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Assessment of the Impact of Electronic Submissions and Data Standards on the Efficiency and Other Performance Attributes of the Human Drug Review Process

FINAL REPORT AND RECOMMENDATIONS

CONSULTING | ANALYTICS | DIGITAL SOLUTIONS | ENGINEERING | CYBER

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EXECUTIVE SUMMARY

MODERNIZING THE REGULATORY REVIEW PROCESS

The Food and Drug Administration (FDA) is responsible for protecting and promoting public health by ensuring that patients and providers have timely and continued access to safe, effective, and high-quality medical products. In support of this mission, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) receives and analyzes thousands of submissions from manufacturers, healthcare professionals, and consumers. Beginning with the Prescription Drug User Fee Act (PDUFA) II reauthorization in 1997, FDA has made a long-term investment to modernize its information technology (IT) systems and infrastructure to facilitate the receipt and review of electronic applications and other submissions for human drugs and biologics.

Assessment Background

In 2011, Booz Allen conducted the initial independent assessment of the impact of FDA's early efforts with the electronic submission and review environment on the drug review process. We found that by fiscal year (FY) 2010, a majority of applications were received in purely electronic format, and recommended that FDA develop additional standards-based tools to realize the benefits of electronic submissions. Additionally, we recommended that FDA provide corresponding training to ensure that reviewers were able to leverage these tools for a more automated, consistent, and efficient review. In 2012, as part of the PDUFA V legislation, FDA made a series of commitments aimed at improving the efficiency of the drug review process through required electronic submissions and standardization of electronic application data.

Under the PDUFA V Reauthorization Performance Goals, FDA committed to assessing the impact of electronic submissions and data standards on the efficiency and other performance attributes of the human drug review process. CDER and CBER have made significant investments to realize the goals of an automated, standards-based review process, and contracted Booz Allen to provide an objective assessment to identify gaps and recommend an actionable path forward for improvement.

Degree of Implementation

Booz Allen assessed the degree of implementation of electronic submissions and data standards by evaluating the number of electronic submissions, use of the electronic common technical document (eCTD) format, and inclusion of standardized study data. Overall, the number of electronically submitted investigational new drugs (INDs) has increased since FY12, but there are significant differences between research and commercial INDs. Research INDs account for 72% (10,935/15,233) of INDs submitted between FY12 and FY16, and 90% (9,872/10,935) of those INDs were submitted in paper. For commercial INDs submitted electronically, the majority were submitted in eCTD format through the Gateway.

FDA received the majority new drug applications (NDAs), biologic license applications (BLAs), and efficacy supplements electronically via the Gateway. Between FY12 and FY16, CDER and CBER received 88% and 92% of submissions electronically through the Gateway, respectively. Between FY03 and FY16, the percentage of electronic original NDAs and NDA efficacy supplements increased significantly, from 7% to 99%. The use of the Gateway, implemented in May 2006, increased significantly during this period. Between FY06 and FY16, the percentage of original NDAs and NDA efficacy supplements submitted electronically via the Gateway rose from 13% to 96%.

Unlike original NDAs and NDA efficacy supplements, the percentage of electronically submitted BLAs and BLA efficacy supplements has not increased quite as dramatically since the majority of submissions have been received electronically since FY03. In FY03, FDA received 54% of submissions electronically, which were not in eCTD format, and in FY16 FDA received 96% of submissions

electronically, almost all in eCTD format. Between FY12 and FY16, only 3% of original BLAs and BLA efficacy supplements were submitted in paper or mixed format.

Currently, FDA does not track submissions with Analysis Data Model (ADaM) data, and as of FY16, the FDA has received nine submissions with Standard for Exchange Nonclinical Data (SEND) data. For both CDER and CBER, the percentage of SDTM submissions increased over time with CBER receiving proportionally fewer Study Data Tabulation Model (SDTM) submissions than CDER. Between FY12 and FY16, CDER received 49% of its submissions with SDTM data whereas CBER only received 21% of its submissions with SDTM data. In FY16, 54% of CDER submissions and 33% of CBER submissions contained at least one study with SDTM data.

Readiness and Completeness of Available Data Standards

Booz Allen assessed the readiness of five submission format and study data standards and five controlled terminology standards, which apply to submissions across the regulatory review process, and to both clinical and non-clinical data. FDA is accepting a version of all of the investigated standards and has already mandated submission of most standards for many application types. As standards are continually evolving, FDA must continuously review newly released standards before providing support. Interviews with FDA staff revealed that FDA provides proactive subject matter expert (SME) input on changes to standards during the Standards Developing Organization (SDO) development process. This collaboration with the SDOs reduces the review time needed for eventual FDA support of new standards. However, without a mock dataset submission from the SDOs that incorporates the updates to be included in the new version of the standard, FDA is not able to fully determine the impact, through testing, that the proposed changes have on their ability to analyze future data with current analysis tools.

Booz Allen performed an in-depth analysis to determine the completeness of the SDTM and SEND standards. For SDTM, we mapped the 44 domains from Study Data Tabulation Model Implementation Guide (SDTMIG) v3.2 to the clinical review sections of the current template. Overall, we found that four key domains (i.e., demographics (DM), disposition (DS), exposure as collected (EC), exposure (EX)) are required to conduct a majority of the analyses in the clinical review. Current SDTM domains (e.g., Adverse Events (AE), Laboratory Test Results (LB), Electrocardiogram Test Results (EG)) appear to provide coverage for the standard safety analyses. However, the assessment of the efficacy portion of the clinical review was somewhat limited since many of the analyses are dependent on specific clinical outcomes. Therapeutic Area standards will continue to play a critical role in the evolution of the SDTM standard's applicability and usefulness by providing specialized domains and variables to facilitate specific analyses for a given indication or therapeutic area (e.g., oncology).

Booz Allen also mapped the 27 domains contained in Standard for Exchange of Nonclinical Data Implementation Guide (SENDIG) v3.0 to the non-clinical review sections of the review template. For most the analyses, reviewers use eight domains within the standard (i.e., DM, DS, EX, pool definition (POOLDEF), trial arm (TA), trial elements (TE), trial summary (TS), trial sets (TX)). At this time, Clinical Data Interchange Standards Consortium (CDISC) has only modeled general toxicity (i.e., single dose and repeat dose) and carcinogenicity studies in the SEND standard. The SEND standard is evolving with input from sponsors, FDA, and SDOs. New versions of the SEND implementation guides continue to add domains to the standard, with the new SENDIGv3.1, which is not yet supported by the FDA, adding the cardiovascular (CV) and respiratory (RE) domains.

Effectiveness of Electronic Review Tools and Training

During the evaluation of FDA review tools and the availability and effectiveness of training, Booz Allen assessed the usefulness of current tools used during the regulatory review process to view, search, and analyze data. In addition to the tools, CDER provides two services (i.e., JumpStart, KickStart) for clinical and non-clinical staff to assist in the review of study data contained in IND, NDA, and BLA submissions. As reviewers continue to receive more submissions with standardized study data, these services provide them with an opportunity to understand the data fitness for their submission early in the review, receive a set of standard exploratory analysis outputs, and familiarize the reviewers with the functionality of the review tools used to generate the outputs.

As the rollout and adoption of new tools and services continues with the projected increase of submissions with standardized data, Booz Allen deployed a survey to understand the general awareness and use of the current tools and services at the FDA. Overall, awareness of clinical review tools (e.g., JMP, JReview, MedDRA-Based Adverse Event Diagnostics (MAED)) was relatively high, most likely due to formal training communications.

To determine the usefulness of current tool outputs to reviewers, Booz Allen assessed the outputs of certain tools. The tool output assessment built upon the data standards completeness assessment by aligning fully-supported and JumpStart service outputs to the data standard domains used to create the output and the standard analyses in the clinical and non-clinical reviews. For the clinical review, the more general analyses (e.g., disposition, demographics) largely have outputs available for staff to use in their reviews. As expected, analyses of efficacy outcome measures have fewer outputs since the analyses are specific for a given indication or therapeutic area (e.g., oncology). For the analyses included within the safety sections, reviewers have a large number of outputs available for use in their review. Non-clinical reviewers have automatically generated visualizations for all general toxicity and carcinogenicity analyses, which are also the areas fully modeled in the SEND standard.

To determine effectiveness of CDER's and CBER's relevant training courses, Booz Allen investigated the percentage of survey respondents that had taken courses for each of the different trainings, as well as the percentage of respondents that were aware of the different training options available. We found that although less than 50% of all respondents had taken each of the different trainings, greater than 50% of the primary clinical and biostatistics reviewers had taken JMP, JReview, Clinical Data Standards, MAED, and GS Review training. Our survey also indicated that 72% of respondents began using the review tool after they had received training for the tool. Of the 28% that did not begin using the tool after training, many noted that timing was the main factor. Beyond applying the knowledge that they learned in their courses, 61% of the survey respondents also shared information they learned in their training courses with their colleagues.

Impact of Standards and Electronic Submissions on the Review Environment

Booz Allen reviewed quantitative and qualitative data from previous assessment activities to measure the impact of the implementation of electronic submissions and data standardization efforts on various performance metrics identified in the regulatory review process, reviewer and sponsor business practices, and reviewer satisfaction with electronic submissions and standardized data. To evaluate impact, we collected data for applications, and conducted a survey and focus groups to collect information related to satisfaction, gains achieved, and business practices from review staff impacted by electronic submissions and data standards. For each phase of the application lifecycle, we collected data and feedback associated with specific activities to determine whether the submission format or inclusion of standardized data affected the reviewer or completion of the activities. The findings were also grouped based on categories that affected review times, such as priority, inclusion in the Program, [1] and receipt of a major amendment.

Over the last few years, primary reviewers at the FDA have experienced a shift in how they access and analyze safety and efficacy data included in submissions. Presently, the majority of submissions come in electronically, with the exclusion of research INDs, and this change led to the need for reviewers to adopt and learn a suite of tools in order to complete their work. Overall, most of the surveyed, primary reviewers spent a majority of their time reviewing electronic applications and many reviewers have experience with standardized data.

Prior to sending in a submission for review, applicants make a number of decisions associated with the application submission format and data that will directly impact FDA staff's ability to review the information. Through the survey and focus groups, reviewers agreed that the FDA should stop accepting paper and make electronic submissions mandatory. Additionally, reviewers indicated their preference for the submission of standardized study data, which is already a requirement for clinical studies started on or after December 17, 2016. Reviewers noted varying levels of submission quality between applicants, and focus group participants described situations where groups within the same sponsor had significant variances in quality, which suggests a lack of standard operating procedures within a company.

When reviewers receive a new application, they determine whether the submission includes not only enough information, but also the correct data to evaluate the safety and efficacy claims made by applicants. When submissions contain standardized data, 87% of surveyed primary clinical reviewers agreed that this type of data improves data fitness. During the filing review period, reviewers can send information requests (IR) to the applicant, classify a concern as a potential review issue, or categorize the problem as a filing issue. For which FDA sent an IR to the applicant, 79% were sent within the first 60 days. Approximately half of those sent within the first 60 days included an IR related to data fitness. Among the submissions with review issues explicitly stated in the letter, 20% were related to data fitness.

[1] PDUFA V Commitment Letter includes performance goals for the different categories of submissions, including applications in the Program. Applications not included in the Program are referred to non-Program applications throughout this report. Retrieved from https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf

The introduction and continued implementation of standardized clinical and non-clinical data in applications has yielded some of the same efficiencies gained by reviewers with electronic submissions. When asked whether this type of data makes it easier to prepare for and complete standard analyses, most primary clinical reviewers strongly agree or agree that standardized data makes a difference in different aspects of their review activities. They believe standardized data makes it easier to complete standard analyses, perform analyses more efficiently, decreases time spent preparing data, and allows more time to conduct additional non-standard analyses.

We also investigated differences in approval rates for original CDER submissions with and without standardized data and found that submissions containing SDTM data, in some cases, generally had higher approval rates compared to non-SDTM submissions with the same designation. For example, standard non-Program submissions with SDTM data had a 61% approval rate whereas submissions with the same designation without SDTM data had only a 50% approval rate.

As the percentage of postmarket submissions sent through the Gateway has steadily increased over time, reviewers may benefit from additional review tools to evaluate postmarket safety data. During focus group sessions, reviewers expressed interest in a tool that could both provide them with an overview of the data and the ability to select detailed information to investigate further.

FDA Readiness to Receive Real-World Evidence

As part of this evaluation, Booz Allen performed a high-level, preliminary assessment of FDA's ability to receive, ingest, and analyze real-world evidence (RWE). RWE "refers to information on health care that is derived from multiple sources outside typical clinical research settings."[2] CDER subject matter experts agreed that RWE could be any clinical information collected outside of a "traditional" clinical study or trial, such as registries, mobile health data, claims data, electronic health records, or historical controls and natural history studies.

Currently, both CDER and CBER are in the process of developing policy to determine the applicability of RWE to regulatory decision-making, as well as their scientific positions regarding this type of data. Due to these ongoing efforts, the readiness assessment identified existing capabilities to receive, ingest, and analyze data that FDA could use for RWE, as well as working groups formed to determine the applicability and potential for incorporating this type of data into the regulatory review of drugs and biologics. Over the next five years, the FDA will need to meet a number of requirements included in the PDUFA IV Commitment Letter and the 21st Century Cures Act associated with use of RWE.

Recommendations

As sponsors continue to increase the proportion of applications submitted with standardized data and the FDA adapts to the evolving regulatory data landscape, future areas of improvement and growth focus on maximizing the gains from data standards implementation and developing a strategy for new sources of data. As standards and the review tools used to analyze the data continue to advance, FDA must adapt its approach to accepting, tracking, and reviewing submissions with data standards. To stay ahead of this change, the FDA can innovate and streamline an approach to training and submissions review to meet and exceed the needs of the dedicated review staff.

The following recommended actions for improvement focus on areas where FDA can make meaningful change to support staff, streamline and enrich processes, and enhance technology for the current and future challenges and opportunities associated with the review of electronic data (Table ES-1).

[2] Sherman et al. "Real-World Evidence – What Is It and What Can It Tell Us?". N Engl J Med. Dec. 8, 2016. 375:2293-2297. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJMsb1609216

Table ES-1: Recommended improvement actions

RECOMMENDATION AREA	KEY FINDINGS	ACTIONS TO IMPROVE
People	• Staff could benefit from an integrated training approach based on feedback associated with timing of courses and linking training content to review work (Section 3.3)	1. Reformat training around work products (e.g., NDA reviews) and provide additional guidance regarding tool output options for completing analyses
	• FDA is in the beginning stages of developing a data strategy for RWE and may need additional resources to support future initiatives (Section 3.5)	2. Based on decisions related to the incorporation and integration of RWE into the regulatory review process, evaluate the need to hire seasoned data scientists to develop and implement a comprehensive data strategy for step change growth in utility of regulatory data, including real-world data and evidence
Process	• Prior to the mandatory requirements for submissions with standardized study data, which took effect on December 17, 2016, CDER and CBER appeared to have different definitions for how to count and track submissions containing standardized data • Current parameters used to count and track standardized study data (i.e., submission contains at least one study with demographics (DM), exposure (EX), and disposition (DS) datasets, and a define.xml file) do not fully align to the published technical rejection criteria (Section 3.1)	3. To improve tracking of submissions with standardized study data, use a validation tool to automatically classify submissions based on the published technical rejection criteria and share the results with reviewers and sponsors, as appropriate
	• Even though submissions pass the technical rejection criteria, they may not have all of the information needed by reviewers to perform their review (Section 3.2)	4. Expand standardized study data technical rejection criteria to include domains that are the most impactful for reviewers and consider long-term approach of implementing the data validation tool upstream so that applications do not enter data systems unless they pass all required checks
	• The vast majority of research INDs are still submitted in paper format, which limits the ability to fully incorporate these submissions into the electronic review environment • The requirement for submitting INDs electronically, which occurs on May 5, 2018, excludes noncommercial INDs (Section 3.1)	5. Evaluate opportunities to make it easier for research IND sponsors to submit electronically

RECOMMENDATION AREA	KEY FINDINGS	ACTIONS TO IMPROVE
Process	• The standards completeness analysis performed for this assessment identified key domains and tool outputs critical for application review analyses • As the standards continue to evolve, FDA will need to continually understand the impact on reviewers and opportunities for improvement (Section 3.1)	6. Conduct a more in-depth analysis of domains, variables, and tool outputs, to build upon the mappings completed for this assessment, including by specific therapeutic areas
	• Oncology reviewers described a pilot for a unified review that integrated all discipline review into a single document • During focus groups sessions, reviewers indicated a need for a more streamlined and less redundant review (Section 3.4)	7. Expand unified review to all CDER divisions to reduce redundancy in reviews
	• FDA may have to adapt review tools based on updated standards • Based on review analyses and tool output mapping, FDA could expand use of recently added domains to enhance outputs (Section 3.2)	8. Request SDOs submit test datasets for updated study data standards (e.g., SDTM) and implementation guides to ensure continued stability and output generation of existing tools
	• OCS and OBI evaluate their training offerings differently (Section 3.3)	9. Implement a consistent approach for evaluating training between Office of Computation Science (OCS) and Office of Business Informatics (OBI) to improve identification of best practices and potential areas for improvement
Technology	• Reviewers have difficulty locating similar submissions (Section 3.4)	10. Make it easier for reviewers to link similar submissions (e.g., with similar indications or mechanisms of action)
	• Reviewers would like increased submission search capabilities (Section 3.4)	11. Consider development of search capabilities where reviewers can search across and within a submission
	• Some review tools perform similar functions • Each review tool requires resources (e.g., training instructors) to maintain and support users (Section 3.3)	12. Identify output redundancies to determine if maintenance of multiple tools is required

1. ASSESSMENT BACKGROUND AND OBJECTIVES

The Food and Drug Administration (FDA) contracted Booz Allen to perform the assessment of impact of electronic submissions and data standards on the efficiency and other performance attributes of the human drug review process to fulfill a Prescription Drug User Fee Act (PDUFA) V commitment.

1.1 Background and Objectives

The FDA is responsible for protecting and promoting public health by ensuring that patients and providers have timely and continued access to safe, effective, and high-quality medical products. In support of this mission, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) receives and analyzes thousands of submissions from manufacturers, healthcare professionals, and consumers. These submissions contain data with various use types (e.g., clinical study data, non-clinical study data), structures (e.g., legacy, standardized), and submission formats (e.g., paper, mixed, electronic), and these variances strain the FDA's ability to conduct cross-study, cross-product, retrospective, and cross-indication analyses during data-driven medical product reviews. To address these challenges and ensure that FDA can continue to achieve its mission and meet the increasing number of mandates, the Agency required a strategy to streamline and optimize the receipt and management of regulatory submissions, including consistent and standardized formats that facilitate a consistent, systematic analysis.

Beginning with the PDUFA II reauthorization in 1997, FDA has made a long-term investment to modernize its information technology (IT) systems and infrastructure to facilitate the receipt of electronic applications and other submissions for human drugs and biologics. In 2011, Booz Allen conducted the initial independent assessment of the impact of FDA's early efforts with electronic submission and review environment on the drug review process.[3] We found that by fiscal year (FY) 2010, a majority of applications were received in purely electronic format, and recommended that FDA develop additional standards-based tools to realize the benefits of electronic submissions. Additionally, we recommended that FDA provide corresponding training to ensure that reviewers were able to leverage these tools for a more automated, consistent, and efficient review. In 2012, as part of the PDUFA V legislation, FDA made a series of commitments aimed at improving the efficiency of the drug review process through required electronic submissions and standardization of electronic application data. In particular, FDA agreed to develop a five-year IT plan to document and prioritize IT-enabled business process change and the associated improvement expectations, and to strengthen requirements for standardized submissions of certain drug and biologic applications. FDA further agreed to develop standardized clinical data terminology through open Standards Developing Organizations (SDOs) to complete clinical data terminology and implementation guides by FY17.

Under the PDUFA V Reauthorization Performance Goals, FDA committed to assessing the impact of electronic submissions and data standards on the efficiency and other performance attributes of the human drug review process. CDER and CBER have made significant investments to realize the goals of an automated, standards-based review process, and contracted Booz Allen to provide an objective assessment to identify gaps and recommend an actionable path forward for improvement.

The key objectives of this evaluation included the assessment of the following:

- The current state of electronic submissions and data standards to enhance the quality and efficiency of reviews of human drugs and biologics, including the availability and usability of data and information.
- Changes in the drug review process compared to the last assessment done during PDUFA IV.
- The progress of CDER and CBER in developing, using, archiving and implementing electronic submissions and data standards.

[3] Assessment of the Impact of the Electronic Submission and Review Environment on the Efficiency and Effectiveness of the Review of Human Drugs – Final Report. Retrieved from https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm272444.pdf

- The impact of FDA reviewer practices and industry sponsor practices on the implementation of electronic submissions and data standards.
- The availability and effectiveness of electronic submissions and review tools training for FDA review staff.
- The progress of developing and implementing data standards such as standardized clinical and non-clinical study data terminology through open standards developing organizations (SDOs).

2. METHODOLOGY

After developing a number of hypotheses, Booz Allen developed an initial cohort that contained all submission types (e.g., NDA, IND, postmarketing) identified for inclusion in the assessment. Additionally, we performed deep dive analyses on a smaller cohort for specific topic areas that we hypothesized would impact certain aspects of submission review. Throughout this evaluation, we relied on FDA data systems, publicly available sources, and input from FDA primary sources, including targeted interviews, surveys, and focus groups. We analyzed data from these various sources to identify key findings, from which we generated recommendations for future improvement.

2.1 Hypotheses Development

Booz Allen began this assessment by developing an initial list of hypotheses to evaluate the impact of electronic submissions and data standards on the regulatory review process for investigational new drug (IND), new drug application (NDA), biologic license application (BLA), and postmarket safety submissions. We conducted a literature review to inform initial hypotheses development and reviewed existing presentations and articles regarding data standards, electronic submissions, and the review process. Based on this literature review, our knowledge of the FDA review process, prior experience performing the previous assessment, experience with data standards, and consultations with FDA leadership, we developed the list of hypotheses to form the starting point for our testing of outputs and outcomes of an electronic, standardized data submissions environment. The hypotheses covered the following impact categories:

- Resources associated with submission and review activities
- Timeframes associated with submission and review activities
- Quality of submission (e.g., number of first cycle approvals, consistency of data submitted, searchability of data submitted, number of information requests)
- FDA services, tools and technology available for use with standardized, electronic data
- Usefulness of electronic submissions, data standards, and tools and technology for data analyses
- Effectiveness of review tools training
- Readiness for real-world evidence (RWE)

We also developed a set of metrics associated with each of these hypotheses to facilitate data collection and analysis. We incorporated feedback from FDA on new hypotheses, including perceived bottlenecks affecting the electronic submissions and data standards implementation. Booz Allen did not assess scientific decisions.

2.2 Summary of Data Sources

The information in this assessment came from review documents, communications, internally generated tracking reports (e.g., data standard submissions), and training course documentation included in FDA systems and internal SharePoint sites. Table 2-1 summarizes the data types, sources, and examples.

Table 2-1: FDA data sources and systems for qualitative and quantitative analysis

DATA TYPE	DATA SOURCE	EXAMPLE DATA ELEMENTS
Submissions, Reviews, and Communications	• Paper, mixed, and electronic submissions and review data contained in data systems such as Document Archiving, Reporting & Regulatory Tracking System DARRTS, Regulatory Management System-Biologics license application (RMS-BLA), and the Electronic Document Room (EDR) • Internal reports generated for identification of submissions with data standards	• Quantitative data such as: – Review actions by Division – Frequency of information requests (IRs) – Review times for paper versus electronic applications – Length of submission review – Number of submissions with data standards
Booz Allen Interviews and Survey	• FDA senior management • Regulatory Project Managers • Review staff • Subject Matter Experts (SME) (e.g., data analysts on the JumpStart team)	• Qualitative data regarding perspective of submission and review process, including best practices: – Issue resolution – Timing of identification and communication – Agreement on how to address – Follow-up to ensure timeliness for completion – Perceived application completeness – Use and preferences of tools and services
Feedback from Focus Groups	• Clinical reviewers	• Perspectives on submission and review process, including best practices
FDA Training Course Evaluations and Surveys	• Course evaluations • Surveys conducted by FDA	• Qualitative data pertaining to the reviewer's opinions of the training program and behavior changes through reviewer interviews/surveys • Quantitative data including: – Time spent in training – Behavior and program outcome metrics

2.3 Cohorts

Based on the variety of submission types and the need for comparisons between submissions included in the previous evaluation and those included in this one, we assessed the impact of electronic submissions and data standards on the review of drug and biologic submissions using three cohorts:

- Baseline Cohort for identification of application types and metrics and comparison purposes
- Study Cohort to gather recent submission data to test hypotheses, make general observations, perform high-level analyses, and develop initial recommendations
- Deep Dive Cohort to perform a more granular evaluation of selected hypotheses and refine initial recommendations

Table 2-2 describes each cohort, including the submission type and timeframe.

Table 2-2: Submission cohorts and descriptions

COHORT NAME	DESCRIPTION
Baseline Cohort	• PDUFA III and IV NDA and BLA original applications and efficacy supplements received as of March 2, 2011 • Main study cohort during the last assessment and used as the baseline to determine change and progress of the electronic submission and data standard implementation

COHORT NAME	DESCRIPTION
Study Cohort	• PDUFA IV and V NDA and BLA original applications and efficacy supplements, along with INDs and postmarket safety submissions, received between October 1, 2011 and September 30, 2016 • Analyzed to test hypotheses regarding the impact of electronic submissions and data standards on the drug and biologic review process, develop findings, and identify recommendations
Deep Dive Cohort	• A subset of submissions included in the Study Cohort analyzed to further test hypotheses, specifically those focused on data standards, tools, services, and training • This subset of the Study Cohort consisted of: – Submissions that received the JumpStart service – Submissions that did not receive the JumpStart service, but contained some standardized data

Figure 2-1 shows the Center designation and the submission types included in the Study and Deep Dive Cohorts.

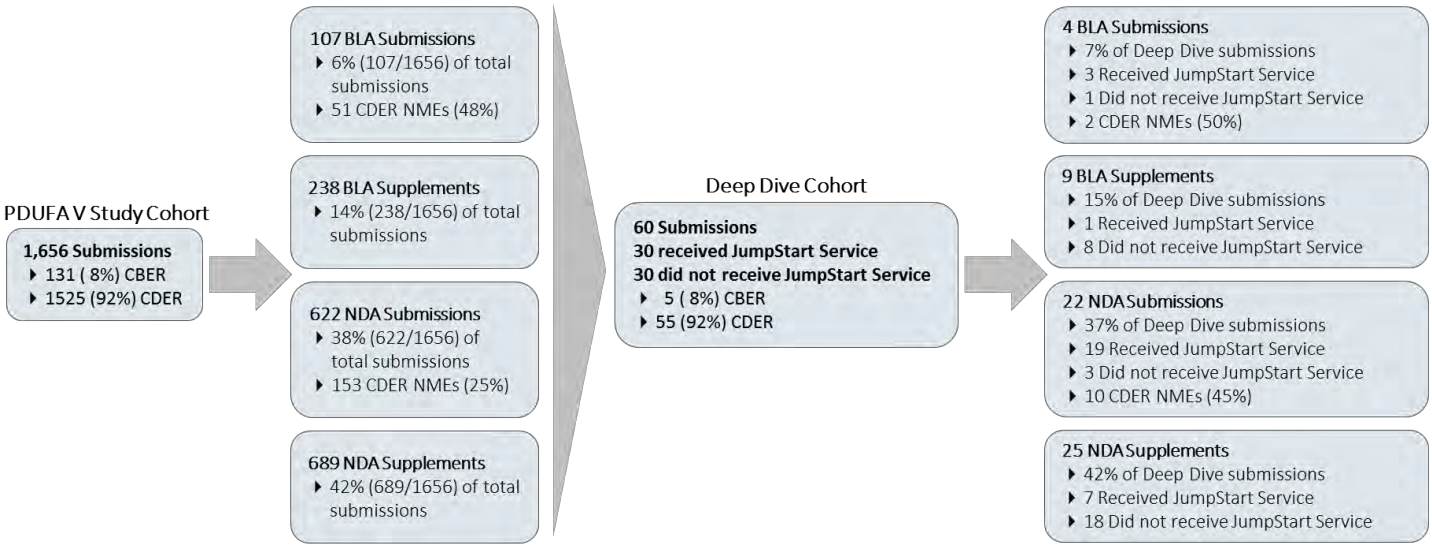


Figure 2-1: Study and Deep Dive Cohorts for assessment

2.4 Data Collection and Analysis Approach

Booz Allen constructed a database to collect information from multiple sources based on the metrics developed in collaboration with the FDA. We used this database to conduct analyses and test the hypotheses for each of the main task areas. The following sections outline the approach to data collection for each of these areas.

DEGREE OF ELECTRONIC SUBMISSIONS AND DATA STANDARDS IMPLEMENTATION

As part of the larger evaluation of FDA's implementation of electronic submissions and data standards and its impact on the new drug review process, Booz Allen assessed the degree of implementation of the following:

- Electronic submission implementation (i.e., percent all electronic, percent paper, and percent combination paper and electronic)
- Study data standard implementation (e.g., percent with Study Data Tabulation Model (SDTM) data, percent with Standard for Exchange of Nonclinical Data (SEND) data)
- Controlled terminology standards implementation (e.g., percent with Medical Dictionary for Regulatory Activities (MedDRA))

Booz Allen analyzed the cohort of submissions received from FY12 to FY16 (i.e., Study Cohort) to compare against the baseline for the submission types. We worked with CDER and CBER to run queries on FDA data systems (e.g., DARRTS, RMS-BLA) to collect the submissions formats (e.g., electronic) and methods of submission (e.g., Gateway) for the cohort.

During this data collection effort, we identified relevant data elements for the queries and reviewed with the FDA to ensure a comprehensive data extract from the system. After development of the final required data elements, we requested execution of the queries in October 2016 to obtain a data set that included all FY16 submissions. Based on Booz Allen's understanding of the limitations for the current systems and tracking methods for submissions with study data standards and controlled terminology standards, we worked with the respective offices in CDER and CBER to obtain access to information used to identify submissions with these standards. Currently, these Centers do not track which submissions include controlled terminology standards so Booz Allen did not analyze the degree of implementation for these standards.

After gaining access to and collecting the necessary data for the selected application types and submission formats and methods, Booz Allen conducted quantitative analyses using descriptive statistics to understand the degree of implementation for electronic submissions and standards. Additionally, we developed findings to identify the degree of implementation, formed logical inferences, where possible and practical, and compared these findings for the Study Cohort to the Baseline Cohort.

READINESS AND COMPLETENESS OF DATA STANDARDS

To assess the readiness of current FDA accepted data standards, Booz Allen focused on five exchange format and study data standards and five controlled terminology standards included in FDA's Data Standards Catalog v4.5.1 (September 29, 2016) and listed below.

Exchange format and study data standards:

- Electronic Common Technical Document (eCTD)
- Individual Case Safety Report (ICSR)
- SDTM
- SEND
- Analysis Data Model (ADaM)

Controlled terminology standards:

- MedDRA
- WHO Drug Dictionary (WHO DD)
- National Drug File – Reference Terminology (NDF-RT)
- Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT)
- Logical Observation Identifiers and Codes (LOINC)

Booz Allen identified the scope of each standard by reviewing SDO and FDA documentation and applicability to the regulatory review process. Additionally, Booz Allen documented the readiness of the data standards based on the stage of adoption (e.g., FDA supported) as determined by publicly available data provided by SDOs and planned requirement dates.

During the assessment, Booz Allen evaluated the following interdependent factors that affect readiness:

- ***Applicability*** of standard to regulatory review process
- ***Continuous improvements*** to existing standards, including potential impact on reviewers, and managed review process for evaluating updates
- ***Collaboration*** with SDOs and other groups impacted
- ***Communication*** to sponsors and public regarding standards

Booz Allen followed the structured approach outlined in Figure 2-2 to determine the completeness of SDTM and SEND. The completeness assessment focused on the standard analyses completed by reviewers during the course of their discipline (i.e., clinical, non-clinical) review. We limited our evaluation to review sections, identified in the most recent version of the review templates, which require analysis (i.e., clinical review – Sections 6 through 8; non-clinical review – Sections 4 through 11). We utilized domains available from the most recent FDA-supported SDTM and SEND implementation guides (i.e., SDTM IGv3.2 and SEND IGv3.0).

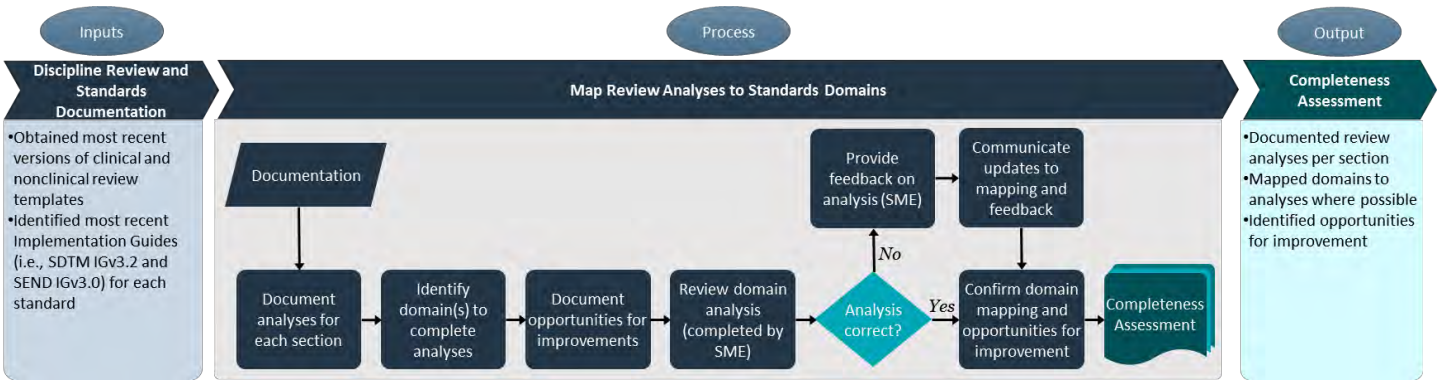


Figure 2-2: Booz Allen approach to data standards completeness assessment

First, Booz Allen documented the analyses required for each section of the discipline review templates (DRT). Next, we identified the SDTM and SEND domains available to complete the required analyses, identifying opportunities for improvement where applicable. Booz Allen then invited FDA SMEs to review and confirm our completeness assessment.

EFFECTIVENESS OF ELECTRONIC REVIEW TOOLS AND TRAINING

Booz Allen evaluated the effectiveness of the electronic review tools and training used to support the regulatory review process. Details on our data collection and analysis approach for reviews tools and training are described in the sections below.

TOOLS

As a first step, Booz Allen created an inventory of FDA-managed review tools, identified the access method (i.e., desktop vs. web-based) and data formats (e.g., file types, standardized) for each one, and whether it can automatically generate standard analyses (e.g., demographics) used in an application review. To determine the awareness and actual use for the tools, we developed and conducted a survey with FDA staff involved in the management and review of submissions. Booz Allen also reviewed previously conducted survey data from Office of Business Informatics (OBI) and Office of Computational Science (OCS) and performed interviews with SMEs to determine usefulness, benefits, and challenges for the tools. These data sources provided insight into reasons for using or not using tools, along with identifying pain points.

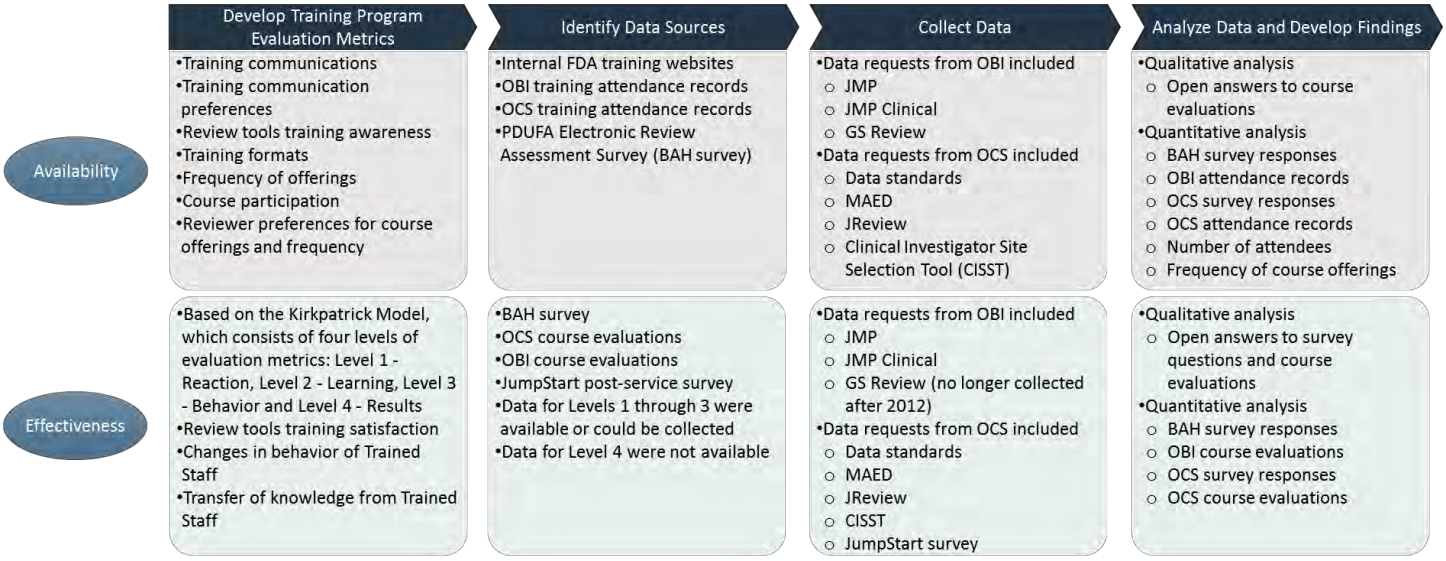
Booz Allen continued to build upon the previous analysis of mapping standard domains to clinical and non-clinical analyses by aligning tool outputs to these same analyses to understand further the tools' usefulness. This effort also identified opportunities for improvement for areas where current outputs do not meet reviewer needs.

For each of the tools, Booz Allen identified and analyzed the data (e.g., format, standard) used by the tool, strengths and limitations, and review activities and/or analyses supported by the tool. While reviewers employ several tools to complete their work, we focused our assessment on tools used to access and analyze data to complete review activities and that the FDA manages enhancements made to the tools and versions used by reviewers. Certain tools that focus on tracking submissions and their associated metadata were not included based on feedback from the FDA Technical Advisory Group (TAG).

TRAINING

Booz Allen evaluated the availability and effectiveness of data standards and review tools training for FDA staff. We identified training program evaluation metrics and data sources to collect and analyze the information. The OBI provides training courses for the tools associated with the review of regulatory submissions information (e.g., JMP) to demonstrate how to complete review activities within the tools. The OCS also offers specific training on analytical tools developed to work with non-standardized and standardized data (e.g., JReview, MAED) and demonstrates how those tools can generate review-specific analyses. Additionally, OCS

collaborates with SDOs to help staff develop a deeper understanding of the study data standards by offering domain specific trainings (e.g., SDTM, SEND, ADaM). We worked closely with the training coordinators in OBI and OCS to gain access to and review course attendance records and evaluations. Figure 2-3 provides an overview for the methodology used for evaluating the effectiveness of the training program associated with the review of electronic submissions and standardized data.



*Note: *Level 1: Reaction – Measures participant reaction to and satisfaction with received training, Level 2: Learning – Evaluates changes in participants' attitudes, knowledge, and/or skills as a result of participating in the training program, Level 3: Behavior – Assesses transfer of knowledge, skills, and/or attitude after completing training, based on performance in the participants' work environment, Level 4: Results – Determines training results based on pre-identified program metrics, such as increased efficiency and/or predictability, or review consistency;*

Figure 2-3: Methodology for evaluating training effectiveness

To assess the training program associated with electronic submissions and data standards, Booz Allen first developed a list of all training courses provided, the type of training, and the course frequency. We based the approach to evaluating training effectiveness on the Kirkpatrick Model, which consists of four levels of evaluation metrics: Reaction, Learning, Behavior, and Results.[4] Each of the four framework levels applies a unique and increasingly complex set of metrics to assess training program utility:

- Level 1: Reaction – Measures participant reaction to and satisfaction with received training
- Level 2: Learning – Evaluates changes in participants' attitudes, knowledge, and/or skills as a result of participating in the training program
- Level 3: Behavior – Assesses transfer of knowledge, skills, and/or attitude after completing training, based on performance in the participants' work environment
- Level 4: Results – Determines training results based on pre-identified program metrics, such as increased efficiency and/or predictability, or review consistency

To collect data related to training effectiveness, Booz Allen worked with FDA training directors and staff to obtain course evaluations and surveys and to review and evaluate training effectiveness at Levels 1 and 2. After analyzing the feedback and results, we categorized the findings into themes and perceptions of the training program, highlighting utility and satisfaction factors, such as the ability to apply learning to completion of reviews, durability of training materials, and approval of format and content.

