FDA Plenary Session

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Ray Wang, Office of Strategic Programs, CDER
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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*

* 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
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.
CBER - CDER Data Standards Strategic Goals

DSP Guiding Principles
1. Use voluntary & consensus-based standards development process
2. Reduce regulation burden by aligning with existing HIT initiatives, laws, regulations, and mandates
3. Adopt or adapt other standards currently in use, when feasible

FDA Strategy Planning & Alignment
- FDA Policy Roadmap
- FDA IT Strategic Plan
- PDUFA
- CDER Strategic Plan
- CBER Strategic Plan

CBER/CDER Data Standards Strategic Goals
- Pre-Market: Incorporate data standards to support more efficient, science-based pre-market review of medical products.
- Post Market: Improve post-market risk mgmt strategies and pharmacovigilance and surveillance of medical products.
- Quality: Implement common data standards to improve the quality and integrity of marketed medical products.
- Innovation: Promote innovation in the development and use of data standards.

Supporting Goals
- Communication: Ensure effective communication and collaboration with stakeholders on DS.
- Management of Info: Improve the management and usability of the volume of information through data standards.

Regulatory Framework
- FDAAA
- FDASIA
- Postmarketing Safety Rule
- 21st Century Cures Act
- Electronic Labeling Rule
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

- Innovations
- Pre-Market
- Quality
- Regulatory Review
- Post Market (Safety Surveillance)

Policy

Management of Information
Communication

Post Approval
Quality Data
- Product
- Substance
- Labeling Data
Supply Chain Data
- Facility
- Production
- Distribution

Pre-Market
Regulatory Review
Post Market (Safety Surveillance)
Data Standards Program *(Externally Published Projects)*

**Innovation**
- Real Word Evidence
- Evaluation of Standards for Regulatory Application

**Pre-Market**
- Study Data Standards Testing
- Source Data Capture from EHRs
- E2B IND Safety Report
- Clinical Outcomes Assessment

**Quality**
- PQ/CMC Data Standardization
- Post Approval Changes Submission Standards

**Policy**
- Technical Conformance Guide
- Data Standards Catalog
- Technical Specifications
- eCTD Submission Standards
- Other Guidance

**Post Market (Safety Surveillance)**
- FAERS II Implementation
- REMS SPL Integration
- Identification of Medicinal Products (IDMP)
- Grant Projects

**Regulatory Review**

**Management of Information**
- Data Governance Project

**Communication**
- Data Standards Webpage
- Action Plan/Annual Assess.
- Public Meetings
- Webinars/Conferences
Data Standards Program Resources

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

FDA Resources for Data Standards

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
FDASIA Guidance Implementation Highlights

**FDASIA Guidance**
- How does FDA plan to implement Section 745A(a) of the FD&C Act?

**eStudy Guidance**
- Binding Guidance—Requires that studies are compliant with the standards outlined in the FDA Data Standards Catalog
- What submission types must be electronic?
- What is the timetable?

**Data Standards Catalog**
- Lists supported and/or required standards.

**Technical Conformance Guide**
- Provides specifications, recommendations, and general considerations on how to submit standardized study data.

**eCTD Guidance**
- 24 months after guidance is finalized, content must be submitted to the Agency electronically in the format specified in the guidance.
DSP – Data Standards View

Innovation
- Data Standards & Terminology
  - SDTM/SENI-D
  - ADaM
  - TAs
- Exchange Standards
  - XML (Define)
  - XPT
  - SPL
  - ICH E2B/ICSR

Quality
- Data Standards
  - FG/CMC
- Exchange Standards
  - HL7 FHIR
- Terminology
  - UNII
  - SPL
  - NCI EVS

Pre-Market
- Data Standards
  - SDTM/SENI-D
  - ADaM
  - TAs
- Exchange Standards
  - XML (Define)
  - XPT
  - SPL
  - ICH E2B/ICSR
- Terminology
  - MEDRT
  - SNOMED CT
  - LOINC
  - MedDRA
  - WHO Drug Global
  - CDISC (EVS)
  - SPL
  - UNII

Regulatory Review
- Data Standards
  - eCTD
  - SPL
  - Pre-market Standards
- Terminology
  - Pre-market Standards

Post-Market (Safety Surveillance)
- Data Standards
  - eCTD
  - SPL
  - Pre-market Standards
- Terminology
  - Pre-market Standards

Management of Information

Communication
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 technologies
- 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
Develop Integration with FDA and External Systems*

(*) For FHIR Submissions Validation Only
Develop Data Feed To All Websites*

- External Systems
- FDA Systems
- Public User
- FDA User
- Industry Submitter
- FDA Public Pages
- FDA Internal Pages
- Review, Search, Report Generation UI
- Submission UI
- Special Purpose APIs
- Review, Search, Report Generation APIs
- Search & Submission APIs
- FHIR Server (FHIR Resources APIs)
- FHIR Repository

* 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)
- Study Data Conformance Analysis (CY2019 Q4)
- New Tools for Industry
- Implementation Timeline
- Summary
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
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.


