Data Standards Strategy

Version: 1.0

Document Date: December 5, 2012

REVISION HISTORY

Version Number	Implemented By	Revision Date	Description of Change
1.0	CDER DSPB	December 5, 2012	Initial Document

The Data Standards Plan (Version 1.1) issued in December, 2010 is superseded by this Strategy and the Data Standards Program Action Plan.

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Executive Summary

The U.S. Food and Drug Administration (FDA) currently receives submissions of original applications and supplements in formats ranging from paper-only to electronic-paper (i.e. pdf), to electronic data, as well as hybrids of the three formats. The variability and unpredictability of format and content of submitted applications present major obstacles to conducting a timely, efficient, and rigorous review. Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research (CDER) has commented that "a lack of standardized data also limits FDA's ability to transition to more standardized approaches to benefit-risk assessment and impedes conduct of safety analyses that inform FDA decisions related to Risk Evaluation and Mitigation Strategies and other post-marketing requirements."[1] Data that conform to standards will allow reviewers to increase review efficiency and consistency and facilitate evaluations across the drug lifecycle.

The purpose of the Data Standards Strategy is to reinforce CDER's on-going commitment to the development, implementation and maintenance of a comprehensive data standards program that will facilitate the efficient and effective review of regulatory submissions such that safe and effective products are available to the market sooner. The Data Standards Plan (Version 1.1) issued in December, 2010 is superseded by this Strategy and the Data Standards Program Action Plan

The scope of this Strategy is limited to the identification of need, development, implementation and maintenance of data standards required for the efficient and effective review of sponsor submissions by CDER. It is aligned with the goals and objectives of the FDA's Strategic Plan, and the performance goals of the PDUFA V Reauthorization as captured in the FDA Safety and Innovation Act (FDASIA).

CDER encourages the development, adoption and consistent implementation of data standards across the drug development value chain, i.e., pre-market data capture to post-market surveillance. Moreover, to maximize the benefits of data standards, there must be a better understanding and specification of the essential clinical information models (i.e., common data elements, their relationships, terminologies, and value sets) that inform data collection for a particular disease state at study protocol design. Clinical information models and associated standards would improve study efficiency, provide consistent data interpretation, enhance quality, and reduce overall costs to all stakeholders and have the impact to effect more rapid access to safe and effective medical products.

CDER's approach to data standards consists of four strategic goals:

1. Support Open, Consensus-Based Data Standards Development
2. Maintain and Promote a Well-Defined Data Standards Governance Function
3. Promote the Electronic Submission of Regulatory Data Using Established Standards
4. Optimize the Regulatory Review Process to Fully Leverage Data Conformed to Standards

CDER's Strategic Data Standards initiatives and their objectives are as follows:

1. Regulatory Data

a) Provide guidance to industry on required electronic data standards under PDUFA V and GDUFA.

[1] Woodcock, J., PDUFA V: Medical Innovation, Jobs, and Patients," Testimony before Sub-committee on Health Committee on Energy and Commerce, US House of Representatives, July, 7, 2011.

b) Create a plan for the development of therapeutic area (TA) Standards.

   i. Collaborate with industry, Standards Development Organizations (SDO) and other stakeholders in the development of TA standards.

   ii. Obtain input through public comment on TA standards and guidance.

c) Collaborate with stakeholders to refine and improve existing core data standards.

d) Publish data validation rules and configuration file for industry use prior to submission; Perform content validation at regulatory submission.

e) Provide guidance to industry on site-level standardized data elements used in the selection clinical sites and / or facilities for inspection as part of a regulatory application or supplement.

2. Study Data Standards Research and Development

a) Develop a pathway for the replacement of SAS XPORT files used for transport of CDISC content with a more robust and flexible transport mechanism.

b) Obtain input through public comment on exchange standards.

c) Provide technical guidance (nonbinding) to industry for conversion from legacy data to SDTM compliant datasets.

3. **Electronic Regulatory Submissions for NDAs, BLAs and ANDAs**

a) Issue draft Guidance in FY2013 specifying the requirement of electronic submission of applications.

b) Obtain input from stakeholders through public comment on electronic submission guidance.

c) Issue final Guidance in FY2013 (planned) specifying the requirement of electronic submission of applications.

d) Obtain input from stakeholders on submission standards for quality sections of applications.

4. Product Identification (Product Dictionary)

a) Evaluate and develop a standalone product dictionary concept of operations utilizing lessons learned from the new Product Dictionary contained within the FDA Adverse Event Reporting System (FAERS); objective is a Product Dictionary available as a resource for other systems.

b) Explore use of the Product Dictionary as a resource by other centers to support safety surveillance and related analysis.