OBI and OCS developed surveys and user training feedback as part of their overall training program to track and evaluate the quality and usefulness of the training. Booz Allen obtained, reviewed, and analyzed this data, which provided some insights into Level 3, but data associated with Level 4 metrics were not available at this time. Additionally, we conducted a survey, which included course participants, and assessed reviewers' satisfaction (Level 1), changes in knowledge and skills (Level 2), as well as both reviewers' and managers' observations and perspectives on knowledge and skills transfer between staff (Level 3).

[4] The Kirkpatrick Model. Retrieved from http://www.kirkpatrickpartners.com/Our-Philosophy/The-Kirkpatrick-Model

IMPACT OF STANDARDS AND ELECTRONIC SUBMISSIONS

As outlined in Figure 2-4, Booz Allen reviewed quantitative and qualitative data to measure the impact of implementing electronic submissions and data standardization efforts on various performance metrics identified in the regulatory review process (e.g., total primary review time), reviewer and sponsor business practices, and reviewer satisfaction with electronic submissions and standardized data. The evaluation of the regulatory review performance portion consisted of mainly quantitative data analysis from FDA data systems. However, to augment the available information for the larger Study Cohort, we performed an in-depth analysis of information requests associated with the applications of the Deep Dive Cohort. Additionally, we piloted an approach to utilize DataFit results as a potential proxy for the degree of data standards implementation for applications included in the Deep Dive Cohort. Evaluation of the business practices and reviewer satisfaction assessments relied on qualitative findings from focus groups, targeted interviews, and survey results. Finally, we investigated two National Institute of Health (NIH) processes to perform best practice benchmarking.

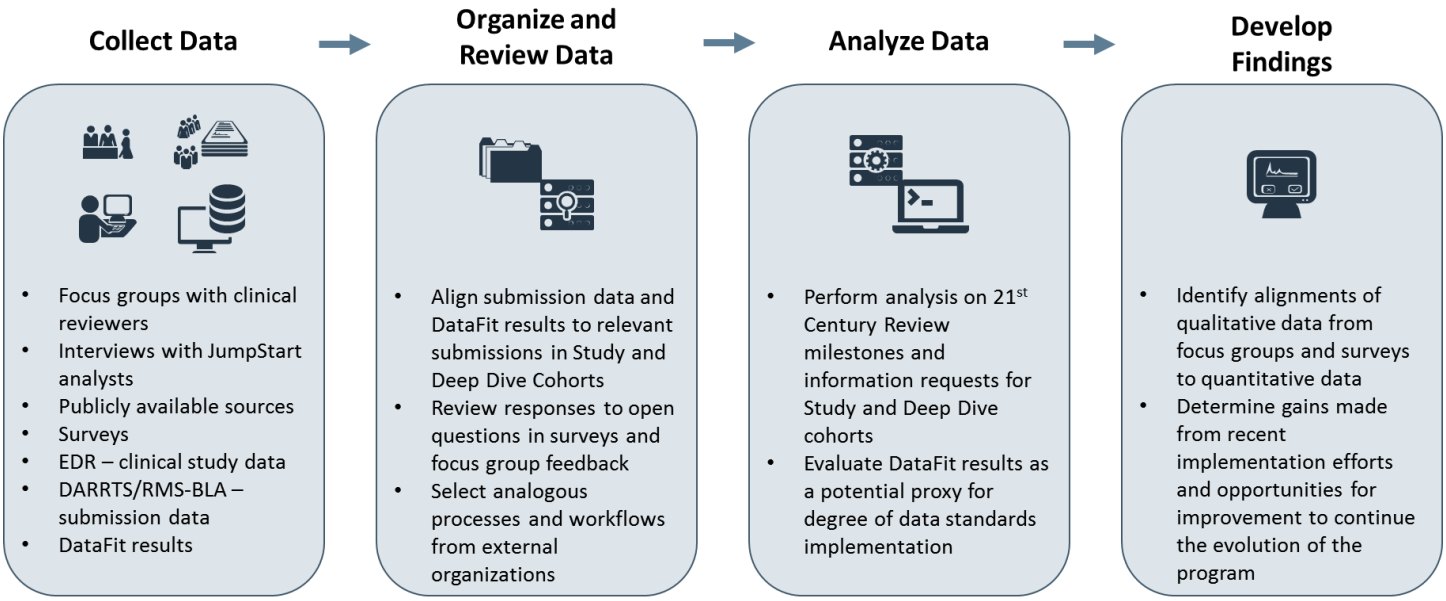


Figure 2-4: Methodology of impact assessment

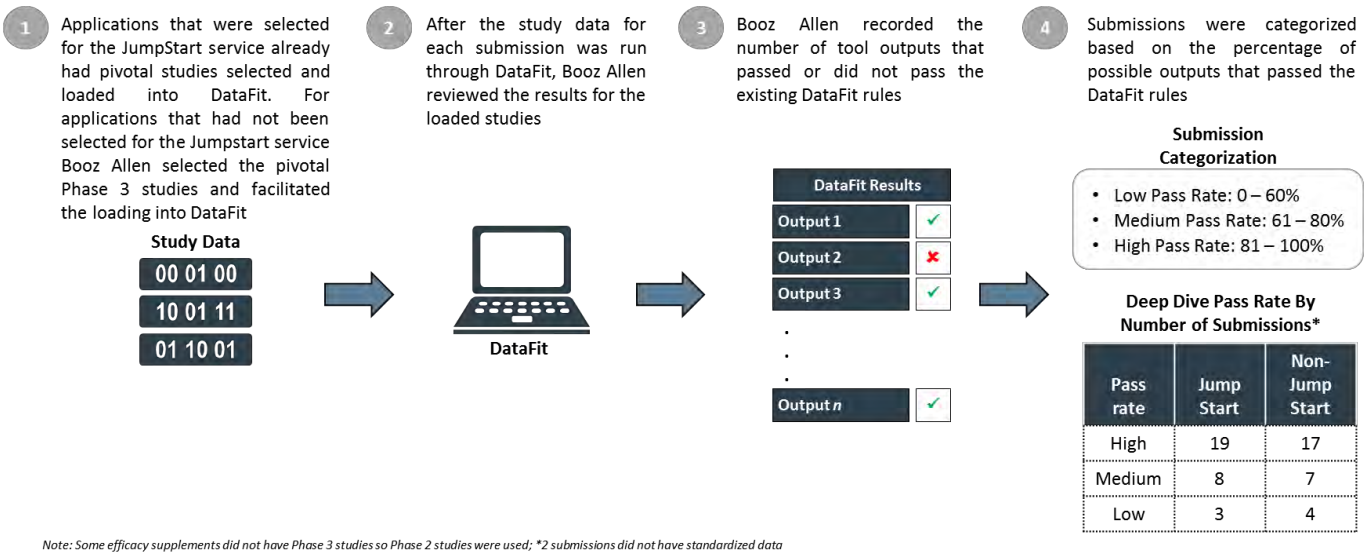
After organizing data from each of the data sources, Booz Allen assessed the impact of electronic submissions and data standards at multiple points throughout the application lifecycle, including the ability of reviewers to meet 21st Century Review milestones. The findings were also grouped based on categories that affected review times, such as priority, inclusion in the Program, and receipt of a major amendment.[5] Where applicable, we aligned qualitative and quantitative data to inform evaluation findings. Additionally, we determined gains made from recent implementation efforts and identified opportunities to improve the current electronic submission and review environment.

DATAFIT PILOT

While FDA collects SDTM classification data, the current classification efforts do not provide insight into the degree of SDTM implementation for each submission. To gain a better understanding of the potential impact of differing degrees of data standardization on various review activities, Booz Allen piloted an approach to categorize Deep Dive Cohort submissions by their DataFit pass rate as a proxy for degree of SDTM standardization. This approach, outlined in Figure 2-5, began with identification of study data to be loaded into the DataFit program. Applications previously selected for the JumpStart service already had pivotal study data loaded into DataFit. For the remaining applications, we identified the pivotal study data and facilitated the loading of this data into DataFit. The DataFit program then checked whether 48 unique JReview, JMP Clinical, and MAED standard analyses outputs could be generated with the study data provided by the applicant. We recorded the number of tool outputs that passed the existing DataFit rules for the studies associated with each application. We then categorized each submission by the total pass rate of all of

[5] PDUFA V Commitment Letter includes performance goals for the different categories of submissions. Retrieved from https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf

the submission's pivotal studies (e.g., if Study 1 had a pass rate of 50% and Study 2 had a pass rate of 100%, the submission pass rate was 75%).



*Note: Some efficacy supplements did not have Phase 3 studies so Phase 2 studies were used; *2 submissions did not have standardized data*

Figure 2-5: Piloted approach to assess degree of data standards implementation per application

FDA READINESS TO RECEIVE REAL-WORLD EVIDENCE

Booz Allen performed a high-level assessment of FDA's readiness to receive RWE. We first identified a current definition of and sources for RWE by performing a literature review. A high-level snapshot of the current state of RWE efforts at FDA was developed by identifying a list of current FDA capabilities for potential use in the ingestion, storage and analysis of this type of data. We also investigated examples of current RWE working groups that include FDA members to highlight attempts toward development of policies and scientific viewpoints.

3. ASSESSMENT FINDINGS

To assess the impact of electronic submissions on review activities, Booz Allen first analyzed the degree of electronic submission and data standards implementation. By also analyzing the readiness and completeness of data standards and the effectiveness of FDA tools and training, we generated a comprehensive viewpoint of the FDA electronic submission and review environment experienced by staff.

3.1 Degree of Implementation

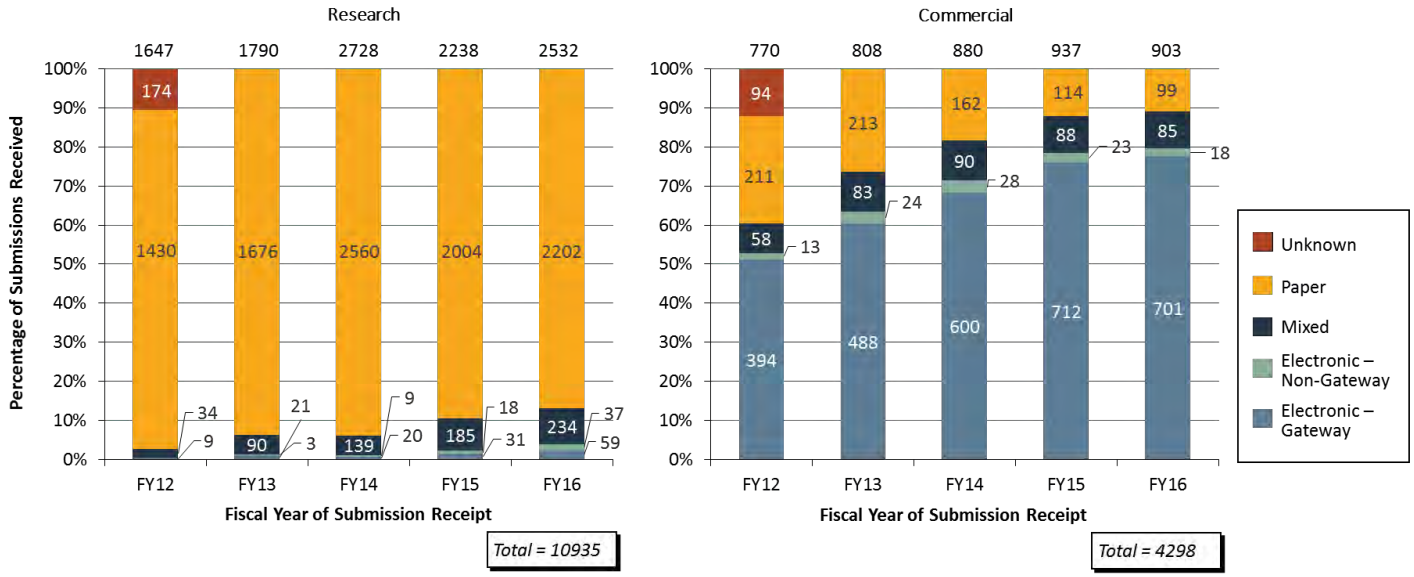
Booz Allen assessed the degree of implementation of electronic submissions and data standards by evaluating the number of electronic submissions, use of the eCTD format, and inclusion of standardized data.

ELECTRONIC SUBMISSIONS

Booz Allen used the Baseline and Study Cohorts to assess the degree of electronic implementation of NDAs, BLAs, efficacy supplements, INDs, and postmarket submissions.[6] The Baseline Cohort provided historical context for the changes in submission patterns observed in the Study Cohort.

The FDA classifies submissions into three different format categories. Electronic submissions have all sections submitted in electronic format. The FDA distinguishes between electronic submissions received via the Electronic Submission Gateway, a portal for sponsors to upload submissions, primarily in eCTD format, and submissions sent to the FDA via other physical media (e.g., CD, tape). Mixed submissions contain a mix of paper and electronic submission components.[7] Paper submissions have all sections submitted in paper format, except for required labeling associated with NDAs, BLAs, and efficacy supplements. For paper submissions, some reviewers request electronic data sets through informal communications.

Overall, the number of electronically submitted INDs has increased since FY12, but there are significant differences between research and commercial INDs. Research INDs account for 72% (10,935/15,233) of INDs submitted between FY12 and FY16, and 90% (9,872/10,935) of those INDs were submitted in paper (Figure 3-1). In contrast, the FDA received only 19% (799/4,298) of commercial INDs in paper format over the same period. The large volume of paper research INDs may be due to a lack of resources or an understanding of how to submit electronic INDs by principle investigators. Between FY12 and FY16, commercial INDs submitted electronically increased from 53% to 80%, whereas electronic research INDs increased from less than 1% to 4%.



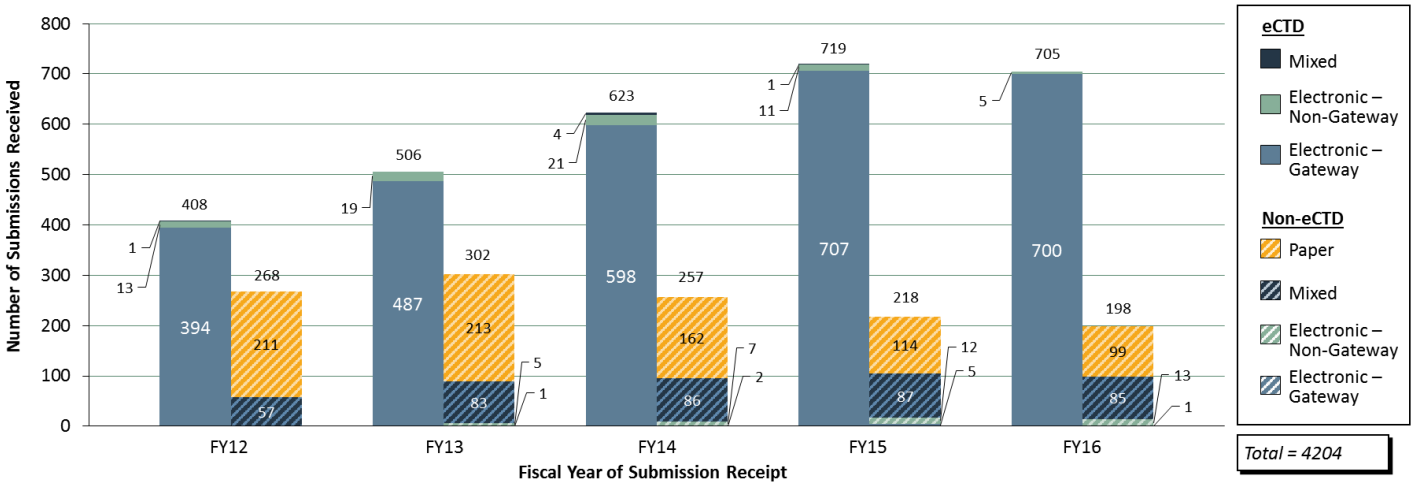
Notes: Since the designation for 27 CDER INDs is unknown, these INDs are not included in either commercial or research sub analyses; Format was not recorded for CBER INDs in FY12
Source: FDA data systems – Study Cohort

Figure 3-1: Research and commercial INDs by submission format and fiscal year

For commercial INDs in the Study Cohort submitted electronically, the majority were submitted in eCTD format through the Gateway (Figure 3-2). Starting in May 2018, sponsors will be required to submit commercial INDs in eCTD format, and non-commercial INDs (e.g., research), including investigator-sponsored INDs and expanded access INDs (e.g., emergency use, treatment), will be exempt.

[6] Postmarket submissions included Periodic Safety Update Reports (PSURs), Periodic Adverse Experience Reports (PAERs), Periodic Adverse Drug Experience Reports (PADERs), and Periodic Benefit-Risk Evaluation Report (PBRERs)

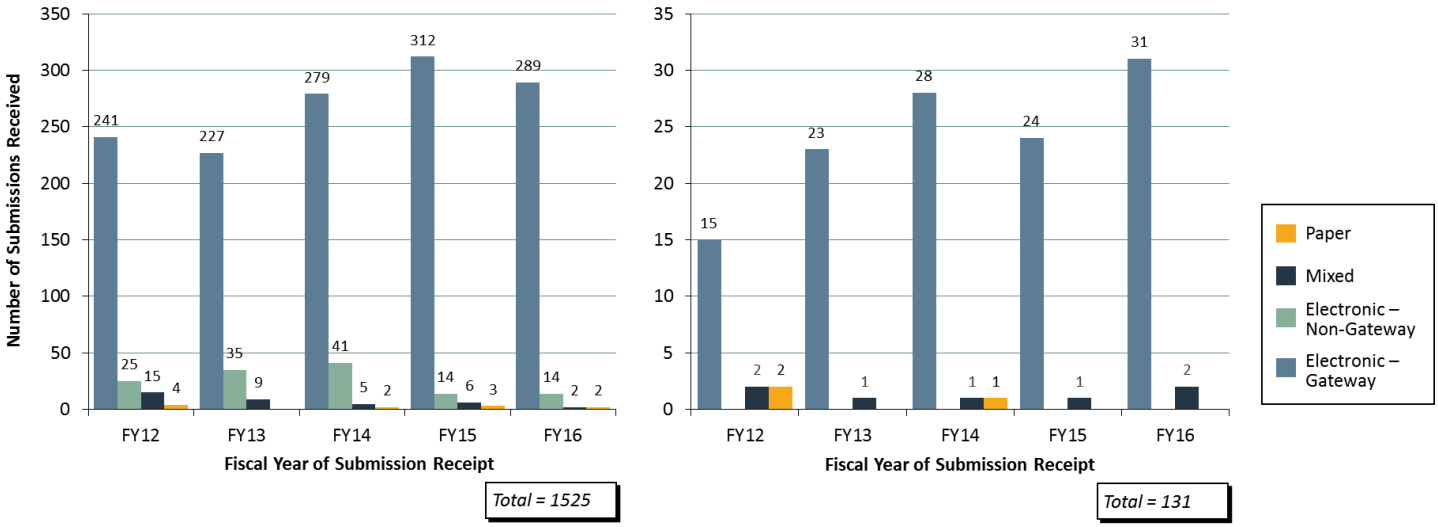
[7] The distribution between electronic and paper submission components can vary greatly, from including only several pages of paper documents with all other elements submitted electronically, to being primarily paper-based with one electronic data set.



Notes: Since the designation for 27 CDER INDs is unknown, these INDs are not included in either commercial or research analyses; eCTD status was not recorded for 94 commercial INDs in FY12
Source: FDA data systems - Study Cohort

Figure 3-2: Commercial INDs by submission and eCTD format

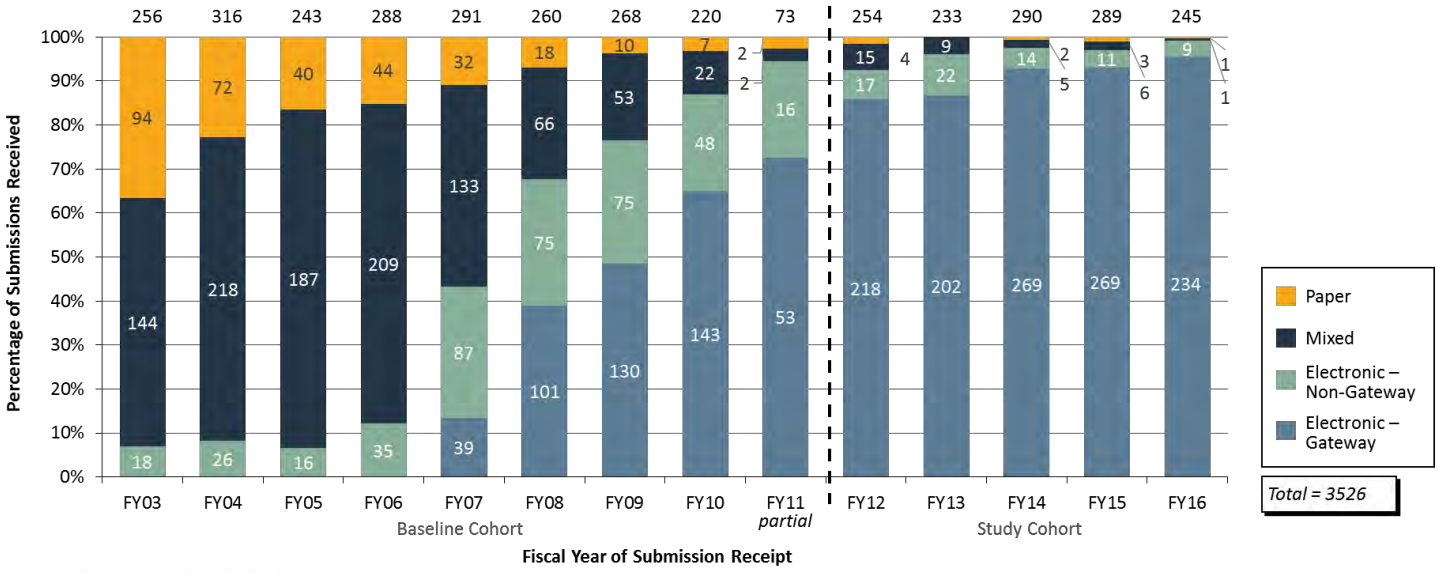
FDA received the majority NDAs, BLAs, and efficacy supplements electronically via the Gateway. Between FY12 and FY16, CDER and CBER received 88% (1348/1525) and 92% (121/131) of submissions electronically through the Gateway, respectively (Figure 3-3).



Source: FDA data systems - Study Cohort

Figure 3-3: Original BLAs, NDAs, and efficacy supplements by Center, submission format, and fiscal year

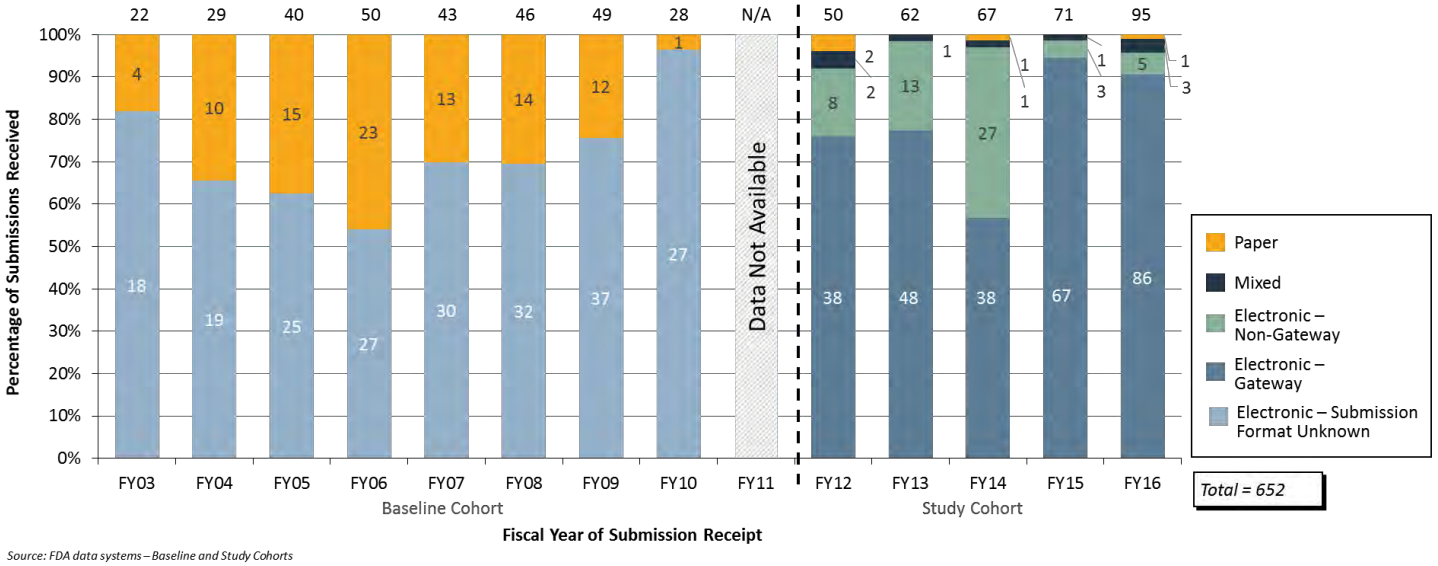
Between FY03 and FY16, the percentage of electronic original NDAs and NDA efficacy supplements increased significantly, from 7% to 99%. In FY16, there was only one submission each for mixed and paper formats (Figure 3-4). Similarly, the use of the Gateway, implemented in May 2006, increased significantly during this period. Between FY06 and FY16, the percentage of original NDAs and NDA efficacy supplements submitted electronically via the Gateway rose from 13% to 96%.



Source: FDA data systems – Baseline and Study Cohorts

Figure 3-4: CDER original NDAs and efficacy supplements for the Baseline and Study Cohorts by submission format and fiscal year

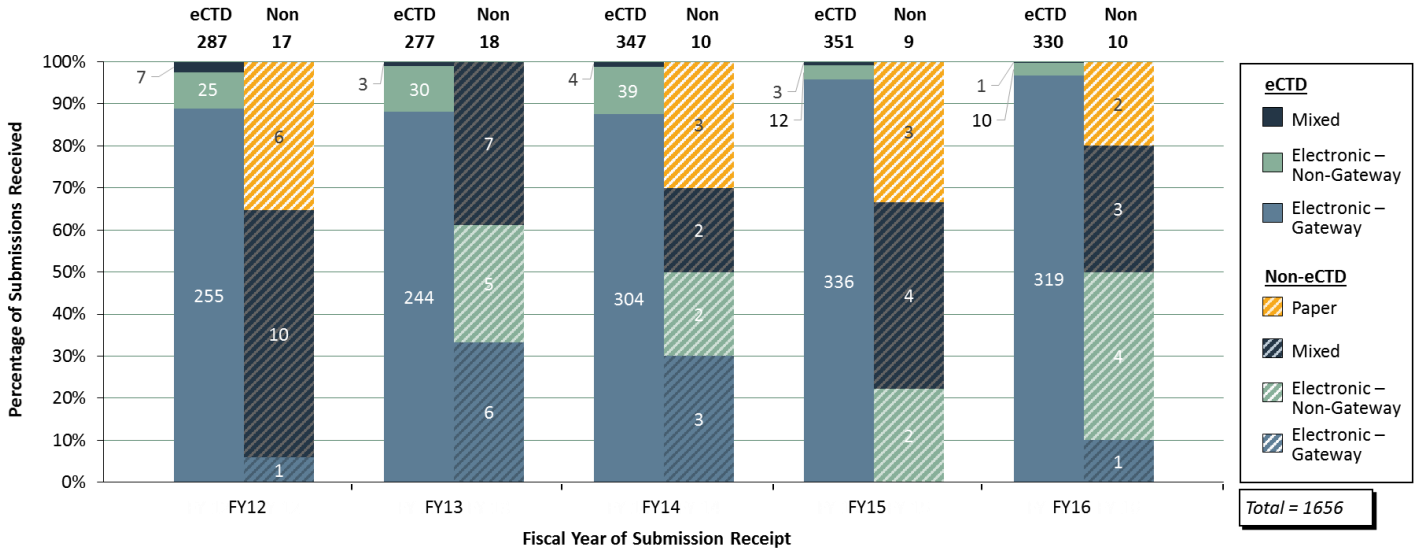
Unlike original NDAs and NDA efficacy supplements, the percentage of electronically submitted BLAs and BLA efficacy supplements has not increased quite as dramatically since the majority of submissions have been received electronically since FY03. In FY03, FDA received 54% of submissions electronically, which were not in eCTD format, and in FY16 FDA received 96% of submissions electronically, almost all in eCTD format (Figure 3-5). Between FY12 and FY16, only 3% of original BLAs and BLA efficacy supplements were submitted in paper or mixed format.



Source: FDA data systems – Baseline and Study Cohorts

Figure 3-5: CDER and CBER original BLAs and efficacy supplements by submission format and fiscal year

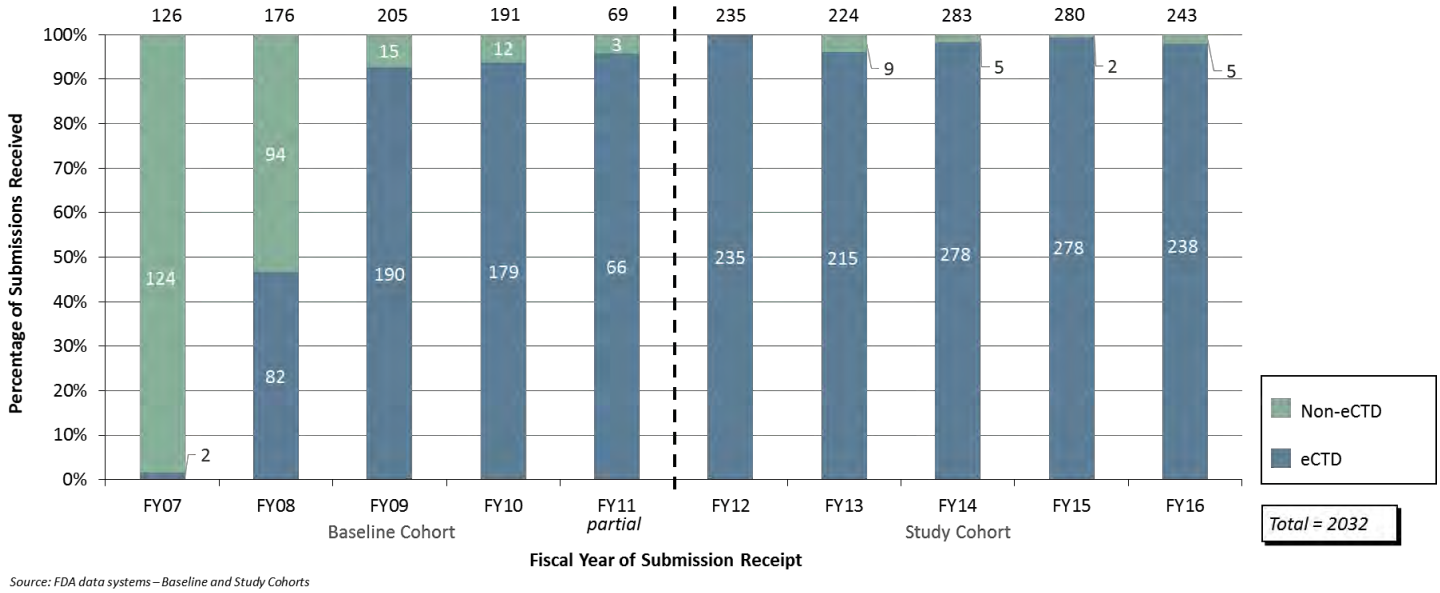
Between FY12 and FY16, FDA received the majority of submissions in eCTD format (96%, 1592/1656) (Figure 3-6). Starting in May 2017, sponsors will be required to submit all NDAs, BLAs and efficacy supplements in eCTD format even if the original submission was not in eCTD format or receive a refuse-to-file.



Source: FDA data systems – Study Cohort

Figure 3-6: CDER and CBER NDAs, BLAs, and efficacy supplements by submission format and fiscal year

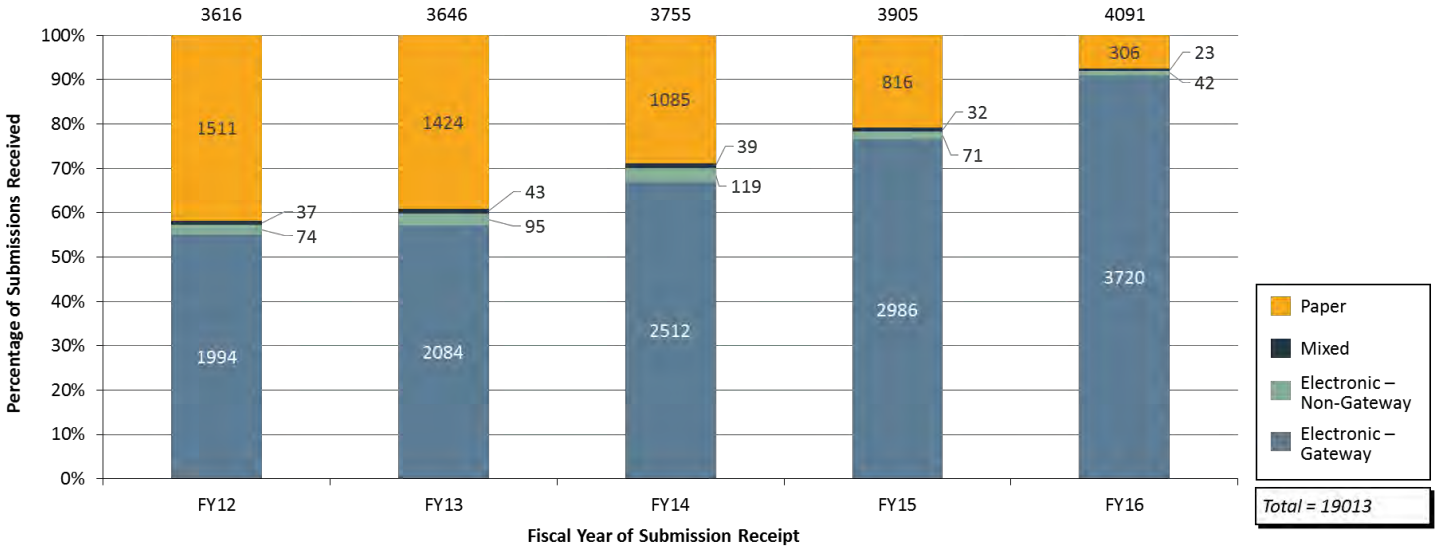
Since FY07, the percentage of CDER NDAs and NDA efficacy supplements submitted in eCTD format has increased considerably from less than 2% of submissions in FY07 to 98% of submissions in FY16, with the largest increases in FY08 and FY09 (Figure 3-7).



Source: FDA data systems – Baseline and Study Cohorts

Figure 3-7: CDER original NDAs and efficacy supplements submitted electronically by eCTD format

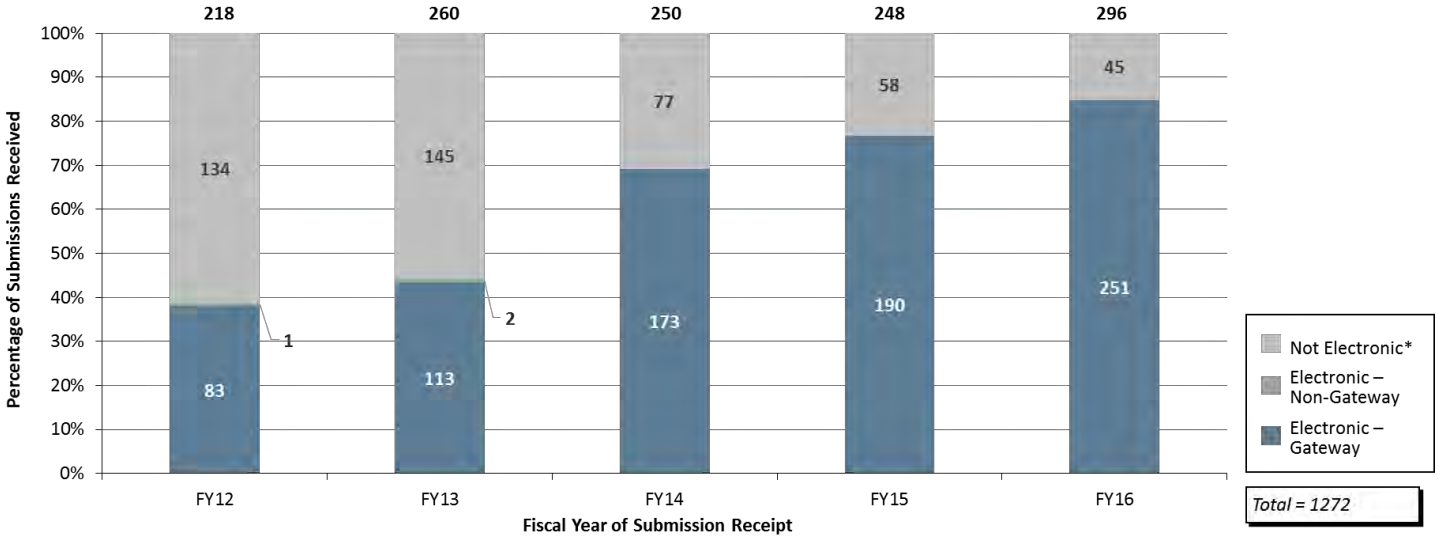
The percentage of CDER postmarket submissions sent electronically through the Gateway has steadily increased over time. In FY16, FDA received more than 90% of the submissions electronically via the Gateway (Figure 3-8).



Source: FDA data systems - Study Cohort

Figure 3-8: CDER postmarket submissions by submission format and fiscal year

Similar to CDER, the percentage of CBER postmarket submissions sent through the Gateway has increased over time. In FY16, 85% were submitted electronically via the Gateway (Figure 3-9). Between FY12 and FY16, FDA only received three postmarket submissions electronically outside of the Gateway.



Notes: CBER Postmarket data does not distinguish between paper and mixed delivery formats, both are categorized as Not Electronic;
Source: FDA data systems – Study Cohort

Figure 3-9: CBER postmarket submissions by delivery format and fiscal year

For NDAs, BLAs, and efficacy supplements, the percentage of electronic, Gateway submissions continued to increase since the last assessment. These trends reflect the progress made by FDA and sponsors to shift away from paper and transition to a more efficient method of sending and receiving electronic submissions. The next section provides an update on the evolving data standards implementation at the FDA.

DATA STANDARDS

The FDA continued to implement data standards for study data through the acceptance of the SDTM and ADaM standards for clinical data and the SEND standard for non-clinical data. The FDA mandated that all studies started on or after December 17, 2016 are

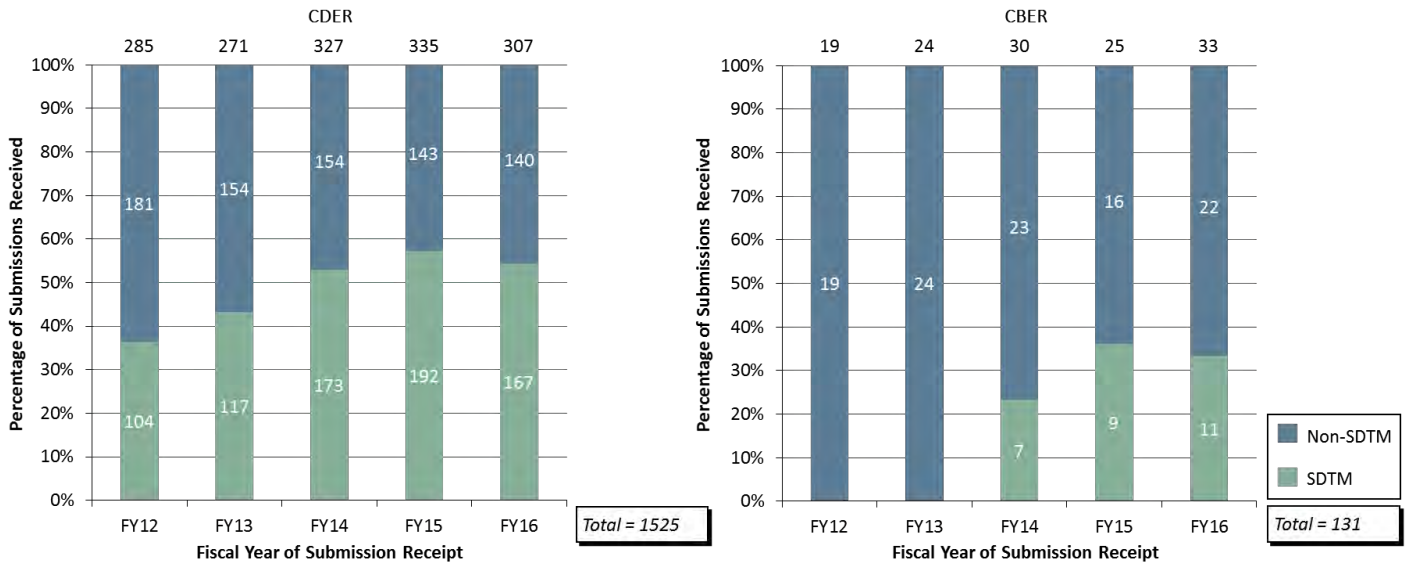
required to use the data standards listed in the FDA Data Standards Catalog or the application may receive a refuse-to-file.[8] The FDA plans to implement a process to check adherence to the rejection criteria at the time of application submission and validation, and it will notify the applicant if the submission is rejected.[9] Submissions may be rejected unless they contain the following:

- A trial summary (TS) dataset for every study
- XPT files with the correct file-tags (i.e., data-tabulations-dataset-sdtm; data-tabulations-dataset-send; analysis-dataset-adam)
- A Demographic dataset (i.e., DM) and define.XML for each study in Module 4, section 4.2 and a Demographic dataset, subject level analysis dataset (ADSL), and define.xml for each study in Module 5, section 5.3
- Only one dataset submitted for each dataset of the same type marked as new

In addition to these criteria, a TS dataset must be included for each study, even if the study started prior to December 17, 2016, and non-clinical legacy data in PDF format should be submitted along with a TS dataset.

