CDER Data Standards Program
2015 Annual Assessment

Final

April 13, 2016

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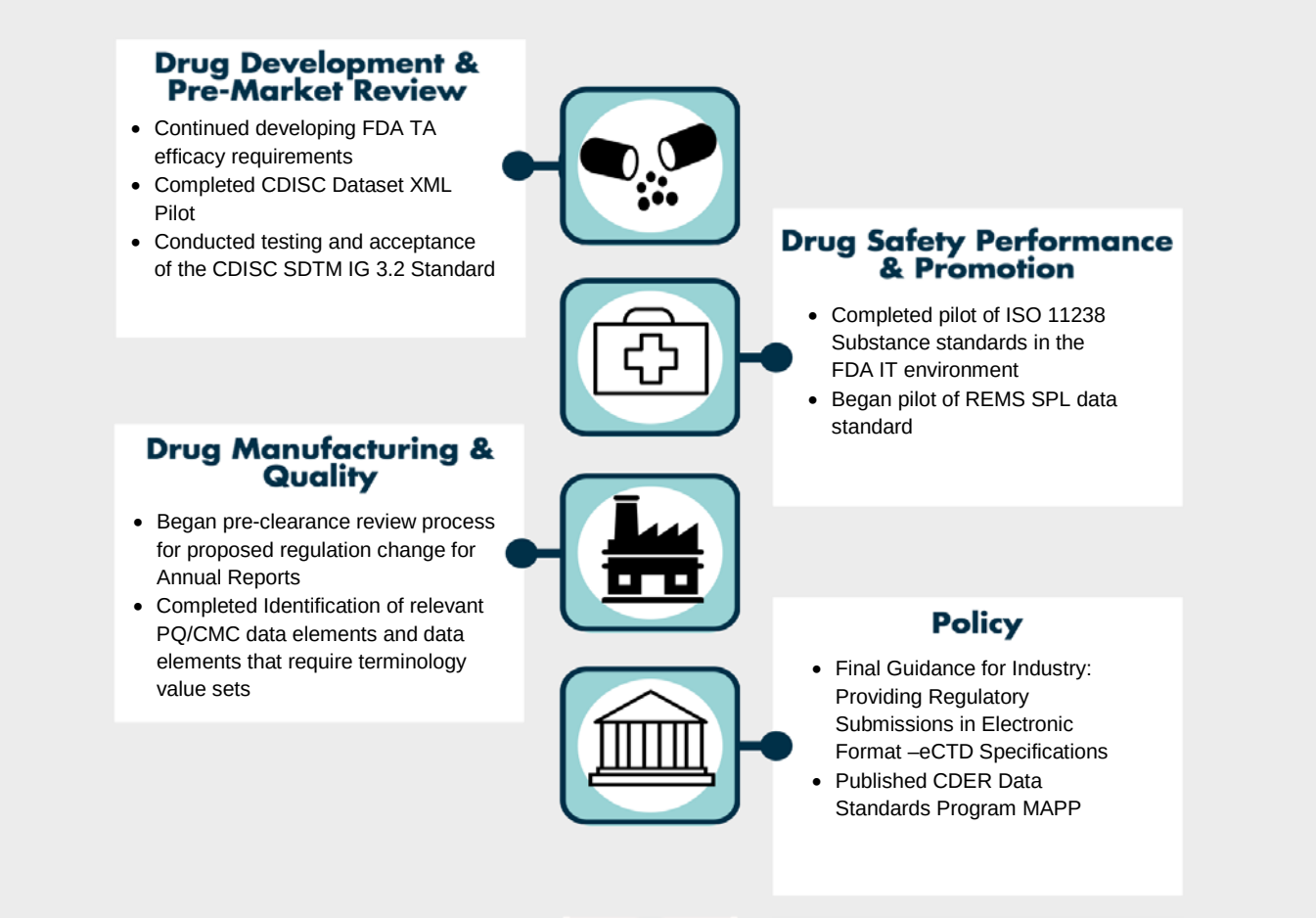
1 Introduction

