

A person wearing blue nitrile gloves is holding a small, clear vial with a red cap. The background is a blurred laboratory setting with various pieces of equipment and containers.

SDTM and SEND – An Integrated View and Approach

PhUSE Connect 2018

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Overview

- ▶ Nonclinical and Clinical Development Phase
- ▶ Regulatory Agency Needs
- ▶ Deliverables to Regulatory Agencies
- ▶ Similarities & Differences
 - Process and Tools
 - Controlled Terminology
 - Domains Structure
 - Trial Design
 - Validation Checks
 - Submitted Documents

Drug Development Process

Investigational New Drug (IND) Application

New Drug Application (NDA)/
Biologics License Application (BLA)

Nonclinical

Phase I

Phase II

Phase III

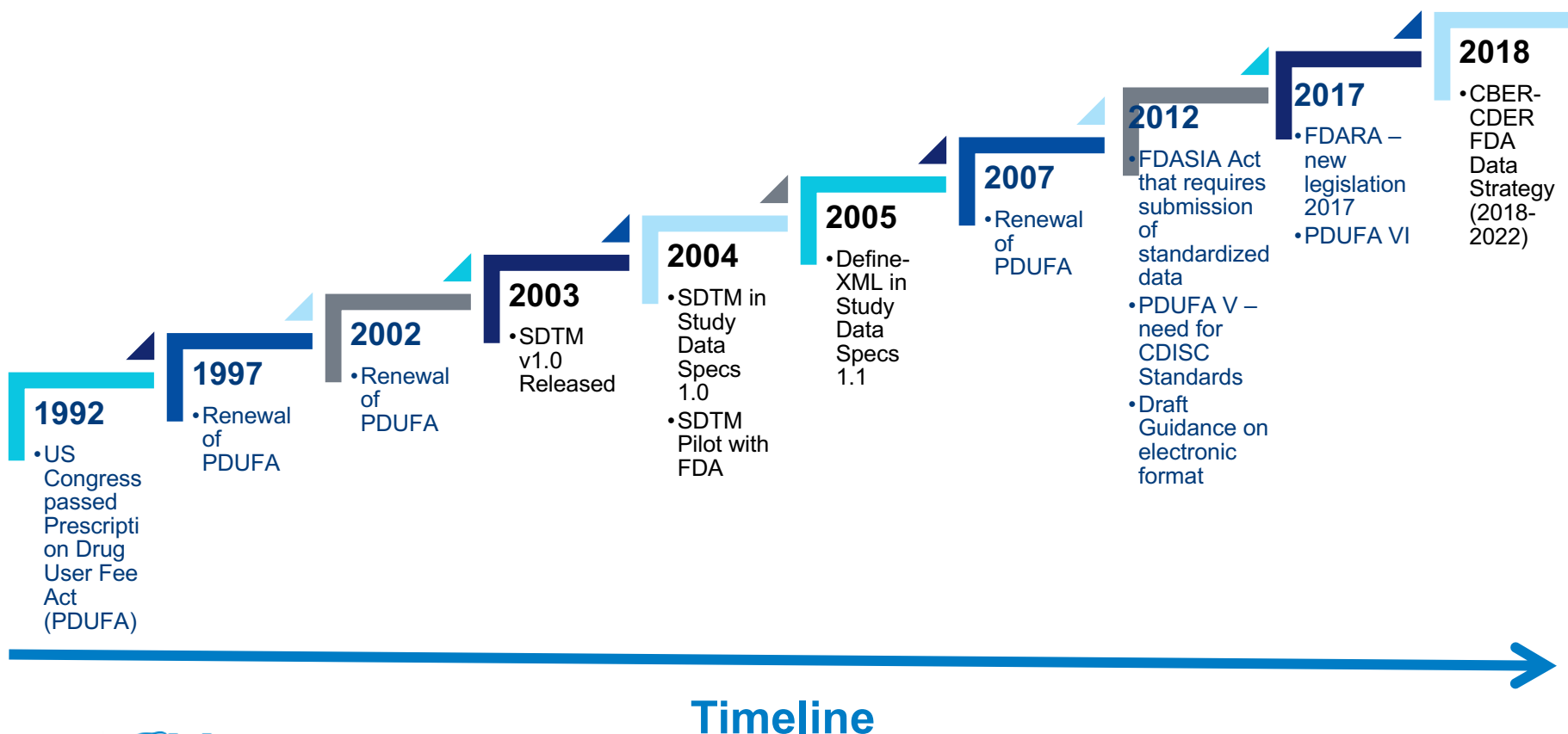
Post Marketing

SENDIG

CDASHIG,
SDTMIG,
ADaMIG

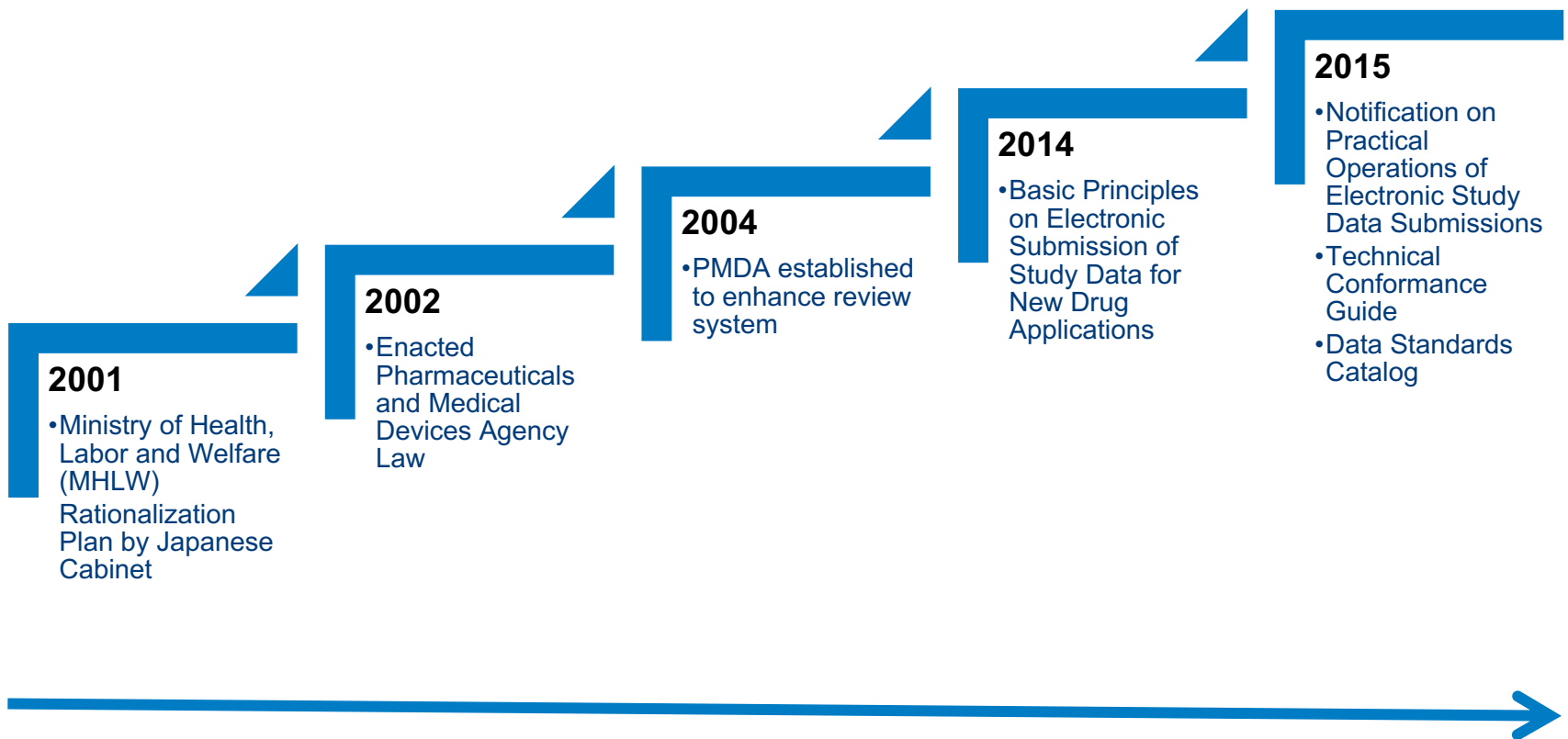
Regulatory Agency: US Food and Drug Administration (FDA)

