CDER Data Standards Program
2021 Annual Assessment

March 2022

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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 study 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.

2021 Summary of Accomplishments

Goal 1

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

- Fully implemented the Technical Rejection Criteria (TRC) in September 2021. The communication of this initiative includes Federal Register Notices and updates to the eStudy Data Guidance, FDA Data Standards Catalog, and three special editions to the Study Data Technical Confromance Guide (sdTCG)
- Updated the sdTCG in March and October 2021
- Evaluated and added CDISC SENDIG-DARTv1.1 to the FDA Data Standards Catalog

Goal 2

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

- Continued the FDA's Adverse Event Reporting System (FAERS) 2 / ICSR implementation effort, defined and communicated regional data elements, established project framework and associated processes
- Launched the FAERS Public Dashboard for COVID-19 emergency use authorization (EUA) products to provide regular updates of adverse event reports submitted to FAERS for drugs and therapeutic biological products used under EUA in COVID-19

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
- Incorporated PQ/CMC requirements into HL7 FHIR Release 5, to be balloted in 2022
- Collaborated 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
- Continued rulemaking effort to improve usability of Post Approval Change submissions

Goal 4

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

- Published a draft guidance for comment, as part of FDA's 21 Century Cures mandate, regarding the use of data standards for the submission of study data containing Real World Data (RWD)
- Conducted feasibility assessment to determine if the uses of the Structured Product Labelling (SPL) standard can be fulfilled by the HL7 FHIR standard
- Continued proof-of-concept assessments of implementation for eSource initiatives to identify best practices to support future developments

Goal 5

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

- Updated the sdTCG five times in 2021
- Maintained updates to the FDA Data Standards Catalog
- Providing Regulatory Submissions in Electronic Format — Standardized Study Data Guidance for Industry (eStudy Data Guidance) was updated to provide for certain accommodations during a HHS-declared Public Health Emergency (PHE)

Goal 6

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

- Refined CDER's Data Governance operating model and its associated workflow processes

- Developed and implemented a Study Data Standards Policy Management Process Standard Operating Procedure to ensure consistency of regulatory clearance activities for electronic submission-related publications

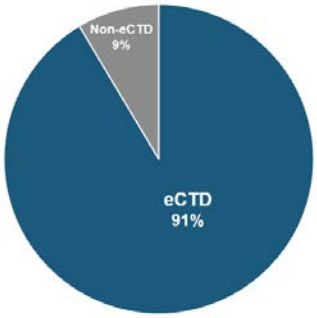
3 Impact of Requiring Standards

FDA continues to implement data standards for study data and submissions and requires applications to use these standards as defined in the FDA Data Standards Catalog. The Data Standards Program's strategic goal areas and objectives were identified as part of an Agency assessment to evaluate 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.

4 2021 Electronic Submission Metrics

Analyses of CDER submissions (excluding promotional marketing and advertising) shows 91% eCTD format, 8% other electronic formats, and 1% paper. There was near 99% compliance with application types required in eCTD.

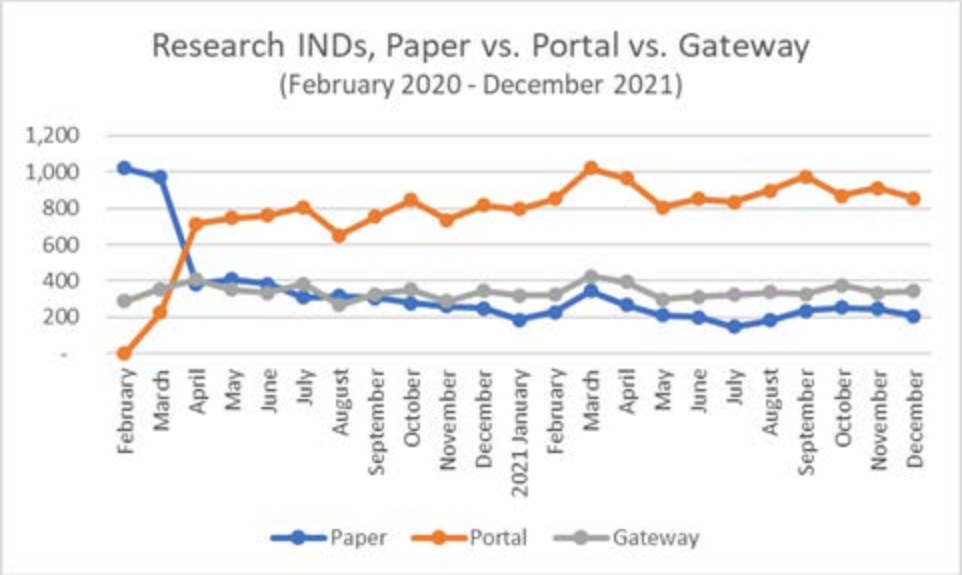
Figure 1. All Submissions to CDER (excluding promotional marketing and advertising)



