CDER Data Standards Program
2016 Annual Assessment

April 28, 2017

Table of Contents

List of Figures

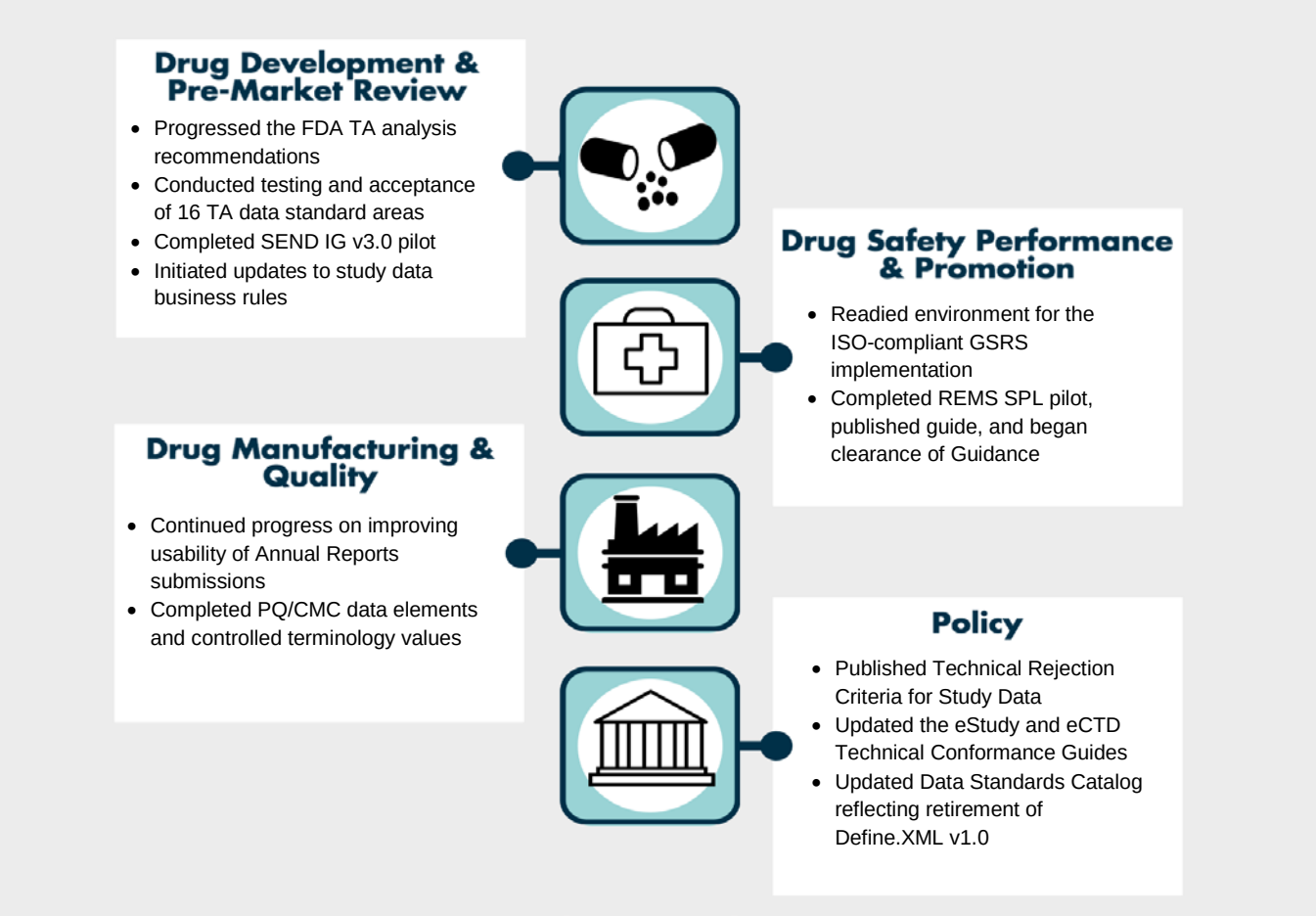
1 Introduction

The Center for Drug Evaluation and Research (CDER) publishes an Annual Assessment for CDER's Data Standards Program to provide a progress update to stakeholders reflecting the last calendar year. The previous year assessment is available on the CDER Data Standards Program 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 five major areas of regulatory business activity of the CDER Strategic Plan. Figure 1 (below) and the following sections highlight program accomplishments.

