Assessment of Combination Product Review Practices in PDUFA VI

Prepared by:

Eastern Research Group, Inc.

110 Hartwell Avenue

Lexington, MA 02420

August 7, 2020

Table of Contents

Executive Summary

Combination products are therapeutic and diagnostic products that contain two or more types of medical products as constituent parts: a drug and device, a drug and biologic, a biologic and device, or all three (drug, biologic, and device). In 1991, the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH) entered into inter-center agreements to provide guidance on the classification and assignment of medical products and clarify jurisdiction over combination products. In 2002, the Office of Combination Products (OCP) was established to help achieve prompt assignment of combination products, promote the development of standardized guidance, support timely premarket reviews by the Centers, and support consistent and appropriate postmarket regulation.

As part of the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI), FDA committed to contracting with an independent third party to assess current combination product review practices. Accordingly, FDA enlisted Eastern Research Group, Inc. (ERG) to conduct such an independent assessment. To do so, ERG developed a set of evaluation questions and metrics, data collection protocols and instruments, and three assessment samples to study:

- **Request for Designation (RFD)/Pre-RFD Sample:** 3 RFD and 46 Pre-RFD reviews completed between September 1, 2018 and January 31, 2020.
- **Inter Center Consult Request (ICCR) Sample:** 86 ICCRs for 17 Investigational New Drugs (INDs), 16 New Drug Applications (NDAs), and 1 Biologics License Application (BLA) for combination products that were active between September 1, 2018 and January 31, 2020.
- **IND/NDA/BLA Sample:** 39 INDs, 27 NDAs, and 9 BLAs that were identified as combination products. INDs in this sample were active between September 1, 2018 and January 31, 2020. Eligible NDAs and BLAs were submitted in PDUFA VI and received a first-cycle action between September 1, 2018 and January 31, 2020.

ERG then collected data for the samples, analyzed the data, answered the evaluation questions, and developed a set of findings and recommendations.

Summary of Results

Pre-RFD and RFD Sample

Sponsors and FDA reviewers generally characterized Pre-RFD and RFD review practices as effective and efficient despite some challenges (described below). They also commented on the value of Pre-RFD and RFD guidance, with most sponsors stating that they used this guidance in preparing their submissions.

Pre-RFDs. In this assessment, sponsors preferred obtaining combination product assessments by means of Pre-RFDs (n=46) much more than RFDs (n=3) for two main reasons: the Pre-RFD process provides more opportunities for interaction with FDA, and submission requirements are more flexible. For 57% of Pre-RFDs, FDA needed to email sponsors one or more requests for more information in order for the submissions to be sufficient for review; a majority of these requests were for further explanation of how

the product works and product components, ingredients, or specifications. In some cases, the need for more data reflected sponsor reluctance to provide information that might not support their desired recommendation for classification and Center assignment. In other cases, particularly for products in early development, the back-and-forth communication helped sponsors characterize their combination products more completely and gain insight into how FDA uses their information to determine product classification and assignment. Due to the need for this back-and-forth for some Pre-RFDs, the time from FDA receipt of the Pre-RFD to acceptance for review varied widely, from 0 to 287 days (mean 27 days, median 9 days), with two outliers being responsible for the bulk of the range. Once FDA accepted Pre-RFDs as complete for review, the Agency usually issued assessment responses within the aspirational 60-day goal for Pre-RFDs. Not surprisingly given the wide variability in time from Pre-RFD receipt to acceptance, the total time from receipt to assessment response also varied widely, from 1 to 348 days (mean 83 days, median 66 days).

For Pre-RFDs, some sponsors appreciated the opportunity to have informal teleconference calls with OCP and Center staff to clarify information about their product or the rationale for the product classification and Center assignment. Other sponsors noted that a teleconference would have been helpful but they did not realize that they needed to request the call. OCP and Center staff stated that informal teleconferences with sponsors were useful for gaining information about a product or explaining their reasoning for Pre-RFD feedback but were not worthwhile if used by the sponsor to present clinical data outside the scope of the primary mode of action determination or to argue legal topics.

In the Pre-RFD process, the primary challenge for FDA reviewers was obtaining enough information from sponsors to be able to initiate the assessment. Most sponsors did not identify challenges. Those who did were mainly sponsors who received FDA Pre-RFD feedback that differed from their desired recommendations. Some of these sponsors commented that it was difficult to learn who in FDA reviewed their Pre-RFDs and which data/studies were used as the basis for the assessment; these sponsors wondered whether appropriate subject matter experts were involved in the assessment and whether they gave adequate weight to data/studies that supported the desired Pre-RFD feedback.

RFDs. In this assessment, sponsors adhered to, and FDA enforced, the 15-page limit for RFDs. OCP filed all three RFDs in the sample within the required 5 business days after receipt and issued designation letters in less than the required 60 calendar days after filing. Thus, the total time from FDA receipt of an RFD to designation decision was 64 to 65 calendar days. Sponsors and FDA staff cited no challenges with RFD reviews.

ICCR Sample

In this assessment, the ICCR process was effective in enabling the Lead Center to obtain information and expertise from the Consulted Center despite many instances of recommended ICCR process timelines not being met. As described further below, technology and other challenges sometimes made the process less efficient than it otherwise could have been.

In the ICCR sample, CDER submitted 86 ICCRs to CDRH. (The sample did not include cases where CBER was the Lead Center or Consulted Center.) Due to partial overlap in the qualifying criteria for the ICCR

sample and IND/NDA/BLA sample, 30 of the 86 ICCRs in the ICCR sample are also represented in the IND/NDA/BLA sample. CDER submitted 56% of the ICCRs within the recommended 7-14 days of application receipt. CDER staff cited two reasons for later-than-recommended ICCR submissions: late notification from a Lead Center submission contact to the Lead Center consult requestor that an ICCR was needed, and initial submission to the wrong group in CDRH, necessitating resubmission to the correct group. Subsequently, CDRH assigned 53% of ICCRs to reviewers within 2-3 days of ICCR form submission; because 44% of ICCR forms were submitted later than recommended, this meant that CDRH assigned 38% of the ICCRs to reviewers within the recommended 9-17 days of application receipt. When CDRH took more than 2-3 days to assign reviewers to ICCRs, staff attributed delays to insufficient information in the ICCR form to decide who best to respond (resulting in a need for communication with the Lead Center to clarify) and inconsistent access to Lead Center databases to review details needed to assign the ICCR. CDRH completed 34% of ICCRs by the date that CDER requested. They sometimes emailed responses so the CDER requestor would receive them as quickly as possible (before official transmittal).

CDER staff generally characterized ICCR practices as reasonably smooth, timely, and high quality once CDRH assigned a reviewer. However, after transition from a SharePoint-based system to a Salesforce-based system, CDER staff were nearly unanimous in characterizing the ICCR submission process in Salesforce as a source of inefficiency, and some found it challenging to discern to whom to submit consults in CDRH. CDRH staff generally characterized ICCR practices as adequately efficient, but noted that accessing data from CDER databases was often difficult, resulting in decreased efficiency and delays. They also noted that insufficient information in ICCRs increased the time it took them to process requests—and that requested due dates were sometimes unreasonably short, though communicating with the CDER contact sometimes revealed leeway. CDRH staff observed that more recent ICCRs have included CDER review milestone dates; this provided context for the requested due dates and helped streamline workload planning.

IND/NDA/BLA Sample

In this assessment, except for the addition of combination product ICCRs, submission and review practices for combination product applications were generally similar to those for noncombination product applications. FDA staff generally characterized combination product reviews as efficient and routine, and sponsors generally characterized their experiences positively, citing FDA's responsive communication practices and timely actions. In preparing combination product applications, sponsors valued FDA's guidances and found industry conferences and PDUFA meetings with FDA to be helpful sources of information.

Like other NDAs and BLAs, combination product applications are expected to meet FDA's standard requirements for a complete application before being filed and reviewed. ERG analyzed NDA and BLA completeness in two ways: by asking FDA review teams for their assessment of the application after the end of the review, and by reviewing FDA Information Requests (IRs) that identified missing data. By FDA review team assessments, 64% of NDAs/BLAs in the sample were complete and adequately organized. The remaining applications had deficiencies in application organization, device data, facility inspection readiness, pharmacology/toxicology data, or product quality microbiology data; FDA reviewers typically

found these issues after filing, while conducting a more in-depth review of the data. By analyzing IRs, ERG estimated that 75% of applications were complete on original submission; many IRs identified Clinical data or patent certification as missing from submissions. The application completeness rates observed in this assessment were slightly lower than those found in a previous assessment of the PDUFA V Program for New Molecular Entity (NME) NDAs and original BLAs; it is unclear whether these differences are meaningful given that the assessments were conducted under different regimes (PDUFA V versus PDUFA VI). Not surprisingly, large sponsors and sponsors with previous combination product application experience were most likely to submit complete NDAs and BLAs in this assessment.

Sponsors interviewed for this assessment cited one challenge with reviews of their combination products: receiving CDRH input near or after the 30-day Safety review or pre-NDA or pre-BLA meeting. Separately, they also suggested that FDA provide new or updated guidance for transdermal devices, topical delivery combination products, outdated IND guidance, amount/thoroughness of device data needed for INDs, and location of device data in the electronic common technical document (eCTD).

Findings and Recommendations

Based on the results of this assessment of combination product review practices, ERG developed a set of findings and recommendations (Table ES-1) organized in two categories: overarching (related to combination product review practices overall) and specific (related to particular aspects of combination product review practices).

Table ES-1. Findings and Recommendations

Type	No.	Finding	Recommendation(s)
Overarching	O1	RFD and Pre-RFD review practices are fundamentally sound, and could be enhanced by some straightforward refinements.	See Recommendations S1, S2, and S3.
	O2	The ICCR process is fundamentally sound, and could be made more efficient by addressing technology challenges and implementing some good practices.	See Recommendations S4 and S5.
	O3	Combination product IND, NDA, and BLA submission and review practices are largely similar to those of noncombination products and are fundamentally sound. Implementing minor refinements to certain guidances and practices could further enhance the combination product application submission and review process.	See Recommendations S6 and S7.
Specific	S1	On first submission, many Pre-RFDs contain insufficient information on which to base a classification and Center assignment feedback, including insufficient information about how the product works and components, ingredients, or specifications.	Develop a good practices document for sponsors for successful Pre-RFDs, including a list of types of information that FDA often requests. Include the good practices when transmitting guidance documents to sponsors.

Type	No.	Finding	Recommendation(s)
	S2	Informal teleconferences between sponsors, OCP, and Center staff provide valuable opportunities to clarify details of the Pre-RFD and product and to determine next steps in product development.	During early contacts about a Pre-RFD, tell sponsor that informal teleconferences must be requested by sponsor. Explain that sponsor may request a teleconference during review to discuss what is needed for submission or afterwards to discuss assessment.
	S3	Sponsors would like to know which FDA personnel were involved in the classification and Center assignment for their Pre-RFD and which types of data and studies served as the basis for the feedback. Providing the latter could increase sponsor understanding of which types of studies and data to submit and reduce the number of unnecessary 510(k)s submitted to CDRH.	At the time of feedback, inform sponsors about which data/studies were relevant to the feedback. *Note: FDA already identifies the decision-maker for Pre-RFD feedback.*
	S4	For ICCRs, technology issues hinder the work of Lead and Consulted Center staff. Frequent challenges are using Salesforce and accessing databases in other Centers. In addition, technology enhancements could help address other challenges, such as ICCR routing and tracking of ICCR work.	Address significant technology challenges: • Salesforce—Expand awareness of support available from ICCR Help Desk and consider providing one-on-one real-time assistance to requestors. • Access to other Center databases—Implement an automated process to identify and request access for reviewers when ICCR reviewer assignment is made. Refine existing technologies to address process inefficiencies: • In Salesforce, provide readily-accessible descriptions of each available CDRH group (e.g., in a reference pane or as a tooltip in the group selection dropdown). • In CDRH, consider how to track ICCR work in the same system as all other CDRH work in order to better track reviewer availability for ICCRs (and better manage workload).
	S5	FDA's internal process guides for ICCRs provide useful information for Lead and Consulted Center staff. Reiterating or establishing some good practices could help ease ICCR timeline pressures.	Reiterate or establish as good practices: • Lead Center: Submit ICCR form as early as possible. • Lead and Consulted Centers: Establish early contact for ICCRs. • Lead Center: Provide planned review milestone dates in ICCRs. • Lead and Consulted Centers: Agree on a due date if feasible for review. • Consulted Center: Email response to Lead Center if deadline is tight. • Lead Center: For continuity, request same consult reviewer for follow-up consults.

Type	No.	Finding	Recommendation(s)
	S6	Sponsors find value in meetings that include CDRH (Consulted Center) staff, noting that this sends a signal of openness to communication.	Where appropriate, include CDRH (Consulted Center) staff in meetings with sponsors (e.g., to discuss device testing issues).
	S7	Combination product sponsors find the following sources to be useful for them in preparing submissions: FDA guidance, industry conferences, meetings with FDA, and previous experience. FDA guidance could be even more useful if new or updated information were provided for certain topics.	Provide new or updated guidance for transdermal devices, topical delivery combination products, amount/thoroughness of device data needed for INDs, and location of device data in eCTD. Continue to share information with combination product sponsors at industry conferences.

1. Introduction

Regulatory History of Combination Products

Combination products are therapeutic and diagnostic products that contain two or more types of medical products as constituent parts: a drug and device, a drug and biologic, a biologic and device, or all three (drug, biologic, and device). Combinations of medical products of the same type (e.g., drug and drug, biologic and biologic, or device and device) and combinations of medical products with non-medical products (e.g., food or cosmetics) are not considered to be combination products.

In 1991, the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH) entered into inter-center agreements to provide guidance on the classification and assignment of medical products and clarify jurisdiction over combination products. Over time, the advent of innovative new therapies and products required FDA to make case-by-case decisions on review jurisdiction. From a technical standpoint, combination products introduced the need to address quality issues across different types of manufacturing facilities; human factors involved in administering multi-component products; bridging studies to address possible pharmacodynamic, pharmacokinetic, and toxicological interactions; and complex labeling to reflect multiple product components. Moreover, because these products require expertise from multiple Centers (which follow different regulations, processes, and pathways for development and review), FDA and sponsors encountered challenges in coordination, management, transparency, consistency, and reconciling differing Center needs during the various stages of drug development, market application review, and postmarketing.

In 2002, the Office of Combination Products (OCP) was established to achieve prompt assignment of combination products, timely premarket reviews, and consistent postmarket regulation and standardized guidance. Since then, FDA has taken further steps to modernize the Agency's combination product review program. For example, FDA:

- *Updated the Inter-Center Consult Request (ICCR) process (2016).* FDA established consult review timelines, developed a tiered consult approach, defined FDA organization roles and responsibilities, facilitated cross-center database access, standardized ICCR forms, and conducted training to familiarize staff with combination product reviews. In continuing support of updating the ICCR process, FDA also created Staff Manual Guide (SMG) 4101 Combination Products Inter-Center Consult Request Process (2018).

- *Formed the Combination Products Policy Council (2016),* which is a decisional authority within FDA to address complex combination product topics and issues.

- *Issued draft and final guidances:* Human Factors Studies and Related Clinical Study Considerations (2016), Current Good Manufacturing Practice Requirements (2017), Classification of Products as Drugs and Devices (2017), Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (2017), How to Prepare a Pre-RFD (2018), Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications (2018), Bridging for Drug-Device and Biologic-Device Combination Products (2019), Requesting FDA Feedback on Combination Products (2019), and Instructions for Use — Patient Labeling for Human Prescription Drug and

Biological Products and Drug-Device and Biologic-Device Combination Products — Content and Format Guidance for Industry (2019).

- *Issued a final rule on postmarketing safety reporting requirements (2019)* to ensure consistent and efficient reporting from combination product sponsors.
- *Developed a Manual of Policies and Procedures (MAPP), Procedures for DMEPA Intra-Center Consult to DMPP on Patient-Oriented Labeling Submitted with Human Factors Validation Study Protocols (2019)* to ensure efficient, effective, and consistent combination product development and review as it relates to patient-oriented labeling, including instructions for use materials, for drug-device and biologic-device combination products regulated by CDER and CBER.
- *Submitted annual performance reports to Congress*[1] *since 2003* summarizing OCP's activities and efforts to ensure the prompt assignment of combination products to Agency Centers, timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of combination products.

PDUFA VI Combination Products Review Practices Assessment

Congress originally enacted the Prescription Drug User Fee Act (PDUFA) in 1992 to help ensure timely review of new drugs and biologics. Since then, Congress has reauthorized PDUFA every five years. In PDUFA V (FYs 2013-2017) and PDUFA VI (FYs 2018–2022), FDA made improvements to the combination product program as described above. An overview of the current combination products regulatory review process appears in Figure 1-1.

As part of PDUFA VI, FDA committed to contracting with an independent third party to assess current combination product review practices. Accordingly, FDA enlisted Eastern Research Group, Inc. (ERG) to conduct such an independent assessment. Specifically, FDA asked ERG to:

1. Using information from both qualitative and quantitative data gathered from interviews and FDA's corporate databases as well as other databases, characterize the current state of the submission and review of combination products process.
2. Collect and analyze qualitative feedback from both FDA review staff and sponsors on what is working well and what is not working well throughout the process; this includes identifying best practices and areas for improvement.
3. Make recommendations for FDA review staff and sponsors on how to improve the process.

