U.S. FOOD & DRUG ADMINISTRATION

2nd Public Meeting on PDUFA VI Electronic Submissions and Data Standards

Building 31, Great Room 1503A
10903 New Hampshire Avenue
Silver Spring, MD 20993

April 10, 2019

Adobe Connect link for online access: https://collaboration.fda.gov/pdufavi/

Disclaimer

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

PDUFA VI Commitment Letter

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022

I. ENSURING THE EFFECTIVENESS OF THE HUMAN DRUG REVIEW PROGRAM
- A. Review Performance Goals
- B. Program For Enhanced Review Transparency And Communication For NME NDAs And Original BLAs
- C. First Cycle Revie
- D. Review Of Pr
- E. Major Dispu
- F. Clinical Hol
- G. Special Proto
- H. Meeting Ma
- I. Enhancing R
- J. Enhancing R Review
- K. Enhancemen

II. ENHANCING MAN
- A. Resource Ca
- B. Financial Tra

III. IMPROVING FDA H
- A. Completion O Augmentation Of System Capacity
- B. Augmentation Of Hiring Staff Capacity And Capability
- C. Complete Establishment Of A Dedicated Function To Ensure Needed Scientific Staffing For Medical Product Review
- D. Set Clear Goals For Drug Review Program Hiring
- E. Comprehensive And Continuous Assessment Of Hiring And Retention

IV. INFORMATION TECHNOLOGY GOALS
- A. Objective
- B. Improve The Predictability And Consistency Of PDUFA Electronic Submission Processes
- C. Enhance Transparency And Accountability Of FDA Electronic Submission And Data Standards Activities

V. IMPROVING FDA PERFORMANCE MANAGEMENT

VI. PROGRESS REPORTING FOR PDUFA VI AND CONTINUING PDUFA V INITIATIVES

VII. DEFINITIONS AND EXPLANATION OF TERMS

IV. INFORMATION TECHNOLOGY GOALS
- A. Objective
- B. Improve The Predictability And Consistency Of PDUFA Electronic Submission Processes
- C. Enhance Transparency And Accountability Of FDA Electronic Submission And Data Standards Activities

https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

PDUFA VI Commitment Letter
Section IV Information Technology Goals

Public Meeting Goal

"Beginning no later than *September 30, 2018*, FDA will hold *annual* public meetings to seek stakeholder input related to electronic submission system past performance, future targets, emerging industry needs and technology initiatives to inform the FDA IT Strategic Plan and published targets."

Agenda

8:00 – 9:00 am **Registration**

9:00 – 9:10 am **Welcome and Opening Remarks**

Ron Fitzmartin
Senior Project Manager
Office of the Director (OD)
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

Session 1. Electronic Submissions Gateway and Electronic Common Technical Document

9:10 – 9:30 am **Electronic Submissions Gateway (ESG)**

This session will focus on the electronic submission process, including key electronic submission milestones and associated sponsor notifications from the completion of its upload to the ESG through the time the submission is made available to the review team.

FDA

La Misha Fields
Program Manager, ESG
Office of Information Management and Technology (OIMT)

Agenda

9:30 – 9:45 am **Electronic Common Technical Document (eCTD)**

This session will provide an update on eCTD, including the transition to the new eCTD viewer and validator software.

FDA

Mark Gray
Senior Project Manager
OD, CBER

9:45 – 10:00 am **Session 1: Open Public Comment**

Agenda

Session 2. **Digital Investigational New Drug (IND): Safety Reporting Program**

This session will focus on the Digital Investigational New Drug (IND) Safety Reporting Program which will implement a digital framework for the electronic submission, review, and tracking of certain IND safety reports required under 21 CFR 312.32.

10:00 – 10:30 am **Program Overview, Implementation and Guidance to Industry**

FDA

Meredith Chuk
Acting Associate Director of Safety,
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs (OND), CDER

Ta-Jen (TJ) Chen
Project Manager
Office of Strategic Programs (OSP), CDER

Virginia Hussong
Chief, Data Standards Staff
OD, CBER

10:30 – 10:45 am **Session 2: Open Public Comment**

10:45 – 11:00 am **BREAK**

Agenda

Session 3. **Pharmaceutical Quality and Chemistry, Manufacturing, and Controls (PQ/CMC) Project**

The goal of the PQ/ CMC project is to establish electronic standards for submitting Pharmaceutical Quality (PQ) and Chemistry & Manufacturing Controls (CMC) data in regulatory applications and to develop and implement a data exchange standard for submission of the data.

11:00 – 11:15 am **Project Overview**

FDA

Scott Gordon
Senior Health Informatics Officer
OSP, CDER

11:15 – 11:30 am **Structured PQ/ CMC Data**

FDA

Norman Schmuff
Associate Director, Office of Process and Facilities (OPF),
Office of Pharmaceutical Quality (OPQ), CDER

11:30 – 11:45 am **Session 3: Open Public Comment**

Agenda

Session 4.	**Data Exchange Standards Projects** This session will focus on projects to assess Fast Healthcare Interoperability Resources (FHIR) for regulatory applications.
11:45 – 12:00 pm	**Overview** **FDA** Boris Brodsky Project Management Officer OSP, CDER
12:00 – 12:15 pm	**Session 4: Open Public Comment**
12:15 – 12:25 pm	**Break**

Agenda

Session 5. **Clinical and Nonclinical Study Data**

This session will focus on the study data standards listed in the FDA Data Standards Catalog are required for clinical and nonclinical studies that started after December 17, 2016. Technical rejection criteria have been developed and added to the existing eCTD validation criteria to enforce compliance to the required study standards.

12:25 – 12:45 pm **Update on Technical Rejection Criteria for Study Data**

FDA

Ethan Chen
Director, Division of Data Management Services and Solutions (DDMSS),
Office of Business Informatics (OBI),
OSP, CDER

Virginia Hussong
Chief, Data Standards Staff
OD, CBER

12:45 – 1:00 pm **Session 5: Open Public Comment**

1:00 pm **ADJOURNED**


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FDA Electronic Submissions Gateway (ESG)

PDUFA VI

Public Meeting on

Electronic Submissions and Data Standards

April 10, 2019

La Misha Fields, Program Manager OIMT

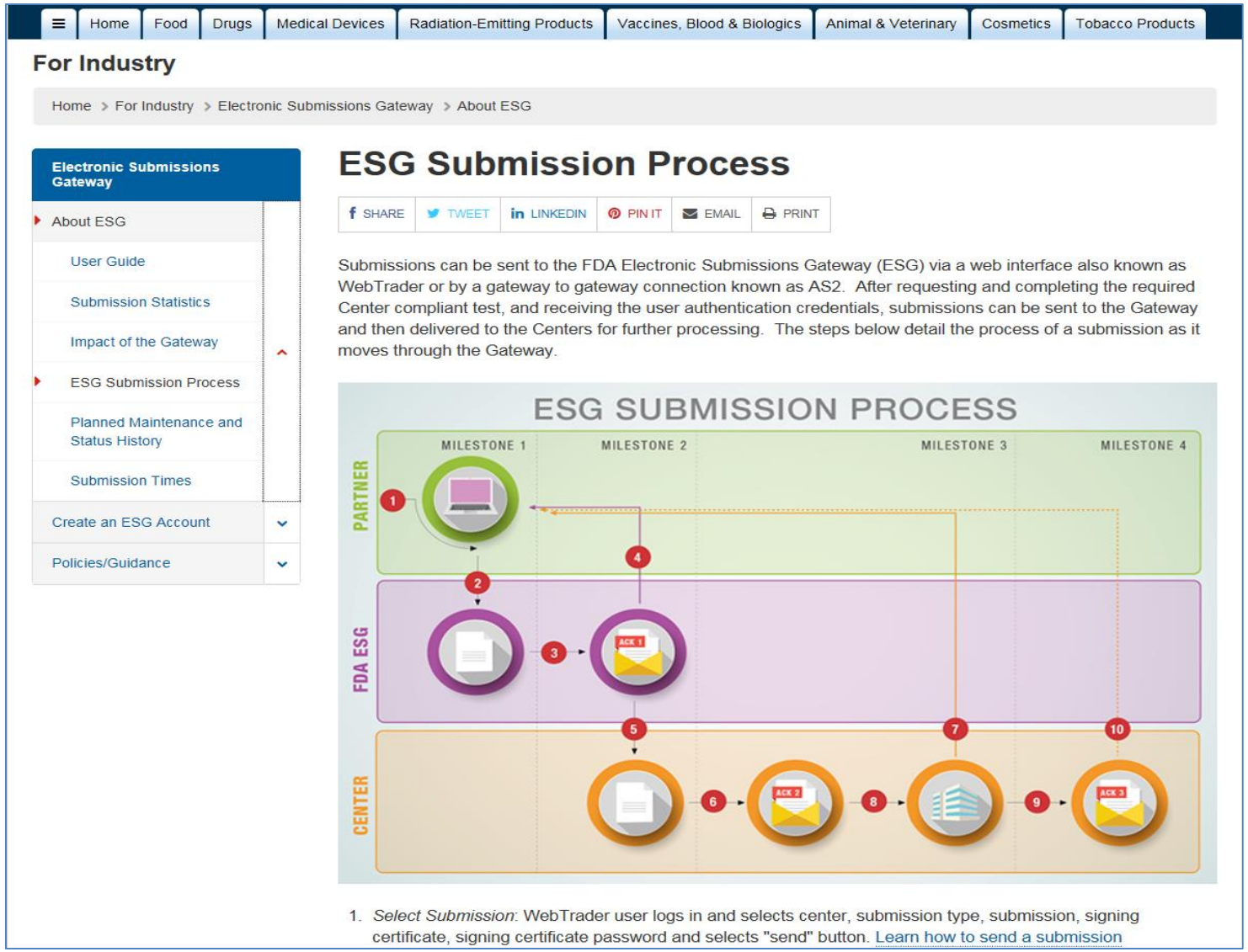
Agenda

- PDUFA VI Update
- System Enhancements

ESG PDUFA VI Goals

#	Goal	Target	Status
1	Publish target timeframes for the 1) expected submission upload duration(s) and 2) timeframe between key milestones and notifications.	Dec 2017	Completed
2	Document and publish the Electronic submission process including key milestones and sponsor notifications .	Dec 2017	Completed
3	Invite industry to provide feedback and/or participate in user acceptance testing in advance of implementing significant changes.	Dec 2017	Completed
4	Document and implement a process to provide ample advance notification on systems and process changes.	Dec 2017	Completed
5	Post, at least annually, historic and current metrics on ESG performance in relation to published targets, characterizations, and volume of submissions.	Dec 2017	Completed
6	Publish targets for and measure ESG availability overall (including schedule downtime) and during business hours (8am to 8pm).	Sept 2018	Completed
7	Communicate electronic submission milestone notifications, including final submission upload status (Note: Acknowledgements)	Sept 2018	Completed
8	Post current ESG operational status on its public website.	Sept 2018	Completed
9	Publish submission instructions in the event of an ESG service disruption.	Sept 2018	Completed

ESG Submission Process



#	Goal	Due Date – Dec 2017
2	Document and publish the Electronic submission process including key milestones and sponsor notifications	

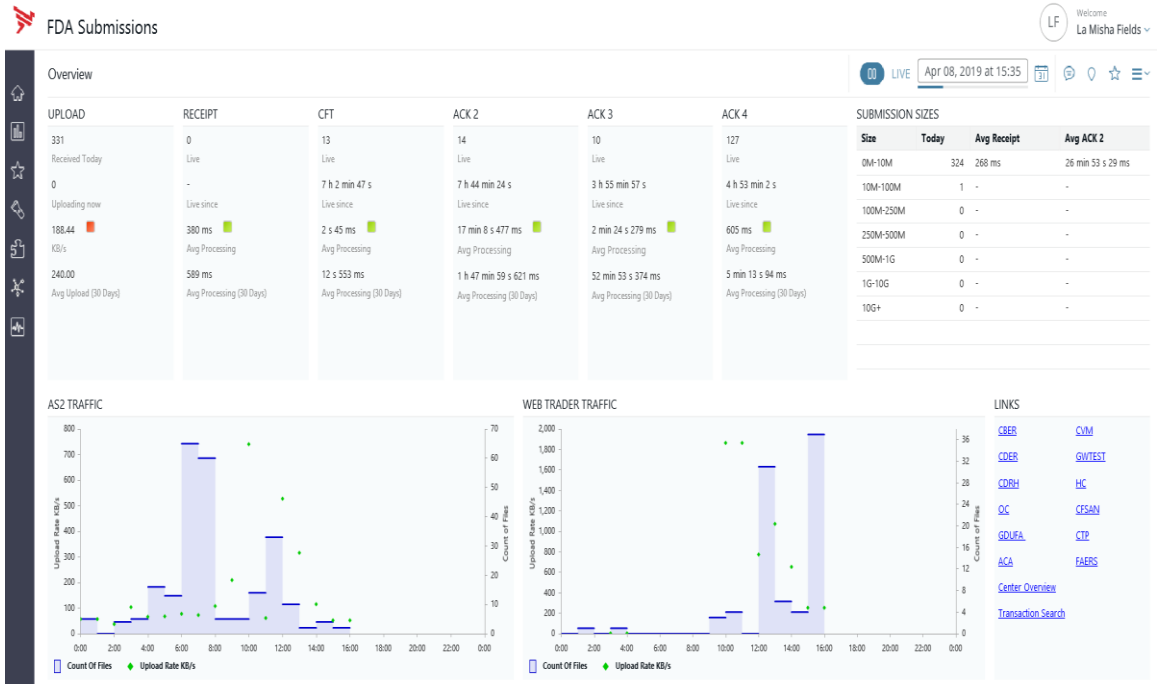
- Hover-over features for additional information
- Key Milestones description

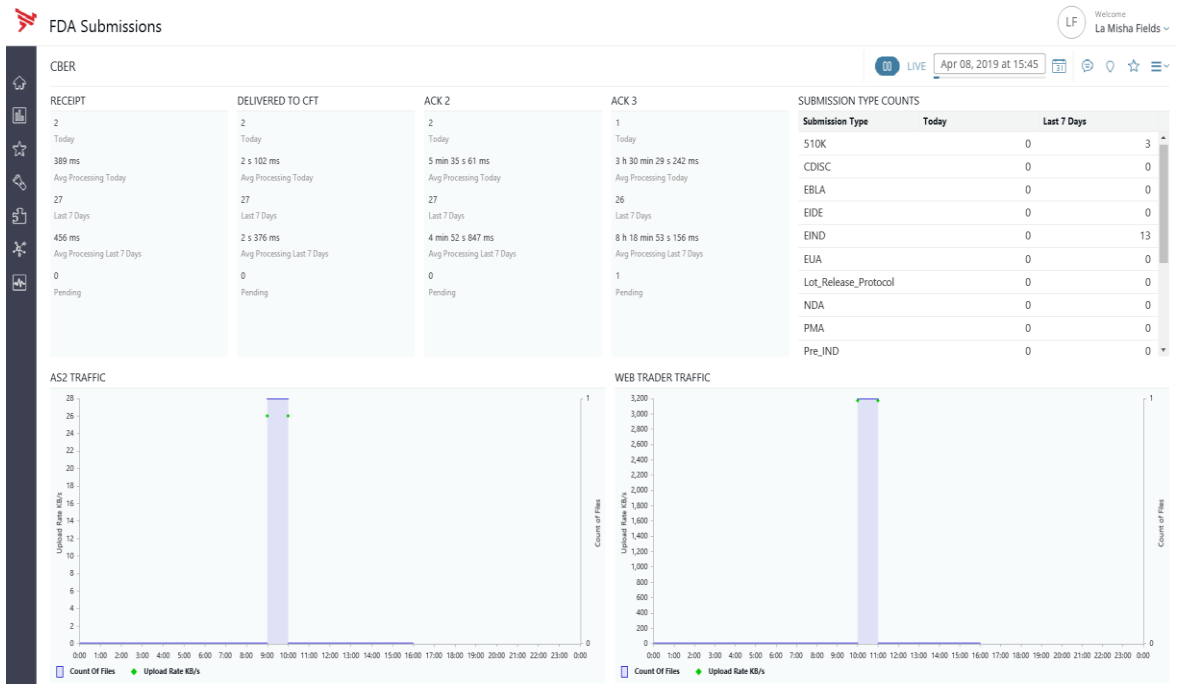
ESG Estimated Submission Processing Time