5. Quality (CMC) Objectives

a) With Industry populate and maintain databases as necessary for facilities, fee assessments and efficiency to support Generic Drug User Fee Act (GDUFA).

b) Develop new and/or enhance existing facility databases (Active Pharmaceutical Ingredient (API) and Final Dosage Form (FDF) manufacturing and clinical/ bioequivalence site) to be populated by industry.

c) Develop a current chemistry manufacturing and controls (CMC) records database to aid in the efficiency of review and inspection.

d) Develop and issue electronic data submission standards.

All of the above initiatives will be supported by the design and implementation of a consistent approach for development, public comment and finalization of electronic standards guidance.

The CDER Data Standards Program Board (DSPB) is responsible for achieving the program's objectives. In order to ensure collaboration, communication and alignment across FDA centers, representatives from the Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH) are participants on the DSPB. A Strategy-linked Action Plan will be developed and will specify the goals/objectives, designated lead responsibility, key milestones and estimated completion dates.

Guidance documents provide assistance to industry and the FDA by clarifying requirements imposed by legislation and regulations. There will be periodic development and issuance of guidance documents on electronic submissions and the standardization of electronic drug application data. It is important for both FDA and regulated industry that guidance documents be developed, internally reviewed / cleared, issued for public comment and finalized in a timely manner. CDER, in collaboration with other Centers, has developed a new process to expedite the clearance of technical resource specifications that provide guidance to industry (e.g., Common Data Standards Issues Document, Study Data Specifications, and other submission related specifications).

Data standards are a critical factor in improving the overall effectiveness and efficiency of the regulatory review process. This Strategy expresses the Center's commitment to the development and use of study data and submission standards, as well as the proactive collaboration with SDOs, industry and other stakeholders to ensure that the standards are optimized to support analysis and decision-making.

1. Introduction

FDA's Strategic Plan (August, 2011)[2], "Advancing Regulatory Science at FDA," defined regulatory science as the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products." The plan outlined eight priorities of regulatory science, including one with an aim to "Harness Diverse Data through Information Sciences to Improve Health Outcomes." FDA receives a vast amount of data from product submissions, adverse event reporting collaboration with outside investigators, and basic research, as well as other sources. The successful integration and analysis of data from these disparate sources would provide knowledge and insight not possible from any one source alone. Harnessing these diverse data demands interoperability across computer systems and harmonization of data standards.

FDA currently receives submissions of original applications and supplements in formats ranging from paper-only, electronic-paper to electronic-data, as well as hybrids of the three formats. The variability and unpredictability of the format and content of submitted application data present major obstacles to conducting a timely, efficient, and rigorous review. Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research has commented that "a lack of standardized data also limits FDA's ability to transition to more standardized approaches to benefit-risk assessment and impedes conduct of safety analyses that inform FDA decisions related to REMS and other post-marketing requirements."[3] Data that conform to standards will allow reviewers to increase review efficiency and consistency and facilitate evaluations across the drug lifecycle.

Within FDA, CDER regulates prescription drugs, including biological therapeutics and generic drugs, as well as over-the-counter products. CDER's mission is to protect and promote public health by ensuring that human drugs are safe and effective for their intended use, meet established quality standards, and are available to patients.

The purpose of this Data Standards Strategy is to reinforce CDER's on-going commitment to the development, implementation and maintenance of a comprehensive data standards program that will facilitate the efficient and effective review of regulatory submissions such that safe and effective products can get to market sooner. The CDER Data Standards Plan (Version 1.1), issued in December 2010, is superseded by this Strategy and accompanying Data Standards Program action plan.

2. Vision

The vision for CDER's data standards program is to create an environment where regulatory data and submission information are based on common standards, are available electronically, and available to support advanced analytics to better inform regulatory decisions to improve public health.

[2] FDA's Strategic Plan (August, 2011), "Advancing Regulatory Science at FDA,"

[3] Woodcock, J., PDUFA V: Medical Innovation, Jobs, and Patients," Testimony before Sub-committee on Health Committee on Energy and Commerce, US House of Representatives, July, 7, 2011.

3. Scope

The scope of this Strategy is limited to the development, implementation and maintenance of data standards required for the efficient and effective review of sponsor regulatory submissions by CDER. It is aligned with the goals and objectives of the FDA's Strategic Plan and the performance goals of the PDUFA V Reauthorization[4] as captured in the FDA Safety and Innovation Act (FDASIA)[5].

