CDER Data Standards Program 2020 Annual Assessment

March 2021

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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.

2020 Summary of Accomplishments

Goal 1

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

- Posted special edition of the Study Data Technical Conformance Guide to address current Public Health Emergency
- Led the Operations Subcommittee (OpSC) through 35 issues resulting in 21 study data policy decisions
- Added CDISC SENDIG-AR (Animal Rule) to FDA Data Standards Catalog (Catalog)
- Added CDISC Define.XML v2.1 to Catalog
- Began support for IEEE BioCompute
- Added two new CDISC Therapeutic Area User Guides (TAUGs) to the sdTCG
- Incorporated PQ/CMC requirements into HL7 FHIR Release 5, to be balloted in 2021

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"
- Published "*The revised technical specifications document Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments*" in December 2020, to include additional data elements, descriptors, and descriptor values for reporting certain IND safety reports as individual case safety reports (ICSRs)

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 mapping PQ/CMC requirements to FHIR resources and development of FHIR exchange standards
- Continued progress on improving usability of Post Approval Change submissions
- Continued working with ISO TC215 WG6 to revise and enhance the ISO Identification of Medicinal Product (IDMP) standards to ensure conformance with FDA regulatory requirements and harmonized global implementation

Goal 4

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

- Continued proof-of-concept assessments of implementation for eSource initiatives to identify best practices to support future development
- Continued feasibility assessment to determine if the uses of the Structured Product Labelling (SPL) standard can be fulfilled by the HL7 FHIR standard
- Complete a draft of advisory guidance, of part of 21 Century Cures, guidance on Data Standards applicable to Real World Evidence and circulate to the respective working group for internal review.

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, July and November of 2020
- Continued updates to the FDA Data Standards Catalog
- The Study Data Technical Rejection Criteria (TRC) has been referenced at many external conferences in 2020 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 (including industry conformance trends in 2020) and the FDA developed Study Data Self-Check Worksheet tool at PHUSE, SBIA, GRx+Biosims, and DIA conferences in 2020
- Updates published to Study Data Guidance in 2020: Providing Regulatory Submissions in Electronic Format — Standardized Study Data Guidance for Industry

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
- Developed a Study Data Standards Policy Document Management Process Standard Operating Procedure to provide the CDER's clearance processes for electronic submission-related documentation. This ensures that study data provided to the FDA as part of a regulatory submission have an associated, defined data standard from the FDA Data Standards Catalog