[1] Combination Products Performance Reports. https://www.fda.gov/about-fda/reports/combination-products-performance-reports

Figure 1-1. Overview of the Combination Product Regulatory Review Process

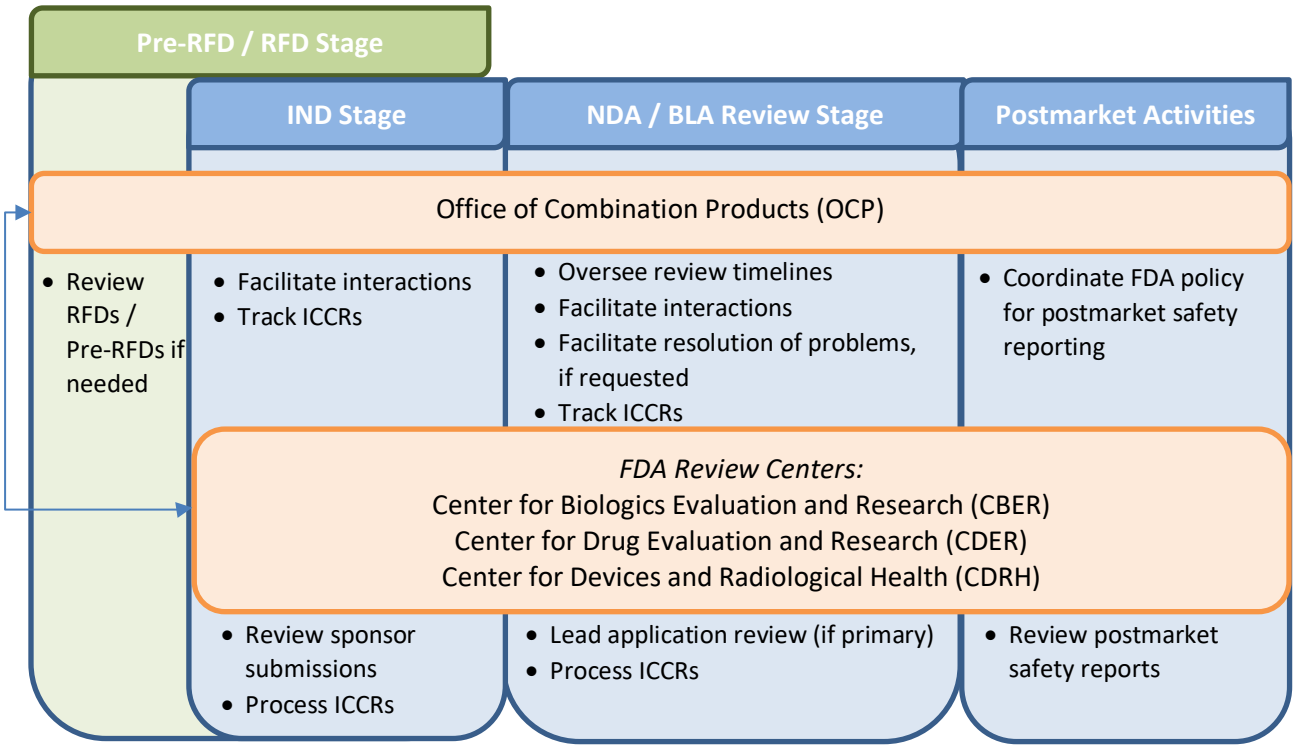


Figure 1a. Request for Designation Process (RFD) and Pre-RFD Process

Requests for Designations (RFDs) & Pre-RFDs:

- RFDs and Pre-RFDs are optional assessments of a regulatory identity or classification and assignment of a product.
- Either legally binding (RFDs) or informal feedback (Pre-RFDs).
- Typically submitted early in product development before an Investigational New Drug (IND) application or Pre-Market Application to determine Lead Center.
- Designation decision made by the Office of Combination Products (OCP).
- In the absence of an RFD or Pre-RFD, sponsors submit applications to the Center that they believe is most appropriate. The Center will notify the sponsor if a different Center should lead the review of their application or refer sponsor to OCP for a jurisdictional determination.

Figure 1b. Inter-Center Consult Request (ICCR) Process

Inter-Center Consult Requests (ICCRs):

- During the clinical development and review of combination products, reviewers may request consults from other Centers.
- These consults request specialized knowledge or expertise from another Center.
- Reviewers in the Consulted Center provide a written review to the Lead Center.
- These consults are tracked via the ICCR process.

ERG operationalized these objectives into measurable assessment questions, listed below.

Assessment Questions

1a. What are current combination product submission and review processes and practices?

1b. To what extent do current combination product submissions and reviews incorporate recommended practices, guidances, and standard operating procedures?

2. How do submission and review practices vary by combination product characteristics such as sponsor size, sponsor experience, combination product category and complexity/novelty, Center involvement/roles, and therapeutic area?

3. How do FDA review staff and sponsors characterize combination product development review and premarketing application review processes?

4. What practices enhance combination product reviews and what challenges hinder reviews?

5. What steps should FDA and sponsors take to improve the combination product review process?

This report describes ERG's assessment combination product review practices under PDUFA VI. The remainder of this report includes:

- Section 2: Methods
- Section 3: Assessment Questions and Answers
- Section 4: Findings and Recommendations
- Appendix A. Acronyms and Glossary
- Appendix B: Evaluation Protocols and Instruments
- Appendix C: Distribution of Traits of Interest in Assessment Samples
- Appendix D: Results

2. Methods

ERG used a systematic process to identify, collect, and analyze comprehensive data for this assessment of combination products review practices. 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 combination products assessment questions. ERG organized these metrics into the following categories: RFD and Pre-RFD submissions and reviews, ICCRs, and combination product applications and reviews.
2. **Develop evaluation protocols and instruments** — The evaluation metrics established a structure for data that needed to be collected to generate results. Accordingly, ERG prepared evaluation protocols and instruments (see Appendix B) to serve as a guide for ERG to obtain descriptive information. This includes collecting data about combination products, sponsor submissions, and FDA reviews, and conducting interviews with sponsors and FDA staff to elicit information and opinions about review practices. For the interviews with combination product sponsors, ERG prepared an Information Collection Request (ICR) for FDA to submit to the Office of Management and Budget (OMB) to request permission to implement this information collection. OMB approved the ICR, assigning an OMB Control Number of 0910-0868.
3. **Create samples** — For this assessment, ERG developed three samples (Table 2-1). ERG built the samples prospectively during the 17-month data collection period of September 1, 2018 to January 31, 2020. For all three samples except the NDA/BLA portion of the third sample, ERG added to the samples each month as follow: (1) identify all new requests/applications that month; (2) randomly select requests/applications (n/17 for each sample) to add; (3) assess conformance of each sample with target distributions for traits of interest; and (4) if some traits are underrepresented, replace requests/applications with others that have underrepresented traits. For the NDA/BLA portion of the third sample, ERG included all combination product NDAs/BLAs that received a first-cycle action during the data collection period.

   Note: Because this assessment represents a commitment for PDUFA VI, ERG included and examined combination products with CDER or CBER (and not CDRH) as the Lead Center.

Table 2-1. Samples for Combination Product Review Assessment

Sample	Description	Sample Size (n)
RFD/Pre-RFD	New RFDs/Pre-RFDs for examination of requests and review practices	49 (3 RFDs, 46 Pre-RFDs)
ICCR	Active commercial INDs and NDAs/BLAs for examination of ICCR practices	34 (17 INDs, 17 NDAs/BLAs)
IND/NDA/BLA	New active commercial INDs/Pre-INDs and NDAs/BLAs with a first-cycle action for examination of applications and review practices	75 (39 INDs/pre-INDs, 36 NDAs/BLAs)

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

- *Sponsor size (by number of employees):* Small (≤500), Medium (501 to 15,000), Large (≥15,001), or Private (not publicly disclosed)
- *Sponsor experience:* Yes (has had at least one combination product NDA/BLA filed), No (has not had a combination product NDA/BLA filed)
- *Combination product category:* 1, 2, 3, 4, 5, 6, 7, 8, 9
- *Lead-Consult Centers:* CDER or CBER as Lead Center, with CDRH or CDER or CBER as Consulted Center
- *Therapeutic area:* As defined by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class

Using data on FY 2017 active commercial combination product INDs, ERG generated target distributions for the traits of interest. In building the three samples each month throughout the assessment period, ERG found that reaching the target distribution was infeasible due to an insufficient number of new combination product INDs, NDAs, and BLAs that represented the traits of interest. Target and actual distributions for traits of interest in the three samples appear in Appendix C.

4. **Collect data** — For each of the three samples, ERG collected both qualitative and quantitative data in accordance with the procedures specified in the data evaluation protocols and instruments. ERG entered quantitative data into an Excel database designed to store the raw data and compute metrics values. 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 in order to generate meaningful information to answer the assessment questions. ERG performed three types of data analysis: (1) descriptive analysis to describe characteristics of RFD and Pre-RFD submissions and reviews, ICCRs, and combination product applications and review; (2) quantitative analysis to compute and analyze evaluation metrics, and to examine differences based on traits of interest (sponsor size, sponsor experience, combination product category and type, Lead-Consult Centers, and therapeutic area); and (3) qualitative analysis to gain insights into current combination product review practices from FDA review teams and sponsors. Results appear in Appendix D. Due to the small sample sizes, the data were insufficient to determine statistical significance, so 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. Assessment Questions and Answers

1a. What are current combination product submission and review processes and practices?

Combination product submission and review processes and practices can be divided into three areas: submission and review of RFDs and assessment of Pre-RFDs, internal FDA review consultation via the ICCR process, and submission and review of combination product INDs, NDAs, and BLAs.

RFD and Pre-RFD Submissions and Reviews/Assessments. Sponsors may utilize the RFD or Pre-RFD process to receive a formal binding (RFD) or informal, non-binding (Pre-RFD) feedback about the regulatory identity or classification of a medical product as a drug, device, biological product, or combination product – and to determine the FDA Center to which a product will be assigned. This process is not required but can be beneficial during early development when classification and Center assignment might be unclear or in dispute. In the absence of an RFD or Pre-RFD, sponsors submit applications to the Center that they believe is most appropriate; the Center will notify the sponsor if a different Center should lead the review of an application. Based on this sample, sponsors preferred obtaining classification and Center assignment through Pre-RFDs (n=46) rather than RFDs (n=3).

Question 1.a: Key Points

Based on the results of this assessment:

- Many sponsors preferred obtaining product classification and Center assignment through Pre-RFDs rather than RFDs, citing the lack of page limits and the opportunity for more interaction with FDA with the Pre-RFD process.
- Pre-RFDs involved more interaction with FDA than RFDs. The overall timeframe varied widely. FDA staff often needed to solicit more information from sponsors prior to accepting Pre-RFDs for review, which sometimes prolonged the timeline. For most Pre-RFDs, once FDA had adequate information to accept it for review, FDA provided feedback within 60 days (as it did for RFDs).
- The ICCR process was effective in enabling the Lead Center to obtain information and expertise from the Consulted Center despite recommended timelines not being met in many cases. Technology and other challenges sometimes made the process less efficient than it otherwise could have been.
- Except for the addition of combination product ICCRs, for both FDA staff and sponsors, review practices for combination product applications were similar to those for noncombination product applications.

- ***RFDs.*** FDA guidance provides information about what sponsors should include in RFDs and imposes a limit of 15 pages per 21 CFR Part 3. When a sponsor submits an RFD, OCP has 5 business days to determine whether to file the RFD (because it is complete enough to proceed to review) or reject it. Upon filing, OCP has 60 calendar days to complete the review and issue a designation letter; if OCP does not provide a designation within 60 days, the sponsor's recommendation for classification or assignment becomes the designation.

  In this assessment, sponsors adhered to and FDA enforced the 15-page limit for RFDs. OCP filed all three RFDs in the assessment sample within the required 5 business days after receipt and issued designation letters in less than the required 60 calendar days after filing. The total time from FDA receipt of an RFD to designation decision was 64 to 65 calendar days.

- ***Pre-RFDs.*** FDA guidance specifies content recommendations for Pre-RFDs (description of product, proposed use or indication for use, manufacturing process and/or source materials, and a description of how the product achieves its intended therapeutic or diagnostic effects) and imposes no page limit. When a sponsor submits a Pre-RFD, OCP may request additional information or clarification in order for the Pre-RFD to be complete for an assessment. Once OCP accepts the Pre-RFD for assessment, the Office strives to provide a preliminary classification or Center assignment within 60 calendar days, though assessments may take longer if necessary. In an email request separate from the Pre-RFD, sponsors may request a meeting or teleconference with OCP prior to submitting their Pre-RFDs or during the review to further explain how their product works.

  In this assessment, OCP asked for additional information from sponsors for 57% of the 46 Pre-RFDs in the sample before accepting the Pre-RFDs for an assessment; for those Pre-RFDs, OCP and sponsors went through one to four rounds of clarification to reach the point of readiness for an assessment. In a majority of cases, FDA requested an explanation of how the product works and a description of product components, ingredients, or specifications. As a result, the time from FDA receipt of the Pre-RFD to acceptance for review varied widely, from 0 to 287 days (mean 27 days, median 9 days). Therefore, the time from FDA receipt to informal feedback varied widely, from 1 to 348 (mean 83 days, median 66 days). Two outliers were responsible for the bulk of the range, as most Pre-RFDs were ready for an assessment within about 20 days and OCP usually responded with preliminary classification and Center assignment feedback within 60 days after acceptance for review. Four sponsors stated that they opted to have a teleconference with OCP in addition to the Pre-RFD to further discuss their products.

Internal FDA Review Consultation via ICCRs. Lead Centers use the ICCR process to consult reviewers from other Centers when specialized knowledge and expertise are needed for combination product review. For some types of combination products, Lead Centers may possess the appropriate expertise, so staff do not request consults. When ICCRs are needed, FDA recommends internal timelines for ICCR submission and ICCR reviewer assignment to encourage the completion of consults in a timely manner. During this assessment, the process for submitting and managing ICCRs changed from a SharePoint-based system to a Salesforce-based system. ERG based the evaluation of ICCR timeliness on task completion records in the Salesforce and SharePoint systems. With the introduction of the new system, users faced challenges related to learning and acclimating to new processes, which sometimes affected the ability of Lead and Consulted Center to process ICCRs within recommended timelines. Since the Salesforce system launched in May 2019, FDA has been making ongoing efforts to support, enhance, and integrate the system into the ICCR process.

In the ICCR sample for this assessment, 86 ICCRs were issued for 34 combination product applications. Due to partial overlap in the qualifying criteria for the ICCR sample and IND/NDA/BLA sample, 30 of the 86 ICCRs in the ICCR sample are also represented in the IND/NDA/BLA sample. In each of the 86 cases, CDER was the Lead Center and CDRH was the Consulted Center. Within CDRH, the Office of Health Technology 3 (OHT3) and Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices (DAGRID) received and processed a majority (65%) of the ICCRs. The Lead Center submitted 56% of ICCRs within FDA-recommended timelines, the Consulted Center assigned 38% of ICCRs to reviewers within FDA-recommended timelines, and the Consulted Center completed 34% of

ICCRs by the date requested by the Lead Center; Consulted Center staff sometimes reached out to the Lead Center to negotiate completion dates when this was feasible for the review schedule. Delays were largely attributable to technology challenges (unintuitive Salesforce system, difficulty accessing databases in other Centers), uncertainty in to whom to submit a consult, a need to communicate with the Lead Center to supplement information in consult requests, and sometimes difficulty balancing heavy workloads.

IND, NDA, and BLA Submissions and Reviews. FDA receives and reviews combination product applications in the IND stage and in the marketing application (NDA and BLA) stage. Combination product applications are initially categorized into one of nine known categories or an additional tenth "unknown" category. The process for this categorization is fluid, as product presentation and categorization may change over time during the IND stage or between the IND and marketing application stages based on changes to the product or its labeling. Depending on the type of combination product, FDA may require sponsors to submit data related to the device constituent, Human Factors (HF) studies, or bridging studies; FDA typically communicates the need for this information to sponsors during IND reviews. Aside from additional activities surrounding consults (in the form of ICCRs), the process for reviewing most combination product applications is similar to that for reviewing noncombination product applications.

Based on data for 39 combination product INDs and 36 combination product NDAs and BLAs collected during this assessment, the most common categories of combination products applications were Type 2–Prefilled Drug Delivery System (45%), Type 1-Convenience Kit or Co-Package (21%), and Type 3–Prefilled Biologic Delivery System (13%). Review practices resembled those for noncombination products; ICCR practices for applications in this sample were similar to those described for the ICCR sample above.

Question 1.b: Key Points

Based on the results of this assessment:

- Sponsors and FDA conformed to RFD guidance in terms of content and timelines.
- About half of Pre-RFDs lacked sufficient information for FDA to initiate a review and make an assessment. Requesting more information sometimes caused delays, but FDA almost always made an assessment within the recommended timeline once a Pre-RFD was accepted for review.
- Lead Centers submitted ICCR forms within recommended timelines for 56% of ICCRs, with delays attributed to late notification of a need for consult and uncertainty about to whom to submit the form. Consulted Centers assigned reviewers within recommended timelines for 38% of ICCRs, with delays attributed to insufficient information in the form and difficulty accessing Lead Center databases.
- About 75% of NDAs/BLAs were complete and 64% were complete and organized on first submission, with deficiencies typically being found after more in-depth review than occurs during the filing review period.
- For NDAs/BLAs, conformance with FDA guidelines was consistent with what reviewers typically experience with noncombination product applications.