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
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

<table>
<thead>
<tr>
<th>Error</th>
<th>Description (Reference to FDA Study Data Technical Rejection Criteria Oct. 2019 version)</th>
<th>Severity Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1734</td>
<td>A Trial Summary (TS) dataset (ts.xpt) with information on study start date (SSD) must be present for each study in required sections*</td>
<td>High</td>
</tr>
<tr>
<td>1735</td>
<td>Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*</td>
<td>High</td>
</tr>
</tbody>
</table>
| 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           |
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

- Per FD&C Act Section 745A(a), sponsors must conform to standards in the FDA Data Standard Catalog
- NDA, BLA, ANDA studies that started after Dec. 17th, 2016
- Commercial IND studies that started after Dec. 17th, 2017

FDA issued “Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry”

- FDA will not accept study data submissions not in compliance with FDA Data Standards Catalog
- FDA emphasized validation rules 1735 and 1789
- FDA introduced the Simplified TS File (simplified ts.xpt) to obtain Study Start Date
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)

<table>
<thead>
<tr>
<th></th>
<th>ANDA</th>
<th>BLA</th>
<th>NDA</th>
<th>Comm IND</th>
<th>All</th>
</tr>
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<tbody>
<tr>
<td>a</td>
<td>Total Number of Submissions with Study Data</td>
<td>623</td>
<td>203</td>
<td>679</td>
<td>700</td>
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<tr>
<td>b</td>
<td>Total Number of Submissions with Study Data in TRC Applicable Sections</td>
<td>582</td>
<td>161</td>
<td>533</td>
<td>645</td>
</tr>
<tr>
<td>c</td>
<td>Total Number Submissions with Critical Errors</td>
<td>181</td>
<td>64</td>
<td>197</td>
<td>156</td>
</tr>
<tr>
<td>d</td>
<td>Error 1734</td>
<td>135</td>
<td>59</td>
<td>195</td>
<td>135</td>
</tr>
<tr>
<td>e</td>
<td>Error 1736</td>
<td>46</td>
<td>5</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>f</td>
<td>Failure Rate (% among submissions with Study Data) [c/a]</td>
<td>29.05%</td>
<td>31.53%</td>
<td>29.01%</td>
<td>22.29%</td>
</tr>
<tr>
<td>g</td>
<td>Failure Rate (% among submissions with Study Data in TRC Applicable section) [c/b]</td>
<td><strong>31.10%</strong></td>
<td><strong>39.75%</strong></td>
<td><strong>36.96%</strong></td>
<td><strong>24.19%</strong></td>
</tr>
</tbody>
</table>

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
Study Data Technical Rejection Criteria are REQUIRED but NOT IMPLEMENTED

FDA published Revised Study Data Technical Rejection Criteria October 2019

- Per FD&C Act Section 745A(a), sponsors must conform to standards in the FDA Data Standard Catalog
- NDA, BLA, ANDA studies that started after Dec. 17th, 2016
- Commercial IND studies that started after Dec. 17th, 2017

Dec. 2014
Dec. 2016 & 2017

Jan. 2019

Oct. 2019

FDA issued “Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry”

- FDA will not accept study data submissions not in compliance with FDA Data Standards Catalog
- FDA emphasized validation rules 1735 and 1789
- FDA introduced the Simplified TS File (simplified ts.xpt) to obtain Study Start Date

- FDA introduced Non-Clinical Study Reports with proper file tags for 1734 Validation
- FDA included SPREFID as a valid source of Study ID in ts.xpt files
- FDA updated guidance for Simplified TS Files (simplified ts.xpt)

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 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:

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>TSPARMCD</th>
<th>TSVAL</th>
<th>TSVALNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>study ID in STF</td>
<td>STSTDTC</td>
<td></td>
<td>Use the value ‘NA’</td>
</tr>
</tbody>
</table>
# SDTRC Revisions: Study Reports

