

CDER Data Standards Plan

Version 1.1

**Office of Planning and Informatics
FDA/CDER
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Revision History

Date	Version	Summary of Changes
March 31,2010	1.0	Original Draft Version
December 15, 2010	1.1	Removed draft watermark. Applied grammatical corrections. Addressed comments on the draft version.

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1 Introduction

The Center for Drug Evaluation and Research (CDER) receives an enormous and growing amount of data in a variety of regulatory submissions from a multitude of sources and in a variety of formats. This wealth of data holds great potential to advance CDER's regulatory and scientific work, but the present lack of standardized data creates significant challenges to realizing that potential. The volume and complexity of drug-related information submitted to CDER for regulatory review is creating significant challenges to the Center's ability to efficiently and effectively perform its critical public health mission.

The lack of standardized data affects CDER's review processes by curtailing a reviewer's ability to perform integral tasks such as rapid acquisition, analysis, storage and reporting of regulatory data. Improved data quality, accessibility and predictability will give reviewers more time to carry out complex analyses, ask in-depth questions and address late-emerging issues. Standardized data will allow reviewers to increase review consistency and perform evaluations across the drug lifecycle. These improvements will improve the Center's performance across key drug regulatory functions and ongoing business operations, including pre-market review, post-market safety, oversight of drug quality, and oversight of drug promotion.

Standardization of data submissions, a requirement for electronic submissions, and a robust computational infrastructure would make significant improvements possible. Facilitating improvements requires careful analysis, advanced planning, project management, expert input, and effective communication among all key stakeholders. In order to be successful, a plan is required to identify, develop, adopt, and maintain data standards that meet CDER "end user" needs.

The objectives of the data standards plan are to establish a comprehensive data standards program at CDER, ensure development of data standards for all key data needed to make regulatory decisions, and ensure successful use of those standardized data. This program is aligned with the principles in standards management at the FDA. From the FDA's perspective, standards should:

- Use voluntary consensus based standards development process in accredited standards development organizations in place of government unique standards unless such standards are inconsistent with law or otherwise impractical;
- Align with existing health information technology initiatives, laws, regulations, and mandates (e.g. executive orders); and
- Coordinate with other standards currently in use.

This document, (Version 1.1) represents the first release of the CDER data standards plan. A draft version (Version 1.0) was developed in March 2010. A public docket was opened to solicit public comments on the draft plan. Four public comments were received during the comment period. In developing Version 1.1, we considered public and internal comments received. We expect that the data standards plan will be revised as needed to address changing needs as a result of scientific and regulatory advances, evolution of data standards, and other such factors.

For the purposes of this plan, data standards are meant to include the following types of standards:

- Data Exchange – This type of standard includes the required content and format in which particular types of data are to be presented and exchanged. Data exchange standards include file format specifications.
- Data Format – This type of standard describes the structure, content, naming conventions, and variable formats for any given data domain.
- Terminology – This type of standard provides controlled vocabularies to improve communications and enhance analytical capabilities

The remainder of this document is organized as follows:

[Section 2](#) provides an overview of major regulatory business functions in CDER that will be target areas for support through further development of the data standards program. The overview does not provide an exhaustive treatment of the areas for data standards and data standards management. Instead, it tries to provide some preliminary context and quantification of the scale of need and opportunity for modernization through standardization of regulatory data submissions.

[Section 3](#) outlines the general approach proposed for development of CDER's comprehensive data standards program. It describes a set of recommended projects, to begin within the first 6 months of CY 2010, to ensure that the basic objectives of the plan are met.

[Section 4](#) describes a proposed program management framework within which CDER's comprehensive data standards program may be developed and sustained. It is intended to evolve into formal specification of CDER "Good Data Standards Management" practices, envisioned as a set of written policies and procedures that constitute a system staff can use to consistently execute rigorous and predictable data standards management processes.

One proposed component of this system includes the establishment of a CDER Data Standards Program Board (DSPB), to oversee the execution of this plan. [Appendix A](#) contains a draft charter for the DSPB, outlining its roles and responsibilities within CDER's existing governance structure.

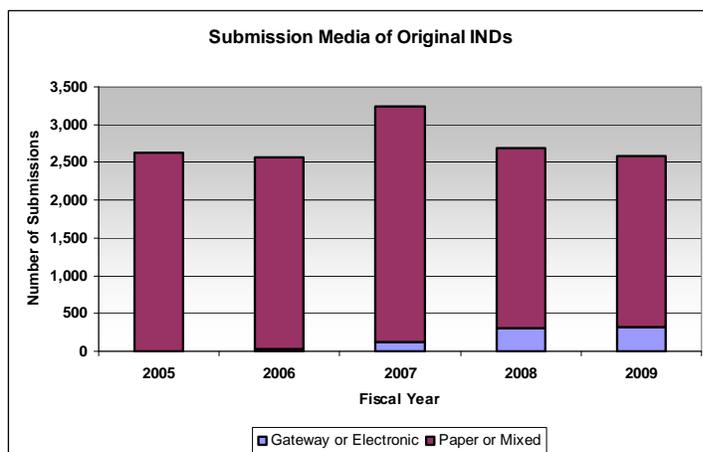
[Appendix B](#) provides additional data on the recent trends in volume and format of CDER data submissions.

2 Current State of Data Submissions and Need for Data Standards

CDER is responsible for ensuring that prescription, generic, and over-the-counter (OTC) drug products are safe, effective, and adequately available to the public. The Center is also responsible for monitoring all drugs that are marketed in the United States for unexpected health risks, and for monitoring and enforcing the quality of drug products. The following section provides an overview of the challenges posed by the lack of standardized data in each CDER regulatory business area.

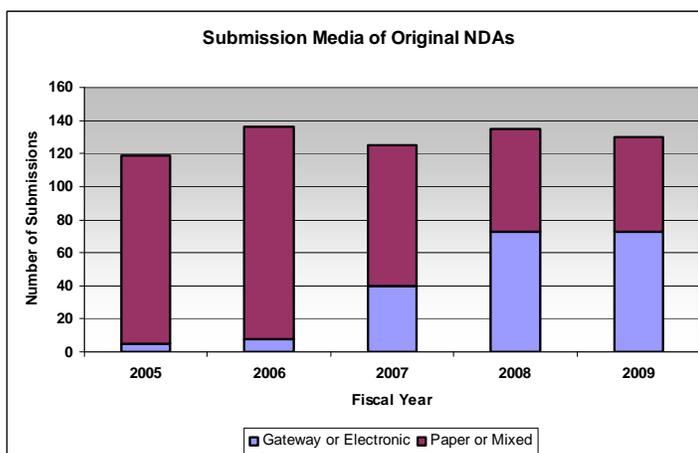
2.1 Trends in Volume and Format of Data Submissions Related to CDER Oversight of Drug Development and Pre-Market Review

CDER is responsible for ensuring the safety of human subjects in clinical trials, the safety and efficacy of new drug and therapeutic biologics, and the pharmaceutical equivalence of generic drug applications.



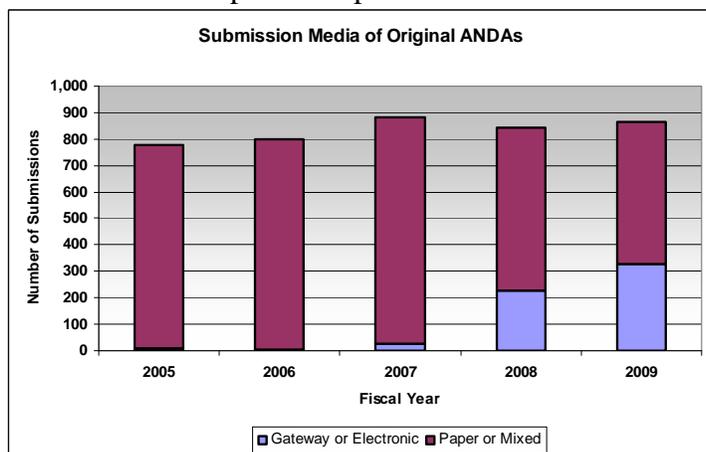
electronic, 84% (2,237) of IND submissions were still paper-based in FY2009, and less than 12% utilized the electronic Common Technical Document (eCTD) format. Of the over 84,000 IND amendments received by CDER in FY 2009, 29% of these submissions were in eCTD format, and over 69% (over 58,000 amendments) were paper-based submissions.

At the completion of the investigational phase, the prospective new drug or therapeutic biologic is submitted to CDER in the form of a New Drug Application (NDA) or Biologic Licensing Application (BLA). These submissions contain an enormous amount of data including patient-level clinical trial data, manufacturing, and quality control data. NDAs are reviewed with the goal of acting within relatively tight timelines.



CDER currently accepts NDAs, BLAs, and their respective supplements as paper-only, electronic-only, and as a hybrid of the two media. Sponsors have increasingly shifted to the submission of original NDAs in electronic format. A fully-electronic NDA submission is about 10 GB on average; a paper-only NDA submission may include several hundred reams of paper. Electronic submissions may or may not be formatted according to the eCTD standard and the enclosed data sets may or may not be formatted according to an existing standard such as the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) or Analysis Data Model (ADaM).

