Data Standards Update

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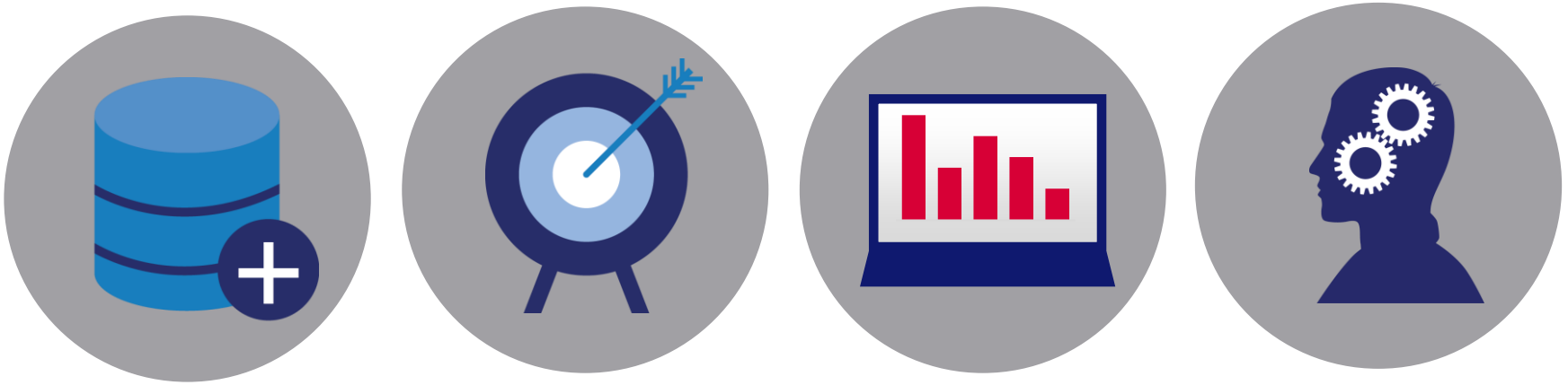
FDA DISCLAIMER

