CDER Data Standards Program
2017 Annual Assessment

FINAL

April 9, 2018

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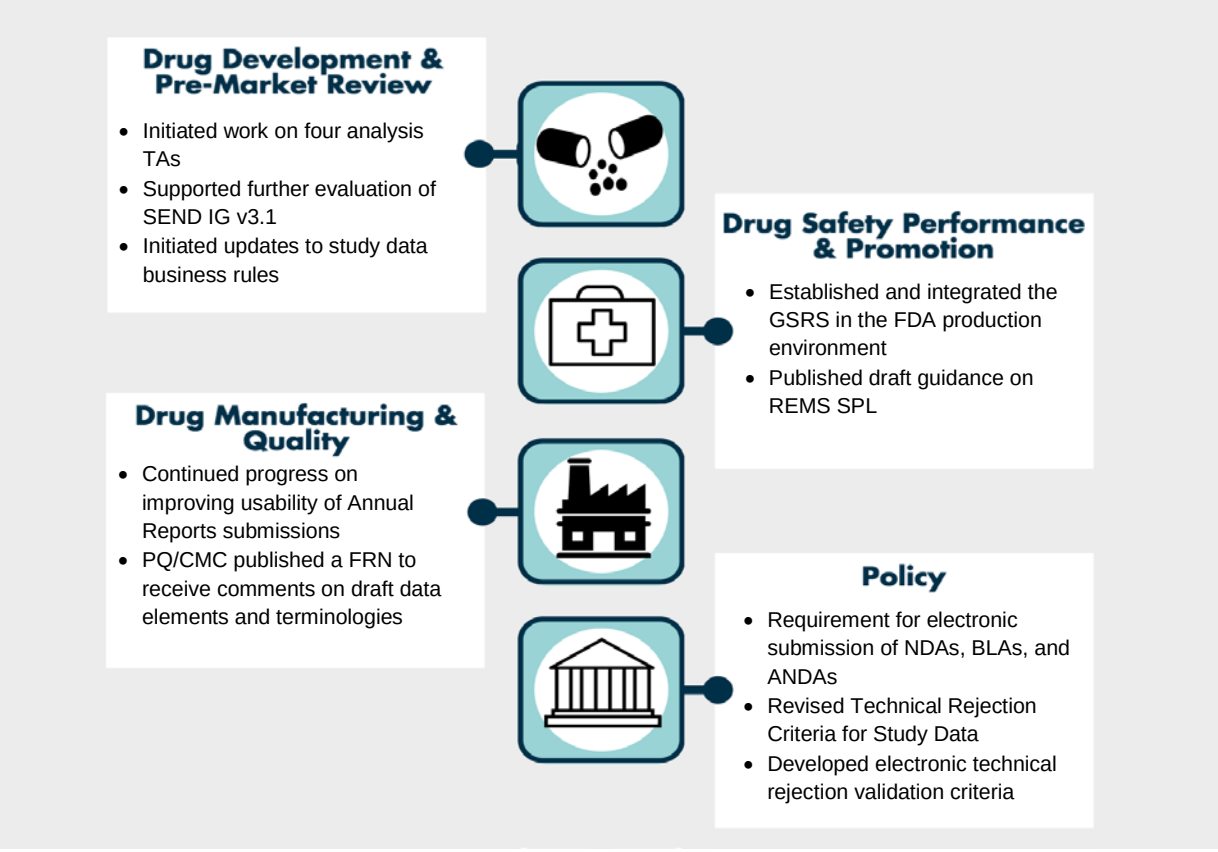
1 Introduction

The Center for Drug Evaluation and Research (CDER) publishes an Annual Assessment for CDER's Data Standards Program (DSP) to provide a progress update to stakeholders reflecting the last calendar year. The previous year assessment is available on the CDER DSP website. Further information for most projects referenced throughout this Annual Assessment is available in the Action Plan.

2 CDER Data Standards Program at a Glance

This assessment highlights the projects and ongoing efforts that cover the identification of need, development, testing, adoption, implementation, and maintenance of data standards required for the efficient and effective review of regulatory submissions. The Annual Assessment is organized to align with the Data Standards Strategy[1] and is mapped to the five major areas of regulatory business activity of the CDER Strategic Plan. Figure 1 (below) and the following sections highlight program accomplishments.

Figure 1. 2017 Summary of Accomplishments



[1] The Annual Assessment reflects accomplishments in 2017, aligned with the CDER Data Standards Strategy 2015-2017. A CBER-CDER Data Standards Strategy FY2018-2022 has been published in 2018.

3 Prescription Drug User Fee Act (PDUFA) V Summary: FY2013 – FY2017

In October 2012, the FDA Safety and Innovation Act (FDASIA) reauthorized the fifth Prescription Drug User Fee Act (PDUFA). FDASIA added section 745A(a) to the Federal Food, Drug, and Cosmetic Act (FD&C Act) and provided FDA with the authority to specify, in guidance, the required electronic format for submitting new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs) and investigational new drug applications (INDs).

