CBER-CDER Data Standards Program 2022 Annual Assessment

February 2023

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1 Introduction

The Center for Drug Evaluation and Research (CDER) publishes an Annual Assessment for CBER-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 CBER-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 highlight the program's accomplishments.

2022 Summary of Accomplishments

Goal 1

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

- Continued evaluation of data standards and properties to assess their ability to meet regulatory review needs, which contributed to three version updates to the FDA Data Standards Catalog
- Assessed alternatives to the XPT file transport format and evaluated the technical considerations for modernizing electronic transport of regulatory submissions

Goal 2

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

- Published two guidance documents, available on theFAERS electronic submission page in preparation for FDA's acceptance of E2B(R3) pre and postmarket ICSR submissions:
  1. Electronic Submission of IND Safety Reports - Technical Conformance Guide
  2. Technical Specifications Document - FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products
- In collaboration with eHealth Exchange, CBER's Biologics Effectiveness and Safety (BEST) platform launched a pilot to connect to production systems of early adopters with the potential to improve AEs reported to the FDA while minimizing the burden on providers and the public.

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 Fast Health Interoperable Resources (FHIR) resources and development of FHIR exchange standards
- FDA released a Federal Register Notice (FRN) in March 2022 that provided the latest PQ/CMC Phase 1 Data elements, controlled terminology, and draft mappings to Health Level 7 (HL7) FHIR
- Collaborated with EMA and WHO-UMC through the Global IDMP Working Group (GIDWG) and conducted five pilot projects to support global implementation of ISO IDMP
- 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.

- Continue to assess HL7 FHIR's capability to fulfill the needs of current regulatory submissions that ultize the Structured Product Lableing (SPL) standard
- Initiated the development of a proof-of-concept intake system to enable testing of submissions in both FHIR and SPL standard
- Co-led the Vulcan Accelerator RWD for Regulatory Submissions track and participated in multiple Vulcan FHIR Connectathons Tracks focusing on Read World Data (RWD)

Goal 5

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

- Posted multiple updates to the FDA Data Standards Catalog
- Published the sdTCG in March and October of 2022
- Published the IND Safety Reports TCG v1.1 and the Bioresearch Monitoring TCG v3.0
- Continued the Agency's public outreach efforts by presenting and participating at industry conferences and forums

Goal 6

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

- Continue the refinement of CDER's Data Governance operating model and its associated workflow processes
- Streamlined the identification of dosage forms by fully aligning its terminologies with National Cancer Institute Enterprise Vocabulary Services (NCI EVS) Codes for IDMP

