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Assessment of the Impact of the Electronic Submission and Review Environment on the Efficiency and Effectiveness of the Review of Human Drugs – Final Report

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Booz | Allen | Hamilton

Table of Contents

EXECUTIVE SUMMARY 1
Assessment Overview 1
Degree of Electronic Implementation 1
Baseline Review Performance 2
Exchange and Content Data Standards 4
Review Tools and Training Analysis 5
Current Organization and Responsibilities 6
Progress against Ideal Electronic Review Environment 6
Recommendations 8

ASSESSMENT OVERVIEW 9
Objectives and Scope 9
Assessment Cohorts 9
Methodology 11

FINDINGS 12
Degree of Electronic Implementation 12
Baseline Review Performance 21
Exchange and Content Data Standards 37
Review Tools and Training Analysis 43
Current Organization and Responsibilities 50

PROGRESS AGAINST IDEAL ELECTRONIC REVIEW ENVIRONMENT 53

RECOMMENDATIONS 56

APPENDIX A: ADDITIONAL ANALYSES 61

APPENDIX B: METHODOLOGY 90

APPENDIX C: HYPOTHESES 94

APPENDIX D: REVIEW DIVISION ACRONYMS 101

APPENDIX E: EXCHANGE AND CONTENT DATA STANDARDS 102

APPENDIX F: DETAILED ELECTRONIC REVIEW TOOL AND TRAINING ANALYSIS 140

APPENDIX G: SURVEY 172

APPENDIX H: PDUFA IV ANALYSIS AND DEEP DIVE COHORT APPLICATIONS 183

Exhibits

Exhibit 1: Overview of Study Cohorts 10
Exhibit 2: Data Gathering and Analysis Methodology 11
Exhibit 3: Format of NDAs by Fiscal Year 13
Exhibit 4: Format of BLAs by Fiscal Year 14
Exhibit 5: Format of NDA Submission by Review Division 15
Exhibit 6: Format of BLA Submissions by Review Division 16
Exhibit 7: Format of NDAs/BLAs from Large Applicants 17
Exhibit 8: Format of NDAs/BLAs from Medium Applicants 19
Exhibit 9: Format of NDAs/BLAs from Small Applicants 20
Exhibit 10: NDA and BLA Approval Rates 22
Exhibit 11: Priority NDA Approval Rate by Fiscal Year, by Submission Format 23
Exhibit 12: Standard NDA Approval Rate by Fiscal Year, by Submission Format 24
Exhibit 13: Priority and Standard BLA Approval Rate by Submission Format, by Fiscal Year 25
Exhibit 14: First Cycle Action for NDAs by Submission Format 26
Exhibit 15: First Cycle Action for BLAs by Submission Format 27
Exhibit 16: Average Time to Approval for Priority NDAs, by Fiscal Year and Submission Format 28
Exhibit 17: Average Time to Approval for Standard NDAs, by Fiscal Year and Submission Format 29
Exhibit 18: Average Time to Approval for CDER BLAs, by Fiscal Year and Submission Format 30
Exhibit 19: Average Time to Approval for CBER BLAs, by Fiscal Year and Submission Format 31
Exhibit 20: Average Time to First Action for NDAs by Submission Format 32
Exhibit 21: Average Time to First Action for BLAs by Submission Format, by Center 33
Exhibit 22: Responses to Survey Question: Does a fully electronic application improve your review experience? 34
Exhibit 23: Printing Habits of Review Staff 35
Exhibit 24: Characteristics of Review Staff that Print Full Sections and/or Applications of Electronic Applications 36
Exhibit 25: Suggestions for Improving Applicants' Electronic Submissions 37
Exhibit 26: Exchange and Content Data Standards Role in NDA/BLA Review Process Lifecycle 39
Exhibit 27: Adoption of eCTD Format and Gateway for Electronic NDAs 40
Exhibit 28: Adoption of SDTM for NDAs 41
Exhibit 29: Overall Approval Rates and Time to Approval for SDTM and Non-SDTM Applications 42
Exhibit 30: Exchange and Content Data Standard Experience by Preference for Applications with Standardized Data 43
Exhibit 31: Review Tools Associated with the Application Review Lifecycle 44
Exhibit 32: Perceived Accessibility of Process Tools 46
Exhibit 33: Survey Respondents Tool Usage, by Discipline 47
Exhibit 34: Reviewers' Perceived Benefits and Proficiency of Most Used Analysis Tools 48
Exhibit 35: Training Course Attendance and Satisfaction with Course Format 49
Exhibit 36: Most Preferred Training Formats 50

Exhibit 37: Responsibilities of CBER and CDER Groups Involved with Electronic Submissions....51
Exhibit 38: Level of Progress towards Potential Ideal Future State....55
Exhibit 39: Format of NDA Submissions by Review Division....62
Exhibit 40: Format of BLA Submissions by Review Division....63
Exhibit 41: Average Time to Approval for NDAs by Submission Format....64
Exhibit 42: Average Time to Approval for Priority NDAs, by Review Division and Submission Format....65
Exhibit 43: Average Time to Approval for Standard NDAs, by Review Division and Submission Format....67
Exhibit 44: Average Time to Approval for BLAs, by Submission Designation and Submission Format....68
Exhibit 45: Average Time to Approval for BLAs, by Submission Designation, Submission Format and Center....69
Exhibit 46: Average Time to Approval for Priority BLAs, by Review Division and Submission Format....70
Exhibit 47: Average Time to Approval for Standard BLAs, by Review Division and Submission Format....71
Exhibit 48: Average Time to First Action for Priority NDAs, by Fiscal Year and Submission Format....72
Exhibit 49: Average Time to First Action for Standard NDAs, by Fiscal Year and Submission Format....73
Exhibit 50: Average Time to First Action for Priority NDAs, by Review Division and Submission Format....74
Exhibit 51: Average Time to First Action for Standard NDAs, by Review Division and Submission Format....76
Exhibit 52: Average Time to First Action for BLAs by Submission Format....77
Exhibit 53: Average Time to First Action for Priority BLAs, by Fiscal Year and Submission Format....78
Exhibit 54: Average Time to First Action for Standard BLAs, by Fiscal Year and Submission Format....79
Exhibit 55: Average Time to First Action for Priority BLAs by Submission Format, by Division....80
Exhibit 56: Average Time to First Action for Standard BLAs by Submission Format, by Division....81
Exhibit 57: Average Time to First Action for BLAs by Submission Type, Submission Designation and Submission Format, by Center....82
Exhibit 58: Time to Approval and Time to First Action for NDAs with SDTM Data....83
Exhibit 59: Reasons for Preferring Electronic Applications....86
Exhibit 60: Reasons for Preferring Standardized Data....86
Exhibit 61: Analysis Tools Usage by Discipline....87
Exhibit 62: IT Barriers Cited by Survey Participants....87
Exhibit 63: Overview of Data Sources....90
Exhibit 64: The eCTD Triangle....109
Exhibit 65: eCTD Viewer....111
Exhibit 66: eCTD and RPS Structures....115
Exhibit 67: CDISC SDTM Standard Domains....122
Exhibit 68: FDA Proposed Goal for Regulatory Submissions Using CDISC-HL7....137

Exhibit 69: Demographics of Survey Respondents....172
Exhibit 70: Survey Respondents' Experience....173
Exhibit 71: Survey of Costs and Benefits Associated with Automated Standards-based eSubmissions....174

Tables

Table 1: Progress against Ideal Electronic Review Environment....7
Table 2: Recommendations....8
Table 3: Submission Format Descriptions....12
Table 4: Accepted and Required Exchange and Content Data Standards....38
Table 5: List of Electronic Review Tools Evaluated....44
Table 6: Progress against Ideal Electronic Review Environment....54
Table 7: Recommendations....57
Table 8: Approval Rate by Submission Format for Priority and Standard NDAs....61
Table 9: Approval Rate by Submission Format for Priority and Standard BLAs....61
Table 10: Percentage of CDER SDTM Applications by Fiscal Year....61
Table 11: Review Activities for Electronic Submissions....84
Table 12: Safety Activities for Electronic NDA Submissions....85
Table 13: CDER Electronic Submission Groups....88
Table 14: CBER Electronic Submission Groups....89
Table 15: Methodology for Excluding Data Elements....92
Table 16: Hypotheses....94
Table 17: FDA Data Standards Working Groups....107
Table 18: Readiness of eCTD....113
Table 19: Strengths/Benefits and Limitations/Challenges for eCTD Submissions....114
Table 20: Readiness of RPS....117
Table 21: Strengths/Benefits and Limitations/Challenges for RPS Submissions....118
Table 22: Readiness of Product Data Stability Standard....120
Table 23: Strengths/Benefits and Limitations/Challenges for Product Stability Data Standard 121
Table 24: Readiness of SDTM....123
Table 25: Strengths/Benefits and Limitations/Challenges for SDTM....124
Table 26: Readiness of SEND....126
Table 27: Strengths/Benefits and Limitations/Challenges for SEND Submissions....127
Table 28: Standardized CDASH Domains....128
Table 29: Readiness of CDASH....129
Table 30: Strengths/Benefits and Limitations/Challenges for CDASH Submissions....130
Table 31: Readiness of ADaM....133
Table 32: Strengths/Benefits and Limitations/Challenges for ADaM Submissions....133
Table 33: Drug Listing and Clinical Data Elements for SPL Documents....135
Table 34: Readiness of SPL....135
Table 35: Strengths/Benefits and Limitations/Challenges for SPL Submissions....136
Table 36: CDISC-HL7 Messages....138
Table 37: Readiness of CDISC-HL7....138
Table 38: Strengths/Benefits and Limitations/Challenges for CDISC-HL7 Submissions....139

EXECUTIVE SUMMARY

This report summarizes an analysis of the impact of the electronic review environment on the review processes, as well as the outputs and outcomes, associated with receipt and review of New Drug Applications (NDAs), Biologics License Applications (BLAs) and efficacy supplements. In partnership with the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), Booz Allen undertook a multi-stage project to evaluate the FDA's current electronic submission and review environment, which included current use of exchange and content data standards, reviewer tools and electronic review training.

Assessment Overview

An evaluation of the efficiency and effectiveness of electronic submissions and review processes in CDER and CBER was performed to identify any challenges in the current FDA system, such as barriers to use. This assessment will allow the FDA to make progress towards their long-term goal of an automated, standards-based information technology environment for the exchange, review, and management of information supporting the process for the review of human drug applications throughout the product life cycle (including approval and post-approval processes). The assessment included all CDER and CBER original applications and efficacy supplements submitted during the PDUFA III and IV timeframe (i.e., October 1, 2002 – September 30, 2012) with a data cut-off date of March 2, 2011. Data used for the analysis were collected through various sources, including action packages, FDA data systems, interviews, focus groups, surveys and publically available sources. Booz Allen used this data to analyze the degree of electronic implementation, impact on review performance and staff, exchange and content data standards and review tools and training to develop recommendations for improvement.

Degree of Electronic Implementation

The degree of electronic implementation was assessed by evaluating the adoption of electronic submissions and adoption by company size. A continued year-over-year increase in receipt of NDA electronic submissions was observed. Moreover, the receipt of electronic submissions via the Electronic Submissions Gateway, rather than electronic media formats (e.g., CDs, DVDs), continued to increase. Since FY03, the percentage of paper and mixed applications declined as the percentage of electronic applications increased. In FY10 and FY11 (partial year), FDA received over 60% (143/220 and 53/73, respectively) of NDA original applications and efficacy supplements electronically through the Gateway. This data indicate that NDA applicants are moving towards adoption of electronic submissions through the Gateway.

Analysis of NDA and BLA application submission formats from FY03 to FY10 indicated a shift from being heavily focused on paper and mixed submission formats during the earlier years to significantly more electronic submissions during recent years as FDA transitioned from PDUFA III to PDUFA IV. Additionally, the proportion of eCTD electronic submissions increased relative to non-eCTD submissions over time for all applicant size groups. Prior to PDUFA IV, a majority of submissions were in mixed format regardless of applicant company size. The most recent results from FY10 and FY11 showed that nearly all submissions from large applicants were

submitted electronically. Similar trends were observed in medium and small applicants, although the transition was not as complete as for large applicants.

Baseline Review Performance

The baseline review performance was assessed to determine whether electronic submissions impact approval rate, time to approval, time to first action and review behavior.

Impact on Approval Rate

NDA and BLA approval rates were evaluated for priority and standard submission designations. For NDAs, priority designated applications had a slightly higher percentage of overall approvals than standard designated applications (80%, 350/438 and 75%, 1026/1364 respectively). Similar to NDAs, BLA priority designated applications demonstrated a higher percentage of approvals compared to standard applications (90%, 73/81 and 83%, 180/216, respectively).

To determine the impact of the submission designation and submission format on NDA approval rates, priority and standard applications were evaluated by fiscal year. The applications were separated out by fiscal year and the number of review cycles required for approval (i.e., first-cycle vs. multiple cycles). Previous analysis of the submission format by fiscal year showed receipt of more paper and mixed applications in earlier years. Therefore, those applications would have more time to reach approval compared to more recently received applications. For both NDAs and BLAs, this analysis showed no apparent impact of submission format on approval rate, regardless of submission designation.

Additionally, Booz Allen examined NDA and BLA submission formats by submissions designation for trends in first cycle actions. Data did not indicate major differences in NDA or BLA first-cycle approval rates for various submission formats in either submission designation. In both priority and standard designated NDA reviews, electronic Gateway formats demonstrated the highest first-cycle approval rates of 71% (55/77) and 66% (162/247), respectively. Among priority designated applications, the electronic non-Gateway format had the lowest first-cycle approval rate (58%, 42/72), followed by mixed formats (62%, 138/223) and paper (62%, 45/72). In contrast, the rate of first-cycle approval for standard designated applications was lowest for paper formats (50%, 87/175) and mixed formats (53%, 365/690). For both priority and standard designated BLAs, the electronic format had slightly higher first-cycle approval rates than paper formats, (73%, 41/56 compared to 67%, 18/27 for priority, and 62%, 99/159 compared to 57%, 37/65 for standard, respectively). Although the first-cycle approval rate for electronic formats was higher, the difference is not large enough to determine a relationship between submission format and first-cycle action. The findings for the impact of submission format on NDA approval rate are consistent with qualitative feedback from reviewers received during focus groups and interviews, indicating that submission format generally does not impact the content of the submission or the approach to the review.

Impact on Time to Approval

For priority and standard designated submissions, available data did not indicate a significant relationship between approval time and submission format for NDA applications. Additionally, no significant trends were found for the impact of electronic submissions on approval times for priority or standard BLA submissions in either CDER or CBER.

Impact on Time to First Action

Within each submission designation for NDAs, there was little variance of time to first action between submission formats in complete response and approval actions. Electronic, Gateway applications that received a complete response under a standard review timeline took on average the longest to reach first action (314 days). In all but the priority complete response category, paper submissions took the shortest average time to first action in all categories, having the shortest overall average of 174 days (priority approval).

The impact of electronic submissions on BLAs' time to first action was also analyzed. Average time to first action for priority applications reviewed by CBER took longer for paper submissions than electronic submissions (185 and 171 days for approvals, and 174 and 164 days for complete response, respectively). In contrast, CDER took longer for priority, electronic submissions than paper submissions (199 and 188 days for approval, and 195 and 183 days for complete response, respectively). Analysis of standard designated applications did not show significant trends for time to first action based on submission format. These slight differences did not indicate an impact of submission format on the average time to first action.

Data analyses did not clearly identify any significant trends between the submission format for NDAs or BLAs and the time to first action. This is consistent with qualitative data received from reviewer focus groups indicating that submission format does not usually impact submission content or FDA's approach to the review.

Impact on Review Staff and Activities

Focus group, interview and survey data were analyzed to determine how reviewers interact with and are impacted by electronic applications (e.g., tools usage, printing habits). The majority of survey respondents (89%, 450/506 respondents) believe electronic applications improve their review. In CBER, 26% (29/110) of those surveyed responded "no" when asked if electronic applications improve their review experience, whereas only 7% (27/396) responded "no" in CDER. Based on review staff responses, reviewers prefer to receive electronic submissions for a number of reasons, primarily due to the ease of accessing and finding information within the review and faster delivery of the application. Further advantages of the electronic submission include eliminating the need for photocopying sections, spending less time searching for documents and requiring less reliance on applicants by reducing the need for obtaining additional copies of paper applications. Focus group participants also noted electronic submission makes it easier to access the application while working remotely, allows reviewers to review labeling on two monitors and enables reviewers to copy and paste data and tables without manual re-entry into a tool or document.

To better understand how electronic applications impact review behavior, survey participants were asked whether they would print some portion of an electronic application. Out of the respondents that answered, 80% (393/ 490) indicated that they print some portion of an electronic submission after receipt.

Survey respondents indicated that applicants could improve their applications by including a thorough table of contents and working hyperlinks that are clearly written and relevant to the review. Furthermore, the review activities would benefit from applications that are submitted in preferred formats and include standardized data.

Exchange and Content Data Standards

To understand the current state of exchange and content data standards at CDER and CBER, the assessment evaluated the role of standards in the review process, the degree of adoption, impact on approval rates and first action and reviewers' preferences for exchange and content data standards.

Exchange and Content Data Standards Role in NDA/BLA Review Process Lifecycle

The use of exchange and content data standards spans the NDA/BLA review process lifecycle and impacts multiple users. Some standards are used throughout the entire review process (e.g., eCTD, SPL), while others may be specific for a type of review (e.g., SDTM, ADaM, SEND). Other exchange and content data standards are still under development and may be implemented in the future at FDA.

Adoption of Exchange and Content Standards

Analysis of electronic submission format and delivery method indicated that applicants are increasingly submitting applications in eCTD format and utilizing the Gateway as a delivery method. In FY04, CDER began accepting applications with standardized clinical trial data in Study Data Tabulation Model (SDTM) format; however, the Center only has a local tracking method and has not yet adopted a formal mechanism to identify and track applications with SDTM data.[1] CBER began accepting applications with SDTM data on May 15, 2010, and as of June 2011, the Center had received five submissions with SDTM data.

Impact of Exchange and Content Data Standards

In priority and standard designated NDA applications, non-SDTM applications had higher overall approval rates, with 81% (332/411) of the non-SDTM group receiving approval compared to 67% (18/27) of the SDTM applications receiving approval among priority applications. Standard applications had slightly lower approval rates for both groups, with an approval rate of 76% (992/1310) for non-SDTM and 63% (34/54) for SDTM. The time to approval was longer for applications with SDTM for both priority and standard submission designations, except in multi-cycle approvals for standard designated applications. However, it should be noted that the sample size for SDTM applications was much smaller than non-SDTM applications and there may be other confounding factors. Some reviewers noted that applications with SDTM data were more complicated applications and they may have also included non-SDTM datasets in the same application. Additionally, SDTM training for reviewers had not been fully implemented until recently.

When asked whether they prefer applications with standardized data versus applications without standardized data, a majority of survey respondents indicated a preference for applications with standardized data, even if they had not had experience with a particular exchange or content data standard. Respondents were also asked why they preferred applications with data standards; results showed that preference did not favor greater depth in analysis, but rather

[1] At the time of data collection, CDER and CBER did not have a formal tracking mechanism in place. As of March 2011, the two Centers improved the tracking of SDTM applications through the use of the define.xml file.

data presentation. The reviewers indicated that they favored standardized data because it was more organized, structured and presented in a familiar format.

Review Tools and Training Analysis

Booz Allen identified currently available electronic review tools and training programs and utilized secondary sources and targeted interviews to evaluate their use in the NDA/BLA review process. The use of tools impacts each phase of the NDA/BLA review process, and FDA reviewers and support staff rely on the tools for management of processes, document tracking, data analysis and creation of visual representations of data. Reviewers and support staff leverage process tools such as Global Submit (GS) Review, Document Archiving, Reporting and Regulatory Tracking System (DARRTS) and Regulatory Management System Biologics License Application (RMS-BLA) from the time of application receipt until FDA takes action on the application. These tools provide staff with the ability to manage, track and archive incoming and outgoing documents related to the application. Process tools also allow review staff to view submissions from the applicant and coordinate review assignments within the review team. When surveyed about the accessibility of process tools, a majority of respondents considered the tools to be consistently accessible. However, CBER tools (i.e., RMS-BLA, CBER EDR) were perceived consistently or sometimes inaccessible more frequently than tools used primarily in CDER (i.e., DARRTS, CDER EDR). In interviews, reviewers indicated difficulties accessing RMS-BLA and CBER EDR. GS Review, used by both Centers, had the lowest rates of perceived inaccessibility. However, reviewers in discipline-specific focus groups indicated they save study reports into a folder on their hard drive to avoid slower connectivity when accessing GS Review.

During the Conduct Review phase of an application review, reviewers utilize multiple analysis tools offered and supported by FDA (e.g., JMP and JReview), which provide reviewers with statistical and graphical analyses focused on clinical trial data.

Outside of the review tools supported by CDER and CBER, reviewers incorporate the functionalities and capabilities of commercially available analysis tools to conduct in-depth analyses and depict data visually to identify trends and outliers. Each tool provides different functionality and capabilities that allow reviewers to conduct the numerous types of analyses required to complete an application review. Clinical and biostatistics reviewers use the majority of tools captured in the 20 most frequently used analysis tools, consistent with the fact that these reviewers must evaluate all portions of the application in order to make a determination on the safety and efficacy of a drug or biologic. Clinical microbiology and safety reviewers in CDER and clinical reviewers and statisticians within CBER utilize the standard statistical software packages (e.g., SAS, JMP). Non-clinical and clinical pharmacology reviewers in CDER and statisticians within CBER use advanced statistics and graphics software (e.g., R, SigmaPlot, S-PLUS) along with specialized software for pharmacodynamic and pharmacokinetic analyses (e.g., Pharsight WinNonlin, NONMEM). Finally, product quality reviewers leverage much of the statistics software used by other reviewers along with software geared specifically toward the analysis of chemical structures (i.e., ChemDraw).

Survey results showed that discipline reviewers and other staff utilized a diverse range of analysis tools to complete or contribute to the application review. The most commonly used tools used across the disciplines include SAS, a common commercially available statistical software package, and JMP, a derivative of the SAS software package supported and offered by CDER and CBER. ChemDraw and Graphpad are also among the top four most frequently

used analysis tools. Survey data revealed that the greatest perceived benefit of these tools varied. A majority of respondents using ChemDraw (54%, 20/37) indicated that the tool allowed for basic review rather than a more in-depth analysis. JMP users indicated that the tool allowed them to perform a more in-depth analysis; however, only 6% (8/130) considered themselves to be experts and over half (73/130) either lacked confidence or rarely used the tool. Respondents indicated the greatest proficiency with Graphpad, with 82% (28/34) self-identifying as expert or capable proficiency.

The role of training as it might relate to the use and proficiency level of process and analysis tools was evaluated by assessing the available options for and reviewer satisfaction with training. CDER and CBER receive feedback via course completion surveys; however, it is unclear if this data is used for program-wide or historical analysis as aggregate data was not available from either Center at the time of this assessment. Out of all training offered for both process and analysis tools, GS Review Hands-On Training had the highest number of responses, with 82 out of 88 (93%) attendees agreeing or strongly agreeing that the course format was appropriate. DARRTS Training for New Users had the second highest response rate, followed by DARRTS Walk-In Sessions, with a vast majority of attendees expressing satisfaction with the course format, both of which were process tool trainings. Although relatively few respondents participated in analysis tool trainings, the majority were satisfied with course format. During focus groups and interviews, some reviewers indicated that the current training was too basic or elementary.

Classroom training in an exercise based/working session format was most preferred, with 292 responses. Walk-in clinics were moderately popular, though self-paced, interactive online courses and learning from a mentor or colleagues ranked above walk-in clinics in preferred format. Classroom training lecture format ranked the lowest of preferred training formats (142 respondents), supporting the attendance and satisfaction data.

Current Organization and Responsibilities

At the time of this report, the roles and responsibilities for managing direction and implementation of the electronic submission program are spread across multiple organizational groups. The lack of clear hierarchy and communication channels has impaired FDA's effectiveness in setting an overall organizational vision for the electronic submission and review environment. Currently, there is no group responsible for an overarching vision, and instead, groups are focused on specific segments of the business process (e.g., marketing application submission, conduct of clinical review, rollout of training for specific tool).

Progress against Ideal Electronic Review Environment

As evidenced by the findings in this report, FDA is moving towards a fully electronic review environment. In order to determine the progress towards this initiative, CDER and CBER should develop a harmonized, transparent vision of the future state of electronic review. At the time of this assessment, an overall vision that encompasses all of the different aspects of electronic review evaluated in this report was not found. In order to determine the progress towards a fully electronic submission and review environment, a vision of the future electronic review environment that incorporates the multiple facets of the new environment must be realized. Therefore, based on the performed analyses and observations from interviews and focus

groups, Booz Allen developed an ideal electronic submission and review environment to assess FDA's progress (Table 1).

Table 1: Progress against Ideal Electronic Review Environment

Area	Ideal Electronic Review Environment Element	Current Progress
Electronic Submissions	▸ All applications submitted electronically	**NDA Original Applications and Efficacy Supplements** ▸ 87% (191/220) of applications submitted electronically in FY10 ▸ 95% (69/73) of applications submitted electronically in FY11 (partial year) **BLA Original Applications and Efficacy Supplements** ▸ 76% (37/49) of applications submitted electronically in FY10 ▸ 96% (27/28)of applications submitted electronically in FY11 (partial)
	▸ All applications submitted through the Gateway	**NDA Original Applications and Efficacy Supplements** ▸ 65% (143/220) of applications submitted through the Gateway in FY10 ▸ 73% (53/73) of applications submitted through the Gateway in FY11 (partial)
Exchange and Content Data Standards	▸ Exchange standard implemented for all electronically submitted applications	**NDA Original Applications and Efficacy Supplements** ▸ 94% (179/191) of electronic applications utilized the eCTD format in FY10 ▸ 90% (66/73) of electronic applications utilized the eCTD format in FY11 (partial year) **BLA Original Applications and Efficacy Supplements**[2] ▸ 19% (5/27) of electronic applications utilized the eCTD format in FY10
	▸ Exchange or content data standard implemented for all incoming non-clinical and clinical data	▸ For those exchange and content data standards that are planned for implementation, CDER and CBER currently accept 50% (2/4) of these standards[3] **NDA Original Applications and Efficacy Supplements** ▸ 10% (22/220) applications submitted with SDTM data in FY10 ▸ 15% (11/73) applications submitted with SDTM data in FY11 (partial year)
Review Tools	▸ Process and analysis tools implemented and utilized for each accepted exchange and content data standard	▸ 100% of accepted standards have associated tools ▸ GS Review used for eCTD ▸ WebSDM Empirica Study, JReview and JMP used for CDISC SDTM ▸ JReview and JMP used for CDISC ADaM
Training	▸ Diverse and effective training available for all process and analysis tools to meet staff needs and preferences	▸ CDER and CBER provide training for all supported process and analysis tools through the HHS Learning Portal - Course format variety is available for select tools; it is unclear if reviewer preferences are considered - Different levels of training (e.g., beginner, expert) are not offered by either center ▸ CDER and CBER receive feedback via course completion surveys; it is unclear if this data is used for program-wide or historical analysis as aggregate data was not available from either Center at the time of this assessment. ▸ External/vendor training is available for unsupported analysis tools

[2] BLA eCTD data for FY11 were not available at the time of data collection

[3] CDASH is not planned for implementation ; CDISC-HL7 will incorporate CDISC SDTM and ADaM

Recommendations

The findings from this assessment indicate an increasing trend in the submission of electronic applications to CDER and CBER. Additionally, the two Centers are in the process of implementing exchange and content data standards critical to the improved efficiency and transparency of the drug and biologic review process. The need for review tools capable of leveraging standardized data to automate analyses and provide more in-depth analyses will increase with expanded standard implementation by the Centers and adoption by applicants. As the standards and tools continue to evolve and mature, the FDA will need to grow and adapt to meet the needs of and realize the efficiencies for review staff.

Recommendations focus on developing a workforce, processes, technologies and infrastructure that can operate effectively in the new and evolving environment (Table 2).

Table 2: Recommendations

Area/ Goal	Recommendations
People *Develop a workforce able to fully and efficiently leverage electronic submission tools and capabilities*	**1.** Develop effective training to ensure new technologies are effectively integrated and staff is comfortable and skilled with process and analysis tools o Support preferred formats o Establish feedback mechanism
Processes *Set up standardized processes to ensure success of the electronic submission program*	**2.** Develop clear roles and responsibilities for managing direction and implementation of the electronic submission program **3.** Develop process metrics and tracking dashboard o Automate reporting and analysis where possible o Develop tool for reviewers to provide process feedback
Technology *Ensure tools and technologies are available to support use of the electronic data*	**4.** Adopt enhanced tools to automatically validate submission data to ensure appropriate application of the standards, reducing administrative burden **5.** Conduct formal hardware and software assessment for review staff and map to current configurations to identify gaps **6.** Continue efforts to review established and cutting edge exchange and content data standards and coordinate the implementation of new standards across CDER and CBER **7.** Synchronize tool development/adoption with standards implementation by simultaneously rolling out review tools that directly utilize the efficiencies for a newly implemented exchange or content data standard **8.** Increase the ability to use automation associated with standards-based review tools
Physical Infrastructure *Ensure physical infrastructure supports needs of the review staff*	**9.** Improve user experience by providing sufficient monitors and network access to support on-site and remote staff **10.** Centralize point of access to data currently stored in multiple databases (e.g., EDR, DARRTS, RMS-BLA) to improve efficiency and consistency of data

ASSESSMENT OVERVIEW

Objectives and Scope

In 1992, FDA enacted the Prescription Drug User Fee Act (PDUFA) to create a more effective drug review process, including the implementation of new information technology resources to allow for the electronic processing of submissions. The 2007 PDUFA IV Reauthorization Performance Goals and Procedures section XIII, Improving FDA Performance Management, requests that the FDA engage an independent expert consultant to assess the impact of the electronic submission and review environment on the efficiency and effectiveness of the overall processes for the review of human drugs. An assessment of the efficiency and effectiveness of electronic submissions and review processes in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) was performed to identify any challenges in the current FDA system, such as barriers to use. This assessment will allow the FDA to make progress towards their long-term goal of an automated, standards-based information technology environment for the exchange, review, and management of information supporting the process for the review of human drug applications throughout the product life cycle (including approval and post-approval processes). In partnership with CDER and CBER, Booz Allen undertook a multi-stage project to evaluate the FDA's current electronic submission and review environment, which included current use of exchange and content data standards, reviewer tools and electronic review training. The scope of this task was to determine the impact of the electronic review environment on the review processes, outputs and outcomes, associated with receipt and review of New Drug Applications (NDAs), Biological License Applications (BLAs) and efficacy supplements. Key objectives included:

- Assess the current impact and estimated potential future impact of the electronic submission and review environment on both efficiency and effectiveness for review of human drugs and biologics.
- Identify whether the impact on reviewer behavior and performance has changed or could further change.
- Determine whether reviewers are using specific electronic review tools and whether this use has changed or could further change.
- Assess how both CDER and CBER have progressed in fully implementing the electronic review environment and how both FDA reviewers and applicants could affect successful implementation.
- Evaluate the effectiveness of the electronic review training programs for FDA review staff.

It is important to note that this study did not, and was not intended to, evaluate the quality of the scientific and medical evaluation or technical merit of the review decision.

Assessment Cohorts

Four cohorts were used during various phases of our assessment. Each of the four cohorts included representation for both CBER and CDER, includes only original applications and

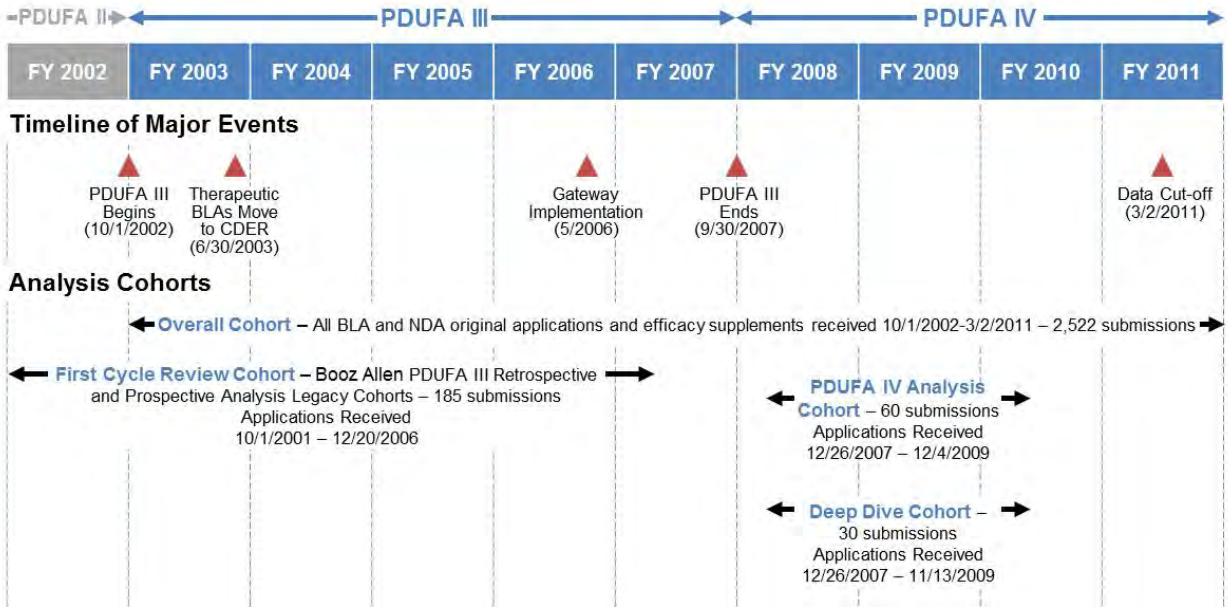
efficacy supplements, and fell within the PDUFA III and IV timeframe (i.e., October 1, 2002 – September 30, 2012).

- **Overall Cohort** – All PDUFA III and IV NDA and BLA original applications and efficacy supplements as of March 2, 2011. (2,522 applications – 2,215 NDAs and 307 BLAs)
- **First Cycle Review Cohort** – Legacy cohort from Booz Allen PDUFA III Retrospective and Prospective Analysis used to identify application characteristics for the other cohorts (185 applications – 136 NDAs and 49 BLAs)
- **PDUFA IV Analysis Cohort** – Cohort for hypotheses testing (60 products – 39 NDAs and 21 BLAs)
- **Deep Dive Cohort** – Subset of PDUFA IV Analysis Cohort for additional hypotheses testing and interview/focus group selection (30 products – 20 NDAs and 10 BLAs)

The First Cycle Review Cohort provided a framework for the types of products and the associated characteristics necessary for in-depth hypothesis testing. This framework was used to help define the PDUFA IV Analysis Cohort of 60 applications, which included a subset of 30 applications that made up the Deep Dive Cohort. Together, these two cohorts were used to assess the hypotheses, in-depth analysis and review staff identification. The Overall Cohort included data available through FDA databases and included all original applications and efficacy supplements that were received during the specified timeframe. This cohort was used for the majority of the analyses presented in this report.

A summary of the timeframes associated with each cohort and major events is presented in Exhibit 1.

Exhibit 1: Overview of Study Cohorts



Methodology

Booz Allen followed a systematic methodology for assessing the impact of the electronic submission and review environment (Exhibit 2).

Exhibit 2: Data Gathering and Analysis Methodology

1. Identify Potential Drivers for Impact of Electronic Submissions	2. Gather Data from Multiple Sources	3. Analyze Data and Test Hypotheses	4. Develop Findings and Recommendations
▸ Develop hypotheses and metrics ▸ Develop product cohorts for hypothesis testing ▸ Refine hypotheses throughout	▸ Collect data from: • Action Packages • Data Systems • Interviews • Focus Groups • Public Sources • Survey	▸ Perform quantitative analyses using basic statistics (e.g., mean, frequency) ▸ Conduct additional qualitative analyses ▸ Develop logical inferences, where possible and practical	▸ Identify the baseline for degree of electronic implementation, review performance, exchange and content data standards, review tools and training ▸ Identify areas for improvement and recommendations

The first step was to develop hypotheses and metrics to evaluate the impact of electronic submissions and to identify product cohorts for testing the hypotheses. Next, the team collected data from multiple sources based on the metrics developed in the first step. In the third step, data were analyzed using quantitative and qualitative methods to test hypotheses. Statistical analyses were limited to single-factor descriptive techniques (e.g., frequency, distribution). Multivariate statistical and data mining techniques were not performed due to the limited sample size of available data and assumed existence of multiple, competing and possibly confounding variables for which data was not readily available (e.g., application quality and complexity, complexity of applicants' responses to information requests during review). Finally, Booz Allen documented findings consistent with the study objectives, focusing on the following areas:

- Degree of Electronic Implementation
- Impact on Review Performance and Staff
- Exchange and Content Data Standards
- Review Tools and Training

Based on these findings, Booz Allen developed recommendations focused on actions that FDA could perform to improve the efficiency and effectiveness of the electronic submission and review environment. A more detailed methodology can be found in Appendix B: Methodology.

FINDINGS

The following sections present the findings from the assessment of the impact of electronic submissions on the review environment. The major findings are organized into the following four main areas:

- Degree of Electronic Implementation
- Baseline Review Performance
- Exchange and Content Standards
- Review Tools and Training

The report includes a review of multiple applications and efficacy supplements in electronic, mixed and paper formats. Table 3 provides an explanation for each of the submission formats.

Table 3: Submission Format Descriptions

Submission Format	Description
Electronic	Applications with all sections submitted in electronic format, submitted through the Gateway or other physical media (e.g., DVD, tape) and accessible through FDA systems.
Mixed	Applications with both paper and electronic submission components. 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.
Paper	Applications with all sections submitted in paper format excluding required labeling[4].

Degree of Electronic Implementation

The degree of electronic implementation was assessed by evaluating the overall adoption of electronic submissions and by applicant size.

Overall Adoption of Electronic Submissions

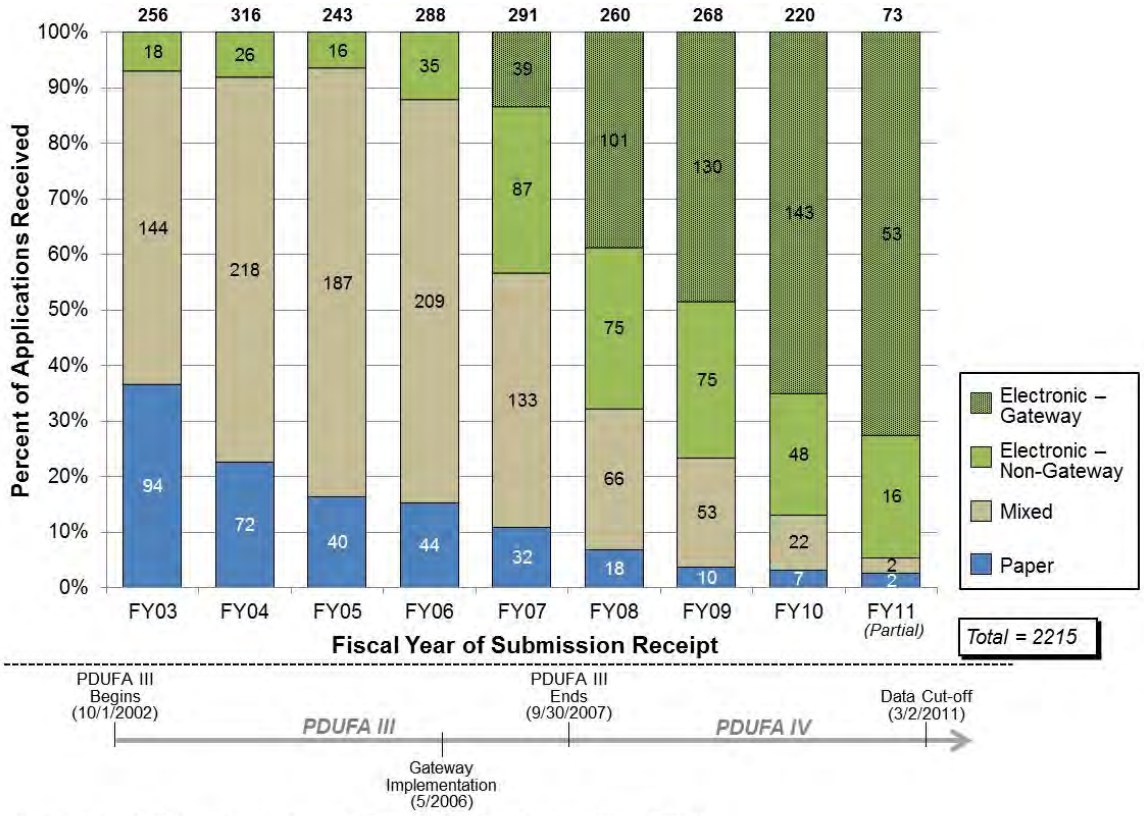
Baseline data were collected for the Overall Cohort to determine the adoption rate of electronically submitted original applications and efficacy supplements for NDAs and BLAs. In May 2006, the Electronic Submissions Gateway (further referred to as the Gateway) was implemented, allowing FDA to receive secure electronic submissions and automatically route them to the proper FDA Center or Office.

From Fiscal Year 2003 (FY03) to FY06, there was a gradual shift from paper to mixed NDA submissions (Exhibit 3). The largest increase in electronic applications occurred in FY07, which coincided with the year FDA began to accept submissions through the Gateway. During that year, the proportion of electronic applications grew by over 30%. In FY10 and FY11, FDA received over 60% (143/220 and 53/73, respectively) of original NDAs and efficacy supplements

[4] For paper applications, some reviewers request electronic data sets through informal communications.

electronically through the Gateway. Data indicate that NDA applicants are moving towards adoption of electronic submissions through the Gateway.

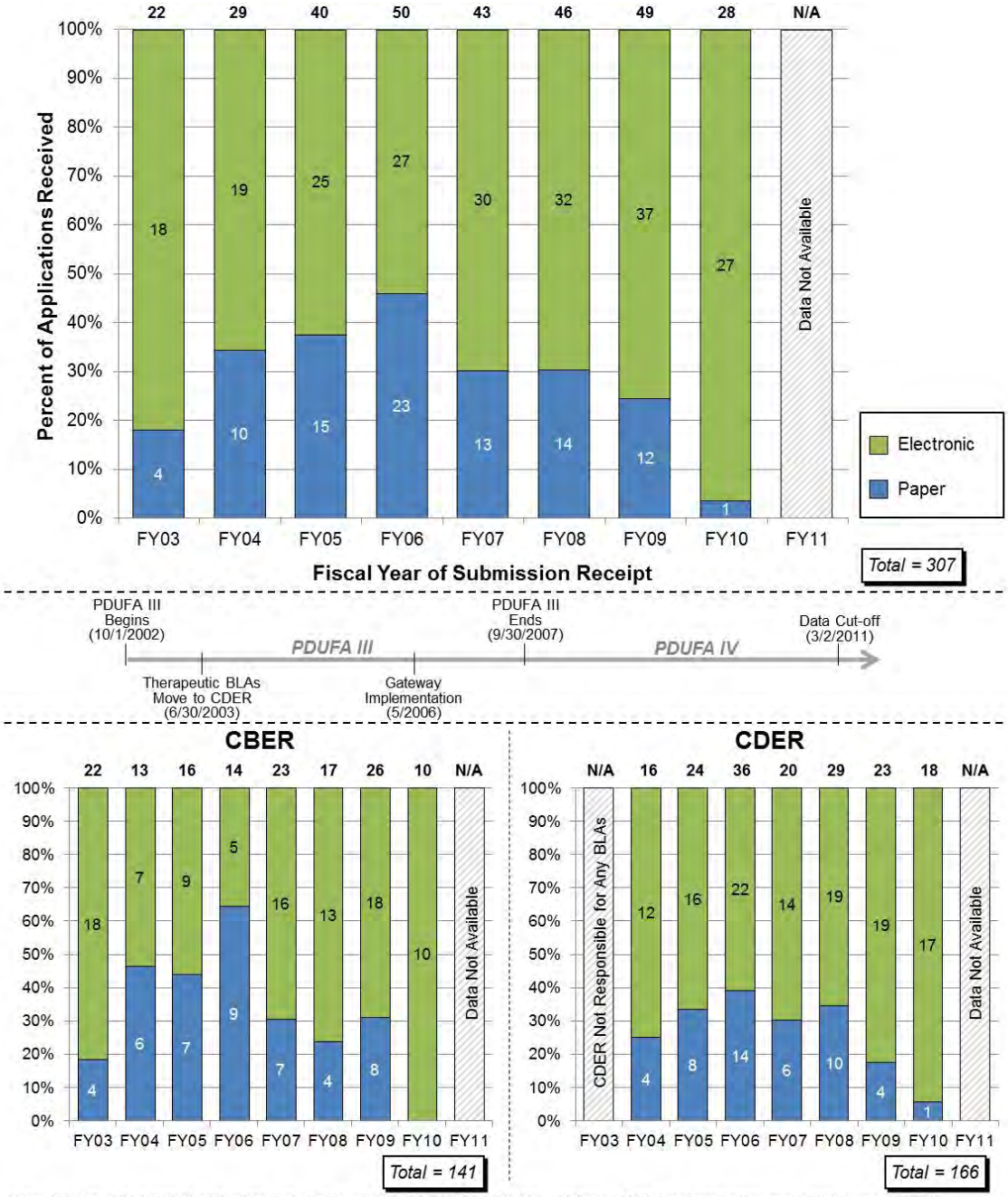
Exhibit 3: Format of NDAs by Fiscal Year



Notes: Includes all NDA original applications and efficacy supplements received 10/1/2002 – 3/2/2011
Source: FDA data systems

For BLAs, the proportion of paper applications gradually increased from FY03 to FY06 (Exhibit 4). After FY06, the overall proportion of electronic applications increased.

Exhibit 4: Format of BLAs by Fiscal Year[5]



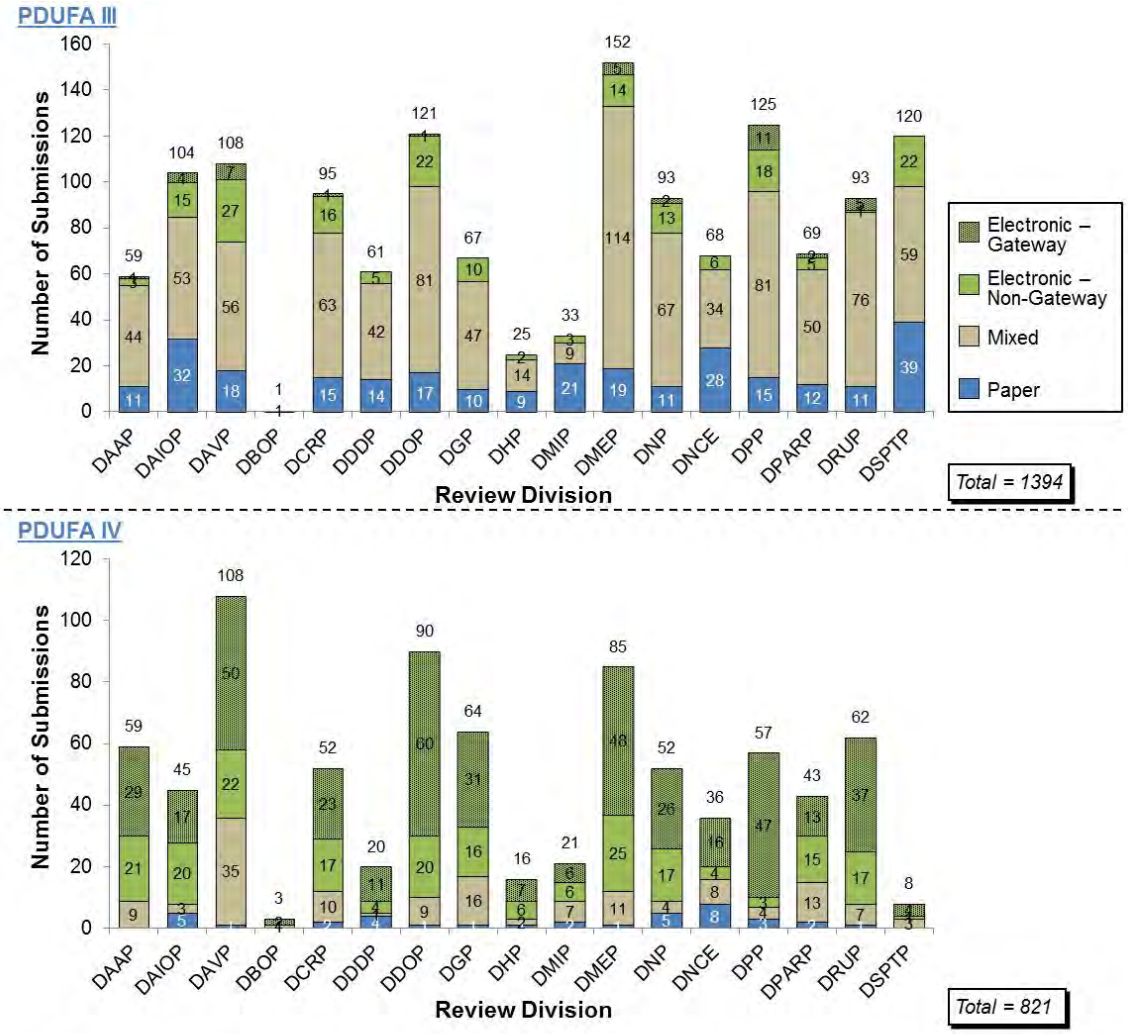
Notes: Includes all BLA original applications and efficacy supplements received 10/1/2002 – 3/2/2011; CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications
Source: FDA data systems

[5] In June 2003, responsibility for the therapeutic biologic applications that resided in the Office of Therapeutics Research and Review (OTRR) was transferred from CBER to CDER, along with much of the corresponding review staff.

While the quantity of electronic BLAs received in FY10 was lower, the year marked the highest proportion of electronic submissions (over 95%, 27/28) for the period assessed. Review of the data by Center did not show any significant trend (see Appendix A: Additional Analyses for additional information).

An analysis of NDA submission formats by review division was performed for both drugs and biologics. The analysis for NDAs, further split into PDUFA III and PDUFA IV timeframes as presented in Exhibit 5, revealed a dramatic shift from primarily mixed submissions during the PDUFA III timeframe to significantly more electronic submissions during the PDUFA IV timeframe. Furthermore, there was a significant increase in receipt of electronic applications through the Gateway.

Exhibit 5: Format of NDA Submission by Review Division[6]

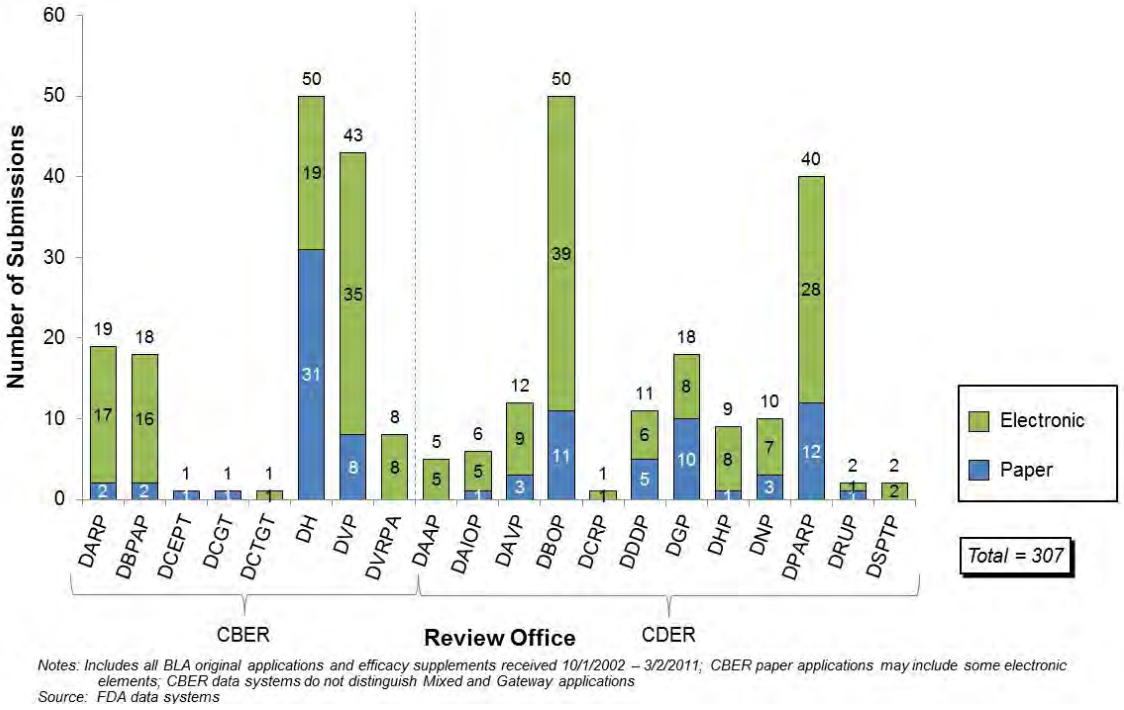


Note: PDUFA III was inclusive of applications received 10/1/2007-9/30/2007; PDUFA IV was inclusive of applications received 10/1/2007-3/2/2011 (data cut-off date)
Source: FDA data systems

[6] DBOP reviews some NDAs that are intended for the treatment and prevention of cancer, as well as treatment of cancer treatment-related symptoms.

The analysis of BLAs by review division, as shown in Exhibit 6[7] revealed that four review divisions (DH, DVP, DBOP, and DPARP) are responsible for the vast majority of applications received. Within CBER, the Division of Hematology (DH) received more paper applications (31 submissions) than any other division in either Center. The Division of Biologic Oncology Products (DBOP), the Division of Viral Products (DVP), and the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) reviewed the largest number of electronic applications.

Exhibit 6: Format of BLA Submissions by Review Division



Notes: Includes all BLA original applications and efficacy supplements received 10/1/2002 – 3/2/2011; CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications
Source: FDA data systems

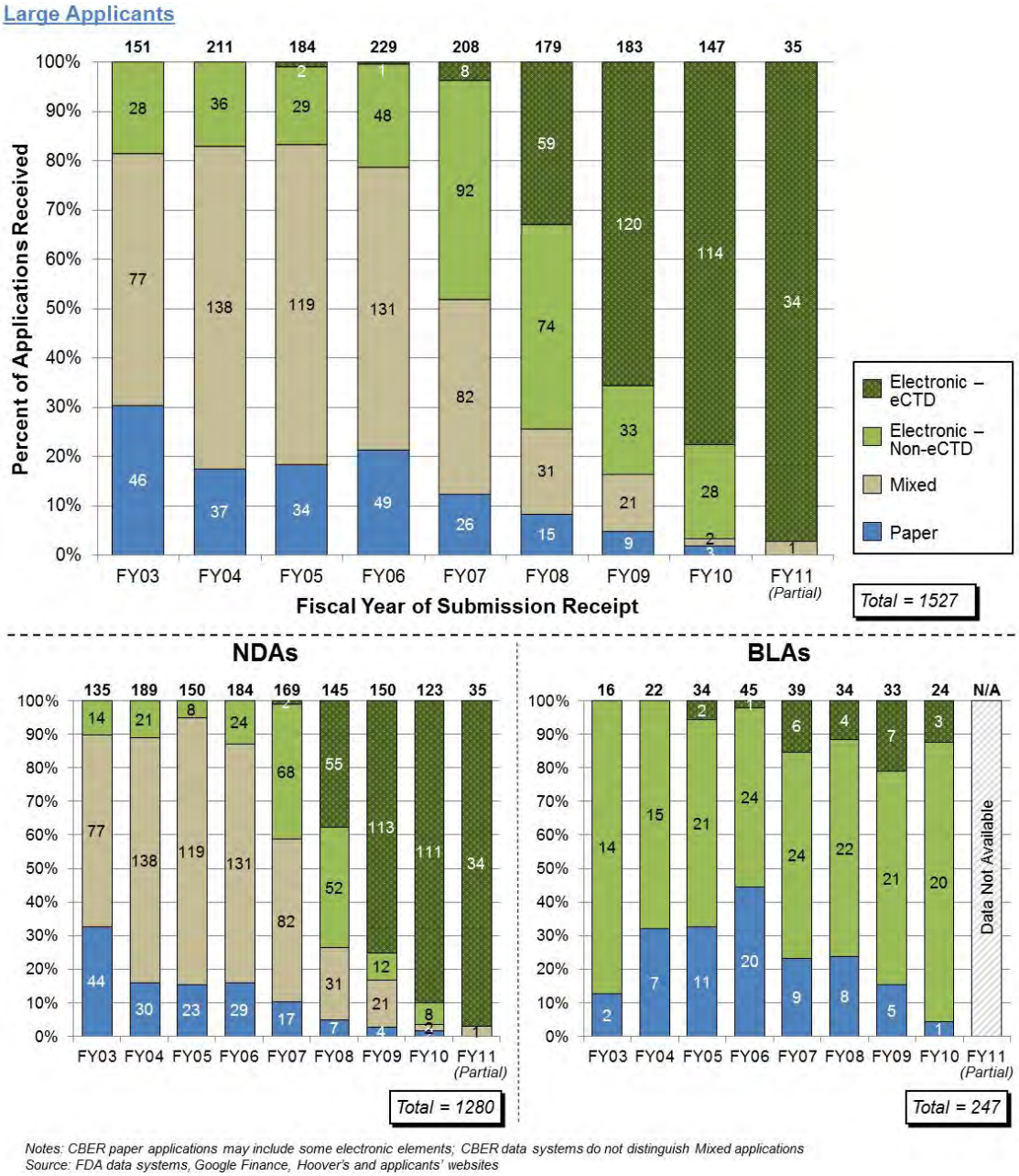
Adoption by Applicant Size

Analysis of NDA and BLA application submission formats over the fiscal years FY03 to FY10 indicated a transition from paper and mixed submission formats, to electronic submissions during later years as FDA transitioned from PDUFA III to PDUFA IV. The percentage of electronic applications submitted also increased proportionately to increasing applicant size. Applicants were categorized as small, medium or large using market capitalization figures as of February 2, 2011. The applicants were defined as small if the market capitalization was less than or equal to $1B, medium if between $1B and $5B and large if greater than $5B. Where market capitalization data were unavailable (i.e., private companies), applicants were categorized by market value using the same parameters as market capitalization; if that data was unavailable, a combination of available data on number of employees and annual sales figures was used to estimate applicant size.

[7] An exhibit in the appendix provides the distribution of BLA applications by review division, for the PDUFA III and PDUFA IV timeframes.

Exhibit 7 illustrates the trend of increasing electronic submissions over mixed or paper formats over time for large applicants.

Exhibit 7: Format of NDAs/BLAs from Large Applicants



Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed applications
Source: FDA data systems, Google Finance, Hoover's and applicants' websites

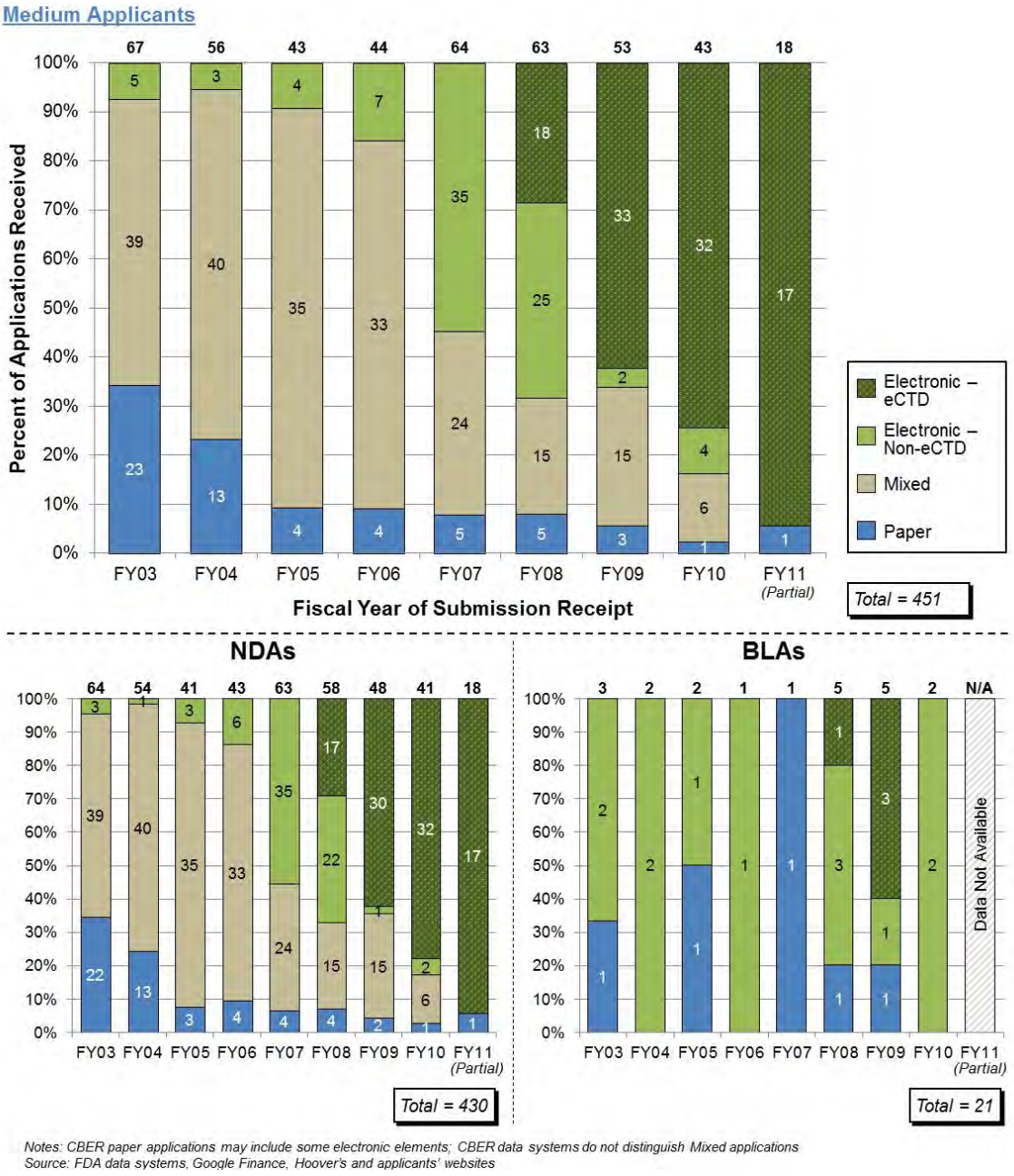
In FY03, the majority of submissions from large applicants were either in paper (31%; 46/151) or mixed (51%; 77/151) format, with only 19% (28/151) of applications submitted in electronic format. Most notably, between FY06 and FY08, which marks the transition period between PDUFA III and PDUFA IV and Gateway implementation, the percentage of electronic submissions more than doubled, from 22% in FY06 to 49% (103/211) in FY07. In FY08, a majority (133 out of 179) of applications were submitted in electronic format. The most recent

results from FY10 and FY11, where nearly all submissions from large applicants are in electronic format, indicate that large applicants have almost exclusively adopted the use of the electronic submission process. Additionally, the proportion of electronic Common Technical Document (eCTD) submissions increased relative to non-eCTD submissions over time.