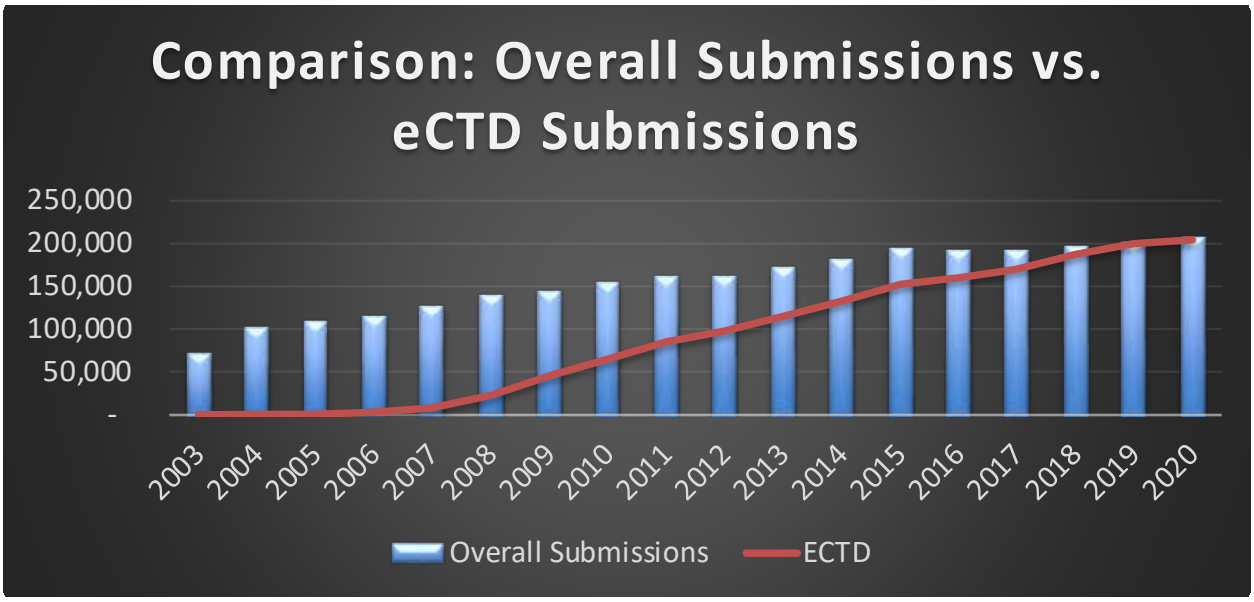
3 Impact of Requiring Standards

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 2020 Electronic Submission Metrics

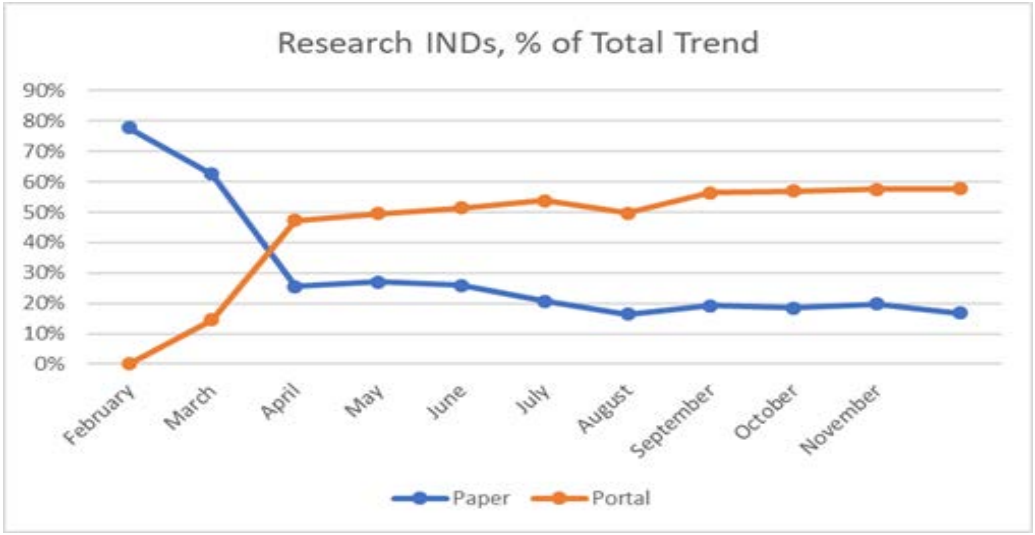
Analyses of FDA's submissions showed a clear trend of improvement in compliance to eCTD format requirements. Excluding non-commercial IND and Type III DMF (these are not required in eCTD), CDER received approximately 205,000 electronic submissions via Electronic Submission Gateway in FY2020. In FY2020, there was near 99% compliance with the eCTD requirement.

Figure 1.



In 2020, CDER expanded electronic options for transmitting non-eCTD submissions. **CDER's NextGen Portal began accepting Non-eCTD submissions to Research IND and DMF Type III applications**. ESG also now accepts non-eCTD DMF Type III. Utilizing CDER NextGen or ESG provides an easier and faster way to transmit a non-eCTD submission compared to paper or physical media (i.e. CD/USB Drive).

Paper Submission of Research INDs dropped from 78% to 17% after the release of CDER NextGen Portal solution during the time period from March to December 2020. The solution sharply decreased the need for staff and RPMs to come to the campus and physically engage, thus improving safety. Paperless benefits were realized on the industry side too by reducing the need to be onsite to print and assemble a physical submission.



5 2020 Data Standards Program Year in Review

The CDER DSP continued to make significant progress in 2020 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 2020 in the planning, development and testing of TAUGs which focus primarily on efficacy review and evaluation of new medical products.

The FDA currently supports 24 TAUGS in section 5 of the sdTCG.