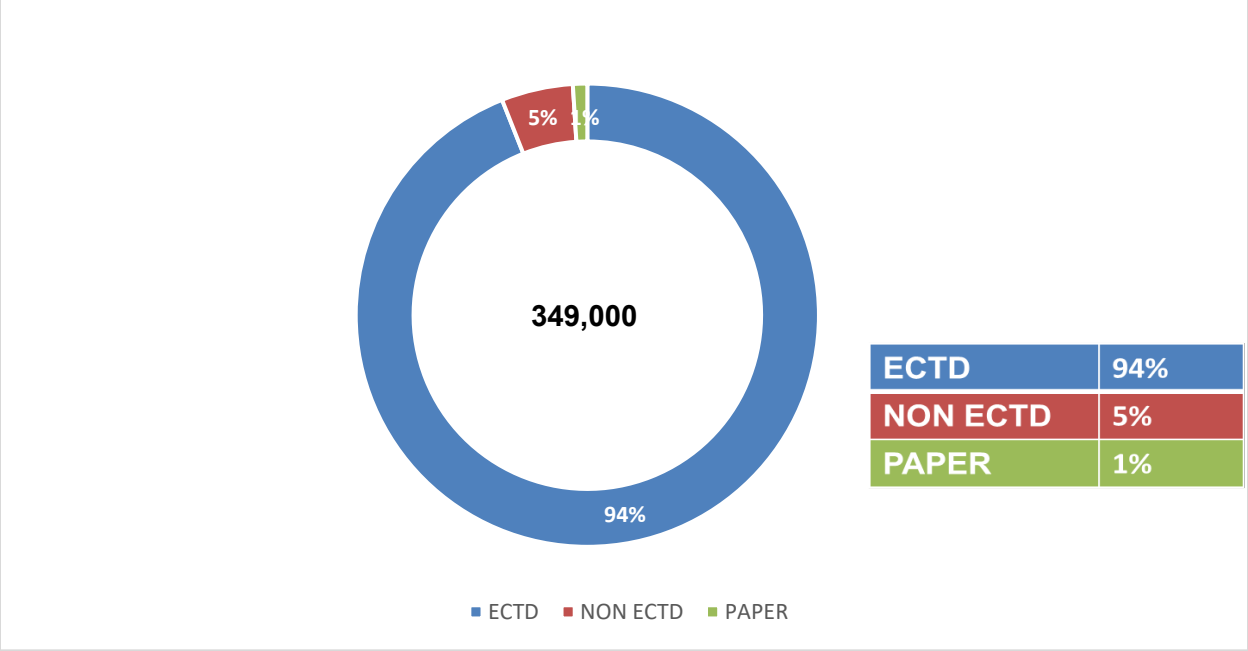
3 Impact of Requiring Standards

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 2022 Electronic Submission Metrics

Analysis of FY2022 data indicated that 94% of all submissions to CDER were in eCTD format, 5% in other electronic formats, and 1% paper. There was near 100% compliance with application types required in eCTD.

Figure 1. Percent of All Submissions to CDER by Electronic Format (FY 2022)



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).

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 2022, CDER continues to see the CDER NextGen Portal as the primary conduit to transmit a non-eCTD Research IND.

5 2022 Data Standards Program (DSP) Year in Review

In 2022, CDER and CBER's DSP continued to make significant progress in multiple fronts including, but not limited to, updates to the FDA Data Standards Catalog and the Study Data Technical Conformance Guide, publishing multiple guidances in the strategic goal areas of study data and postmarket pharmacovigilance and surveillance. The PQ/CMC project reached a significant milestone as it published a FRN containing the complete set of PQ/CMC Phase 1 data elements and controlled terminology. Five pilot projects where completed through the Agency's collaboration with EMA and WHO-UMC to further investigate solutions that will enable more effective global implementation of ISO IDMP standards. CDER also Initiated the development of a proof-of-concept system to better understand the technical considerations of enabling dual submissions in both SPL and FHIR standards. Details on all major data standards program initiatives are highlighted in the sections below.

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 external data models, implementation guides, terminologies, and other standards related properties. Significant progress continued in 2022 in evaluating new versions of existing standards, new externally developed standards and related documents, as well as developing and publishing FDA-authored technical specifications. In addition, the FDA has maintained an up-to -Study Data Technical Conformance Guide (sdTCG) and FDA Data Standards Catalog.

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 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.

CDER and CBER completed a joint assessment of alternatives to the XPT file transport format. The project evaluated the technical capability to enable the enhanced ability for electronic

transport of regulatory submissions and assess, at a high level, the effort required for a transition to a new standard including whether transitioning to an intermediate standard will provide value to the Agency. The scope included all review processes that use Transport V5 XPT files for all clinical, non-clinical, and generics files. Results from this assessment suggested that amongst the three candidate file formats analyzed (SAS XPT V8, JSON, XML), JSON will likely yield the greatest long term benefit followed by XML. However, more in-depth evaluations and technical pilots are needed and planning activities are underway.

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 biological 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 continued to maintain 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 drug and therapeutic biological products used under EUA in COVID-19. FDA also published the following guidance documents to FAERS electronic submission page in preparation for FDA's acceptance of E2B(R3) pre- and post-market ICSR submissions: Electronic Submission of IND Safety Reports - Technical Conformance Guide; and Technical Specifications Document - FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products.

In support of CBER's mission for post-market safety surveillance, in 2021, the Biologics Effectiveness and Safety (BEST) Innovative Methods (IM) initiative developed and tested the BEST platform, a proof-of-concept adverse events validation and reporting system. The BEST platform aims to utilize health information exchanges to improve the quality of AE reports submitted to CBER. The BEST platform uses the emerging HL7 FHIR standards to request and receive additional clinical data from health providers to enrich the AE reported cases. In 2022, in collaboration with eHealth Exchange, the largest health information exchange network in the United States, the BEST platform launched a pilot to connect to production systems of early adopters. The BEST platform has the potential to improve AEs reported to the FDA while minimizing the burden on providers and the public.

