Regulatory Submissions, Information, and Document Management Forum

February 10-12 2020 | North Bethesda, MD

FDA Plenary Session

Ron Fitzmartin, Office of the Director, CBER (chair)

Ray Wang, Office of Strategic Programs, CDER

Scott Gordon, Office of Strategic Programs, CDER

Ethan Chen, Office of Business Informatics, CDER

DIA

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From Commissioner Stephen Hahn (30 Jan 2020)

*"One of the most important resources for our work lies in the **power of data**. I strongly believe that we need to do everything we can to **attain more and better data** for the work we're doing, to be more proactive in gathering data, and to be more creative and thorough in our analysis of it.*

*"By harnessing this power, we can **improve our regulatory decision-making**…"*

Data & Terminology Standards in the Medicinal Product Development Lifecycle*

RESEARCH

INVESTIGATIONAL

REGULATORY REVIEW

POST-MARKET

* Examples of standards used in product development

CDER-CBER Data Standards Program Overview

Ray Wang
Team Lead
Data Standards Program
Office of Strategic Programs
Center for Drug Evaluation & Research

CBER - CDER Data Standards Mission

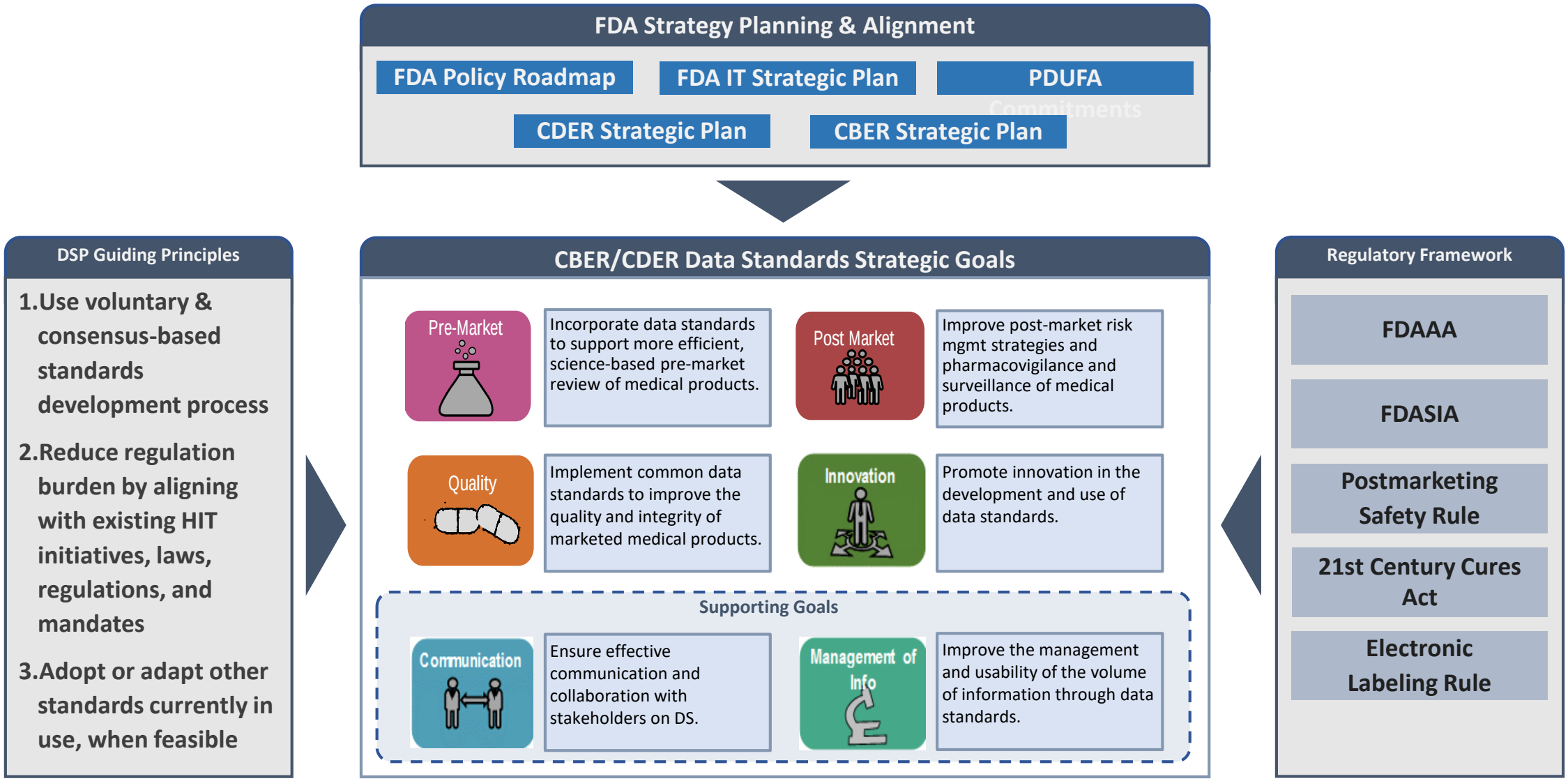
The FDA CDER Data Standards Program promotes electronic information exchange standards and terminologies to enable the effective and efficient use of regulatory submissions through stakeholder collaboration, policy development, and project implementation.

Develop

Collaborate

Implement

CBER - CDER Data Standards Strategic Goals



Goal 1: Pre-Market Standards *(Example Projects)*

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

Therapeutic Area (TA) Assessments

- Priority TAs identified by CDER that could benefit from further standardization, and is developed through the Coalition for Accelerating Standards and Therapies (CFAST) initiative using CDISC standards.

Standard for Exchange of Nonclinical Data (SEND)

- SEND is the nonclinical implementation of the CDISC Study Data Tabulation Model. It provides a format that is standard, predictable and consistent across studies and submissions.
  - Required by CDER in NDAs, ANDAs, BLAs, and INDs, but, currently, not by CBER.
  - Joint CBER-CDISC-Industry expert working team formed to evaluate SEND to support the needs of CBER nonclinical reviewers.
  - Initiated a proof of concept with industry to gain experience with SEND, explore ways to review data in the standard, and to leverage common analytic tools.

Goal 1: Pre-Market Standards *(Example Projects)*

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

Clinical Outcome Assessment (COA) Project

- COAs capture patient experience data in Phase I-III of clinical trials in drug development programs. CDER's project is focused on the development and evaluation of COAs submitted in support of regulatory submissions.

Goal 2: Post Market Standards *(Example Projects)*

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

FDA Adverse Event Reporting System (FAERS) Program

- FAERS is a mission critical system for FDA and supports CDER/CBER's post-marketing safety surveillance program for all marketed drug and therapeutic biologic products.
  - The FAERS II program was initiated with the goal of implementing a digital framework for pre and post marketing safety reports with enhanced data analytics and signal management lifecycle solutions.
  - All phases of IND Safety Report Pilot are complete; Draft IND Safety Report Guidance published

Identification of Medicinal Products (IDMP) Project

- 5 related standards (MPID, PhPID, SubID, Dosage Form, Units) that are used together to define, characterize, and uniquely identify regulated medicinal product for human use across different regions. Several national regulators are collaborating with the end-goal of global implementation of this standard.

Goal 3: Quality Standards *(Example Projects)*

Implement common data standards to improve the quality and integrity of marketed medical products.

Pharmaceutical Quality / Chemistry Manufacturing and Control (PQ/CMC) Project

- Cross-Center initiative involving reviewers from CDER, CBER and CVM with a goal of establishing electronic standards for submitting PQ/CMC data.
  - Develop standardized data elements, terminologies, and data structures for PQ/CMC submissions.
  - Implement a data exchange standard for submitting PQ/CMC data.
  - Industry Proof of Concept testing of FHIR underway.
  - Project Opportunity Proposal to ICH for standardized Quality data underway.

Post Approval Changes Submission Standards

- This CBER-CDER project is focused on improving submission requirements to ensure that essential facility, production information, and an up-to-date view of the CMC process are captured completely, and in a format that is conducive to electronic receipt, storage and usage.

Goal 4: Innovation *(Example Projects)*

Promote innovation in the development and use of data standards.

Biomedical Research Integrated Domain Group (BRIDG) Initiative

- The BRIDG model represents a shared view of the concepts of pre-clinical, clinical, and translational research, and is also being used to support development of interoperable data exchange standards and technology solutions.

Real World Evidence / Real World Data

- eSource Data - CDER is supporting two 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.
- eSource (FHIR Accelerator) – Joint effort with Industry stakeholders and government agencies to plan and implement FHIR accelerated projects that the FDA will participate in.
- Common Data Model Harmonization (CDMH) project – Collaborative effort involving NCATS, NCI, NLM, the ONC and is led by FDA, with an objective of creating a proof of concept solution that enables a researcher to make a single query usable across data from four distinct CDM research formats.

Goal 5: Communication *(Example Projects)*

Ensure effective communication and collaboration with stakeholders on data standards.

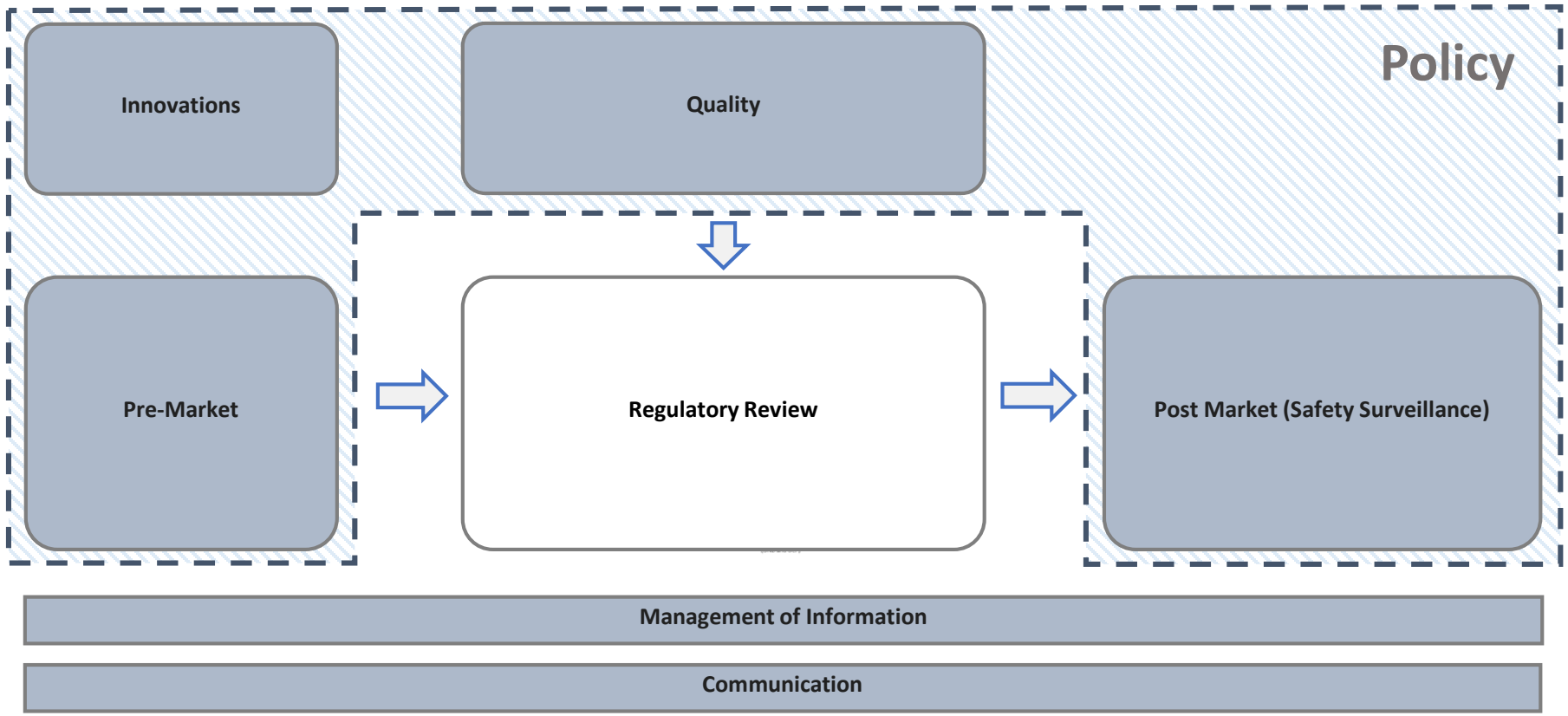
- Technical Rejection Criteria for Study Data – Specifies the conformance requirement for study data submissions.
- Data Standards Catalog – Lists the data standards and terminologies that FDA supports for use in regulatory submissions.
- Technical Conformance Guide – Provides specifications, recommendations and general considerations on how to submit standardized study data using standards listed in the data standards catalog.
- Conferences, Public Meetings, Webinars

