CDER Data Standards Program
2019 Annual Assessment

March 2020

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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's 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 and is mapped to the six major areas of regulatory business activity of the CBER-CDER Strategic Plan. The following sections below highlight program accomplishments.

2019 Summary of Accomplishments

Goal 1

Goal 1: Incorporate data standards to support more efficient, science-based pre-market review of medical products.

- Completed assessments for nine Therapeutic Area User Guides (TAUGs)
- Supported further evaluation of SENDIG v3.1
- Updated FDA Business Rules
- Clinical Outcome Assessment (COA) – Completed three Questionnaire, Rating, & Scales (QRS) assessments

Goal 2

Goal 2: Improve the post-market risk management strategies and pharmacovigilance and surveillance of medical products by using data standards.

- Initiated the FDA's Adverse Event Reporting System (FAERS) 2 / ICSR Implementation effort, defined and communicated regional data elements, established project framework and associated processes
- Completed Electronic IND Safety Report Pilot and published Draft "Providing Regulatory Submissions in Electronic Format: IND Safety Reports: Guidance for Industry"

Goal 3

Goal 3: Implement common data standards to improve the quality and integrity of marketed medical products.

- Pharmaceutical Quality/Chemistry, Manufacturing, and Controls (PQ/CMC) continued review of comments on draft data elements and terminologies and conducted a public meeting on Standardized Data
- Continued progress on improving usability of Post Approval Change submissions
- Continued assessment of Identification of Medicinal Product (IDMP) standards to ensure conformance with FDA regulatory requirements

Goal 4

Goal 4: Promote innovation in the development and use of data standards.

- Collaborated with HL7 Biomedical Research and Regulation (BR&R) workgroup to develop Fast Healthcare Interoperability Resources (FHIR) resources to represent the full scope of clinical research semantics
- Assessed proof-of-concept implementation for eSource initiatives to identify best practices to support future development
- Completed most of the foundational design and implementation milestones for the Common Data Model Harmonization (CDMH) project
- Conducted a feasiblility assessment to determine if the uses of the Structured Product Labelling (SPL) standard can be fulfilled by the HL7 FHIR standard

Goal 5

Goal 5: Ensure effective communication and collaboration with stakeholders on data standards

- The Study Data Technical Conformance Guide (sdTCG) was updated in March and October of 2019
- Continued updates to the FDA Data Standards Catalog
- Developed and updated the Study Data Technical Rejection Criteria (TRC) to promote stakeholder understanding of eCTD Validation Criteria applied to submissions containing standardized study data
- Collaborated with PHUSE on updates to the TRC and a publicly available tool to help stakeholders meet requirements
- Presented on the TRC and the FDA developed Study Data Self-Check Worksheet tool at PHUSE, SBIA, GRx+Biosims, and DIA conferences in 2019

Goal 6

Goal 6: Improve the management and usability of the volume of information through data standards

- Continued the development and refinement of CDER's Data Governance operating model and its associated workflow processes

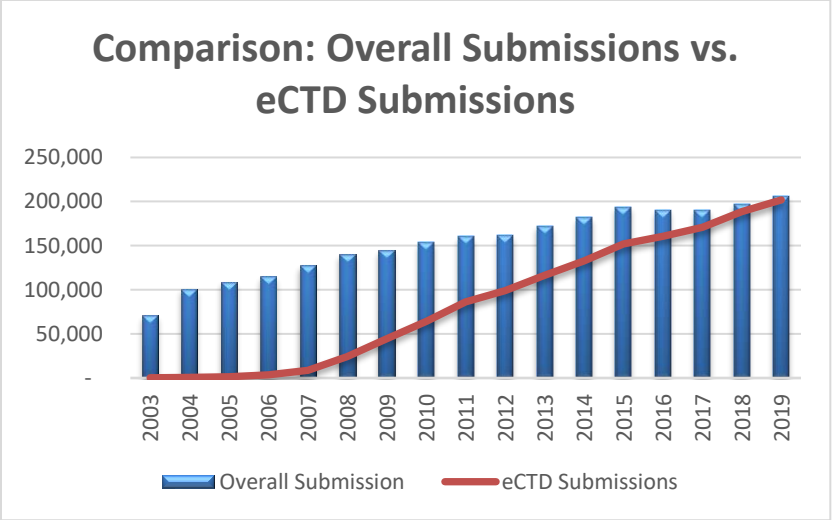
3 Impact of Requiring Standards

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, which assessed the degree of implementation of electronic submissions and data standards, the readiness of data standards, effectiveness of electronic 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.