Figure 1. 2016 Summary of Accomplishments



3 2016 Data Standards Program Year in Review

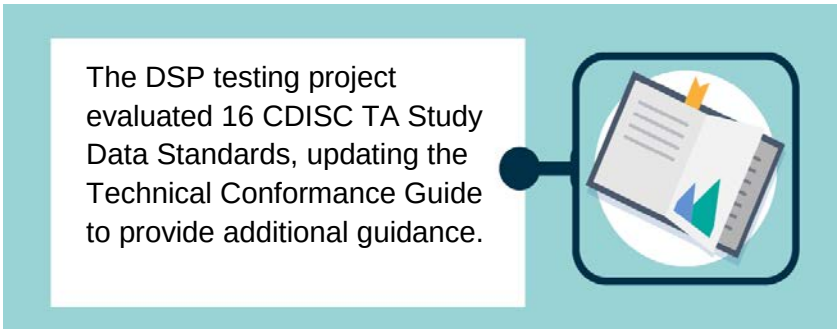
The CDER Data Standards Program made significant overall progress in 2016 which is highlighted below. The published Guidance and Technical Specifications updates along with standard operating procedures and templates, supported the program as it continued to focus on participating in the development and testing of standards and evaluating standards which has led to several updates of the Data Standards Catalog.

3.1 Drug Development and Pre-Market Review

The Prescription Drug User Fee Act (PDUFA) V Performance Goals indicate FDA will develop standardized clinical data terminology for distinct Therapeutic Areas (TAs) in collaboration with Standards Development Organizations (SDOs). Significant progress continued in 2016 in the planning, development and testing of TA data standards which focus primarily on efficacy review and evaluation of new medical products.

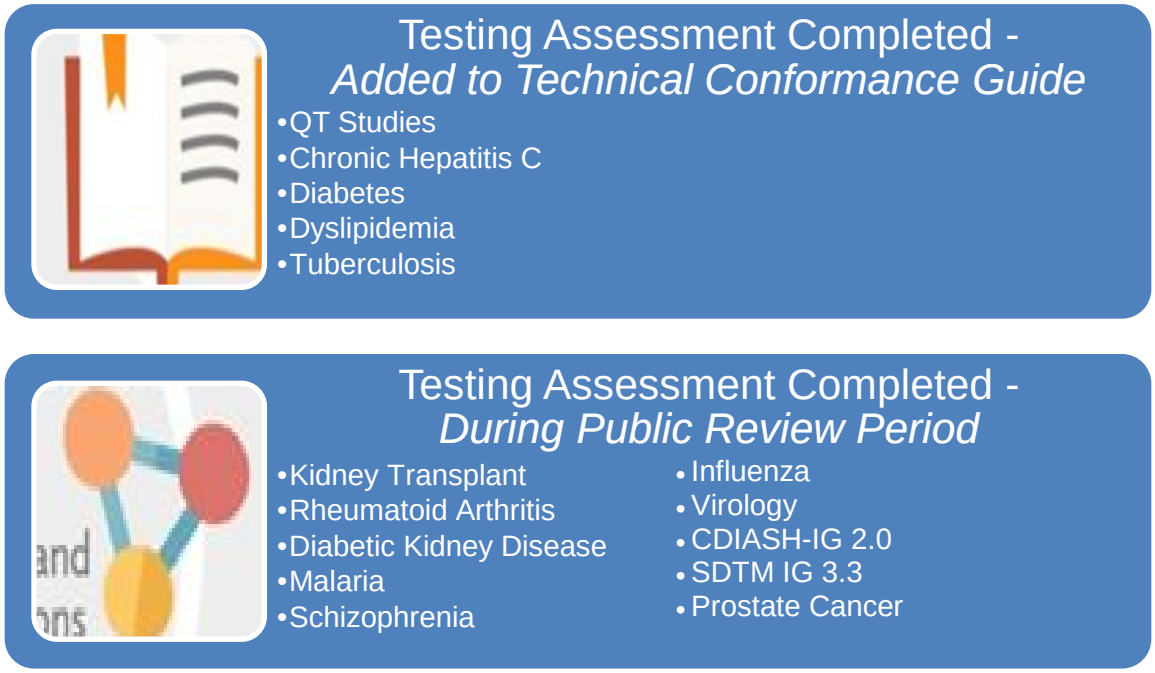
The list of the prioritized TAs and their development status was updated to reflect progress made and changes in CDER priorities. Of the 54 TAs on this list, 42 have commenced either within FDA to capture business needs or in collaboration with external parties to develop standards. FDA completed recommendations for 24 TAs based on the input of its Review Divisions. The relevant recommendations documents are provided to serve as input to the project scope in SDO projects, ensuring Review Division input early in each project.