Goal 6: Management of Information

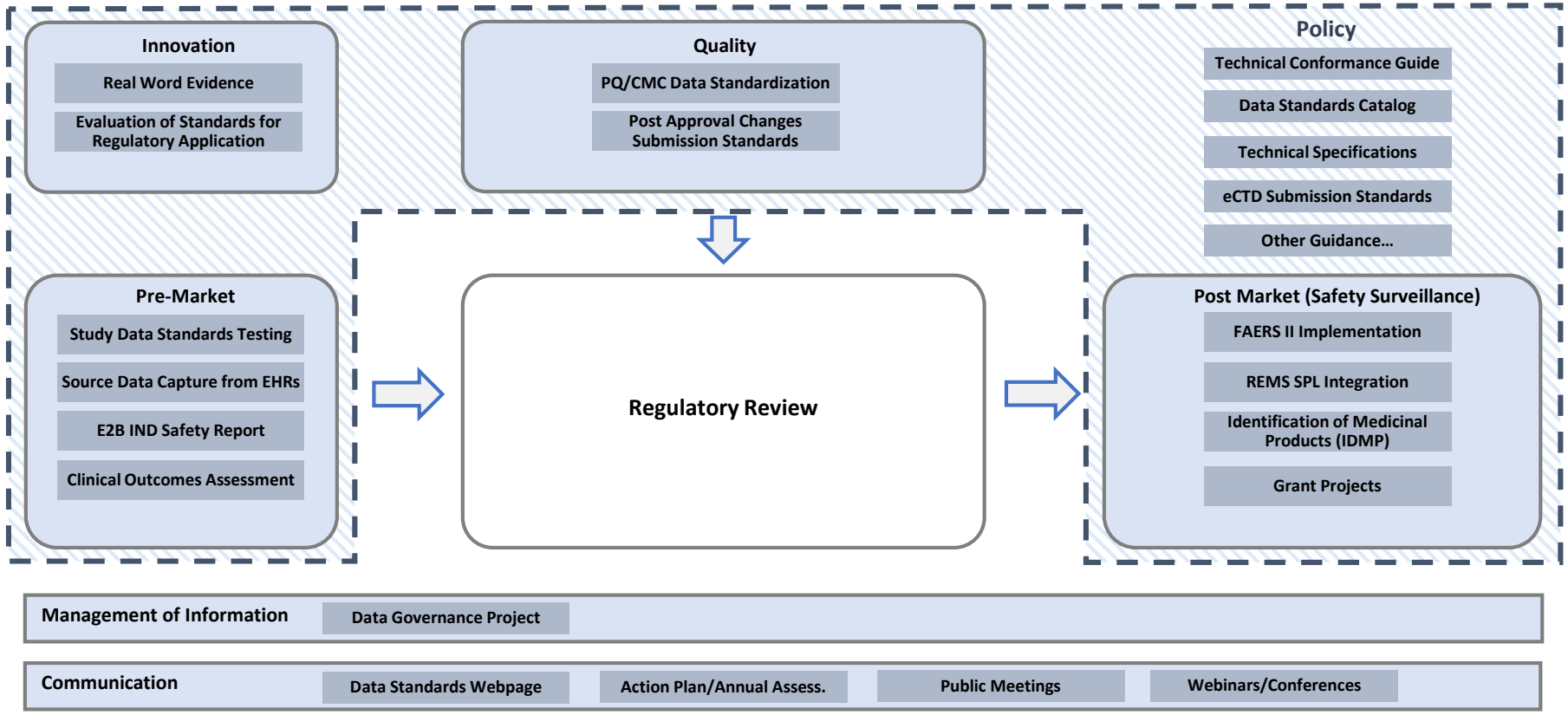
Improve the management and usability of the volume of information through data standards.

- Data Governance – Develop an operating model to manage business/informatics decisions involving regulatory submission data and metadata, and support the implementation of this data governance framework across CDER.

Data Standards Program Operating Environment

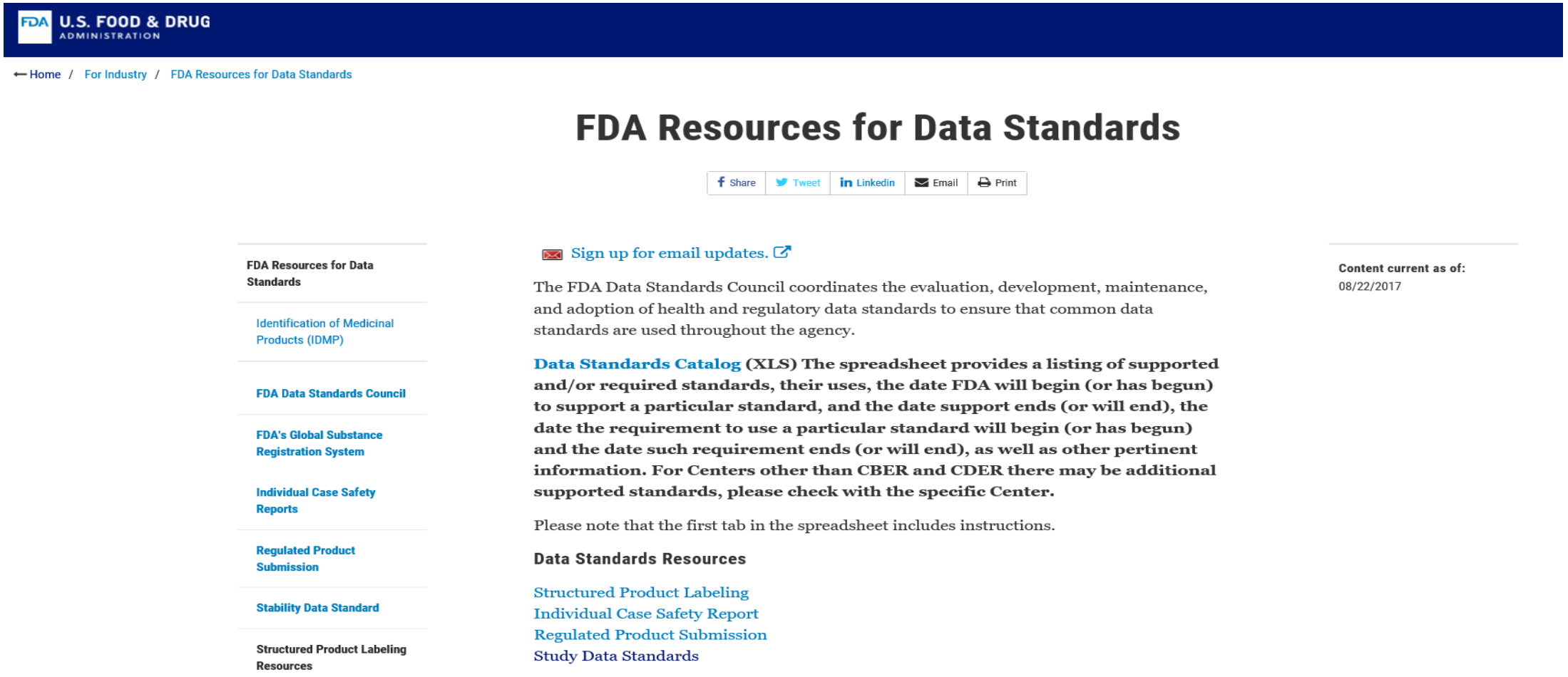


Data Standards Program *(Externally Published Projects)*



Data Standards Program Resources

- [FDA Resources for Data Standards](https://www.fda.gov/industry/fda-resources-data-standards) *(https://www.fda.gov/industry/fda-resources-data-standards)*



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← Home / For Industry / FDA Resources for Data Standards

FDA Resources for Data Standards

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FDA Resources for Data Standards

Identification of Medicinal Products (IDMP)

FDA Data Standards Council

FDA's Global Substance Registration System

Individual Case Safety Reports

Regulated Product Submission

Stability Data Standard

Structured Product Labeling Resources

Sign up for email updates.

The FDA Data Standards Council coordinates the evaluation, development, maintenance, and adoption of health and regulatory data standards to ensure that common data standards are used throughout the agency.

Data Standards Catalog (XLS) The spreadsheet provides a listing of supported and/or required standards, their uses, the date FDA will begin (or has begun) to support a particular standard, and the date support ends (or will end), the date the requirement to use a particular standard will begin (or has begun) and the date such requirement ends (or will end), as well as other pertinent information. For Centers other than CBER and CDER there may be additional supported standards, please check with the specific Center.

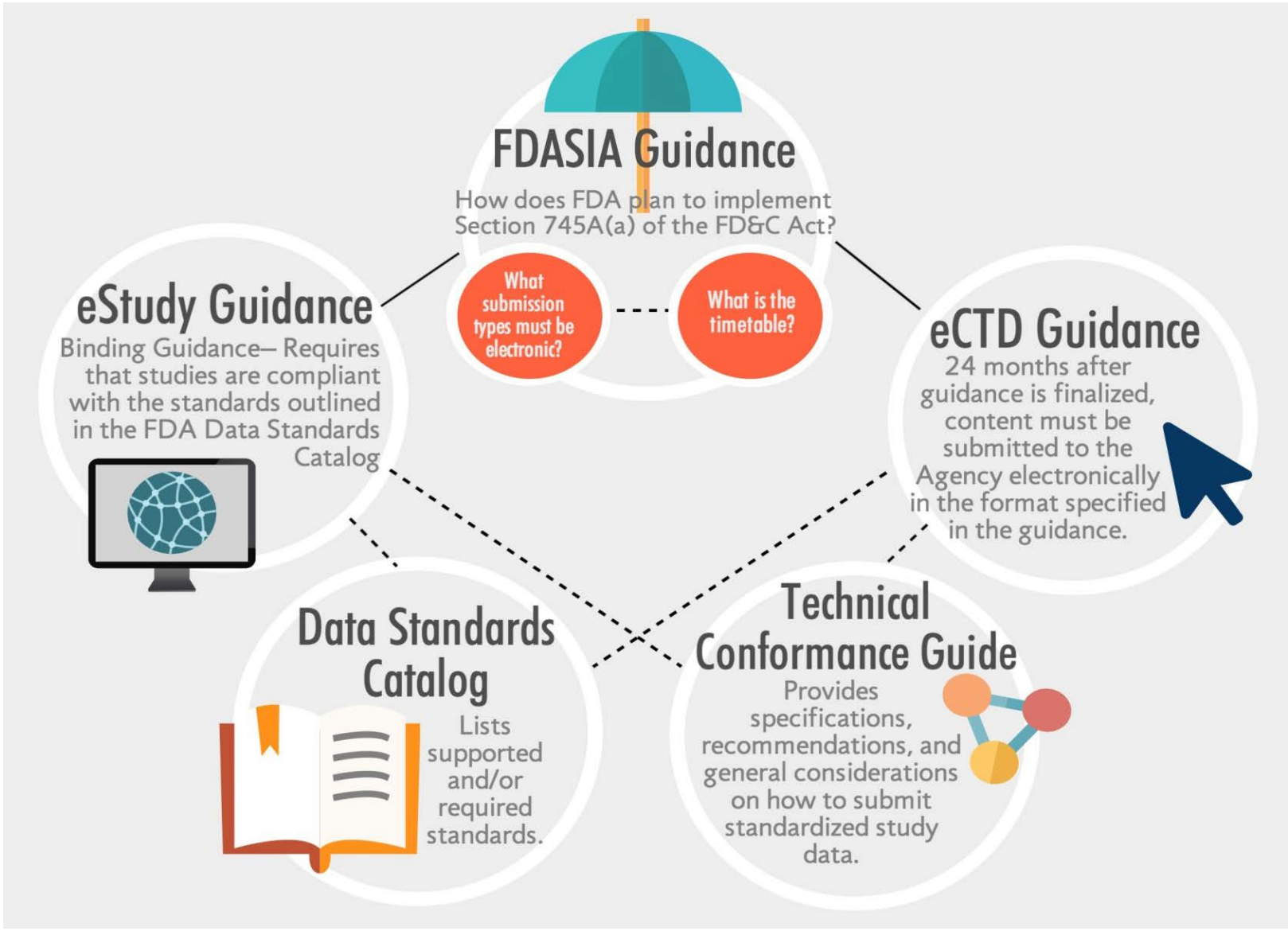
Please note that the first tab in the spreadsheet includes instructions.

Data Standards Resources

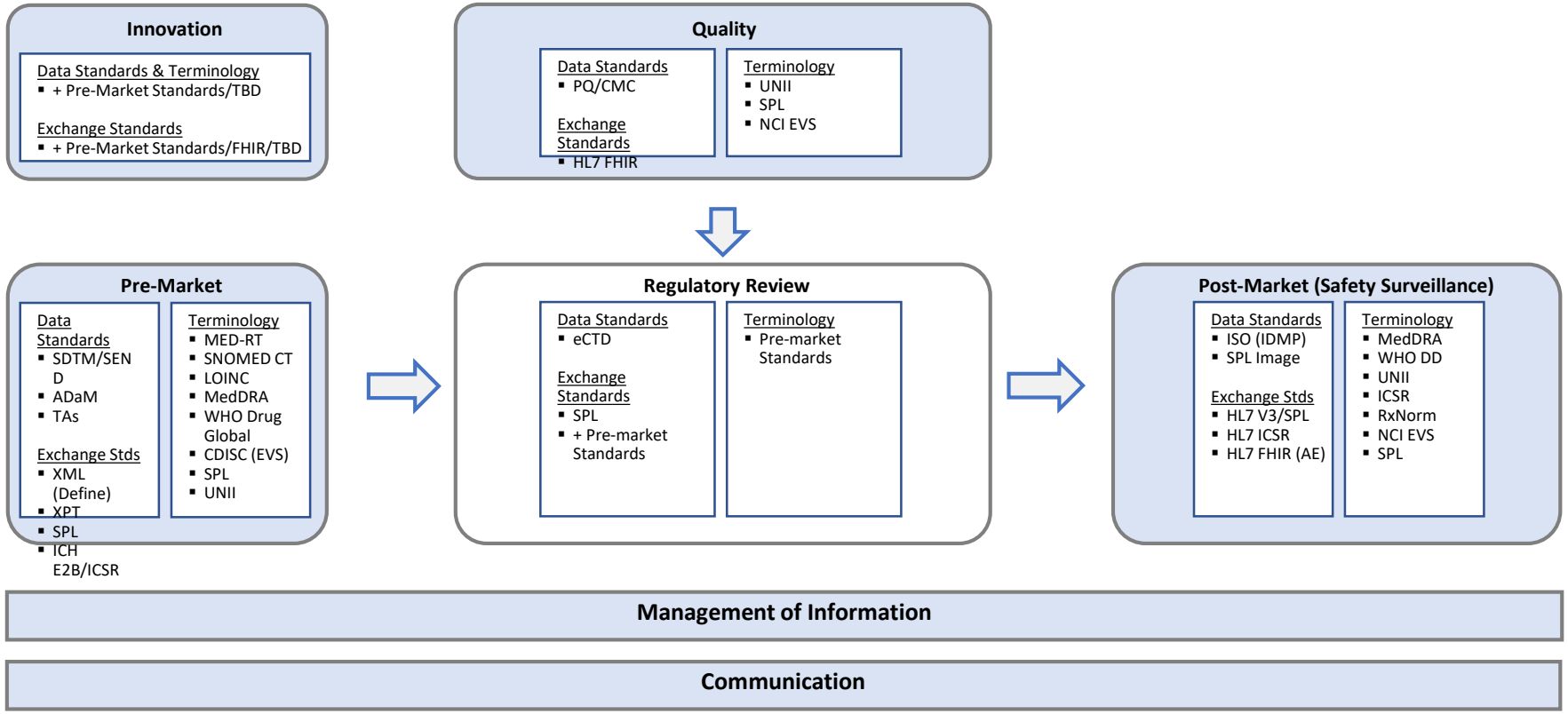
Structured Product Labeling
Individual Case Safety Report
Regulated Product Submission
Study Data Standards