When the initial period of patent and market exclusivity expires, an innovator product may be subject to generic competition. CDER reviews



CDER reviews Abbreviated New Drug Applications (ANDAs) for generic products to ensure they are bioequivalent to the innovator product. The annual number of ANDAs submitted to the agency has grown by nearly three-fold since 2001. Like their innovator counterparts, ANDAs are often subject to manufacturing and labeling supplements. While progress has been made in moving ANDAs and their supplements towards eCTD submissions and away from paper-based submissions, much progress remains to be made. See Appendix

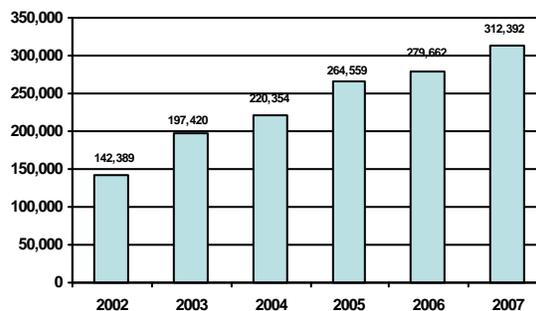
B for additional information on data submission trends.

2.2 Trends in Scope of Oversight of Drug Quality Driving Need for Better Data

CDER has several regulatory inspection responsibilities including: drug product distribution; imported products and import facilities; plants where drugs are manufactured, packed, tested, and stored; and clinical investigator sites.

The globalization of regulated industry operations has created significant challenges for CDER's oversight of drug quality. For example, between FY2002 and 2007, the number of FDA-regulated foreign drug facilities doubled, including a 7-fold increase in drug facilities in China and a 25-fold increase in facilities in India. Due to resource constraints, the FDA is able to inspect less than 1% of the current 321,000 drug import lines.

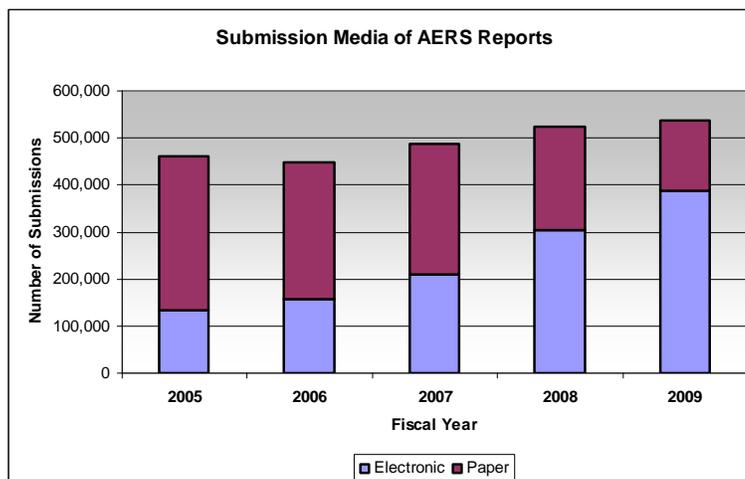
Receipt of manufacturing, investigator site, and facility data in standardized form will enable a multi-level aggregation of characteristics across manufacturers, applications, and clinical studies, which will enable a more-informed selection of sites, plants, and facilities to be inspected.



Growth in Drug Import Lines 2002-2007

2.3 Trends in Volume and Format of Submissions Related to Oversight of Post-Market Drug Safety

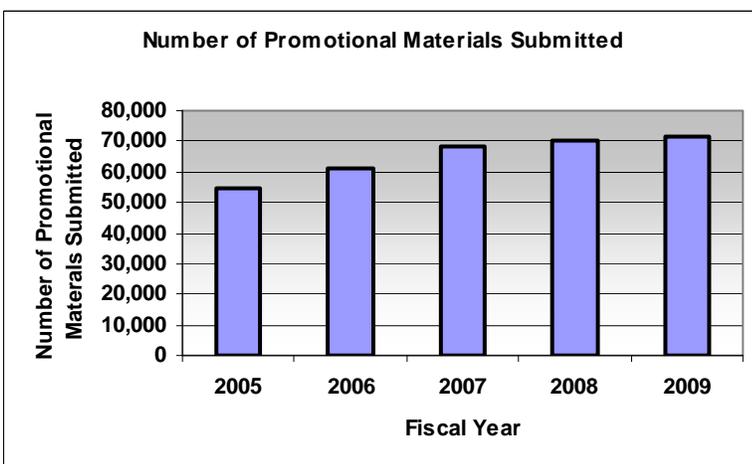
CDER conducts a range of activities to detect safety concerns that emerge after a drug has been approved. Since the Adverse Event Reporting System (AERS) data are currently coded according to International Conference on Harmonization (ICH) E2B(M) guidance, adoption of data standards for premarket studies will allow the integration of clinical study data with the observational data gathered in the post-market AERS system. While a growing proportion of these individual case safety reports are being submitted to the FDA in electronic format, a significant proportion are still submitted in paper format.



CDER also works to ensure the safe use of drug products by preventing medication errors due to brand name and/or labeling confusion. Electronic product labeling, enabled by data standards and related processes, will enable CDER to further reduce the risk of medical mistakes. CDER has already adopted the HL7 Structured Product Labeling (SPL) standard to support its drug labeling and drug registration and listing processes.

2.4 Trends in Volume of Sponsor Submissions Related to Oversight of Drug Promotion

CDER regulates the drug information, advertisements, and other promotional materials distributed to physicians, healthcare professionals, and consumers. CDER received 71,759 promotional materials in FY09, a 31% increase over FY05.



All of these drug regulatory areas present opportunities for enhancement from the potential availability of standardized electronic data. The section that follows outlines a general approach to CDER data standards development and describes specific projects to be pursued in the near term.

3 Approach to Data Standards Management

3.1 General Approach

With an increasing volume of submissions, CDER must transition to standardized electronic regulatory submissions in order to meet strict regulatory deadlines. This section outlines a proposal for a CDER Data Standards Program. Associated projects and activities should adhere to the following three guiding principles:

1. Projects should be focused on addressing end-user requirements. This “reviewer-centered” approach should work from requirements to specifications to implementation, to produce the most useful standards to support modern regulatory work.
2. Data standards projects and activities should be focused on concrete near-term improvements that benefit pre-market drug review and other regulatory functions. The projects with near-term benefits should align with the Center’s long-range informatics goals.
3. Data standards-related decisions and standards-related processes should be clear, predictable, and widely communicated in a timely manner to all stakeholders. Moreover, the timeline associated with data standards adoption should be made clear to both internal and external stakeholders, such that these organizations can prepare to adopt these data standards.

A holistic approach to developing data standards to facilitate effective, efficient, and forward-looking regulatory decision making consists of four objectives:

- **Ensure that useful, publicly-available data standards exist.** An early and necessary step toward that objective involves developing an inventory of data elements required for drug regulatory decision making, and building on this inventory to establish data standards for all data needed to make regulatory decisions. FDA reviewers must have the opportunity to review the candidate terminology and related implementation guides in order to ensure that the proposed standards meet their scientific and regulatory requirements.
- **Ensure that there is a well-defined standards adoption process in place.** A well-defined standards adoption process must consider the impact of adoption on CDER’s core business processes and the associated regulatory burden. The process must clearly address the goal of adopting a given standard, the changes necessary to the business and review processes, the tools required to integrate the standard, an implementation schedule that is sensitive to the abilities of the stakeholders to successfully implement the standard (while still maintaining forward momentum) and a well-defined, comprehensive communication plan that addresses outreach and education.
- **Ensure that regulatory data is submitted according to those standards.** To ensure that CDER receives regulatory submissions in the expected form, the Center needs to align related

regulatory guidance to industry, conduct outreach and training on standards and tools for our reviewers, and provide compliance checklists for both reviewers and sponsors.

- **Ensure that regulatory review processes can fully leverage the standardized data.** To fully utilize standardized data, reviewers need to be able to load, access, and manipulate electronic submissions. This requires planning to ensure the needed server infrastructure is in place, software tools are developed and tested with end-user input, and end-users are trained in the adoption and use of data standards and review tools. It also requires that regulatory business processes be reviewed for potential enhancement with expanded access to better-quality data and new analytic tools.

The rest of this section outlines the priority efforts viewed as necessary to jump start a comprehensive CDER data standards program. Section 4 outlines a proposed structure to establish this program and to ensure coordination of its activities.

3.2 Priority Efforts for the Next 2 Years

To advance toward fully standardized data as rapidly as possible, the following priority projects¹ are proposed for CY 2010 and 2011. The projects outlined below contain differing degrees of specificity, reflecting that these efforts are at various stages of development and readiness:

- Revise the PDUFA IT 5-year plan to clarify for key stakeholders FDA plans for continued and expanded use of regulatory submissions using CDISC standards through FY 2013 and beyond. **(Section 3.2.1)**
- Establish new regulatory requirements for electronic submissions of all study data included in submitted NDAs, BLAs, and ANDAs. **(Section 3.2.2)**
- Establish a CDER Data Standards Program Board (DSPB) to oversee all CDER data standards projects and activities **(Section 3.2.3)**
- Develop a baseline inventory of data standards needs for all of CDER regulatory operations. **(Section 3.2.4)**
- Establish a basic set of clear processes to support data standards development and implementation that would engage all key stakeholders. **(Section 3.2.5)**

By the end of the first two year period, these processes and activities should be incorporated into a functioning comprehensive data standards program that is integrated with and directly supportive of the CDER regulatory mission.

¹ Selection, definition and scope of the projects outlined below responds to the expressed priorities of CDER, from information collected from Senior Leadership, the Computational Science Center Board, subject matter experts in attendance of a CDER Mini-Retreat on Strategy for Clinical Data Standards, and interviews with end-users and support office staff. Importantly it is also informed by activities currently underway among sister agencies, data standard organizations, sponsors, contract research organizations, and academic research centers.