In the data provided to Booz Allen for this assessment, CDER defined an SDTM submission as an application (i.e., original NDAs, BLAs, efficacy supplements) that contains at least one study with demographics (DM), exposure (EX), and disposition (DS) datasets, as well as a define.xml. CBER defined an SDTM submission as an application where the sponsor claimed it included SDTM data. The FDA does not currently track submissions with ADaM data, and as of FY16, the FDA has received four NDAs and BLAs and five INDs with SEND data.[10]

For both CDER and CBER, the percentage of submissions with SDTM data, as defined above, increased over time with CBER receiving proportionally fewer SDTM submissions than CDER. Between FY12 and FY16, CDER received 49% (753/1525) of its submissions with SDTM data whereas CBER only received 21% (27/131) of its submissions with SDTM data (Figure 3-10). In FY16, 54% of CDER submissions and 33% of CBER submissions contained at least one study with SDTM data.



Source: FDA data systems - Study Cohort

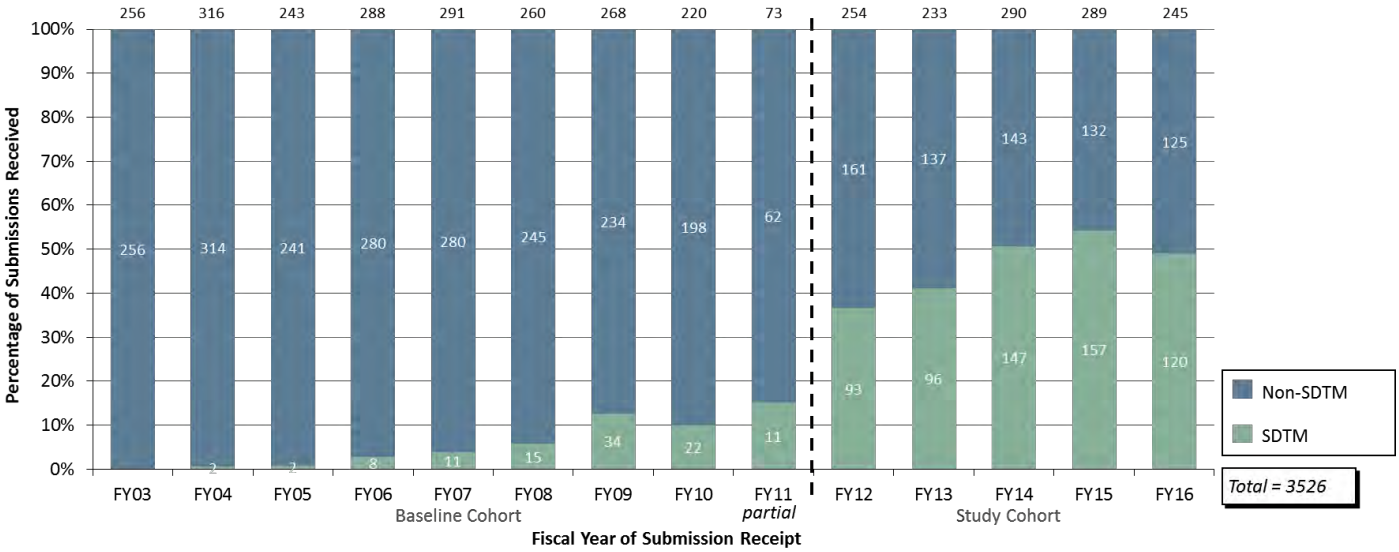
Figure 3-10: Original NDAs, BLAs, and efficacy supplements by Center, submission format and fiscal year

Between the Baseline and Study Cohorts, there was a distinct increase in the percentage of submissions with SDTM data. In FY16 49% of original NDAs and efficacy supplement submissions contained SDTM data (Figure 3-11).

[8] Providing Regulatory Submissions in Electronic Format – Standardized Study Data Guidance. Retrieved from https://www.fda.gov/downloads/drugs/guidances/ucm292334.pdf

[9] FDA Technical Rejection Criteria. Retrieved from https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf

[10] Submission data tracked by OCS



Source: FDA data systems - Study Cohort

Figure 3-11: CDER original NDAs and efficacy supplements by fiscal year and submissions with SDTM data

FDA and applicants are making steady progress towards implementing standardized data. The increases in the number of NDAs, BLAs and efficacy supplements with standardized data creates an opportunity to further streamline the electronic review environment with the creation and use of tools that utilize this type of data. With the staged implementation of the technical rejection criteria and the eCTD submission, the percentage of electronic submissions in eCTD format with SDTM data should increase significantly in the coming years.

3.2 Readiness and Completeness of Available Data Standards

During the evaluation of available data standards, Booz Allen assessed the readiness of data standards by leveraging publicly available information to determine the current and future state of the standards as well as FDA's support of the released standards. Additionally, Booz Allen evaluated the completeness of SDTM and SEND by assessing whether each standard contained domains needed to perform each of the required clinical and non-clinical analyses. The following sections include the findings from the assessment of the readiness and completeness of available data standards.

READINESS

Booz Allen assessed the readiness of five submission format and study data standards and five controlled terminology standards. Table 3-1 shows the individual scope of each of the 10 standards as they relate to specific portions of the regulatory review process and applicable disciplines. Together, the standards apply to submissions across the regulatory review process and apply to both clinical and non-clinical data. Additionally, the table displays the current and future state of the investigated standards. FDA is accepting a version of all the investigated standards and has already mandated submission of most standards for many application types. Since FDA must review new versions of standards released by SDOs, as in the case of SEND, there can be a lag between the release of a new version of a standard and integration of the updated version into FDA processes (see also Appendix E, Figure 5-9, Figure 5-10, and Figure 5-11).

Table 3-1: Current and future state of standards

STANDARD	PHASE OF REGULATORY REVIEW PROCESS	APPLICABLE DISCIPLINE(S)	CURRENT VERSION ACCEPTED BY FDA*	CURRENT VERSION RELEASED BY SDO	RELEASE DATE OF CURRENT VERSION	DATE STANDARD MANDATED BY FDA
Submission Format and Study Data Standards						
eCTD	INDs, NDAs, BLAs, Abbreviated New Drug Application (ANDAs), master files, postmarket	All	eCTD v3.2.2 Implementation Guide (IG): M2 eCTD Electronic Common Technical Document Specifications	eCTD v4.0 IG v1.1 Released for planning purposes	1/20/2016	NDAs, BLAs, and ANDAs: 5/5/2017 Commercial INDs and master files: 5/5/2018
ICSR	Postmarket	Clinical	Release 2 IG: ICH E2B(R3) v5.01**	Release 2 IG: ICH E2B(R3) v5.01	12/2011 04/12/2013	Not listed
SDTM	INDs, NDAs, BLAs, ANDAs	Clinical	SDTM v1.4 SDTMIG v3.2	SDTM v1.5 to specifically support SENDIG v3.1 SDTMIG v3.2	7/5/2016	NDAs, BLAs, ANDAs: 12/17/2016 Commercial INDs: 12/17/2017
SEND	INDs, NDAs, BLAs, ANDAs	Non-clinical	CDER: SDTM v1.2 CDER: SENDIG v3.0	SDTM v1.5 SENDIG v3.1	7/7/2016	NDAs, BLAs, ANDAs: 12/17/2016 Commercial INDs: 12/17/2017
ADaM	INDs, NDAs, BLAs, ANDAs	Clinical	ADaM v2.1 ADaMIG v1.0	ADaM v2.1 ADaMIG v1.1	12/17/2009 2/12/2016	NDAs, BLAs, ANDAs: 12/17/2016 Commercial INDs: 12/17/2017
Terminology Standards						
MedDRA	INDs, NDAs, BLAs, ANDAs, postmarket	Clinical	8 or later	19.1	9/2016	NDAs, BLAs, ANDAs: 12/17/2016 Commercial INDs: 12/17/2017
WHO DD	INDs, NDAs, BLAs, ANDAs, postmarket	Clinical	CDER: Latest Version	December 1, 2016 release	12/1/2016	NDAs, BLAs, ANDAs: 3/15/2018 Commercial INDs: 3/15/2019
NDF-RT	INDs, NDAs, BLAs, ANDAs	Clinical and Non-clinical	CDER: Latest Version	12/2016 release	12/2016	NDAs, BLAs, ANDAs: 12/17/2016 Commercial INDs: 12/17/2017
SNOMED CT	INDs, NDAs, BLAs, ANDAs	Clinical	None listed	September 2016 US Edition	9/2016	NDAs, BLAs, ANDAs: 12/17/2016 Commercial INDs: 12/17/2017
LOINC	INDs, NDAs, BLAs, ANDAs	Clinical	Latest Version	2.58	12/21/2016	NDAs, BLAs, ANDAs: 3/15/2018 Commercial INDs: 3/15/2019

Notes: Information current as of February 10, 2017;
**CDER and CBER unless otherwise noted;*
*** Although not explicitly stated in the FDA Data Standards Catalog v4.5.1 as (R3), accompanying FDA guidance refers to (R3) v5.01*
Source: FDA Data Standards Catalog v4.5.1, CDISC website, see additional standard specific references in Appendix E, Table 5-4

To provide updated standards guidance to industry, the FDA developed a number of documents to communicate the proper methods for the formatting and submission of standardized data, listed in Table 3-2. In many cases, a single document covers multiple standards, which minimizes the number of documents that require updates or tracking by industry. For example, the Data Standards Catalog provides a quick reference to the current version of standards supported by the FDA.

Table 3-2: Communication documents for data standards

DOCUMENT	APPLICABLE STANDARDS
eCTD Technical Conformance Guide	eCTD
Guidance to Industry Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications	eCTD
Study Data Technical Conformance Guide	All
Providing Regulatory Submissions in Electronic Format – Standardized Study Data	All
Technical Rejection Criteria for Study Data	eCTD, SDTM, SEND, ADaM
FDA Specific SDTM Validation Rules	SDTM
FDA Specific SEND Validation Rules	SEND
FDA Data Standards Catalog	All
Study Data Standards: What You Need To Know	SDTM, SEND, ADaM
Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments	ICSR
Steps to Submitting ICSRs Electronically in the XML Format	ICSR
CDER Data Standards Action Plan v2.2	All

Source: FDA website

As standards are continually evolving, FDA must continuously review newly released standards before providing support. As outlined in Figure 3-12, interviews with FDA staff revealed that FDA provides proactive SME input on changes to standards during the SDO development process. For example, FDA holds monthly meetings with Clinical Data Interchange Standards Consortium (CDISC), the SDO in charge of SDTM, SEND, ADaM, and the therapeutic area standards, to discuss improvements to future versions of the standards and any other prioritized changes. This collaboration with the SDOs reduces the review time needed for eventual FDA support of new standards. Specifically for the therapeutic area standards, the FDA conducts additional meetings with CDISC during initial development phases, separate from the monthly meetings held with CDISC, to provide input early in the process to ensure accurate and comprehensive changes to the standard.

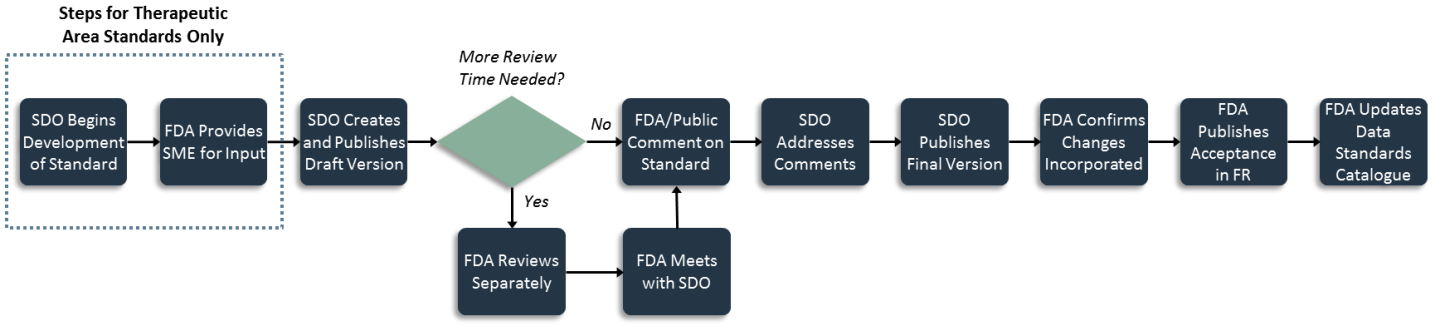
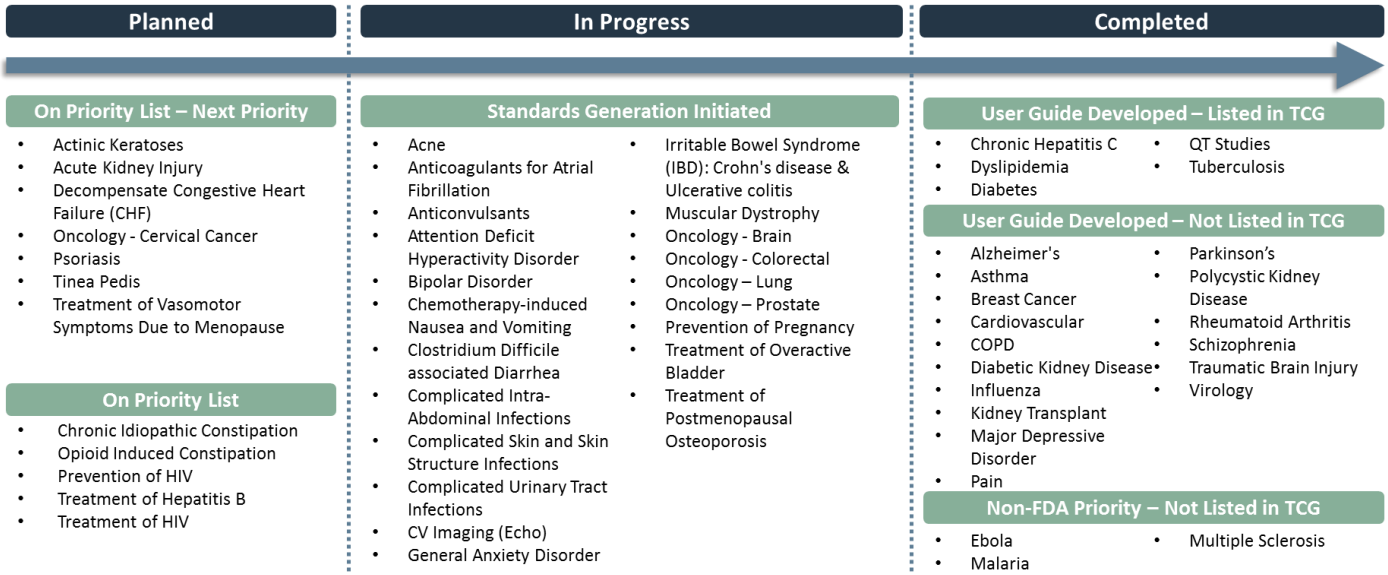


Figure 3-12: Data standards development and review process

This collaborative process prepares the FDA for the changes that will be implemented in future versions of standards. However, without a mock dataset submission from the SDOs that incorporates the updates to be included in the new version of the standard, FDA is not able to fully determine the impact, through testing, that the proposed changes have on their ability to analyze future data with current analysis tools.

To provide specialized guidance under the SDTM standard, CDISC is also generating therapeutic area user guides to outline considerations specific to certain disease areas. As outlined in Figure 3-13, CDISC has released 25 user guides and is in the process of

generating an additional 21 guides (see also Appendix F, Table 5-5 and Table 5-6). The therapeutic area standards for user guide generation were prioritized based on a number of factors, including previous project initiation and FDA review division feedback.[11]



Note: Current as of February 10, 2017
Source: CDISC website, FDA Therapeutic Area (Disease/Domain) Data Standards Prioritization April 19, 2016

Figure 3-13: Therapeutic area user guide development progress

Beyond the previously mentioned SDO interactions, FDA also holds internal meetings and collaborates with other organizations as part of a number of initiatives to continually develop new standards and enrich currently implemented standards. Internally, FDA created an FDA Data Standards Advisory Board (DSAB) and the CDER Data Standards Program Board (DSPB), which monitor standards implementation across FDA. Externally through Pharmaceutical Users Software Exchange (PhUSE), FDA collaborates with industry on several initiatives. Along with CDISC, FDA is also a member of the Coalition for Accelerating Standards and Therapies (CFAST) initiative involved in developing the therapeutic area standards.

COMPLETENESS

Booz Allen followed a structured approach to determine the completeness of SDTM and SEND. Appendices C and D contain the full clinical and non-clinical analyses whereas a summary of each analysis is provided below.

SDTM

Booz Allen mapped the 44 domains from SDTMIGv3.2 to the clinical review sections of the current template. Overall, we found that four key domains (i.e., DM, DS, exposure as collected (EC), EX) are required to conduct a majority of the analyses in the clinical review. Current SDTM domains (e.g., Adverse Events (AE), Laboratory Test Results (LB), Electrocardiogram Test Results (EG)) appear to provide coverage for the standard safety analyses. However, the assessment of the efficacy portion of the clinical review was somewhat limited since many of the analyses are dependent on specific clinical outcomes. Of the six review sections that contained analyses that varied by therapeutic area or pharmacological class, five are included in the efficacy sections of the clinical review template. Since the current SDTM structure does not enable clinical reviewers to conduct consistent efficacy analyses, they will often use a domain in the ADaM dataset. Therapeutic area standards will continue to play a critical role in the evolution of the SDTM standard's applicability and usefulness by providing specialized domains and variables to facilitate specific analyses for a given indication or therapeutic area (e.g., oncology).

SEND

Booz Allen mapped the 27 domains contained in SENDIGv3.0 to the non-clinical review sections of the review template. For a majority of the analyses, reviewers use eight domains within the standard (i.e., DM, DS, EX, pool definition (POOLDEF), trial arm (TA),

[11] Therapeutic Area Data Standards Roadmap (version 11, April 19, 2016). Retrieved from https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM297084.pdf

trial elements (TE), TS, trial sets (TX)). At this time, CDISC has only modeled general toxicity (i.e., single dose and repeat dose) and carcinogenicity studies in the SEND standard. We found nine analyses from the non-clinical review template that are not yet modeled in SEND. We also determined that five analyses from the non-clinical review template that may vary by therapeutic area or pharmacological class.

The SEND standard is evolving with input from sponsors, FDA, and SDOs. New versions of the SEND implementation guides continue to add domains to the standard, with the new SENDIGv3.1, which is not yet supported by the FDA, adding the cardiovascular (CV) and respiratory (RE) domains. Additionally, 13 sponsors and FDA non-clinical reviewers across multiple divisions participated in a recent FDA Fit-for-Use Pilot to identify current challenges of SEND implementation.[12] After reviewers had experience reviewing pilot applications with SEND data, they identified a list of domains in need of improvement. These included clinical observations (CL), macroscopic findings (MA), microscopic findings (MI), pharmacokinetics concentrations (PC), and tumor findings (TF).[13] On these and other potential issues, FDA continues to collaborate with sponsors through a PhUSE working group to modify SEND to meet the non-clinical reviewers' needs.

3.3 Effectiveness of Electronic Review Tools and Training

During the evaluation of FDA review tools and the availability and effectiveness of training, Booz Allen assessed the usefulness of current tools used during the regulatory review process to view, search, and analyze data. Additionally, the training associated with electronic submissions, data standards, and review tools was evaluated to determine the adequacy of course offerings across the subject areas and assess the usefulness and applicability of the information presented to review staff.

The following sections include the findings from the assessment of the tools and training program associated with electronic submissions and data standards.

TOOLS ASSESSMENT

The assessment of CDER and CBER managed tools associated with electronic submissions and data standards started with the creation of a tool inventory.[14] Table 3-3 includes a list of tools included in this evaluation.[15]

Table 3-3: Review tools at CDER and CBER

TOOL	DESCRIPTION	EXAMPLE FUNCTIONALITY AND OUTPUTS	STANDARD ANALYSIS OUTPUTS PROVIDED WITH STANDARDIZED DATA*
JMP	Statistical software program that allows the reviewers to easily open data files (e.g., .xpt, .sas7bdat, .xls), view data, perform analyses, and generate graphs	• Variety of analyses through a user interface (e.g., using certain functions with the tool, the reviewer may quickly obtain a high-level view of the application data and then select more detailed analyses) • Ability to visually inspect data in each submitted dataset	No

[12] Elaine Thompson. CDISC-PhUSE Fit for Use Pilot. Retrieved from https://wiki.cdisc.org/display/NSFFUW/Nonclinical+%28SEND%29+Fit+for+Use+Workstream+Home

[13] Elaine Thompson. SEND Challenges. Retrieved from https://wiki.cdisc.org/display/NSFFUW/Nonclinical+%28SEND%29+Fit+for+Use+Workstream+Home

[14] Booz Allen defined "FDA managed tools" as tools for which FDA manages enhancements made to the tools and versions used by reviewers

[15] This list contains a mix of COTS tools with customized solutions to specifically meet the needs of review staff and in-house products. SAS is included in this list as the SAS Analysis Panels are managed by FDA. Portes stores the latest version of the standardized data for a submission and could be used by a reviewer to access this data.

TOOL	DESCRIPTION	EXAMPLE FUNCTIONALITY AND OUTPUTS	STANDARD ANALYSIS OUTPUTS PROVIDED WITH STANDARDIZED DATA*
JMP Clinical	Desktop application that offers data discovery, analysis and reporting for pre-clinical, clinical and post-market data	Reports include those from the following functional categories: • Cross domain • Demographics and visits • Events • Findings • Interventions • Patient recruitment	Yes
JReview	Web-based review tool that allows users to tabulate, visualize, and analyze safety and efficacy data	• Data visualizations of adverse events, disposition, concomitant medications, exposure and lab results; Hy's Law visualization; risk benefit graphics and relative risk plots • Graphical patient profiles with a time-oriented display with duration bars and trend plots with normal range for labs • JReview Standard Analysis Catalog provides a series of over 40 automatic standard analyses in interactive tables, listings, and graphical figures for studies with SDTM data	Yes
MedDRA-Based Adverse Events Diagnostics (MAED)	Performs a series of exploratory adverse event analyses on data from clinical trials and non-denominator databases (such as AERS-type data)	• Signal Detection using SMQ (standardized MedDRA query) counts at broad or narrow levels • Adverse event (AE) counts at subject level or event level by treatment groups, such as preferred term/high level term/high group level term/SOC (system organ class) • AE counts with primary MedDRA coding or primary & secondary coding • Risk difference (RD), relative risk (RR), and odds-ratio (OR)	Yes
Statistical Analysis Software (SAS), including SAS Analysis Panels	SAS - software suite developed by the SAS Institute for advanced analytics SAS Analysis Panels – scripts developed to perform standard analyses for clinical reviewers and generate Excel outputs for use within the review	SAS Analysis Panels • MedDRA at a Glance • AE Toxicity Analysis Panel • AE Severity Analysis Panel • Disposition Analysis Panel	Yes (for SAS Analysis Panels)
Janus Non-clinical	Enables visualization and analytics for the toxicology studies (e.g., general toxicology and carcinogenicity studies)	Current outputs and visualizations include: • Summary • Tabular View • Graph or Visualization • SEND Table Display	Yes

TOOL	DESCRIPTION	EXAMPLE FUNCTIONALITY AND OUTPUTS	STANDARD ANALYSIS OUTPUTS PROVIDED WITH STANDARDIZED DATA*
CISST	Assists OND review staff and clinical site inspection coordinators in the Office of Scientific Investigations in the decision-making process for site selection	Risk-ranked list of clinical sites for inspection	Yes[16]
Janus CTR	Supports the automated extraction, transformation, loading, management, and integration of clinical trials data and facilitates the timely creation of custom "data marts" to support a variety of regulatory review and meta-analysis needs	Provides access to tools and standard analyses usually performed during the regulatory review of a human drug	Yes

*Standard analyses includes analyses commonly completed by reviewers for application reviews (e.g., demographics, adverse events)

In addition to these tools, CDER provides two services for clinical and non-clinical staff to assist in the review of study data contained in IND, NDA, and BLA submissions: JumpStart and KickStart. As reviewers continue to receive more submissions with standardized study data, these services provide them with an opportunity to understand the data fitness for their submission early in the review, receive a set of standard analysis outputs, and familiarize the reviewers with the functionality of the review tools used to generate the outputs.[17] Table 3-4 provides a summary of the services.

Table 3-4: JumpStart and KickStart services

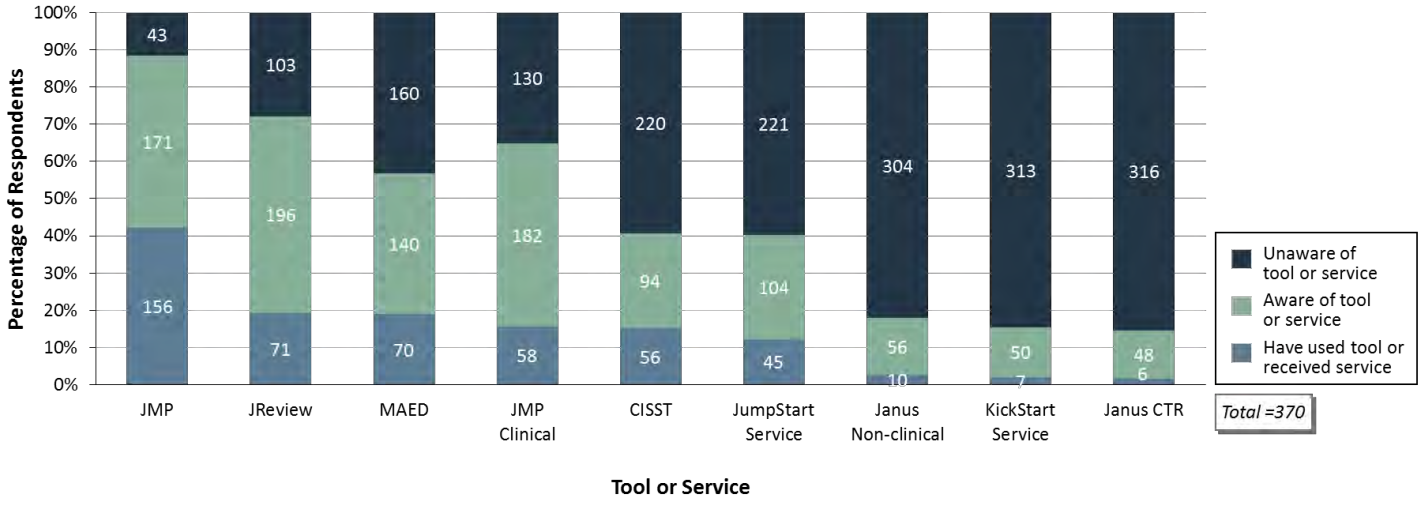
	JUMPSTART SERVICE	KICKSTART SERVICE
Purpose	Assess the data fitness and provide core data analyses of clinical study data early in the drug review process and provide review teams with outputs and tools for their review	Assess the data fitness of non-clinical study data and provide review teams with visualizations for their review
Features	• Assess SDTM study data fitness using DataFit to identify data quality issues and clinical relevance • Perform universal or common analyses and provide review team with outputs and visualizations • Set up review tools • Orient the review team to outputs and tools • Support review team communications about the clinical data to the sponsor	• Assess SEND study data fitness using DataFit and other tools to assess data quality • Provide review team with visualizations for the study reports • Assist with data exploration in Janus Non-clinical • Provide support and training for review tools and use of SEND data • Support review team communications about the SEND data to the sponsor
Year service started	2014	2016 (pilot started in 2014)

[16] Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning. Retrieved from https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/ucm332466.pdf

[17] Data fitness refers to the degree to which a submission contains relevant data to perform analyses

	JUMPSTART SERVICE	KICKSTART SERVICE
Use to date	94 submissions that have received the service	13 Fit for Use pilot and 9 submissions
Data Standard Requirements	SDTM data for up to four studies included with a submission	SEND data included with a submission

As the rollout and adoption of new tools and services continues with the projected increase of submissions with standardized data, Booz Allen sought to understand the general awareness and use of the current tools and services at the FDA. During the survey conducted for the assessment, we asked respondents whether they were aware of a tool or service and if they have used a tool or service. If respondents did not indicate that they were aware or used a tool or service, we categorized them as unaware. The survey focused on tools and services managed by FDA to collect data and develop findings where the Agency could make changes to improve functionality or offerings.[18] Overall, awareness of clinical review tools (e.g., JMP, JReview, MAED) was relatively high, most likely due to formal training communications (Figure 3-14).



Source: PDUFA Electronic Review Assessment Survey

Figure 3-14: Awareness and use of FDA managed tools and services

In addition to awareness and use of tools and services, Booz Allen surveyed respondents to determine the best way to communicate new offerings. The survey indicated that 74% of respondents believe that email is the best way to notify reviewers of new tools and services. As adoption and use for FDA managed review tools and services expands, the organization will need to continue to evolve the tools based on available technologies and the outputs on the ever-changing data standards to meet more reviewers' needs.

To determine the usefulness of current tool outputs to reviewers, Booz Allen assessed the outputs of certain tools. The tool output assessment expanded the data standards completeness assessment, outlined in Section 3.2, by aligning fully-supported and JumpStart outputs to the data standard domains used to create the output and the standard analyses in the clinical and non-clinical reviews. We defined fully supported tools with the following criteria to ensure the analysis focused on mature and fully implemented tools:

- Access available to all reviewers
- Formal training available for all reviewers
- Automatically generates standard outputs or visualizations
- User guide, manual or training presentation available for all reviewers

[18] Although SAS is consistently used by biostatistics reviewers to both analyze data and communicate with sponsors, since FDA does not offer in-house training nor does it make changes to the software (except for SAS Analysis Panels, which are scripts used during JumpStart), SAS was not included in the survey.

After applying this definition to the list of currently managed FDA tools, Booz Allen used JReview and MAED for clinical reviews and Janus Non-clinical for non-clinical reviews to conduct the analysis. Additional JumpStart outputs from the Statistical Analysis System (SAS) Analysis Panels were included to provide an understanding of other standard outputs that reviewers could potentially use to support standard review analyses. The assessment focused on those review sections and analyses where we had already identified clinical data standard domains that could support the given analysis. Appendix C and D include the comprehensive list of the analyses, domains, and available outputs.

For the clinical review, the more general efficacy analyses (e.g., disposition, demographics) largely have outputs available for staff to use in their reviews. As expected, analyses of efficacy outcome measures have fewer outputs since the analyses are specific for a given indication or therapeutic area (e.g., oncology). For the analyses included within the safety sections, reviewers have a large number of outputs available for use in their review. Non-clinical reviewers have automatically generated visualizations for all general toxicity and carcinogenicity analyses, which are also the areas fully modeled in the SEND standard.

Throughout this assessment, Booz Allen collected feedback from reviewers and SMEs, including JumpStart analysts, on the perceived benefits and challenges of the tools managed by the FDA. The intention was to collect specific pain points experienced by staff that use these tools on a regular basis to identify opportunities for improvement. For example, reviewers noted that JMP does not provide any standard analyses for reviews and the outputs need to be created manually. FDA is currently in the process of rolling out JMP Clinical, which addresses this concern and should help to drive adoption for this tool. Table 3-5 summarizes the feedback received during the survey, interviews, and focus groups on the benefits and challenges of the tools.

Table 3-5: Reviewer and SME feedback on benefits and challenges of current tools

TOOLS	BENEFITS	CHALLENGES
JMP	• Can ingest and analyze non-standardized and standardized data • Easy to share analyses with others if they have an account	• No standard analyses provided to reviewers – outputs need to be created manually • "JMP would be amazing if could do the same as JReview in terms of using multiple datasets at the same time" – Clinical Reviewer
JMP Clinical	• Unlike other tools, reviewers can just double-click to run an analyses • Can combine datasets across the application to gives a more integrated view of the submission data • Reviewers like the graphic patient profiles to view data across all domains on a timeline	• Ingests standardized data, which in the future, with more adherence to and adoption of the standard, will allow developers to create more standardized and automated analyses • Currently there is no server to house the tool so users are required to load data into the tool which can discourage use • Easier to use consistently, if used intermittently users often need to relearn the tool
JReview	• Can ingest and analyze non-standardized and standardized data • Can share analyses with other users that have accounts • Reviewers like the graphic patient profiles to view data across all domains on a timeline • Standard analysis catalogue for clinical review continues to expand	• Easier to use consistently, if used intermittently users often need to relearn the tool • Methods for generating outputs are not easily viewed by reviewers and occur on the backend • Requires more resources – need to "point" to specific data depending on analyses • "JReview is not intuitive, and although the class teaches how to follow directions, it does not provide a deeper understanding of how JReview works... in particular nuances of why certain steps are taken, and how it would differ if slight changes in the steps were made"- OCS Training attendance evaluation data FY13-16 JReview Mod 2
MAED	• Can use standardized and non-standardized data • Provides the ability to perform custom queries • "One of the more popular tools, reviewers are comfortable using it, have received little negative feedback" – JumpStart Team	• Limited to adverse event data analysis • Reviewers need to understand their data to effectively use the tool and outputs

Janus Non-clinical	• Provides visual representation of the non-clinical study reports that can be used to view the data and pasted into the review	• Not currently available to all non-clinical reviewers – only those that receive the KickStart Service • "Role out Janus Non-clinical :-)" – Non-clinical Primary Reviewer
SAS Analysis Panels	• MedDRA at a Glance output provides a look at the MedDRA hierarchy in a way that no other tool can currently	• Outputs from tools are only available to reviewers who have applications that receive the JumpStart Service

We asked primary reviewers if they used the outputs generated from the listed FDA tools in their review and whether or not they modified the output. Out of those reviewers surveyed, 11% (12/114) indicated that they would use the outputs without any modification while 75% (85/114) noted that they modify the output before using it in their review. For the 15% (17/114) of reviewers that said that they do not use the output in their review, some provided comments that there was useful information in the outputs, but they prefer to create the charts and tables using SAS or Microsoft Office applications.

The usefulness of the tools is also dependent on the effectiveness of the tool training, which we assessed in the section below.

TRAINING EFFECTIVENESS

Both OCS and OBI offer courses pertaining to specific review tools and data standards. Table 3-6 and Table 3-7 display the courses associated with the previously investigated review tools and standards offered by OCS and OBI, respectively.

Table 3-6: OCS training course offerings

REVIEW TOOL OR STANDARD	COURSE TITLE	FORMAT	FREQUENCY (OFFERINGS PER YEAR)*
Review Tools Training			
JReview	• Module 1: Introduction to JReview • Module 2: Using Graphical Patient Profiles with JReview • Module 3: Creating Tables with JReview • Module 4: Creating Graphs with JReview • Module 5: Using the JReview Standard Analysis Catalog	Exercise-Based Class	4-5
	• JReview Clinic: How to Create Laboratory Shift Tables	Clinic	3
MAED	• Introduction to MAED • MAED for Advanced Users	Exercise-Based Class	8-9
	• MAED Clinic • MAED Bring Your Own NDA (BYONDA) Sessions	Clinic	16
CISST	• CDER's Clinical Investigator Site Selection Tool Training	Exercise-Based Class	3
Data Standards Training			
Clinical Data Standards	• Module 1: Introduction to Standard Data and Your Review • Module 2: Working with Standard Clinical Data in a Clinical Review • Module 3: Working with Standard Analysis Data in a Clinical Review	Lecture-Based Class	2
Non-Clinical Data Standards	• Module 1: SEND Basic • Module 2: SEND Basic	Lecture-Based Class	1

*Note: *Based on FY15 for Non-Clinical Data Standards and FY16 data provided by OCS for all others*
Source: OCS Training Data

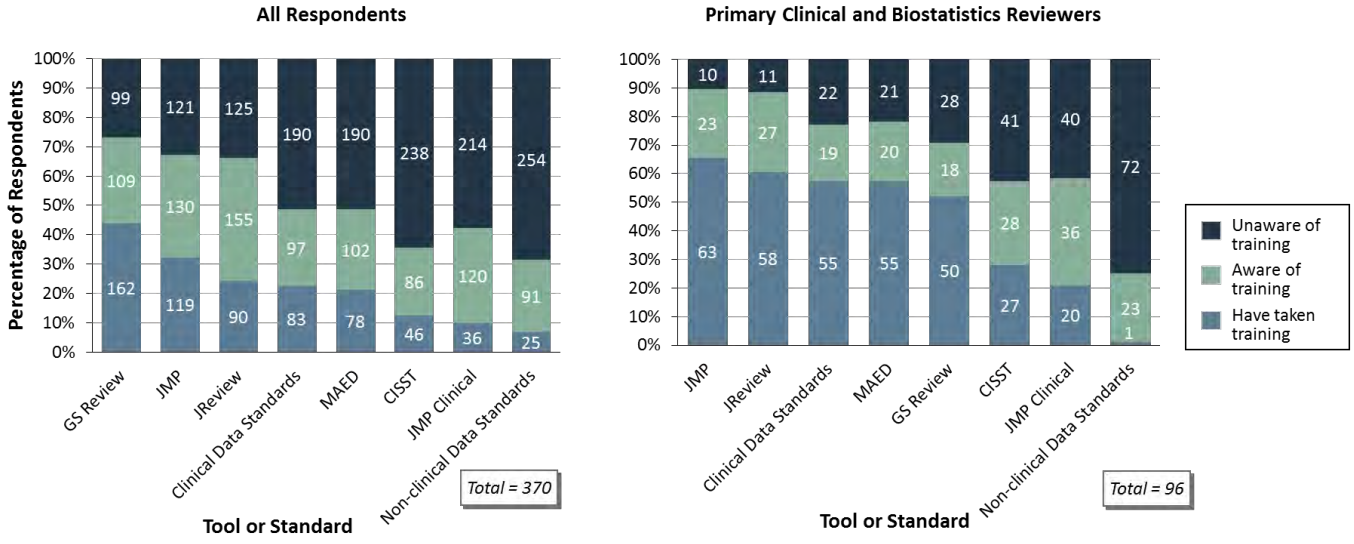
Table 3-7: OBI training course offerings

REVIEW TOOL OR STANDARD	COURSE TITLE	FORMAT	FREQUENCY (OFFERINGS PER YEAR)*
Ongoing Trainings			
JMP	• JMP Trainings 1 – 9	Exercised-Based Class	2-3
eCTD / GS Review	• GS Review Hands-on Training	Exercise-Based Class	10
	• eCTD Viewer - GS Review Walk-in Clinics	Clinic	17
	• On-on-One Training	One-on-One	As requested
Pilot Trainings			
JMP Clinical	• JMP Clinical Module 1 • JMP Clinical Module 2 • JMP Clinical Module 3	Exercise-Based Class	6

*Note: *Based on FY16 data*
Source: OBI Training Data

OCS and OBI offer training in formats ranging from walk-in clinics to exercise based lectures. As of FY16, OBI began piloting a new course for JMP Clinical as they plan to expand access to this tool among interested reviewers. As FDA offers courses several times a year, it is not surprising that 78% of the respondents to the Booz Allen survey answered that courses are available when they need to take them. Of those respondents that answered courses are not available when they need to take them, many noted that training might not always be at the same time they need to use a tool, limiting the courses' usefulness. Additionally, respondents most often cited courses for JMP and JMP Clinical as needed more frequently. This feedback will likely be less of a concern for staff once FDA transitions their JMP Clinical pilot training to an on-going training offering.