Content current as of:
08/22/2017

FDASIA Guidance Implementation Highlights



DSP – Data Standards View



The Implementation of Structured Product Labeling (SPL) in HL7 FHIR

Gideon Scott Gordon, PhD
Senior Health Informatics Officer
Office of Strategic Programs
Center For Drug Evaluation and Research

February 10, 2020

SPL FHIR Implementation - Background

- SPL is critical and heavily utilized at FDA
- SPL is currently implemented in HL7 V3 (Version 3)
- HL7 V3 data exchange format was intended as the next generation HL7 message standard
- However, HL7 V3 is being superseded by HL7 FHIR (Fast Healthcare Interoperability Resources)
  - Risk of reduced tools and implementation support for V3 technogies
- FDA is conducting an assessment of SPL implementation in FHIR
  - Ensure sustainability and uninterrupted support for SPL use cases
  - Support the exchange of product data with international regulators
    - E.g. EMA and Health Canada
- Early planning underway to ensure a transition that will be gradual and deliberate
  - Concurrent support for both formats until full adoption

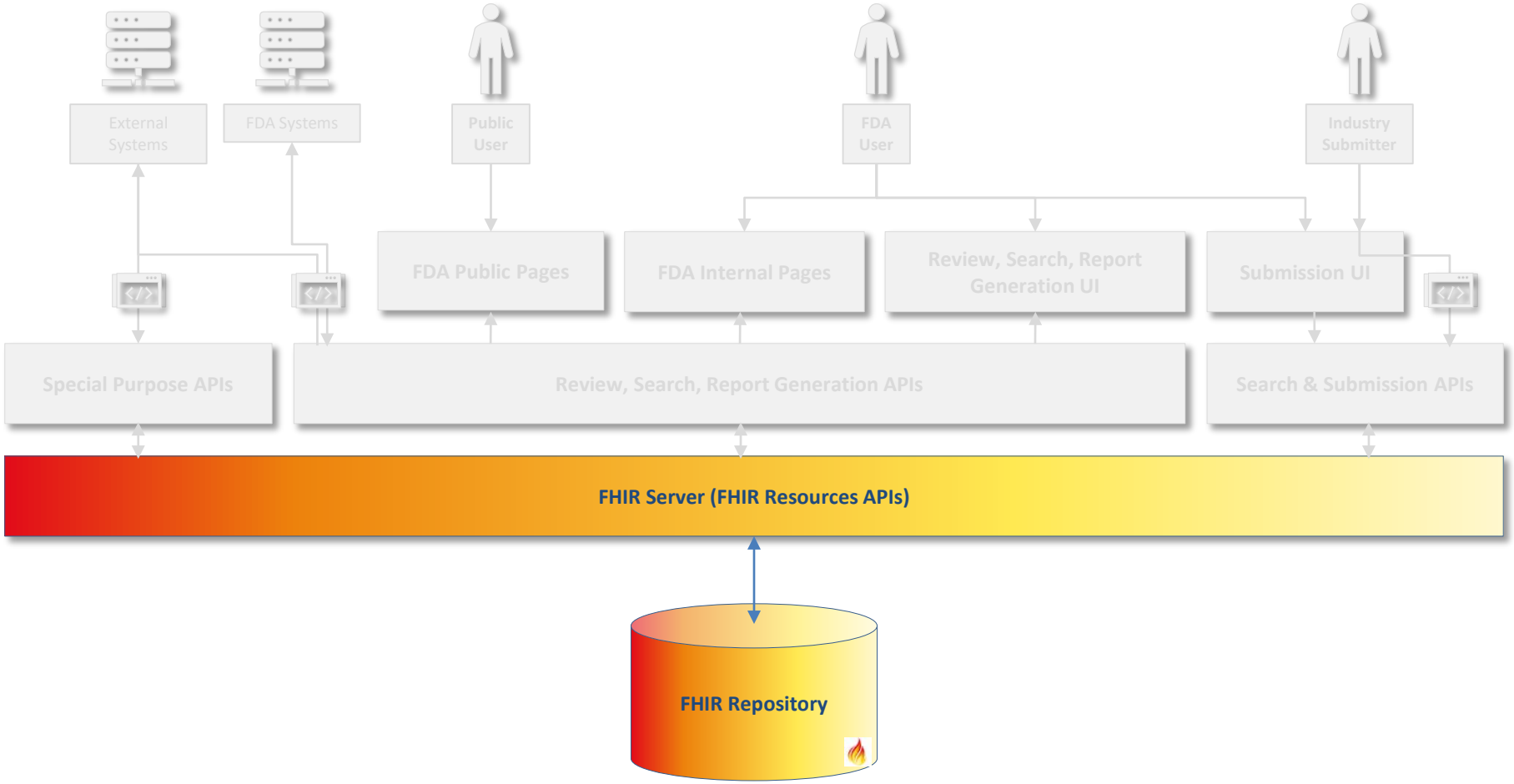
The Primary Focus on the Label Use Case

- **Submit a Drug or Biologic Label**
- Request an NDC Labeler Code
- Register an Establishment
- Submit GDUFA Facility Self-Identification
- Submit Lot Distribution Data (LDD)
- Submit Wholesale Drug Distribution Reports
- Submit a Device Label
- Submit SPL Index documents
- Submit Risk Evaluation and Mitigation Strategies Document

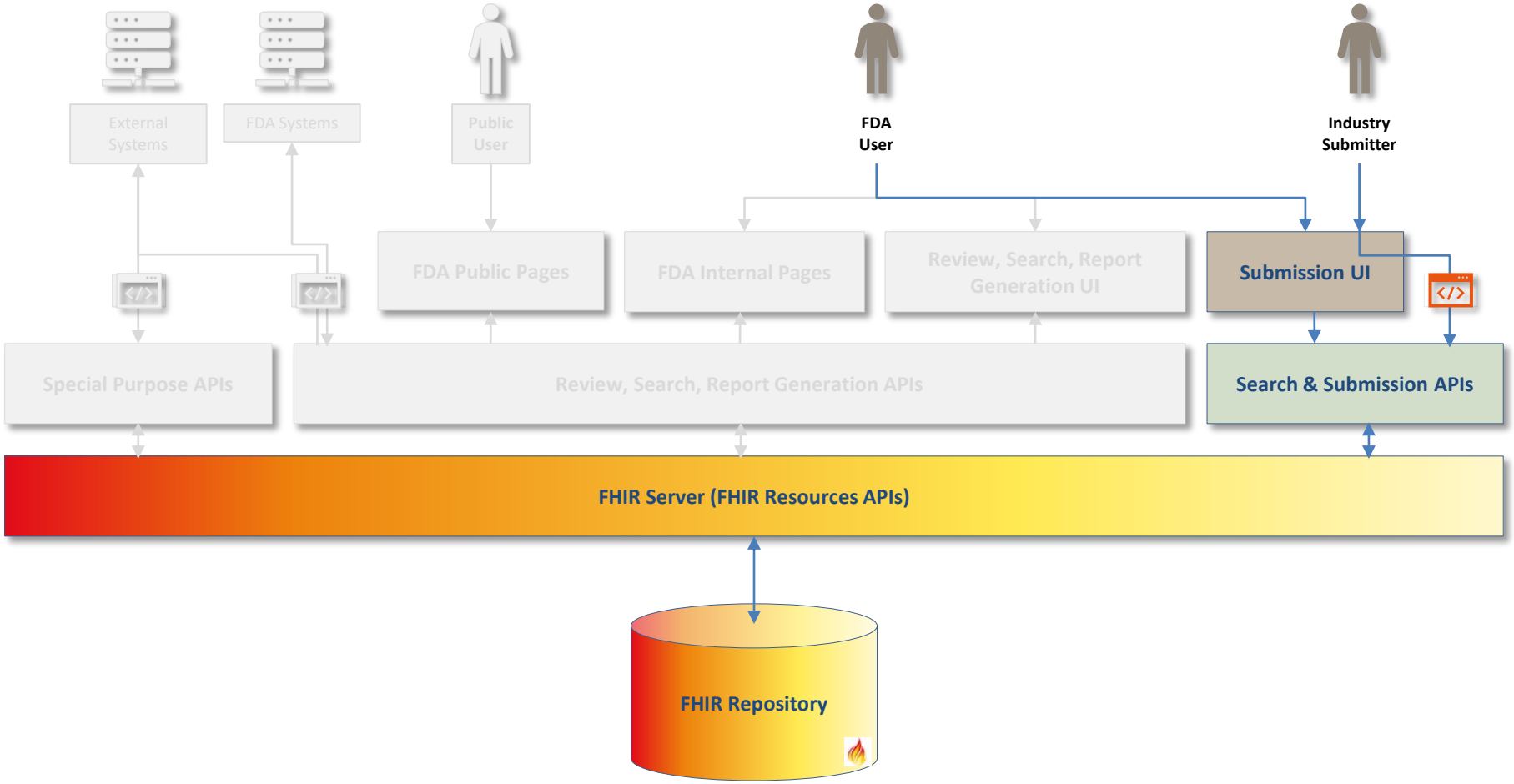
Proposal for transitioning from V3-based messaging to FHIR-based

- Long-term multi-phase transition
  - Ample transition period with data available in both V3 and FHIR formats
  - No disruption to the systems relying on SPL (e.g. Drugs@FDA, DailyMed)
- Phase I – Enable dual submissions
  - Submissions, validation, storage, integration with other systems
  - Data synchronization between the old and the new environments
    - Convert FHIR submissions to SPL V3 after they are validated and stored in the FHIR repository,
- Phase II – Implement reporting requirements
  - Search, review, and reporting on FHIR submissions (FDA internal)
  - Integration with other FDA systems
- Phase III – Complete transition to SPL-FHIR
  - Publishing of SPL data to external websites in FHIR format
  - Enable all system interfaces in FHIR

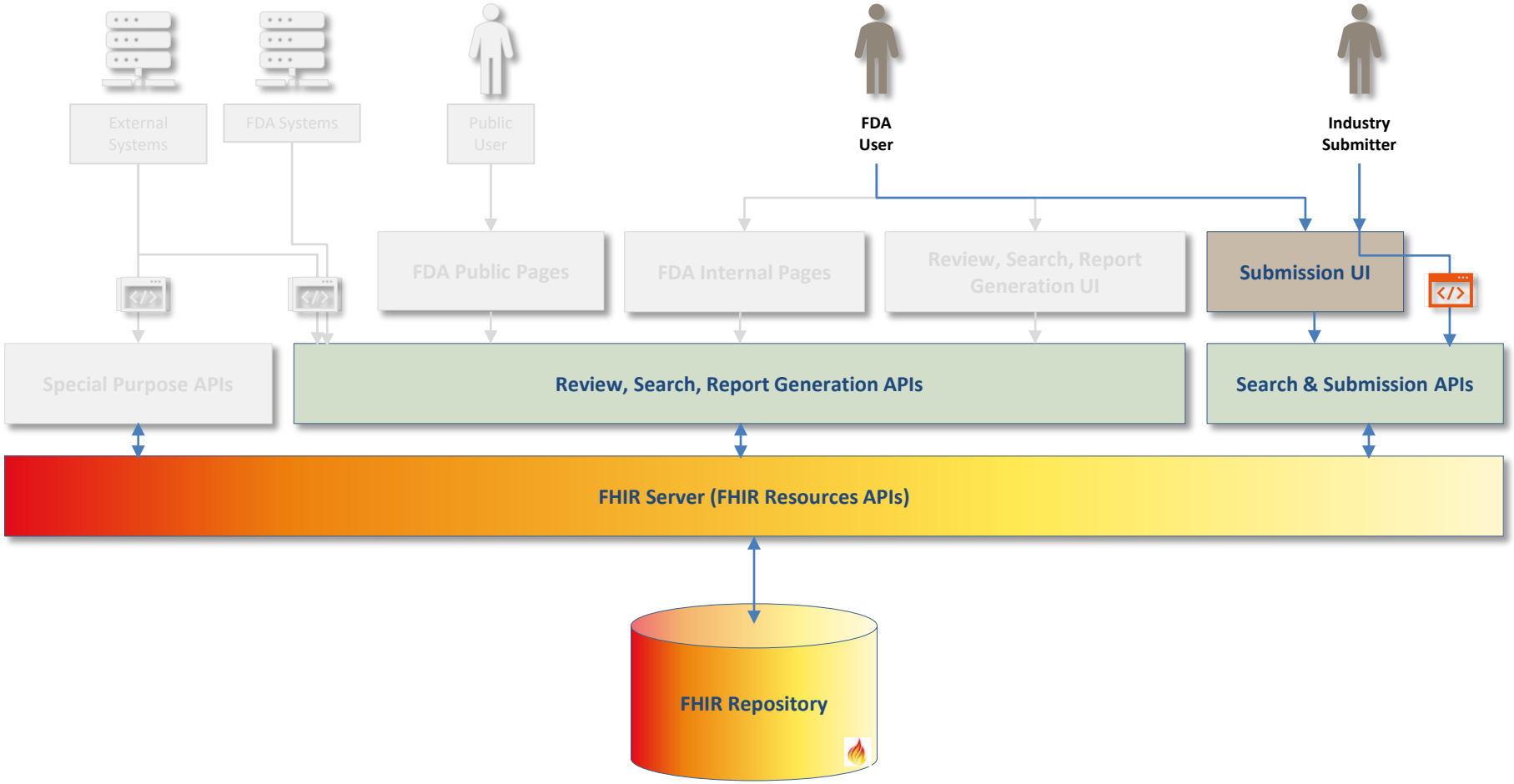
Develop FHIR Repository and Resources API



Develop FHIR Submission Capability (IU and API)