CDER expanded the FDA recommendations for the operational efficacy endpoints, in order to include the derived and compound endpoints generally used in statistical analyses. In 2016 CDER initiated work on four analysis TAs, all of which will be completed in early 2017.



The Center continued to implement and refine its comprehensive testing approach to ensure that data standards meet FDA's needs as well as to assess impact to the current review environment and tools. The Clinical Data Interchange Standards Consortium (CDISC) foundational standards and TA extensions were prioritized for testing by the Study Data Standards Working Group; when possible, testing activities were conducted while the standard was available for public review. In 2016, the Study Data Standards Working Group tested 16 study data standards leading to updates in the Technical Conformance Guide for five (5) TAs supported by FDA.

Figure 2. Study Data Standards Tested in 2016



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

The Business Validation Rules (BVR) Working Group maintains and updates the business rules which are used to ensure that the study data are compliant, useful, and will support meaningful review and analysis. An updated business rules document is in review and will be published on the Study Data Standards Resources web page when complete. The BVR Working Group periodically considers other lists of validation and conformance rules to enhance the current list of rules. Any stakeholder can present content to the CCB for consideration by emailing cder-edata@fda.hhs.gov. New versions of the documents will be published as they are available.

The Bioanalytical Methods project developed draft guidance, "Providing Regulatory Submissions in Electronic Format-Standardized Bioanalytical Data", which provides guidance for a valid electronic submission of standardized bioanalytical data. The Guidance is expected to begin clearance in 2017. The bioanalytical data are the results of analytical methods for bioanalysis that provide a quantitative determination of the quantity of drugs and their metabolites in biological fluids (e.g., bioanalytical method validation of the analytic). The submission of data in a standardized format will increase the efficiency of FDA's review of

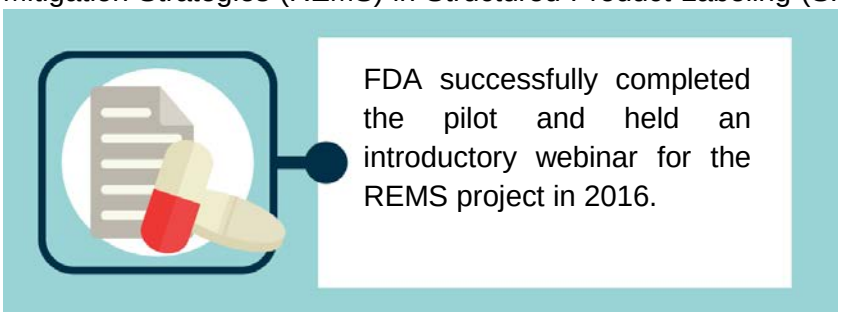
bioanalytical data contained in the bioequivalence (BE) submissions to Abbreviated New Drug Applications (ANDAs).