1b. To what extent do current combination product submissions and reviews incorporate recommended practices, guidances, and standard operating procedures?

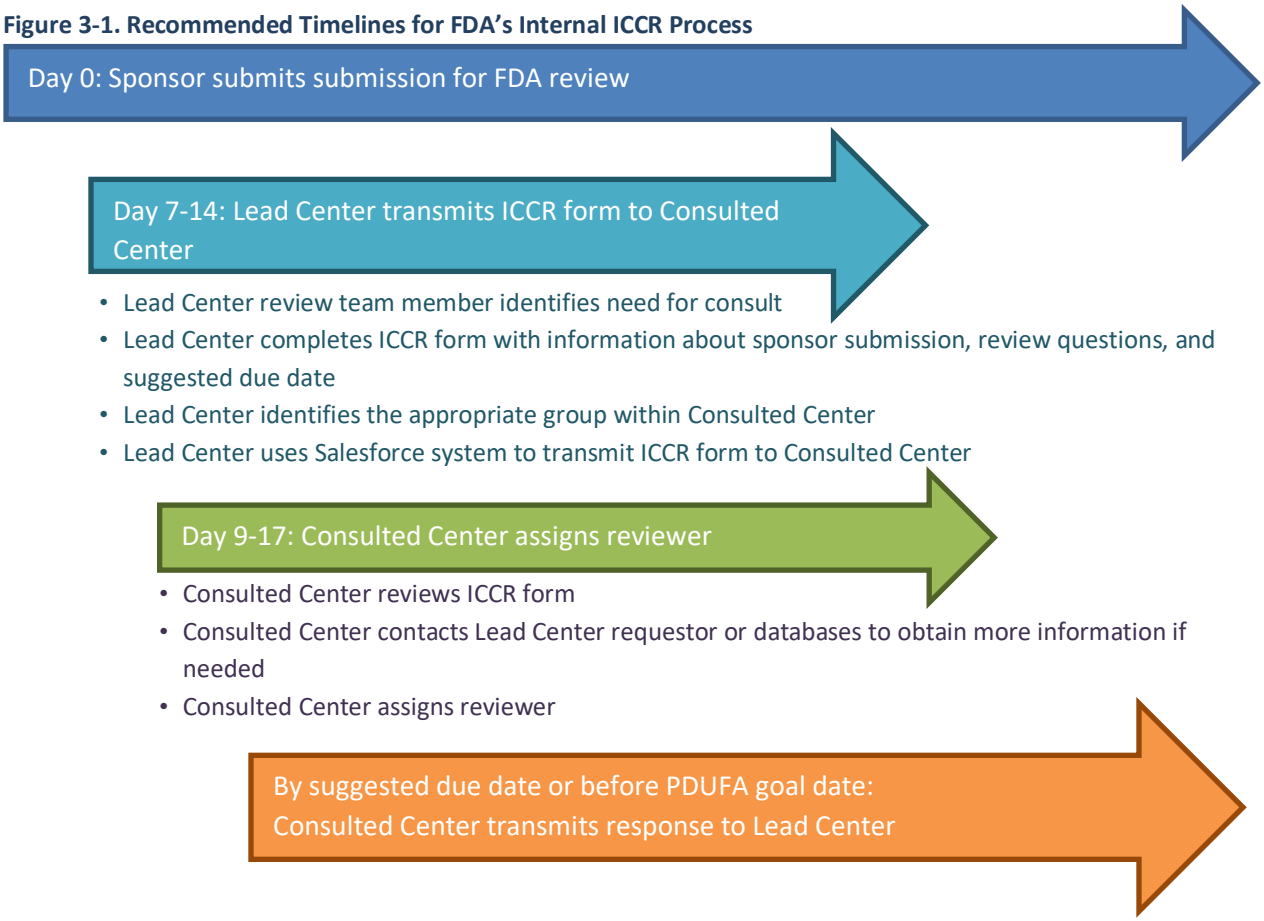
In this assessment, adherence to recommended practices, guidances, and standard operating procedures varied by assessment sample.

RFD and Pre-RFD Submissions and Reviews/ Assessments. In this assessment, most sponsors

consulted FDA guidance in preparing their RFD and Pre-RFD submissions. In accordance with published guidance, OCP assessed all three filed RFDs for adherence to RFD requirements within 5 business days of submission and issued designation letters within the 60-day goal (58 to 59 calendar days after the filing date). For Pre-RFDs, 43% of submissions did not need additional rounds of clarification and the remaining 57% needed one to four clarification rounds to be considered complete enough to initiate an assessment. In these clarification rounds, FDA asked for more data to support the Pre-RFD (most often, additional information about how the product works or additional information on product components, specifications, and ingredients). In some cases, the need for more data reflected sponsor reluctance to provide information that might not support their recommendation for classification and Center assignment. In other cases, particularly for products in early development, the back-and-forth communication helped sponsors characterize their combination products more completely and gain insight into how FDA uses their information to assess product classification and Center assignment. Once FDA accepted Pre-RFDs as complete, the Agency usually issued feedback within the aspirational 60-day goal for Pre-RFDs. In three cases, reviews took considerably longer (105 to 188 days).

Internal FDA Review Consultation via ICCRs. In this assessment, FDA's review Centers struggled to meet two timelines recommended in internal FDA process guides for completing ICCR activities (Figure 3-1):

Figure 3-1. Recommended Timelines for FDA's Internal ICCR Process



- ***Lead Center transmittal of the ICCR form to the Consulted Center 7 to 14 days after receipt of a submission from a sponsor:*** The Lead Center transmitted 56% of ICCR forms (n=86) to the Consulted Center within the recommended timeline. CDER staff cited two reasons for later-than-recommended ICCR transmittal: (1) late notification from a Lead Center submission contact to the Lead Center consult requestor that an ICCR was needed, and (2) initial submission to the wrong group in the Consulted Center, necessitating resubmission to the correct group.
- ***Consulted Center assignment of the ICCR to a reviewer 9 to 17 days after receipt of submission:*** The Consulted Center assigned 38% of ICCRs to reviewers within the recommended timeline. CDRH staff attributed delays to late submission of the ICCR form (reducing the time available to assign a reviewer within the recommended timeline), insufficient information in the ICCR form to decide who best to respond (resulting in a need for communication with the Lead Center to clarify), and inconsistent access to Lead Center databases to review details needed to assign the ICCR.

IND, NDA, and BLA Submissions and Reviews. In this assessment, sponsor and FDA conformance with guidance for submission content and review timelines was generally similar to that experienced with noncombination product reviews. Like other NDAs and BLAs, combination product applications are expected to meet FDA's standard requirements for a complete application before being filed and reviewed. ERG analyzed NDA and BLA completeness in two ways:

- ***By asking FDA review teams for their assessment*** of the application after the end of the review. Using FDA reviewer assessments as the measure, 64% of NDAs/BLAs in the sample were complete and adequately organized. The remaining applications had deficiencies in application organization, device data, facility inspection readiness, pharmacology/toxicology data, or product quality microbiology data; FDA reviewers typically found these issues after filing, while conducting a more in-depth review of the data.
- ***By reviewing FDA Information Requests (IRs) that identified missing NDA/BLA data.*** Using an absence of FDA IRs for missing information as the measure, ERG estimated that 75% of applications were complete on original submission; many IRs (n=24) identified clinical data (25%) or patent certification (21%) as missing from submissions.

ERG found no ICCRs for 20 of 75 INDs/NDAs/BLAs in this sample; most applications without ICCRs (17 of 20) were INDs. For certain types of combination products, the Lead Centers need not submit ICCRs to other Centers when the appropriate knowledge and expertise are available in the Lead Center. Of the 20 applications without ICCRs in the sample, 11 fell into that category; it is likely that the remaining 9 applications (all INDs) did not require ICCRs due to the stage of development. For applications with ICCRs, adherence to recommended ICCR timelines was similar to that found for ICCRs in the ICCR sample (described above).

2. How do submission and review practices vary by combination product characteristics such as sponsor size, sponsor experience, combination product category and complexity/novelty, Center involvement/roles, and therapeutic area?

Question 2: Key Points

Based on the results of this assessment:

- Sponsors that are large or have previous combination product application experience tended to submit more complete Pre-RFDs and applications.
- Product complexity might be associated with differences in the extent to which FDA needed to ask for more information from sponsors (for Pre-RFDs), but data were insufficient to determine whether the differences were meaningful.

In this assessment, submission and review practices were generally consistent across sponsor size, sponsor experience, combination product category, Center involvement/roles, and therapeutic area. Nevertheless, some possible patterns in the frequency or duration of review process steps emerged. Due to the small number of combination products in each subgroup by trait of interest, ERG could not assess the statistical significance of these patterns or verify whether the differences were meaningful.

Sponsor Size and Sponsor Experience. Likely owing to their familiarity with FDA's processes and expectations, large companies and those with previous combination product application experience tended to submit more complete documents than other sponsors:

- *Pre-RFDs:* On average these sponsors required fewer rounds of clarification with FDA, which contributed to a shorter time from Pre-RFD receipt to acceptance and Pre-RFD feedback.
- *ICCRs:* On average, applications submitted by large sponsors had more ICCRs than applications submitted by smaller sponsors, possibly due to the greater complexity of their products.
- *NDAs/BLAs:* Large sponsors and sponsors with previous combination product application experience were associated with a greater proportion of complete applications than other sponsors.

Combination Product Category. Within Pre-RFDs, Type 4 and Type 5 products (devices coated, impregnated or otherwise combined with a drug or biologic) were generally associated with more rounds of clarification with FDA than other types of products, possibly because these products were more complex. In contrast, co-packaged (Type 1) and prefilled biologic delivery device systems (Type 3) had the fewest number of clarification rounds. In the ICCR sample, Type 2 (Prefilled Drug Delivery System) products had a higher mean number of days from application submission to ICCR submission than the overall sample.

Lead Center. For Pre-RFDs in the RFD/Pre-RFD sample with CDER eventually assigned as the Lead Center, the time from acceptance to feedback was shorter than for Pre-RFDs with CBER as the assigned Lead Center. For applications in the IND/NDA/BLA sample, applications with CBER as the Lead Center had fewer IRs and amendments than CDER-led reviews; this might be an artifact of differences in how CBER and CDER record IRs and amendments in their databases. Data were insufficient to determine whether these differences were meaningful.

Therapeutic Area. For Pre-RFDs, the mean number of rounds of clarification with FDA varied by therapeutic area. Products in the "endocrine disorders", "injury, poisoning and procedural complications", and "nervous system disorders" therapeutic areas had multiple clarification rounds, while Pre-RFDs in the "immune system disorders" and "metabolism and nutrition disorders" therapeutic areas had no clarification rounds. Within the ICCR sample, applications in the "infection and infestations" therapeutic area were associated with a smaller mean number of days from application receipt to ICCRs submission than the sample as a whole. Differences might be due to the level of complexity of the products, but data were insufficient to determine whether the differences were meaningful.

3. How do FDA review staff and sponsors characterize combination product drug development review and premarketing application review processes?

In this assessment, most FDA staff and sponsors viewed current combination product review practices favorably.

RFD and Pre-RFD Reviews/Assessments. Many sponsors interviewed for this assessment had favorable opinions of the Pre-RFD process, often highlighting the flexibility of FDA's recommendations for submission content and the perceived efficiency relative to the RFD process. For Pre-RFDs, some sponsors appreciated the opportunity to have informal teleconference calls with OCP and Center personnel in order to clarify information about their product, the rationale for the product classification and Center assignment, or next steps for development. Other sponsors of Pre-RFDs noted that a teleconference would have been helpful but did not realize they needed to request the call. For both RFDs and Pre-RFDs, nearly all sponsors who were interviewed noted that they used FDA guidance in preparing their submissions.

Question 3: Key Points

Based on the results of this assessment:

- Overall, most FDA staff and sponsors characterized combination product review practices in favorable terms.
- Many sponsors and FDA (OCP and Center) staff characterized RFD review and Pre-RFD assessment practices as effective and efficient despite some challenges.
- Lead Center and Consulted Center staff characterized ICCR practices as effective, but cited technology issues (challenges with Salesforce, difficulty accessing databases in other Centers) as sources of inefficiency. Uncertainty about to whom to submit ICCR forms and insufficient information in ICCR forms also contributed to inefficiency.
- FDA reviewers characterized combination product review practices as similar to those for noncombination products—mostly routine. Sponsors characterized reviews as positive, responsive, and timely.

OCP and Center staff characterized current RFD review and Pre-RFD assessment practices as effective and efficient, while also noting that individual cases can be difficult to process due to insufficient data from sponsors. These staff also noted that informal teleconferences with sponsors were useful for gaining information about a product or explaining their reasoning for their feedback, but calls were not worthwhile if used by the sponsor to present clinical data outside the scope of the primary mode of action determination or to argue legal topics.

Internal FDA Review Consultation via ICCRs. Lead Center staff generally characterized ICCR practices as reasonably smooth, timely, and high quality once the Consulted Center assigned a reviewer. However, after transitioning from a SharePoint-based system to a Salesforce-based system, staff were nearly

unanimous in characterizing the ICCR submission process in Salesforce as a source of inefficiency, and some found it challenging to discern to whom to submit consults in the Consulted Center. Consulted Center staff generally characterized ICCR practices as adequately efficient, but noted that accessing data from Lead Center databases was difficult, resulting in decreased efficiency and delays. Consulted Center staff also noted that insufficient information in ICCR forms increased the time it took for them to process requests—and that requested due dates were sometimes unreasonably short, though communicating with the Lead Center contact sometimes revealed leeway in those timelines. Consulted Center staff observed that more recent ICCRs have included Lead Center milestone dates; this provided context for the requested due dates and helped streamline workload planning.

IND, NDA, and BLA Reviews. FDA reviewers commented that review practices for combination products and noncombination products are similar, so they focused on the main difference: ICCRs. Their comments about ICCRs mirrored those described above. Sponsors generally characterized their combination product review experiences positively, often citing FDA's responsive communication practices and timely actions. In preparing applications, sponsors valued FDA's combination product guidances and found industry conferences and PDUFA meetings with FDA to be helpful sources of information. Many sponsors who had submitted combination product applications in the past also leveraged that experience to facilitate the submission and review of their applications.

4. What practices enhance combination product reviews, what challenges hinder reviews, and what steps can FDA and sponsors take to improve these processes moving forward?

Table 3-1 presents a summary of good practices, challenges, and suggestions for combination product reviews. This table reflects feedback conveyed by FDA staff and sponsors interviewed for this assessment. ERG considered the totality of all perspectives and data to develop our findings and recommendations (Section 4).

Table 3-1. Good Practices, Challenges, and Suggestions for Combination Product Reviews Based on Assessment
(from the perspective of FDA staff and sponsors interviewed for this assessment)

Practice Area	Good Practices	Challenges	Suggestions
RFD and Pre-RFD Reviews	• FDA providing RFD/Pre-RFD guidance documents to sponsors • Sponsor, OCP, and Center holding informal teleconferences during or after Pre-RFD process	• FDA obtaining necessary information from sponsor • Sponsors learning who reviewed Pre-RFD and which data/studies were basis for classification and Center assignment to understand whether the entirety of data was considered by appropriate subject matter experts	• Hold informal sponsor-OCP-Center teleconferences for more Pre-RFDs • FDA share information with sponsor about who reviewed Pre-RFD and which data/studies were basis for feedback
ICCRs	• Lead Center submitting ICCR form as early as possible • Lead Center establishing early contact between Lead Center contact person and Consulted Center reviewer • Lead Center providing planned review milestone dates in ICCR • Consulted Center negotiating due date for review if feasible • Consulted Center emailing response to Lead Center if deadline is tight	• Lead Center using Salesforce (unintuitive) • Lead Center knowing who to send ICCR form to in Consulted Center • ICCR form lacking enough information for Consulted Center to decide to whom to assign consult • Consulted Center accessing databases in other Centers • Aggressive due dates for the Consulted Center • In Consulted Center, balancing workload with external ICCR requests	• Lead Center submit ICCR form as early as possible • Lead and Consulted Centers establish early contact for ICCR • Lead Center provide planned review milestone dates in ICCR • Consulted Center negotiate due date if feasible for review • Consulted Center email response to Lead Center if deadline is tight
IND and NDA/BLA Reviews	• Lead Center requesting same consult reviewer if an application has multiple ICCRs • Lead Center including CDRH (Consulted Center) staff in some meetings with sponsor	• For FDA, same as above • Sponsor receiving CDRH input near/after 30-day Safety review or pre-NDA/BLA meeting	• FDA provide new or updated guidance for transdermal devices, topical delivery combination products, outdated IND guidance, amount/thoroughness of device data needed for INDs, and location of device data in eCTD

4. Findings and Recommendations

Based on an integrated evaluation of all perspectives and data collected during this assessment of combination product review practices, ERG developed a set of findings and recommendations organized in two categories: overarching (related to combination product review practices overall) and specific (related to particular aspects of combination product review practices). These appear in Table 4-1.