3.2.1 Revise the PDUFA IT 5-year Plan to clarify FDA plans for continued and expanded use of available data standards for regulatory submissions through FY 2013 and beyond.

As part of the 2007 reauthorization of the Prescription Drug User Fee Act (PDUFA), FDA committed to issue a 5-year plan for further enhancement of information technology (IT) to support the process for the review of human drugs. This public document was intended make agency plans for both systems and standards more transparent and predictable to external stakeholders who must also develop systems and use standards that will align with those of FDA.

The 2009 assessment of the PDUFA IT 5-year Plan caused confusion and concern among both external and internal stakeholders because it implied a shift to the submission of study data formatted in accordance with CDISC-HL7 standards within the next few years. More recent internal analysis revealed that the transition to CDISC-HL7 standards will take longer than initially estimated. The PDUFA IT 5-year Plan therefore needed revision to make clear CDER and CBER's intention to continue refining, improving, and expanding the use of CDISC standards for regulatory submissions for the process of human drug review in the near-term, e.g., through FY 2013 and beyond.

The PDUFA Information Management Working Group (PIMWG) published an abbreviated update to the PDUFA IT 5-year Plan in May 2010. Planning for a more comprehensive update is underway.

3.2.2 Establish new regulatory requirements for electronic submission of study data associated with NDAs, BLAs and ANDAs

The existence of data standards that can be used in sponsor application submissions is necessary -- but is not sufficient -- to achieve the goal of standardized electronic regulatory submissions to CDER. The Center will not achieve the full public health benefits nor the potential efficiencies of electronic review unless all sponsor submissions are electronic and standardized. This requires a change in FDA regulations. Thus, another critical near-term project involves the publication of an Advanced Notice of Proposed Rulemaking to require electronic submissions of all study data submitted to FDA. This rulemaking will be a joint undertaking by CDER and CBER. In addition to this rulemaking CDER and CBER would anticipate further clarifying expectations for standardized data submissions via guidance to industry.

3.2.3 Establish a CDER Data Standards Program Board (DSPB) to oversee all CDER data standards projects and activities

This data standards plan calls for the establishment of a CDER Data Standards Program Board (DSPB) to oversee the ongoing planning, coordination and progress-tracking of Center data standards projects, ensure timely reporting to the CDER Computational Science Center (CSC) Board and to the CDER Executive Committee, and ensure compliance of Center standards projects with the newly established good practices for standards development.

In addition to these Center-internal functions, the DSPB will provide an effective interface with the FDA Data Standards Council (DSC). According to its 2003 charter, the FDA DSC is responsible for coordinating the evaluation, adoption or development and maintenance of health and regulatory data standards supporting the Agency's mission. Historically, however, the representation by FDA Centers, including CDER, has been inconsistent and typically driven by the specific data standard in development. Members of CDER CSC Board have recently identified the need for coordinated Center-level representation to the DSC as a critical ingredient for improved data standards planning at CDER. The proposed CDER DSPB will provide a focal point for coordination and communication of CDER priorities to the FDA DSC.

The CDER DSPB held its initial meeting in July 2010. The DSPB Charter is included in Appendix A.

3.2.4 Inventory data standards needs for CDER.

The goal of this project is to develop an inventory of CDER needs for data standards, beginning with the data submitted by regulated industry. (Note that a later project will address greater standardization of information in CDER-generated regulatory work products.) The inventory will be developed by working with all CDER offices building on key process inputs identified in earlier CDER strategic planning and Computational Science Center road-map interviews conducted in FY 2009.

This plan proposes two concurrent methods for conducting an inventory of the Center's data standard needs:

- A narrowly-focused, therapeutic-area based approach that focuses on specific disease areas (such as tuberculosis, polycystic kidney disease, acute coronary syndrome, oncology, Alzheimer's disease, Parkinson's disease, and diabetes) in which existing work groups have already begun work on standardizing terminology and standardized formats
- A broadly-focused approach centered around drug regulatory business functions and related decision-making. This approach will begin with the scientific and regulatory needs of reviewers in various disciplines and will use these end-user driven requirements as the specifications for the data to be collected, and specifications for the format of submitted data.
 - Related to the broader inventory effort, the Center will review all current and planned rulemaking and guidance development to ensure that planned standards efforts are coordinated with future policy plans.

Together, these approaches should identify therapeutic areas and disciplines where substantial standards development has already taken place, areas where some work has been done, and areas that lack systematic standards development programs. The inventory activities have begun and will include an assessment of needs related to existing standards the Center currently accepts.

3.2.5 Establish a basic set of clear processes to support data standards development and implementation that would engage all key stakeholders

In order to begin a Center-wide process that is clear, predictable, and aggressive in advancing the availability and utility of data standards and standardized data submissions, the Center needs to establish some initial procedures and baseline capabilities. These include the following:

- Develop and initiate a process for prioritization of data standards development activities.

- Develop documentation, guidance, and training materials prior to the roll-out of any data standard.
- Develop and implement a communications strategy to support roll-out of the Center data standards program.
- Establish a clear process for data standards development that engages all key stakeholders.

The subsections that follow provide additional discussion of these initial tasks.

3.2.6 Develop and initiate a process for prioritization of data standards development activities

Because of the multitude of potential data standards development efforts that exist, it will be critical that CDER develop a process for prioritizing its data standards development activities. Prioritization of efforts will likely be based on several factors including: impact on regulatory review process; resource intensiveness; ability to leverage and partner with outside stakeholders; and the current stage of data standard development efforts in disease specific areas.

In the near term, priority should be allocated according to several principles, including:

- Placing emphasis on specific disease areas in which existing groups have already made substantial progress on standardizing terminology and data fields. Among others, these disease areas include tuberculosis, polycystic kidney disease, acute coronary syndrome, oncology, Alzheimer's disease, Parkinson's disease, and diabetes.
- Developing standards in disease areas with relatively large development pipeline would offer substantial return on investment for the Center. If it is anticipated that more NDAs and BLAs will be submitted in a particular therapeutic areas in coming years, standards development now will save substantial time for reviewers in the future. Future marketing application activity might be forecast, for example, by the number of active INDs by therapeutic area in recent years.
- Focusing on other mission-critical areas that can offer a significant improvements in public health, or where substantial development work has already begun and can be built upon to develop needed standards with a relatively modest additional investment of resources. Implementation of data standards should improve the quality of submitted data, and enable reviewers to access the data more quickly to conduct more thorough and timely reviews.

Preparation Activities

Prior to the roll out of any particular data standard, specific deliverables must be in place to support the implementation of the data standard. These deliverables include:

- Guidance to Industry on the expected format of standardized data.
- Training programs and supporting materials (checklists, templates, and specifications. documents) for review divisions to structure data standard-related discussions prior to submission and during the review process.
- Tools to automate data quality checks at the point of submission.
- Post-review debrief template to incorporate reviewers' feedback on data quality.
- A structured database to track implementation problems.

Each of these deliverables is further described below.

3.2.6.1 Guidance to Industry

In conjunction with the publication of a proposed rule requiring electronic submission of sponsor study data, CDER would develop and publish Guidance to Industry that provides more specific information on the data standards to be implemented. The contents of the guidance will be informed by various activities contained in the CDER data standards plan, including the data standards development process and the implementation assessment process.

This guidance will be provided to industry with sufficient lead time to allow sponsors to understand the requirements of the guidance and obtain clarification prior to the implementation date for the data standard.

3.2.6.2 Training programs and supporting materials for reviewers

Supporting documents under development include reviewer check-lists that can be used in pre-NDA meetings with sponsors to reinforce FDA requirements for the format and content of regulatory submissions. Check lists and supporting documentation will help sponsors prepare data for submission by explicitly describing CDER's data preferences and facilitate and inform discussions with sponsors at key points during the product development process. Documents already in existence or currently under development include: Study Data Specifications Document; Analysis Data Specifications Document; [eCTD Validation Specifications](#); and the Standard Data Template for reviewers/divisions.

To ensure the successful uptake of new data standards, training will be offered to reviewers to introduce the standard. Training programs will be tailored to the specific standard being rolled out, and incorporate the above supporting documentation as applicable.

3.2.6.3 Tools to automate data standards conformance checks at submission

Currently, the CDER process to identify CDISC submissions is labor intensive: A weekly report is generated and sent to an individual in the Office of Business Process Support, who reviews the sponsor's cover letter to determine if the application datasets are in SDTM format, and then performs spot checks on a few relevant files to determine if the submission is SDTM-compliant. In the near future, an OpenCDISC validation tool will be rolled out to replace the current labor-intensive review, and perform the initial data assessment.

Systematic, automatic, and regular checks of the format of submitted data will generate a better understanding of several key factors related to data standards adoption, including the rate of uptake of standardized data by sponsors, the degree of adherence to the specified standards, the ability of reviewers to use standard-specific advanced review methods/tools, and the adequacy of the current standards to represent clinical trial data. A formal process for tracking and characterizing standardized submissions to CDER is necessary to successfully transition to a more advanced regulatory process which takes full advantage of the benefits of high quality standardized data.

3.2.6.4 Post-review debrief template to assess reviewers' experience

Systematic assessment of the utility of a particular standard or the quality of a particular submission requires systematic collection of reviewers' experiences after the conclusion of the review process. Development of a post-review debrief template will ensure that the information required to improve the standard and improve future submissions will be collected in a form amenable to analysis. This

template should include the reviewers' impressions of the assessment of data quality, the utility of the standard, suggestions for improvement, and other relevant information.