Components that may be affected by this Strategy include, for example, electronic submissions, data repositories, data dictionaries, as well as statistical and scientific tools for data integration, visualization, analysis, reporting and archive.

For the purpose of this Strategy, data standards encompass four broad categories: 1. exchange/transport; 2. format; 3. analysis; and 4. terminology/ vocabulary.

1. Exchange/Transport: A standard way of exchanging data between computer systems. May describe the information classes/attributes/data elements, and relationships necessary to achieve the unambiguous exchange of information between disparate information systems.
2. Format: the way that information is encoded in an electronic file or message. Specifications of a format permit the file to be written according to a standard, opened for use or alteration, and written back to a storage medium for later access.
3. Analysis: A standard presentation of the data intended to support analysis. It includes extraction, transformation, and derivations of the collected data.
4. Terminology: A "terminology standard" is the specification for commonly agreed-upon vocabulary to be used in another data standard or family of data standards. Terminology standards specify the key concepts that are represented as preferred terms, definitions, synonyms, codes, and the code system that must be used in order to ensure a common understanding of a given data standard.

The internal and external stakeholders for this strategy, its implementation and/or its impact include:

> **FDA**: CDER, other Medical Product Centers and Office of the Commissioner/Office of Information Management (OIM).
>
> **External**: Sponsors, Standards Development Organizations (SDOs), Contract Research Organizations (CROs), technology vendors, other governmental agencies, and the public.

The scope of this Strategy may be revised, as needed, due to changing business needs within the FDA in general and the regulated industry in particular.

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[4] PDUFA V Reauthorization: 2013-2017
http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

[5] FDASIA
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm20027187.htm

4. CDER Data Standards Principles

The CDER Data Standards program is aligned with the principles in standards management at the FDA. From the FDA's perspective, standards should:

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

5. Data Standards Goals

CDER's Data Standards Goals are listed below.

5.1 Support Open, Consensus-Based Data Standards Development

To enable and enhance the ability to integrate, analyze, report and share regulatory information, open, consensus-based data standards are required. CDER's support will foster collaboration with regulated industry, SDOs and other stakeholders, such as ICH to develop standards for study data, including therapeutic areas and study types, as well as for other data required in electronic regulatory submissions. The benefit of using data standards must be recognized and must deliver value. CDER reviewers must have the opportunity to review the standards and related implementation guides in order to ensure that they meet rigorous scientific and regulatory requirements.

5.2 Maintain and Promote a Well-Defined Data Standards Governance Function

The CDER data standards governance provides a framework of policies, procedures, accountabilities, and decision rights for the lifecycle management of standards. Well-defined, recognized, and transparent governance must underpin the management of regulatory data and submissions. Leadership must support and communicate the governance to all stakeholders. Good governance promotes the understanding and management of standards from both the regulatory science and industry perspectives, as well as the value of standards in enabling more confidence in overall quality of the data.

5.3 Promote the Electronic Submission of Regulatory Data Using Established Standards

To ensure that CDER receives standard electronic regulatory submissions and data conforming to supported standards, CDER and other centers must be work with regulated industry in clearly articulated regulatory guidance and technical specification.

5.4 Optimize the Regulatory Review Process to Fully Leverage Data Conformed to Standards

To fully utilize and benefit from electronic submissions and standardized data, reviewers must have: 1. training in the specific data standards and structure; and 2. training in the review, and analysis of standardized data. Moreover, based on the needs of the reviewers, the computational environment must be optimized for review and the use of advanced analytics through software tools that have been acquired/developed, tested, and trained for.

6. Where We Are Today

CDER is seeing increases in the number of electronic submissions each year. The FDA Electronic Submissions Gateway (ESG) is an Agency-wide solution for accepting electronic regulatory submissions over the internet. The FDA ESG enables the secure submission of regulatory information for review. In 2011 CDER received 93,503 submissions through the ESG which is approximately a 45% increase from 2010.[6] This data indicate that applicants are rapidly moving towards adoption of electronic submissions.

While IND submissions have become increasingly electronic, approximately 47% of IND submissions were still paper-based in FY2011, and less than 53% utilized the electronic Common Technical Document (eCTD) format.[7]

In FY2011, approximately 75% of NDA submissions to CDER were electronic and approximately 90% of the BLAs were electronic. In the first few months of FY2012, CDER received approximately 78% electronic NDAs and 92% electronic BLAs.[8]

These electronic submissions may or may not conform to the electronic common technical document (eCTD) standard, they may or may not contain electronic datasets (as opposed to pdf tabulations), and the enclosed data sets may or may not conform to CDER-supported standards such as the CDISC SDTM, SEND or ADaM. In fiscal year 2011, only approximately 32% of electronic submissions monthly contained ADaM datasets, and only approximately 39% average of monthly electronic submissions contained SDTM data sets.[9]

The predictability of the efficiency of the regulatory review process relies heavily on the degree of standardization of sponsor submissions. Non-standardized information limits the ability to transition to more standardized approaches to benefit-risk assessment and impedes conduct of safety analyses that inform FDA decisions related to monitoring during the IND phase, NDA phase, Risk, Evaluation, and Mitigation Strategy (REMS) and other post-marketing requirements.