Table 4-1. Findings and Recommendations

Type	No.	Finding	Recommendation(s)
Overarching	O1	RFD and Pre-RFD review practices are fundamentally sound, and could be enhanced by some straightforward refinements.	See Recommendations S1, S2, and S3.
	O2	The ICCR process is fundamentally sound, and could be made more efficient by addressing technology challenges and implementing some good practices.	See Recommendations S4 and S5.
	O3	Combination product IND, NDA, and BLA submission and review practices are largely similar to those of noncombination products and are fundamentally sound. Implementing minor refinements to certain guidances and practices could further enhance the combination product application submission and review process.	See Recommendations S6 and S7.
Specific	S1	On first submission, many Pre-RFDs contain insufficient information on which to base a classification and Center assignment feedback, including insufficient information about how the product works and components, ingredients, or specifications.	Develop a good practices document for sponsors for successful Pre-RFDs, including a list of types of information that FDA often requests. Include the good practices when transmitting guidance documents to sponsors.
	S2	Informal teleconferences between sponsors, OCP, and Center staff provide valuable opportunities to clarify details of the Pre-RFD and product and to determine next steps in product development.	During early contacts about a Pre-RFD, tell sponsor that informal teleconferences must be requested by sponsor. Explain that sponsor may request a teleconference during review to discuss what is needed for submission or afterwards to discuss assessment.
	S3	Sponsors would like to know which FDA personnel were involved in the classification and Center assignment for their Pre-RFD and which types of data and studies served as the basis for the feedback. Providing the latter could increase sponsor understanding of which types of studies and data to submit and reduce the number of unnecessary 510(k)s submitted to CDRH.	At the time of feedback, inform sponsors about which data/studies were relevant to the feedback. *Note: FDA already identifies the decision-maker for Pre-RFD feedback.*

	S4	For ICCRs, technology issues hinder the work of Lead and Consulted Center staff. Frequent challenges are using Salesforce and accessing databases in other Centers. In addition, technology enhancements could help address other challenges, such as ICCR routing and tracking of ICCR work.	Address significant technology challenges: • Salesforce—Expand awareness of support available from ICCR Help Desk, and consider providing one-on-one real-time assistance to requestors. • Access to other Center databases—Implement an automated process to identify and request access for reviewers when ICCR reviewer assignment is made. Refine existing technologies to address process inefficiencies: • In Salesforce, provide readily-accessible descriptions of each available CDRH group (e.g., in a reference pane or as a tooltip in the group selection dropdown). • In CDRH, consider how to track ICCR work in the same system as all other CDRH work in order to better track reviewer availability for ICCRs (and better manage workload).
	S5	FDA's internal process guides for ICCRs provide useful information for Lead and Consulted Center staff. Reiterating or establishing some good practices could help ease ICCR timeline pressures.	Reiterate or establish as good practices: • Lead Center: Submit ICCR form as early as possible. • Lead and Consulted Centers: Establish early contact for ICCRs. • Lead Center: Provide planned review milestone dates in ICCRs. • Lead and Consulted Centers: Agree on a due date if feasible for review. • Consulted Center: Email response to Lead Center if deadline is tight. • Lead Center: For continuity, request same consult reviewer for follow-up consults.
	S6	Sponsors find value in meetings that include CDRH (Consulted Center) staff, noting that this sends a signal of openness to communication.	Where appropriate, include CDRH (Consulted Center) staff in meetings with sponsors (e.g., to discuss device testing issues).
	S7	Combination product sponsors find the following sources to be useful for them in preparing submissions: FDA guidance, industry conferences, meetings with FDA, and previous experience. FDA guidance could be even more useful if new or updated information were provided for certain topics.	Provide new or updated guidance for transdermal devices, topical delivery combination products, amount/thoroughness of device data needed for INDs, and location of device data in eCTD. Continue to share information with combination product sponsors at industry conferences.

Appendix A. Acronyms and Glossary

Acronym	Term
AP	Approval
BIRAMS	Biologics Investigational Related Applications Management System
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CMC	Chemistry, Manufacturing, and Controls
CR	Complete Response
CSS	Controlled Substance Staff
CTS	Center Tracking System
DAGRID	Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DMEPA	Division of Medication Error Prevention and Analysis
eCTD	Electronic Common Technical Document
EIR	Establishment Inspection Report
ERG	Eastern Research Group, Inc.
EDR	Electronic Document Room
FDA	Food and Drug Administration
FY	Fiscal Year

HF	Human Factors
ICCR	Inter-Center Consult Request
ICR	Information Collection Request
IND	Investigational New Drug
IR	Information Request
MAPP	Manual of Policies and Procedures
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NME	New Molecular Entity
OAP	Office of Antimicrobial Products
OCP	Office of Combination Products
ODEI	Office of Drug Evaluation I
ODEII	Office of Drug Evaluation II
ODEIII	Office of Drug Evaluation III
ODEIV	Office of Drug Evaluation IV
OHOP	Office of Hematology and Oncology Products
OHT3	Office of Health Technology 3
OND	Office of New Drugs
OMB	Office of Management and Budget
OPQ	Office of Pharmaceutical Quality
ORA	Office of Regulatory Affairs
OSAR	Online Search and Retrieval
OSE	Office of Surveillance and Epidemiology
PADSS	Performance Analysis and Data Services Staff

PDUFA	Prescription Drug User Fee Act
PMC	Postmarketing commitments
PMR	Postmarketing requirements
Pre-RFD	Pre-Request for Designation
RFD	Request for Designation
RIMS	Regulatory Information Management Staff
RPM	Regulatory Project Manager
SMG	Staff Manual Guide
SOP	Standard Operating Procedure

Glossary

30-Day Safety Review: Period when FDA reviewers assess a new IND protocol for safety before the clinical trial can proceed. If this review raises safety concerns, the IND can be placed on Clinical Hold until the issues are resolved. FDA may issue non-hold comments in the "Study May Proceed" letter.

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

Approval (AP): 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.

Biological Product: A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Biologics License 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 for human use and ensures that these products are safe, effective, and available to those who need them.

Center for Devices and Radiological Health (CDRH): FDA organization that regulates medical devices and radiation-emitting products and ensures that these products are high-quality, safe, and accessible.

Center Tracking System (CTS): The workflow and work management system used by CDRH to track the progress of industry submitted premarket documents, as well as other regulatory activities.

Combination Product: A product comprised of any combination of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device, and a biological product. Combination products are further divided into types:

1. Type 1: Convenience Kit or Co-Package – *Drug and device are provided as individual constituent parts within the same package.*
2. Type 2: Prefilled Drug Delivery Device/System – *Drug is filled into or otherwise combined with the device AND the sole purpose of the device is to deliver drug.*
3. Type 3: Prefilled Biologic Delivery Device/System – *Biological product is filled into or otherwise combined with the device AND the sole purpose of the device is to deliver biological product.*
4. Type 4: Device Coated/Impregnated/Otherwise Combined with Drug – *Device has an additional function in addition to delivering the drug.*
5. Type 5: Device Coated/Impregnated/Otherwise Combined with Biologic – *Device has an additional function in addition to delivering the drug.*
6. Type 6: Drug/Biologic Combination.
7. Type 7: Separate Products Requiring Cross Labeling.
8. Type 8: Possible Combination Based on Cross Labeling of Separate Products.
9. Type 9: Other Type of Part 3 Combination Product – *Combination product not otherwise described.*

Complete Response (CR): FDA regulatory action on an application (in this case, an original BLA or NDA) 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.

Device: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory which is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. A device does not achieve its primary intended purpose through chemical action within or on the body and is not dependent on being metabolized for the achievement of its primary intended purposes.

Discipline: A scientific review team responsible for specific aspects of an application. For the purpose of the 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
- Non-clinical
- Pharm/Tox
- Human Pharmacokinetics
- Bioavailability
- Facilities
- Other

The organization of these scientific review teams differs in CDER and CBER, but both organizations address the same range of subject matter.

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 evaluation.

Drug: A product intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. 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 PDUFA VI assessment of combination products.

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

Electronic Document Room (EDR): Internal database for storing and managing sponsor submitted IND, NDA, and BLA records. EDR serves as a source of application history and regulatory information for ERG's assessment of combination product review practices.

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.

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

ICCR Database (Salesforce): Updated database housing Inter-Center Consults and relevant documentation. Launched in May 2019.

ICCR Resource Center (SharePoint): Legacy database housing Inter-Center Consults and relevant documentation.

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

Inter-Center Consult Requests (ICCRs): Consults that occur between CDER, CBER, or CDRH. The ICCR process is used for investigational and marketing applications for combination products and may also be used for review of combination product postmarket issues or for the review of noncombination products that will benefit from agency expertise that resides in another center.

Interview: For this assessment, face-to-face or telephone interview that ERG conducted with sponsor representatives or FDA reviewers. The purpose of the interview was to gather sponsor and FDA review team opinions and experiences (including good practices, challenges, and suggestions) on combination product practices.

Inspection: For this assessment, relevant inspections include pre-license and pre-approval inspections supporting the review of original BLAs and NDAs.

Issue: 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 Combination Products (OCP): FDA office within the Office of the Commissioner with the purpose of ensuring prompt assignment of combination products to review Centers, timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of combination products.

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

Office of New Drugs (OND): Office within FDA's CDER responsible for providing regulatory oversight for investigational studies during drug development and making decisions regarding marketing approval for new drugs, including decisions related to changes to already marketed products. During this assessment, OND's reviewing offices included the Office of Drug Evaluation I/II/III/IV, Office of Antimicrobial Products, and Office of Hematology and Oncology Products. In May 2020, OND review offices underwent reorganization, so they now have different names.

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

Office of Surveillance and Epidemiology (OSE): Office at FDA within CDER responsible for maintaining a system of 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. Through their Division of Medication Error Prevention and Analysis (DMEPA), OSE is also responsible for Human Factor reviews. Other activities include updating drug labeling, providing information to the community, implementing or revising a risk management program, and reevaluating approval or marketing decisions.

Performance Analysis and Data Services Staff (PADSS): Group within CDER that serves as the technical experts and coordinates information reports internally, from corporate data bases, and for other government agencies and the public.

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.

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

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

Primary Mode of Action (PMOA): The single mode of action of a combination product that provides greatest contribution to the overall therapeutic action of the product.

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 of these primary review disciplines.*

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

- Analytical similarity
- Biopharmaceutics
- Chemistry
- Chemistry, manufacturing, and controls
- Immunogenicity
- Microbiology (quality)
- Product quality
- Quality

[The] Program: First implemented on October 1, 2012, the Program was a new review model established by FDA under the fifth iteration of the Prescription Drug User Fee Act intended to improve review transparency and communications between FDA review teams and applicants. See also "Prescription Drug User Fee Act (PDUFA)".

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. See "Regulatory Action / Regulatory Outcome."

Regulatory Action / Regulatory Outcome: The regulatory decision that FDA issues on an application. This includes an action that closes the PDUFA goal (AP, CR, WD) and an action issued before complete review of the application (RTF, WF).

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

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.

[Pre-] Request for Designation (RFD): A Pre-RFD is an informal process to assess classification of a medical product as a drug, device, biological product, or combination product as well as Center assignment. The

Pre-RFD provides preliminary, non-binding feedback. An RFD is a formal process that provides a legally binding decision for a product's classification and Center assignment.

Review Cycle: Period from application receipt to regulatory action, during which an FDA review team reviews the application for filing and then regulatory action.

Sponsor: For the purposes of this assessment, the sponsor is the person or entity who takes responsibility for and initiates an RFD, Pre-RFD, IND, NDA, or BLA.

Therapeutic Area: In an effort to standardize drug and disease information, therapeutic areas group diseases and conditions into broader, overarching categories. In this assessment, ERG used therapeutic areas as defined by MedDRA System Organ Class.

Appendix B: Evaluation Protocols and Instruments

Table B-1. Combination Products Review Practices Assessment Protocols and Instruments

Evaluation Protocol	Associated Data Collection Instruments	Data Sources	Purpose
RFDs and pre-RFDs	RFD/Pre-RFD Data	OCP: Jurisdictional Determinations – RFD and Informal database CDRH: Center Tracking System (CTS)	Collect descriptive data (to characterize cohort and analyze/compare subsets with traits of interest) and data for fields to characterize RFD/Pre-RFD completeness and review process, time, and outcome
ICCRs	IND ICCRs NDA/BLA ICCRs	ICCR Resource Center (SharePoint) ICCR database (Salesforce) CDRH: CTS	Collect descriptive data (to characterize INDs and NDAs/BLAs in cohort and compare subsets by traits of interest) and data for fields to characterize volume, compliance with SMGs, and ICCR process and timeliness. ICCR timeliness evaluation based on completion of task in Salesforce/SharePoint.
Application Reviews	Applications Conformance with Guidances (SMGs, MAPPs, SOPs, etc.)* Information Requests and Amendments Facilities and Inspections Human Factors Bridging Studies Labeling	CDER: Document Archiving and Regulatory Reporting Tracking System (DARRTS), Panorama, Electronic Document Room (EDR), and Performance Analysis and Data Services Staff (PADSS) CBER: EDR, Biologics Investigational Related Applications Management System (BIRAMS), and Regulatory Information Management Staff (RIMS) OCP: Jurisdictional Determinations – RFD and Informal database ORA: Online Search and Retrieval (OSAR) System ICCR Resource Center (SharePoint) ICCR database (Salesforce)	Collect descriptive data (as above) and data to characterize applications (completeness, errors, adherence to FDA advice, etc.), reviews (IRs and amendments, inspections, conformance with guidances, etc.), and other topics of interest (RFDs, human factors, bridging studies, labeling)

Evaluation Protocol	Associated Data Collection Instruments	Data Sources	Purpose
		CDRH: CTS	
Interviews	Interview Script-RFD/Pre-RFD: FDA Interview Script-RFD/Pre-RFD: Sponsor Interview Script-ICCR: Lead Center Interview Script-ICCR: Consulted Center Interview Script-IND/NDA/BLA: FDA Interview Script-IND/NDA/BLA: Sponsor	Interviews with FDA reviewers (CBER, CDER, CDRH, and OCP) Interviews with sponsors and sponsor representatives	Collect feedback about specific aspects of requests/applications and reviews as well as other feedback about review experiences, challenges and pain points, lessons learned, good practices, suggestions, and other comments

*SMG = Staff Manual Guide. MAPP = Manual of Policies and Procedures. SOP = Standard Operating Procedures.

Appendix C: Distribution of Traits of Interest in Assessment Samples

Table C-1. Distribution of Traits of Interest in Combination Products Review Practices Assessment Samples

Traits	Categories	RFD/Pre-RFD Sample (n=49)	ICCR Sample (n=34)	IND/NDA/BLA Sample (n=75)	Target Distribution
Sponsor size	Small	37%	38%	44%	21% to 31%
	Medium	6%	3%	7%	5% to 15%
	Large	12%	26%	36%	37% to 47%
	Private	45%	32%	13%	17% to 27%
Sponsor experience	Yes	6%	32%	32%	36% to 46%
	No	94%	68%	68%	54% to 64%
Combination product category	1 - Convenience kit or co-package	8%	15%	21%	25% to 35%
	2 - Prefilled drug delivery device/system	29%	56%	45%	18% to 28%
	3 - Prefilled biologic delivery device/system	6%	3%	13%	1% to 7%
	4 - Device coated/impregnate/otherwise combined with drug	37%	3%	0%	6% to 16%
	5 - Device coated/otherwise combined with biologic	6%	0%	1%	1% to 8%
	6 - Drug/biologic combination	0%	3%	9%	13% to 23%
	7 - Separate products requiring cross labeling	2%	0%	3%	1% to 5%

Traits	Categories	RFD/Pre-RFD Sample (n=49)	ICCR Sample (n=34)	IND/NDA/BLA Sample (n=75)	Target Distribution
	8 - Possible combination based on cross labeling of separate products	0%	0%	1%	6% to 16%
	9 - Other type of Part 3 combination product	12%	21%	5%	1% to 7%
Lead-Consult Centers	CBER-CDER	0%	0%	3%	1% to 8%
	CBER-CDRH	12%	0%	8%	1% to 10%
	CBER-CDER/CDRH	4%	0%	0%	1% to 8%
	CBER-Unknown	0%	0%	1%	N/A
	CDER-CBER	0%	0%	3%	1% to 8%
	CDER-CDRH	84%	100%	83%	79% to 89%
	CDER-CBER/CDRH	0%	0%	1%	1% to 8%
	CDER-Unknown	0%	0%	1%	N/A
Therapeutic area	Blood and lymphatic system disorders	0%	0%	3%	1% to 6%
	Congenital, familial and genetic disorders	0%	0%	1%	1% to 6%
	Ear and labyrinth disorders	0%	0%	1%	N/A
	Endocrine disorders	2%	9%	4%	1% to 7%
	Eye disorders	8%	6%	3%	N/A
	Gastrointestinal disorders	12%	3%	3%	N/A
	General disorders and administration site conditions	0%	0%	0%	1% to 8%

Traits	Categories	RFD/Pre-RFD Sample (n=49)	ICCR Sample (n=34)	IND/NDA/BLA Sample (n=75)	Target Distribution
	Hepatobiliary disorders	0%	0%	1%	6% to 16%
	Immune system disorders	2%	0%	1%	1% to 6%
	Infections and infestations	10%	18%	13%	1% to 6%
	Injury, poisoning and procedural complications	14%	3%	1%	1% to 6%
	Investigations	2%	0%	1%	N/A
	Metabolism and nutrition disorders	2%	0%	8%	1% to 8%
	Musculoskeletal and connective tissue disorders	8%	0%	4%	2% to 12%
	Neoplasms benign, malignant and unspecified (including cysts and polyps)	0%	6%	11%	37% to 47%
	Nervous system disorders	2%	6%	15%	1% to 10%
	Psychiatric disorders	0%	12%	9%	1% to 8%
	Renal and urinary disorders	0%	3%	0%	1% to 7%
	Reproductive system and breast disorders	2%	3%	1%	N/A
	Respiratory, thoracic and mediastinal disorders	0%	3%	7%	3% to 13%
	Skin and subcutaneous tissue disorders	10%	3%	5%	2% to 12%
	Surgical and medical procedures	24%	12%	7%	1% to 8%
	Vascular disorders	0%	3%	1%	N/A

Appendix D: Results

For the PDUVA VI combination product review practices assessment, ERG collected and analyzed results for three samples of combination products for which CDER or CBER was the Lead Center:

- **RFD/Pre-RFD Sample (n=49):** 3 RFD and 46 Pre-RFD reviews completed between September 1, 2018 and January 31, 2020.
- **ICCR Sample (n=34):** 17 INDs, 16 NDAs, and 1 BLA that were active between September 1, 2018 and January 31, 2020. These applications were associated with 86 ICCRs.
- **IND/NDA/BLA Sample (n=75):** 39 INDs, 27 NDAs, and 9 BLAs that were identified as combination products. INDs in this sample were active between September 1, 2018 and January 31, 2020. Eligible NDAs and BLAs were those submitted in PDUFA VI and received a first-cycle action between September 1, 2018 and January 31, 2020.