3.2.6.5 Structured database for implementation problems and insufficiencies

A structured database needs to be developed to store the information gathered at the point of submission (via the automated data standards conformance checks) and after the conclusion of the review cycle (via the post-review debrief template). The design of the database needs to take into account any metrics that will be drawn from the collected data. These include metrics related to data standards conformance and data quality.

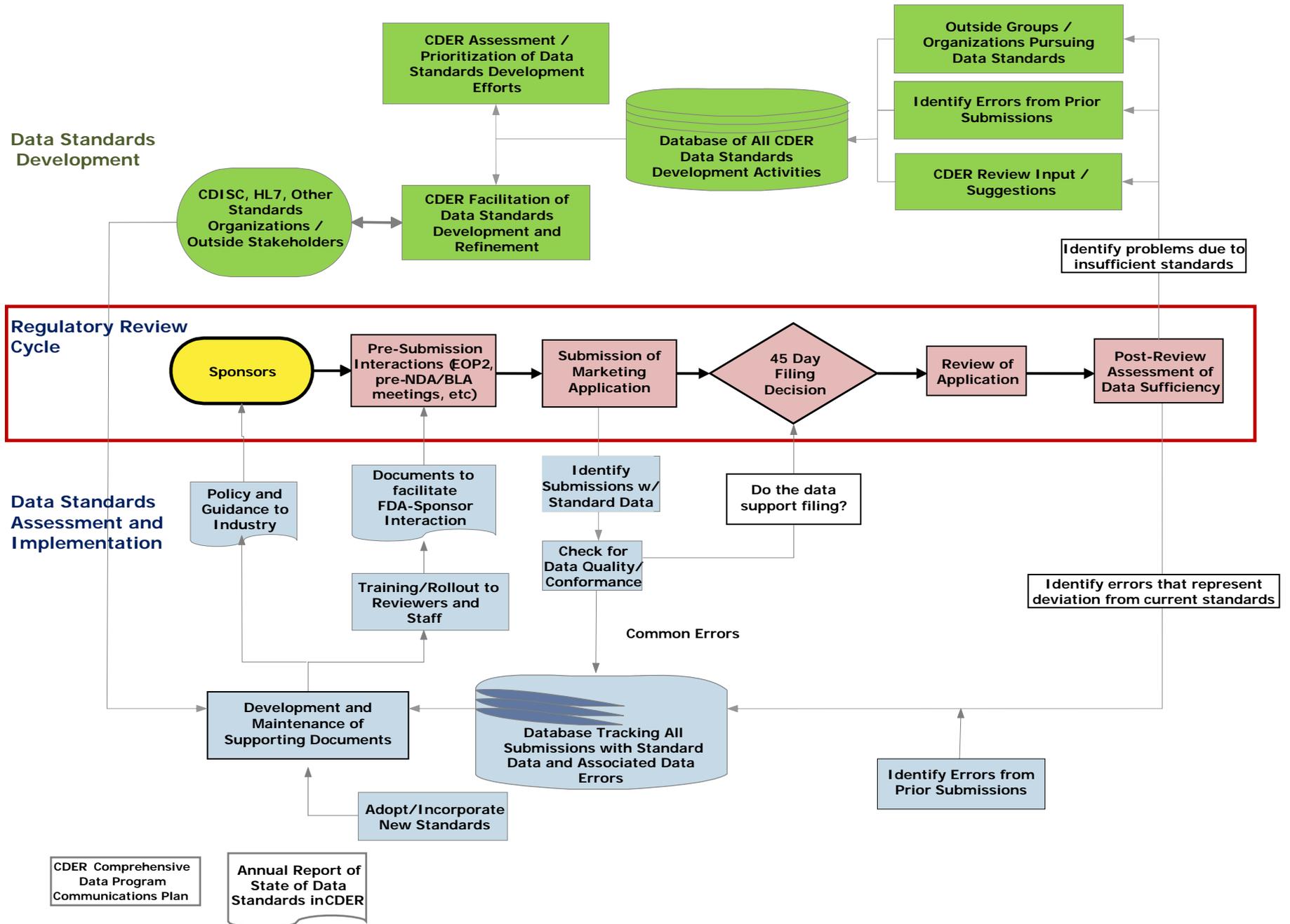
3.2.7 Develop and implement a communications strategy to support roll-out of the Center data standards program.

This purpose of this project is to establish a robust communication structure to support the Center's data standards goals. Well-timed communications, crafted for the intended audience in terms of content and length, will be developed for internal and external stakeholders. Communications materials should be developed to clearly articulate CDER understanding of how data standards decisions impact stakeholders, in conjunction with development of an inventory and calendar of critical stakeholder communication opportunities, for both internal and external audiences.

This project will be executed in consultation with the Office of Communications. A central feature of this communication strategy would be regular interaction and support from the CSC Communications Team, comprised of members of the CSC Board, OTS, OND, OCOMM, OCTEC, and OBPS. This team will serve as a resource and will facilitate communication of data standards efforts which may include, but will not be limited to, data standards updates, training resources, and presentations.

To maximize the effectiveness of communications related to standards it is critical that CDER remove ambiguity in published data standards. For example, CDER reviewers should be empowered to work with standards development organizations such as CDISC to remove ambiguity in the SDTM and ADaM implementation guides. Similarly, review divisions should be encouraged to provide additional data specification documents to ensure that the data managers in the sponsor or CRO clearly understand CDER's data requirements.

Figure 1. Example of pre-market review and refinement of data standards



3.2.8 Establish a clear process for data standards implementation that engages all stakeholders

Figure 1 illustrates key steps in the integration of data standards development work (in green) and data standards implementation and assessment (in blue) into CDER's regulatory review cycle. These key steps correspond to the preparation activities identified Section 3.2.7, and include:

- Providing guidance for industry on the preferred format of standardized data.
- Offering training for reviewers to support the adoption of data standards across all CDER regulatory processes.
- Implementing a process to identify and track all submissions that include standardized data and rapidly assess quality and conformance to data standards at the time of submission.
- Updating databases to keep track of the data standards themselves, data standards development activities, and problems with existing standards or the implementation of existing standards.

Since data standards will evolve as scientific and regulatory needs change, this process is designed to be iterative and build upon the learning experiences gained from prior reviews. Data standards development, implementation, and assessment affect the review cycle at three points: prior to submission; at submission; and after the conclusion of the review process.

Figure 1 shows that prior to submission CDER will provide training to reviewers and guidance to industry. The sponsor will be provided with a comprehensive set of guidance documents describing the format and content of the standardized data preferred for NDAs and BLAs submitted to CDER review divisions. During pre-submission interactions between the sponsor and the review division, CDER reviewers will be expected to refer to checklists and training materials that will allow them to provide the sponsor with clear answers to questions related to the format and content of standardized data submissions.

When a submission is received, CDER will use automated tools to identify submissions with standardized data. To the extent possible, these tools will be open-source, such that sponsors, CROs, and others will be able to perform the CDER validation checks prior to submission. All submissions will be checked for data quality and their degree of conformance to existing guidance. As Figure 1 proposes, the results of this initial data quality assessment will be discussed at the 45-day filing meeting, and any errors generated during the data evaluation process will be entered into a tracking database.

At the conclusion of the review process, an assessment of the data sufficiency will allow CDER to identify data-related problems that arose during the review process. These problems will generally fall into two categories: problems due to deviations from current standards (which can be addressed through the blue implementation process in Figure 1); and problems due to ambiguity or inadequacy in the current standard specification (which can be addressed through the green standards development process in Figure 1).

CDER will analyze various measures derived from the databases identified in Figure 1 to develop measurements and reporting requirements. These requirements would include the timing of reports, ownership for creation of reports, and presentation of results to relevant persons/audiences, as well as determining what data elements to track for assessment of process efficiency. This would include review of the requirements of the business processes to which the standards are being applied.

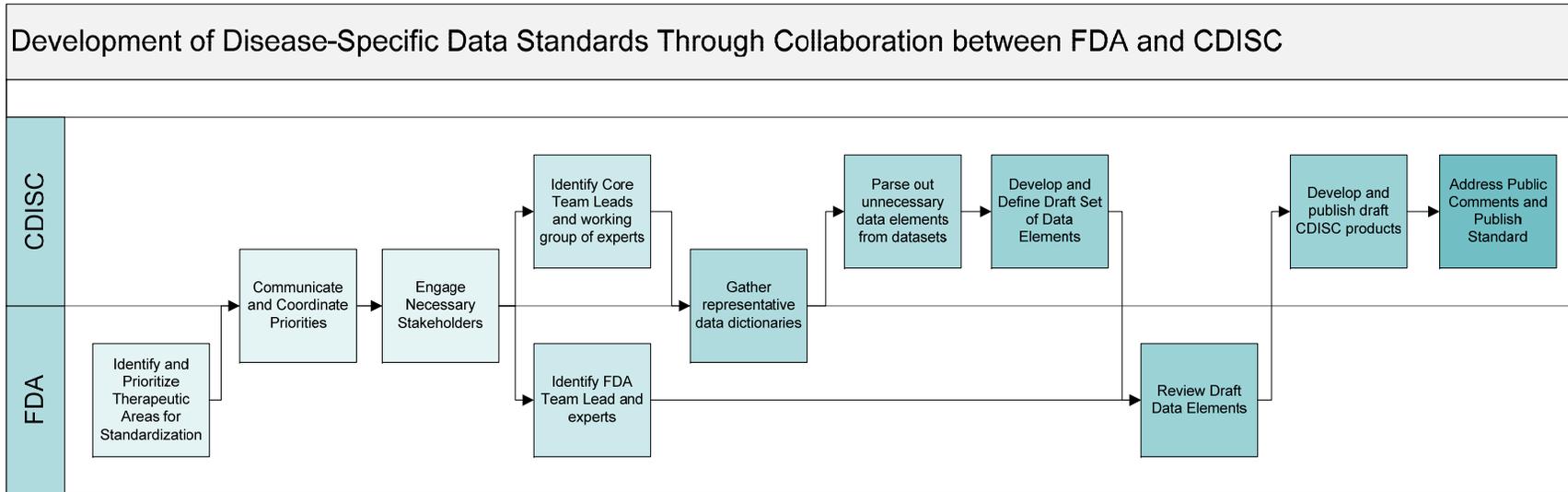
3.2.9 Establish a clear process for data standards development (good data standards development practices) and implementation that engages all key stakeholders

Where current standard specifications are not available or not adequate, CDER will need to engage appropriate SDOs, (e.g., CDISC) as well as industry to take full advantage of the capabilities offered by the formal SDO process.