Under the PDUFA V performance goals, FDA agreed to publish guidance document on standards and format of electronic submission of application, further develop clinical and non-clinical terminology standards, and periodically publish final guidance specifying formats sponsors must use to submit data in applications.

Table 1 lists the performance goals areas defined in the PDUFA V Commitments and accomplishments the data standards program achieved in those areas.

Table 1. PDUFA V Goals & Accomplishments

Performance Goal	Accomplishments
Format of electronic submissions: electronic Comment Technical Document (eCTD)	✓ Published draft guidance on January 3, 2013 ✓ Reissued draft guidance on July 25, 2014 ✓ Issued final guidance on May 5, 2015 ✓ Published eCTD Technical Conformance Guide (TCG) in October 2015 ✓ Revised timetable to require Master File (MF) submissions in eCTD form to May 5, 2018 in April 2017
Guidance on Standards, Formats, Terminologies that Sponsors Must Use to Submit Data in Applications	Published Final Guidance and Technical Specifications in 2014, including: ✓ Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act ✓ Providing Regulatory Submissions in Electronic Format – Standardized Study Data ✓ Posted Study Data TCG, Data Standards Catalog, and Data Standards Action Plan These binding guidances became effective for NDAs, BLAs, and ANDAs in 2016.

Performance Goal	Accomplishments
Clinical Terminology Standards	**2013** ✓ Published Therapeutic Areas (TA) Standards Initiative Project Plan, 1st version (for public comment) ✓ Participation in the Coalition for Accelerating Therapies & Standards ✓ Initiated internal projects to develop FDA TA recommendations based on FDA's priority list **2014-2017** ✓ Published TA Project Plan, 2nd and 3rd Versions ✓ Continued internal and external projects ✓ Posted the PDUFA V Therapeutic Area Standards Initiative Summary Report – FY2012-FY2017 on September 8, 2017
Other Data Standards	**2015** ✓ Established FDA Identification of Medicinal Products (IDMP) Implementation Group to oversee IDMP implementation **2016** ✓ Established European Medicines Agency /FDA Global Substance Registration System (GSRS) Collaboration Agreement **2017** ✓ Established FDA Substance Registration Scientific Review Board ✓ Established FDA Substance Registration System Technical Control Board ✓ Implemented FDA GSRS in production

4 Impact of Requiring Standards

As described in the previous section, FDA continues to implement data standards for study data and submissions and requires applications use these standards as defined in the FDA data standards catalog. In 2017 FDA published the Assessment of the Impact of Electronic Submissions and Data Standards on the Efficiency and Other Performance Attributes of the Human Drug Review Process[2], which assessed the degree of implementation of electronic submissions and data standards, the readiness of data standards, effectiveness of electronic

[2] https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm564913.pdf

review tools and training, and impact of standards and electronic submission on the review environment. The assessment identified potential actions to consider for improving the FDA electronic submission and review environment.

5 2017 Data Standards Program Year in Review

The CDER DSP continued to make significant progress in 2017 which is highlighted in the sections below. The published Guidance and Technical Specifications updates along with standard operating procedures and templates, supported the program as it continued to focus on participating in the development and testing of standards and evaluating standards which has led to several updates of the FDA Data Standards Catalog.

5.1 Drug Development and Pre-Market Review

The Prescription Drug User Fee Act V Performance Goals indicate FDA will develop standardized clinical data terminology for distinct TAs in collaboration with Standards Development Organizations (SDOs). Significant progress continued in 2017 in the planning, development and testing of TA data standards which focus primarily on efficacy review and evaluation of new medical products.

The list of the prioritized TAs and their development status was updated to reflect progress made and changes in CDER priorities. Of the 55 TAs on this list, 45 have commenced either within FDA to capture business needs or in collaboration with external parties to develop standards. The relevant recommendations documents are provided to serve as input to the project scope in SDO projects, ensuring Review Division input early in each project.

CDER expanded the FDA recommendations for the operational efficacy endpoints, in order to include the derived and compound endpoints generally used in statistical analyses. In 2017 CDER initiated work on four analysis TAs (Rheumatoid Arthritis, Prostate Cancer, Lung Cancer, and Colorectal Cancer), all of which were completed in May 2017.

The Center continued to implement and refine its comprehensive testing approach to ensure that data standards meet FDA's needs as well as to assess impact to the current review environment and tools. The Clinical Data Interchange Standards Consortium (CDISC) foundational standards and TA extensions were prioritized for testing by the Study Data Standards Working Group, when possible, testing activities were conducted while the standard was available for public review. In 2017, the Study Data Standards Working Group testing 16 study data standards leading to updates in the Technical Conformance Guide for seven (7) TAs supported by FDA.