When NDA applications were analyzed separately from BLA applications, the trends in increasing percentage of electronic format over time mirrored the results found in the total number of applications. However, though more limited in quantity, BLA data revealed that a majority of applications were submitted in electronic format since FY03. The lowest number 55% (25/45) of electronic submissions was observed in FY06. From FY06 to FY10, the proportion of electronic BLA submissions increased, similar to NDA data.

Exhibit 8 provides a detailed analysis of NDA and BLA submissions from FY03 through FY11 for medium applicants. Although the overall trends are similar to those seen in large applicant submissions, medium applicants appeared to use mixed format submissions more frequently.

Exhibit 8: Format of NDAs/BLAs from Medium Applicants

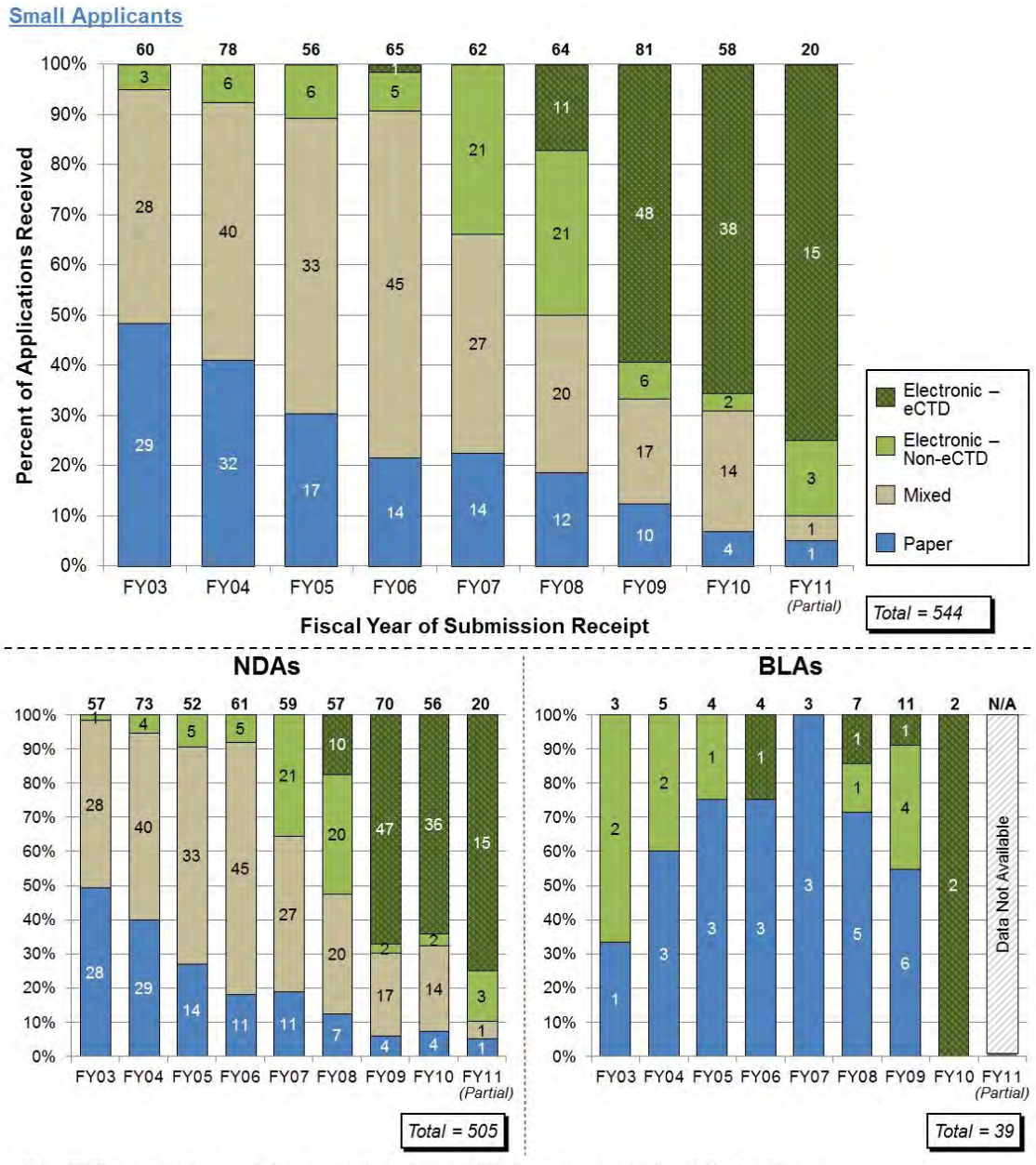


The majority of total applications submitted by medium applicants between FY03 and FY06 were in mixed format. The most significant change in submission formats was observed between FY06, where the majority (75%; 33/44) of applications were mixed format, and FY07, where the majority (55%; 35/64) of applications were in electronic format. Similar to large sponsors, medium applicants shifted towards a predominantly electronic submission format over time, concurrent with the transition from PDUFA III to PDUFA IV, with nearly all applications submitted in electronic format in FY10 and FY11. As observed in large applicants, the proportion of eCTD electronic submissions increased relative to non-eCTD submissions over time, and all electronic submissions submitted in FY11 were in eCTD format.

No significant distinctions were found when NDA data alone were analyzed for medium applicants, which is consistent considering NDA applications made up 95% (430/451) of the medium sample. The BLA data were too limited to detect any trends in application formats over time.

Application submission trends for small applicants is consistent with trends observed in large and medium applicants, with an increased use of the electronic submission format over time, as depicted in Exhibit 9.

Exhibit 9: Format of NDAs/BLAs from Small Applicants



Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed applications
Source: FDA data systems, Google Finance, Hoover's and applicants' websites

As observed for large and medium applicants, the most significant changes in submission behavior for small applicants occurred between FY06 and FY08 during the transition period from PDUFA III to PDUFA IV. In FY06, a greater proportion of submissions were in paper format (22%, 14/65) than electronic (9%, 6/65). During FY07, the number of electronic submissions more than tripled to 34% (21/62). The proportion of submissions in electronic format continued to increase steadily between FY08 and FY11, similar to trends seen in Exhibit 7 and Exhibit 8 for large and medium applicants, respectively. Again, eCTD electronic submissions increased in proportion relative to non-eCTD submission over time. NDA data alone mirrored the overall trends for formats, while BLA data for small applicants are likely too limited to conclude any trends in submission format at this time.

Despite the common trend of increasing proportion of electronic submissions over time, there was a notable difference in the rate at which different sized applicants transitioned to electronic submissions. Specifically, large applicants appeared to transition at a faster rate than small applicants. By FY08, nearly three-quarters (133/179) of applications from large applicants were submitted electronically, whereas 68% (43/63) of medium and 50% (32/64) of small firms' applications were submitted electronically.

The correlation between applicant size and degree of electronic submission suggests that large applicants more readily submit electronically than small applicants. The data also show a decrease in the amount of mixed format submissions between the PDUFA III and PDUFA IV timeframes. Although the majority of applications submitted during PDUFA III were mixed format across different sized applicants, the proportion of mixed submissions decreased as electronic submissions increased. Interestingly, small applicants had a tendency to submit paper applications more frequently during PDUFA III, whereas medium- and large-size applicants submitted approximately the same proportion of paper applications as electronic during this timeframe.

Baseline Review Performance

The baseline review performance was assessed to determine how electronic submissions impact approval, time to action, time to approval and review behavior.

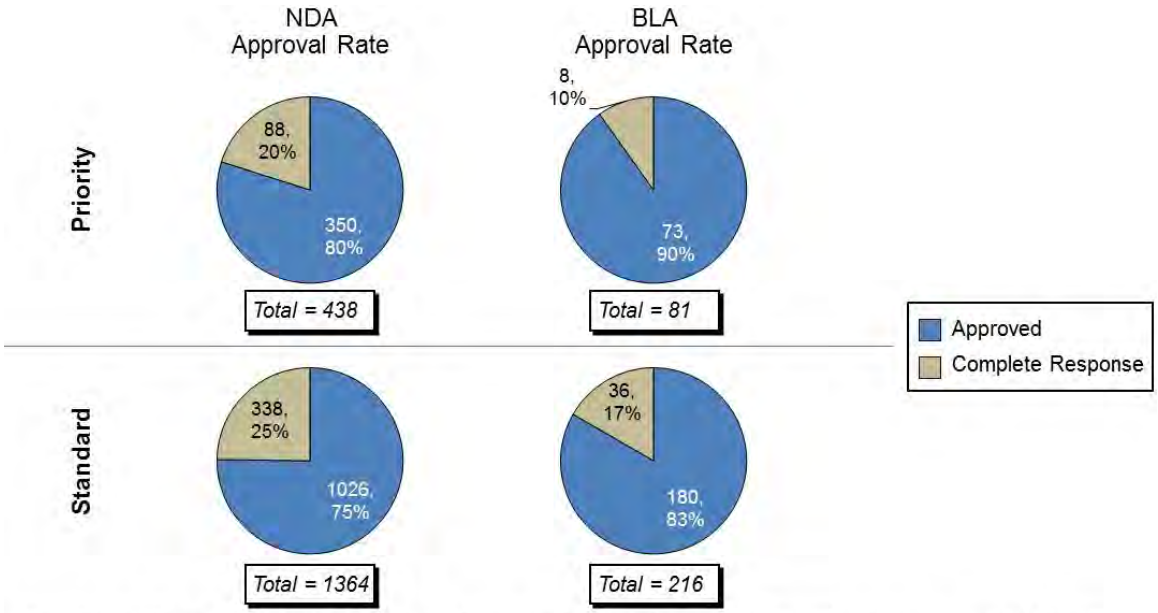
Impact on Approval Rate

Booz Allen hypothesized that electronic submissions may impact the quality of the application and subsequently increase the approval rate. In order to determine whether the electronic review process fosters higher-quality applications and/or reduces time to approval as compared to paper submissions, Booz Allen measured the approval rate for NDAs and BLAs in the overall cohort against the following factors:

- Submission designation (i.e., priority, standard)
- First-cycle action
- Average time to approval
- Average time to first action
- Impact on review staff

Applications included in the Overall Cohort were original NDA and BLA submissions and efficacy supplements that received action within the data cut-off timeframe. NDA and BLA approval rates were evaluated for priority and standard submission designations (Exhibit 10).[8]

Exhibit 10: NDA and BLA Approval Rates



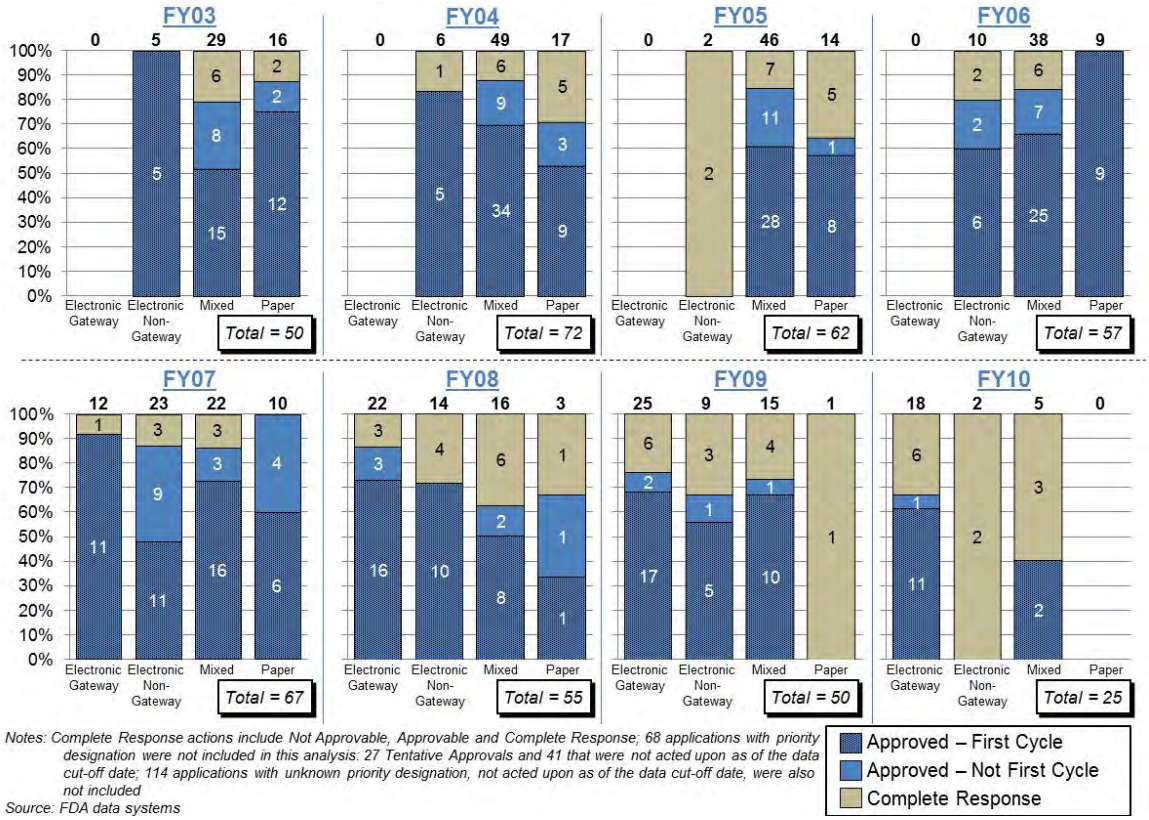
Notes: Complete Response actions include Not Approvable, Approvable and Complete Response. For NDAs, 413 applications were not included in this analysis: 55 Tentative Approvals and 358 that were not acted upon as of the data cut-off date. For BLAs, 10 applications, withdrawn after the first cycle action, were not included in this analysis
Source: FDA data systems

For NDAs, priority designated applications had a slightly higher percentage of overall approvals than standard designated applications (80%, 350/438 and 75%, 1026/1364 respectively). Similar to NDAs, BLA priority designated applications demonstrated a higher percentage of approvals compared to standard applications (90%, 73/81 and 83%, 180/216, respectively).

To determine the impact of the submission designation and submission format on NDA approval rates, priority and standard applications were evaluated by fiscal year. The applications were separated out by fiscal year and the number of review cycles required for approval (i.e., first-cycle vs. multiple cycles). The analysis of the submission format by fiscal year (Exhibit 3) showed receipt of more paper and mixed applications in earlier years. Therefore, those applications would have more time to reach approval compared to more recently received applications. Priority designated NDA submissions were evaluated over the course of FY03 through FY10 in Exhibit 11.

[8] Applications that received first action before 74 days of receipt of the submission were excluded from the approval rate analysis.

Exhibit 11: Priority NDA Approval Rate by Fiscal Year, by Submission Format

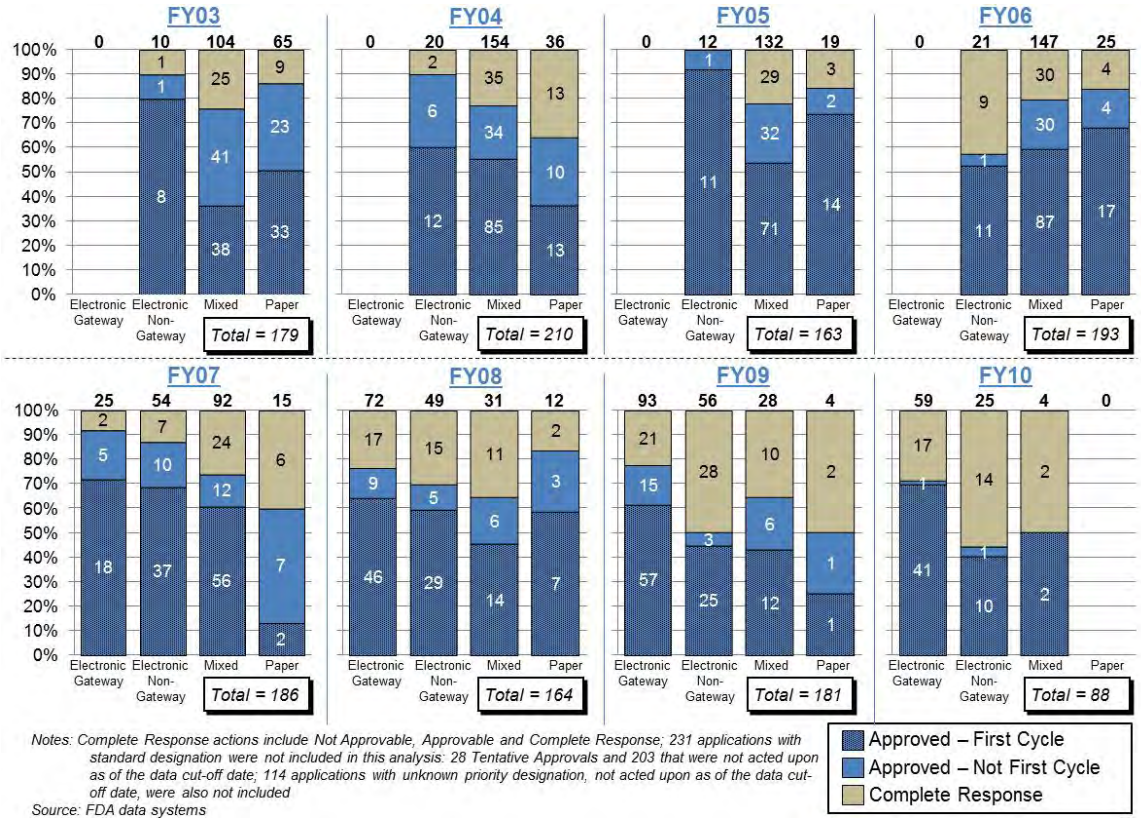


Notes: Complete Response actions include Not Approvable, Approvable and Complete Response; 68 applications with priority designation were not included in this analysis: 27 Tentative Approvals and 41 that were not acted upon as of the data cut-off date; 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included

Source: FDA data systems

No significant trends were found for the impact of submission format on approval rates for priority NDAs. The same factors were assessed for standard designated NDA submissions over the course of FY03 through FY10 (Exhibit 12).

Exhibit 12: Standard NDA Approval Rate by Fiscal Year, by Submission Format



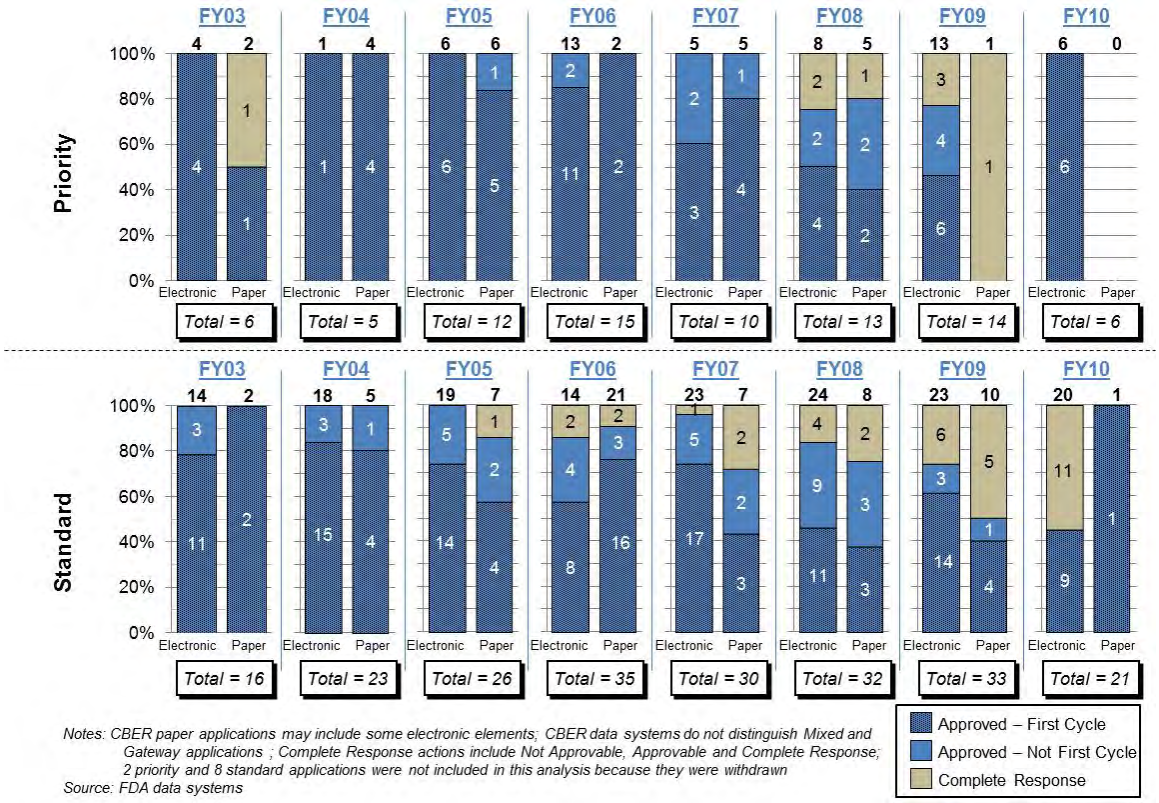
Notes: Complete Response actions include Not Approvable, Approvable and Complete Response; 231 applications with standard designation were not included in this analysis: 28 Tentative Approvals and 203 that were not acted upon as of the data cut-off date; 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included

Source: FDA data systems

Data did not indicate major differences in NDA approval rates for various submission formats in either submission designation (see Appendix A: Additional Analyses for a table detailing overall percentages). The findings for the impact of submission format on NDA approval rate were consistent with qualitative feedback from reviewers received during focus groups and interviews, which indicated that submission format generally does not impact the content of the submission or the approach to the review.

BLA approval rates were assessed for trends in submission format by submission designation (Exhibit 13) (see Appendix A: Additional Analyses for a table detailing overall percentages).

Exhibit 13: Priority and Standard BLA Approval Rate by Submission Format, by Fiscal Year

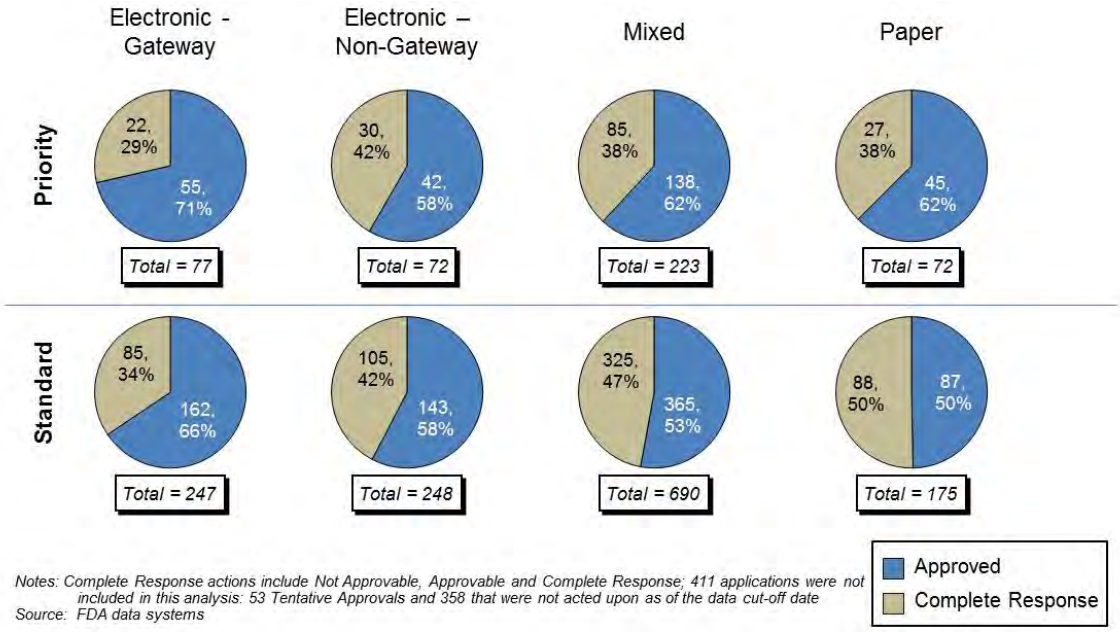


Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications ; Complete Response actions include Not Approvable, Approvable and Complete Response; 2 priority and 8 standard applications were not included in this analysis because they were withdrawn
Source: FDA data systems

Similar to NDAs, data did not indicate major differences in BLA approval rates for various submission formats in either submission designation.

Booz Allen examined NDA submission formats by submission designation for trends in first cycle actions (Exhibit 14). [9]

Exhibit 14: First Cycle Action for NDAs by Submission Format



Notes: Complete Response actions include Not Approvable, Approvable and Complete Response; 411 applications were not included in this analysis: 53 Tentative Approvals and 358 that were not acted upon as of the data cut-off date
Source: FDA data systems

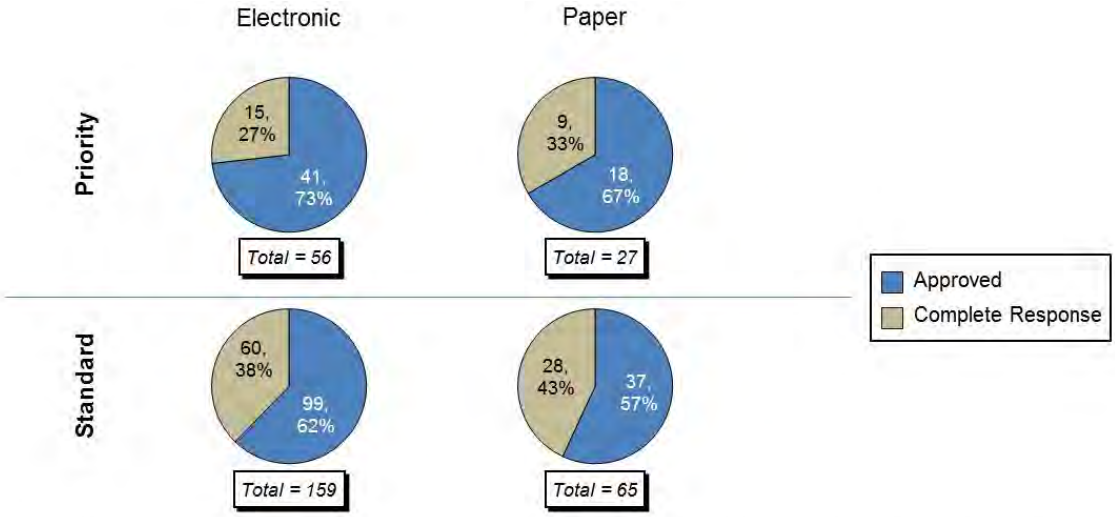
For all submission formats, approval rates of priority designated applications were greater than or equal to standard designated application approval rates. In a prior evaluation, Booz Allen observed that priority review designation, which is given to applications for products that offer major advances in treatment or provide a treatment where no adequate therapy exists, had the most significant impact on first-cycle approval rates. [10] In both priority and standard designated application reviews, electronic Gateway formats demonstrated the highest first-cycle approval rates of 71% (55/77) and 66% (162/247), respectively. Among priority designated applications, the electronic non-Gateway format had the lowest first-cycle approval rate (58%, 42/72), followed by mixed formats (62%, 138/223) and paper (62%, 45/72). In contrast, the rate of first-cycle approval for standard designated applications was lowest for paper formats (50%, 87/175) and mixed formats (53%, 365/690).

[9] Applications acted on in fewer than 74 days from application receipt or over 90 days after the goal date, more than 273 days for priority and more than 393 days for standard, were excluded from the first-cycle analyses. Many applications over 90 days of the goal date had altered timelines due to special circumstances (e.g., withdrawn applications, previous refuse-to file decision made and received date wasn't changed in database and late payment of user fees), and therefore, might have misrepresented the data.

[10] Independent Evaluation of FDA's Prescription Drug User Fee Act III – Evaluations & Initiatives – First Cycle Review Performance Study. Booz Allen Hamilton (July 2008).

BLA first cycle actions were analyzed to identify possible trends between approval rates and submission formats for standard and priority designated application reviews (Exhibit 15).

Exhibit 15: First Cycle Action for BLAs by Submission Format



Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; Complete Response actions include Not Approvable, Approvable ,and Complete Response; all 307 applications are included in this analysis
Source: FDA data systems

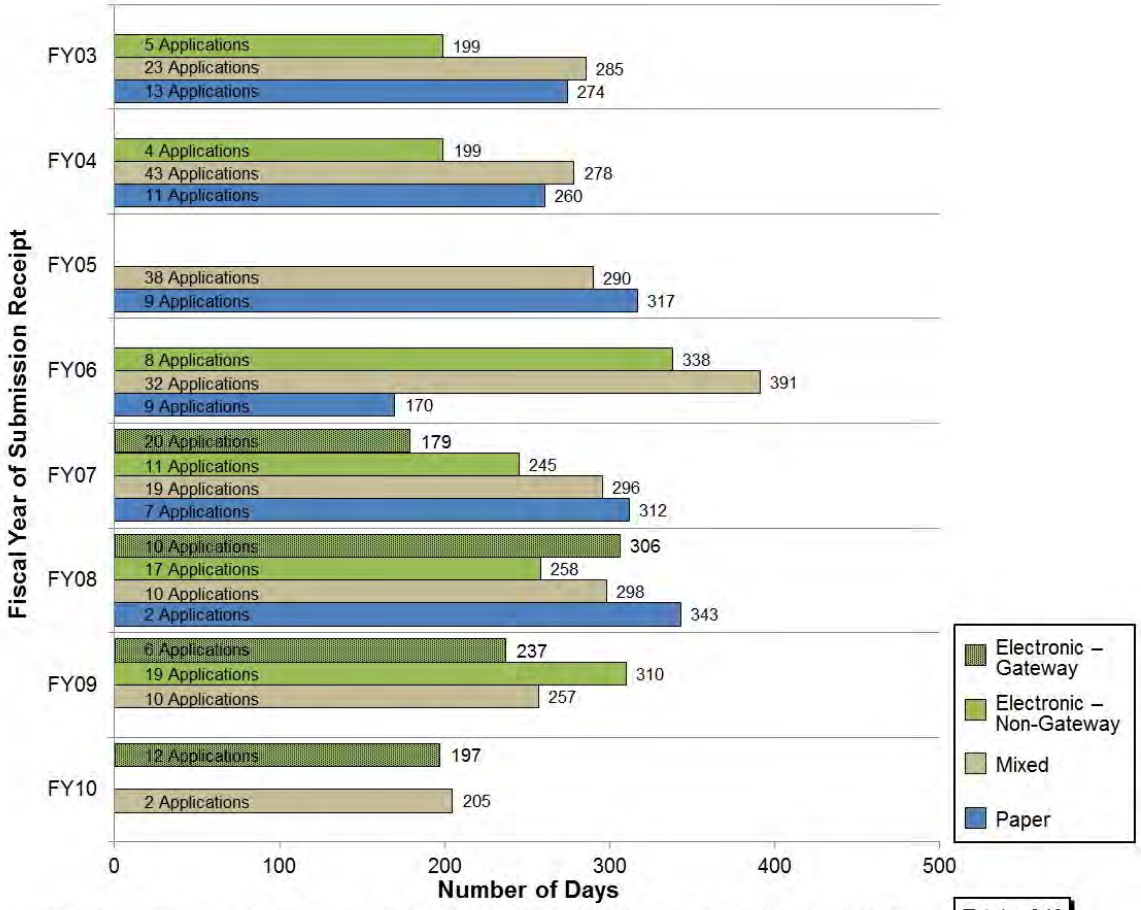
Similar to NDA findings, priority BLAs had slightly higher first-cycle approval rates than standard designated applications for both electronic and paper submissions. For both priority and standard designated applications, the electronic format had slightly higher first-cycle approval rates than paper formats (73%, 41/56 compared to 67%, 18/27 for priority, and 62%, 99/159 compared to 57%, 37/65 for standard, respectively). Although the first-cycle approval rate for electronic formats was higher, the difference was not large enough to determine a relationship between submission format and first-cycle action.

Analyses of NDA and BLA approval rates for priority and standard designated application reviews did not demonstrate any definitive relationship between the approval rate and submission format. The electronic non-Gateway format had the lowest approval rate out of all formats for NDA submissions, while the electronic format had a slightly higher approval rate for first-cycle BLAs compared to paper formats. The slight variations in approval rate across submission formats supports the qualitative data from focus groups indicating that format does not usually impact submission content or FDA's approach to the review. Future assessments can follow these variables over time to determine if stronger trends emerge or confirm whether approval rate is independent from submission format.

Impact on Time to Approval

The time to approval for NDAs by submission format was analyzed to determine impact. An analysis of the average time to approval assessed the impact of submission format over time, from FY03 through FY10, for priority (Exhibit 16) and standard (Exhibit 17) NDA submissions.

Exhibit 16: Average Time to Approval for Priority NDAs, by Fiscal Year and Submission Format



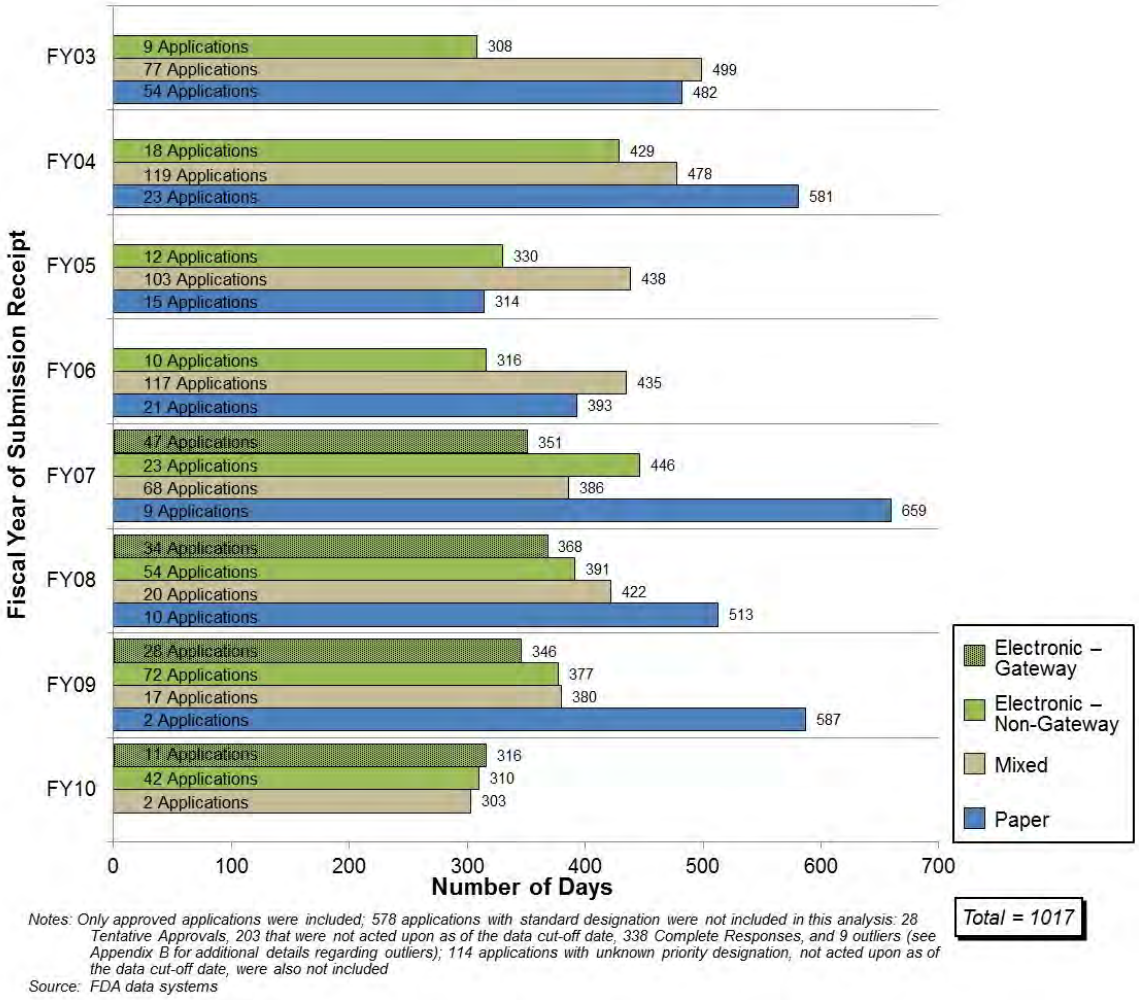
Notes: Only approved applications were included; 166 applications with priority designation were not included in this analysis: 27 Tentative Approvals, 41 that were not acted upon as of the data cut-off date, 88 Complete Responses, and 10 outliers (see Appendix B for additional details regarding outliers); 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included

Source: FDA data systems

For priority applications, the number of paper submissions decreased steadily over time, from 13 applications in FY03 to two applications in FY08, and no applications in FY09 or FY10. Similarly, the number of mixed format submissions declined over the fiscal years, as the number of electronic submissions saw an increase from only five applications in FY03 to 25 applications in FY09. The average time to approval was generally longer for paper and mixed submissions as compared to electronic submissions each year, with the exception of FY06 where electronic submissions required nearly twice as long as paper NDAs for approval.

The same factors were assessed for standard designated NDA submissions over the course of FY03 through FY10, as shown in Exhibit 17.

Exhibit 17: Average Time to Approval for Standard NDAs, by Fiscal Year and Submission Format



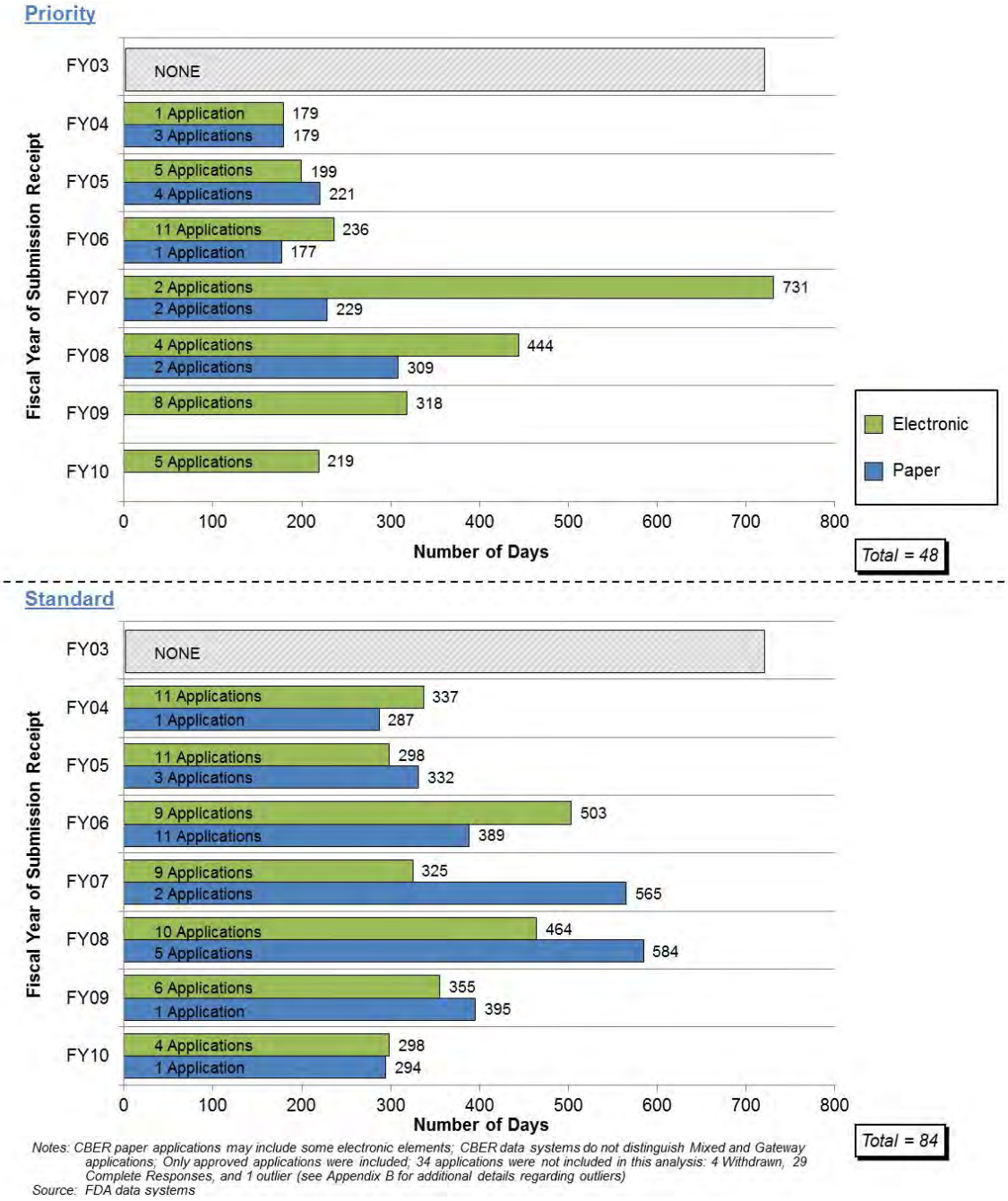
Notes: Only approved applications were included; 578 applications with standard designation were not included in this analysis: 28 Tentative Approvals, 203 that were not acted upon as of the data cut-off date, 338 Complete Responses, and 9 outliers (see Appendix B for additional details regarding outliers); 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included
Source: FDA data systems

The number of standard NDA paper submissions decreased steadily over time, from 54 applications in FY03 to two applications in FY09, and none submitted in FY10. Similarly, the number of mixed format submissions declined over the fiscal years, from 77 applications in FY03 to only two applications in FY10. The number of electronic submissions saw an increase from nine applications in FY03 to 53 applications in FY10. With the exception of FY05 and FY10, where there were no paper submissions, paper NDA submissions designated standard status took on average longer for approval than electronic format submissions. The longest average time to approval was 659 days for paper submissions in FY07, and the shortest average time to approval was 303 days for mixed submissions in FY10.

Approval times were also assessed for electronic and paper original BLA applications and efficacy supplements by review designation, Center and fiscal year. Exhibit 18 shows the

average time to approval for priority and standard BLA submissions in CDER over time, from FY03 to FY10.[11]

Exhibit 18: Average Time to Approval for CDER BLAs, by Fiscal Year and Submission Format



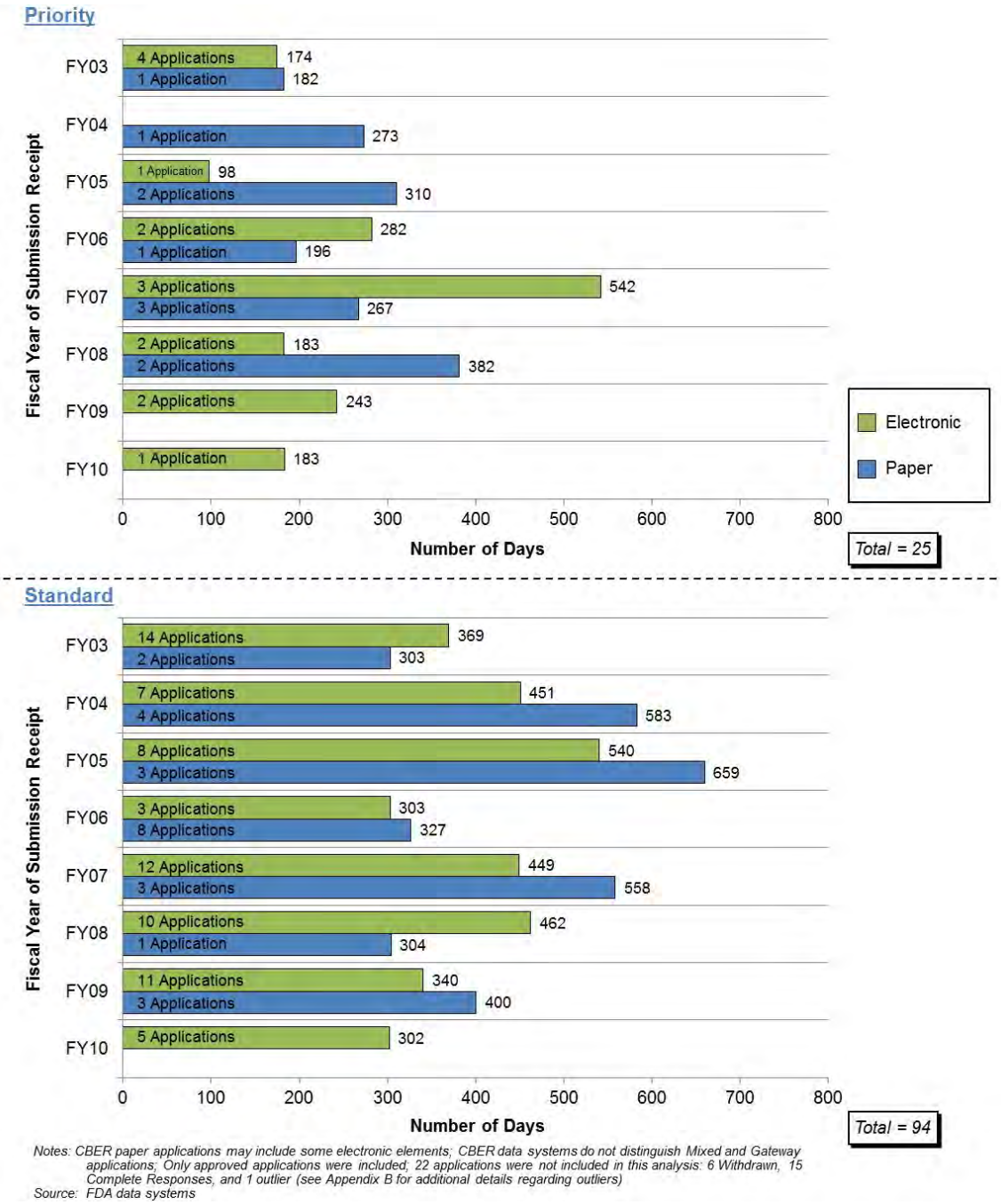
Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; Only approved applications were included; 34 applications were not included in this analysis: 4 Withdrawn, 29 Complete Responses, and 1 outlier (see Appendix B for additional details regarding outliers)
Source: FDA data systems

[11] There were no BLA submissions received by CDER in FY03, and there were no priority designated paper BLA submissions received by CDER in FY09 and FY10.

No significant trends were found for the impact of electronic submissions on approval times for priority or standard BLA submissions in CDER.

Additionally, no significant trends were found for the impact of electronic submissions on approval times for priority or standard BLA submissions in CBER (Exhibit 19).

Exhibit 19: Average Time to Approval for CBER BLAs, by Fiscal Year and Submission Format



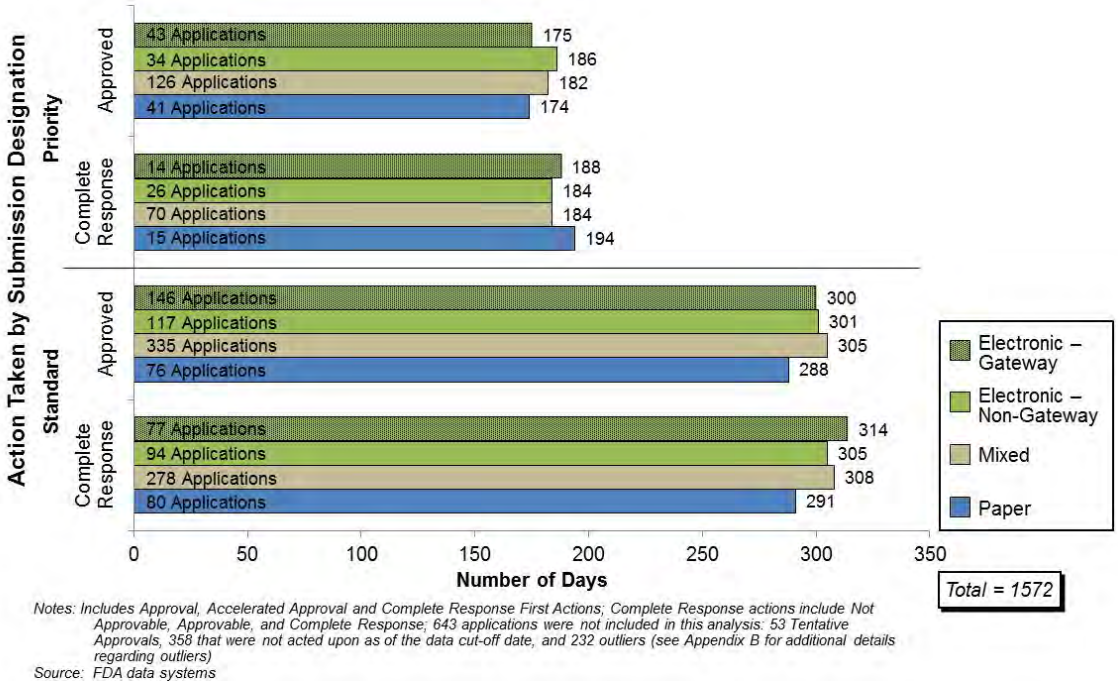
Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; Only approved applications were included; 22 applications were not included in this analysis: 6 Withdrawn, 15 Complete Responses, and 1 outlier (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Reviewer interviews revealed that some believed electronic submissions allowed them to review more efficiently because of the ability to immediately access and easily navigate the application. While some reviewers did not cite any difference in review time, some estimated that they spent up to twice as long reviewing applications that were not electronic.

Impact on Time to First Action

Booz Allen examined application data to evaluate the impact of electronic submissions on the time to first action for NDAs and BLAs as part of the baseline review performance analysis. The average time to first action for NDAs was analyzed to determine the impact of electronic submissions (Exhibit 20).

Exhibit 20: Average Time to First Action for NDAs by Submission Format

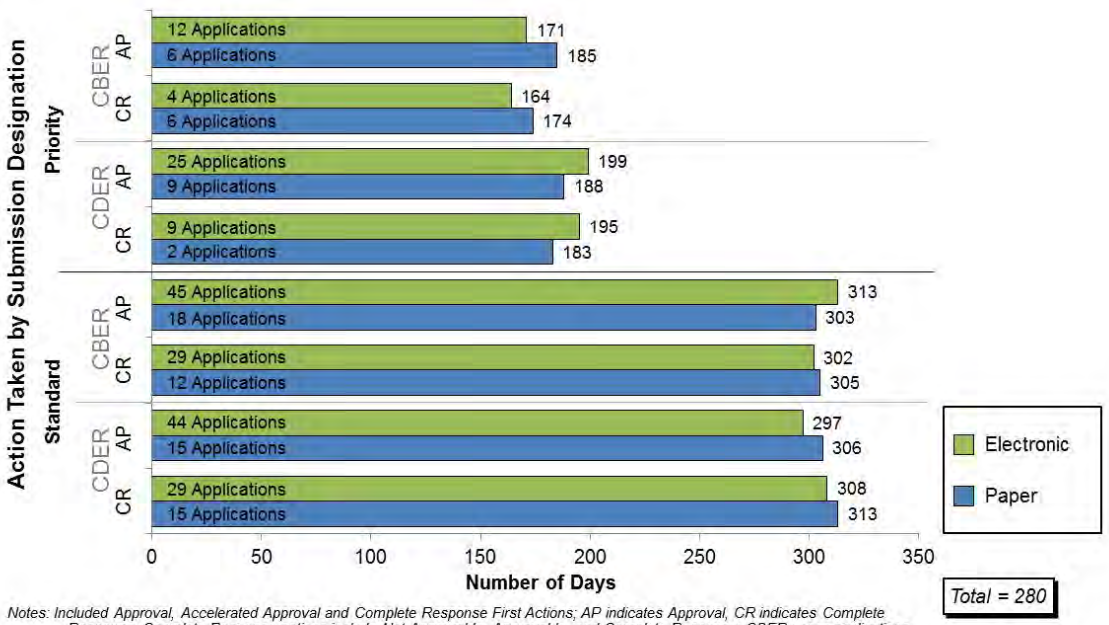


Notes: Includes Approval, Accelerated Approval and Complete Response First Actions; Complete Response actions include Not Approvable, Approvable, and Complete Response; 643 applications were not included in this analysis: 53 Tentative Approvals, 358 that were not acted upon as of the data cut-off date, and 232 outliers (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Within each submission designation, there was little variance in time to first action between submission formats for complete response and approval actions. Electronic, Gateway applications that received a complete response under a standard review timeline took on average the longest to reach first action (314 days). In all but the priority complete response category, paper format submissions took the shortest average time to first action, having the shortest overall average of 174 days (priority approval). Additional analyses around time to first action for NDAs by fiscal year and division are included in Appendix A. No clear trends were observed for the priority NDA time to first action analysis.

Booz Allen also analyzed the impact of submission format on time to first action for BLAs by Center (Exhibit 21).

Exhibit 21: Average Time to First Action for BLAs by Submission Format, by Center



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; AP indicates Approval, CR indicates Complete Response; Complete Response actions include Not Approvable, Approvable, and Complete Response; CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; 27 applications, considered outliers, were not included in this analysis (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Average time to first action for priority applications reviewed by CBER took longer for paper submissions than electronic submissions (185 and 171 days for approvals, and 174 and 164 days for complete response, respectively). In contrast, CDER took longer for priority, electronic submissions than paper submissions (199 and 188 days for approval, and 195 and 183 days for complete response, respectively). Standard applications did not demonstrate substantial trends for submission format and time to first action. These slight differences did not indicate an impact of submission format on the average time to first action. Additional analyses for average time to first action for BLAs are included in Appendix A.

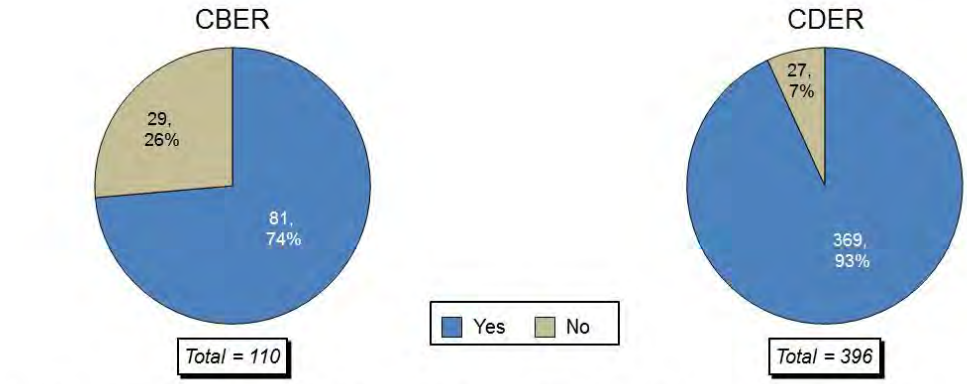
Data analyses did not clearly identify any trends between the submission format for NDAs or BLAs and time to first action. This is consistent with qualitative data received from reviewer focus groups indicating that submission format does not usually impact submission content or FDA's approach to the review. Future assessments can follow these variables over time to determine if stronger trends emerge or confirm whether time to first action is independent from submission format.

Impact on Review Staff and Activities

Booz Allen assessed the effectiveness of review training programs on the electronic review process for FDA review staff during and after implementation of the fully electronic standardized review environment. The impact on review staff was determined by evaluating the current training programs for FDA staff related to electronic submissions and review environment. The impact on review activities was limited to the examination of the impact of the automated standards-based review environment on the quality of the activities. To determine the effectiveness of the electronic review process, feedback was obtained, analyzed and synthesized from review staff through the use of focus groups, targeted interviews and a web-based survey.

The data from the survey were analyzed along with feedback received from interviews and focus groups to determine how reviewers interact with and are impacted by electronic applications (e.g., tools usage, printing habits). Based on review staff responses, reviewers prefer to receive electronic submissions for a number of reasons, primarily the ease of accessing and finding information within the review and faster delivery of the application (Exhibit 22). During interviews and focus groups, review staff indicated that divisions can operate more independently of each other when accessing an electronic application that requires input from multiple divisions. Additionally, reviewers noted the benefits of accessing an application while working remotely.

Exhibit 22: Responses to Survey Question: Does a fully electronic application improve your review experience?



Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

The majority of respondents, 89% (450 out of 506 respondents), believe electronic applications improve their review. In CBER, 26% (29/110) of those surveyed responded “no” when asked if electronic applications improve their review experience, whereas only 7% (27/396) responded “no” in CDER. Survey results indicate that the percentage of “no” responses increased slightly in proportion to the increasing number of years of review experience at FDA, from 22% with zero-to-two years of experience to 29% with ten or more years of experience. Of the respondents who indicated “no,” 43% (24/56) had reviews consisting of mostly paper submissions, and 61% (34/56) indicated that IT negatively impacted their electronic review. These findings suggest there is a difference in perception between the two Centers on electronic review process efficiency.

When asked why they prefer electronic applications, respondents indicated it was because they were able to access applications more quickly and locate information more easily. The primary reasons for this preference based on survey results include:

- Makes it easier to search and find information applicable to my review
- Reduces the time it takes to get a copy from another member of the review team (e.g., reviewer or RPM)
- Makes it easier to work from home by not having to transport paper documents
- Reduces the time it takes to search the document room
- Reduces the time it takes to receive the initial submission from the applicant for review

Complete data from the survey results for this analysis can be found in Appendix A: Additional Analyses. Similar responses were received during focus groups and interviews with review staff.

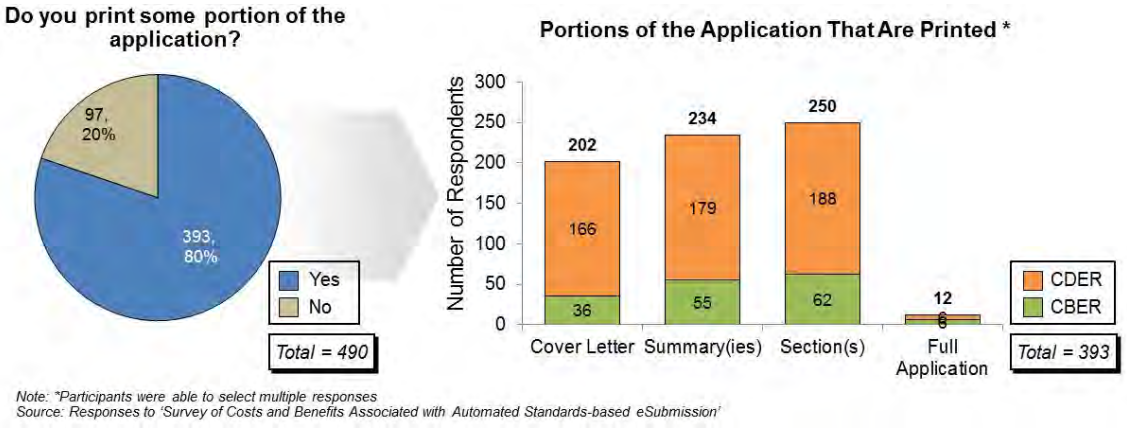
In addition to the reasons listed above, focus group respondents also noted that electronic submissions make it easier to run preliminary checks on an application to ensure that reviewers have the necessary information, review labeling on two monitors and enable them to copy and paste data and tables without manual re-entry into a tool or document.

Booz Allen evaluated the review performance using the parameters of review times and consult cycle times for electronic Common Technical Document (eCTD) and Study Data Tabulation Model (SDTM) submissions. Both standard and priority designated applications were compared for each submission format, but no key findings emerged from these analyses. Detailed results are presented in Appendix A: Additional Analyses.

Review Staff Printing Habits

The majority of survey respondents reported that they print some portion of an electronic submission after receipt. Exhibit 23 provides a detailed look at the printing habits of review staff based on survey results.

Exhibit 23: Printing Habits of Review Staff

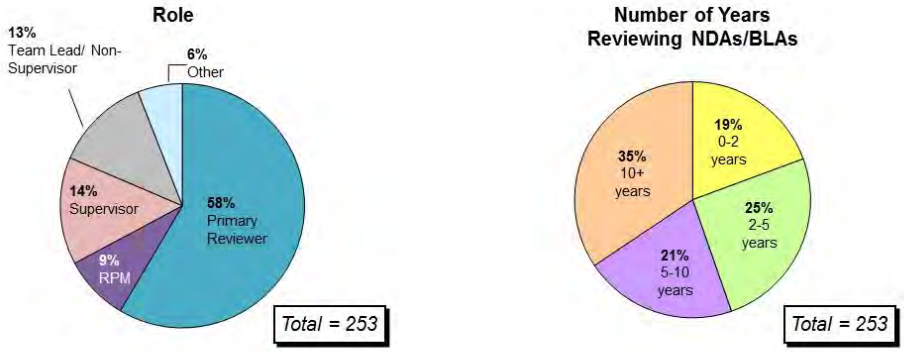


*Note: *Participants were able to select multiple responses*
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Survey respondents were asked whether they would print some portion of an electronic application. Out of the respondents that answered the question, 80% (393/ 490) indicated that they print some portion of an electronic submission after receipt. Although printing appears to be prominent, it is important to note that only 2% (12 out of 490; 6 from each Center) stated that they would print the full application. The cover letter, summaries and individual sections were printed at similar rates among each center. When reviewers were asked which portions of the summaries or sections were most commonly printed, reviewers indicated elements necessary for the specific review (e.g., Clinical Section, Labeling), data tables, and administrative portions were commonly printed. Focus group findings confirmed that discipline reviewers often print the labeling sections and data tables that would be re-entered manually for easy access during the review. Additionally, discipline reviewers also typically print definitions and other materials they will need to reference or mark-up at meetings.