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**. 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).

Figure 2: Paper Submissions 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. In 2021, CDER continues to see the CDER NextGen Portal as the primary conduit to transmit a non-eCTD Research IND. The solution sharply decreased the need for staff and RPMs to come to the campus and physically engage, thus improving safety. Paperless benefits were also realized on the industry side by reducing the need to be onsite to print and assemble a physical submission.

Figure 2. Paper Submissions of Research INDs



5 2021 Data Standards Program Year in Review

In 2021, the CDER DSP continued to make significant progress in multiple fronts including, but not limited to, updating the eStudy data guidance and the Study Data Technical Conformance Guide, publishing a draft CDER/CBER guidance regarding real-world data/evidence for regulatory submissions, and conducting a Global PhPID pilot with WHO-UMC as part of the IDMP project. Details on all major data standards program initiatives are highlighted in the sections below. In addition to publishing new and updated Guidance documents and standard operating procedures and templates, the DSP 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 evaluate and participate as a stakeholder in the development of therapeutic area user guides (TAUGs) and communicate to Industry our technical requirements for therapeutic areas. Significant progress continued in 2021 in testing of new versions of existing standards, evaluating new externally developed standards-related documents, and developing and publishing FDA-authored technical specifications.

Following CDER's announcement to support SENDIG v3.1 in August of 2017, FDA has continued to improve the sdTCG.

The FDA Business Rules Change Control Board (BR 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.

CDER's Clinical Outcome Assessment (COA) project evaluates data collection instruments used by industry and health care to measure or asses patient outcomes. These outcomes are often the endpoints supporting regulatory submissions. The Questionnaires, Ratings and Scales (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 can come from instruments qualified by the COA Project, existing standards, or therapeutic area extensions. Well-defined dataset structures ensure that data submitted to the Agency is fit-for-purpose. The Agency collaborates with industry to develop these dataset structures through the QRS effort.

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

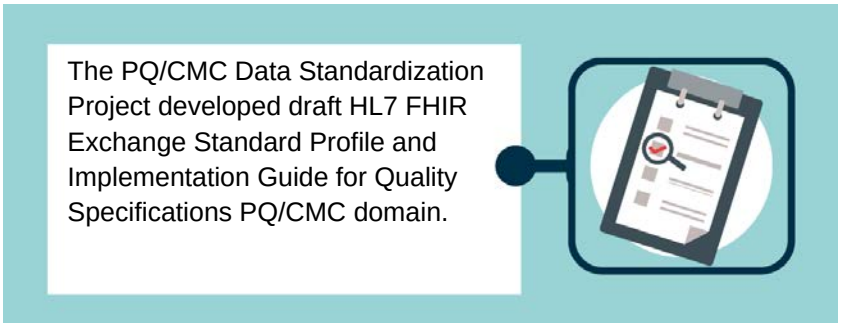
FAERS is a mission critical system for FDA. FAERS supports CDER/CBER's post-marketing safety surveillance program for all marketed drug and therapeutic biologic products. The FAERS II program was initiated to provide a modernized system for safety surveillance, including pre-market and post-market safety 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.

Since the inception of the FAERS II program, a highly interactive and user friendly FAERS Public Dashboard was launched 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.

In response to the COVID-19 pandemic, FDA launched the FAERS Public Dashboard for COVID-19 emergency use authorization (EUA) products. The COVID-19 EUA FAERS Public Dashboard provides weekly updates of adverse event reports submitted to FAERS for drugs and therapeutic biological products used under EUA in COVID-19.