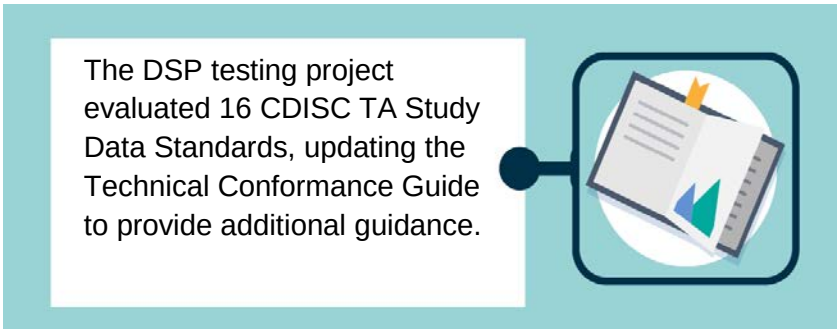
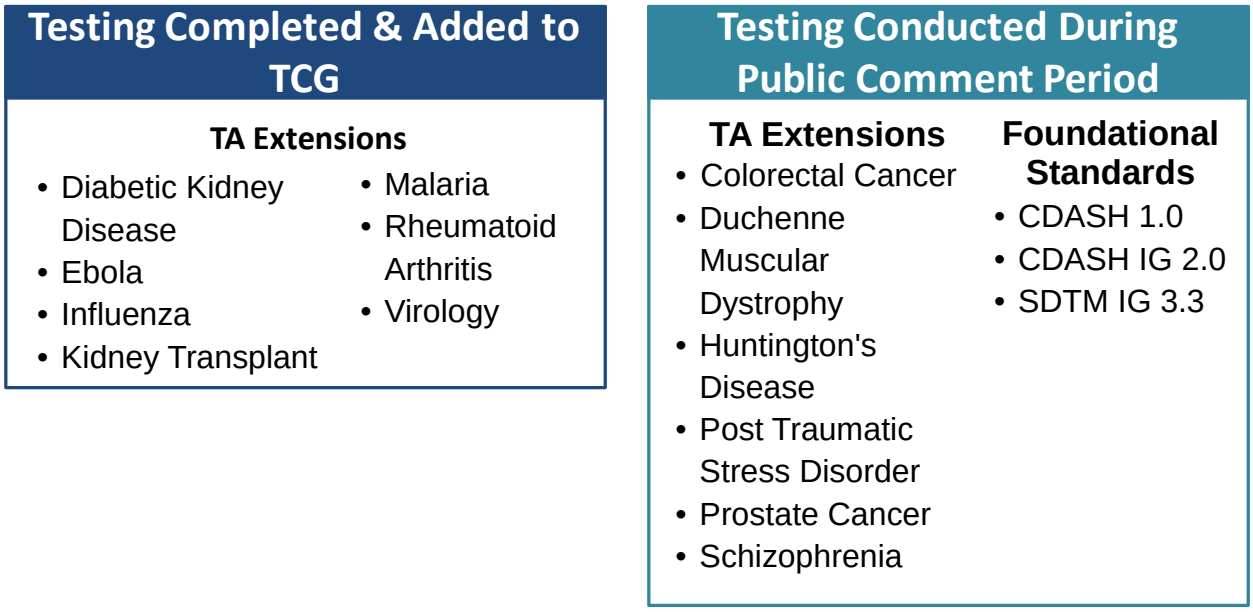


Figure 2. Study Data Standards Tested in 2017



The CDER Office of Computational Science collaborated with CDISC and the Pharmaceutical Users Software Exchange (PhUSE) Nonclinical Test Submissions Workgroup to pilot the Standard for Exchange of Nonclinical Data Implementation Guide (SENDIG) v3.0. This pilot enabled FDA to receive valuable sample data to test readiness of software and processes. It resulted in improvements to the Technical Conformance Guide and further supported evaluation of the SENDIG v3.1. Having sample data enabled CDER to identify improvements to internal tools and services and for the group to identify areas of further development. Information about this pilot as well as FDA and community findings are available in the Nonclinical (SEND) Fit for Use Workstream Wiki Page. Following this pilot and evaluation of SENDIG v3.1, CDER announced support for SENDIG v3.1 and end of support for SENDIG v3.0 in August 2017.

In addition to testing the SEND foundational standard, CDER is collaborating with Critical Path Institute and CDISC to develop improved data standards for Animal Efficacy Studies and Natural History Studies for Animal Rule studies. This project is in the development stage and is planning to publish a Standard for Exchange of Nonclinical Data Implementation Guide: Animal Rule.

The FDA Business Rules (BR) Change Control Board (CCB) maintains and updates the list of business rules on the Study Data Standards Resources website which are used to communicate in a human-readable format the Agency's business needs and practices around regulatory review. The goals of the BR CCB are to help industry understand how best to submit study data that are compliant, useful, and will support meaningful review and analysis and mature existing data standards along these same lines. Regulatory review is a complex and multi-faceted task, the BR CCB focuses on one piece of the process at a time and works with subject matter experts in that area to distill any business rules that are appropriate across the Agency. The list of business rules has been updated twice in 2017; first to align with the Office of Minority Health's guidance on Race and Ethnicity published in 2016 (published Spring 2017) and second to update SEND-