Develop Review, Search, and Report Generation



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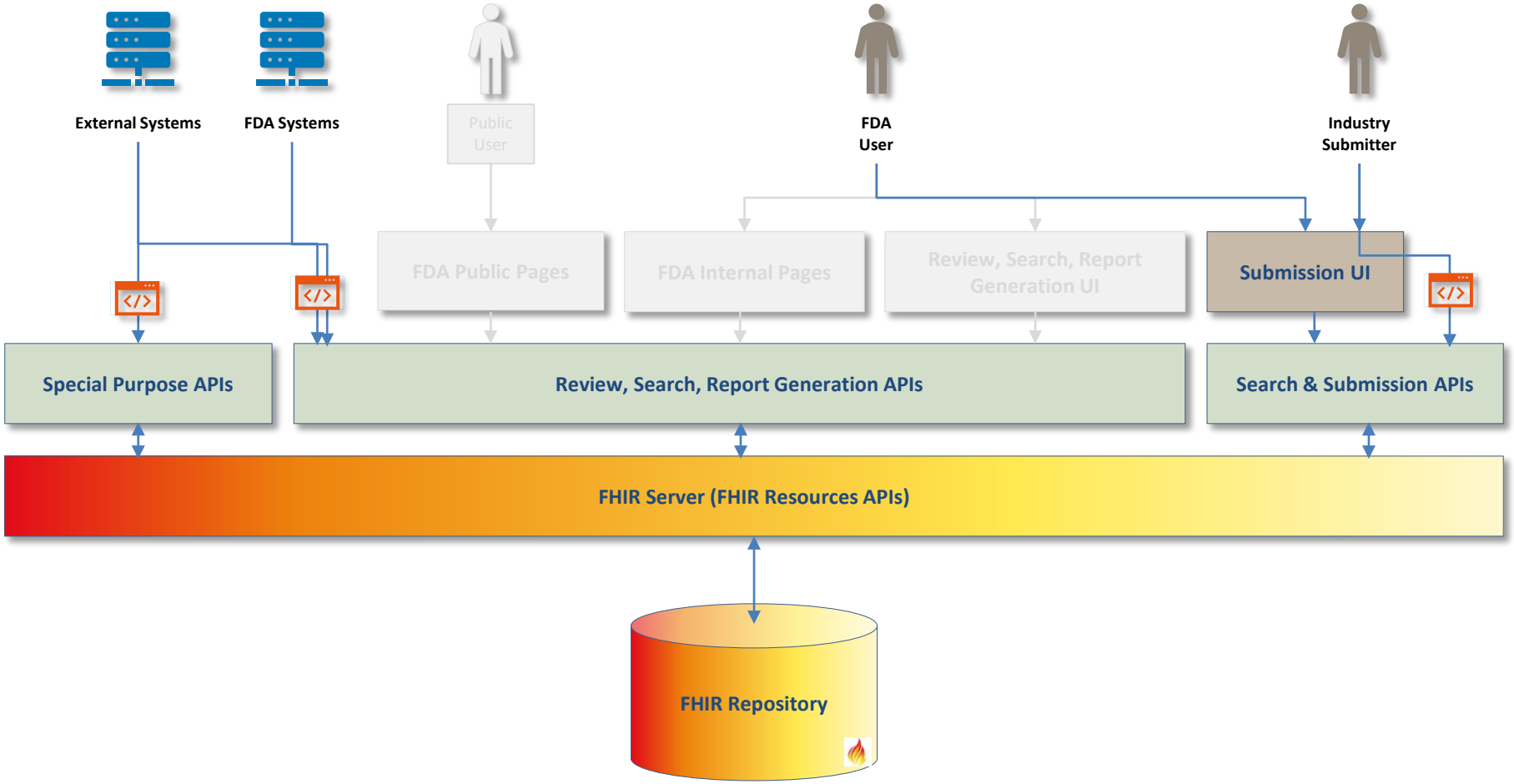
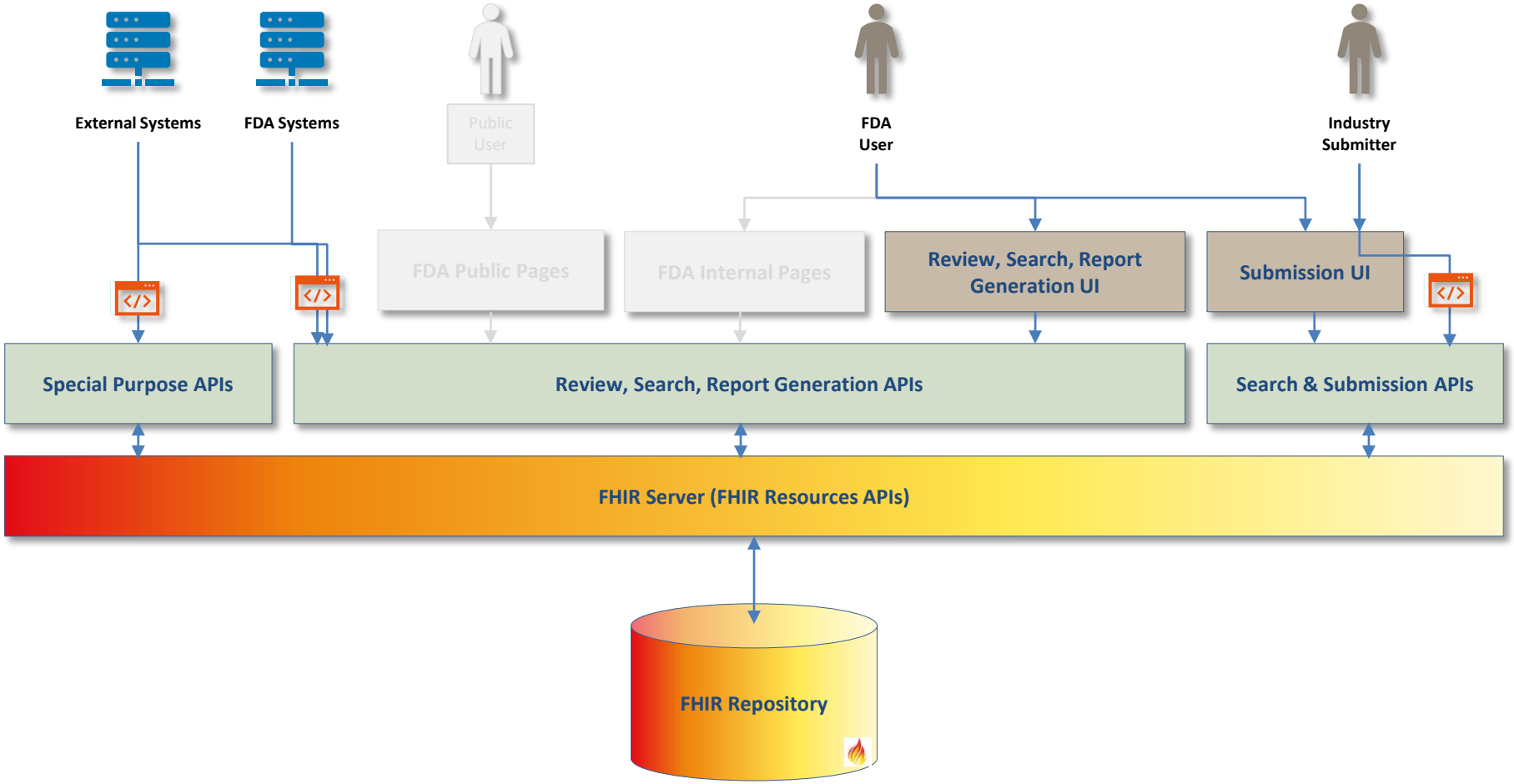
Develop Integration with FDA and External Systems*

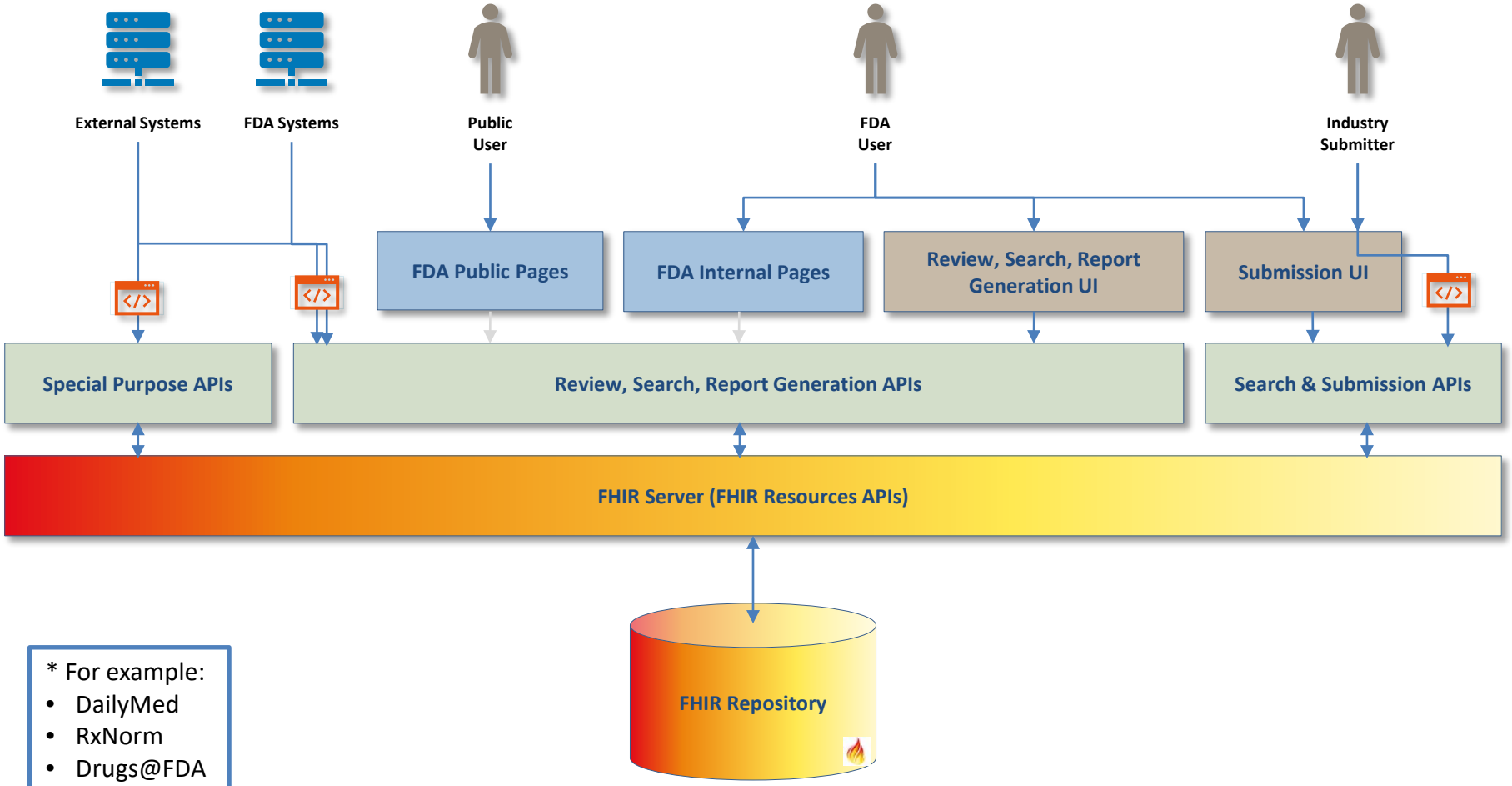


(*) For FHIR Submissions Validation Only)

Develop Review, Search, Reports IU



Develop Data Feed To All Websites*



* For example:
- DailyMed
- RxNorm
- Drugs@FDA

Next Step in the SPL FHIR Implementation

- Detail and finalize an architectural approach to the FHIR implementation of labeling submissions
- Conduct gap analysis between the present SPL requirements and the existing HL7 FHIR resources
- Prototype an architectural design
  - Ensure no interference with the present SPL capabilities
  - Support full integration of the data submitted via the new FHIR pathway and the present V3 submissions
- Implement a limited proof-of-concept
  - Use real industry-sourced data to receive, process, validate, and distribute a FHIR-based electronic label
  - Demonstrate functional equivalence to the SPL mechanisms
- Identify new labeling use cases to implement in FHIR

Potential Advantages of the Transition

- Reduces complexity of current submission process
- Has the flexibility to adapt to new products characteristics
- Allows for advanced submission functions
- Opens integration opportunities:
  - Simplify management of organizations data within the FDA
  - Facilitate Integration with OND label reviews operations
  - Better integration with other centers' product label system
- Eliminates duplicate storage and processing of label data
- Potentially allows for integration with clinical trial data

Advantages of Proposed Implementation Approach

- Gradual parallel implementation
- Gradual introduction of FHIR submissions
- No disruption to current systems
- Least interruptions to current users
- Allows for ample, and extensible, adaptation period

Technical Rejection Criteria for Study Data

Ethan Chen
Office of Business Informatics
Center for Drug Evaluation and Research

Agenda

- Study Data Technical Rejection Criteria (SDTRC)
- Study Data Conformance Statistics (CY2018 and CY2019 Q1-Q3)
- Revised Technical Rejection Criteria for Study Data (Oct. 2019)
- Study Data Conformance Analysis (CY2019 Q4)
- New Tools for Industry
- Implementation Timeline
- Summary

Purpose of eCTD and Study Data Requirements

- Reviewing study data in a timely manner is critical for FDA's review process (e.g. Reviewers have 30 days to review an IND application)

- When sponsors submit data to the FDA in a reliable and accessible format, it improves efficiency and consistency of review decisions

- CDISC Standards enable FDA to streamline the review process:
  - Reduce time for reviewers to locate and identify study data
  - Reduce the burden on sponsors and reviewers from IRs (Information Requests)
  - Reduce review time by enabling the use of COTS reviewer's tools such as JReview, JMP Clinical, etc. to automate review analyses
  - Support data driven decisions by applying data mining and data analytic techniques

"The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities."