Application Type	Submission Type	Submission Size Range	Avg Submission Size (compressed)	Upload Duration (Avg; Target: 6 Hrs)	Deliver Receipt to User (Avg; Target: 2 Hrs)	Delivery to Centers (Avg; Target: 2 Hrs 55 Mins)	Delivery Ack2 to User (Avg; Target: 5 Mins)	Delivery Ack3 to User (Avg; Target: 1 Hrs)	Total Duration (Avg; Target: 12 Hrs)
NDA	Original	5GB +	7.09 GB	1.9 hrs	17 mins	10 mins	57 mins	5.1 hrs	8.4 hrs
		1GB to 5GB	2.32 GB	1.4 hrs	3 mins	12 mins	32 mins	5.1 hrs	7.2 hrs
		up to 1GB	244 MB	49 sec	46 sec	4 sec	9 mins	3.4 hrs	3.6 hrs
	Amendment	5GB+	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		1GB to 5GB	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		up to 1GB	63.83MB	47 sec	3 sec	3 sec	9 mins	2.9 hrs	3 hrs
	Supplement	5GB+	15.49 GB	1.4 hrs	18 mins	25 mins	2.1 hrs	8.2 hrs	12.4 hrs
		1GB to 5GB	1.86 GB	18 mins	2 mins	2 mins	48 mins	8.3 hrs	9.5 hrs
		up to 1GB	20.16 MB	24 sec	1 min	4 sec	11 mins	3.8 hrs	4 hrs
BLA	Original	5GB+	8.96GB	2.9 hrs	19 mins	10 mins	34 mins	2.5 hrs	6.4 hrs
		1GB - 5GB	2.25GB	39 mins	4 mins	3 mins	31 mins	8.6 hrs	9.9 hrs
		up to 1GB	1.2GB	31 sec	1 mins	3 sec	10 mins	2.9 hrs	3.1 hrs
	Amendment	5GB+	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		1GB - 5GB	3.45GB	33 mins	5 mins	3 mins	26 mins	1.4 hrs	2.5 hrs
		up to 1GB	14.58MB	22 sec	8 mins	6 sec	18 mins	3.7 hrs	4.1 hrs
	Supplement	5GB+	7.50GB	1.7 hrs	15 mins	8 mins	1 hrs	2 hrs	5.2 hrs
		1GB - 5GB	1.8GB	39 mins	3 mins	2 mins	18 min	2.3 hrs	3.4 hrs
		up to 1GB	31.17MB	37 sec	44 sec	25 sec	9 mins	3.7 hrs	3.9 hrs

#	Goal	Due Date - Dec 2017
1	Publish target timeframes for: 1) Expected submission upload duration(s) 2) Timeframe between key milestones and notifications	

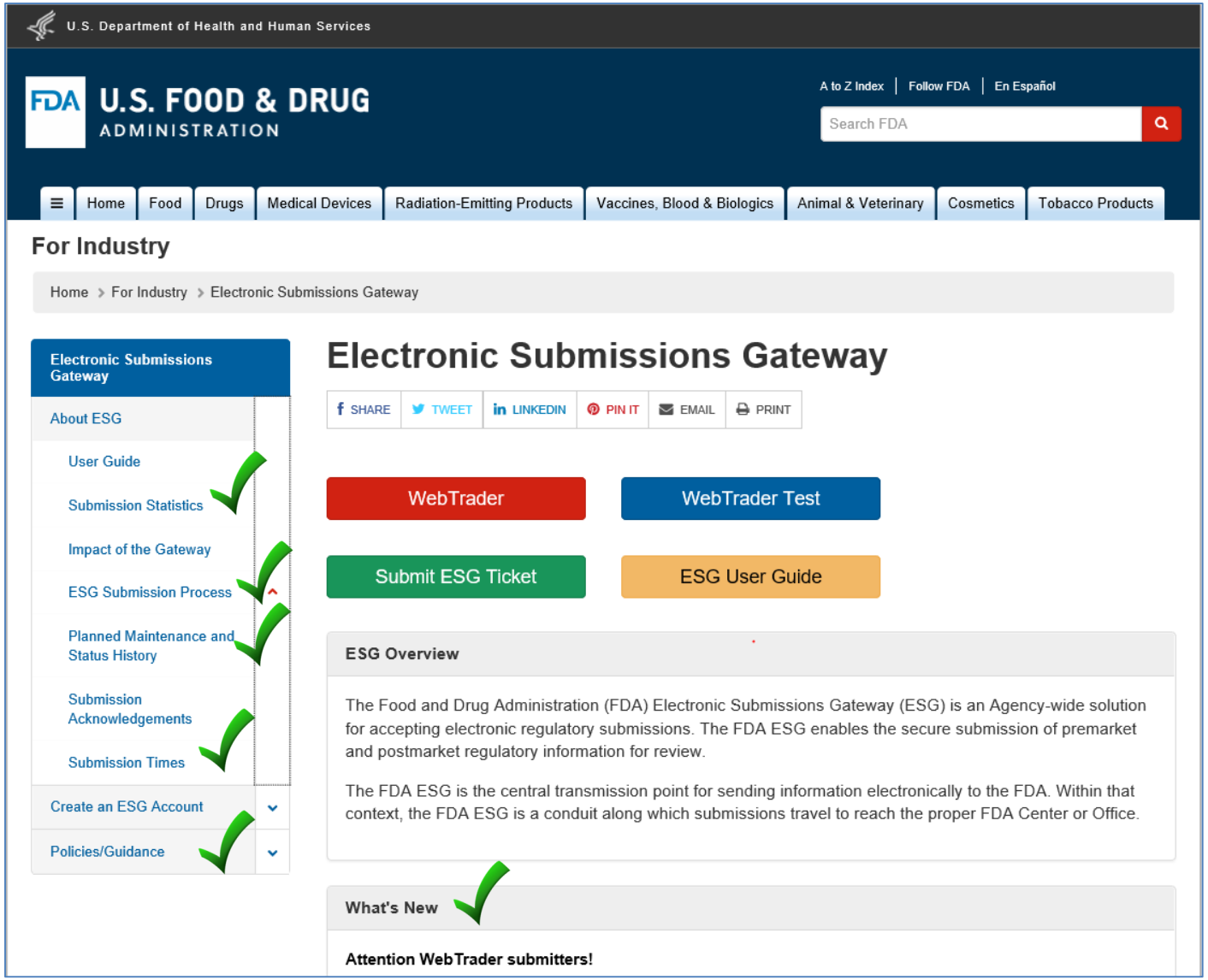
- Various sized files
- Application/ Submission Type (ex. NDA/Orig)
- WT/AS2





Operational Intelligence

ESG Website Resources



#	Goal	Due Date – Dec 2017
2	Document and publish the Electronic submission process including key milestones and sponsor notifications	
3	Invite industry to provide feedback and/or participate in user acceptance testing in advance of implementing significant changes	
4	Document and implement a process to provide ample advance notification on systems and process changes	
5	Post, at least annually, historic and current metrics on ESG performance in relation to published targets, characterizations, and volume of submissions	

#	Goal	Due Date – Sept 2018
6	Publish targets for and measure ESG availability overall (including schedule downtime) and during business hours	
7	Communicate electronic submission milestone notifications, including final submission upload status	
8	Post current ESG operational status on its public website	
9	Publish submission instructions in the event of an ESG service disruption	

Enhancements

- Year in Review
  - CBER 3rd Ack
  - Large File (Folder submission)
  - Infrastructure Optimization
  - Operational Intelligence Dashboards
  - External Help Desk with FAQs
  - Multi-thread Processing (May)

- Enhancements
  - Two Way Communications
  - Large File Prototype
    - 100 GB+
  - Cloud
  - Junior Admin

Help Desk and Website Resources

Website: http://www.fda.gov/esg/
Help Desk: ESGHelpDesk@fda.hhs.gov

ESG Submission Times
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/AboutESG/ucm590817.htm

ESG Submission Process
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/AboutESG/ucm572950.htm

ESG What's New
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

Submission Statistics
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/AboutESG/ucm110653.htm

Planned Maintenance
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/AboutESG/ucm367545.htm

Outage Notification and Disruption Policy
https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/PoliciesGuidance/ucm610190.htm

Thank you

U.S. FOOD & DRUG ADMINISTRATION

FDA Electronic Common Technical (eCTD) Update

PDUFA VI
Public Meeting on
Electronic Submissions and Data Standards

April 10, 2018

Mark Gray, Senior Project Manager CBER/OD/BSS

Agenda

- eCTD Guidance & Specification Updates
- Vendor Tool Transition
- eCTD v4.0 Update

eCTD Guidance & Specification Updates

- eCTD 745A(a) Guidance
  - Requirement to submit using the eCTD format
  - Revision 6 (January 2019):

    Extends the timeline to May 5, 2020 for Type III Drug Master Files
  - Revision 7 (In progress)

    Long-term and short-term waivers

- FDA Regional Module 1 Specifications
  - Added “REMS Supplement” Submission Type and Sub-Types
  - Implementation Date TBD

eCTD Vendor Tool Transition

- What's been completed
  - Implementation of infrastructure
  - Integration with Center systems and processes
  - Importing CDER & CBER sequences
    Over 1.5 million sequences have been imported
  - Super User training & testing
  - Communication and training plans
- What's next
  - Performance testing
  - Delta sequence imports
  - User Training
    Over 125 hands-on training sessions
  - Production rollout
  - User Support

eCTD v4.0 Update

- International Council for Harmonisation (ICH) standards development discussions
  - ICSR (E2B(R3)) and eCTD v4.0 based on Health Level Seven International (HL7) version 3 messaging standard
  - FHIR (Fast Healthcare Interoperable Resources) is HL7's new/future messaging standard
  - ICH M2 is developing recommendations on HL7 FHIR
  - Recommendations will be reviewed during the ICH June meeting

- eCTD v4.0
  - No region is currently accepting eCTD v4.0 messages
  - Regional implementations planned for late 2020 - 2022
  - ICH M8 reviewing implementation options

FDA eCTD Websites

- FDA eCTD Webpage (http://www.fda.gov/ectd)
  - eCTD Guidance & Technical Conformance Guide
  - eCTD Submission Standards
    - Specifications
    - Validation Criteria
    - ICH & FDA DTDs
  - Notices
- FDA eCTD v4.0 Webpage
  (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm309911.htm)
  - FDA Regional Implementation Package
    - Implementation Guide
    - Code List (Spreadsheet and Genericode Files)
    - XML Samples
  - Link to ICH eCTD v4.0 webpage

Digital IND Safety Reporting Program

PDUFA VI Public Meeting on
Electronic Submissions and Data Standards
April 10, 2019

Meredith K. Chuk, M.D.
Acting Associate Director for Safety, OHOP/OND/CDER/FDA

Outline

- Background
- Implementation plans
  - Description of new process
  - Pilot
  - Requirements and timelines for implementation
  - Data flow
  - Types of IND safety reports to be sent to FAERS
- Data elements for IND safety reports using ICH E2B(R2)

IND Safety Reports

Sponsors of clinical trials are required to submit
IND safety reports as per 21 CFR 312.32

Current Process: **PDFs in eCTD format**	**New Process:** **ICH E2B XML files to FAERS**

• Inefficient and labor intensive review
 	
• Lack of universal tracking system
	• Allows for use of data visualization and analytic tools for review and tracking
	
	• In addition:
	  • Leverages existing processes in use for postmarket safety reporting (ICH E2B data standards & FDA gateway)
	  • Complies with existing federal regulations 21 CFR 312.32(c)(1)(v)

Process Pilot

Phase I Feb. 2016 to July 2016 **OHOP–OSE** **Proof of Concept**	**Phase II** Sept. 2017 to July 2019 **Technical Pilot**	**Phase III** Aug. 2019 to Sept. 2019 **End-to-End Testing Pilot**
Stage 1: PDF safety reports manually converted to E2B format Subsequently transmitted to a pre-production environment in FAERS **Stage 2**: Four sponsors each submitted ten safety reports in ICH E2B(R2) format to the FAERS pre-production environment with confirmation of successful processing of data elements	Five participants (Genentech, Merck, AZ, Bayer, and Novartis) participated in parallel submission pilot **Purpose**: • Develop IND safety report E2B submission specifications • Configure FAERS to accept IND safety reports • Develop/finalize technical specification document	Worked through PIMWG to identify sponsors to participate in Phase III pilot testing **Purpose**: Successful submission, processing, routing, and documentation IND of safety report review Ensure the following: • Successful E2B IND safety report receipt, processing, and coding • Reviewer notifications • Review and documentation

Requirements and Timelines

- **Required change in format under 745A(a) of FD&C Act**
  - Sponsors of commercial INDs must submit specified[1] IND safety reports to FAERS by one of two methods:
    - Electronic Submissions Gateway (ESG)

      or
    - Safety Reporting Portal (SRP)
  - Effective 24 months after publication of final guidance

- Goal to begin voluntary submissions in October 2019
  - Date to be published on FAERS website 30 days prior