Figure 3. Study Data Standards Tested in 2020

Added to sdTCG or Catalog	Agency Provide Public Comments
Properties	**Properties**
• CDISC SENDIG-AR and SDTM v1.8 • CDISC Heart Failure TAUG • CDISC Psoriasis TAUG • CDISC Acute Kidney TAUG • Acute Kidney Injury TAUG • Psoriasis TAUG • Acute Kidney Injury v1.0 TAUG Comments • Heart Failure TAUG	• CDISC Acute Kidney TAUG • CDISC Metadata Submission Guide v2.0 • ADaMIG v1.2 and OCCDS v1.0 Added to DSC

Following CDER's announcement to support SENDIG v3.1 in August of 2017, FDA has continued to improve the Study Data Technical Conformance Guide.

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. The QRS effort, is one that develops well-characterized analysis dataset structures for data collection instruments related to the conduct of a trial. These dataset structures often support existing standards and TAUGs and may also be used across standards and TAUGs. Well-defined dataset structures ensure that data is submitted to the Agency fit-for-purpose. The Agency collaborates with industry to develop these dataset structures through the QRS effort. During 2020, the DSP pivoted to align its participation in QRS development with study data standards properties already supported by Agency policy. The priority TA list is also being revisited.

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 computable data standards for PQ/CMC submissions, ensuring consistent representation of concepts. In 2020 the project applied revisions to FHIR profiles based on lessons learned from the 2019 PQ/CMC Proof-of-Concept (PoC) testing with 7 PhRMA industry participants and continued working with HL7 Workgroups to incorporate PQ/CMC requirements into FHIR.

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

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. FDA continued assessment of IDMP standards to ensure conformance with FDA regulatory requirements. In 2020, working with ISO TC215 WG6, developed a potential solution to represent pharmaceutical dose form to generate global PhPID for all regions. There will be a pilot project with the proposed solution for feasibility study and reflect findings in the relevant ISO standards and technical specifications.

The Post Approval Changes rulemaking project seeks to improve the usability of post approval submissions data by ensuring essential information is captured completely in a format conducive to electronic receipt, storage and usage. This project is in the proposed rule stage and is 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. The BR&R facilitates the development of common standards and the maintenance and enhancement of the research-focused domain analysis model for clinical research information management across a variety of organizations, including national and international government agencies and regulatory bodies, private researchers, research organizations, sponsored research, CROs and other interested entities. A shared semantic view is essential if the clinical research community, both for itself and as part of the larger healthcare and life sciences communities, is to achieve computable semantic interoperability. The BR&R will

seek to assure that related or supportive standards produced by other HL7 groups are robust enough to accommodate their use in regulated clinical research through participation as appropriate, including ballots. The group also monitors information interchange standards developed outside of HL7, and attempt harmonization of information content and representation of such standards with the HL7 content and representation.

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 is 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 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.

FDA has been also mandated by the 21st Century Cures Act of 2016 and the FDA Reauthorization Act of 2017 to evaluate and provide guidance for the use of "Real World Data" (RWD) to support innovation and efficiencies in clinical research, submissions to FDA, and post-approval studies. Real World Data is data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Some of the most prominent sources of RWD are Electronic Health Records (EHR) systems used by the vast majority of hospitals and primary care clinics in the United States and insurance claims databases used to document and pay for medical care. Many other sources of RWD also exist and continue to emerge. With this consideration, 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. As part of this effort FDA is assessing the gaps between RWD and currently

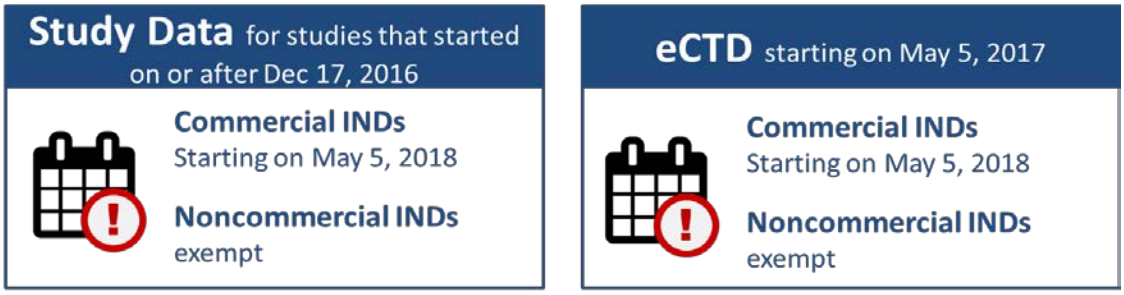
accepted data standards at FDA and the opportunities for supporting the needs of RWD use for research and regulatory submissions. Additionally, under this effort, a draft of advisory guidance on Data Standards applicable to Real World Evidence is planned.