Source: https://www.ich.org/products/ctd.html

FDA Guidance and Data Standards Catalog

- **Per FD&C Act Section 745A(a), drug application sponsors must use the standards defined in the FDA Data Standards Catalog starting 24 months after final guidance for a specific submission type.**

- **FDA issued "Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry" in December 2014.**

- **Sponsors must conform to standards in the FDA Data Standards Catalog:**
  - NDA, BLA, ANDA studies that started after December 17th, 2016
  - Commercial IND studies started after December 17th, 2017

FDA Study Data Technical Rejection Criteria (SDTRC)

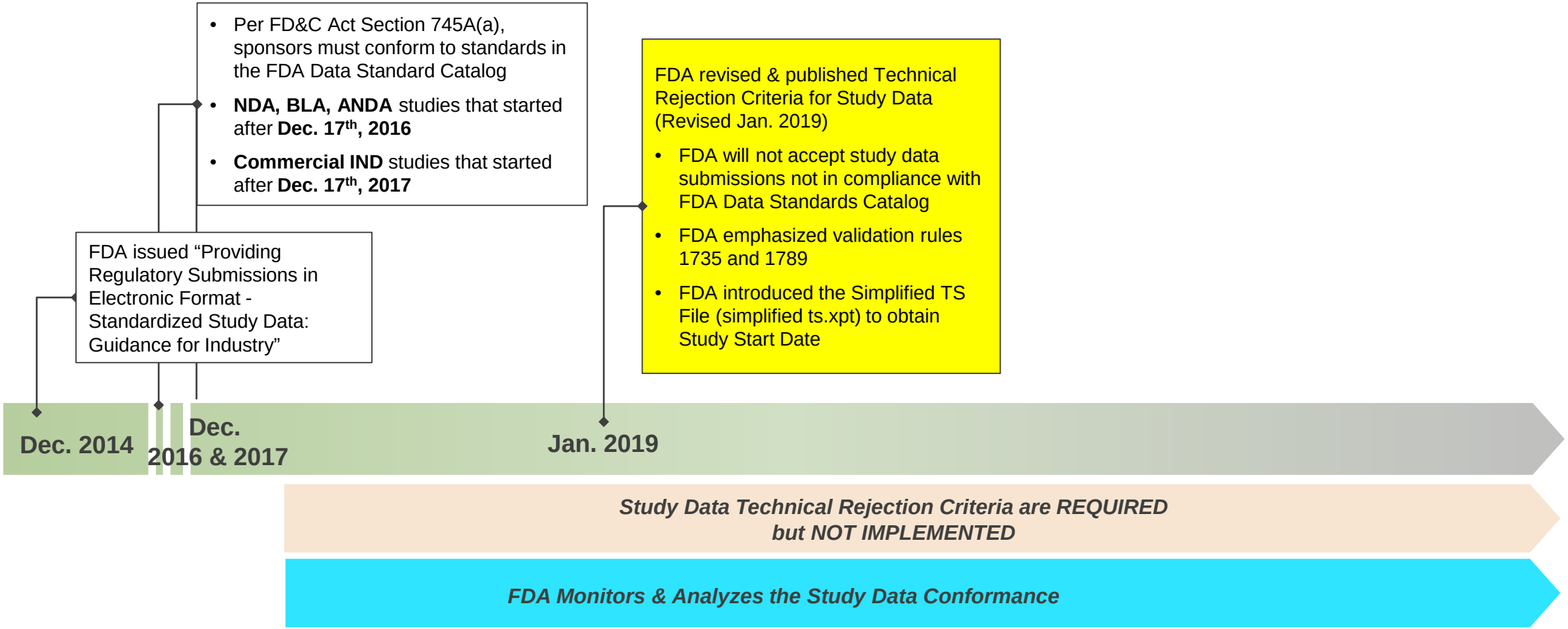
- Study Data Technical Conformance Guide provides technical recommendations for submitting study data according to CDISC standards
- Technical Rejection Criteria for Study Data provides the conditions under which FDA will not accept submissions with study data

Error	Description (Reference to FDA Study Data Technical Rejection Criteria Oct. 2019 version)	Severity Level
1734	A Trial Summary (TS) dataset (ts.xpt) with information on study start date (SSD) must be present for each study in required sections*	**High**
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*	**High**
1736	For SEND data, a DM dataset and define xml must be submitted in required sections* For SDTM data, a DM dataset and define.xml must be submitted in required sections* For ADaM data, an ADSL dataset and define.xml must be submitted in required sections*	**High**
1789	Study files must be referenced in a Study Tagging File (STF). STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.4 Literature references, and 5.3.6 Postmarketing reports	**High**

Technical Rejection Criteria Revisions Timeline

❖ FDA published Revised Study Data Technical Rejection Criteria in January 2019

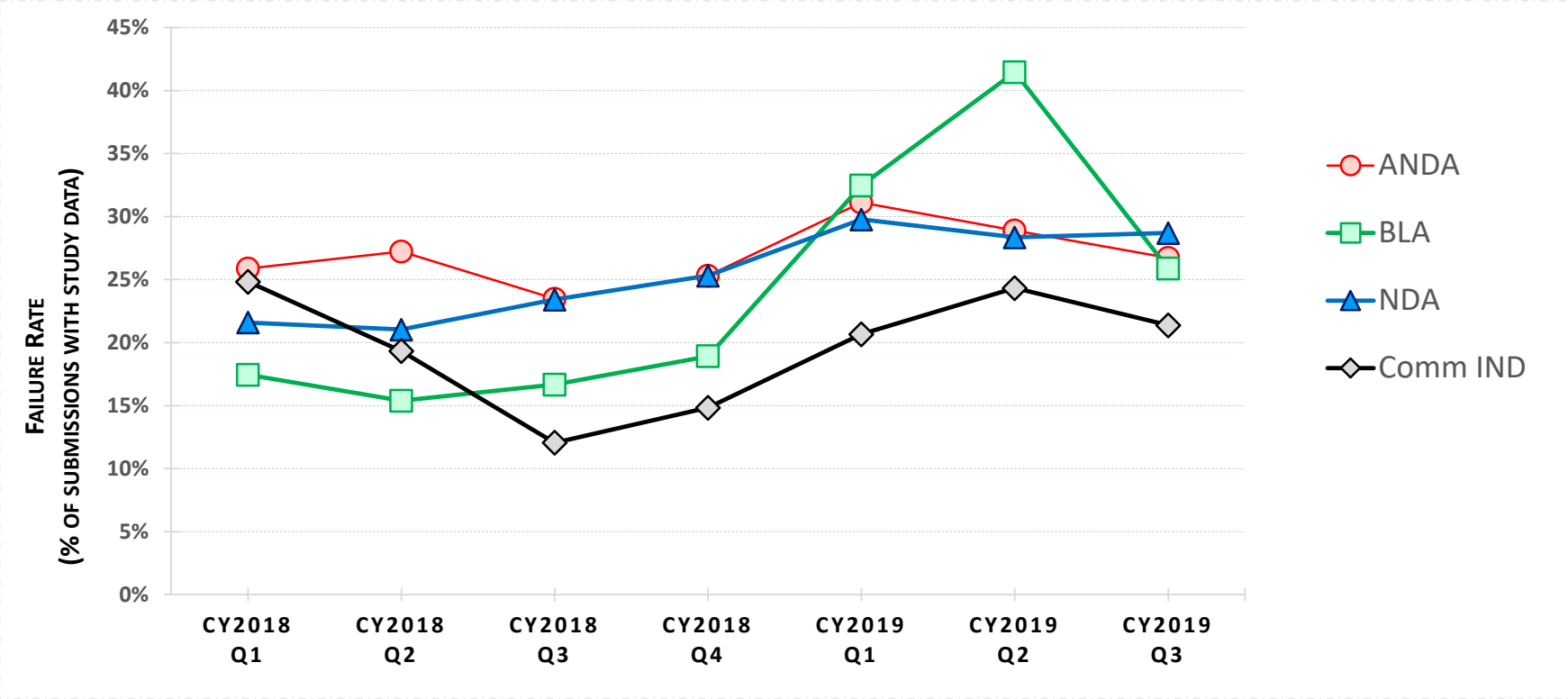
Note: When a submission is technically-rejected, the submission sequence is not transferred into the FDA electronic document rooms



Study Data Technical Rejection Criteria Conformance Statistics and Trend CY2018 and CY2019 (Q1-Q3)

CY2018 & 2019 Q1-Q3 Conformance Trend for Validation Errors 1734 & 1736

TRC validation failure rate have increased between Q1- Q3 2019 (based on TRC version Jan. 2019)



Notes:

1) CY2018 & CY2019 (Q1-Q3) analysis was conducted according to the TRC (Revised Jan. 2019)
2) Analysis includes NDA, BLA, ANDA and Commercial IND Sequence received by CDER between 1/1/2018 and 9/30/2019
3) Validation of error 1736 is not performed if a study has Error 1734
4) Definition of Study Data - .xpt files present in eCTD modules 4 or 5

2019 Q1-Q3 Conformance Analysis for Validation Errors 1734 & 1736

- ANDA, NDA, BLA, and Commercial IND Submissions received by CDER between 1/1/2019 and 09/30/2019, were assessed for conformance to the two high-level errors as revised in the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

		ANDA	BLA	NDA	Comm IND	All
a	**Total Number of Submissions with Study Data**	623	203	679	700	2205
b	**Total Number of Submissions with Study Data in TRC Applicable Sections**	582	161	533	645	1921
c	**Total Number Submissions with Critical Errors**	181	64	197	156	598
d	**Error 1734**	135	59	195	135	524
e	**Error 1736**	46	5	2	21	74
f	**Failure Rate (% among submissions with Study Data) [c/a]**	29.05%	31.53%	29.01%	22.29%	27.12%
g	**Failure Rate (% among submissions with Study Data in TRC Applicable section) [c/b]**	**31.10%**	**39.75%**	**36.96%**	**24.19%**	**31.13%**

Notes:

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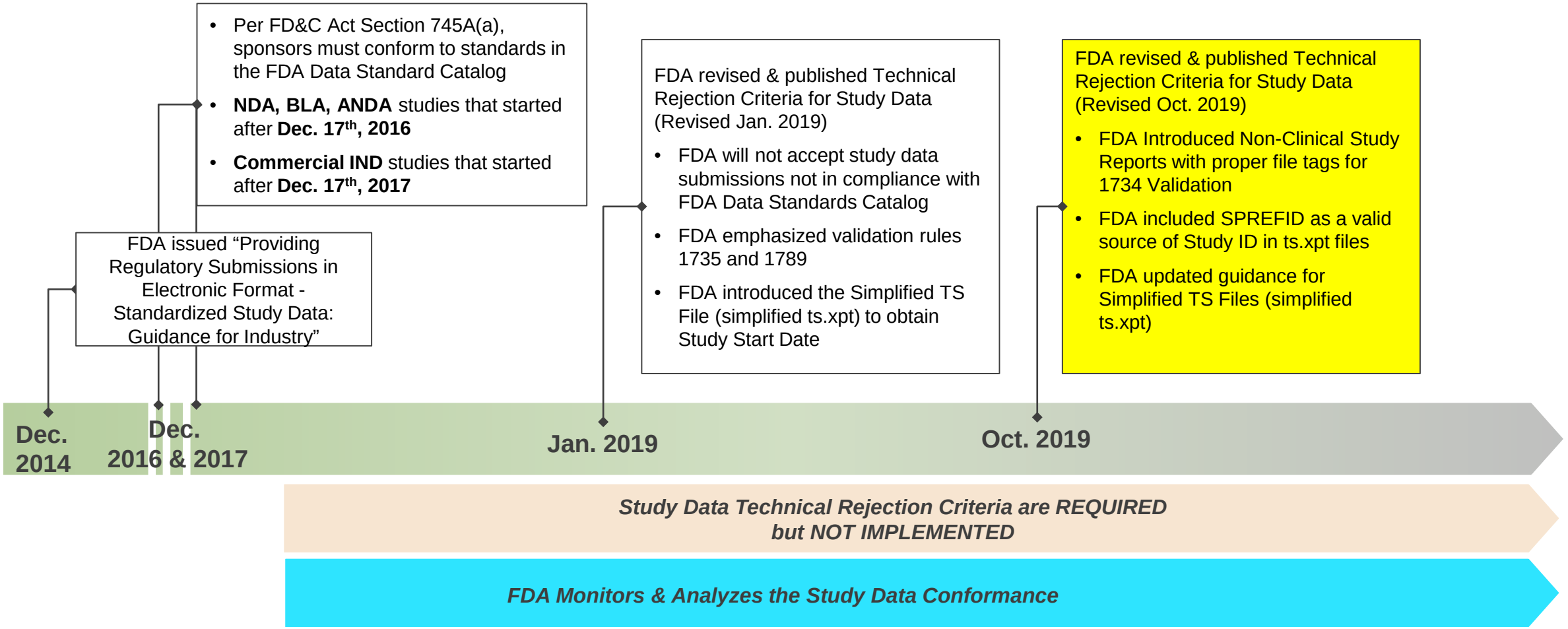
4) Definition of Study Data - .xpt files present in eCTD modules 4 or 5

Technical Rejection Criteria Revisions Timeline

❖ FDA published Revised Study Data Technical Rejection Criteria October 2019



Note: When a submission is technically-rejected, the submission sequence is not transferred into the FDA electronic document rooms

Qualification and Exemption for Non-Clinical Studies

- Nonclinical study that are required to qualify for TRC including any study in module 4 ECTD modules 4.2.3.1, 4.2.3.2, or 4.2.3.4 that includes one of the one of the following three file tags

‘pre-clinical-study-report’ | ‘legacy-clinical-study-report’ | ‘study-report-body’

- The qualifying non-clinical study must be submitted according to SEND specification.
- Certain Non-Clinical studies are exempted for TRC (See Study Data Technical Conformance Guide Section 8.2.2 for details https://www.fda.gov/media/131872/download):
  - Non-Clinical Studies does not require SEND Data
  - Non-Clinical Study Initiation Dates not relevant
- A simplified ts.xpt must submitted for exempted Non-Clinical Studies as below:

STUDYID	TSPARMCD	TSVAL	TSVALNF
study ID in STF	STSTDTC		Use the value ‘NA’