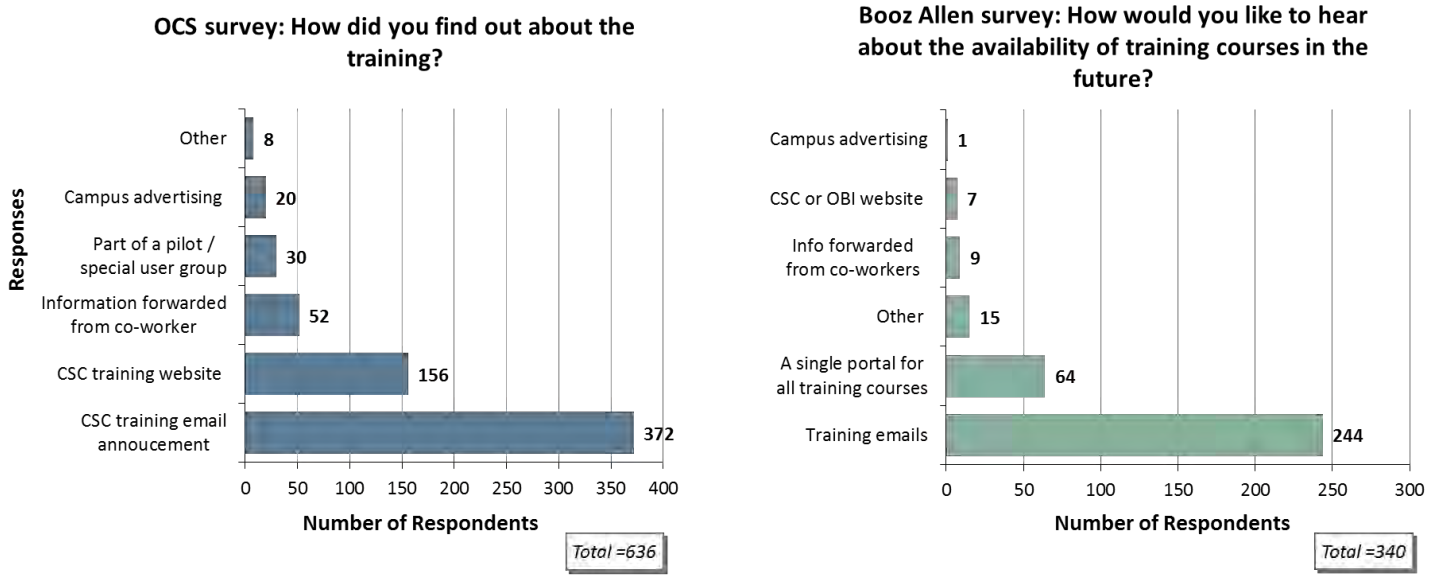
To determine effectiveness of the training courses, Booz Allen investigated the percentage of survey respondents that had taken courses for each of the different trainings, as well as the percentage of respondents that were aware of the different training options available. As shown in Figure 3-15, we found that although less than 50% of all respondents had taken each of the different trainings, greater than 50% of the primary clinical and biostatistics reviewers had taken JMP, JReview, Clinical Data Standards, MAED, and GS Review training. Whereas more respondents were aware of training courses than had taken them, most primary and clinical reviewers had actually taken the offered courses.



Source: PDUFA Electronic Review Assessment Survey

Figure 3-15: Training attendance and awareness of tool and standards training

To assess effectiveness of FDA training communications, Booz Allen leveraged data provided by OCS training survey respondents. As illustrated in Figure 3-16, participants of OCS training courses usually found out about the training that they attended from email announcements. We surveyed respondents to determine if the way staff actually find out about training is also the way they prefer to find out about training. We found that the majority of respondents also want to hear about training opportunities by email announcements.

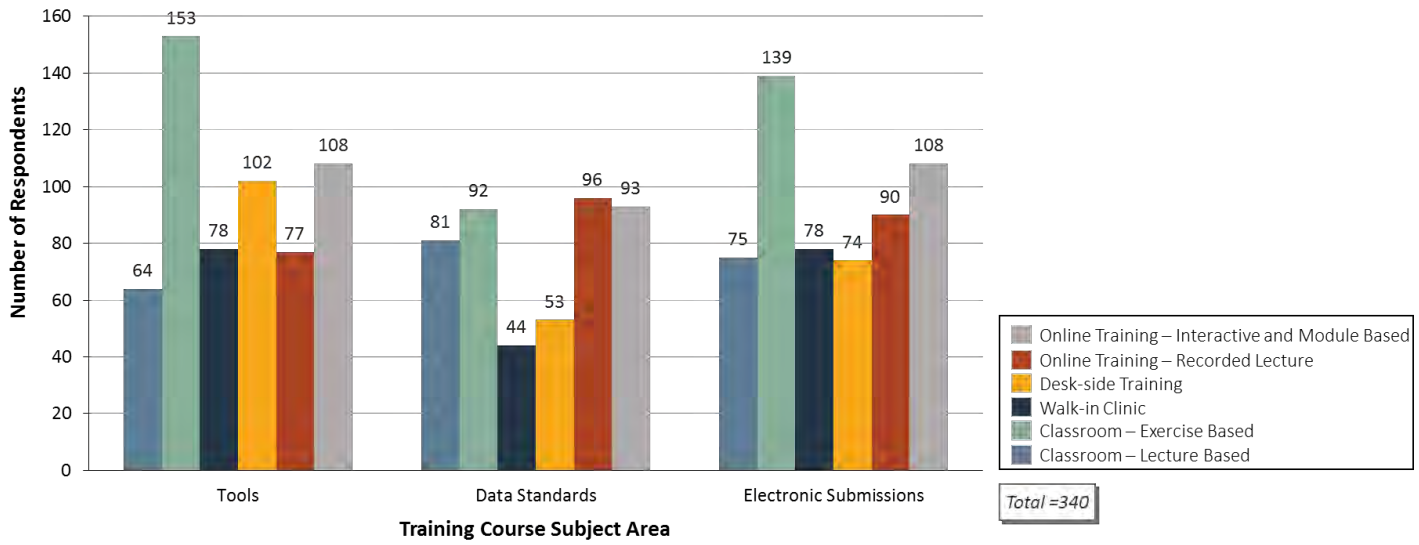


*Notes: *Participant numbers do not reflect unique participants*
Sources: FY14-FY16 OCS Training Survey Data, PDUFA Electronic Review Assessment Survey

Figure 3-16: Training communication methods - actual and preferred

Booz Allen surveyed respondents to determine which training format they find to be most effective for review tool and data standards training. As seen in Figure 3-17, survey respondents prefer exercise based and interactive trainings for tools and electronic submissions. OCS and OBI offer their tools and electronic submissions courses in the preferred training format (i.e., classroom - exercise based). This finding is also consistent with the previous independent assessment that showed strong satisfaction with the course format of attended training courses.[19] While no clear preference emerged for data standards training, most of the respondents did not believe desk-side training or walk-in clinics would be the most effective format for teaching this topic. Currently, OCS provides the data standards courses as lecture-based classes.

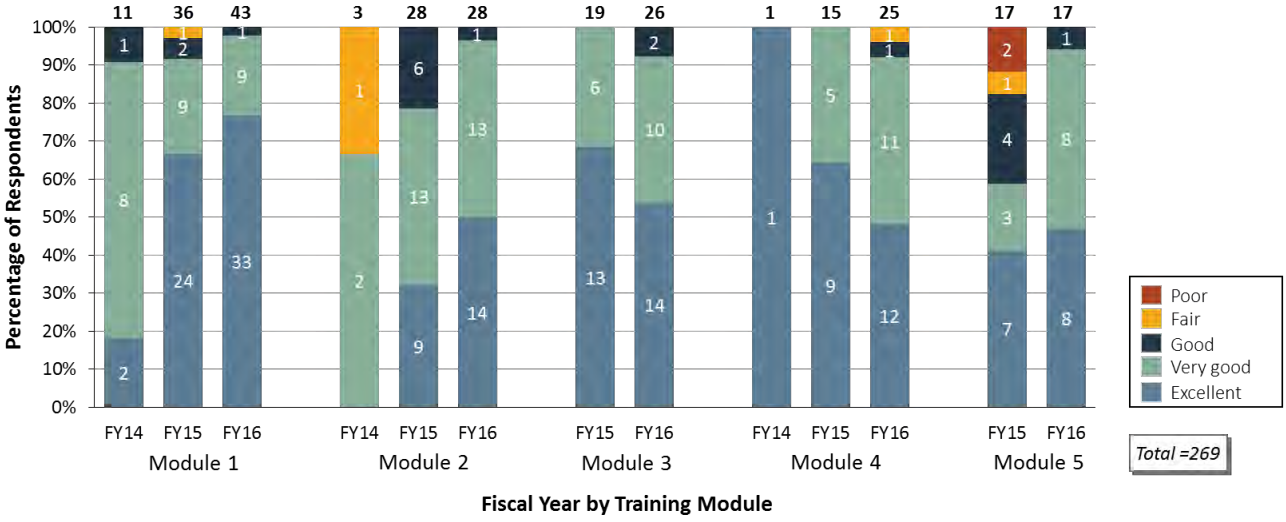
[19]Assessment of the Impact of the Electronic Submission and Review Environment on the Efficiency and Effectiveness of the Review of Human Drugs – Final Report (September 9, 2011). Retrieved from https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm272444.pdf



Source: PDUFA Electronic Review Assessment Survey

Figure 3-17: Reviewer perception of most effective training formats

Our evaluation of training effectiveness based on Kirkpatrick Levels 1 and 2 relied on information provided by FDA from course evaluations. Although OCS and OBI utilize surveys with different questions, both sets of surveys measure participant reactions to and satisfaction with recently completed training. We investigated the OCS JReview evaluation data from the question: How would you rate the course? As illustrated in Figure 3-18 for JReview training, course attendees that filled out course evaluations had mostly positive reviews, with modules 1, 2, and 5 ratings improving over time. Similar to the data for JReview, for the additional OCS and OBI courses, we found the FDA data to be very positive regarding overall course ratings, instructor satisfaction, and perceived ability of participants to apply the knowledge they learned from the courses. However, during focus group sessions, clinical reviewers voiced concerns about selecting the proper tool and output during the completion of their review since courses do not currently link outputs with sections of the review. For example, based on a focus group comment, it appears that while instructors are familiar with the functionality of the tool, some may not be familiar with the contents and requirements of a submission review.



Notes: Total number does not reflect unique participants
Source: OCS Training Attendance and Evaluation Data

Figure 3-18: JReview training ratings

Part of our evaluation of FDA training based on Kirkpatrick Model Level 3 included survey questions addressing changes in respondents' behavior after receiving review tool training. As shown in Figure 3-19, 72% of respondents answered that they did begin using the review tool after they had received training for the tool. This finding shows that, through the training courses, participants received knowledge that changed their behavior in their work environment. Of the 28% that answered No, many noted that timing is a main factor for why they would not be able to use tools after receiving training. For example, if there is a long time

between when a reviewer takes the course and the next time they are assigned an application for which they can use the tool, they may forgot the specifics of the training.

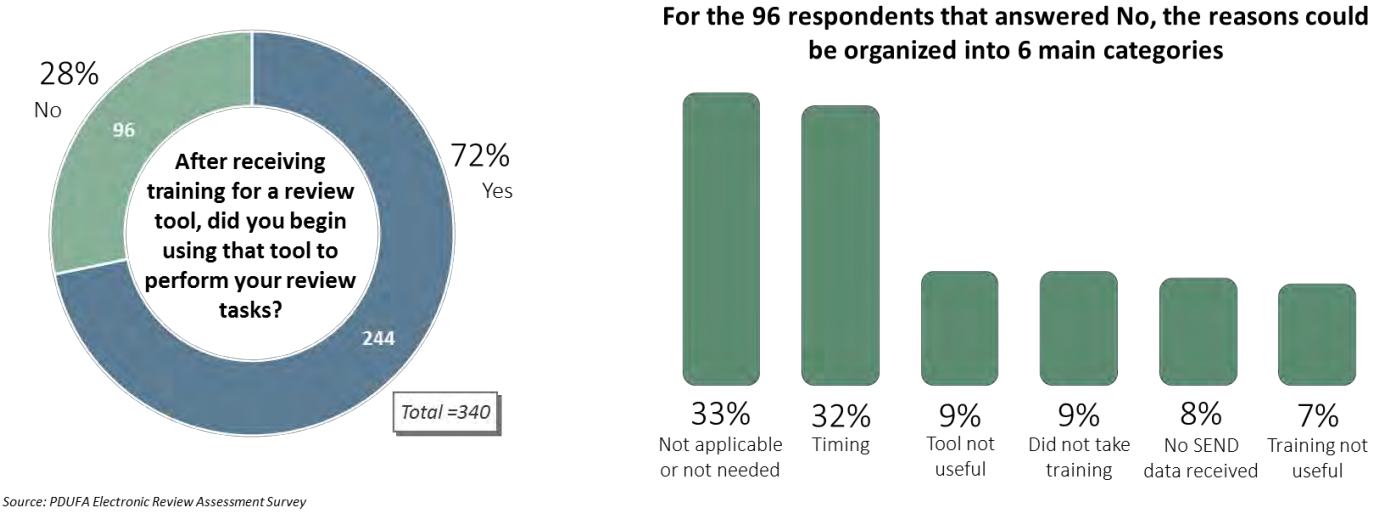


Figure 3-19: Survey respondents' tool use after training course completion

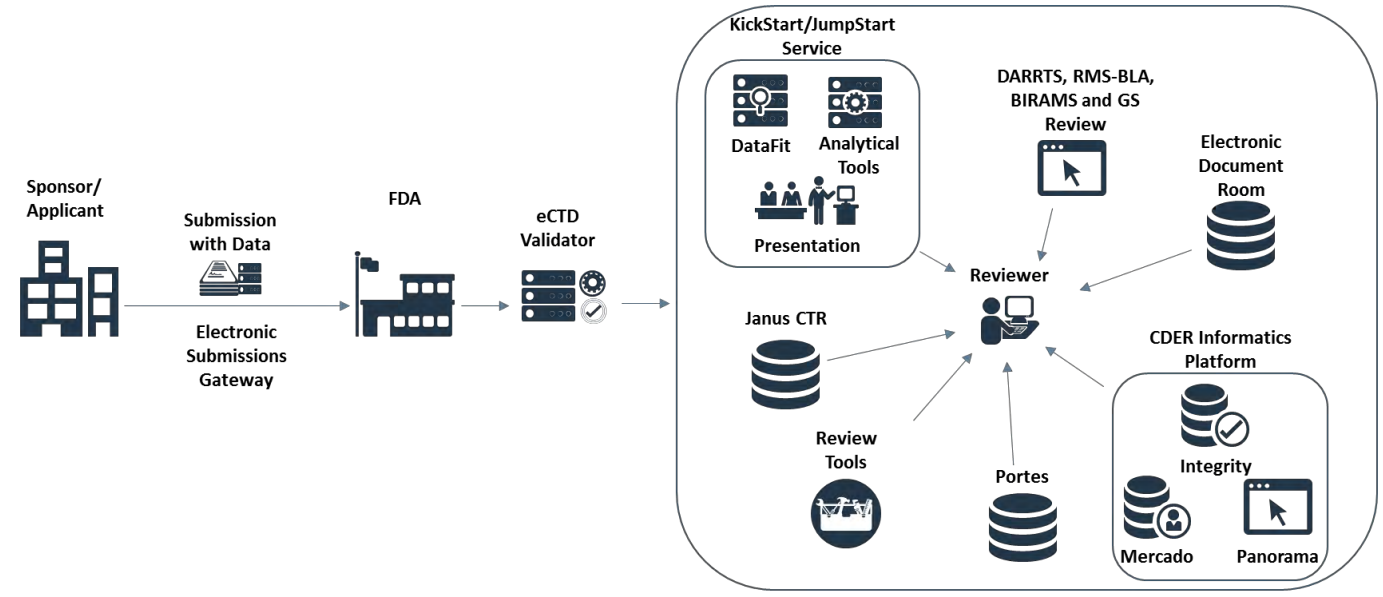
Beyond applying the knowledge they learned in their courses, 61% of the survey respondents also shared information they learned in their training courses with their colleagues. Respondents mentioned sharing information from a number of different courses and sharing information both verbally and by providing colleagues with slides and handouts they received from the trainings.

Based on FDA collected data and information collected from the Booz Allen survey and focus groups, it appears that reviewers believe the overall communication around, format of, and content of the distinct data standards and analysis tools training courses are largely effective. While reviewers generally had positive feedback, the concerns raised during the survey and focus groups related to course timing and applicability of tools or outputs during the review indicate potential opportunities for improvement that may increase training effectiveness. Additionally, there still appears to be a large percentage of surveyed staff that have not taken many of the available training courses. When asked whether staff had reviewed submissions with either SDTM or ADaM data, approximately 20% of respondents answered that they were unsure, suggesting many staff members would benefit from attending data standards training.

Along with standards implementation and effective analysis tools, reviewer training is a critical component that affects the successful implementation of an effective review environment across the application lifecycle.

3.4 Impact of Standards and Electronic Submissions on the Review Environment

The lifecycle of electronic submission data originates with sponsors and applicants compiling, organizing and transmitting the data to the FDA. After being sent through the Gateway, the submission, if properly formatted, passes through the eCTD Validator and enters FDA data systems. Once the data enters these systems, reviewers can access and analyze the information through various tools to view and analyze data required for their review. Additionally, reviewers of submissions selected for the JumpStart or KickStart service have access to additional tool results. Booz Allen constructed this submission data lifecycle view to understand the various touch points where FDA reviewers can interact with the data required to complete their work. Figure 3-20 provides an overview of this lifecycle.

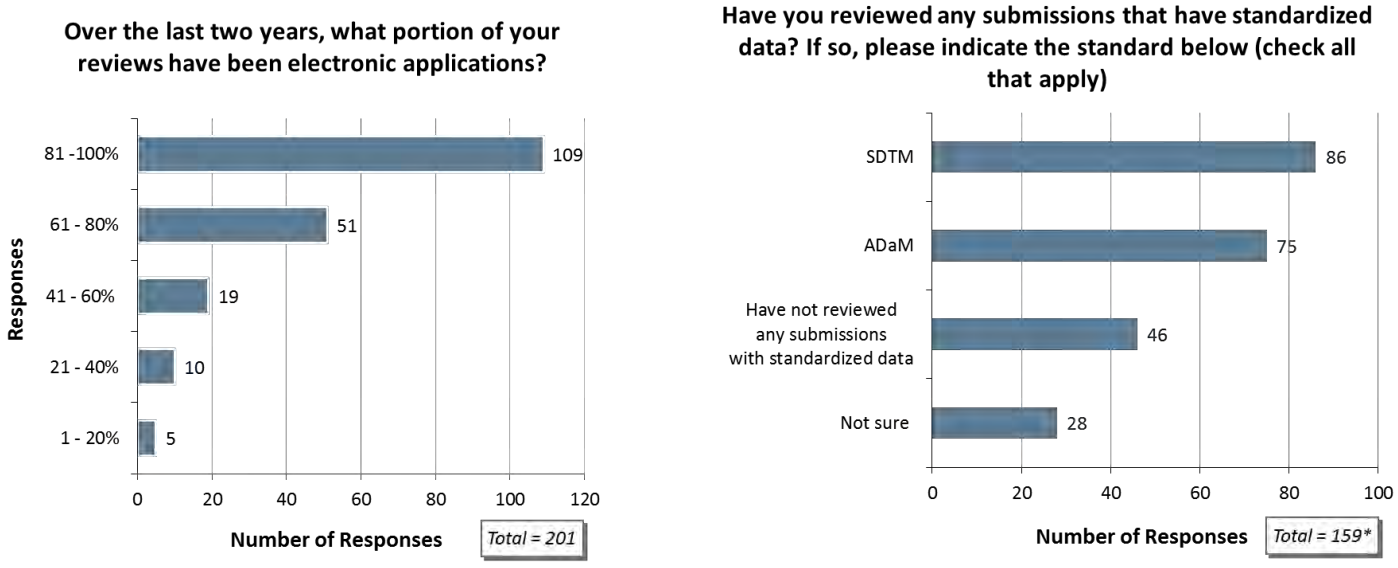


Note: Sponsors may use a contract research organization (CROs) to submit applications with standardized data, which may introduce additional data issues

Figure 3-20: Flow of submission data through CDER and CBER

To measure the impact of the implementation of electronic submissions and data standardization efforts, Booz Allen reviewed quantitative and qualitative data from previous assessment activities to analyze various performance metrics and processes associated with regulatory data review, reviewer and sponsor business practices, and reviewer satisfaction. We collected data for applications included in the Study and Deep Dive cohorts, and conducted a survey and focus groups to collect information related to satisfaction, gains achieved, and business practices from review, staff impacted by electronic submissions and data standards. Additionally, we identified and categorized specific business practices that may affect implementation and benchmarked submission processes against other organizations.

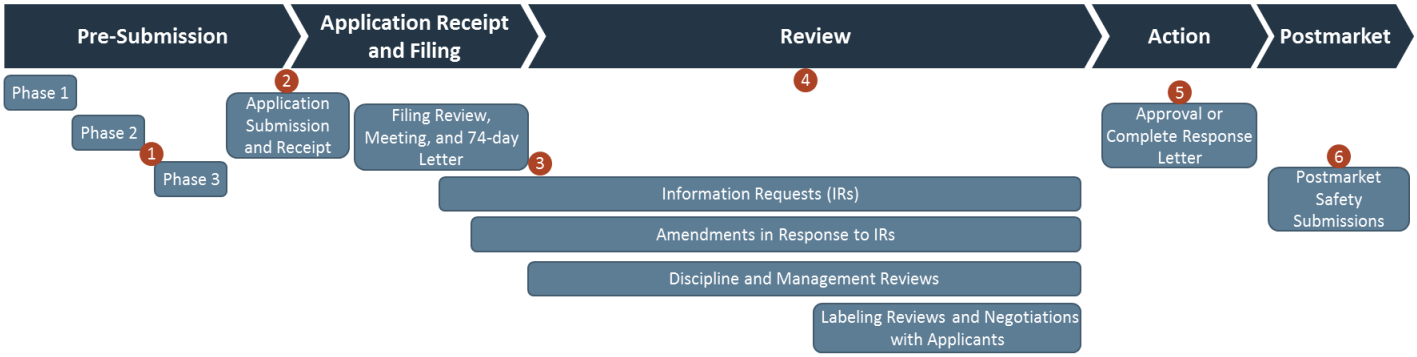
Over the last few years, primary reviewers at the FDA have experienced a shift in how they access and analyze safety and efficacy data included in submissions. Presently, the majority of submissions come in electronically, with the exclusion of research INDs, and this change led to the need for reviewers to adopt and learn a suite of tools to complete their work more efficiently. Figure 3-21 shows surveyed primary reviewers' experience with electronic applications and standardized data. Overall, most of the surveyed, primary reviewers spent a majority of their time reviewing electronic applications and many reviewers have experience with standardized data.



*Notes: *42 survey participants did not answer the question*
Source: PDUFA Electronic Review Assessment Survey

Figure 3-21: Primary reviewers' experience with electronic applications and standardized data

Booz Allen organized the impact assessment findings around different activities throughout the application lifecycle. For each phase of the lifecycle, we collected data and feedback associated with specific activities to determine whether the submission format or inclusion of standardized data affected the reviewer or completion of the activities. Figure 3-22 summarizes the different phases of the application lifecycle, associated review activities, and areas analyzed for potential impact.



	ACTIVITY	IMPACT ANALYSIS
1	Conduct pre-submission meetings	• Timing of data standards discussion
2	Submit and receive application	• Benchmarking – data validation • Gains and best practices from receiving electronic submissions with standardized data
3	Perform filing review	• IR timing, frequency, and type • 74-day letters – refuse-to-file by format and types of review issues

	ACTIVITY	IMPACT ANALYSIS
4	Complete review	• Gains and best practices • Benchmarking – data storage and review • Discipline review template feedback • Types of IRs and major amendments by format • Timing of primary review completion by format
5	Take action	• Approval rates and timing by format
6	Monitor safety post-approval	• Feedback on reviewing safety reports

Figure 3-22: Impact assessment areas throughout the application lifecycle

The following sections provide detailed findings for our impact analysis associated with each phase and corresponding review activities.

PRE-SUBMISSION

Prior to sending in a submission for review, applicants make a number of decisions associated with the application submission format and data that will directly impact FDA staff's ability to review the information. Through the survey and focus groups, reviewers agreed that the FDA should stop receiving paper and make electronic submissions mandatory. Additionally, reviewers indicated their preference for the submission of study standardized data, which is already a requirement for clinical and non-clinical studies started on or after December 17, 2016.

Reviewers noted varying levels of submission quality between applicants, and focus group participants described situations where groups within the same company had significant variances in quality, which suggests a lack of standard operating procedures within a company. One survey respondent stated that the "use of standardized data all depends on whether the Sponsor/Applicant cared enough to do a good job with it." Some reviewers agreed that the Study Data Reviewers Guide (SDRG) could be helpful, but many times, the applicants note errors in the data, but do not address them in the guide.

Pre-submission Business Practices based on Focus Group Responses

- During End-of-Phase 2 (EOP2) meeting, the oncology divisions specify or provide the following:
  - data that applicants need to include
  - specific analyses they want to see
  - information on data standards
- JumpStart analysts noted that the best time to have the discussion for data standards would be during the EOP2 meeting since discussions that occur at the Pre-NDA meeting are probably too late to change how safety data collection occurs and the Pre-IND meetings may be too early since the SDTM standard is evolving

APPLICATION RECEIPT AND FILING

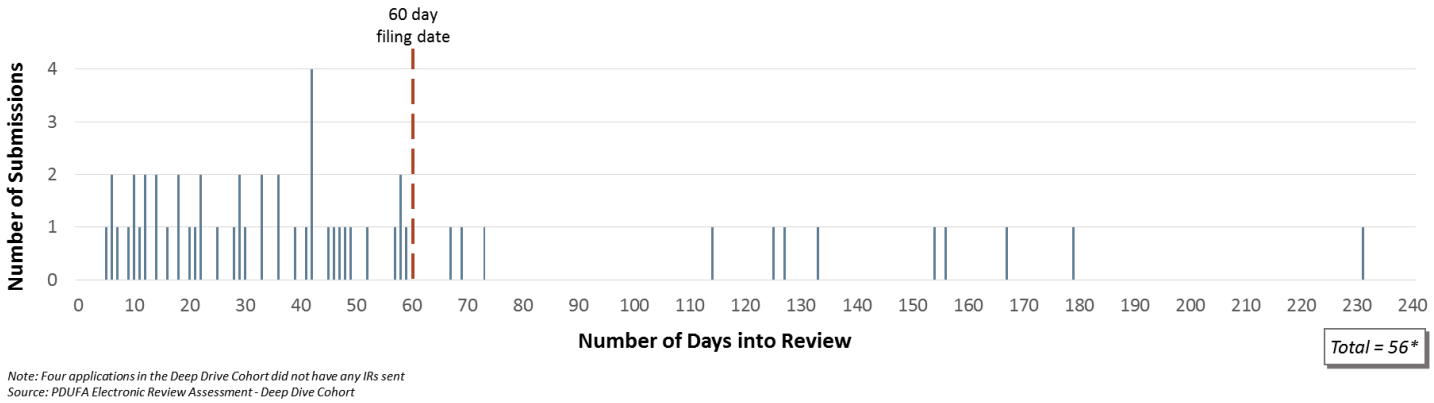
When reviewers receive a new application, they determine whether the submission includes not only enough information, but also the correct data to evaluate the safety and efficacy claims made by applicants. When submissions contain standardized data, 87% (45/52) of surveyed, primary clinical reviewers either strongly agreed or agreed that this type of data improves data fitness. In a

clinical reviewer focus group, one participant commented that they were unsure whether or not it was more complete, but that it was easier to see what was submitted and what was missing from the application. This respondent also noted that the tools used for the JumpStart service were helpful in determining the data fitness for a submission.

Application Receipt and Filing Business Practices based on Focus Group Responses

- Reviewers believed it was helpful for sponsors to submit mock datasets so they could review the information prior to the filing period and that doing so could prevent Complete Responses
- Reviewers appreciated being able to ask sponsors about the location of information within an application when an Application Orientation Meeting was held

As reviewers initiate their assessment of the safety and efficacy data provided by the applicant, they begin by reviewing the information to determine if there is sufficient evidence to complete a substantive review to support the claims for the proposed indication. While conducting their filing reviews, they identify issues with the application and determine the severity of the issue. During this period, reviewers can send IRs to the applicant for issues, classify a concern as a potential review issue, or, where there are serious deficiencies in the application, categorize the problem as a filing issue. Booz Allen conducted an analysis on the initial IR communications sent by the FDA for applications included in the Deep Dive cohort. The date of the first IR communication was recorded along with whether the communication included a request related to data fitness (e.g., missing data). As shown in Figure 3-23, most of the initial IRs occurred within the first 60 days for submissions in the cohort, and for applications where an information request was sent to the applicant, 79% (44/56) were sent within the first 60 days. Almost half (48%, 21/44) of those sent within the first 60 days included an IR related to data fitness. Only one out of 12 of the applications where the first IR communication was sent after 60 days included a data fitness IR.



Note: Four applications in the Deep Drive Cohort did not have any IRs sent
Source: PDUFA Electronic Review Assessment - Deep Dive Cohort

Figure 3-23: Timing of initial IR communications

Booz Allen determined the average number of days into the review when a 74-day letter or RTF letter was sent for all submission formats and for submissions with and without SDTM data. While the number of RTF letters are low, submission format did not appear to affect the number of RTF letters issued (Appendix E, Table 5-7). Interestingly, CDER original applications with SDTM data have a lower percentage of RTF letters than applications without SDTM data (Table 3-8).

Table 3-8: Percentage of refuse-to-file submissions by SDTM inclusion

	% RTFS (RTFS/TOTAL SUBMISSIONS)	
SUBMISSION TYPE	SDTM	NON-SDTM
CDER		
Original	2% (7/378)	9% (28/304)
Efficacy Supplement	1% (3/375)	2% (11/468)
CBER		
Original	0% (0/16)	0% (0/31)
Efficacy Supplement	0% (0/11)	3%* (2/73)

*Only 2 CBER BLA Submissions received an "Unacceptable for Filing" action

As shown in Table 3-9, inclusion of SDTM data did not seem to affect timing significantly for the 74-day letter and similar findings were observed for submission format (Appendix E, Table 5-8).

Table 3-9: Average number of days into review 74-day letter sent by SDTM inclusion

		AVERAGE NUMBER OF DAYS INTO REVIEW 74-DAY LETTER SENT* (NUMBER OF SUBMISSIONS)	
SUBMISSION TYPE	PRIORITY	SDTM	NON-SDTM
CDER			
Original	Priority	60 (98)	61 (47)
	Standard	70 (247)	69 (188)
Efficacy Supplement	Priority	59 (106)	59 (57)
	Standard	67 (114)	67 (163)
CBER			
Original	Priority	59 (1)	57 (10)
	Standard	55 (14)	56 (20)
Efficacy Supplement	Priority	NA (0)	88 (2)
	Standard	58 (10)	58 (66)

*Excludes submissions that received a refuse-to-file, no user fee was received, was unacceptable for filing, applicant was in arrears, the submission was withdrawn and, or the filing letter date was missing at the time when the data was pulled (11/4/16)

For the Deep Dive Cohort, Booz Allen reviewed and analyzed the potential review issues identified in the 74-day letters. For the 20 submissions with review issues explicitly stated in the letter, 20% were related to data fitness. We also performed an analysis that categorized the Deep Dive submissions by pass rate, and it did not appear to affect the 74-day letter sent date. Interestingly, 79% (27/34) of reviewers that went through the JumpStart service and participated in the post-service survey said that the service

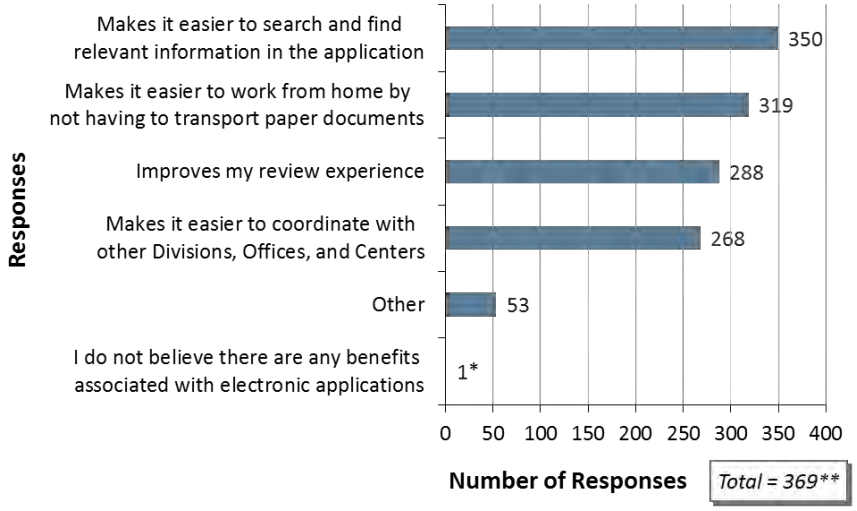
increased their confidence in making a filing decision with respect to data quality and reviewability. During the survey, we asked reviewers if there were any reasons why they would not request a service like JumpStart or KickStart, since it is not available for all submissions, but appeared to add value to the review. While many of the reviewers (50/124) would request the service for all applications, we found that some of the reviewers did not know what was included in the service (47/124) or how to request it (31/124). A smaller number of reviewers indicated they would prefer to perform their own data evaluation (15/124) or they were discouraged from requesting since not all applications can receive the service (14/124).

After receiving an application and making a decision on whether to file it, FDA staff initiate their review to evaluate the applicant's claims based on the data provided.

REVIEW

During the impact assessment, Booz Allen evaluated how electronic submissions and data standards affect review staffs' ability to complete efficient and effective application reviews. Reviewers described the multiple benefits experienced during the review of an electronic submission. These benefits can be organized into themes that include accessibility to the information included in the application, ability to easily share the information and coordinate with other groups, and flexibility in work locations.

Figure 3-24 shows survey responses from staff when asked about the benefits of electronic submissions.

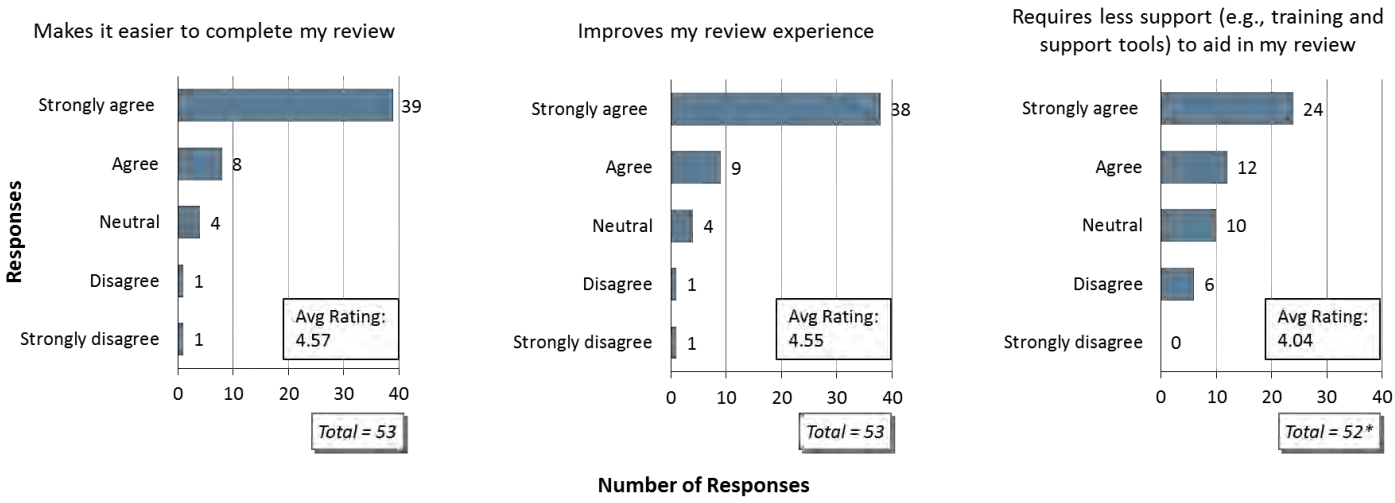


*Notes: *This respondent also selected other benefits to electronic applications; **1 respondent only selected N/A*
Source: PDUFA Electronic Review Assessment Survey

Figure 3-24: Benefits of electronic applications based on survey responses

Respondents overwhelmingly believed that the information within an electronic submission was easier to search and find, as compared to paper and mixed submissions. The responses in the survey indicate that the submission of electronic applications leads to increased productivity throughout the review process and an improved user experience. Notably, reviewers mentioned the ability to cut and paste important figures and tables into their review and improved coordination within their own team members, not just other divisions, offices, or Centers. Additionally, respondents noted the benefit of having easier access to previous submissions, years after a review is completed. Some respondents used this question as an opportunity to provide feedback about improvements that could be made, such as the ability to perform a global search on all text within in application and the need to convert previously submitted paper applications into electronic versions.

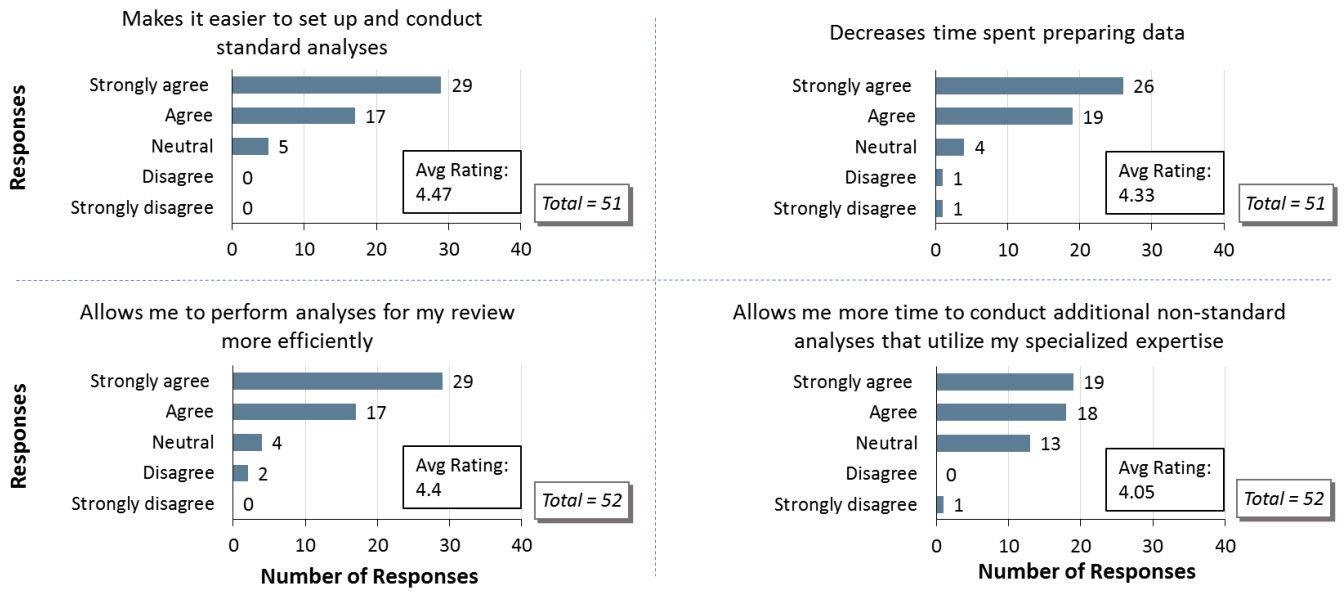
The introduction and continued implementation of standardized clinical and non-clinical data in applications has led to some of the same efficiencies experienced by reviewers with electronic submissions. Surveyed clinical primary reviewers strongly agree and agree that this type of data improves ease of use (89%, 47/53), their review experience (89%, 47/53), and require less support (69%, 36/52). Figure 3-25 provides the average ratings of clinical reviewers' agreement with potential benefits of standardized data.



*Note: *1 respondent answered N/A. 27 primary reviewers did not answer theses questions; Average rating obtained from assigning values of 1-5 for strongly disagree to strongly agree responses*
Source: PDUFA Electronic Review Assessment Survey

Figure 3-25: Impact of standardized data on overall review for primary clinical reviewers

Booz Allen included survey questions to further understand the specific efficiencies gained from standardized data. When asked whether this type of data makes it easier to prepare for and complete standard analyses, most primary clinical reviewers strongly agree or agree the standardized data makes a difference in these aspects of their review activities. They believe standardized data makes it easier to complete standard analyses (90%, 46/51), perform analyses more efficiently (88%, 46/52), decreases time spent preparing data (88%, 45/51), and allows more time to conduct additional non-standard analyses (73%, 37/52). Figure 3-26 shows the results for these survey questions.



*Note: *27 primary reviewers did not answer the question, 1-2 reviewers responded N/A to each response; Average rating obtained from assigning values of 1-5 for strongly disagree to strongly agree responses*
Source: PDUFA Electronic Review Assessment Survey

Figure 3-26: Impact of standardized data on review time and analyses for primary clinical reviewers

During focus group sessions, primary clinical reviewers provided some deeper insight into some of the challenges they experience when reviewing SDTM data and provided suggestions for improvement. One reviewer noted that the dataset is often uninterpretable because it is copied from the case report forms (CRFs) and the parameters can be in different units. Other reviewers agreed and indicated that they sometimes use the analysis datasets when the units have not been properly converted. All of the reviewers agreed that the SDTM data should include properly converted units and identify it is one of biggest challenges with applicant data.