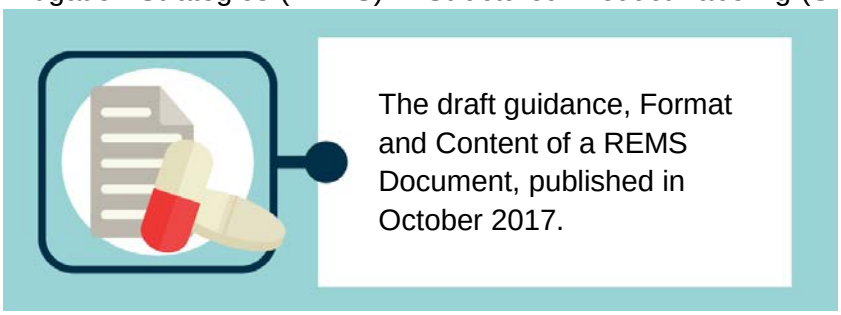
specific content (finalized December 2017). New versions of the documents will be published as they are available.

5.2 Drug Safety Performance and Promotion

Projects in this regulatory business area support the oversight of post-market risk management strategies as well as drug marketing and promotion which includes pharmacovigilance and surveillance.

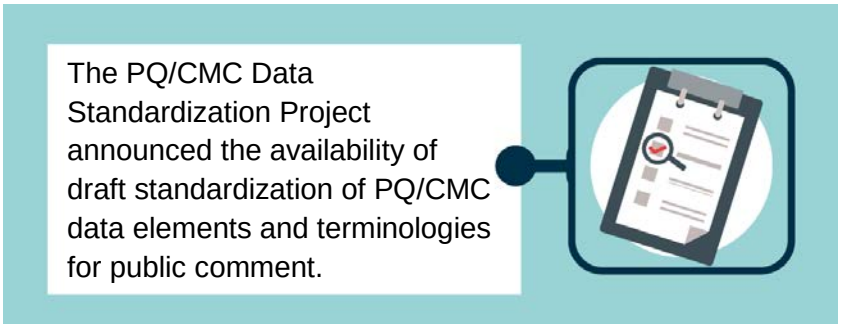
Based on the Center's commitment to implement the International Organization for Standardization (ISO) 11238 Substance Identification Standard, FDA established and integrated the GSRS in the FDA production environment in February. The GSRS is co-developed by National Institutes of Health (NIH)/ National Center for Advancing Translational Sciences (NCATS) and FDA with contributions from international regulators, academia, standard bodies, and experts. This system release is anticipated to include Specified Substance Group 1 registration activity. Substance identification is the lynchpin associating data related to products, biology, manufacturing, and submissions. This mission critical system will ensure that substances are consistently described, uniquely identified, shareable with other regulatory authorities and managed as critical source data in FDA.

The CDER project to capture and submit structured information about Risk Evaluation and Mitigation Strategies (REMS) in Structured Product Labeling (SPL) was completed in 2016 with the publishing of a revised implementation guide describing how sponsors, healthcare information systems developers, and other stakeholders can share REMS information leveraging SPL. Prior to completing the REMS project, FDA successfully completed a pilot with nine companies, this information was covered during an introductory webinar for the REMS project in August 2016. Ultimately, FDA hopes that the incorporation of REMS information into SPL will have numerous benefits for both sponsors and the healthcare providers and patients who participate in REMS programs. For sponsors, SPL will simplify the creation of standardized REMS documents, facilitating more efficient review of those documents. For participants in the REMS, REMS information in SPL will help clarify what the REMS requires by describing those requirements in a standardized way. Draft guidance, Format and Content of a REMS Document, published in October 2017 (FDA-2009-D-0461) and once finalized will require sponsors to submit REMS documents in SPL format.



The Annual Report project seeks to improve the usability of Annual Report submissions pertaining to Distribution data, Field Alert Reports, and Pharmaceutical Quality & Chemistry, Manufacturing, and Controls (PQ/CMC) information. The project will ensure that essential facility location and production information, and an up-to-date view of the CMC process are captured completely and in a format conducive to electronic receipt, storage and usage. This project continues to assess and refine the proposed changes that are undergoing internal agency reviews.

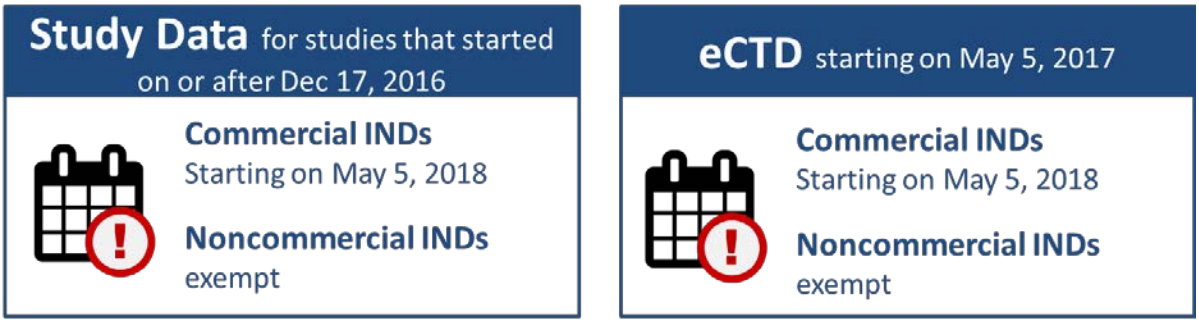
The PQ/CMC Data Elements and Terminologies Data Standardization Project continued work related to characterizing data elements and terminologies for information used in support of Module 3 of eCTD based drug applications. An overall goal of this initiative is the development of standardized, structured and computable data standards for PQ/CMC submissions, ensuring consistent representation of concepts. In July 2017, the project announced availability of draft data elements and terminologies for public comment[3].