Roadmap for Standardized data

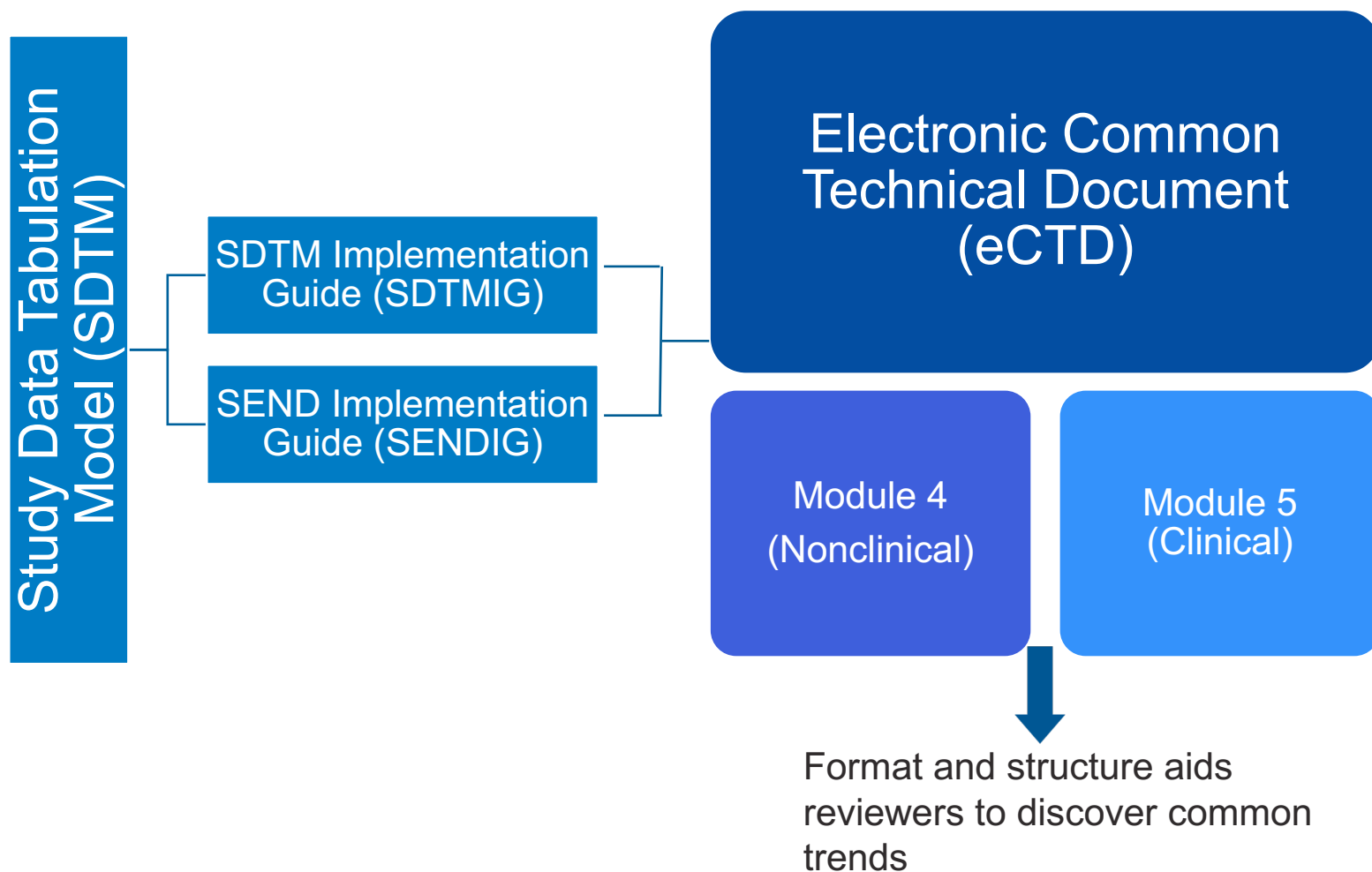


Regulatory Agency - Pharmaceuticals and Medical Devices Agency (PMDA):