The Center for Drug Evaluation and Research (CDER) publishes an Annual Assessment for CDER's Data Standards Program and reflects the progress made since the last assessment. The previous year assessment is available on the CDER Data Standards Program website. The focus of this document is to provide stakeholders with an update on CDER's progress over the last calendar year. The Data Standards Strategy was updated and published in 2015 reflecting the Data Standards Program's continued growth. 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. 2015 Summary of Accomplishments



3 2015 Data Standards Program Year in Review

The CDER Data Standards Program made significant overall progress in 2015 which is highlighted below. The publication of Guidance and Technical Specifications along with standard operating procedures and templates, supported the program as it continued to focus on participating in the development of standards and testing 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 Standard Development Organizations (SDOs). Significant progress continued in 2015 in the planning and development of TA data standards which focus primarily on requirements for the efficacy review and evaluation of new medical products. The third version of the *Therapeutic Area Standards Initiative Project Plan* (Project Plan*)*, published in October 2015, is an update to the original document for guiding all major aspects of FDA's multi-year initiative to develop and implement TA standards to support the regulatory review process for drugs and biologics.

The list of the prioritized TAs and their development status was revised to reflect progress made and changes in CDER priorities. This list will continue to be revised periodically. Of the 53 TAs on this list, 41 have commenced either within FDA to capture business needs or in collaboration with external parties to develop standards. FDA completed or has underway recommendations for 24 TAs based on the expressed preference of the FDA Review Divisions. When standards projects are initiated by SDOs, the relevant requirements document is provided to serve as input to the project scope ensuring Review Division input early in each project.

CDER continues to expand the FDA recommendations for the operational efficacy endpoints, in order to include the derived and compound endpoints generally used in statistical analyses. The current effort, expected to document the FDA CDER analysis needs for five priority TAs, builds on the outcomes and the methodology used in developing analysis specification for a virology TA (Hepatitis C) in 2015.

The DSP testing project evaluated several standards leading to updates of the Data Standards Catalog and TCG.

The Center continued to implement and refine its comprehensive testing approach to ensure that data standards meet FDA's requirements as well as confirm its ability to process, review and archive the format, standard, or terminology. The Clinical Data Interchange Standards Consortium (CDISC) foundational standards and TA use cases were prioritized for testing by the Study Data Standards Working Group. In some cases testing activities were conducted before the standard was published (e.g., during SDO public review stage) which helped ensure the final standards meet FDA needs. This also facilitates later testing and acceptance efforts which can focus on

outcomes from previous reviews. The CDISC Study Data Tabulation Model (SDTM) Implementation Guide (IG) 3.2 and Associated Person (SDTMIG-AP v1) as well as therapeutic use cases for Chronic Hepatitis C and Dyslipidemia completed the testing and acceptance phase. FDA CDER supports for SDTMIG 3.2 is published in the latest Data Standards Catalog, and supports for Chronic Hepatitis C and Dyslipidemia is announced via Study Data Technical Conformance Guide (TCG).

Based on the findings from the Meaningful Use (MU) standards (terminologies) assessment, the Center announced the Logical Observation Identifiers Names and Codes (LOINC) terminology will be required for laboratory test data in studies that start after March 2018, and that FDA is now encouraging sponsors and applicants to provide World Health Organization (WHO) Drug Dictionary codes for concomitant medication data in investigational studies provided in regulatory submissions. The working group is undertaking a review and anticipated update to the FDA Data Standards Manual (DSM) website.

Ongoing efforts continued for non-clinical data standards as the Standard for the Exchange of Nonclinical Data (SEND) Cardiovascular and Respiratory Safety Pharmacology Pilot team successfully executed its proposed plan to receive sample data for review. While the pilot project plan was developed, the Center has prioritized efforts on implementation of the base SEND standard. The pilot plan work will resume following base standard implementation. To support ongoing implementation efforts, CDER published an update of the Center-defined validation rules for SEND formatted files to reflect refinements in the severity level for some rules.

The SEND and SDTM validation rule documents are both available on the Study Data Standards Resources web page. These documents reflect a list of human readable business rules that describe how standardized data are needed to support review activities. They are maintained by a Change Control Board (CCB) that 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.