SDTRC Revisions: Study Reports

Introduced the Study Report File Tag Criteria					
Study Start Date	**Application Type**	**Data Type**	**Study Sections**	**Expectation by Center**	
				CDER	**CBER**
Prior to or on 17-Dec-2017	Commercial INDs	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied
		Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1z, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will not be applied	
After 17-Dec-2017	Commercial INDs	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a full TS	Rejection criteria will not be applied
		Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3,	Rejection criteria will not be applied	
Prior to or on 17-Dec-2016	NDA, BLA, ANDA	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied if a study report with the proper file tags and/or an xpt file is submitted. Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	Rejection criteria will not be applied
		Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will be applied; submit a simplified TS if the study contains an xpt dataset (other than the ts.xpt)	
After 17-Dec-2016	NDA, BLA, ANDA	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	Rejection criteria will be applied; submit a full TS	Rejection criteria will not be applied
		Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rejection criteria will be applied; submit a full TS	

Included Additional Reference for Study ID Match

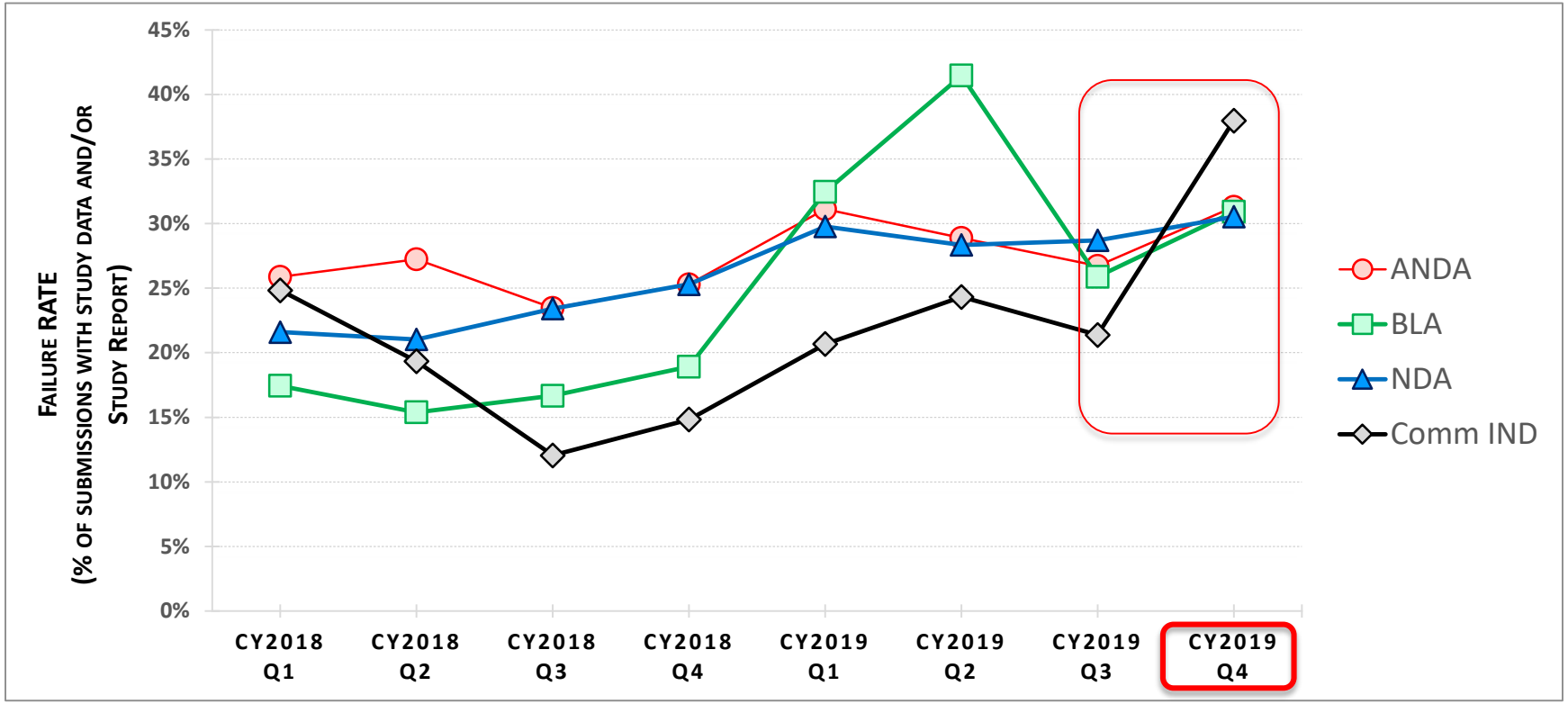
- Feedback from industry pointed scenarios where ts.xpt study-id may not be able to matched (Ex. when a study is bought by another company and the study id is already established)
- Proposed solution with feedback was inclusion of Sponsor Reference ID (SPREFID) parameter to match the STF study-id
- After analysis, SPREFID parameter matching with STF study-id added to October 2019 SDTRC revision

Included SPREFID for Study ID matching	
TRC January 2019	**TRC October 2019**
If a file is referenced within a study section in Module 4 or 5, a STF and ts.xpt must be present to identify the study ID and SSD to which the file belongs. The ts.xpt and STF need to contain matching study ID values.	If a file is referenced within a study section in Module 4 or 5, a STF and ts.xpt must be present to identify the study ID and SSD to which the file belongs. The ts.xpt needs to contain either a study ID (STUDYID) or Sponsor Reference ID (SPREFID) value that matches with the STF study ID.

Study Data Technical Rejection Criteria Conformance Statistics and Trend CY2019 (Q4)

CY2018 & CY2019 Conformance Trend for Validation Errors 1734 & 1736

- TRC Validation Conformance failure rate have increased in Q4 because of introduction of study reports for 1734 in the revised TRC (Oct. 2019)



Notes:

1) CY2018 & CY2019 (Q1-Q3) analysis was conducted according to the TRC (Revised Jan. 2019)
2) CY2019 (Q4) analysis was conducted according to the TRC (Revised Oct. 2019)
3) Analysis includes NDA, BLA, ANDA and Commercial IND Sequence received by CDER between 1/1/2018 and 12/31/2019
4) Validation of error 1736 is not performed if a study has Error 1734
5) M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in the submission
6) M5 Definition of Study Data - .xpt files present in the submission

2019 Q4 Conformance Analysis for Validation Errors 1734 & 1736

- Commercial IND's have a large number of studies subjected to TRC due to study reports

		ANDA	BLA	NDA	Comm IND	All
a	**Total Number of Submissions with Study Data and/or Study Report**	230	110	262	827	1429
b	**Total Number of Submissions with Study Data and/or Study Report in TRC Applicable section**	213	80	192	480	965
c	**Total Number Submissions with Critical Errors**	72	34	80	314	500
d	**Error 1734**	55	27	73	293	448
f	**Error 1736**	17	7	7	21	52
g	**Failure Rate (% among submissions with Study Data and/or study Report)**	31.30%	30.91%	30.53%	37.97%	34.99%
h	**Failure Rate (% among submissions with Study Data and/or study Report in TRC Applicable sections)**	33.80%	42.50%	41.67%	65.42%	51.81%

Notes:

(1) One drug application could contain multiple submissions throughout its review life-cycle, such as original, supplements, and amendments;
(2) Analysis includes NDA, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2019 and 12/31/2019
(3) A submission with multiple studies can report both Errors 1734 and 1736. In this instance, the submission is counted only once at the submission level when calculating failure rate
(4) M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in submission
(5) M5 Definition of Study Data - .xpt files present in the submission
(6) Analysis is conducted according to the revised TRC (Revised Oct. 2019)

2019 (Q1-Q3) vs 2019 Q4 Study Level Comparison

A large number of non-clinical studies fail 1734 because of expectation of a ts.xpt for Non-Clinical studies when a study report is submitted as per revised TRC (Oct. 2019)

		CY2019 (Q1-Q3)		CY2019 (Q4)	
		Nonclinical (m4)	Clinical (m5)	Nonclinical (m4)	Clinical (m5)
a	**Total Number of Studies**	1778	3959	10,128	1513
b	**Total Number of Studies in TRC Applicable Sections**	1648	2983	1623	1135
c	**Total Number Studies with Critical Errors**	283	782	940	290
d	**Error 1734**	253	655	903	239
f	**Error 1736**	30	127	37	51
g	**Error Rate [c/a] (% among Total Number of Studies)**	15.92%	19.75%	9.28%	19.17%
h	**Error Rate (% among failed studies with Study Data* Data in TRC Applicable Sections) [c/b]**	**17.17%**	**26.22%**	**57.92%**	**25.55%**

Notes:

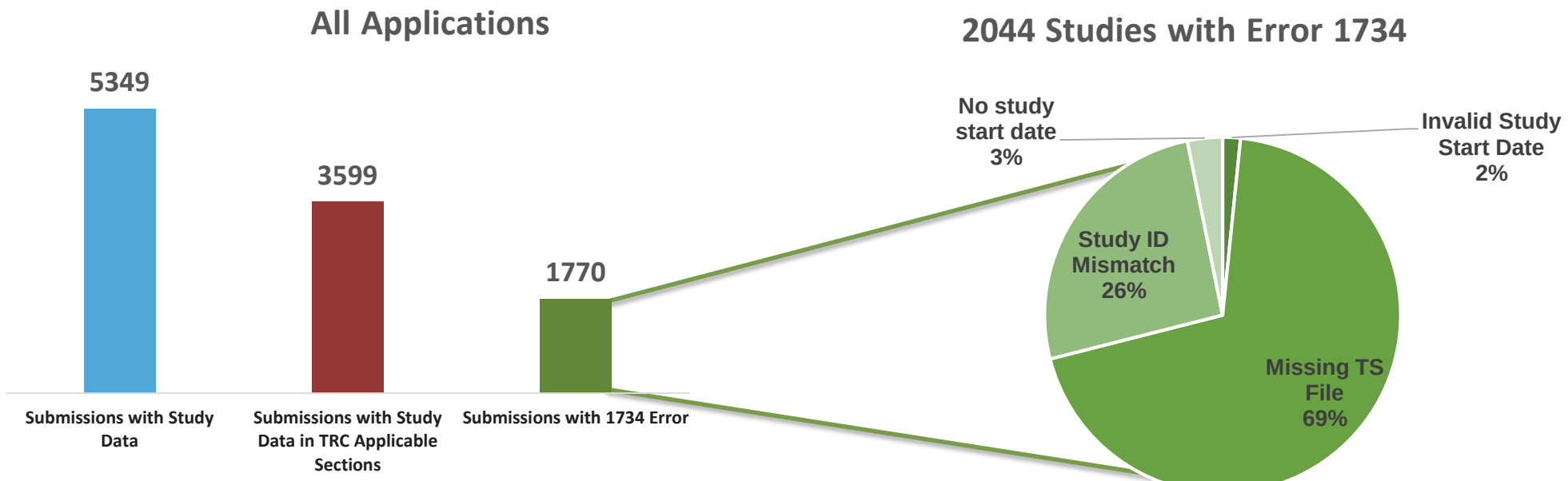
(1) Analysis includes NDA submissions received by CDER between 1/1/2019 and 12/31/2019
(2) Validation of errors 1735 and 1736 is not performed if a study has Error 1734
(3) A submission with multiple studies can report Errors 1734, 1735 and/or 1736. In this instance, the submission is counted only once at the submission level when calculating failure rate
(4) Analysis is conducted according to the revised TRC (Revised Oct. 2019)
(5) M4 Definition of Study Data - .xpt files and/or a Study Report tagged as pre-clinical-study-report, legacy-clinical-study-report, or study-report-body present in submission
(6) M5 Definition of Study Data - .xpt files present in the submission

Top Error Reason for TRC Rule 1734

CY2019 Error Reasons for Validation Rule 1734

Error	Description
1734	Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*

- **Common error reason for all application type:**
  - A missing ts.xpt file
  - Study ID Mismatch between TS and STF



1734 Common error reason – A missing TS file

- A Simplified ts.xpt file would be expected in cases in which a non-clinical study report submitted is not required to include accompanying SEND datasets
- **Simplified ts.xpt**
  Sponsors should submit a dataset named 'ts.xpt' with four variables: STUDYID, TSPARMCD, TSVAL, and TSVALNF. Exempted non-clinical studies should submit a simplified ts.xpt file with TSVALNF value as "NA"

Example of Simplified ts.xpt Dataset

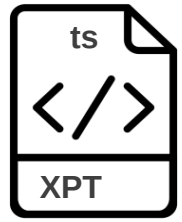
STUDYID	TSPARMCD	TSVAL	TSVALNF
•Study ID in STF File	•SSTDTC for a clinical study •STSTDTC for a nonclinical study	•Format: yyyy-mm-dd •Left blank when study start date is not available or irrelevant	• Left blank when study start date is provided in TSVAL •"NA"

References:
FDA Study Data Technical Conformance Guide (Section 8 and Appendices C Version 4.4, Oct 2019)
FDA Study Data Technical Rejection Criteria (Revised Oct. 2019)

Example - Simplified ts.xpt with and without Study Start Date

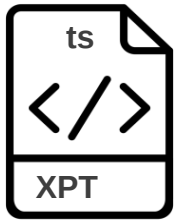
- Example of a Simplified TS file submitted for a non-clinical study with study-id “S107” in the STF file

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	S107	STSTDTC	2014-10-26	



- Example of a Simplified TS file submitted for a non-clinical study with study-id “S107” in the STF file without a study start date

	STUDYID	TSPARMCD	TSVAL	TSVALNF
1	S108	STSTDTC		NA



Self-Check Worksheet Example for Simplified TS

- **Section 4** in the Self-Check Worksheet Provides more guidance to sponsors/applicants to check for the expectation from a Simplified TS file

Study ID in TS = S107

Study Start Date= 2019-01-01

Simplified TS File

4l. Study ID (STUDYID) in TS File*:
S107

4m. Does Study ID (study-id) in STF (Field 3d) and TS Files Match?*
☒ Yes ☐ No
Referenced Validation Error Number 1734
*If you answered "No" in **Field 4m**, Validation Rule 1734 FAILS. Do not proceed.*

4n. Is there a Value in TSVALNF?
☐ Yes ☒ No
*If you answered "No" in **Field 4n**, and there is no value in TSVALNF, proceed to **Field 4p** to enter the Study Start Date (SSD).*

4o. Is the Value in TSVALNF "NA"?
☐ Yes ☐ No
Referenced Validation Error Number 1734
*If you answered "Yes" in **Field 4n** and "No" in **Field 4o**, Validation Rule 1734 FAILS. Do not proceed.*

4p. Study Start Date in TS File:
2019-01-01
The Study Start Date (SSD) should follow the ISO 8601 standard that provides, at a minimum, the year, month, and date for the study start date (yyyy-mm-dd).