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 2021, the project continued mapping PQ/CMC requirements to FHIR resources and development of FHIR exchange standards, and all requirements for PQ/CMC Phase 1 data domains were entered into FHIR R4B and R5 ballots.



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 conducted a Global PhPID pilot with WHO-UMC to assess alternative solutions for ISO IDMP standards. The findings and recommendations are now included in the draft revision of ISO 11239 and TS20440 for further balloting. The agency also collaborated with EMA and WHO-UMC to establishe a Global IDMP Working Group (GIDWG) to assess and promote global implementation of ISO IDMP standards based on the success of Global PhPID project and Global Vaccine Initiative. GIDWG planned five projects to further investigate solutions and processes to address identified gaps of ISO IDMP standards, and to work with ISO TC215 to improve IDMP standards for global implementation.

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-chaired and continues to actively participate in 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 is to achieve

computable semantic interoperability, both for itself and as part of the larger healthcare and life sciences communities. 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. The group also monitors information interchange standards developed outside of HL7 and attempts harmonization of information content and representation of such standards with the HL7 content and representation.

As part of CDER's participation with HL7, the HL7 FHIR "accelerator" program for clinical research, "Vulcan," was jointly created by academia, 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. In 2021, CDER also participated in FHIR connectathon tracks covering RWD and adverse events.

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 and mobile apps. One of the larger potential sources of eSource data are 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.

A number of initiatives exist to help mitigate these challenges, including CDER's supported 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 automated approaches demonstrate relevant improvements in efficiencies and potential returns on investment versus the current manual methodology. One of these ongoing projects, Source Data Capture from EHRs: Using Standardized Clinical Research Data, is part of an existing phase 3 trial and is also used in clinical investigations related to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and disease (COVID-19). Throughout 2021, the project made significant strides in system development, specifying the data elements to be incorporated in 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. Iterative proof-of-concept implementations were 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 RWD to support innovation and efficiencies in clinical research, submissions to FDA, and post-approval studies. RWD 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)

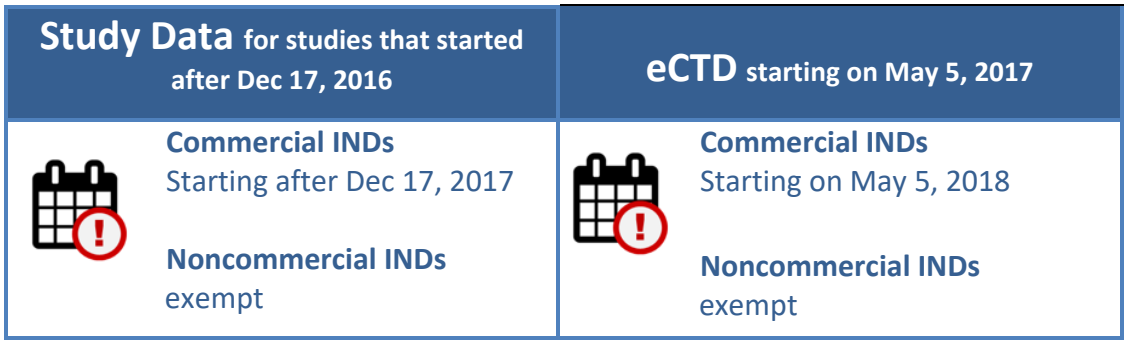
systems used by the vast majority of hospitals and primary care clinics in the United States and insurance claims databases used to document and pay for medical care. Many other sources of RWD also exist and continue to emerge. With this consideration, CDER is working to outline the conceptual and logistical groundwork around efforts that began in 2018, culminating in the first output, the Framework for FDA's Real-World Evidence Program. 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. Under this effort, in 2021 CDER published a draft guidance for comment regarding the use of data standards for the submission of study data containing RWD.