One of the efforts that this plan proposes includes a narrowly focused, therapeutic-area based approach that focuses on specific disease areas (such as tuberculosis, polycystic kidney disease, acute coronary syndrome, oncology, Alzheimer's disease, Parkinson's disease, and diabetes) in which existing groups have already begun work on standardizing terminology and standardized formats.

Figure 2 illustrates how the process of data standards development for a particular therapeutic area could proceed, with FDA working in collaboration with CDISC and other stakeholders.

Figure 2



Identify and Prioritize Therapeutic Areas for Standardization: FDA senior management at the Center level will collaborate to identify and prioritize target diseases and therapeutic areas that lack adequate data standards.

Communicate and Coordinate Priorities: FDA will communicate its priorities with CDISC. FDA and CDISC will determine the level of resources and time needed to develop standards for the targeted therapeutic areas. (Note: Collaboration with CDISC is an example; FDA plans to collaborate with additional SDOs as appropriate.)

Engage Necessary Stakeholders: FDA will publish a notice in the Federal Register informing stakeholders of the data standards development effort, and requesting that stakeholders share existing data dictionaries being used in specified priority therapeutic areas. FDA will continue to communicate with external stakeholders on an ongoing basis through existing venues such as meetings of the DIA, HL7, CDISC and others.

Identify Core Team Leads and Working Group Experts, Identify FDA Team Leads and Working Group Experts: FDA and CDISC will identify project managers and subject matter experts to participate, and assign project managers able to commit sufficient time to the project.

Gather Representative Controlled Vocabularies: FDA will use the public docket to gather representative controlled vocabularies from industry and other stakeholders. FDA and CDISC will establish and enforce a set of criteria to determine which controlled vocabularies will form the basis of the standard. Additionally, FDA will work to ensure that there are established and well-defined governance processes around these vocabularies.

Parse Out Unnecessary Data Elements from Data Dictionaries: CDISC will parse out unnecessary data elements from the selected data dictionaries. These include elements that are irrelevant, duplicative, or already incorporated into existing CDISC standards.

Develop and Finalize Draft Set of Data Elements: The remaining data elements will form the basis of a draft set of data elements to be incorporated into the standard. CDISC data standards experts and subject matter experts will work to further parse and refine the data elements.

Review Draft Data Elements: FDA will conduct a final review of the draft data elements prior to their development into CDISC products. CDISC may convene stakeholder focus groups--to conduct additional reviews of the draft data elements.

Develop and publish draft CDISC products: CDISC will develop draft data elements into CDISC products, including SDTM domains and CDASH case report forms. Draft versions of these products will be published and made available for public comment.

Address Public Comments and Publish Standard: CDISC will address public comments and publish the finalized standard.

3.3 Incorporate processes into an ongoing, comprehensive program.

Following the initial development of some core procedures to enable a rapid start-up of CDER data standards work, particularly in the area of pre-market drug review, the Center will work to incorporate these components into a comprehensive program that provides a system for implementation, training, troubleshooting, learning about where current standards need specific further improvement, and providing well-coordinated feedback to SDOs and other stakeholders.

Accomplishing this would include transitioning the initially established processes described above into on-going execution and updating activities, based on new needs, new findings, and other developments that enable the Center to streamline and otherwise improve its approach.

- Continued tracking and analysis of the format, quality and standards-conformance of all submissions to CDER.
- Continued assessment of data standards needs across all of CDER, and reporting these findings to agency management. This process should include the ability to identify areas where current data standards are in need of further refinement as well as areas where no current data standards exist and therefore need to be developed.
- Conducting periodic review and updating of the prioritization of data standards development activities, to take account of potential changes in Center needs and priorities.
- Continued maintenance of the databases for on-going data standards-related data, meta-data, and standards development activities, and development of reports for Center management based on summarization and analysis of this data.
- Conducting on-going training of reviewers and roll-out of data standards processes, supporting documents, and activities, and evaluation and continued enhancement of these processes based on reviewer feedback.
- Continued implementation and collection of feedback on the communications plan developed to enhance the success of the data standards program.
- On-going operation, evaluation and improvement of the proposed “concept of operations” for governance of data standards development and lifecycle management. (See Section 4).

The Center is committed to working throughout the standards development and implementation processes with stakeholders to develop appropriate data standards adoption, testing and implementation plans with phase-in periods and to maintain clear communication of data submission expectations between CDER and sponsors.

4 Concept of Operations

In order to improve data quality as quickly as possible this plan puts forth a concept of operations to support and leverage existing standards and ongoing projects while developing the necessary infrastructure to meet long-term goals. This includes:

- *Identifying and supporting regulatory business requirements* – Data standards development to support CDER’s mission must be planned, prioritized, specified, tested and implemented to maximize regulatory decision-maker support and practical business value, beginning in the near-term. This means that regulatory requirements and end-user needs, as well as current technological and resource realities drive planning and implementation.
- *Developing organizational infrastructure to sustain good progress and good process* – Clear and efficient procedures need to be developed and proper oversight must be established to ensure implementation of good data standards practices in CDER’s operating environment.
- *Early consultation and planning for needed regulatory policy changes* – Policy development should be properly planned and sequenced with other data standardization efforts to enable smooth and expeditious data standards adoption and utilization. This requires early analysis and consultation with Center regulatory policy experts in parallel with consultations with scientific subject matter experts. Without timely regulatory changes consistent with current statutory authority, standard adoption will be delayed and incomplete and the value of data standards efforts will be likewise diminished.
- *Communicating data standards needs and plans to all stakeholders* – To minimize implementation costs and maximize the benefit from new data standards, CDER must work to ensure all key stakeholders are engaged. This will require ongoing efforts to ensure clear and consistent communication both within CDER and with external stakeholders. The development of this data standards plan will help accomplish this.

These processes must move forward in a synchronized manner to ensure the smoothest and most expeditious data standards development, adoption, and utilization effort. The proposed program management framework would be designed to ensure that.

4.1 Program Management Framework

Any single data standard development, adoption and utilization effort presents complex management challenges. CDER requires a program and project management and governance structure that can efficiently deliver practical results while adroitly managing the complexity of a portfolio of data standards projects. The adopted structure should also provide the flexibility to incorporate continuous learning and process improvement.

This section of the CDER data standards plan outlines principles for a good standards development and management process. Because a data standard, like information systems, needs to be well-designed, tested, implemented and updated as user needs change, we have proposed a “life cycle” management approach informed by existing processes. For example, the US Department of Health and Human Services (HHS) Enterprise Performance Lifecycle (EPLC) offers a framework for rigorous application of project management and best practices to information technology governance².

Another example is offered by the Systems Development Lifecycle (SDLC), a systems engineering framework for planning and controlling the creation of an information system³. A third model we’ve drawn on is the Project Integration Management model espoused by the Project Management Body of Knowledge⁴. Elements of these or similar models could be adapted to the CDER data standards program, to provide the necessary structure to advance and manage a portfolio of data standards-related efforts.

The following discusses a high-level example of how the EPLC could be shaped to create a CDER Data Standards Management Lifecycle system to support CDER’s comprehensive data standards program. This model is intended to provide the proposed DSPB with a starting point in defining the requisite management and governance structure to apply to the processes described in Diagram 1 of Section 3. Data standards projects currently underway will be supported and evaluated as this infrastructure is developed, thus providing critical process engineering information, from which lifecycle processes may be developed. This approach allows CDER to maximize the benefits of ongoing efforts while a fully functional process and structure for Data Standards Management Lifecycle is developed.

The EPLC has been developed by HHS to provide a consistent yet flexible framework for improving the quality of IT project planning and execution while reducing risks. It consists of ten lifecycle phases within which activities, responsibilities, reviews, and deliverables are defined. The schematic below follows the spirit of the EPLC framework but is tailored to CDER’s data standards projects (See Figure 4-1). It consists of nine lifecycle phases.