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Why Data Standards



Predictability + Traceability + Common Tools + Communication

= More efficient & transparent review process

Data Standards Governance in CDER

Data Standards Advisory Board

CBER Data Standards Committee

CDER Data Standards Program Board

CDRH
CFSAN
CVM

Operations Committee

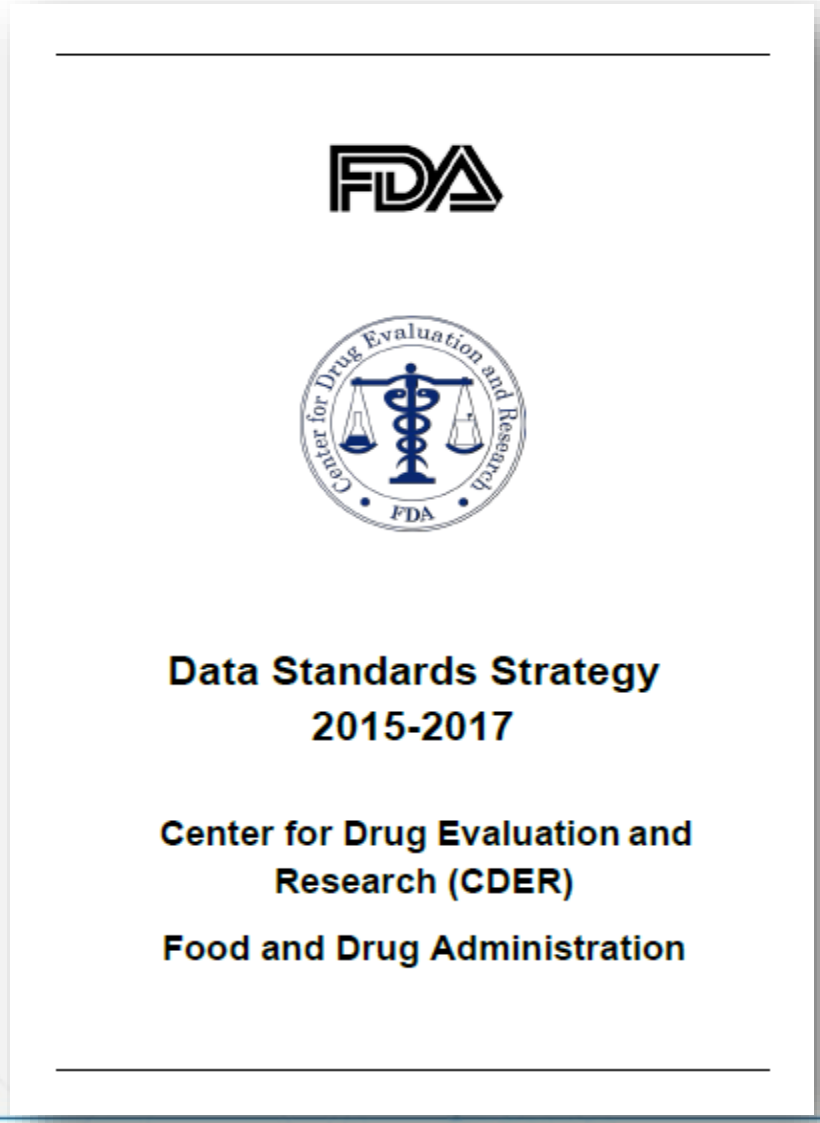
Validation Rules Group

Study Data Standards Group

Terminology Group

Conformance Guide Group

Data Standards Strategy and Action Plan



Data Standards Program Portfolio*

Drug Development and Pre-Market Review