3.2 Drug Safety Performance and Promotion

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

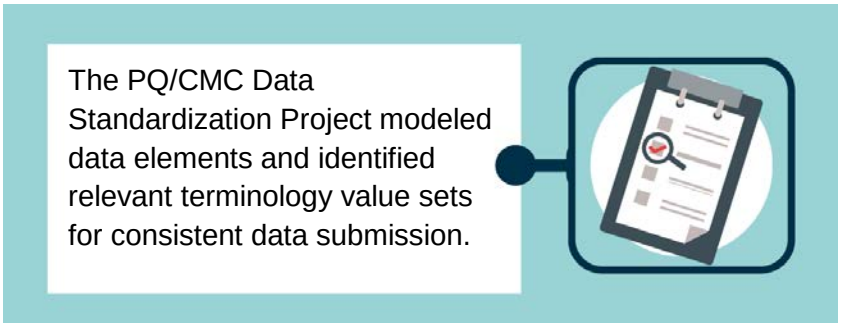
Based on the Center's commitment to implement the International Organization for Standardization (ISO) 11238 Substance Identification Standard, a pilot was executed using the Global Substance Registration System (GSRS) and the Center prepared for implementing the release of GSRS at FDA in early 2017. The GSRS is co-developed by National Institutes of Health (NIH)/ National Center for Advancing Translational Sciences (NCATS) and FDA with contributions from international regulators, academia, standard bodies, and experts. This system release is anticipated to include Specified Substance Group 1 registration activity. Substance identification is the lynchpin associating data related to products, biology, manufacturing, and submissions. This mission critical system will ensure that substances are consistently described, uniquely identified, shareable with other regulatory authorities and managed as critical source data in FDA.

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



The Annual Report project seeks to improve the usability of Annual Report submissions pertaining to Distribution Data, Field Alert Reports, and Pharmaceutical Quality & Chemistry, Manufacturing, and Controls (PQ/CMC) information. The project will ensure that essential facility location and production information is captured completely and in a format conducive to electronic receipt, storage and usage.

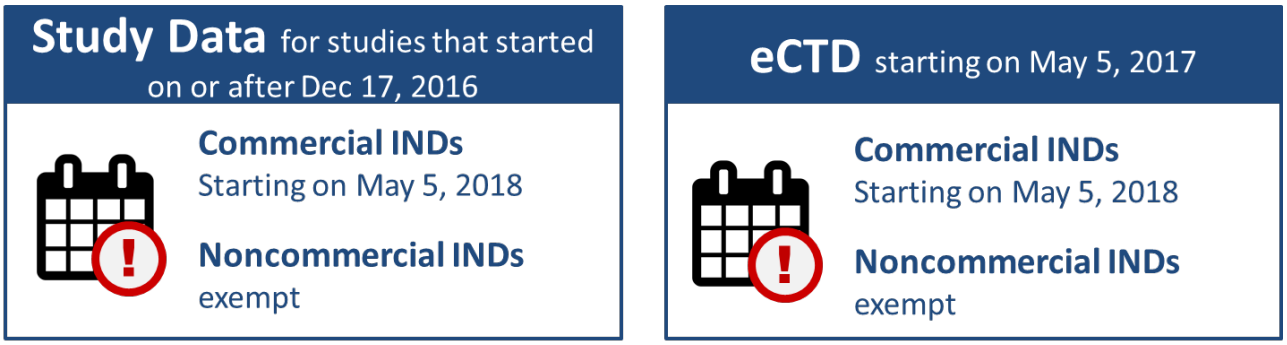
PQ/CMC Data Standardization Project was commenced to identify and standardize data elements and terminologies for information used in support of Module 3 of electronic Common Technical Document (eCTD) based drug applications. An overall goal of this initiative is the development of standardized, structured and computable data standards for PQ/CMC submissions, ensuring consistent representation of concepts. In 2016, the project completed identification and modeling of relevant data elements and controlled terminology value sets. The project anticipates publishing a Federal Register (FR) Notice in 2017 to receive comment on draft data elements and terminologies. In 2017, the project will test and implement data exchange standards for PQ/CMC data.