Analyses were performed to identify the characteristics of review staff that print either full sections of an application or the entire electronic application. Exhibit 24 depicts printing habits based on the role and the number of years reviewing NDAs/BLAs indicated by survey respondents.

Exhibit 24: Characteristics of Review Staff that Print Full Sections and/or Applications of Electronic Applications



Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Of the 253 survey respondents who reported that they print full sections and/or applications, the majority (58%) are primary reviewers. Supervisors, team leads and Regulatory Project Managers (RPMs) reported printing full sections or applications to a significantly lower degree than primary review staff. Exhibit 24 also shows a trend of printing related to the number of years FDA staff have reviewed applications. As review experiences increases, so do these printing practices. Of the 253 survey respondents, those who reported printing the most (35%) had ten or more years of review experience at the FDA. In contrast, reviewers with the fewest years of experience (two years or fewer), were the least likely to print, making up only 19% of the 253 reviewers printing full sections or applications.

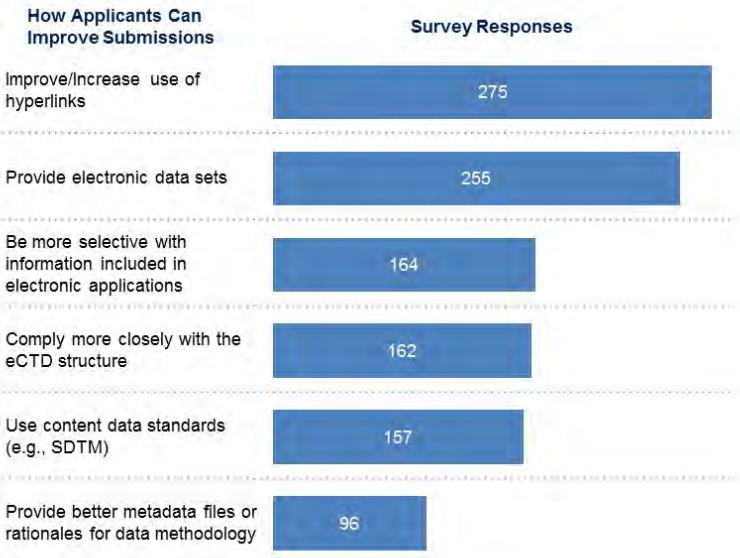
Issues Identified by Review Staff and Suggestions for Improvement

Data from the survey, interviews and focus groups provided insight into factors that impacted the review environment and led to developing recommendations for improving the electronic application review process. Several challenges were noted through the deep-dive data collection that impact electronic submissions and the review environment. Focus group respondents noted that data sets are often misplaced by the applicant (e.g., in the wrong folder or in separate folders) and show up incorrectly in GS Review, making it more difficult to review when two submissions are not stored next to each other in the same folder. Another challenge identified was that dates in the lifecycle view of the eCTD submission in GS Review and DARRTS do not directly link and occasionally do not match. Respondents also informed Booz Allen that DARRTS frequently requires timed out users to sign back in and reviewers waste time logging back in repeatedly. However, the time outs were added by FDA to enhance network security.

Survey respondents suggested modifying electronic exchange tools, training formats and IT support to better facilitate reviews. Discipline reviewers interviewed in focus groups suggested the use of standardized data sets in accepted formats because data standards save time on the upfront analyses. Confirming that an application has all of the necessary data for review and determining which data will be used for review takes less time when a standard is used. Consolidating documents in a central repository across CDER and CBER was also recommended as a way to improve the review environment. Focus group reviewers found it helpful if paper-only volumes of BLAs, NDAs, and Investigational New Drugs (INDs) could be scanned and electronically stored. In particular, they noted it would be more transparent and

useful if there was one central location for these files rather than using both RMS-BLA and DARRTS. Survey respondents and focus group reviewers supported the recommendation to promote the submission of electronic INDs. Discipline reviewers suggested that FDA mandate the electronic submission of all INDs since shorter review times for an IND makes immediate access critical.[12]

Exhibit 25: Suggestions for Improving Applicants' Electronic Submissions



Notes: Participants were able to select multiple responses
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

In order to improve applications, survey respondents suggested applicants provide electronic data sets and improve their use of hyperlinks. Applicants could improve their applications by providing better data that are organized with a thorough table of contents and working hyperlinks that are clearly written and relevant to the review. Furthermore, the respondents felt the review process would improve if applications were submitted in preferred formats and included more standardized data. Reviewers in focus groups remarked that applicants sometimes overburden reviewers with unnecessary data and they need to streamline summary sections. Applicants could increase the traceability of datasets by providing metadata and detailed variable definitions. In order to assist applicants in creating applications that include important components, focus group reviewers suggested that FDA develop supportive guidelines for industry on how and in what formats to submit data and reports for each discipline review.

Exchange and Content Data Standards

In order to provide a comprehensive assessment of exchange and content data standards, the Booz Allen team leveraged publically available data provided by the standards development organizations, FDA internal web resources and other public sources to document the readiness

[12] Focus group respondents noted that shortening review time by submitting electronic INDs would be especially useful in cases when a clinical hold is issued.

and current stage of adoption for each standard (See Appendix E: Exchange and Content Data Standards). The assessment was limited to the nine data standards selected by the FDA Technical Advisory Group (TAG). Table 4 lists the exchange and content standards along with their status.

Table 4: Accepted and Required Exchange and Content Data Standards[13]

Standard	Status
Electronic Common Technical Document (eCTD)	Required for All Electronic Submissions (CDER) Accepted (CBER)
Regulated Product Submission (RPS)	Not Accepted
Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM)	Accepted
CDISC Analysis Data Model (ADaM)	Accepted
Standard for Exchange of Nonclinical Data (SEND)	In Pilot (CDER) Not Accepted (CBER)
Product Stability Data Standard (PSDS)	Not Accepted
Clinical Data Acquisition Standards Harmonization (CDASH)	Not Accepted[14]
Structured Product Labeling (SPL)	Required
CDISC-HL7	Not Accepted

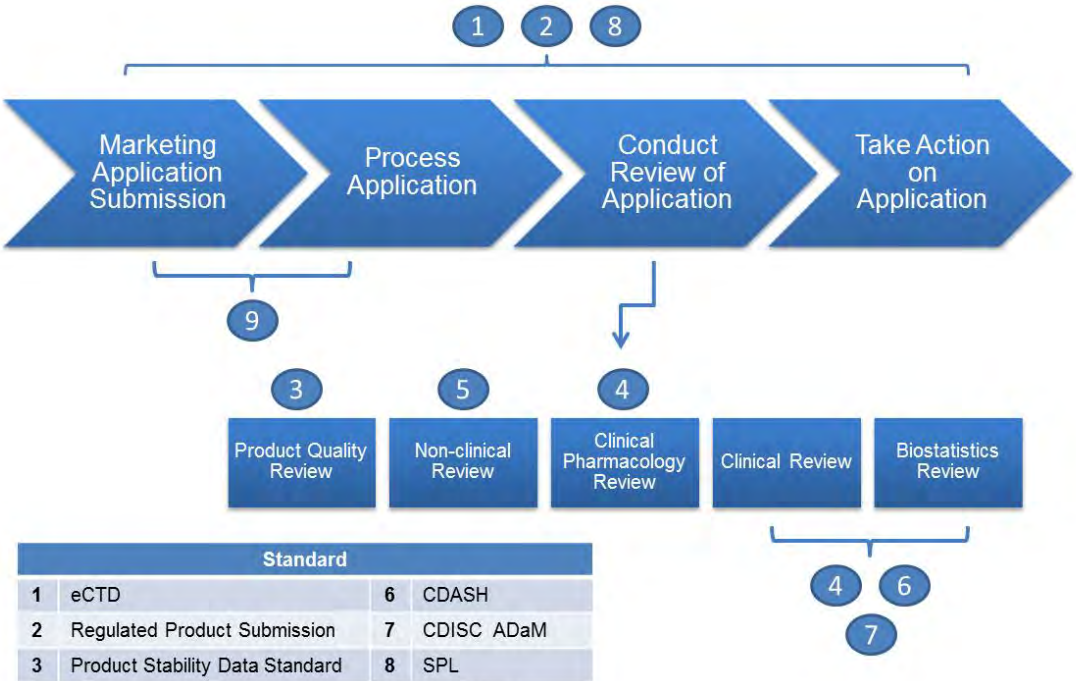
Exchange and Content Data Standards Role in NDA/BLA Review Process Lifecycle

This section provides an overview of each standard and its use in relation to the NDA/BLA review process. Exhibit 26 presents the review process lifecycle and the exchange and content data standards that correspond with each review process step.

[13] CDER began accepting eCTD submissions in October 2003. As of January 1, 2008, applicants submitting electronically are required to send new NDA, IND, ANDA, BLA, Annual Report, and DMF submissions in eCTD format to CDER. However, they can apply for a waiver to submit their application in paper. CDER has accepted SDTM data since July 2004 and effective December 2010 CBER completed a rolling implementation for SDTM that started in May 2010.

[14] CDER and CBER indicated that there are no plans to implement CDASH.

Exhibit 26: Exchange and Content Data Standards Role in NDA/BLA Review Process Lifecycle



Standard			
1	eCTD	6	CDASH
2	Regulated Product Submission	7	CDISC ADaM
3	Product Stability Data Standard	8	SPL
4	CDISC SDTM	9	CDISC-HL7
5	SEND		

*Note: * CDASH is used for the upfront data collection during clinical trials and consistent mapping to SDTM data*

The use of exchange and content data standards spans the NDA/BLA review process lifecycle, impacting multiple users. From receipt of the application submission to the point at which action is taken, applicants and FDA staff currently leverage the eCTD for electronic applications and SPL for product labeling. In the future, these users may work with RPS, which is expected to be the next major version of the eCTD, and CDISC-HL7, which may be the data exchange standard used to generate a data repository within the Janus system, which is currently under development. During review of an application, discipline reviewers work with multiple data sets provided in different file formats and structures. Currently, CDER and CBER accept clinical trial tabulation and analysis data sets submitted in the CDISC SDTM and ADaM formats which impact clinical pharmacology, clinical, and biostatistics reviewers who are responsible for reviewing applications with these data sets. Data may be collected using CDASH, a data collection standard that maps to SDTM. As more standards are adopted by the FDA, product quality reviewers may interact with data in the Product Stability Data Standard format and non-clinical reviewers will review data in the SEND format. Standards generated by a single sponsoring organization (e.g., CDISC, HL7) work in conjunction with one another to address the full review lifecycle.

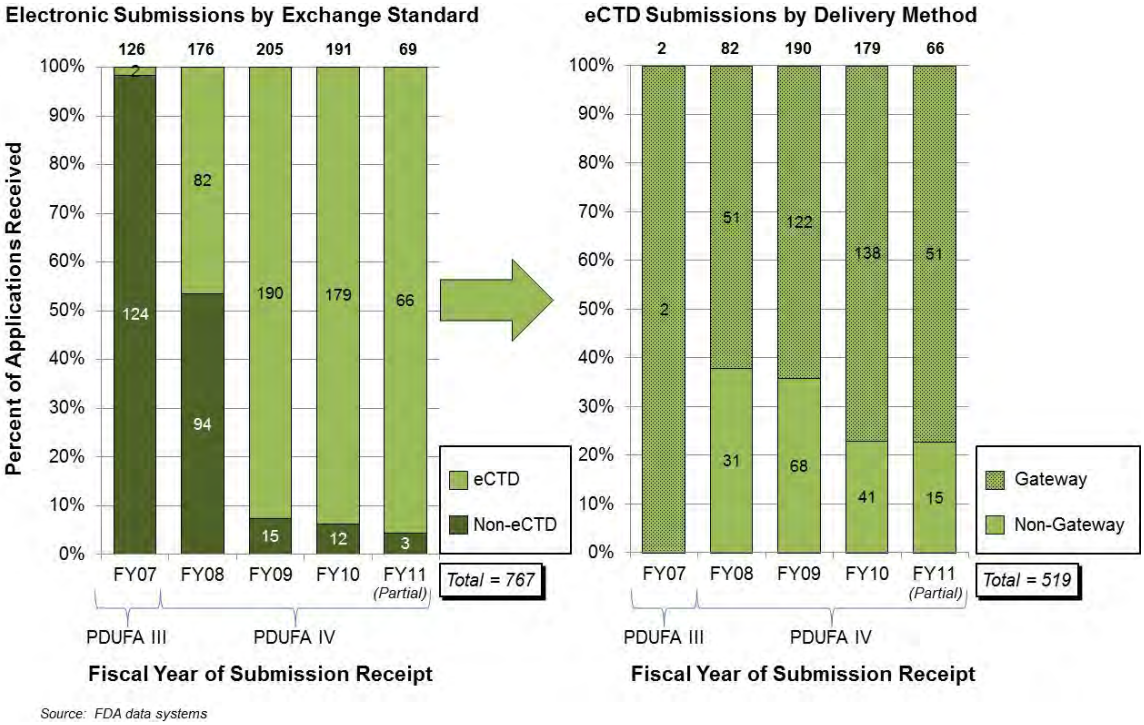
Adoption of Exchange and Content Data Standards

Booz Allen performed an analysis of the Overall Cohort to determine the number of electronic NDA applications submitted in eCTD format between FY07 to FY11.[15] Additionally, the eCTD

[15] The analysis is limited to applications submitted between FY07 to FY11 due to the lack of verifiable data available in FDA data systems before this time period.

submissions were analyzed to determine the delivery method (i.e., Gateway, non-Gateway). The findings are summarized in Exhibit 27.

Exhibit 27: Adoption of eCTD Format and Gateway for Electronic NDAs



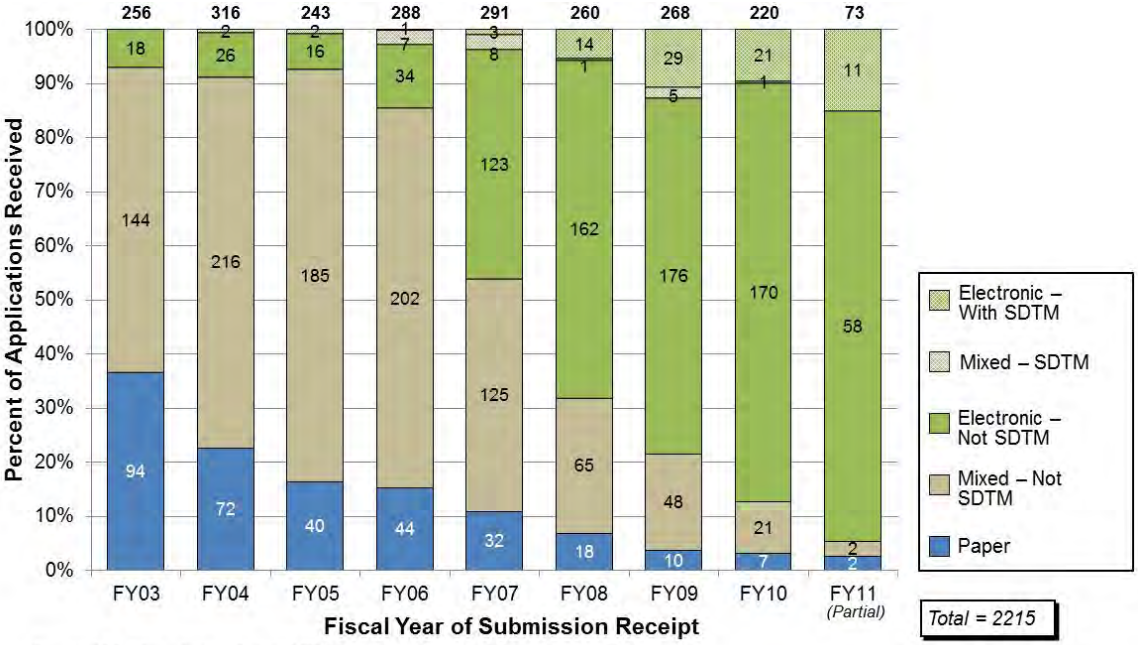
Source: FDA data systems

The analysis of electronic submission format and delivery method indicates that applicants are increasingly submitting applications in eCTD format and a majority of eCTD applications have been submitted through the Gateway. Since FY09, over 90% of electronic submissions have been in eCTD format, and the number is increasing over time. Booz Allen speculates that applicants are becoming more familiar with the eCTD format and developing more confidence using Gateway as a delivery method.

In FY04, CDER began accepting applications with standardized clinical trial data in SDTM format; however, the Center only has a local tracking method and has not yet adopted a formal mechanism to identify and track applications with SDTM data. The data are captured when an applicant indicates in the cover letter that the application includes SDTM data or a review team member verifies submission of SDTM data. The application number and review division are then placed in an internal spreadsheet.[16] Exhibit 28 shows the adoption of SDTM by applications from FY03 to FY11 (see Appendix A: Additional Analyses for a table detailing percentage of SDTM applications over time). The SDTM data were only available for NDAs through the end of December 2010.

[16] At the time of data collection, CDER and CBER did not have a formal tracking mechanism in place. As of March 2011, the two Centers automated the tracking of SDTM applications through the use of the define.xml file.

Exhibit 28: Adoption of SDTM for NDAs



Source: FDA data systems and internal SDTM data tracking spreadsheets

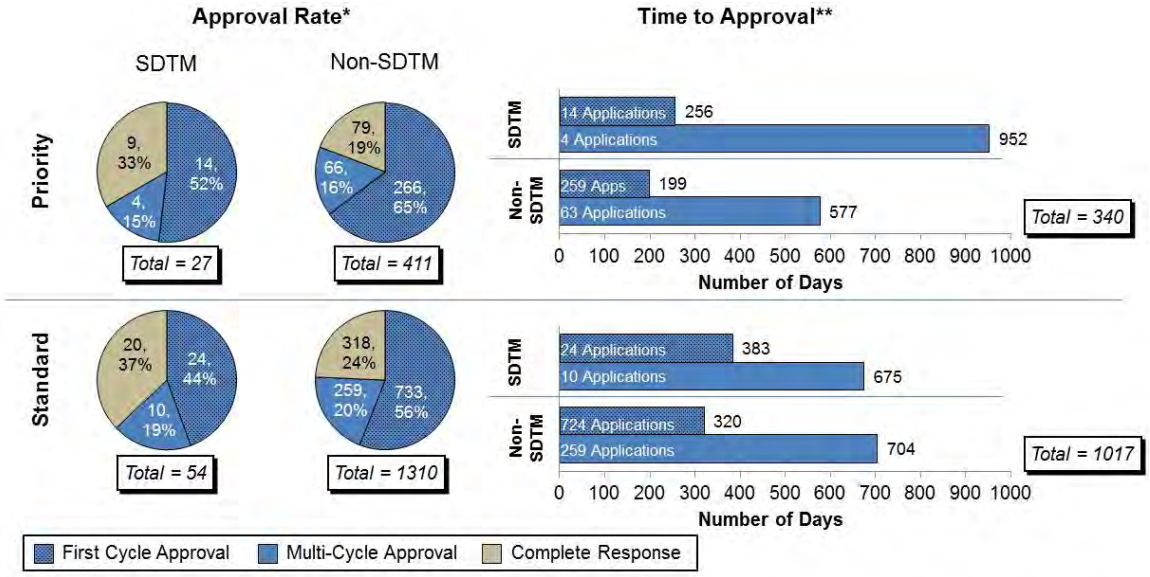
Overall, the data indicate that applications with SDTM data increased between FY03 and FY11. If the number of applications with SDTM data continues to follow the trend for FY11, then the total number for FY11 could approach or surpass the highest number of applications received in a fiscal year. The trend shows that applicants are slowly increasing the use of SDTM in recent years.

CBER began accepting applications with SDTM data on May 15, 2010, and as of June 2011, the Center had received five submissions with SDTM data. CBER has an established business process to identify, manage and validate SDTM and ADaM formatted submission.

Impact of Exchange and Content Data Standards

Booz Allen performed an analysis on the Overall Cohort and identified submissions that included SDTM data sets within the applications. The overall approval rate and time to approval were determined along with the first action and time to first action for SDTM and non-SDTM applications (Exhibit 29).

Exhibit 29: Overall Approval Rates and Time to Approval for SDTM and Non-SDTM Applications



Notes: SDTM data is only available for NDA submissions

** Complete Response actions include Not Approvable, Approvable and Complete Response; 413 applications were not included in this analysis: 55 Tentative Approvals and 358 that were not acted upon as of the data cut-off date*

***858 applications were not included in this analysis: 55 Tentative Approvals, 358 that were not acted upon as of the data cut-off date, and 445 outliers (see Appendix B for additional details regarding outliers)*

Source: FDA data systems and internal SDTM data tracking spreadsheets

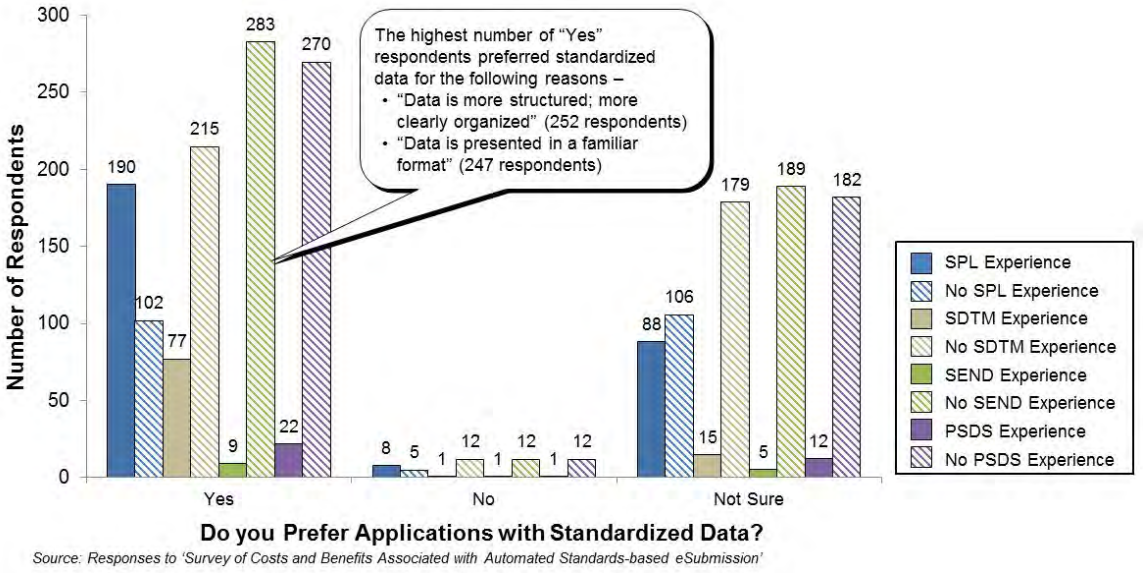
In priority and standard applications, non-SDTM applications had higher overall approval rates, with 81% (332/411) of the non-SDTM group receiving approvals compared to 67% (18/27) of the SDTM applications receiving approval among priority applications. Standard applications had slightly lower approval rates for both groups, with an approval rate of 76% (992/1310) for non-SDTM and 63% (34/54) for SDTM. The time to approval was longer for applications with SDTM for both priority and standard submission designations, except in multi-cycle approvals for standard designated applications (see Appendix A: Additional Analyses for time to approval and time to first action by submission format).

Given the findings, it should be noted that the sample size for SDTM applications was much smaller than non-SDTM applications and there may be other confounding factors. Some reviewers noted that applications with SDTM data were more complicated applications and they may have also included non-SDTM datasets in the same application. Additionally, SDTM training for reviewers had not been fully implemented until recently. FDA should perform these analyses as the availability of larger sample sizes increases since the number of applications with SDTM data sets only recently showed a trend towards increased adoption.

When asked whether they prefer applications with standardized data versus applications without standardized data, a majority of survey respondents indicated a preference for applications with

standardized data, even if they had not had experience with a particular exchange or content data standard (Exhibit 30).

Exhibit 30: Exchange and Content Data Standard Experience by Preference for Applications with Standardized Data



Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Respondents were also asked why they preferred applications with exchange and content data standards; results showed that preference did not favor greater depth in analysis, but rather favored data presentation. The reviewers indicated that they favored the standardized data because it was more organized, structured and presented in a familiar format. Refer to Appendix A: Additional Analyses for a full list of responses regarding preferences for receiving applications with standardized data.

Review Tools and Training Analysis

Booz Allen identified currently available electronic review tools and training programs and utilized secondary sources and targeted interviews to evaluate their use in the NDA/BLA review process (See Appendix F: Detailed Electronic Review Tool and Training Analyses). A recent study conducted by the CDER Computational Science Center (CSC) and IBM was used to help identify the top analysis tools used for medical product review. The three most used process tools and the 20 most frequently used analysis tools from this study were evaluated in this report (Table 5).[17] Two other analysis tools (i.e., WebSDM/Empirica Study, JMP Clinical) were added to the evaluation based on potential implementation of these tools in CDER and CBER.

[17] Survey Results and Analysis for FDA CDER Computational Science Tools Survey (n=389), January 2009.

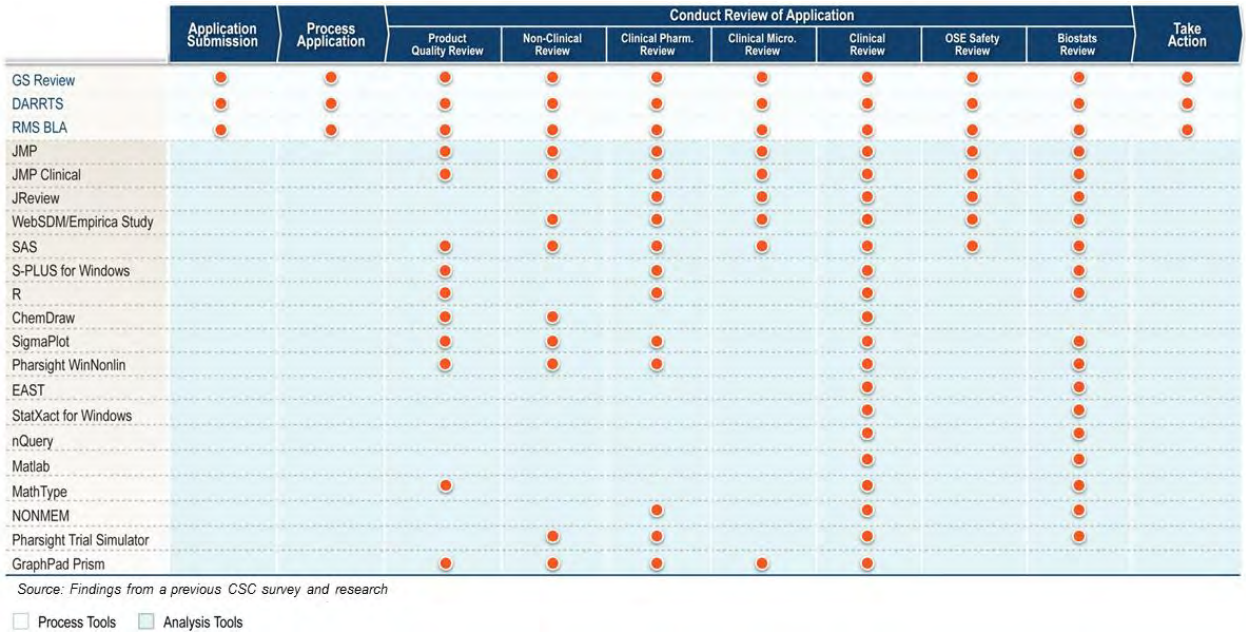
Table 5: List of Electronic Review Tools Evaluated

Process Tools	Analysis Tools	
▸ GS Review	▸ JMP	▸ ChemDraw
▸ DARRTS	▸ JMP Clinical	▸ SigmaPlot
▸ RMS-BLA	▸ JReview	▸ Pharsight WinNonlin
	▸ WedSDM/Empirica Study	▸ EAST
	▸ SAS	▸ StatXact For Windows
	- Base SAS	▸ nQuery
	- SAS/STAT	▸ Matlab
	- SAS/GRAPH	▸ Mathtype
	- SAS/IML	▸ NONMEM
	- SAS System Viewer	▸ Pharsight Trial Simulator
	- S-PLUS	▸ Graphpad Prism
	▸ R	

Role of Electronic Review Tools and Training in the NDA/BLA Review Process

This section provides an overview of each tool and its use in relation to the NDA/BLA review process. Exhibit 31 presents the review process lifecycle and the tools that correspond with each review process step.

Exhibit 31: Review Tools Associated with the Application Review Lifecycle



The use of tools impacts each phase of the NDA/BLA review process, and FDA reviewers and support staff rely on the tools for management of processes, document tracking, data analysis and creation of visual representations of data. Reviewers and support staff leverage process tools such as GS Review, DARRTS and RMS-BLA from the time of application receipt until FDA takes action on the application. Process tools are tools that support business processes by providing staff the ability to manage, track and archive incoming and outgoing documents related to the application. The tools also allow review staff to view submissions from the

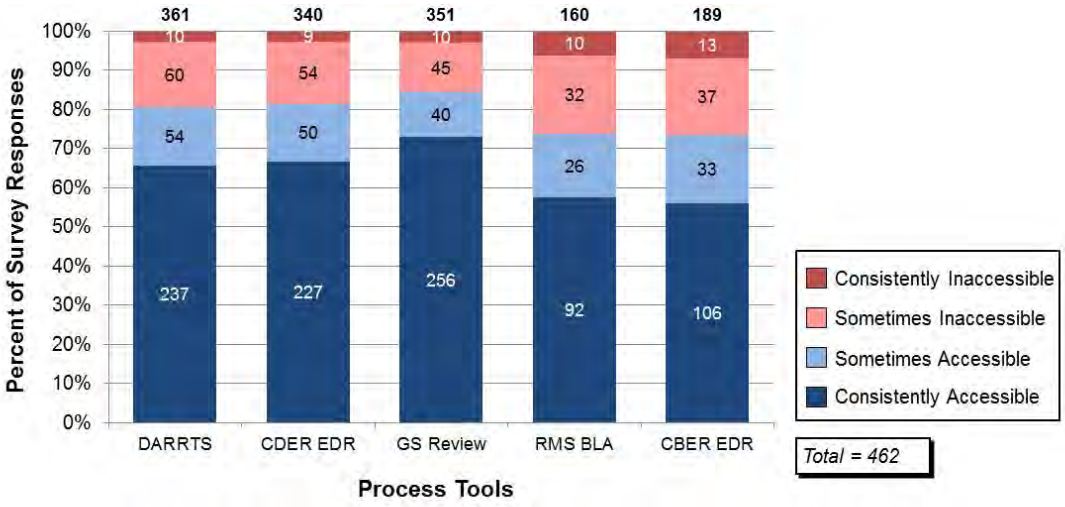
applicant and coordinate review assignments within the review team. During the Conduct Review phase of an application review, reviewers utilize multiple analysis tools offered and supported by FDA. These tools, which include JMP, JReview and WebSDM/Empirica Study (rollout and support development in process), provide reviewers with statistical and graphical analyses focused on clinical trial data. Additionally, CDER and CBER are evaluating the possible implementation of JMP Clinical as a review tool for staff.

Outside of the review tools supported by CDER and CBER, reviewers incorporate the functionalities and capabilities of commercially available analysis tools to conduct in-depth analyses and depict data visually to identify trends and outliers. Each tool provides different functionality and capabilities that allow reviewers to conduct the numerous types of analyses required to complete an application review. As evidenced in Exhibit 31 above, the clinical and biostatistics reviewers use the majority of tools captured in the 20 most frequently used analysis tools, consistent with the fact that these reviewers must evaluate all portions of the application in order to make a determination on the safety and efficacy of a drug or biologic. The clinical microbiology and safety reviewers in CDER and clinical reviewers and statisticians within CBER utilize the standard statistical software packages (e.g., SAS, JMP). Non-clinical and clinical pharmacology reviewers in CDER and statisticians within CBER use advanced statistics and graphics software (e.g., R, SigmaPlot, S-PLUS) along with specialized software for pharmacodynamic and pharmacokinetic analyses (e.g., Pharsight WinNonlin, NONMEM). Finally, product quality reviewers leverage much of the statistics software used by other reviewers along with software geared specifically toward the analysis of chemical structures (i.e., ChemDraw).

After identifying the most frequently used process and analysis tools, Booz Allen conducted stakeholder interviews, held discipline-specific focus groups and issued a survey to understand how review staff learn and interact with the tools in order to effectively and efficiently review NDA and BLA applications.

As part of the survey, participants were asked to rate how consistently they were able to access select process tools (Appendix G: Survey). Accessibility to these web-based tools is pivotal to performing the required review tasks and directly impacts review efficiency.

Exhibit 32: Perceived Accessibility of Process Tools

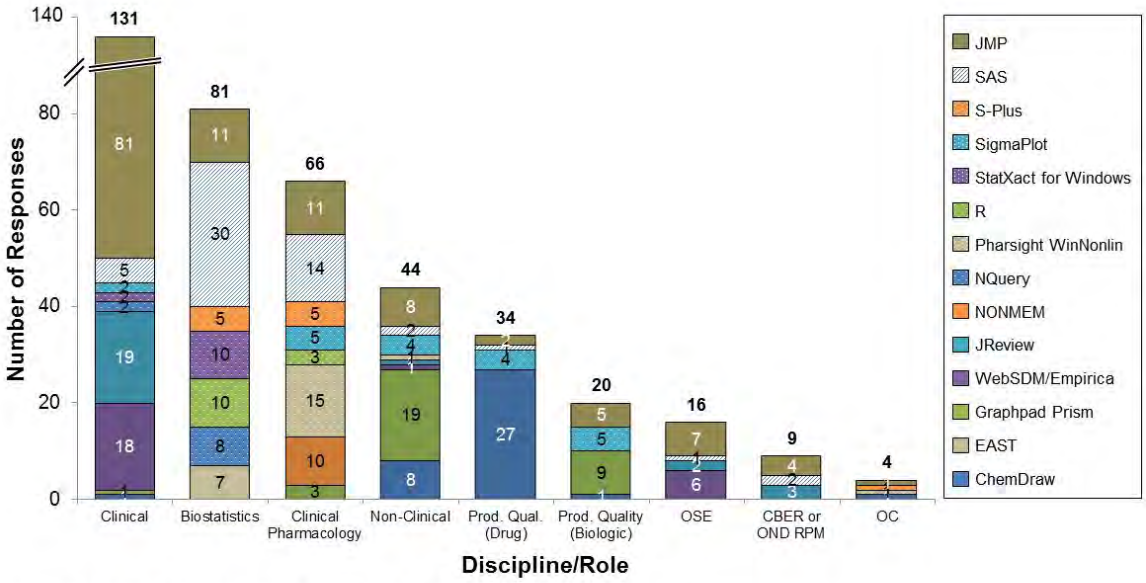


Notes: Data excludes 'N/A- Do not use' option. Respondents were not required to rate all five process tools; 42 respondents did not answer any portion of the question and 2 respondents answered 'N/A- Do not use' for all five process tools
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Assessment of feedback received through the survey, presented in Exhibit 32, indicated that although perceived accessibility to the five process tools is generally positive, there are opportunities for improvement. In focus groups and interviews across disciplines, reviewers commonly indicated that they save study reports into a folder on their hard drive to avoid slower connectivity when accessing GS Review.

In order to ensure a complete understanding of the tools being used, the survey also requested feedback regarding analysis tools. Survey participants were asked to select their three most frequently used analysis tools and to answer a set of corresponding questions. Understanding which tools are and are not used, as well as the disciplines that use them, may be important considerations when deciding whether to continue or discontinue offerings or support for specified tools. Exhibit 33 presents the data captured through the survey, portraying how many survey respondents from each discipline indicated frequently using each analysis tool.

Exhibit 33: Survey Respondents Tool Usage, by Discipline

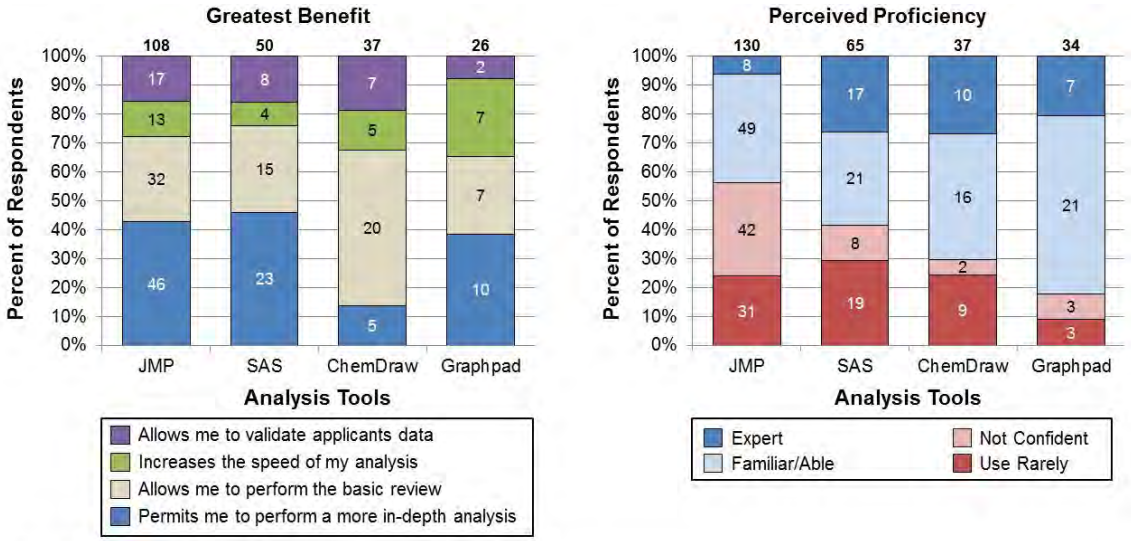


Notes: Facility (Biologic) and DDMAC were surveyed but did not cite the use of any tools
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Survey results showed that discipline reviewers and other staff utilize a diverse range of analysis tools to complete or contribute to the application review. The most commonly used tools across the disciplines include SAS, a commonly used statistical software package, and JMP, a derivative of the SAS software package supported and offered by CDER and CBER. ChemDraw and Graphpad were also among the top four most frequently used analysis tools (See Appendix A for additional analysis on tool usage).

To gain a better understanding of the advantages of the four most popular analysis tools used by review staff, respondents were asked to identify the benefits of these analysis tools and indicate their level of proficiency with each tool (Exhibit 34). JMP users indicated that the tool allowed them to perform a more in-depth analysis; however, only 6% (8/130) considered themselves to be experts and over half (73/130) either lacked confidence or rarely used the tool. Respondents indicated the greatest proficiency with Graphpad Prism, with 82% (28/34) self-identifying as expert or capable proficiency. A majority of respondents using ChemDraw (54%, 20/37) indicated that the tool allowed for basic review rather than a more in-depth analysis.

Exhibit 34: Reviewers' Perceived Benefits and Proficiency of Most Used Analysis Tools

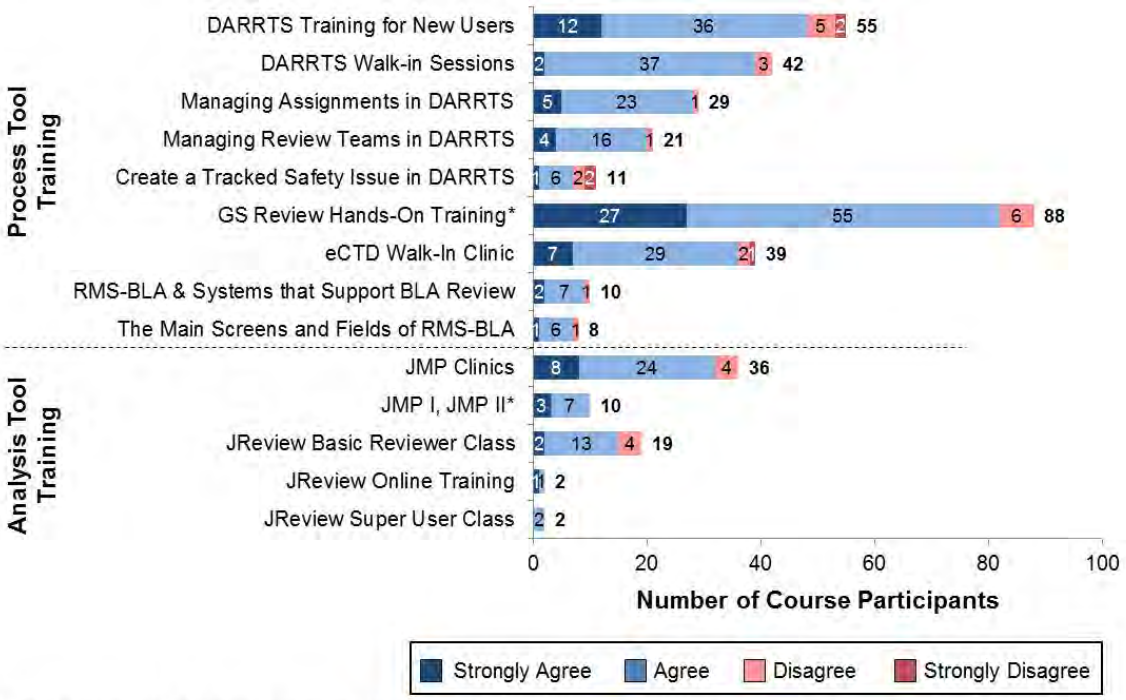


Notes: Analysis performed on the top 4 tools, identified using survey data
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

The role of training as it might relate to use and proficiency level of process and analysis tools was evaluated by assessing the available options for and reviewer satisfaction with training. Profiles of each tool include a list of available training options, which can be found in Appendix F: Detailed Electronic Review Tool and Training Analysis. Where formal corresponding training courses exist, a summary of the curriculum and evaluation also follows the section. CDER and CBER receive feedback via course completion surveys; however, it is unclear if this data is used for program-wide or historical analysis as aggregate data was not available from either Center at the time of this assessment. Data from the Survey of Costs and Benefits Associated with Automated Standards-based eSubmissions were used to evaluate course satisfaction (Exhibit 35).

In the survey, respondents were asked to indicate two courses they attended in the past year and rate their satisfaction with the selected course format (Exhibit 35). In this analysis, nine training courses were evaluated for process tools and five were evaluated for analysis tools.

Exhibit 35: Training Course Attendance and Satisfaction with Course Format

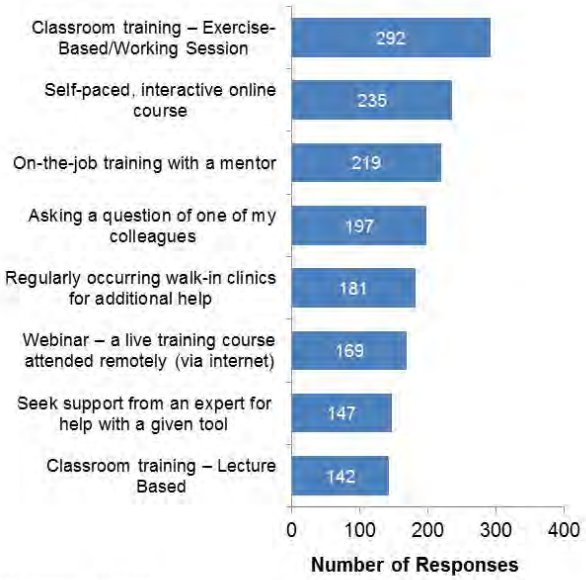


*Notes: Fewer respondents rated the course format than attended the course.
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

In addition to a wider variety of course offerings, a greater number of participants attended process tool training than analysis tool training. Out of all training offered for both process and analysis tools, GS Review Hands-On Training had the highest number of responses, with 82 out of 88 attendees agreeing or strongly agreeing that the course format was appropriate. DARRTS Training for New Users had the second highest response rate, followed by DARRTS Walk-In Sessions, with a vast majority of attendees expressing satisfaction with the course format, both of which were process tool trainings. Although relatively few respondents participated in analysis tool trainings, the majority were satisfied with course format. During focus groups and interviews, some reviewers indicated that the current training was too basic or elementary.

When the courses were categorized by format, walk-in clinics had the greatest number of participants, followed by the classroom exercise based format. A majority of respondents agreed or strongly agreed that the course format was appropriate for both categories. Classroom lecture based formats were attended least frequently and had the largest portion of respondents indicating disagreement or strong disagreement with appropriateness of course format. When compared to a survey question asking participants to identify the most preferred training methods for electronic review tools, there were some similarities with attendance and satisfaction data (Exhibit 36).

Exhibit 36: Most Preferred Training Formats



Notes: Participants were able to select multiple responses
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

For example, classroom training in an exercise based/working session format was most preferred, with 292 responses. Walk-in clinics were moderately popular, though self-paced, interactive online courses and learning from a mentor or colleagues ranked above walk-in clinics in preferred format. Classroom training lecture format ranked the lowest of preferred training formats (142 respondents), supporting the attendance and satisfaction data.

Current Organization and Responsibilities

As of July 2011, there are a number of formal FDA groups playing an active role in defining the future of electronic submissions and exchange and content data standards within the FDA. Each group has been designed to meet a specific need and has responsibilities ranging from strategy development, to coordination, to providing lifecycle support in a specific area such as electronic submissions or IT systems. The groups range in size, authority, available resources and scope, both in breadth and depth. Some were created to support another group within the same arena, in which case the communication channels appeared strong; however, other groups are much larger and only a portion of their focus includes electronic submissions and exchange and content data standards.

Groups at the FDA-level lead the electronic submission and exchange and content data standard initiatives for all Centers. They are comprised of Center representatives who work to develop a FDA-wide strategy and to coordinate Center-level groups to ensure alignment. In doing so, each group has a specified purpose:

- **FDA Data Standards Council (DSC)** – Coordinates FDA-wide health and regulatory information standardization and utilization activities; promotes development of an FDA-wide integrated business and data element architecture; addresses data policy issues raised at the HHS Data Council

- **Interim Informatics Governance Board (IIGB)** – Oversees all FDA activities related to business automation planning, acquisition, and implementation decisions; acts as the delegated Information Technology Investment Review Board (ITIRB) for FDA bioinformatics activities; coordinates FDA representatives to the various groups and councils

- **PDUFA Information Management Working Group (PIMWG)** – Reviews PDUFA IT programs and related budget; comprised of OIM, and CDER/CBER representatives

- **Scientific Computing Board (SCB)** – Defines and coordinates FDA-wide scientific IT; collaborates with Office of Information Management (OIM) and OAGS to identify and develop policies and procedures and advise the Office of the Chief Scientist (OCS) and IGB

Groups at the Center-level develop and implement Center or Office-level strategies. They do so while influencing one or more of the following: electronic submissions and exchange standards, content data standards, IT systems and training. Exhibit 37 presents the groups involved and the areas that fall within their scope of responsibilities.

Exhibit 37: Responsibilities of CBER and CDER Groups Involved with Electronic Submissions

Responsibilities											
General Focus											
Strategy & Policy Development											
Compliance Monitoring (incl. alignment with strategy)											
Process Development											
Daily Support											
Coordination (between other offices or groups)											
Advisory											
Analytics – metrics, analysis, reporting											
Primary Areas of Influence											
Electronic Submissions & Exchange Standards											
Content Data Standards											
IT Systems – process tools, review tools											
Training- tool & review process											
Office/Groups											
CDER											
CDER Data Standard Program Board (DSPB)			✓	✓	✓		✓			✓	
Information Management Advisory Board (IMAB)		✓			✓		✓			✓	
Computational Science Center (CSC) Board	✓	✓	✓				✓	✓	✓	✓	
Office of Planning and Informatics (OPI)		✓		✓					✓		✓
Office of Business Informatics (OBI)		✓		✓		✓	✓				✓
Division of Project Development (DPD)		✓							✓		
Division of Regulatory Review Support (DRRS)	✓	✓		✓	✓	✓	✓	✓	✓		
Office of Planning and Analysis (OPA)				✓			✓				✓
CBER											
Review Management (RM) [within Office of the Director]	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Information Management Coordinating Committee (IMCC)		✓		✓		✓	✓		✓		✓
Review Management Coordinating Committee (RMCC)		✓	✓	✓		✓	✓		✓		✓
Regulatory Information Management Staff (RIMS)	✓	✓			✓	✓	✓	✓		✓	
Office of Communications (OCOD)	✓						✓			✓	

Notes: Participants may be involved in more than one group

In CDER, the DSPB oversees ongoing planning and coordination of Center exchange and content data standards projects and ensures a coordinated CDER representation to the FDA

DSC. The Office of Planning and Analysis (OPI), which falls within the Office of Planning and Informatics (OPI), directs the Center's long-range planning processes and coordinates with the long-range planning process of FDA's Office of Commissioner and DHHS. The remaining groups, including OPI, influence the Center's IT systems. Available data shows that there is an attempt to differentiate between the types of systems influenced and the stage at which the influence occurs, but it appears as if there are some areas of overlap.

CBER's Review Management, within the Office of the Director, manages the Center's application review process, which includes coordination of Center activities in external standards organizations. CBER also has two coordinating committees, IMCC and RMCC, which may help to develop strategies for their specific focus area and provide recommendations to CBER management. Each coordinating committee includes members who serve as Center representatives on FDA-level groups including the FDA DSC. The Regulatory Information Management Staff (RIMS) oversee CBER's regulatory information databases (e.g., RMS-BLA) and provide corresponding training. The Office of Communications (OCOD) oversees the CBER's intranet and internet websites and manages review training, which includes reaching out to CDER to coordinate training for tools (e.g., GS Review).

In both Centers, several groups were created primarily to facilitate communication between OIM and all of the different Offices and groups within the Centers. Additionally, some individuals serve on multiple committees and groups in CDER and CBER. However, the existing lack of internal transparency hindered an evaluation of the effectiveness of the approach. Comprehensive information pertaining to the roles and responsibilities, overall hierarchy, communication channels and overall purpose of each group related to electronic submissions, exchange and content data standards, review tools and training was not clearly presented, regularly updated or readily available. Further details for each of the groups can be found in Appendix A.

PROGRESS AGAINST IDEAL ELECTRONIC REVIEW ENVIRONMENT

As evidenced by the findings in this report, FDA is moving towards a fully electronic review environment. In order to determine the progress towards this initiative, CDER and CBER should develop a harmonized, transparent vision of the future state of electronic review. At the time of this assessment, an overall vision that encompasses all of the different aspects of electronic review evaluated in this report was not found. In order to determine the progress towards a fully electronic submission and review environment, a vision of the future electronic review environment that incorporates the multiple facets of the new environment must be realized. Therefore, based on the performed analyses and observations from interviews and focus groups, Booz Allen developed an ideal electronic submission and review environment to assess FDA's progress (Table 6).

Table 6: Progress against Ideal Electronic Review Environment

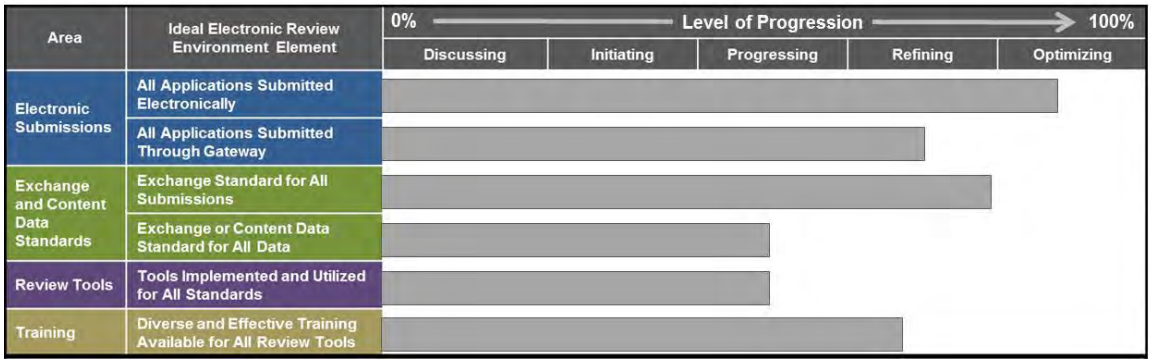
Area	Ideal Electronic Review Environment Element	Current Progress
Electronic Submissions	▸ All applications submitted electronically	**NDA Original Applications and Efficacy Supplements** ▸ 87% (191/220) of applications submitted electronically in FY10 ▸ 95% (69/73) of applications submitted electronically in FY11 (partial year) **BLA Original Applications and Efficacy Supplements** ▸ 76% (37/49) of applications submitted electronically in FY10 ▸ 96% (27/28)of applications submitted electronically in FY11 (partial)
	▸ All applications submitted through the Gateway	**NDA Original Applications and Efficacy Supplements** ▸ 65% (143/220) of applications submitted through the Gateway in FY10 ▸ 73% (53/73) of applications submitted through the Gateway in FY11 (partial)
Exchange and Content Data Standards	▸ Exchange standard implemented for all electronically submitted applications	**NDA Original Applications and Efficacy Supplements** ▸ 94% (179/191) of electronic applications utilized the eCTD format in FY10 ▸ 90% (66/73) of electronic applications utilized the eCTD format in FY11 (partial year) **BLA Original Applications and Efficacy Supplements**[18] ▸ 19% (5/27) of electronic applications utilized the eCTD format in FY10
	▸ Exchange or content data standard implemented for all incoming non-clinical and clinical data	▸ For those exchange and content data standards that are planned for implementation, CDER and CBER currently accept 50% (2/4) of these standards[19] **NDA Original Applications and Efficacy Supplements** ▸ 10% (22/220) applications submitted with SDTM data in FY10 ▸ 15% (11/73) applications submitted with SDTM data in FY11 (partial year)
Review Tools	▸ Process and analysis tools implemented and utilized for each accepted exchange and content data standard	▸ 100% of accepted standards have associated tools ▸ GS Review used for eCTD ▸ WebSDM Empirica Study, JReview and JMP used for CDISC SDTM ▸ JReview and JMP used for CDISC ADaM
Training	▸ Diverse and effective training available for all process and analysis tools to meet staff needs and preferences	▸ CDER and CBER provide training for all supported process and analysis tools through the HHS Learning Portal - Course format variety is available for select tools; it is unclear if reviewer preferences are considered - Different levels of training (e.g., beginner, expert) are not offered by either center ▸ CDER and CBER receive feedback via course completion surveys; it is unclear if this data is used for program-wide or historical analysis as aggregate data was not available from either Center at the time of this assessment. ▸ External/vendor training is available for unsupported analysis tools

[18] BLA eCTD data for FY11 were not available at the time of data collection

[19] CDASH is not planned for implementation ; CDISC-HL7 will incorporate CDISC SDTM and ADaM

The exhibit below provides a graphical representation of FDA's current progress towards this potential ideal future state based on the information outlined in the table above (Exhibit 38).

Exhibit 38: Level of Progress towards Potential Ideal Future State



RECOMMENDATIONS

The findings from this assessment indicate an increasing trend in the submission of electronic applications to CDER and CBER. Additionally, the two Centers are in the process of implementing exchange and content data standards critical to the improved efficiency and transparency of the drug and biologic review process. The need for review tools capable of leveraging standardized data to automate analyses and provide more in-depth analyses will increase with expanded standard implementation by the Centers and adoption by applicants. As the standards and tools continue to evolve and mature, the FDA will need to grow and adapt to meet the needs and realize the efficiencies for the review staff.

Some of the current benefits of electronic submissions and standards include:

- Reduced administrative burden when locating and accessing documents
- Improved ability to search within documents for material
- Improved navigation within the application due to consistent formatting
- Reduced amount of time spent organizing data for review

Other potential future benefits of increased adoption of content data standards include:

- Automation or semi-automation of some clinical, pre-clinical and clinical pharmacology data analyses
- Familiarity with the data format for improved manipulation and navigation
- Integration with external data and databases
- Improved data quality and accessibility

The following recommendations focus on developing a workforce, processes, technologies and infrastructure that can operate effectively in the new and evolving environment (Table 7).

Table 7: Recommendations

Area/ Goal	Recommendations
People *Develop a workforce able to fully and efficiently leverage electronic submission tools and capabilities*	**1.** Develop effective training to ensure new technologies are effectively integrated and staff is comfortable and skilled with process and analysis tools o Support preferred formats o Establish feedback mechanism
Processes *Set up standardized processes to ensure success of the electronic submission program*	**2.** Develop clear roles and responsibilities for managing direction and implementation of the electronic submission program o Electronic submission tracking and analysis o Exchange and content data standard research, planning and implementation o Review tool research, development/procurement, implementation and monitoring o Training related to electronic submissions, exchange and content data standards and review tools o Harmonization of communication across CBER and CDER o Outreach efforts with industry **3.** Develop process metrics and tracking dashboard o Automate reporting and analysis where possible o Develop tool for reviewers to provide process feedback
Technology *Ensure tools and technologies are available to support use of the electronic data*	**4.** Adopt enhanced tools to automatically validate submission data to ensure appropriate application of the standards, reducing administrative burden **5.** Conduct formal hardware and software assessment for review staff and map to current configurations to identify gaps **6.** Continue efforts to review established and cutting edge exchange and content data standards and coordinate the implementation of new standards across CDER and CBER **7.** Synchronize tool development/adoption with standards implementation by simultaneously rolling out review tools that directly utilize the efficiencies for a newly implemented exchange or content data standard **8.** Increase the ability to use automation associated with standards-based review tools
Physical Infrastructure *Ensure physical infrastructure supports needs of the review staff*	**9.** Improve user experience by providing sufficient monitors and network access to support on-site and remote staff **10.** Centralize point of access to data currently stored in multiple databases (e.g., EDR, DARRTS, RMS-BLA) to improve efficiency and consistency of data

People

In order to perform their review activities and ensure the availability of safe and effective drugs and biologics to the public, the FDA workforce performs a multitude of general and highly-specialized services to complete an application review. In addition, the staff must interact with complex technologies. Therefore, FDA should invest in effective training for staff to assure the new technologies are effectively integrated into the review process and reviewers realize the benefits of the new tools. For example, the FDA could implement an instructional design model (e.g., ADDIE) so the training would be specifically targeted for the particular staff taking the

course and evaluated to make sure all the goals of the training have been met. During focus groups, reviewers indicated a need for discipline-specific training with sessions targeted towards varying skill levels (e.g., beginner, intermediate, expert). Additionally, survey data revealed that reviewers preferred exercised-based classroom training and self-paced, interactive online training. Analysis of training efficacy data uncovered a need for a formal feedback mechanism to capture feedback from staff after course completion. After capturing the feedback, FDA should track and analyze the data to determine the needs and preferences of the review staff.

Processes

As discussed in the findings, there are multiple groups, councils and offices working to improve the electronic submission process, all with potentially competing priorities. The fragmentation created by these different groups reduces the efficiency and effectiveness of any well intentioned electronic submission initiative. Any effort to drive change and progress associated with electronic submissions needs to be comprehensive and include a concerted effort with individuals working on exchange and content data standards, review tools and training. All of these components work interdependently to create an electronic review environment that allows FDA staff to effectively process, analyze, review and act on applications. However, FDA needs to clearly differentiate the roles and responsibilities of the involved parties as they relate to electronic submissions, exchange and content data standards, review tools and training to lessen the possibility of redundant work efforts for each of the components. After identifying and clearly communicating the roles and responsibilities to the designated groups, FDA should ensure that transparent and harmonized communication between the two Centers effectively reaches review staff so they have a comprehensive understanding of the different initiatives and the impact on their work (e.g., review tool availability). For example, the group designated to work on the research, planning and implementation of exchange and content data standards could regularly meet with the recently established Data Standards Leads for each review division and Points of Contact in the Office of Biostatistics. The group could also develop MaPPs and guidances (e.g., data submission formats) related to the exchange and content data standards. Finally, FDA should engage in interactive outreach sessions (e.g., focus groups, conferences) with industry, advocacy groups and standard development organizations to gain a better understanding of their perspective, priorities and insight on electronic submissions, standards and associated tools.

While performing this assessment, specific and accurate data for submission format, applicant size, applications with standardized data and applicants' previous experience with electronic submissions (e.g., electronic INDs) proved challenging to obtain in order to conduct analyses. FDA should determine the metrics necessary for strategic decision-making and develop a dashboard to automatically collect the data, which can be used to perform critical analyses needed to make decisions regarding the electronic submission initiative (e.g., exchange and content data standard implementation). The dashboard could also pull data from external websites (e.g., financial sites for applicant size data) and provide data for the FDA-Transparency-Results-Accountability-Credibility-Knowledge Sharing (TRACK) initiative.[20] For example, the dashboard metrics could cover four main areas related to electronic submissions:

- Application characteristics (e.g., submission format, application size, standards used)

[20] FDA currently reports on SDTM data.

- Review characteristics (e.g., number and type of analyses performed by discipline per application, number and type of information requests sent during review)
- Review tools (e.g., tools used during review of an application)
- Training (e.g., courses attended, course feedback/rating)

Technology

Currently, the FDA has not adopted automated validation tools for all exchange and content data standards.[21] In order to reduce the administrative burden on reviewers and support staff, FDA should implement or utilize currently available data validation tools. Upon receipt of the application, the data within the electronic submission should be validated prior to delivery to review staff to ensure the appropriate application of the given standard. FDA should use automated validation tools for all accepted exchange and content data standards.

During review staff interviews and discipline-specific focus groups, reviewers and RPMs indicated that they were using older computer equipment and older application versions to complete their reviews. Reviewers raised concerns that the older hardware and software was not able to adequately handle the larger file sizes or effectively run the new applications without significant processing strain.[22] FDA should conduct a formal assessment to map application requirements to hardware and software configurations and identify any gaps to what is currently available or used by review staff.