5.3 Policy, Planning and Governance

On December 17, 2016, the first requirement implemented under the provisions of FDASIA that authorized the electronic submission of information for NDAs, BLAs, and ANDAs went into effect requiring clinical and nonclinical trials that started on or after that date to use the standards in the FDA Data Standards Catalog. Requirements for submissions to use the electronic eCTD format began on May 5, 2017. Figure 3 highlights these implementation dates.

Figure 3. Implementation Dates – Update



To ensure that submissions meet expected requirements, CDER and Center for Biologics Evaluation and Research (CBER) will validate submissions upon receipt and will assess conformance to required study data standards. The Technical Rejection Criteria for Study Data was published in November 2016 (revised in March 2017) and outlines the approach and validations planned for study data. During 2017 CDER and CBER initiated the development of the electronic technical rejection validation criteria and started testing.

[3] Draft Standardization of Pharmaceutical Quality/Chemistry Manufacturing and Control Data Elements and Terminologies; Request for Comments (FDA-2017-N-2166)

To ensure that current information continues to be available, new versions of the technical specifications associated with Providing Regulatory Submissions in Electronic Format — Standardized Study Data guidance (eStudy Guidance), specifically the *Data Standards Catalog* and *Study Data TCG,* were updated in 2017. The documents provide a detailed revision history but in general reflect feedback from industry and FDA staff as well as results of testing and acceptance activities discussed above. Figure 4 highlights the new versions published in 2017.

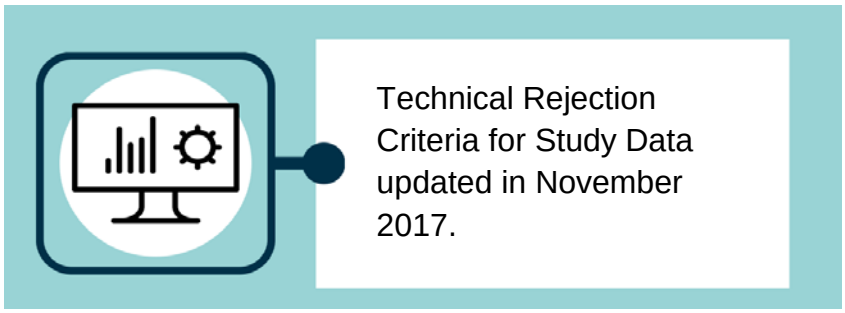
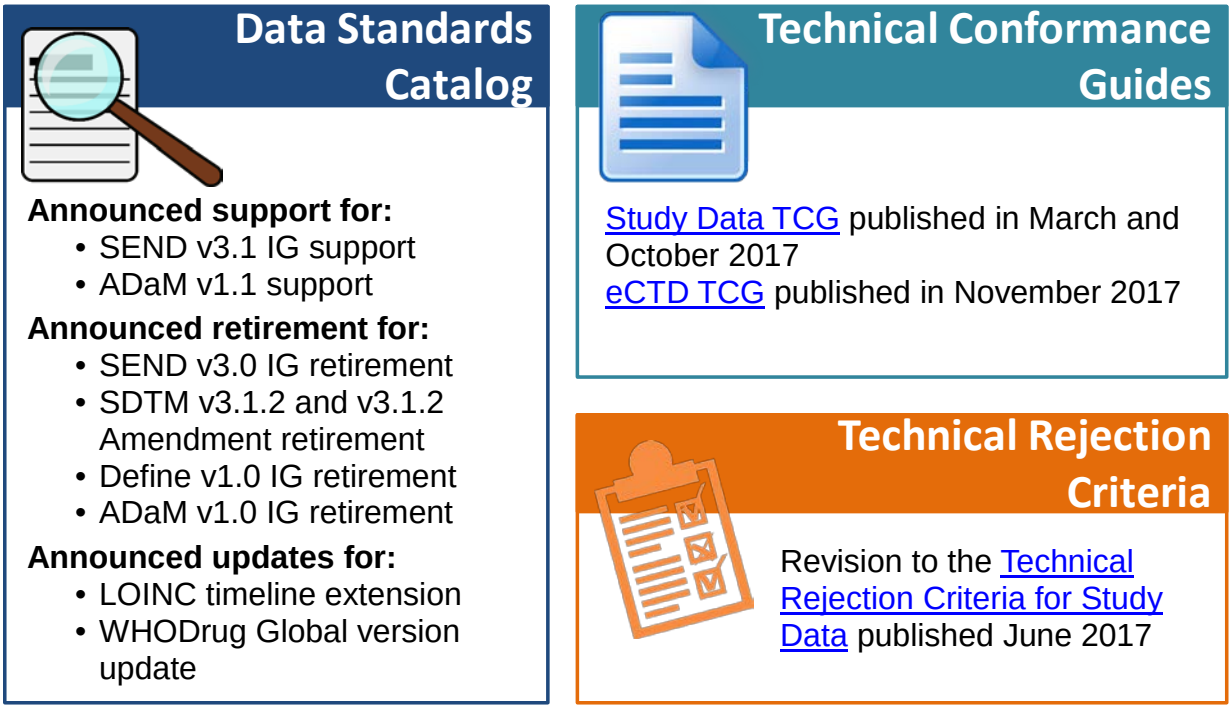