4 2019 Electronic Submission Metrics

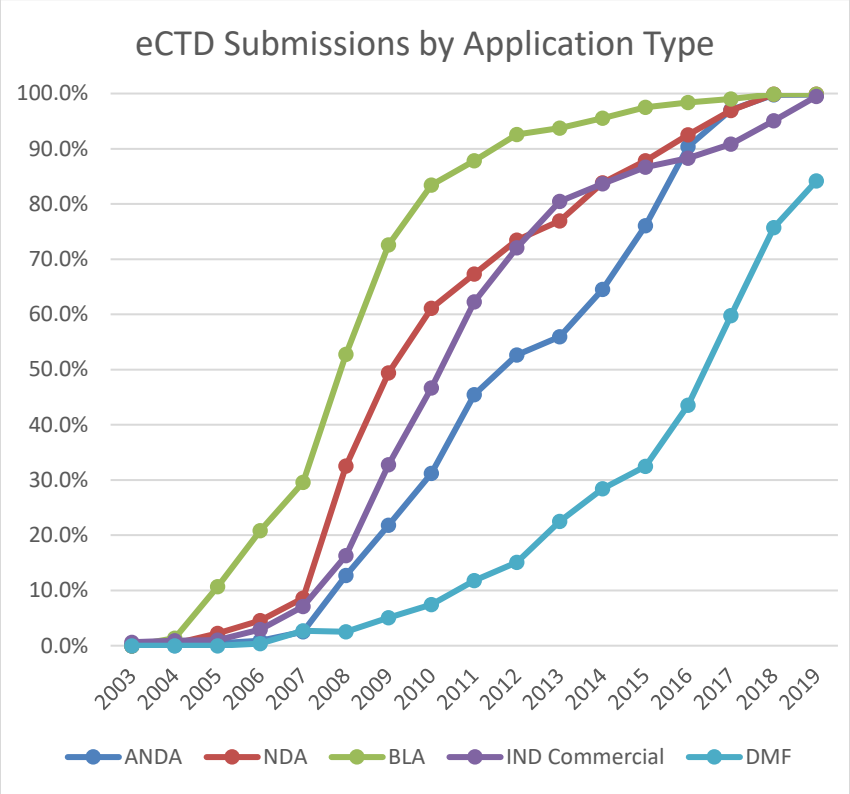
Analyses of FDA's submissions showed a clear trend of improvement in compliance to eCTD format requirements. CDER receives approximately 205,000 electronic submissions via Electronic Submission Gateway annually. In FY2019, about 98% were in eCTD.

Figure 1.



Further analyzing the FY2019 submission metrics by application type, nearly 99% of the regulatory submissions for NDA, BLA, ANDA, Commercial IND, and DMFs Type II/IV/V were in eCTD.

Figure 2.



5 2019 Data Standards Program Year in Review

The CDER DSP continued to make significant progress in 2019 which is highlighted in the sections below. The published Guidance documents and 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 Goal 1: Incorporate data standards to support more efficient, science-based pre-market review of medical products

The Prescription Drug User Fee Act (PDUFA) VI Performance Goals indicate FDA will develop and update therapeutic area user guides (TAUGs) to include the appropriate content for the analysis data standards used in submission and review. Significant progress continued in 2019 in the planning, development and testing of TAUGs which focus primarily on efficacy review and evaluation of new medical products.

The list of TAUGs that address each prioritized therapeutic area was updated to reflect progress made. Of the fifty-five therapeutic areas on this list, forty-eight have commenced either within FDA to capture business needs or in collaboration with external parties to develop standards Therapeutic Area User Guides. The relevant recommendations documents are provided to serve

as input to the project scope in external projects, ensuring Review Division input early in each project.

The Center continued to implement and refine its comprehensive testing approach to ensure that data standards and TAUGs 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 Therapeutic Area extensions (also called TAUGs) were prioritized for testing by the Study Data Standards Working Group, when possible, testing activities were conducted while the TAUG was available for public review. In 2019, the Study Data Standards Working Group assessed four TAUGs leading to updates in the Study Data Technical Conformance Guide.