[1] Those that contain individual patient data

Communication Plan

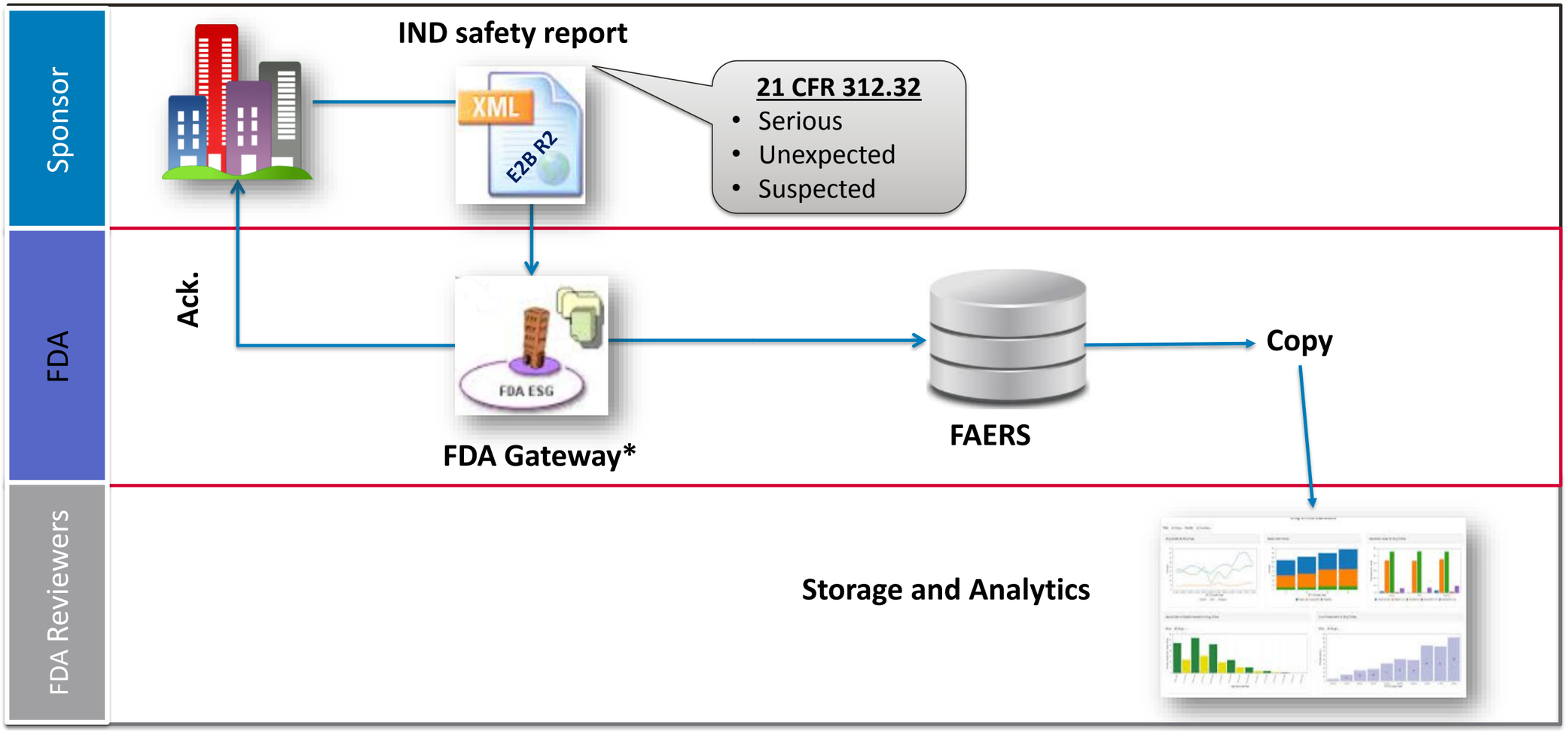
- Draft Guidance with technical conformance guide (TCG) and updated technical specifications to be published together ahead of October 2019

- Updated FAERS website with link to page with information specific to IND safety reports
  - Guidance, TCG, tech specs, use cases, FAQs

- SBIA Webinar

- Other FDA communications

IND Safety Report Data Flow



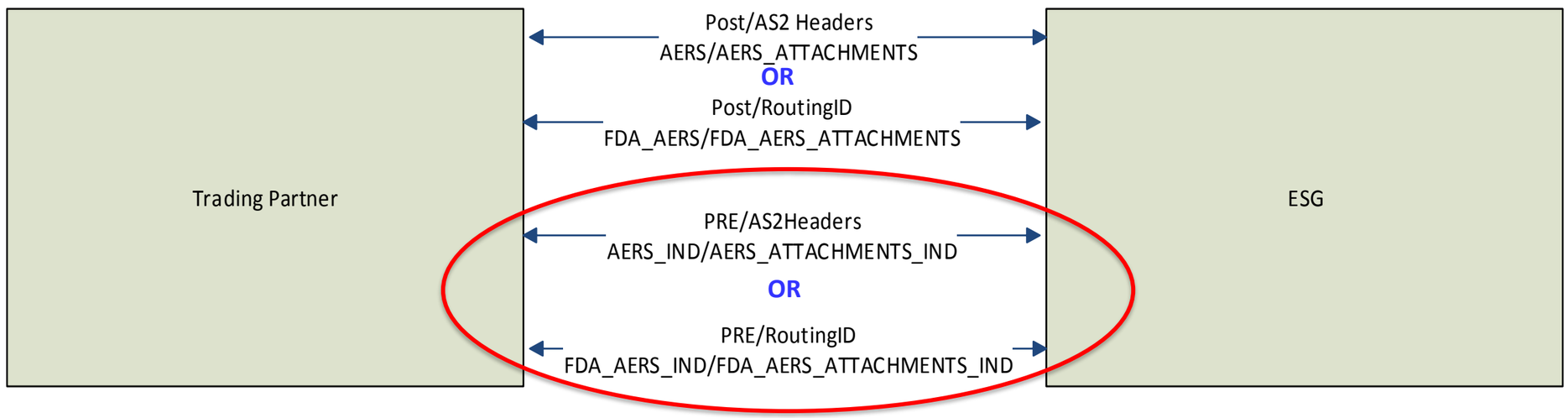
Ack= Acknowledgement
FAERS= FDA Adverse Event Reporting System
*= separate submission path for IND safety reports

Goal to begin accepting E2B(R2) reports = October 2019

Separate Submission Paths for IND and Postmarket Safety Reports

- FDA has defined new header attributes and routing IDs for IND safety reports and attachments

- Two pathways allow separation of premarket from postmarket reports as premarket reports will NOT be posted to the public dashboard



Where to Submit IND Safety Reports

Type of IND safety report	Submit to FAERS	Submit in eCTD format
A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (21 CFR 312.32(c)(1)(i)(A)	X	
One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug 21 CFR 312.32(c)(1)(i)(B)	X	
An aggregate analysis of specific events observed in a clinical trial (known consequences of the underlying disease or condition) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group. (21 CFR 312.32(c)(1)(i)(C)	X	
Findings from other studies (21 CFR 312.32(c)(1)(ii))		X
Findings from animal or in vitro testing (21 CFR 312.32(c)(1)(iii))		X
Increased rate of occurrence of serious suspected adverse reactions (21 CFR 312.32(c)(1)(iv))		X

Technical Specifications

- *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments** will be updated with information for IND reporting

- Data elements for IND number(s)
  - IND number where the event occurred (A.2.3.2)
    - Required to be a valid IND number for processing and routing
  - IND number(s) for cross-referenced IND(s)
    - Repeat A.2.3.2 and A.2.3.3 as many times as needed for other relevant INDs

*https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM601820.pdf

Technical Specifications

- E2B(R2) variables for premarket reporting
  - IND number where event occurred
  - Repeat as needed for cross-referenced IND numbers

Data Element	DTD Descriptor 2.1	Title	Field Length	Element Values for DTD 2.1	Notes
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	35AN	IND Number Under Which the Clinical Trial where the Event Occurred is Conducted For Reports Submitted from an Aggregate Analysis (312.32(c)(1)(i)(C)) from Trials Conducted Under More Than One IND, Use The “Parent” IND Number[1]	Include the Acronym "IND" Followed by a Space and then the IND number for the Application (e.g. IND 123456) Do not populate the Data Element B.4.k.4.1<drugauthorizationnumb> for IND Safety Reports
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s)/ Event(s) were Observed	1N	1= Clinical Trials 2= Individual Patient Use (*e.g. ‘Compassionate Use’ or ‘Named Patient Basis’*) 3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*) 4= Report from Aggregate Analysis 312.32©(1)(i)(C) 5= cross-referenced INDs	Required if Element Value for A.1.4 is 2=Report from Study If Element Value 4 is Chosen, A.1.9 Should = 1.

Technical Specifications

- E2B(R2) variables for premarket reporting
  - Type of report
    - Report from study
  - Expedited criteria
    - New regional data element values (7 and 15 day)
  - Clinical trial identification
    - eCTD study tag name and abbreviated trial name

Data Element	DTD Descriptor 2.1	Title	Field Length	Element Values for DTD 2.1	Notes
A.1.4	<reporttype>	Type of Report	1N	1=Spontaneous 2=Report from Study 3=Other 4=Not Available to Sender (unknown)	Use Element Value 2 for Report from Study
A.1.9	<fulfillexpeditecriteria>	Does this Case Fulfill the Local Criteria for an Expedited Report?	1N	1=Yes 2=No 4=5-Day 5=30-Day 6=7-Day	Use Element Values 1 for 15-Day Expedited Use Element Values 6 for 7-Day Expedited
A.2.3.1	<studyname>	Study Name	100AN	Study ID Associated with eCTD, Study Tagging File (STF) As Used in eCTD Submissions Concatenated using "#" with Abbreviated Trial Name	Use the Format eCTD study ID# Abbreviated Trial Name

Technical Specifications

- Causality assessment
  - At least one product should be a suspect product
  - Default to sponsor assessment
  - Include investigator assessment in B.5.2
  - Recommend binary response (suspected/not suspected)

Data Element	DTD Descriptor 2.1	Title	Field Length	Element Values for DTD 2.1	Notes
B.4.k.18	<drugreactionrelatedness>	Relatedness of drug to reaction/ event			For IND Safety Reports, at Least one Suspect Product should have Relatedness of Drug to Reaction/ Event
B.4.k.18.1a	<drugreactionassesmeddra version>	MedDRA Version for Reaction Assessed	8AN		
B.4.k.18.1b	<drugreactionasses>	Reaction Assessed	250AN		
B.4.k.18.2	<drugassessmentsource>	Source of Assessment	60AN		Default to Sponsor and Include Investigator Assessment in B.5.2
B.4.k.18.3	<drugassessmentmethod>	Method of Assessment	35AN		
B.4.k.18.4	<drugresult>	Result	35AN	1= Suspected 2= Not suspected	

Technical Specifications

- Narrative fields
  - Construct narratives that fit within character limitations
  - Rationale for sponsor assessment should be in B.5.4

Data Element	DTD Descriptor 2.1	Title	Field Length	Notes
B.5.1	<narrativeincludeclinical>	Case Narrative Including Clinical Course, Therapeutic Measure, Outcome and Additional Relevant Information	20,000 AN	ICSR Attachments can be Submitted with additional Information that exceeds the character limitations of 20,000 AN though FDA strongly encourages sponsors to construct narratives that fit within E2B character limitations. Sponsors should not submit attachments for narratives instead of using this field.
B.5.4	<sendercomment>	Sender's comments	2000 AN	Rationale for Sponsor's causality assessment should be in this field

Technical Specifications

- Investigational product identification
  - Active substance, product information

Data Element	DTD Descriptor 2.1	Title	Field Length	Notes
B.4.k.2.1	<medicinalproduct>	Proprietary Medicinal Product Name	70AN	Use Company Product Code if no Established Name, for Multi-Ingredient Products, or if Name Exceeds Character Length
B.4.k.2.2	<activesubstancename>	Active drug Substance Name	100AN	

Technical Specifications

- Reports from aggregate analysis
  - One ‘index’ report with individual ICSRs linked to this report
  - Use ‘parent IND’ number as primary IND
  - New regional data values for study type
  - Patient identifier is ‘aggregate’

Data Element	DTD Descriptor 2.1	Title	Field Length	Element Values for DTD 2.1	Notes
A.1.12	<linkreportnumb>	Identification Number of the Report Which is Linked to This Report	100AN		Used to Link all Individual Cases (safetyreportid) That Make Up an IND Safety Report Submitted as a Result of an Aggregate Analysis as per 312.32(c)(1)(i)(C)
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	35AN	IND Number Under Which the Clinical Trial where the Event Occurred is Conducted For Reports Submitted from an Aggregate Analysis (312.32(c)(1)(i)(C)) from Trials Conducted Under More Than One IND, Use The “Parent” IND Number	Include the Acronym "IND" Followed by a Space and then the IND number for the Application (e.g. IND 123456) Do not populate the Data Element B.4.k.4.1<drugauthorizationnumb> for IND Safety Reports
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s)/ Event(s) were Observed	1N	1= Clinical Trials 2= Individual Patient Use (*e.g. ‘Compassionate Use’ or ‘Named Patient Basis’*) 3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*) 4= Report from Aggregate Analysis 312.32(c)(1)(i)(C)	Required if Element Value for A.1.4 is 2=Report from Study If Element Value 4 is Chosen, A.1.9 Should = 1.
B.1.1	<patientinitial>	Patient Identifier	10AN		For a Report from an Aggregate Analysis, The Element Value Should Be “AGGREGATE”

Benefits to Industry

- Efficiency gains in processing and submission
  - Direct electronic submission to FDA from PV
    - no 1571 or cover letter
  - Ability to automate submission compliance and tracking within safety database
  - Eliminates need to send duplicate reports

- More comprehensive and structured formatting than Medwatch form

- Consistent with format for NDA/BLA and ex-US submissions

Questions

Digital IND Safety Reporting Up Versioning

PDUFA VI Public Meeting on
Electronic Submissions and Data Standards
April 10, 2019

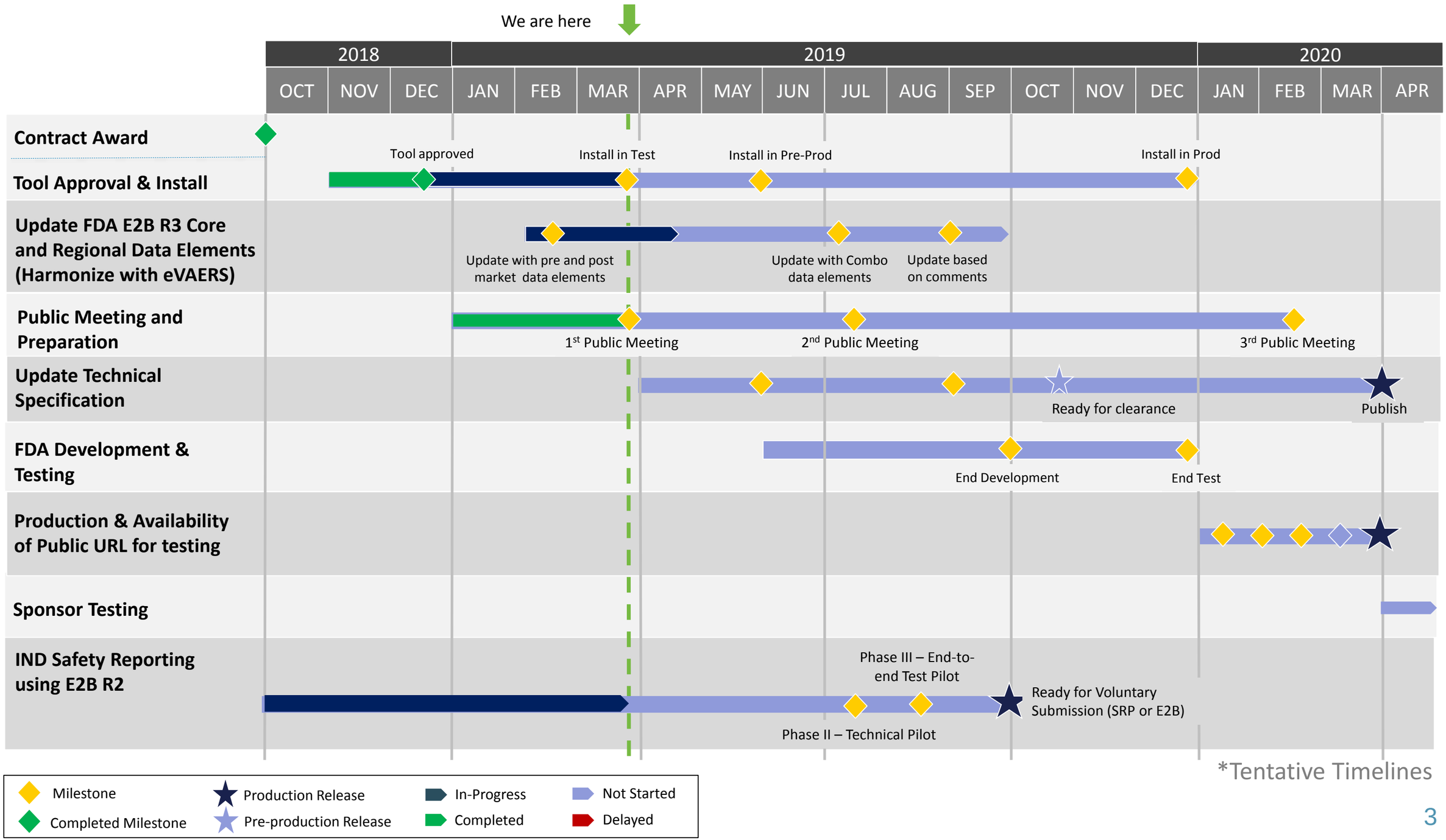
Ta-Jen (TJ) Chen
Project Management Officer, OSP/CDER/FDA