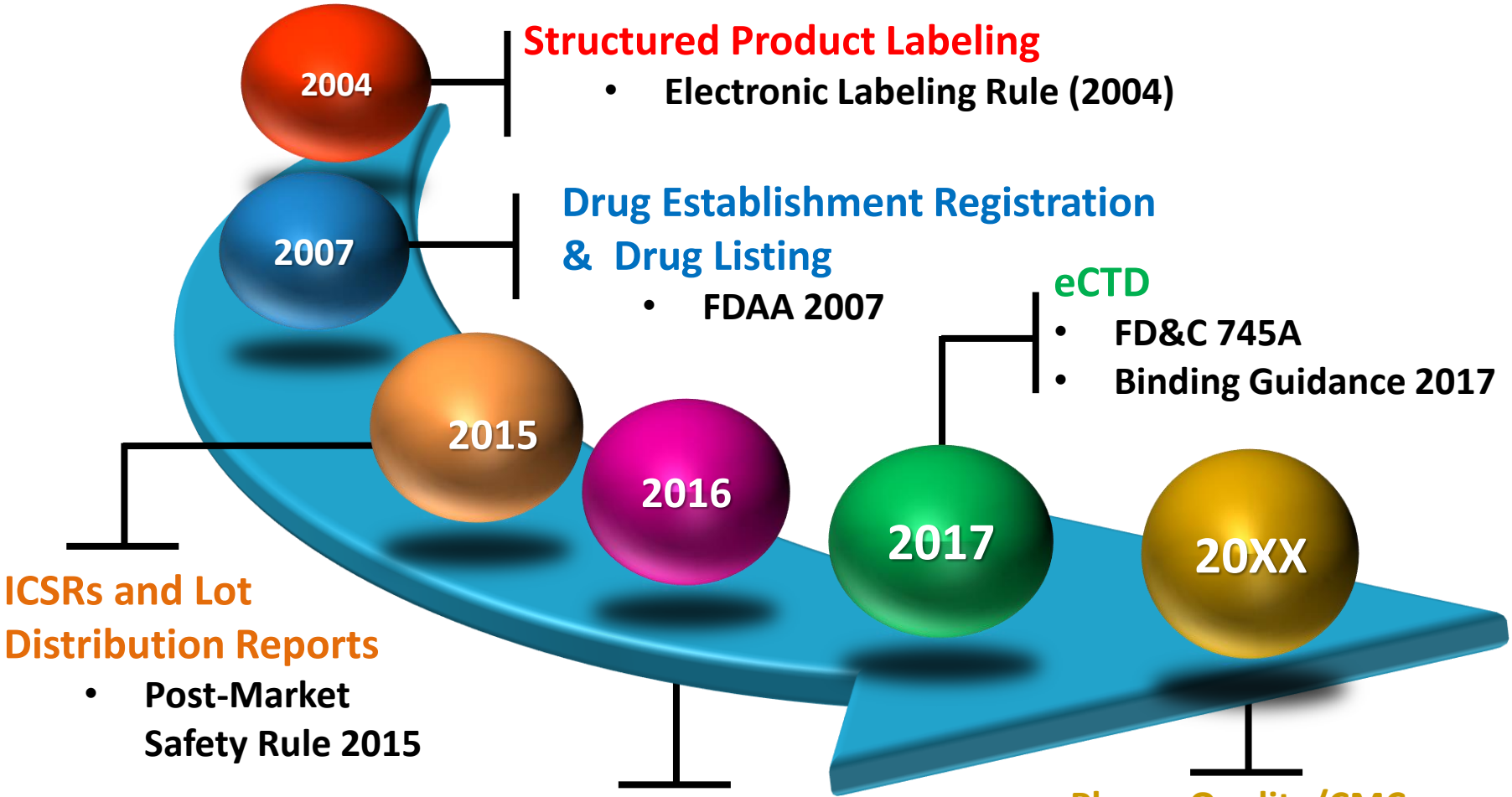
Drug Safety Performance and Promotion

Drug Manufacturing and Quality

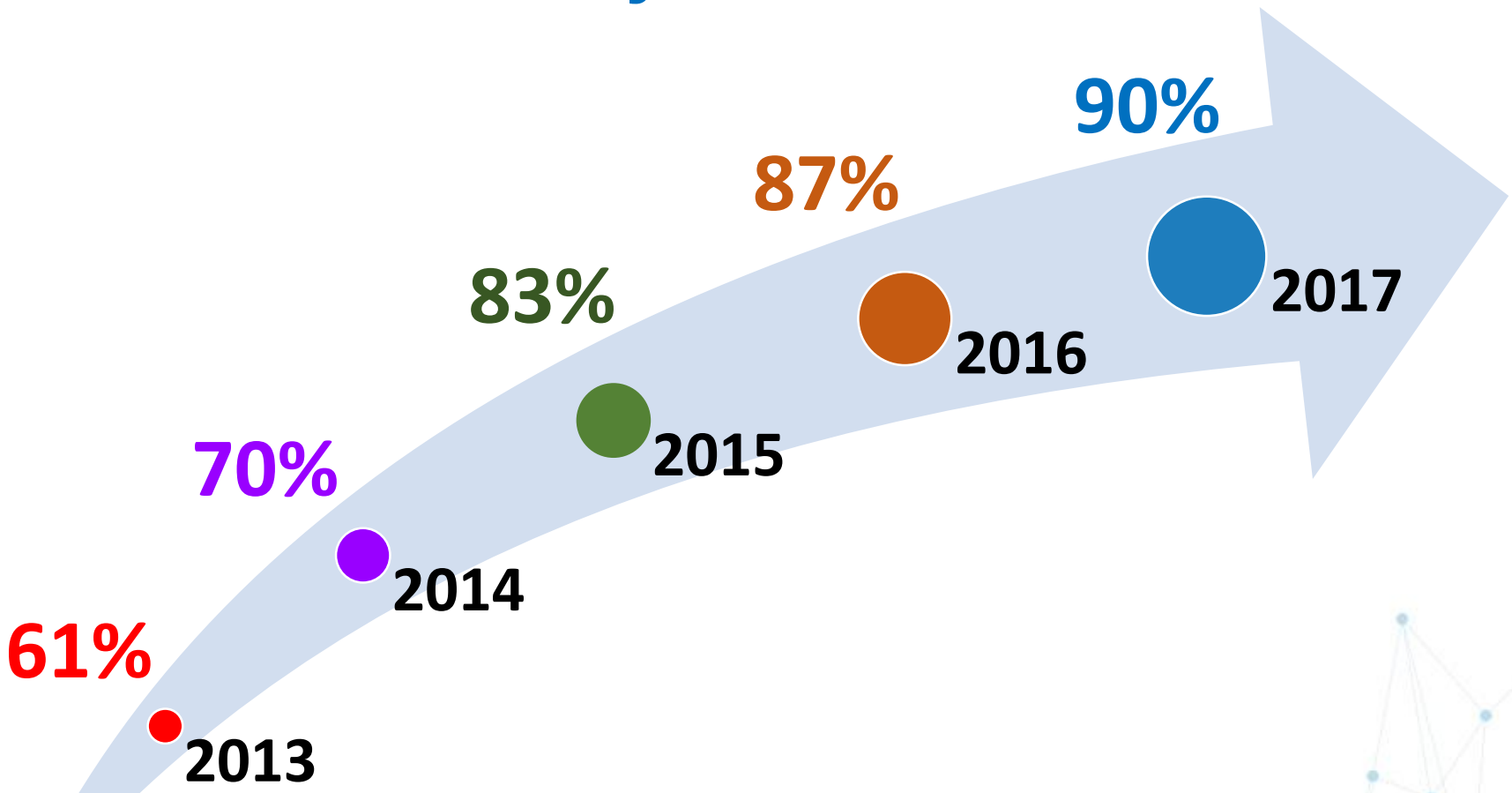
Policy

- Full list: https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm249979.htm

Road to Required Electronic Submission Standards

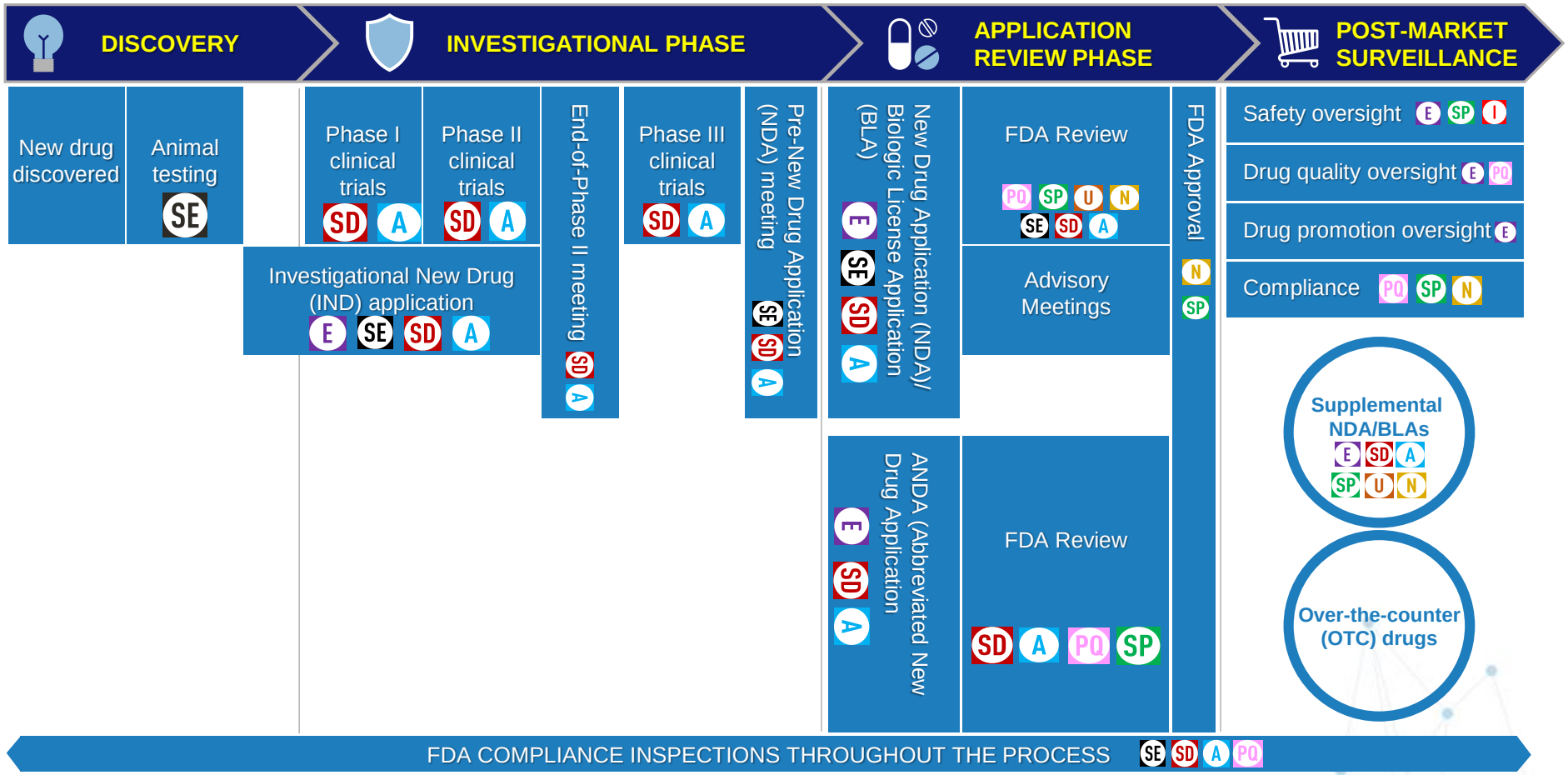


Percent of New NDA Submissions with Standardized Study Data - FY13- FY17*



* **<u>One or more</u>** explicitly stated **SDTM** studies (or study data structure that resembled SDTM) in NEW NDAs. FY2013-F2017(Q1-Q2), Source: Office of Business Informatics, CDER