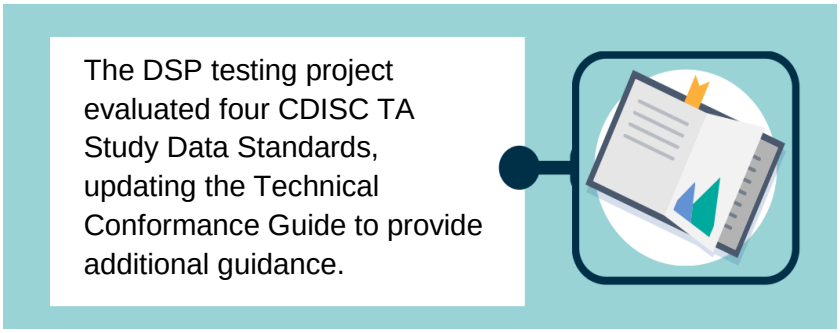
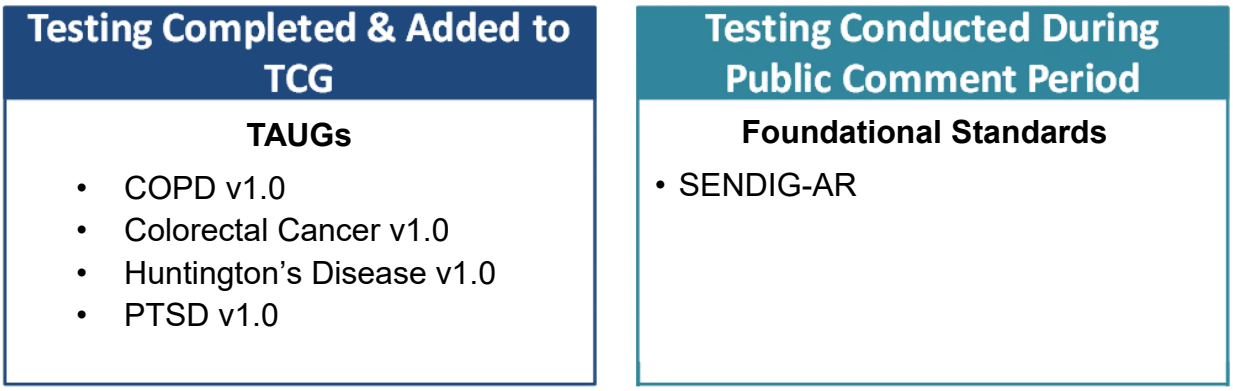


Figure 3. Study Data Standards Tested in 2019



Following CDER's announcement to support SENDIG v3.1 in August of 2017, FDA has continued to improve the Study Data Technical Conformance Guide and further support evaluations of the SENDIG v3.1. In 2018, CDER Office of Computational Science (OCS) conducted a comparison of the SENDIG v3.0 and SENDIG v3.1 to analyze the differences and the potential impacts on the DataFit tool. Furthermore, SENDIG v3.1 was assessed for impacts that the new version will have on Janus.

In addition to testing the SEND foundational standard, CDER collaborated 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 was completed in 2019 and has published a Standard for Exchange of Nonclinical Data Implementation Guide: Animal Rule(SENDIG-ARv1.0).

The FDA Business Rules 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 once in 2019.

CDER's Clinical Outcome Assessment project is focused on the development and evaluation of COAs submitted in support of regulatory submissions. COAs capture patient experience data in Phase I-III of clinical trials in drug development programs. The purpose of COAs is to assess treatment efficacy, treatment safety and tolerability, and used to formulate labelling claim language. During 2019, three QRS supplements were completed.

5.2 Goal 2: Improve the post-market risk management strategies and pharmacovigilance and surveillance of medical products by using data standards.

FAERS is a mission critical system for FDA, it supports the CDER/CBER's post-marketing safety surveillance program for all marketed drug and therapeutic biologic products. The FAERS II program is initiated in fall 2018 to provide a modernized system for safety surveillance including pre-market and post-market safety reports along with product quality defect reports. The goal for the system is to become a one-stop shop solution for intake, triage, and case processing. It will also allow for enhanced and unified data analytics and signal management lifecycle solution utilizing ICH E2B R3 standard.

Meanwhile, a highly interactive and user friendly FAERS Public Dashboard was launched in 2018 to provide the general public access to information related to human adverse events reported to the FDA by the pharmaceutical industry, healthcare providers and consumers.