FAERS II - Objectives

- FAERS II - a mission critical system for CDER/CBER
- Provide a modernized system for:
  - surveillance of **pre-market** and **post-market** safety reports along with **product quality defect** reports
  - one-stop shop solution for intake, triage and case processing
  - allows for **enhanced and unified data analytics** and **signal management lifecycle** solution
- Achieve compliant with data standards - ICH E2B R3

HHS has designated FAERS II as a Modernization Priority

FAERS II - E2B R3 Roadmap*

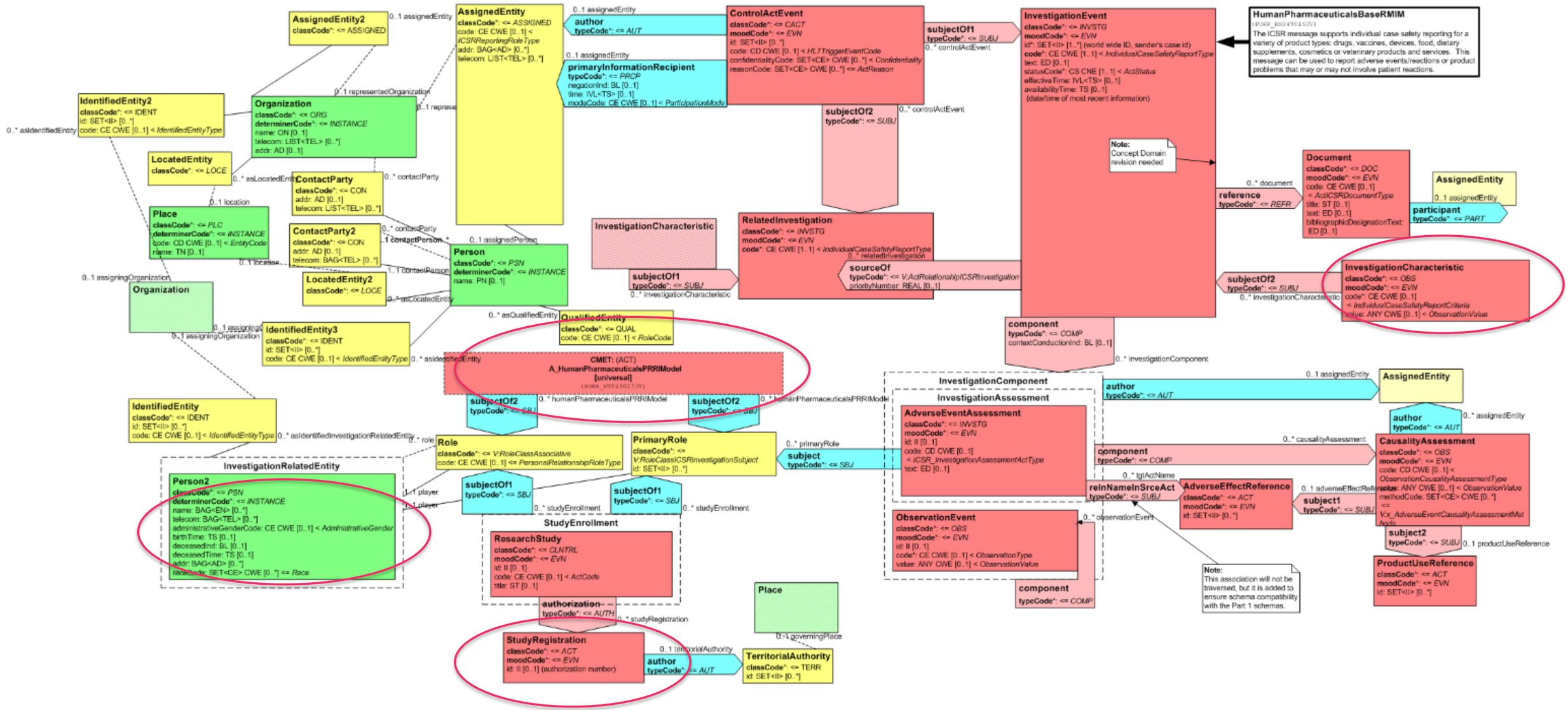


*Tentative Timelines

ICH E2B Up Versioning Resource

- ICH E2B(R3) IG Package
  - http://estri.ich.org/e2br3/E2B(R3)_IG_Complete_Package_v1_07.zip
  - Appendix I (B) ICH ICSR Backwards and Forwards Compatibility (BFC) Recommendations
  - Appendix I (H) ICH ICSR BFC conversion

FDA Report Type and Combination Product Flag



Administrative and Identification Elements

R2 Element	R2 Element Name	Data Type	Element Values for DTD 2.1	R3 Element	R3 Element Name	Data Type	Element Values
A.1.9	Does This Case Fulfill the Local Criteria for an Expedited Report?	1N	1=yes (expedited) 2=no (non-expedited) 4=5-Day 5=30-Day	C.1.7	Does This Case Fulfil the Local Criteria for an Expedited Report?	Boolean	False, True, NI
				FDA.C.1.7.1	FDA Report Type (MedWatch G.7)	1N	1=15-Day 2=Periodic 4=5-Day 5=30-Day 6=7-day
A.1.0.1	Sender's (case) Safety Report Unique Identifier (safety report identifier)	100AN	Manufacturer Control Number (MCN)	C.1.1	Sender's (case) Safety Report Unique Identifier	100AN	
A.1.10.1	Regulatory Authority's Case Report Number	100AN		C.1.8.1	Worldwide Unique Case Identification Number	100AN	
A.1.10.2	Other Sender's Case Report Number	100AN		C.1.8.2	First Sender of This Case	1N	1=Regulator 2=Other
A.3.1.2	Sender Identifier (sender organization)	60AN		C.3.2	Sender's Organisation	100AN	

Administrative and Identification Elements for IND Safety Report

R2 Element	R2 Element Name	Data Type	Element Values for DTD 2.1	R3 Element	R3 Element Name	Data Type	Values
A.1.4	Type of report	1N	1=Spontaneous 2=Report from study 3=Other 4=Not available to sender (unknown)	C.1.7	Type of report	1N	1=Spontaneous 2=Report from study 3=Other 4=Not available to sender (unknown)
A.2.3.1	Study name	100AN		C.5.2	Study name	2000AN	Study ID Associated with eCTD, study tagging file (STF) concatenated with abbreviated trial name using "#"
A.2.3.3	Study type in which the reaction(s)/event (s) were observed	1N		C.5.4	Study type where reaction(s)/event(s) were observed	1N	1=Clinical trials 2=Individual patient use(e.g. 'compassionate use' or 'named patient basis') 3=Other studies (e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring) Required if Element Value for A.1.4 is 2=Report from study
A.2.3.2	Sponsor study number	35AN	IND number under which the clinical trial where the event occurred is conducted	FDA.C.5.5	IND or PANDA # where AE Occurred	10AN	IND number under which the clinical trial where the event occurred is conducted
				FDA.c.5.r.6	IND # for other INDs with same suspect product	10AN	Repeatable

Patient Race and Ethnicity

Section D: Patient Characteristics

a. FDA.D.11.r. : Patient Race Code

- Identifies the race of the patient and a patient can have one or more race
- Data length and Type: 10AN
- Value Allowed: C16352 = African American, C41259 = American Indian or Alaska Native, C1260 = Asian, C1219 = Native Hawaiian or Other Pacific Islander, C41261 = White
- Conformance: Mandatory
- Business Rule: Must use a valid value or HL7 null flavor. NullFlavors: UNK, MSK, OTH

b. FDA.D.12: Patient Ethnicity Code

- Identifies the ethnicity of the patient
- Data length and Type: 10AN
- Value Allowed: C17459 = Hispanic or Latino, C41222 = Non Hispanic or Latino
- Conformance: Mandatory
- Business Rule: Must use a valid value or HL7 null flavor

Receiver Information

- E2B(R2) batch level information maps to E2B(R3) N.1.x
  - ***Batch Sender Identifier N.1.3***
  - Senders should use the Data Universal Numbering System (DUNS) number for N.1.3 using the Dun and Bradstreet (D&B) Object Identifier1.3.6.1.4.1.519.1.
- E2B(R2) message Level (A.3.2.1, A.3.2.2, and A.3.2.3) to N.2.r.3 in R3
  - ***Message Receiver Identifier N.2.r.3***
  - FDA uses two different message receiver identifiers for test and production submissions. These identifiers are:
    - For Test ICSR Submissions: ZZFDATST
    - For Production ICSR Submissions: ZZFDA

Testing Plan and Method

- No compliance date has been set for R3 submission
- Sponsors can start testing anytime after March 2020
- FDA to provide a validator to pre test sender's ICSR
  - Validator can be accessed via public URL
- Once validated Sponsor's can submit ICSRs in preproduction environment and receive Acks
- Sponsor's continue to submit ICSRs in R2 format until ready for R3

Testing Plan and Method

- Sponsor's must test both premarket and postmarket (including combo product) ICSRs
- Sponsor's must notify FDA when ready for first production submission to FDA
- In future, FDA plan to conduct cross regional testing
- All question during testing must be sent to eprompt@fda.hhs.gov

Next Steps

- Invite comments via the docket on topics discussed in March 2019 ePrompt meeting by April 25, 2019
- Update schema with regional elements
- Update FDA Regional Implementation Specifications for ICH E2B(R3) Implementation
  - Incorporate comments received via the docket
- Prepare for the next meeting on July 17, 2019
  - Discuss data elements related to combination product
- Prepare sample regional E2B R3 data files
- Contact: eprompt@fda.hhs.gov after the docket timeframe

Pharmaceutical Quality and Chemistry, Manufacturing, and Controls (PQ/CMC) Project Overview

G. Scott Gordon
Data Standards Team
Office of Strategic Programs
CDER

PQ/CMC Project

Goal:

- Establish electronic standards for submitting Pharmaceutical Quality (PQ) and Chemistry & Manufacturing Controls (CMC) data
- Provide for pre-population of assessment templates
- Build a PQ/CMC knowledge-base

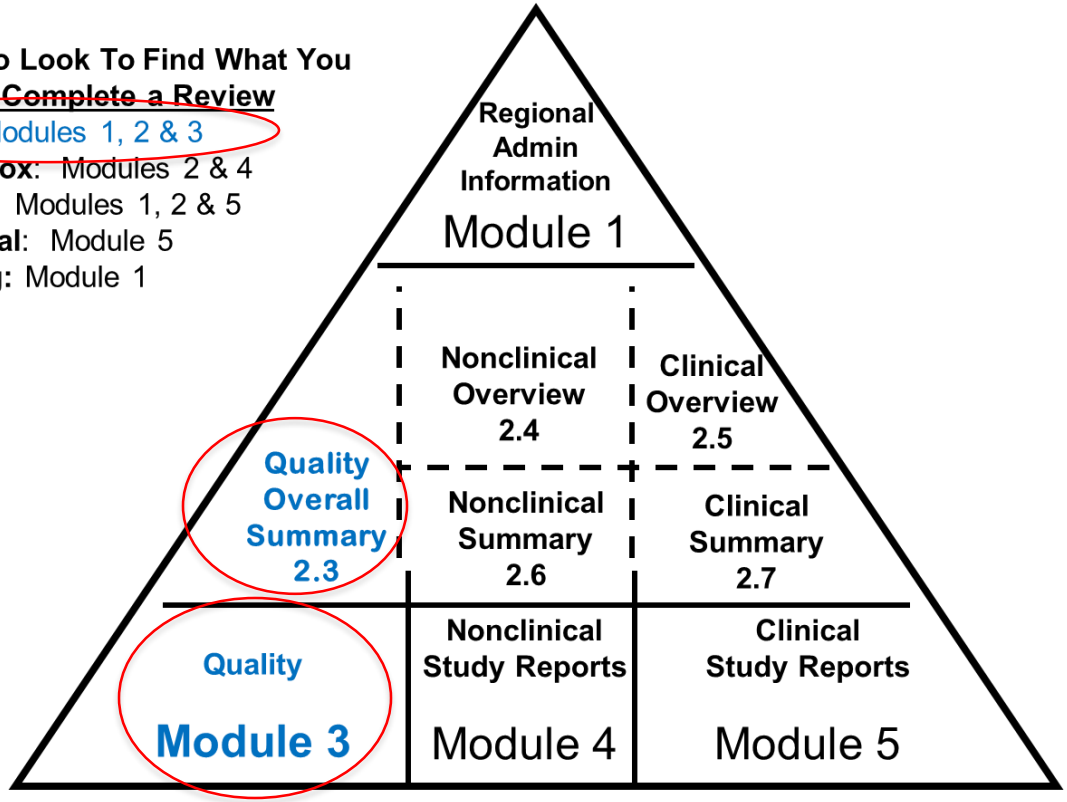
Objectives:

- Develop structured data standards for PQ/CMC
- Implement a data exchange standard for submitting PQ/CMC data