The Data Standards Plan (Version 1.1) outlined a number of key objectives to be accomplished in the 2010-2012 timeframe. The status of each objective was reported in the 2011 Assessment of CDER's Data Standards Program (January 12, 2012)[10]. The objectives and status is included:

1. 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. Status: Completed.
2. Establish new regulatory requirements for electronic submissions of all study data included in NDAs, BLAs, and ANDAs submitted to the Agency. Status: In Process.

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[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm110653.htm

[7] PDUFA IV IT Metrics: FY 2011. Presentation delivered by Edward Hallissey, PDUFA Program Manager. 02 2012-02-24 Quarterly Industry Report Metrics.ppt.

[8] PDUFA IV IT Metrics: FY 2011.

[9] http://www.accessdata.fda.gov/FDATrack/track?program=cder&id=CDER-OB-NDAs-BLAs-and-Efficacy-Supplements-with-Electronic-Datasets-Available

[10] 2011 Assessment of CDER's Data Standards Program (January 12, 2012)

3. Establish a CDER Data Standards Program Board (DSPB) to oversee all CDER data standards projects and activities. Status: Completed.
4. Develop a baseline inventory of data standards needs for all of CDER regulatory operations. Status: Completed.
5. Establish a basic set of clear processes to support data standards development and implementation that would engage all key stakeholders. Status: Key processes established.

Since the initial publication of CDER's Data Standards Plan, CDER has continued to collaborate with Sponsors and SDOs to promote standards-based electronic submissions including standardized study data. Although CDER encourages the submission of study data conforming to CDISC developed standards, research that address current and future reviewer needs is on-going. This includes such aspects such as the challenge of conducting multi-dimensional review and analyses at the study level. These more complex analyses will allow reviewers to gain a better understanding of the relationships between endpoints, across studies and submissions. Moreover, development of clinical information models for particular disease states to inform data collection during a study, using standards, would improve efficiency, support consistent data interpretation, enhance data quality, and reduce overall costs. The ability to identify and develop predictable and essential data elements for particular disease states and study types allows for the use of specialized tools and supports consistent data interpretation.

The goals of the PDUFA V Reauthorization are specific on the need for: enhanced communication between FDA and Sponsors; evaluation of innovative scientific and medical methodologies to expedite the regulatory review process; and continued enhancements to the drug safety system. Moreover, and key to CDER's data standards strategy, FDASIA Section 1136 and the PDUFA V Reauthorization require electronic submissions and the need for drug application data to conform to standards.

Looking forward, the road ahead for regulatory data standards will be challenging. CDER has an established data standards governance model, but is constantly looking to streamline and improve upon the model, both within CDER and with our counterpart medical product centers and the Agency. The challenge will be to maintain effective governance of this effort while collaborating with the external stakeholders, including industry sponsors, academia, government researchers, and SDOs.

7. Road Ahead

CDER encourages the development, adoption and consistent implementation of data standards across the drug development process, e.g. nonclinical to clinical studies, pre-market data capture to post-market surveillance. In addition, there must be a better understanding and specification of the clinical information models needed to inform standard data collection for a particular study type or disease state at study protocol design. These models and standards should improve study efficiency, provide consistent data interpretation, enhance quality, reduce overall costs to stakeholders and have the impact to effect more rapid access to safe and effective medical products.

CDER encourages on-going research and development on data standards and innovative technologies to enhance review process by improving the analytical and visualization tools available to reviewers, as well as regulated industry. To truly leverage data and submission standards research and implementation requires collaboration of all stakeholders, including government, industry, SDOs, and technology providers. CDER is committed to proactive communication and collaboration.

CDER's data standards program is focused on realizing its vision by delivering on its goals and its objectives. The established data standards governance body, DSPB, is responsible for the strategy, objectives, implementation and communication.

8. Key Data Standards Programs and Objectives

The five key data standards program areas and objectives are described below: 1. Regulatory Data, 2. Study Data Standards Research and Development, 3. Electronic Regulatory Submissions for NDAs, BLAs and ANDAs, 4. Product Identification and 5. Quality (CMC).