Roadmap for Standardized data



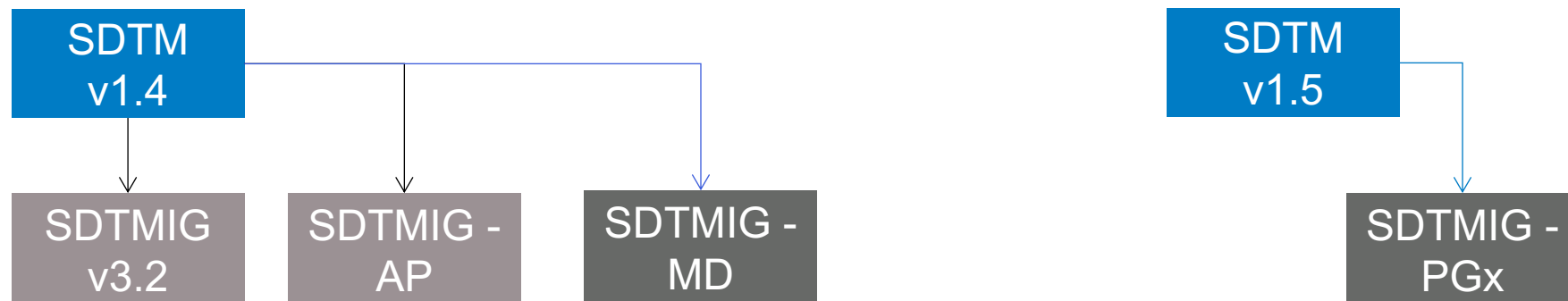
SDTM and SEND Data Standards



Deliverables to Regulatory Agencies

FDA*	PMDA**
CLINICAL: • SDTM Datasets v3.1.2, v3.1.3, v3.2 • Define XML 2.0 • aCRF.pdf • Study Data Reviewer's Guide (cSDRG) • ADaM Datasets v1.0, v1.1 • Define XML 2.0 • Analysis Data Reviewer's Guide (ADRG)	CLINICAL • SDTM Datasets v3.2 • Define XML 2.0 • aCRF.pdf • Study Data Reviewer's Guide (cSDRG) • ADaM Datasets 1.0 • Define XML 2.0 • Analysis Data Reviewer's Guide (ADRG)
NONCLINICAL: • SEND 3.0, 3.1 Datasets • Define XML 2.0 • Study Data Reviewer's Guide (nSDRG)	NONCLINICAL: None
Study Data Standardization Plan (SDSP): • Assists FDA in identifying potential data standardization issues • FDA Study Data Technical Conformance guide describes SDSP needs • PhUSE has developed the SDSP Template • Describes both clinical and nonclinical studies within a program • Sponsors may initiate discussions at pre-IND meeting • FDA CBER expects SDSP Appendix no later than end-of-Ph2 meeting	<i>* Based on current versions of:</i> ❖ FDA Data Standards Catalog v5.0 ❖ FDA Study Data Technical Conformance Guide v4.1 March 2018 <i>**Based on current versions of:</i> ❖ PMDA Data Standards Catalog v March 2017 ❖ PMDA Study Data Technical Conformance Guide v Aug 2016

SDTM and IG Development (Clinical)



New special purpose domains + New Variables added to SDTMIG-MD

Therapeutic Area User Guides Releases (Provisional)

Each user guide states the different implementation guides and identifies new domains, variables needed for that particular Therapeutic Area