PQ/CMC Scope: Module 3 of eCTD

Where to Look To Find What You Need to Complete a Review

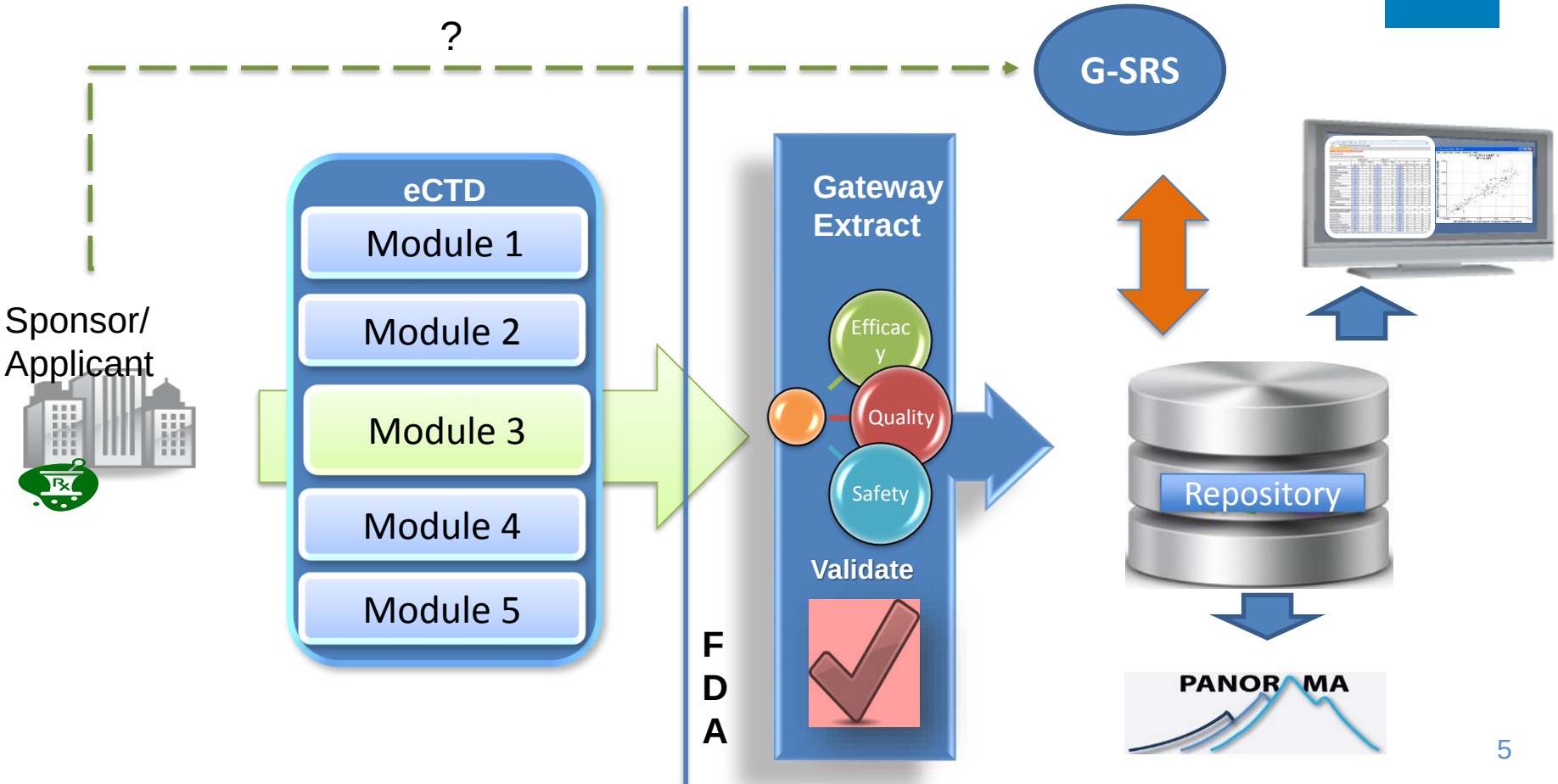
CMC: Modules 1, 2 & 3
Pharm/Tox: Modules 2 & 4
Clinical: Modules 1, 2 & 5
Statistical: Module 5
Labeling: Module 1



Expected Benefits

- FDA
  - Receives consistent high-quality data that can be consumed by computer systems without data entry and interpretations
  - Enables much-needed technology improvements to support quality assessments
  - Improves crisis response
- Stakeholders
  - Provides consistent exchange formats for:
    - Internal data management & storage (e.g. in LIMS)
    - Data exchange with CMOs (Contract Manufacturing Organizations)
  - Ensures industry and FDA are using the “same data”

Future State with Structured Data



Where We Are (1 of 4)

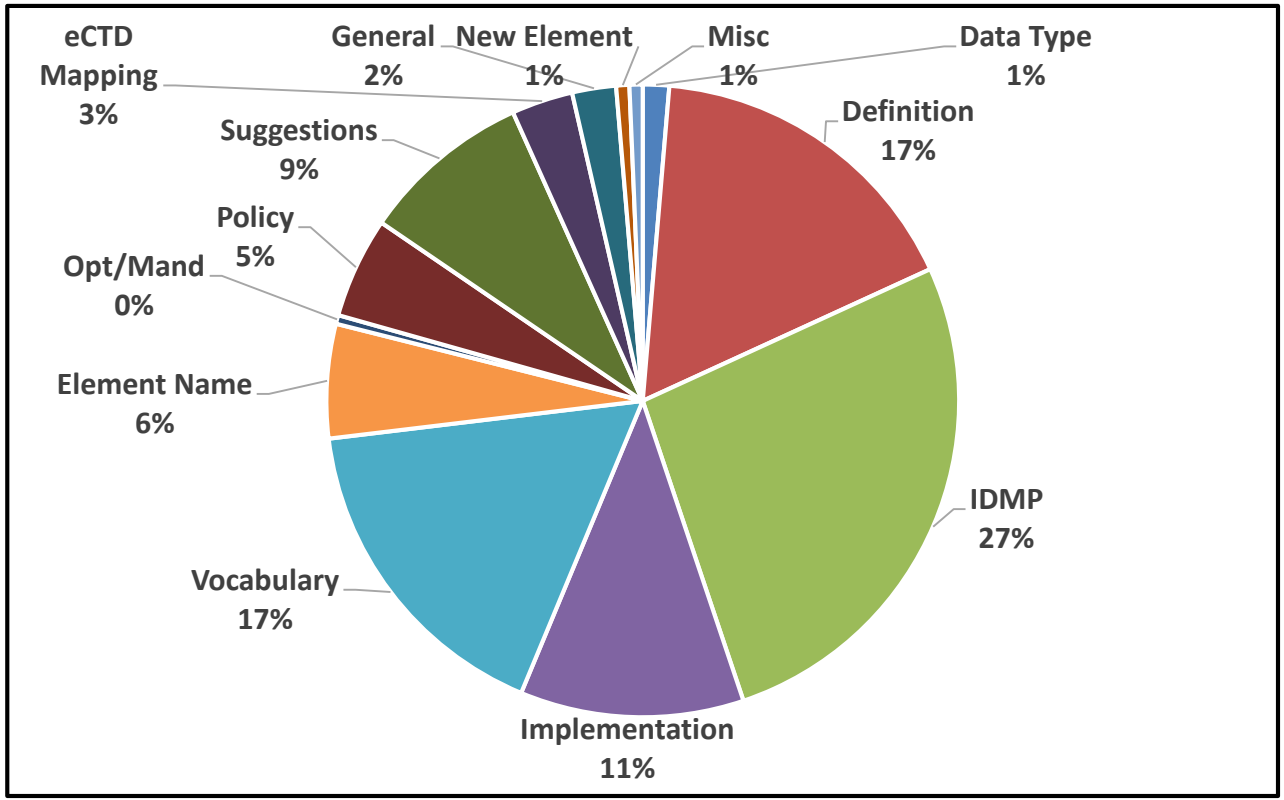
- The cross-center initiative involves FDA reviewers from CDER, CBER and CVM
- Over 150 data elements within eCTD Module 3 (CMC) were analyzed, definitions identified, and controlled terminologies developed where appropriate
- PQ/CMC Data Elements & Controlled Terminology was published for public comment in July 2017
  - https://www.regulations.gov/document?D=FDA_FRDOC_0001-7545

Where We Are (2 of 4): Public Comments Summary

- 11 Organizations provided over 480 comments
  - Overall a positive response to structuring and standardization of CMC data
  - Detailed review of comments resulted in a number of changes

- Some general themes:
  1. Need FDA's overall strategic plan
  2. Avoid duplication of effort and submission
  3. Plans for global harmonization for regulators
  4. Harmonize with IDMP
  5. FDA asking for more than what is in the dossier
  6. Terms are small molecule centric
  7. Provide flexibility in adding new data elements and terminology
  8. Collaborate with Allotrope and leverage that work, where relevant

Where We Are (3 of 4): Public Comments by Categories



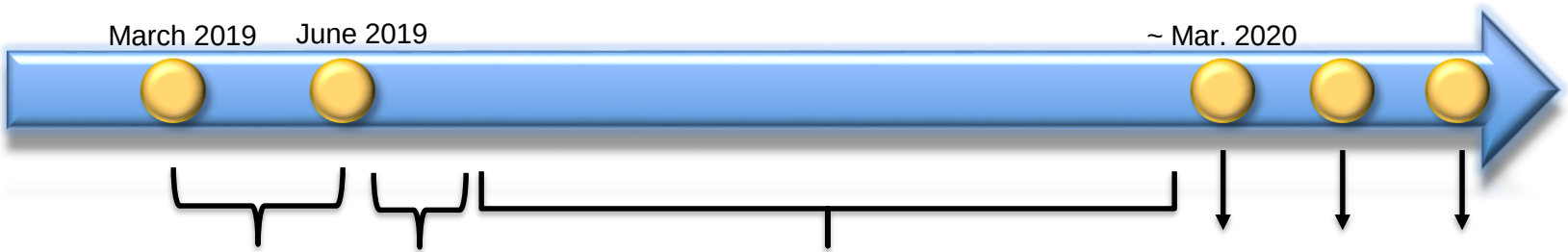
Where We Are (4 of 4)

- Harmonizing with ISO IDMP, where feasible
  - Detailed mapping complete (83 pages)
  - Initial interactive session with industry April 3
- Discussion within ICH M2 about a potential quality topic
  - M2 project opportunity proposal in progress
- Several possible electronic data exchange mechanisms evaluated

Next Steps

- Continue to reconcile PQ/CMC with IDMP where possible
- Develop & test PQ/CMC Data Exchange Standard
  - Originally considered HL7 SPL but unable to address full requirements
  - Evaluating HL7 FHIR as an alternate option
  - Proof of concept using Quality Specification will inform next steps for rest of PQ/CMC
- Develop draft guidance(s)

Draft Timeline for PQ/CMC



Industry participation for FHIR proof-of-concept (Subset of PQ/CMC - Phased approach)

Assess feasibility of FHIR

- End-to-end system test using FHIR
- Continue data exchange development
- Continued testing with Industry
- Develop draft guidance

DRAFT Guidance for Specifications

Followed by rounds of guidance for subsequent domains

Longer Term

- This project covers 1/3rd of submitted CMC data
- Other CMC data may be addressed in future
  - For example: manufacturing process

Structured PQ/CMC Data

Norman R. Schmuff
CDER, Office of Pharmaceutical Quality
Office of Process and Facilities
April 10, 2019

Goals

- PQ/CMC
  - Establish electronic standards for submitting Pharmaceutical Quality (PQ) and Chemistry & Manufacturing Controls (CMC) data
- KASA
  - Establish a structured pre-populated assessment template
  - Establish risk-ranking algorithms
  - Move assessments from narrative stories to structured documents, suitable for knowledge-management

Objectives

- PQ/CMC: Structured submission data for
  - Pre-population of review templates
  - Building a product quality knowledge-base
  - Implement a technical exchange standard
- KASA
  - Providing structured assessment & eliminate text-based narratives
  - Establish algorithms to facilitate risk identification & mitigation
  - Capture knowledge from assessments

Scope

- PQ/CMC
  - Long-term: Most data in CTD Module 3
  - Present: Specifications, stability, components & composition
- KASA
  - Long-term: All OPQ assessments
  - Present: Limited number of ANDAs

PQ/CMC data in eCTD Module 3 and Module 2 QOS

- Specification(drug substance/drug product/excipients)
- Batch Analysis (drug substance/drug product)
- Stability(drug substance/drug product)
- Nomenclature of Drug Substance
- Composition of Drug Product
- Batch Formula
- Impurities
- Manufacturing Process
- Annual BLA Lot Distribution Report
- CMC Changes in Annual Report – NDA/ANDA/BLA/NADA/ANADA
- Analytical Procedure Validation
- Facility Information

Note:
- Stability Analysis supported by extant HL7 eStability message (to be revised)
- Deferred to next version of PQ/CMC

eCTD Module 3 Sections

3.2.S DRUG SUBSTANCE (NM, MANF)

- ***3.2.S.1 General Information (nm, manf)***
  - 3.2.S.1.1 Nomenclature (nm, manf)
  - 3.2.S.1.2 Structure (nm, manf)
  - 3.2.S.1.3 General Properties (nm, manf)
- ***3.2.S.2 Manufacture (nm, manf)***
  - 3.2.S.2.1 Manufacturers (nm, manf)
  - 3.2.S.2.2 Description of Manuf Process and Controls (nm, manf)
  - 3.2.S.2.3 Control of Materials (nm, manf)
  - 3.2.S.2.4 Controls of Critical Steps and Intermediates (nm, manf)
  - 3.2.S.2.5 Process Validation and/or Evaluation (nm, manf)
  - 3.2.S.2.6 Manufacturing Process Development (nm, manf)
- ***3.2.S.3 Characterisation (nm, manf)***
  - 3.2.S.3.1 Elucidation of Str and other Characteristics (nm, manf)
  - 3.2.S.3.2 Impurities (nm, manf)
- ***3.2.S.4 Control of Drug Substance (nm, manf)***
  - 3.2.S.4.1 Specification (nm, manf)
  - 3.2.S.4.2 Analytical Procedures (nm, manf)
  - 3.2.S.4.3 Validation of Analytical Procedures (nm, manf)
  - 3.2.S.4.4 Batch Analyses (nm, manf)
  - 3.2.S.4.5 Justification of Specification (nm, manf)
- ***3.2.S.5 Reference Standards or Materials (nm, manf)***
- ***3.2.S.6 Container Closure System (nm, manf)***
- ***3.2.S.7 Stability (nm, manf)***
  - 3.2.S.7.1 Stability Summary and Conclusions (nm, manf)
  - 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (nm, manf)
  - 3.2.S.7.3 Stability Data (nm, manf)

Top Priority

2nd Priority

Extant HL7 Standard

3.2.P DRUG PRODUCT (NM, DF)