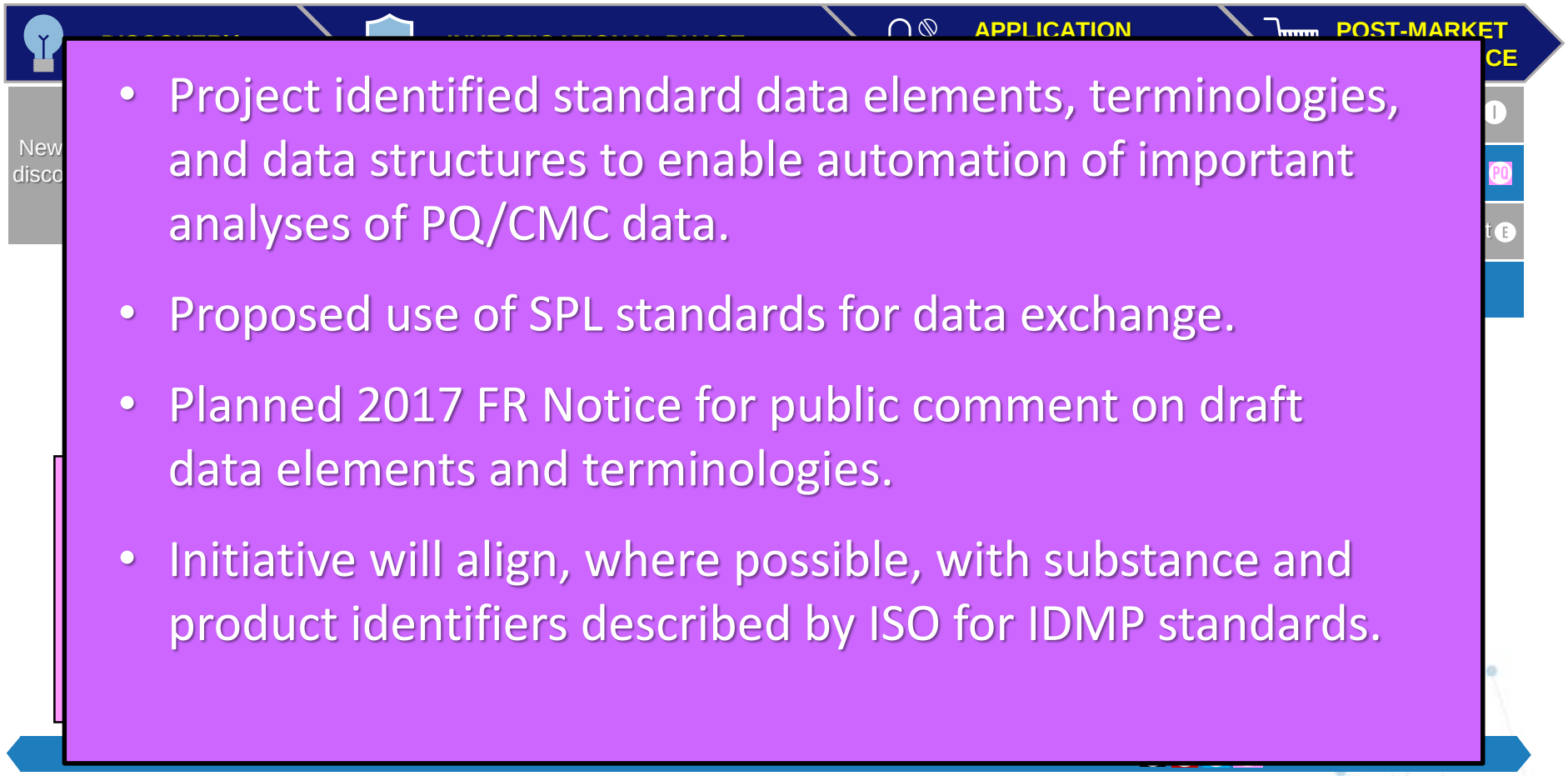
Project Updates for Standards in the Drug Development Lifecycle