8.1 Regulatory Data

8.1.1 Provide Guidance to Industry on Data Standards

CDER will develop and periodically publish a cross-center draft guidance to industry on data standards – that will be required under FDASIA / PDUFA V Reauthorization. Further, under GDUFA, guidance will be provided to industry on the development and publication of electronic data submission standards.

8.1.2 Study Data Standards

CDER has identified the need to develop therapeutic and disease area data standards to facilitate the evaluation of medical products. These content standards are primarily intended to support the assessments of new products in specific therapeutic areas, but may have other uses as well. CDER fully expects that the existing "cross-cutting" CDISC domains will be enhanced to be more robust and will include new "cross-cutting" concepts as they are indentified during the TA standards development. CDER initially prioritized 55 key diseases/domains where data standardization can most effectively support our regulatory review activities.

To facilitate this objective, CDER has established a small grants program to fund projects that develop disease/domain specific therapeutic area data standards. Results are expected within one year of award for each project, unless extensions are granted. Future awards are subject to receipt of qualified applications and availability of funds. To date, CDER has awarded six grants across five therapeutic areas (virology, cardiovascular imaging, schizophrenia, major depressive disorder, cardiovascular endpoints).

PDUFA V commitments state that FDA will standardize therapeutic areas and provide guidance requiring electronic submission of clinical study data in standardized form. Traditionally, clinical study data submitted to CDER is in a format that is unique to each individual sponsor; furthermore the data quality varies. For these reasons, it has not been possible for CDER to undertake a wholesale attempt at improving data analysis efficiency and consistency through automation. Attempts to encourage sponsor adoption of available clinical trial data standards (CDISC/SDTM) for submission of product application have managed to improve the standardization of submitted data. However, such a voluntary approach has proven insufficient to support both the current business requirements as well as efforts to modernize the review environment.

8.1.3 Data Validation Project

This pilot project is design to assess whether the Sponsor-submitted data is "fit for use" by the regulatory reviewers. This involves ensuring that the data to support a particular review activity is present, conforms to standards, and that there are no quality issues. Reviewers will receive a report during the first week of submission and prior to filing decision notifying them of the "fit for

use" status. FDA will publish OpenCDISC validation rules and configuration file for Sponsors to use prior to regulatory submission.

8.1.4 Standard for Exchange of Nonclinical Data (SEND)

SEND provides a standardized presentation of general toxicology and carcinogenicity study data tabulations in an electronic format. CDER supports SEND as the preferred format for general toxicology and carcinogenicity studies.

There are several SEND projects focused on a more effective, efficient and consistent review of nonclinical data:

1. Implement SEND: This project has rolled out the developed SEND standard for general toxicity and carcinogenicity including processes and tools; the project will include Guidance;
2. Enhance SEND standard: This project's aim is to enhance the existing standard to cover reproductive toxicity and safety pharmacology studies;
3. Nonclinical Information Management System (NIMS): provides nonclinical study data management, analysis, search, and visualization functionality to reviewers. Project will continue to support and enhance NIMS for additional study types.

8.1.5 Site-Level Standardized Data Elements

PDUFA V Reauthorization Section XII.F requires the development of terminology standards for data other than clinical data. CDER will collaborate with stakeholders to identify other areas that would benefit from standardized data, develop draft guidance for public comment and issue final guidance. For example, one such area is standardized data elements for site selection by the Office of Scientific Investigations (OSI). Prior to selecting sites for inspection, OSI must have timely access to adequate and accurate data in NDA and BLA submissions. Assignments for foreign and domestic inspections must be issued as early in the submission review clock as possible to ensure the availability of inspection results to inform OSI's recommendations regarding data integrity. NDA/BLA submissions frequently do not contain all the information that is needed to support inspections or this information is provided in non-standard formats that makes it difficult to use.

CDER will conduct a gap analysis of clinical site-level data submitted by Sponsors versus the data needed by OSI to select site's for inspection. A draft guidance on the content and format of the data needed will be published to provide clarity for industry on the goals, objectives, and scope of OSI's site selection program.

Regulatory Data Objectives

a) Provide guidance to industry on required electronic data standards under PDUFA V and GDUFA.

b) Create a plan for the development of therapeutic area (TA) Standards.

   i) Collaborate with industry, Standards Development Organizations (SDO) and other stakeholders in the development of TA standards.

   ii) Obtain input through public comment on TA standards and guidance.

c) Collaborate with stakeholders to refine and improve existing core data standards.

d) Publish data validation rules and configuration file for industry use prior to submission; Perform content validation at regulatory submission.

e) Provide guidance to industry on site-level standardized data elements used in the selection clinical sites and / or facilities for inspection as part of a regulatory application or supplement.