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 2022, the project finalized PQ/CMC Phase 1 requirements of FHIR resources and development of FHIR exchange standards, and all requirements for PQ/CMC Phase 1 data domains were included in the FHIR R5 ballot. In March 2022, FDA released a FRN [https://www.regulations.gov/document/FDA-2022-N-0297-0001] that provides the updated PQ/CMC Phase 1 Data elements and controlled terminology as well as Draft mappings [Data Elements & Terminologies Document] to HL7 FHIR. The focus of the 2022 FRN was to seek industry input on the FHIR mappings.

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, the Agency continues to participate and promote 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 established the GIDWG (Global IDMP Working Group) to assess and promote global implementation of ISO IDMP standards based on the success of Global PhPID project and Global Vaccine Initiative. GIDWG conducted five projects to further investigate solutions and processes to address identified gaps of ISO IDMP standards, and work with ISO TC215 to improve IDMP standards for global implementation.

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 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. 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 standards.

As part of CDER's participation with HL7, the HL7 FHIR Accelerator program for clinical research was jointly created by academia, sponsors, regulatory and translational researchers organizations, including TransCelerate Biopharma, 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. Since 2021, CDER also participates in multiple Vulcan FHIR connectathon tracks including those focusing on RWD (which FDA also co-leads) 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 drug and biological products.

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 2022, the project continued to make 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 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 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 is also investigating approaches to better align data standards for submission to FDA with the many sources of 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 labeling. 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 standard. As HL7 is transitioning to the more advanced FHIR 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. The FDA is creating a proof-of-concept intake system that would allow for the submission of the new FHIR standard as well as the SPL standard.

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

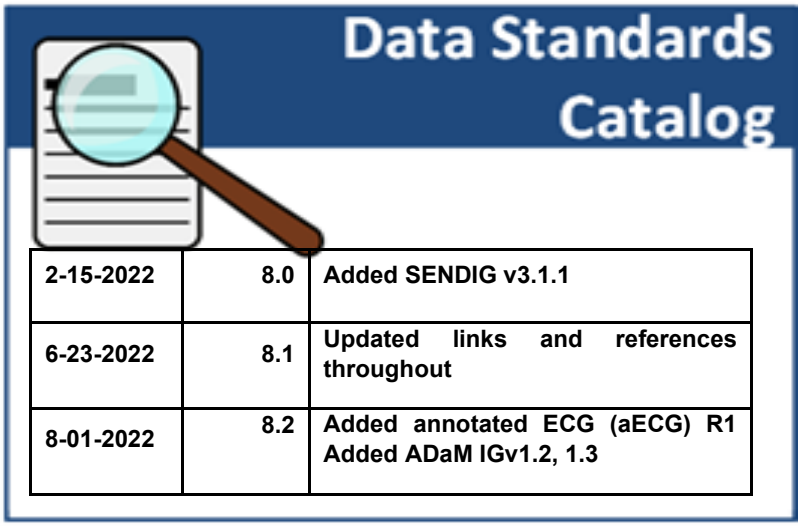
On December 17, 2016, the first requirement implemented under the provisions of FDASIA that authorized the electronic submission of information for NDAs, BLAs, and ANDAs went into effect, requiring clinical and nonclinical trials that started after that date to use the standards in the FDA Data Standards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

To ensure that submissions meet expected requirements, CDER and CBER added eCTD validations to check submissions upon receipt and assess conformance to required study data standards. The Technical Rejection Criteria 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. In 2022, FDA continued its outreach by presenting at numerous conferences and forums.

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 2022. The FDA Data Standards 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 FDA Data Standards Catalog.

Figure 2. Updates to Data Standards Catalog



The Data Standards Program 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.

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 2022, 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. CDER also streamlined the identification of dosage forms by fully aligning its terminologies with National Cancer Institute Enterprise Vocabulary Services' Codes for IDMP.