Sponsor Business Practices Affecting Review Activities

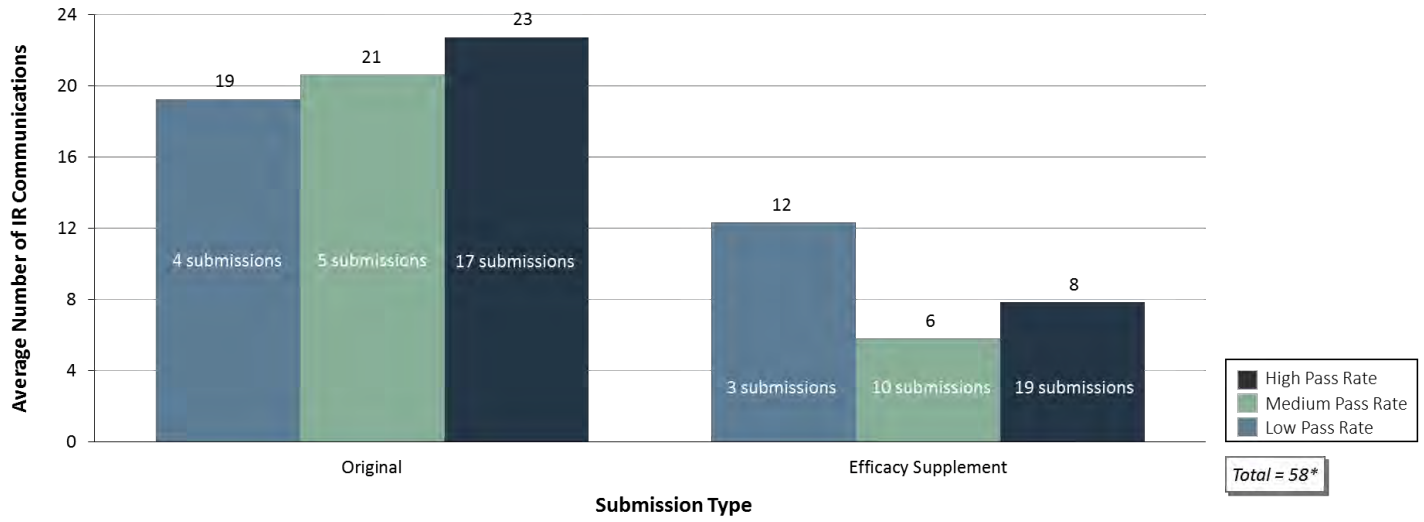
- Reviewers believe current SDRGs are not useful but could become so if flagged terms and abbreviations are defined
- Reviewers would like "plain language" explanations of steps sponsors take when performing analyses, not just the SAS code

While conducting the focus groups, Booz Allen asked reviewers to provide feedback for the current clinical review template (CRT). The feedback suggested that the template helps to guide from big picture items down to more granular information, the general feedback indicated unnecessary redundancies across the document. Reviewers cited multiple instances where the template requires them to copy information from other discipline reviews and repeats sponsor information from the application without any analysis. Booz Allen observed examples of these critiques while performing the mapping of review analyses to SDTM domains, with the addition of similar analyses between the safety and efficacy sections that may leave the placement of the information up to interpretation and reduce consistency between reviews. Booz Allen also noted the absence of suggested tools and outputs for use when completing the analyses. OCS and OND developed a new review template that provides references to tools, outputs, and relevant documents (e.g., guidances). This new review template, the Clinical Review Template Analysis References (CRTAR), is currently under review internally and should address many of the concerns reviewers voiced during the focus groups once rolled out.

FDA Business Practices Associated Review Activities

- Several reviewers had positive experiences when the oncology divisions piloted a unified review where reviewers from all disciplines (e.g., clinical, quality) completed all of their reviews in one document
- The review team made updates and modifications to their sections within the single template using SharePoint
- Other reviewers were extremely interested in also piloting this approach
- CBER also uses the unified review approach

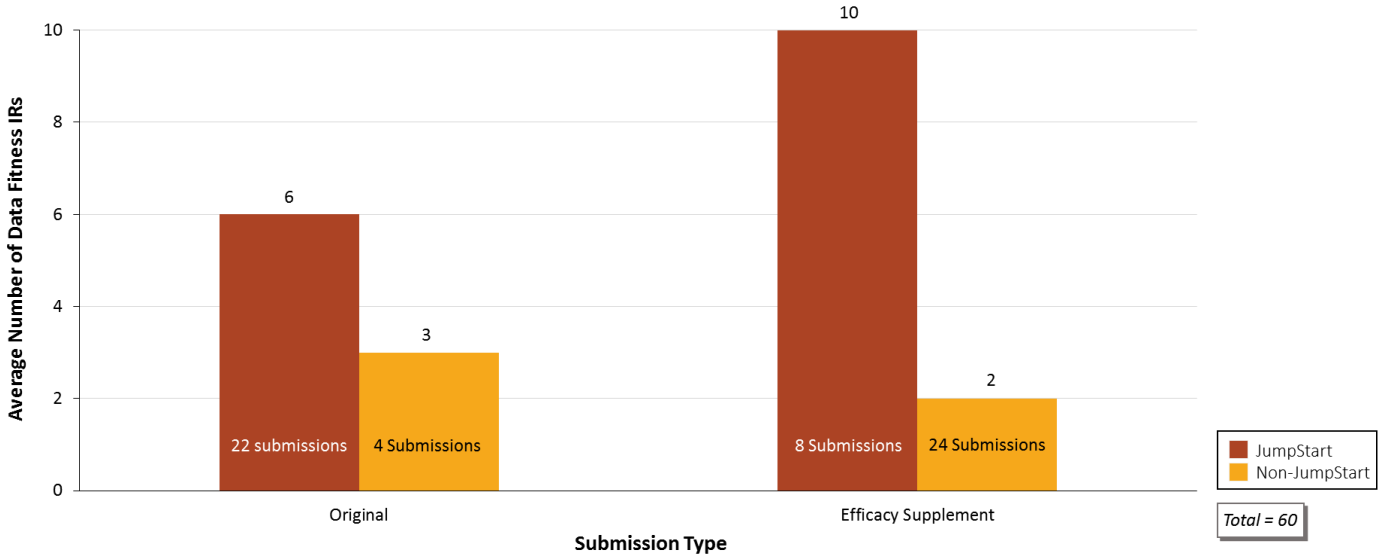
As reviewers sort through and evaluate the safety and efficacy data provided by the applicant, they identify gaps in the data that require further explanation. As previously discussed, Booz Allen piloted a methodology for categorizing applications by their relative data fitness based on the number of outputs that could be generated with the data, which resulted in the high, medium and low pass rate categories. We performed an analysis to determine whether those applications in the low pass rate category would have more IR communications. While the pass rate did not appear to have an effect on the number of IR communications, original applications had more IRs sent compared to efficacy supplements, most likely due to the volume of data and familiarity associated with an original application.



*Notes: *2 deep dive submissions do not contain standardized data, which contained 19 and 3 IR communications*
Source: PDUFA Electronic Review Assessment Deep Dive Cohort Analysis

Figure 3-27: Average number of IR communications by submission type and pass rate

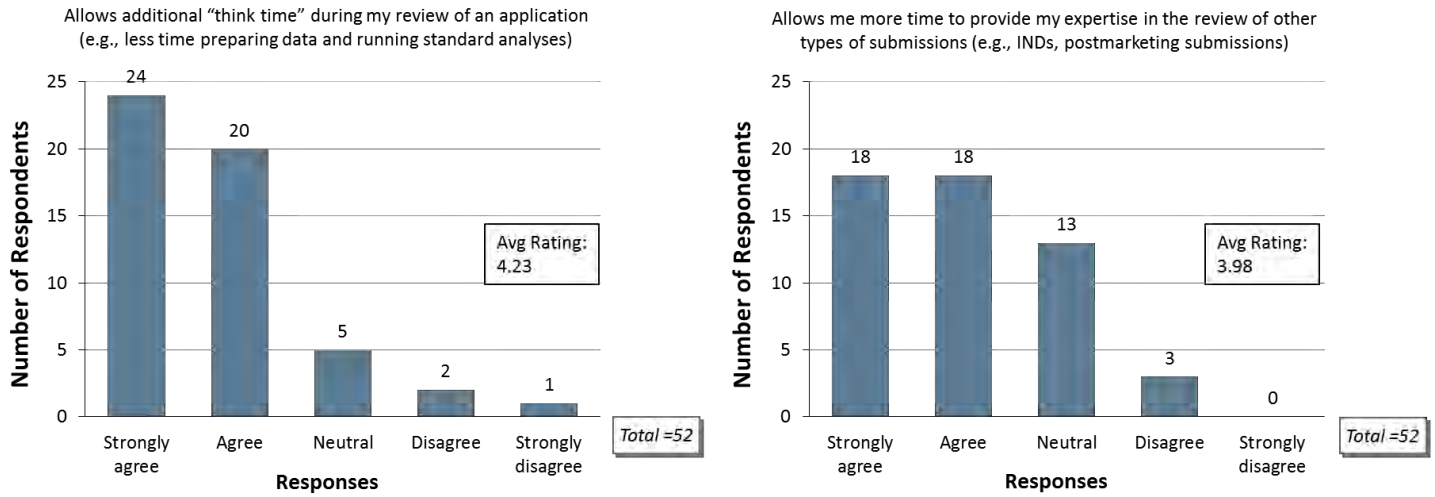
Booz Allen also assessed whether applications that went through the JumpStart service had more individual IRs related to data fitness compared to non-JumpStart applications. Figure 3-28 shows, on average, applications in the Deep Dive Cohort that were associated with the JumpStart service had a higher number of data fitness IRs sent to the applicant. This finding suggests that the JumpStart service assists reviewers in identifying meaningful data fitness issues. We performed additional analysis that showed the pass rate for JumpStart and non-JumpStart applications did not appear to affect the number of data fitness IRs sent (Appendix E, Figure 5-12).



Source: PDUFA Electronic Review Assessment Deep Dive Cohort Analysis

Figure 3-28: Average number of data fitness IRs by submission type and JumpStart experience

During the survey, Booz Allen asked respondents if applications with standardized data allows for additional "think time" during their review as potentially less time is spent preparing and running standard analyzes on the data. For the most part, primary clinical reviewers strongly agreed or agreed (85%, 44/52) with this concept. While fewer reviewers strongly agreed or agreed (69%, 36/52), most responded that they had more time to devote to the review of other submissions types (e.g., INDs) when an application they were reviewing had standardized data.



*Notes: *27 primary reviewers did not answer the question, Average rating obtained from assigning values of 1-5 for strongly disagree to strongly agree responses*
Source: PDUFA Electronic Review Assessment Survey

Figure 3-29: Primary clinical reviewers' perceptions of review time spent with standardized data

As reviewers continue to assess the safety and efficacy data during the course of an application review, some applicants submit amendments that can introduce a significant amount of information not previously seen in the application. If the new information

constitutes a major amendment, the FDA extends the goal date by three months. Booz Allen performed analyses on whether submission format or the inclusion of standardized data in an application affected the occurrence of major amendments. For submission format, since the majority of applications received by FDA were in electronic format, there appeared to be no meaningful difference (see Appendix A, Table 5-9). Additionally, the inclusion of standardized data did not affect the submission of major amendments to applications (see Appendix A, Table 5-10).

Booz Allen collected and analyzed additional data to determine the effect of submission format and inclusion of standardized data on a number of milestones associated with application review. We did not observe any significant impact associated with the submission format and primary clinical review completion time since the majority of submissions were electronic (See Appendix A, Table 5-11 and Table 5-12). Table 3-10 includes the average primary review completion times organized by applications with and without SDTM data. For priority original applications with standardized data, the review times are shorter than applications without standardized data.

Table 3-10: Average time to primary clinical review completion for CDER original applications by SDTM inclusion*

			AVERAGE TIME TO PRIMARY CLINICAL REVIEW COMPLETION IN DAYS (NUMBER OF SUBMISSIONS)	
DESIGNATION	**APPLICATION TYPE**	**EXPECTED PRIMARY COMPLETION***	**SDTM**	**NON-SDTM**
Priority / Non-Program	NDAs and BLAs	152	123 (15)	140 (16)
	NDAs and BLAs with Major Amendments	Variable	148 (2)	NA (0)
Priority / Program	NDAs and BLAs	213	152 (49)	173 (13)
	NDAs and BLAs with Major Amendments	Variable	155 (2)	157 (3)
Standard / Non-Program	NDAs and BLAs	243	254 (119)	237 (96)
	NDAs and BLAs with Major Amendments	Variable	261 (4)	123 (3)
Standard / Program	NDAs and BLAs	304	257 (60)	234 (8)
	NDAs and BLAs with Major Amendments	Variable	254 (2)	NA (0)

*Based on primary review completion times from Appendix A of the"21st Century Review Process Desk Reference Guide"; Excludes submissions that received a refuse-to-file, no user fee was received, was unacceptable for filing, applicant was in arrears, the clinical review date was missing, or the clinical review date was after the action date (e.g., data entry error)
Source: FDA data systems - Study Cohort

Additionally, Booz Allen survey questions addressed whether submissions with standardized data make it easier to respond to consult requests or make it easier to prepare for advisory committee meetings. Primary reviewer responses were generally distributed between strongly agree, agree and neutral (See Appendix E, Figure 5-13).

After completing their review of an application, FDA staff then decide what action to take on the submission.

ACTION

Booz Allen investigated the effect that submission format and standardized data had on a variety of review action metrics, including:

- First cycle approval rate
- Average time to first action
- Average time to first cycle approval

We categorized submissions based on their priority and Program designation as well as whether or not they contained major amendments. The low number of CBER applications with SDTM data limited the ability to observe any meaningful differences in the analyses performed below (Appendix E, Table 5-17, Table 5-18, Table 5-24, Table 5-25, and Table 5-31).

FIRST CYCLE APPROVAL RATE

With the low number of paper and mixed submission in the Study Cohort, approval rate differences by submission format could not be determined for either CDER or CBER original submissions or efficacy supplements (see Appendix F, Table 5-13, Table 5-14, Table 5-15, and Table 5-16). However, as may be expected, original CDER Program applications had higher approval rates than non-Program applications.

We also investigated differences in first cycle approval rates for original CDER submissions with and without standardized data and found that, in some cases, submissions containing SDTM data had higher first cycle approval rates compared to non-SDTM submissions with the same designation (Table 3-11). For example, standard non-Program submissions with SDTM data had a 61% approval rate whereas submissions with the same designation without SDTM data had only a 50% approval rate. Two exceptions to this trend were standard, non-Program applications with major amendments, which had similar approval rates (76% vs 77%) and priority, Program submissions with major amendments and standardized data, which had lower approval rates than non-SDTM submissions (92% vs 100%).

Table 3-11: First cycle approval rates for CDER original applications by SDTM inclusion, priority and Program designation

			% OF ACTION* (NUMBER OF ACTIONS / TOTAL NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	ACTION	SDTM	NON-SDTM
Priority / Non-Program	NDAs and BLAs	Approval	78% (18/23)	71% (15/21)
		CR	22% (5/23)	29% (6/21)
	NDAs and BLAs with Major Amendments	Approval	100% (4/4)	75% (3/4)
		CR	0% (0/4)	25% (1/4)
Priority / Program	NDAs and BLAs	Approval	96% (44/46)	92% (11/12)
		CR	4% (2/46)	8% (1/12)
	NDAs and BLAs with Major Amendments	Approval	92% (11/12)	100% (4/4)
		CR	8% (1/12)	0% (0/4)
Standard / Non-Program	NDAs and BLAs	Approval	61% (77/127)	50% (58/117)
		CR	39% (50/127)	50% (59/117)
	NDAs and BLAs with Major Amendments	Approval	76% (16/21)	77% (10/13)
		CR	24% (5/21)	23% (3/13)
Standard / Program	NDAs and BLAs	Approval	72% (38/53)	57% (4/7)
		CR	28% (15/53)	43% (3/7)
	NDAs and BLAs with Major Amendments	Approval	100% (4/4)	100% (2/2)
		CR	0% (0/4)	0% (0/2)

*Only includes submissions with the following actions: approved, complete response

The inclusion of SDTM data for CDER efficacy supplements did not have a meaningful difference on first cycle approval rate (Table 3-12).

Table 3-12: First cycle approval rates for CDER efficacy supplements by SDTM inclusion, priority and Program designation

			% OF ACTION* (NUMBER OF ACTIONS / TOTAL NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	ACTION	SDTM	NON-SDTM
Priority / Non-Program	NDAs and BLAs	Approval	93% (98/105)	95% (60/63)
		CR	7% (7/105)	5% (3/63)
	NDAs and BLAs with Major Amendments	Approval	80% (4/5)	100% (4/4)
		CR	20% (1/5)	0% (0/4)
Standard / Non-Program	NDAs and BLAs	Approval	85% (144/169)	86% (220/255)
		CR	15% (25/169)	14% (35/255)
	NDAs and BLAs with Major Amendments	Approval	75% (6/8)	92% (11/12)
		CR	25% (2/8)	8% (1/12)

*Only includes submissions with the following actions: approved, complete response

Efficacy supplements without major amendments had similar approval rates (93% vs 95% for priority submissions and 85% vs 86% for standard submissions). Non-SDTM efficacy supplements with major amendments had higher approval rates than SDTM submissions with the same designation (100% vs 80% for priority submissions and 92% vs 75% for standard submissions).

AVERAGE TIME TO FIRST ACTION

Booz Allen investigated the impact of submission format on average time to first action (Appendix F, Table 5-19, Table 5-20, Table 5-21, and Table 5-22). Again, without large numbers of paper or mixed original submissions, we could not determine average time to first action differences based on submission format.

Interestingly, when analyzing average time to first action based on inclusion of standardized data in the submission, we found that priority submissions, without major amendments, with SDTM data had much shorter average times to first action than for non-SDTM submissions (160 vs 175 days or 212 vs 232 days for non-Program and Program applications, respectively) (see Table 3-13). In contrast, standard submissions without major amendments either had similar (365 vs 367 days for Program applications) or longer (306 vs 295 days for non-Program applications) average number of days to first action. FDA sometimes completed the first action for original submissions with major amendments after the projected time, especially for non-program submissions with SDTM data (305 vs a projected 274 days for non-Program applications and 427 vs a projected 395 days for Program applications). Booz Allen saw similar trends for CDER efficacy supplements (Appendix F, Table 5-23).

Table 3-13: Time to first action for CDER original applications by SDTM inclusion, priority and Program designation

			AVG. # OF DAYS TO FIRST ACTION* (NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	SDTM	NON-SDTM
Priority / Non-Program	NDAs and BLAs	183	160 (23)	175 (20)
	NDAs and BLAs with Major Amendments	274	305 (4)	274 (4)
Priority / Program	NDAs and BLAs	243	212 (46)	232 (12)
	NDAs and BLAs with Major Amendments	335	340 (12)	361 (4)
Standard / Non-Program	NDAs and BLAs	304	306 (127)	295 (117)
	NDAs and BLAs with Major Amendments	395	427 (21)	389 (13)
Standard / Program	NDAs and BLAs	365	365 (53)	367 (7)
	NDAs and BLAs with Major Amendments	456	454 (4)	455 (2)

*Excludes submissions that received a refuse-to-file, no user fee was received, submission was unacceptable for filing, applicant was in arrears, or submission was withdrawn

**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"

AVERAGE TIME TO FIRST CYCLE APPROVAL

Booz Allen analyzed the impact of submission format on average time to first cycle approval (see Appendix F, Table 5-26, Table 5-27, Table 5-28, and Table 5-29). We saw similar trends for average time to first cycle approval as for time to first action. Without larger numbers of paper or mixed original submissions, we could not determine average time to first cycle approval differences based on submission format.

When performing analysis on average time to first action based on inclusion of standardized data in the submission, we found that priority submissions without major amendments with SDTM data had much shorter average times to first cycle approval than for non-SDTM submissions (154 vs 174 days or 211 vs 230 days for non-Program and Program applications, respectively) (Table 3-14). In contrast, standard submissions without major amendments either had similar (i.e., 366 vs 365 days for Program applications) or longer (i.e., 307 vs 291 days for non-Program applications) average number of days to first cycle approval. FDA sometimes completed the first cycle approval for original submissions with major amendments after the projected time, especially for non-program submissions with SDTM data (i.e., 305 vs a projected 274 days for non-Program applications and 421 vs a projected 395 days for Program applications). We saw similar trends for CDER efficacy supplements (see Appendix F, Table 5-30).

Table 3-14: Time to first cycle approval for CDER original applications by SDTM inclusion, priority and Program designation

			AVG. # OF DAYS TO FIRST APPROVAL* (NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	SDTM	NON-SDTM
Priority / Non-Program	NDAs and BLAs	183	154 (18)	174 (14)
	NDAs and BLAs with Major Amendments	274	305 (4)	275 (3)
Priority / Program	NDAs and BLAs	243	211 (44)	230 (11)
	NDAs and BLAs with Major Amendments	335	340 (11)	361 (4)
Standard / Non-Program	NDAs and BLAs	304	307 (77)	291 (58)
	NDAs and BLAs with Major Amendments	395	421 (16)	388 (10)
Standard / Program	NDAs and BLAs	365	366 (38)	365 (4)
	NDAs and BLAs with Major Amendments	456	454 (4)	455 (2)

*Excludes submissions that received a refuse-to-file, no user fee was received, submission was unacceptable for filing, applicant was in arrears, or submission was withdrawn

**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"

POSTMARKET

As the percentage of postmarket submissions sent through the Gateway has steadily increased over time (see Figure 3-8 and Figure 3-9), reviewers may benefit from additional review tools to evaluate postmarket safety data. Booz Allen sought to learn if reviewers would be interested in the development of a tool, as well as functionalities of that tool, by posing questions to focus group participants. The focus group discussion touched on a number of topics, including the use of current tools to analyze data. One primary reviewer noted that when they use Empirica, it would only display the main event and not the other adverse events from the report. Another reviewer hoped a review tool would allow him to compare the background adverse event rate to other drugs in the same class to put the data into context. Reviewers appear to want a tool that could both provide them with an overview of the data and the ability to select detailed information to investigate further. Such a tool could increase the gains reviewers experience in the transition from paper to electronic postmarket safety submissions.

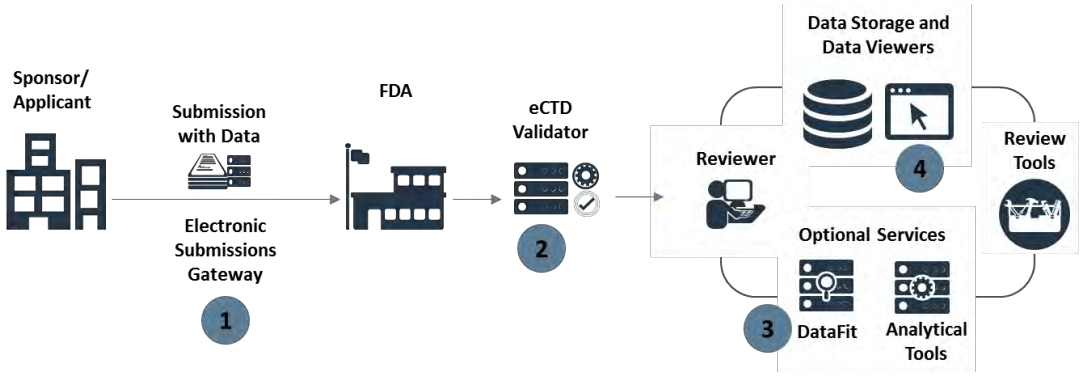
BENCHMARKING

Booz Allen benchmarked best practices for the ingestion, storage, and processing of standardized data against two processes at the NIH.

The first process is the Data and Specimen Hub (DASH) utilized by the National Institute of Child Health and Human Development (NICHD). DASH is a cloud-hosted infrastructure for the standardized submission and sharing of NICHD-funded study data, such as clinical trial data. Contained within DASH is a data preparation tool (DPT) for validation of incoming submissions prior to ingestion into DASH. Researchers submitting study data are required to use the DPT to organize and validate their data. The researcher is notified if a specific error in their submission prevents upload and has the ability to iteratively update their submission until it meets all of the DPT's validation criteria.[20]

[20] NICHD DASH. Retrieved from https://dash.nichd.nih.gov/

As outlined in Figure 3-30, DASH and the DPT are analogous to some of FDA's current tools and processes for handling standardized data. DASH is similar to the Gateway, but unlike the Gateway, DASH not only ingests data, but also serves as a hub for storing and sharing data via a cloud infrastructure. DASH's DPT has similarities to FDA's eCTD Validator by testing all submissions uploaded by the researcher. Additionally, DPT's automated validation of submissions has some similarities to DataFit, except the process is automated and occurs before a submission has been ingested into the system. Finally, DASH serves a data storage role and by utilizing a cloud solution, which minimizes the impact the storage and processing of large volumes of data have on the performance of the system.



1	**Data Ingestion and Sharing:** DASH not only ingests data, but also serves as a hub for sharing data via a cloud infrastructure	3	**Validation Results:** DPT is an automated validation tool that alerts the submitter to errors before a study has been uploaded and prevents ingestion of a study unless it meets all of the validation criteria
2	**Data Validation:** DASH tests all submissions uploaded by a researcher, not only a single test submission. Submission validation checks file integrity and structure of the submission	4	**Big Data Approach:** DASH's use of a cloud infrastructure reduces the impact the storage and processing of large volumes of data have on a system

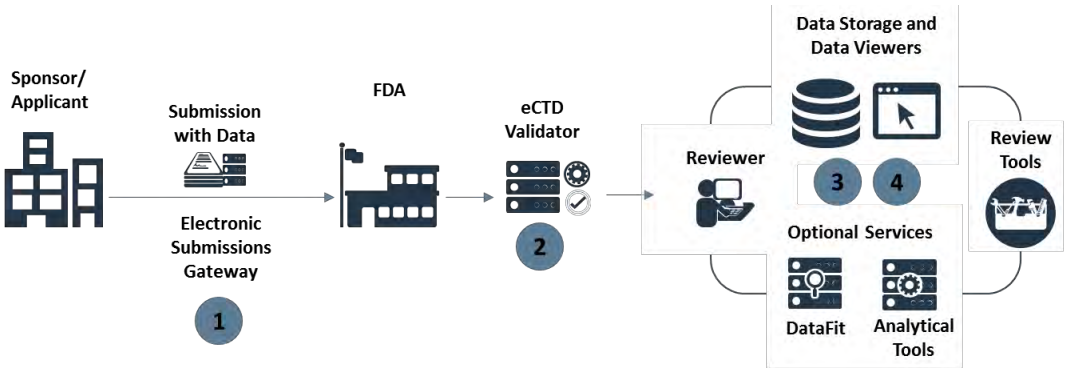
Source: Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, https://dash.nichd.nih.gov/

Figure 3-30: DASH similarities and differences against FDA electronic submission process

The second process that Booz Allen investigated was NIH's database of Genotypes and Phenotypes (dbGaP) created by the National Center for Biotechnology Information.[21] NCBI data housed in this database include individual-level genotypic and phenotype data, analysis results and general study information (including protocols).[22] For this database, Genomic Program Administrators work with Principal Investigators (PIs) to register their studies and submit their data.[23] During the submission process, dbGaP curators reconcile data conflicts in consultation with the data submitters.[24] dbGaP then makes data available on their website, with individual-level data only available to PIs with authorized access.[25] dbGaP is linked to two tools, a data browser and PheGenI, a tool that links relevant data from several NCBI-housed databases.[26] Additionally, to link data that share consent groups, disease area or funding project, dbGaP also generates Collections (e.g., Open Translational Science in Schizophrenia (OPTICS)).[27]

dbGaP employs a number of practices akin to FDA data ingestion, storage and review processes (see Figure 3-31). Highlighted differences between the dbGaP and FDA processes may also be considerations for FDA to adapt to their current processes. For example, dbGaP's informative files names allow users to determine certain aspects of the contents of the files before opening.[28] FDA has both an eCTD validator before data is accepted and DataFit to investigate potential data fitness issues in a submitted application, dbGaP has a more intensive data screen before accepting data to the database. Their process is resource intensive with an automated as well as a human assessment of the data.[29]

[21] dbGaP. Retrieved from https://www.ncbi.nlm.nih.gov/gap/
[22] Tryka et al. "The Database of Genotypes and Phenotypes (dbGaP) and PheGenI." The NCBI Handbook [Internet] 2nd edition. August 15, 2013. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK154410/
[23] dbGaP submission process. Retrieved from https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetPdf.cgi?document_name=HowToSubmit.pdf
[24] Tryka et al. "The Database of Genotypes and Phenotypes (dbGaP) and PheGenI." The NCBI Handbook [Internet] 2nd edition. August 15, 2013. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK154410/
[25] Ibid
[26] Ibid
[27] dbGaP Collections. Retrieved from https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetCollectionList.cgi
[28] Tryka et al. "The Database of Genotypes and Phenotypes (dbGaP) and PheGenI." The NCBI Handbook [Internet] 2nd edition. August 15, 2013. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK154410/
[29] Ibid



dbGaP Considerations Affecting Storage and Review

1	**Informative File Names:** Genotype file names contain pieces that reflect the content of the file (e.g., the genotype accession, the consent code)	3	**Data Linkages:** Facilitated by the XML format of submitted documents, dbGaP staff curate documents to provide live links to other relevant internal information as well as to external resources
2	**Data Validation:** Submitted phenotypic data is subject to automated as well as human assessment	4	**Search Capabilities:** All public studies can be queried from the homepage by either using simple keywords or multiple search fields

Source: dbGaP https://www.ncbi.nlm.nih.gov/gap ; Tryka et al. "The Database of Genotypes and Phenotypes (dbGaP) and PheGenI." The NCBI Handbook [Internet] 2nd edition. August 15, 2013.; Mailman et al. "The NCBI dbGaP database of genotypes and phenotypes." Nat Genet. 2007 Oct; 39(10): 1181-1186.

Figure 3-31: dbGaP similarities and differences against FDA electronic submission process

As dbGaP's role is not to analyze but to collect and disseminate information, they largely focus their efforts towards curating the data to make research on their site easier for users.[30] To this end, dbGaP provides live links to internal and external related resources, similar to FDA's data systems linking certain information related to application numbers and applicable INDs. [31] Finally, users can search dbGaP using either simple keywords or multiple search fields.[32]

Features highlighted from both NIH processes provide insight into the business practices of a different agency tasked with ingestion, storage and review of standardized data. Although both processes have slightly different outcomes than those at FDA, there may be an opportunity to learn from these processes to improve data interactions.

3.5 FDA Readiness to Receive Real-World Evidence

As part of this evaluation, Booz Allen performed a high-level, preliminary assessment of FDA's ability to receive, ingest, and analyze real-world evidence. According to an article written by Sherman et al., which included multiple coauthors from the FDA, titled "Real-World Evidence – What Is it and What Can It Tell us?", RWE "refers to information on health care that is derived from multiple sources outside typical clinical research settings".[33] CDER SME agreed that RWE could be any clinical information collected outside of a "traditional" clinical study or trial. Data sources for RWE could include the following:

- **Registries:** Patient data pertaining to either a certain product or disease
- **Mobile:** Data collected from personal devices and mobile health applications
- **Claims:** Patient data collected for claims and billing purposes
- **Electronic Health Records:** Patient health records kept by clinicians
- **Historical:** Data from historical controls and natural history studies

[30] Ibid
[31] Ibid
[32] Ibid
[33] Sherman et al. "Real-World Evidence – What Is It and What Can It Tell Us?". N Engl J Med. Dec. 8, 2016. 375:2293-2297. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJMsb1609216

At this time, both CDER and CBER are in the process of developing policy to determine the applicability of RWE to regulatory decision-making, as well as their scientific positions regarding this type of data. Due to these current efforts, the readiness assessment focused on identifying current capabilities to receive, ingest, and analyze data and working groups formed to determine the applicability and potential for incorporating this type of data into the regulatory review of drugs and biologics. Over the next five years, the FDA will need to meet a number of requirements included in the PDUFA IV Commitment Letter and the 21st Century Cures Act associated with use of RWE. [34]

While CDER and CBER have capabilities available for review of RWE, the policy decisions, such as the methods for accessing and interpreting the data, limit the ability to complete a full evaluation. Due to the inability to identify the full scope or amount of data that could be coming in, Booz Allen, based on feedback from the FDA, limited the readiness assessment to focus on existing capabilities and working groups engaged in the development of scientific and policy decisions for the applicability of RWE in a regulatory context. Table 3-15 includes a list of current capabilities at CDER and CBER available for use in the review of RWE.

Table 3-15: Current capabilities applicable to RWE

CAPABILITY	DESCRIPTION	CONSIDERATIONS PRIOR TO IMPLEMENTATION OF RWE REVIEW
Ingestion and Validation		
Electronic Submission Gateway	Provides a centralized communications portal for secure transmission of electronic regulatory submissions (e.g., eCTD applications) and enables the receipt, acknowledgement, routing, and notification of a Center for the submission	• Volume and velocity of any new data in addition to current submission data • Data types and format (e.g., standardized)
Event Data Management (EDM)	• An online portal where users or external groups can submit information directly to Panorama • Information is entered into a form within the portal and then a Panorama project can be created • Currently, the capability is for external stakeholders to submit drug shortage information • Future functionality may include the ability to ingest an email and create a Panorama project based off the information included in the email	• Volume and velocity of any new data in addition to current submission data • Data types and format (e.g., standardized) • Work flow and products (e.g., programs, projects, tasks) associated with RWE outside of application reviews
DataFit	Web-based tool that automatically detects new data in Portes via Application Programming Interface (API) and then processes and validates the data using FDA/CDISC business and conformance rules	• Volume and velocity of any new data in addition to current submission data An assessment of data format and identification of validation rules for RWE will be necessary to ensure appropriate use of DataFit

[34] PDUFA IV Commitment Letter Requirements: 1) By the end of FY 2018, hold one or more public workshops to discuss RWE issues with relevant stakeholders, 2) By the end of FY 2019, initiate activities to address RWE concerns and considerations, 3) By the end of FY 2021, release draft guidance on the contribution of RWE to regulatory submissions; 21st Century Cures Act Requirements: 1) By December 2018, implement a program to evaluate the potential use of RWE to support approval of new indications for approved products and postapproval study requirements, 2) By December 2021, release draft guidance regarding when sponsors may rely on RWE and describing standards for collection and analysis

CAPABILITY	DESCRIPTION	CONSIDERATIONS PRIOR TO IMPLEMENTATION OF RWE REVIEW
Data Storage		
Janus CTR	Supports the automated extraction, transformation, loading, management, and integration of clinical trials data and facilitates the timely creation of custom "data marts" to support a variety of regulatory review and meta-analysis needs	• Volume and velocity of the data • Data types and format (e.g., standardized) • Organization and ability to search data • Interaction and interoperability with analytical tools • Implications of agreements with other organizations for off-site storage of source data
EDR	Database that provides the ability to search through submission data for INDs, NDAs, and BLAs through a folder structure organized by submission numbers and eCTD sequence numbers	
Mercado	An integrated data warehouse with analytics tools that allows for flexible querying, reporting and analysis	
Portes	• Provides a library or location for new incoming datasets to be automatically loaded and data to be categorized by study and version • Once the new data sets are loaded, the review staff is notified and can access this data via any of the commercial off-the-shelf (COTS) tools used in CDER such as JMP, JReview, and MAED	
Analysis		
SAS Analysis Panels	SAS scripts developed to perform standard analyses for clinical reviewers and generate Excel outputs for use within the review	• Current implementation uses only CDISC STDM and ADaM data • Not currently available to review staff outside of the JumpStart service
Empirica Signal	Web-based tool used to provide a data-mining capability for detecting safety signals in adverse event postmarketing data	• Can use data in XLS, PDF, and Rich Text Format file types • Access requires registration by interested users • No formal training for users
Tableau	Enables the ability to create data visualizations with any data	• Can use data in XLS, PDF, and Rich Text Format file types • Not currently disseminated to all users • No formal training for users
JMP	Statistical software program that allows the reviewers to easily open data files (e.g., .xpt, .sas7bdat, .xls), view data, and perform analyses, and generate graphs	• Can use data in XLS, PDF, and Rich Text Format file types • Access requires registration by interested users • Formal training for users
JMP Clinical	Desktop application that offers data discovery, analysis and reporting for pre-clinical, clinical and post-market data	• Automatically generated standard outputs require standardized data • Standard analyses available based on clinical reviews • Not currently available to all review staff
MAED	Web-based review tool that performs a series of exploratory adverse event analyses on data from clinical trials and non-denominator databases (such as FAERS-type data)	• Can incorporate multiple data types and formats (e.g., standardized, non-standardized) • Standard analyses available based on clinical reviews • Assess requires registration by interested users • Formal training available for users

CAPABILITY	DESCRIPTION	CONSIDERATIONS PRIOR TO IMPLEMENTATION OF RWE REVIEW
JReview	Web-based review tool that allows users to tabulate, visualize, and analyze safety and efficacy data	• Can incorporate multiple data types and formats (e.g., standardized, non-standardized) • Standard analyses available based on clinical reviews • Formal training available for users

As previously noted, both CDER and CBER are in the process of developing RWE policy as well as their scientific positions regarding this type of data. As part of this effort, FDA has a number of internal and external working groups focused on RWE initiatives (see Table 3-16 for select examples). While internal working groups are focusing on FDA RWE strategy and internal Health IT projects, the BRIDG working group is an example of a collaboration focused on interoperability.

Table 3-16: Example internal and external RWE working groups

WORKING GROUP NAME	KEY MEMBERS	FOCUS AND INITIATIVES
CDER Health Information Technology (Health IT) Board	CDER staff, including representatives from the Office of Translational Sciences (OTS) and Office of Strategic Programs	Identify and prioritize CDER Health IT projects
RWE Working Group	CDER staff, including representatives from Office of the Center Director, OTS, and OND	RWE strategy for CDER
HL7 Biomedical Research and Integrated Domain Group (BRIDG)	• FDA • CDISC • HL7 Regulated Clinical Research Information Management Technical Committee (RCRIM) Work Group • National Cancer Institute (NCI)	Collaborative working group to develop a model that supports interoperability among different data systems and data types (e.g. CDISC data standards)

As FDA continues to prepare for large-scale receipt of RWE, the Agency will be able to build upon current technical capabilities and utilize current working groups to develop data strategy policies.

4. RECOMMENDATIONS

ACTIONS TO IMPROVE

The impact assessment of FDA's implementation of electronic submissions and data standards revealed several potential areas of improvement. Based on these findings, we identified 12 potential actions to improve the FDA electronic submission and review environment.

As sponsors continue to increase their submission of applications with data standards and the FDA adapts to the evolving regulatory data landscape, future areas of improvement and growth focus on maximizing the gains from data standards implementation and developing a strategy for new sources of data. As standards and the review tools used to analyze the data continue to advance, FDA must adapt its approach to accepting, tracking, and reviewing submissions with data standards. To stay ahead of this change, the FDA has the opportunity to innovate and streamline an approach to training and submissions review to meet and exceed the needs of the dedicated review staff.

The following recommended actions for improvement focus on areas where FDA can make meaningful change to support staff, streamline and enrich processes, and enhance technology for the current and future challenges and opportunities associated with the review of electronic data. (Table 4-1).

Table 4-1: Recommended improvement actions

RECOMMENDATION AREA	KEY FINDINGS	ACTIONS TO IMPROVE
People	• Staff could benefit from an integrated training approach based on feedback associated with timing of courses and linking training content to review work (Section 3.3)	1. Reformat training around work products (e.g., NDA reviews) and provide additional guidance regarding tool output options for completing analyses
	• FDA is in the beginning stages of developing a data strategy for RWE and may need additional resources to support future initiatives (Section 3.5)	2. Based on decisions related to the incorporation and integration of RWE into the regulatory review process, evaluate the need to hire seasoned data scientists to develop and implement a comprehensive data strategy for step change growth in utility of regulatory data, including real-world data and evidence
Process	• Prior to the mandatory requirements for submissions with standardized study data, which took effect on December 17, 2016, CDER and CBER appeared to have different definitions for how to count and track submissions containing standardized data • Current parameters used to count and track standardized study data (i.e., submission contains at least one study with demographics (DM), exposure (EX), and disposition (DS) datasets, and a define.xml file) do not fully align to the published technical rejection criteria (Section 3.1)	3. To improve tracking of submissions with standardized study data, use a validation tool to automatically classify submissions based on the published technical rejection criteria and share the results with reviewers and sponsors, as appropriate
	• Even though submissions pass the technical rejection criteria, they may not have all of the information needed by reviewers to perform their review (Section 3.2)	4. Expand standardized study data technical rejection criteria to include domains that are the most impactful for reviewers and consider long-term approach of implementing the data validation tool upstream so that applications do not enter data systems unless they pass all required checks
	• The vast majority of research INDs are still submitted in paper format, which limits the ability to fully incorporate these submissions into the electronic review environment • The requirement for submitting INDs electronically, which occurs on May 5, 2018, excludes noncommercial INDs (Section 3.1)	5. Evaluate opportunities to make it easier for research IND sponsors to submit electronically

RECOMMENDATION AREA	KEY FINDINGS	ACTIONS TO IMPROVE
Process	• The standards completeness analysis performed for this assessment identified key domains and tool outputs critical for application review analyses • As the standards continue to evolve, FDA will need to continually understand the impact on reviewers and opportunities for improvement (Section 3.1)	6. Conduct a more in-depth analysis of domains, variables, and tool outputs, to build upon the mappings completed for this assessment, including by specific therapeutic areas
	• Oncology reviewers described a pilot for a unified review that integrated all discipline review into a single document • During focus groups sessions, reviewers indicated a need for a more streamlined and less redundant review (Section 3.4)	7. Expand unified review to all CDER divisions to reduce redundancy in reviews
	• FDA may have to adapt review tools based on updated standards • Based on review analyses and tool output mapping, FDA could expand use of recently added domains to enhance outputs (Section 3.2)	8. Request SDOs submit test datasets for updated study data standards (e.g., SDTM) and implementation guides to ensure continued stability and output generation of existing tools
	• OCS and OBI evaluate their training offerings differently (Section 3.3)	9. Implement a consistent approach for evaluating training between Office of Computation Science (OCS) and Office of Business Informatics (OBI) to improve identification of best practices and potential areas for improvement
Technology	• Reviewers have difficulty locating similar submissions (Section 3.4)	10. Make it easier for reviewers to link similar submissions (e.g., with similar indications or mechanisms of action)
	• Reviewers would like increased submission search capabilities (Section 3.4)	11. Consider development of search capabilities where reviewers can search across and within a submission
	• Some review tools perform similar functions • Each review tool requires resources (e.g., training instructors) to maintain and support users (Section 3.3)	12. Identify output redundancies to determine if maintenance of multiple tools is required

The following sections provide additional details to the recommended actions summarized in the table above.