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 is the current standard behind a range of information processed by FDA and public information systems, and is 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 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

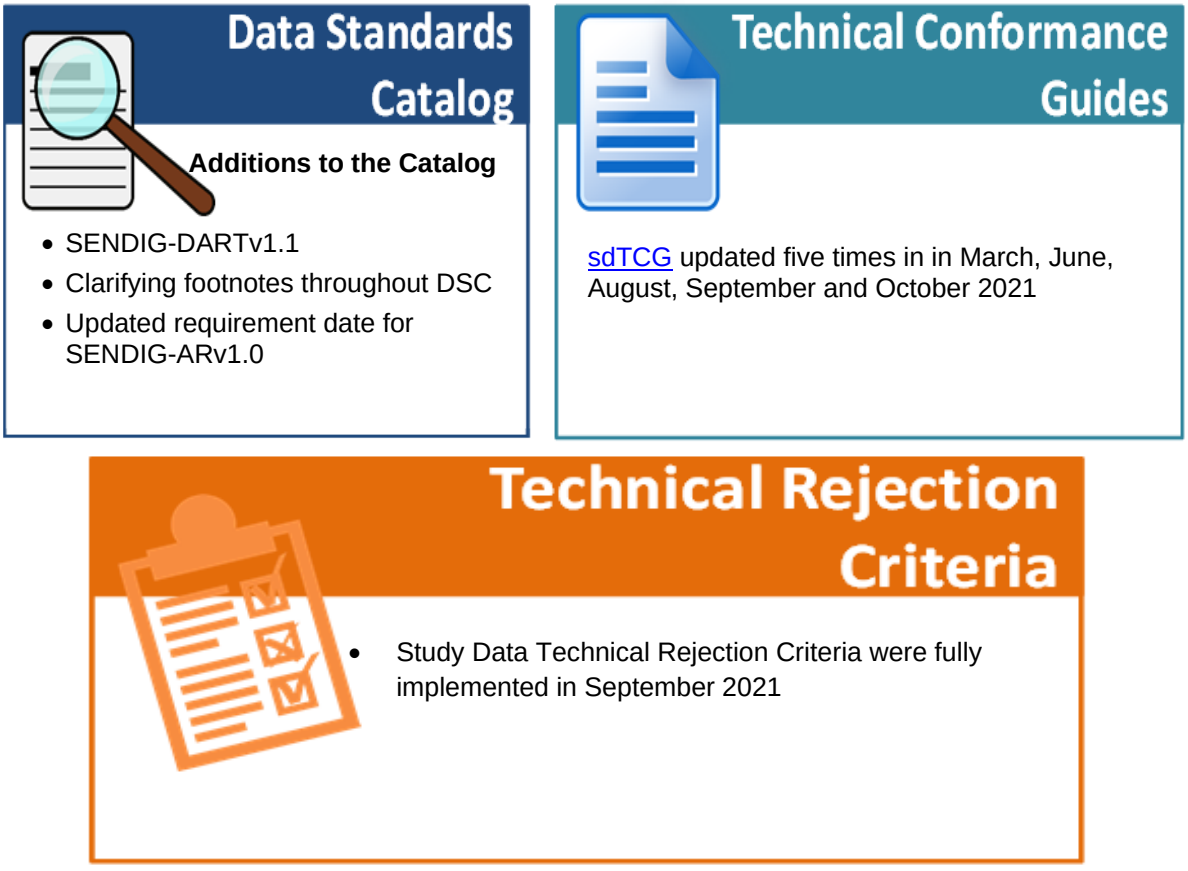


To ensure that submissions meet expected requirements, CDER and Center for Biologics Evaluation and Research (CBER) added eCTD validations to check submissions upon receipt

and assess conformance to required study data standards. The TRC for Study Data were originally published in November 2016 and outlined the approach and validations for study data. During 2017, CDER and CBER initiated the development of additional eCTD validation criteria that were fully implemented in September 2021 after extensive communication with industry via conferences, FDA websites, eData/eSub help desks, and Federal Register Notice.

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 sdTCG, were updated throughout 2021. The FDA Data Standards Catalog (Catalog) lists the study data standards, exchange formats, and terminologies that FDA supports and requires for use in regulatory submissions. The sdTCG provides specifications, recommendations and general considerations on how to submit standardized study data using the Catalog.

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



The Action Plan, updated quarterly, continued to highlight progress across the program as progress has been made to the Center's strategic goals. The Data Standards Operations Subcommittee continued to conduct data standards policy activities and coordinate operations with other governance bodies such as the Study Data Standards Testing, Catalog, and sdTCG workgroups.