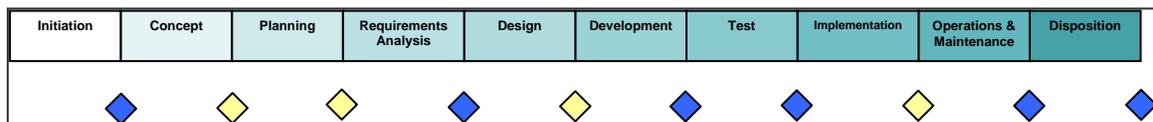
² The Enterprise Performance Lifecycle Framework- Overview Document, HHS.
http://www.hhs.gov/ocio/eplc/eplc_framework_v1point2.pdf. Retrieved December 20, 2009

³ Selecting a Development Approach. HHS, CMS.
<http://www.cms.hhs.gov/SystemLifecycleFramework/Downloads/SelectingDevelopmentApproach.pdf>, Retrieved December 20, 2009

⁴ Guide to the Project Management Body of Knowledge – Third Edition. (2004) Project Management Institute, Newtown Square, PA

4.1.1 Figure 3.1 Illustrative Phases of “Data Standards Management Lifecycle”

The figure below depicts the stages that would comprise the proposed Data Standards Management Lifecycle, and the discussion provides a brief description of the activities contemplated at each stage. The blue (or darker colored) diamonds depict that exit criteria are applied to ensure appropriate progression of data standards projects through the lifecycle. The yellow (or lighter colored) diamonds indicate that a formal Stage Gate Review is also a part of the exit criteria.



The phases of the EPLC applied to data standards management at CDER may involve the following:

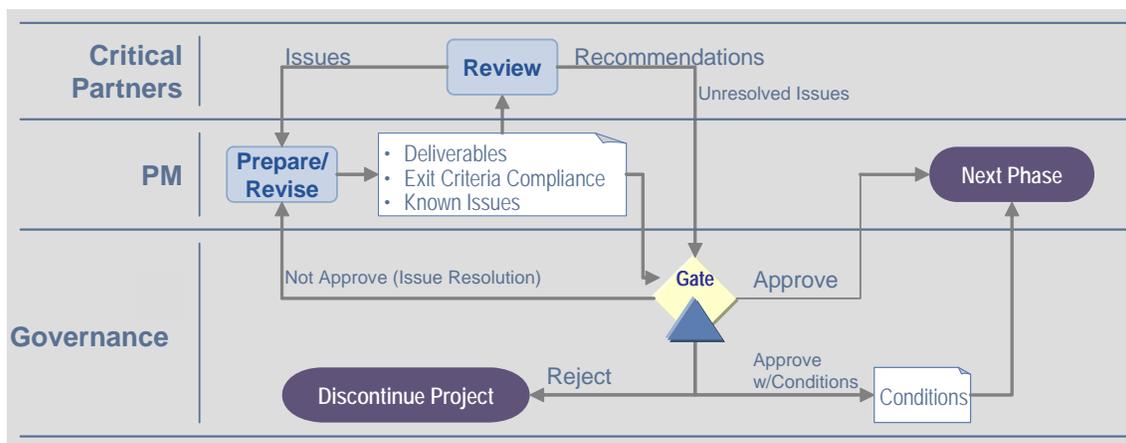
1. **Initiation** begins with identification of the data standards need. This might be based on analysis of CDER data standard priorities, or be triggered by external factors, such as development of a drug-relevant standard by an external stakeholder. It might also be triggered by periodic review of existing data standards and identification of the need for updating.
2. **Concept** entails development of the user business case for the standard development and is the first phase that would ideally require stage-gate review and approval before the project proceeds any further. Consideration should be given to the formation of an industry-side business case that helps improve the prospects of success.
3. **Planning** entails complete development of a full project management plan incorporating business and related policy requirements, training, communications, infrastructure and resources required for the project.
4. **Requirements Analysis** develops a detailed analysis of functional and supporting requirements. This may include identification of specific decision process requirements, hardware and software requirements, policy, regulatory, training, and communications needs.
5. **Design** develops design documents and would typically involve active participation with data standards organizations development organizations (SDOs) and the FDA DSC. This phase would include more detailed internal specification of regulatory and policy needs, and training and communications plans.
6. **Development** would entail participation in standard development typically in collaboration with other stakeholders and related SDOs, and includes preparations for pilot testing of a proposed new standard.
7. **Testing** involves the proto-type data standard and related deliverables and recommends refinements as necessary, based on analysis of the results of pilots,

8. **Implementation** rolls out an operations-ready version of the standard and includes pre-testing and assurance of the readiness of needed systems infrastructure, policy requirements, internal user training, external stakeholder advance awareness and readiness, to ensure successful initiation of the use of the new data standard.
9. **Operations & Maintenance** consists of ongoing oversight and analysis of systems, processes and standards to ensure data standards and all supporting and implementing systems are fully optimized. This includes tracking, reporting and evaluation programs that will inform a periodic prioritization review that will be a critical component of the CDER Data Standards Management Lifecycle.

4.2 Stage Gate Reviews

An important feature of the EPLC framework is the *stage-gate review*. As a project moves from one phase into the next, a review is required to ensure phase objectives have been met, plans for the next phase are laying the foundation for success, and strategies have been developed to mitigate potential risks inherent in the coming phase. A schematic of this process is shown in Figure 4-2⁵ below.

4.2.1 Figure 3-2 Illustrative Process for Stage Gate Reviews



As this schematic shows, if the objective of the exiting phase and the plan for the coming phase has not been adequately accomplished or sufficiently articulated, the stage gate

⁵ From Enterprise Performance Life Cycle Framework, page 19.
http://www.hhs.gov/ocio/eplc/eplc_framework_v1point2.pdf . Retrieved December 10, 2009

review will flag these issues and either 1) require resolution before the project may proceed into the next phase, 2) allow the project to continue into the next phase under specified conditions, or 3) if warranted the project can be discontinued. This will ensure quality control, and risk management, and will provide an avenue to cancel a project and free up resources if the prospect of successful project completion diminishes below an acceptable threshold.

4.3 Participant Roles in Proposed Data Standards Lifecycle Management

Effective and efficient management of a portfolio of data standards projects will require coordinated efforts and clear roles for multiple participants within and outside FDA.⁶

- **FDA Data Standards Council** – develops technical aspects of specific data exchange standards for the FDA.
- **CDER Data Standard Program Board (DSPB)** – provides consistent oversight of CDER data standards activities, recommends resource investments, policies, and procedures for interaction with outside stakeholders; and recommends and oversees implementation of CDER business processes to iteratively define, adopt, and enforce standards.
- **CDER Data Standards Project Teams.** This plan envisions the formation of project teams organized around specific data standards efforts that are identified as priorities by CDER senior management, to the DSPB. The work plans developed and executed by these teams will be centrally tracked by the CDER DSPB. The DSPB will both oversee teams' progress and to ensure that teams are adequately resourced to perform the work they have been assigned.
- **CDER Regulatory End Users and Other Internal Subject Matter Experts** – provide critical substantive input, identifying which data elements need data standards, and other critical regulatory business requirements. They also play a key role in reviewing draft data standards and dictionaries, can inform implementation training requirements, and play a critical role in acceptance testing.
- **FDA/ CDER Regulatory Policy Experts** -- advise data standards projects and consultation to the DSPB at appropriate stages to ensure timely identification of and planning for any changes in regulations or guidance that may be needed to fully implement a new data standard, or to provide adequate advance notice and communication to regulated industry.

⁶ From Enterprise Performance Life Cycle Framework, page 5.
http://www.hhs.gov/ocio/eplc/eplc_framework_v1point2.pdf . Retrieved December 10, 2009

- **External Stakeholders** – includes data standards organizations, other government agencies, health care professionals, patient advocates, academic researchers and regulated industry. These entities provide important perspectives and relevant expertise, and often share FDA’s public health goals and aligned business objectives. Engaging in timely and effective communications and collaboration can reduce the time and costs and increase the success of FDA/CDER data standards efforts.
- **FDA/ CDER Technical Experts** – provide a wide range of critical support including but not limited to advance analysis of technical requirements to support database and tool development, staffing needs including project management, data management and statistical analysis, planning for needed computing infrastructure capacity, financial and contract requirements, and planning and implementation of communications to various stakeholder groups. As is evident by the diversity of these needs, the technical experts to be consulted and engaged span a range of offices and will likely consist of different work groups with appropriate specific assignments that are part of a data standards project plan.

While an effective management system will require significantly more thought, detail, and definition, the approach above lays the foundation for a system that will facilitate project and portfolio tracking, management, strategic decision making. Each project and each phase within each project could be tracked with the use of a visual dashboard-like display. This will allow the DSPB to monitor the status of all current ongoing efforts at any given time, which, in turn, should provide a comprehensive picture of the development of all the pieces of the data standards puzzle and enable the DSPB to provide effect enterprise oversight and cogent strategic direction to both short-term/ early-win projects and longer term goals.

Appendix A: CDER Data Standards Program Board (DSPB)

CHARTER

CHARTER DEFINITION

This document defines the CDER Data Standards Program Board's (DSPB) charter. The charter is intended to be used as:

1. A statement of the CDER DSPB's purpose, authority, membership, role, and responsibilities;
2. An aid in communicating the CDER DSPB's charter internally to CDER staff and externally to other Agency officials; and
3. A reference guide of the responsibilities of the DSPB's members to assure clarity of roles and expectations for member contributions.

BACKGROUND

Modernization of CDER business processes requires better quality information. To more effectively use the information FDA receives from regulated industry, the Center must develop modern bioinformatics. Data standards are a critical component of information management. A modern regulatory informatics environment requires more effective management of information related to regulatory decision making.

The degree to which common standards enable improved use of data and support enhanced decisions is a function of how well the standards are developed, adopted, and implemented. Currently, CDER lacks adequate data standards, rigorous processes to develop standards, an entity authorized to make and communicate standards decisions, organized representation and communication to external stakeholders, and comprehensive regulations to require electronic submissions. Current data standards efforts are piecemeal, lacking the organizational support necessary to be successfully realized.