3.3 Policy, Planning and Governance

On December 17, 2016 the first requirement implemented under the provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA) that authorized the electronic submission of information for New Drug Applications (NDAs), Biologics License Applications (BLAs) and Abbreviated New Drug Applications (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 will begin in May 2017. Figure 3 highlights these implementation dates.

Figure 3. Implementation Dates - Update



To ensure that submissions meet expected requirements, CDER and CBER will validate submissions upon receipt and will assess conformance to required study data standards. The Technical Rejection Criteria for Study Data was published in November 2016 (revised March 2017) and outlines the approach and validations planned for study data.

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 2016. The documents provide a detailed revision history but in general reflect feedback from industry and FDA staff as well as results of testing and acceptance activities discussed above. Figure 4 highlights the new versions published in 2016.

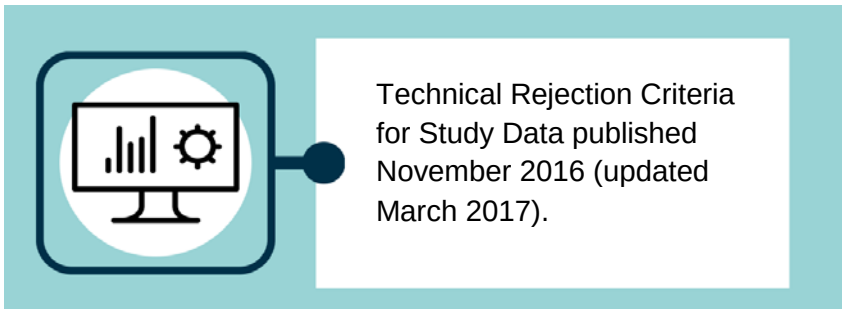
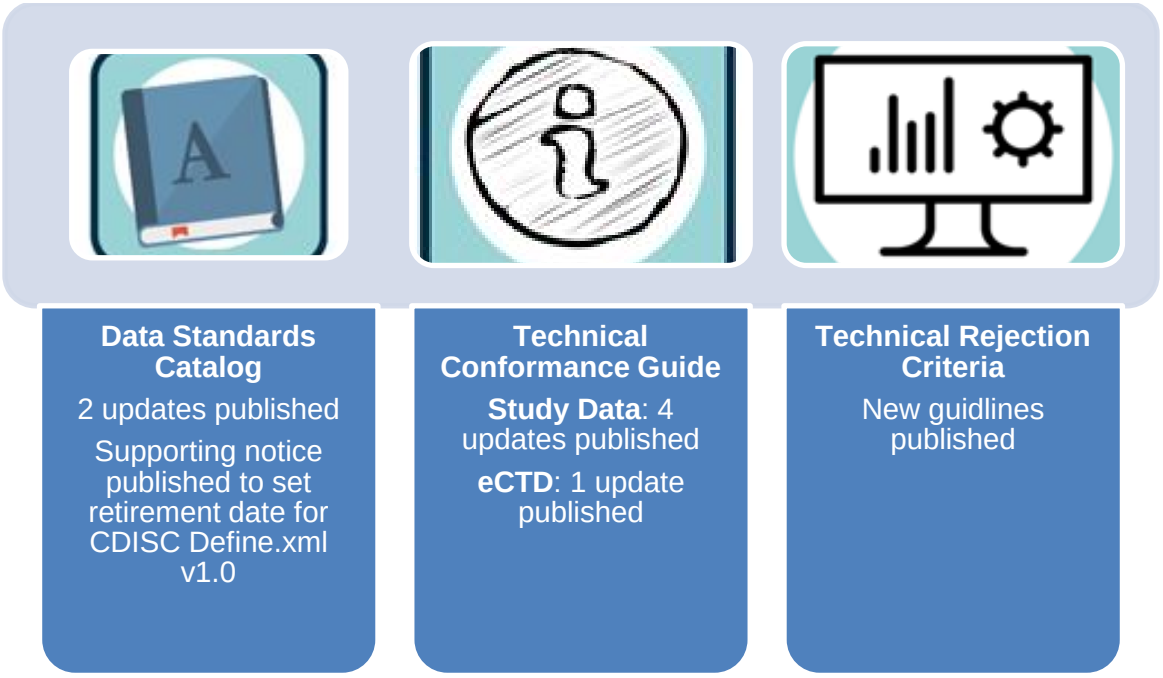