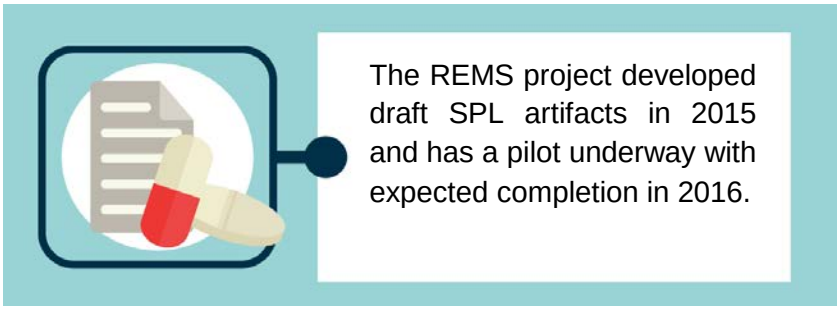
The Bioanalytical Methods project has made noteworthy progress leading to completed draft guidance, Providing Regulatory Submissions in Electronic Format-Standardized Bioanalytical Data, which defines the requirements for a valid electronic submission of standardized bioanalytical data. The Guidance is expected to begin clearance in 2016. 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 listed 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, a pilot was successfully completed based on the Global Substance Registration System (GSRS) and the Center is now working towards the first production release of GSRS at FDA. Substance is the primary lynchpin for 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.

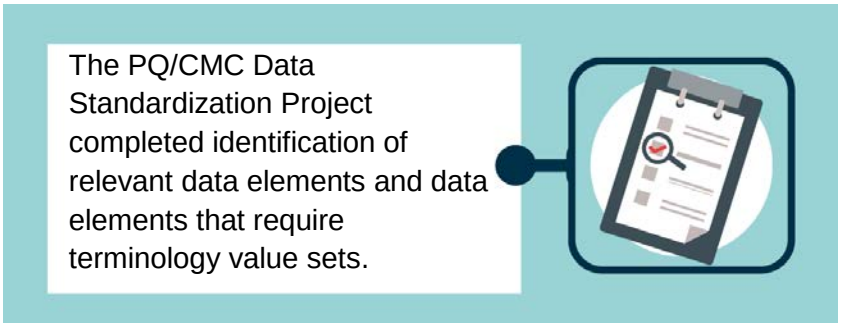
The CDER project to capture and submit structured information about Risk Evaluation and Mitigation Strategies (REMS) and official FDA-approved REMS Documents in Structured Product Labeling (SPL) continued to make progress in 2015. The project developed draft SPL artifacts including style sheet, data elements and controlled terminology. The Pilot is underway and targeted for completion at the end of 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.



3.3 Drug Manufacturing and Quality

With the authorization of the Generic Drug User Fee Act (GDUFA), CDER completed an internal assessment of the generic drug review process with an emphasis on data usage and submission quality. Per recommendations from the assessment, the Annual Report Project was initiated to improve the efficient use and review of submission data.

The Annual Report project serves to improve data quality of Annual Report submissions pertaining to Distribution data, Field Alert Reports, and CMC information through changes to the underlying regulatory requirements. 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. The project is currently in the internal review steps for the proposed regulation changes.