5.3 Goal 3: Implement common data standards to improve the quality and integrity of marketed medical products.

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

The PQ/CMC Data Standardization Project developed draft HL7 FHIR Exchange Standard Profile and Implementation Guide for Quality Specifications PQ/CMC domain.

computable data standards for PQ/CMC submissions, ensuring consistent representation of concepts. In 2019 the project executed testing of a PQ/CMC Proof-of-Concept (PoC) with 7 PhRMA industry participants, demonstrating successful end-to-end creation, submission, and report generation using structured PQ/CMC data and built out PQ/CMC content standard to include eStability data elements.

As FDA focuses on the challenges of the global supply chain and foreign sourcing of medicinal products, FDA continues to participate and promote the conformance to international harmonized IDMP to ensure the safety of medications throughout the world. In 2019, FDA continued assessment of IDMP standards to ensure conformance with FDA regulatory requirements.

The Annual Report project seeks to improve the usability of Annual Report submissions pertaining to Distribution data, Field Alert Reports, and 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.

5.4 Goal 4: Promote innovation in the development and use of data standards.

CDER co-leads the HL7 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 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 has funded and overseen a successful grant aimed at harmonizing BRIDG clinical research semantics with the existing healthcare delivery artifacts implemented in FHIR, a modern HL7 standard for exchanging healthcare information electronically. The team has mapped the core BRIDG classes to FHIR resources, worked with the BR&R to develop FHIR resources to fill in the identified gaps (such as the semantics of research studies and research subjects), and subsequently balloted them at HL7.

eSource data (electronic source data) refers to the use of electronically recorded information as a source of data directly transferred to data systems used for clinical trials. The device or system that records the original data can include many items such as wearable devices, mobile apps. One of the larger potential sources of eSource data is Electronic Health Records (EHR) systems. 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 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. To mitigate this challenge, an HL7 FHIR "accelerator" program for clinical research , "Vulcan," was jointly created by sites, sponsors, regulatory and translational researchers organizations, including TransCelerate Biopharma (TCB), FDA, NIH, JHU, HL7, CDISC, as well as several large professional societies. CDER is actively involved in Vulcan, participating in its Steering Committee, Advisory Board, and Technical Expert group, to ensure that the solution are aligned with our regulatory review needs. CDER is also 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 and 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 is currently ongoing, 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 2019, the project made significant strides in 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. Proof-of-concept implementation was assessed for the best practices to build upon in continued development.

Real World Data (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 began in 2018, culminating in the first output, the Framework for FDA's Real-World Evidence Program released December 2018.

The Common Data Model (CDM) Harmonization project started in 2017 to build a data infrastructure for conducting research using RWD derived from the delivery of health care in routine clinical settings. The objective of this project was 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. Funded by the Patient-Centered Outcomes Research Trust Fund (PCORTF) the project was 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. This first phase project completed work in 2019 and a full report of its delvierables, achievements, and lessons learned is expected to be posted on the PCORTF Reports website (https://aspe.hhs.gov/patient-centered-outcomes-research-trust-fund-reports) in early 2020.

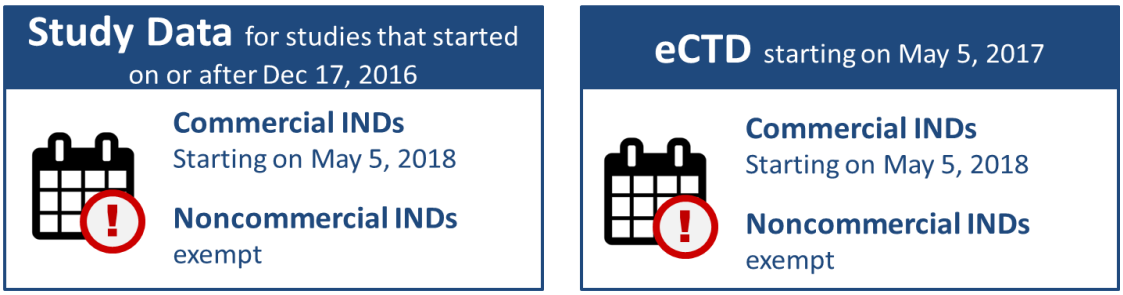
This Patient-Centered Outcomes Research Trust Fund (PCORTF) project is a collaborative effort involving five organizations: FDA, NCATS, National Cancer Institute, National Library of Medicine, and the Office of the National Coordinator and is led by FDA.