- *3.2.P.1 Description and Composition of the DP (nm, df)*
- *3.2.P.2 Pharmaceutical Development (nm, df)*
- *3.2.P.3 Manufacture (nm, df)*
  - 3.2.P.3.1 Manufacturer(s) (nm, df)
  - 3.2.P.3.2 Batch Formula (nm, df)
  - 3.2.P.3.3 Description of Manuf Process and Process Controls (nm, df)
  - 3.2.P.3.4 Controls of Critical Steps and Intermediates (nm, df)
  - 3.2.P.3.5 Process Validation and/or Evaluation (nm, df)
- *3.2.P.4 Control of Excipients (nm, df)*
  - 3.2.P.4.1 Specifications (nm, df)
  - 3.2.P.4.2 Analytical Procedures (nm, df)
  - 3.2.P.4.3 Validation of Analytical Procedures (nm, df)
  - 3.2.P.4.4 Justification of Specifications (nm, df)
  - 3.2.P.4.5 Excipients of Human or Animal Origin (nm, df)
  - 3.2.P.4.6 Novel Excipients (nm, df)
- *3.2.P.5 Control of Drug Product (nm, df)*
  - 3.2.P.5.1 Specification(s) (nm, df)
  - 3.2.P.5.2 Analytical Procedures (nm, df)
  - 3.2.P.5.3 Validation of Analytical Procedures (nm, df)
  - 3.2.P.5.4 Batch Analyses (nm, df)
  - 3.2.P.5.5 Characterisation of Impurities (nm, df)
  - 3.2.P.5.6 Justification of Specification(s) (nm, df)
- *3.2.P.6 Reference Standards or Materials (nm, df)*
- *3.2.P.7 Container Closure System (nm, df)*
- *3.2.P.8 Stability (nm, df)*
  - 3.2.P.8.1 Stability Summary and Conclusion (nm, df)
  - 3.2.P.8.2 Post-approval Stability Protocol and Commitment
  - 3.2.P.8.3 Stability Data (nm, df)