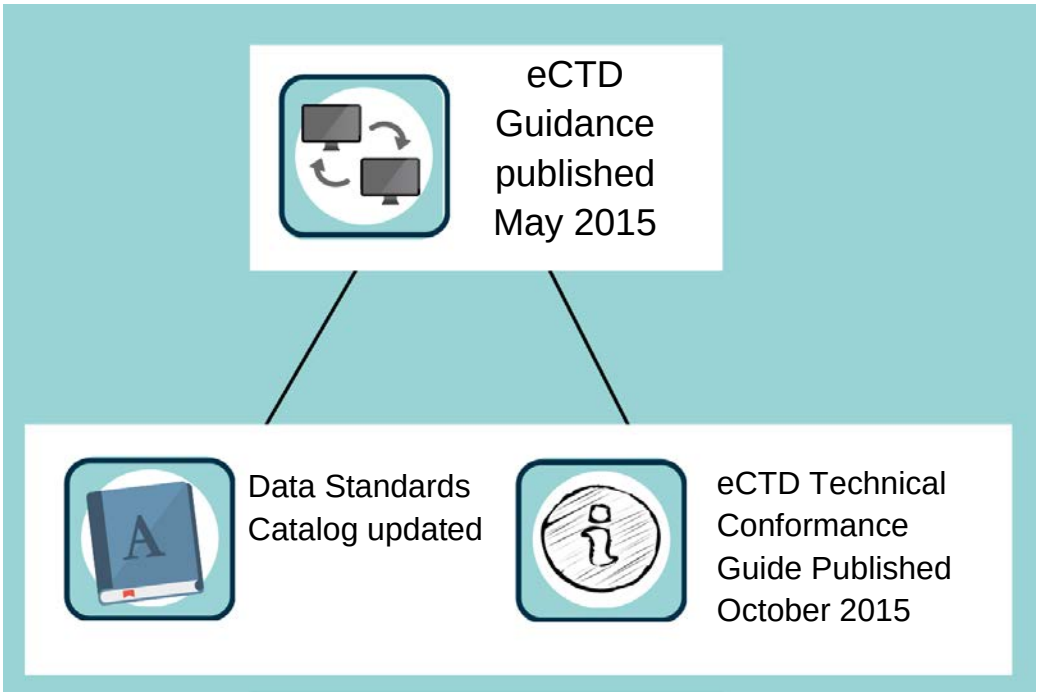


PQ/CMC Data Standardization Project was commenced to identify and standardize data elements and terminologies for information commonly used in support of drug application submissions. An overall goal of this initiative is the development of structured and computable data standards for PQ/CMC, ensuring consistent representation of concepts common among internal FDA systems. To date, relevant data elements and data elements that require terminology value sets have been identified. In the 3rd Quarter of 2016, there is a plan to publish a Federal Register Notice to receive comment on defintions and terminiogies. In the next year, the project will evaluate data exchange standards for PQ/CMC data.

3.4 Policy, Planning and Governance

In 2015, to implement the provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA) that authorized the electronic submission of information for certain Investigational New Drugs (INDs), New Drug Applications (NDAs), Biologics License Applications (BLAs) and Abbreviated New Drug Applications (ANDAs), CDER and the Center for Biologics Evaluation and Research (CBER) developed and in May 2015 published the Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format – electronic Common Technical Document (eCTD) Specifications (eCTD Guidance). Further technical instructions were included in a separate eCTD technical conformance guide published in October 2015. The timeframes for requiring electronic submissions in eCTD format are established with the publication of the final eCTD Guidance. Submissions after May 2017 for NDAs, BLAs, and ANDAs and May 2018 for certain INDs must be in eCTD format.

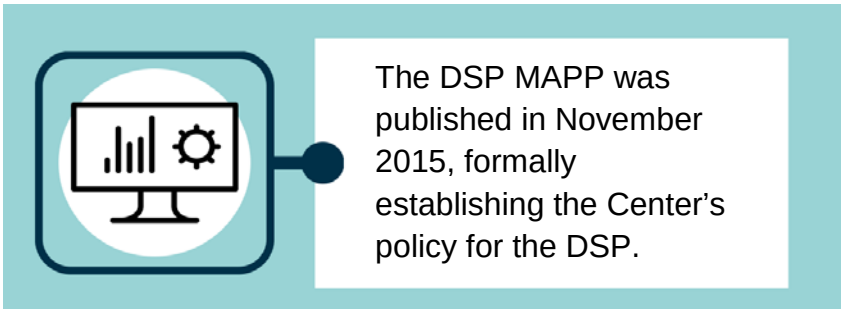
Figure 2. eCTD Guidance Accomplishment Highlights



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 published in 2015. The documents capture a detailed change history but in general reflected feedback to comments and results of testing and acceptance activities discussed above.