ERG presents the results as follows:

D.1 RFD/Pre-RFD Sample: RFD and Pre-RFD Submissions and Reviews

Key Points

- Sponsors submitted many more Pre-RFDs (46) than RFDs (3), citing the lack of page limits and the desire for a more interactive process.
- Pre-RFD and RFD processes were quicker (or needed fewer rounds of clarification) with larger and more experienced sponsors, with applications eventually assigned to CDER, and with certain types of combination products and therapeutic areas.
- For Pre-RFDs, 43% were complete on submission; with one to four rounds of clarification needed for the other Pre-RFDs, the mean number of clarification rounds per Pre-RFD was 0.8. The mean time from receipt to acceptance was 27 days, and the mean time from acceptance to feedback was 56 days.
- All three RFDs in the sample were deemed complete enough to be filed. The mean time from receipt to filing was 4 business days, and the mean time from filing to designation decision was 59 calendar days.
- *Characterizations of review practices:* RFD and Pre-RFD process and guidance are well established and useful.
- *Good practices:* Providing RFD/Pre-RFD guidance documents to sponsors. Informal teleconferences during or after the Pre-RFD process.
- *Challenges:* FDA obtaining necessary information from the sponsor, resulting in time-consuming rounds of clarification for Pre-RFDs. Sponsors learning who reviewed Pre-RFD and on which data/studies the feedback was based.
- *Suggestions:* OCP, Center, and sponsor hold informal teleconferences for more Pre-RFDs. FDA share information with sponsor about who reviewed Pre-RFD and which data/studies on which the feedback was based.

Sponsors may request a preliminary assessment from FDA's OCP to determine the classification of a medical product as a drug, device, biological product, or combination product as well the product's assignment to the appropriate Center for premarket review and regulation. This can be achieved through a formal and legally binding RFD process or through an informal, non-binding Pre-RFD process.

ERG collected data on 49 RFDs and Pre-RFDs during the 17-month data collection period of September 1, 2018 to January 31, 2020. The sample included 3 RFDs and 46 Pre-RFDs for combination products with CDER or CBER assigned as Lead Centers; this reflected the distribution of RFDs and Pre-RFDs in the universe from which the sample was drawn. Data on metrics related to RFDs and Pre-RFDs appear in Table D-1.

Table D-1. Data for Evaluation Metrics Related to RFDs (n=3) and Pre-RFDs (n=46) in RFD/Pre-RFD Sample for Combination Product Review Practices Assessment

Metrics	n	Result
Percent of filed RFDs that are filed on the first submission*	3 RFDs	100%
Number of business days from RFD receipt to file: **Mean**	3 RFDs	4 business days
Number of business days from RFD receipt to file: **Median**		4 business days
Number of business days from RFD receipt to file: **Range**		0 business days [4, 4]
Number of calendar days from RFD file to decision: **Mean**	3 RFDs	59 calendar days

Metrics	n	Result
Number of calendar days from RFD file to decision: **Median**		59 calendar days
Number of calendar days from RFD file to decision: **Range**		1 calendar day [58, 59]
Total number of calendar days from RFD receipt to decision: **Mean**	3 RFDs	65 calendar days**
Total number of calendar days from RFD receipt to decision: **Median**		65 calendar days**
Total number of calendar days from RFD receipt to decision: **Range**		1 calendar day [64, 65]**
Percent of Pre-RFDs that are complete on the first submission	46 Pre-RFDs	43%
Number of Pre-RFD data request/clarification rounds per Pre-RFD: **Mean**	46 Pre-RFDs	0.8
Number of Pre-RFD data request/clarification rounds per Pre-RFD: **Median**		1
Number of Pre-RFD data request/clarification rounds per Pre-RFD: **Range**		4 [0, 4]
Number of calendar days from Pre-RFD receipt to be complete: **Mean**	46 Pre-RFDs	27 calendar days***
Number of calendar days from Pre-RFD receipt to be complete: **Median**		9 calendar days***
Number of calendar days from Pre-RFD receipt to be complete: **Range**		287 calendar days [0, 287]***
Number of calendar days from Pre-RFD complete to feedback: **Mean**	46 Pre-RFDs	56 calendar days
Number of calendar days from Pre-RFD complete to feedback: **Median**		58 calendar days
Number of calendar days from Pre-RFD complete to feedback: **Range**		188 calendar days [0, 188]
Total number of calendar days from Pre-RFD receipt to feedback: **Mean**	46 Pre-RFDs	83 calendar days***
Total number of calendar days from Pre-RFD receipt to feedback: **Median**		66 calendar days***
Total number of calendar days from Pre-RFD receipt to feedback: **Range**		347 calendar days [1, 348]***

*Only filed RFDs were included in the sample; unfiled RFDs were not included because they did not differentiate between non-combination and combination products.

**FDA tracks the time from RFD receipt to filing in business days, and from filing to decision in calendar days. ERG believes that the total time involved in the RFD process from receipt to decision is also of interest; to calculate that value, ERG calculated the number of calendar days from the RFD receipt date to the decision date for every RFD, then calculated the mean, median, and range for all the RFDs in the sample.

***FDA tracks some Pre-RFD metrics in business days. ERG believes that the total time involved in the Pre-RFD process from receipt to complete – and from receipt to feedback – is also of interest. To calculate those values, ERG calculated the number of calendar days from the Pre-RFD receipt date to the complete date (or the feedback date) for every Pre-RFD, then calculated the mean, median, and range for all the Pre-RFDs in the sample.

Completeness of RFDs and Pre-RFDs. FDA guidance[1] specifies types of information for sponsors to include in RFDs and imposes a limit of 15 pages. For Pre-RFDs, FDA guidance specifies content recommendations (description of product, proposed use or indication for use, manufacturing process and/or source materials, and a description of how the product achieves its intended therapeutic or diagnostic effects) and imposes no page limit; in any case, Pre-RFDs should provide adequate information for FDA to provide classification and Center assignment feedback. If needed, FDA may request additional information from the sponsor. FDA did so for 26 of 46 Pre-RFDs (57%) in the sample; in a majority of cases, FDA requested more information about how the product works and product components, ingredients, or specifications (Table D-2) because the information originally provided was insufficient for FDA to use to provide classification and Center assignment feedback for the combination product. Table D-2 and Figure D-1 present the types of information that FDA requested from sponsors.

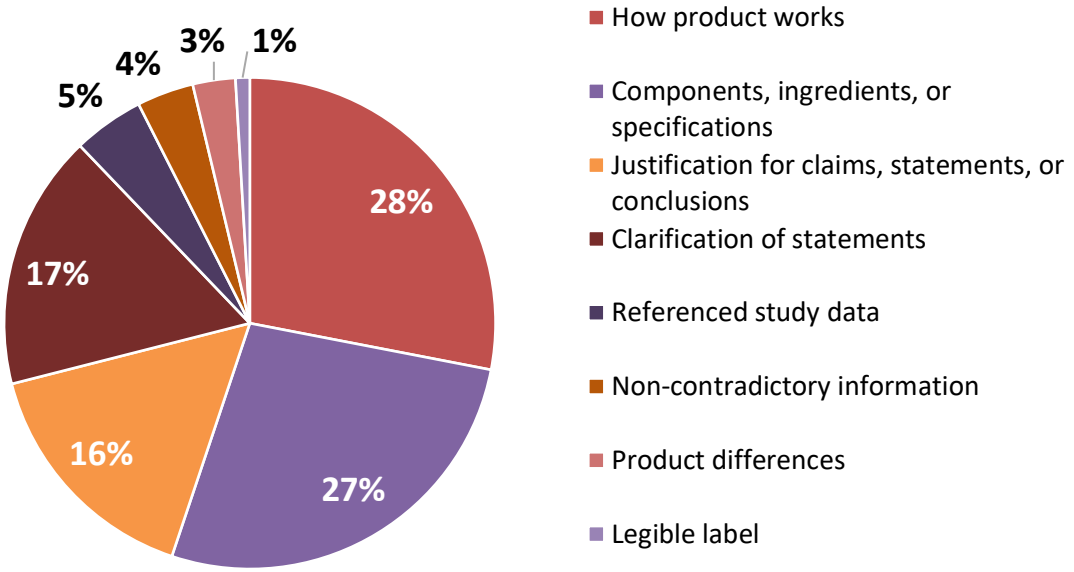
Table D-2. Completeness of Pre-RFDs (n=46) in RFD/Pre-RFD Sample for Combination Product Review Practices Assessment

Pre-RFD Metrics	Result
Percent of Pre-RFDs that are complete on the first submission	43%
For Pre-RFDs that are not complete (n=26), percent where a missing item is:*	
How product works (19)	73%
Components, ingredients, or specifications (16)	61%
Justification for claims, statements, or conclusions (9)	35%
Clarification of statements (9)	35%
Referenced study data (4)	15%
Reconciling of contradictory information (3)	11%
Product differences (3)	11%
Legible label (1)	4%

*Of the 26 Pre-RFDs that were not complete on first submission, 16 Pre-RFDs had more than one type of missing item. In most cases, the sponsor provided some data for the "missing" item; FDA requested more information because data provided was insufficient to provide feedback.

[1] U. S. Food and Drug Administration. (2018). How to Prepare a Request for Designation (RFD) Guidance for Industry.

Figure D-1. Items that FDA Requested in Clarification Emails (n=107) for Pre-RFDs (n=46) in RFD/Pre-RFD Sample for Combination Product Review Practices Assessment



Timing. Per FDA guidance, FDA should file an RFD within 5 business days of receipt and make a designation decision within 60 calendar days of filing. The mean time from receipt to filing for RFDs was 4 business days (median 4 business days, range 0 business days [4, 4]). The mean time from filing to decision for RFDs was 59 days (median 59 days, range 1 day [58, 59]).

FDA accepts a Pre-RFD for review once all the basic information is provided and strives to provide feedback within 60 calendar days after the Pre-RFD is complete. The mean time from receipt to acceptance was longer for Pre-RFDs than for RFDs in the sample; this was because FDA asked for one or more clarifications from sponsors for 26 of the 46 Pre-RFDs. The mean time from receipt to acceptance for Pre-RFDs was 16 days (median 8 days, range 72 days [0, 72]); two Pre-RFDs with over 200 days from receipt to acceptance were omitted from these calculations as outliers. In these cases, the sponsors took additional time to generate data to answer FDA's clarification questions. The time from Pre-RFD acceptance to feedback was similar to that for RFD filing to decision. The mean time from acceptance to feedback for Pre-RFDs was 50 days (median 57 days, range 69 days [0,69]); three Pre-RFDs with over 100 days from acceptance to feedback were omitted from these calculations as outliers. Reasons for delays included FDA needing more time to discuss internally and, in one case, to accommodate a meeting with the sponsor.

Interview Feedback. In interviews, FDA staff and sponsors generally characterized the RFD and Pre-RFD process as well established and useful. Sponsors expressed a preference for the informal Pre-RFD process, citing that this process is potentially faster and provides more opportunity for discussion with FDA. Both sponsors and FDA agreed that the Agency's guidance was helpful in preparing submissions and in answering sponsor questions.

FDA staff and sponsors cited helpful practices related to the RFD and Pre-RFD process:

- Both FDA staff and sponsors commented that providing guidance documents that detail expected RFD and Pre-RFD content and specific timeline expectations allowed sponsors to prepare for the process and anticipate FDA feedback. Nearly all of the sponsors who were interviewed said that they used the guidance to prepare their submission.
- Some sponsors indicated that the option to have a teleconference with OCP and Center personnel during or after the Pre-RFD review process was helpful. These conversations enabled sponsors and FDA staff to clarify details about the product, FDA's assessment, or potential next steps for development. In four interviews, sponsors indicated that they had a teleconference with OCP; sponsors in other interviews suggested that having a call would have been helpful but thought it was automatically included in the Pre-RFD process; that is, they did not realize they needed to request a call. *Note: FDA staff generally agreed that these calls were useful, but noted that calls were not worthwhile if, for example, the sponsor used the calls to present clinical data outside the scope of the primary mode of action determination or to argue legal topics.*

Sponsors and FDA reviewers cited some challenges with the RFD and Pre-RFD process. FDA reviewers stated that occasionally it can be challenging to obtain the necessary information from the sponsor, resulting in multiple rounds of clarification requests; some sponsors expressed reluctance to submit more information than necessary at an early stage of development. By the end of the process, some sponsors found that it was not always apparent who reviewed the RFD or Pre-RFD, nor was it always clear what information FDA staff used to evaluate classification and Center assignment. In these cases, FDA's RFD decision or Pre-RFD feedback differed from that desired by the sponsors, and the sponsors wondered whether FDA included needed subject matter experts or gave adequate weight to data that supported their desired classification and Center assignment.

Sponsors and FDA reviewers had two suggestions for improving the Pre-RFD process:

- Continue to expand the practice of holding informal teleconferences between sponsors, OCP, and Center staff, both during and after the Pre-RFD assessment. *These teleconferences are an opportunity for FDA and sponsors to clarify details of the Pre-RFD and product, FDA*'s assessment, *and next steps in product development.*
- Inform sponsors of which FDA personnel assess classification and Center assignment and which types of data and studies are relevant to the Pre-RFD feedback. *This will increase sponsor understanding of which types of studies and data to submit and reduce the number of unnecessary 510(k)s submitted to CDRH.*

Patterns by Traits of Interest. ERG analyzed the data to identify any patterns by traits of interest in the sample of RFDs and Pre-RFDs. Due to the small sample size, ERG found no patterns for RFDs. ERG found some variations by traits of interest among Pre-RFDs. For Pre-RFDs, at this sample size the number of cases in each subgroup by trait of interest was too small for these patterns to be statistically significant:

- ***Sponsor Size:*** Pre-RFDs from large sponsors were associated with fewer rounds of clarification (n=6, mean 0.5) than those from small companies (n=17, mean 1.1), as well as a shorter time from receipt to decision (mean 51 versus 72 days, respectively). This might be due to the greater regulatory affairs resources that large sponsors can direct to their development programs.
- ***Sponsor Experience:*** Sponsors who had previous experience with combination product applications experienced a shorter duration from receipt to Pre-RFD filing (n=3, mean 4 days versus n=43, 28 days) and from receipt to a Pre-RFD decision (mean 38 days versus 86 days) than sponsors without previous experience. Additionally, Pre-RFDs from sponsors with previous experience had fewer rounds of clarification (mean 0.3 rounds versus 0.8 rounds) than sponsors without previous experience. This might be due to a greater familiarity with FDA expectations.
- ***Lead Center:*** Time from acceptance to decision was shorter for Pre-RFDs with CDER as the Lead Center (n=39, mean 52 days) than those with CBER as the Lead Center (n=7, mean 75 days). This result was primarily driven by a single Pre-RFD that was under review for 188 days and assigned to CBER as the Lead Center.
- ***Combination Product Category:*** Type 1 and Type 3 combination product Pre-RFDs were associated with fewer rounds of clarification (n=4, mean 0.3 rounds and n=3, 0.3 rounds, respectively) than Type 4 and Type 5 combination product Pre-RFDs (n=17, mean 1.1 and n=2, 1.5, respectively) (Table D-3). Due to the small numbers in each category, it is unclear whether these differences represent a pattern based on product complexity or insignificant scatter that would not be observable with a larger sample.
- ***Therapeutic Area:*** The mean number of rounds of clarification needed for Pre-RFDs varied by therapeutic area (Table D-4). The mean for the RFD/Pre-RFD Sample as a whole was 0.8. As above, due to the small numbers in each category, it is unclear whether these differences represent a real pattern or insignificant scatter.