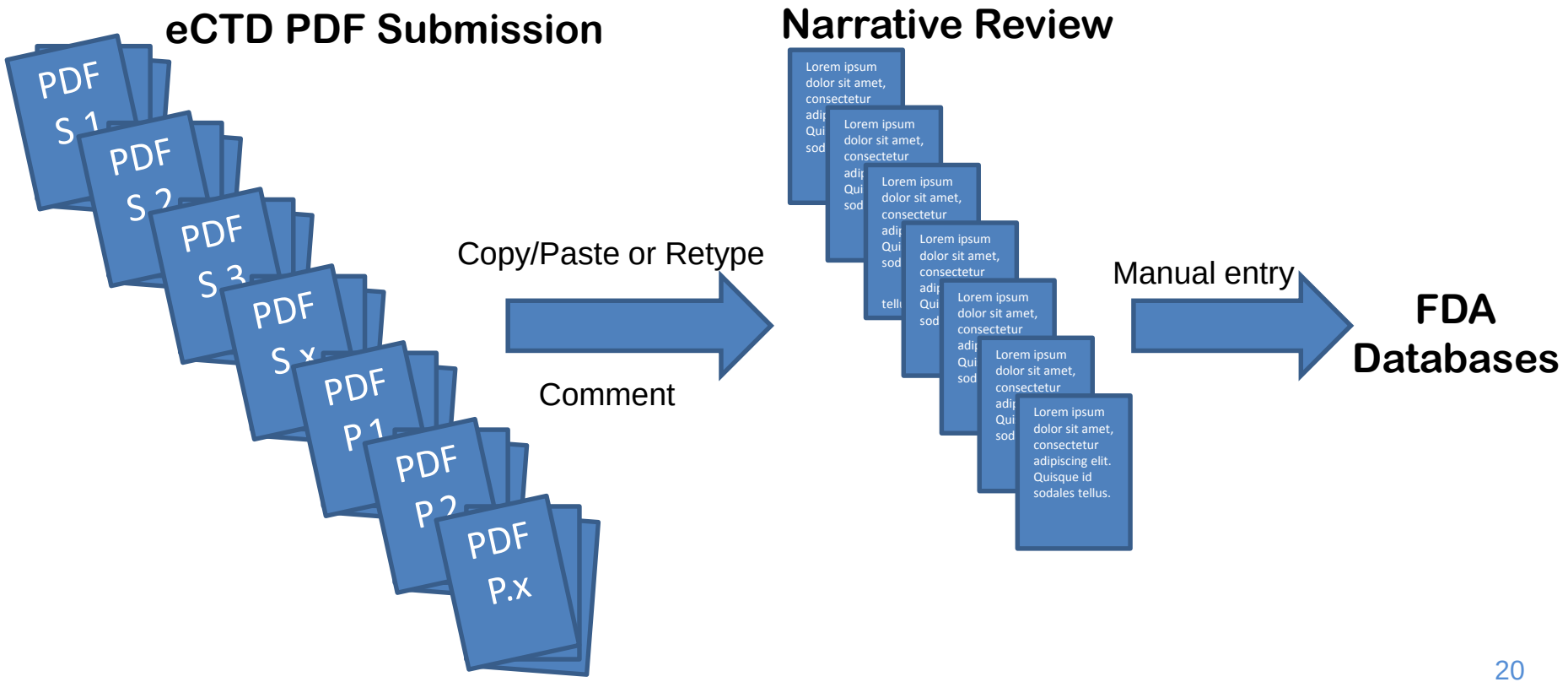
FDA

2nd Priority

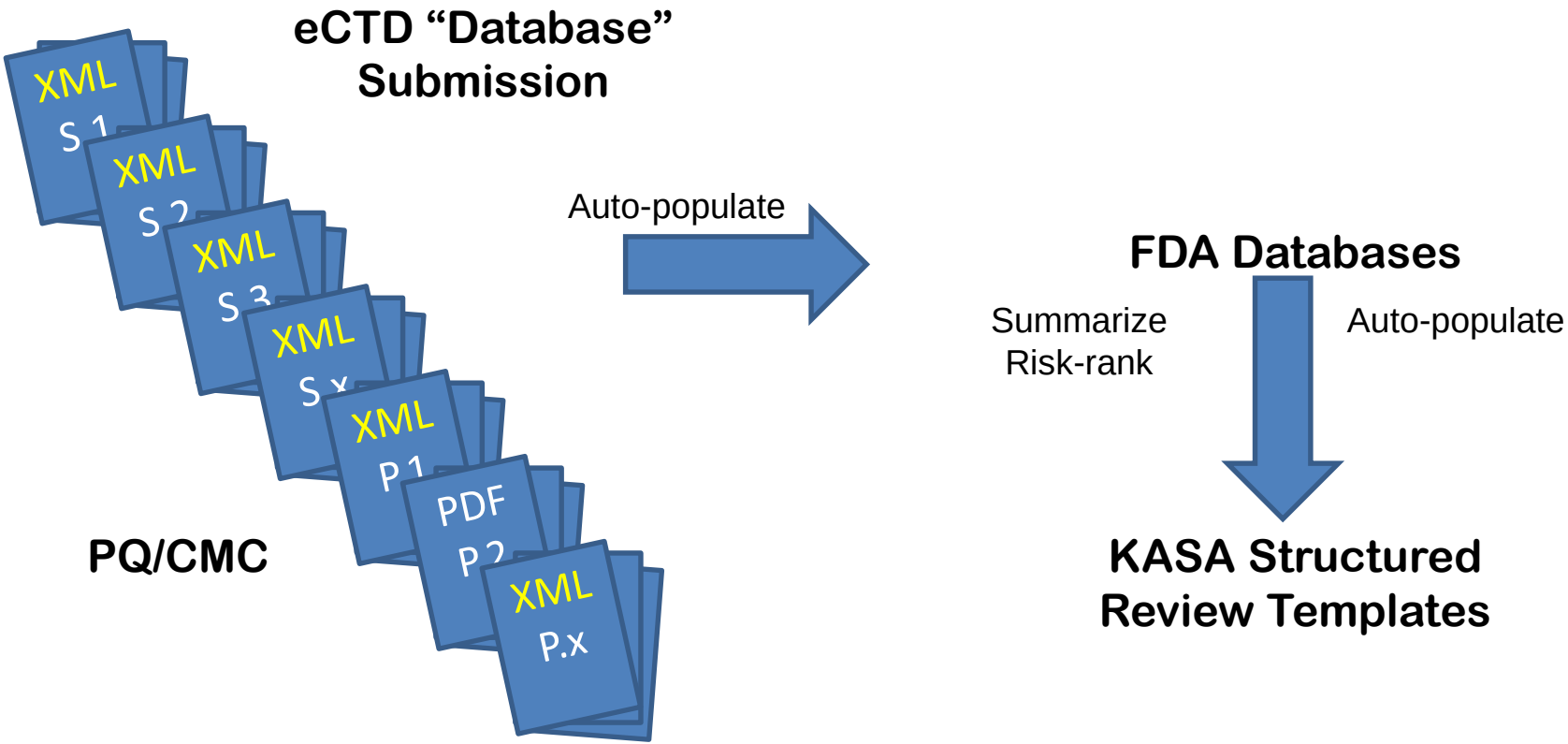
Top Priority

Extant HL7 Standard

Current Module 3 Submission Model

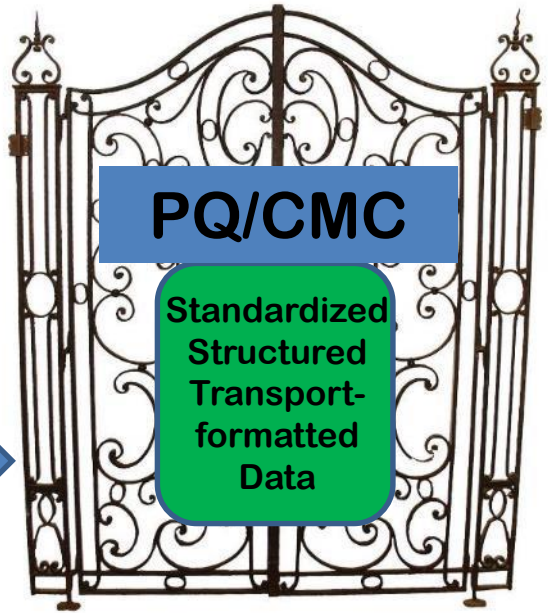


Future Module 3 Submission Model



Future State: Information Flow

Applicant's Regulatory Information Management System

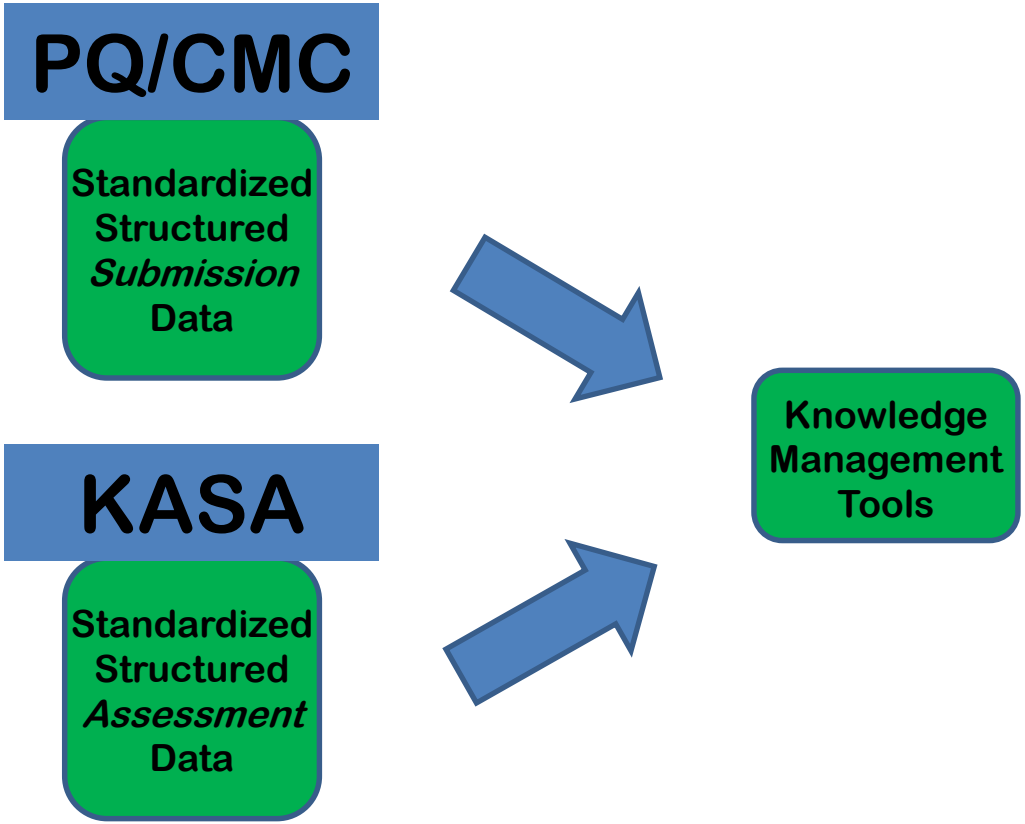


FDA Electronic Submission Gateway

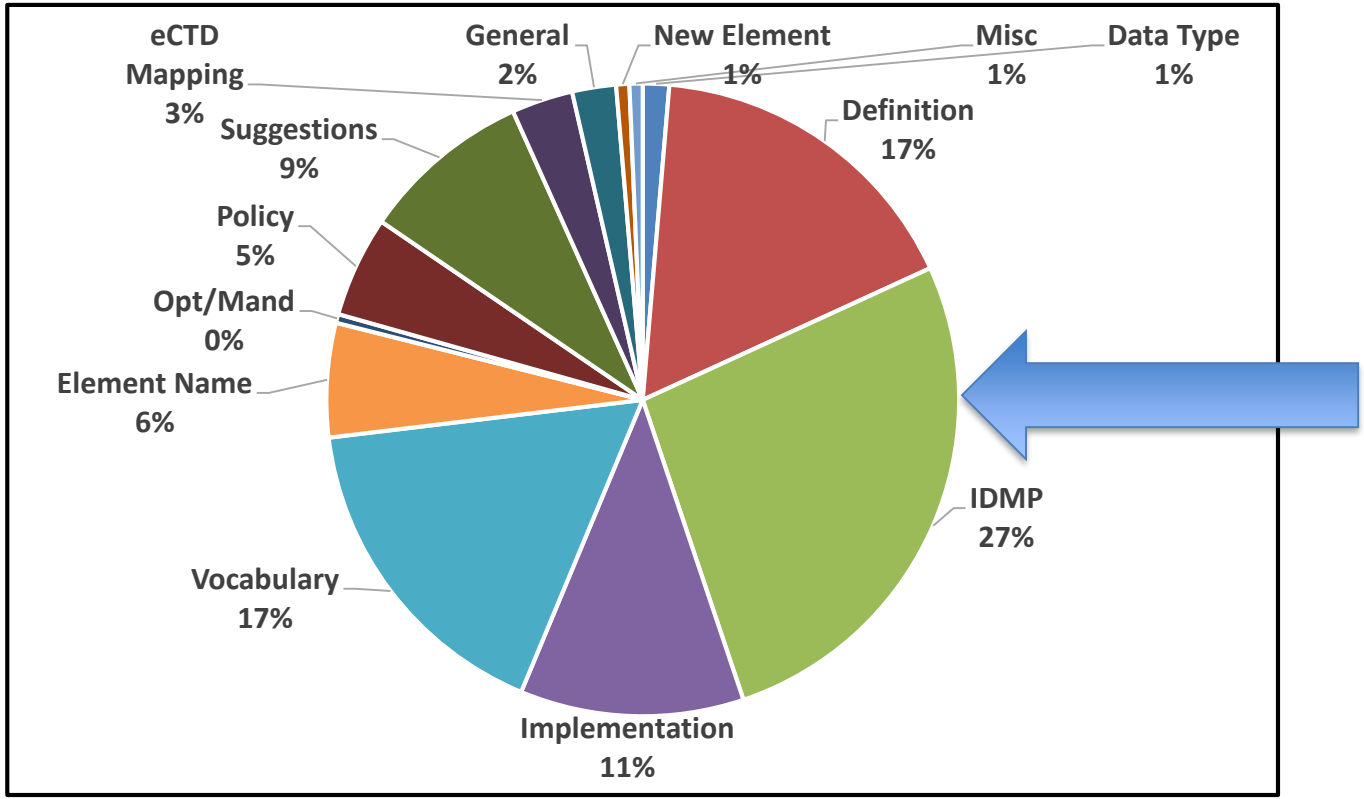
KASA OPQ Template

Pre-populated Review Template

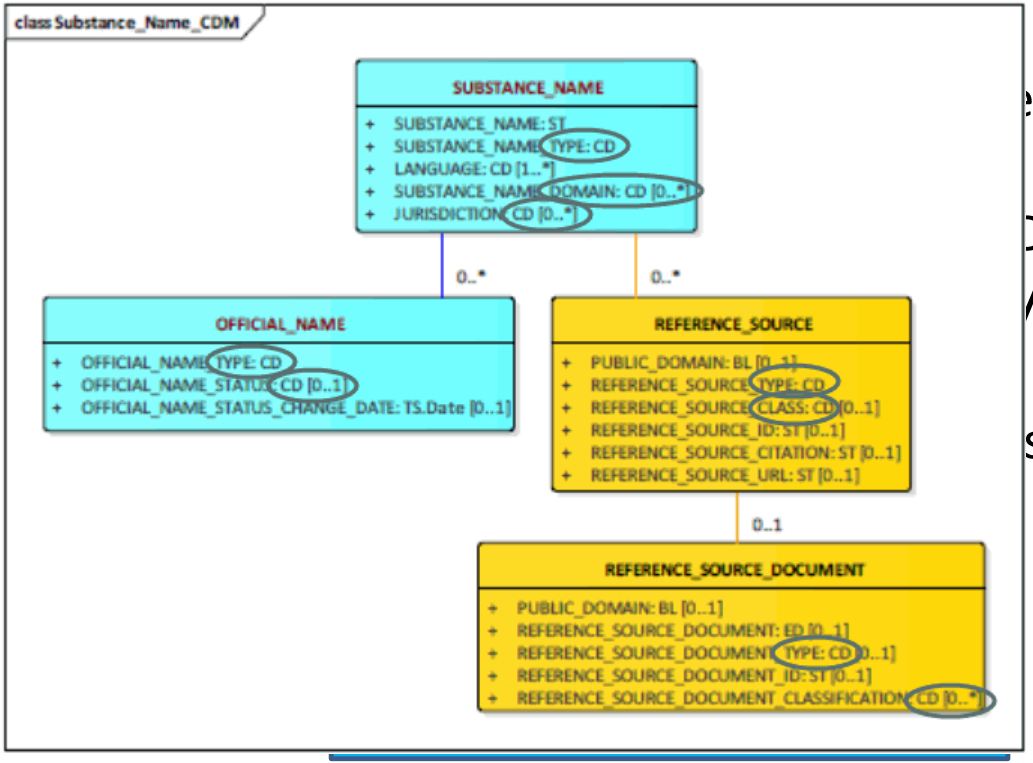
Future State: Data Flow



Public Comments by Categories



PQ/CMC IDMP Challenges

- 

ers from PQ/CMC

D) undefined

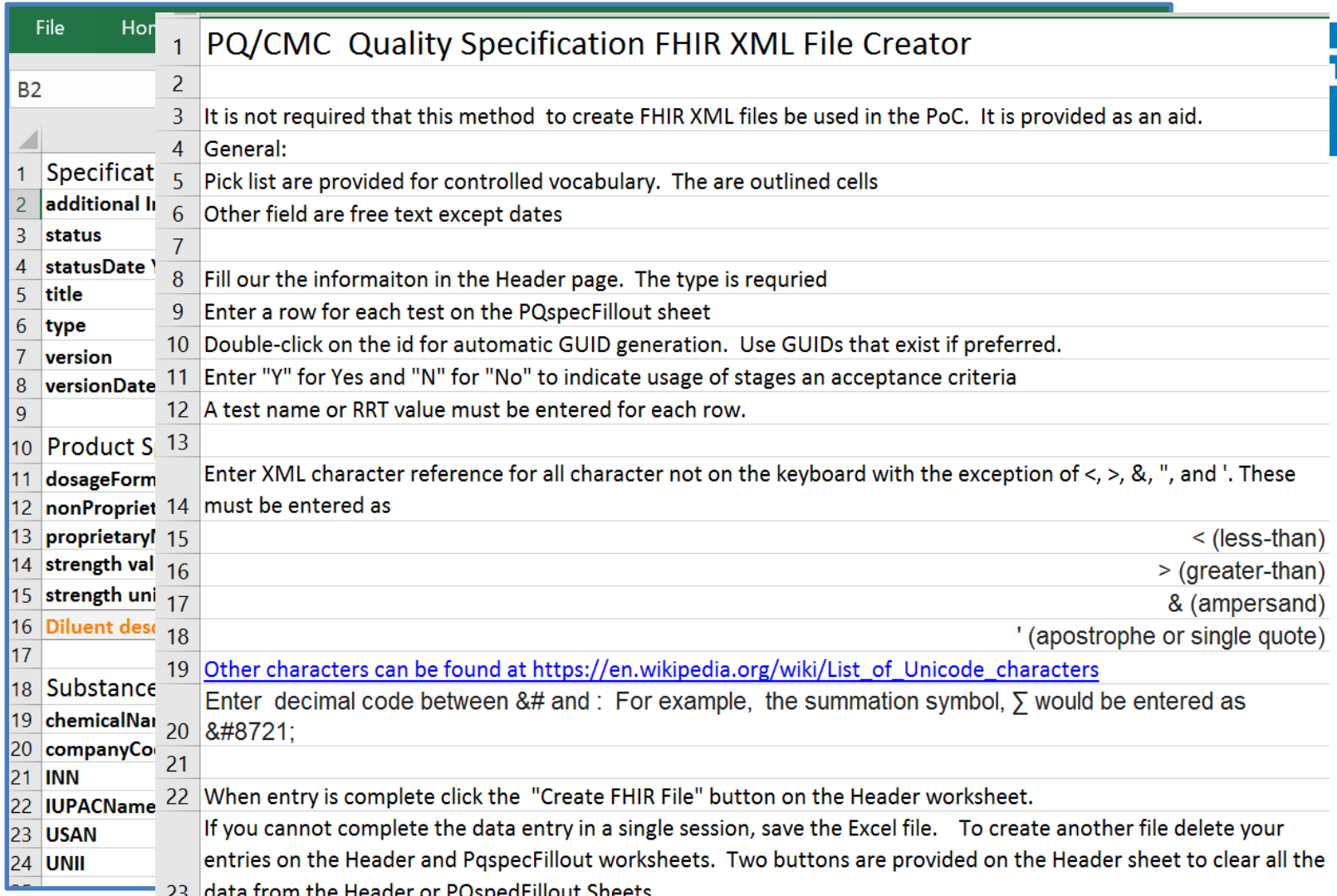
MP

s)

Data Element Name	Data Element Name Definition	Data type	FDA ISO IDMP 11238/11615 Mapping	Industry IDMP Comments
Batch or Lot Number (Bulk Batch ID)	A combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined. [Source : Adapted reference: 21 CFR 210.3 Definitions (4/1/2014)]	Text	GAP Note: FDA term is a broader, more general term than the BAID, and would sit higher in a hierarchy. It is not restricted to Medicinal Product (packaged stuff), although it incorporates both BAID1 and BAID2. For an unboxed bottle or vial, it probably corresponds to BAID2 (immediate container); for a boxed container (bottle or vial) probably BAID1 (outer). As was previously said, in many cases the value would be the same in our system because at this level the lot number generally represents the drug in its container, and for single container/multiple same container, that carries over to any additional packaging. The NDC# would perhaps distinguish single/multiple container instances. (we are excluding multi-unit shipping cartons here)	Comment (Sanofi): Batch or Lot numbers are often used interchangeably. Although synonymous, suggest some guidance be provided for the purpose of harmonization. For example, Lot is often used for bulk materials and Batch is often used for packaged products. Or define that Lot is normally used for drug substance and Batch is normally used for drug product. It is not clear how this element aligns with ISO 11615:2017 regarding Medicinal Products or ISO 11238:2017 regarding Substances. ISO 11615:2017 uses the term “Batch identifier” and the abbreviation “BAID” and applies this term to “Medicinal Products” and to “Investigational Medicinal Products” in the ISO 11615:2017 standard (see section 9.6.2.7). Note that IDMP does not seem to have a “bulk batch ID”. Proposed change: Provide clarification regarding the interchangeability of the terms batch and lot number. Ensure alignment of PQ/CMC terms with ISO 11615:2017 or explain the mapping of the FDA terms PQ/CMC data elements to those used in the IDMP standards.

Where We Are

- PQ/CMC
  - Working with HL7 on FHIR message
  - Proof of Concept using XML FHIR implementation
    - Limited to specification
    - Tcons with seven PhRMA participants
      - Initial calls completed
      - “Deep-dive” calls ongoing
    - Submissions expected by June
- KASA
  - Template refinement
  - Data mining for impurity ID and acceptance criteria


File
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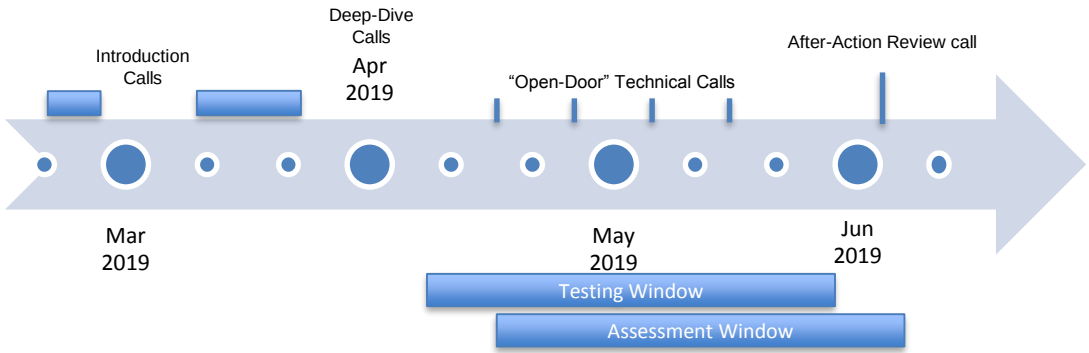
1 Specificat
2 additional I
3 status
4 statusDate
5 title
6 type
7 version
8 versionDate
9
10 Product S
11 dosageForm
12 nonPropriet
13 proprietaryI
14 strength val
15 strength uni
16 Diluent des
17
18 Substance
19 chemicalNa
20 companyCo
21 INN
22 IUPACName
23 USAN
24 UNII
1 PQ/CMC Quality Specification FHIR XML File Creator
2
3 It is not required that this method to create FHIR XML files be used in the PoC. It is provided as an aid.
4 General:
5 Pick list are provided for controlled vocabulary. The are outlined cells
6 Other field are free text except dates
7
8 Fill our the informaiton in the Header page. The type is requried
9 Enter a row for each test on the PQspecFillout sheet
10 Double-click on the id for automatic GUID generation. Use GUIDs that exist if preferred.
11 Enter "Y" for Yes and "N" for "No" to indicate usage of stages an acceptance criteria
12 A test name or RRT value must be entered for each row.
13
14 Enter XML character reference for all character not on the keyboard with the exception of <, >, &, ", and '. These must be entered as
15 < (less-than)
16 > (greater-than)
17 & (ampersand)
18 ' (apostrophe or single quote)
19 Other characters can be found at https://en.wikipedia.org/wiki/List_of_Unicode_characters
20 Enter decimal code between &# and : For example, the summation symbol, ∑ would be entered as ∑
21
22 When entry is complete click the "Create FHIR File" button on the Header worksheet.
23 If you cannot complete the data entry in a single session, save the Excel file. To create another file delete your entries on the Header and PqspecFillout worksheets. Two buttons are provided on the Header sheet to clear all the data from the Header or PQspedFillout Sheets

PQ/CMC PoC Timeline



U.S. FOOD & DRUG ADMINISTRATION

Evaluation of HL7 FHIR Exchange Standard for Regulatory Applications

PDUFA VI Public Meeting

April 10, 2019

Health Level Seven International (HL7)

- HL7 is a healthcare standards development organization
  - An ANSI-accredited SDO
- Provides a framework for the exchange of electronic health information
- The primary objective to support clinical practice
  - Management, delivery and evaluation of health services
- Members include providers, vendors, payers, and regulatory agencies
  - Represented across 35 countries

HL7 V3 Exchange Format

- HL7 Version 3 (V3) exchange standard
  - Utilized by several FDA applications (e.g. SPL and ICRS)
- However, HL7 V3 is aging
  - Low uptake outside of regulatory agencies
  - Overly complex for the regulatory submission needs
  - Limited support horizon (tools, training, implementors)
  - Superseded by the next version – FHIR
- FDA interest in FHIR is primarily based on its wide uptake
  - In line with the federal guidelines to adopt voluntary consensus standards*

(*) In conformance with the OMB Circular A–119 "Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities

HL7 FHIR*

- Fast Healthcare Interoperability Resources (FHIR)
- Combines features of previous HL7 versions
- Strong focus on fast implementation
- Facilitates flexible real-time exchange
  - Mobile devices, web-based applications, cloud communications, and EHRs
  - E.g. downloads of EHR data through Apple's Health app
- Easily understood human-readable format
- Specification is free for use with no restrictions
- Global community of developers and implementers
- Rapidly adopted by healthcare community

(*) Adapted from the HL7 public materials and presentations

Major components of FHIR

- Resource
  - A shared human-readable set of metadata components
  - E.g. Patient, Substance, Questionnaire, AdverseEvent
- Profile
  - Refines Resources for specific use cases
- Document
  - A collection of FHIR records
  - Can be securely signed by users
- Message
  - Supports communication of content between systems
- API (application programming interface)
  - Enables external parties to access distributed data

FHIR Current Status

- The evaluation of standards is forward-looking
  - Requires good understanding of the degree of maturity
- FHIR R4 has just passed the HL7 normative ballot
  - Ready to be submitted to ANSI as a normative standard
  - Ensures backward compatibility in the future
    - For applications that implement the normative sections of R4
- FHIR R5 expected to be published in Q3 2020
  - Will move more content to the normative status
- ONC* is expected to require the use of FHIR APIs
  - Evidenced in the ONC Notice of Proposed Rulemaking
  - Significantly expanding the scope of EHR certification

(*) The Office of the National Coordinator for Health Information Technology

FHIR for SPL

- Structured Product Labeling (SPL)
  - Critical and heavily utilized FDA V3 standard
- FDA is evaluating the use of FHIR for SPL
  - To ensure continuous support for the SPL use cases
  - To support data exchange with international regulators who have adopted FHIR
- Mapping SPL contents to FHIR for select use cases
  - Identifying existing FHIR resources
  - Conducting gap analysis with the FDA requirements
  - Developing proof-of-concept FHIR artifacts