Figure 4. Summary of Updates to Data Standards Catalog, TCG, and new Technical Rejection Criteria



As part of its role in defining and governing CDER's Data Standards program, the Data Standards Program Board (DSPB) has plans to update the Data Standards Strategy document in 2017. The Action Plan, updated quarterly continued to highlight progress across the program as progress has been made to the Center's strategy. The Data Standards Operations Subcommittee (OpSC) continued to conduct primary operations on behalf of the DSPB. The Study Data Standards and Technical Conformance Guide workgroups were very active all year supporting testing and updates to the guide that were published. All progress and decisions are briefed to the DSPB quarterly or on an as needed basis.

The Data Standards Program (DSP) conducted an annual review of the Data Standards Program Manual of Policies and Procedures and supporting standard operating procedures (SOPs) to determine if any refinements were needed. Minor changes were incorporated into the SOPs indicate a lessons learned activity for each project.

The Program continued its communication efforts by creating a series of fact sheets related to study data, eCTD, master files, and the electronic gateway, working on a new data standards video, and an interactive Drug Lifecycle webpage that shows what standards are applicable in different areas of the drug lifecycle.

3.4 Other Standards Areas

3.4.1 Alternative Transport Formats

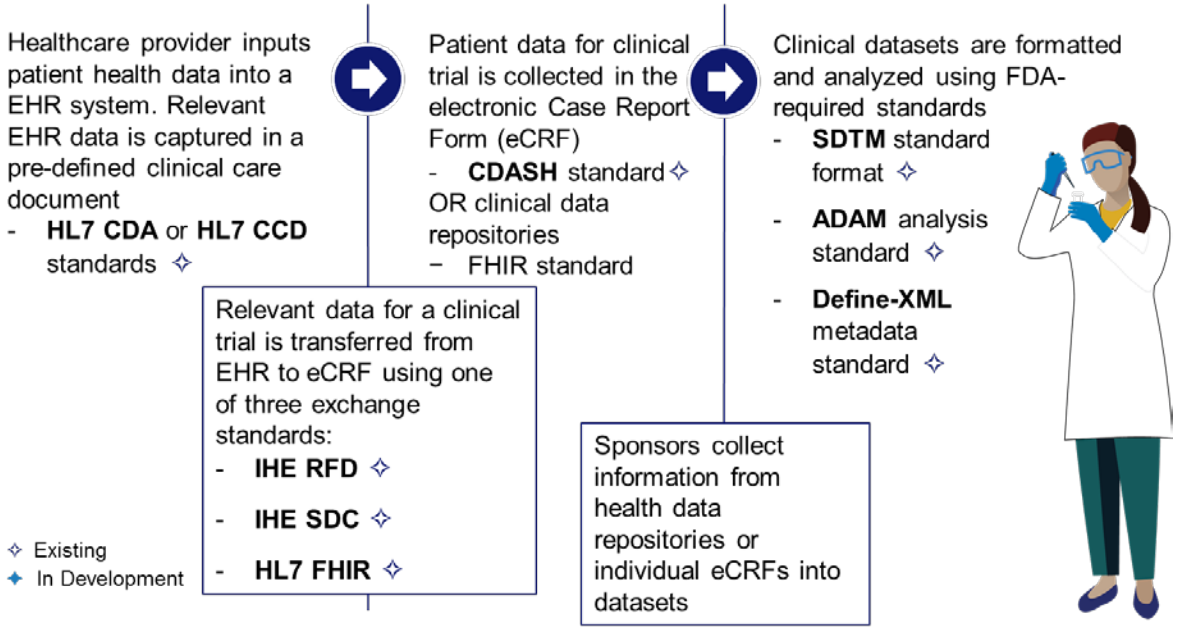
In 2014-2015 FDA conducted a pilot to evaluate the CDISC Dataset-XML. The final report for that pilot outlined that additional testing is needed to evaluate cost versus effectiveness of DS-XML as an alternate transport format and determined that several pilots would be needed to evaluate new transport formats before a decision is made to support a new format. The PhUSE collaboration added the evaluation of alternate transport formats as a project to further this evaluation. Project progressed in 2016, with PhUSE planning to submit results to the FDA in 2017.