To be effective, data standards development and implementation requires sustained organizational attention and senior leadership. Establishment of the CDER Data

Standards Program Board arose out of the identified need for Center-level planning and coordination of its data standards activities.

PURPOSE

The purpose of the CDER Data Standards Program Board is to:

1. Provide consistent oversight of CDER data standards activities;
2. Recommend resource investments, policies, and procedures which enable CDER to proactively participate in data standards development with external stakeholders;
3. Ensure development of data standards for all key data needed to make regulatory decisions; and
4. Recommend and oversee implementation of CDER business processes which will iteratively define, adopt, and enforce those standards.

MEMBERSHIP AND ORGANIZATION

1. The Chair of the DSPB will be appointed by the Center Director. The Chair is responsible for directing the activities of the DSPB.
2. Board members will be comprised of senior leadership from each major discipline or business area of CDER. Board members will serve at the discretion of their supervisor or CDER Office Director. Nominees for Board members will be submitted to the Chair for approval.
3. The DSPB Project Teams will carry out the work of the data standards plan. Project Teams will be comprised as appropriate to efficiently meet the needs of the project. Project Team members will likely include data standard end users, and may also include data analysts, process analysts, and a project manager. Project Teams will generally be constituted for the performance period of the specified data standards project. The DSPB will form and dissolve Project Teams as needed.
4. The DSPB may form subcommittees – reporting to the DSPB – to provide more direct management oversight of data standards development or implementation work or other standards program administrative/operational functions in a specific area and for a specific duration.

- a. A charter will be established to clarify the purpose, responsibilities, scope, and membership of such subcommittees.

ROLES AND RESPONSIBILITIES

The DSPB will report to the CDER Executive Committee. The remit of the Data Standards Program Board is to:

1. Conduct planning, tracking, analysis, and reporting of annual resources invested in data standards projects and results achieved through these project;
2. Update the Executive Committee on the state of the CDER data standards program and Recommend data standard program priorities to the Executive Committee; Issues that cannot be resolved by the DSPB will be presented to the executive committee and/or the Center Director for resolution;
3. Oversee CDER Data Standards Plan execution and periodic plan updates, as needed;
4. Establish, direct, and review progress of DSPB Project Teams;
 - a. Providing template for project proposals;
 - b. Reviewing and approving CDER data standards project proposals;
 - c. Reviewing and approving DSPB Project Team project plans;
 - d. Conducting high-level stage-gate review of the work progresses of Project Teams; and
 - e. Providing direction and feedback to Project Teams.
5. Communicate and coordinate with both internal and external stakeholders and Standards Development Organizations;
6. Ensure and coordinate participation and influence the development of national and international standards that impact CDER with the relevant Standards Development Organizations (SDO);
7. Ensure effective communication to support sustained Center attention to data standards development and implementation needs.

DSPB Member Responsibilities

1. DSPB members will prepare for, attend, and proactively participate in DSPB meetings and activities.

2. DSPB members will serve as an active liaison between their home Office, other CDER cross-center working groups, external partners, and the DSPB. It is the responsibility for members to bring matters that impact CDER and the FDA to the DSPB for discussion so that the DSPB may adequately respond.
3. Depending on the subject matter to be discussed, DSPB members may bring subject matter experts whose role will be to participate, as needed, on particular topics. Every effort will be made to have no more participants than reasonably necessary and members will share the names of new participants with the DSPB project manager 1 week prior to the meeting, if possible.
4. DSPB members will align around DSPB/EC ratified positions and consistently communicate those positions to stakeholders.

DSPB Manager

A DSPB Manager will be appointed to provide support for the Board. The DSPB manager has primary responsibility for:

- a. Coordinating and supporting data standards program projects;
- b. Tracking and reporting data standards project information to the DSPB;
- c. Scheduling DSPB meetings and communicating the agenda prior to each meeting;
- d. Following up on DSPB assignments and action items assigned to Project Teams;
- e. Preparing DSPB documents;
- f. Maintaining the roster of the DSPB and its Project Teams;
- g. Maintaining a repository that includes meeting notes, a log and status of issues discussed and actions assigned, and other such documents.
- h. Distributing meeting minutes that will summarize key topics of discussion, including substantive proposals, as well as any significant controversies or differences of opinion and action items.

PROCEDURES

Meetings:

1. The DSPB will meet monthly.

2. Project Team Leads will provide the DSPB with quarterly updates.
3. Special meetings may be scheduled at the discretion of the Chair.

Meeting agenda:

1. Proposed agenda items may be submitted by a Board member or be developed by the Chair
2. The Chair will determine the applicability of a proposed item and decide if it will be included on the agenda.
3. Agenda items generally will be submitted at least one week in advance. It will be indicated on the agenda if this is a decision meeting. Action documents will be provided to the Board members and assistants at least 4 working days before a meeting.

Voting:

1. DSPB members will vote on issues brought to the board for review.
2. Agenda items intended for voting will be identified as such on the agenda.
3. Prior to voting on an issue, DSPB members will work together to ensure that issues of significance to any CDER discipline or business area are fairly considered.
4. DSPB members who cannot be present for the vote will convey their vote and proxy (or decision to abstain) to another DSPB member or the DSPB manager prior to the vote.
5. DSPB members may abstain from voting on issues that are not of significant importance to their Office Director.
6. The Chair may close voting in the absence of a DSPB member's vote when the Chair judges that the issue is not of significant importance to that member's discipline or business area.
7. For voting purposes, a quorum is achieved if at least 50% of voting members have cast a vote.
8. Agreements will be reached through a simple majority of voting members.
9. Issues of significant disagreement will be referred to the CDER Executive Committee.

Appendix A: DSPB Charter Revision History:

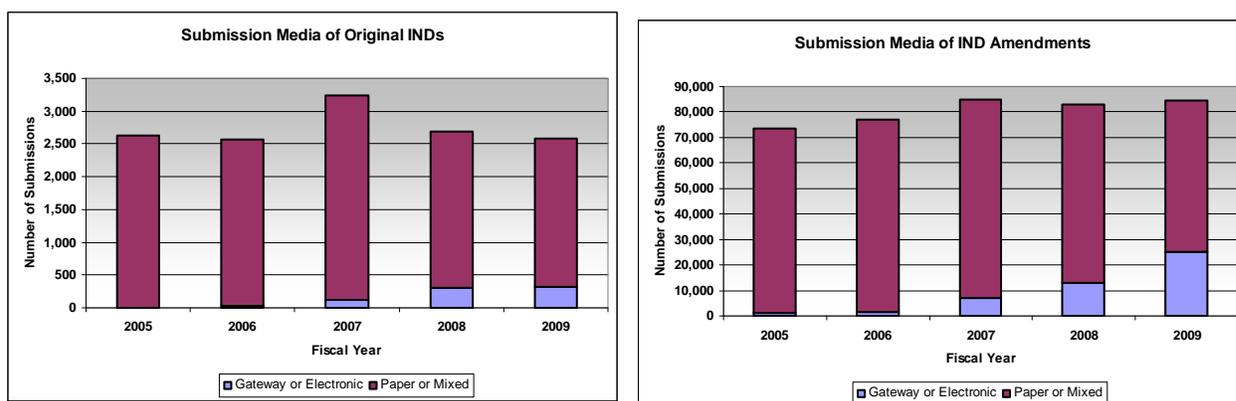
Date	Version	Summary of Changes
March 31,2010	1.0	Original Draft Version
December 15, 2010	1.1	Removed draft watermark. Revised as discussed and approved by the Data Standards Program Board.

Appendix B: Trends in the Format of Submissions

The following charts display trends in the transition to electronic submissions among Investigational New Drug applications, New Drug Applications, Abbreviated New Drug Applications, Drug Master Files, and their respective supplements.

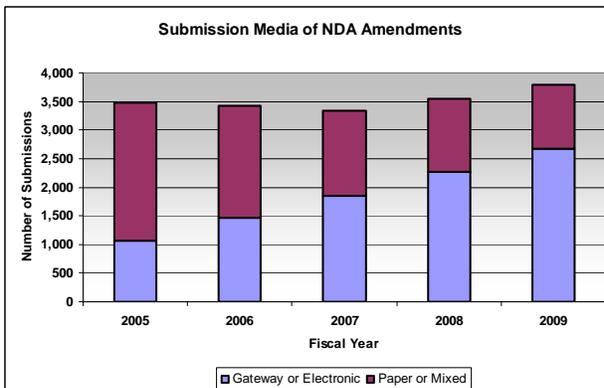
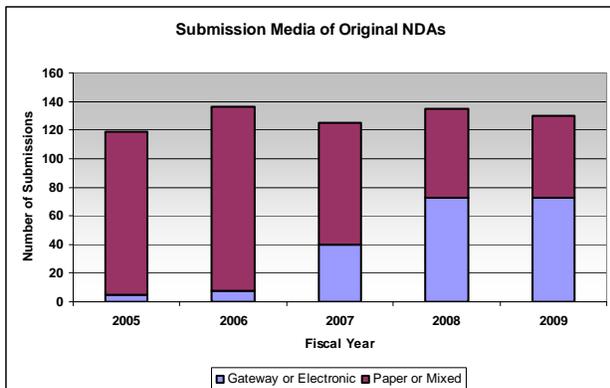
B-1 Investigational New Drug applications (INDs)

INDs are submitted when a drug sponsor is prepared to test a new molecule in humans for the first time. IND amendments are submitted over the course of the IND-phase which can last many years. IND-phase submissions have lagged behind NDAs in their transition to electronic submissions. In fiscal year 2009, only 12.5% of original INDs and 29.7% of IND amendments were submitted in a fully-electronic format.