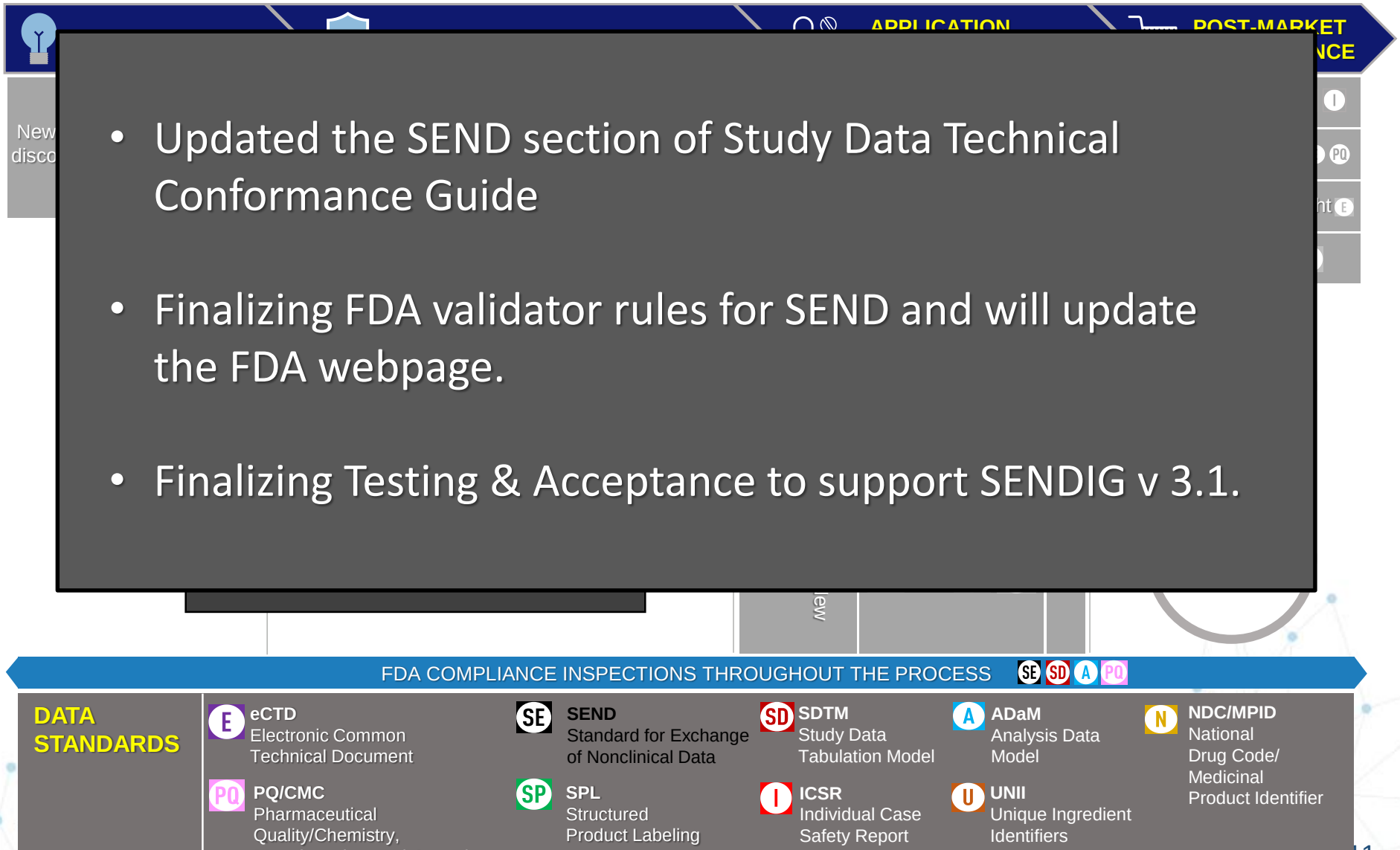
DATA STANDARDS

- **E** — **eCTD** Electronic Common Technical Document
- **SE** — **SEND** Standard for Exchange of Nonclinical Data
- **SD** — **SDTM** Study Data Tabulation Model
- **A** — **ADaM** Analysis Data Model
- **N** — **NDC/MPID** National Drug Code/ Medicinal Product Identifier
- **PQ** — **PQ/CMC** Pharmaceutical Quality/Chemistry, Manufacturing, and Controls
- **SP** — **SPL** Structured Product Labeling
- **I** — **ICSR** Individual Case Safety Report
- **U** — **UNII** Unique Ingredient Identifiers