Figure 4. Updates to Data Standards Catalog, TCG, and Technical Rejection Criteria



As part of its role in defining and governing CDER's Data Standards program, the Data Standards Program Board (DSPB) updated the Data Standards Strategy document in 2017 to create a joint CBER-CDER Data Standards Strategy. The Action Plan, updated quarterly, continued to highlight progress across the program as progress has been made to the Center's strategy. The Action Plan will be updated in 2018 to align with the CBER-CDER Data Standards Strategy. The Data Standards Operations Subcommittee continued to conduct primary operations on behalf of the DSPB. The Study Data Standards and TCG workgroups remained very active all year supporting testing and updates to the guide that were published. All progress and decisions are

briefed to the DSPB quarterly or on an as needed basis. In 2018, the DSPB will meet on a bi-monthly basis.

The DSP conducted an annual review of the Data Standards Program Manual of Policies and Procedures and supporting standard operating procedures (SOPs) to assess the need for updates or refinements. Minor updates and process step clarifications were incorporated into the SOPs.

The DSP continued its communication efforts by refining the study data standards resource webpage. The program is developing a series of fact sheets related to study data, eCTD, MFs, electronic gateway, creating a new data standards video and refining the interactive Drug Lifecycle webpage.

5.4 Other Standards Areas

5.4.1 Alternative Transport Formats

In 2014-2015 FDA conducted a pilot to evaluate the CDISC Dataset-XML. The final report for that pilot outlined that additional testing is needed to evaluate cost versus effectiveness of DS-XML as an alternate transport format and determined that several pilots would be needed to evaluate new transport formats before a decision is made to support a new format. The PhUSE collaboration added the evaluation of alternate transport formats as a project to further this evaluation. Project progressed in 2017, with PhUSE publishing, a white paper recommending SAS V8 Transport.

5.4.2 Source Data Capture

A large amount of clinical trials participant data, which needs to be entered in research electronic case report forms (eCRFs), already exists in healthcare provider's Electronic Health Records (EHR) systems. However, EHR and eCRF data are generally collected in separate, non-compatible formats and exist in separate systems. This results in patient information being manually re-entered into the eCRF system, dramatically slowing down workflow and increasing the risk of inaccuracies due to duplicate entry. This is a major barrier to research on real-world use of drugs and biologics.

CDER is supporting two projects that aim to demonstrate approaches for collecting eCRF data, stored on research Electronic Data Collection (EDC) systems, directly from an EHR system in an FDA-compliant way. These projects will also demonstrate relevant improvements in efficiencies and potential returns on investment from using an automated approach versus the current manual methodology.

One of these projects, Transforming Research Through eSource and Standards, plans to collaborate with clinical research sites and organizations to develop and evaluate EHR-to-EDC solutions in conjunction with ongoing research. The project objective is to use identified metrics to measure the relative benefits of using an EHR-to-EDC solution compared to traditional manual entry methods. The second project, Source Data Capture from EHRs: Using Standardized Clinical Research Data, has similar overall goals and is being performed as part of an existing

phase 3 trial. In 2017, the project made significant strides in initial system development, specifying the data elements to be incorporated an EHR-to-EDC system for pilot testing, and working through the complexities of their EHR system Applied Program Interfaces to allow bi-directional communication between systems.