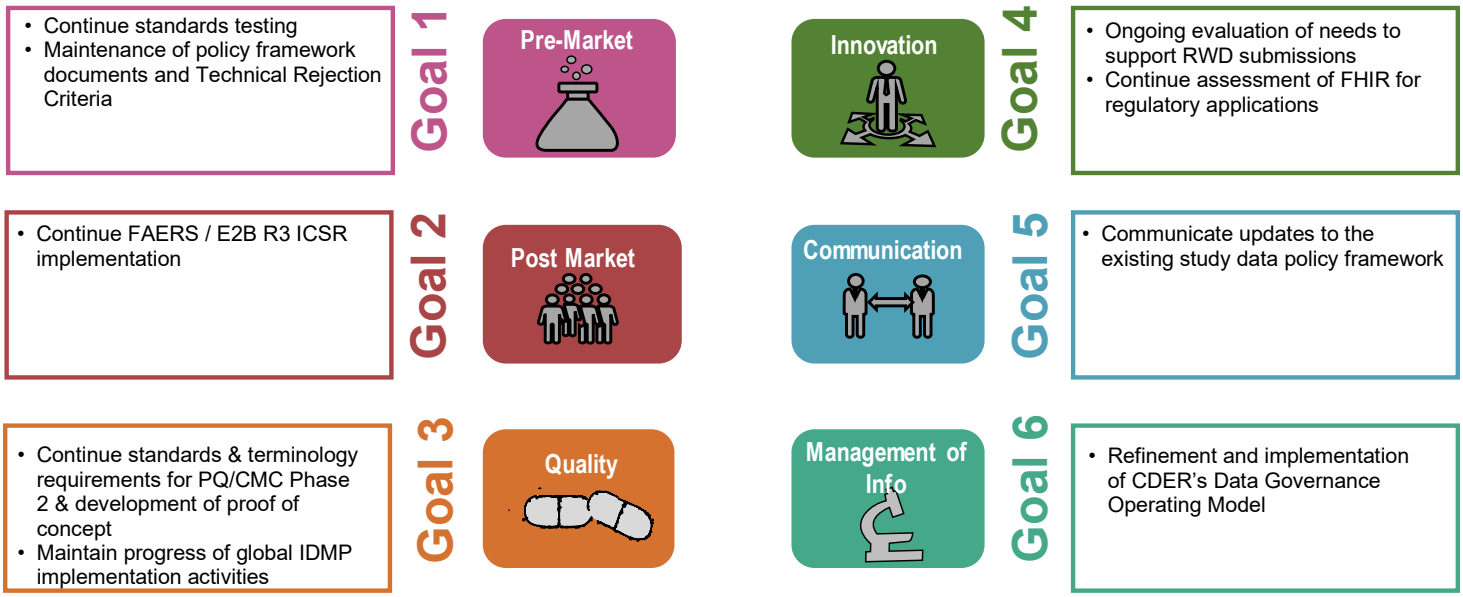
For 2023, this initiative will focus on establishing a common product data dictionary for internal use and continue to refine the model's scope and processes based on feedback and lessons learned, and implement data governance best practices across CDER offices.

6 Moving Forward - 2023 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, conformance guides, and relevant standards information, the TCG will be updated in March and October of 2023. FDA webpages (e.g., PDUFA VII Informatics page, Study Data Standards Resources, PQ/CMC, IDMP Webpage) will be updated throughout 2023. 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 3. 2023 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 2023, see the DSP Action Plan published quarterly on the CDER Data Standards Program webpage.

Appendix A: Glossary of Acronyms

ANDA	Abbreviated New Drug Application
BEST - IM	Biologics Effectiveness and Safety - Innovative Methods
BLA	Biologics License Application
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 Form
eCTD	Electronic Common Technical Document
EDC	Electronic Data Collection
EHR	Electronic Health Record
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FAERS	FDA's Adverse Event Reporting System
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
NCATS	National Center for Advancing Translational Sciences
NDA	New Drug Application
NIH	National Institutes of Health
PDUFA	Prescription Drug User Fee Act
PhUSE	Pharmaceutical Users Software Exchange
PQ/CMC	Pharmaceutical Quality/ Chemistry, Manufacturing, and Controls
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 Procedure
SPL	Structured Product Labeling
TA	Therapeutic Area
TCG	Technical Conformance Guide
TRC	Technical Rejection Criteria
WHO UMC	World Health Organization Uppsala Monitoring Centre