4.1 People

1. Reformat training around work products (e.g., NDA reviews) and provide additional guidance regarding tool output options for completing analyses. To realize the gains from increased submission of standardized data, the CDER and CBER workforce must be trained to utilize the available analysis tools effectively and efficiently. While reviewers generally had positive feedback about the distinct training courses, they raised concerns about the timing of the course along with the ability to immediately apply the knowledge gained to their work and the ability to link useful tools and outputs to specific analyses required for their review. To this end, FDA should consider redesigning their training around specific work products (e.g., an NDA/BLA review). Based on reviewer feedback, the training course should follow the process used for completing a review. For example, in the beginning of a course

focused on NDA/BLA/efficacy supplement clinical reviews, the training would teach the reviewers about data standards. Then, it would go through the applicable review sections and show the reviewer how to use different tools and what outputs are available for each section. Throughout the assessment, reviewers consistently mentioned challenges associated with lag time between taking a course and having a submission where they could use the tool. Therefore, the training should be modularized based on the review process so that reviewers can easily refer back to the material. If resources permit, the FDA should develop online, interactive, and module-based training for on-demand use by reviewers.

2. Based on decisions related to the incorporation and integration of RWE into the regulatory review process, evaluate the need to hire seasoned data scientists to develop and implement a comprehensive data strategy for step change growth in utility of regulatory data, including real-world data and evidence. Depending on outcomes of current policy and scientific efforts around RWE, FDA should consider hiring a team of seasoned data scientists to develop and implement a comprehensive data strategy for existing and planned data efforts. Additionally, these data scientists would be able to assess and implement analytic capabilities for disparate data, including RWE, and ensure a comprehensive infrastructure is in place to meet the needs of the rapidly changing review environment. This team could also drive step change growth in the ingestion, management, and analysis of regulatory data, including clinical information related to real-world data and evidence.

4.2 Processes

3. To improve tracking of submissions with standardized study data, use a validation tool to automatically classify submissions based on the published technical rejection criteria and share the results with reviewers and sponsors, as appropriate. FDA should also consider certain process improvements that could enhance reviewer experiences with electronic submissions and data standardized study data. Prior to the mandatory requirements for submissions with standardized study data, which took effect on December 17, 2016, CDER and CBER appeared to have different definitions for counting and tracking submissions containing standardized data. The parameters currently used to count and track submissions with standardized data do not fully align to the published technical rejection criteria. Since CDER and CBER collaboratively developed the technical rejection criteria for submissions with standardized data, the Centers should use these criteria moving forward to classify submissions. Additionally, they should use a validation tool at the initial receipt of a submission to automatically classify the study data based on these defined parameters. Beyond the classification of submissions using the technical rejection criteria, the tool should provide meaningful results to reviewers related to the data fitness of the submission by identifying the ability to generate specific review tool outputs based on the submitted data. The validation tool should organize these results using the application number, receipt date, and, if applicable, the supplement number. The FDA should consider methods for communicating the validation results with sponsors to establish a feedback loop for continuous improvement. Finally, this information should also be available to all reviewers so they can understand the data fitness of the submissions they need to review.

4. Expand standardized study data technical rejection criteria to include domains that are the most impactful for reviewers and consider long-term approach of implementing the data validation tool upstream so that applications do not enter data systems unless they pass all required checks. FDA should also consider expanding the technical rejection criteria to include domains that are the most impactful for reviewers. For example, based on our analysis, they should consider including DM, DS, EX, EC, trial summary, AE, LB, EG, and define.xml for the SDTM standard. The FDA should make it possible for sponsors to waive these requirements depending on the characteristics of their studies. For example, if the applicant submits studies that might not have all of these domains (e.g., extension study, safety update), then this information should be captured in the define.xml so they can be excluded from the validation check. As part of the long-term strategy, FDA should consider implementing the data validation tool upstream and not allow an applicant to submit an application unless they pass all the checks or have the proper waivers in place.

5. Evaluate opportunities to make it easier for research IND sponsors to submit electronically. Booz Allen determined that although most commercial INDs are now submitted electronically, the vast majority of research INDs (which represent the most of INDs submitted overall) are still submitted in paper format. The FDA should identify an approach for facilitating or assisting research sponsors (e.g., using a tool that helps research sponsors compile an electronic IND, conduct webinars, develop guidances) to submit electronically. While the amount of data is generally much less compared to a commercial IND, the overall burden on the system (e.g., manual processing and data input required for paper submissions) could be significant and automatic ingestion of these submission types could introduce efficiencies, reduce costs, and improve review experiences.

6. Conduct a more in-depth analysis of domains, variables, and tool outputs, to build upon the mappings completed for this assessment, including by specific therapeutic areas. Booz Allen was able to identify potential areas for improvement based on the SDTM and SEND analyses at the variable level with JReview, MAED, and SAS Analysis Panel Updates. FDA should continue to build upon the analysis conducted for this assessment to identify additional opportunities for improvement for reviewers. The Agency should conduct a more in-depth analysis of domains, specific variables, and tool outputs from additional tools. To be comprehensive, this in-depth analysis should focus on specific therapeutic areas since the types of analyses/outputs may vary. Additionally, the analysis should be expanded to include Therapeutic Area Standards as they are implemented at CDER and CBER.

7. Expand unified review to all CDER divisions to reduce redundancy in reviews. Based on the feedback and interest from reviewers regarding the unified review, FDA should consider expanding the pilot to other CDER review divisions. This type of review has the opportunity to reduce the redundancies currently experienced by reviewers. Additionally, a new review template designed for the unified review should provide suggestions for resources, tools, and outputs, as detailed in the current version of the CRTAR. If implemented, the new template should be incorporated into the recommended work product training redesign to put forth a comprehensive approach for application review.

8. Request SDOs submit test datasets for updated study data standards (e.g., SDTM, SEND, ADaM) and implementation guides to ensure continued stability and output generation of existing tools. Even though FDA closely collaborates with SDOs to continuously improve standards, FDA does not know the full extent to which changes to the standard will affect their reviewers and use of review tools. One way to facilitate reviewers' transition to new standards would be to require SDOs to submit test datasets for updated standards. With these test datasets, FDA could begin to make necessary adjustments to analysis tools before reviewers receive submissions conforming to updated standards. Additionally, tool outputs could be developed or enhanced using recently added domains.

9. Implement a consistent approach for evaluating training between OCS and OBI to improve identification of best practices and potential areas for improvement. In addition to the proposed changes related to the processes FDA uses to receive submission data, the FDA should consider making some adjustments to data collection related to training feedback. Currently, OCS and OBI training evaluation surveys contain different questions to measure participant reactions to and satisfaction with recently completed training courses. Consistent evaluations across Centers will allow for a more meaningful assessment of training best practices and areas for improvement. Additionally, to more fully understand the effectiveness of current training, FDA should consider modifying their current training evaluations to collect data that assesses transfer of knowledge, skills, and/or attitude after completing training, based on performance in the participants' work environment (i.e., Kirkpatrick Level 3 – Behavior).

4.3 Technology

10. Make it easier for reviewers to link similar submissions (e.g., with similar indications or mechanisms of action). FDA should consider additional improvements to their technology capabilities to support reviewers. For instance, based on focus group feedback, FDA may consider making it easier for reviewers to link similar submissions. Applications with similar indications, mechanisms of action, and active moieties can provide reviewers insight into potential review considerations as well as improve consistency across reviews.

11. Consider development of search capabilities where reviewers can search across and within a submission. Focus group participants, as well as some survey respondents, believed one improvement to see increased gains from an electronic submissions and data standards environment was to improve the search functionality both within and across submissions. FDA should consider expanding and modifying their search functions with input from reviewers. This modification could lead to a more effective review.

12. Identify output redundancies to determine if maintenance of multiple tools is required. In addition to making improvements to existing capabilities, FDA should analyze their current review tools for output redundancies. Training for and maintenance of tools is resource intensive, and FDA should consider consolidating redundant tools (e.g., JReview and JMP Clinical appear to have similar purposes). FDA will need to investigate reviewer preferences for each potentially redundant tool to retain superior analysis features after consolidation. Fewer tool outputs options may also provide a more streamlined approach for the new review template and the work product training recommended above.

5. APPENDICES

The sections below include additional information and analyses to support the assessment findings and recommendations.

5.1 Appendix A: Glossary

Table 5-1 includes a glossary of terms used in this assessment.

Table 5-1: Glossary of terms

TERM	DEFINITION
ADaM	Analysis data model
ADME	Absorption, Distribution, Metabolism, Excretion
ADSL	Subject level analysis dataset
AE	Adverse event
ANDA	Abbreviated new drug application
API	Application programming interface
BG	Body Weight Gain
BIRAMS	Biologics Investigational and Related Applications Management System
BLA	Biologics license application
BRIDG	HL7 Biomedical Research and Integrated Domain Group
BW	Body Weight
BYONDA	Bring your own NDA
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDISC	Clinical data interchange standards consortium
CFAST	Coalition For Accelerating Standards and Therapies
CISST	Clinical investigator site selection tool
CL	Clinical Observations
CM	Concomitant and Prior Medications
COTS	Commercial-off-the-shelf
CRF	Case report form
CRT	Clinical review template
CRTAR	Clinical review template analysis references
CV	Cardiovascular
DAAAP	Division of Anesthesia, Analgesia, and Addiction (CDER)
DAIP	Division of Anti-Infective Products (CDER)

TERM	DEFINITION
DARRTS	Document Archiving, Reporting & Regulatory Tracking System
DASH	Data and Specimen Hub
DAVP	Division of Anti-Viral Products (CDER)
dbGaP	Database of genotypes and phenotypes
DBPAP	Division of Bacterial, Parasitic, and Allergenic Products (CBER)
DBRUP	Division of Bone, Reproductive and Urologic Products (CDER)
DCEPT	Division of Clinical Evaluation and Pharmacology/Toxicology (CBER)
DCGT	Division of Cellular and Gene Therapies (CBER)
DCRP	Division of Cardiovascular and Renal Products (CDER)
DD	Death Details
DDDP	Division of Dermatology and Dental Products (CDER)
DGIEP	Division of Gastroenterology and Inborn Error Products (CDER)
DH	Division of Hematology (CBER)
DHCR	Division of Hematology and Clinical Review (CBER)
DHOT	Division of Hematology, Oncology, Toxicology (CDER)
DHP	Division of Hematology Products (CDER)
DHRR	Division of Hematology Research and Review (CBER)
DM	Demographics
DMEP	Division of Metabolism and Endocrinology Products (CDER)
DMIP	Division of Medical Imaging Products (CDER)
DNCE	Division of Nonprescription Clinical Evaluation (CDER)
DNDP	Division of Nonprescription Drug Products (CDER)
DNP	Division of Neurology Products (CDER)
DNRD	Division of Nonprescription Regulation and Development (CDER)
DOP1	Division of Oncology Products (1) (CDER)
DOP2	Division of Oncology Products (2) (CDER)
DPARP	Division of Pulmonary Allergy and Rheumatology (CDER)
DPMH	Division of Pediatric and Maternal Health (CDER)
DPP	Division of Psychiatry Products (CDER)
DPT	Data preparation tool
DRPM	Division of Regulatory Project Management (CBER)
DRT	Discipline review template
DS	Disposition
DSAB	Data Standards Advisory Board
DSPB	Data Standards Program Board

TERM	DEFINITION
DTOP	Division of Transplant and Ophthalmology Products (CDER)
DV	Protocol Deviations
DVP	Division of Viral Products Applications (CBER)
DVRPA	Division of Vaccines and Related Products (CBER)
EC	Exposure as Collected
ECG	Electrocardiograms
eCTD	Electronic common technical document
EDM	Event data management
EDR	Electronic document review
EG	ECG Test Results
ESRE	Electronic submissions review environment
EOP	End-of-phase
EX	Exposure
FA	Findings About
FAERS	FDA adverse event reporting system
FDA	Food and Drug Administration
FW	Food and Water Consumption
FY	Fiscal year
GPP	Graphical Patient Profile
ICH E2B	International Conference on Harmonization standard for transmission of electronic individual case safety reports
ICSR	Individual case safety reports
IG	Implementation Guide
IHTSDO	International health terminology
IND	Investigational new drug
IR	Information request
IS	Immunogenicity Specimen Assessments
IT	Information technology
LB	Laboratory Test Results
LOINC	Logical Observation Identifiers Names and Codes
MA	Macroscopic Finding
MAED	MedDRA-Based Adverse Event Diagnostics
MB	Microbiology Specimen
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
MI	Microscopic Findings

TERM	DEFINITION
MO	Morphology
MS	Microbiology Susceptibility Test
MSSO	Maintenance and support services organization
NCI	National cancer institute
NDA	New drug application
NDF-RT	National Drug File – Reference Terminology
NICHD	National Institute of Child Health and Human Development
NIH	National institutes of health
NME	New molecular entity
OBE	Office of Biostatistics and Epidemiology (CBER)
OBI	Office of Business Informatics (CDER)
OBRR	Office of Blood Research and Review (CBER)
OC	Office of Compliance or Office of Communications (CDER)
OCBQ	Office of Compliance and Biologics Quality (CBER)
OCD	Office of the Center Director (CDER)
OCOD	Office of Communication, Outreach and Development (CBER)
OCS	Office of Computational Science (CDER)
OGD	Office of Generic Drugs (CDER)
OM	Office of Management (CBER)
OM	Organ Measurement
OMP	Office of Medical Policy (CDER)
OND	Office of New Drugs (CDER)
OPQ	Office of Pharmaceutical Quality (CDER)
OPTICS	Open Translational Science in Schizophrenia
ORP	Office of Regulatory Policy (CDER)
OSE	Office of Surveillance and Epidemiology (CDER)
OSP	Office of Strategic Programs (CDER)
OSP	Office of strategic planning
OTAT	Office of Tissues and Advanced Therapies (CBER)
OTS	Office of Translational Science (CDER)
OVRR	Office of Vaccines Research and Review (CBER)
PADER	Periodic Adverse Drug Experience Reports
PAER	Periodic Adverse Experience Reports
PAG	Program advisory group
PBRER	Periodic Benefit-Risk Evaluation Report

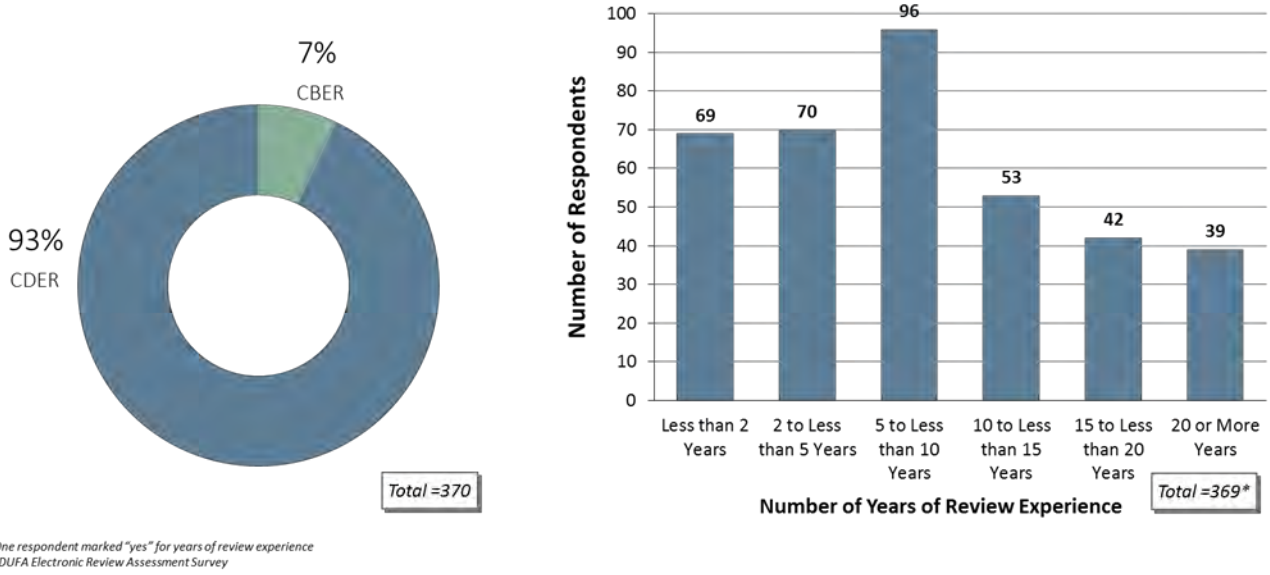
TERM	DEFINITION
PC	Pharmacokinetics Concentrations
PDUFA	Prescription Drug User Fee Act
PE	Physical Examination
PhUSE	Pharmaceutical Users Software Exchange
PI	Principal investigator
PK	Pharmacokinetics
PM	Palpable Masses
POOLDEF	Pool definition
PP	Pharmacokinetics Parameters
PR	Procedure
PSUR	Periodic Safety Update Reports
QS	Questionnaires
RE	Respiratory
RMS-BLA	Regulatory Management System- Biologics license application
RP	Reproductive System Findings
RS	Disease Response
RTF	Refuse-to-file
RWE	Real world evidence
SAE	Serious adverse events
SAS	Statistical analysis software
SC	Subject Characteristics
SDO	Standards developing organization
SDRG	Study data reviewer's guide
SDTM	Study data tabulation model
SE	Subject Elements
SEND	Standard for exchange of non-clinical data
SME	Subject matter expert
SMQ	Standardized MedDRA query
SNOMED CT	Systematized Nomenclature of Medicine – Clinical Terms
SOC	System organ class
SS	Subject Status
SU	Substance Use
SUPPMA	Supplemental qualifiers macroscopic findings
SUPPMI	Supplemental qualifiers microscopic findings
SV	Subject Visits

TERM	DEFINITION
TA	Trial arm
TAG	Technical advisory group
TD	Trial Disease Assessments
TE	Trial elements
TEAS	Treatment emergent adverse events and adverse reactions
TF	Tumor Findings
TR	Tumor Response
TS	Trial summary
TU	Tumor Identification
TX	Trial sets
VS	Vital Signs
WHO	World Health Organization
WHO DD	WHO Drug Dictionary

5.2 Appendix B: Survey Respondents

This section contains additional demographic information for survey respondents.

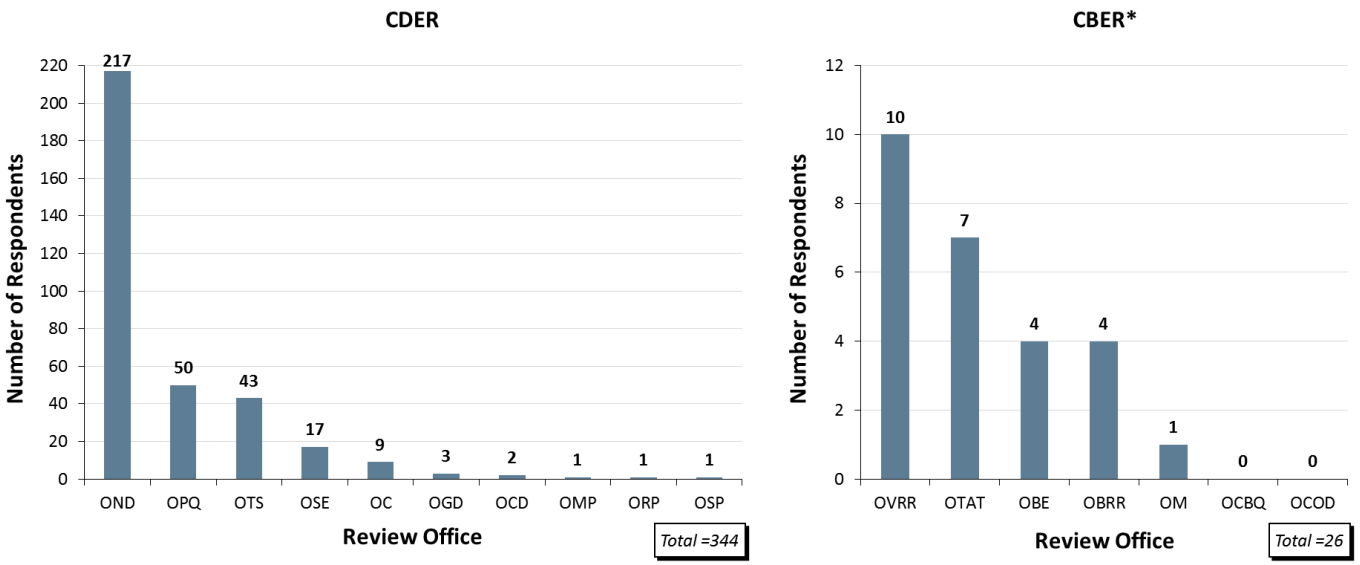
Staff from CDER and CBER offices, selected by the FDA TAG, received the survey. More than 90% of respondents were aligned to CDER (Figure 5 1). Approximately 38% (139/369) of survey respondents had less than five years of experience.



*Notes: *One respondent marked "yes" for years of review experience*
Source: PDUFA Electronic Review Assessment Survey

Figure 5-1: Survey respondents by Center and years of experience

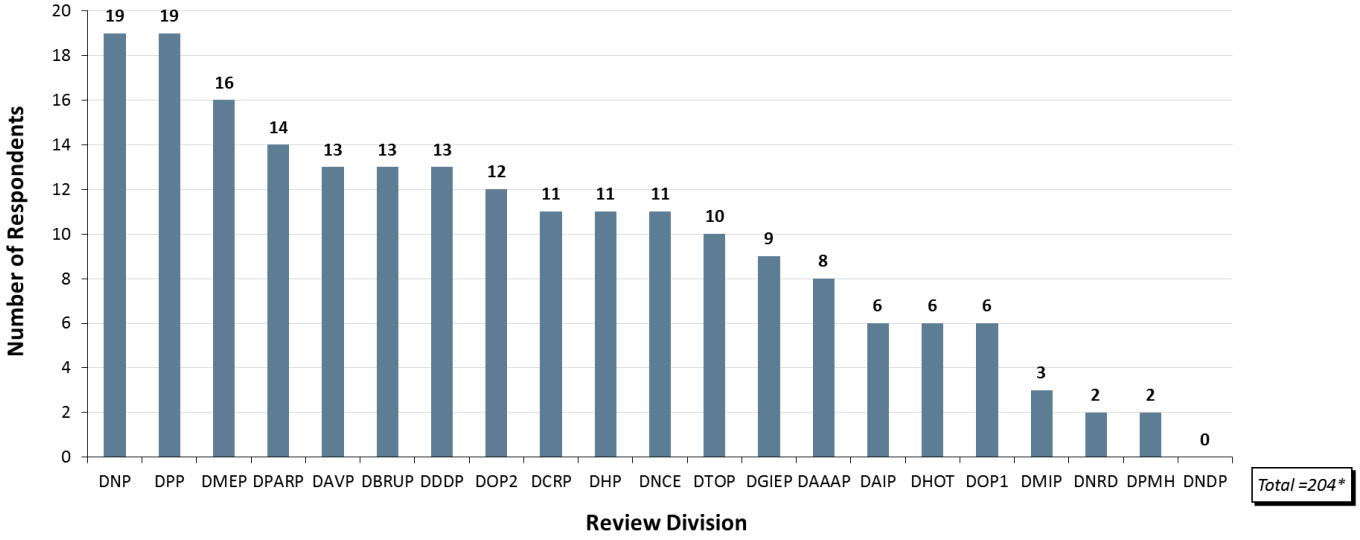
The majority of CDER respondents (63%, 217/344) aligned to the OND (Figure 5-2). Most CBER respondents aligned to the Office of Vaccines Research and Review (OVRR) (38%, 10/26) and Office of Tissues and Advanced Therapies (OTAT) (27%, 7/26).



*Notes: *The PDUFA Electronic Review Assessment Survey was only sent to select CBER offices*
Source: PDUFA Electronic Review Assessment Survey

Figure 5-2: Survey respondents by Center and office

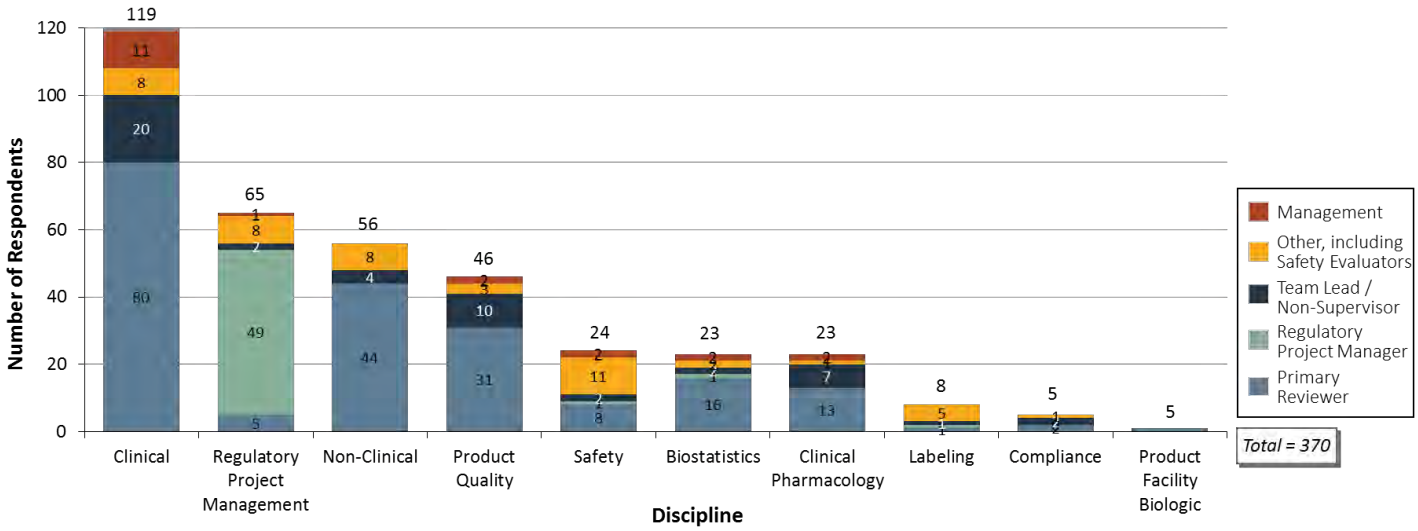
There were respondents for all selected divisions, except for the Division of Nonprescription Drug Products (DNDP) (Figure 5-3).



*Notes: *13 respondents from OND did not select a review and designated one of the following offices or groups: OND Immediate Office, Therapeutics Biologics and Biosimilars Staff, Office of Antimicrobial Products, and Office of Drug Evaluation IV*
Source: PDUFA Electronic Review Assessment Survey

Figure 5-3: Survey respondents in OND by review division

The majority of respondents were primary reviewers (54%, 201/370) (Figure 5-4).



Source: PDUFA Electronic Review Assessment Survey

Figure 5-4: Survey respondents by discipline and role

Booz Allen designed and distributed the PDUFA Electronic Review Assessment Survey to capture data from a variety of disciplines, roles, and length of review experience. A large portion of survey respondents classified themselves as primary clinical reviewers, a key demographic for assessing the impact of electronic submissions and standardized data have on the review process.

5.3 Appendix C: Clinical Review Sections and Analyses Mapped to SDTM Standard and Tool Outputs

Table 5-2 provides a mapping of sections in the clinical review and standard analyses to SDTM domains and tool outputs.

Table 5-2: Clinical review sections and analyses mapped to SDTM standard and tool outputs

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
6.1.2	Study Results – Compliance with Good Clinical Practices	No standard analyses	Not applicable		
	Study Results – Financial Disclosure	No standard analyses	Not applicable		
	Study Results	Patient Disposition	DM, DS, EX	JReview • Box Whiskers Plot Time to DS Events by Arm Page by Event • Time to <DS Event> by Arm	SAS Analysis Panel - Disposition • Disposition Event by Arm for All Subjects • Disposition Event by Arm for Exposed Subjects • Time to Disposition Event for All Subjects • Time to Disposition Event for Exposed Subjects SAS Analysis Panel – Demographics • Age Groups by Disposition • Sex by Disposition • Race by Disposition • Ethnicity by Disposition • Country by Disposition • Site ID by Disposition

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
6.1.2 cont.	Study Results cont.	Protocol Violations / Deviations	DM, DS	JReview • Dropouts Disposition Event Standard Terms • Dropouts: Disposition Events Standard Terms 2D Bar Chart • Dropouts: Relative Frequency DS Events • Dropouts Disposition Event <Standard Terms> • Box Whiskers Plot Time to DS Events by Arm Page By Event • Time to <DS Events> by Arm	SAS Analysis Panel - Demographics • Age Groups by Disposition • Sex by Disposition • Race by Disposition • Ethnicity by Disposition • Country by Disposition • Site ID by Disposition
			DV	None	None
		Table of Demographic Characteristics	DM, DS	None	SAS Analysis Panel – Demographics • Overview • Age Groups • Age Groups by Disposition • Age Stats • Sex • Sex by Disposition • Race • Race by Disposition • Ethnicity • Ethnicity by Disposition • Country • Country by Disposition • Site ID • Site ID by Disposition • Country and Site ID
	Study Results - Baseline entry criteria (e.g., duration, stage, and severity of disease)	No standard analyses	Not applicable		

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
6.1.2 cont.	Study Results – Other Baseline Patient Characteristics	No standard analyses	Not applicable		
	Study Results	Comorbid Conditions	DM, MH	None	None
		Concomitant Treatments	CM, DM, DS	JReview • Graphical Patient Profile (GPP)	None
	Study Results - Baseline laboratory measurements not part of entry criteria	No standard analyses	Not applicable		
	Study Results	Treatment compliance	TD, TS	None	None
		Concomitant medications	CM, DM, DS	JReview • GPP	None
		Rescue medications	CM, DM	JReview • GPP	None
	Study Results – Efficacy Results - Primary Endpoints	• Analysis of success on the primary endpoint • Effects in demographic subpopulations • Effects in other subgroups • Time-related effects • Distribution of effect size • Analysis by population • Handling missing data • Analysis by site • Potential confounding factors or identified associations • Time of enrollment • Considerations for composite endpoints	Analyses vary by therapeutic area or pharmacological class		

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
6.1.2 cont.	Study Results – Data Quality and Integrity – Reviewers' Assessment	Refer to analyses for Efficacy Results - Primary Endpoints with site exclusions			
	Study Results – Secondary and Other Endpoints	• Analysis of success on the primary endpoint • Effects in demographic subpopulations • Effects in other subgroups • Time-related effects • Distribution of effect size • Analysis by population • Handling missing data • Analysis by site • Potential confounding factors or identified associations • Time of enrollment • Considerations for composite endpoints	Analyses vary by therapeutic area or pharmacological class		
	Study Results	Dose / Dose-Response	DM, DS, EC, EX, PC, PR	None	None
		Durability of Response	DM, DS, EC, EX, RS	None	None
		Persistence of Effect	DM, DS, EC, EX, RS	None	None
	Study Results – Additional Analyses Conducted on the Individual Trial	No standard analyses	Not applicable		

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
7.1.1	Study Results – Primary Endpoints	• Analysis of success on the primary endpoint • Effects in demographic subpopulations • Effects in other subgroups • Time-related effects • Distribution of effect size • Analysis by population • Handling missing data • Analysis by site • Potential confounding factors or identified associations • Time of enrollment • Considerations for composite endpoints	Analyses vary by therapeutic area or pharmacological class		
7.1.2	Study Results – Secondary and Other Endpoints	Analysis of success on the secondary or other endpoint	Analyses vary by therapeutic area or pharmacological class		
7.1.3	Subpopulations	• Analysis by major demographic factors (e.g., age, sex, and race/ethnicity) • Analysis by predefined or relevant characteristics (e.g., disease severity, non-responders to existing treatments, treatment-naïve, concomitant illnesses, concomitant drugs, body weight, renal or hepatic function) • Pooled Analyses	CM, DD, DM, DS, EC, EG, EX, FA, IS, LB, MB, MI, MO, MS, PE, PR, QS, RP, RS, SC, SE, SS, SU, SV, TR, TU, VS	None	None
7.1.4	Dose and Dose-Response	Dose and Dose-Response	DM, DS, EC, EX, PC, PR	None	None

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
7.1.5	Onset, Duration, and Durability of Efficacy Effects	• Time to onset of treatment effect • Persistence of clinical efficacy with continuous treatment • Persistence of clinical benefit after the treatment has been stopped or withheld	DM, DS, EC, EX, RS	None	None
7.2.1	Considerations on Benefit in the Postmarket Setting	No standard analyses	Not applicable		
7.2.2	Other Relevant Benefits	No standard analyses	Not applicable		
7.3	Integrated Assessment of Effectiveness	Not a standard analysis - based on findings from previous sections specific to the endpoints	Analyses vary by therapeutic area or pharmacological class		
8.1	Safety Review Approach	No standard analyses	Not applicable		
8.2.1	Overall Exposure	Safety Population, Size, and Denominators	DM, DS	JReview • Dropouts Disposition Event Standard Terms • Dropouts: Disposition Events Standard Terms 2D Bar Chart • Dropouts: Relative Frequency DS Events • Dropouts Disposition Event <Standard Terms> • Box Whiskers Plot Time to DS Events by Arm Page By Event • Time to <DS Events> by Arm	SAS Analysis Panel – Demographics • Overview

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.2.1 cont.	Overall Exposure cont.	Safety Population, Size, and Denominators cont.	DM, DS, EX	None	SAS Analysis Panel – Disposition • Disposition Event by Arm for All Subjects • Disposition Event by Arm for Exposed Subjects
			EC	None	None
		Duration of exposure[35]	DM, DS, EC, EX	None	SAS Analysis Panel – Disposition • Time to Disposition Event for All Subjects • Time to Disposition Event for Exposed Subjects
			EC	None	None
8.2.2	Relevant Characteristics of the Safety Population	Demographic and Baseline Disease Characteristics for Safety Population	Refer to Study Results Domains for Section 6		
		• Severity of illness/disease • Concomitant illness • Use of relevant concomitant medications	CM, DM, MH	None	None

[35]The following outputs are not currently used for the JumpStart service, but do exist: SAS Analysis Panel – Exposure: Planned arm vs actual treatment and Dose changes during study

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.2.2 cont.	Relevant Characteristics of the Safety Population cont.	BMI / weight	DM, VS	JReview • Vital Signs Baseline Values Box Whiskers Plot • DBP vs SBP Plot with Normal Range Grid • DBP Baseline vs Max Value Scatter Plot • SBP Baseline vs Max Value Scatter Plot • Heart Rate Baseline vs Max Value Scatter Plot • DBP Baseline vs Min Value Scatter Plot • SBP Baseline vs Min Value Scatter Plot • Heart Rate Baseline vs Min Value Scatter Plot • Vitals Max Change from Baseline Page By Test by Actual Treatment • Vitals Max Percent Change from Baseline Page By Test by Actual Treatment • Vitals Min Change from Baseline Page By Test by Actual Treatment • Vitals Min Percent Change from Baseline Page By Test by Actual Treatment • Diastolic BP greater than 90 by Actual Arm • Systolic BP greater than 140 by Actual Arm	None
		Renal dysfunction	LB	None	None

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.2.2 cont.	Relevant Characteristics of the Safety Population cont.	Hepatic dysfunction	DM, LB	JReview • Liver Function BL Box Whisker by Actual Trt • Liver Tests Baseline vs Max Value Scatter Plot by ARM • Liver Tests Baseline vs Min Value Scatter Plot by ARM • Liver Tests Mean Line Summary vs VisitNumber Plot by ARM • Liver Tests Box Whiskers Plot vs VisitNum by ARM • Liver Testst Max Chg from Baseline • Liver Tests Min Chg from Baseline • Liver Tests Max Percent Change from Baseline • Min Percent Change from Baseline • Liver Tests Mean + Std Dev vs Visitnum by Arm • Hy's Law Plots: ALT/BILI/ALP • Hy's Law Plots: AST/BILI/ALP • Hy's Law Plots: ALT/BILI • Hy's Law Plots: AST/BILI • Hy's Law Patient Listing • ALP Shift from Baseline • ALT Shift from Baseline • AST Shift from Baseline • BILI Shift from Baseline • Hy's Law Table	SAS Analysis Panel - Liver Lab • Liver lab tests greater than upper limit of normal • Possible Hy's law cases • Max Post baseline lab test vs baseline lab tests • Maximum AST and ALT vs Maximum TB Lab Test Results per Subject Charts • Maximum Lab Test Results per Subject by Study Day • Subject with post-baseline lab tests who were missing baseline lab tests • Subjects with no post-baseline lab tests who had baseline lab tests • Subjects with no lab tests • Lab tests missing upper limit of normal • ALP lab tests missing lower limit of normal • Missing or zero lab test results • Visit Number Distribution
8.2.3	Adequacy of the Safety Database	No standard analyses	Not applicable		
8.3.2	Categorization of Adverse Events	Evaluation of coding of adverse events	AE	None	SAS Analysis Panel • MedDRA at a Glance

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.3.3	Routine Clinical Tests	No standard analyses	Not applicable		
8.4.1	Deaths	Number of deaths and identification of subjects	AE, CM, DM, LB	JReview • GPP to Review Deaths	None
			DD	None	None
8.4.2	Serious Adverse Events (SAEs)	• Table of SAEs categorized by MedDRA hierarchy • Overall rate of SAEs • Rate of specific SAEs for each treatment group • Number of SAEs in critical subgroups • Rate of SAEs by dose	AE, DM	JReview • SAE Incident Percent Rate by Preferred Term vs ARM • SAE Incident Percent Rate by SOC vs ARM • SAE Percentage Rates by Arm for Specified SOC MAED • SAE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • SAE SMQ analysis (broad, algorithmic, narrow)	SAS Analysis Panel • MedDRA at a Glance SAS Analysis Panel - AE Toxicity • Toxicity Grade Summary • PT Analysis by Tox Grade • Two term MedDRA Analysis SAS Analysis Panel - AE Severity • SAEs by ARM • SAEs by Severity
8.4.3	Dropouts and/or Discontinuations Due to Adverse Events	Discontinuations	DM, DS	JReview • Dropouts Disposition Event Standard Terms • Dropouts: Disposition Events Standard Terms 2D Bar Chart • Dropouts: Relative Frequency DS Events • Dropouts Disposition Event <Standard Terms> • Box Whiskers Plot Time to DS Events by Arm Page By Event • Time to <DS Events> by Arm	SAS Analysis Panel – Demographics • Age Groups by Disposition • Sex by Disposition • Race by Disposition • Ethnicity by Disposition • Country by Disposition • Site ID by Disposition

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.4.4	Significant Adverse Events	Overall rate of significant AEs	AE, DM, EX	JReview • SAE Incident Percent Rate by Preferred Term vs ARM • SAE Incident Percent Rate by SOC vs ARM • SAE Percentage Rates by Arm for Specified SOC MAED • SAE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • SAE SMQ analysis (broad, algorithmic, narrow)	SAS Analysis Panel • MedDRA at a Glance SAS Analysis Panel - AE Toxicity • Toxicity Grade Summary • PT Analysis by Tox Grade • Two term MedDRA Analysis SAS Analysis Panel - AE Severity • SAEs by ARM • SAEs by Severity

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.4.5	Treatment Emergent Adverse Events (TEAEs) and Adverse Reactions	TEAEs	AE, DM, EX	JReview • SAE Incident Percent Rate by Preferred Term vs ARM • SAE Incident Percent Rate by SOC vs ARM • SAE Percentage Rates by Arm for Specified SOC • AE Incident Rates by Arm • AE SOC Rates by Arm Descending sort on Totals • AE Coding Tables • AE Coding Table by Body System or Organ Class MAED • SAE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • SAE SMQ analysis (broad, algorithmic, narrow) • AE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • AE SMQ analysis (broad, algorithmic, narrow)	SAS Analysis Panel • MedDRA at a Glance SAS Analysis Panel - AE Toxicity • Toxicity Grade Summary • PT Analysis by Tox Grade • Two term MedDRA Analysis SAS Analysis Panel - AE Severity • SAEs by ARM • SAEs by Severity • AEs by ARM • AEs by Severity

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.4.6	Laboratory Findings	Clinical laboratory abnormalities	DM, LB	JReview • Liver Function BL Box Whisker by Actual Trt • Liver Tests Baseline vs Max Value Scatter Plot by ARM • Liver Tests Baseline vs Min Value Scatter Plot by ARM • Liver Tests Mean Line Summary vs VisitNumber Plot by ARM • Liver Tests Box Whiskers Plot vs VisitNum by ARM • Liver Testst Max Chg from Baseline • Liver Tests Min Chg from Baseline • Liver Tests Max Percent Change from Baseline • Min Percent Change from Baseline • Liver Tests Mean + Std Dev vs Visitnum by Arm • ALP Shift from Baseline • ALT Shift from Baseline • AST Shift from Baseline • BILI Shift from Baseline	SAS Analysis Panel - Liver Lab • Liver lab tests greater than upper limit of normal • Max Post baseline lab test vs baseline lab tests • Maximum AST and ALT vs Maximum TB Lab Test Results per Subject Charts • Maximum Lab Test Results per Subject by Study Day • Subject with post-baseline lab tests who were missing baseline lab tests • Subjects with no post-baseline lab tests who had baseline lab tests • Subjects with no lab tests • Lab tests missing upper limit of normal • ALP lab tests missing lower limit of normal • Missing or zero lab test results • Visit Number Distribution
		Potential Hy's Law cases	DM, LB	JReview • Hy's Law Plots: ALT/BILI/ALP • Hy's Law Plots: AST/BILI/ALP • Hy's Law Plots: ALT/BILI • Hy's Law Plots: AST/BILI • Hy's Law Patient Listing • Hy's Law Table	None