5.4.3 BRIDG Working Group and BRIDG Architectural Review

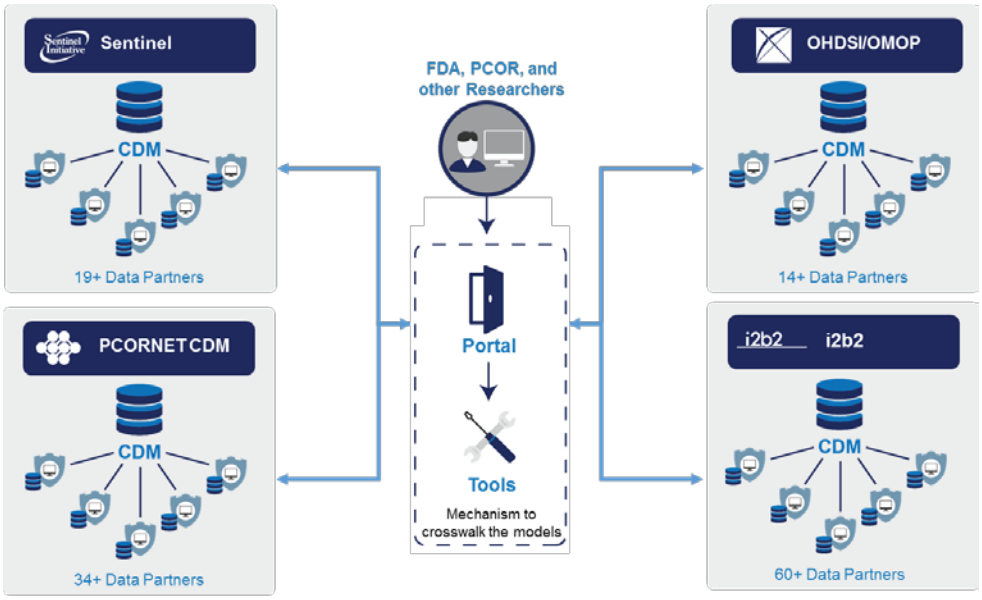
CDER co-leads the HL7 Biomedical Research and Regulation (BR&R) workgroup. The BR&R areas of interest encompass clinical and translational research, both regulated and non-regulated, and the subsequent regulatory submissions and information exchanges to bring new products to market and to ensure safe use throughout the product lifecycle. BR&R creates and promotes standards to facilitate biomedical research and any subsequent regulatory evaluation of the safety, efficacy and quality of medical products that may arise from research. BR&R maintains the Biomedical Research Integrated Domain Group (BRIDG) information model representing a shared view of the concepts of basic, pre-clinical, clinical, and translational research. This structured information model is being used to support development of data exchange standards and technology solutions that will enable semantic interoperability within the biomedical/clinical research arena and between research and the healthcare arena.

In collaboration with the BR&R workgroup, CDER currently has a project to support the architecture review of BRIDG to make it more sustainable, accessible and usable model. The project identified an initial list of BRIDG model re-architecture changes and developed approaches to expanding use of BRIDG in biomedical research by linking to pre-existing standards (termed “modelling by reference”). The project objectives also include harmonizing BRIDG with the Fast Healthcare Interoperability Resources (FHIR), a modern HL7 standard for exchanging healthcare information electronically. In 2017, the project mapped 80% of BRIDG classes to FHIR resources and worked with the HL7 BR&R workgroup to develop use cases/scenario in clinical research where FHIR resources could be leveraged. Additionally, the project worked with the HL7 BR&R workgroup to update two FHIR resources which were to be subsequently balloted at HL7 in January 2018.

5.4.4 Common Data Model Harmonization

The Common Data Model (CDM) Harmonization project started in 2017 to build a data infrastructure for conducting research using Real World Data (RWD) derived from the delivery of health care in routine clinical settings. Shown in Figure 5, the objective of this project is to create a proof of concept solution that enables a researcher to make a single query usable across data from four distinct CDM research formats - FDA’s Sentinel CDM, the Observational Health Data Sciences and Informatics CDM, PCORnet CDM, and the Accrual of Patients to Clinical Trials i2b2 CDM.

Figure 5. CDHM Concept



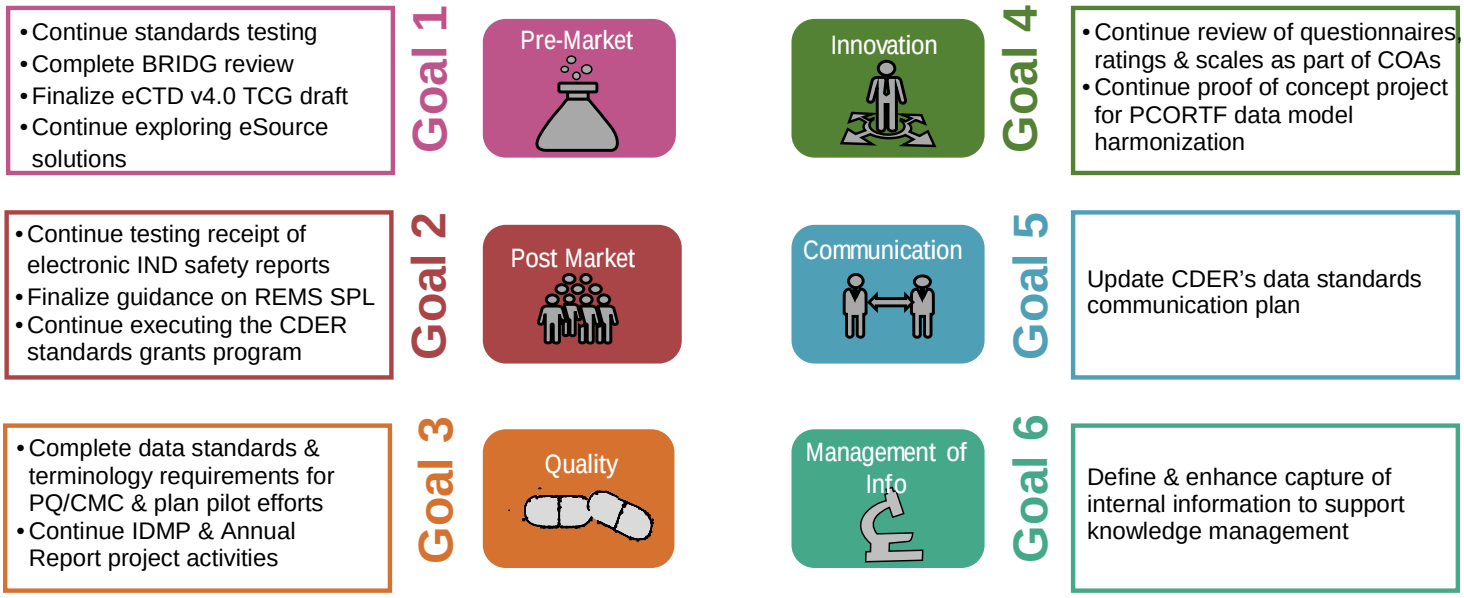
This Patient-Centered Outcomes Research Trust Fund (PCORTF) project is a collaborative effort involving five organizations: FDA, NCATS, National Cancer Institute, National Library of Medicine, and the Office of the National Coordinator and is led by FDA. The project has worked to define requirements, determine the architectural approach, conduct a tools evaluation, and continues core data mapping activities.