## Introduced the Study Report File Tag Criteria

<table>
<thead>
<tr>
<th>Study Start Date</th>
<th>Application Type</th>
<th>Data Type</th>
<th>Study Sections</th>
<th>Expectation by Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to or on 17-Dec-2017</td>
<td>Commercial INDs</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>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)</td>
</tr>
<tr>
<td>After 17-Dec-2017</td>
<td>Commercial INDs</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>Rejection criteria will be applied; submit a full TS</td>
</tr>
<tr>
<td>Prior to or on 17-Dec-2016</td>
<td>NDA, BLA, ANDA</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>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)</td>
</tr>
<tr>
<td>After 17-Dec-2016</td>
<td>NDA, BLA, ANDA</td>
<td>Nonclinical</td>
<td>4.2.3.1, 4.2.3.2, 4.2.3.4</td>
<td>Rejection criteria will be applied; submit a full TS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical</td>
<td>5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.5.1, 5.3.5.2</td>
<td>Rejection criteria will not be applied</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical</td>
<td>5.3.1.1, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.5.1, 5.3.5.2</td>
<td>Rejection criteria will not be applied</td>
</tr>
<tr>
<td></td>
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<td>Clinical</td>
<td>5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.5.1, 5.3.5.2</td>
<td>Rejection criteria will not be applied</td>
</tr>
<tr>
<td></td>
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<td>Clinical</td>
<td>5.3.1.1, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.5.1, 5.3.5.2</td>
<td>Rejection criteria will not be applied</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Included SPREFID for Study ID matching</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRC January 2019</strong></td>
</tr>
<tr>
<td>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. <strong>The ts.xpt and STF need to contain matching study ID values.</strong></td>
</tr>
</tbody>
</table>
Study Data Technical Rejection Criteria Conformance Statistics and Trend CY2019 (Q4)
TRC Validation Conformance failure rate have increased in Q4 because of introduction of study reports for 1734 in the revised TRC (Oct. 2019)
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

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

**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)

<table>
<thead>
<tr>
<th></th>
<th>CY2019 (Q1-Q3)</th>
<th>CY2019 (Q4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonclinical (m4)</td>
<td>Clinical (m5)</td>
</tr>
<tr>
<td>a Total Number of Studies</td>
<td>1778</td>
<td>3959</td>
</tr>
<tr>
<td>b Total Number of Studies in TRC Applicable Sections</td>
<td>1648</td>
<td>2983</td>
</tr>
<tr>
<td>c Total Number Studies with Critical Errors</td>
<td>283</td>
<td>782</td>
</tr>
<tr>
<td>d Error 1734</td>
<td>253</td>
<td>655</td>
</tr>
<tr>
<td>f Error 1736</td>
<td>30</td>
<td>127</td>
</tr>
<tr>
<td>g Error Rate [c/a] (% among Total Number of Studies)</td>
<td>15.92%</td>
<td>19.75%</td>
</tr>
<tr>
<td>h Error Rate (% among failed studies with Study Data* Data in TRC Applicable Sections) [c/b]</td>
<td>17.17%</td>
<td>26.22%</td>
</tr>
</tbody>
</table>

**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
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**

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>TSPARMCD</th>
<th>TSVAL</th>
<th>TSVALNF</th>
</tr>
</thead>
</table>
| • 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 without a study start date.

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>TSPARMCD</th>
<th>TSVAL</th>
<th>TSVALNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>S107</td>
<td>STSTDTC</td>
<td>2014-10-26</td>
<td></td>
</tr>
</tbody>
</table>

- 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.

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>TSPARMCD</th>
<th>TSVAL</th>
<th>TSVALNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>S108</td>
<td>STSTDTC</td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>
Section 4 in the Self-Check Worksheet Provides more guidance to sponsors/applicants to check for the expectation from a Simplified TS file

<table>
<thead>
<tr>
<th>Study ID in TS = S107</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Study Start Date= 2019-01-01</th>
</tr>
</thead>
</table>
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
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

<table>
<thead>
<tr>
<th>Full TS File</th>
</tr>
</thead>
<tbody>
<tr>
<td>4f. Study ID (STUDYID) in TS File*: pqr-456</td>
</tr>
<tr>
<td>4g. Does Study ID (study-id) in STF (Field 3d) and TS Files Match?*</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>4h. If Study ID does Not Match, What is the Value of SPREFID in TS File?</td>
</tr>
<tr>
<td>S107</td>
</tr>
<tr>
<td>4i. Does Study ID (study-id) in STF (Field 3d) and SPREFID Match?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