FDA maintains and updates its data standards to ensure continuous support of critical regulatory functions in light of exchange standards technology enhancements and upgrades. For example, FDA has been proactively reviewing the technology behind the Structured Product Labelling (SPL) standard used to support a wide range of regulatory uses including labelling. SPL powers a range of information FDA and public information systems. SPL is currently implemented using the HL7 Version 3 (v3) standard. As HL7 is transitioning to a more advanced FHIR (Fast Healthcare Interoperable Resources) standard, FDA is performing its due diligence by conducting an assessment of the FHIR capability to support the full range of current functions and, potentially, new use cases in a more efficient, robust, and sustainable way.

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

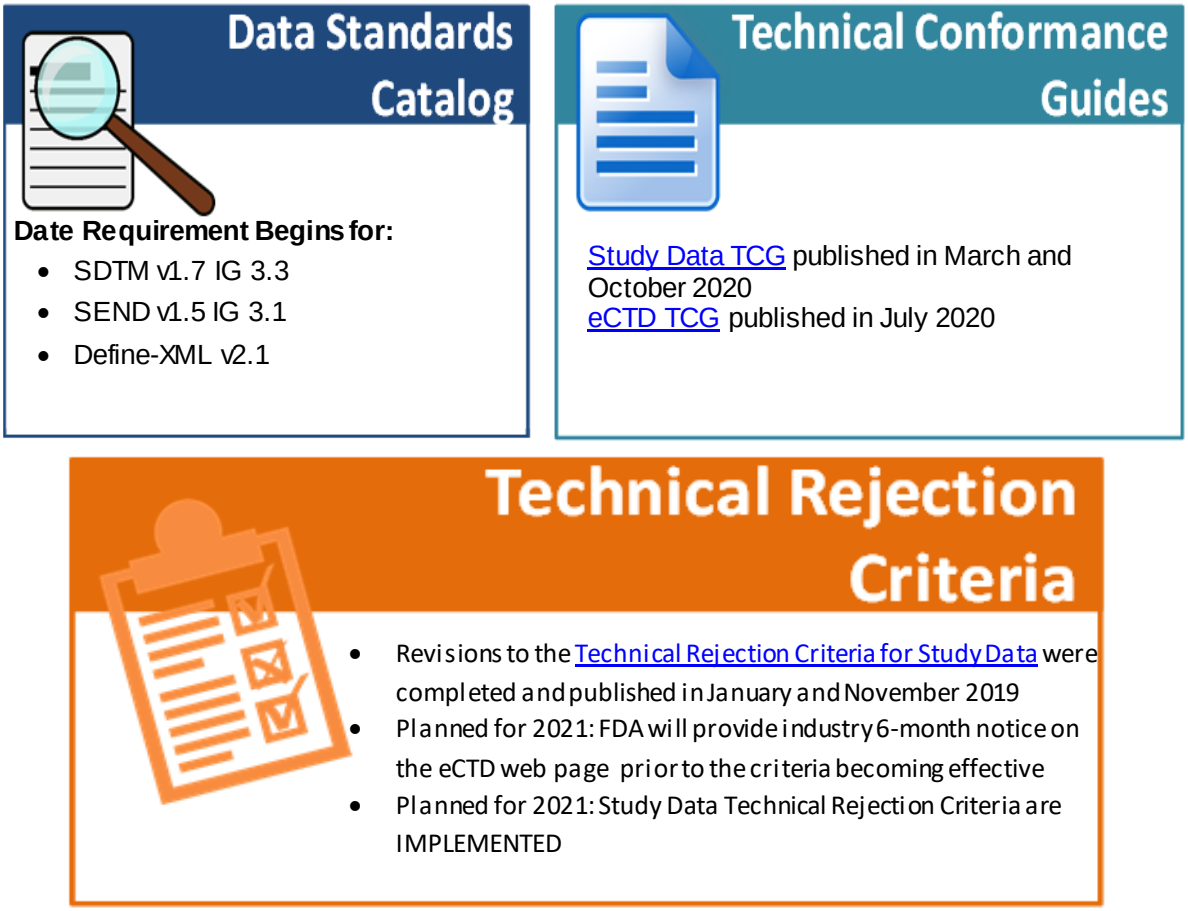


To ensure that submissions meet expected requirements, CDER and Center for Biologics Evaluation and Research (CBER) will validate submissions upon receipt and will assess conformance to required study data standards. The Technical Rejection Criteria for Study Data was published in November 2016 and outlines 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 2020. 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 2020.