6 Moving Forward - 2018 CDER Data Standards Program Direction

With required electronic study data standards and electronic submissions in effect or coming into effect, respectively, CDER continues to focus on ensuring that the review environment is capable to support receipt, processing and review of all electronic data. Continued collaboration with SDOs and stakeholders to ensure long-term sustainability of supported data standards, as well as the testing of new standards and terminologies will be a key focus of the DSP.

To support communication of new technical specifications and conformance guides, as well as relevant standards information, webinars are planned in 2018 corresponding to the March and November updates of the TCG, new FDA webpage updates (e.g., PDUFA VI Informatics webpage) are planned for deployment throughout 2018. These updates will ensure a consistent external web presence, revised materials, and interactive tools for both internal and external stakeholders. Figure 6 highlights focus areas in 2018.

Figure 6. 2018 Direction Highlights



In addition to these project areas, the Center is committed to continuing support for demonstration efforts that highlight standards-based technology solutions for collection of related healthcare and clinical research information. Both the 21st Century Cures Act and PDUFA VI Commitment Letter mandate the development of a framework and guidance for the use of Real RWD and the evidence generated from RWD, Real World Evidence, for use in clinical research and regulatory work. In short, RWD is data gathered in everyday settings, not generated by research protocol-driven methods, such as entries into patient EHRs during routine visits. CDER is working to outline the conceptual and logistical groundwork around efforts that would begin in 2018. For updates on this, and other ongoing projects ongoing in 2018, see the DSP Action Plan published quarterly on the CDER Data Standards Program webpage.

Appendix A: Glossary of Acronyms

ANDA	Abbreviated New Drug Applications
BLA	Biologics License Applications
BR	Business Rules
BR&R	HL7 Biomedical Research and Regulation Group
BRIDG	Biomedical Research Integrated Domain Group
CBER	Center for Biologics Evaluation and Research
CCB	Change Control Board
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDM	Common Data Model
COA	Clinical Outcomes Assessment
DSP	Data Standards Program
DSPB	Data Standards Program Board
eCRF	Electronic Case Report Forms
eCTD	Electronic Common Technical Document
EDC	Electronic Data Collection
EHR	Electronic Health Record
FDASIA	Food and Drug Administration Safety and Innovation Act
FD&C Act	Federal Food, Drug, and Cosmetic Act
FHIR	Fast Healthcare Interoperability Resources
FRN	Federal Register Notices
FY	Fiscal Year
GSRS	Global Substance Registration System
IDMP	Identification of Medicinal Product
IND	Investigational New Drug
ISO	International Organization for Standardization
MF	Master File
NCATS	National Center for Advancing Translational Sciences
NDA	New Drug Applications
NIH	National Institutes of Health
PCORTF	Patient-Centered Outcomes Research Trust Fund
PDUFA	Prescription Drug User Fee Act
PhUSE	Pharmaceutical Users Software Exchange
PQ/CMC	Pharmaceutical Quality/ Chemistry, Manufacturing, and Controls
REMS	Risk Evaluation and Mitigation Strategies
RWD	Real World Data
RWE	Real World Evidence
SDO	Standards Development Organization
SEND	Standard for Exchange of Nonclinical Data
SENDIG	Standard for Exchange of Nonclinical Data Implementation Guide
SOP	Standard Operating Procedures
SPL	Structured Product Labeling
TA	Therapeutic Area
TCG	Technical Conformance Guide