Table D-2. Mean Number of Rounds of Clarification for Pre-RFDs (n=46) in RFD/Pre-RFD Sample for Combination Product Review Practices Assessment, by Combination Product Category

Combination Product Category	Mean Number of Clarification Rounds
Type 5: Device Combined with Biologic (n=2)	1.5
Type 4: Device Combined with Drug (n=17)	1.1
Type 7: Separate Products Requiring Cross Labeling (n=1)	1.0
Type 9: Other Type of Part 3 Combination Product (n=5)	0.8
Type 2: Prefilled Drug Delivery System (n=14)	0.6
Type 3: Prefilled Biologic Delivery Device System (n=3)	0.3
Type 1: Convenience Kit or Co-Packaged (n=4)	0.3

Table D-3. Mean Number of Rounds of Clarification for Pre-RFDs (n=46) in RFD/Pre-RFD Sample for Combination Product Review Practices Assessment, by Therapeutic Area

Therapeutic Area	Mean Number of Clarification Rounds
Endocrine disorders (n=1)	2.0
Injury, poisoning and procedural complications (n=7)	2.0
Nervous system disorders (n=1)	2.0
Investigations (n=1)	1.0
Reproductive system and breast disorders (n=1)	1.0
Eye disorders (n=4)	0.8
Gastrointestinal disorders (n=6)	0.7
Surgical and medical procedures (n=11)	0.6
Musculoskeletal and connective tissue disorders (n=2)	0.5
Skin and subcutaneous tissue disorders (n=5)	0.4
Infections and infestations (n=5)	0.2
Immune system disorders (n=1)	0
Metabolism and nutrition disorders (n=1)	0

D.2 ICCR Sample: Internal FDA Review Consultation via ICCRs

Key Points

- Based on recommended timelines in internal FDA process guides for ICCRs, Lead Centers submitted 56% of ICCRs on time, Consulted Centers assigned 38% of ICCRs to reviewers on time, and Consulted Centers completed 34% of ICCRs by the requested due dates.
- All applications in the ICCR sample had one or more ICCRs. In no case did an application have all three ICCR activities (see above) completed on time for all its ICCRs.
- Together, CDRH's OHT3 and DAGRID received 65% of the ICCRs.
- *Characterizations of ICCR process:* Process itself is strong, but challenges lead to inefficiencies and delays. Quality of consults has improved, and quality of responses is high.
- *Good practices:* Lead Center submitting ICCR form as early as possible, providing planned review milestone dates in ICCR forms, and being in contact with assigned reviewer. Consulted Center being in contact with requestor from Lead Center, negotiating due date if feasible, and emailing response to Lead Center if deadlines are tight.
- *Challenges:* Lead Center using Salesforce (unintuitive) and knowing to whom to send ICCR form in Consulted Center. Consulted Center finding insufficient information in ICCR form to know to whom to assign consult, accessing databases in other Centers, managing aggressive due dates, and balancing existing workload with external ICCR requests.
- *Suggestions:* Same as good practices.

For a given combination product, FDA staff in the Lead Center are responsible for reviewing submissions for the product. When Lead Center staff need specialized knowledge and expertise not available in their own Center, they may request a consult from reviewers in another Center via the ICCR process. The three main steps are: Lead Center submits an ICCR form (consult request), the Consulted Center assigns the consult to a reviewer, and the Consulted Center completes the request.

For this assessment, ERG examined all 86 ICCRs for a sample of 34 active commercial combination product INDs (n=17), NDAs (n=16), and BLAs (n=1) where CDER was the Lead Center and CDRH was the Consulted Center. Due to partial overlap in the qualifying criteria for the ICCR sample and IND/NDA/BLA sample, 30 of the 86 ICCRs are also part of the IND/NDA/BLA sample. The sample included no cases in which CBER was the Lead Center or Consulted Center. Table D-5 shows ICCR metric results.

Table D-5. Data for Evaluation Metrics for ICCRs (n=86) for INDs (n=17), NDAs (n=16), and BLAs (n=1) in ICCR Sample for Combination Product Review Practices Assessment

Metrics	n	Result
Number of days from NDA/BLA submission or issue receipt to combination product ICCR submission: **Mean**	86 ICCRs with submission dates	19.8 days
Number of days from NDA/BLA submission or issue receipt to combination product ICCR submission: **Median**		8.5 days
Number of days from NDA/BLA submission or issue receipt to combination product ICCR submission: **Range**		167 days [0, 167]

Metrics	n	Result
Number of days from ICCR submission to reviewer assignment: **Mean**	80 ICCRs with reviewer assignment dates	9.1 days
Number of days from ICCR submission to reviewer assignment: **Median**		3 days
Number of days from ICCR submission to reviewer assignment: **Range**		188 days [0, 188]
Number of days from ICCR completion to requested due date: **Mean**	53 ICCRs with due dates and completion dates	-7.2 days
Number of days from ICCR completion to requested due date: **Median**		0 days
Number of days from ICCR completion to requested due date: **Range**		266 days [-98, 168]
Number of days from ICCR completion to PDUFA goal date*: **Mean**	31 ICCRs with PDUFA goal dates and completion dates	13.0 days
Number of days from ICCR completion to PDUFA goal date*: **Median**		3 days
Number of days from ICCR completion to PDUFA goal date*: **Range**		352 days [-93, 259]
Percent of ICCR submissions on time**	86 ICCRs with submission dates	56%
Percent of ICCR assignments on time**	80 ICCRs with assignment dates	38%
Percent of ICCR responses on time**	53 ICCRs with due dates and completion dates	34%
Number of ICCRs per application: **Mean**	34 INDs/NDAs/BLAs	2.5
Number of ICCRs per application: **Median**		2
Number of ICCRs per application: **Range**		10 [1, 11]
Percent of applications with all ICCR actions on time**	34 INDs/NDAs/BLAs	0%
Percent of combination product submissions with no ICCRs	34 INDs/NDAs/BLAs	0%

*PDUFA goal date of the NDA/BLA submission or issue receipt, if applicable.

**Criteria: ICCR submitted by Day 14 (BLA/NDA) or Day 7 (IND), ICCR assigned by Day 17 (BLA/NDA) or Day 9 (IND), ICCR completed by "Consult Due Date".

ICCR Process Timelines. Per internal FDA process guides for ICCRs, Lead Centers should submit the ICCR form to the Consulted Center 7 to 14 days after receipt of a submission; Consulted Centers should assign a reviewer to the consult 2 or 3 days later, which translates to 9 to 17 days after the receipt of the submission (Table D-6). For this assessment, ERG based the evaluation of ICCR timeliness on task completion records in the Salesforce and SharePoint systems. If FDA staff completed a task without indicating this in the Salesforce or SharePoint system, ERG would record task completion as late. ERG has no evidence to support that this situation did or did not occur in this sample.

Table D-6. CDER Recommended Timelines* Compared to Mean Timelines for ICCRs (n=86) in ICCR Sample for Combination Product Review Practices Assessment

Submission Type	ICCR Form Submission Goal	ICCR Form Submission in Sample (Mean)	ICCR Reviewer Assignment Goal	ICCR Reviewer Assignment in Sample (Mean)
IND originals	Day 7	7.8 days	Day 9	10 days
IND amendments	Day 14	30 days	Day 17	39 days
PDUFA (Type A-C) meeting requests, including Pre-INDs	Day 10	15 days	Day 12	18 days
NDA/BLA – NME & Non-NME	Day 14	21 days	Day 17	36 days

**Intercenter Consult Request (ICCR) Process for CDER*, May 2019.
NME: New Molecular Entity

In the ICCR Sample, the Lead Center (CDER) submitted a majority (56%) of ICCR forms within the recommended 7 to 14 days of application, amendment, or meeting request receipt. Of the ICCRs submitted later than that, most were submitted 15 to 68 days after application receipt. In interviews, CDER staff cited two reasons for later-than-recommended ICCR form submissions: (1) late notification from a Lead Center submission contact to the Lead Center consult requestor that an ICCR was needed, and (2) initial submission to the wrong group in the Consulted Center, necessitating resubmission to the correct group. In a few extreme cases, CDER submitted ICCRs forms three to six months after IND receipt; these cases involved a quality information amendment for a single IND.

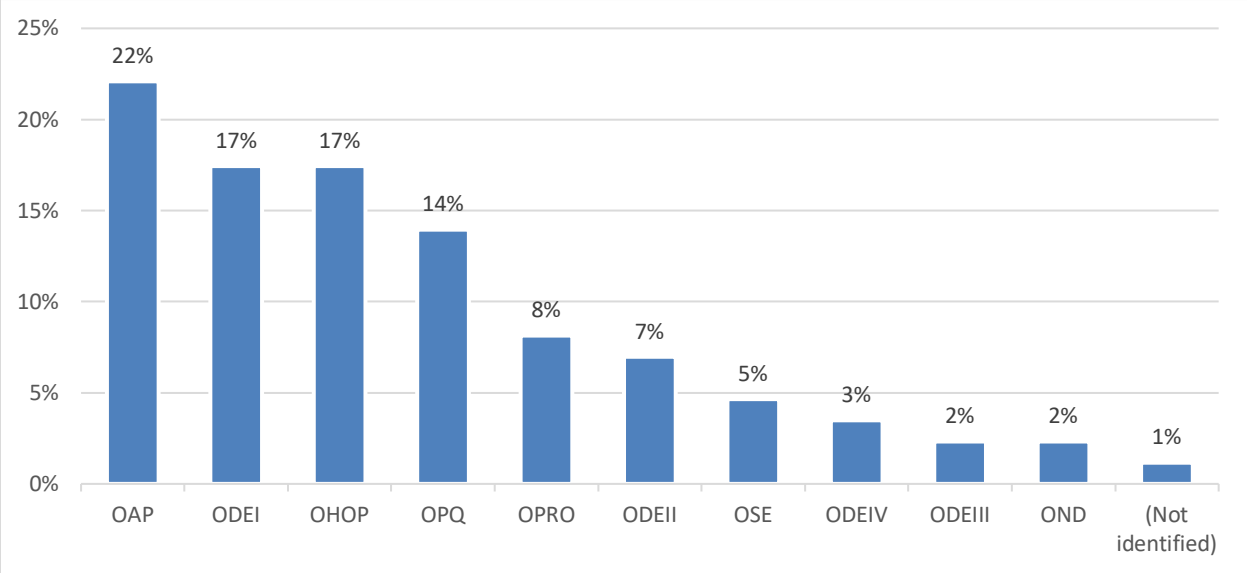
In the ICCR Sample, the Consulted Center (CDRH) assigned 38% of ICCRs to reviewers within the recommended 9 to 17 days of application, amendment, or meeting request receipt. Some of the delays were due to late receipt of ICCR forms. Therefore, ERG calculated the percentage of cases where CDRH assigned ICCRs to reviewers within 2 to 3 days: 53%. CDRH assigned most of the other ICCRs to reviewers 4 to 46 days after ICCR form submission; one ICCR was assigned 188 days after ICCR form submission. In interviews, CDRH staff attributed delays to insufficient information in the ICCR form to decide who best to respond (resulting in a need for communication with the Lead Center to clarify) and inconsistent access to Lead Center databases to review details needed to assign the ICCR.

In their ICCRs, Lead Centers may request specific due dates for Consulted Center responses. On average, the Consulted Center completed the ICCRs 7.2 days after the requested due dates and 13.0 days before the PDUFA goal dates for the NDAs/BLAs. In interviews, CDRH staff commented that heavy workloads

and competing priorities sometimes prevented them from completing ICCRs by the requested due dates. In addition, in some cases the requested due date was much earlier than the PDUFA goal date for the application, causing some CDRH staff to wonder whether the early date was necessary. In situations of heavy workload, competing priorities, or early due dates, some CDRH staff reached out to Lead Center staff to extend the date if that was feasible for the application review timeline. Interviewees also noted that they sometimes emailed their responses to the Lead Center so they could use this information before the consult was officially closed out at a later date.

Review Office Distribution. At the Lead Center (CDER), three CDER OND offices (OAP, ODEI, and OHOP) collectively generated 56% of the ICCRs in the ICCR Sample; OPQ, including OPRO, generated 22% of the ICCRs (Figure D-2). Two organizations (OHT3 and DAGRID) in the Consulted Center (CDRH) received 65% of the ICCRs (Figure D-3). During this assessment, CDRH underwent a reorganization to more efficiently regulate products by structuring itself around types of products rather stages in a product's life cycle. As such, CDRH review organizations in this data are a mix of old names from the Office of Device Evaluation's divisions and new names from the Office of Product Evaluation and Quality's sub-offices.

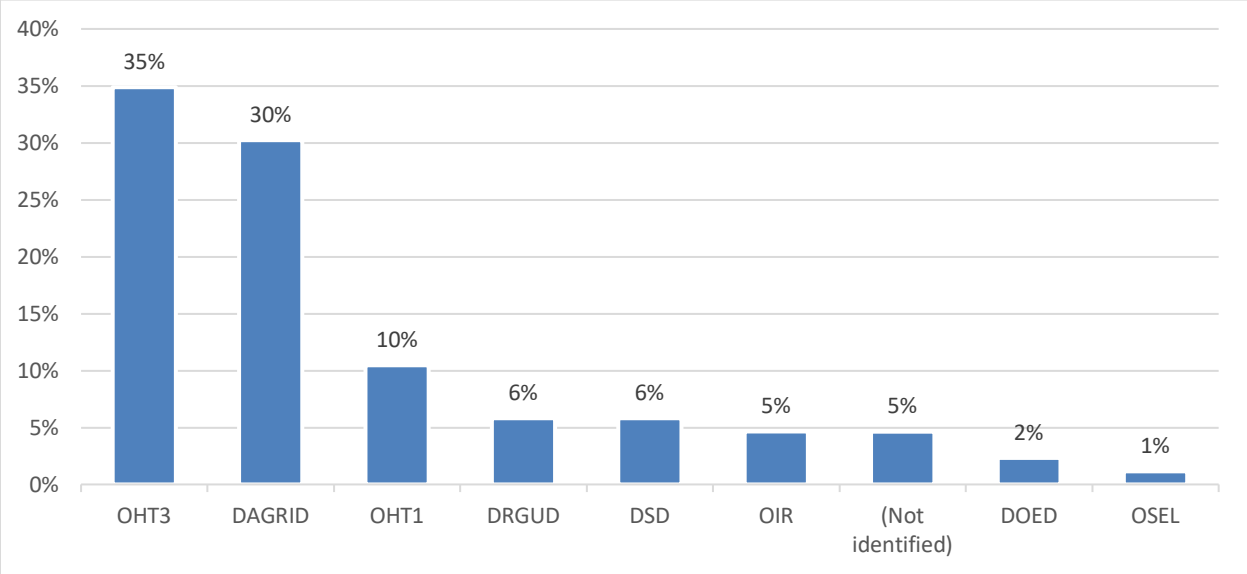
Figure D-2. ICCRs (n=86) in ICCR Sample for Combination Product Review Practices Assessment, by Office* in Lead Center (CDER) that Generated the ICCRs



*Based on the "Lead Center Organization" field in the ICCR at the time of the review; therefore, organizations include a mix of those from before and after the CDRH reorganization that took place during this assessment.

OAP: Office of Antimicrobial Products, ODEI: Office of Drug Evaluation I, OHOP: Office of Hematology and Oncology Products, OPQ: Office of Pharmaceutical Quality, OPRO: Office of Program and Regulatory Operations, ODEII: Office of Drug Evaluation II, OSE: Office of Surveillance and Epidemiology, ODEIV: Office of Drug Evaluation IV, ODEIII: Office of Drug Evaluation III, OND: Office of New Drugs.

Figure D-3. ICCRs (n=86) in ICCR Sample for Combination Product Review Practices Assessment, by Organization* in Consulted Center (CDRH) that Received the ICCRs



*Based on the "Primary Reviewer Organization" field in the ICCR.

OHT3: Office of Health Technology 3, DAGRID: Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices, OHT1: Office of Health Technology 1, DRGUD: Division of Reproductive, Gastro-Renal, and Urological Devices, DSD: Division of Surgical Devices, OIR: Office of In-vitro Diagnostics and Radiological Health, DOED: Division of Ophthalmic and Ear, Nose and Throat Devices, OSEL: Office of Science and Engineering Laboratories.

ICCR Quality. In interviews, most Lead Center (CDER) staff stated that they appreciated the complete and comprehensive reviews that they received from the Consulted Center (CDRH); many remarked that the process was very smooth once they were able to contact the assigned reviewer. Some Consulted Center (CDRH) staff commented that some ICCRs from CDER lacked sufficient timeline details; near the end of the assessment, interviewees observed that the quality of the ICCRs had improved with greater inclusion of the Lead Center's planned review milestone dates, which helped consult reviewers manage their workload. CDRH staff also noted that spending time resolving problems accessing CDER data subtracted from valuable review time, making it more difficult to complete ICCRs in a timely manner.

ICCR Interview Feedback. Table D-7 presents major themes expressed by Lead and Consulted Center staff in interviews.