As part of an effort to improve internal stakeholder communication, the Data Standards Program conducted a review of its policies and process, as well as their supporting standard operating procedures (SOPs) to assess the need for updates or refinements. Revisions and process step clarifications were incorporated into the SOPs.

The Data Standards Program 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 with the goal of developing and implementing a data governance framework across CDER data domains such as Facilities Data and Products Data. In 2021, the project continued to refine the Data Governance operating model and collaborate with other enterprise level data governance efforts within CDER to improve data management processes. For 2022, this initiative will continue to refine the model's scope and processes based on feedback and lessons learned, explore opportunities to expand the model to include other additional data domains, and implement data governance best practices across CDER offices.

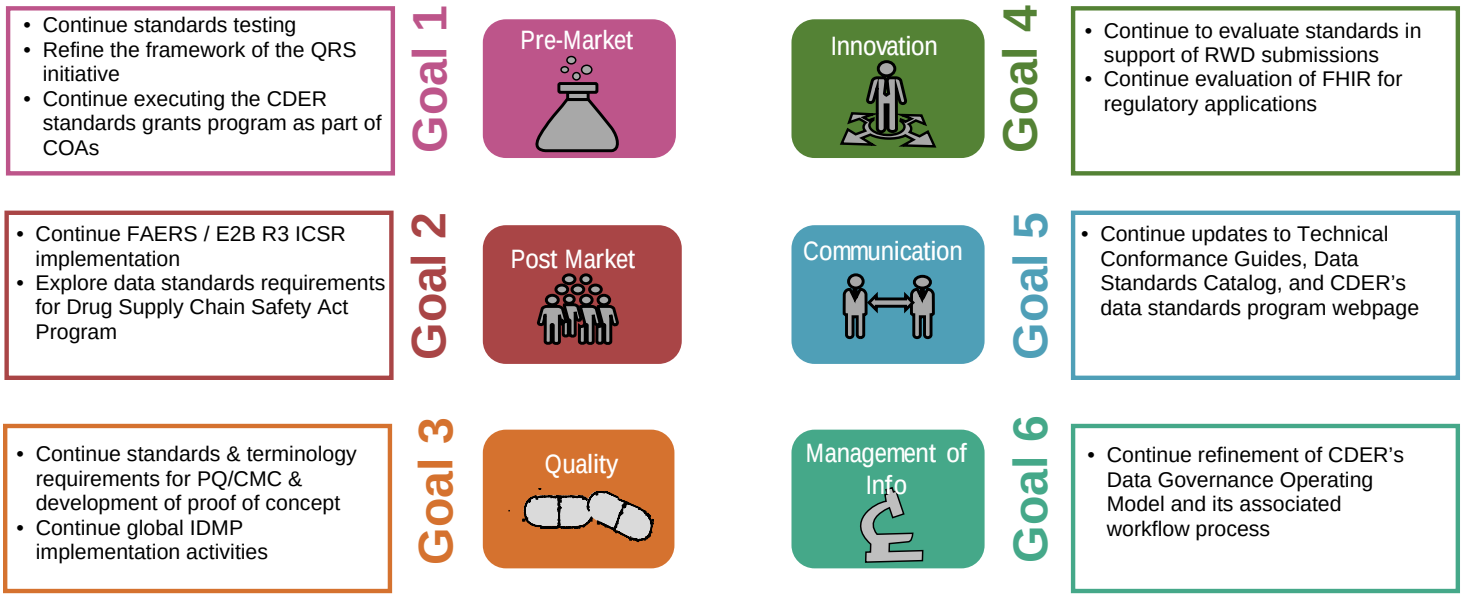
The Study Data Standards Policy Document Management Process Standard Operating Procedure was developed to provide CDER offices with a common understanding of the definition and legal authority for each document type governing study data submission and allow for standardized clearance processes for electronic submission-related documentation.

6 Moving Forward - 2022 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 of supporting 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 2022. New FDA webpage updates (e.g., PDUFA VI Informatics webpage) are planned for deployment throughout 2022. These updates will ensure a consistent external web presence, revised materials, and interactive tools for both internal and external stakeholders. Figure 5 highlights a summary of the focus areas activities for 2022.

Figure 5. 2022 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 in 2022, 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
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