8.2 Study Data Standards Research and Development

CDER recognizes the need to identify a pathway for moving away from SAS XPORT files to a more robust and flexible transport mechanism for CDISC content and certain other study data currently submitted in PDF format. For example, ongoing research and development work on the HL7 study data standards project indicates that HL7 version 3, including the Clinical Document Architecture (CDA), may be a promising future solution for the exchange of study data, including enhanced interoperability with EHRs and other healthcare systems. This is one alternative of several solutions that are being considered, and for which public input is being sought. CDER will conduct a careful evaluation of the cost-benefit of potential migration to a new exchange format – on both FDA and regulated industry – to inform possible next steps. A determination of whether and how to proceed will be based on an evaluation of alternatives against FDA study information exchange requirements and proposals for further development or adoption.

Ongoing research and Development projects include development and testing the potential for HL7 v3-compliant specifications, including structured documents such as Clinical Document Architecture, Release 2 (CDA R2), for SDTM and SEND defined content and additional information currently exchanged using PDF. These projects include the exchange of: Patient Narrative, Clinical Investigator Qualification Information, Structured Protocol Information, and Subject Data.

As noted above, Sponsors are increasingly submitting study data to the FDA using CDISC SDTM and ADaM standards. However, in many cases the data were collected or integrated in a non-standardized format and have to be converted to standard formats based on the SDTM and ADaM Implementation Guides. Sponsor's legacy data conversion to SDTM and ADaM for submission should result in added benefit to the submission of non-standardized data only. For FDA reviewers and Sponsors, the benefit should be an improvement in reviewer efficiency and better understanding of the data. To help address the challenge that data relevancy and traceability need to be preserved while legacy data conversion is performed, guidelines and expectations, and best practices will be incorporated in a technical resource document.

Study Data Standards Research and Development Objectives

a) Develop a pathway for the replacement of SAS XPORT files used for transport of CDISC content with a more robust and flexible transport mechanism.

b) Obtain input through public comment on data exchange standards.

c) Provide technical guidance (nonbinding) to industry for conversion from legacy data to SDTM compliant datasets.

8.3 Electronic Regulatory Submissions for INDs, NDAs, BLAs and ANDAs

PDUFA V reauthorization and GDUFA includes a phased-in requirement for standards-based, fully electronic submissions for all marketing and investigational applications. CDER realizes that there are significant investments required to change regulatory submission and review software. Initially FDA draft guidance planned for FY2013 shall specify that electronic submission of applications is required in eCTD version 3.2.2.

Looking towards the future of the eCTD standard, eCTD version 4.0 will be based on the Health Level Seven International (HL7) Regulated Product Submission (RPS) exchange standard. The HL7 RPS exchange message was developed, with FDA sponsorship, to provide regulatory authorities the ability to exchange regulatory information with sponsors. The exchange message defines the framework for regulatory information using predefined parameters to identify and catalog submission information and can be tailored to the format requirements for specific application types. The RPS message enables the FDA to organize the content of a regulatory submission so that reviewers will be able to consistently locate discipline-specific content and defines the submission information for the efficient processing and review of regulatory submissions.

Currently, members and observers of the International Conference on Harmonisation (ICH) are testing the eCTD version 4.0 to ensure that the RPS exchange standard fully meets the ICH requirements. After successful testing, the RPS standard will be balloted as a Normative HL7 Standard. ICH will finalize the eCTD v4.0 Implementation Guide, and FDA will finalize our Module 1 regional implementation guide. The current ICH plan is to complete this process in late 2014 and FDA is targeting 2015 for initial acceptance of eCTD v4.0 submissions.

Electronic Regulatory Submissions for NDAs, BLAs and ANDAs Objectives

a) Issue draft Guidance in FY2013 specifying the requirement of electronic submission of applications.

b) Obtain input from stakeholders through public comment on electronic submission guidance.

c) Issue final Guidance in FY2013 (planned) specifying the requirement of electronic submission of applications.

d) Obtain input from stakeholders on submission standards for quality sections of applications.

8.4 Product Identification (Product Dictionary)

The roll-out of the FDA Adverse Event Reporting System (FAERS) introduces a companion Product Dictionary (PD) providing a comprehensive listing of CDER/CBER regulated products and product information. The PD additionally includes reported foreign product names maintained by the World Health Organization (WHO). The scope encompasses the functional requirements needed for the product dictionary to be used by FDA for validating, mapping, and coding the medical products listed in adverse event reports (including more than six million reports already submitted to FDA are available in FAERS). FAERS PD will improve the quality of post-market adverse event data, and increase efficiency for validating reported products and retrieving reports.