FDA is also reviewing how to ensure the continued utility of it's primary data standards for internal and external data transfer during a period expected to bring significant changes and advancement in data standards for regulatory purposes. The Structured Product Labelling (SPL) standard is used for a wide range of uses at FDA including, but not at all limited to, support for labelling changes. It powers a range of information systems within and between FDA Centers as well as to external and public facing information systems. SPL is currently powered by the HL7 Version 3 (v3) standards. Because HL7's primary focus has shifted to the newer and more technically powerful FHIR standard (Fast Healthcare Interoperable Resources), FDA is performing due diligence by performing an assessment of the capability of FHIR to, at minimum, support the same functions and uses as are currently allowed by SPL based on v3. Results of this and continuing work will help FDA determine the best paths to ensuring SPL will be supportable for the long term.

5.5 Goal 5: Ensure effective communication and collaboration with stakeholders on data standards

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 4 highlights these implementation dates.

Figure 4. Implementation Dates – Update

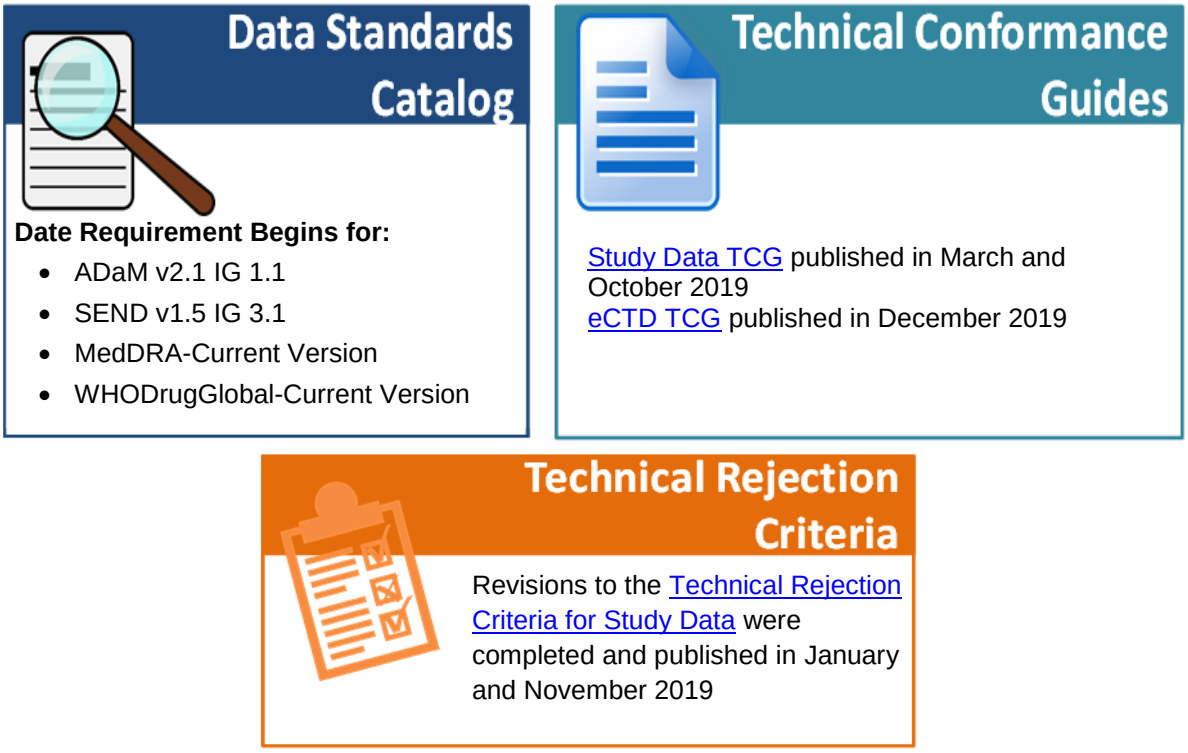


To ensure that submissions meet expected requirements, CDER and Center for Biologics Evaluation and Research (CBER) will validate submissions upon receipt and will assess conformance to required study data standards. The Technical Rejection Criteria for Study Data was published in November 2016 and outlines 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.