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, re-charter in 2020 as the Data Standards & Data Governance Board (DSDG), 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 2020 to align with the CBER-CDER Data Standards Strategy. The Data Standards Operations Subcommittee continued to conduct primary operations on behalf of the DSDG. 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 DSDG 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 2020, the project has completed the development of the Data Governance operating model and launched CDER's Data Standards & Data Governance Board, replacing its predecessor, the Data Standards Program Board. In 2021, this initiative 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.

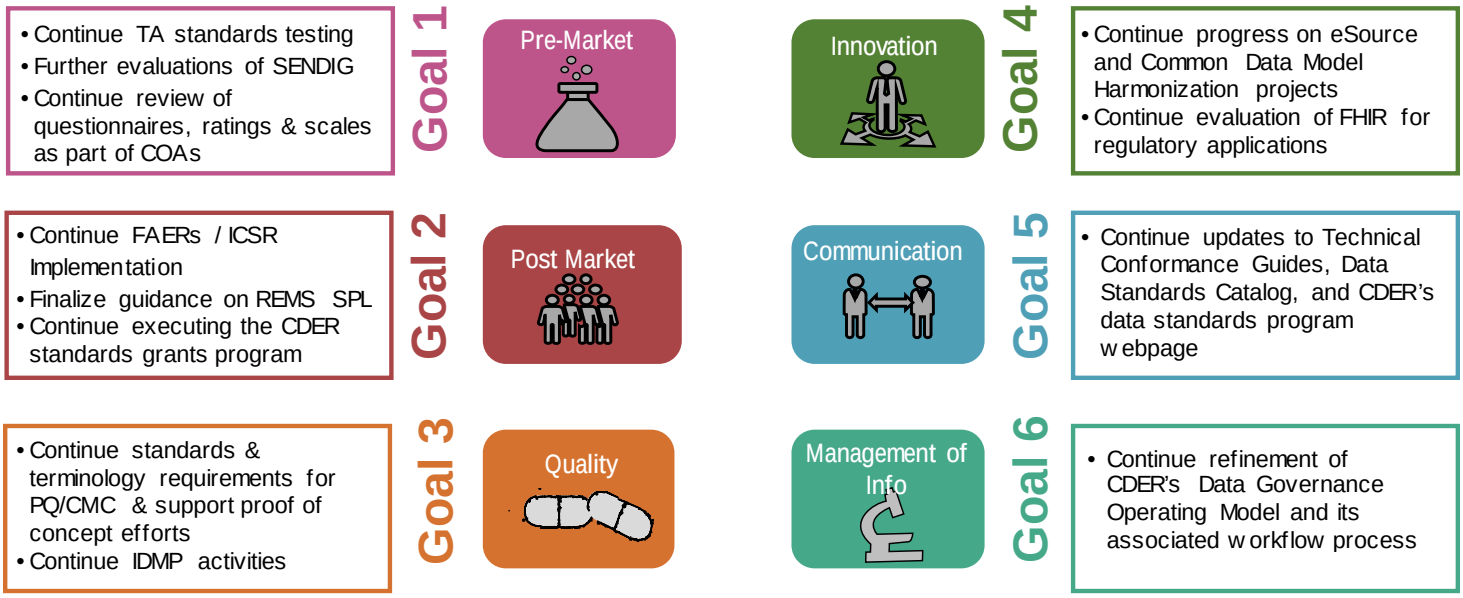
To standardize the management and procedures surrounding the study data standards policy document clearance process, a Study Data Standards Policy Document Management Process Standard Operating Procedure is under clearance. This Standard Operating Procedure will provide CDER with an understanding of the definition and legal authority for each document type governing study data submission and allow for standardized clearance processes for electronic submission-related documentation.

6 Moving Forward - 2021 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 2021, new FDA webpage updates (e.g., PDUFA VI Informatics webpage) are planned for deployment throughout 2021. 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 2021.

Figure 6. 2021 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 2021, 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
DSDG	Data Standards & Data Governance 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