Table D-7. Lead Center (n=28) and Consulted Center (n=29) Feedback from Interviews for ICCR Sample for Combination Product Review Practices Assessment

Lead Center (CDER) Feedback	Consulted Center (CDRH) Feedback
ICCR process timeliness: • Need for consult is generally identified as soon as possible • Consult responses are usually received on time	ICCR process timeliness: • Requested due dates range from aggressive (days) to reasonable (weeks) • Timeline can sometimes be extended, if requested by reviewers and Lead Center can accommodate request
Process efficiency: • Salesforce platform is unintuitive and a source of inefficiency in the ICCR process • Frequent Salesforce users will become more proficient with experience, but occasional users might not improve	Process efficiency: • Overall consult process is adequately efficient • Inconsistent access to Lead Center databases delays review and decreases efficiency
Good practices: • Establish and maintain contact with the assigned reviewer	Good practices: • Lead Center submitting ICCR form as early as possible • Contacting Lead Center requestor for support with consult • Lead Center including planned review milestone dates in ICCR form • Emailing response to Lead Center (before consult is closed) when deadlines are tight
Challenges: • Adjusting to using Salesforce for ICCRs • Knowing which group in CDRH to send ICCRs to	Challenges: • Insufficient information in ICCR forms to determine to whom to assign the ICCR • Accessing CDER databases • Aggressive requested due dates • Balancing external ICCRs with internal workload

Patterns by Traits of Interest. ERG identified the following patterns by traits of interest in the sample of ICCRs. At this sample size, the number of ICCRs in each subgroup by trait of interest was too small for these patterns to be statistically significant:

- ***Sponsor Size and Experience:*** All large sponsors in this sample had experience submitting combination product applications, and applications from these sponsors had a greater number of ICCRs (n=9, mean 4.1) than applications from small, medium, and private sponsors (n=25, mean 2.0). This might have been due to the complexity of their products.
- ***Combination Product Category:*** Type 2 combination product applications were associated with a greater number of days from application submission to ICCR submission (n=19, mean 28.9 days)

than applications in the full sample (n=34, mean 19.8 days). This might be due to CDER reviewer familiarity with the classes of drugs involved, then having questions about the device constituents only later in the review.

- ***Therapeutic Area:*** Applications in the "infections and infestations" therapeutic area were associated with a lower number of days from application submission to ICCR submission (n=6, mean 10.7 days) than applications in the full sample (n=34, mean 19.8 days). This might be due to the products having characteristics that could quickly and easily be determined as requiring specialized knowledge from another Center.

D.3 IND/NDA/BLA Sample: Combination Product Applications and Reviews

Key Points

- ERG estimated the percentage of combination product NDAs/BLAs complete on original submission in two ways:
  - Based on FDA reviewer opinions given in interviews—64% were complete and adequately organized on original submission, with the remainder incomplete due to issues with application organization, specific device data, facility inspection readiness, pharmacology/toxicology data errors, or product quality microbiology data.
  - Based on an analysis of IRs that FDA issued during the filing period—75% were complete on original submission, with IRs identifying types of missing data from the remainder as clinical (28%), patent certification (28%), and unspecified (22%).
- Applications submitted by large or experienced sponsors were more likely to be complete and organized than applications from smaller sponsors or sponsors without previous combination product experience.
- Over the entire review period, the largest proportion of IR items (37%) pertained to Clinical issues, while the majority of amendment items (58%) submitted by sponsors pertained to Product Quality.
- *Characterization of IND/NDA/BLA review practices:* Review practices are well established and work well. The ICCR process is useful, but involves some challenges (see Section D.2).
- *Good practices:* For FDA, generally same as Section D.2, with addition of requesting same consult reviewer if an application has multiple ICCRs. For the sponsor, including CDRH staff in some meetings is helpful.
- *Challenges:* For FDA, same as Section D.2. For sponsor, receiving CDRH input near/after 30-day Safety review or pre-NDA/BLA meeting.
- *Suggestions:* Provide new or updated guidances (see list on page D-25).

For the IND/NDA/BLA sample, ERG collected data for 39 active commercial combination product INDs (7 CBER, 32 CDER) and 36 combination product NDAs and BLAs (2 CBER, 34 CDER). The INDs represented a sample of INDs active during the assessment period; the NDAs and BLAs were all those with a first-cycle action (Approval, Complete Response, or Withdrawal After Filing) during the assessment period. Data for IND/NDA/BLA sample metrics appear in Table D-8.

Table D-8. Data for Evaluation Metrics for Application Reviews (n=75; 39 INDs, 36 NDAs/BLAs) in IND/NDA/BLA Sample for Combination Product Review Practices Assessment

Metrics	N	Result
Percent of INDs and NDAs/BLAs with Pre-RFD	75 INDs/NDAs/BLAs	1.3%
Percent of INDs and NDAs/BLAs with RFD	75 INDs/NDAs/BLAs	4.0%
Percent of INDs and NDAs/BLAs identified as combination products by sponsors	75 INDs/NDAs/BLAs	60%
Percent of NDAs/BLAs deemed complete on original submission by FDA reviewers	28 NDAs/BLAs with interviews	64%
Percent of NDAs/BLAs considered complete based on analysis of IRs issued during the filing period	36 NDAs/BLAs	75%

Metrics	N	Result
Number of quality deficiencies identified by IRs for NDAs/BLAs: **Mean**	551 IRs	0.09
Number of quality deficiencies identified by IRs for NDAs/BLAs: **Median**		0
Number of quality deficiencies identified by IRs for NDAs/BLAs: **Range**		8 [0, 8]
Number of quality deficiencies identified by IRs during filing period of NDAs/BLAs: **Mean**	107 IRs in filing period	0.1
Number of quality deficiencies identified by IRs during filing period of NDAs/BLAs: **Median**		0
Number of quality deficiencies identified by IRs during filing period of NDAs/BLAs: **Range**		2 [0, 2]
Distribution of types of quality deficiencies in original submission of NDA/BLA		*(Table D-9)*
Number of IRs per IND: **Mean**	39 INDs	3.2
Number of IRs per IND: **Median**		2
Number of IRs per IND: **Range**		22 [0, 22]
Number of IRs per NDA/BLA: **Mean**	36 NDAs/BLAs	15.3
Number of IRs per NDA/BLA: **Median**		10.5
Number of IRs per NDA/BLA: **Range**		71 [0, 71]
Number of IR items per IND: **Mean**	39 INDs	10.4
Number of IR items per IND: **Median**		6
Number of IR items per IND: **Range**		58 [0, 58]
Number of IR items per NDA/BLA: **Mean**	36 NDAs/BLAs	32.7
Number of IR items per NDA/BLA: **Median**		20
Number of IR items per NDA/BLA: **Range**		154 [0, 154]
Distribution of topics among IRs for INDs or NDAs/BLAs		*(Figure D-6)*
Temporal distribution of IRs throughout IND or NDA/BLA review		*(Figures D-4 and D-5)*
Number of amendments per IND: **Mean**	39 INDs	4.7
Number of amendments per IND: **Median**		4
Number of amendments per IND: **Range**		18 [0, 18]
Number of amendments per NDA/BLA: **Mean**	36 NDAs/BLAs	33.7
Number of amendments per NDA/BLA: **Median**		30

Metrics	N	Result
Number of amendments per NDA/BLA: **Range**		86 [0, 86]
Number of amendment items per IND: **Mean**	39 INDs	11.5
Number of amendment items per IND: **Median**		7
Number of amendment items per IND: **Range**		60 [0, 60]
Number of amendment items per NDA/BLA: **Mean**	36 NDAs/BLAs	93.4
Number of amendment items per NDA/BLA: **Median**		81
Number of amendment items per NDA/BLA: **Range**		382 [0, 382]
Distribution of topics among IND or NDA/BLA amendments		*(Figure D-7)*
Temporal distribution of IND or NDA/BLA amendments throughout review		*(Figures D-4 and D-5)*
Number of months between NDA/BLA facility consult submission and facility consult completion: **Mean**	23 facility consults	4.5 months
Number of months between NDA/BLA facility consult submission and facility consult completion: **Median**		3.8 months
Number of months between NDA/BLA facility consult submission and facility consult completion: **Range**		10.9 months [0.7, 11.6]
Distribution of NDA/BLA facility inspection milestones		*(Figure D-8)*
Number of HF consults issued within/to CDER per IND or NDA/BLA: **Mean**	75 INDs/NDAs/BLAs	0.01
Number of HF consults issued within/to CDER per IND or NDA/BLA: **Median**		0
Number of HF consults issued within/to CDER per IND or NDA/BLA: **Range**		1 [0, 1]
Number of HF consults issued to CDRH per IND or NDA/BLA: **Mean**	75 INDs/NDAs/BLAs	0
Number of HF consults issued to CDRH per IND or NDA/BLA: **Median**		0
Number of HF consults issued to CDRH per IND or NDA/BLA: **Range**		N/A
Percent of INDs and NDAs/BLAs with all ICCR actions on time**	55 INDs/NDAs/BLAs with ICCRs	7.3%
Percent of combination product IND and NDA/BLA submissions with no ICCRs	75 INDs/NDAs/BLAs	27%

**Criteria: ICCR submitted by Day 14 (BLA/NDA) or Day 7 (IND), ICCR assigned by Day 17 (BLA/NDA) or Day 9 (IND), and ICCR completed by "Consult Due Date"

Combination Product Applications with an RFD or Pre-RFD. In this sample of combination product applications, very few were associated with a Pre-RFD (1.3%, 1 of 75) or RFD (4.0%, 3 of 75). This might be due to a combination of factors, including (1) sponsors using outdated FDA forms that do not include the RFD identification field, (2) sponsors who might not fill in the RFD identification field, and (3) inclusion of combination products in early development, before the application stage.

Combination Products Identified by Sponsors in INDs and NDAs/BLAs. Sponsors identified their applications as combination products in 60% (45 of 75) of submissions. Of the 45 submissions where sponsors identified their product as a combination, 23 matched the combination product category listed in FDA databases, 16 were written comments (e.g., "combination product," "drug-device combination product," or "auto-injector"), and 6 specified a different combination product category than what was listed in FDA databases.

Completeness and Quality of NDAs/BLAs. ERG examined combination product application completeness and quality in two ways:

- *By asking FDA review teams for their assessment of the application.* In interviews, FDA review teams described 64% of the NDAs/BLAs in the sample as complete and adequately organized. With the remaining 36% of NDAs/BLAs, FDA review teams cited difficulties with application organization, specific device data, facility inspection readiness, pharmacology/toxicology data errors, or product quality microbiology data.
- *By reviewing FDA IRs that identified missing NDA/BLA data.* Based on this analysis, ERG estimated that 75% of applications were complete on original submission. For the remaining 25% of NDAs and BLAs, Table D-9 presents the data types that IRs identified as missing.

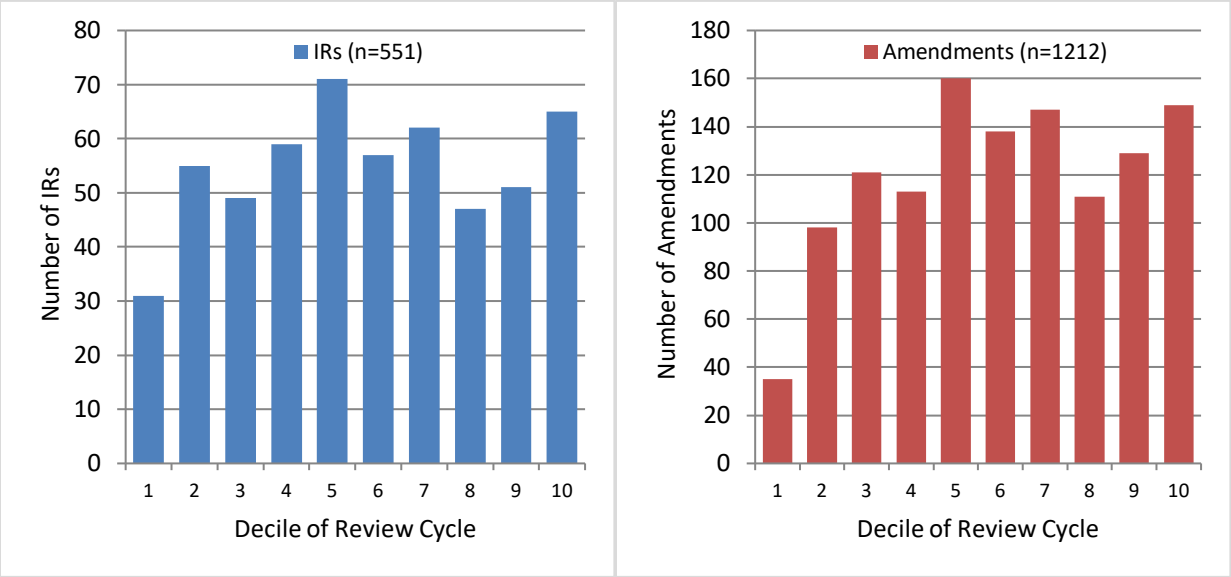
Table D-9. Types of Items that IRs Identified as Missing from NDAs/BLAs on Original Submission (n=18) in IND/NDA/BLA Sample for Combination Product Review Practices Assessment

Missing Items	Result
For IRs that identify missing items from an NDA/BLA on original submission, percent where a missing item is:	
Clinical data	28%
Patent certification	28%
Unspecified data	22%
Review and summary of clinical information to support Pregnancy, Lactation, and Females and Males of Reproductive Potential labeling sections	11%
Comparative analysis report and human factors validation study report	6%
Product quality microbiology data	6%

These estimates of completeness of combination product NDAs/BLAs are slightly lower than the estimate developed for NDAs/BLAs in PDUFA V: 86% based on interviews with FDA reviewers.[2]

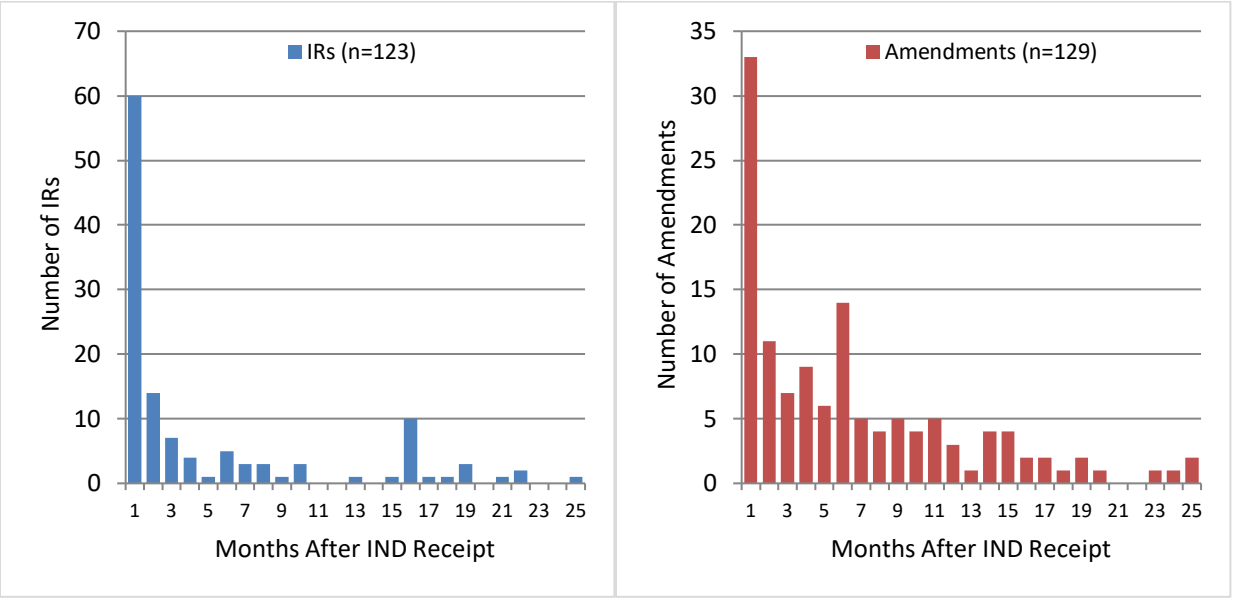
IRs and Amendments for INDs and NDAs/BLAs. An integral part of the FDA review process is the exchange of information between FDA and sponsors in the form of IRs and amendments. Figure D-4 displays the distribution of IRs and amendments for 36 NDAs/BLAs over the course of the review cycle, normalized to deciles of the review cycle to account for different review timelines (Priority, Standard, with or without a Major Amendment). IRs and amendments do not typically exhibit a one-to-one relationship; the greater number of amendments compared to IRs can be largely attributed to multiple partial responses to individual IRs. The relatively low activity in the first month of review compared to higher levels of activity throughout the rest of the review cycle is in line with patterns seen with noncombination product application reviews. In Figure D-5, the distribution of IRs and amendments for INDs exhibits a different pattern from NDAs and BLAs, with a lower volume and a greater proportion occurring in the first month after IND submission. This is not surprising because of the level and timing of information exchange that is expected during the 30-day Safety review.