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 2019. The Data Standards Catalog lists the data standards

and terminologies that FDA supports for use in regulatory submissions to better enable the evaluation of safety, effectiveness, and quality of FDA-regulated products. The Study Data TCG provides specifications, recommendations and general considerations on how to submit standardized study data using standards listed in the data standards catalog. These 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 5 highlights the new versions published in 2019.

Figure 5. 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 was 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 bi-monthly or on an as needed 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 and the interactive Drug Lifecycle webpage.

5.6 Goal 6: Improve management and usability of the volume of information through data standards.

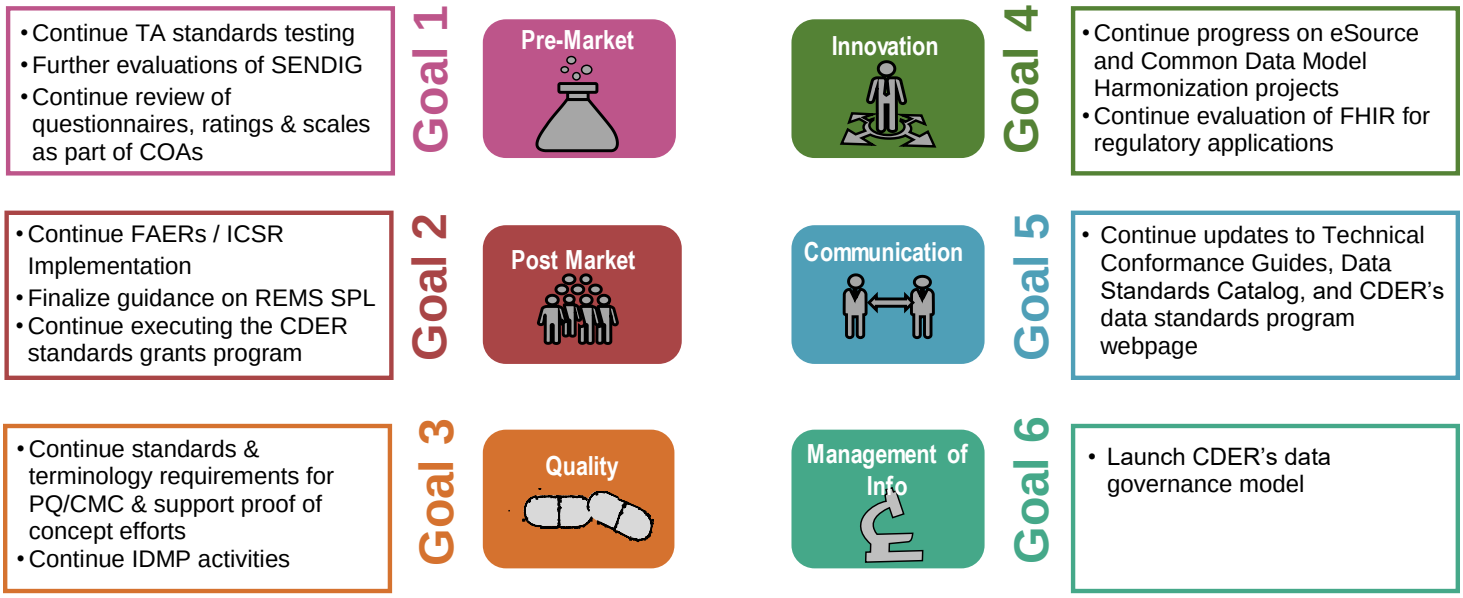
The CDER Data Governance project was initiated in 2018 with the objective of developing and implementing a data governance framework across CDER data domains such as Facilities Data and Products Data, etc. The preliminary assessment of the current state was completed in 2018, in 2019, the project has completed the development of the Data Governance operating model and its associated workflow processes. The initiative is expected to launch in the first quarter of 2020, and will continue to refine the model's scope and processes based on feedback and lessons learned, as well as explore opportunities to expand the model to include other additional data domains and activities.

6 Moving Forward - 2020 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, TCG will be updated in March and October of 2020, new FDA webpage updates (e.g., PDUFA VI Informatics webpage) are planned for deployment throughout 2019. 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 2019.

Figure 6. 2020 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. For updates on this, and other ongoing projects ongoing in 2019, 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
FAERS	FDA's Adverse Event Reporting System
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