Project Updates for Standards in the Drug Development Lifecycle

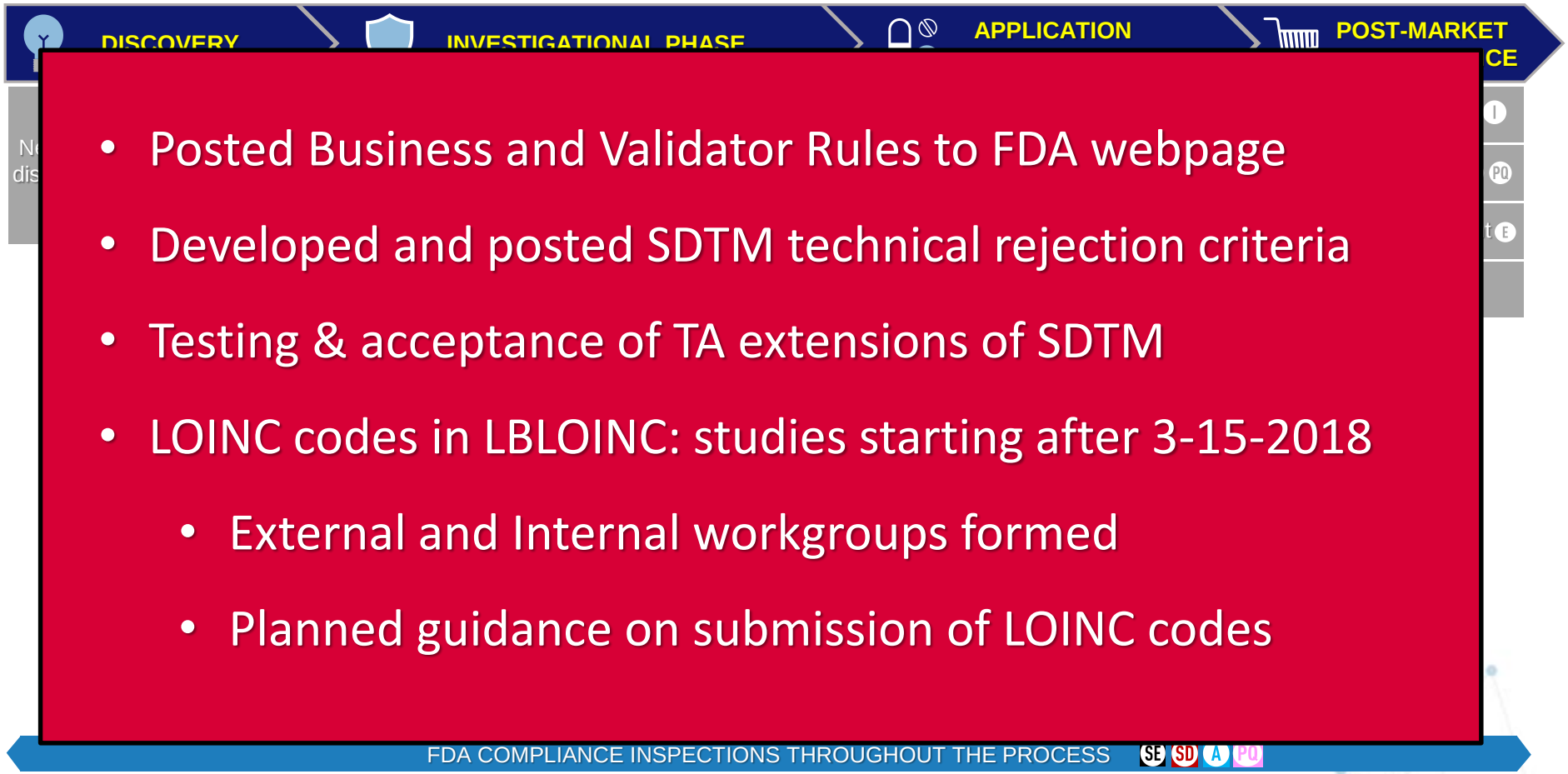


Project Updates for Standards in the Drug Development Lifecycle



- Updated the SEND section of Study Data Technical Conformance Guide
- Finalizing FDA validator rules for SEND and will update the FDA webpage.
- Finalizing Testing & Acceptance to support SENDIG v 3.1.

Project Updates for Standards in the Drug Development Lifecycle



Project Updates for Standards in the Drug Development Lifecycle

- Integrating Risk, Evaluation and Mitigation Strategies into SPL
  - Completed the pilot and now able to receive REMS in SPL format.
  - Guidance is in development.
- Draft Guidance on Submission of Manufacturing Establishment Information published December 2016
  - Requires: Establishment Name and Address, Unique Facility Identifier, PoC, Operations being conducted

FDA COMPLIANCE INSPECTIONS THROUGHOUT THE PROCESS SE SD A PQ

DATA STANDARDS

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FDA'S THERAPEUTIC AREA (TA) STANDARDS PROJECT

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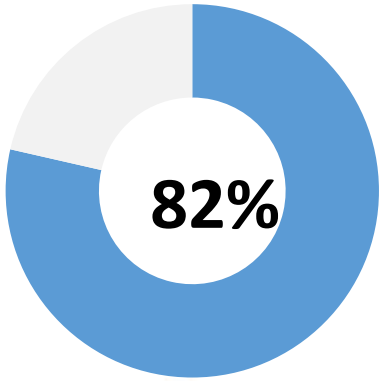
Overview

In 2012, as part of a PDUFA V commitment, CDER compiled a prioritized list of disease and therapeutic areas (TAs) for which standardization was needed.

Approach

Focus is on regulatory review needs

Current Status



Of the 55 TAs* prioritized, 45 have been initiated as of April 2017

CFAST Key Players

CDISC, C-Path, NIH, FDA, TransCelerate, Duke, HL7 and many other stakeholders

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM297093.pdf

FDA'S THERAPEUTIC AREA STANDARDS PROJECT

TA's Supported by FDA*

- QT Studies
- Chronic Hepatitis C
- Diabetes
- Dyslipidemia
- Tuberculosis
- Diabetic Kidney Disease
- Ebola
- Kidney Transplant
- Malaria

TA Standards in FDA Review - 2017

- Asthma
- Breast Cancer
- Colorectal Cancer
- CV Study
- CV Imaging
- Duchenne's MD
- Prostate Cancer
- Schizophrenia
- Virology

*May, 2017- listed in Technical Conformance Guide

eCTD Technical Rejection of Submissions

FDA can Refuse to File (RTF) or Refuse to Receive (RTR) an Application for Non-Conformance to Standardized Study Data

eStudy Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs in the formats in the Data Standards Catalo

…so we will start with eCTD technical rejection of submissions

eCTD Technical Rejection of Submissions

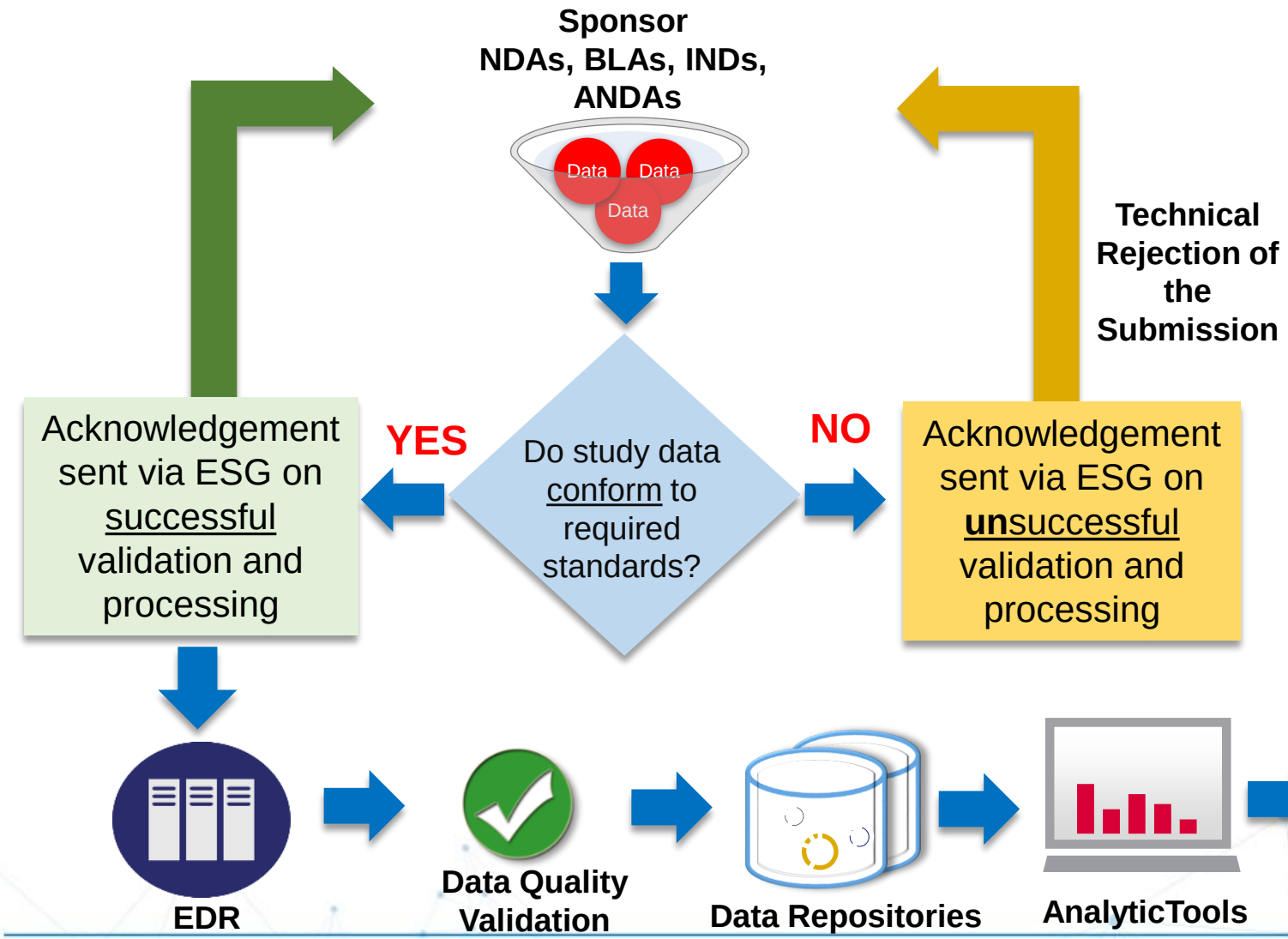
- CDER has been validating incoming submissions for conformance to *eCTD format* for **~8** yrs.
  - If a submission fails eCTD format validation a technical rejection notice will be sent to the submitter.
  - eCTD validation occurs upon receipt of the submission, prior to being written to the EDR and review division notification.
- The same process will be used for validating submissions for conformance to study data standards.
- It is NOT the same as RTF or RTR.