4q. If Study Start Date Exists, Is it in Valid Format *(yyyy-mm-dd)*?
☒ Yes ☐ No
Referenced Validation Error Number 1734
*If you answered "No" in **Field 4q**, Validation Rule 1734 FAILS. Do not proceed.*

TRC Introduced SPREFID to Match STF Study ID with ts.xpt

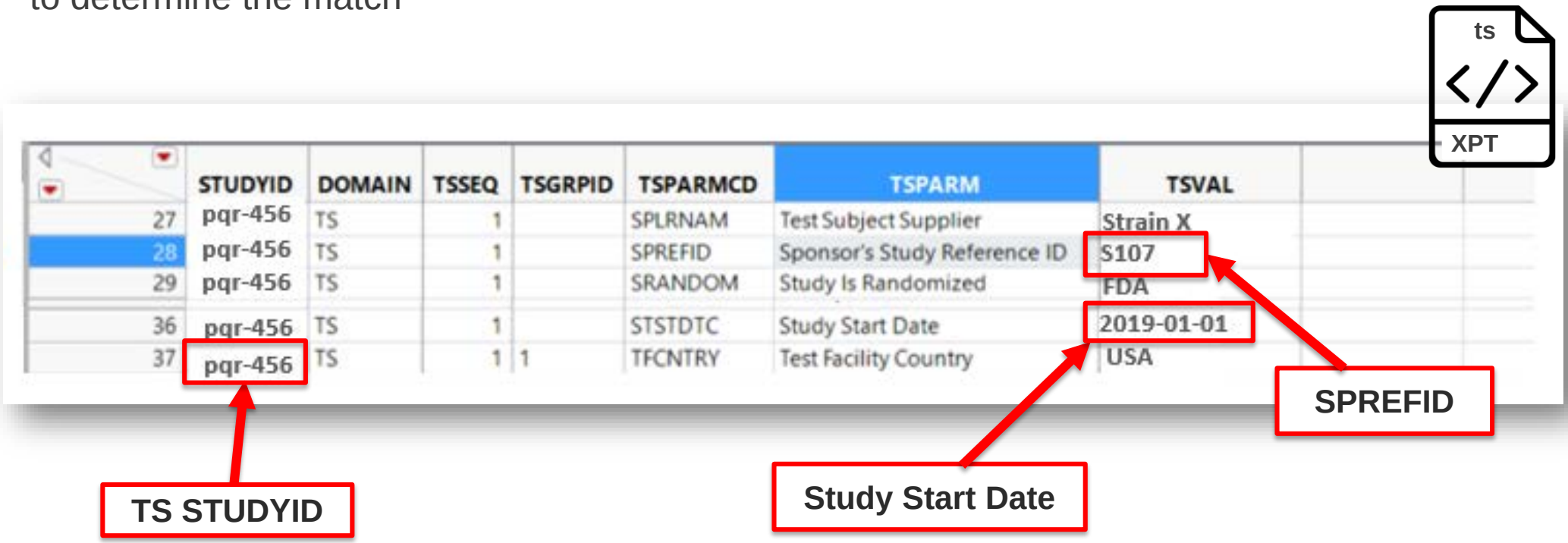
Example in Revised TRC -SPREFID for Study ID matching

A study in standardized format is submitted to FDA and the study files are referenced in a STF, a ts.xpt dataset is included in the study. The SPREFID in the ts.xpt dataset matches the study ID (study-id) in the STF. The Study Start Date in the ts.xpt is in SDTM or SEND format and the study begins after December 17, 2016, for NDAs, BLAs, and ANDAs (or December 17, 2017, for Commercial INDs).

- Additional parameter in the ts.xpt for matching study id with STF study id to pass validation 1734
  - The SPREFID parameter allows for an alternate way for Sponsors provide a matching study id
  - Multiple SPREFID values are allowed in the ts.xpt

1734 Common Error Reason – Study ID Mismatch

- This is an example of a Full TS file submitted for a non-clinical study with study-id “S107” in the STF file
- The variable **STUDYID** does not match with STF study-id but SPREFID parameter “S107” is provided to determine the match



Self-Check Worksheet Example for Full TS

- **Section 4** in the Self-Check Worksheet Provides more guidance to sponsors/applicants to check for the expectation from a full TS file
- for e.g. Study ID in STF = S107

✖ Study ID in TS = pqr-456

✓ Study ID in SPREFID= S107

Full TS File

4f. Study ID (STUDYID) in TS File*:
pqr-456

4g. Does Study ID (study-id) in STF (Field 3d) and TS Files Match?*
☐ Yes ☒ No
Referenced Validation Error Number 1734

4h. If Study ID does Not Match, What is the Value of SPREFID in TS File?
S107

4i. Does Study ID (study-id) in STF (Field 3d) and SPREFID Match?
☒ Yes ☐ No
*If you answered "No" in **Field 4g and Field 4i**, Validation Rule 1734 FAILS. Do not proceed.*
Referenced Validation Error Number 1734

4j. Study Start Date in TS File:
2019-01-01
*If you do not have a Study Start Date in **Field 4j,** Validation Rule 1734 FAILS. Do not proceed.*
Referenced Validation Error Number 1734

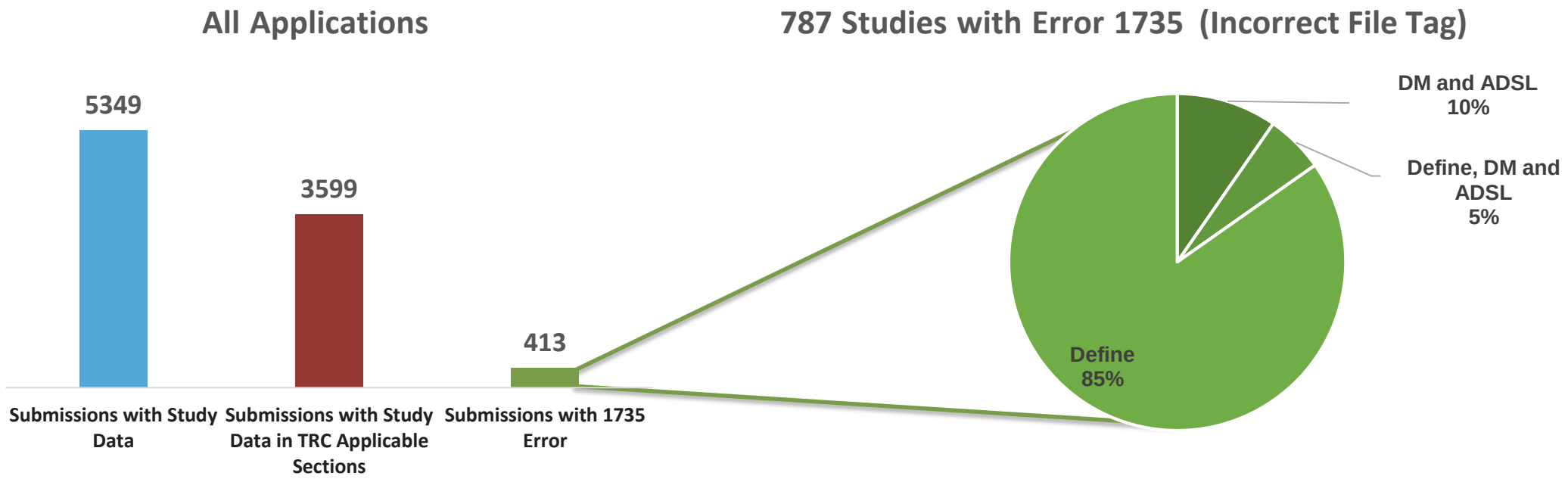
4k. If Study Start Date Exists, Is it in Valid Format (*yyyy-mm-dd*)?
☒ Yes ☐ No
*If you answered "No" in **Field 4k**, Validation Rule 1734 FAILS. Do not proceed.*
The Study Start Date (SSD) should follow the ISO 8601 standard that provides, at a minimum, the year, month, and day for the study start date (yyyy-mm-dd).
Referenced Validation Error Number 1734

Top Error Reason for TRC Rule 1735

CY2019 Error Reasons for Validation Rule 1735

Error	Description
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*

- **Common error reason for all application type:**
  - An incorrect file tag for a define.xml file
  - An incorrect file tag for a DM and ADSL file



Self-Check Worksheet Example

- **Section 5** in the Self-Check Worksheet Provides more guidance to sponsors/applicants to check for the proper file tags for standardized dataset as well as the associated define.xml file

Verify SEND Dataset File Tag

5d. Are the STF File-Tags for the SEND Datasets "data-tabulation-dataset-send"?*
☒ Yes ☐ No

5e. Is the STF File-Tag for the Define File "data-tabulation-data-definition"?*
☒ Yes ☐ No

*If you answered "No" in **Fields 5d or 5e**, Validation Rule 1735 FAILS.*

Referenced Validation Error Number 1735

Verify SDTM Dataset File Tag

5h. Are the STF File-Tags for the SDTM Datasets "data-tabulation-dataset-sdtm"?*
☒ Yes ☐ No

5i. Is the STF File-Tag for the Define File "data-tabulation-data-definition?*
☒ Yes ☐ No

*If you answered "No" in **Fields 5h or 5i**, Validation Rule 1735 FAILS.*

Referenced Validation Error Number 1735

Verify ADaM Dataset File Tag

5l. Are the STF File-Tags for the ADaM Datasets "analysis-dataset-adam"?*
☒ Yes ☐ No

5m. Is the STF File-tag for the Define File "analysis-data-definition"?*
☒ Yes ☐ No

*If you answered "No" in **Fields 5l or 5m**, Validation Rule 1735 FAILS*

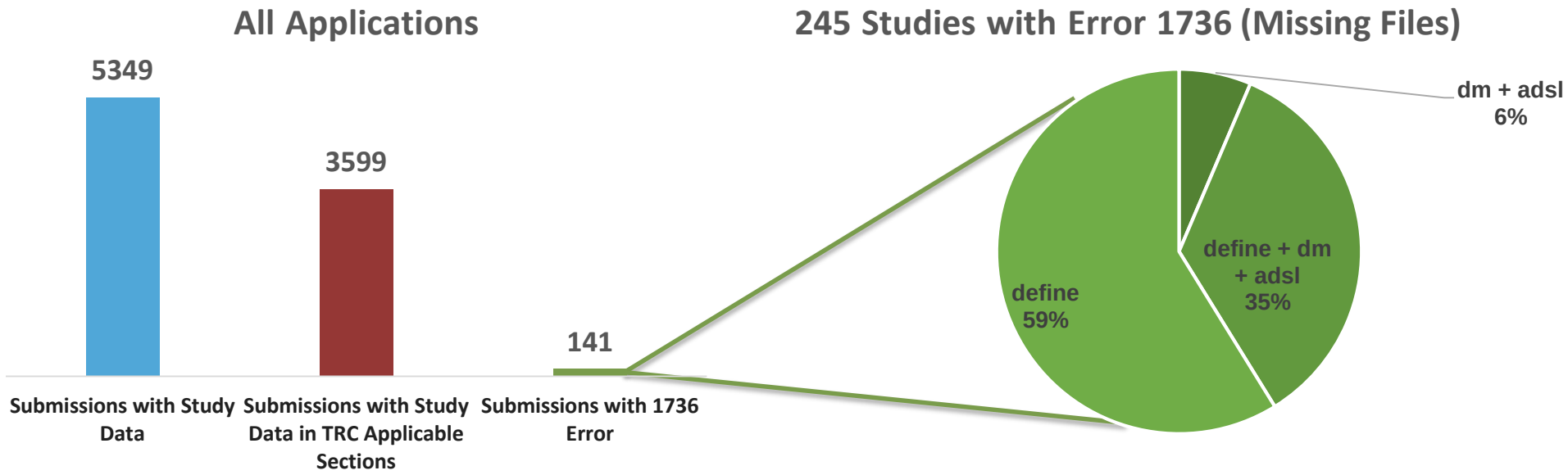
Referenced Validation Error Number 1735

Top Error Reason for TRC Rule 1736

CY2019 CDER Error Reasons for Validation Rule 1736

Error	Description
1736	For SEND data, a DM dataset and define xml must be submitted in required sections* For SDTM data, a DM dataset and define.xml must be submitted in required sections* For ADaM data, an ADSL dataset and define.xml must be submitted in required sections*

- **Common error reason for all application type:**
  - A missing define.xml files
  - A missing define.xml, dm.xpt, and/or adsl.xpt files



Self-Check Worksheet Example

- **Section 5** in the Self-Check Worksheet Provides more guidance to sponsors/applicants to check for the DM and/or ADSL for standardized dataset as well as the associated Define file

Verify DM and Define for SEND

Nonclinical (m4)

Tabulation (SEND datasets)

5b. Is DM File Included?*	5c. Is Define File Included?*	
☒ Yes ☐ No	☒ Yes ☐ No	Referenced Validation Error Number 1736

*If you answered "No" in **Fields 5b or 5c**, Validation Rule 1736 FAILS. Proceed to **Fields 5d and 5e** for Validation Rule 1735.*

Verify DM and Define for SDTM

Clinical (m5)

Tabulation (SDTM datasets)

5f. Is DM File Included?*	5g. Is Define File Included?*	
☒ Yes ☐ No	☒ Yes ☐ No	Referenced Validation Error Number 1736

*If you answered "No" in **Fields 5f or 5g**, Validation Rule 1736 FAILS. Proceed to Fields **5h and 5i** for Validation Rule 1735.*

Verify DM and Define for ADaM

Analysis (ADaM datasets)

5j. Is ADSL File Included?*	5k. Is Define File Included?*	
☒ Yes ☐ No	☒ Yes ☐ No	Referenced Validation Error Number 1736

*If you answered "No" in **Fields 5j or 5k**, Validation Rule 1736 FAILS. Proceed to **Fields 5l and 5m** for Validation Rule 1735.*

Additional Tools for Industry

Tools for Industry

FDA has developed tools to help sponsors meet updated study data standard requirements and provide more transparency on the validation process