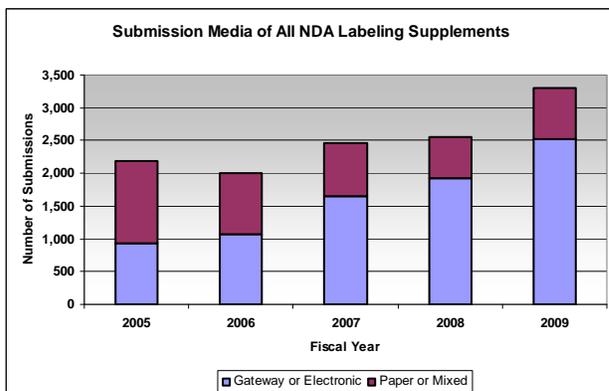
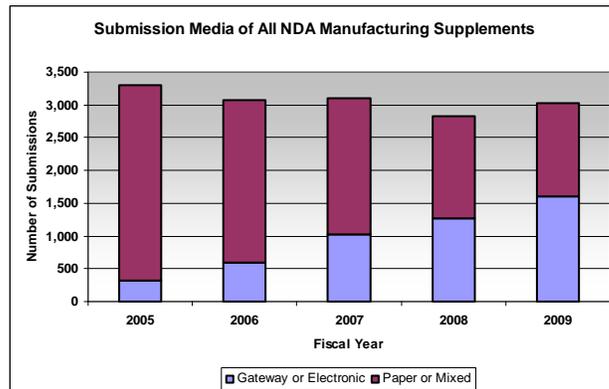
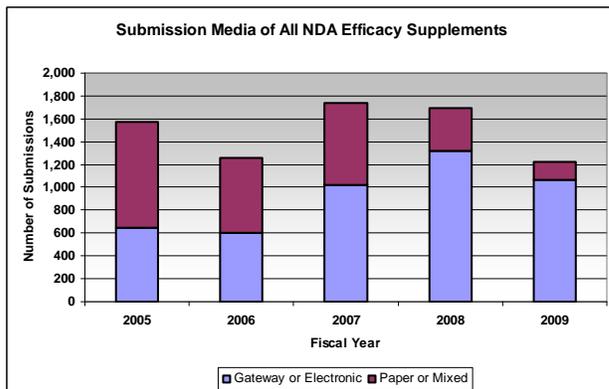
B-2 New Drug Applications (NDAs)

NDAs are submitted when a sponsor seeks approval to market a new drug product. The submissions tend to be very large – consisting of tens of boxes of paper documents or over 10 gigabytes of electronic files. These submissions include important product information such as chemical makeup, manufacturing processes, and clinical trial data. NDAs have made steady progress towards electronic submissions – in fiscal year 2009 56.2% of original NDAs and 70% of NDA amendments were submitted in a fully-electronic format.



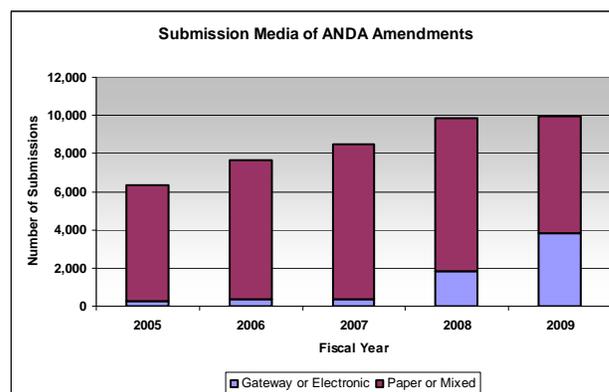
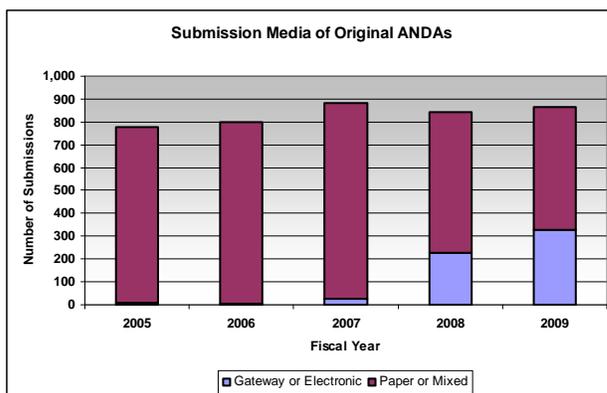
B-2a New Drug Supplements

After a new drug product gains marketing approval it often is subject to a number of supplements. Efficacy supplements are submitted to gain approval for a new indication. These applications are substantial, akin to the efficacy piece of the NDA review process. A labeling supplement may be submitted if a sponsor would like to change the labeling of their product. Manufacturing supplements are submitted when a sponsor would like to change their manufacturing process. Each of these supplements has an original submission that may also be subject to amendments. In fiscal year 2009, 86.9% of all 1,227 original efficacy supplements and their amendments, 76.4% of all 3,303 original labeling supplements and their amendments, and 53.2% of all 3,020 original manufacturing supplements and their amendments were submitted in a fully-electronic format.



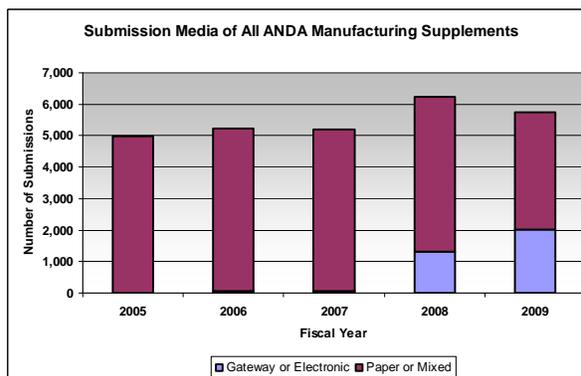
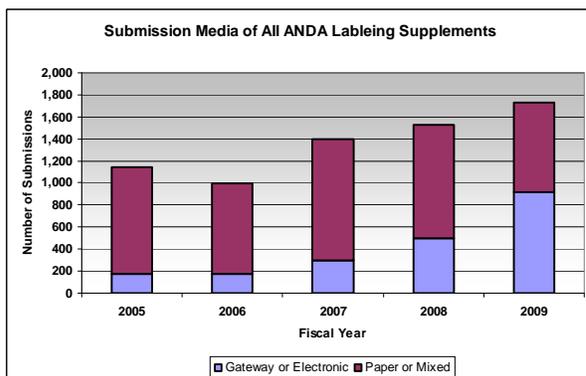
B-3 Abbreviated New Drug Applications (ANDAs)

After the expiration of any patent and marketing exclusivity a drug product is often subject to generic competition. These competitors must first get an Abbreviated New Drug Application approved before they can market their generic version. Original ANDAs are commonly also subject to amendment submissions. In fiscal year 2009, 37.7% of 865 original ANDAs and 38.4% of 9,977 ANDA amendments were submitted in a fully-electronic format.



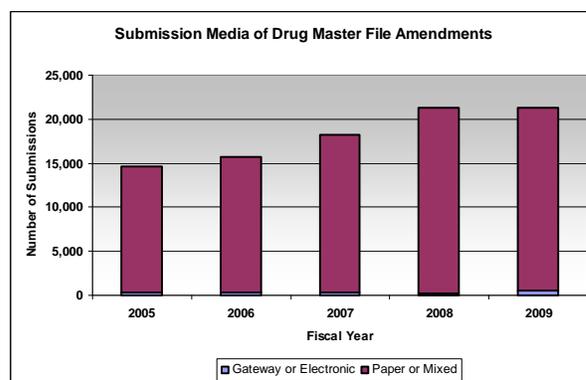
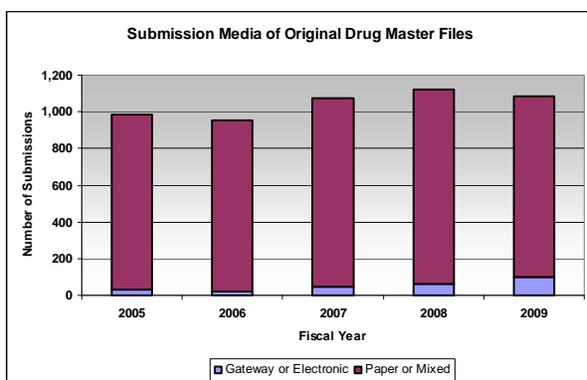
B-3a Abbreviated New Drug Supplements

Like NDAs, ANDAs are also frequently subject to labeling or manufacturing supplements. In fiscal year 2009, 52.9% of 1,720 original labeling supplements and their amendments, and 35.1% of 5,754 original manufacturing supplements and their amendments were submitted in a fully-electronic format.



B-4 Drug Master Files (DMFs)

A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The submission of a DMF is not required by law or FDA regulation. These submissions have lagged behind other submission types in their transition to fully-electronic formats. In fiscal year 2009, only 9.4% of 1,086 original DMFs and 2.7% of 21,296 DMF amendments were submitted in a fully-electronic format.



Appendix B: Revision History

Date	Version	Summary of Changes
March 31, 2010	1.0	Original Draft Version
December 15, 2010	1.1	Removed draft watermark.