The next generation PD is envisioned to be an independent resource, easily accessible by other systems and supporting a fuller spectrum of product identification needs. This will be supported by the ISO/HL7 Identification of Medicinal Product (IDMP) standards, championed by ICH and currently under final review within the participating SDOs and ICH.

Product Identification (Product Dictionary) Objectives

a) Evaluate and develop a standalone product dictionary concept of operations utilizing lessons learned from the new Product Dictionary contained within the FDA Adverse Event Reporting System (FAERS); objective is a Product Dictionary available as a resource for other systems.

b) Explore use of the Product Dictionary as a resource by other centers to support safety surveillance and related analysis.

8.5 Quality (CMC)

The CMC data and information submitted in an application are focused on ensuring continued product quality (i.e., the identity, strength, quality, purity, and potency). The information submitted includes: 1) description and composition of the drug product / substance, (2)

manufacture, (3) control of excipients, (4) control of drug products / substance, (5) reference standards or materials, (6) container closure systems, and (7) stability.

Quality (CMC) Objectives

a) With Industry, populate and maintain databases as necessary for facilities, fee assessments and efficiency to support GDUFA.
b) Develop new and/or enhance existing facility databases (API and FDF manufacturing and clinical/ bioequivalence site) to be populated by industry. These databases will, at a minimum, contain information for generics-related firms, including addresses and Data Universal Numbering System (DUNS) numbers, and will link facilities to DMFs and ANDAs and will contain other information as necessary.
c) Develop a current chemistry, manufacturing and controls (CMC) records database to aid in the efficiency of review and inspection.
d) FDA will develop and issue electronic data submission standards.

9. Policy and Process

Guidance documents provide assistance to regulated industry and the FDA by clarifying requirements imposed by legislation and regulations. These documents explain the FDA's current policy on the topic addressed in the document. There will be periodic development and issuance of guidance documents on electronic submissions and the standardization of electronic drug application data. It is important for both FDA and regulated industry that guidance documents be developed, internally reviewed / cleared, issued for public comment and finalized in a timely manner.

CDER, in collaboration with other Centers, has developed a new process to expedite the clearance of technical resource specifications that provide guidance to industry (e.g., Common Data Standards Issues Document, Study Data Specifications, and other submission related specifications).

10. Collaboration with Stakeholders

Medical product research and development is an increasingly complex and costly scientific and regulatory process. It is generally accepted that the current cost to a sponsor to research and develop a medical product exceeds $1 billion and consumes 8-10 years. With these ever-increasing research & development (R&D) costs, regulated industry is looking to FDA to improve the efficiency, transparency, and predictability of its regulatory review process. Sponsors have had to find innovative and cost-effective ways to research and develop products such as through process improvements often supported by technology developments and partnerships.

PDUFA V promotes enhanced communications between FDA and sponsors with respect to electronic submissions and electronic data. FDA will seek public input on standard submission formats and study data standards, as well as review and input on the draft guidance documents.

The Data Standards Program Board (DSPB) has established a Communication Plan that provides a framework to support the successful execution of the data standards program. The framework addresses the information needs of internal and external stakeholders and outlines the requirements of communications efforts to reach and inform each group, as well as to receive feedback. The plan is a key tool for promoting support, cooperation, participation, coordination and transparency among all stakeholders.

11. Data Standards Governance

11.1 CDER Data Standards Program Board

The CDER DSPB, established in late 2010, is responsible for the portfolio of CDER data standards projects. The DSPB is chaired by a member of the CDER Office of Planning & Informatics. In order to ensure collaboration, communication and alignment across FDA centers, representatives from CBER and CDRH are participants on the DSPB. As stated in its charter the DSPB is responsible for the oversight of CDER's data standards activities. The DSPB:

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

In addition to the overall governance, the DSPB establishes consistent processes for data standards development, implementation and maintenance. Processes ensure that affected stakeholders and dependencies are identified and planned into the project. For example, there may be a need for regulation or policy changes, additional stakeholders (e.g., SDOs) or coordination with the Computational Sciences Center or the CDER Project Management Office if the project requires tools or other technology needs. At a high level, identification of the need, business case development, and alternative solution analyses work to determine whether a new standard must be developed, changed, or if an existing standard can meet the identified need. Depending on the project, a pilot or proof of concept testing may be needed to assess overall impact and business value. Finally, adoption and implementation steps, critical for rollout of any change or new standard, is prepared.