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.4.7	Vital Signs	Analysis of vital sign measurements	DM, VS	JReview • Vital Signs Baseline Values Box Whiskers Plot • DBP vs SBP Plot with Normal Range Grid • DBP Baseline vs Max Value Scatter Plot • SBP Baseline vs Max Value Scatter Plot • Heart Rate Baseline vs Max Value Scatter Plot • DBP Baseline vs Min Value Scatter Plot • SBP Baseline vs Min Value Scatter Plot • Heart Rate Baseline vs Min Value Scatter Plot • Vitals Max Change from Baseline Page By Test by Actual Treatment • Vitals Max Percent Change from Baseline Page By Test by Actual Treatment • Vitals Min Change from Baseline Page By Test by Actual Treatment • Vitals Min Percent Change from Baseline Page By Test by Actual Treatment • Diastolic BP greater than 90 by Actual Arm • Systolic BP greater than 140 by Actual Arm	None
8.4.8	Electrocardiograms (ECGs)	ECG findings	EG	None	None
8.4.9	QT	QT finding	EG	None	None
8.4.10	Immunogenicity	Incidence of antibody formation	IS	None	None

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.4.10 cont.	Immunogenicity cont.	Consequences of antibody formation and potential for adverse events related to antibody formation	AE, IS	None	None
8.5	Analysis of Submission-Specific Safety Issues	No standard analyses (refer to previous safety sections for possible analyses that may be included)	Not applicable		
8.6	Safety Analyses by Demographic Subgroups	Safety information for demographic interactions (e.g., age, sex, racial and ethnic subgroups)	AE, DM	None	None
8.7	Specific Safety Studies/Clinical Trials	No standard analyses	Not applicable		
8.8.1	Human Carcinogenicity or Tumor Development	Treated as adverse events	AE, DM, EX	Refer to adverse event analyses	

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.8.2	Human Reproduction and Pregnancy	Number of non-serious and serious pregnancy events	AE, DS, DM	JReview • Dropouts Disposition Event Standard Terms • Dropouts: Disposition Events Standard Terms 2D Bar Chart • Dropouts: Relative Frequency DS Events • Dropouts Disposition Event <Standard Terms> • Box Whiskers Plot Time to DS Events by Arm Page By Event • Time to <DS Events> by Arm MAED • SAE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • SAE SMQ analysis (broad, algorithmic, narrow) • AE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • AE SMQ analysis (broad, algorithmic, narrow	SAS Analysis Panel • MedDRA at a Glance
8.8.3	Pediatrics and Assessment of Effects on Growth	Refer to analyses from previous sections with focus on pediatric populations			

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.8.4	Overdose, Drug Abuse Potential, Withdrawal, and Rebound	Overdose	AE, DM, DS, EX	JReview • SAE Incident Percent Rate by Preferred Term vs ARM • SAE Incident Percent Rate by SOC vs ARM • SAE Percentage Rates by Arm for Specified SOC • AE Incident Rates by Arm • AE SOC Rates by Arm Descending sort on Totals • AE Coding Tables • AE Coding Table by Body System or Organ Class MAED • SAE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • SAE SMQ analysis (broad, algorithmic, narrow) • AE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • AE SMQ analysis (broad, algorithmic, narrow)	SAS Analysis Panel • MedDRA at a Glance SAS Analysis Panel - AE Toxicity • Toxicity Grade Summary • PT Analysis by Tox Grade • Two term MedDRA Analysis SAS Analysis Panel - AE Severity • SAEs by ARM • SAEs by Severity • AEs by ARM • AEs by Severity
8.9.1	Safety Concerns Identified Through Postmarket Experience	No standard analyses	Not applicable		

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.9.2	Expectations on Safety in the Postmarket Setting	Any potential safety issues that could cause concern when considering how the drug may be used in the postmarket setting	AE, DM, DS, EX	JReview • SAE Incident Percent Rate by Preferred Term vs ARM • SAE Incident Percent Rate by SOC vs ARM • SAE Percentage Rates by Arm for Specified SOC • AE Incident Rates by Arm • AE SOC Rates by Arm Descending sort on Totals • AE Coding Tables • AE Coding Table by Body System or Organ Class MAED • SAE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • SAE SMQ analysis (broad, algorithmic, narrow) • AE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • AE SMQ analysis (broad, algorithmic, narrow)	SAS Analysis Panel • MedDRA at a Glance SAS Analysis Panel - AE Toxicity • Toxicity Grade Summary • PT Analysis by Tox Grade • Two term MedDRA Analysis SAS Analysis Panel - AE Severity • SAEs by ARM • SAEs by Severity • AEs by ARM • AEs by Severity
8.10	Additional Safety Issues From Other Disciplines	Not a standard analysis	Not applicable		

SECTION #	REVIEW SECTION	ANALYSES	DOMAIN AVAILABLE FOR ANALYSES	OUTPUTS FROM FULLY SUPPORTED TOOLS	ADDITIONAL JUMPSTART SERVICE OUTPUTS
8.11	Integrated Assessment of Safety	Based on findings from analyses in previous sections	AE, DM, DS, EX	JReview • SAE Incident Percent Rate by Preferred Term vs ARM • SAE Incident Percent Rate by SOC vs ARM • SAE Percentage Rates by Arm for Specified SOC • AE Incident Rates by Arm • AE SOC Rates by Arm Descending sort on Totals • AE Coding Tables • AE Coding Table by Body System or Organ Class MAED • SAE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • SAE SMQ analysis (broad, algorithmic, narrow) • AE Analysis for each MedDRA Hierarchy Level (PT, HLT, HLGT, SOC) • AE SMQ analysis (broad, algorithmic, narrow)	SAS Analysis Panel • MedDRA at a Glance SAS Analysis Panel - AE Toxicity • Toxicity Grade Summary • PT Analysis by Tox Grade • Two term MedDRA Analysis SAS Analysis Panel - AE Severity • SAEs by ARM • SAEs by Severity • AEs by ARM • AEs by Severity

5.4 Appendix D: Non-clinical Review Sections and Analyses Mapped to SEND Standard and Tool Outputs

Table 5-3 provides a mapping of sections in the non-clinical review and standard analyses to SEND domains and tool outputs.

Table 5-3: Non-clinical review sections and analyses mapped to SEND standard and tool outputs

SECTION #	REVIEW SECTION	ANALYSES	DESIGN, INTERVENTIONS, AND EVENT DOMAINS AVAILABLE FOR ANALYSES	SEND FINDINGS DOMAINS AVAILABLE FOR ANALYSES	JANUS NON-CLINICAL OUTPUTS/VIEWS* BASED ON FINDINGS DOMAINS
4.1	Primary Pharmacology	No standard analyses	Not applicable		
4.2	Secondary Pharmacology	No standard analyses	Not applicable		
4.3	Safety Pharmacology	Safety Pharmacology	Not modeled in SEND		
5.1	PK/ADME	PK/ADME	Not modeled in SEND		
5.2	Toxicokinetics	Toxicokinetics	Not modeled in SEND		
6.1	Single-Dose Toxicity	Key Study Findings	No standard analyses		
		Mortality	DM, DS, EX, POOLDEF, TA, TE, TS, TX	DD	SEND Table Display Output
		Clinical Signs	DM, DS, EX, POOLDEF, TA, TE, TS, TX	CL	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Body Weights	DM, DS, EX, POOLDEF, TA, TE, TS, TX	BG, BW	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Feed Consumption	DM, DS, EX, POOLDEF, TA, TE, TS, TX	FW	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Ophthalmoscopy	DM, DS, EX, POOLDEF, TA, TE, TS, TX	CL	Summary, Tabular View, Graph or Visualization, SEND Table Display
		ECG	DM, DS, EX, POOLDEF, TA, TE, TS, TX	EG	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Hematology	DM, DS, EX, POOLDEF, TA, TE, TS, TX	LB	Summary, Tabular View, Graph or Visualization, SEND Table Display

SECTION #	REVIEW SECTION	ANALYSES	DESIGN, INTERVENTIONS, AND EVENT DOMAINS AVAILABLE FOR ANALYSES	SEND FINDINGS DOMAINS AVAILABLE FOR ANALYSES	JANUS NON-CLINICAL OUTPUTS/VIEWS* BASED ON FINDINGS DOMAINS
6.1		Clinical Chemistry	DM, DS, EX, POOLDEF, TA, TE, TS, TX	LB	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Urinalysis	DM, DS, EX, POOLDEF, TA, TE, TS, TX	LB	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Gross Pathology	DM, DS, EX, POOLDEF, TA, TE, TS, TX	MA, PM, SUPPMA	MA and SUPPMA: Summary, Tabular View, Graph or Visualization, SEND Table Display PM – No outputs currently available
		Organ Weights	DM, DS, EX, POOLDEF, TA, TE, TS, TX	OM	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Histopathology • Adequate Battery • Peer Review • Histological Findings	DM, DS, EX, POOLDEF, TA, TE, TS, TX	MI, SUPPMI, TF	MI and SUPPMI: Summary, Tabular View, Graph or Visualization, SEND Table Display TF: Summary, Tabular View, SEND Table Display
		Special Evaluation	Analyses vary by therapeutic area or pharmacological class		
		Toxicokinetics	DM, DS, EX, POOLDEF, TA, TE, TS, TX	PC, PP	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Dosing Solution Analysis	DM, DS, EX, POOLDEF, TA, TE, TS, TX	Not applicable	Not applicable
6.2	Single-Dose Toxicity	Key Study Findings	No standard analyses		
		Mortality	DM, DS, EX, POOLDEF, TA, TE, TS, TX	DD	SEND Table Display Output
		Clinical Signs	DM, DS, EX, POOLDEF, TA, TE, TS, TX	CL	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Body Weights	DM, DS, EX, POOLDEF, TA, TE, TS, TX	BG, BW	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Feed Consumption	DM, DS, EX, POOLDEF, TA, TE, TS, TX	FW	Summary, Tabular View, Graph or Visualization, SEND Table Display

SECTION #	REVIEW SECTION	ANALYSES	DESIGN, INTERVENTIONS, AND EVENT DOMAINS AVAILABLE FOR ANALYSES	SEND FINDINGS DOMAINS AVAILABLE FOR ANALYSES	JANUS NON-CLINICAL OUTPUTS/VIEWS* BASED ON FINDINGS DOMAINS
6.2		Ophthalmoscopy	DM, DS, EX, POOLDEF, TA, TE, TS, TX	CL	Summary, Tabular View, Graph or Visualization, SEND Table Display
		ECG	DM, DS, EX, POOLDEF, TA, TE, TS, TX	EG	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Hematology	DM, DS, EX, POOLDEF, TA, TE, TS, TX	LB	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Clinical Chemistry	DM, DS, EX, POOLDEF, TA, TE, TS, TX	LB	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Urinalysis	DM, DS, EX, POOLDEF, TA, TE, TS, TX	LB	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Gross Pathology	DM, DS, EX, POOLDEF, TA, TE, TS, TX	MA, PM, SUPPMA	MA and SUPPMA: Summary, Tabular View, Graph or Visualization, SEND Table Display PM: No outputs currently available
		Organ Weights	DM, DS, EX, POOLDEF, TA, TE, TS, TX	OM	Summary, Tabular View, Graph or Visualization, SEND Table Display
		• Histopathology • Adequate Battery • Peer Review • Histological Findings	DM, DS, EX, POOLDEF, TA, TE, TS, TX	MI, SUPPMI, TF	MI and SUPPMI: Summary, Tabular View, Graph or Visualization, SEND Table Display TF: Summary, Tabular View, SEND Table Display
		Special Evaluation	Analyses vary by therapeutic area or pharmacological class		
		Toxicokinetics	DM, DS, EX, POOLDEF, TA, TE, TS, TX	PC, PP	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Dosing Solution Analysis	DM, DS, EX, POOLDEF, TA, TE, TS, TX	Not applicable	Not applicable
7.1	In vitro Reverse Mutation Assay	Key Study Findings	No standard analyses		
		Study Validity	No standard analyses		

SECTION #	REVIEW SECTION	ANALYSES	DESIGN, INTERVENTIONS, AND EVENT DOMAINS AVAILABLE FOR ANALYSES	SEND FINDINGS DOMAINS AVAILABLE FOR ANALYSES	JANUS NON-CLINICAL OUTPUTS/VIEWS* BASED ON FINDINGS DOMAINS
7.1	in Bacterial Cells (Ames)	Results	Not modeled in SEND		
7.2	In vitro Assays in Mammalian Cells	Key Study Findings	No standard analyses		
		Study Validity	No standard analyses		
		Results	Not modeled in SEND		
7.3	In vivo Clastogenicity Assay in Rodents (Micronucleus Assay)	Key Study Findings	No standard analyses		
		Study Validity	No standard analyses		
		Results	Not modeled in SEND		
7.4	Other Genetic Toxicity Studies	Not standard analyses	No standard analyses		
8	Carcinogenicity	Key Study Findings	No standard analyses		
		Adequacy of Carcinogenicity Study	No standard analyses		
		Appropriateness of Test Models	No standard analyses		
		Evaluation of Tumor Findings	DM, DS, EX, POOLDEF, TA, TE, TS, TX	CL, MA, MI, PM, SUPPMA, SUPPMI	CL, MA, MI, SUPPMA and SUPPMI: Summary, Tabular View, Graph or Visualization, SEND Table Display PM: No outputs currently available
		Mortality	DM, DS, EX, POOLDEF, TA, TE, TS, TX	DD	SEND Table Display Output
		Clinical Signs	DM, DS, EX, POOLDEF, TA, TE, TS, TX	CL	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Body Weights	DM, DS, EX, POOLDEF, TA, TE, TS, TX	BG, BW	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Feed Consumption	DM, DS, EX, POOLDEF, TA, TE, TS, TX	FW	Summary, Tabular View, Graph or Visualization, SEND Table Display

SECTION #	REVIEW SECTION	ANALYSES	DESIGN, INTERVENTIONS, AND EVENT DOMAINS AVAILABLE FOR ANALYSES	SEND FINDINGS DOMAINS AVAILABLE FOR ANALYSES	JANUS NON-CLINICAL OUTPUTS/VIEWS* BASED ON FINDINGS DOMAINS
8		Gross Pathology	DM, DS, EX, POOLDEF, TA, TE, TS, TX	MA, PM, SUPPMA	MA and SUPPMA: Summary, Tabular View, Graph or Visualization, SEND Table Display PM: No outputs currently available
		Histopathology • Peer Review • Neoplastic • Non Neoplastic	DM, DS, EX, POOLDEF, TA, TE, TS, TX	MI, SUPPMI, TF	MI and SUPPMI: SEND Table Display Output TF – Summary, Tabular View, SEND Table Display
		Special Evaluation	Analyses vary by therapeutic area or pharmacological class		
		Toxicokinetics	DM, DS, EX, POOLDEF, TA, TE, TS, TX	PC, PP	Summary, Tabular View, Graph or Visualization, SEND Table Display
		Dosing Solution Analysis	DM, DS, EX, POOLDEF, TA, TE, TS, TX	Not applicable	Not applicable
9.1	Fertility and Early Embryonic Development	Key Study Findings	No standard analyses		
		Mortality	Not modeled in SEND		
		Clinical Signs	Not modeled in SEND		
		Body Weights	Not modeled in SEND		
		Feed Consumption	Not modeled in SEND		
		Toxicokinetics	Not modeled in SEND		
		Dosing Solution Analysis	Not modeled in SEND		
		Necropsy	Not modeled in SEND		
9.2	Embryonic Fetal Development	Key Study Findings	No standard analyses		
		Mortality	Not modeled in SEND		
		Clinical Signs	Not modeled in SEND		
		Body Weights	Not modeled in SEND		

SECTION #	REVIEW SECTION	ANALYSES	DESIGN, INTERVENTIONS, AND EVENT DOMAINS AVAILABLE FOR ANALYSES	SEND FINDINGS DOMAINS AVAILABLE FOR ANALYSES	JANUS NON-CLINICAL OUTPUTS/VIEWS* BASED ON FINDINGS DOMAINS
9.2		Feed Consumption		Not modeled in SEND	
		Toxicokinetics		Not modeled in SEND	
		Dosing Solution Analysis		Not modeled in SEND	
		Necropsy		Not modeled in SEND	
		Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)		Not modeled in SEND	
		Offspring (Malformations, Variations, etc.)		Not modeled in SEND	
9.3	Prenatal and Postnatal Development	Key Study Findings		No standard analyses	
		Observations and Results (Optional Table)		Not modeled in SEND	
10	Special Toxicology Studies	Not standard		No standard analyses	
11	Integrated Summary and Safety Evaluation	Not applicable		No standard analyses	

* Summary, Tabular View, Graph or Visualization, and SEND Table Display are all of the available outputs/views

5.5 Appendix E: Additional Analyses

Booz Allen selected applications for the Deep Dive Cohort to ensure similar distribution of application type and submission subtype, review division, and Center compared to the Study Cohort (Figure 5-5). The 60 submissions selected for the Deep Dive Cohort represent 21 out of 26 review divisions across CBER and CDER.

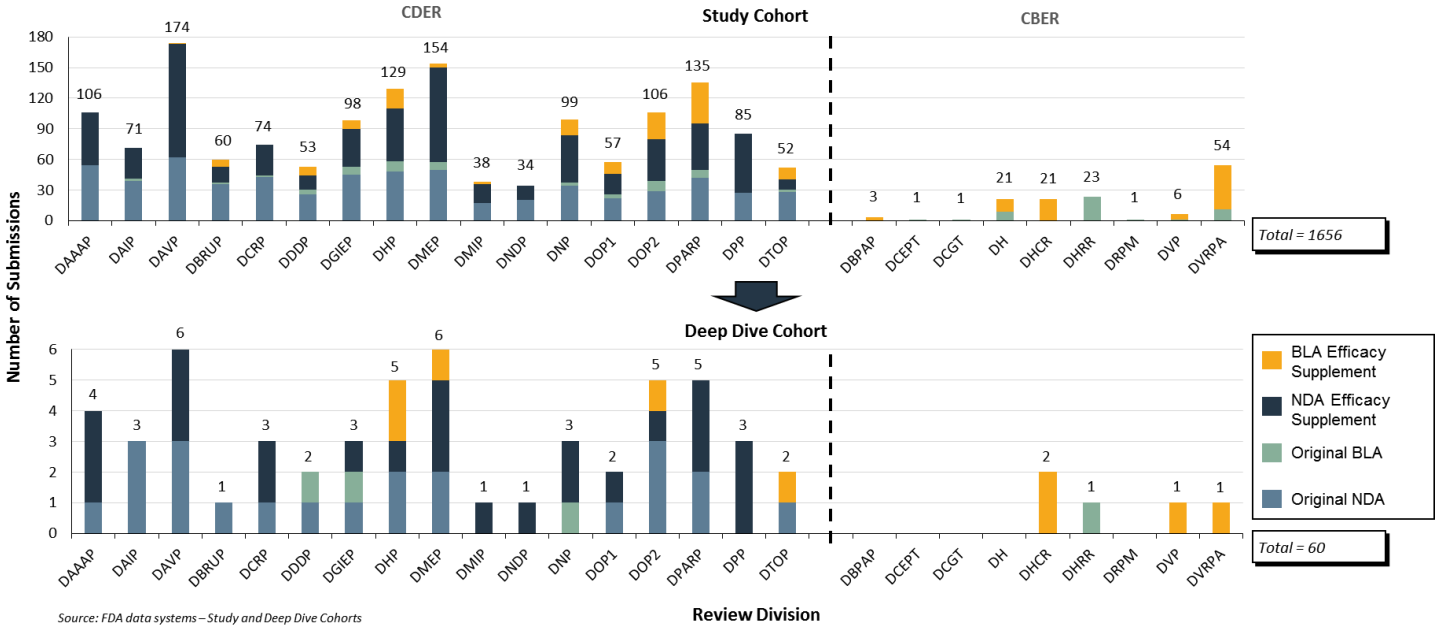
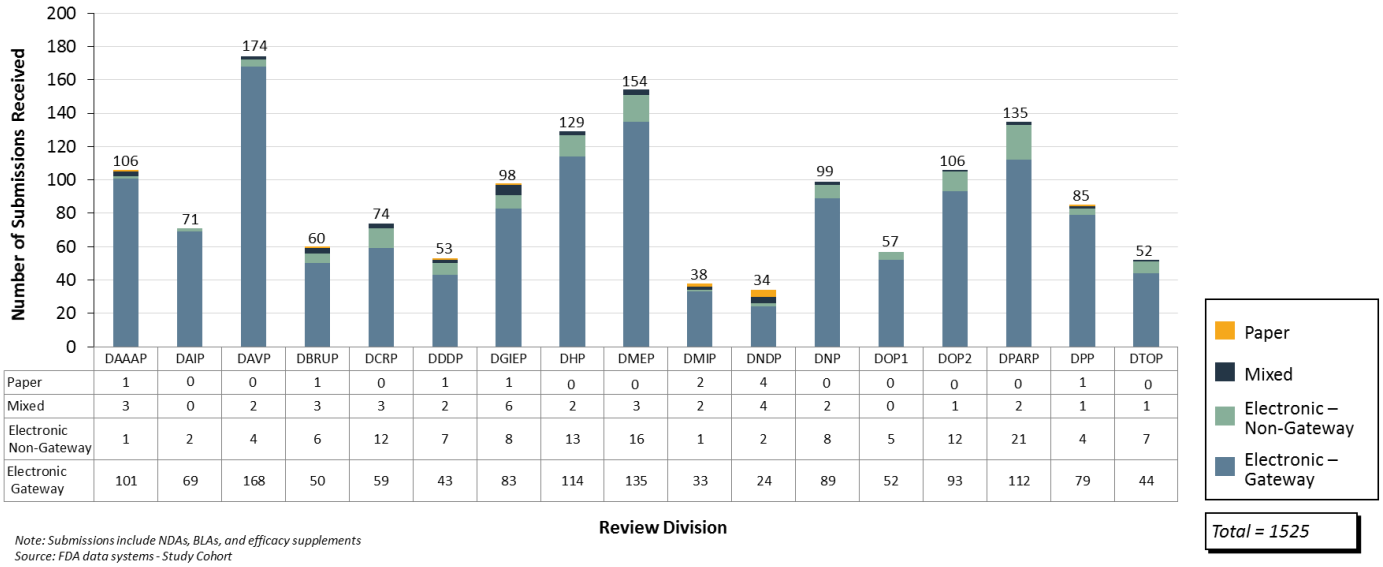


Figure 5-5: Study and Deep Dive Cohorts by Center, review division, application type, and submission subtype

CDER review divisions receive the majority of submissions electronically through the Gateway (Figure 5-6).

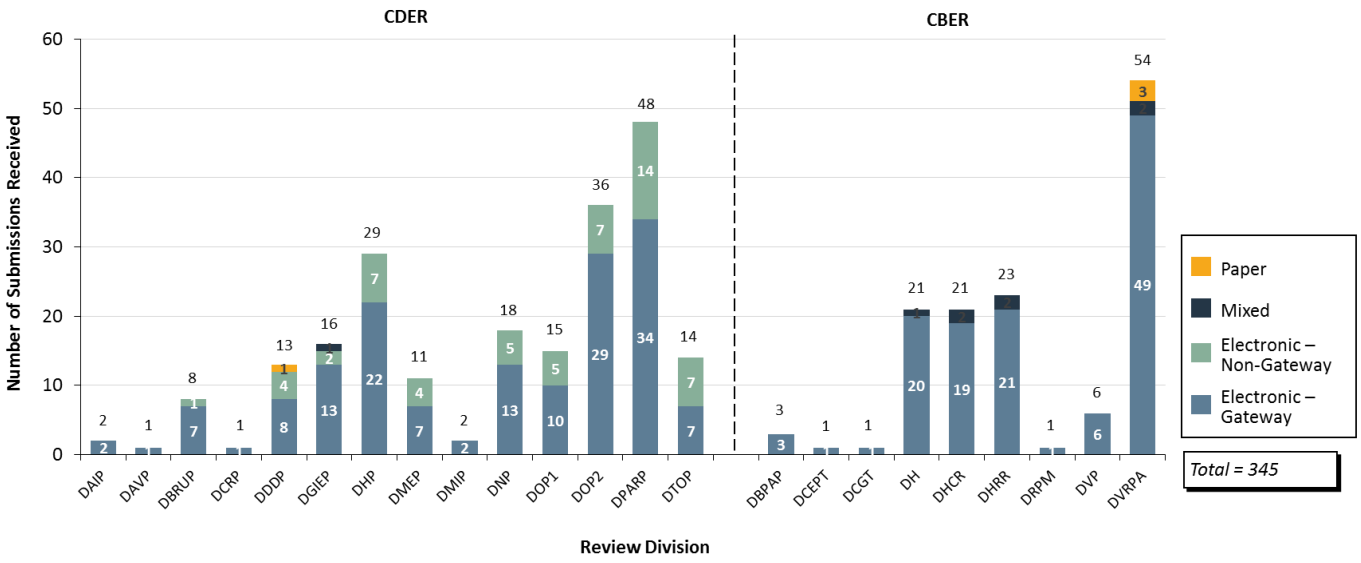


	DAAAP	DAIP	DAVP	DBRUP	DCRP	DDDP	DGIEP	DHP	DMEP	DMIP	DNDP	DNP	DOP1	DOP2	DPARP	DPP	DTOP
Paper	1	0	0	1	0	1	1	0	0	2	4	0	0	0	0	1	0
Mixed	3	0	2	3	3	2	6	2	3	2	4	2	0	1	2	1	1
Electronic Non-Gateway	1	2	4	6	12	7	8	13	16	1	2	8	5	12	21	4	7
Electronic Gateway	101	69	168	50	59	43	83	114	135	33	24	89	52	93	112	79	44

Note: Submissions include NDAs, BLAs, and efficacy supplements
Source: FDA data systems - Study Cohort

Figure 5-6: CDER Study Cohort submissions by review division and submission format

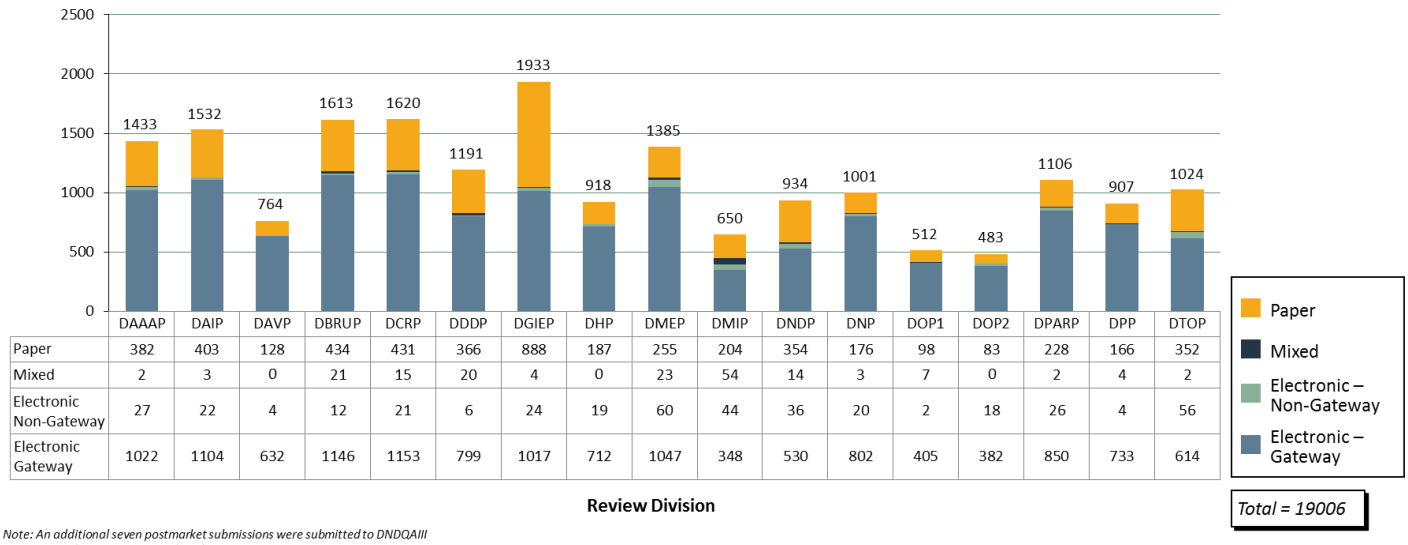
Across review divisions, the FDA received the vast majority of BLAs submissions electronically; 73% of CDER original BLAs and efficacy supplements and 92% of CBER original BLAs and efficacy supplements were submitted electronically through the Gateway (Figure 5-7).



Source: FDA data systems - Study Cohort

Figure 5-7: CDER and CBER original BLAs and efficacy supplements by submission format

The percentage of postmarket submissions received through the Gateway varies by review division; DGIEP receives almost half non-electronic submissions while DAVP, DOP1, and DOP2 receives almost all electronic submissions (Figure 5-8).

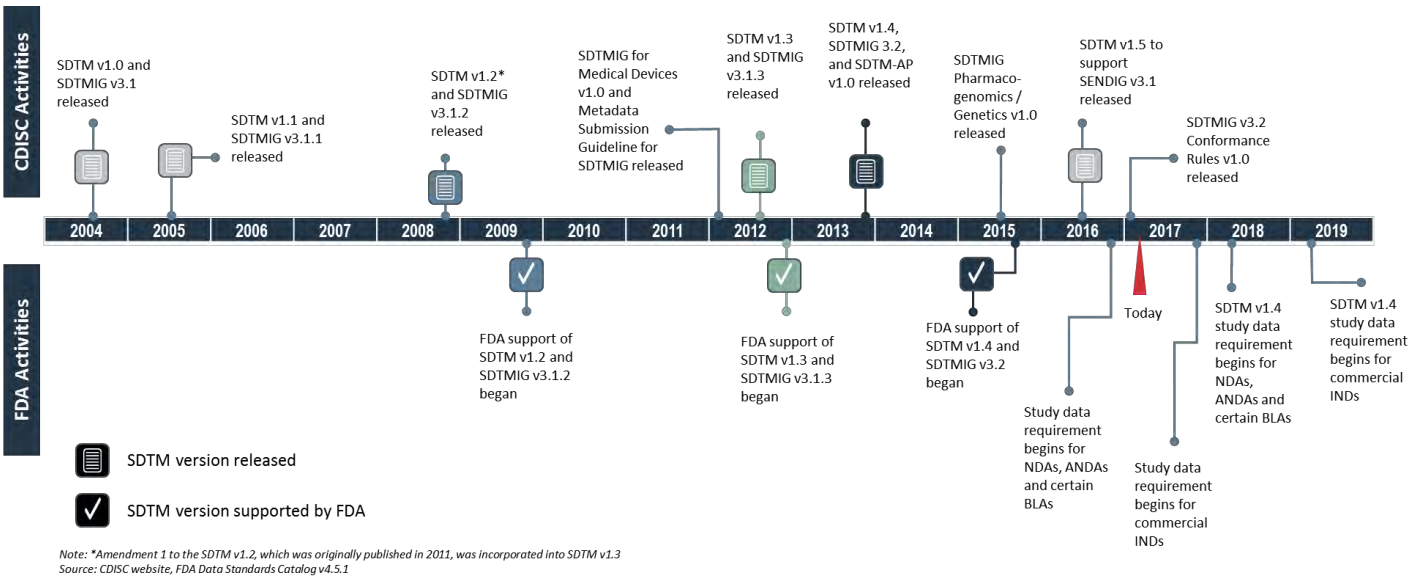


	DAAAP	DAIP	DAVP	DBRUP	DCRP	DDDP	DGIEP	DHP	DMEP	DMIP	DNDP	DNP	DOP1	DOP2	DPARP	DPP	DTOP
Paper	382	403	128	434	431	366	888	187	255	204	354	176	98	83	228	166	352
Mixed	2	3	0	21	15	20	4	0	23	54	14	3	7	0	2	4	2
Electronic Non-Gateway	27	22	4	12	21	6	24	19	60	44	36	20	2	18	26	4	56
Electronic Gateway	1022	1104	632	1146	1153	799	1017	712	1047	348	530	802	405	382	850	733	614

Note: An additional seven postmarket submissions were submitted to DNDQAIII
Source: FDA data systems – Study Cohort

Figure 5-8: CDER postmarket submissions by review division and submission format

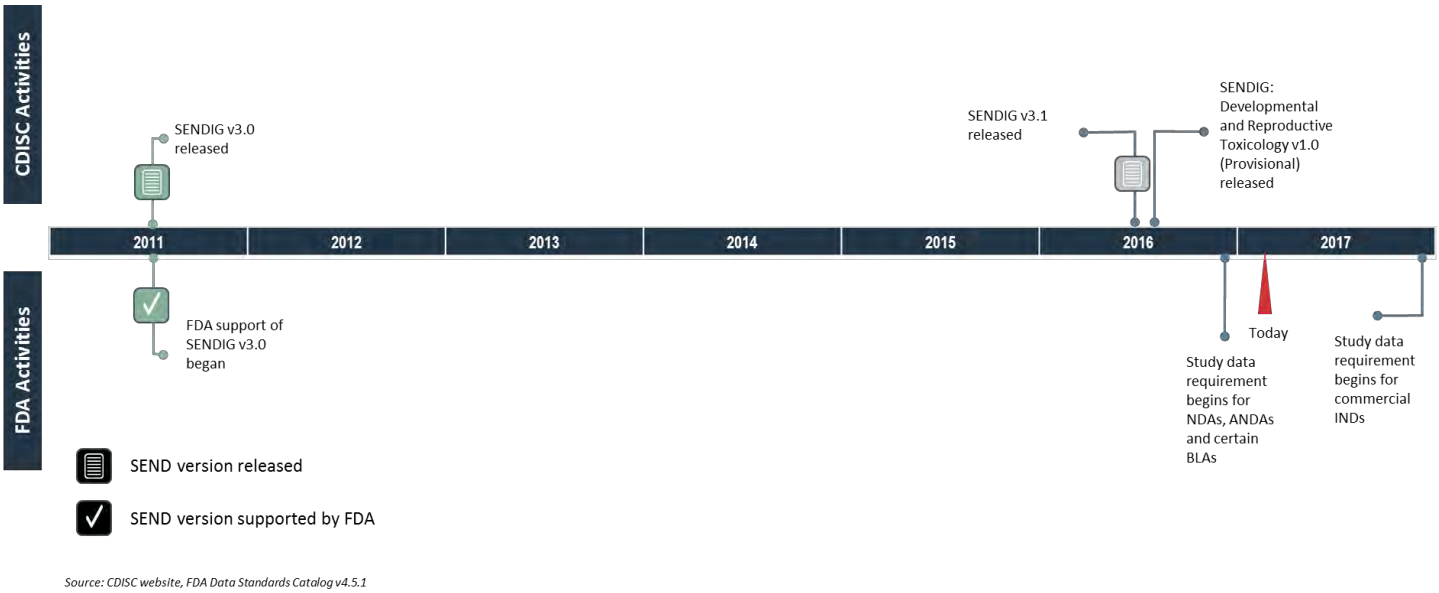
The SDTM standard has gone through several iterations over the years. All studies starting after December 16, 2016 for NDAs, ANDAs, and some BLAS are required to have standardized study data (i.e., SDTM, ADaM, SEND) (Figure 5-9). After December 16, 2017, commercial INDs are required to have standardized study data.



*Note: *Amendment 1 to the SDTM v1.2, which was originally published in 2011, was incorporated into SDTM v1.3*
Source: CDISC website, FDA Data Standards Catalog v4.5.1

Figure 5-9: Evolution of the SDTM standard since 2004

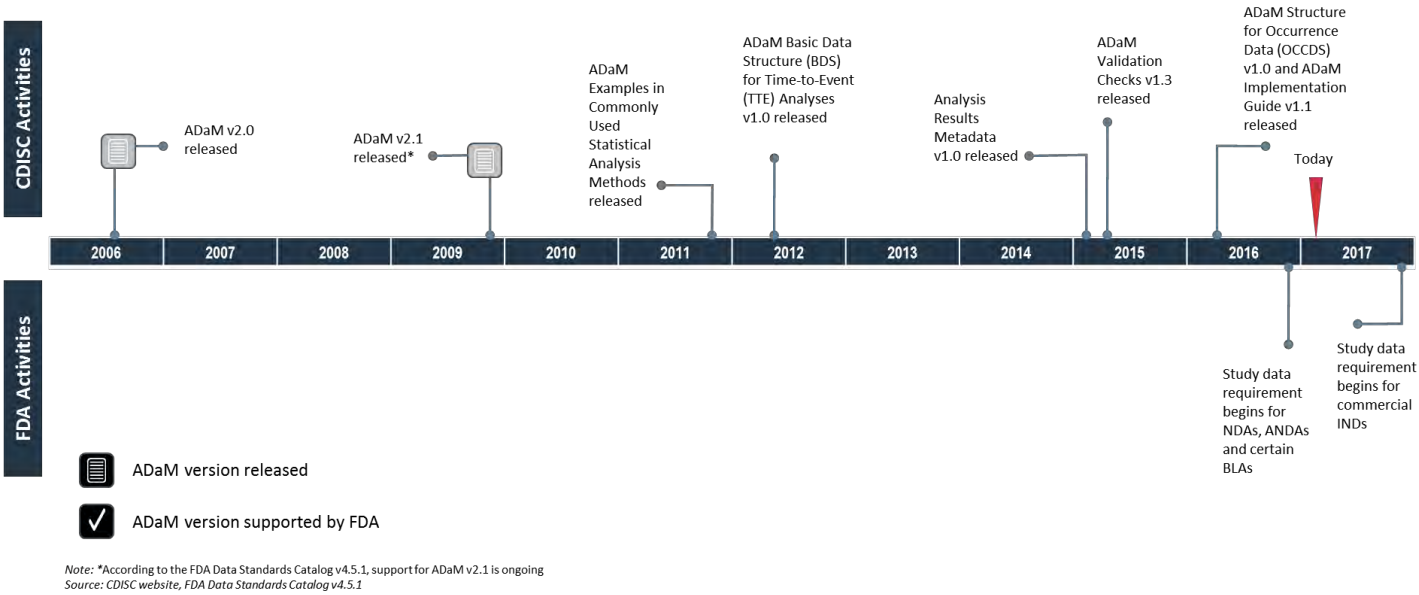
Although the SEND standard is less mature than the SDTM standard, sponsors will still be required to provide standardized data for all non-clinical studies initiated after December 16, 2016 for NDAs, ANDAs, and some BLAs and after December 16, 2017 for commercial INDs (Figure 5-10).



Source: CDISC website, FDA Data Standards Catalog v4.5.1

Figure 5-10: Evolution of the SEND standard since 2011

The ADaM standard for clinical analysis datasets has the same requirement as the SDTM and SEND standards (Figure 5-11).



Note: *According to the FDA Data Standards Catalog v4.5.1, support for ADaM v2.1 is ongoing
Source: CDISC website, FDA Data Standards Catalog v4.5.1

Figure 5-11: Evolution of the ADaM standard since 2006

FDA utilizes a variety of standards to streamline submission data for the review process (Table 5-4).