eCTD Technical Rejection of Submissions

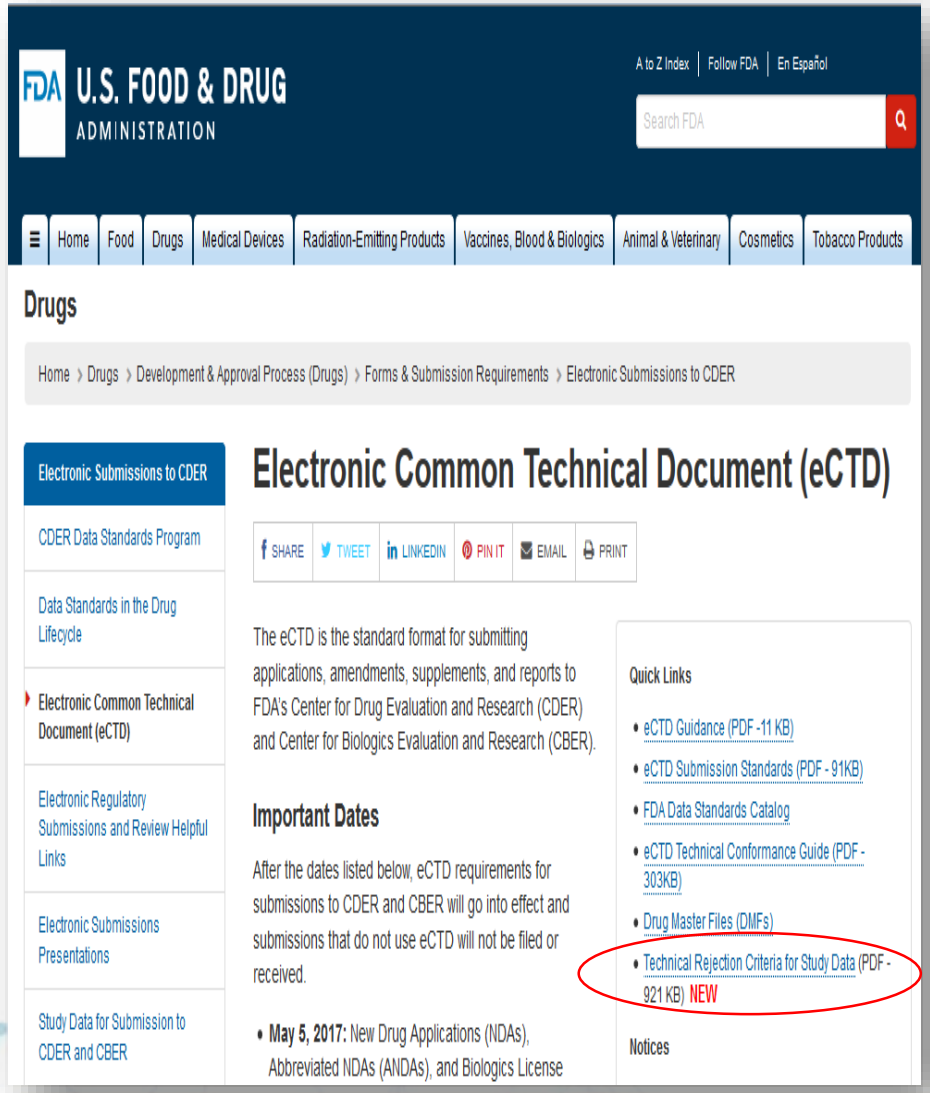
- Sponsors will be able to correct the technical errors and re-submit
- For study data standards validation, FDA will notify submitters, at least 30 days, prior to ‘going live” with the technical rejection of submissions.