To facilitate the day-to-day data standards operations activities, the DSPB created an Operations Subcommittee comprised of end-user representatives from the CDER Office of Business informatics (OBI) eData team, the CDER Computational Science Center (CSC), and the DSPB, and with participants from CBER and CDRH to ensure cross-center coordination. The Subcommittee monitors and supports standards development and implementation projects, identifies, tracks and addresses (or coordinates) resolution to standards-related issues, maintains sound collaborative relationships and communications with external partners, and recommends modifications to standards and resources that are supported, or are under consideration for support, by CDER.

The Subcommittee works in conjunction with a cross-center Change Coordination Group that coordinates the development and posting of study data standards resources for those standards supported by CDER, CBER and CDRH. This cross-center collaboration promotes consistent, consolidated information for external stakeholders.

11.2 FDA Data Standards Council

The FDA Data Standards Council (DSC), an agency-wide group, facilitates connecting FDA internal stakeholders with common needs, and coordinating enterprise-wide regulatory data standards with appropriate healthcare standards, with a focus on HL7 V3 exchange. Key members of the DSPB participate on the DSC.

12. Assumptions and Constraints

12.1 Assumptions

The following assumptions were made in preparing the Data Standards Strategy:

1. CDER Executive Leadership and other agency leadership support the outlined strategy and endorse the active participation of critical SDOs and needed staff from Center programs.
2. The DSPB will ensure the timely execution of the Strategy's Action Plan;
3. The DSPB will adhere to the Data Standards Communications Plan; and
4. Program participants will work toward established timelines, as well as comply with approved charters, policies and procedures.

12.2 Constraints

The following constraints may eliminate or delay one or more approved projects:

1. The required CDER staff and support resources are not available as expected, or severely limited;
2. A reduced CDER budget and staffing requires that efforts be reduced accordingly;
3. Required resources from external stakeholders are not available or severely limited;
4. External environmental factors (e.g., regulatory, legislative, economic, technological) arise that directly impact one or more key programs.

13. Implementation

As discussed previously, the 2011 Assessment of CDER's Data Standards Program identified priority activities. The Strategic Goals listed in this document reflect that assessment, stakeholder consultations, and proposed PDUFA V reauthorization commitments. Overall, the data standards implementation strategy is iterative and measured, working to address the needs of the organization and delivering the business value to achieve the identified goals.

The CDER DSPB is responsible for ensuring the implementation of the Data Standards Strategy through Center-level planning and organization of identified priority projects and activities. Through this governance process, the DSPB's membership expertise ensures that the portfolio of data standards projects aligns with the goals, periodically evaluates if the portfolio is achieving the Center's goals, and assesses gaps (e.g., through a broad environmental scan) in the portfolio. They also provide the appropriate oversight and guidance for projects.

A Strategy-linked Action Plan will be developed and will specify the goals / objectives, designated lead responsibility, key milestones and estimated completion dates.

14. Conclusion

Data standards are a critical factor in improving the overall effectiveness and efficiency of the regulatory review process. This Strategy expresses the Center's commitment to the development and use of study data and submission standards, as well as the proactive collaboration with SDOs, industry and other stakeholders to ensure that the standards are optimized to support analysis and decision-making.

Appendix – Acronym List

ADaM	Analysis Dataset Model
API	Active Pharmaceutical Ingredient
CBER	Center for Biologics Evaluation and Research
CDA	Clinical Document Architecture
CDASH	Clinical Data Acquisition Standards Harmonization
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDRH	Center for Devices and Radiological Health
CRO	Contract Research Organization
CSC	Computational Sciences Center
DMF	Drug Master File
DSC	Data Standards Council
DSPB	Data Standards Program Board
eCTD	Electronic Common Technical Document
EHR	Electronic Health Record
FDASIA	FDA Safety and Innovation Act
FDF	Finished Dosage Form
FAERS	FDA Adverse Event Reporting System
GDUFA	Generic Drug User Fee Act
HL7	Health Level 7
ICH	International Conference on Harmonisation
IDMP	Identification of Medicinal Product
NIMS	Nonclinical Information Management System
OSI	Office of Scientific Investigations
PDUFA	Prescription Drug User Fee Act
REMS	Risk Evaluation & Mitigation Strategy
RPS	Regulated Product Submission
SDO	Standards Development Organization
SDTM	Standard Data Tabulation Model
SEND	Standard for Exchange of Non-clinical Data
Sponsors	Regulated Industry
SPL	Structured Product Labeling