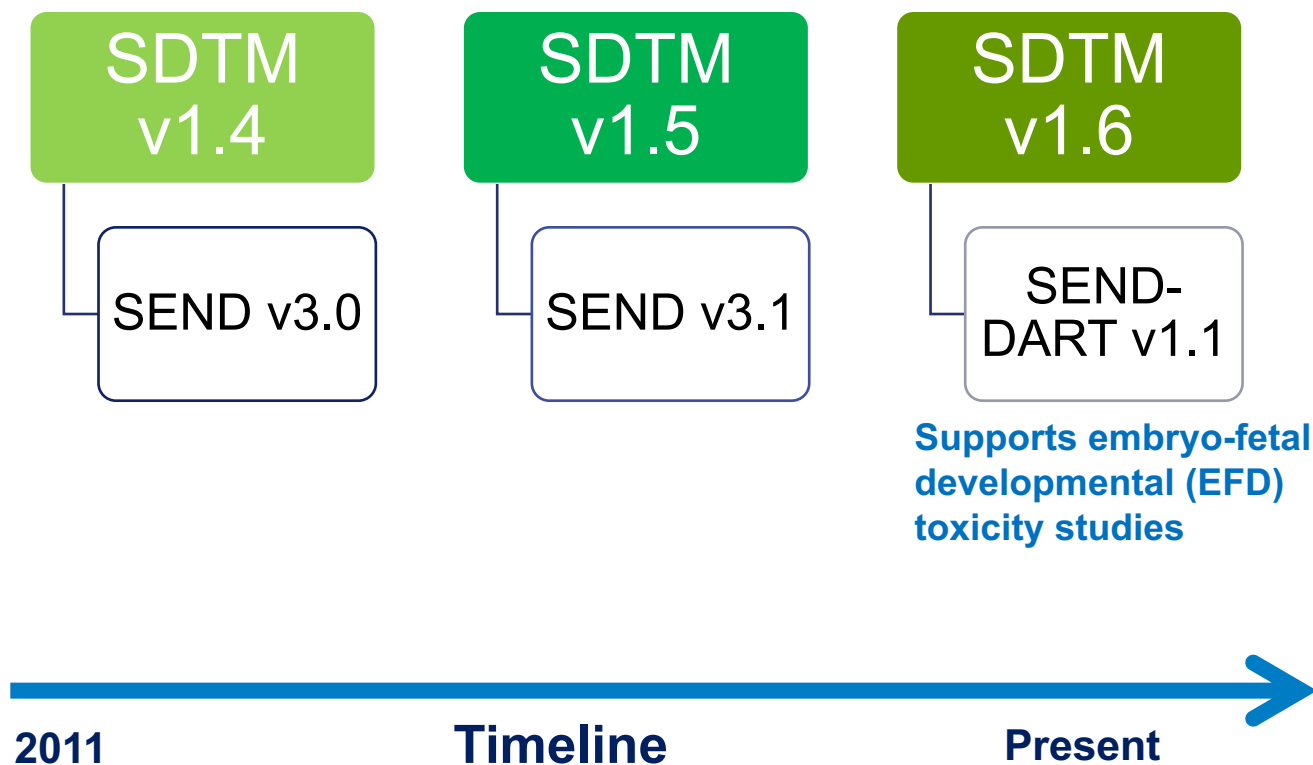
2013

Timeline

Present

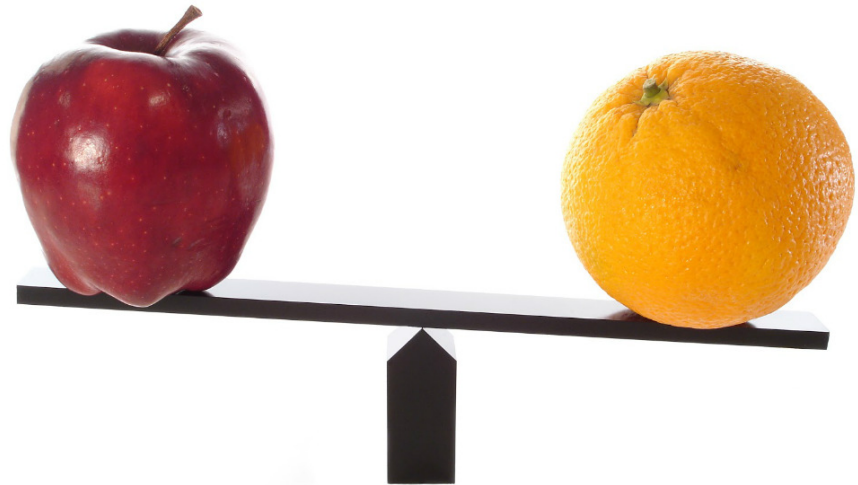
SDTM1.5 has new variables needed due to SEND 3.1

SDTM and IG Development (Nonclinical)