Figure D-4. Timing of IRs (n=551) and Amendments (n=1,212) During NDA and BLA Reviews (n=36) in IND/NDA/BLA Sample for Combination Product Review Practices Assessment



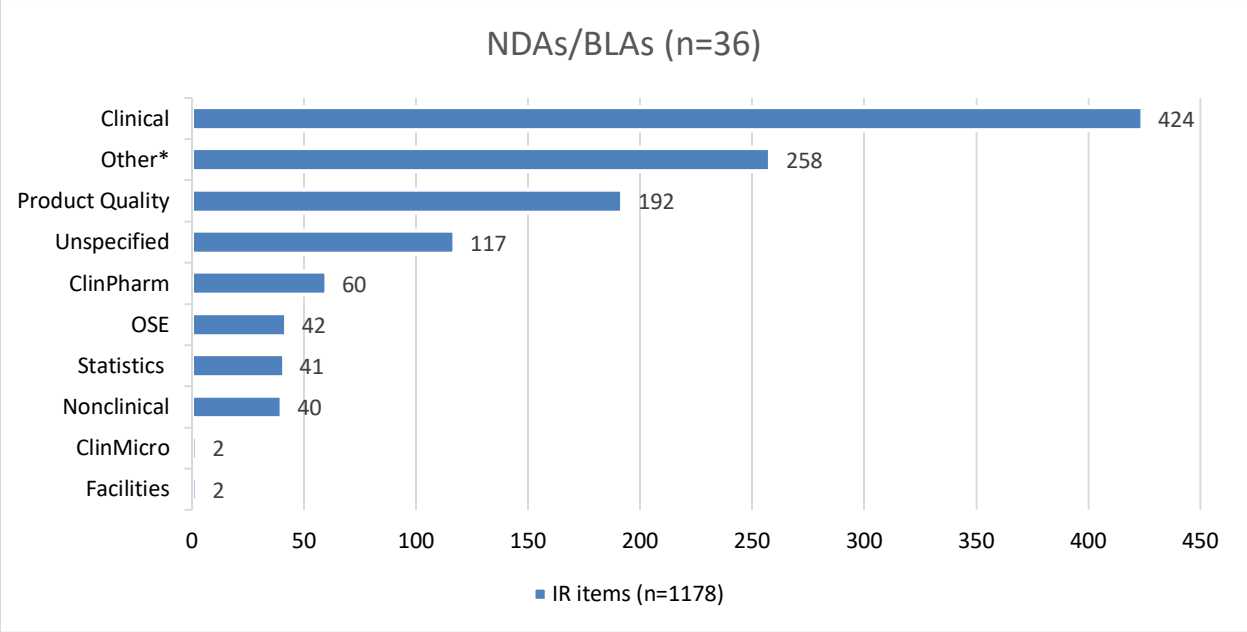
[2] *Final Assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs in PDUFA V*, 2016

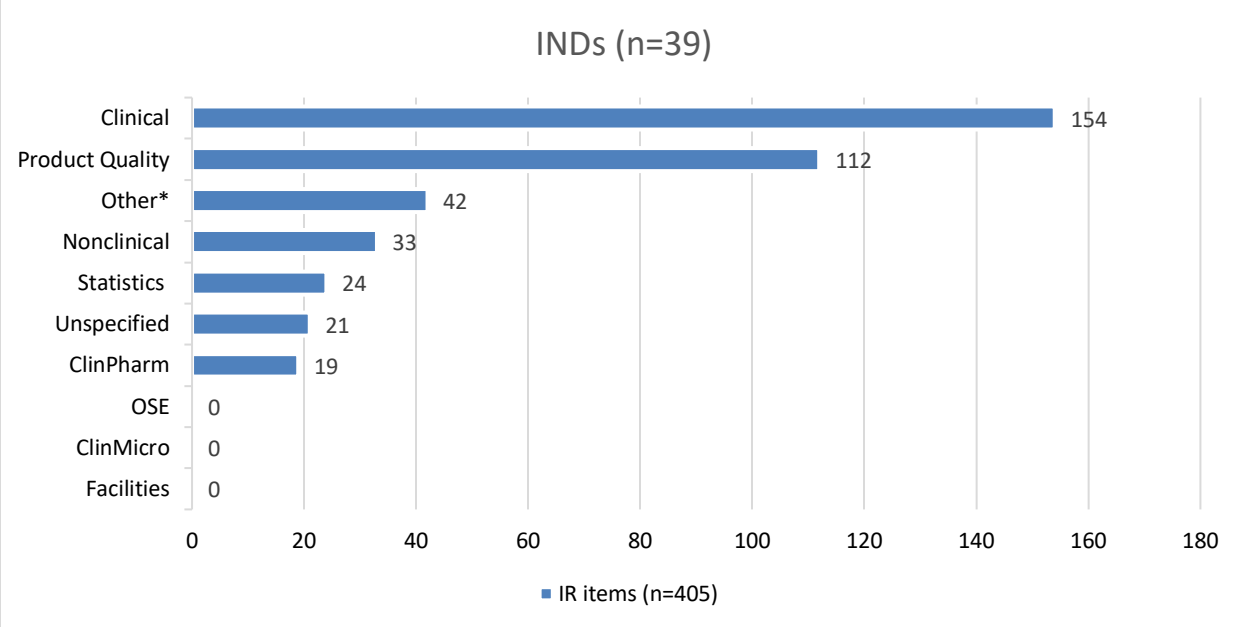
Figure D-5. Timing of IRs (n=123) and Amendments (n=129) During IND Reviews (n=39) in IND/NDA/BLA Sample for Combination Product Review Practices Assessment



IRs often contained numbered or bulleted lists of multiple items for sponsors to address, and sponsors usually responded in a similar manner with multiple items in amendment submissions. Figures D-6 and D-7 present the distribution of IR and amendment items by topic for the 75 INDs, NDAs, and BLAs in the IND/NDA/BLA Sample. These distributions were similar for INDs and NDAs/BLAs, except for the disproportionate number of Product Quality amendment items for NDAs and BLAs. This might be due to a greater need for this type of information during the application review period, when FDA reviewers are assessing whether product quality practices, procedures, and controls are adequate to ensure safety upon product manufacture for marketing.

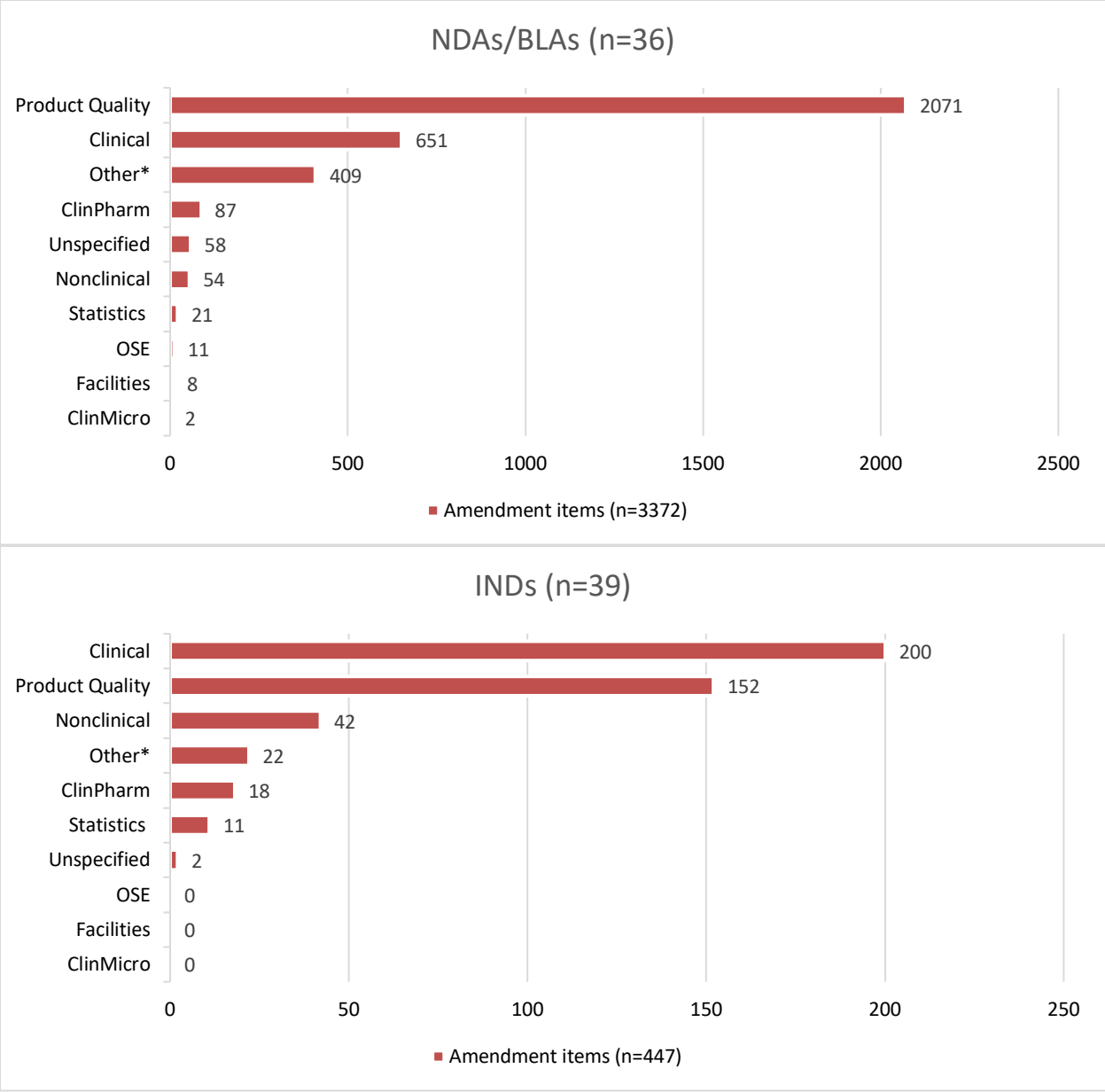
Figure D-6. Distribution of IR Item Topics (n=1,583) During IND, NDA, and BLA Reviews (n=75) in IND/NDA/BLA Sample for Combination Product Review Practices Assessment





**Other includes labeling, REMS, OCP, Division of Medical Policy Programs, pediatrics, postmarketing requirements (PMR)/postmarketing commitments (PMC), proprietary name, nonproprietary name, Controlled Substance Staff (CSS), patent verification, administrative, and CDRH.*

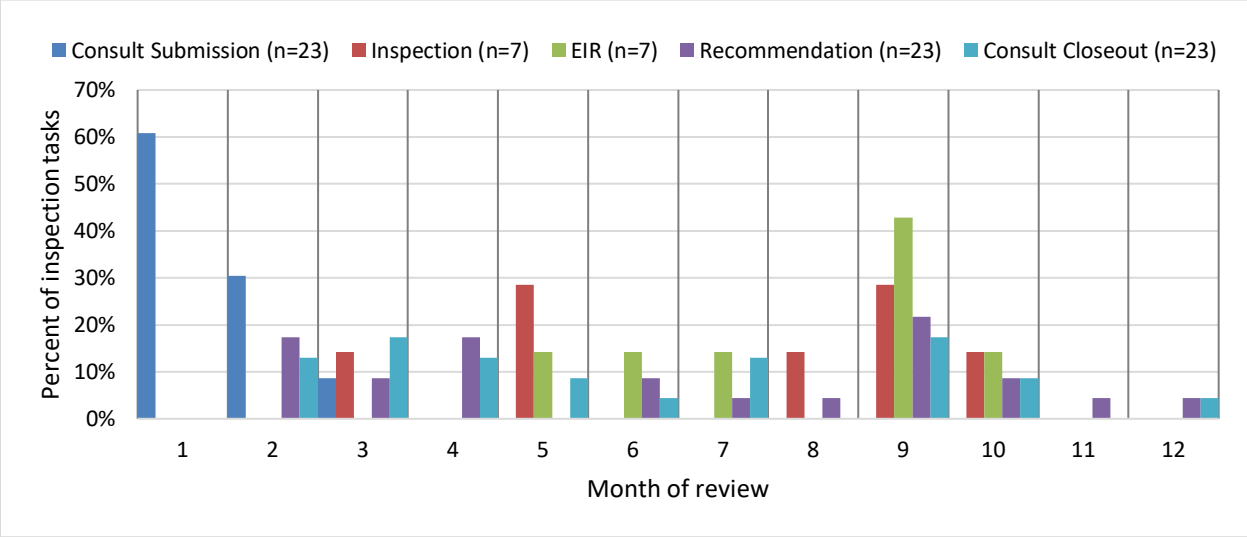
Figure D-7. Distribution of Amendment Item Topics (n=3,819) During IND, NDA, and BLA Reviews (n=75) in IND/NDA/BLA Sample for Combination Product Review Practices Assessment



**Other includes labeling, REMS, OCP, pediatrics, PMR/PMC, proprietary name, nonproprietary name, CSS, patent, administrative, CDRH, and human factors.*

Facility Consults and Inspections for NDAs/BLAs. For NDAs/BLAs in the IND/NDA/BLA sample, during the review period CDER submitted 23 facility consult requests to CDRH in the form of ICCRs. For many of these consults, CDRH reviewed the facility data and concluded that premarketing inspections were not needed. Inspections resulted from seven facility consults; the inspections occurred 3 to 10 months after application receipt, with Establishment Inspection Reports (EIRs) completed 0.2 to 2.1 months after inspections. CDRH made recommendations based on inspection results 7 to 11 months after application receipt (Figure D-8). The timing of these inspection activities generally conformed to FDA guidance.

Figure D-8. Timing of Facility Inspection Milestones for Applications with Device Facility Consults (n=23) in IND/NDA/BLA Sample for Combination Product Review Practices Assessment



Human Factors (HF) Consults. In the IND/NDA/BLA sample, CDER and CBER submitted no ICCRs for HF consults to CDRH, and CBER submitted one HF ICCR to CDER's Division of Medication Error Prevention and Analysis (DMEPA). Within CDER, HF consults to DMEPA were preempted by incorporating DMEPA staff into the OND review team as a standard practice.

Combination Product Applications with ICCRs. In the IND/NDA/BLA sample, 73% of applications (55 of 75) were associated with ICCRs; because some applications had multiple ICCRs, the total number of ICCRs was 102. Due to partial overlap in the qualifying criteria for the IND/NDA/BLA sample and ICCR sample, 30 of the 102 ICCRs (for 15 applications) were also represented in the ICCR sample. Examining the 102 ICCRs independently of their parent applications, 48% of ICCR forms were submitted on time, 37% of ICCRs were assigned to reviewers on time, and 46% of ICCRs were completed by the requested due dates. Of the applications with ICCRs, 7.3% (4 of 55) were associated with ICCRs that had all activities (submission, assignment, and completion) on time. *Note: See Section D.2 for the recommended timelines for these ICCR activities.*

ERG found no ICCRs for 27% of applications (20 of 75) in the IND/NDA/BLA sample; most of the applications without ICCRs (17 of 20) were INDs. For certain types of combination products, the Lead Centers need not submit ICCRs to other Centers when the appropriate knowledge and expertise are available in the Lead Center. Of the 20 applications without ICCRs in the sample, 11 fell in that category. It is likely that the remaining 9 applications (all INDs) did not yet require ICCRs due to the stage of development.

Interview Feedback. ERG interviewed FDA staff and sponsors to gather insight into current combination product application and review practices. Common themes gathered from interviews appear in Table D-10. FDA reviewers generally commented that review practices for combination products were similar to those for noncombination products, except for the addition of combination product ICCRs. Therefore, they focused on ICCRs; their feedback was consistent with that obtained for the ICCR sample (Section D.2 of this document).

Table D-10. FDA Review Team (n=48) and Sponsor (n=44) Feedback from Interviews from IND/NDA/BLA Sample for Combination Product Review Practices Assessment

FDA Review Team Feedback
General feedback about combination product review practices: • Combination product review practices are similar to those for noncombination products, with these practices being well established and smooth most of the time General feedback about combination product ICCR process: • Consults usually worked well once a reviewer was assigned • Lack of access to Lead Center databases was a common obstacle for Consulted Center reviewers • CDRH is not consulted or needed for some device types Helpful practices that facilitate ICCR process: • Lead Centers identifying consult needs and involving consulted reviewers as early as possible • Lead Centers should contact and directly communicate with consult reviewer • Lead Centers maintaining continuity in consult reviews by requesting the same consult reviewer Challenges in ICCR process: • Timing of ICCR submission was sometimes affected by difficulties in identifying the correct group within CDRH to send the consult to • Access to databases in other Centers • Learning to use Salesforce for ICCRs
Sponsor Feedback
General feedback: • Overall experience was positive Useful information sources for preparing combination product applications: • FDA combination product guidance • Industry conferences • Meetings with FDA • Previous experience Some sponsors requested new or updated guidance for: • Transdermal devices • Topical delivery combination products • Outdated IND guidance that references paper submissions • Amount/thoroughness of device data needed for INDs • Location of device data in eCTD Common communication about FDA-sponsor communication: • Contact and communication usually established long before NDA or BLA submission • During application review, sponsors primarily communicated with Clinical and Quality RPMs • CDRH's presence at some meetings demonstrated an openness to communicate Challenges: • Receiving relatively late comments or advice from CDRH near or after 30-day Safety reviews or after Pre-BLA/NDA meetings (occasional comment)

Patterns by Traits of Interest. ERG identified the following patterns by traits of interest in the sample of combination product applications and reviews. At this sample size, the number of applications in each subgroup by trait of interest was too small for these patterns to be statistically significant:

- ***Sponsor Size:*** Based on FDA reviewers' assessments in interviews (n=28), large sponsors (61%) were more likely than small, medium, and private sponsors (39%) to submit complete applications. This might be due to a greater level of regulatory affairs resources available in large sponsors.
- ***Sponsor Experience:*** Based on FDA reviewers' assessments in interviews (n=28), sponsors who had previous experience with combination product applications (58%) were more likely than sponsors without previous combination product experience (44%) to submit complete applications. This might be due to the greater familiarity with FDA expectations that comes with experience.
- ***Lead Center:*** Combination product application reviews led by CBER had fewer IRs and amendments (n=9, mean 4.8 IRs and 11.8 amendments) than those led by CDER (n=66, mean 9.6 IRs and 19.5 amendments). This might be an artifact of differences in how CBER and CDER record IRs and amendments in their databases.