If you answered “No” in **Field 4g and Field 4i**, Validation Rule 1734 FAILS. Do not proceed.

| 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.

| 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).*
Top Error Reason for TRC Rule 1735
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

<table>
<thead>
<tr>
<th>Error</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1735</td>
<td>Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*</td>
</tr>
</tbody>
</table>

All Applications

- Submissions with Study Data: 5349
- Submissions with Study Data in TRC Applicable Sections: 3599
- Submissions with 1735 Error: 413

787 Studies with Error 1735 (Incorrect File Tag)

- Define: 85%
- Define, DM and ADSL: 5%
- DM and ADSL: 10%
**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

| 5d. Are the STF File-Tags for the SEND Dataset "data-tabulation-dataset-send"? |
|-------------------|-----------------|
| Yes ♡ No           |                 |
| Reference: Validation Error Number 1735 |

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

| 5e. Is the STF File-Tag for the Define File "data-tabulation-data-definition"? |
|-------------------|-----------------|
| Yes ♡ No           |                 |
| Reference: Validation Error Number 1735 |

| 5h. Are the STF File-Tags for the SDTM Dataset "data-tabulation-dataset-sdtm"? |
|-------------------|-----------------|
| Yes ♡ No           |                 |
| Reference: Validation Error Number 1735 |

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

| 5i. Is the STF File-Tag for the Define File "data-tabulation-data-definition"? |
|-------------------|-----------------|
| Yes ♡ No           |                 |
| Reference: Validation Error Number 1735 |

| 5l. Are the STF File-Tags for the ADaM Dataset "analysis-dataset-adam"? |
|-------------------|-----------------|
| Yes ♡ No           |                 |
| Reference: Validation Error Number 1735 |

If you answered "No" in Fields 5l or 5m, Validation Rule 1735 FAILS.
Top Error Reason for TRC Rule 1736
Common error reason for all application type:

- A missing define.xml files
- A missing define.xml, dm.xpt, and/or adsl.xpt files
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.

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonclinical (m4)</td>
<td>Verify DM and Define for SEND</td>
</tr>
<tr>
<td>Clinical (m5)</td>
<td>Verify DM and Define for SDTM</td>
</tr>
<tr>
<td>Analysis (ADaM datasets)</td>
<td>Verify DM and Define for ADaM</td>
</tr>
</tbody>
</table>

- **Nonclinical (m4)**
  - **Tabulation (SEND datasets)**
    - 5b. Is DM File Included?**
      - Yes ☒ |
    - 5c. Is Define File Included?**
      - Yes ☒ |

  - **Validation Rule 1736**
    - Referenced Validation Error Number 1736

- **Clinical (m5)**
  - **Tabulation (SDTM datasets)**
    - 5f. Is DM File Included?**
      - Yes ☒ |
    - 5g. Is Define File Included?**
      - Yes ☒ |

- **Analysis (ADaM datasets)**
  - 5j. Is ADSL File Included?**
    - Yes ☒ |
  - 5k. Is Define File Included?**
    - Yes ☒ |
Additional Tools for Industry
FDA has developed tools to help sponsors meet updated study data standard requirements and provide more transparency on the validation process.

   
   **Purpose:** To clarify the requirements for eCTD Validation of submissions with study data and to provide 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.
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/](https://geotiger.shinyapps.io/07_genTS/)
TRC 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

Implementation Timeline

- **Dec. 2014**
  - Per FD&C Act Section 745A(a), sponsors must conform to standards in the FDA Data Standard Catalog
  - NDA, BLA, ANDA studies that started after Dec. 17th, 2016
  - Commercial IND studies that started after Dec. 17th, 2017

- **Dec. 2016 & 2017**
  - FDA issued “Providing Regulatory Submissions in Electronic Format - Standardized Study Data: Guidance for Industry”

- **Oct. 2019**
  - FDA published Study Data Self-Check Worksheet & Instruction

- **Mid to Late 2020**
  - FDA will give the industry 90 days’ notice on the eCTD website prior to the criteria becoming effective

- **TBD**
  - Study Data Technical Rejection Criteria are Implemented*

- **Dec. 2016 & 2017**
  - Study Data Technical Rejection Criteria are REQUIRED but NOT IMPLEMENTED

**FDA Monitors & Analyzes the Study Data Conformance**
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/GUIDANCECOMPLIANCE/REGULATORYINFORMATION/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/GUIDANCECOMPLIANCE/REGULATORYINFORMATION/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