As part of its role in defining and governing CDER's Data Standards program, the Data Standards Program Board (DSPB) reviewed and updated its Data Standards Strategy document for 2015-2017. The document replaces the last version from 2012 and highlights the Center's focus areas, strategy, and related initiatives. The Action Plan, published quarterly, was revised to align with the strategy and provide a progress update to relevant initiatives. The Data Standards Operations Subcommittee (OpSC) continued to conduct primary operations on behalf of the DSPB. To gain efficiencies and be able to manage changes to technical specifications and support testing needs, the OpSC established two standing committees and forms ad hoc committees to address actions defined by the OpSC. Examples of ad hoc committees include groups to update the Technical Conformance Guide and to develop a new Manual of Policies and Procedures (MAPP) related to rejections of electronic submissions. The Study Data Workgroup is key to study data standards testing activities and interfacing with CDISC. The Terminology Workgroup meets on an as needed basis to address terminology requests or questions. All progress and decisions are briefed to the DSPB quarterly or on an as needed basis.

The Data Standards Program (DSP) had worked to establish standard operating procedures to provide consistency in how new projects were identified, approved and included a general framework for operations. To ensure this was consistent and transparent in CDER, a new MAPP was developed and published: CDER Data Standards Program. This MAPP outlines the Center's policy and outlines the relevant procedures and references to support the policy. This publication was a milestone in formally establishing the Center's policy for the data standards program. In addition to the publication of the MAPP, the SOPs underwent a review one year after being initially developed to incorporate lessons learned and address any needed refinements. The changes made reflected the revised DSPB charter and maturing testing procedures.



The Program continued its communication efforts presenting eight additional program overviews to internal CDER audiences. These presentations allowed the Data Standards Team to share its vision and inform other offices about projects relevant to them, allowing better insight into the many aspects of the drug development lifecycle data standards affects. In addition to these "Road Shows" the Data Standards Program underwent an internal and external website refresh with updated content, announcements, and project spotlights. Looking forward to 2016, the Data Standards Program will be hosting its first-ever Data Standards Half Day, which will feature four interactive workshops geared towards anyone interested in learning more about how data standards play an integral role in streamlining the drug development and application process.

3.5 Other Standards Areas

3.5.1 DS-XML Pilot

The pilot project to evaluate the CDISC Dataset-XML was conducted during 2014 and a final report was published in April 2015. The objectives were to evaluate the utility of DS-XML as a replacement transport format for Statistical Analysis Software (SAS) XPORT. The report outlined that additional testing is needed to evaluate cost versus effectiveness of DS-XML as an alternate transport format. FDA envisions conducting several pilots to evaluate new transport formats before a decision is made to support a new format. The Pharmaceutical Users Software Exchange (PhUSE) collaboration has added the evaluation of alternate transport formats as a project to further this evaluation.

3.5.2 Source Data Capture

On June 26, 2015, the Center published a notice entitled Source Data Capture from Electronic Health Records: Using Standardized Clinical Research Data in the *Federal Register* (Vol. 80:123, June 26, 2015). The purpose of this notice is to elicit demonstration projects to test and evaluate performance of end-to-end Electronic Health Record (EHR)-to-Electronic Data Capture (EDC) single-point data capture approaches in a standards-based, regulated clinical research environment. CDER created the Source Data Capture from EHRs webpage which provides background and information on the effort as well as feedback received from the published FR notice.