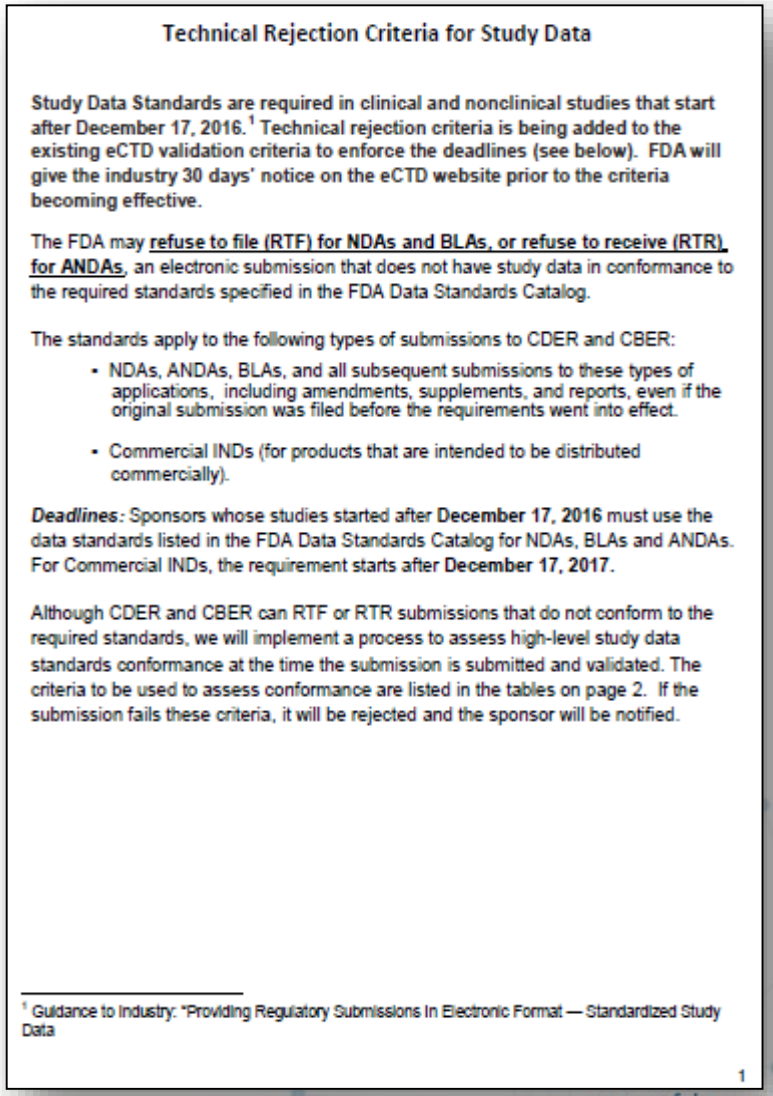
eCTD Technical Rejection…

How will it work?



eCTD Technical Rejection Criteria for Study Data Standards





Technical Rejection Criteria for Study Data

Study Data Standards are required in clinical and nonclinical studies that start after December 17, 2016.[1] Technical rejection criteria is being added to the existing eCTD validation criteria to enforce the deadlines (see below). FDA will give the industry 30 days' notice on the eCTD website prior to the criteria becoming effective.

The FDA may **refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs**, an electronic submission that does not have study data in conformance to the required standards specified in the FDA Data Standards Catalog.

The standards apply to the following types of submissions to CDER and CBER:

- NDAs, ANDAs, BLAs, and all subsequent submissions to these types of applications, including amendments, supplements, and reports, even if the original submission was filed before the requirements went into effect.
- Commercial INDs (for products that are intended to be distributed commercially).

Deadlines: Sponsors whose studies started after **December 17, 2016** must use the data standards listed in the FDA Data Standards Catalog for NDAs, BLAs and ANDAs. For Commercial INDs, the requirement starts after **December 17, 2017.**

Although CDER and CBER can RTF or RTR submissions that do not conform to the required standards, we will implement a process to assess high-level study data standards conformance at the time the submission is submitted and validated. The criteria to be used to assess conformance are listed in the tables on page 2. If the submission fails these criteria, it will be rejected and the sponsor will be notified.

[1] Guidance to Industry: "Providing Regulatory Submissions in Electronic Format — Standardized Study Data

1

https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm153574.htm

eCTD Module Sections Included and Excluded

IMPORTANT

A Trial Summary dataset (ts.xpt) must be presented for each study in sections identified below *even if the study started prior to December 17, 2016*. Nonclinical legacy data submitted in PDF format should be submitted with a TS dataset.

Study data validation **WILL APPLY** to the following eCTD sections:

- 4.2 Study Reports
- 5.3 Clinical Study Reports and Related Information

Study data validation **WILL NOT APPLY** to the following eCTD sections:

- 4.2.1 Pharmacology
- 4.2.2 Pharmacokinetics
- 4.2.3.3 Genotoxicity
- 4.2.3.5 Reproductive and Developmental Toxicity
- 4.2.3.6 Local Tolerance
- 4.2.3.7 Other Toxicity Studies
- 5.3.1.3 In Vitro – in Vivo correlation Study reports and related information
- 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies
- 5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials
- 5.3.3.5 Population PK study reports and related information
- 5.3.5.3 Reports of Analyses of Data from More than One Study
- 5.3.5.4 Other Study Reports and Related Information
- 5.3.6 Reports of Postmarketing Experience

eCTD Data Validation Criteria and Severity

High	Demographic dataset (DM) and the define.xml must be submitted in Module 4 for nonclinical data; DM dataset, the subject-level analysis dataset (ADSL) and define.xml must be submitted in Module 5 for clinical data
High	Trial Summary (TS) dataset must be present for each study in eCTD section 4.2 and 5.3
Medium	Correct STF file-tags must be used for all standardized datasets in section 4.2 and 5.3 • Data-tabulations-dataset-sdtm • Data-tabulations-dataset-send • Analysis-dataset-adam
Medium	For each study in eCTD section 4.2 and section 5.3, no more than one dataset of the same name should be submitted as new.

Thank You

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