Although many of the exchange and content data standards have not yet been fully implemented, preliminary findings indicate that reviewers prefer to work with standardized data and spend less time preparing the data for their review. The reduction in preparation time did not appear to have an effect on the overall review time and the limited data prevented further analysis. However, the potential benefits (e.g., automated analyses) for standardized data may eventually lead to less time spent analyzing the data and more time spent investigating any inconsistencies within the data (e.g., safety signals, efficacy endpoint) to expand the safety and efficacy profile of the drug or biologic.

With an increase in the implementation and adoption of exchange and content data standards, FDA will need to synchronize the availability of review tools that effectively and efficiently interact with the newly implemented standard. Otherwise, the efficiencies gained by using standardized data will not be fully realized. Additionally, FDA has the opportunity to further increase the ability to use automation in currently available tools (e.g., JReview) through expanded access to reviewers and proper training.

Physical Infrastructure

When surveyed about accessibility to tools available on the network, review staff indicated that there were times when the critical review tools were inaccessible. Staff that work remotely revealed that network reliability and connectivity have improved in recent years; however, they stated that network issues continue to cause disruptions in their ability to access tools and

[21] Currently, FDA has automated validation for eCTD. Recently, FDA began using OpenCDISC for SDTM and ADaM data validation.

[22] FDA representatives indicate that the issue may be related to applicants' development of the SDTM xpt files. FDA analysis shows that SDTM dataset size may be reduced by 60 to 90%.

information. FDA should ensure that sufficient monitors and network access are in place to support review staff while completing application reviews.

FDA should also consider consolidating databases (i.e., CDER and CBER EDR, DARRTS, RMS-BLA) utilized by both CDER and CBER review staff.[23] For the most part, both Centers follow the same review process (i.e., Good Review Management Principles and Practices) and timelines for original applications and supplements. Therefore, the FDA could reduce redundancies by eliminating databases where the same functionalities and capabilities exist or could be implemented in another database. The two Centers could reduce resources dedicated to maintaining the two databases and eliminate the need to train staff on separate databases performing the same functions.

[23] During the completion of this report, CDER integrated the CDER EDR into DARRTS.

APPENDIX A: ADDITIONAL ANALYSES

The following exhibits include additional analyses performed to evaluate variations in the findings.

Table 8: Approval Rate by Submission Format for Priority and Standard NDAs

	Submission Format	Paper	Mixed	Electronic – Non- Gateway	Electronic - Gateway
Priority	Approval	80%	81%	76%	79%
	Complete Response	20%	19%	24%	21%
Standard	Approval	78%	76%	69%	77%
	Complete Response	22%	24%	31%	23%

Table 9: Approval Rate by Submission Format for Priority and Standard BLAs

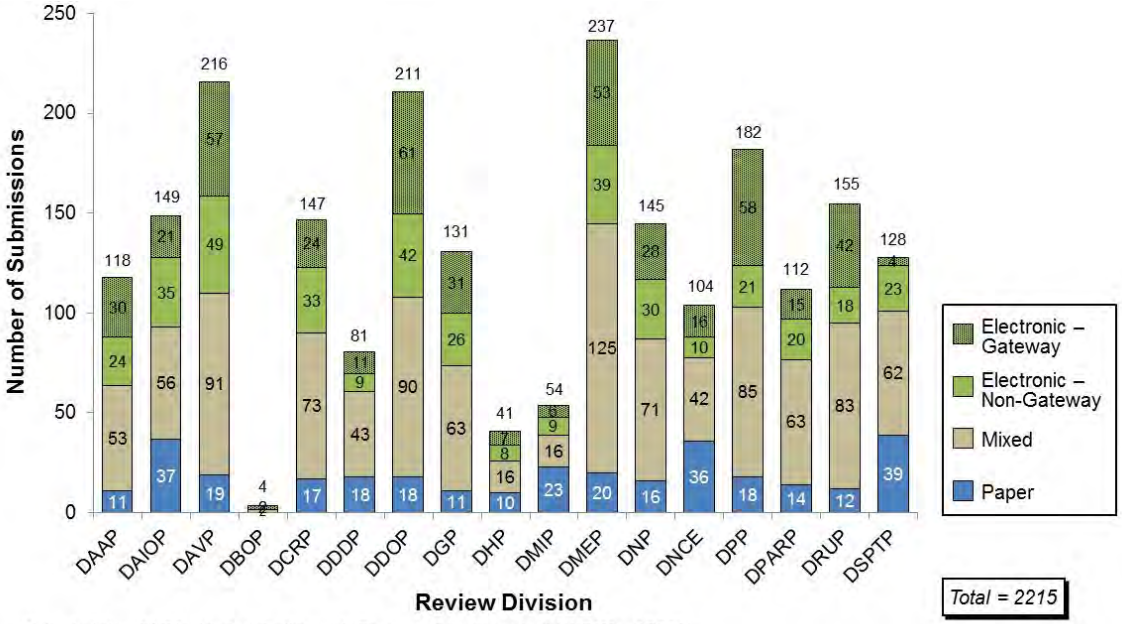
	Submission Format	Paper	Electronic
Priority	Approval	88%	91%
	Complete Response	12%	9%
Standard	Approval	80%	85%
	Complete Response	20%	15%

Table 10: Percentage of CDER SDTM Applications by Fiscal Year

Fiscal Year of Submission Receipt	Percentage of SDTM Applications
FY03	0.0%
FY04	0.6%
FY05	0.8%
FY06	2.8%
FY07	3.8%
FY08	5.8%
FY09	12.7%
FY10	10.0%
FY11	15.1%

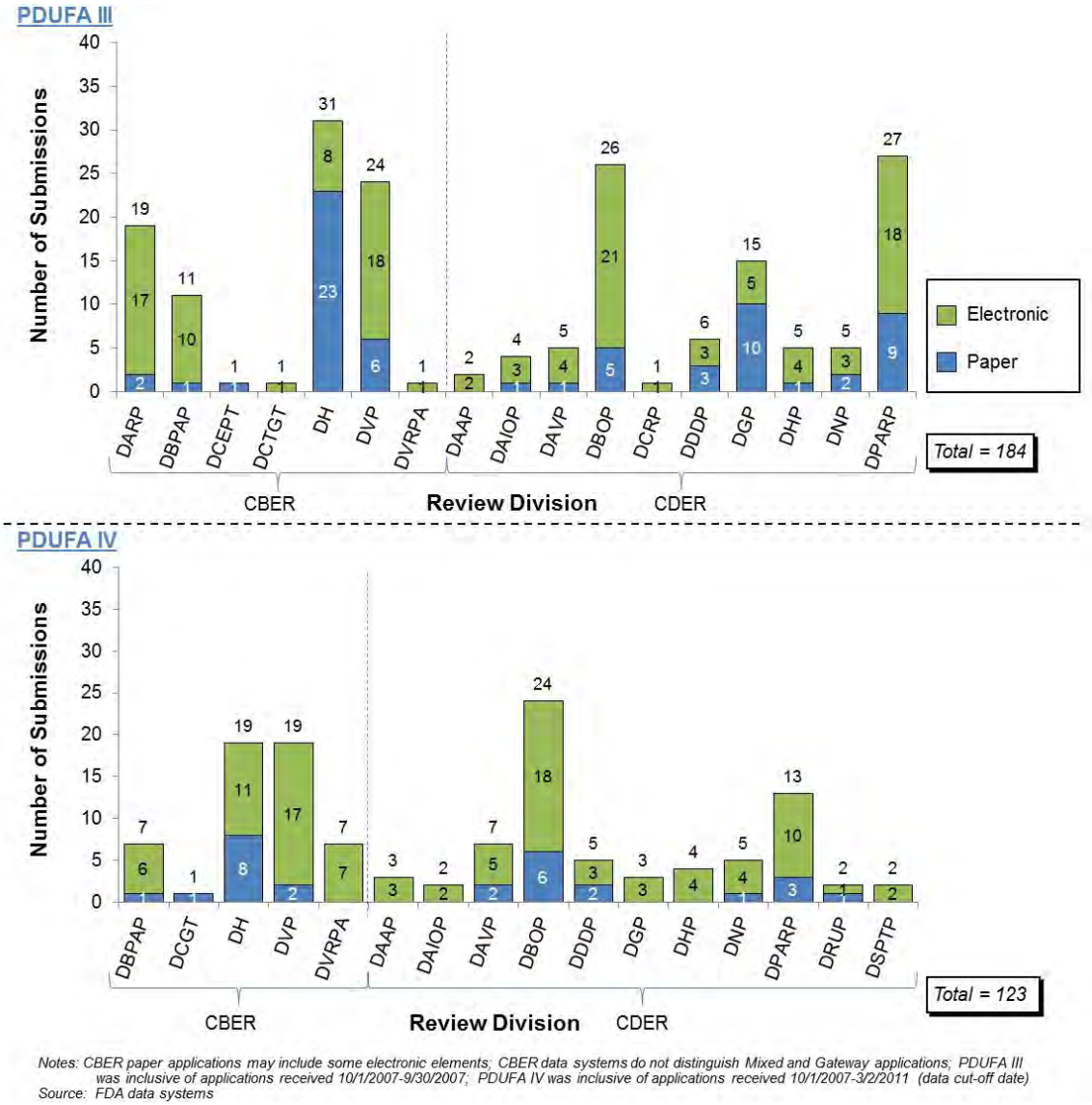
An overview of the 2215 NDAs submitted during the PDUFA III and PDUFA IV timeframes is shown by review division in Exhibit 39 and Exhibit 40.

Exhibit 39: Format of NDA Submissions by Review Division



Notes: Includes all NDA original applications and efficacy supplements received 10/1/2002 – 3/2/2011
Source: FDA data systems

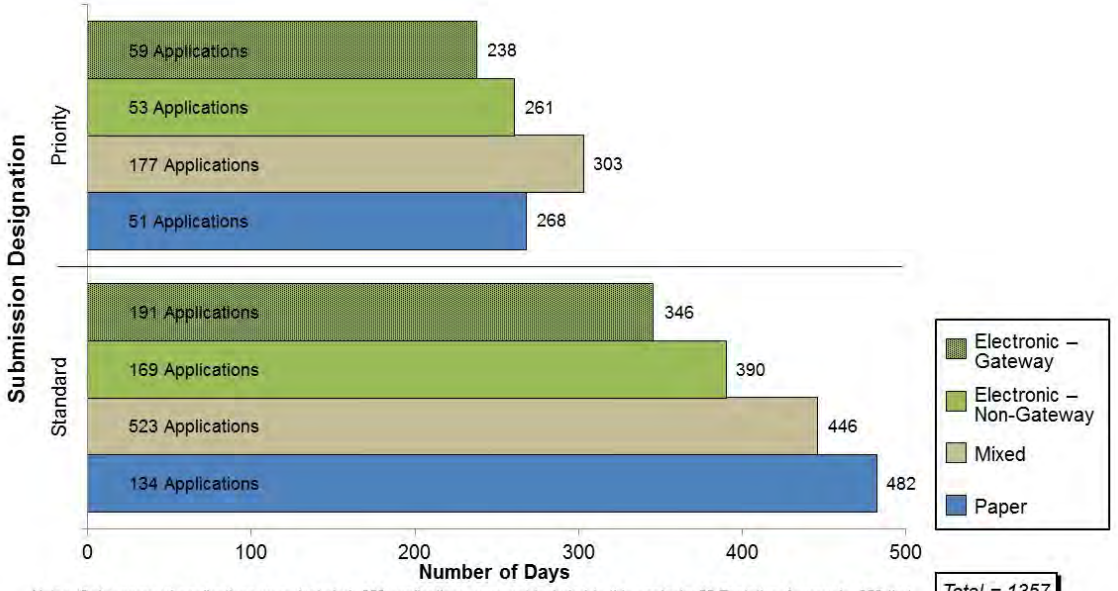
Exhibit 40: Format of BLA Submissions by Review Division



Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; PDUFA III was inclusive of applications received 10/1/2007-9/30/2007; PDUFA IV was inclusive of applications received 10/1/2007-3/2/2011 (data cut-off date)
Source: FDA data systems

NDAs were analyzed by submission format to determine impact on time to approval. Exhibit 41 shows an overview of the average time to approval for standard and priority NDAs.

Exhibit 41: Average Time to Approval for NDAs by Submission Format

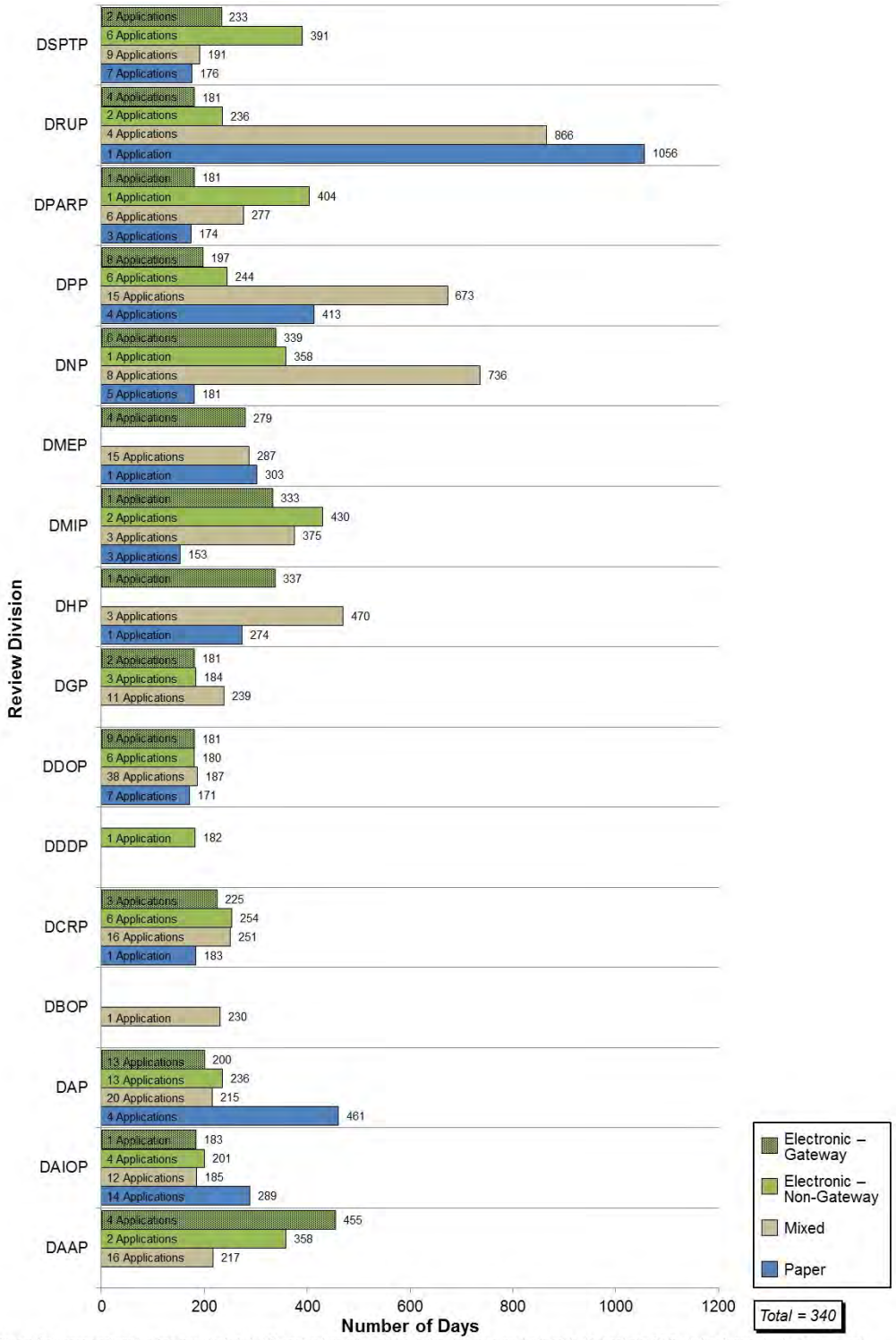


Notes: Only approved applications were included; 858 applications were not included in this analysis: 55 Tentative Approvals, 358 that were not acted upon as of the data cut-off date, 426 Complete Responses, and 19 outliers (see Appendix B for additional details regarding outliers)
Source: FDA data systems

For priority and standard designated reviews, available data did not indicate a significant relationship between approval time and submission format for NDA applications. Analysis of the Overall Cohort data revealed that application submission format has limited impact on the time it takes to approve an application designated priority, although it does show an effect on applications designated standard. Applications submitted in paper format averaged the longest review times (482 days) for standard designated NDAs, and mixed applications averaged the longest review times (303 days) for priority designated NDAs. For applications designated standard, average time to approval decreased in proportion to the degree of electronic submission, with electronic Gateway submissions having the shortest review time (346 days), followed by electronic non-Gateway submissions (390 days), and mixed submissions (446 days). This suggests a trend toward decreasing time to approval with the degree of electronic implementation (electronic Gateway being the highest degree, and paper being the lowest) for standard NDAs. Tracking this data over time with greater sample sizes will strengthen the validity of these findings.

Approval times were also assessed for priority-classified NDAs (Exhibit 42) by review division. All but two review divisions, DBOP and DDDP, had a mixture of paper and electronic priority designated NDA submissions. For the remaining review divisions, there was no apparent trend in average approval times when comparing paper submissions to electronic or mixed format submissions. Some review divisions had mixed applications (i.e., DRUP, DPP, DNP, DHP) that took a significant time to approve compared to mixed applications in other divisions. The application with the longest review time (1056 days) was a paper NDA submission to DRUP.

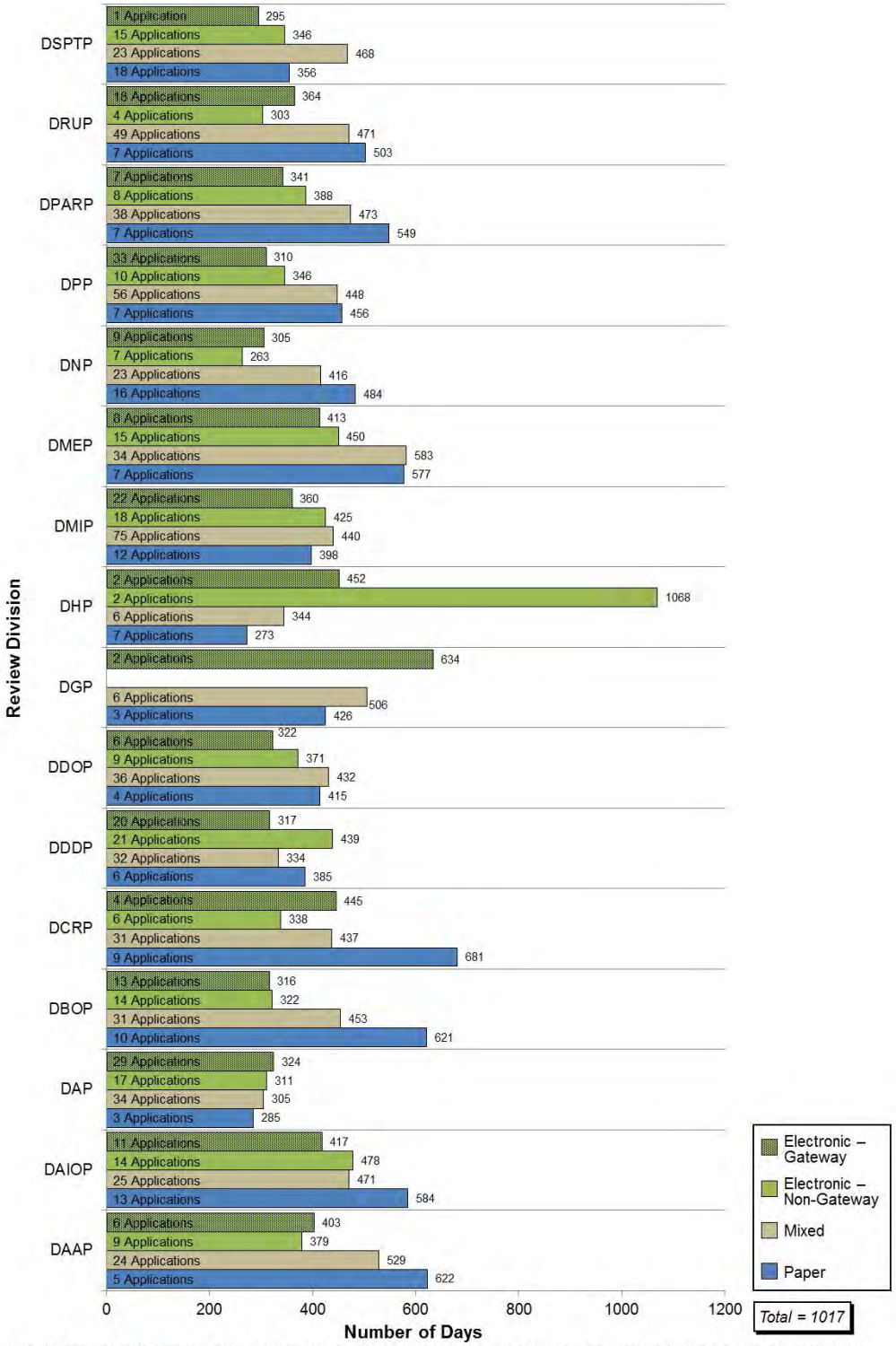
Exhibit 42: Average Time to Approval for Priority NDAs, by Review Division and Submission Format



Notes: Only approved applications were included; 166 applications with priority designation were not included in this analysis: 27 Tentative Approvals, 41 that were not acted upon as of the data cut-off date, 88 Complete Responses, and 10 outliers (see Appendix B for additional details regarding outliers); 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included
Source: FDA data systems

Approval times by review division were also assessed for NDAs designated standard review status (Exhibit 43). Every submission format was represented in each review division for the standard designated NDA cohort except for DGP, which lacked electronic non-Gateway submissions. Like the priority cohort, there was no definitive impact of submission format on average time to approval, although it does appear that paper submissions had on average longer review times than electronic submissions in most review divisions.

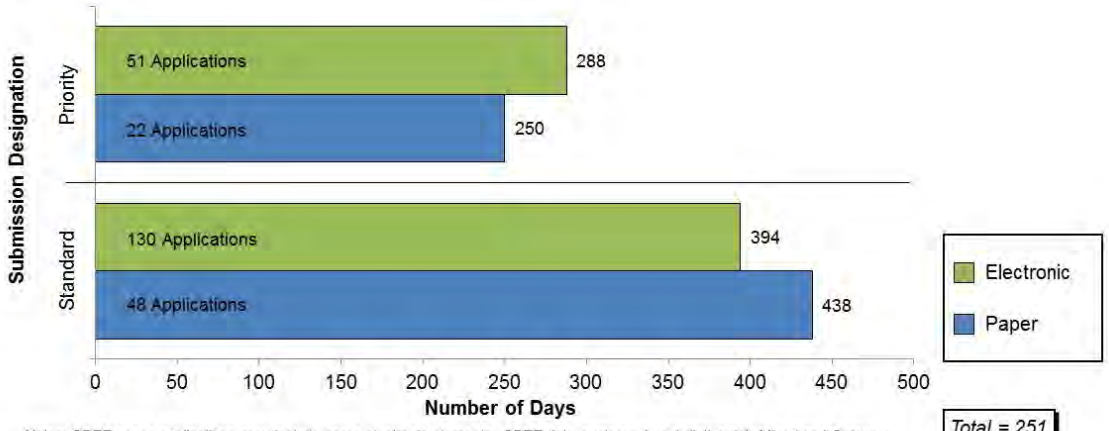
Exhibit 43: Average Time to Approval for Standard NDAs, by Review Division and Submission Format



Notes: Only approved applications were included; 578 applications with standard designation were not included in this analysis: 28 Tentative Approvals, 203 that were not acted upon as of the data cut-off date, 338 Complete Responses, and 9 outliers (see Appendix B for additional details regarding outliers); 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included
Source: FDA data systems

Time to approval was evaluated by submission format to identify trends for BLAs in Exhibit 44. The total number of applications in CDER and CBER was analyzed as well as the total number of priority and standard review designation applications for BLA submissions. Exhibit 45 shows an overview of the average time to approval for standard and priority BLAs in the Overall Cohort.

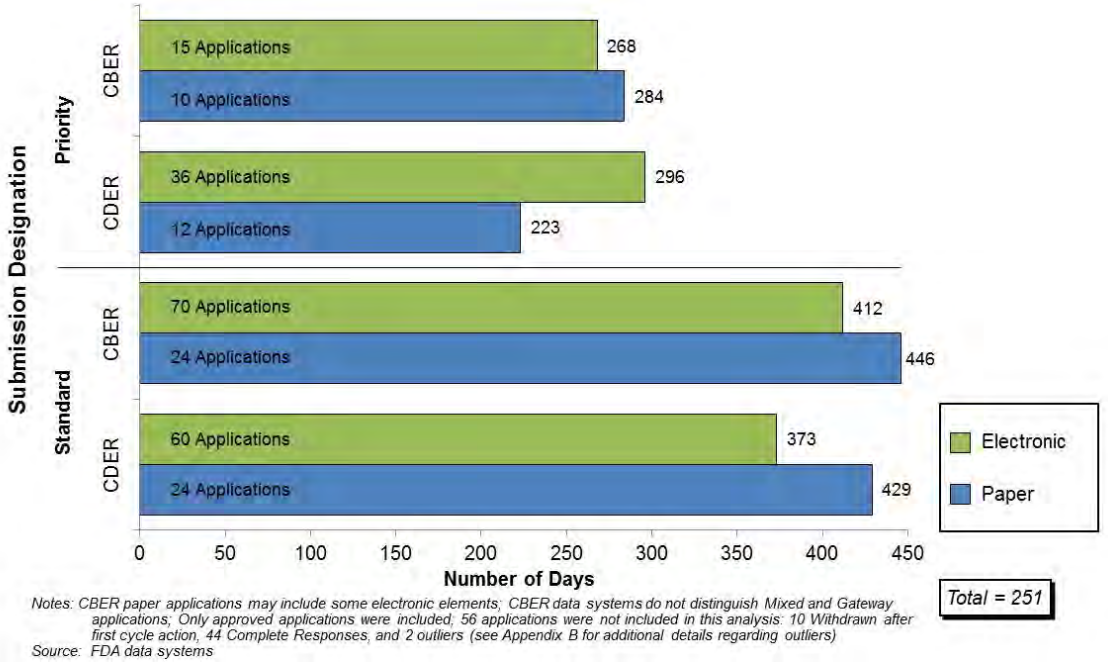
Exhibit 44: Average Time to Approval for BLAs, by Submission Designation and Submission Format



Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; Only approved applications were included; 56 applications were not included in this analysis: 10 Withdrawn after first cycle action, 44 Complete Responses, and 2 outliers (see Appendix B for additional details regarding outliers)
Source: FDA data systems

The analysis of time to approval for priority designated review BLAs revealed that paper applications took less time on average (250 days) to approve than electronic submissions (288 days). In contrast, electronic applications took less time on average (394 days) than paper applications (438 days) to approve for applications designated standard. No significant differences were found between CDER and CBER approval times for priority or standard designated applications (Exhibit 45).

Exhibit 45: Average Time to Approval for BLAs, by Submission Designation, Submission Format and Center

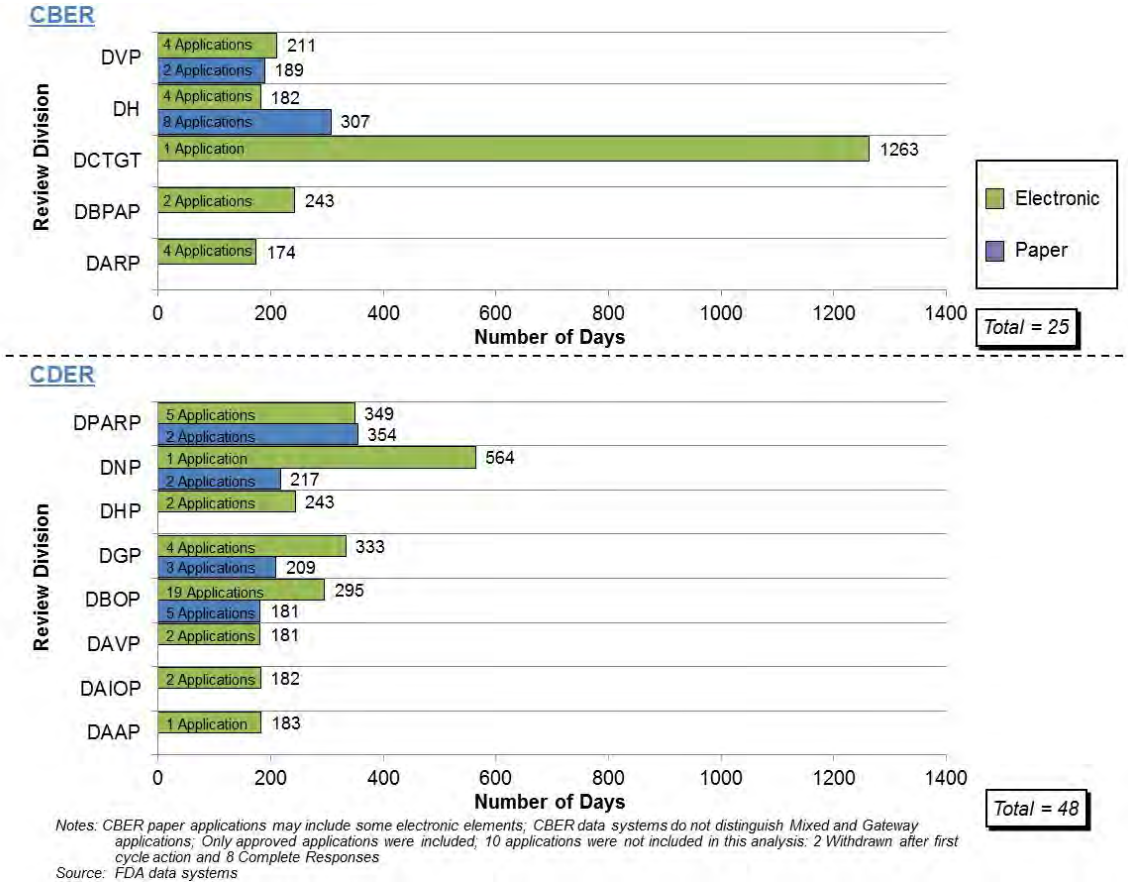


Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; Only approved applications were included; 56 applications were not included in this analysis: 10 Withdrawn after first cycle action, 44 Complete Responses, and 2 outliers (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Priority designated applications reviewed by CDER took an average of 73 days longer to approve for electronic versus paper applications; however, electronic submissions for standard designated applications were approved on average 56 days earlier than paper submissions in CDER.

Further analysis of time to approval was conducted for paper and electronic submissions in CDER and CBER based on review divisions and review designation. Exhibit 46 reveals the average time to approval for priority applications in CDER and CBER across review divisions. In CBER, only two review divisions (DH and DVP) contained priority paper submissions. The priority status application with the longest time (1263 days) to approval was in DCTGT within CBER and was an electronic submission.

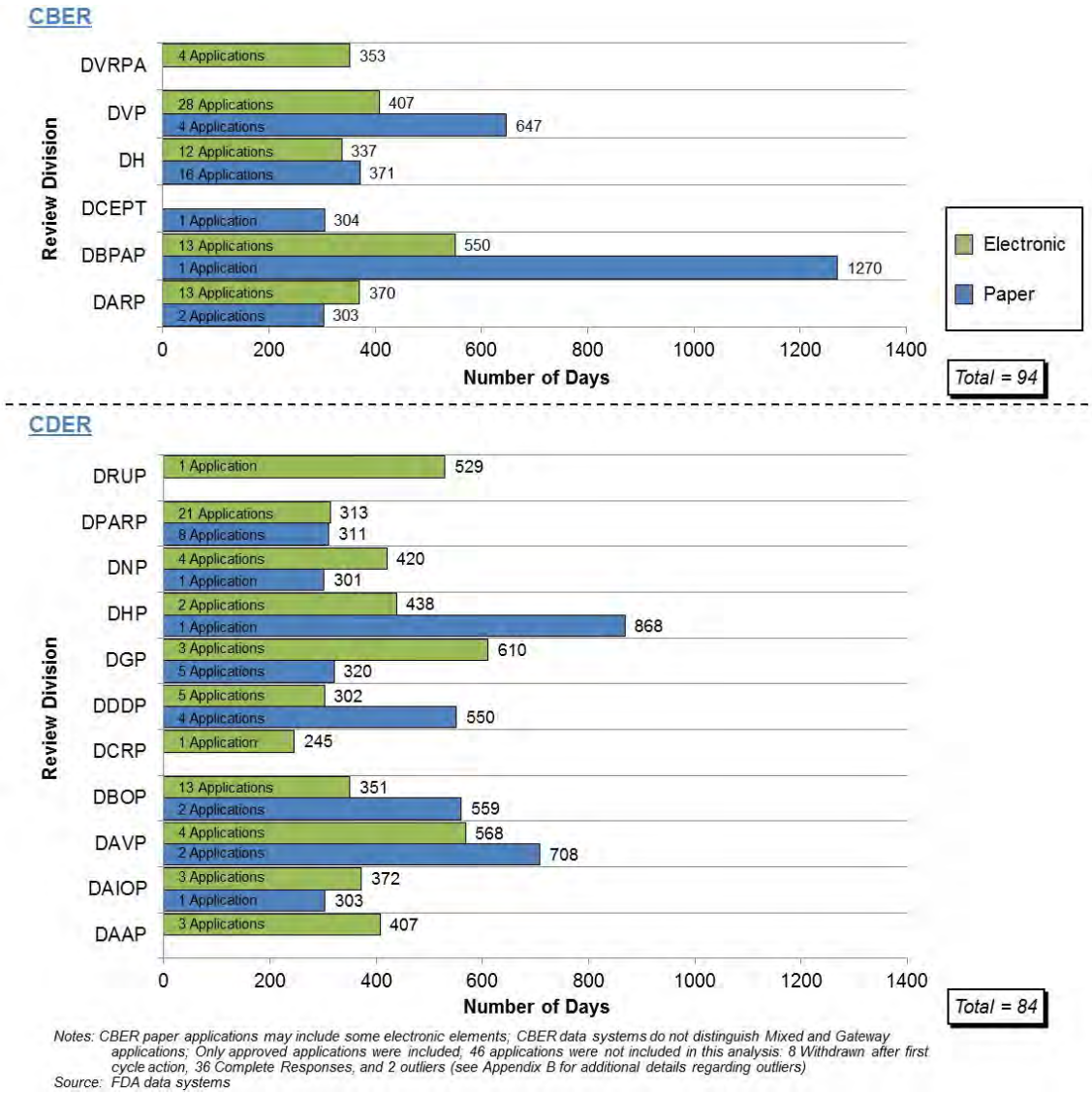
Exhibit 46: Average Time to Approval for Priority BLAs, by Review Division and Submission Format



Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; Only approved applications were included; 10 applications were not included in this analysis: 2 Withdrawn after first cycle action and 8 Complete Responses
Source: FDA data systems

The standard status application with the longest time (1270 days) to approval was in DBPAP within CBER and was a paper submission, as shown in Exhibit 47.

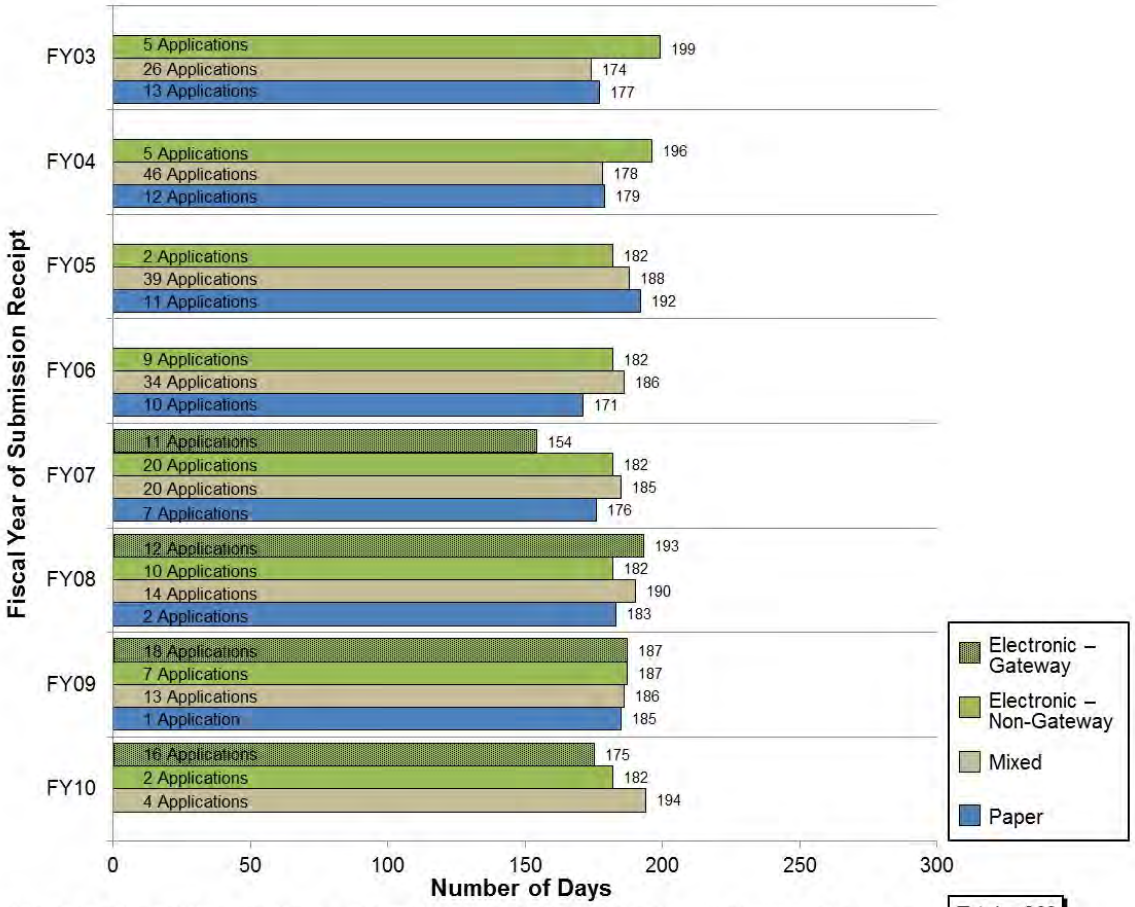
Exhibit 47: Average Time to Approval for Standard BLAs, by Review Division and Submission Format



Notes: CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; Only approved applications were included; 46 applications were not included in this analysis: 8 Withdrawn after first cycle action, 36 Complete Responses, and 2 outliers (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Time to first action for priority NDAs was analyzed by fiscal year (FY03-FY10) to further identify trends in submission format (Exhibit 48). The first electronic Gateway applications appeared in FY07, consisting of 11 applications having the shortest average time to first action (154 days) in the sample. However, in the following years (FY08, FY09, FY10), the electronic Gateway format did not demonstrate a consistent advantage in time to first action compared to other submission formats (193 days, 187 days, 175 days, respectively). No other clear trends were observed for the priority-designated NDA time to first action over time.

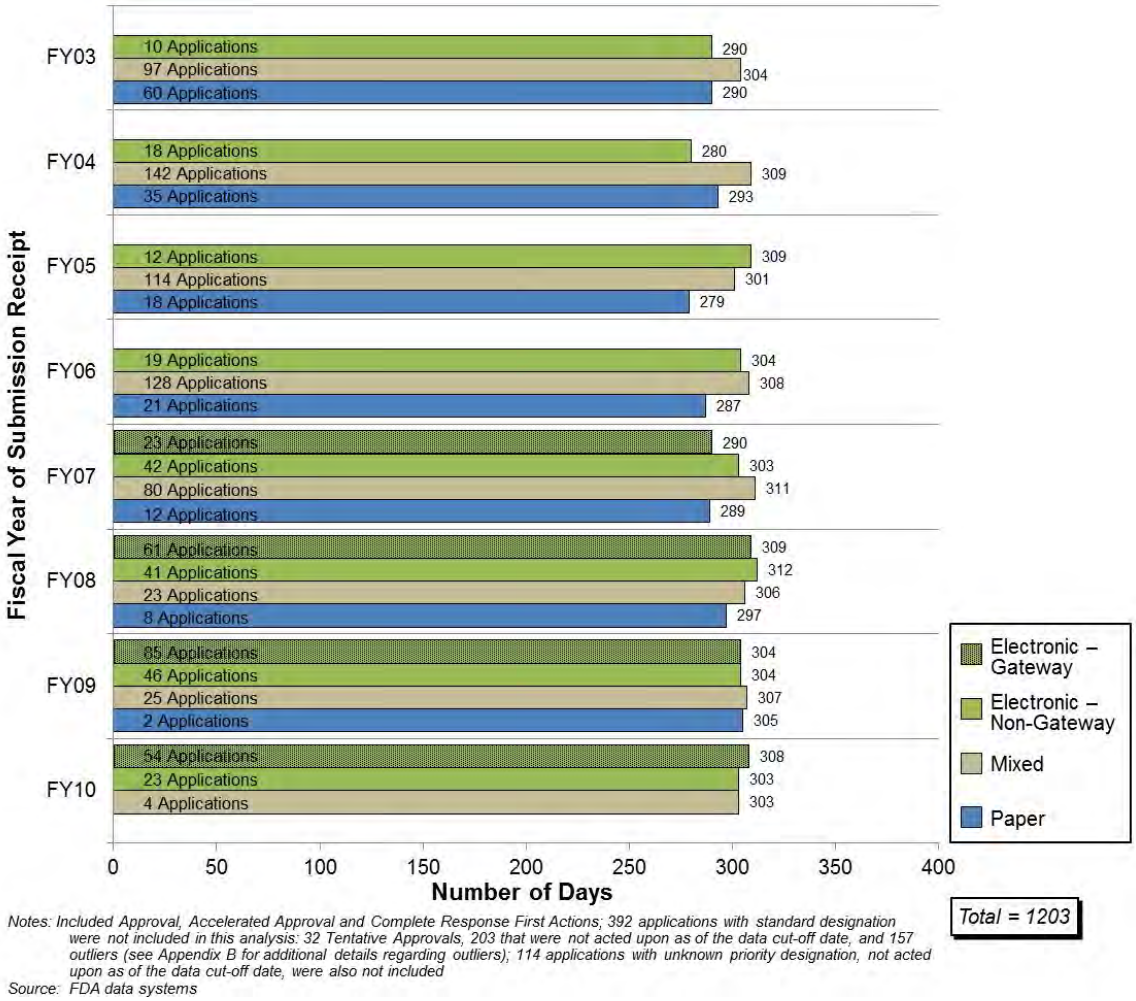
Exhibit 48: Average Time to First Action for Priority NDAs, by Fiscal Year and Submission Format



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; 137 applications with priority designation were not included in this analysis: 21 Tentative Approvals, 41 that were not acted upon as of the data cut-off date, and 75 outliers (see Appendix B for additional details regarding outliers); 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included
Source: FDA data systems

Standard NDAs' time to first action was also tracked in fiscal years FY03-FY10 to evaluate the impact of electronic submissions (Exhibit 49). The range of the average time to first action for standard NDAs was narrow compared to priority submissions (Exhibit 48), with a low of 279 days in FY05 for paper submissions and a high of 311 days in FY07 for mixed format. Over the eight years analyzed, paper submissions had the shortest average time to first action in five of the years (FY03, FY05, FY06, FY07, and FY08) compared to other submission formats. Mixed formats had the longest average time to first action compared to other formats in five of the eight years analyzed (FY03, FY04, FY06, FY07, and FY09). No clear trends were observed for the standard-designated NDA time to first action over time.

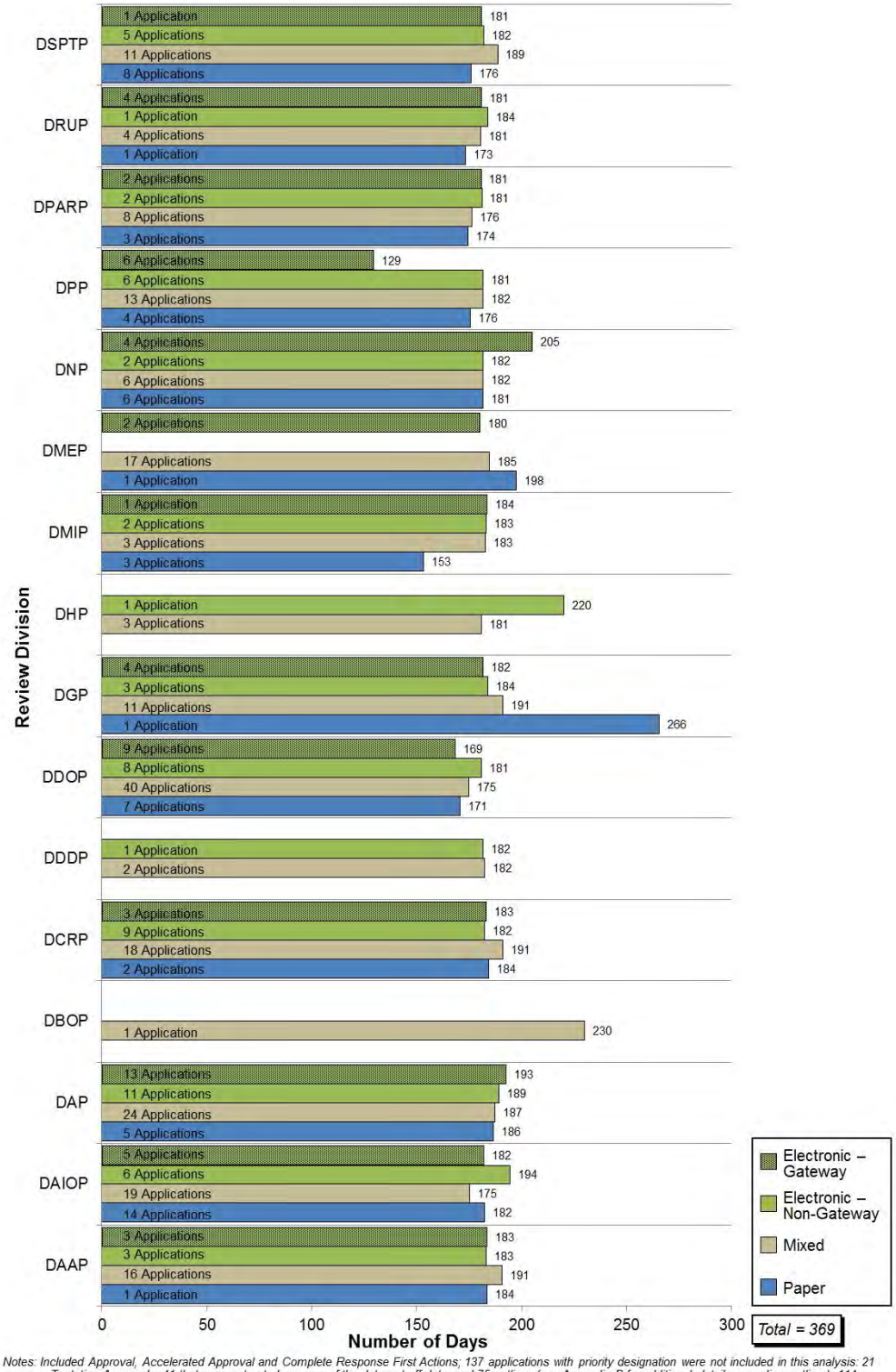
Exhibit 49: Average Time to First Action for Standard NDAs, by Fiscal Year and Submission Format



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; 392 applications with standard designation were not included in this analysis: 32 Tentative Approvals, 203 that were not acted upon as of the data cut-off date, and 157 outliers (see Appendix B for additional details regarding outliers); 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included
Source: FDA data systems

When priority applications were categorized by division (Exhibit 50), a few individual applications took a substantially longer time to first action, including a paper submission in DGP (266 days), a mixed submission in DBOP (230 days), and an electronic non-Gateway submission in DHP (220 days). Given that these were individual applications, they were not representative of the responsible Division's time to first action or the submission format as a whole. Despite these outliers, there was great variation in the average time to first action by submission format between Divisions and there were no trends.

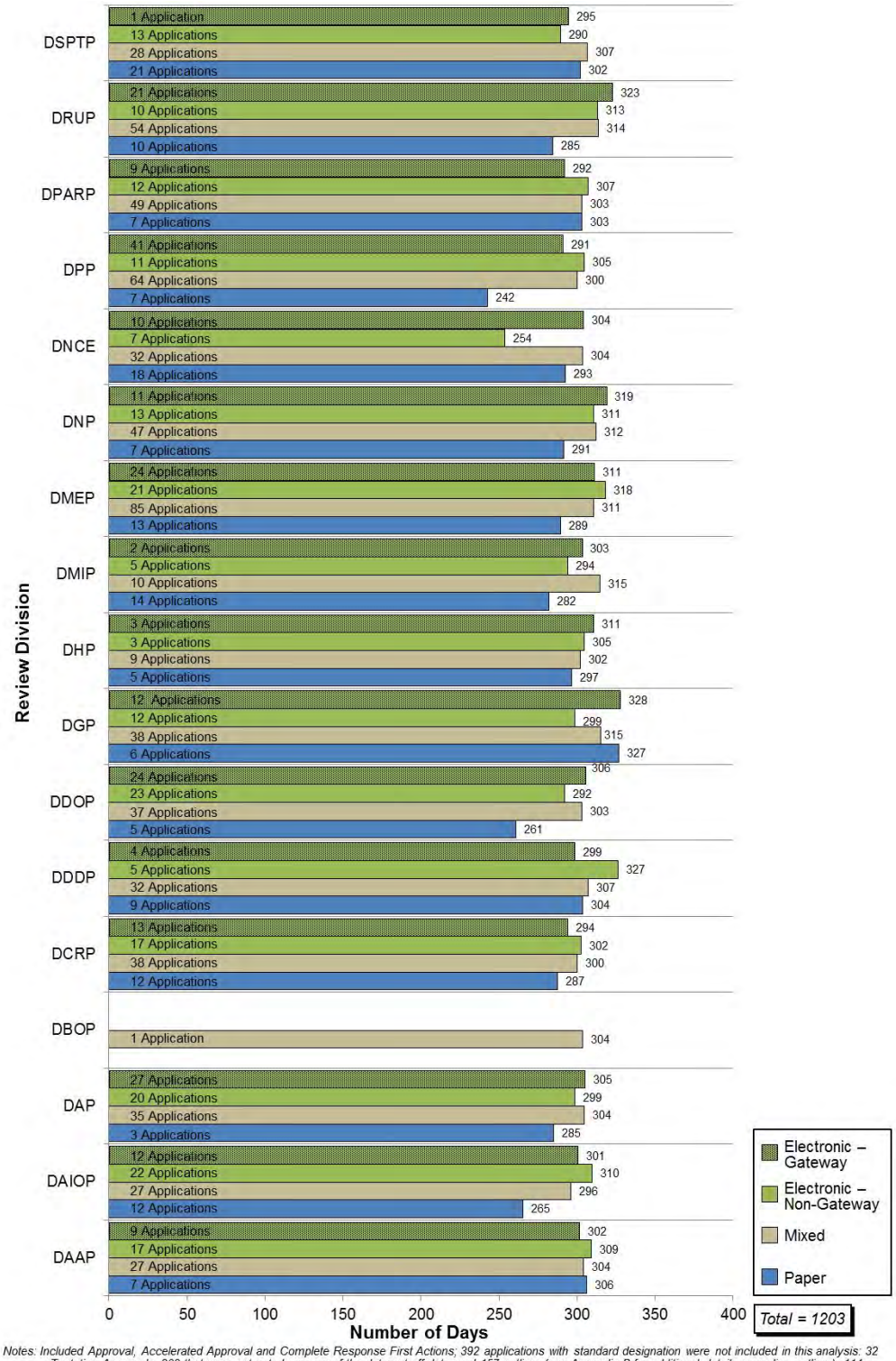
Exhibit 50: Average Time to First Action for Priority NDAs, by Review Division and Submission Format



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; 137 applications with priority designation were not included in this analysis: 21 Tentative Approvals, 41 that were not acted upon as of the data cut-off date, and 75 outliers (see Appendix B for additional details regarding outliers); 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included
Source: FDA data systems

Similarly, standard NDAs' time to first action varied and no Division appeared to have a longer or shorter review time based on application type (Exhibit 51). However, in 10 of the 17 Divisions evaluated, paper submissions had the shortest time to action compared to other submission formats. No other relationships were identified, and future analysis may determine a possible impact of submission format on time to first action by Division.

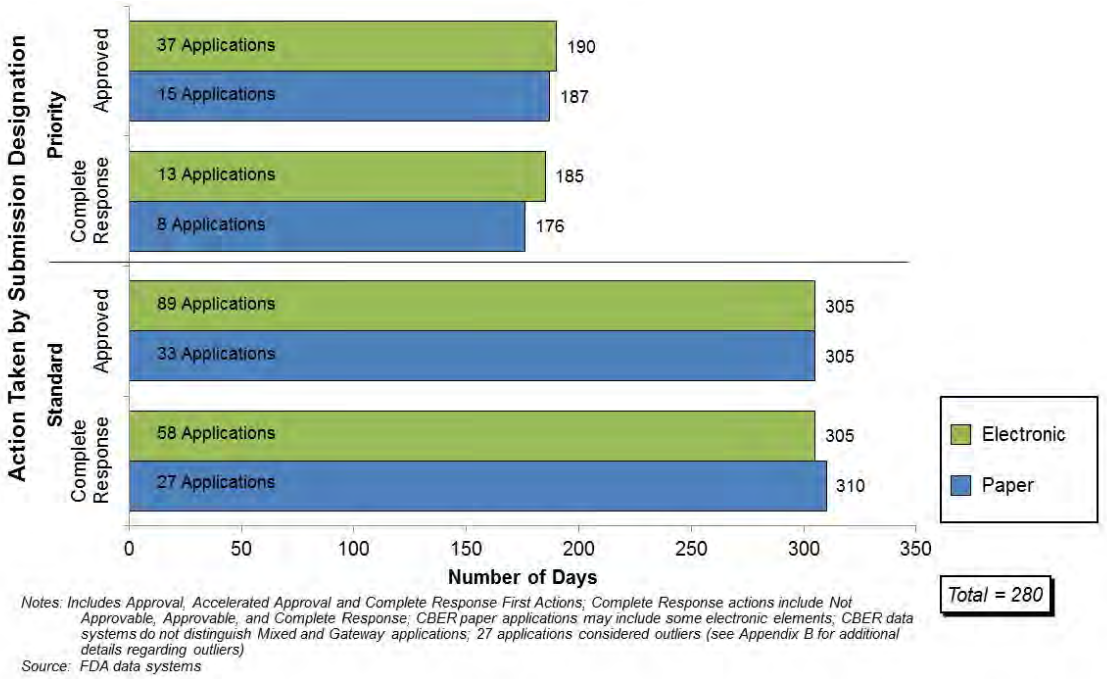
Exhibit 51: Average Time to First Action for Standard NDAs, by Review Division and Submission Format



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; 392 applications with standard designation were not included in this analysis: 32 Tentative Approvals, 203 that were not acted upon as of the data cut-off date, and 157 outliers (see Appendix B for additional details regarding outliers); 114 applications with unknown priority designation, not acted upon as of the data cut-off date, were also not included
Source: FDA data systems

To evaluate the impact of electronic submissions on BLAs' time to first action, BLA data, combined from CBER and CDER, were analyzed by submission designation and action type (Exhibit 52).

Exhibit 52: Average Time to First Action for BLAs by Submission Format

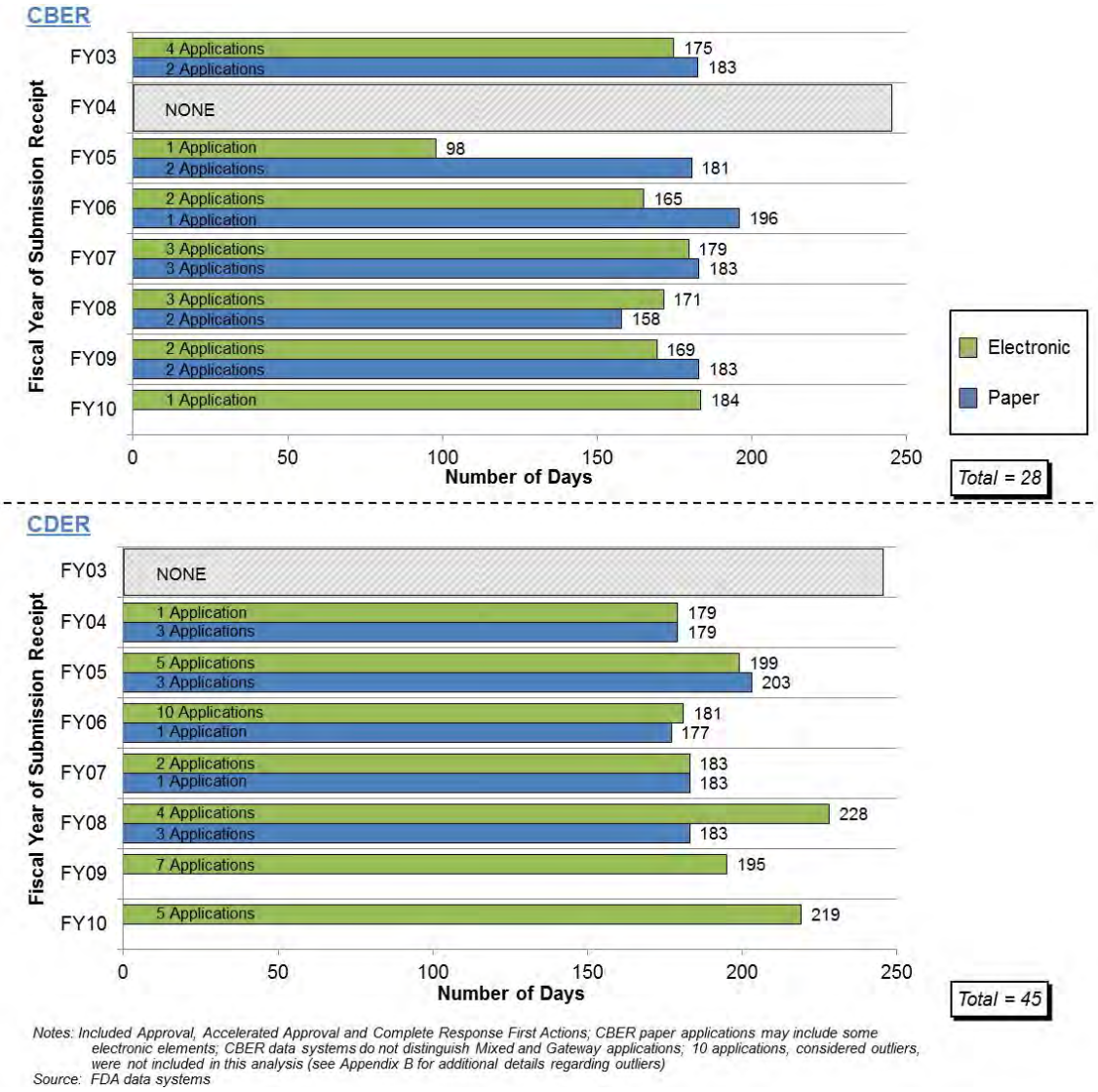


Notes: Includes Approval, Accelerated Approval and Complete Response First Actions; Complete Response actions include Not Approvable, Approvable, and Complete Response; CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; 27 applications considered outliers (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Priority designated, electronic applications took slightly longer to reach first action than paper applications for approvals (averaging 190 and 187 days, respectively) and complete responses (averaging 185 and 176 days, respectively). In standard designated application actions, the paper applications took an average of five days longer to reach a complete response first action. These slight differences did not indicate an impact of submission format on the average time to first action.

To observe the impact of submission formats of priority BLAs on average time to action in various years by Center, Booz Allen separated the data from FY03 to FY10 (Exhibit 53). During five of the fiscal years in CBER (FY03, FY05, FY06, FY07 and FY09), paper submissions had longer times to first action than electronic submissions. No trends were observed in CDER. Limited data for both Centers make it difficult to identify relationships between time to action and submission format.