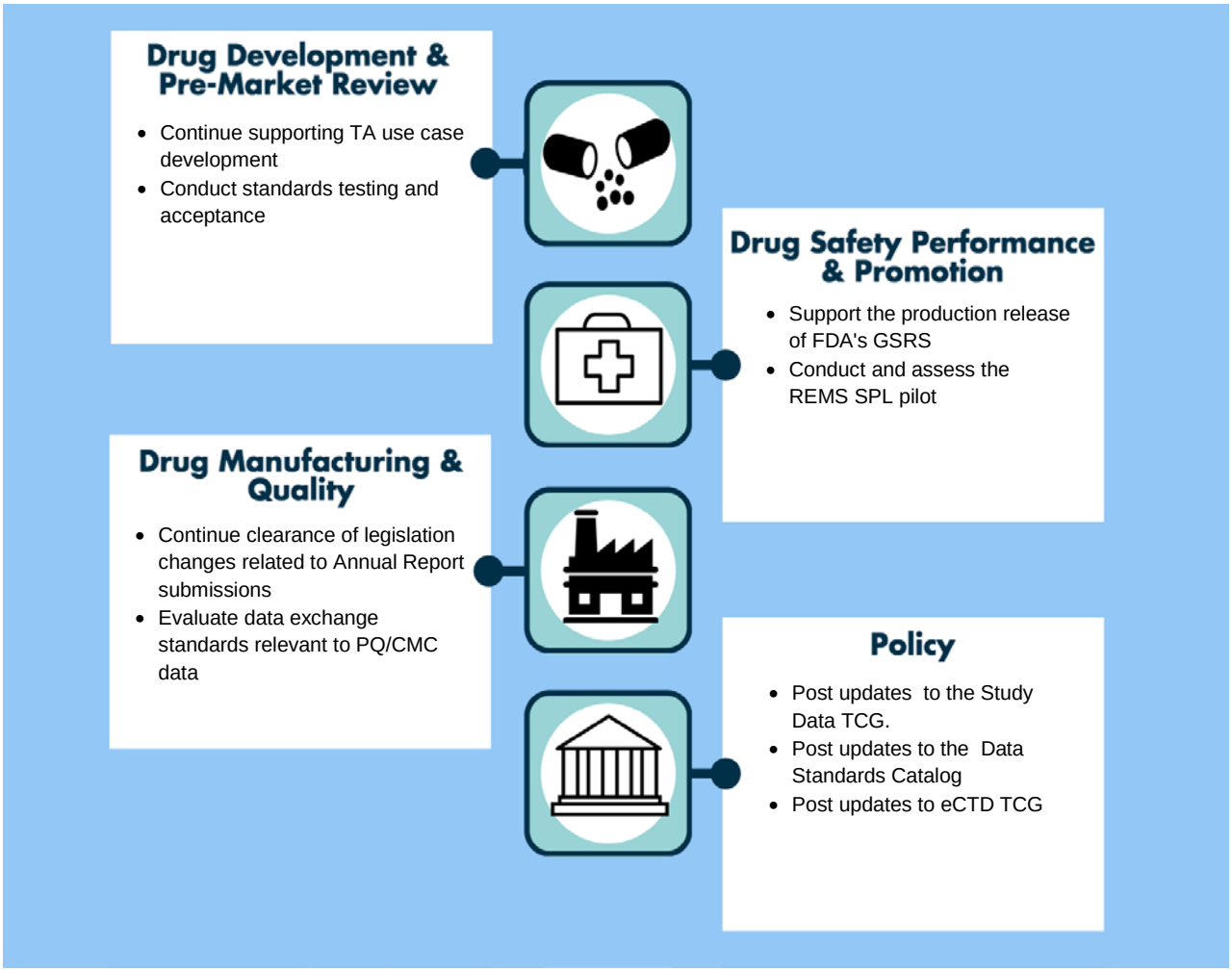
3.5.3 BRIDG Working Group

CDER co-leads the Health Level Seven (HL7) Biomedical Research Integrated Domain Group (BRIDG) Work Group (along with NCI, other stakeholders including CDISC and HL7), to improve and ensure viability of the BRIDG 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. In 2015 BRIDG was released as ISO standards, approved as a HL7 Draft Standards for Trial Use, and NCI launched a BRIDG Imaging pilot project.

4 Moving Forward - 2016 CDER Data Standards Program Direction

With the publication of eCTD Guidance, CDER is focused on ensuring that the review environment is in place to support receipt and processing of all data electronically. There will continue to be significant effort in supporting standards development projects and on the testing and acceptance of standards and terminologies. To ensure there is consistent awareness of upcoming deadlines as well as relevant standards information, new communications are planned for deployment in the summer of 2016. These will ensure a consistent external web presence, revised materials, and interactive tools for both internal and external stakeholders. The program already began collecting feedback from a broad range of stakeholders to support these communication efforts. The figure below highlights planned activities in 2016 in the four strategic areas:

Figure 3. 2016 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.