Table 5-4: List of data standards by version, standard evolution, governing body, scope of standard, and readiness

STANDARD	VERSION	STANDARD EVOLUTION	GOVERNING BODY	SCOPE OF STANDARD	READINESS
eCTD[36]	• Supported version: 3.2.2 (IG: M2 eCTD Electronic Common Technical Document Specifications) • Release date of supported version: 7/16/08 • Most recent version: 4.0 (IG v1.1) • Release date of most recent version: 1/20/2016	• Version 3.0 released October 2003 • Four subsequent versions released, ending with Version 3.2.2 • FDA is providing the ICH eCTD v4.0 Implementation Package for planning purposes. FDA will request formal comments on the package	ICH	Throughout the medical product lifecycle	• Date requirement begins: 5/5/2017 for NDAs, ANDAs, and certain BLAs, 5/5/2018 for commercial INDs • FDA issued guides and guidances: eCTD Technical Conformance Guide, Guidance to Industry Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

[36] FDA Data Standards Catalog v4.5.1; eCTD v4.0. Retrieved from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm309911.htm; ICH eCTD v4.0 Step 4 page. Retrieved from http://estri.ich.org/new-eCTD/index.htm; ICH M2 EWG eCTD Specification. Retrieved from http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf

STANDARD	VERSION	STANDARD EVOLUTION	GOVERNING BODY	SCOPE OF STANDARD	READINESS
SDTM[37]	• Supported version: SDTM 1.4 (SDTMIG 3.2) • Release date of supported version: 11/26/2013 • Most recent version: SDTM 1.5 (SENDIG 3.1) • Release date of most recent version: 6/27/2016	• Version 1.0 released 6/25/2004 • Four subsequent versions released, ending with Version 1.4 Final • CDISC has released Version 1.5 to specifically support SENDIG v3.1	CDISC	Clinical study datasets	• Date requirement begins: 12/17/2016 for NDAs, ANDAs and certain BLAs, 12/17/2017 for certain INDs for Versions 1.3 and 1.2; 3/15/2018 for NDAs, ANDAs, and certain BLAs, 3/15/2019 for certain INDs for Version 1.4 • FDA issued guides and guidances: Study Data Technical Conformance Guide, Providing Regulatory Submissions in Electronic Format – Standardized Study Data
SEND[38]	• Supported version: SENDIG 3.0 (SDTM 1.2) • Release date of supported version: 06/17/2011 • Most recent version: SENDIG 3.1 (SDTM 1.5) • Release date of most recent version: 6/27/2016	• SENDIG v3.0 is based upon v1.2 of SDTM • SENDIG 3.1 is based upon v1.5 of SDTM • CDISC also released Version 1.0 Provisional of SENDIG: Developmental and Reproductive Toxicology on 8/01/2016	CDISC	Animal study datasets	• Date requirement begins: 12/17/2016 for NDAs, ANDAs, and certain BLAs; 12/17/2017 for certain INDs • FDA issued guides and guidances: Study Data Technical Conformance Guide, Providing Regulatory Submissions in Electronic Format – Standardized Study Data

[37] CDISC SDTM. Retrieved from https://www.cdisc.org/standards/foundational/sdtm; CDISC SDTMIG. Retrieved from https://www.cdisc.org/standards/foundational/sdtmig; FDA Data Standards Catalog v4.5.1
[38] CDISC SEND. Retrieved from https://www.cdisc.org/standards/foundational/send; FDA Data Standards Catalog v4.5.1

STANDARD	VERSION	STANDARD EVOLUTION	GOVERNING BODY	SCOPE OF STANDARD	READINESS
ADaM[39]	• Supported version: 2.1 (IG v1.0) • Release date of supported version: 12/17/2009 • Most recent version: same as above (IG v1.1) • Release date of most recent version: same as above (12/12/2016)	• Version 2.0 Draft released 2/15/2006 • Four subsequent versions released, ending in Version 2.1 Final	CDISC	Clinical study datasets	• Date requirement begins: 12/17/2016 for NDAs, ANDAs, and certain BLAs; 12/17/2017 for certain INDs • FDA issued guides and guidances: Study Data Technical Conformance Guide, Providing Regulatory Submissions in Electronic Format – Standardized Study Data

[39] CDISC ADaM. Retrieved from https://www.cdisc.org/standards/foundational/adam; FDA Data Standards Catalog v4.5.1

STANDARD	VERSION	STANDARD EVOLUTION	GOVERNING BODY	SCOPE OF STANDARD	READINESS
ICSR[40]	• Supported version: Release 2 (IG: ICH E2B(R3)[41] v5.01) • Release date of supported version: 12/2011 (04/12/2013) • Most recent version: same as above • Release date of most recent version: same as above	• E2B guideline released in 1997 • Revised versions released in 2000 and 2001 resulting in E2B(R2) guideline • E2B(R3) released for public consultation in May 2005, revisions resulted in v5.01	ICH E2B	Postmarket	• Date requirement begins: ICSRs must be submitted electronically starting 6/10/2015 • FDA issued guides and guidances: E2B(R3) Electronic Transmission of ICSRs Implementation Guide – Data Elements and Message Specification; Appendix I (B) to the ICH E2B(R3) ICSRs Implementation Guide – Backwards and Forwards Compatibility; FDA Regional Implementation Specifications for ICH E2B(R3) Implementation – Postmarket Submission of Individual Case Safety Reports for Drugs and Biologics, Excluding Vaccines; Providing Submissions in Electronic Format – Postmarket Non-Expedited ICSRs Technical Questions and Answers

[40] FDA Adverse Events Reporting System Electronic Submissions. Retrieved from http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm; Individual Case Safety Reports. Retrieved from http://www.fda.gov/ForIndustry/DataStandards/IndividualCaseSafetyReports/default.htm, E2B(R3) ICSR Specification and Related Filed. Retrieved from http://estri.ich.org/e2br3/index.htm; FDA Data Standards Catalog v4.5.1

[41] Although not explicitly stated in the FDA Data Standards Catalog v4.5.1 as (R3), accompanying FDA guidance refers to (R3) v5.01

STANDARD	VERSION	STANDARD EVOLUTION	GOVERNING BODY	SCOPE OF STANDARD	READINESS
MedDRA[42]	• Supported version: 8 or later • Release date of supported version: 3/1/2005 for version 8 • Most recent version: 19.1 • Release date of most recent version: 9/2016	• 10/1994 - ICH adopted MedDRA Version 1.0 • New versions are released bi-annually in March and September	Maintenance and Support Services Organization (MSSO)	• Adverse events • Applicable SDTM and SEND domains: AE	• Date requirement begins: 12/17/2016 for NDAs, ANDAs, and certain BLAs, 12/17/2017 for certain INDs • FDA issued guides and guidances: Study Data Technical Conformance Guide, Providing Regulatory Submissions in Electronic Format – Standardized Study Data
WHO DD[43]	• Supported version: Latest version • Release date of supported version: 12/1/2016 • Most recent version: December 1, 2016 release • Release date of most recent version: same as above	• Contains data from 1968 onwards • New versions released quarterly • Has evolved into WHODrug Enhanced which, from 2017, will include records from WHODrug Herbal	World Health Organization (WHO)	• Medication • Applicable SDTM and SEND domains: CM	• Date requirement begins: 3/15/2018 for NDAs, ANDAs, and certain BLAs, 3/15/2019 for certain INDs • FDA issued guides and guidances: Study Data Technical Conformance Guide, Providing Regulatory Submissions in Electronic Format – Standardized Study Data

[42] MedDRA Support Documentation. Retrieved from http://www.meddra.org/how-to-use/support-documentation; Eugene Sefanov. The 6 Annual Release Dates For MedDRA And WHO Drug. Life Sciences Blog. May 7, 2015. Retrieved from http://blogs.perficient.com/lifesciences/2015/05/07/the-6-annual-release-dates-for-meddra-and-who-drug/; FDA Data Standards Catalog v4.5.1

[43] WHODrug Portfolio. Retrieved from https://www.who-umc.org/whodrug/whodrug-portfolio/whodrug-global/whodrug-enhanced/; Eugene Sefanov. The 6 Annual Release Dates For MedDRA And WHO Drug. Life Sciences Blog. May 7, 2015. Retrieved from http://blogs.perficient.com/lifesciences/2015/05/07/the-6-annual-release-dates-for-meddra-and-who-drug/; FDA Data Standards Catalog v4.5.1

STANDARD	VERSION	STANDARD EVOLUTION	GOVERNING BODY	SCOPE OF STANDARD	READINESS
NDF-RT[44]	• Supported version: Latest version • Release date of supported version: 12/2016 • Most recent version: 12/2016 release • Release date of most recent version: same as above	• Released 10 times per calendar year	Department of Veterans Affairs/ Veterans Health Administration	• Pharmacological class • Applicable SDTM and SEND domains: CM, TS	• Date requirement begins: 12/17/2016 for NDAs, ANDAs, and certain BLAs, 12/17/2017 for certain INDs • FDA issued guides and guidances: Study Data Technical Conformance Guide, Providing Regulatory Submissions in Electronic Format – Standardized Study Data
SNOMED CT[45]	• Supported version: Latest version • Release date of supported version: 9/2016 • Most recent version: September 2016 US Edition of SNOMED CT • Release date of most recent version: same as above	• International and US specific releases • The current US release is the last time Release Format 1 will be used. Moving forward, Release Format 2, which supports the creation of reference sets, will be the only release format	International Health Terminology Standards Development Organisation (IHTSDO)	• Indications and usage • Applicable SDTM and SEND domains: TS	• Date requirement begins: 12/17/2016 for NDAs, ANDAs, and certain BLAs, 12/17/2017 for certain INDs • FDA issued guides and guidances: Study Data Technical Conformance Guide, Providing Regulatory Submissions in Electronic Format – Standardized Study Data

[44] NDF-RT Documentation. Retrieved from https://evs.nci.nih.gov/ftp1/NDF-RT/NDF-RT%20Documentation.pdf; FDA Data Standards Catalog v4.5.1
[45] SNOMED CT United States Edition. Retrieved from https://www.nlm.nih.gov/healthit/snomedct/us_edition.html; FDA Data Standards Catalog v4.5.1

STANDARD	VERSION	STANDARD EVOLUTION	GOVERNING BODY	SCOPE OF STANDARD	READINESS
LOINC[46]	• Supported version: Latest version • Release date of supported version: 12/21/2016 • Most recent version: LOINC 2.58 • Release date of most recent version: same as above	• Initiated in 1994 • New versions released in December and June	Regenstrief Institute	• Laboratory tests • Applicable SDTM and SEND domains: LB	• Date requirement begins: 3/15/2018 for NDAs, ANDAs, and certain BLAs, 3/15/2019 for certain INDs • FDA issued guides and guidances: Study Data Technical Conformance Guide, Providing Regulatory Submissions in Electronic Format – Standardized Study Data

[46] LOINC. Retrieved from https://loinc.org/; FDA Data Standards Catalog v4.5.1

FDA included five therapeutic area standards in the Study Data Technical Conformance Guide (Table 5-5).

Table 5-5: Therapeutic area standards detailed in the Study Data Technical Conformance Guide (as of February 2017)

DISEASE STANDARD	MOST RECENT VERSION OF IMPLEMENTATION GUIDE	RELEASE DATE OF MOST RECENT VERSION	STANDARD EVOLUTION
Diabetes	1.0 Provisional	9/11/2014	• Version 1.0 Draft released 4/3/2014 for public review • ADaM Supplement Version 1.0 Draft released 7/17/2015 for public review • ADaM Supplement Version 1.0 Provisional released 12/18/2015
QT Studies	1.0 Provisional	12/8/2014	Draft released 7/31/2014 for public review
Chronic Hepatitis C	1.0 Provisional	4/8/2015	Draft released 12/15/2014 for public review
Dyslipidemia	1.0 Provisional	6/19/2015	Draft released 3/13/2015 for public review
Tuberculosis	2.0 Provisional	2/26/2016	• Version 1.0 Provisional released 6/29/2012 • Version 2.0 Draft released 1/12/2015 for public review

There are user guides are available for another 19 therapeutic area standards in addition to the five standards outlined in the Study Data Technical Conformance Guide (Table 5-6).

Table 5-6: Therapeutic area standards with user guides available (as of February 2017)

DISEASE STANDARD	MOST RECENT VERSION OF IMPLEMENTATION GUIDE	RELEASE DATE OF MOST RECENT VERSION	STANDARD EVOLUTION
Parkinson's	1.0 Provisional	12/18/2012	Draft released 8/9/2012 for public review
Polycystic Kidney Disease	1.0 Provisional	2/26/2013	Draft released 10/22/2012 for public review
Asthma	1.0 Provisional	11/26/2013	Draft released 9/13/2013
Alzheimer's	2.0	12/16/2013	• Version 1.0 released 9/9/2011 • 2.0 Draft released for public review 10/4/2013
Multiple Sclerosis*	1.0 Provisional	5/2/2014	• Draft released 1/17/2014 for internal review • Draft released 2/28/2014 for public review
Cardiovascular	1.0 Provisional	10/17/2014	Draft released 4/7/2014 for public review
Influenza	1.0 Provisional	11/25/2014	Draft released 9/15/2014 for public review
Breast Cancer	1.0 Provisional	5/16/2015	Draft released 11/2/2015
Schizophrenia	1.0 Provisional	6/9/2015	Draft released 2/16/2015 for public review
Virology	2.0 Provisional	9/30/2015	1.0 Provisional released 12/6/2012
Traumatic Brain Injury	1.0 Provisional	12/2/2015	Draft released 7/13/2015 for public review
COPD	1.0 Provisional	1/26/2016	Draft released 10/30/2015 for public review
Kidney Transplant	1.0 Provisional	10/31/2016	Draft released 5/23/2016 for public review
Rheumatoid Arthritis	1.0 Provisional	11/14/2016	Draft released 5/17/2016 for public review
Major Depressive Disorder	1.0 Provisional	12/5/2016	Draft released 7/5/2016 for public review

DISEASE STANDARD	MOST RECENT VERSION OF IMPLEMENTATION GUIDE	RELEASE DATE OF MOST RECENT VERSION	STANDARD EVOLUTION
Diabetic Kidney Disease	1.0 Provisional	12/13/2016	Draft released 12/9/2016 for public review
Pain	1.1 Provisional	12/13/2016	• 1.0 Draft released 8/7/2012 for public review • 1.1 Draft released 8/1/2016
Ebola*	1.0 Provisional	12/19/2016	Draft released 9/30/2016 for public review
Malaria*	1.0 Provisional	1/9/2017	Draft released 6/27/2016 for public review

**Non-FDA priority*
Source: CDISC website

No meaningful differences were observed when analyzing the impact of submission format on the number of RTF letters (Table 5-7).

Table 5-7: Percentage of RTF submissions by submission format

	% RTFS (RTFS/TOTAL SUBMISSIONS)		
SUBMISSION TYPE	PAPER	MIXED	ELECTRONIC
CDER			
Original	40% (2/5)	5% (1/19)	5% (32/658)
Efficacy Supplement	17% (1/6)	0% (0/18)	2% (13/819)
CBER			
Original	0% (0/0)	0% (0/3)	0% (0/44)
Efficacy Supplement	66%* (2/3)	0% (0/4)	0% (0/77)

**Only 2 CBER BLA Submissions received an "Unacceptable for Filing" action*
Source: FDA data systems - Study Cohort

As shown in Table 5-8, the submissions format did not seem to affect timing significantly for the 74-day letter and any clear trends were not discernible since the majority of submissions were sent in electronically.

Table 5-8: Average number of days into review 74-day letter sent by submission format and Center

		AVERAGE NUMBER OF DAYS INTO REVIEW 74-DAY LETTER SENT (NUMBER OF SUBMISSIONS)		
SUBMISSION TYPE	PRIORITY	PAPER	MIXED	ELECTRONIC
CDER				
Original	Priority	NA (0)	74 (2)	60 (144)
	Standard	NA (0)	71 (11)	69 (429)
Efficacy Supplement	Priority	NA (0)	49 (1)	59 (163)
	Standard	74 (1)	66 (7)	67 (269)

CBER				
Original	Priority	NA (0)	57 (1)	57 (10)
	Standard	NA (0)	49 (1)	56 (33)
Efficacy Supplement	Priority	NA (0)	NA (0)	88 (2)
	Standard	NA (0)	55 (4)	58 (72)

Notes: Excludes submissions that received a refuse-to-file, no user fee was received, was unacceptable for filing, applicant was in arrears, the submission was withdrawn and, or the filing letter date was missing at the time when the data was pulled (11/4/16)
Source: FDA data systems - Study Cohort

While submissions format did not affect the number of major amendments, almost 40% of CBER Original BLAs had a major amendment whereas only 12% of CDER Original BLAs had a major amendment (Table 5-9).

Table 5-9: Percentage of major amendments by submission type and format

	% MAJOR AMENDMENTS (SUBMISSIONS WITH MAJOR AMENDMENTS/TOTAL SUBMISSIONS)*		
SUBMISSION TYPE	**PAPER**	**MIXED**	**ELECTRONIC**
CDER			
Original NDA	0% (0/0)	17% (2/12)	11% (56/530)
NDA Efficacy Supplement	0% (0/3)	17% (2/12)	4% (22/579)
Original BLA	0% (0/0)	0% (0/1)	12% (6/52)
BLA Efficacy Supplement	0% (0/1)	0% (0/0)	4% (6/143)
CBER			
Original BLA	0% (0/0)	0% (0/3)	39% (17/44)
BLA Efficacy Supplement	0% (0/1)	0% (0/4)	6% (5/77)

*Excludes submissions that received a refuse-to-file, no user fee was received, was unacceptable for filing, or applicant was in arrears
Source: FDA data systems - Study Cohort

Major amendments occurred with a similar frequency between submissions with and without SDTM data (Table 5-10).

Table 5-10: Percentage of major amendments by submission type and inclusion of standardized data

	% MAJOR AMENDMENTS (SUBMISSIONS WITH MAJOR AMENDMENTS/TOTAL SUBMISSIONS)*	
SUBMISSION TYPE	**SDTM**	**NON-SDTM**
CDER		
Original NDA	11% (35/309)	10% (23/233)
NDA Efficacy Supplement	4% (10/257)	4% (14/337)
Original BLA	14% (6/44)	0% (0/9)
BLA Efficacy Supplement	3% (3/88)	5% (3/56)
CBER		
Original BLA	31% (5/16)	39% (12/31)
BLA Efficacy Supplement	0% (0/11)	7% (5/71)

*Excludes submissions that received a refuse-to-file, no user fee was received, was unacceptable for filing, or applicant was in arrears
Source: FDA data systems - Study Cohort

Primary clinical review completion times for electronic submissions appear lower than the expected times; however, after further review, the review time may be due to accelerated approvals and data entry errors in DARRTS (e.g., filing reviews marked as primary reviews) (Table 5-11).

Table 5-11: Average time to primary clinical review completion for CDER original applications by submission format

			AVERAGE TIME TO PRIMARY CLINICAL REVIEW COMPLETION IN DAYS (NUMBER OF SUBMISSIONS)*		
DESIGNATION	APPLICATION TYPE	EXPECTED PRIMARY REVIEW COMPLETION TIME**	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	NDAs and BLAs	152	NA (0)	NA (0)	132 (31)
	NDAs and BLAs with Major Amendments	Variable	NA (0)	NA (0)	148 (2)
Priority / Program	NDAs and BLAs	213	NA (0)	NA (0)	157 (62)
	NDAs and BLAs with Major Amendments	Variable	NA (0)	NA (0)	156 (5)
Standard / Non-Program	NDAs and BLAs	243	NA (0)	274 (5)	246 (210)
	NDAs and BLAs with Major Amendments	Variable	NA (0)	NA (0)	201 (7)
Standard / Program	NDAs and BLAs	304	NA (0)	NA (0)	254 (68)
	NDAs and BLAs with Major Amendments	Variable	NA (0)	NA (0)	254 (2)

*Excludes submissions that received a refuse-to-file, no user fee was received, submission was unacceptable for filing, applicant was in arrears, the clinical review date was missing, or the clinical review date was after the action date (e.g., clear data entry error)
**Based on primary review completion times from Appendix A of the"21st Century Review Process Desk Reference Guide
Source: FDA data systems - Study Cohort

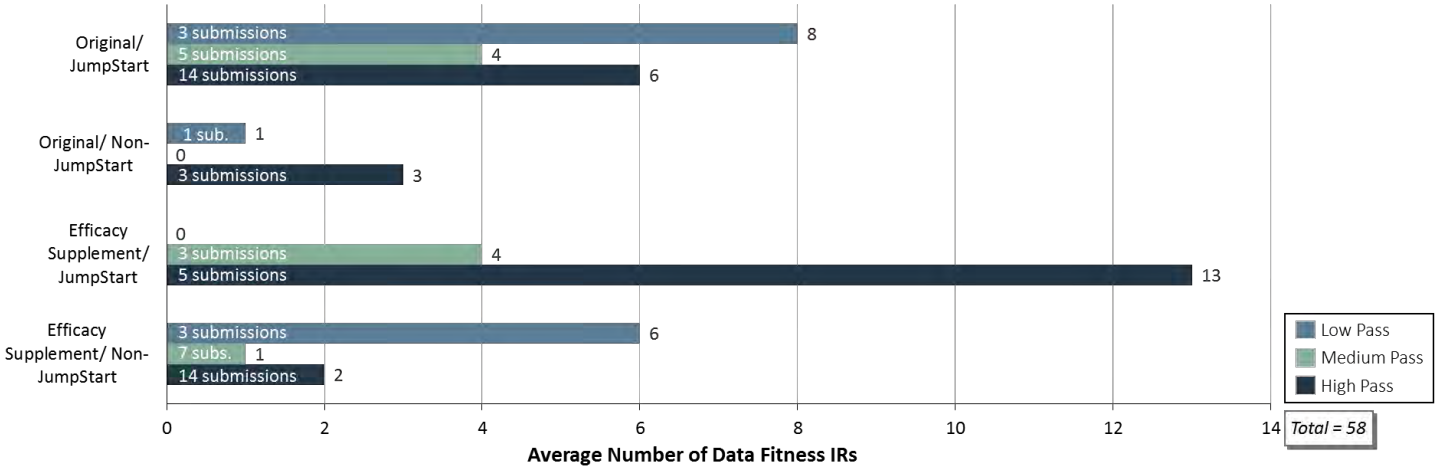
Primary clinical review completion times for electronic submissions were near the expected primary completion timelines (Table 5-12).

Table 5-12: Average time to primary clinical review completion for CDER efficacy supplements by submission format

			AVERAGE TIME TO PRIMARY CLINICAL REVIEW COMPLETION IN DAYS (NUMBER OF SUBMISSIONS)*		
DESIGNATION	APPLICATION TYPE	EXPECTED PRIMARY REVIEW COMPLETION TIME**	PAPER	MIXED	ELECTRONIC
Priority /Non-Program	NDAs and BLAs	152	NA (0)	158 (1)	151 (141)
	NDAs and BLAs with Major Amendments	Variable	NA (0)	NA (0)	151 (3)
Standard /Non-Program	NDAs and BLAs	243	225 (2)	286 (8)	247 (334)
	NDAs and BLAs with Major Amendments	Variable	NA (0)	278 (1)	271 (2)

*Excludes submissions that received a refuse-to-file, no user fee was received, submission was unacceptable for filing, applicant was in arrears, the clinical review date was missing, or the clinical review date was after the action date (e.g., clear data entry error)
**Based on primary review completion times from Appendix A of the"21st Century Review Process Desk Reference Guide
Source: FDA data systems - Study Cohort

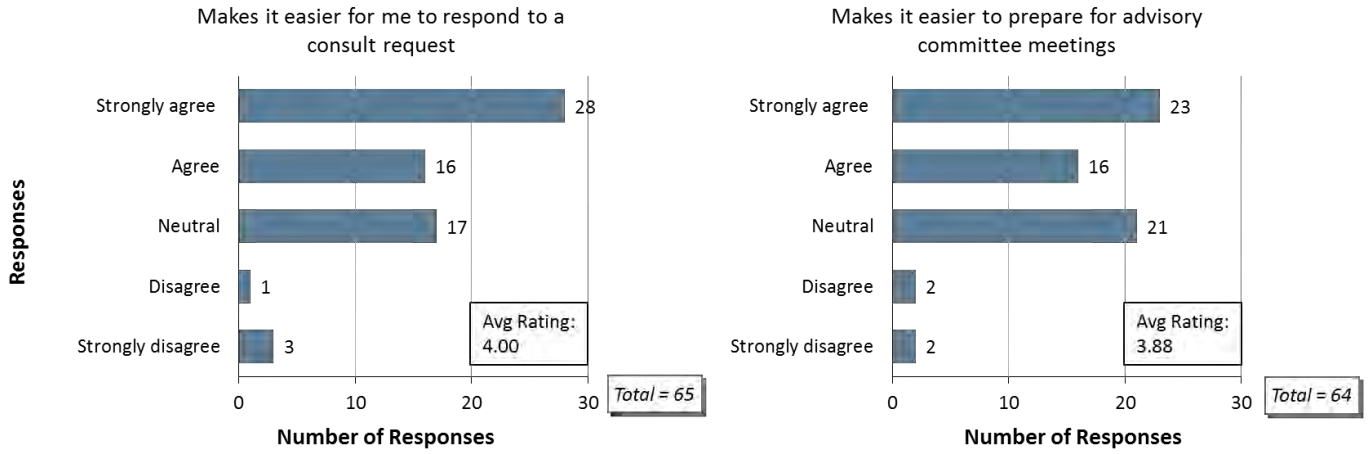
Pass rate did not affect the number of data fitness IRs (Figure 5-12).



Note: 2 deep dive submissions did not contain standardized data
Source: PDUFA Electronic Review Assessment Deep Dive Cohort Analysis

Figure 5-12: Average number of data fitness IRs by submission type, JumpStart status, and pass rate

Sixty-eight percent (44/65) of survey respondents strongly agreed or agreed that standardized data makes it easier for them to respond to a consult request (Figure 5-13). Sixty-one percent (39/64) of survey respondents strongly agreed or agreed that standardized data makes it easier to prepare for advisory committee meetings.



Note: 115 and 116 reviewers did not answer the questions respectively and 21 answered N/A
Source: PDUFA Electronic Review Assessment Survey

Figure 5-13: Impact of standardized data on primary reviewers

Most applications were received in electronic format and differences in first cycle approval rates were not evident (Table 5-13, Table 5-14, Table 5-15, Table 5-16, Table 5-17).

Table 5-13: First cycle approval rates for CDER original applications by submission format, priority and Program designation

			% OF ACTION* (NUMBER OF ACTIONS / TOTAL NUMBER OF SUBMISSIONS)		
DESIGNATION	**APPLICATION TYPE**	**ACTION**	**PAPER**	**MIXED**	**ELECTRONIC**
Priority / Non-Program	NDAs and BLAs	Approval	0% (0/0)	0% (0/0)	75% (33/44)
		CR	0% (0/0)	0% (0/0)	25% (11/44)
	NDAs and BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)	88% (7/8)
		CR	0% (0/0)	0% (0/0)	13% (1/8)
Priority / Program	NDAs and BLAs	Approval	0% (0/0)	0% (0/0)	95% (55/58)
		CR	0% (0/0)	0% (0/0)	5% (3/58)
	NDAs and BLAs with Major Amendments	Approval	0% (0/0)	100% (1/1)	93% (14/15)
		CR	0% (0/0)	0% (0/1)	7% (1/15)
Standard / Non-Program	NDAs and BLAs	Approval	0% (0/0)	57% (4/7)	55% (131/237)
		CR	0% (0/0)	43% (3/7)	45% (106/237)
	NDAs and BLAs with Major Amendments	Approval	0% (0/0)	100% (1/1)	76% (25/33)
		CR	0% (0/0)	0% (0/1)	24% (8/33)
Standard / Program	NDAs and BLAs	Approval	0% (0/0)	0% (0/0)	70% (42/60)
		CR	0% (0/0)	0% (0/0)	30% (18/60)
	NDAs and BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)	38% (6/16)
		CR	0% (0/0)	0% (0/0)	63% (10/16)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
Source: FDA data systems - Study Cohort

Table 5-14: First cycle approval rates for CBER original applications by submission format, priority and Program designation

			% OF ACTION* (NUMBER OF ACTIONS / TOTAL NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	ACTION	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	BLAs	Approval	0% (0/0)	0% (0/0)	100% (2/2)
		CR	0% (0/0)	0% (0/0)	0% (0/2)
	BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)	0% (0/0)
		CR	0% (0/0)	0% (0/0)	0% (0/0)
Priority / Program	BLAs	Approval	0% (0/0)	0% (0/1)	67% (4/6)
		CR	0% (0/0)	100% (1/1)	33% (2/6)
	BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)	50% (1/2)
		CR	0% (0/0)	0% (0/0)	50% (1/2)
Standard / Non-Program	BLAs	Approval	0% (0/0)	0% (0/2)	100% (1/1)
		CR	0% (0/0)	100% (2/2)	0% (0/1)
	BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)	60% (3/5)
		CR	0% (0/0)	0% (0/0)	40% (2/5)
Standard / Program	BLAs	Approval	0% (0/0)	0% (0/0)	64% (9/14)
		CR	0% (0/0)	0% (0/0)	36% (5/14)
	BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)	80% (8/10)
		CR	0% (0/0)	0% (0/0)	20% (2/10)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
Source: FDA data systems - Study Cohort

Table 5-15: First cycle approval rates for CDER efficacy supplement applications by submission format, priority and Program designation

			% OF ACTION* (NUMBER OF ACTIONS / TOTAL NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	ACTION	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	NDAs and BLAs	Approval	0% (0/0)	100% (1/1)	94% (157/167)
		CR	0% (0/0)	0% (0/1)	6%(10/167)
	NDAs and BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)	89% (8/9)
		CR	0% (0/0)	0% (0/0)	11% (1/9)
Standard / Non-Program	NDAs and BLAs	Approval	100% (3/3)	78% (7/9)	86% (354/412)
		CR	0% (0/0)	22% (2/9)	14% (58/412)
	NDAs and BLAs with Major Amendments	Approval	0% (0/0)	100% (2/2)	83% (15/18)
		CR	0% (0/0)	0% (0/2)	17% (3/18)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
Source: FDA data systems - Study Cohort

Table 5-16: First cycle approval rates for CBER efficacy supplement applications by submission format, priority and Program designation

			% OF ACTION* (NUMBER OF ACTIONS / TOTAL NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	ACTION	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	BLAs	Approval	0% (0/0)	0% (0/0)	100% (2/2)
		CR	0% (0/0)	0% (0/0)	0% (0/2)
	BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)	0% (0/0)
		CR	0% (0/0)	0% (0/0)	0% (0/0)
Standard / Non-Program	BLAs	Approval	100% (1/1)	100% (3/3)	87% (60/69)
		CR	0% (0/1)	0% (0/3)	13% (9/69)
	BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)	80% (4/5)
		CR	0% (0/0)	0% (0/0)	20% (1/5)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
Source: FDA data systems - Study Cohort

Table 5-17: First cycle approval rates for CBER original applications by SDTM inclusion, priority and Program designation

			% OF ACTION* (NUMBER OF ACTIONS / TOTAL NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	ACTION	SDTM	NON-SDTM
Priority / Non-Program	BLAs	Approval	0% (0/0)	100% (2/2)
		CR	0% (0/0)	0% (0/2)
	BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)
		CR	0% (0/0)	0% (0/0)
Priority / Program	BLAs	Approval	0% (0/1)	67% (4/6)
		CR	100% (1/1)	33% (2/6)
	BLAs with Major Amendments	Approval	0% (0/0)	50% (1/2)
		CR	0% (0/0)	50% (1/2)
Standard / Non-Program	BLAs	Approval	0% (0/0)	33% (1/3)
		CR	0% (0/0)	67% (2/3)
	BLAs with Major Amendments	Approval	0% (0/0)	60% (3/5)
		CR	0% (0/0)	40% (2/5)
Standard / Program	BLAs	Approval	57% (4/7)	71% (5/7)
		CR	43% (3/7)	29% (2/7)
	BLAs with Major Amendments	Approval	100% (5/5)	60% (3/5)
		CR	0% (0/5)	40% (2/5)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
Source: FDA data systems - Study Cohort

The low number of CBER applications with SDTM data limited the ability to observe any meaningful differences in the analysis performed below (Table 5-18).

Table 5-18: First cycle approval rates for CBER efficacy supplement applications by SDTM inclusion, priority and Program designation

			% OF ACTION* (NUMBER OF ACTIONS / TOTAL NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	ACTION	SDTM	NON-SDTM
Priority / Non-Program	BLAs	Approval	0% (0/0)	100% (2/2)
		CR	0% (0/0)	0% (0/2)
	BLAs with Major Amendments	Approval	0% (0/0)	0% (0/0)
		CR	0% (0/0)	0% (0/0)
Standard / Non-Program	BLAs	Approval	67% (6/9)	91% (58/64)
		CR	33% (3/9)	9% (6/64)
	BLAs with Major Amendments	Approval	0% (0/0)	80% (4/5)
		CR	0% (0/0)	20% (1/5)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
Source: FDA data systems - Study Cohort

With the low number of paper and mixed submission in the Study Cohort, approval rate differences by submission format could not be determined for either CDER or CBER original submissions or efficacy supplements times (Table 5-19, Table 5-20, Table 5-21, Table 5-22).

Table 5-19: Time to first action for CDER original applications by submission format, priority, and Program designation

			AVG. # OF DAYS TO FIRST ACTION* (NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	NDAs and BLAs	183	NA (0)	NA (0)	167 (43)
	NDAs and BLAs with Major Amendments	274	NA (0)	NA (0)	289 (8)
Priority / Program	NDAs and BLAs	243	NA (0)	NA (0)	216 (58)
	NDAs and BLAs with Major Amendments	335	NA (0)	334 (1)	346 (15)
Standard / Non-Program	NDAs and BLAs	304	NA (0)	304 (7)	301 (237)
	NDAs and BLAs with Major Amendments	395	NA (0)	396 (1)	413 (33)
Standard / Program	NDAs and BLAs	365	NA (0)	NA (0)	365 (60)
	NDAs and BLAs with Major Amendments	456	NA (0)	NA (0)	454 (6)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

Table 5-20: Time to first action for CBER original applications by submission format, priority, and Program designation

			AVG. # OF DAYS TO FIRST ACTION* (NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	BLAs	183	NA (0)	NA (0)	179 (2)
	BLAs with Major Amendments	274	NA (0)	NA (0)	NA (0)
Priority / Program	BLAs	243	NA (0)	242 (1)	210 (6)
	BLAs with Major Amendments	335	NA (0)	NA (0)	286 (2)
Standard / Non-Program	BLAs	304	NA (0)	261 (2)	300 (1)
	BLAs with Major Amendments	395	NA (0)	NA (0)	369 (5)
Standard / Program	BLAs	365	NA (0)	NA (0)	344 (14)
	BLAs with Major Amendments	456	NA (0)	NA (0)	444 (10)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

Table 5-21: Time to first action for CDER efficacy supplements by submission format, priority, and Program designation

			AVG. # OF DAYS TO FIRST ACTION* (NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	NDAs and BLAs	183	NA (0)	181 (1)	179 (166)
	NDAs and BLAs with Major Amendments	274	NA (0)	NA (0)	264 (9)
Standard / Non-Program	NDAs and BLAs	304	304 (3)	332 (9)	293 (412)
	NDAs and BLAs with Major Amendments	395	NA (0)	388 (2)	391 (18)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

Table 5-22: Time to first action for CBER efficacy supplements by submission format, priority, and Program designation

			AVG. # OF DAYS TO FIRST ACTION* (NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	BLAs	183	NA (0)	NA (0)	182 (2)
	BLAs with Major Amendments	274	NA (0)	NA (0)	NA (0)
Standard / Non-Program	BLAs	304	371 (1)	304 (3)	300 (69)
	BLAs with Major Amendments	395	NA (0)	NA (0)	372 (5)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

On average, CDER priority, non-program efficacy supplements with SDTM data had slightly less time to first action compared to supplements without SDTM data (Table 5-23).

Table 5-23: Time to first action for CDER efficacy supplements by SDTM inclusion, priority, and Program designation

			AVG. # OF DAYS TO FIRST ACTION* (NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	SDTM	NON-SDTM
Priority / Non-Program	NDAs and BLAs	183	175 (105)	186 (62)
	NDAs and BLAs with Major Amendments	274	270 (5)	258 (4)
Standard / Non-Program	NDAs and BLAs	304	295 (169)	293 (255)
	NDAs and BLAs with Major Amendments	395	395 (8)	387 (12)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

The low number of CBER applications with SDTM data limited the ability to observe any meaningful differences in the analysis performed below (Table 5-24, Table 5-25).

Table 5-24: Time to first action for CBER original applications by SDTM inclusion, priority, and Program designation

			AVG. # OF DAYS TO FIRST ACTION* (NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	SDTM	NON-SDTM
Priority / Non-Program	BLAs	183	NA (0)	179 (2)
	BLAs with Major Amendments	274	NA (0)	NA (0)
Priority / Program	BLAs	243	217 (1)	214 (6)
	BLAs with Major Amendments	335	NA (0)	286 (2)
Standard / Non-Program	BLAs	304	NA (0)	274 (3)
	BLAs with Major Amendments	395	NA (0)	369 (5)
Standard / Program	BLAs	365	349 (7)	338 (7)
	BLAs with Major Amendments	456	455 (5)	433 (5)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

Table 5-25: Time to first action for CBER efficacy supplements by SDTM inclusion, priority, and Program designation

			AVG. # OF DAYS TO FIRST ACTION* (NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	SDTM	NON-SDTM
Priority / Non-Program	BLAs	183	NA (0)	182 (2)
	BLAs with Major Amendments	274	NA (0)	NA (0)
Standard / Non-Program	BLAs	304	302 (9)	302 (64)
	BLAs with Major Amendments	395	NA (0)	372 (5)

* Only includes submissions that received a complete response (i.e., complete response, approvable, not approved), approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

With the low number of paper and mixed submission in the Study Cohort, approval rate differences by submission format could not be determined for either CDER or CBER original submissions or efficacy supplements times (Table 5-26, Table 5-27, Table 5-28, Table 5-29).

Table 5-26: Time to first cycle approval for CDER original applications by submission format, priority, and Program designation

			AVG. # OF DAYS TO FIRST APPROVAL* (NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	NDAs and BLAs	183	NA (0)	NA (0)	163 (32)
	NDAs and BLAs with Major Amendments	274	NA (0)	NA (0)	292 (7)
Priority / Program	NDAs and BLAs	243	NA (0)	NA (0)	215 (55)
	NDAs and BLAs with Major Amendments	335	NA (0)	334 (1)	347 (14)
Standard / Non-Program	NDAs and BLAs	304	NA (0)	304 (4)	300 (131)
	NDAs and BLAs with Major Amendments	395	NA (0)	396 (1)	409 (25)
Standard / Program	NDAs and BLAs	365	NA (0)	NA (0)	366 (42)
	NDAs and BLAs with Major Amendments	456	NA (0)	NA (0)	454 (6)

*Only includes submissions that received first cycle approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

Table 5-27: Time to first cycle approval for CBER original applications by submission format, priority, and Program designation

			AVG. # OF DAYS TO FIRST APPROVAL* (NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	BLAs	183	NA (0)	NA (0)	179 (2)
	BLAs with Major Amendments	274	NA (0)	NA (0)	NA (0)
Priority / Program	BLAs	243	NA (0)	NA (0)	200 (4)
	BLAs with Major Amendments	335	NA (0)	NA (0)	332 (1)
Standard / Non-Program	BLAs	304	NA (0)	NA (0)	300 (1)
	BLAs with Major Amendments	395	NA (0)	NA (0)	383 (3)
Standard / Program	BLAs	365	NA (0)	NA (0)	360 (9)
	BLAs with Major Amendments	456	NA (0)	NA (0)	455 (8)

*Only includes submissions that received first cycle approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

Table 5-28: Time to first cycle approval for CDER efficacy supplements by submission format, priority, and Program designation

			AVG. # OF DAYS TO FIRST APPROVAL* (NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	NDAs and BLAs	183	NA (0)	181 (1)	180 (156)
	NDAs and BLAs with Major Amendments	274	NA (0)	NA (0)	263 (8)
Standard / Non-Program	NDAs and BLAs	304	304 (3)	341 (7)	290 (354)
	NDAs and BLAs with Major Amendments	395	NA (0)	388 (2)	390 (15)

*Only includes submissions that received first cycle approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

Table 5-29: Time to first cycle approval for CBER efficacy supplements by submission format, priority, and Program designation

			AVG. # OF DAYS TO FIRST APPROVAL* (NUMBER OF SUBMISSIONS)		
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	PAPER	MIXED	ELECTRONIC
Priority / Non-Program	BLAs	183	NA (0)	NA (0)	182 (2)
	BLAs with Major Amendments	274	NA (0)	NA (0)	NA (0)
Standard / Non-Program	BLAs	304	371 (1)	304 (3)	300 (60)
	BLAs with Major Amendments	395	NA (0)	NA (0)	390 (4)

*Only includes submissions that received first cycle approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

For average time to first action, priority submissions without major amendments with SDTM data had shorter average times to first action than for non-SDTM submissions (Table 5-30).

Table 5-30: Time to first cycle approval for CDER efficacy supplements by SDTM inclusion, priority, and Program designation

			AVG. # OF DAYS TO FIRST CYCLE APPROVAL* (NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	SDTM	NON-SDTM
Priority / Non-Program	NDAs and BLAs	183	175 (98)	188 (59)
	NDAs and BLAs with Major Amendments	274	269 (4)	258 (4)
Standard / Non-Program	NDAs and BLAs	304	293 (144)	289 (220)
	NDAs and BLAs with Major Amendments	395	395 (6)	387 (11)

*Only includes submissions that received first cycle approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

The low number of CBER applications with SDTM data limited the ability to observe any meaningful differences in the analysis performed below (Table 5-31).

Table 5-31: Time to first cycle approval for CBER original applications by SDTM inclusion, priority, and Program designation

			AVG. # OF DAYS TO FIRST APPROVAL* (NUMBER OF SUBMISSIONS)	
DESIGNATION	APPLICATION TYPE	PROJECTED TIME TO COMPLETION**	SDTM	NON-SDTM
Priority / Non-Program	BLAs	183	NA (0)	179 (2)
	BLAs with Major Amendments	274	NA (0)	NA (0)
Priority / Program	BLAs	243	NA (0)	200 (4)
	BLAs with Major Amendments	335	NA (0)	332 (1)
Standard / Non-Program	BLAs	304	NA (0)	300 (1)
	BLAs with Major Amendments	395	NA (0)	383 (3)
Standard / Program	BLAs	365	353 (4)	365 (5)
	BLAs with Major Amendments	456	455 (5)	455 (3)

*Only includes submissions that received first cycle approval
**Based on projected completion times from the"21st Century Review Process Desk Reference Guide"
Source: FDA data systems - Study Cohort

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