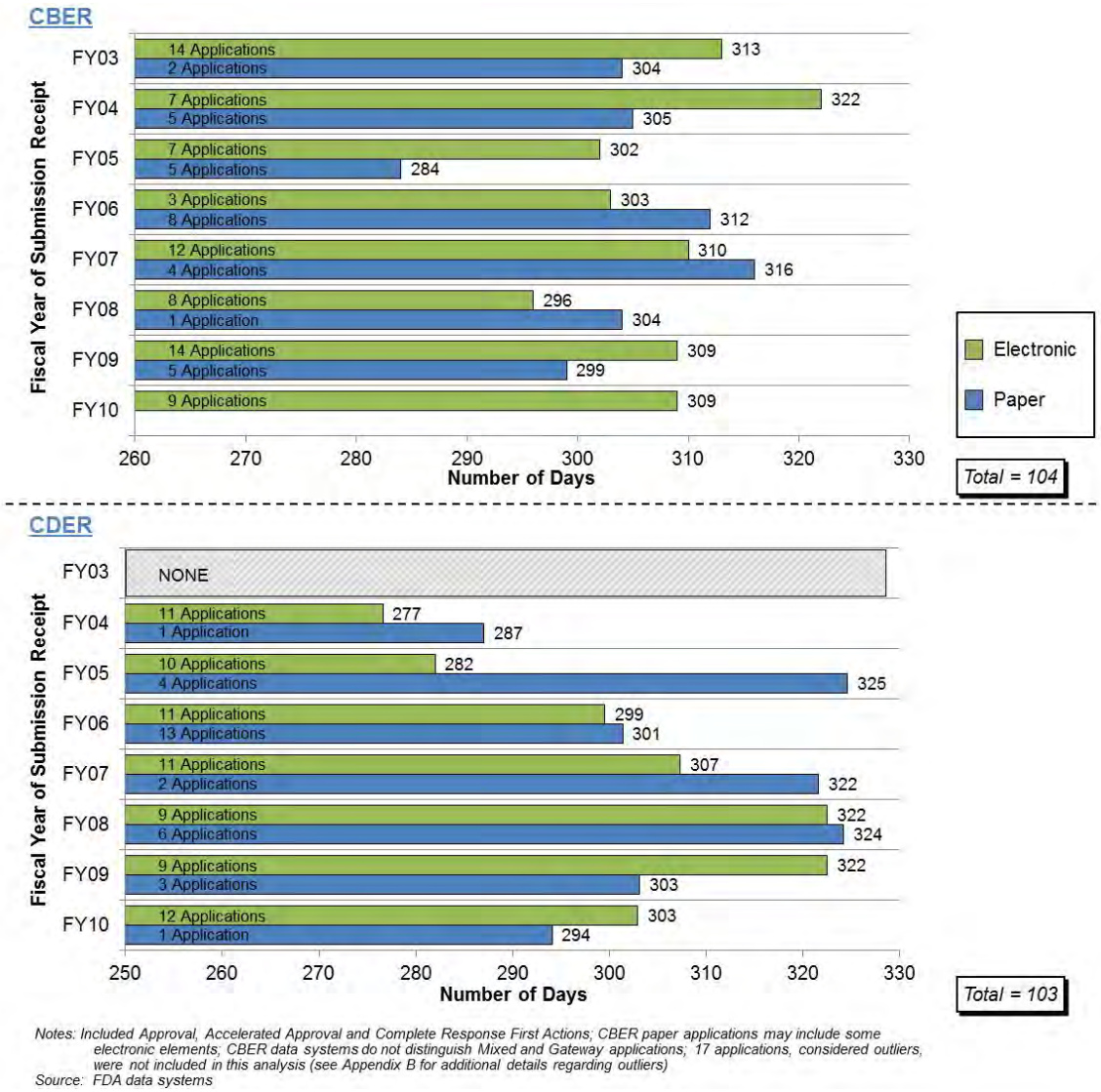
Exhibit 53: Average Time to First Action for Priority BLAs, by Fiscal Year and Submission Format



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; 10 applications, considered outliers, were not included in this analysis (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Standard BLAs were also analyzed for trends between submission type and time to first action for each Center (Exhibit 54). In CDER, paper format standard BLAs had longer average times to action than electronic format standard BLAs in five of the years (FY04, FY05, FY06, FY07, and FY08). No major trends were observed in CBER standard applications, as time to action data varied from year to year for both submission formats.

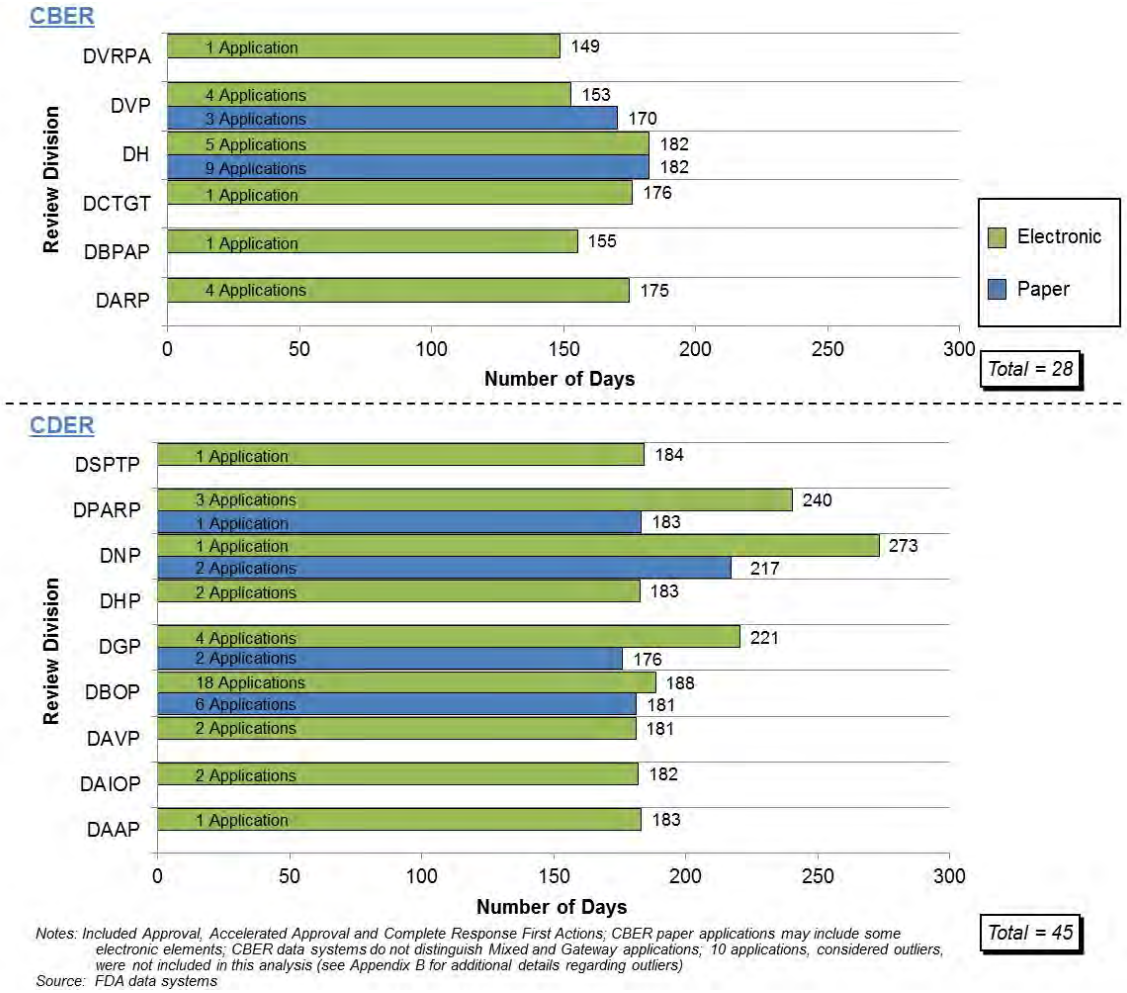
Exhibit 54: Average Time to First Action for Standard BLAs, by Fiscal Year and Submission Format



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; 17 applications, considered outliers, were not included in this analysis (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Booz Allen also analyzed priority BLAs for relationships between submission type by each Division and average time to first action (Exhibit 55). Of the six Divisions in CBER, only DVP and DH received paper submissions in addition to electronic formats. The average time to first action in DH was equal for electronic and paper formats; in DVP, paper applications were slightly longer (170 days) than electronic (153 days). Four Divisions in CDER (DPARP, DNP, DGP and DBOP) received paper BLA submissions in addition to electronic formats, and in all Divisions, paper submissions had shorter average times to action than electronic formats.

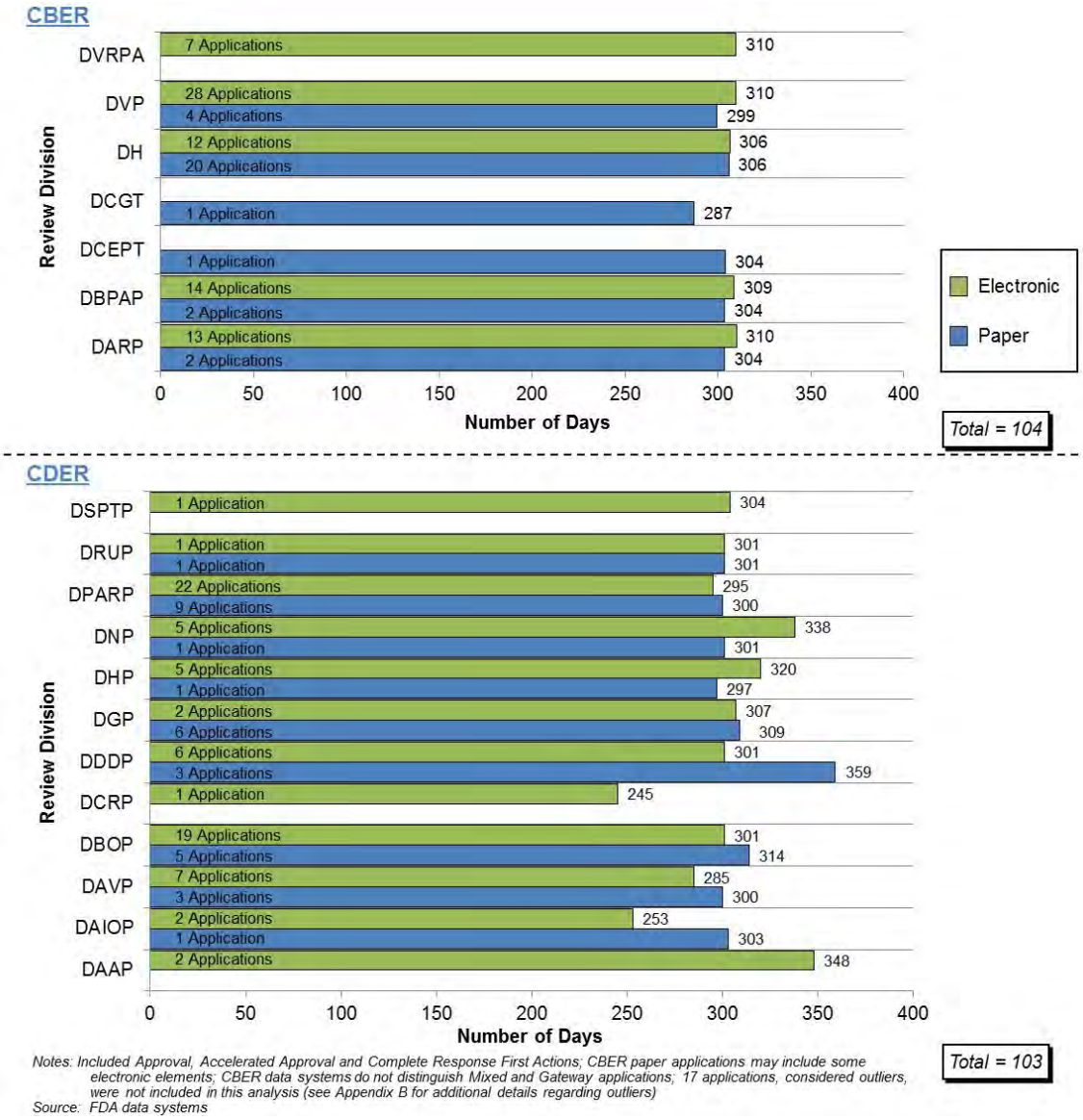
Exhibit 55: Average Time to First Action for Priority BLAs by Submission Format, by Division



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; 10 applications, considered outliers, were not included in this analysis (see Appendix B for additional details regarding outliers)
Source: FDA data systems

When standard BLAs were examined by Division, four Divisions in CBER (DVP, DH, DBPAP, and DARP) had both electronic and paper submission formats (Exhibit 56). In all four Divisions, the electronic formats were slightly longer or equal to the length of time to first action of paper formats. In CDER, nine Divisions received both paper and electronic formats. In six Divisions (DPARP, DGP, DDDP, DBOP, DAVP and DAIOP) the paper submissions took longer than electronic submissions.

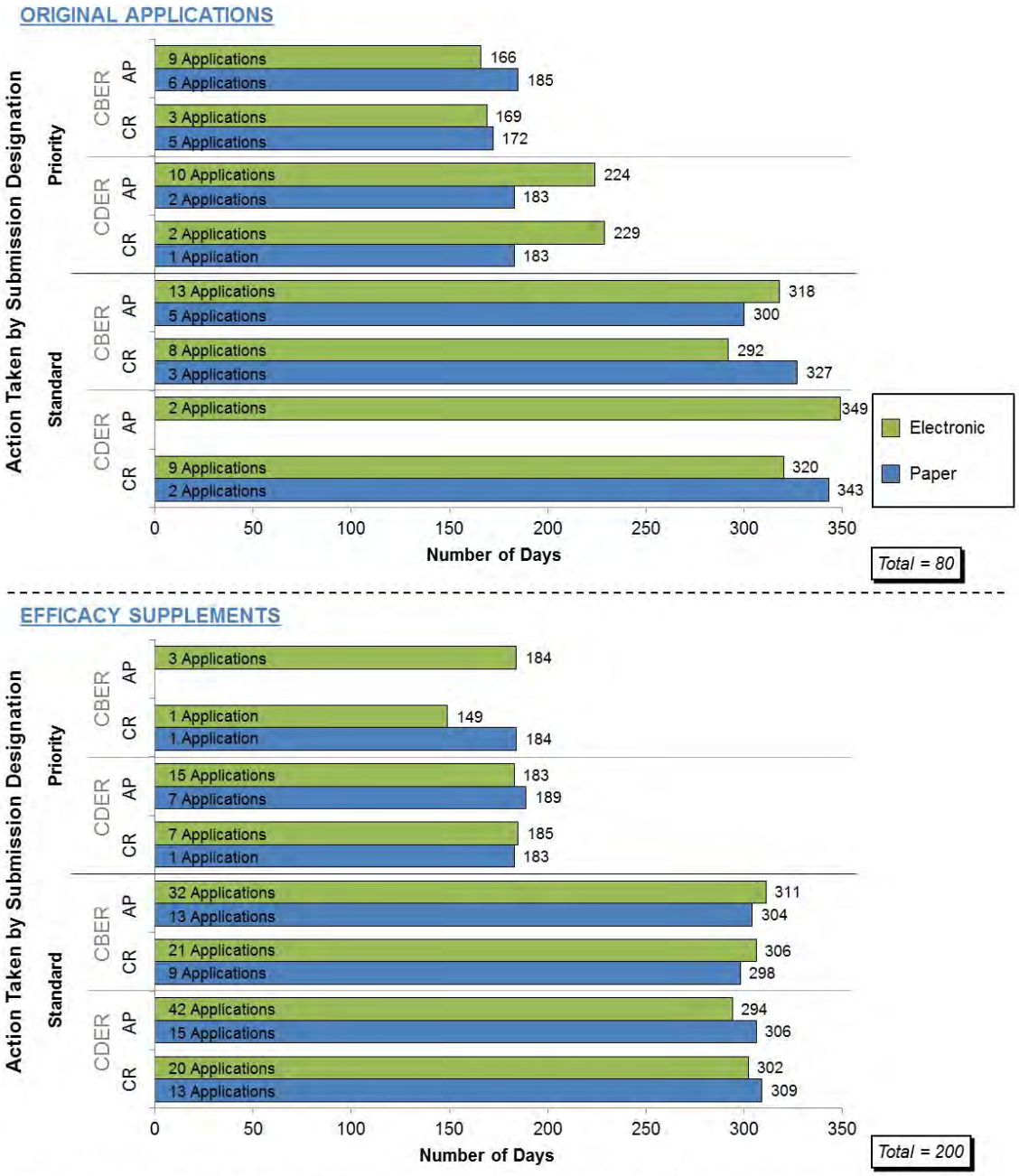
Exhibit 56: Average Time to First Action for Standard BLAs by Submission Format, by Division



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; 17 applications, considered outliers, were not included in this analysis (see Appendix B for additional details regarding outliers)
Source: FDA data systems

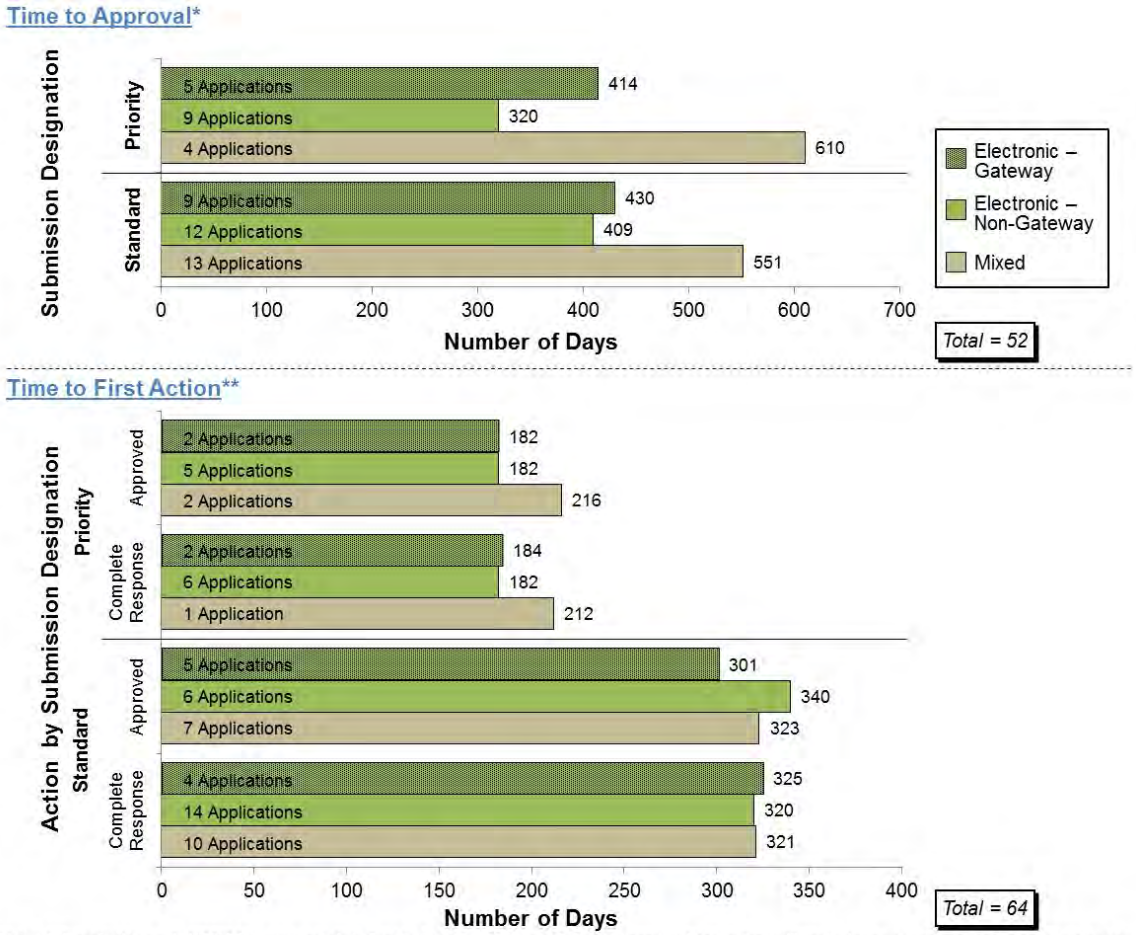
The impact of electronic submissions on average time to first action was also analyzed by Center by original applications and efficacy supplements (Exhibit 57). Clear trends were not observed in the original application or efficacy supplement data, although the electronic format took longer in CDER for priority BLA original applications compared to paper format (224 and 183 for approvals, and 229 and 183 for complete responses, respectively).

Exhibit 57: Average Time to First Action for BLAs by Submission Type, Submission Designation and Submission Format, by Center



Notes: Included Approval, Accelerated Approval and Complete Response First Actions; AP indicates Approval, CR indicates Complete Response; CBER paper applications may include some electronic elements; CBER data systems do not distinguish Mixed and Gateway applications; 27 applications, considered outliers, were not included in this analysis (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Exhibit 58: Time to Approval and Time to First Action for NDAs with SDTM Data



Notes: 105 applications with SDTM data were included. Time to Approval analysis included only approved applications; 53 applications were not included: 24 not acted upon as of the data cut-off date and 29 Complete Responses. Time to First Action analysis included Approval, Accelerated Approval and Complete Response First Actions; 41 applications were not included: 24 that were not acted upon as of the data cut-off date and 17 outliers (see Appendix B for additional details regarding outliers)
Source: FDA data systems

Electronic submissions (i.e., Gateway and non-Gateway) with SDTM data sets reached final approval in a shorter time compared to mixed submissions. This trend was also observed in time to first action for priority applications, where electronic approved and complete response applications reached action in fewer days than mixed formats; however, no trend was observed for standard applications.

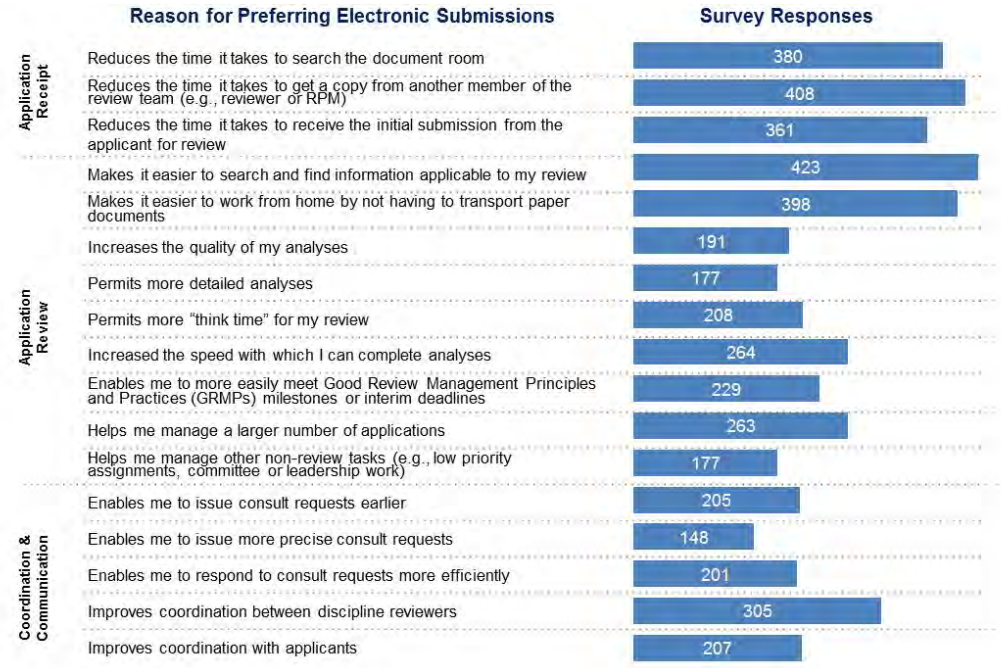
Table 11: Review Activities for Electronic Submissions

	Electronic		eCTD		SDTM	
	Priority	Standard	Priority	Standard	Priority	Standard
Total Number of Applications	9	18	9	16	5	7
Average Day in Application Review at Which Specified Reviews were Completed						
CMC/Product Quality Review *27 Applications*	**173** *9 Applications*	**260** *15 Applications*	**173** *9 Applications*	**260** *14 Applications*	**149** *5 Applications*	**279** *7 Applications*
Non-Clinical/Pharm.-Tox. Review *23 Applications*	**173** *8 Applications*	**261** *13 Applications*	**173** *8 Applications*	**261** *13 Applications*	**174** *5 Applications*	**241** *5 Applications*
Clinical Review *27 Applications*	**192** *9 Applications*	**298** *17 Applications*	**192** *9 Applications*	**298** *16 Applications*	**176** *5 Applications*	**287** *5 Applications*
Biometrics Review *27 Applications*	**163** *9 Applications*	**283** *16 Applications*	**163** *9 Applications*	**282** *15 Applications*	**163** *5 Applications*	**268** *5 Applications*
Clinical Pharmacology Review *26 Applications*	**173** *9 Applications*	**260** *14 Applications*	**173** *9 Applications*	**260** *13 Applications*	**154** *5 Applications*	**278** *7 Applications*
Microbiology Review *12 Applications*	**170** *3 Applications*	**290** *7 Applications*	**170** *3 Applications*	**290** *7 Applications*	**153** *3 Applications*	**293** *1 Applications*
Average Day in Application Review at Which Specified Consults were Requested						
OSE (DMEPA) Consult *12 Applications*	**47** *6 Applications*	**45** *6 Applications*	**47** *6 Applications*	**45** *6 Applications*	**66** *3 Applications*	**61** *3 Applications*
DSI Consult *14 Applications*	**32** *5 Applications*	**57** *7 Applications*	**32** *5 Applications*	**57** *7 Applications*	**23** *4 Applications*	**43** *3 Applications*
DDMAC Consult *16 Applications*	**47** *7 Applications*	**98** *7 Applications*	**47** *7 Applications*	**98** *7 Applications*	**35** *5 Applications*	**148** *4 Applications*
Patient Labeling (DRISK) Consult *7 Applications*	**33** *2 Applications*	**69** *5 Applications*	**33** *2 Applications*	**69** *5 Applications*	**N/A** *0 Applications*	**67** *3 Applications*
Average # of Days in Consult Review Cycles						
OSE (DMEPA) Proprietary Name Consult *11 Applications*	**186** *5 Applications*	**96** *6 Applications*	**186** *5 Applications*	**96** *6 Applications*	**103** *3 Applications*	**111** *3 Applications*
OSE (DMEPA) Label and Labeling Consult *10 Applications*	**137** *5 Applications*	**193** *5 Applications*	**137** *5 Applications*	**193** *5 Applications*	**153** *3 Applications*	**221** *3 Applications*
DSI Consult *14 Applications*	**110** *5 Applications*	**188** *7 Applications*	**110** *5 Applications*	**188** *7 Applications*	**101** *4 Applications*	**184** *3 Applications*
DDMAC Consult *13 Applications*	**116** *6 Applications*	**141** *5 Applications*	**116** *6 Applications*	**141** *5 Applications*	**145** *4 Applications*	**100** *4 Applications*
Patient Labeling (DRISK) Consult *5 Applications*	**114** *1 Applications*	**201** *3 Applications*	**114** *1 Applications*	**201** *3 Applications*	**N/A** *0 Applications*	**201** *3 Applications*

Table 12: Safety Activities for Electronic NDA Submissions

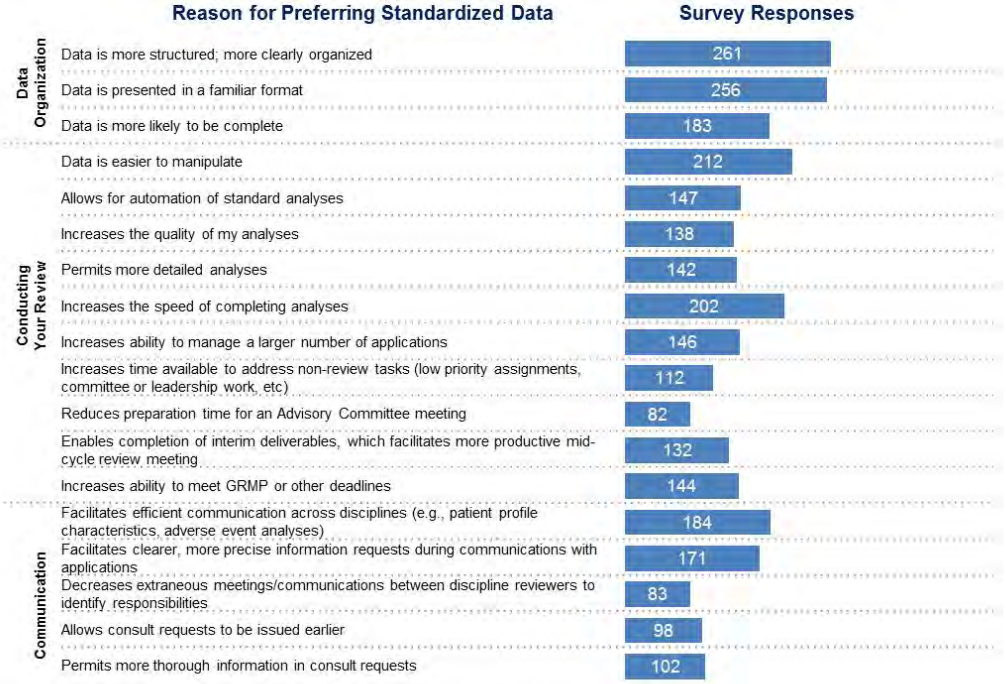
	Electronic		eCTD		SDTM	
	Priority	Standard	Priority	Standard	Priority	Standard
Total Number of Applications	10	19	10	17	5	8
Safety						
# of Applications with REMS *6 Applications*	3	2	3	2	2	2
# of Applications that had REMS submitted with application *3 Applications*	0	1	0	1	1	2
# of Applications with REMS issued within the first cycle (when not initially submitted with application) *4 Applications*	3	0	3	0	2	0
# of Applications with PMRs/PMCs *18 Applications*	8	7	8	7	3	2
# of Applications with FDAAA PMRs *8 Applications*	4	3	4	3	2	2
Average # of FDAAA PMRs	2	1	2	1	2	1
Average # of non-FDAAA PMRs	1	1	1	1	0	0
Average # of PMCs	2	0	2	1	2	0
Note: no ETASUs						

Exhibit 59: Reasons for Preferring Electronic Applications



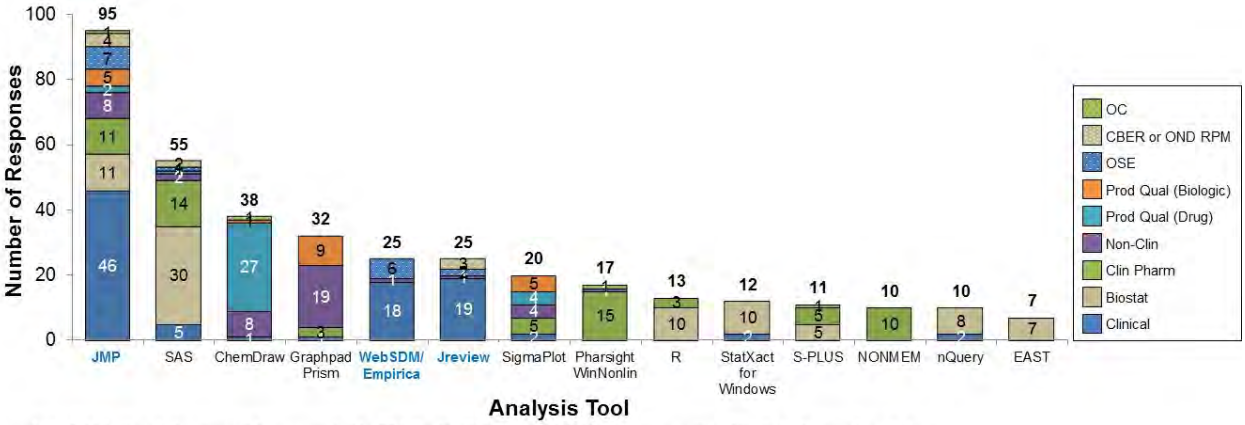
Notes: Respondents were able to make multiple selections
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Exhibit 60: Reasons for Preferring Standardized Data



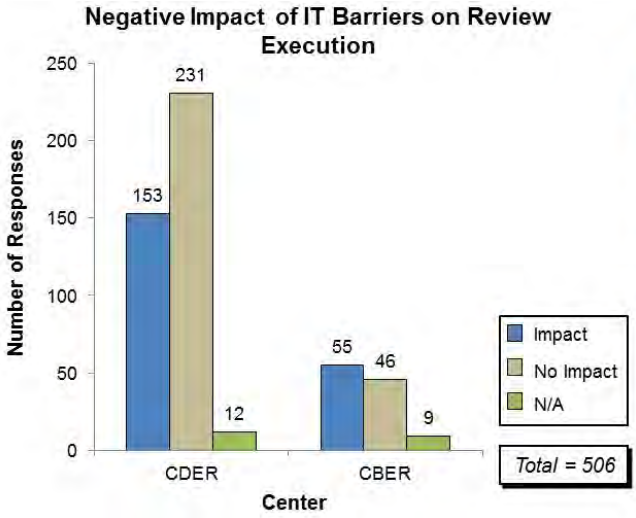
Notes: Respondents were able to make multiple selections
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Exhibit 61: Analysis Tools Usage by Discipline



Note: Bold Analysis tools represent those supported by FDA; Facility (Biologic) and DDMAC were surveyed but did not cite the use of any tools
Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Exhibit 62: IT Barriers Cited by Survey Participants



Most Cited Barriers

Most Cited IT Barriers	Number of Responses
1. Broken printers/scanners	91
2. Inactive electronic links (i.e., dead links)	88
3. Inconsistent access to database or analysis tool due to server or connectivity issues	86
4. Difficulty loading page (e.g., slow loading or error messages)	85
5. File errors (e.g., corrupt files, missing files)	78

Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Table 13: CDER Electronic Submission Groups

Organization	Mission, Scope, or Purpose
CDER Data Standard Program Board (DSPB)	− Interfaces with the FDA DSC, providing CDER representation inclusive of a coordinated, holistic, center-level approach − Oversees the ongoing planning, coordination and progress-tracking of center data standards projects, ensures timely reporting to the CSC Board and to the CDER Executive Committee, and ensures compliance of center standards projects with the newly established good practices for standards development
Information Management Advisory Board (IMAB)	− Reviews IT project proposals, shares information with CDER business Units, CSC, CDER IT Liaison and other committees, and makes recommendations to the Senior Management Team (SMT) − Once projects are approved, the IMAB coordinates these proposals with the OBI, Division of Project Development, and the project sponsor − Documents and maintains a CDER strategic IT plan
Computational Science Center (CSC) Board	− Provides oversight and direction for the development of CDER's computing capabilities, including both infrastructure and operations − Ensures alignment with Center and Agency initiatives (e.g., JANUS Clinical Data Repository), and coordinates with OIM and the various governance bodies (e.g., IMAB, and the FDA DSC)
Office of Planning and Informatics (OPI)	− Directs CDER Planning and Analysis Office and OBI − Develops, installs, and monitors Center-wide business process and performance tracking systems
Office of Business Informatics (OBI)	− Develops and implements IT systems that provide access to and analysis of regulatory data − Acts as CDER strategic business liaison to the FDA OIM − Chairs and coordinates CDER's review and prioritization of business IT system needs, CDER IT Investment Review Board functions and recommendations regarding IT investment prioritization
Division of Project Development (DPD)	− Develops IM project proposals and provides staff to coordinate IT systems development projects − Develops and maintains the business and data layers of the enterprise architecture − Standardizes business information management processes
Division of Regulatory Review Support (DRRS)	− Provides hands-on support to the Center's electronic submission and review software applications − Conducts electronic submission and review training for review and support personnel − Provides guidance on electronic submission issues to FDA staff and Industry − Identifies and addresses local computing requirements
Office of Planning nd Analysis (OPA)	− Directs the agency long-range planning processes, including strategic and program planning, and coordinates with FDA's Office of Commissioner and DHHS long-range planning process

Table 14: CBER Electronic Submission Groups

Organization	Mission, Scope, or Purpose
Review Management (RM)	− Manages CBER application review process, ensuring it is effective and compliant with business policies − Develops guidance, regulations and SOPs associated with the review process and IM − Coordinates management of Center activities in external standards organizations and represents CBER in several arenas of national and international data standards formulation and implementation − Develops and conducts product review training and provides support personnel for electronic submission and review − Oversees CBER document control and records management programs
Information Management Coordinating Committee (IMCC)	− Defines IT strategic goals, prioritizes projects, and develops budget recommendations − Provides a forum for CBER offices to discuss IM-related policies and procedures − Liaison with other agency information management (IM) initiatives
Review Management Coordinating Committee (RMCC)	− Provides a forum for all CBER offices to participate in discussions of review management issues − Brings draft policy recommendations to CBER management for final decisions − Contains a Business Process Subcommittee that reviews/identifies business process-specific issues and presents recommendations at RMCC meetings
Regulatory Information Management Staff (RIMS)	− Oversees CBER's regulatory information databases (e.g., BIRAMS, CRMTS, RMS-BLA) and creates corresponding performance reports − Provides training for database users
Office of Communications, Outreach and Development (OCOD)	− Manages CBER staff professional and management training programs and policies − Maintains CBER intranet and internet websites − Collaborates with Center groups for external communications

APPENDIX B: METHODOLOGY

The following sections provide additional details of our four step methodology, with particular focus on the specific factors analyzed and the data sources used to support the analysis.

Step 1: Identify Potential Impact of Electronic Submissions

The first step consisted of generating hypotheses of potential impact of electronic submissions on application reviews and review staff and identifying the metrics appropriate for hypothesis testing. Booz Allen generated the initial study hypotheses based on knowledge of the FDA review process (e.g., PDUFA III Retrospective and Prospective Analysis) and electronic submissions, as well as consultation with FDA leadership. These hypotheses evolved throughout the duration of the assessment based on observations, additional analysis and feedback from FDA staff. The hypotheses can be separated into three major categories: Resources Associated with Submission and Review Activities, Timeframes Associated with Submission and Review Activities and Quality of Submission. The full list of hypotheses is included in Appendix C: Hypotheses.

Step 2: Gather Data

In conducting this analysis, Booz Allen used multiple sources of data: FDA action packages, FDA data systems, publicly available data sources, review team focus groups, review team input and review team interviews. Specific data sources are summarized in Exhibit 63.

Exhibit 63: Overview of Data Sources

Data Source	Description of Data Source and Use
FDA Action Packages	A source of data for the 60 and 30 product cohorts was FDA-compiled product Action Packages which contain records of FDA internal and FDA-applicant communications and application review documents.
FDA Data Systems that Support Application Review	During the data collection for all cohorts, FDA data systems that support NDA and BLA application review were used as a primary source of information on submission format and review communications and activities.
Publicly Available Data Sources	Data sources such as company and financial tracking (e.g., Google Finance) websites were used to supplement product and applicant profiles (e.g., company size).
Review Team Focus Groups – Discipline Specific	Booz Allen conducted six focus group meetings with FDA reviewers and RPMs, selected from the deep dive cohort, to gather perspectives on the electronic submission and review environment.
Review Team Input	Where feasible and not available through other sources, input from FDA Regulatory Project Managers (RPMs) and other review team members was solicited to capture application review activities.
Review Team Interviews	Booz Allen conducted interviews with review teams from one NDA and one BLA, selected from the deep dive cohort, to gather feedback regarding electronic submissions and review and to prioritize topics for focus group discussions.

Booz Allen used a set of refined hypotheses[24] that are aligned to specific Good Review Management Principles and Practices (GRMPs) activities and/or types of discipline review as the foundation for the survey and focus groups regarding the impact, costs and benefits associated with automated standards-based review environment. In determining benefits and costs of the electronic review process,[25] Booz Allen designed and distributed a web-based survey (see Appendix F) to a subset of CDER and CBER review staff to collect data.

To ensure widespread input into the final report and to confirm previous findings, this multi-question survey was distributed across CDER and CBER. The survey objectives were to:

- Develop a multi-subject questionnaire for cross-discipline participants
- Address multiple task analysis components
- Seek to understand measurable changes (e.g., time to perform function, amount and use of resources, and quality of reviews)

Booz Allen identified a subset of NDAs and BLAs for which a more detailed data collection was conducted via interviews and/or focus groups. The deep-dive analysis included eight targeted interviews and six discipline-specific focus groups[26] aimed at refining hypotheses regarding the impact of electronic submissions on the review environment, as well as identifying recommendations to improve the efficiency and effectiveness of the electronic submission and review process. Additionally, as part of this deep dive, the impact on reviewer behavior and performance was assessed for any changes.

Step 3: Analyze Data and Test Hypotheses

Data were analyzed using both quantitative and qualitative methods to test hypotheses developed. However, when using the PDUFA IV Analysis cohort and Deep Dive cohort, the small numbers of product applications limited the ability to demonstrate statistically significant analyses. As such, most quantitative analyses were limited to basic statistics (e.g., mean, frequency, range). Where possible and practical, the assessment draws logical inferences based on Booz Allen observations and discussions with FDA. However, the small number of product applications (and subsets of applications) impacted the ability to generalize conclusions in some instances. In the process of testing hypotheses through data collection and analysis, we were unable to test some hypotheses based on inadequate data quality or insufficient data.

As a result, our report focuses heavily on data analyses of the Overall Cohort of 2,522 original applications and efficacy supplements, for both BLAs and NDAs. During our analysis, we identified a number of factors that may have led to inaccurate findings. A number of outliers deemed non-critical for our purposes were not included in specified analyses. The table below provides additional information.

[24] Booz Allen used the GRMPs Level Automated Standards-based Environment and an understanding of the GRMPs and 21st Century Review to develop these hypotheses.
[25] e.g., Changes in: time to perform function, amount and use of scientific resources and other support, quality and consistency of the reviews.
[26] Focus groups were held with the following disciplines: Non-clinical, Product Quality, RPM, Biostatistics, Clinical, Clinical Pharmacology

Table 15: Methodology for Excluding Data Elements

Data Not Included (i.e., data cuts)	Types of Analyses			
	Approval Rate	First Cycle Action	Time to Approval	Time to First Action
Outliers				
≤74 days: The PDUFA goal date for communicating to applicants any significant review deficiencies identified during the filing review is 74 days after the date of application receipt. The filing review is a preliminary review, and it is not possible to review a full original application or efficacy supplement in that timeframe. Applications that received actions within the first 74 days faced special circumstances (e.g., prior submissions to other applications already in the process of review)			19 NDAs 2 BLAs	26 NDAs 2 BLAs
>273 days: The PDUFA goal date for a first action for priority applications is 6 months or 183 days (6*365/12). If a major amendment is received, the clock is extended 90 days, pushing the first action goal date to day 273. Applications acted on after day 273 were found to have altered timelines due to special circumstances (e.g., withdrawn applications, previous refuse-to file decision made and received date wasn't changed in database, or late payments of user fees) that may have created inaccurate representations in our data.				63 NDAs 10 BLAs
>394 days: The PDUFA goal date for a first action for standard applications is 10 months or 304 days (10*365/12). If a major amendment is received, the clock is extended 90 days, pushing the first action goal date to day 394. Applications acted on after day 394 were found to have altered timelines due to special circumstances (e.g., withdrawn applications, previous refuse-to file decision made and received date wasn't changed in database or late payments of user fees) that may have created inaccurate representations in our data.				143 NDAs 15 BLAs
Other				
No Action: An NDA submission has been received and is in the process of being processed and/or reviewed by FDA. However, as of the March 2, 2011 data cut-off date for the overall cohort, there have been no actions issued by FDA.	358 NDAs	358 NDAs	358 NDAs	358 NDAs
Tentative Approval: An NDA submission has been tentatively approved, meaning that although a product meets all of the safety, efficacy, and manufacturing quality standards required for marketing in the U.S., existing patents and/or proprietary issues currently prevent marketing of the product in the US. This accounted for a small fraction of applications, and because it was neither approved for US market nor required additional changes before additional review, it was not included in our analysis.	55 NDAs	53 NDAs	55 NDAs	53 NDAs
Withdrawn: A BLA submission has been withdrawn from market and acknowledged as withdrawn by FDA.	10 BLAs	0 BLAs	10 BLAs	10 BLAs

Step 4: Develop Recommendations

While many hypotheses were initially developed, only those hypotheses that had notable findings were highlighted. Using both qualitative and quantitative analyses, Booz Allen generated findings consistent with the study objectives, focusing on the following areas:

- Degree of Electronic Implementation
- Impact on Review Performance and Review Staff
- Exchange and Content Data Standards
- Review Tools and Training

Based on these findings, Booz Allen developed recommendations focused on actions that FDA could perform to address our findings, particularly to improve the efficiency and effectiveness of the electronic submission and review environment. Recommendations were categorized based on people, processes, technologies and infrastructure.

APPENDIX C: HYPOTHESES

Each hypothesis is accompanied by the anticipated metrics for assessment, as well as the data sources that were used or evaluated for testing (Table 16). Some hypotheses were tested, of these some had significant findings and others did not. Some hypotheses could not be tested, either because appropriate data did not exist or the quality and quantity of such data was insufficient. Each analysis is marked with a status that details the analysis outcome:

- Analyzed with Findings (AF)
- Analyzed with no Findings (ANF)
- Not Analyzed (NA) due to insufficient data

Table 16: Hypotheses

	Hypothesis	Description/Rationale	Metrics	Data Source	Status
1.0	**Resources Associated with Submission and Review Activities**				
1.1	**Types of Resources Needed**				
1.1.1	**Level of experience**: In an automated standards-based electronic submission and review environment (ASBESRE), discipline reviewer experience with conducting standard analyses is less/more important	• Supporting tools that enable reviews to be conducted may allow less experienced reviewers to be as proficient at conducting standard analyses as experienced reviewers or more experience may be required due to an increase in number and type of standard analyses.	• Experience/ Expertise required to independently conduct a review • Reviewers' responses	• Interviews • Survey	NA
1.1.2	**New Staff:** Training new staff to conduct reviews in ASBESRE will require less/more time spent to reach full productivity	• Use of standards-based clinical data may or may not eliminate the need for new discipline reviewers to be familiar with more than one data standard or electronic submission type	• Amount of training time needed to get a reviewer up to full productivity	• Interviews • Training evaluations	NA

	Hypothesis	Description/Rationale	Metrics	Data Source	Status
1.2	**Number of Resources Needed**				
1.2.1	**Standard Analyses:** Conducting standard analyses for a review will be faster/slower in an ASBESRE and therefore require fewer/more resources	• With an increase/decrease in review time spent on standard analyses, a reviewer can direct time and efforts differently	• Change in time (e.g., minimal, moderate, significant) needed to conduct standard analyses vs. SME projection of time needed in future state	• Interviews • Survey	NA
1.2.2	**Extra Analyses:** Reviewers with applications containing standards based data will need to/not need to conduct additional analyses	• Reviewers will have more/less time to conduct additional analyses in an ASBESRE	• Reviewers' responses	• Interviews • Survey	AF
1.2.3	**Support Resources:** More/fewer resources will be required to support reviewers, tools and training in an ASBESRE	• Reviewers, tools and training programs will require more/less support staff in an ASBESRE	• Resource to reviewer ratio	• Interviews • Survey	NA
2.0	**Timeframes Associated with Submission and Review Activities**				
A2.0.1	**GRMPs Milestone Compliant:** Applications reviewed in an ASBESRE are more/less likely to comply with GRMPs milestones	• Electronic submissions may/may not impact the ability for reviewers to meet GRMPs milestone dates	• Compliance to GRMPs milestones	• PDUFA TO1	AF
2.1	**Pre-Submission**				
2.1.1	**Approval Cycles:** Applications with electronically submitted, standards-based IND files are more/less likely to have first-cycle approval	• Sponsors that submit electronically are more/less likely to have higher quality applications	• First cycle approval rate • IND submissions in eCTD format	• DARRTS • RMS BLA • BLA Product File	NA
2.1.2	**Issues Identified:** Applications with electronically submitted, standards-based IND files are more likely to have fewer issues identified during the review process	• Fewer/more data calls (e.g., information requests (IRs), 74-day letter issues)	• Number of IRs • Number of 74-day letter issues	• DARRTS • RMS BLA • BLA Product File	NA

	Hypothesis	Description/Rationale	Metrics	Data Source	Status
2.1.3	**Sample Electronic Submission:** Applications that submitted a sample electronic application are more/less likely to have first-cycle approvals	• Electronic application organizational issues will/will not be resolved prior to marketing application submission increasing likelihood of a high quality application	• First-cycle approval rate	• Office of Business Informatics Access Database • RMS BLA • BLA Product File	NA
2.2	**Filing Determination and Review Planning Phase**				
2.2.1	**74-day Letter Issues:** Electronically submitted standards-based applications are more /less likely to have more 74-day letter issues	• Standards based data and better organization will improve/not impact the speed and quality of issue identification	• 74-day letter issues	• DARRTS • RMS BLA • BLA Product File	ANF
2.2.2	**Refusal-to-File:** Electronically submitted standards-based applications are more/less likely to have fewer Refuse-to-File actions	• Standards based data and better organization will improve/not impact the speed and quality of issue identification permitting reviewer more time to work with sponsor	• Refuse-to-File letters	• DARRTS • RMS BLA • BLA Product File	ANF
2.2.3	**Consult Review Questions:** ASBESRE applications will have more/less targeted questions for non-standard, content specific consults	• Electronic data will/will not allow review team to focus questions for non-standard, content specific consults	• Reviewers' responses	• Interviews • Survey	ANF
2.2.4	**Consult Request Processing Time :** In an ASBESRE, standard consult request completion times are more/less likely to meet GRMPs completion time frames	• Less/More time needed to complete a request due to electronically, standardized available data and processing	• Completion time of consult requests	• DARRTS • RMS BLA • BLA Product File	ANF
2.2.5	**Internal Communication:** Applications with electronically submitted standards-based applications are less/more likely to require meetings and communications between discipline reviewers to identify review responsibilities	• Less/More information will be incorrectly labeled under the wrong heading and assigned to the inappropriate discipline for review	• Current number of mislabeled application sections and headers • Reviewers' responses	• DARRTS • RMS BLA • BLA Product File • Interviews • Survey	NA

	Hypothesis	Description/Rationale	Metrics	Data Source	Status
2.3	**Review Phase**				
2.3.1	**IR Timing:** Products in an ASBESRE are more/less likely to have IRs sent earlier in review	• Issues are identified more/less quickly because of access to data	• Number of days IR letters sent into the review	• DARRTS • RMS BLA • BLA Product File	ANF
2.3.2	**IR Frequency:** Products in an ASBESRE are more /less likely to have IRs	• Additional analyses may raise more questions by reviewers or less confusion around how material is organized	• Number of IRs	• DARRTS • RMS BLA • BLA Product File	ANF
2.3.3	**Amendment Frequency:** Products in an ASBESRE are more/less likely to have fewer major amendments.	• In an ASBESRE, applicants may submit more/less amendments based on ease/difficulty of data transmission and IRs from review staff	• Number of amendments submitted	• DARRTS • RMS BLA	ANF
2.3.4	**Deficiency Identification:** Products in an ASBESRE are more/less likely to identify major deficiencies by the mid-cycle meeting	• Applications in an ASBESRE are more/less transparent	• Major deficiencies identified by mid-cycle meeting	• DARRTS • RMS BLA • BLA Product File	NA
2.3.5	**Accessibility:** Product data in an ASBESRE are more likely to be easily accessed and manipulated by the review team, both during the review and when referenced post-action preventing delays	• ASBERE applications are more structured and data is easily identified and utilized	• Reviewers' response	• Interviews • Survey	AF
2.3.6	**Review Tools:** Interface with currently available tools causes review to take longer than when paper-based… … overall … explore by discipline	• Explore in more detail for each of the tools assessed	• Time required to use tool vs. paper based review.	• Dependent on selected tools	ANF
2.3.7	**Consult Completion:** Consult completion time is more likely be reduced/increased in an ASBESRE	• Less/more time spent receiving and analyzing the data	• Reviewers' responses	• Interviews • Survey	AF

	Hypothesis	Description/Rationale	Metrics	Data Source	Status
2.3.8	**Mid-cycle Findings:** Mid-cycle meetings will be more/less productive in an ASBESRE review environment as materials will be easier/harder to review prior to the meeting resulting in a more/less robust discussion	• Data can be manipulated more/less efficiently because of faster/slower access to standardized data.	• Reviewers' responses	• Interviews • Survey	ANF
2.3.9	**Issue Resolution:** Issues identified during the review process are more/less likely to be resolved faster/slower in an ASBESRE	• Since applicants are notified of issues earlier/later, higher/lower likelihood of earlier/later resolution	• Time to resolve issue	• DARRTS • RMS BLA • BLA Product File	NA
2.4	**Advisory Committee (AC) Phase**				
2.4.1	**AC Preparation:** In an ASBESRE, there will/will not be a reduction in preparation time for an AC meeting	• Preparation is less/more burdensome for applications in an ASBESRE	• Reviewers' responses	• Interviews • Survey	ANF ANF
2.5	**Action Phase**				
2.5.1	**Approval Cycle:** Applications with electronically submitted standards-based data are more likely to have first-cycle approvals	• Reviewers will identify and resolve issues faster	• Approval vs. CR	• DARRTS • RMS BLA • BLA Product File • Action Letter	AF
2.5.2	**Number of PMRs/PMCs:** Applications with electronically submitted standards-based data are more likely to have fewer/more PMRs /PMCs	• Reviewers will/will not identify and resolve issues sooner in the review cycle	• Number of PMRs PMCs • Timing of issue identification • Reviewers' responses	• DARRTS • RMS BLA • BLA Product File • Action Letter • Interviews • Surveys	ANF

	Hypothesis	Description/Rationale	Metrics	Data Source	Status
2.5.3	**Number of Deficiencies:** Applications with electronically submitted standards-based data are more likely to have fewer/more deficiencies if action is CR	• Reviewers will/will not identify and resolve issues sooner in the review cycle	• Number of Deficiencies • Timing of issue identification • Reviewers' responses	• DARRTS • RMS BLA • BLA Product File • Action Letter • Interviews • Survey	ANF
2.5.4	**REMS Identification:** For ASBESRE applications that did not initially submit a REMS, one will/will not be identified during the first cycle review as compared to paper applications	• Reviewers will identify and resolve issues faster	• Percentage of products with a REMS approved first-cycle	• Action Letter	ANF
2.5.5	**Labeling:** Labeling reviews and need for negotiations are more/less likely to be identified more quickly in an ASBESRE	• Reviewers may or may not be able to review and analyze data faster leading to an earlier identified need for labeling discussions	• Timing and occurrence of labeling meetings	• DARRTS • RMS BLA • BLA Product File • Interviews	ANF
2.6	**Post-Action Phase**				
3.0	**Quality of Submission**				
3.1	**Overall Quality:** Applications in an ASBESRE are more/less likely to be a higher quality submissions	• System structure will/will not require application completeness and standardization of data	• Reviewers' responses	• Interviews • Survey	AF
3.2	**Table of Contents Quality:** Applications that include a table of contents that is well-organized and easy to navigate in an ASBESRE are/are not higher quality applications	• A well-structured and easy to navigate table of contents is/is not a proxy for a well-organized application	• Reviewers' responses	• Interviews • Survey • DARRTS • RMS BLA • BLA Product File	ANF

	Hypothesis	Description/Rationale	Metrics	Data Source	Status
3.3	**Technical Contact:** Applicants with a designated Technical Contact in an ASBESRE will/will not submit higher quality applications	• Applicants that dedicate staff to specifically focus on electronic submissions will be more informed about electronic submissions and more willing to engage FDA	• Listing of Technical Contact in Application • Reviewers' responses	• DARRTS • RMS BLA • BLA Product File • Interviews • Survey	NA
3.4	**Manual Processing:** Electronic applications that are processed manually as a result of validation issues will/will not be of lower quality	• Applications that have validation issues will/will not have other issues throughout the application	• Reviewers' responses	• Interviews • Survey • Submission Log Files (submission error rates)	NA
3.5	**Applicant Experience Level:** In an ASBESRE, applicants that have more experience (i.e., have submitted multiple electronic applications) with electronic applications will submit higher quality applications	• Applicants with more electronic submission experience will/will not have resolved issues experienced by applicants with little to no electronic submission experience • The writing and structure of an application received from an applicant with more experience could potentially be better	• Reviewers' responses	• DARRTS • RMS BLA • BLA Product File • Interviews • Survey	ANF
3.6	**Rigidity of Electronic Submission:** ASBESRE application format is/is not potentially overly structured forcing sponsors to exclude valuable review information in order to conform	• The structure of an electronic submission may/may not limit what a sponsor may send or is required to send	• Increase in application file sizes year over year	• DARRTS • RMS BLA	NA
3.7	**Fewer Submission Errors:** Applications in an ASBERE will have a lower percentage of errors than current electronic and paper submissions	• Structure itself is likely to be more clear, system will likely be calibrated to accept fewer errors	• SME response	• Interviews with technology staff SMEs	NA

APPENDIX D: REVIEW DIVISION ACRONYMS

Review Divisions	
CDER	
DAAP	Division of Anesthesia and Analgesia Products
DAIOP	Division of Anti-infective and Ophthalmology Products
DAVP	Division of Anti-Viral Products
DBOP	Division of Biologic Oncology Products
DCRP	Division of Cardiovascular and Renal Products
DDDP	Division of Dermatology and Dental Products
DDOP	Division of Drug Oncology Products
DGP	Division of Gastroenterology Products
DHP	Division of Hematology Products
DMIP	Division of Medical Imaging Products
DMEP	Division of Metabolism and Endocrinology Products
DNP	Division of Neurology Products
DNCE	Division of Nonprescription Clinical Evaluation
DPP	Division of Psychiatry Products
DPARP	Division of Pulmonary, Allergy and Rheumatology Products
DRUP	Division of Reproductive and Urologic Products
DSPTP	Division of Special Pathogens and Transplant Products
CBER	
DARP	Division of Application Review and Policy
DBPAP	Division of Bacterial, Parasitic and Allergenic Products
DCEPT	Division of Clinical Evaluation and Pharmacology/Toxicology
DCGT	Division of Cellular and Gene Therapies
DH	Division of Hematology
DVP	Division of Viral Products
DVRPA	Division of Vaccines and Related Product Applications

APPENDIX E: EXCHANGE AND CONTENT DATA STANDARDS

A brief overview of each standard, as well as its readiness and completeness to support the NDA/BLA review process, is detailed below.

eCTD

Overview	The Common Technical Document (CTD) is a standardized table of contents that provides a logical way of organizing regulatory information at the document/page level. The CTD is similar to a table of contents, organizing information into five modules. The eCTD provides a mechanism for delivering the CTD electronically, utilizing an Extensible Markup Language (XML)-based backbone which replaces the PDF table of contents used in earlier versions of electronic applications.
Readiness	**Mature:** eCTD is a mature standard that is used by many countries for pharmaceutical applications. The current version, Version 3.2.2, was released in January 2004.
Completeness	Strengths: • Provides consistency between documents • Facilitates reuse of documents • Relieves challenges associated with paper distribution • Accepted by multiple regulatory agencies Limitations: • Limits change in granularity • Uses a fixed metadata structure • Is difficult to distribute to non-FDA consult reviewers • Does not accommodate placeholders for non-electronic components of a regulatory submission that is not electronic • Does not support two-way communication

RPS

Overview	RPS is an exchange standard developed by the FDA and the Health Level 7 International Regulated Clinical Research Information Management (HL7 RCRIM) working group. RPS is intended to serve as a universal submission standard or exchange message, transferable across all FDA Centers, and used for both any type of regulated product, human or animal products, making it transferable across all FDA Centers. It is intended to be the next major version of the eCTD standard and therefore users should not recognize any difference, excluding any enhancements offered by the next eCTD version. The standard helps FDA meet PDUFA IV and FDAAA requirements, to facilitate two-way electronic communication and reduce the dependence on paper by allowing FDA reviewers to source and review all documentation electronically.[27] Additionally, the standard aims to be international in scope.
Readiness	**Emerging**: RPS is scheduled for full adoption in early 2013. The latest release, Release 2, is presently in Draft Standard for Trial Use (DTSU).
Completeness	Strengths: • Provides structural flexibility with no fixed element names or hierarchical structure • Is accepted internationally • Allows for easier submission updates • Supports two-way communication • Supports differentiated submissions to multiple regulatory agencies Limitations: • Compiling, validating, and viewing tools are complex and critical to access information • Hierarchy is inferred by the review system • Is difficult to distribute to non-FDA consult reviewers

[27] (n.d.). *RPS Data Exchange Standards Initiatives: Regulated Product Submission (RPS) Standard Status* [PDF document]. Retrieved from http://www.fda.gov/downloads/ForIndustry/DataStandards/RegulatedProductSubmission/UCM174101.pdf

Product Stability Data Standard

Overview	Product stability data submitted by drug and biologic applicants confirms the shelf life of the product and provides information regarding the quality of a drug substance or drug product under different conditions, within specific time frames. As with other data submitted to the FDA, stability data is submitted either in paper or electronic format, in PDF or SAS transport format. The latter electronic format allows product quality reviewers the ability to perform statistical analyses. Over time, FDA reviewers discovered that data submitted in different formats was not always identical.[28] Therefore, the Stability Data Standards Working Group, in conjunction with HL7, developed a project to standardize the electronic format of stability data "so that FDA will be able to view the information as it appears on paper or electronic paper as well as [to] directly analyze the data."[29] The format and information contained in stability data reports can vary drastically between Companies and even within the same company or the same product over time. This will standardize the format and types of information for all stability reports.
Readiness	**Emerging**: The current version, HL7 Drug Stability Reporting Version 3, Release 1, was released in January 2009.
Completeness	Strengths: • Integrates with other standards (i.e., eCTD and RPS) • Eliminates inconsistencies • Potentially increases review efficiency Limitations: • Relies on eCTD and the current version of RPS, resulting in one-way communication • Requires an additional tool for developing exchange messages

SDTM

Overview	The CDISC SDTM data standard seeks to address issues surrounding data organization and formatting by grouping clinical trial observations into domains. Domain datasets include, "both raw (as originally collected) and derived values (i.e., converted into standard units, or computed on the basis of multiple values, such as an average).[30] Datasets may usually be grouped into three general observation classes: Interventions, Events, and Findings; datasets categorized as special-purpose datasets do not belong in any of the three general observation classes.
Readiness	**Mature:** SDTM has been designed to be backward compatible. The current version, Version 1.2, was released on November 12, 2008.
Completeness	Strengths: • Allows for automation during analyses • Increases efficiency for reviewers and applicants Limitations: • Does not include mandatory structure to ensure consistent adoption • SAS XPT restrictions reduce standard's benefits • Not based on a Well-Structured Data Model • Includes an ambiguous implementation guide, resulting in inconsistent standard application • Used as an exchange and analysis standard

[28] FDA Data Council. (2003, December 1). *Project Description - Stability Data Standards* [PDF document]. Retrieved from http://inside.fda.gov:9003/downloads/ProgramsInitiatives/CommitteesWorkgroups/DataStandardsCouncil/UCM166879.pdf
[29] Ibid
[30] CDISC Submission Data Standards Team. (2008, November 12). *Study Data Tabulation Model Implementation Guide: Human Clinical Trials* [PDF document]. Retrieved from http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/ComputationalScienceCenter/ucm171013.htm

SEND

Overview	SEND, an expansion of the SDTM standard, is used for submission of data from non-clinical studies, focusing on data from animal toxicology studies, though it may be expanded to safety pharmacology studies. The intent of SEND, like that of similar standards, is to create a common organization scheme, increasing the accuracy of interpretation and decreasing the time required to evaluate the safety and efficacy of the product. Because SEND is based on the SDTM standard, data that arrives at the FDA is in tabulation format, requiring an additional analytics tool to extract the information into a format suitable for review.[31]
Readiness	**Emerging:** Version 3.0, a draft for public comment, is expected to become the production version in the second quarter of 2011.
Completeness	Strengths: • Leverages currently accepted standards • Fills gap in non-clinical data standards Limitations: • Requires development and use additional analytics tools to be effective • SAS XPT restrictions reduce standard's benefits

CDASH

Overview	CDASH is a collaborative project supported by multiple international organizations and led by CDISC. The driver behind CDASH is differences and diversity in Case Report Forms (CRFs) around the world. The use of non-standard CRFs, in many cases, leads to differences in the use of SDTM as different controlled terminology is applied across domains. CDASH focuses on developing a series of content standards including name, definition, and metadata for a basic set of global data collection fields on clinical trial CRFs.[32] CDASH provides recommended standards for data spanning16 non-therapeutic specific domains (e.g., adverse events, demographic) for CRFs that map to SDTM standards for transferring data.
Readiness	**Emerging:** Version 2.0 is in development; Version 1.0 was released in October 2008.
Completeness	Strengths: • Leverages currently accepted standards • Standardizes data up early in the application process • Permits centralized data storage and sharing • Eliminates duplicate clinical data entry • Reduces research errors Limitations: • Requires development and use of data entry tools in order to be effective • Does not automatically map to SDTM • Is limited to non-therapeutic specific domains

[31] Ibid
[32] Brownley, Clinton W. (n.d.) *BRIDGing CDASH to SAS: How Harmonizing Clinical Trial and Healthcare Standards May Impact SAS Users*. Retrieved from http://www.wuss.org/proceedings09/09WUSSProceedings/papers/cdi/CDI-Brownley.pdf

ADaM

Overview	ADaM is a set of guidelines and examples for analysis datasets (AD) used to generate statistical results. ADs are generated as part of clinical trials. Summaries of these datasets are used to generate efficacy and safety data, used as part of the review process. Standardization of the ADaM model permits review of analyzed data and allows for replication of analyses, tables, and graphics with significantly less effort.[33] It also supports "traceability", or a clear linage of the data from collection to results, and integrates into one of the data classifications supported by eCTD.
Readiness	**Emerging:** Version 2.1 was released in 2008.
Completeness	Strengths: • Promotes linkages between datasets from different review phases • Leverages currently accepted standards • Allows applicant discretion in data and variable selection Limitations: • Is limited to one-way variable creations • Difficult to convert non-ADAM analysis data set • Requires development and use additional analytics tools to be effective • SAS XPT restrictions reduce standards benefits

SPL

Overview	The Structure Product Labeling (SPL) is a document markup standard that was developed by HL7 and is based on extensible markup language (XML). The standard specifies the structure and semantics of the package insert and contents of labeling. When submitting marketing applications or labeling supplements, applicants are required to submit the content of labeling in SPL format. Additionally, unless an applicant is granted a waiver, they must submit drug establishment registration and drug listing information electronically, in SPL format. SPL allows for "both the human readability of the content and facilitates machine processing of that content". The machine readable portions of the SPL document include drug listing data elements and clinical data elements.
Readiness	**Mature:** Release 4 became available on 3/23/2009.
Completeness	Strengths: • Improved information exchange • Labeling revisions efficiency • Data efficiency • improved dissemination of product labeling Limitations: • Has limited search functionality for related terms

[33] CDISC Analysis Data Model Team. (2009, December 17). *CDISC Analysis Data Model Version 2.1* [PDF document]. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/854651256c2654c94b03e6da1be6e145/download/analysis_data_model_v2.1.pdf

CDISC-HL7

Overview	CDISC-HL7 study data standard supports data exchange between researchers and the FDA. Human and animal study data will be stored in the forthcoming Janus data warehouse; a repository which allows users to generate views such that data may be further analyzed using different tools. One of FDA's goals for developing and adopting standards based on HL7 Reference Information Model (RIM) is to support meaningful information representation and exchange between systems used by clinical researchers, FDA and health care providers.
Readiness	**In Development:** The Study Design, Study Participation, and Subject Data exchange standards passed the HL7 September 2009 ballot cycle as Draft Standard for Trial Use (DSTU).
Completeness	Strengths: • Based on a well-structured information model • Able to support more analyses of interest • Supports harmonization with other HL7 standards • Promotes long-term interoperability with electronic heath record systems Limitations: • More complex to implement • High transition costs

Stakeholders Engaged in NDA/BLA Data Standards

The development and implementation of data standards for drug and biologic development require multiple stakeholders, to assure these standards are integrated into research, clinical trials, application review, and post-market safety. Key stakeholders involved in the development process include: standards development organizations (SDOs), FDA, and the biotechnology and pharmaceutical industry. Interaction and communication between these groups will be integral to the continued development and adoption of data standards applicable to drugs and biologics.