Sponsor reviews Study Data Standard Resources:

- **Revised Study Data Technical Rejection Criteria with eCTD Validation Table**
- **Study Data Self-Check Worksheet & Instruction**

Sponsor submits a eCTD and/or Standardized Data Sample to the FDA for validation

After review, FDA will provide with feedback, highlighting the errors found during the processing of the sample submission

Sponsor submits an application with study data

1. **Revised Study Data Technical Rejection Criteria (Revised Oct. 2019)**

   Purpose: To clarify the requirements for eCTD Validation of submissions with study data and to provided examples (**Appendix 1 and 2**) to illustrate the requirements

2. **TRC Self-Check Worksheet & Instruction**

   Purpose: To help sponsors understand criteria for submissions with study data to pass the updated TRC

3. **eCTD and/or Standardized Data Sample Validation**

   Purpose: To help sponsors validate their sample submissions and receive feedback with identified errors

Tools Available to create a Simplified TS File

FDA Guide for creating a Simplified TS File

- **Purpose** – The *Simplified ts.xpt Creation Guide* is a resource that FDA is providing industry to help create a simplified TS file using free and open-source software
  - R or Python
- This Guide provides step by step instructions to install the necessary software to create and view the simplified ts.xpt file
- Users can simply copy paste the code from the guide to generate the simplified ts.xpt
- This guide is intended for users with non programming background to create the simplified ts.xpt with ease
- This link to this Guide will be available on the FDA's Web Page

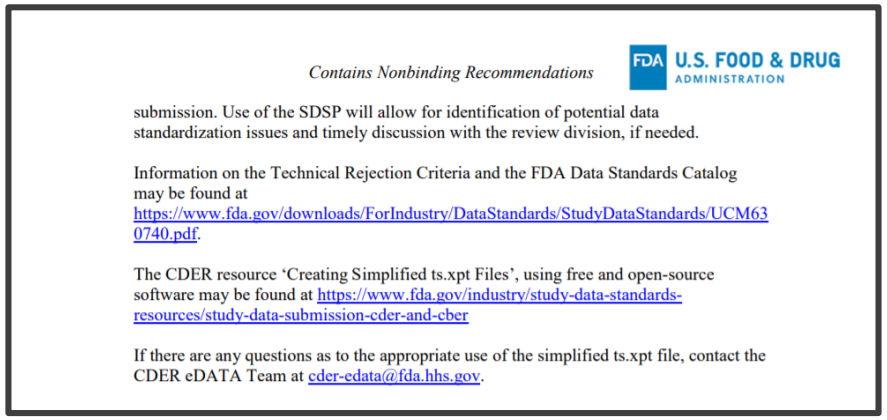
  - *Study Data for Submission to CDER and CBER*

Publicly available Tool

- PhUSE utility to generate Simplified TS file

https://geotiger.shinyapps.io/07_genTS/

Study Data TCG (Oct 2019) references this Guide



Contains Nonbinding Recommendations

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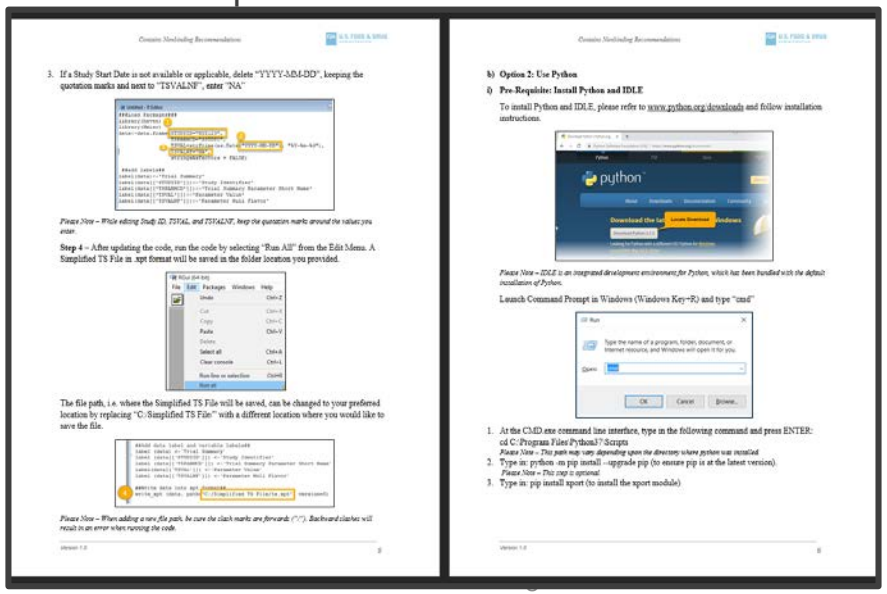
submission. Use of the SDSP will allow for identification of potential data standardization issues and timely discussion with the review division, if needed.

Information on the Technical Rejection Criteria and the FDA Data Standards Catalog may be found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630740.pdf.

The CDER resource 'Creating Simplified ts.xpt Files', using free and open-source software may be found at https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

If there are any questions as to the appropriate use of the simplified ts.xpt file, contact the CDER eDATA Team at cder-edata@fda.hhs.gov.

Simplified TS File Creation Guide



FDA Tools - Study Data Self-Check Worksheet & Instructions (Revised Nov. 2019)

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For Industry

Home > For Industry > Data Standards > Study Data Standards

Study Data Standards

- Study Data for Submission to CDER and CBER
- Study Data Research and Collaborations
- Janus
- Study Design Standard
- Study Participation Standard
- Subject Data Standard

Study Data for Submission to CDER and CBER

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Data standards enable FDA to modernize and streamline the review process. They also enable more consistent use of analysis tools to better view drug data and highlight areas of concern.

Study data standards describe a standard way to exchange clinical and nonclinical research data between computer systems. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.

FDA is instituting new requirements for data standards that will apply to most study data submitted to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Stay Connected

If you have study data questions for CDER, please contact the CDER eDATA Team at cder-edata@fda.hhs.gov.

For electronic submissions, contact the CDER Electronic Submission (ESUB) Support Team at esub@fda.hhs.gov.

If you have study data questions for CBER, please contact CBER-edata@fda.hhs.gov.

For electronic submissions, contact CBER ESUB at esubprep@fda.hhs.gov.

Beginning after the dates specified below, FDA may refuse to file for New Drug Applications (NDAs) and Biologics License Applications (BLAs) or refuse to receive for Abbreviated NDAs (ANDAs) any electronic submission whose study data do not conform to the required standards specified in the FDA Data Standards Catalog. See the Technical Rejection Criteria for Study Data (pdf) for more information. FDA conducted an analysis of study data conformance on submissions received during a specified time period and developed a presentation on the overall conformance results. Study Data Conformance (PDF). To assist sponsors when submitting study data FDA has created the Technical Rejection Criteria Self-Check Worksheet (PDF) and Worksheet Instructions (PDF).

CDER and CBER strongly encourage Investigational New Drug (IND) sponsors and NDA applicants to consider the implementation and use of study data standards as early as possible in the product development life cycle so that data standards are accounted for in the design, conduct, and analysis of studies.

- Sponsors whose studies start after Dec. 17, 2016, must submit data in the data formats supported by FDA and listed in the FDA Data Standards Catalog. This applies to NDAs, BLAs, ANDAs, and subsequent submissions to

"Technical Rejection Criteria for Study Data" (Oct 2019)
https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm630740.pdf"

"Technical Rejection Criteria Self-Check Worksheet" (Nov 2019)
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf

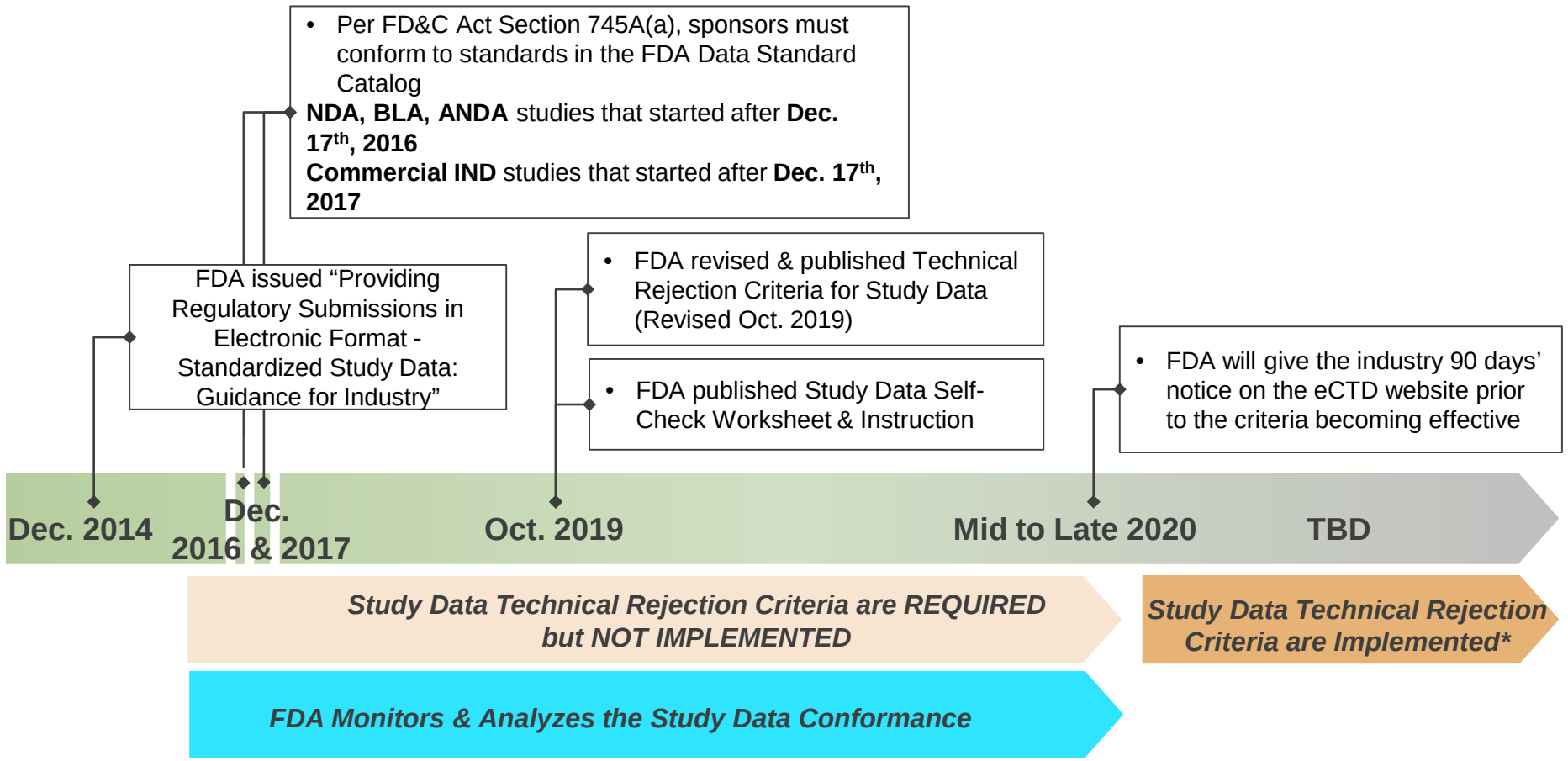
"Technical Rejection Criteria Self-Check Worksheet Instructions" (Nov 2019)
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf

TRC Implementation Timeline

Implementation Timeline

FDA published Revised Study Data Technical Rejection Criteria (Revised Oct. 2019) and Study Data Self-Check Worksheet to assist sponsors with the TRC Conformance

** Note: When a submission is technically-rejected, the submission sequence is not transferred into the FDA electronic document rooms*



Summary

- Overall conformance for Errors 1734,1735 and 1736 has increased
- FDA requires the submission of standardized Study Data as defined in the FDA Data Standard Catalog
- FDA has not rejected any submission that contains errors as reflected in this analysis.
- FDA plans to use technical rejection criteria to identify applications that are not fulfilling this requirement
- FDA published Study Data Self-Check Worksheet to help sponsors to follow the revised TRC
- FDA published Simplified TS file creation guide and utility to Generate Simplified TS file

TIP

To avoid validation errors, it is important for sponsors and applicants to understand the requirements specified in guidance and recommendations for submitting study data in the Study Data Technical Conformance Guide.

References

- **“Providing Regulatory Submissions In Electronic Format - Standardized Study Data: Guidance For Industry”**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/DRUGS/GUIDANCECOMPLIANCEREGULATORYINFORMATION/GUIDANCES/UCM292334.PDF
- **“Providing Regulatory Submissions In Electronic Format - Submissions Under Section 745a(a) Of The FD&C Act: Guidance For Industry”**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/DRUGS/GUIDANCECOMPLIANCEREGULATORYINFORMATION/GUIDANCES/UCM384686.PDF
- **“Technical Rejection Criteria For Study Data”**
  HTTPS://WWW.FDA.GOV/MEDIA/100743/DOWNLOAD
- **“Study Data Technical Conformance Guide”**
  HTTPS://WWW.FDA.GOV/MEDIA/131872/DOWNLOAD
- **“FDA Data Standards Catalog”**
  HTTPS://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/DEFAULT.HTM
- **“Technical Rejection Criteria Self-Check Worksheet”**
  HTTPS://WWW.FDA.GOV/MEDIA/123098/DOWNLOAD
- **“Technical Rejection Criteria Self-Check Worksheet Instructions”**
  HTTPS://WWW.FDA.GOV/MEDIA/123099/DOWNLOAD

Recommended Readings

- **For FDA instruction of Study Data submission, Self-Check Worksheet and Simplified TS file creation guide see the FDA "Study Data for Submission to CDER and CBER" page at:** HTTPS://WWW.FDA.GOV/INDUSTRY/STUDY-DATA-STANDARDS-RESOURCES/STUDY-DATA-SUBMISSION-CDER-AND-CBER

- **For the full list of Study Data standards, see the FDA "Study Data Standards Resources" page at:** HTTPS://WWW.FDA.GOV/INDUSTRY/FDA-RESOURCES-DATA-STANDARDS/STUDY-DATA-STANDARDS-RESOURCES


Thank you