3.4.2 Source Data Capture

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

Figure 5 shows a general conceptual approach of how Health IT data standards could address current barriers.

Figure 5: Health IT Data Standards: How It Could Work



CDER is supporting projects that would connect these two formats without data entry. One project, CDISC's Transforming Research Through eSource and Standards Project, is performing a prospective clinical trial that integrates the EHR and EDC systems, leveraging the Healthcare Link solution (CDISC, Integrating the Healthcare Enterprise (IHE), Health Level Seven (HL7)). The objectives of this project are to demonstrate the viability and value of eSource data capture in regulated research as well as to encourage its use and ultimately implement the vision of leveraging EHR and other Health IT data in regulated clinical research.

Another project, Source Data Capture from EHRs: Using Standardized Clinical Research Data, seeks to demonstrate an approach to collecting data for clinical trials that populates an electronic data collection (EDC) system directly from an EHR system in an FDA-compliant way using RFD, which provides a method for gathering data within a user's current application (in this case the EHR) to meet the requirements of an external system (in this case the EDC). The demonstration will be done in collaboration with the University of California at San Francisco Medical Center (UCSF) as part of a phase 3 trial in breast cancer.

These projects started in 2016 and expect to make significant progress towards their objectives in 2017.

3.4.3 BRIDG Working Group

CDER co-leads the HL7 Biomedical Research Integrated Domain Group (BRIDG) Work Group to improve and ensure viability of a clinical research domain analysis model, an essential effort to enhance sustainability of clinical research standards, and to help harmonize clinical research and healthcare standards. The BRIDG model is an 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