Standards Development Organizations

There are two SDOs, the Clinical Data Standards Exchange Consortium (CDISC) and the Health Level 7 International (HL7), that are responsible for many of the standards that are currently used in other industries and proposed for use in drug and biologic applications.

CDISC

CDISC oversees the development and support of the following data standards:

- SDTM
- BRIDG Model
- SEND
- CDASH
- ADaM

CDISC Mission Statement

"CDISC is a global, open, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata. The CDISC mission is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare. CDISC standards are vendor-neutral, platform-independent and freely available via the CDISC website."[34]

[34] Clinical Data Standards Exchange Consortium (CDISC). (n.d.). *The mission is to develop and support data standards for medical research.* Retrieved from http://www.cdisc.org/mission-and-principles

HL7

In addition, HL7 oversees the development of the following data standards:

- Product Stability Data Standard
- RPS
- SPL
- CDISC HL7[36]

HL7 Mission Statement
Mission: *"HL7 provides standards for interoperability that improve care delivery, optimize workflow, reduce ambiguity and enhance knowledge transfer among all of our stakeholders, including healthcare providers, government agencies, the vendor community, fellow SDOs and patients. In all of our processes we exhibit timeliness, scientific rigor and technical expertise without compromising transparency, accountability, practicality, or our willingness to put the needs of our stakeholders first."*[35]

FDA

There are several working groups within FDA's CDER and CBER, examining data standards adoption and implementation. The following groups are focused on the data standards included in this document:

- Analysis File Submission Working Group
- CDER Data Standards Program Board (DSPB)
- CDER Computational Science Center (CSC)
- FDA Data Standards Council (DSC)
- Interim Informatics Governance Board (IIGB)
- RPS Working Group
- Stability Data Standards Working Group
- Study Data Work Group

Each of the working groups listed above is responsible for specific aspects of data standards adoption and implementation. Many of the groups regularly communicate with one another, ensuring a consistent data standards approach across the FDA. Table 17 below outlines each working groups' mission or purpose within the FDA.

Table 17: FDA Data Standards Working Groups

Group	Mission/Purpose
Analysis File Submission Working Group	"The primary focus of the Analysis Files Submission Working Group is improving analysis datasets routinely submitted as part of an NDA/BLA. This group is not developing data standards but is interested in promoting standards."[37]
CDER DSPB	▸ "Provide consistent oversight of CDER data standards activities ▸ Recommend resource investments, policies, and procedures which enable CDER to proactively participate in data standards development with external stakeholders ▸ Recommend and oversee implementation of CDER business processes which will iteratively define, adopt, and enforce those standards"[38]

[35] Health Level Seven (HL7) International. (n.d.). *About Health Level Seven International.* Retrieved from http://www.hl7.org/about/index.cfm?ref=nav
[36] The CDISC HL7 Data Standard capitalizes on both CDISC and HL7 standards to provide a method for exchanging data between researchers and FDA. The standard relies on the HL7 exchange message and leverages CDISC data standards.
[37] (2011, January 14). *Data Standards*. Retrieved from http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/ComputationalScienceCenter/ucm171013.htm
[38] Office of Planning and Informatics, (2010, March 30). *CDER Data Standards Plan Version 1.0* [PDF document]. Retrieved from http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Drugs/ComputationalScienceCenter/UCM207834.pdf

Group	Mission/Purpose
CDER CSC	CDER's strategy for computational science is focused on: ▸ "Defining the requirements for and ensuring development of the IT infrastructure needed to enable 21st century computing operations ▸ Building technical expertise to enhance CDER's capabilities to use modern scientific computing tools to advance the science of safety at every stage of the drug life cycle. ▸ Driving change through key projects to develop and implement needed data standards, increase electronic submissions and access to electronic data, provide and expand use of electronic review tools and measure impact and value. ▸ Developing a resource for CDER to support review tool management, best practice development, review tool development, and consultation needs."[39]
FDA DSC	"To coordinate the evaluation, development, maintenance, and adoption of health and regulatory data standards to ensure that common data standards are used throughout the agency and the standards are consistent with those used outside the FDA. This is accomplished through strategically focused and systematic analysis of health and regulatory data standards requirements, evaluation of existing standards and adoption or development and maintenance of standards. This function operates at the direction of the FDA Management Council through the Business Process Planning Group (BPP) and provides timely, accurate and comprehensive analysis to BPP."[40]
IIGB	"We oversee the planning and management of FDA's information technology/investment management activities to move in a coordinated manner towards a highly automated mission-supportive information management environment. We will increase the standardization of technology, data and applications to the extent feasible, and achieve the most efficient and effective use of resources across the agency. We will ensure that our activities are communicated FDA-wide."[41]
RPS Working Group	To create codes and implement the R2 modifications through R3.[42]
Stability Data Standards Working Group	"To improve the efficiency of stability data evaluation by standardizing the format of the stability data. The group will work with HL7 to develop a standard that is consistent with version 3 of the HL7 Reference Information Model."[43]
Study Data Work Group	The goal of the group to improve the coordination and communication (internal and external) of all study data standards activities at FDA. This is intended to be an agency-level group with representation of all Centers that review study data submissions.

[39] (n.d.). *CDER Computational Science Center (CSC).* Retrieved from http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/ComputationalScienceCenter/default.htm
[40] (n.d.). *FDA Data Standards Council's Charter*. Retrieved from http://inside.fda.gov:9003/ProgramsInitiatives/CommitteesWorkgroups/DataStandardsCouncil/ucm166867.htm
[41] (2010, October 25). *Interim Informatics Governance Board*. Retrieved from http://inside.fda.gov:9003/ProgramsInitiatives/CommitteesWorkgroups/BioinformaticsBoardandBusinessReviewBoard/ucm011170.htm
[42] (n.d.). *RPS Data Exchange Standards Initiatives: Regulated Product Submission (RPS) Standard Status* [PDF document]. Retrieved from http://www.fda.gov/downloads/ForIndustry/DataStandards/RegulatedProductSubmission/UCM174101.pdf
[43] (n.d.). *Data Standards Council*. Retrieved from http://inside.fda.gov:9003/ProgramsInitiatives/CommitteesWorkgroups/DataStandardsCouncil/ucm166878.htm

Industry

Industry is a critical stakeholder, both in data standard development and usage. Pharmaceutical and biotechnology companies contribute to the development of standards in many ways. First, industry representatives are actively involved in proposing areas where standards would be relevant and the types of standards that would improve their ability to generate a well written and credible application. Secondly, applicants allow their staff to participate in standard organizations' working groups and boards of directors, and they provide public comment to draft and current production versions of standards. This type of feedback is critical to ensure the standard is valid and understood clearly and consistently. Finally, industry uses the standards. Initially, data standard applications may occur as part of a pilot, which requires close collaboration with regulatory agencies. In later stages, this occurs when standardized data is incorporated into submissions either voluntarily, as agreed upon with reviewers during pre-submission meetings, or as required by regulatory agencies.

Scope, Readiness and Completeness of Standards

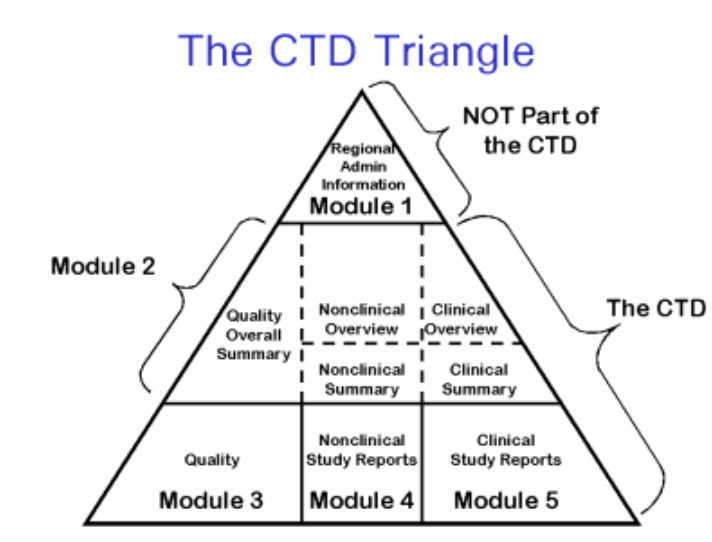
The following section provides a detailed overview of each of the eight profiled data standards. This includes each standard's scope, relationship to the NDA/BLA review process, readiness, and strengths and limitations.

eCTD

Overview of Standard

The Common Technical Document (CTD) is a standardized formatting tool that provides a logical way of ordering and organizing regulatory information at the document file level. It is similar to a table of contents, organizing information into five modules (See Exhibit 64), and can be used in both paper and electronic formats.

Exhibit 64: The eCTD Triangle



The CTD modules provide a specific location for application information, enabling reviewers to quickly locate information:

- Module 1: Administrative Information
- Module 2: Common Technical Document Summaries
- Module 3: Quality
- Module 4: Nonclinical Study Reports
- Module 5: Clinical Study Reports

Each module provides a technical taxonomy for categorizing information and documents, for example in section 2.3.S.1 quality data on drug substance manufacturing is stored and nonclinical toxicology study reports are stored in section 4.2.3.

The electronic Common Technical Document (eCTD) provides a mechanism for delivering the CTD electronically. The eCTD provides a logical way of ordering and organizing information and the document/page level. The eCTD utilizing an Extensible Markup Language (XML)-based backbone which replaces the PDF Table of Contents used in earlier versions of electronic applications. eCTD accommodates the following file formats:

- PDF for reports and forms
- SAS XPORT (version 5) transport files (XPT) for datasets
- ASCII text files (e.g., SAS program files, NONMEM control files) using txt for the file extension
- XML for documents, data, and document information files
- Stylesheets (XSL) and document type definition (DTD) for the XML document information files
- Microsoft Word for draft labeling44

Some important concepts for using the eCTD standard include granularity, metadata, and leaf.

- **Granularity** describes the level in which content is broken into individual files in the eCTD submission; higher granularity indicates that there are more files

- **Metadata** is descriptive information about data files. In the eCTD, metadata is provided in various locations:
  - Module 1: submission level metadata
  - Modules 2-5: heading level metadata
  - All leaf elements in modules 1-5: document/file level metadata
  - Modules 4 & 5: study tagging files

- A **Leaf** is a section of the XML backbone containing all of the metadata associated with an individual file, including a link to the physical file. A leaf does not need to contain metadata – it can be a reference to another file. The ability to create a pointer to a

[44] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2008, June). *Guidance for Industry Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* [PDF document]. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf

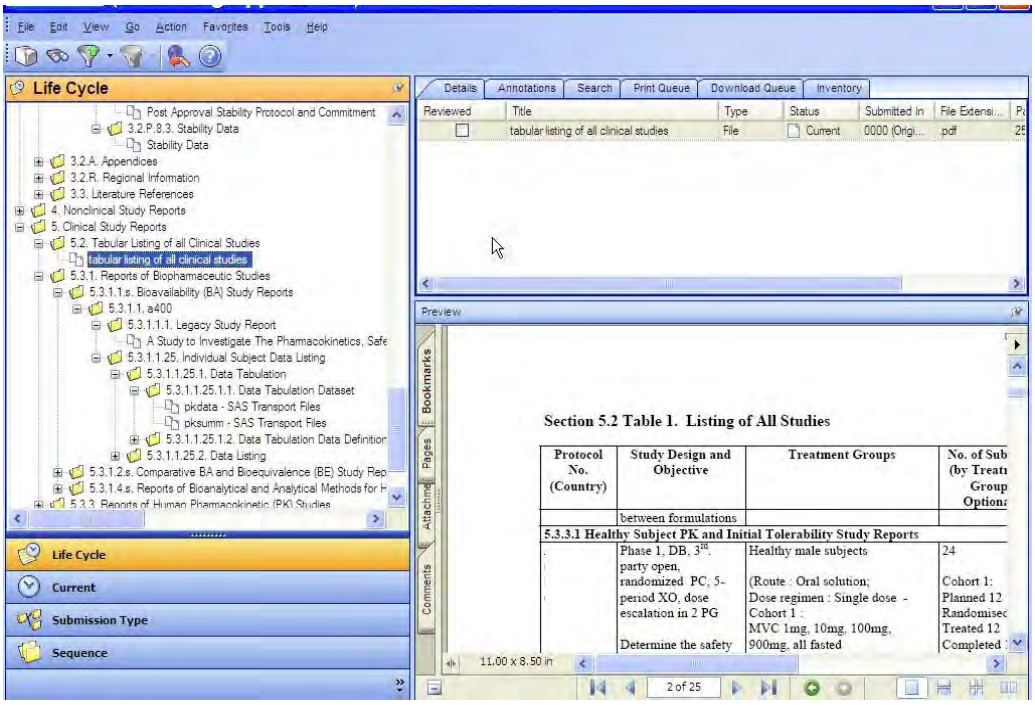
specific file by using a leaf is helpful when the same document is referenced in multiple sections of an application.[45]

Three types of tools are commonly used when working with eCTD; each tool can be used separately.

- **eCTD Compiler:** Develops the eCTD by creating the XML backbone using the document type definitions (DTD), metadata, and references to required style sheets
- **eCTD Validator:** Used to validate the presence of all required files and metadata and to validate the eCTD backbone against the DTD
- **eCTD Viewer:** Provides reviewers with a view of the application data and allows XML backbone information to be displayed in an alternate view, one more meaningful and helpful to reviewers

The tools used by industry to compile and validate eCTD submissions can be different than the tools FDA uses to view the eCTD (i.e. GS Review). [46] As its eCTD Viewer, FDA currently utilizes version 4.1.0 of the Review™ application, developed by Global Submit. Review.™ This tool allows reviewers to navigate the application using three panes (See Exhibit 65).

Exhibit 65: eCTD Viewer[47]



[45] Aitken, John & Smerkanich, Nancy. (2010, October 28-29). Tutorial #1: eCTD Basics. *9th Annual Electronic Submissions Conference: Working Together Towards a Global Strategy.*
[46] Ibid
[47] Duggan, Donovan. (n.d.). *Getting Started With eCTD* [PDF document]. Retrieved from http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM229720.pdf

The Navigation pane presents the contents of submission, changing to display and "will display different trees depending upon the view you select".[48] The Details pane has five tabs. The most important of these is the Details tab which provides additional information about the selected folder or document selected in the Navigation pane.[49] Finally, the Preview pane "displays the source document."[50]

eCTD Metadata Operators
New – Used for files submitted for the first time to the application
Append- Used to add information to a previously submitted file
Replace* – Used to replace a previously submitted file with an updated version (e.g., updated labeling)
Delete* – Removes a file from the current view of the application
**Note: Files are removed from the current view of the application but remain in the application sequence*

The XML backbone for an eCTD submission allows applicants to add new files to the backbone sequence, append files to existing files (i.e., add information), replace files, and delete files within a sequence.[51] These operations provide the applicant with the flexibility to modify their submission and provide FDA with the most relevant and up-to-date information required for an application review.

Scope of Standard in NDA/BLA Review Process

The eCTD standard is used throughout the medical product lifecycle. As of January 2010, the FDA eCTD standard applies to the following submission types:

- New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- Biologics License Application (BLA)
- Investigational New Drug (IND)
- Drug Master File (DMF) and related submissions

[48] GlobalSubmit Inc. (n.d.). *Global Submit Review Training Guide 4.0* [PDF document]. Retrieved from http://inside.fda.gov:9003/downloads/CDER/OfficeofBusinessProcessSupport/UCM044505.pdf
[49] Ibid
[50] Ibid
[51] Duggan, Donovan. (n.d.). *Getting Started With eCTD* [PDF document]. Retrieved from http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM229720.pdf

Readiness

Table 18: Readiness of eCTD

Readiness of eCTD			
Current Version:	Version 3.2.2	**Release Date:**	January 13, 2004
Highlighted Features/Changes:	Release 3 provided a revision of the Annex: Granularity Document.		
Current Users:	The CTD standard is currently used by the US FDA, EU, Japan, Canada and Switzerland and is under consideration for adoption by several others. Countries are at different levels in their ability to accept eCTD submissions.		
Standard Evolution:	The CTD was agreed upon in November 2000 by the ICH Steering Committee. The standard is defined in "ICH Topic M4L Common Technical Document for the Registration of Pharmaceuticals for Human Use." Edits to the numbering and section headers were made for consistency of use in September 2002. A revision to the granularity document was approved in January 2004. [52] As of 1/1/08, sponsors and applicants submitting electronically are required to send new NDA, IND, ANDA, BLA, Annual Report, and DMF submissions in eCTD format to CDER (refer to Memo 33 in the Electronic Submissions Public Docket number 92-0251). Paper is still acceptable as an alternative to electronic submission. Waivers are available for those applicants who would like to submit electronically, but are unable to do so in eCTD format by the deadline.[53] According to the FDA website, the current version of eCTD, Version 3.2 (file name: ich-ectd-3-2.dtd), has been supported since November 2003.[54] Work began on an update to eCTD, Version 3.3, in 2005. Major business requirements were identified during this process, including: ▸ Create two-way electronic interaction between applicants and regulators ▸ Develop a message structure that better matches business needs ▸ Better manage quirks/problems in current lifecycle model 'In 2008, ICH, by agreeing to work with HL7 and other standards development organizations will merge the next major version of eCTD with RPS'. [55]		
Governing Body:	CTD was developed by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.		
Process for Changes:	The ICH Steering Committee provides updates/modification to the standards as deemed necessary. The proposed changes are released for public comment before finalizing changes. A complete change control process is adopted by ICH.		
Relationship to Other Standards:	eCTD relies on the CTD as defined by ICH		
Related Tools:	eCTD Compiler eCTD Validator eCTD Viewer (e.g., GS Review)		

[52] (2004, January 13). *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4* [PDF document]. Retrieved from http://private.ich.org/LOB/media/MEDIA554.pdf
[53] (2009, June 18). *Electronic Submissions > eCTD Submission Waivers.* Retrieved from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm163186.htm.
[54] (2010, December 10). *Electronic Submissions > Electronic Common Technical Document (ECTD)*. Retrieved from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm#guidancespecs
[55] Williams, Geoff. (2010, October 28-29). RPS: An ICH Perspective and Release 3. *DIA 9th Annual Electronic Submissions Conference.*

Strengths and Limitations

Table 19: Strengths/Benefits and Limitations/Challenges for eCTD Submissions

Strength Description	Impact
1. **Provides consistency between documents due to the same standardized format –** Consistency of the CTD structure allows reviewers to quickly find needed information within the application. During Booz Allen interview and focus groups FDA staff noted eCTD: ▸ Provides rapid access and easy management access ▸ Facilitates finding information and lifecycle management	High
2. **Facilitates reuse of documents –** Applicants are able to link to IND submissions and other files without submitting them in duplicate.	Medium
3. **Relieves challenges associated with paper distribution** – Electronically submitted documents are available to any person on the review team and do not have the burden associated with inter-office mail of paper documents. Additionally, electronically submitted documents are more accessible than paper volumes stored in the document room or offsite storage.	High
4. **Accepted by multiple regulatory agencies –** The eCTD is currently accepted in the EU, Canada, US, and Japan and is being expanded to other countries.	High
5. **Multiple vendor and tool options--**Standard and format is supported by multiple tools and vendors. However, FDA uses Global Submit Review and applicants may find it beneficial to use this system to ensure that their view of the application is the same as reviewers.	High

Limitation Description[56]	Impact
1. **Limits change in granularity -** The level of document granularity (i.e. a single PDF) can be defined early in the product development process but cannot be changed over time as the product development progresses. This can lead to challenges when amendments are submitted to the application because the entire granule needs to be updated, even if only a small part of the document has changed.	Medium
2. **Fixed metadata structure –** The eCTD has a fixed, hierarchical metadata structure. When changes to the application are needed, individual granules need to be deleted and re-added.	Medium
3. **Does not support non-electronic application components--**Does not accommodate placeholders for components of a regulatory submission that are not electronic (e.g., samples of production lots, promotional advertising samples, faxes).	Medium
4. **Difficult to distribute to non-FDA consult reviewers--** The standard and the underlying infrastructure do not accommodate the need to bring in consult reviewers who are unable to access FDA systems. Additionally, the submission cannot be separated and distributed easily so that it can be viewed outside the FDA infrastructure or electronic document rooms.	Low
5. **Standard is limited by the quality of current viewer tool –** Since an application submission is submitted in many smaller files, a viewer is needed to review the submission. Functional or interface limitations associated with a viewer impact the ease of conducting the review; paper printouts do not bear these same limitations. During Booz Allen interviews and focus groups, FDA staff noted: ▸ "An eCTD is difficult to navigate" ▸ "It is hard to make sure you reviewed everything"; reviewers would like to have a mechanism to flag pages reviewed ▸ Can't highlight specific text and can't copy sections onto a hard drive and retain links without copying all of the sections	High

[56] Finkle, Joel. (2010, October 28-29). RPS – More than an Envelope. *DIA 9th Annual Electronic Submissions Conference: Working Together Towards a Global Strategy Conference.*

Limitation Description[56]	Impact
6. **Applicant submissions are not fully standardized–** Variations in applicant's implementation of eCTD can increase the time reviewers spend finding information. There are too many small documents and the changes in files are not always apparent. During Booz Allen interview and focus groups FDA staff noted: ▸ Diversity of strategies, (e.g., Quality Overall Summary, Amendments, Supplements, INDs [don't include all data here, use Module 3]) ▸ Diversity of data presentation ▸ Diversity of leaf naming conventions	Medium
7. **Does not support two-way communication –** Two-way communication between FDA and applicants is not currently supported requiring communication, and tracking of that communication through multiple systems.	Low

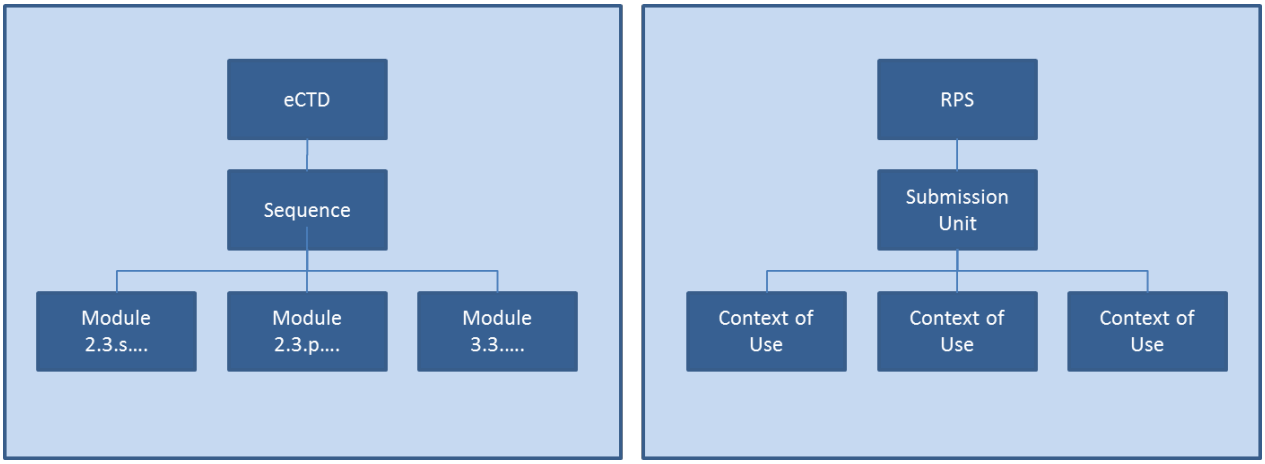
Impact	Evaluation Criteria
Low	Strength or limitation affects very few individuals' ability to read, understand, analyze or process the data.
Medium	Strength or limitation affects multiple individuals' ability to read, understand, analyze or process the data within a stakeholder group
High	Strength or limitation affects multiple stakeholders' ability to read, understand, analyze or process the data

Regulatory Product Submission (RPS)

Overview of Standard

Regulatory Product Submission (RPS) is a product information submission framework developed jointly by the FDA and the HL7 Regulated Clinical Research Information Management (HL7 RCRIM) working group. RPS is a flexible, open framework permitting controlled context of use lists and key words or "pointers" to more easily and consistently guide reviewers when conducting an electronic review. The RPS structure also easily facilitates granular changes to a file or files and allows an applicant to reference additional files or applications already documented by the FDA. However, RPS, does not have fixed element names or a hierarchical structure. (See Exhibit 66)

Exhibit 66: eCTD and RPS Structures



RPS is an evolution of the eCTD standard and so the user should not recognize any difference when eCTD transitions to RPS, with the exception of any enhancements offered by the next version. RPS intends to be a universal submission standard, or exchange message, for any type of regulated product, human or animal, making it transferable across all FDA Centers. The standard helps FDA meet PDUFA IV and FDAAA regulations, to facilitate two-way electronic communication, and reduces the dependence on paper by allowing FDA reviewers to source and review all documentation electronically.[57] Additionally, RPS aims to be international in scope. In 2009, the International Conference on Harmonization (ICH) cited that RPS would be the next major version of eCTD.[58]

RPS provides an electronic "envelope" for exchanging documents between applicants and the FDA. This includes a status code, indicating the status or progress of the regulatory action (e.g., acceptance, approval, or withdrawal). However, according to HL7 and FDA documentation, RPS uses different location indicators and replaces the XML tags and sequences used in eCTD.

Scope of Standard in NDA/BLA Review Process

The RPS exchange standard scope includes animal and human products, including but not limited to food additives, human therapeutics, veterinary products, and medical devices. Worldwide use of the same model for all product types to all regulatory authorities is the goal of HL7.[59]

[57] (n.d.). *RPS Data Exchange Standards Initiatives: Regulated Product Submission (RPS) Standard Status* [PDF document]. Retrieved from http://www.fda.gov/downloads/ForIndustry/DataStandards/RegulatedProductSubmission/UCM174101.pdf
[58] (2009, 13 November). *Product RR RPS*. Retrieved from http://wiki.hl7.org/index.php?title=Product_RR_RPS
[59] (n.d.). *FDA Data Exchange Standards Initiatives: Regulated Product Submission (RPS) Standard Status* [PDF document]. Retrieved from http://www.fda.gov/downloads/ForIndustry/DtaStandards/RegulatedProductSubmission/UCM174101.pdf

Readiness

Table 20: Readiness of RPS

Readiness of RPS			
Current Version:	RPS Release 2 (R2)	**Release Date:**	October 2008
Highlighted Features/Changes:	The primary PDUFA goal met through R2 is to generate, exchange, and classify two-way communication between the FDA and applicants including all correspondence using the same electronic format		
Current Users:	FDA		
Standard Evolution:	RPS has an operational schedule consisting of three releases. FDA documentation indicates that the Agency is presently accepting DSTU for Release 2 (R2).[60] **RPS Release 1 (R1)** passed ballot in May 2007 and an HL7 Normative Standard. It became an American National Standards Institute (ANSI) standard in 2008. This version provided the ability to cross reference applicant material, conform to the submission lifecycle, manage trans-BLAs (CBER), and correct and modify attributes.[61] **RPS Release 2 (R2)** was initiated in late 2008 and, at the time of this report, was nearing the end of its Draft Standards for Trial Use (DSTU). R2 originally aimed to meet PDUFA goals and core ICH requirements. The primary PDUFA goal of this release was to generate, exchange, and classify two-way communication between the FDA and applicants including all correspondence using the same electronic format. This included the ability to conduct and tag discussion around submission activities, communication of regulatory actions, and requests for additional information. [62] This release also offered referencing capability both within a document and through hyperlinks, between documents in an application, submission, or submission unit and documents within an external warehouse and the ability to capture basic product information.[63] *Since not all requirements of R2 were achieved, FDA deferred implementation until release of R3*. **RPS Release 3(R3)** was initiated in 2009 and is planned for an adoption ballot in May 2012.This version address nine areas of improvement:, including: ▸ Two way communications ▸ Referencing of other applications ▸ Lifecycle management improvements ▸ Improvements to submission metadata ▸ Improvement to hyperlinking ▸ ICH requirements for the eCTD next major version'[64] Additional regional/domain requirements		
Governing Body:	HL7		
Process for Changes:	RPS follows a structured process for updates including requirement gathering, specification design, testing, and balloting.		
Relationship to Other Standards:	Will be integrated into the Next Major Version (NMV) of eCTD		
Related Tools:	RPS Compiler RPS Validator RPS Viewer (e.g., GS Review)		

[60] (n.d.). *FDA Data Exchange Standards Initiatives: Regulated Product Submission (RPS) Standard Status* [PDF document]. Retrieved from http://www.fda.gov/downloads/ForIndustry/DtaStandards/RegulatedProductSubmission/UCM174101.pdf
[61] Ibid
[62] (2010, August 25). *HL7 RPS R2 Project Scope* Retrieved from http://wiki.hl7.org/index.php?title=RPS_R2_Project
[63] Ibid
[64] Williams, Geoff. (2010, October 28-29). RPS: An ICH Perspective and Release 3. *DIA 9th Annual Electronic Submissions Conference.*

Completeness – Strengths and Limitations

Table 21: Strengths/Benefits and Limitations/Challenges for RPS Submissions

Strength Description	Impact
1. **Structural flexibility and increasing consistency –** The RPS standard has no fixed element names and no hierarchical structure. The flexibility of RPS allows its use to be extended beyond drugs and biologics to any type of regulated data. Unlike eCTD which relies on a rigid hierarchical structure that is more useful for drugs and biologics, RPS is a more flexible framework, permitting the use controlled context of use lists and key words or "pointers" to more easily and consistently guide reviewers when conducting an electronic review.[65]	High
2. **International Acceptance –** Because RPS is in development as a universal international standard through an open development process, it will be adopted and implemented by more international participants. This will likely increase the usage beyond ICH member countries.	Medium
3. **Easier Submission Updates –** RPS structure facilitates minor changes (i.e., granularity and metadata) to a file or files without deleting and resubmitting documents. Additionally, a single document can replace multiple documents, decreasing the time it takes reviewers to identify information and the effort associated with applicants' resubmissions.[66]	Medium
4. **Two-way Communication –** Permits the dissemination of formal and informal communication between the regulatory agency and applicant, which may provide addition information in support of workload and deadline management.	Medium

Limitation Description[67]	Impact
1. Complex tools to compile, validate, and view RPS are critical to access information – Compared to paper files, the multi-file format of RPS submission creates a reliance on viewing tools to access application information. RPS Validator and RPS View are still under development, as are other infrastructure required to support larger submissions.	High
2. Hierarchy is inferred by the Review System – There is no guarantee that review and assembly display the same information. Without a standard structure or hierarchy (e.g., eCTD), referencing other applications implies that applicants know where 'other' applications are stored.	High
3. Difficult to distribute to non-FDA consult reviewers – The standard and underlying infrastructure do not accommodate SGE consult reviewers who are unable to access FDA systems. Additionally, the submission cannot be easily separated and distributed so that it can be viewed outside the FDA infrastructure or electronic document rooms.	Low

Impact	Evaluation Criteria
Low	Strength or limitation affects very few individuals' ability to read, understand, analyze or process the data
Medium	Strength or limitation affects multiple individuals' ability to read, understand, analyze or process the data within a stakeholder group
High	Strength or limitation affects multiple stakeholders' ability to read, understand, analyze or process the data

Product Stability Data Standard (eStability)

Overview of Standard

Product stability data submitted by drug and biologic applicants confirms the shelf life of the product and provides information regarding the quality of a drug substance or drug product

[65] (2009, 13 November 2009). *Product RR RPS*. Retrieved from http://wiki.hl7.org/index.php?title=Product_RR_RPS#Summary
[66] Ibid
[67] Ibid

under different conditions, within specific time frames. As with other data submitted to the FDA, stability data is submitted either in paper or electronic format, in PDF or SAS transport format. The latter electronic format allows product quality reviewers the ability to perform statistical analyses. Over time, FDA reviewers discovered that data submitted in different formats was not always identical.[68] Therefore, the FDA Stability Data Standards Working Group, in conjunction with HL7, developed a project to standardize the electronic format of stability data "so that FDA will be able to view the information as it appears on paper or electronic paper as well as [to] directly analyze the data."[69] The format and information contained in stability data reports can vary drastically between companies and even within the same company or the same product over time. This will standardize the format and types of information for all stability reports.

Scope of Standard in NDA/BLA Review Process

The Product Stability Data Standard will allow FDA product quality reviewers to analyze and review stability data in a standardized format.

[68] FDA Data Council. (2003, December 1). *Project Description - Stability Data Standards* [PDF document]. Retrieved from http://inside.fda.gov:9003/downloads/ProgramsInitiatives/CommitteesWorkgroups/DataStandardsCouncil/UCM166879.pdf
[69] Ibid

Readiness

Table 22: Readiness of Product Data Stability Standard

Readiness of Product Data Stability Standard			
Current Version:	HL7 Drug Stability Reporting Release 2 (R2)[70]	**Release Date:**	January 2009
Highlighted Features/Changes:	Incorporates changes and rectifies deficiencies in the message that were identified during the 2006 FDA Pilot.		
Current Users:	FDA – Pilot (Docket No. 2006N-0181 (Product Stability; Data: Notice of Pilot))		
Standard Evolution:	The Product Stability Data Standard has undergone two releases: ▸ January 2001 - Development of HL7 Stability Standard started ▸ January 2005 - Stability Standard Release 1 (R1) passes HL7 Committee ballot ▸ May 2005 - Stability Standard (R1) passes HL7 Membership ballot ▸ September 2005 - HL7 Stability Standard (R1) is ANSI approved and 1st public draft of Implementation Guide ▸ September 2006 - Kick-Off meeting for the Product Stability Data Pilot ▸ May 2006 - Published FR notice (Docket No. 2006N-0181 (Product Stability; Data: Notice of Pilot)) ▸ May 2008 - Product Stability Data Pilot Project Completion Announcement ▸ January 2009 - Stability Standard (R2) as Draft Standard for Trial Use (DSTU) and Implementation Guide Pass ballot"[71] ▸ May 2010 - Stability Standard (R2)passed normative ballot ▸ October 2010 - Stability Standard (R2) Implementation Guide Pass ballot		
Governing Body:	Regulated Clinical Research Information Management (RCRIM) technical committee in HL7		
Process for Changes:	The Product Stability Data Standard follows a structured process for updates including requirement gathering, specification design, testing, and balloting.		
Relationship to Other Standards:	HL7 version 3 reference information model[72]		
Related Tools:	Input Tool – ▸ "Will allow the entry and reporting of stability data as an XML file ▸ Will allow users to enter data and build a stability message that can be validated against the PORT_MT090002UV01 schema ▸ Will support the two interactions possible with the message: send and revise"[73] ▸ Stopped work on Input Tool, environment and version dependent. Once FDA requires, software vendors will create. Style Sheet - ▸ For viewing XML stability file ▸ Can display the data in a flat file and display as a CSV file ▸ Data in flat file can be copied to Excel, display selected column(s), or display data for a specific test Business Rules (schematron) - ▸ Allow XML eStability file to be validated to the W3C schema and the FDA business rules to submit to FDA ▸ Validation Procedures Document		

[70] eStability Working Group. (n.d.) *Stability Data Standard Implementation Guide v1.6* [PDF document]. Retrieved from http://www.fda.gov/ForIndustry/DataStandards/StabilityDataStandard/default.htm
[71] Gregory, Norman. (n.d.). *Establishment of Health Level 7 (HL7) Standard for Submission of XML Stability Data* [PDF document]. Retrieved from http://www.fda.gov/ForIndustry/DataStandards/StabilityDataStandard/default.htm
[72] (n.d.). *Product Stability Data Pilot Project Completion Announcement* [PDF document]. Retrieved from http://www.fda.gov/ForIndustry/DataStandards/StabilityDataStandard/default.htm
[73] (n.d.). *Stability Data Standard Message Input Tool User Requirements 6.2* [PDF document]. Retrieved from http://www.fda.gov/ForIndustry/DataStandards/StabilityDataStandard/default.htm

Completeness – Strengths and Limitations

Table 23: Strengths/Benefits and Limitations/Challenges for Product Stability Data Standard

Strength Description	Impact
1. **Integration with other formatting standards –** The Product Stability Data Standard can work in conjunction with eCTD and RPS.[74]	High
2. **Eliminate inconsistencies** – Utilizing the standard will eliminate differences found between paper and electronic submissions.[75]	Medium
3. **Potential for review efficiency** – The organization of data will be standardized, enabling product quality reviewers to use review tools.[76]	Medium

Limitation Description	Impact
1. **One way communication** – Because eCTD and the current version of RPS do not support two-way communication, communication can only occur between: ▸ Contractor → Company ▸ Company → Company ▸ Company → Regulatory Agency[77]	High
2. **Tool required** – Applicants may be required to develop or acquire a tool to develop the exchange message.	Low

Impact	Evaluation Criteria
Low	Strength or limitation affects very few individuals' ability to read, understand, analyze or process the data
Medium	Strength or limitation affects multiple individuals' ability to read, understand, analyze or process the data within a stakeholder group
High	Strength or limitation affects multiple stakeholders' ability to read, understand, analyze or process the data

Study Data Tabulation Model (SDTM)

Overview of the Model

Clinical trial data is the cornerstone for clinical, biostatistics and clinical pharmacology reviewers when conducting the safety and efficacy review for a drug or biologic. Without a standardized format for the clinical trial data, reviewers can inefficiently use review time trying to reconcile the data and perform simple analyses due to inconsistent formatting within and between datasets. The CDISC Study Data Tabulation Model (SDTM) seeks to address the issues around data organization and formatting by grouping clinical trial observations into domains. The CDISC SDTM Implementation Guide explains:

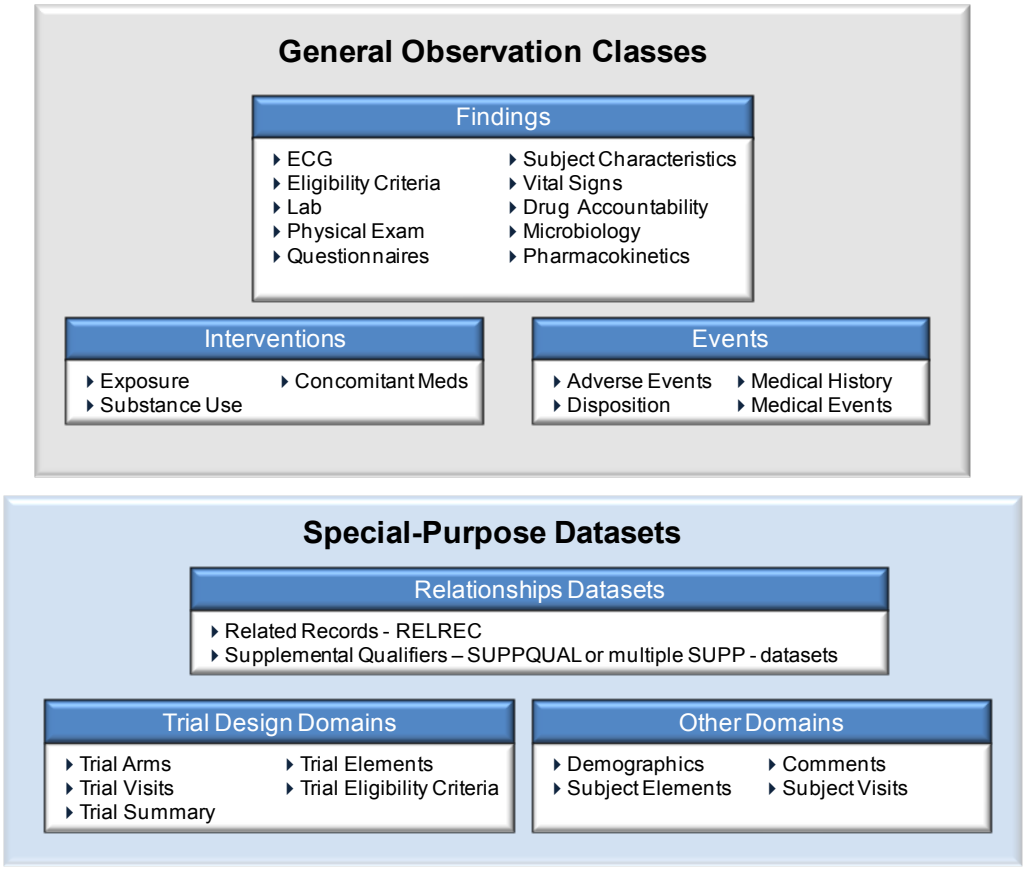
> "Observations about study subjects are normally collected for all subjects in a series of domains. A domain is defined as a collection of logically related observations with a common topic. The logic of the relationship may pertain to the scientific subject matter of the data or to its role in the trial. Each domain is represented by a single dataset. Each

[74] (n.d.). *Stability Data Standard Implementation Guide v1.6* [PDF document]. Retrieved from http://www.fda.gov/ForIndustry/DataStandards/StabilityDataStandard/default.htm
[75] (n.d.). *Product Stability Data Pilot Project Completion Announcement* [PDF document]. Retrieved from http://www.fda.gov/ForIndustry/DataStandards/StabilityDataStandard/default.htm
[76] Ibid
[77] (n.d.). *Stability Data Standard Implementation Guide v1.6* [PDF document]. Retrieved from http://www.fda.gov/ForIndustry/DataStandards/StabilityDataStandard/default.htm

domain dataset is distinguished by a unique, two-character code that should be used consistently throughout the submission."[78]

The referenced domain datasets include, "both raw (as originally collected) and derived values (e.g., converted into standard units, or computed on the basis of multiple values, such as an average)".[79] For the most part, datasets can be grouped into three general observation classes: Interventions, Events and Findings. However, there are some datasets, categorized as special-purpose datasets, which do not belong in the general observation classes. Exhibit 67 below shows some of the standard domains/datasets grouped into either one of the three general observation classes or special-purpose datasets:

Exhibit 67: CDISC SDTM Standard Domains[80]



[78] CDISC Submission Data Standards Team. (2008, November 12). *Study Data Tabulation Model Implementation Guide: Human Clinical Trials* [PDF document]. Retrieved from http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/ComputationalScienceCenter/ucm171013.htm
[79] Ibid
[80] CDISC Submission Data Standards Team. (2008, November 12). *Clinical Data Interchange Standards Consortium (CDISC) SDTM Implementation Guide: Human Clinical Trials* [PDF document]. Retrieved from http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/ComputationalScienceCenter/ucm171013.htm

Scope of Standard in NDA/BLA Review Process

By categorizing datasets and grouping them into a standardized format, clinical pharmacology, clinical, and biostatistics reviewers will be able to locate datasets that apply to their portion of the application review. The data standard also allows for the use of specialized review tools that can pull data from the standardized domains (i.e., datasets).

Readiness

Table 24: Readiness of SDTM

Readiness of SDTM			
Current Version:	Study Data Tabulation Model, Version 1.2 (SDTM v1.2)	**Release Date:**	November 12, 2008
Highlighted Features/Changes:	▸ Designed to be backward compatible ▸ Includes the following new variables: --PRESP, --VAMT, --VAMTU, --OBJ, --STRTPT,--STTPT, --ENRTPT, --ENTPT, TIVERS, and TSGRPID ▸ Includes numerous text corrections, clarifications, and some reordering, including the transfer of domains for Subject Elements and Subject Visits[81]		
Current Users:	FDA – CDER (IG 3.1.2) and CBER (IG 3.1.1)		
Standard Evolution:	SDTM has an operational schedule of three releases. At the time of this deliverable, the CDISC website indicates that the FDA can accept SDTM Version 1.2. ▸ **Version 1.0:** This version was released on June 25, 2004 and included changes identified during the comment period ▸ **Version 1.1 Final:** This final version was released on April 28, 2005 and included corrections to comments from the public comment period ▸ **Version 1.2 Final:** The draft version was released on July 10, 2007 for comments and the final version was released on November 12, 2008 with corrections addressing the comments from the draft version.[82]		
Governing Body:	CDISC		
Process for Changes:	1. Draft version release 2. Public comment period 3. Correction made based on comments 4. Final version release		
Relationship to Other Standards:	Descendant of CDISC Submission Data Standards or Submission Domain Models[83]		
Related Tools:	WebSDM JReview JMP		

[81] CDISC Submission Data Standards Team. (2008, November 12). *Study Data Tabulation Model v1.2* [PDF document]. Retrieved from http://www.cdisc.org/content1209
[82] Ibid
[83] Ibid

Completeness – Strengths and Limitations

Table 25: Strengths/Benefits and Limitations/Challenges for SDTM

Strength Description	Impact
1. **Permits automation of analyses** – With standardized clinical trial data, standard analyses (e.g., demographics) can be performed using review tools that extract and analyze the data. Additionally, review tools can be updated to perform specific, in-depth analyses.	Medium
2. **Promotes review efficiency** – Reviewers don't have to expend review time organizing data, as it is already easily interpreted due to its standardized format. Instead, the reviewer has the opportunity to conduct more in-depth analyses and contemplate the results of the analyses. During Booz Allen interviews and focus groups, FDA staff noted: ▸ "Everything is the same" ▸ Able to become "familiar with the format" ▸ Familiarity with format and terminology ▸ "Can find what I need and link databases with headers" ▸ Helped to facilitate the review An FDA presentation noted the following: ▸ "Easy to find the data" ▸ "Improved efficiency & more 'think time'"	Medium
3. **Generates efficiencies for applicants** – Applicants experience some of the following efficiencies when using standardized clinical trial data: ▸ Streamlines data management and data transfers ▸ Facilitates generating analyses and listings ▸ Potential for faster application preparation[84]	Medium

Limitation Description	Impact
1. **Standard may not be robust enough** – Because clinical trial data standards are rather new, the standard may not be robust enough for all situations.	High
2. **No requirements for applicant adoption and compliance** – Applicants are not required use SDTM formatted data when submitting an application. Additionally, some applicants do not comply with all aspects of the data standard, either by choice or as a result of inconsistencies in the [sometimes misleading] implementation guide. During Booz Allen interviews and focus groups, FDA staff noted: ▸ "Seventy percent of sponsors [applicants] are not using the data standard" ▸ Applicants resistant to adopt standards due to changing environment ▸ FDA needs to develop a validation tool to determine whether the applicant adhered to the CDISC SDTM standard and by how much ▸ FDA staff need to make sure definition file matched the data	High
3. **Requires use of analysis tools to be effective--** Because SDTM relies on tabulation data, it requires the use of specially designed analysis tools to support efficient and effective reviews of clinical trial data.	High
4. **Produces disparate patient profiles** – The SDTM format breaks up clinical trial data into specific domains which do not allow presentation of the full patient profile. During Booz Allen interviews and focus groups, FDA staff noted: ▸ Data for individual patients has been "chopped up" and split into different sections ▸ Data standard may not be organized in the best interest of the reviewer	Medium

[84] CDISC Submission Data Standards Team. (2008, November 12). *Study Data Tabulation Model v1.2* [PDF document]. Retrieved from http://www.cdisc.org/content1209

Limitation Description	Impact
5. SAS XPT restrictions reduce standard benefits – SDTM datasets are delivered in SAS XPT files. Field and file size limitations and lack of an audit trail for changes may inhibit applicants and reviewers. It is unclear if the pending release of SAS transport will remedy many of these issues. During Booz Allen interviews and focus groups, FDA staff noted: ▸ SAS transport file (version 5) o Character limits o Field limits o Metadata can't be associated with file o File size limitations o No audit trail An FDA presentation noted the following: ▸ "Flat" 2-dimensional files are not the best way to represent clinical data ▸ Some meaning is lost when exchanging flat files, making certain analyses difficult or impossible"[85]	High
6. Not based on a well-structured data model – Because the SDTM standard is not based on a well-structured data model, compared to a relational data model, the standard has a number of disadvantages: • Inflexible • New requirements or data domain require changes to: o data model o implementation guide o database • Addition of new requirements can be costly and time consuming[86]	High
7. Ambiguous implementation guide – As structured and presented, the implementation guide does not provide clear and concise instructions for implementing SDTM	Medium
8. Used as an exchange and analysis standard – The SDTM standard currently fulfills two roles as an exchange and analysis standard. Since the requirements for both are different, SDTM is not particularly robust as either an exchange or analysis standard.[87]	High

Standard for Exchange of Nonclinical Data (SEND)

Overview of the Standard

SEND, an expansion of the SDTM standard, is used for submission of data from non-clinical studies, focusing on data from animal toxicology studies, though it may be expanded to safety pharmacology studies. The intent of SEND, like that of similar standards, is to create a common organization scheme for data, increasing the accuracy of interpretation and decreasing the time required to evaluate the safety and efficacy of the product. Because SEND is based on the SDTM standard, data that arrives at the FDA is in tabulation format, requiring an additional analytics tool to extract the information into a format suitable for review.[88]

[85] (2010, October 27). *CDISC Standards for Dummies* [PDF document]. Retrieved from http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ONDLearningandCareerDevelopment/UCM234435.pdf
[86] Oliva, M.D, Armando. (n.d.). *Information and Data Modeling - Implications for CDER's Long-Term Information Management Strategy*.
[87] Ibid
[88] CDISC Standard for Exchange of Nonclinical Data Team. (2009, March 12). *CDISC Standard for Exchange of Nonclinical Data Implementation Guide (Version 3.0 Draft A)*. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/333019e937e4a85fcfb8574ea9aa24d7/misc/send_3.0_draft_a.pdf

Scope of the Standard in NDA/BLA Process

SEND standard is used by non-clinical reviewers during the non-clinical review portion of the NDA/BLA application review process.

Readiness

Table 26: Readiness of SEND

Readiness of SEND			
Current Version:	v. 3.0	**Release Date:**	May 19, 2011
Highlighted Features/Changes:	• V 3.0 was created as part of the Phase II FDA CDER pilot • Current implementation guide incorporates feedback from FDA		
Current Users:	FDA (CDER) – pilot participants only		
Standard Evolution:	• Standard development initiated in 2003 • FDA launched two pilots in 2003 and 2007 in CDER that produced implementation guides and early tools to support data analysis of the SEND format. [89] [90] • CDISC released for public review the updated SEND v3.0 Implementation Guide (IG) in December 2010 that incorporates findings from the pilot.[91] At the close of the review period in February 2011, CDISC will update and release the new, official CDISC production version. • CVM has launched a pilot; CDRH and CFSAN are examining their non-clinical data standards requirements. • CBER has not yet conducted a pilot but intends to implement in the future capitalizing on the lessons learned of other FDA Centers.		
Governing Body:	CDISC SEND Team		
Process for Changes:	• SEND is updated based on feedback and recommendations from FDA pilots as well as solicited public comments on production versions by domain experts. • The SEND Team reviews the comments and determines if they are relevant and within scope. • Revisions and additions are incorporated into the next release		
Relationship to Other Standards:	• Developed in conjunction with CDSIC SDTM Version 1.2		
Related Tools:	• ToxVision		

[89] (2010, November 4). *Standard for Exchange of Non-Clinical Data*. Retrieved from http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm155320.htm
[90] CDISC Standard for Exchange of Nonclinical Data Team. (2010, December 20). *CDISC Standard for Exchange of Nonclinical Data Implementation Guide (V3.0) - DRAFT FOR PUBLIC REVIEW*. Retrieved from http://www.cdisc.org/send
[91] Ibid

Completeness – Strengths and Limitations

Table 27: Strengths/Benefits and Limitations/Challenges for SEND Submissions

Strength Description	Impact
1. **Leverages currently accepted standards -** SEND utilizes the SDTM model which is a credible, FDA accepted and utilized format for both FDA CBER and CBER. The two FDA pilots and multiple Centers involved with SEND development indicate the perceived value of the CDISC standards and their compatibility with NDA/BLA review efforts[92].	High
2. **Fills gap in non-clinical data standards –** SEND offers a standard for nonclinical data an area which lacked recognized standards.	High

Limitation Description	Impact
1. **Requires development and use of analysis tools to be effective -** Because SEND relies on tabulation data, it requires the use of specially designed analysis tools to support efficient and effective review of nonclinical data	Low
2. **SAS XPT restrictions create reduce standard benefits -** SEND datasets are delivered in SAS transport files. Field and file size limitations and lack of an audit trail for changes can inhibit applicants and slow reviewers. It is unclear if the pending new release of SAS transport will remedy many of these issues.	Medium

Impact	Evaluation Criteria
Low	Strength or limitation affects very few individuals' ability to read, understand, analyze or process the data
Medium	Strength or limitation affects multiple individuals' ability to read, understand, analyze or process the data within a stakeholder group
High	Strength or limitation affects multiple stakeholders' ability to read, understand, analyze or process the data

Clinical Data Acquisition Standards Harmonization (CDASH)

Overview of the Standard

The Clinical Data Acquisition Standards Harmonization (CDASH) is a collaborative project supported by multiple international organizations and led by CDISC to develop a clinical data collection standard. The driver behind CDASH is differences and diversity in Case Report Forms (CRFs) around the world. The use of non-standard CRFs, in many cases, leads to differences in data collection and when clinical data standards were used, they were often inconsistently applied.

CDASH is a series of content standards including name, definition, and metadata for a basic set of global data collection fields on clinical trial CRFs.[93] CDASH provides recommended standards for data spanning 16 non-therapeutic specific domains (e.g., adverse events, demographic, etc.) for CRFs that map to SDTM domains for transfer of clinical data to regulatory agencies. Table 28 below lists the standardized domain areas CDASH encompasses that map to SDTM. By nature of its standardization, CDASH supports electronic data collection and electronic CRFs.

[92] (2010, February 1). *FDA CDER/CBER – CDISC Executive Committee Meeting* [PDF document]. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/d3c7e8b6690f991da920e7e60dee0568/misc/fda_cdiscmeeting1feb10summarybodfin.pdf

[93] Brownley, Clinton W. (n.d.) *BRIDGing CDASH to SAS: How Harmonizing Clinical Trial and Healthcare Standards May Impact SAS Users*. Retrieved from http://www.wuss.org/proceedings09/09WUSSProceedings/papers/cdi/CDI-Brownley.pdf

Table 28: Standardized CDASH Domains[94]

CDASH Domains
Adverse Events (AE)
Inclusion and Exclusion Criteria (IE)
Comments (CO)
Prior and Concomitant Medications (CM)
Demographics (DM)
Disposition (DS)
Drug Accountability (DA)
ECG Test Results (EG)
Exposure (EX)
Vital Signs (VS)
Laboratory Test Results (LB)
Medical History (MH)
Physical Examination (PE)
Protocol Deviations (DV)
Subject Characteristics (SC)
Substance Use (SU)

CDASH is intended for use by Clinical Investigators, Medical Monitors, Clinical Research Study Coordinators, Clinical Data Managers, Clinical Data and Statistical Programmers, Biostatisticians, Drug Safety, Case Report Form (CRF) designers and other functions involved with the design, collection or analysis of clinical trials. However, regulatory agency personnel benefit from use of the standard.[95] CDASH can increase sponsor accuracy in upfront data collection and consistent mapping to SDTM, which results in higher better quality data sets for regulatory reviewers.

Scope of the Standard in NDA/BLA Process

The CDASH standard is not used directly in the NDA/BLA review process. Instead, resulting SDTM data is leveraged by clinical pharmacology, clinical, and biostatistics reviewers to locate datasets that apply to their portion of the application review.

[94] CDISC CDASH Core and Domain Teams. (2008, October 1).*Clinical Data Acquisition Standards Harmonization (CDASH) V 1.0* [PDF document]. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/9b32bc345908ac4c31ce72b529a3d995/misc/cdash_std_1_0_2008_10_01.pdf
[95] Ibid

Readiness

The second version of the CDASH standard is still in development at this time.