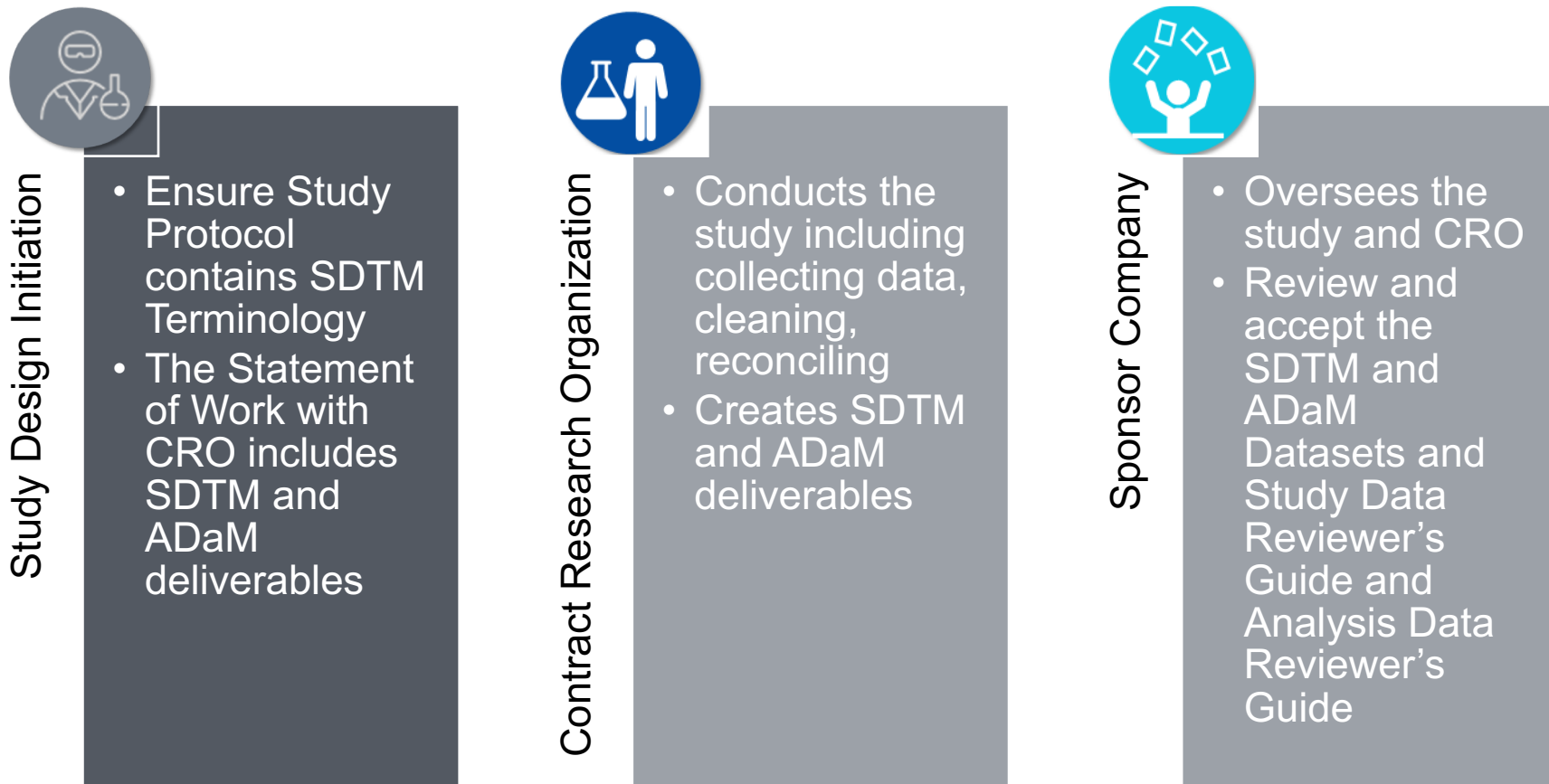


Similarities and Differences

“Share our similarities and celebrate our differences” – M. Scott Peck

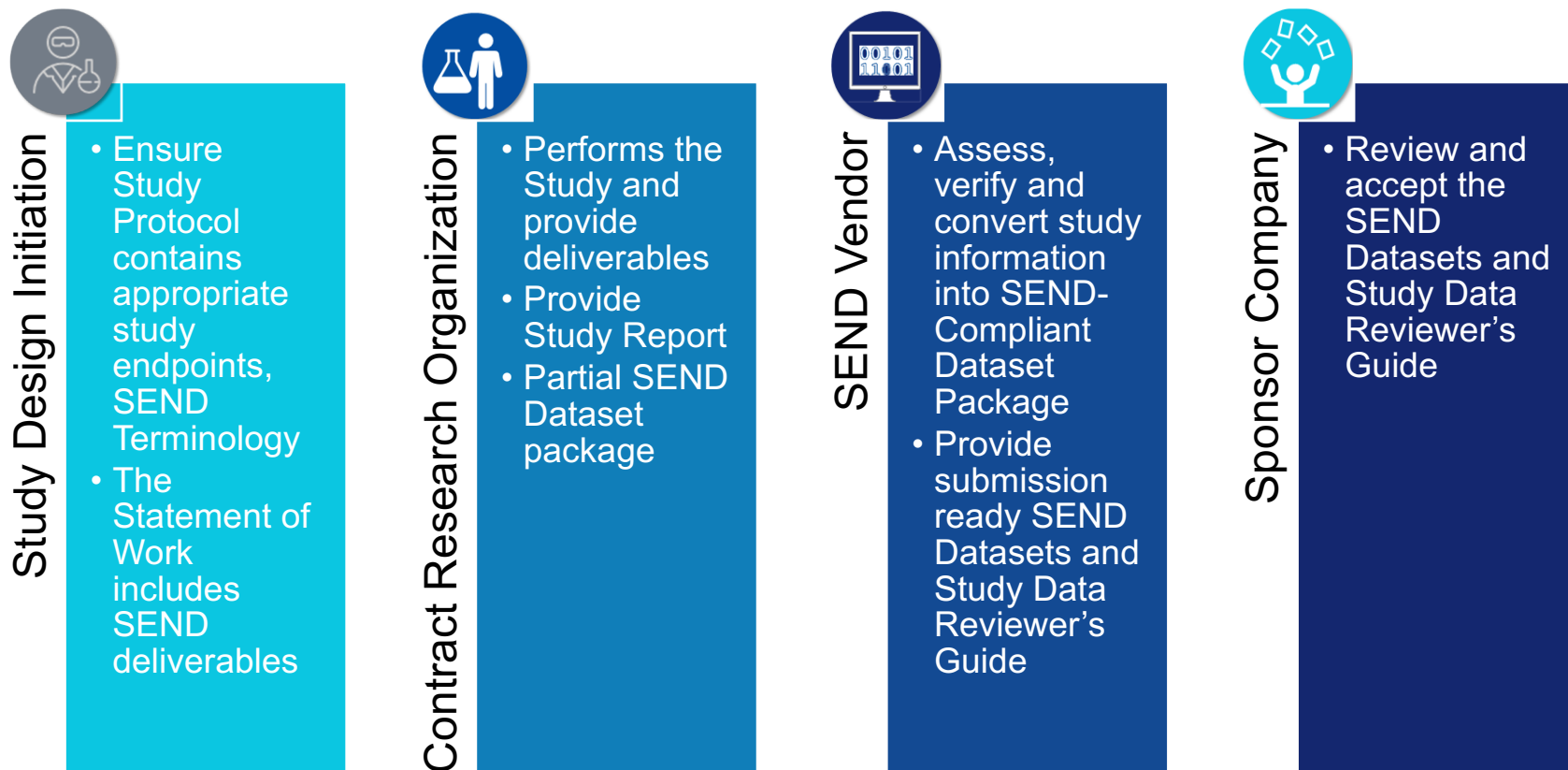


Process and Tools used for SDTM deliverables (Clinical)



ROLES AND RESPONSIBILITIES OF CLINICAL RESEARCH

Process and Tools used for SEND deliverables (Nonclinical)



ROLES AND RESPONSIBILITIES OF NONCLINICAL RESEARCH

Controlled Terminology (CT)

NCI CDISC Controlled Terminology – Set of standard expressions (values)

- Using common CT helps compare and visualize the data across clinical and nonclinical
 - Comparing SDTM CT v2018-03-30 and SEND CT v2018-03-30
 - 34 codelists are common between SDTM V3.2 and SEND 3.1
 - 18 codelists have similar codelist names but the code terms are specific to each standard
- For Nonclinical studies, there are other organizations such as International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) – composed of toxicological pathology societies across the world developing terminologies by providing a standardized nomenclature for the findings

Domains Structure

Comparing SDTMIG 3.2 and SEND 3.1 Models

SDTM Domains (only)

Interventions General Observation Class

Concomitant Medications (CM)
Exposure as Collected (EC)
Procedures (PR)
Substance Use (SU)

Events General Observation Class

Adverse Events (AE) Medical History (MH)

Protocol Clinical Events
Deviations (DV) (CE)

Findings General Observation Class

Drug Accountability (DA) Morphology (MO)

Immunogenicity Inclusion/Exclusion not
Specimen Assessments met (IE)
(IS)

Microbiology Microbiology Specimen
Susceptibility Test (MS) (MB)

Questionnaires (QS) Disease Response (RS)

Physical Examination (PE) Reproductive System
Findings (RP)

Subject Status (SS) Tumor Results (TR),
Tumor Identification
(TU)

Findings About
Findings About (FA)

Trial Design Domains

Trial Inclusion/Exclusion Criteria (TI)
Trial Disease Assessment (TD)
Trial Visits (TV)

Common Domains

Special Purpose Domains

Comments (CO)
Demographics (DM)