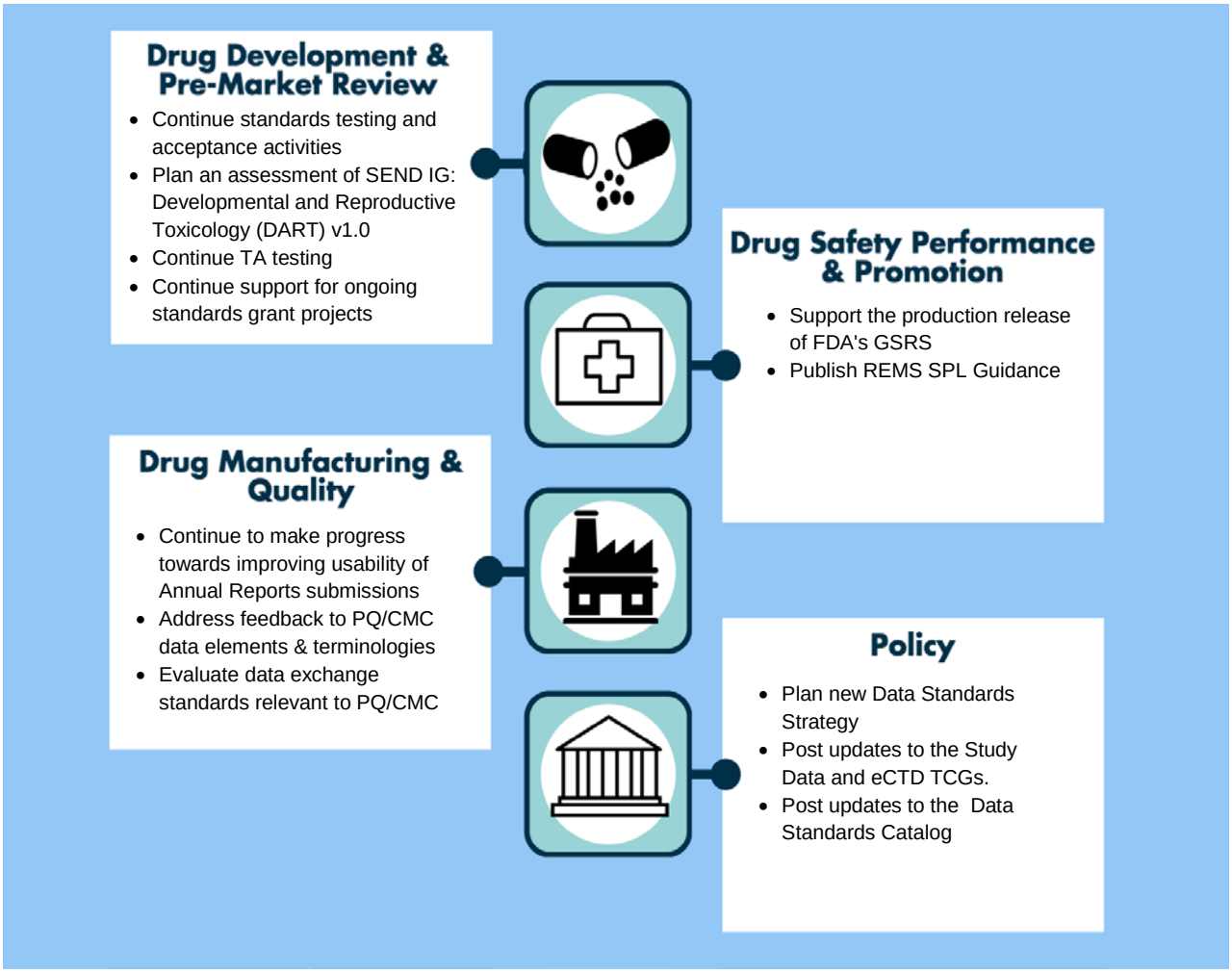
technology solutions that will enable semantic interoperability within the biomedical/clinical research arena and between research and the healthcare arena. CDER is presently managing a grant on performing the architectural review of the BRIDG model, to ensure that BRIDG meets the objective of sustainability and interoperability in the biomedical domain and provides the foundation of shared understanding of the domain, including the development of specific design recommendations for re-architecting the BRIDG model. In early 2017, the BRIDG work group will merge with the HL7 Regulated Clinical Research Information Management (RCRIM), forming a new HL7 work group, Biomedical Research & Regulation (BR&R).

4 Moving Forward - 2017 CDER Data Standards Program Direction

With required electronic study data standards and electronic submissions in effect or coming into effect, respectively, CDER is focused on ensuring that the review environment is capable to support receipt, processing and review of all electronic data. It is also anticipated that efforts will continue for further standardization of submission data and structures as well as internally generated 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 Data Standards Program.

To support communication of new technical specifications and conformance guides, as well as relevant standards information, new FDA webpage updates are planned for deployment throughout 2017. 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 2017.

Figure 6. 2017 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. One project launching in 2017 is the Common Data Model (CDM) Harmonization project which is looking to build a data infrastructure for conducting research using Real World Data derived from the delivery of health care in routine clinical settings. The objective is to develop a method to harmonize the Common Data Models of various networks (e.g., Sentinel), allowing researchers to simply ask research questions on much larger amounts of Real World Data than currently possible, leveraging open standards and controlled terminologies to advance Patient-Centered Outcomes Research.