Table 29: Readiness of CDASH

Readiness of CDASH			
Current Version:	v. 1.0	**Release Date:**	10/2008
Highlighted Features/Changes:	• This release represents the initial version of the standard.		
Current Users:	Selected Applicants		
Standard Evolution:	• Standard development initiated in 2008 and originated from the FDA Critical Path Opportunity List in 2006, Opportunity #45 Consensus on Standards for Case Report Forms (CRFs) explains that inconsistencies between CRFs can result in expensive inefficiencies and errors that slow the review process.[96] Additionally, most CRFs were submitted in paper format deterring FDA's PDUFA goal to transition to a fully electronic review. • The initial version represents consensus-based standards development process with comments from organizations in all of the ICH regions (US, Europe and Japan). • CDISC and domain teams are in the process of collecting feedback from CDASH users in order to create version 1.1.of the standard. • This updated version was due for release in the third quarter of 2010 but is not yet available.[97] • FDA is not presently piloting, or intending to pilot, this standard.		
Governing Body:	CDISC CDASH Core Team		
Process for Changes:	• CDASH is updated based on solicited comments and recommendations from domain experts on the current production or draft production version. • The CDASH Core Team reviews the comments and determines if they are relevant and within scope. • Revisions and additions are incorporated into the next release		
Relationship to Other Standards:	• Developed in conjunction with CDSIC SDTM • CDISC ODM		
Related Tools:	N/A		

[96] Food and Drug Administration. (2006, March). *Clinical Path Opportunities List*. Retrieved from http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathinitiative/CriticalPathOpportunitiesReports/UCM077258.pdf

[97] (n.d.). *CDASH*. Retrieved from http://www.cdisc.org/cdash

Completeness – Strengths and Limitations

Table 30: Strengths/Benefits and Limitations/Challenges for CDASH Submissions

Strength Description	Impact
1. **Leverages currently accepted standards -** CDASH is related to SDTM, which is a credible, FDA accepted and utilized data standard format for both FDA CBER and CBER.	High
2. **Standardizes data early in the study cycle–** CDASH is applied during the study start up and data collection therefore making it easier to have consistent, standardized data throughout the IND/NDA/BLA review process. This streamlines application development for applicants and potentially facilitates a more efficient application review. According to a PhRMA-Gartner-CDISC project, when standards are implemented in the study startup stage there can be a study cycle time reduction of up to 8.1 months and a per study cost savings of $9 million.[98]	High
3. **Permits centralized data storage and sharing –** CDASH standardization permits centralized data storage within a regulatory agency and, when extended, international permits global data sharing in a meaningful way.	High
4. **Eliminates duplicate clinical data entry –** Because CDASH requires a standard case report form, it minimizes the need for duplicate data entry. This, in turn, reduces inefficiencies and errors that originate from data manipulation.[99]	Medium
5. **Reduces research errors -** Researchers can use standard data elements in electronic health records to pre-populate case report forms which reduce the cost and likelihood of data entry errors.[100]	Low

Limitation Description	Impact
1. **Requires development and use of analysis tools to be effective -** Because SDTM relies on tabulation data, it requires the use of specially designed data processing tools to convert CDASH data to SDTM data in a timely way for review.	Low
2. **Does not automatically map to SDTM -** In order for CDASH data to be transferable applicants must be vigilant throughout the study process to ensure alignment with SDTM. For example, electronic data capture systems (EDCs) need to have supporting eCRFs that are aligned with SDTM domains.[101]	Medium
3. **Limited to non-therapeutic areas –** CDASH only standardizes non therapeutic specific domains which can create variation at the therapeutic level that generate inconsistencies in how therapeutic-specific data are collected across different sponsors and different studies	Medium

Impact	Evaluation Criteria
Low	Strength or limitation affects very few individuals' ability to read, understand, analyze or process the data
Medium	Strength or limitation affects multiple individuals' ability to read, understand, analyze or process the data within a stakeholder group
High	Strength or limitation affects multiple stakeholders' ability to read, understand, analyze or process the data

[98] Kush, Rebecca Daniels et al. (2006, September). *Business Case for CDISC Standards: Summary PhRMA-Gartner-CDISC Project* [PDF document]. Retrieved from: http://www.cdisc.org/stuff/contentmgr/files/0/ff2953ea8dbc8e81080f0e44ba6714c7/misc/businesscasesummarywebmar09.pdf
[99] Brownley, Clinton W. (n.d.) *BRIDGing CDASH to SAS: How Harmonizing Clinical Trial and Healthcare Standards May Impact SAS Users*. Retrieved from http://www.wuss.org/proceedings09/09WUSSProceedings/papers/cdi/CDI-Brownley.pdf
[100] Ibid.
[101] De Bondt, Joris. (n.d.)*CDASH: The Rising Star*. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/023f7975ace4051a1777d42df7e53343/misc/cdash_the_rising_star.pdf

Analysis Data Model (ADaM)

Overview of the Standard

The Analysis Data Model (ADaM) was developed by CDISC. It is a set of data variable guidelines and examples for analysis datasets (AD) used to generate statistical results. ADs are generated as part of clinical trials and summaries of these datasets are used to generate efficacy and safety data that is used as part of the review process. There are various types of ADs depending on the intent of the applicant, for example an outcome measure or a detailed analysis of a subset of the population. As a result, AD consistency, clarity, and link to sources data are critical but difficult to achieve without standardization. Standardization of the ADaM model permits review of analyzed data and allows for replication of analyses, tables, and graphics with significantly less effort. [102] It also generates a clear linage of the data from collection to results.

ADaM integrates into one of the data classifications supported by eCTD. The eCTD application submission format permits submission of four data classifications:

- data tabulations
- data listings
- analysis data sets
- subject profiles

SDTM standardizes study tabulation while ADaM standardizes data derivation and analysis. SDTM is not designed to support complex statistical analysis or such activities as analysis windows, complicated algorithms, and imputation of missing values. However, ADaM uses SDTM controlled vocabulary and adds the attributes, variables, and data structures needed for statistical analysis.[103] ADaM datasets and accompanying metadata (information describing the data) incorporate derived and collected data from various SDTM domains and/or other ADaM datasets into one dataset that can be easily analyzed.[104]

Due to the interconnection of SDTM domains and ADaM model analysis datasets, there are multiple methods for the development of ADs including parallel generation of the analysis and tabulation datasets, sequential generation, or a hybrid method.[105] Results of the 2006 CDISC SDTM/ADaM Pilot Project with the FDA revealed that reviewers determined that the most effective approach to developing the analysis datasets was to use STDM domains as inputs into ADaM datasets to ensure a strong and clear link to the data source.[106]

[102] CDISC Analysis Data Model Team. (2009, December 17). *CDISC Analysis Data Model Version 2.1* [PDF document]. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/854651256c2654c94b03e6da1be6e145/download/analysis_data_model_v2.1.pdf
[103] Kenny, Susan J. and Michael A. Litzsinger. (n.d.). *Strategies for Implementing SDTM and ADaM Standards* [PDF document]. Retrieved from http://www.pharmasug.org/2005/FC03.pdf
[104] CDISC Analysis Data Model Team. (2009, December 17). *CDISC Analysis Data Model Version 2.1* [PDF document]. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/854651256c2654c94b03e6da1be6e145/download/analysis_data_model_v2.1.pdf
[105] Kenny, Susan J. and Michael A. Litzsinger. (n.d.). *Strategies for Implementing SDTM and ADaM Standards* [PDF document]. Retrieved from http://www.pharmasug.org/2005/FC03.pdf
[106] (2009, January 31). *CDISC SDTM/ADaM Pilot Project* [PDF Document]. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/df91a087c6df43275288267c9fe92180/misc/sdtmadampilotprojectreport.pdf

Additionally, ADaM requirements support reviewers in conducting a credible and efficient review.[107]

1. **ADaM datasets, variables and metadata must be traceable-**-When combined properly with SDTM domains, ADaM allows reviewers to be able to trace analysis variables and the individual data points that make up the dataset back to their origins more quickly and easily. Traceability increases further when combined with the use of the CDASH standard. Applicants must also provide the method used to create derived or imputed data and information used for analyses.

2. **ADaM data structures must be clear**—While a standardized data analysis framework is not required to create transparency, CDSIC provides two standardized data structures: subject-level analysis dataset (ADSL) and the Basic Data Structure (BDS). FDA CDER requires applicants to submit the ADSL dataset along with other supporting analysis datasets.

CDISC defined the required characteristics for the standard variables in the ADSL and BDS data structures. These are standard variables that are frequently needed in analysis datasets. The ADaM standard requires that their outlined variable names be used with a variable that contains listed content. It is expected that applicants will discuss potential analysis datasets and structures with reviewers in advance of submission to meet these requirements.

Scope of the Standard in NDA/BLA Process

The ADaM standard may be used by clinical reviewers and biostatisticians during the clinical review, the clinical and biostatistics review portion of the NDA/BLA application review process.

[107] CDISC Analysis Data Model Team. (2009, December 17). *Analysis* Data Model (ADaM) Implementation *Guide* [PDF Document]. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/854651256c2654c94b03e6da1be6e145/download/adam_implementation_guide_v1.0.pdf

Readiness

Table 31: Readiness of ADaM

Readiness of ADaM			
Current Version:	v. 2.1	**Release Date:**	2008
Highlighted Features/Changes:	• Incorporates the results of the CDER SDTM/ADaM pilot project		
Current Users:	FDA (CDER and CBER)		
Standard Evolution:	• Standard development initiated in 2004. Since inception, ADaM development has been encouraged and informed by FDA statistical and medical reviewers who participate in ADaM meetings as active participants in development and who have participated in CDISC-FDA pilots. • In 2005, ADaM v0.7 was released for comment. • In 2006 CDISC conducted a SDTM/ADaM Pilot Project with the FDA (CDER) and Industry. The objective of the pilot was to examine how well CDISC-adherent datasets submissions and associated metadata, and structure met the needs and the expectations of both medical and statistical FDA reviewers. • In 2008 results of the pilot were incorporated into the new release version • In May 2010 CDER started accepting ADaM data sets. • In December 2010 CBER started accepting ADaM data sets		
Governing Body:	CDISC ADaM Team		
Process for Changes:	• Development and revisions to ADaM have been thus far been generated through participation of FDA statistical and medical reviewers in CDSIC meetings or pilot projects. • It is anticipated that future releases will be updated based on solicited comments and recommendations from domain experts on the current production or draft production version.		
Relationship to Other Standards:	• Developed in conjunction with CDSIC SDTM v 1.2		
Related Tools and References:	• SAS Transport • ADaM Implementation Guide • ADaM Validation Checks • FDA Study Data Specifications • CDER Analysis Data Request Document • CDER Data Standards Checklist		

Completeness – Strengths and Limitations

Table 32: Strengths/Benefits and Limitations/Challenges for ADaM Submissions

Strength Description	Impact
1. **Promotes a clear linkages between datasets –**ADaM generates linkages at two levels—analysis variable and data—which links analysis results, the analysis datasets, and the SDTM domains. This helps reviewers verify and confirm results are credible and viable.	High
2. **Leverages currently accepted standards –** When ADaM data is generated or derived from SDTM data and not legacy data sets it produces FDA accepted and utilized data standard format for both FDA CBER and CBER. When CDASH is harmonized with SDTM, ADaM datasets have even greater transparency.	High
3. **Allows applicant discretion in data and variable selection—**Applicants are provided the flexibility to submit the appropriate data and variables necessary to support their analysis as long as they adhere to the ADaM domains. CDISC and FDA encourage early meetings with regulatory reviewers to design the right submission.	Medium

Limitation Description	Impact
1. **Limited to one-way variables creation -** Variables that have been derived or imputed in ADaM datasets cannot be copied back into the SDTM source data as this introduces circular dependencies that may disassociate important relationships between variables.[108]	High
2. **Difficult to convert non-ADaM analysis data sets -** Converting analysis datasets not generated in ADaM into an ADaM format is quite timely and difficult. To confirm the accuracy it is necessary to repeat some statistical analyses. CBER reports that ADaM data created from legacy data sets is confusing and requires the submission of the original legacy data or for the applicant to resubmit their ADaM data using SDTM.	High
3. **Requires development and use additional analytics tools to be effective -** Because ADaM relies on tabulation data, it requires the use of specially designed analysis tools to generate production data for reviewers in a timely way.	Medium
4. **SAS XPT restrictions reduce standard benefits -** ADaM datasets are delivered in SAS XPT files. Field and file size limitations and lack of an audit trail for changes can inhibit applicants and slow reviewers. It is unclear if the pending new release of SAS XPT will remedy many of these issues.	Medium

Impact	Evaluation Criteria
Low	Strength or limitation affects very few individuals' ability to read, understand, analyze or process the data
Medium	Strength or limitation affects multiple individuals' ability to read, understand, analyze or process the data within a stakeholder group
High	Strength or limitation affects multiple stakeholders' ability to read, understand, analyze or process the data

Structured Product Labeling (SPL)

Overview of the Standard

The Structure Product Labeling (SPL) is a document markup standard that was developed by HL7 and is based on extensible markup language (XML). The standard specifies the structure and semantics of the package insert or content of labeling, which is the labeling required under 21 CFR 200.100(d)(3), including text, tables and figures, and provides important information about the drug or biologic. Applicants are required to submit the content of labeling in SPL format when submitting marketing applications, including NDAs, BLAs and supplements with labeling. Additionally, unless an applicant is granted a waiver, it must submit drug establishment registration and drug listing information electronically in SPL format.[109] SPL allows for "both the human readability of the content and facilitates machine processing of that content".[110] The machine readable portions of the SPL document include drug listing data elements and clinical data elements. Table 33 below outlines the coded information included in each of the elements.

[108] CDISC Data Analysis Team. (2009, December 17). CDISC Analysis Data Model Version 2.1. Retrieved from http://www.cdisc.org/stuff/contentmgr/files/0/854651256c2654c94b03e6da1be6e145/download/analysis_data_model_v2.1.pdf
[109] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2005, April). *Guidance for Industry Providing Regulatory Submissions in Electronic Format — Drug Establishment Registration and Drug Listing* [PDF document]. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072331.pdf
[110] HL7. (2010, May 31). *Product SPL – HL7Wiki*. Retrieved from http://wiki.hl7.org/index.php?title=Product_SPL

Table 33: Drug Listing and Clinical Data Elements for SPL Documents[111]

Drug Listing Data Elements	Clinical Data Elements
Product and Generic Names	Indications and Use
Ingredients and Strengths	Contraindications
Dosage Forms	Drug Interactions
Routes of Administration	Warning
Appearance	Precautions
DEA Schedule	Use in Special Populations
Packaging Quantity and Type	

Scope of the Standard in NDA/BLA Process

The SPL standard is required for submission of the content of labeling (i.e., package insert) and the drug establishment registration and drug listing information for marketing applications and supplements. FDA recommends that applicants submit the required content of labeling through the drug establishment registration and drug listing system since it may be duplicative of the labeling required for the listing information. The applicant can then reference the SPL labeling file for the content of labeling requirement.[112] FDA review staff converts the SPL version of the package insert into a PDF version for review of the labeling. When an application or supplement is approved, the action letter includes the final version of the package insert and requests the sponsor to submit a final SPL version as a post-approval submission. FDA staff review the final SPL version and compare to the package insert included in the action letter to ensure consistency. The final SPL is automatically uploaded to the National Library of Medicine website.

Readiness

Table 34: Readiness of SPL

Readiness of SPL			
Current Version:	Release 4	**Release Date:**	3/23/2009
Highlighted Features/Changes:	• Clarified proprietary and nonproprietary names • Changed Drug Listing data elements to Product data elements • Added terminologies for FDA tracking system, Code of Federal Regulations, SPL image[113]		
Current Users:	CDER (implemented October 31, 2005) and CBER (implemented October 15, 2008) Review Staff		
Standard Evolution:	• The SPL Working Group was formed in January 2004 • **Release 1:** Designated as ANSI/HL7 SPL, R1-2004 and approved 8/17/2004 • **Release 2:** Designated as ANSI/HL7 V3 SPL, R2-2005 and approved 5/23/05 • **Release 3:** Designated as ANSI/HL7 V3 SPL, R3-2007 and approved 6/1/07 • **Release 4:** Designated as ANSI/HL7 V3 SPL, R4-2009 and approved 3/23/09[114]		
Governing Body:	HL7 SPL Team		

[111] HL7. (2010, May 31). *Product SPL – HL7Wiki*. Retrieved from http://wiki.hl7.org/index.php?title=Product_SPL
[112] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2005, April). *Guidance for Industry Providing Regulatory Submissions in Electronic Format — Drug Establishment Registration and Drug Listing* [PDF document]. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072331.pdf
[113] HL7 RCRIM Working Group. (2009, April). *HL7 Version 3 Implementation Guide: Structured Product Labeling, Release 4* [PDF Document]. Retrieved from http://www.hl7.org/documentcenter/private/standards/SPL/V3_IG_SPL_R4_2009.pdf
[114] HL7. (n.d.). *ANSI Approved Standards*. Retrieved from http://www.hl7.org/implement/standards/ansiapproved.cfm

Readiness of SPL	
Process for Changes:	SPL follows a structured process for updates including, requirement gathering, specification design, testing and balloting.
Relationship to Other Standards:	HL7 version 3 Reference Information Model
Related Tools:	Electronic Drug Establishment Registration and Drug Listing System (eLIST)

Completeness – Strengths and Limitations

Table 35: Strengths/Benefits and Limitations/Challenges for SPL Submissions

Strength Description	Impact
1. **Improved information exchange** – SPL allows information exchange to occur between computer systems which provide opportunities for additional functionality not realized with other formats (e.g., PDF).[115]	High
2. **Labeling revision efficiency** – When an applicant needs to revise the labeling for a drug or biologic, it can submit only those sections that need revision. Additionally, comparisons of the revised label to the original label can be automated.[116]	High
3. **Data efficiency –** Content of labeling and product data elements for listing included in a single document	High
4. **Improved dissemination of product labeling** – SPL provides the ability to efficiently upload updated labeling information and potentially improve risk management of products[117]	High

Limitation Description	Impact
1. **Limited search functionality for related terms -** When searching the content of labeling, certain related terms will not be displayed when conducting a search (e.g., hepatotoxicity and liver toxicity)[118]. However, FDA is in the process of implementing indexing elements to mitigate this limitation.	Medium

Impact	Evaluation Criteria
Low	Strength or limitation affects very few individuals' ability to read, understand, analyze or process the data
Medium	Strength or limitation affects multiple individuals' ability to read, understand, analyze or process the data within a stakeholder group
High	Strength or limitation affects multiple stakeholders' ability to read, understand, analyze or process the data

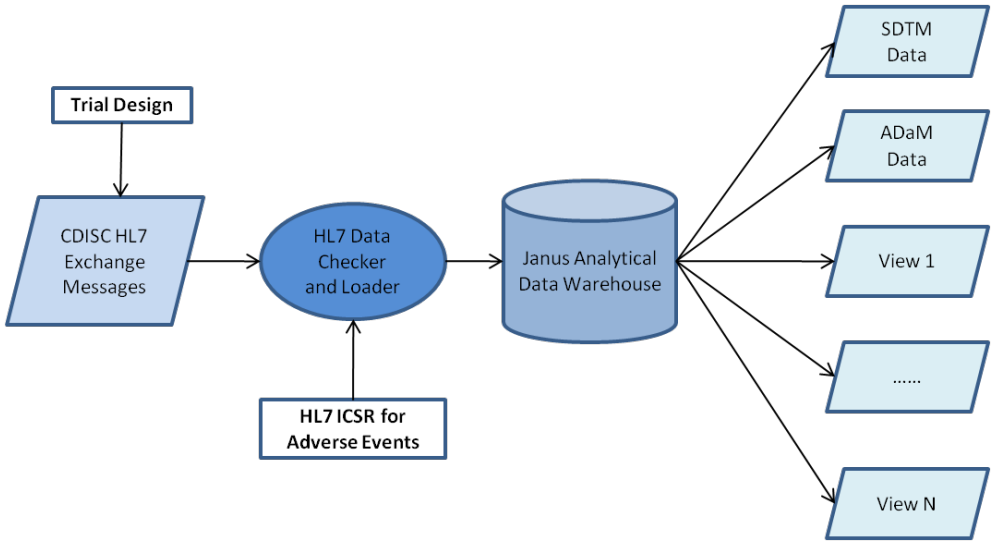
[115] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2005, April). *Guidance for Industry Providing Regulatory Submissions in Electronic Format — Content of Labeling* [PDF document]. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072331.pdf
[116] Ibid
[117] HL7. (2010, May 31). *Product SPL – HL7Wiki*. Retrieved from http://wiki.hl7.org/index.php?title=Product_SPL
[118] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2008, June). *Guidance for Industry Indexing Structured Product Labeling* [PDF document]. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072317.pdf

CDISC-HL7

Overview of the Standard

The purpose of the CDISC-HL7 study data standard is to exchange data between researchers and FDA. "CDISC-HL7 is a joint CDISC-FDA-sponsored project within HL7 to harmonize CDISC study data standards with HL7 version 3 XML exchange standard for healthcare information." [119] CDISC-HL7 leverages the Health Level Seven (HL7) Reference Information Model (RIM) to support meaningful information representation and exchange between systems in use by clinical researchers, FDA (Janus data warehouse) and health care providers (electronic health record systems). The use of the HL7 XML will result in a more "multi-dimensional" or "multi-relational" representation of clinical data rather than the flat files associated with SAS XPT.[120] The human and animal study data contained in the new structure will include all CDISC content (e.g., SDTM, ADaM, etc.) where appropriate and stored in the Janus data warehouse, a repository, which allows users to generate views for analysis with different end-user tools. Exhibit 68 below offers a view of the proposed, future FDA data submission process using CDISC-HL7.

Exhibit 68: FDA Proposed Goal for Regulatory Submissions Using CDISC-HL7[121]



There are currently three draft messages the HL7 has developed as part of the project—study design, study participation, and subject data. A fourth message leverages the existing mature HL7 Individual Case Safety Report (ICSR) data standard for adverse event information. Table 36 below discusses these messages and their corresponding reference standards.

[119] Oliva, Armando, M.D. and Mitra Rocha, Ph.D. (n.d.). *The CDISC-HL7 Project: What is it? How Does it Affect CDER?*
[120] Ibid
[121] Oliva, Armando, M.D. (n.d.). *CDISC HL7 Project FDA Perspective*. Retrieved from http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM155318.pdf

Table 36: CDISC-HL7 Messages[122]

CDISC HL7 Exchange Messages		
Message	**Definition**	**Reference Standard**
Study Design	What is going to be done?	• CDISC SDTM/CDASH • HL7 Clinical Statement CMET • Clinical Trial Enrollment • HL7 SPL • define.xml
Study Participation	Who is involved in the conduct of the study?	• CT Lab • Clinical Trial Enrollment define.xml
Subject Data	What was observed during the study?	• CDISC SDTM • ADaM • Clinical Statement CMET • ICSR • SPL • define.xml
ICSR	Study AE Reports	• SPL

Initial requirements of the standard were gathered using the BRIDG model and additional developed standard requirements will be harmonized back into the BRIDG model.

Scope of the Standard in NDA/BLA Process

CDISC HL7 standard may be used by FDA data managers to facilitate validation and loading of study data into the Janus data warehouse. Clinical reviewers and biostatisticians will benefit from the availability of highly predictable (i.e. low variability) SDTM, ADaM and other views of the data during their review.

Readiness

Table 37: Readiness of CDISC-HL7

Readiness of CDISC-HL7	
Current Version:	Draft Standard for Trial Use (DSTU). **Release Date:** September 2009
Highlighted Features/Changes:	• Three exchange messages: Study Design, Study Participation, and Subject Data
Current Users:	Currently in Development
Standard Evolution:[123]	• Fall 2007 – CDISC-HL7 Project launched in HL7 • Fall 2009 – CDISC-HL7 passed HL7 ballot as Draft Standards for Trial Use (DSTU) – Currently available for testing and early adoption • October 2010 – Study Participation Implementation Guide informative ballot • Jan 2011 – Study Design Implementation Guide informative ballot and Subject Data harmonize with CDA R3 (Clinical Document Architecture) • 2010-2012 – Testing Planned
Governing Body:	HL7; CDISC; FDA
Process for Changes:	Release version of standard is not yet available and is presently under review through DSTU. Changes and additions are approved through balloting process
Relationship to Other Standards:	Leverages several CDISC and HL7 Standards (see Table 19 for complete list)
Related Tools:	• Janus/CTR data warehouse (in development)

[122] Oliva, Armando, M.D. (n.d.). *CDISC HL7 Project FDA Perspective*. Retrieved from http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM155318.pdf
[123] Oliva, Armando, M.D. and Mitra Rocha, Ph.D. (n.d.). *The CDISC-HL7 Project: What is it? How Does it Affect CDER?*

Completeness – Strengths and Limitations

Table 38: Strengths/Benefits and Limitations/Challenges for CDISC-HL7 Submissions

Strength Description	Impact
1. **Based on a well-structured information model—**HL7 is an ANSI accredited, open, consensus based Standards Development Organization and the RIM model on which CDISC HL7 is based is widely used and respected in the healthcare industry**.**	High
2. **Able to support more analyses of interest—**The extraction of standardize data from a central warehouse creates more flexibility and a greater depth of data analysis. Reviewers will benefit from more predictable (less variable) SDTM and ADaM views and the ability to generate other analysis views of interest.	High
3. **Promotes Long term interoperability with electronic heath record systems** – Integrates across the lifecycle permitting communication and semantic interoperability between researchers, regulatory agencies and sponsors	High
4. **Supports harmonization with other HL7 standards at FDA –** This includes RPS, SPL, ISCR. The use of the BRIDG model ensures continued harmonization as the standard develops.	Medium

Limitation Description	Impact
1. **More complex to implement**—Unlike content data standards currently in use, CDISC HL7 requires the harmonization and interoperability of many standards. To operationalize the standard, development of a data warehouse and data viewer is necessary.	High
2. **High transition costs—** In addition to the associated costs of the necessary IT infrastructure development, switching costs for data managers to adopt new processes and learn new tools to process CDISC-HL7 data will be incurred	Medium

Impact	Evaluation Criteria
Low	Strength or limitation affects very few individuals' ability to read, understand, analyze or process the data
Medium	Strength or limitation affects multiple individuals' ability to read, understand, analyze or process the data within a stakeholder group
High	Strength or limitation affects multiple stakeholders' ability to read, understand, analyze or process the data

APPENDIX F: DETAILED ELECTRONIC REVIEW TOOL AND TRAINING ANALYSIS

This section contains details about the 21 tools profiled in this report. As previously mentioned, there are two types of tools featured in this review, process tools and analytical tools, which are defined below.

- Process Tools—Tools that store, organize, track electronic NDA/BLA application materials and status of review activities. These tools allow reviewers to access and view application contents throughout the review lifecycle.

- Analytical Tools—Tools that support application data review, manipulation, analysis and reporting. Different analytical tools may be used at different phases of the review lifecycle, particularly the sub-steps of the “conduct review” phase.

The first three tools are process tools and FDA tailored systems related to NDA/BLA submissions, while the remainders are analytical tools. The analytical tools are typically commercial off-the-shelf products and include clinical trial design and review tools as well as statistics and graphics software.

For each profiled tool we offer an overview of the tool including the current version, a brief description, impact on the review process, data inputs and outputs, relationship to other tools, a summary of strengths and limitations (if available), and a list of available training options. Where a formal, corresponding training course exists, a summary of the curriculum and evaluation also follows within the section.

GS Review

Global Submit (GS) Review, a commercially available tool, is the software tool used to view electronically submitted eCTD documents from applicants at FDA. FDA worked with Global Submit to tailor this viewer to the needs of a FDA reviewer.

Current Version:	• Version 4.1.0
FDA Users:	• Review and Support Staff
Brief Description:	• Viewing application for the review of submissions in eCTD format that offers among its features advanced dossier lifecycle management, online reviewing capabilities, and easier navigation of the submission
Impact on Review Process:	• Review staff utilizes GS Review to open and view eCTD submissions for NDA and BLA applications from sponsors.
Relationship to Other Tools:	• GS Reviews launches from DARRTS and RMS-BLA when the user requests access to an eCTD submission.
Data Standards Utilized:	• eCTD
Training Offered:	• GS Review Hands-on Training (CDER and CBER) • eCTD Walk-In Clinic: Understanding the eCTD and Global Submit Review Software (CDER and CBER)
Tool Strengths	• Minimal Training Required – Users with basic computer skills are able to use the software with minimal training • Compatibility – GS Review is compatible with all software that produces eCTD compliant submissions
Tool Limitations	• Navigation and Manipulation – New reviewers and reviewers with little electronic submission experience may initially find the user interface challenging when navigating through an application. Additionally, while reviewers can annotate sections they are unable to save certain changes (e.g., highlight) to an application when viewing it within the tool. Reviewers are also unable to save specific sections of an application to their desktop without losing the links to other sections unless the reviewer copies all linked sections. • Review Progress – Reviewers are unable to determine which sections of an application they have reviewed and must track this information on their own.

The eSubmission Team offers multiple training options to introduce and support users with the eCTD and GS Review software. These range from high-level overviews both in new reviewer training to tactical hands on sessions designed to help users experience the features and process of using the system. In addition to the formal courses listed below, the team also provides one-on-one support to individuals and divisions as needed. Additional support materials include the GS Review operations manual.

The primary classroom-based training options are described below:

GS Review Hands-On Training

Course Details	**Format:** Classroom (Computer Lab) **Review Process Steps Impacted:** All Review Steps **Intended Audience:** Discipline Reviewers; RPMs, Project Managers **Sponsoring Office:** CDER and CBER **Frequency:** Monthly **Point of Contact:** Valerie Gooding
Training Objectives	• Introduce key features required for conducting an electronic review • Highlight time-saving features • Increase comfort level with tool navigation • Offer a tactical experience to facilitate learning
Course Description	The goal of this three-hour session is to teach new reviewers how to use the software to conduct reviews and can be used as a "refresher" for more experienced reviewers. The session covers the following system aspects and functionality: • Launch GS Review via Network and DARRTS • Identifying the 4 Panes and their functionalities (Navigation, Details, Preview and Sequence View) • Locating submissions using 4 different views (Sequence, Current, Lifecycle and Submission Type) • Viewing a document's lifecycle (Replace, Append, Withdrawn and Current files) • Use of the Inventory tab • Sorting files based on name, type, status, date, etc., • Printing a document or batch documents (print queue tab) • Use of the Review flag • Emailing a document link from GS Review • Searching the entire application using GS Review and Adobe Acrobat • Saving a document or downloading batch documents (download queue) • Creating annotations • Organizing folders/documents using "filter" and "favorite" functions
Training Effectiveness	• Participants complete evaluation forms • Since the launch of the course two years ago, the feedback received through both the evaluations and anecdotally has been incredibly positive. • Reviewer focus groups confirmed that navigation instructions and time saving features such as bookmarks are very valuable.

eCTD Walk-In Clinic: Understanding the eCTD and Global Submit Software

Course Details	**Format:** Classroom (Computer Lab) **Review Process Steps Impacted:** All Review Steps **Intended Audience:** Discipline Reviewers and Project Managers **Sponsoring Office:** CDER and CBER **Frequency:** Monthly **Point of Contact:** Valerie Gooding/Jared Lantzy
Training Objectives	• Introduce eCTD and GS Review • Learn how to open and view an eCTD submission • Provide reference materials • Answer participant questions
Course Description	The goal of the session is a high-level overview of eCTD and GS Review and answer participant questions around these areas. The session includes a brief overview of the eCTD and a demonstration of the most critical features of GS Review. Participants are given copies of the presentation and other reference materials for day-to-day use. The topics in this session include: • Accessing an eCTD submission, • Specifying view settings to suit your preference, • Searching printing, downloading and filtering submissions • Responding to specific participant questions
Training Evaluation	• Since the launch of the course, feedback received has been positive.

DARRTS

The Document Archiving, Reporting and Regulatory Tracking System (DARRTS) is a custom built solution for the FDA CDER. The goal of DARRTS is to provide users with a fully integrated system combining tracking of incoming submissions, outgoing communications and document generation for all Investigational New Drug Applications, New Drug Applications, Abbreviated New Drug Applications, and Biologicals License Applications. DARRTS is a web-based system providing flexible capabilities that meet CDER's current business processes as determined by legal and regulatory requirements.[124]

[124] Prescription Drug User Fee Act (PDUFA) IV Drug Safety Five-Year Plan 2008-2012, 2009 Update of Activities, June 2010.

Current Version:	• Release 3.1.4
FDA Users:	• Review and support staff
Brief Description:	• Fully electronic workflow tracking and information management system to receive, log, track, assign, process, and manage official submissions with internal and external stakeholders.
Impact on Review Process:	• Manages the regulatory process through tracking of INDs, NDAs and supplements • DARRTS tracks - Supporting documentation (Sponsor submissions, Safety issues) - Reviewer assignments - Work plans - Goals - Status - Reviews - Outgoing correspondence - Postmarketing Requirements/Commitments • Meetings
Relationship to Other Tools:	• Users can launch GS Review from within DARRTS for eCTD submissions
Data Standards Utilized:	• Not Applicable
Training Offered:	• Classroom Training (CDER) - DARRTS Training for New Users - DARRTS Advanced RPM Training for RPMs • Walk-in Sessions (CDER) - DARRTS Add Function Training - DARRTS Check-In: Focus on Linking Rules - DARRTS Consult Review Training - DARRTS Mass Assignments Training - DARRTS Meeting Training - DARRTS Search Training - DARRTS TSI Policy & Check-In Procedure • Online Training (CDER) - Managing Review Teams in DARRTS - Managing Assignments in DARRTS - Create a Tracked Safety Issue in DARRTS - One-on-one Training (CDER)
Tool Strengths	• Document Tracking – DARRTS provides users with a way to track all formal and some informal documentation between sponsors and FDA (i.e., CDER, CBER (only INDs)). • Document Archive – DARRTS allows CDER and CBER to archive documentation related to the review of drugs and biologics. For internal and outgoing documents, users can access electronic versions of the documents. For incoming documents submitted electronically, users can view and copy the submissions.
Tool Limitations	• Limited Report Outputs – Users are unable to create reports utilizing all of the data available in DARRTS. The user must select from a list of pre-defined reports which may not contain all of the data they are trying to evaluate.

As DARRTS is a central part of the CDER IND and NDA review process, CDER OBI offers multiple courses designed for different experience levels and types of users. This includes classroom courses profiled below, targeting walk in sessions and several online, on-demand options (e.g., review team and assignment management). The walk-in sessions on specific topics include:

- Add Function Training
- Focus on Linking Rules
- Consult Review Training
- Mass Assignments Training

- DARRTS Meeting Training
- TSI Policy & Check-In Procedure

The CDER OBI team also offers support to answer questions, provides one-on-one or team and division training upon request. The DARRTS/OBI team has also assembled an extensive resource Center on inside.fda.gov which includes a help Center and supporting supplemental materials such as FAQs and "hot topics" documents.

DARRTS Training for New Users

Course Details	**Format:** Classroom **Review Process Steps Impacted:** All review steps **Intended Audience:** Reviewers; RPMs and Project Managers **Sponsoring Office:** CDER OBI **Frequency:** Monthly **Point of Contact:** Samantha Gordon
Training Description/ Objectives	This three-hour, instructor-led course provides an overview of the system and its basic feature. Course contents include: • Introduce major system features of DARRTS • Introduce basic DARRTS terminology and • Provide an overview of the system. • Demonstrate necessary, basic functions (i.e., log on, screen navigation, basic searches, reports) • Teach monitoring communications, including reviews, consult requests, consult reviews, meeting minutes.
Training Effectiveness	• TBD

DARRTS Advanced RPM Training for RPMs

Course Details	**Format:** Classroom **Review Process Steps Impacted:** All review steps **Intended Audience:** RPMs **Sponsoring Office:** CDER OBI **Frequency:** Monthly **Point of Contact:** Samantha Gordon
Training Description/ Objectives	DARRTS 3.1.2 introduces a new functionality role for Regulatory Project Managers (RPMs) called the Advanced RPM Role. All interested RPMs must complete training prior to being granted this role. Course contents include: • Update Submission Classification (Original Submission Only) • Maintain Submission Responsible Organization • Update Supplement Categories (Levels 1, 2, & 3) • Set Supplement Subtype FDA/Applicant
Training Effectiveness	• TBD

RMS-BLA

The Review Management System for Biological License Applications (RMS-BLA) supports CBER's managed review process for the review and approval of applications for biological derived drugs, blood products, and IVD Test Kits (the BLAs) that are regulated by CBER under 21 CFR parts 601 and 820, respectively . RMS-BLA is a custom developed application for FDA CBER.

Current Version:	• Release R5.6 CHDC PROD 2010.1
FDA Users:	• Review and support staff
Brief Description:	• System supports CBER's Managed Review Process for the review and approval of applications for biological derived drugs, blood products, and IVD Test Kits (the BLAs) that are regulated by CBER
Impact on Review Process:	RMS/BLA provides capabilities to users to: • Assign the following: - Submission Tracking Numbers (STNs) to all BLA Original Applications (OA) - Supplements (BLS) - Amendments - Product Correspondence (PC) - Annual Reports (AR) - Postmarketing Requirements/Commitments • Perform the following: - Enter, update and query essential data on submissions, applicants, products, facilities, communications, contacts and review committees - Establish and track review milestones - Record User Fee information - Track postmarketing requirements and commitments[125]
Relationship to Other Tools:	• Users can launch GS Review from within RMS-BLA for eCTD submissions
Data Standards Utilized:	• Not Applicable
Training Offered:	• Online Training (CBER) – A Tour of Major Screens and Fields of RMS-BLA – RMS-BLA: An Overview of RMS-BLA and the Systems that Support BLA Review
Tool Strengths	• To be collected through reviewer interviews and survey
Tool Limitations	• Separate Archiving System Required – Unlike DARRTS, users cannot access archived documents (e.g., incoming, outgoing). A separate system must be accessed in order to view archived documents.

Approximately 3 years ago, CBER reviewers indicated that they lacked sufficient time to attend classroom courses and would prefer online training. CBER responded by designing two, on-demand on-line courses for RMS-BLA partnership with GEOLearning, a Canadian-based firm. In addition to these two courses, CBER offers monthly brown bag sessions on CBER systems with topics determined by CBER reviewers. CBER also offers one-on-one consultations and support either in person or via telephone. Additional support materials include the RMS-BLA dictionary and the RMS-BLA operational threads document.

[125] Carter, Vicky. (n.d.). *What does RMS/BLA mean?* [PDF document]. Retrieved from http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Drugs/ProjectManagement/UCM232161.pdf

A Tour of the Main Screens and Fields of RMS-BLA

Course Details	**Format**: On-Line **Review Process Steps Impacted:** All review steps **Intended Audience:** Reviewers; RPMs and Project Managers **Sponsoring Office:** CBER **Frequency:** On Demand **Point of Contact:** Carla Vincent
Training Objectives	• Introduce major system screens including field definitions • Increase understanding the major operations and features in each screen, particularly required fields • Increase data input quality • Test knowledge retention
Training Description	The topics in this session are listed below and the course typically takes two hours to complete. CBER course designers also integrated interactive elements into the curriculum. After completing several screens of information, users are presented with interactive scenarios. • Explore the main RMS-BLA screens • Discover how to enter new submissions • Assign the review schedule • Manage the milestone and communication screens • Use the product information screen • Explore the facility information screen • Discover how to add manufacturing activities into a facility • Manage postmarketing requirements • Run reports and queries • Search for STNs
Training Effectiveness	• Formal and informal feedback on all RMS-BLA courses is limited. • CBER RIMS recently drafted a course evaluation form that was administered to a small set of participants; less than half completed the survey.

RMS-BLA: An Overview of RMS-BLA and the Systems that Support BLA Review

Course Details	**Format**: On-Line **Review Process Steps Impacted:** All review steps **Intended Audience:** Reviewers; RPMs and Project Managers **Sponsoring Office:** CBER **Frequency:** On Demand **Point of Contact:** Carla Vincent
Training Objectives	• Introduce the BLA review systems in the context of the process • Understand the interrelationship between systems and reporting • Increase data input quality • Test knowledge retention
Training Description	The topics in this session are listed below and the course typically takes two hours to complete. CBER course designers also integrated interactive elements into the curriculum. After completing several screens of information, users are presented with interactive scenarios. • Describe what a BLA is as well as its components and numbering schema • Discuss the review management process • Identify the purpose of CBER's core systems • Discuss how RMS-BLA and the systems associated with review management are used • Identify the types of submissions which require user fees and those which carry performance goals.
Training Effectiveness	• Formal and informal feedback on all RMS-BLA courses is limited. • CBER OPS recently drafted a course evaluation form that was administered to a small set of participants; less than half completed the survey.

JMP

JMP (pronounced “jump”), a commercially available tool, is statistical software that links statistics to interactive graphics, allowing the user to visualize and explore the data. FDA provides reviewers with the JMP application on their desktop.

Current Version:	• Version 7.0 (used at FDA)
FDA Users:	• Clinical, Biostatistics, Clinical Microbiology, Clinical Pharmacology, Safety, Product Quality and Non-clinical Reviewers
Brief Description:	• Statistical software package for non-SAS programmers used to review electronic data
Impact on Review Process:	• Provides clinical, biostatistics and clinical pharmacology reviewers the ability to analyze and manipulate safety and efficacy data critical for their review. JMP includes the following: - a spreadsheet for viewing, editing, entering and manipulating data - a broad range of graphical and statistical methods for data analysis - options to highlight and display subsets of the data - tools to sort and combine tables - a calculator for each table column to compute values - a facility for grouping data and performing subgroup analyses - tools for moving analysis results between applications and for printing[126]
Data Inputs	• Multiple dataset types (e.g., .jmp, SAS files (e.g., .sas, .xpt))
Data Outputs	• Adverse Events Data Analysis • Laboratory Data Analysis • Exposure Data Analysis • Efficacy Data Analysis
Relationship to Other Tools:	• SAS applications
Data Standards Utilized:	• SDTM, ADaM
Training Offered:	• FDA Office of Business Process Support training course (CDER) - JMP - JMP Clinics
Tool Strengths	• Data Flexibility – Can interpret standardized and non-standardized data
Tool Limitations	• To be collected through reviewer interviews and survey

CDER OBI offers a formal, classroom based two-part JMP course designed to teach reviewers how to use JMP to review electronic data. In addition, OBI offers additional topically-based clinics, examples of which are below:

- Clinic 1: Join Datasets
- Clinic 2: Calculate difference in LB test values between baseline and particular time point
- Clinic 3: Transform datasets to calculate difference between measurements
- Clinic 4: Convert format of date variables to calculate elapsed time
- Clinic 5: Identify LB Test Data outside NR limits and Create AE Counts table for these subjects
- Clinic 6: " Tables | Summary " tool
- Clinic 7: Basic Statistical tools and functions

[126] (n.d.). *Introduction to JMP – Version 6.0 (Includes Analysis of CDISC/SDTM Data)* [PDF Document]. Retrieved from http://inside.fda.gov:9003/downloads/CDER/OfficeofBusinessProcessSupport/UCM044520.pdf

JMP I, JMP II

Course Details	**Format**: Classroom **Review Process Steps Impacted:** Clinical Review **Intended Audience:** Clinical Reviewer; those Using CDISC datasets **Sponsoring Office:** CDER **Frequency:** Several Times Per Year **Point of Contact:** Scott Runyan
Training Description	The JMP course consists of two 3-hour sessions approximately one week apart. The course is taught in the computer lab with hands-on instruction using actual data submitted for review • Prior completion of the EDAT course (Electronic Data Analysis Training) and/or familiarity with electronic datasets is recommended • Learn how to use a variety of JMP functions to analyze electronic data • Basic functions of summary tables, graphs, statistical tests, and the formula calculator • Focus on adverse event, laboratory, exposure, and efficacy data
Training Effectiveness	• TBD

JMP Clinical

JMP Clinical, a commercially available tool, is statistical software that provides advanced data visualization and can create reports from SDTM data. FDA is evaluating the use of JMP Clinical by reviewers.

Current Version:	• Version 2.1 – Pilot testing at CDER and CBER
FDA Users:	• Clinical, Biostatistics, Clinical Microbiology, Clinical Pharmacology, Safety, Product Quality and Non-clinical Reviewers
Brief Description:	• JMP Clinical "links advanced statistics and graphics, enabling sophisticated analysis in a user-friendly environment. JMP Clinical creates reports from multiple types of datasets including SDTM and ADaM datasets which are Clinical Data Interchange Standards Consortium (CDSIC) data standards. This facilitates communication between clinicians and biostatisticians at the sponsor organization and, subsequently, between sponsors and FDA reviewers. Interactive graphs offer multiple views of patient profiles and reveal hidden patterns in drug-drug and drug-disease interactions."[127]
Impact on Review Process:	• Statistical software package for non-SAS programmers used to review electronic data
Data Inputs	• Multiple dataset types (e.g., JMP files (.jmp), SAS files (e.g., .sas, .xpt)
Data Outputs	• Adverse Events Analysis • Lab Analysis • Incidence Indicators Analysis • Patient Profiles Analysis
Relationship to Other Tools:	• Based on JMP
Data Standards Utilized:	• CDISC Standards (e.g., SDTM, ADaM)
Training Offered:	• None
Tool Strengths	• Individual Patient Profiles – Allows the user to display detailed information about a patient's adverse events, lab tests and concomitant medications • Window Management – Text and graphics can be displayed in the same window • Intelligent Scrolling – Titles for reports remain visible until the report is no longer displayed on the screen • Interactive Graphs and Plots – Users can select a point or a group of points
Tool Limitations	• Value for additional functionality only exists for SDTM formatted data

JReview

JReview, a web-enabled version of Integrated Review™ (iReview) developed by Integrated Clinical Systems, Inc., is a client/server data review tool that allows the user to access, review, report, graph and analyze data from clinical database management systems. JReview is commercially available and made available to FDA review staff on an internal website.

[127] SAS Institute Inc. (2010). *JMP® Clinical 2.1 – Product Brief* [PDF Document]. Retrieved from http://www.jmp.com/software/clinical/pdf/104419_jmpclinical_0410.pdf

Current Version:	• JReview – Version 9.1.4-1003
FDA Users:	• Biostatistics, Clinical, Clinical Microbiology and Clinical Pharmacology Reviewers
Brief Description:	• "JReview® is the web-enabled version of Integrated Review™ (iReview). It allows users to view, create, print, and interact with their Integrated Review™ objects locally on an Intranet or securely over the Internet. JReview® can be run in two different modes of operation (authoring and non-authoring) in addition to two modes of communication (clear-text and SSL)."[128] • "Integrated Review™ (iReview) is a fully integrated client/server data review tool. The product makes it easy to access, review, report, graph, and statistically analyze clinical data from clinical database management systems. Integrated Review™ supports ongoing monitoring of data quality and patient safety and may be used to explore data visually to identify trends."[129]
Impact on Review Process:	• FDA reviewers can use and JReview "to support ongoing monitoring of data quality and patient safety and to explore data visually to identify trends".[130]
Data Inputs	• SAS files (e.g., .xpt)
Data Outputs	The following reports can be generated: • Detail Data Listing - one report line for each patient observation • A Summary Listing - one report line containing summary information • Formatted Detail Data Listing - one report line for each patient observation with applied formatting • Formatted Summary Listing - one report line containing summary information with applied formatting • Patient Visit Data Report - patient results organized by patient ID and visit where multiple visit panels are easily joined and displayed per row
Relationship to Other Tools:	• User can register "in-house" SAS programs and run them in JReview environment[131]
Data Standards Utilized:	• CDISC Standards (i.e., SDTM, ADaM)
Training Offered:	• Web Based Training (CDER and CBER) • Online Clinic (CDER and CBER) • Classroom Training (CDER and CBER) - JReview Basic Reviewer Class - JReview Super User Class
Tool Strengths	• Data Flexibility – Can interpret standardized and non-standardized data • Patient profiles – The user can drill down to individual patient profiles
Tool Limitations	• Internet connectivity – The user must have access to an internet connection in order to use JReview

FDA offers two classroom sessions, several topic-specific online training, and clinic options (in person and online) for JReview. Classroom-based training offers instruction to new users as well as those with more advanced skills. Online, on-demand training options include the following topics:

[128] Integrated Clinical Systems, Inc. (2011). *Integrated Review™ (iReview)* [PDF Document]. Retrieved from http://www.i-review.com/index.php?option=com_content&task=view&id=26&Itemid=35
[129] Integrated Clinical Systems, Inc. (2011). *Integrated Review™ (iReview)* [PDF Document]. Retrieved from http://www.i-review.com/index.php?option=com_content&task=view&id=25&Itemid=34
[130] Integrated Clinical Systems, Inc. (2009). *Exploring Clinical Data using Integrated Review™ Version 9 – Core Concepts I* [PDF Document]. Retrieved from http://fdswa127/default.htm
[131] Integrated Clinical Systems, Inc. (2009). *JReview™ Super User Class* [PDF Document]. Retrieved from http://fdswa127/default.htm

- Patient Selection Criteria (PSC)
- Saving
- Selected Browsers (Data & Notes, Crosstabs, Graph, Patient Profile, Report, Risk Assessment)
- Output Filter
- Advanced Lessons

Additional reference materials include the User Manual v9.1.2 and the iReview Core Concepts Manual. The Computational Science Center (CSC) is presently developing a CDISC/JReview training course that will integrate the formal JReview training with an overview of CDSIC and two hour sessions on SDTM and ADaM datasets.

JReview Basic Reviewer Class

Course Details	**Format**: Classroom **Review Process Steps Impacted:** Clinical Review **Intended Audience:** Clinical Reviewer; Those Using CDISC datasets **Sponsoring Office:** CDER and CBER **Frequency:** Several Times Per Year **Point of Contact:** Scott Runyan and David Wanyoike
Training Description	This two-day introductory course is intended for those that are new to using J-Review or have a limited knowledge of the software, have a basic understanding of Clinical Trials and/or have a need to review clinical data. The course provides an overview of the following system features: • Data Browser • Notes Browser • Selecting Patients • Saving and Opening Objects • Report Browser –Detail Reports, Summary Report and Patient Visit Data Reports • Filters • New Items and Pivot Panels • Crosstab Browser • Graph Browser • Patient Profile Browser • Practical Scenario Exercises
Training Effectiveness	• TBD

JReview Super User Class

Course Details	**Format**: Classroom **Review Process Steps Impacted:** Clinical Review **Intended Audience:** Clinical Reviewer; Those Using CDISC datasets **Sponsoring Office:** CDER and CBER **Frequency:** Several Times Per Year **Point of Contact:** Scott Runyan and David Wanyoike
Training Description	This one-day course is intended for those that have taken the Basic Training Courses, have a basic understanding of SQL, and will be responsible for creating more advanced objects within JReview. The course provides an overview of the following advanced system features: • JR Special Functions(New Item, Join Logic, Custom Join Logic for Specific Objects, ImportSQL, Define Pivot Panel, New Range) • Prompting Output Filters • Graphical Patient Profile Templates • Exercises to reinforce above
Training Effectiveness	• TBD

WebSDM/Empirica Study

WebSDM, a commercially available tool, provides validation for SDTM formatted study data. The application, developed under a Cooperative Research and Development Agreement with the FDA, ensures that files conform to the SDTM data standard. Additionally, Empirica Study, built upon the WebSDM electronic data submission platform, provides screening for safety issues in clinical trial data.

Current Version:	• Release 3.0
FDA Users:	• Biostatistics, Clinical Pharmacology, Safety and Clinical Reviewers
Brief Description:	• "WebSDM allows users to load SDTM-format study data, check and correct errors and inconsistencies, and browse data in a variety of tabular and graphical formats. Users may browse studies one-at-a-time or perform pooling of data across studies for combined analysis."[132] • "The Empirica Study system integrates data from clinical trials into a CDISC SDTM-compliant data repository and performs automated screening for potential safety issues."[133] The "tool provides an effective means for detecting potential safety problems early in the pre-marketing clinical trial stage."[134]

[132] Phase Forward – Oracle Corporation. (n.d.). *Applied Data Standards – WebSDM – Phase Forward.* Retrieved from http://www.phaseforward.com/products/clinical/ads/
[133] Phase Forward – Oracle Corporation. (n.d.). *Clinical Trials Signal Detection (CTSD) – Electronic Submission Platform – Phase Forward.* Retrieved from http://www.phaseforward.com/products/safety/study/default.aspx
[134] Ibid

Impact on Review Process:	• Provides analyses and graphical representations of data for a more robust safety analysis when conducting an application review • "Web-based, intuitive visual interface improves visibility of safety data • Rapidly navigate from aggregate displays to individual patient profiles • Supports detailed review of adverse events, clinically significant lab results, ECGs and vital signs data • Powerful signal detection techniques • Automated screening based on disproportionality analysis • Availability of exposure data provides denominators • Simple 2x2 table statistics • Subgroup by age, gender, race, medical history or concomitant medications • Allows evaluation of potential safety signals for adverse events or clinically significant lab, ECG or vital signs associated with study treatment • Sector map graphical display facilitates data interpretation"[135]
Data Inputs	• SAS files (e.g., .sas, .xpt) • Define.XML
Data Outputs	• Clinically Significant Lab Analysis • Clinically Significant Vitals Analysis • Hy's Law Analysis • Lab Change from Baseline Analysis • MedDRA HLGT, HLT, PT and SOC Analyses • QT Interval Prolongation Analysis • Subject Disposition Analysis • Vitals Change from Baseline Analysis • Subgroup Analysis (e.g., sex, race, age, medical history, concomitant medications, indication (for a study pool only))
Relationship to Other Tools:	• None
Data Standards Utilized:	• SDTM
Training Offered:	• WebSDM 3.0 Training Slides available on FDA intranet
Tool Strengths	• To be collected through reviewer interviews and survey
Tool Limitations	• Cannot load or validate data that does not have a valid define.xml file • SDTM only – Can only interpret SDTM data

SAS

SAS, commercially available software developed by the SAS Institute Inc., provides users with an integrated system of software products to perform statistical analysis. The software allows FDA reviewers to perform in-depth analysis and generate visuals for applications reviews and presentations.

[135] Phase Forward – Lincoln Safety Group. (n.d.). *Safety Review using WebSDM / Empirica™ Study.* Retrieved from http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm053180.htm

Current Version:	• Base SAS 9.2 • SAS/STAT 9.22 • SAS/GRAPH 9.21 • SAS/IML 9.22 • SAS System Viewer 9.1 (SAS Universal Viewer for SAS 9.2)
FDA Users:	• Biostatistics, Clinical, Clinical Microbiology, Clinical Pharmacology, Safety, Product Quality, Non-clinical Reviewers and Support Staff
Brief Description:	• Base SAS: "Provides a scalable, integrated software environment specially designed for data access, transformation and reporting. It includes a fourth-generation programming language; ready-to-use programs for data manipulation, information storage and retrieval, descriptive statistics and report writing; and a powerful macro facility that reduces programming time"[136] • SAS/STAT: "From traditional statistical analysis of variance and predictive modeling to exact methods and statistical visualization techniques, SAS/STAT software is designed for both specialized and enterprise wide analytical needs. SAS/STAT software provides a complete, comprehensive set of tools that can meet the data analysis needs of the entire organization."[137] • SAS/GRAPH: "SAS/GRAPH software delivers high-impact visuals, enabling decision makers to gain a quick understanding of critical business issues. The solution meets the needs of both business analysts and IT managers by creating highly customizable, presentation-style visuals, regardless of information location, computing platform or format of the results."[138] • SAS/IML: "SAS/IML software provides a powerful and flexible matrix programming language in a dynamic environment for programmers, statisticians, researchers and high-end analysts. The SAS/IML Studio interface provides interactive programming and exploratory data analysis. Simple syntax makes it easy to translate mathematical formulas into SAS program statements. In addition, users can submit R code within SAS, enabling experimentation with new methods."[139] • SAS System Viewer: "In the FDA's general guidance for electronic submissions, the SAS System Viewer is listed as one of the tools used by the agency to view SAS XPORT transport files and SAS data sets directly. The Viewer allows a user to view files without invoking the SAS System or having any other SAS System software installed."[140]
Impact on Review Process:	• SAS software allows discipline reviewers to perform in-depth statistical analyses and view the data graphically to identify trends and inconsistencies when conducting an application review. Additionally, the SAS System Viewer allows support staff to access and view the data.
Data Inputs	• SAS files (e.g., .sas, .xpt)

[136] SAS Institute, Inc. (n.d.). *Base SAS® Software*. Retrieved from http://www.sas.com/technologies/bi/appdev/base/
[137] SAS Institute, Inc. (n.d.). *Statistical Analysis with SAS/STAT® Software*. Retrieved from http://www.sas.com/technologies/analytics/statistics/stat/index.html
[138] SAS Institute, Inc. (n.d.). *SAS/GRAPH® Software*. Retrieved from http://www.sas.com/technologies/bi/query_reporting/graph/index.html
[139] SAS Institute, Inc. (n.d.). *SAS/IML®*. Retrieved from http://www.sas.com/technologies/analytics/statistics/iml/index.html
[140] SAS Institute, Inc. (n.d.). *SAS System Viewer Included in FDA Guidance Recommendations*. Retrieved from http://www.sas.com/industry/government/fda/fdaviewer.html

Data Outputs	Multiple analyses including: - Analysis of variance - Mixed models - Regression - Categorical data analysis - Bayesian analysis - Multivariate analysis - Survival analysis - Psychometric analysis - Cluster analysis - Nonparametric analysis - Survey data analysis - Multiple imputation for missing values - Study planning
Relationship to Other Tools:	• SAS software able to receive R code
Data Standards Utilized:	• CDISC standards using the SAS Clinical Standards Toolkit[141]
Training Offered:	• None
Tool Strengths	• To be collected through reviewer interviews and survey
Tool Limitations	• To be collected through reviewer interviews and survey

S-PLUS for Windows

S-PLUS for Windows is commercially available software and distributed by MS MIAMI. The software was developed to work with commonly used analytical software (e.g., Excel) to provide graphical displays of the data. The software allows the user to import data from multiple data sources and export graphics in multiple file formats.

Current Version:	• Version 8.2
FDA Users:	• Clinical, Biostatistics, Clinical Pharmacology, Non-clinical and Safety Reviewers
Brief Description:	• Software package for "Exploratory Data Analysis, Statistical Modeling, Rapid Prototyping, Analytic Development, and Business Intelligence."[142]
Impact on Review Process:	• S-PLUS software allows discipline reviewers to perform in-depth statistical analyses and view the data graphically to identify trends and inconsistencies when conducting an application review.

[141] SAS Institute, Inc. (n.d.). *SAS® and the Clinical Data Interchange Standards Consortium (CDISC)*. Retrieved from http://www.sas.com/industry/life-sciences/cdisc/index.html
[142] MS Miami, (2009). *The Power and Flexibility of S-PLUS. Retrieved from http://www.msmiami.com/directory.cfm?CategoryID=42&gclid=CIanjoDHyaYCFYHb4Aodshf2Hw*

Data Inputs	• S-PLUS can import data from multiple data sources including: - SAS - SPSS - Excel - Text (ASCII) - Quattro Pro - Paradox - Lotus 1-2-3 - dBase - Sigma Plot - Systat - STATA - Gauss - Access - MATLAB - LIM - Bloomberg - FAME - Minitab - FoxPro - Epi Info - Oracle - Sybase - DB2 - SQL Server - ODBC[143]
Data Outputs	• S-Plus can perform over 4,200 data analysis and statistical functions[144] and export graphics in the following formats: - Windows Bitmap (.BMP) - Encapsulated PostScript (.EPS) - CompuServe (.GIF) - GEM Bitmap (.IMG) - JPEG (.JPG) - Adobe Photoshop (.PSD) - Adobe PDF (.PDF) - HP Printer Control Language (.PCL) - PaintBrush (.PCX) - Tagged Image Format (.TIF) - True Vision Targa (.TGA) - Windows Metafile (.WMF) - Portable Network Graphics (.PNG)[145]
Relationship to Other Tools:	• S-Plus can import and export data from the following tools: - SAS - Sigma Plot - MATLAB - Excel
Data Standards Utilized:	• None
Training Offered:	• None
Tool Strengths	• Import and Export Capabilities – The software allows the user to import from multiple data sources and export graphics into multiple file formats. These capabilities provide users with a flexible environment for analyzing and generating graphical displays of data.
Tool Limitations	• To be collected through reviewer interviews and survey

[143] MS Miami, (2009). *S-Plus Datasheet* [PDF Document]. *Retrieved from* http://www.msmiami.com/custom/downloads/splus6-pdf.pdf
[144] MS Miami, (2009). *The Power and Flexibility of S-PLUS. Retrieved from* *http://www.msmiami.com/directory.cfm?CategoryID=42&gclid=CIanjoDHyaYCFYHb4Aodshf2Hw*
[145] MS Miami, (2009). *S-Plus Datasheet* [PDF Document]. *Retrieved from* http://www.msmiami.com/custom/downloads/splus6-pdf.pdf

R

R is a free software environment for statistical analysis and graphic creation. Additionally, the R language offers users an open source method to conduct research in statistical methodology. The software provides the user with an environment where statistical techniques can be implemented.

Current Version:	• Version 2.12.1
FDA Users:	• Clinical, Biostatistics, Clinical Pharmacology and Product Quality Reviewers
Brief Description:	• "R is an integrated suite of software facilities for data manipulation, calculation and graphical display. Among other things it has - an effective data handling and storage facility, - a suite of operators for calculations on arrays, in particular matrices, - large, coherent, integrated collection of intermediate tools for data analysis, - graphical facilities for data analysis and display either directly at the computer or on hardcopy, and - a well-developed, simple and effective programming language (called `S') which includes conditionals, loops, user defined recursive functions and input and output facilities. (Indeed most of the system supplied functions are themselves written in the S language.)"[146]
Impact on Review Process:	• R provides discipline reviewers an environment where modern and classical techniques can be utilized either through the base environment or through the use of packages.[147] The base environment allows the user to perform standard statistical and graphic functions. Additionally, "there are hundreds of contributed packages for R, written by many different authors. Some of these packages implement specialized statistical methods, others give access to data or hardware, and others are designed to complement textbooks."[148]
Data Inputs	• Multiple data formats (e.g., .txt, .XML, .csv)
Data Outputs	• A number of statistical procedures including: - linear and generalized linear models - nonlinear regression models - time series analysis - classical parametric and nonparametric tests - clustering - smoothing
Relationship to Other Tools:	• Users can utilize SAS/IML Studio "to integrate R functionality with SAS/IML or SAS programs" and "exchange data between SAS and R as data sets or matrices."[149]
Data Standards Utilized:	• None
Training Offered:	• None
Tool Strengths	• Easy High Quality Plot Creation – Can produce well-designed, publication-quality plots that include symbols and formulas
Tool Limitations	• To be collected through reviewer interviews and survey

[146] (n.d.). *The R Project for Statistical Computing.* Retrieved from http://www.r-project.org/
[147] Ibid
[148] Ibid
[149] SAS Institute, Inc. (2011). *R Interface Now Available in SAS/IML® Studio*. Retrieved from http://support.sas.com/rnd/app/studio/Rinterface2.html

ChemDraw

ChemDraw is a commercially available drawing suite by CambridgeSoft used to create stereochemically correct structures from chemical names. The software also provides the ability to perform additional analyses by using the chemical structure.

Current Version:	• Version 12.0
FDA Users:	• Clinical and Product Quality Reviewers
Brief Description:	• ChemDraw is a "structure drawing suite" which includes "advanced prediction tools and full Web integration"[150]
Impact on Review Process:	• ChemDraw allows product quality reviewers to create visual representations of chemical structures and provides additional functionality related to the chemical structure.
Data Inputs	• Chemical structure
Data Outputs	• ChemDraw provides the ability to: - "create publication quality graphics featuring chemical structures and labware elements - automatically calculate and update stoichiometry data for chemical reactions - draw and modify peptide and nucleotide sequences using single or three letter codes - preview chemical structure in 3D - perform dynamic database lookups on structure - predict proton and carbon-13 NMR spectra from structures, with splitting patterns and chemical shifts identified and linked to the structure"[151]
Relationship to Other Tools:	• Functionality with Excel
Data Standards Utilized:	• Not Applicable
Training Offered:	• None
Tool Strengths	• To be collected through reviewer interviews and survey
Tool Limitations	• To be collected through reviewer interviews and survey

SigmaPlot

SigmaPlot is a commercially available software package from Systat Software Inc. used for scientific graphing and data analysis. The package includes graphing templates and utilities to help non-statisticians perform data analysis. The graphing capabilities allow for detailed graph customization and creation of publication quality graphs.