Subject Elements (SE)

Interventions General Observation Class

Exposure (EX)

Events General Observation Class

Disposition (DS)

Findings General Observation Class

Death Details (DD) Laboratory Test
Results (LB)
Microscopic Pharmacokinetic
Findings (MI) Concentrations (PC)
Pharmacokinetic Subject Characteristics (SC)
Parameters (PP) ECG Test Results (EG)
Vital Signs (VS)

Trial Design Domains

Trial Elements (TE)
Trial Summary (TS)
Trial Arms (TA)

Relationship Datasets

Related Records (RELREC)
Supplemental qualifiers
(SUPP-) datasets

SEND Domains (only)*

Findings General Observation Class

Body Weight (BW)
Body Weight Gain (BG)
Clinical Observations (CL)
Food and Water Consumption (FW)
Macroscopic Findings (MA)
Organ Measurements (OM)
Palpable Masses (PM)
Tumor Findings (TF)
Cardiovascular Test Results (CV)
Respiratory Test Results (RE)

Trial Design Domains

Trial Sets (TX)

Relationship Datasets

Pool Definition (POOLDEF)

* DART 1.0 domains not included

Trial Design

FDA Study Data Technical Conformance guide V5.0 states

“The Trial Summary (TS) dataset will be used to determine the time of study start. The requirement to submit using a particular study data standard is dependent on its support by FDA as listed in the Catalog at the time of study start. TSPARMCD = SSTDTC will allow the determination of the study start date and should be included in all SDTM submissions. Sponsors submitting legacy data (See section 8.3.2) should provide a TS dataset (ts.xpt) which includes the study start date in the form of SSTDTC (TSPARMCD = SSTDTC) and TSVAL= ‘yyyy-mm-dd’”

- Clinical studies use
 - All Trial Design datasets except Trial Sets (TX)
- Nonclinical studies use
 - Trial Arms (TA), Trial Sets (TX), Trial Elements (TE) and Trial Summary (TS)
- FDA has announced the addition of Technical Rejection Criteria to the existing eCTD validation criteria to ensure study data conformance validation. One of the checks is “Trial Summary (TS) dataset must be presented for each study in Module 4 or 5.”

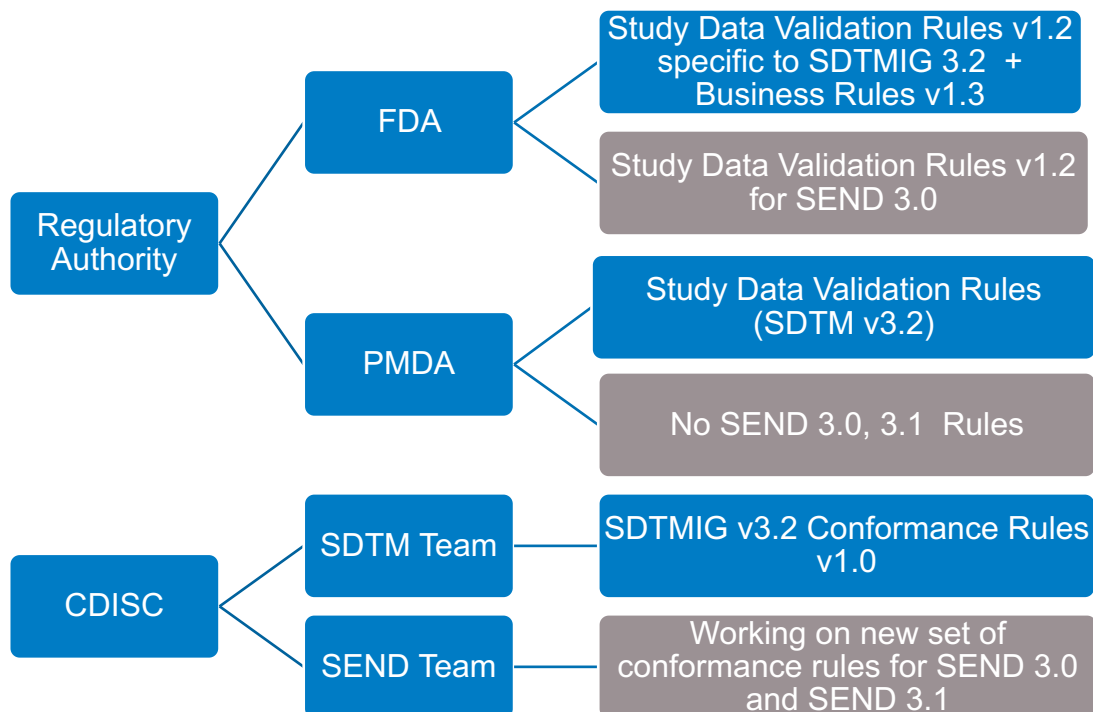


For more information on FDA Technical Rejection Criteria:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf>

Validation Checks

- Checks the conformance to CDISC Model
- Validator Tools available check compliance or conformance to CDISC Standards (SDTMIG, SEND, ADaM, Define-XML)
- Validation report generated produces the results of validation. These findings should be explained in the Study Data Reviewers Guide.
 - *FDA suggests cSDRG for clinical and nSDRG for nonclinical*



Best Practices

- Keep track of the
 - commonly released agency documents
 - understand what constitutes a requirement versus a guidance
 - released CDISC Implementation Guides (IGs) and related documents
- At Shire, we established a Data Standards Governance Model
 - provides a cross-functional forum for discussing specific needs and solutions
 - helps to propagate throughout the organization some of the challenges discussed in industry forums (e.g. PhUSE, CDISC)
- Volunteer in CDISC and/or PhUSE groups to learn and collaborate on how to handle such changes.

Best Practices

- Understand external CRO partner and vendor capability
 - how they affect the submission-ready package creation
 - ensure proper oversight capabilities to ensure quality and timing of the deliverables
- Industry Resources available
 - collaborate with groups or SMEs who support delivery of standardized data on clinical and nonclinical studies to understand the intricacies of the model and implementations
 - attend courses/webinars to develop topic-specific skills and learn about the changes

Conclusion

- Understand the **agency requirements** for data standards, changing landscape of CDISC, and internal company needs
- As SEND is fairly new requirement to the industry. Organizations have to create new processes to support this requirement.
 - Helpful to **collaborate** with clinical teams as they are submitting standardized study data (SDTM) since 2004
 - Understand **deliverables** and oversee the vendors
- Sponsor organizations have to build processes that are **lean and adaptable** to this changing landscape which can support global standardized study data submissions.
- Consistent use of format and standard within the nonclinical and clinical modules supports regulatory agencies review times. Having a **robust Data Standards Governance** process, supports overall standards development and helps to ensure quality data submissions.