Current Version:	• Version 12.0
FDA Users:	• Clinical, Biostatistics, Clinical Pharmacology, Product Quality and Non-clinical Reviewers
Brief Description:	• "SigmaPlot is a scientific data analysis and graphing software package with advanced curve fitting, a vector-based programming language, macro capability and over 50 frequently used statistical tests. SigmaPlot has the analytical features necessary to extract the important Information' and includes "over 100 graph types and a user interface which allows detailed manipulation of every graph object."[152]

[150] CambridgeSoft. (n.d.). *Chem & Bio Office 2010 featuring ChemBioDraw & E-Notebook* [PDF Document]. Retrieved from http://www.cambridgesoft.com/literature/pdf/FeatureSheet12E.pdf
[151] Ibid
[152] Systat Software Inc. (n.d.). *SigmaPlot – Exact Graphs and Data Analysis – Leader in Niche Scientific Graphing* [PDF Document]. Retrieved from http://www.sigmaplot.com/products/sigmaplot/sigmaplot_12_brochure.pdf

Impact on Review Process:	• SigmaPlot allows discipline reviewers to perform in-depth analyses and create graphical representations of the analyses for their review.
Data Inputs	• Multiple data formats (e.g., SAS and Minitab files, OBDC, Microsoft Access MDB)
Data Outputs	• SigmaPlot can: • Create multiple graph types - radar plots - dot density graphs - 2D vector plots - 3D mesh plots - Weibull axis scales to plot Weibull distributions - selective positive direction for polar plots - reciprocal scales - area plots - function plotter - 2D filled contour - waterfall/high-low-close - ternary plots/3D mesh • Perform data analysis - enzyme kinetics module - weighting methods - parameter covariance matrix and confidence intervals in reports - implicit function curve fitting - non-parametric one sample t-test - Deming regression allowing errors in both x and y - normal distribution comparison for quality control - parallel line analysis - Bland-Altman method for method comparison - p value improvement for Dennett's test and improved 3-way ANOVA - worksheet row and column titles from transform language - new root() and implicit() transform language functions - global curve fitting - complete advisory statistical analysis - standard curves macro - dynamic fit wizard - find the global minimum - ROC curve analysis - probability transform functions - piecewise linear regression - 2, 3, 4 & 5-segment models - statistical results for nonlinear curve-fitting - multi-line equations - simultaneously solve for a range of values - ligand binding analysis - equation solver to evaluate mathematical equations - six smoothing routines for 2d data - seven smoothing routines for 3d data - quick transforms for point-and-click data transformations - enhanced histogram wizard - regression wizard for curve-fitting - summary statistics • Export - Enhanced PDF of graphs and reports - HTML for reports - Graphs[153]
Relationship to Other Tools:	• Not Applicable

[153] Systat Software Inc. (n.d.). *SigmaPlot- Upgrade Comparison*. Retrieved from http://www.sigmaplot.com/products/sigmaplot/upgrade-compa.php

Data Standards Utilized:	• None
Training Offered:	• None
Tool Strengths	• Extensive Graphing Capabilities – The software provides a user friendly interface along with a graphing wizard to create high-quality, customizable graphs
Tool Limitations	• To be collected through reviewer interviews and survey

Pharsight WinNonlin

Pharsight WinNonlin is a commercially available statistics software package focused on pharmacokinetic (PK), pharmacodynamic (PD) and noncompartmental analysis. The package includes a library of PK, PD and PK/PD models and allows the user to create custom models for additional data analysis.

Current Version:	• Version 5.2
FDA Users:	• Clinical, Clinical Pharmacology, Product Quality and Non-clinical Reviewers
Brief Description:	• WinNonlin can perform "pharmacokinetic, pharmacodynamic, and noncompartmental analysis" and includes an "extensive library of built-in PK, PD and PK/PD models"[154]. "WinNonlin supports custom, user-defined models to address any kind of data."[155]
Impact on Review Process:	• WinNonlin allows the discipline reviewer to perform pharmacokinetic (PK), pharmacodynamic (PD) and noncompartmental analyses to complete their review.
Data Inputs	• Multiple data formats (e.g., ASCII, Excel, SAS transport)
Data Outputs	• WinNonlin can: - Perform compartmental modeling - PK models - PD models - Noncompartmental Analysis - PK/PD Link Models - Indirect response models - Simultaneous PK/PD link models - Additional model libraries, as needed - Analysis of variance/general linear models/bioequivalence - Export Worksheets - Create presentation-quality graphics - scatter plots - bar charts - histograms - other high-resolution plots - Tables that contain or combine data listings and summary statistics in a variety of formats[156]
Relationship to Other Tools:	• Can export to S-PLUS, SigmaPlot and NONMEM[157]
Data Standards Utilized:	• None
Training Offered:	• None
Tool Strengths	• To be collected through reviewer interviews and survey
Tool Limitations	• To be collected through reviewer interviews and survey

[154] Tripos, L.P. (2010). *Pharsight Products: WinNonlin*. Retrieved from http://www.pharsight.com/products/prod_winnonlin_home.php
[155] Ibid
[156] Tripos, L.P. (2010). *Pharsight – WinNonlin® 5.2* [PDF Document]. Retrieved from http://www.pharsight.com/library/WNL_DS.pdf
[157] Ibid

EAST

EAST is a commercial off-the-shelf software from Cytel for clinical trial design. The software was first launched in 1995 as a way to support the "early stoppage" of a futile clinical trial. The tool is one of the most widely used software packages of its kind and is in use at more than 100 applicant companies, research Centers and regulatory agencies, including the FDA.

Current Version:	• Version 5
FDA Users:	• Clinical and Biostatistics Reviewers
Brief Description:	• EAST is clinical trial design software which supports simulation and monitoring of adaptive, group sequential and fixed sample size trials. Features include: - Trial Design—supports multiple trials, calculates sample size, and permits selection of stopping boundaries - Interim Monitoring Module—dashboard monitors tracking and testing of confidence intervals and stopping boundaries to make educated decisions - Simulation—understand the implications of possible trial designs
Impact on Review Process:	• Provides confidence and validity for clinical trial design including number and selection of subjects, dosing decisions, confidence levels, etc.
Data Inputs	• Product information and characteristics • Purpose/Type of trial (e.g., preventive, screening, treatment, etc.) • Trial phase (e.g., 0, I, II, II) • Study design (e.g., randomized, blind, placebo-controlled) • Sample size, demographics, and other relevant information • Dosage (single, multiple, and amounts)
Data Outputs	• Excel-based design comparisons/scenarios • Initial sample size and stopping boundaries • Re-computed stopping boundaries, error spent, conditional power and post-hoc power • Conditional power and repeated confidence intervals • Adjusted p-values • Confidence intervals and point estimates at the end of the study
Relationship to Other Tools:	• EAST is compatible with several optional modules - East® Adapt, East® • Surv, East® SurvAdapt, East® Xact.
Data Standards Utilized:	• None
Training Offered:	• According to the manufacturer, Cytel, "experts periodically train FDA statisticians in East® use, along with advances in the statistics of adaptive, dose-finding, and group sequential designs."[158]
Tool Strengths	• Supports review by multiple audiences—includes visualization tools to increase understanding of proposed trial designs by trial planners, clinical operators and regulators. • Generates confidence around trials with smaller sample sizes—offers special design scenarios for small sample size studies and generates valid, large-scale studies with smaller sample sizes. • Permits mid-course correction—monitoring features permit review and mid-course corrections during simulations (at intervals) or post simulation review and analysis.
Tool Limitations	• To be collected through reviewer interviews and survey

[158] (n.d.) *East Version 5: Improve Complex Clinical Trial Planning*. Retrieved from http://www.cytel.com/Software/East.aspx

StatXact for Windows

StatXact is a commercial-off-the-shelf product from Cytel that offers a wide range of validated statistical exact tests. The product may be used for a variety of fields including medical, scientific, engineering and mathematics and is comparable to, yet more expansive than, SAS offerings.

Current Version:	• Version 9
FDA Users:	• Clinical and Biostatistics Reviewers
Brief Description:	• StatXact is a statistical software tool used for small-sample categorical and nonparametric data problem solving. The tool offers more than 140 different validated statistical tests and procedures and a user friendly interface to make analysis quicker than comparable packages.[159] Recent enhancements include: - R integration to support R scripts - New methods including unique to StatXact offerings - Compatibility with newer Microsoft products
Impact on Review Process:	• With comparable features to many SAS and excel functions, StatXact may be leveraged throughout the conduct review phase of the NDA/BLA lifecycle
Data Inputs	• Original data or data collected in another software package (see Relationship to Other Tools)
Data Outputs	Outputs from 140 statistical tests, from the following category of equations (see StatXact Website for full list of tests): • One-sample Goodness-of-Fit • Paired Samples • Two Independent Samples • K Related Samples • K Independent Samples • One-Sample Rates and Proportions • Poisson Rates • Two Independent Binomials • Stratied 2x2 Tables • C Ordered Binomials (with or without strata) • Two Ordered Multinomials (with or without strata) • Unordered RxC Table • Single Ordered RxC Table • Doubly Ordered RxC Table • Stratifed RxC Tables • Correlated Categorical Data • Measures of Association (nominal) • Measures of Association (ordinal) • Measures of Agreement • Power & Sample Size
Relationship to Other Tools:	• StatXact supports original data or data created in the following software packages: - ASCII - Excel - LogXact or Egret - Lotus 1-2-3 - SAS data sets - SAS transport data - SPSS - STATA - SYSTAT

[159] (n.d.) StatXact 9 Tests Compared to SAS Software. Retrieved from http://www.cytel.com/Software/StatXact.aspx

Data Standards Utilized:	• None
Training Offered:	• None
Tool Strengths	• Permits unique sorting, filtering and manipulation—DataEditor feature allows direct editing of the cells of a contingency table and the he DataEditor menu contains sorting and filtering properties, and other data manipulation features are geared towards clinical researchers attempting to subset the data.[160] • Facilitates easy test execution—This tool groups statistical procedures according to what they solve so users can select the type of statistical problem and the file format from a menu. This supports easy navigation of the more than 140 tests available and quickly executes. • Geared toward biological sciences—Due to the breadth of the analysis offerings which are heavy on the non-parametric, tool is ideal for clinical and epidemiological data. According to a product review, "many biological and physical scientists will find this of use and, as the routines are available through SAS, many statisticians as well."[161]
Tool Limitations	• Limited graphic capabilities—According to one review of the product, the tool only supports standard analytic plots such as the histogram, box, line, scatter, and stem and leaf.[162] Therefore a separate graphics program may be necessary

nQuery

nQuery Advisor is a commercial off-the-shelf product from Statistical Solutions that assists users in generating power and sample size calculation. The product was designed by professional statisticians to facilitate easier generation of sample sizes and can be used to ensure validity in samples generated for clinical trials.

Current Version:	• Version 7.0
FDA Users:	• Biostatistics and Clinical Reviewers
Brief Description:	• nQuery Advisor generates power and sample size calculations across a wide variety of statistical analyses and when paired with Statistical Solutions nTerim product this extends to group sequential trials. • The tool offers sample size justification statement support and scenario evaluation. • A unique feature generates randomized lists and an automated function for mixed block sizes to ensure double blind study maintenance.[163] • nQuery is on the Computational Science Center's list of data analysis tools available for use by FDA employees.
Impact on Review Process:	• Provides confidence and validity of selected sample and sample size.
Data Inputs	• Study design detail • Analysis, method, parameters and expected differences • Alternative values for effect size can be entered for sensitivity analysis
Data Outputs	• Results of selected tests: – One-group, paired and repeated measures tests and confidence intervals for means – Two-group tests and confidence intervals for means – One and two group and crossover designs, non-inferiority and equivalence tests

[160] Wass, John. (n.d.) StatXact: *Statistical Software for Exact Nonparametric Inference*. Scientific Computing. Retrieved from http://www.scientificcomputing.com/statxact-statistical-software.aspx
[161] Wass, John. (n.d.) StatXact: *Statistical Software for Exact Nonparametric Inference*. Scientific Computing. Retrieved from http://www.scientificcomputing.com/statxact-statistical-software.aspx
[162] Wass, John. (n.d.) StatXact: *Statistical Software for Exact Nonparametric Inference*. Scientific Computing. Retrieved from http://www.scientificcomputing.com/statxact-statistical-software.aspx
[163] (n.d.). NQuery Advisor + NTerim. Retrieved from http://www.statistical-solutions-software.com/products-page/nquery-advisor-sample-size-software/

	– Multiple group tests and confidence intervals for means – One-group and paired tests and confidence intervals for proportions – Two-group tests and confidence intervals for proportions – Multiple group tests – One-sided non-inferiority tests for survival hazard ratio – Dichotomous outcome methods using Intraclass Kappa – Continuous outcome methods using Pearson r – Logistic Regression – Linear Regression • Range of scenarios displayed in tables and plots to enhance decision-making • Sample size decision report (once decision is made)
Relationship to Other Tools:	• Pairs with nTerim, a Statistical Solutions product
Data Standards Utilized:	• None
Training Offered:	• None
Tool Strengths	• Generates only necessary scenarios-- nQuery Advisor uses closed form solutions for calculating sample size as much as possible. This ensures nQuery Advisor only generates scenarios where appropriate, for example with survival analysis.[164]
Tool Limitations	• Limited types of analysis-- nQuery Advisor does not perform in-depth statistical analysis, it is used for calculating power and sample size as compared to the more expansive EAST product.

Matlab

Matlab is a commercial-of-the shelf tool by MathWorks that is used for algorithm development, data visualization, data analysis, and numeric computation. Matlab has a broad spectrum of applications including signal and image processing and computational biology. Matlab's high level computing language is considered easier to use than computer programming languages

Current Version:	• Version 7.11
FDA Users:	• Biostatistics, Clinical Pharmacology, Clinical and Product Quality Reviewers
Brief Description:	• Matlab is a computing language for numeric computation and visualization. The tool permits users to: - Develop Algorithms without low level administrative activities - Conduct Data Analysis with the use of interactive tools and command-line functions - Conduct Data Visualization using 2-D and 3-D plotting functions, 3-D volume visualization functions, tools for interactively creating plots - Perform Numeric Computation contains mathematical and statistical functions to support all common science operations. Add-on toolboxes provide specialized computations such as curve-fitting. • The tool also provides features for documenting and sharing work with others. Matlab supports publishing in HTML, Word, LaTEX, and other formats.
Impact on Review Process:	• Matlab may be leveraged throughout the conduct review phase of the NDA/BLA lifecycle

[164] (n.d.). FAQ. Retrieved from http://www.statistical-solutions-software.com/nquery-advisor-sample-size-software/support-info/faq/

Data Inputs	• Matlab supports the use of data multiple formats: - Microsoft Excel; ASCII text or binary files - Image, sound, and video files; and scientific files, such as HDF and HDF5 - Data from Web pages and XML - Hardware devices, such as serial ports or sound card • Live streaming media
Data Outputs	• Tested, referenced and validated data analysis.
Relationship to Other Tools:	• MATLAB supports integration with external applications and languages, such as C, C++, Fortran, Java, COM, and Microsoft Excel
Data Standards Utilized:	• None
Training Offered:	• None
Tool Strengths	• To be collected through reviewer interviews and survey
Tool Limitations	• To be collected through reviewer interviews and survey

MathType

Mathtype is a commercial off-the shelf equation editing software developed by Design Science. Mathtype is a more advanced version of Equation Editor, which Design Science licensed to Microsoft in 1991 and is found in its Microsoft Word product. The product can be used with various media to quickly generate and display equations.

Current Version:	• Version 6.7
FDA Users:	• Biostatistics, Clinical and Product Quality Reviewers
Brief Description:	• MathType is a powerful interactive equation editor creates mathematical notation for word processing, web pages, desktop publishing, presentations, eLearning, and for TeX, LaTeX, and MathML documents. MathType is currently compatible with 400 different applications and website types previous described making cutting, pasting, and editing of existing equation.[165] Users are able to create equations by: - Handwriting recognition - Point and Click automatic formatting - Keyboard shortcuts - Copy and pasted from other applications (including the Microsoft Office toolbar/ribbon) - Find and insert function - MathType permits customization of the equation style including font and color features. • MathType also has stylistic features such as color and exclusive fonts to design and emphasize parts or entire equations
Impact on Review Process:	• MathType expedites the creation, editing/fixing and publishing of equations for interim reports, final application review report, correspondence, etc.
Data Inputs	• Equation type determined by the reviewer or specific portion of NDA/BLA application
Data Outputs	• Presentation ready equation for review reports • Edits to sponsor/applicant submitted equations
Relationship to Other Tools:	• Compatible with 400 applications, tools and websites (see website for full list)
Data Standards Utilized:	• None
Training Offered:	• None

[165] (n.d). MathType. Retrieved from http://www.dessci.com/en/products/mathtype/default.htm

Tool Strengths	• Quickly creates equations—Users can choose templates from MathType pick lists and typing into their empty slots, using keyboard shortcuts for symbols and commands, or typing TeX language directly into Microsoft Word. MathType automatically applies mathematical spacing rules.[166]
Tool Limitations	• Does not pair with analysis tools—MathType is an editor and publishing tool but does not integrate directly with statistical analysis tools requiring the use of potentially two or more tools to generate and display analysis.

NONMEM

NONMEM is a commercial off-the-shelf population pharmacokinetic (PK)/ pharmacodynamic (PD) modeling tool. This tool was developed by the University of California San Francisco and is now exclusively licensed by ICON. NONMEM is considered the "gold standard" for this type of analysis and has directed pharmaceutical research since its development in1970s.[167]

Current Version:	• Version 7.0
FDA Users:	• Biostatistics, Clinical Pharmacology, Clinical and Product Quality Reviewers
Brief Description:	• NONMEM is a modeling tool used in population pharmacokinetic (PK)/ pharmacodynamic (PD) analysis. • Two additional parts to the software compute predictions for population PK and PD data (PREDPP) and preprocessor (NM-TRAN) that organizes and manages the inputs to the other two parts of the tool. • Features of this version of tool include: – "Improved incidence of success in problems using the first-order conditional estimation method. – Improved incidence of completion when using the "Super Problem" feature. – Exact likelihood maximization methods, such as importance sampling expectation maximization (EM), and stochastic approximation EM. – Full three stage hierarchical Markov Chain Monte Carlo (MCMC) methods. – Additional result files, with number of significant digits selectable by the user, and which can be easily read by post-processing programs. – Numbers of data items per data record increased to 50. – Label names may be as large as 10 characters. – Initial parameter entries in the control stream file may be of any numerical format."[168]
Impact on Review Process:	• NONMEM allows the discipline reviewer to perform PK and PD analyses to complete their review.
Data Inputs	• Data is defined by the user
Data Outputs	• PK and PD Analyses
Relationship to Other Tools:	• Can be used with SAS
Data Standards Utilized:	• None
Training Offered:	• None

[166] (n.d). *MathType 6.7*. Retrieved from http://www.downloadatoz.com/home-education_directory/mathtype/reviews.html
[167] (n.d.) NONMEM. Retrieved from http://www.iconplc.com/technology/products/nonmem/
[168] Ibid

Tool Strengths	• Reduces need for certain coding activities – "Use of PREDPP obviates the need for the user to code kinetic-type equations and it also allows complicated patient-type data to be easily used."[169] • Automates with SAS products for better post analysis--The automation of NONMEM with SAS is especially efficient and time-saving for population PK/PD. This can reduce errors and the need for additional quality assurance activities.
Tool Limitations	• Requires use of system with significant computing power - NONMEM® analyses can be timely (hours, days) depending the problem and computer processing power. Therefore, ICON Products advises users to employ a machine with sufficient available memory. "For multiprocessor and multi-core environments 3-4 Gb of memory may be needed to accommodate several simultaneous NONMEM® runs."[170] • Does not support pre- and post-processing activities-- NONMEM algorithm is critical for population analysis workflow, data assembly, and pre and post processing are functions that are not adequately supported and therefore typically handled outside of NONMEM.[171]

Pharsight Trial Simulator

Pharsight Trial Simulator is a commercial-off-the-shelf software tool for trial design and analysis. In 2005, CDER used the Simulator software as part of a "modeling effort related to an undisclosed anti-HIV drug, in preparation for an end-of-Phase IIa meeting."[172] Pharsight extended a preexisting Cooperative Research and Development Agreement (CRADA) with CDER to create a platform for multiple Pharsight products and other vendors' products.

Current Version:	• Version 2.2.1
FDA Users:	• Biostatistics, Clinical Pharmacology, Clinical and Non-clinical Reviewers
Brief Description:	• Pharsight Trail Simulator is a Computer-Assisted Trial Design tool that consolidates multiple sub tools to support a clinical study team with study design, statistical and sensitivity analyses, "what if" scenarios, and cross team communication. Simulator supports access of preexisting information and uses preloaded models and equations to reduce workloads. Features include: - Drug Action Modeling—graphical interface, pre-loaded PK/PD models, and ability to add equations using simple expression or FORTRAN language - Protocol Design—supports multiple design scenarios, permits cross Center enrollment screening, and various dosing schemes - Integrated Study Analysis Plans—built in and customizable study plans with Microsoft Word reporting features - "What If" Scenarios—options include population variability, drug model variability, and control; system supports any number of scenarios - Simulation Results Analysis—cross replication and scenario comparisons with additional manipulation tools such as filtering, sorting and exporting • Pharsight has extended its CRADA with FDA CDER to support the Critical Path Initiative. As part of this agreement Pharsight will provide the FDA with software for the analysis, visualization, storage, reporting and review of PK/PD data.
Impact on Review Process:	• Provides confidence and validity for clinical trial and clinical safety reviews including number and selection of subjects, dosing decisions, confidence levels, etc.

[169] Ibid
[170] (n.d.) NONMEM. Retrieved from http://www.iconplc.com/technology/products/nonmem/
[171] Xiao, Alan J and Jill B Fiedler-Kelly. (n.d.). *Integration of SAS® and NONMEM® for Automation of Population Pharmacokinetic/Pharmacodynamic Modeling on UNIX Systems.* Retrieved from http://www.nesug.org/proceedings/nesug02/ph/ph015.pdf
[172] (n.d.). *FDA-Pharsight CRADA*. Retrieved from http://www.pharsight.com/criticalpath/crada.php

Data Inputs	• Product information and characteristics • Purpose/Type of trial (e.g., preventive, screening, treatment, etc.) • Trial phase (e.g., 0, I, II, II) • Study design (e.g., randomized, blind, placebo-controlled) • Sample size, demographics, and other relevant information • Dosage (single, multiple, and amounts)
Data Outputs	• Drug effects as a function of dose(s), disease processes, time and subject characteristics. • Compliance and dropouts based on drug effects or time • Multiple, reusable scenarios and simulations
Relationship to Other Tools:	• Compatible with multiple statistical tools including SAS, S-PLUS, NONMEM, WinNonlin.
Data Standards Utilized:	• None
Training Offered:	• None
Tool Strengths	• Easy to assemble drug models – Easy to build customized drug models through a visually based graphic interface. Models are generated by "adding and connecting model blocks to define functions of subject characteristics, treatments and formulations, drug and disease actions, placebo effects and random factors." [173]
Tool Limitations	• FDA sponsored product set—FDA/Pharsight CRADA for multiple tools ensures that the full suite, not just a single tool is supported by FDA. This increases the power and functionality of the simulator tool and increases communication abilities with non-clinical peers

GraphPad Prism

GraphPad Prism is a commercial off-the-shelf multi-purpose scientific graphics tool by GraphPad Software. The tool is popular among scientists as it is specifically designed for non-statisticians requiring statistical analysis to validate their work. GraphPad reports that more than 100,000 scientists currently use the program worldwide.[174]

Current Version:	• Version 5
FDA Users:	• Clinical, Clinical Microbiology, Clinical Pharmacology, Product Quality and Non-clinical Reviewers
Brief Description:	• GraphPad Prism is statistical software and a graphing tool originally designed for biological studies. The system contains similar features and outputs of traditional biostatistics, curve fitting and graphics but is designed for non-statisticians providing support as needed during the analysis process. Features of the program include: - Non-linear regression tools including advanced fitting options and multiple examples - Statistics commonly used by clinicians and laboratories - Two dimensional scientific graphs including a page layout tool for reporting - Analysis organization tool saves files logically and logs analysis process as well as results
Impact on Review Process:	• GraphPad Prism may be leveraged throughout the conduct review phase of the NDA/BLA lifecycle
Data Inputs	• Data is defined by the user
Data Outputs	• Outcomes of statistical tests and analysis • Two dimensional graphics reports (wmf, emf, pdf, eps, tif, jpg, png, bmp or pcx format)

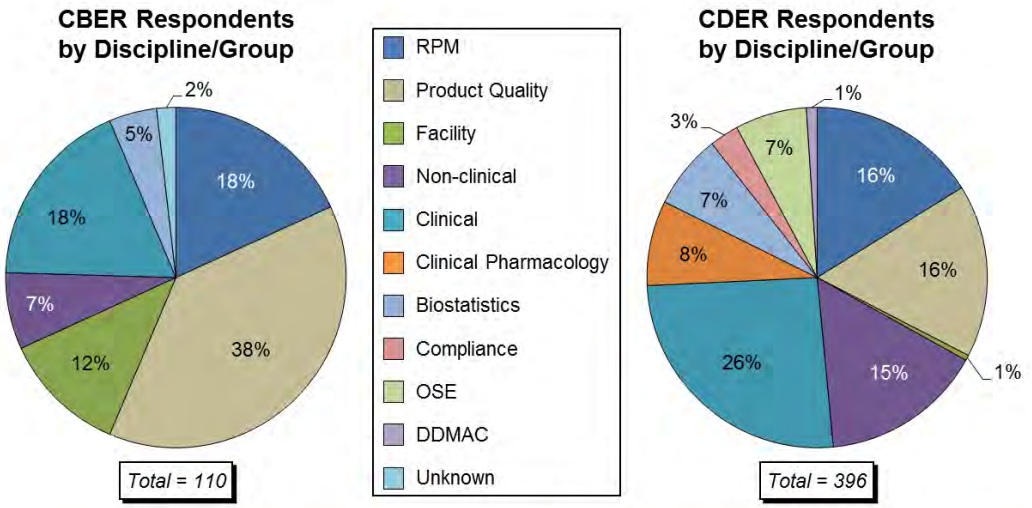
[173] (n.d.) NONMEM. Retrieved from http://www.iconplc.com/technology/products/nonmem/
[174] (n.d.). *GraphPad Prism*. http://www.graphpad.com/prism/prism.htm

Relationship to Other Tools:	• Compatible with Microsoft Excel
Data Standards Utilized:	• None
Training Offered:	• None
Tool Strengths	• Designed for biostatistics – Program is intended for biochemical and biological studies and therefore does not consume space with statistically heavy analyses that may not be relevant. • Requires only modest computer requirements—Software only needs 30MB of hard drive and a minimum of 128 MB of RAM. The version runs on Windows 2000, XP, Vista or Mac. • Integrated help feature—Software does not come with manuals and instead relies on a robust help menu, online FAQ database, and video tutorial. • Accessible "notes" feature—"Flag" feature allows the user t to append notes to each dataset detailing its format and analysis. One review noted that this feature is very accessible compared to other, similar programs.[175]
Tool Limitations	• Designed for smaller datasets – Data importation can be difficult and is most effective through cut and paste of data which can be difficult for larger datasets that exist for certain disciplines.

[175] Wass, John D. (n.d.). *Graphpad Prism: A Very Nice Little Package*. Retrieved from http://www.scientificcomputing.com/graphpad-prism-a-very-nice-little.aspx

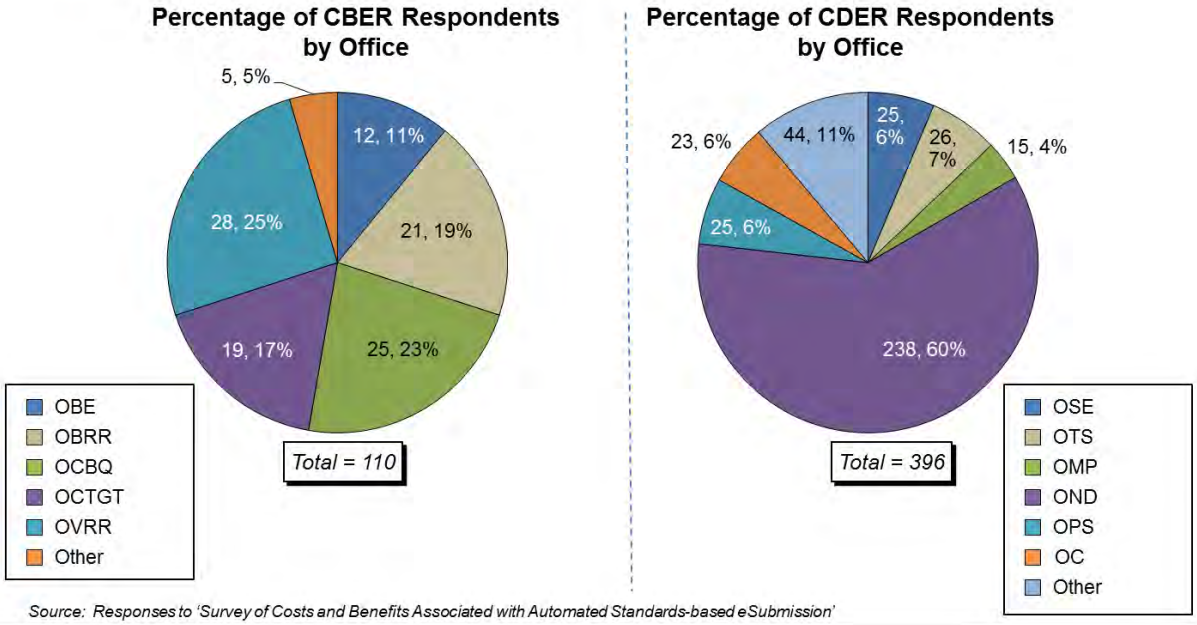
APPENDIX G: SURVEY

Exhibit 69: Demographics of Survey Respondents



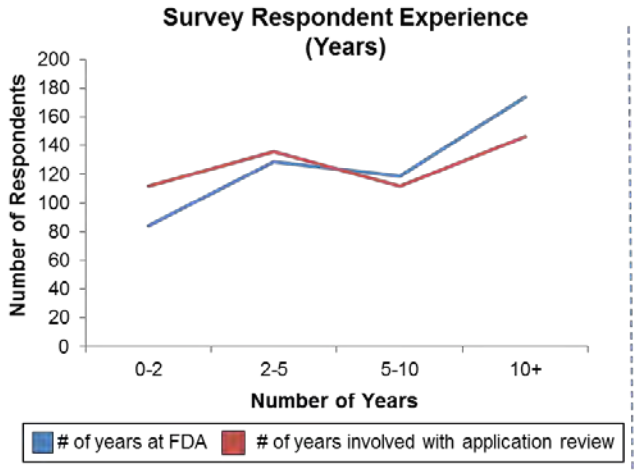
Number of Respondents by Discipline/Group

	RPM	Product Quality	Facility	Non-clinical	Clinical	Clin. Pharm.	Biostats	Comp-liance	OSE	DDMAC	Unknown	Total
CBER	20	42	13	8	20	0	5	0	0	0	2	110
CDER	64	65	2	61	102	32	28	11	27	4	0	396

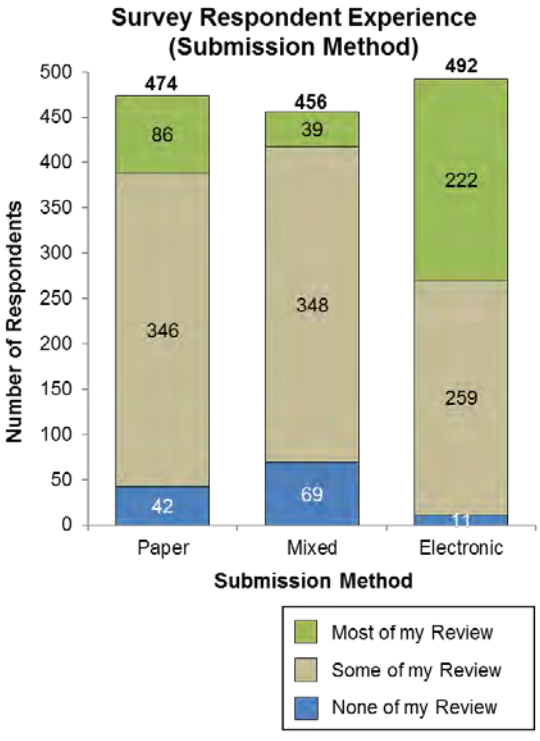


Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Exhibit 70: Survey Respondents' Experience

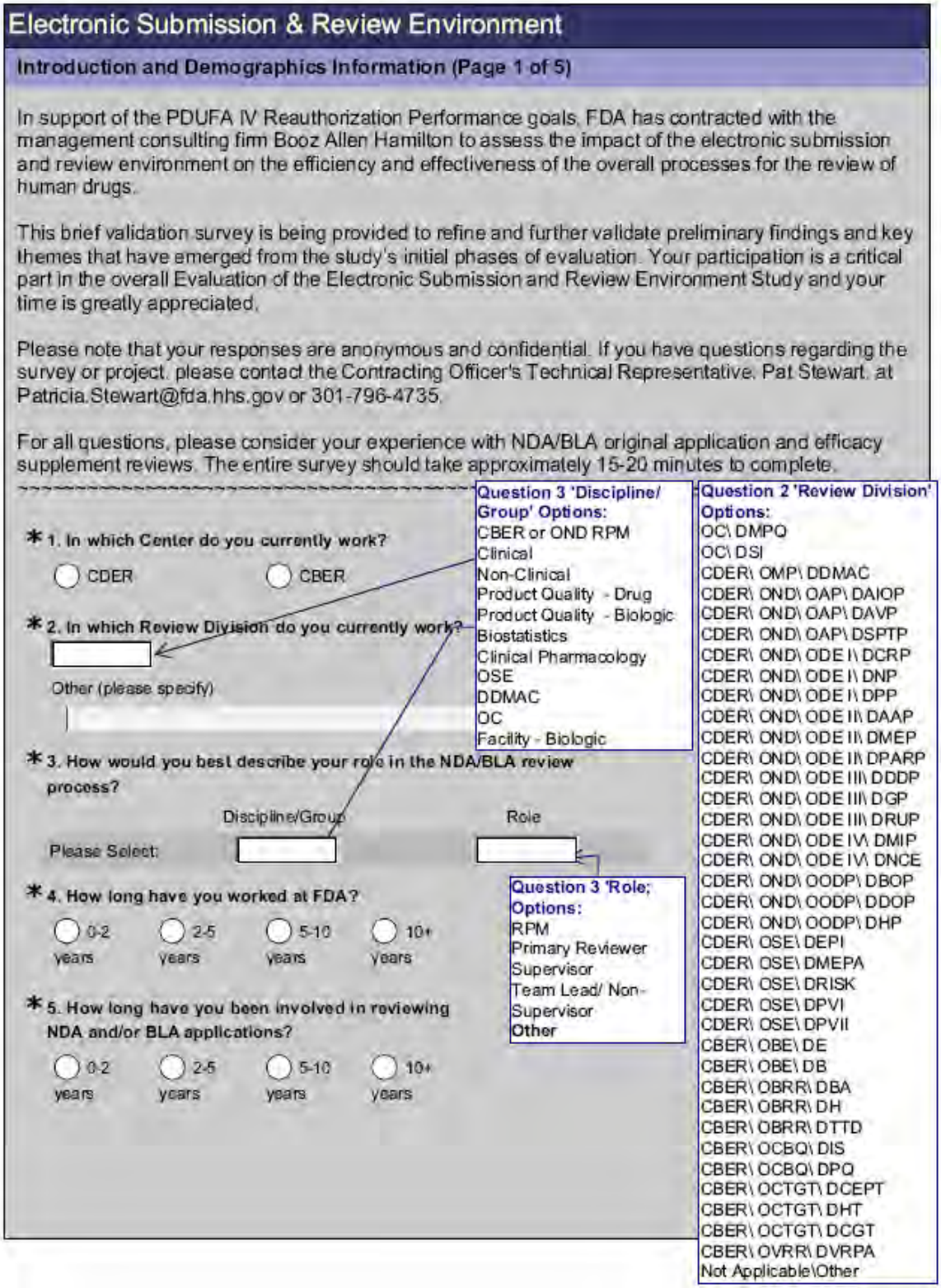


	0-2 years (% of total)	2-5 years (% of total)	5-10 years (% of total)	10+ years (% of total)	Total
Number of years at FDA	84 (17%)	129 (25%)	119 (24%)	174 (34%)	506 (100%)
Number of years involved in application review	112 (22%)	136 (27%)	112 (22%)	146 (29%)	506 (100%)



Source: Responses to 'Survey of Costs and Benefits Associated with Automated Standards-based eSubmission'

Exhibit 71: Survey of Costs and Benefits Associated with Automated Standards-based eSubmissions



Electronic Submission & Review Environment

Electronic Application Submissions (Page 2 of 5)

Instructions: Please base responses on original applications and efficacy supplements you have reviewed

Definitions:

Electronic – Original applications or efficacy supplements with ALL sections submitted in electronic format, accessible through GS Review or EDR

Mixed – Original applications or efficacy supplements with some sections submitted in paper format, and some sections submitted electronically, not counting labeling and datasets

Paper – Original applications or efficacy supplements with all sections submitted in paper format (note- labeling and datasets may still be submitted electronically)
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* 6. During your tenure at FDA, what has been your experience with review of Paper, Mixed, and Electronic applications?

Each format comprises what portion of your review?

	MOST of my review	SOME of my review	NONE of my review
Electronic	◯	◯	◯
Mixed	◯	◯	◯
Paper	◯	◯	◯

* 7. Does the fully electronic application format improve your experience with the review process?

◯ Yes

◯ No

Why?

* 8. In your experience, what are the benefits of reviewing a fully electronic application?

◯ I believe the benefits are (CHECK ALL THAT APPLY IN THE SECTIONS BELOW)

◯ Not Applicable; I have not reviewed electronic applications

◯ I do not believe there are any associated benefits
~~~~~~

Electronic Submission & Review Environment

Application Receipt:

- ☐ Reduces the time it takes to search the document room
- ☐ Reduces the time it takes to get a copy from another member of the review team (e.g., reviewer or RPM)
- ☐ Reduces the time it takes to receive the initial submission from the applicant for review

Application Review:

- ☐ Makes it easier to search and find information applicable to my review
- ☐ Makes it easier to work from home by not having to transport paper documents
- ☐ Increases the quality of my analyses
- ☐ Permits more detailed analyses
- ☐ Permits more "think time" for my review
- ☐ Increased the speed with which I can complete analyses
- ☐ Enables me to more easily meet Good Review Management Principles and Practices (GRMPs) milestones or interim deadlines
- ☐ Helps me manage a larger number of applications
- ☐ Helps me manage other non-review tasks (e.g., low priority assignments, committee or leadership work)

Coordination & Communication:

- ☐ Enables me to issue consult requests earlier
- ☐ Enables me to issue more precise consult requests
- ☐ Enables me to respond to consult requests more efficiently
- ☐ Improves coordination between discipline reviewers
- ☐ Improves coordination with applicants

Other (please specify)

* **9. If you receive an electronic application, do you print any of it?**

- ◯ Yes
- ◯ No
- ◯ Not Applicable

Electronic Submission & Review Environment

If "Yes", what portions do you print? Check all that apply.

- ☐ Cover Letter
- ☐ Summary(ies)
- ☐ Section(s)
- ☐ Full Application

Please specify which Summary(ies) and/or Section(s) you print.

*** 10. Do technology barriers prevent you from performing an efficient review of an electronic submission?**

- ◯ Yes
- ◯ No
- ◯ Not Applicable

If "Yes", please indicate which technology barriers apply.

- ☐ Lack of access rights to a database or analysis tool
- ☐ Inconsistent access to database or analysis tool due to server or connectivity issues
- ☐ Difficulty loading page (e.g., slow loading or error messages)
- ☐ Inactive electronic links (i.e., dead links)
- ☐ File errors (e.g., corrupt files, missing files)
- ☐ Duplicate files (e.g., submission records)
- ☐ Non-receipt or delays in receiving notification of an incoming application
- ☐ Inability to make notes or flag a file for reference in GS Review only
- ☐ Inability to share parts or sections of an electronic file with other reviewers or consults
- ☐ Review tools are not supported by office or division
- ☐ FDA does not provide support for a tool
- ☐ Lack of duplicate monitors
- ☐ Broken printers/scanners
- ☐ Other (please specify)

Electronic Submission & Review Environment

Data Standards (Page 3 of 5)

Instructions: Please base responses on original applications and efficacy supplements you have reviewed

Definitions:

Data Standards are documented agreements on representations, formats, and definitions of common health data. Standards are typically defined, developed and maintained by non-profit organizations such as Clinical Data Interchange Standards Consortium (CDISC) and Health Level Seven International (HL7).

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* 11. Have you reviewed any original applications or efficacy supplements that conform to the data standards below?

	Yes	No
Structured Product Labeling (SPL)	◯	◯
Study Data Tabulation Model (SDTM)	◯	◯
Standard for Exchange of Nonclinical Data (SEND)	◯	◯
Product Stability Data Standard	◯	◯

* 12. Do you (or would you) prefer applications that contain standardized data?

◯ Yes

◯ Not Sure

◯ No. Please provide an explanation:

If "Yes", check all benefits that apply.

Data Organization:

☐ Data is more structured; more clearly organized

☐ Data is presented in a familiar format

☐ Data is more likely to be complete
~~~~~~

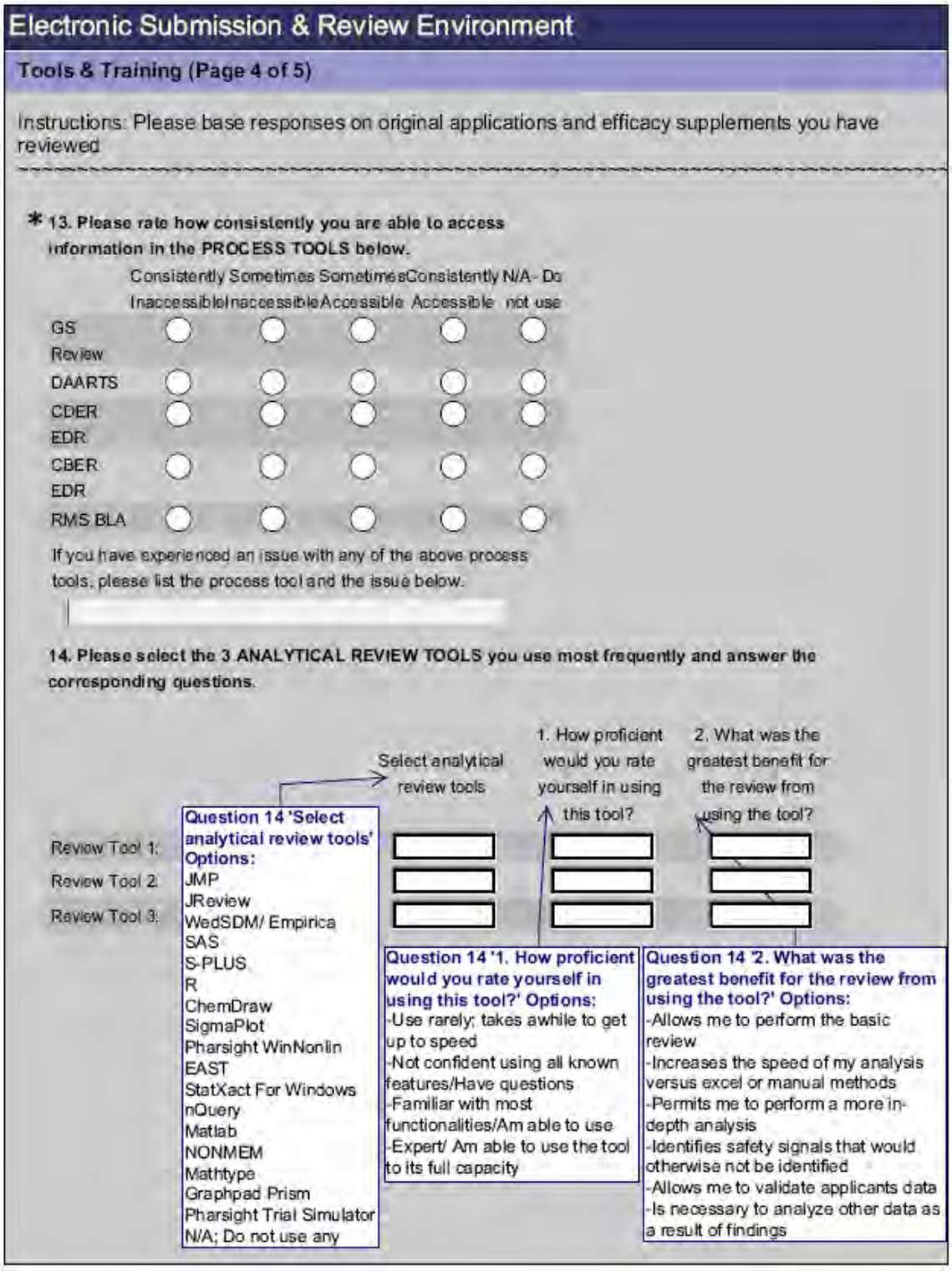
Electronic Submission & Review Environment

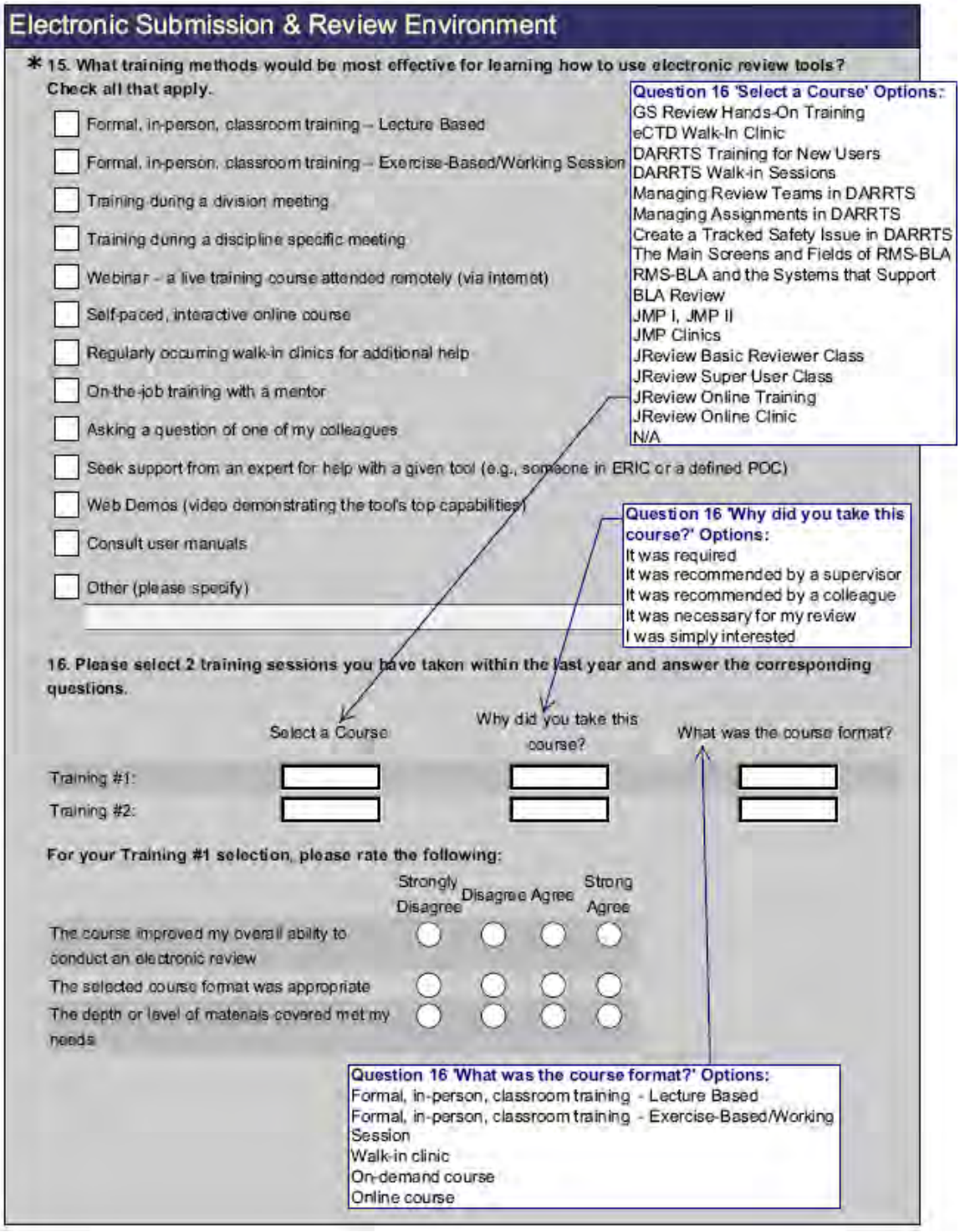
Conducting Your Review:

- ☐ Data is easier to manipulate
- ☐ Allows for automation of standard analyses
- ☐ Increases the quality of my analyses
- ☐ Permits more detailed analyses
- ☐ Increases the speed of completing analyses
- ☐ Increases ability to manage a larger number of applications
- ☐ Increases time available to address non-review tasks (low priority assignments, committee or leadership work, etc)
- ☐ Reduces preparation time for an Advisory Committee meeting
- ☐ Enables completion of interim deliverables, which facilitates more productive mid-cycle review meeting
- ☐ Increases ability to meet GRMP or other deadlines

Communication:

- ☐ Facilitates efficient communication across disciplines (e.g., patient profile characteristics, adverse event analyses)
- ☐ Facilitates clearer, more precise information requests during communications with applications
- ☐ Decreases extraneous meetings/communications between discipline reviewers to identify responsibilities
- ☐ Allows consult requests to be issued earlier
- ☐ Permits more thorough information in consult requests
- ☐ Other (please specify) _____


Electronic Submission & Review Environment
Tools & Training (Page 4 of 5)
Instructions: Please base responses on original applications and efficacy supplements you have reviewed
* 13. Please rate how consistently you are able to access information in the PROCESS TOOLS below.
Consistently Inaccessible
Sometimes Inaccessible
Sometimes Accessible
Consistently Accessible
N/A - Do not use
GS Review
DAARTS
CDER EDR
CBER EDR
RMS BLA
If you have experienced an issue with any of the above process tools, please list the process tool and the issue below.
14. Please select the 3 ANALYTICAL REVIEW TOOLS you use most frequently and answer the corresponding questions.
Select analytical review tools
1. How proficient would you rate yourself in using this tool?
2. What was the greatest benefit for the review from using the tool?
Review Tool 1:
Review Tool 2:
Review Tool 3:
Question 14 'Select analytical review tools' Options:
JMP
JReview
WedSDM/ Empirica
SAS
S-PLUS
R
ChemDraw
SigmaPlot
Pharsight WinNonlin
EAST
StatXact For Windows
nQuery
Matlab
NONMEM
Mathtype
Graphpad Prism
Pharsight Trial Simulator
N/A; Do not use any
Question 14 '1. How proficient would you rate yourself in using this tool?' Options:
-Use rarely; takes awhile to get up to speed
-Not confident using all known features/Have questions
-Familiar with most functionalities/Am able to use
-Expert/ Am able to use the tool to its full capacity
Question 14 '2. What was the greatest benefit for the review from using the tool?' Options:
-Allows me to perform the basic review
-Increases the speed of my analysis versus excel or manual methods
-Permits me to perform a more in-depth analysis
-Identifies safety signals that would otherwise not be identified
-Allows me to validate applicants data
-Is necessary to analyze other data as a result of findings


Electronic Submission & Review Environment
* 15. What training methods would be most effective for learning how to use electronic review tools? Check all that apply.
Formal, in-person, classroom training – Lecture Based
Formal, in-person, classroom training – Exercise-Based/Working Session
Training during a division meeting
Training during a discipline specific meeting
Webinar – a live training course attended remotely (via internet)
Self-paced, interactive online course
Regularly occurring walk-in clinics for additional help
On-the-job training with a mentor
Asking a question of one of my colleagues
Seek support from an expert for help with a given tool (e.g., someone in ERIC or a defined POC)
Web Demos (video demonstrating the tool's top capabilities)
Consult user manuals
Other (please specify)
Question 16 'Select a Course' Options:
GS Review Hands-On Training
eCTD Walk-In Clinic
DARRTS Training for New Users
DARRTS Walk-in Sessions
Managing Review Teams in DARRTS
Managing Assignments in DARRTS
Create a Tracked Safety Issue in DARRTS
The Main Screens and Fields of RMS-BLA
RMS-BLA and the Systems that Support
BLA Review
JMP I, JMP II
JMP Clinics
JReview Basic Reviewer Class
JReview Super User Class
JReview Online Training
JReview Online Clinic
N/A
Question 16 'Why did you take this course?' Options:
It was required
It was recommended by a supervisor
It was recommended by a colleague
It was necessary for my review
I was simply interested
16. Please select 2 training sessions you have taken within the last year and answer the corresponding questions.
Select a Course
Why did you take this course?
What was the course format?
Training #1:
Training #2:
For your Training #1 selection, please rate the following:
Strongly Disagree
Disagree
Agree
Strong Agree
The course improved my overall ability to conduct an electronic review
The selected course format was appropriate
The depth or level of materials covered met my needs
Question 16 'What was the course format?' Options:
Formal, in-person, classroom training - Lecture Based
Formal, in-person, classroom training - Exercise-Based/Working Session
Walk-in clinic
On-demand course
Online course

Electronic Submission & Review Environment

For your Training #2 selection, please rate the following:

	Strongly Disagree	Disagree	Agree	Strong Agree
The course improved my overall ability to conduct an electronic review	○	○	○	○
The selected course format was appropriate	○	○	○	○
The depth or level of materials covered met my needs	○	○	○	○

*** 17. How would you like to learn about currently offered training courses? Check all that apply.**

- ☐ Centralized training website
- ☐ Email with a course list and schedule
- ☐ Other (please specify)

Electronic Submission & Review Environment

Conclusion (Page 5 of 5)

18. What can applicants do to improve their electronic applications? Check all that apply.

- ☐ Be more selective with information included in electronic application
- ☐ Comply more closely with the eCTD structure
- ☐ Provide electronic data sets
- ☐ Provide better metadata files or rationales for data methodology
- ☐ Use content data standards (e.g., SDTM)
- ☐ Improve/Increase use of hyperlinks
- ☐ Other (please specify)

19. In your opinion, how can electronic submissions, review process, tools, or training be improved?

20. Are there any additional analyses which, if automated, would assist with your review?

21. Please provide any additional feedback regarding this survey or the study overall in the space below.

APPENDIX H: PDUFA IV ANALYSIS AND DEEP DIVE COHORT APPLICATIONS

NDA/ BLA	Application Number	Division	Seq #	Trade Name	Applicant	Submission Format	Gate-way	Deep Dive
NDA	20449	DDOP	059	TAXOTERE	SANOFI AVENTIS US LLC	Electronic	✓	✓
NDA	20873	DHP	019	ANGIOMAX	THE MEDICINES CO	Electronic		
NDA	20965	DDDP	007	LEVULAN KERASTICK	DUSA PHARMACEUTICALS INC	Paper		
NDA	21425	DMIP	017	ULTRAVIST INJECTION	BAYER HEALTHCARE PHARMACEUTICALS	Electronic	✓	✓
NDA	21572	DAIOP	023	CUBICIN	CUBIST PHARMACEUTICALS INC	Electronic		
NDA	[redacted]	DHP	000	[redacted]	[redacted]	Electronic		✓
NDA	21947	DAAP	008	FENTORA	CEPHALON INC	Electronic		✓
NDA	22009	DNCE	002	ANTHELIOS 40	LOREAL USA PRODUCTS INC	Paper		
NDA	22187	DAVP	001	Intelence	TIBOTEC INC	Electronic		✓
NDA	22250	DNP	000	AMPYRA	ACORDA THERAPEUTICS INC	Electronic		✓
NDA	[redacted]	DNCE	000	[redacted]	[redacted]	Paper		
NDA	22307	DCRP	000	Effient	ELI LILLY AND CO	Electronic		✓
NDA	[redacted]	DNP	000	[redacted]	[redacted]	Electronic		✓
NDA	22350	DMEP	000	ONGLYZA	BRISTOL MYERS SQUIBB CO	Electronic		
NDA	22352	DPARP	000	COLCRYS	AR HOLDING CO INC	Electronic		✓
NDA	[redacted]	DAIOP	000	[redacted]	[redacted]	Electronic		✓
NDA	[redacted]	DDOP	000	[redacted]	[redacted]	Mixed		✓
NDA	22377	DNP	000	ALSUMA	KING PHARMACEUTICALS INC	Paper		
NDA	[redacted]	DRUP	000	[redacted]	[redacted]	Electronic		
NDA	22383	DPARP	000	ARCAPTA NEOHALER	NOVARTIS PHARMACEUTICALS CORP	Electronic	✓	
NDA	22395	DAAP	000	QUTENZA	NEUROGESX INC	Electronic		
NDA	22404	DSPTP	000	Oravig	Bioalliance Pharma	Electronic		
NDA	22411	DPP	000	Oleptro	LABOPHARM INC	Mixed		
NDA	[redacted]	DMEP	000	[redacted]	[redacted]	Electronic		✓
NDA	22430	DRUP	000	LYSTEDA	FERRING PHARMACEUTICALS INC	Electronic		✓
NDA	22436	DAVP	000	ACYCLOVIR AND HYDROCORTISONE CREAM, 5%/1% TOPICAL	MEDA PHARMACEUTICALS INC	Electronic		
NDA	[redacted]	DMIP	000	[redacted]	[redacted]	Electronic		✓
NDA	22468	DDOP	000	FOLOTYN	ALLOS THERAPEUTICS INC	Electronic	✓	

NDA/ BLA	Application Number	Division	Seq #	Trade Name	Applicant	Submission Format	Gate-way	Deep Dive
NDA	22470	DNCE	000	NEXCEDE	NOVARTIS CONSUMER HEALTH INC	Electronic		
NDA	[redacted]	DGP	000	[redacted]	[redacted]	Electronic	✓	✓
NDA	[redacted]	DPP	000	[redacted]	[redacted]	Mixed		✓
NDA	22511	DGP	000	VIMOVO	ASTRAZENECA LP	Electronic		
NDA	22554	DGP	000	XIFAXAN	SALIX PHARMACEUTICALS INC	Mixed		
NDA	22555	DMIP	000	HEXVIX	PHOTOCURE ASA	Electronic	✓	
NDA	22565	DNCE	000	Advil Congestion Relief	WYETH CONSUMER HEALTHCARE	Electronic	✓	✓
NDA	22571	DDDP	000	CUVPOSA ORAL SOLUTION	SHIONOGI PHARMA INC	Electronic	✓	✓
NDA	22575	DGP	000	VPRIV	SHIRE HUMAN GENETIC THERAPIES INC	Electronic	✓	✓
NDA	22581	DCRP	000	PHOSLYRA	FRESENIUS MEDICAL CARE NORTH AMERICA	Mixed		
NDA	50824	DSPTP	000	N/A	DAVA PHARMACEUTICALS INC	Mixed		✓
BLA	103000	DDDP	5194	BOTOX	ALLERGAN, INC	Electronic	✓	
BLA	103174	DBA	5520	Prolastin-C	Talecris Biotherapeutics, Inc.	Electronic	✓	✓
BLA	103606	DVRPA	5374	VAQTA	MERCK & CO., INC.	Electronic	✓	✓
BLA	103788	DBA	5144	CROFAB	PROTHERICS INC	Paper		
BLA	125019	DBOP	0156	ZEVALIN	Spectrum Pharmaceuticals, Inc.	Electronic		
BLA	125108	DVRPA	0341	ProQuad	Merck Sharp & Dohme Corp.	Electronic	✓	✓
BLA	125288	DSPTP	000	Belatacept	Bristol-Myers Squibb	Electronic		✓
BLA	125293	DPARP	000	KRYSTEXXA	Savient Pharmaceuticals	Electronic	✓	✓
BLA	125300	DVRPA	000	MENVEO	NOVARTIS VACCINES AND DIAGNOSTICS, INC.	Electronic		
BLA	125325	DBA	000	GLASSIA	KAMADA LTD. #1826	Electronic		✓
BLA	125326	DBOP	000	ARZERRA	GLAXO GROUP LIMITED D/B/A GLAXOSMITHKLINE #1809	Electronic		✓
BLA	125329	DBA	000	GAMMAPLEX	BIO PRODUCTS LABORATORY	Paper		
BLA	125338	DPARP	000	XIAFLEX	Auxilium Pharmaceuticals, Inc.	Electronic		
BLA	125347	DVRPA	000	HIBERIX	GlaxoSmithKline Biologicals	Electronic		
BLA	125348	DCGT	000	Isolagen Therapy	Fibrocell Technologies, Inc.	Paper		
BLA	125350	DBA	000	Hizentra	CSL Behring AG	Electronic	✓	✓
BLA	125351	DBA	000	TachoSil PTS 042	Nycomed Danmark ApS	Electronic		

NDA/ BLA	Application Number	Division	Seq #	Trade Name	Applicant	Submission Format	Gate-way	Deep Dive
BLA	125354	DVRPA	000	Coccidioidin SD	Allermed Laboratories	Electronic		✓
BLA	125360	DNP	000	XEOMIN	MERZ PHARMACEUTICALS GMBH	Electronic	✓	
BLA	[redacted]	DVRPA	000	[redacted]	[redacted]	Electronic		✓
BLA	[redacted]	DAVP	000	[redacted]	[redacted]	Electronic		