FHIR for Source Data Capture

- Using EHR-to-EDC single point data capture
  - FDA expressed interest in June 2015 *
- TransCelerate BioPharma (TCB) eSource initiative
  - Optimizing the use of electronic data sources
  - Supporting more efficient data gathering practices
- HL7 and TCB are collaborating to advance the use of eSource in clinical trials
  - Promoting the use of FHIR-enabled EHRs in clinical research to facilitate interoperability

(*) Federal Register Notice "Source Data Capture from Electronic Health Records: Using Standardized Clinical Research Data", Docket No. FDA–2015–N–1887

FHIR for Biomedical Research

- The Biomedical Research Integrated Domain Group (BRIDG) model
  - Captures semantics of clinical and translational research
  - Stakeholders include NCI, FDA, CDISC, HL7, and ISO
- FDA supported the mapping of BRIDG classes to FHIR resources
  - Assessed the feasibility of exchanging protocol-driven and basic life science research semantics with FHIR
- Conducted under the HL7 Biomedical Research & Regulation (BR&R) WG
  - Focused on ensuring the comprehensive coverage of biomedical research and regulatory use cases

FHIR for IDMP

- The EU has endorsed FHIR for the implementation of ISO IDMP standards
- The European Medicines Agency (EMA) and HL7 are jointly developing IDMP FHIR resources
  - Substance Specification (supporting ISO 11238)
    - Definitions of substances, manufacturing processes and ingredients
  - Medicinal Product (supporting ISO 11615)
    - Definitions of products, their submissions to regulators, authorization activities, ingredients, packaging, etc.
- FDA plans to implement the IDMP FHIR standard
  - To allow the exchange of substance and product data with EMA

FHIR for PQ/CMC

- PQ/CMC contains multiple domains
  - E.g. substance and product information
- Need to harmonize information flow within CDER, across FDA, and between international regulators
  - E.g. substance registration and product listing
  - Would help support submission of each piece of information to FDA once
- Presently piloting the Specification domain in FHIR
  - Utilizes stable (high-level of maturity) FHIR resources
  - Independent of ongoing developments (e.g. Product)

FHIR for Adverse Event reporting

- Individual Case Safety Report (ICSR)
  - Captures information about adverse events (AE) that are reported to regulatory agencies
  - Supports reporting from a variety of sources
    - Consumers, hospitals, contract research organizations, clinicians or pharmaceutical product and medical device manufacturers
- FHIR AE resource is currently developed by HL7
  - Intended to enable AE exchange between health care providers (including PIs), sponsors, and manufacturers
  - Will also support voluntary reporting to regulators
  - FDA continuous participation ensures alignment with the ICSR semantics and regulatory needs

Update on Technical Rejection Criteria for Study Data

Presented to: Public Meeting on
Electronic Submissions and Data Standards

Ethan Chen, Office of Business Informatics, CDER
Virginia Hussong, Data Standards Program, CBER

April 10, 2019

Disclaimer

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

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

Study Data Conformance from Previous Analysis

- **Study Data was assessed for:**
  - NDA, BLA, and ANDA Submissions received from 12/18/2016 to 3/31/2018
  - Commercial IND Submissions received from 12/18/2017 to 3/31/2018
  - No duplicates
- **Conformance was checked against the existing two high-level validation rules as described in the Technical Rejection Criteria for Study Data**
  - 1734 – TS Dataset & Correct Study Start Date must be present
  - 1736 – DM Dataset, ADSL Dataset and define.xml must be present

Overall Conformance Statistics from Previous Analysis

Error	Description
1734	Trial Summary (TS) dataset must be present for each study in eCTD section 4.2 and 5.3
1736	Demographic dataset (DM) and the define.xml must be submitted in Module 4 for nonclinical data; DM dataset, the subject-level analysis dataset (ADSL) and define.xml must be submitted in Module 5 for clinical data

	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	1,126	1,446	473	176	3,221
Total Number Submissions with Critical Errors	302	551	138	41	1,032
Error 1734	290	506	137	35	968
Error 1736	14	63	1	6	84
Failure Rate (% among submissions with Study Data)	26.8%	38.1%	29.2%	23.3%	32.0%

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, and ANDA submissions received by CDER between 12/18/2016 and 3/31/2018, and commercial IND submissions received by CDER between 12/18/2017 and 3/31/2018

(3) Validation of error 1736 of a study is not performed if a study has Error 1734

(4) 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

Reference: FDA Study Data Technical Rejection Criteria (Revised May 2018)

CY2018 Conformance Analysis for Validation Errors 1734 & 1736

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

** Refer to the latest Technical Rejection Criteria for Study Data*

	NDA	ANDA	BLA	Comm. IND	All
Total Number of Submissions with Study Data	**877**	**1078**	**291**	**649**	**2895**
Total Number Submissions with Critical Errors	**195**	**266**	**50**	**113**	**624**
Error 1734	**185**	**186**	**48**	**96**	**515**
Error 1736	**16**	**88**	**2**	**18**	**124**
Failure Rate (% among submissions with Study Data)	**22.2%**	**24.7%**	**17.2%**	**17.4%**	**21.6%**

Notes:

(1) Analysis includes NDA, BLA, ANDA and Commercial IND submissions received by CDER between 1/1/2018 and 12/31/2018

(2) Validation of error 1736 is not performed if a study has Error 1734

(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) Analysis is conducted according to the revised TRC (Revised Jan. 2019)

Reference: FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

CY2018 Conformance Analysis of IND, NDA, BLA and ANDA Submission Studies: Errors 1734, 1735 & 1736

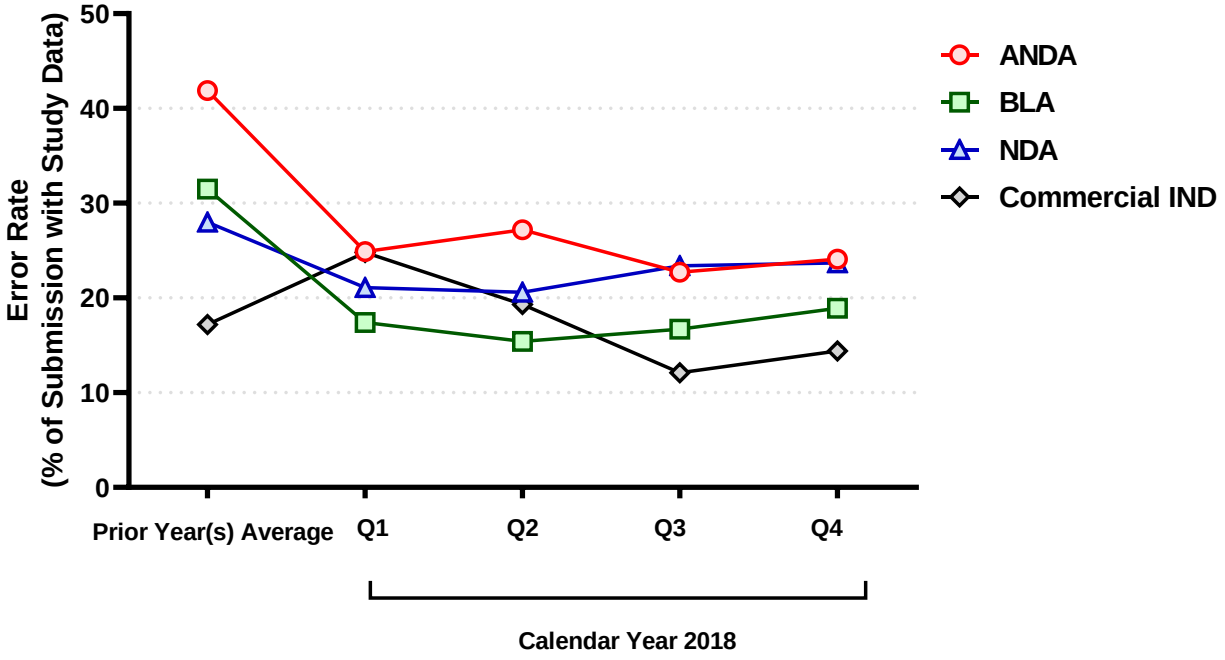
Error	Description
1734	Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for required sections*
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*
1736	For SEND data, a DM dataset and define 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*

** Refer to the latest Technical Rejection Criteria for Study Data*

	IND		NDA		BLA		ANDA	
	Nonclin (m4)	Clin (m5)	Nonclin (m4)	Clin (m5)	Nonclin (m4)	Clin (m5)	Nonclin (m4)	Clin (m5)
Total Number of Studies	883	288	403	1810	12	206	N/A	1004
Total Number Studies with Critical Errors	105	98	38	390	3	51	N/A	673
Error 1734	65	85	33	321	2	46	N/A	186
Error 1735	36	2	6	53	0	5	N/A	497
Error 1736	11	13	1	35	1	1	N/A	88
Error Rate (% among Total Number of Studies)	11.9%	34.0%	9.7%	21.6%	25.0%	24.8%	N/A	67.0%

Overall Conformance Trend for Validation Errors 1734 & 1736

- Submissions with study data received during CY2018 showed overall decreases in Validation Errors 1734 and 1736 compared to prior years' average error rate



Notes:

(1) Prior year(s) average uses data from the previous analysis, but excludes any submissions received in 2018

(2) CY2018 analysis is conducted according to the revised TRC (Revised Jan. 2019)

Summary of 1734 and 1736 Conformance Trend

- The failure rate for Errors 1734 and 1736 for all application types received in CY2018 is 21.6%
- Overall conformance for Errors 1734 and 1736 improved compared to the previous analysis (previous years' average of 68.0% vs. CY2018's average of 78.4%)
- FDA has identified the need to provide additional clarifications on TRC to help Industry meet study data requirements and continue to improve the conformance trend over time
  - Revision to TRC
    - Details on 1734 and 1736
    - Emphasis on Error 1735
    - Inclusion of Error 1789
    - Inclusion of **Table 1** eCTD Technical Rejection Criteria for Study Data Expectation
    - Inclusion of **Appendix 1** Examples of Validation Findings in Study Data
    - Inclusion of **Appendix 2** Examples of ts.xpt datasets
  - **Additional Tools**: Self-Check Worksheet and Instructions for Study Data

Summary of Latest Revisions to the Technical Rejection Criteria for Study Data (Revised Jan. 2019)

Error	Description (Reference to FDA Study Data Technical Rejection Criteria May 2018 version)	Severity Level
1734	Trial Summary (TS) dataset must be present for each study in eCTD section 4.2 and 5.3	High
1736	Demographic dataset (DM) and the define.xml must be submitted in Module 4 for nonclinical data; DM dataset, the subject-level analysis dataset (ADSL) and define.xml must be submitted in Module 5 for clinical data	High

Error	Description (Reference to FDA Study Data Technical Rejection Criteria Jan. 2019 version)	Severity Level
1734	Trial Summary (TS) dataset (ts.xpt) with information on study start date must be present for 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**	STF Files must be submitted in a study section. STF s are not required for required sections*	**High**

** Refer to the latest Technical Rejection Criteria for Study Data*

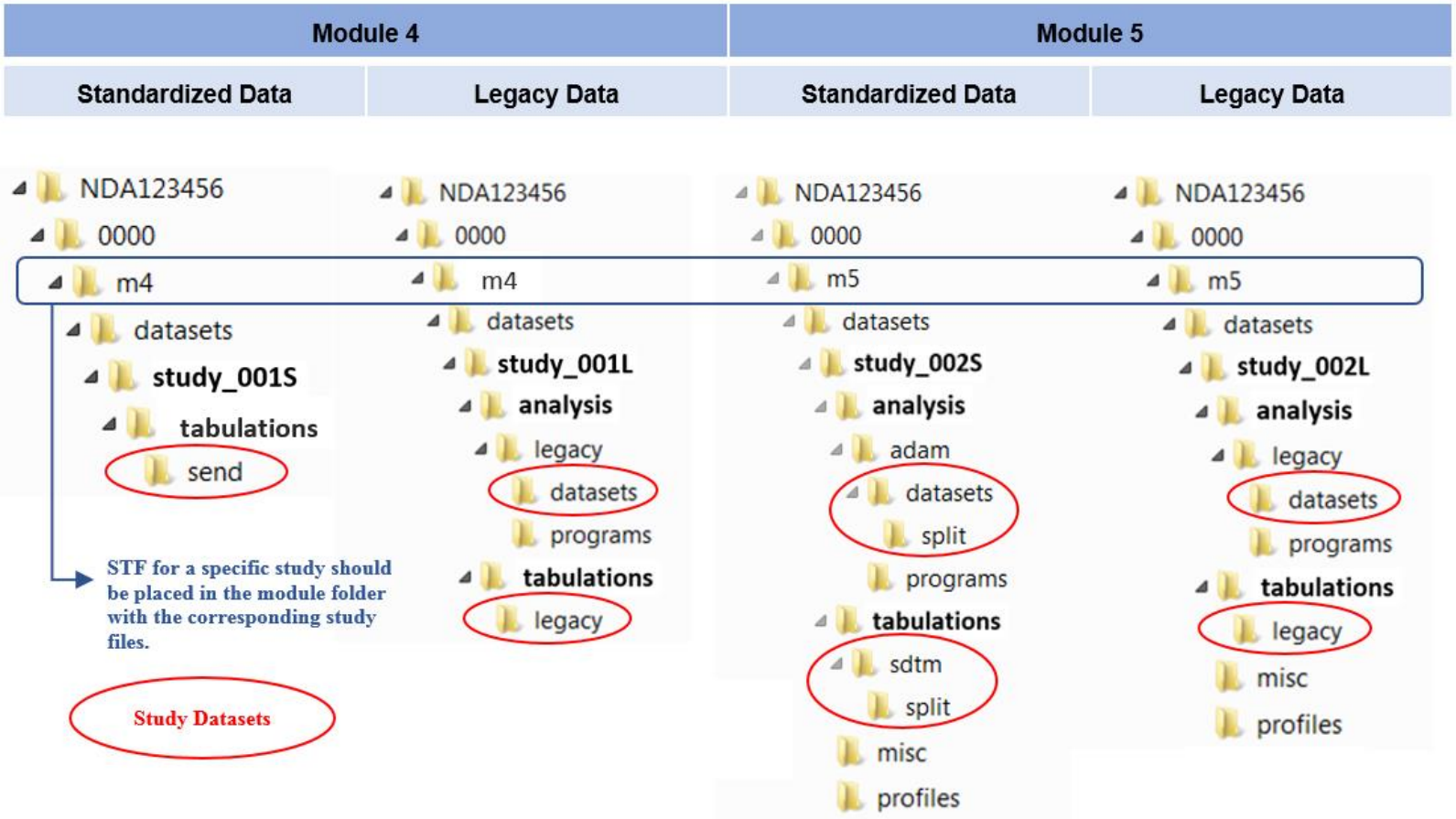
*** From Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specification, Section J: Datasets must only be provided in modules 3, 4, or 5 and not in modules 1 or 2*

Reference:

FDA Study Data Technical Rejection Criteria (Revised May 2018)
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Folder Structure for Module 4 and Module 5

- STF files and their associated datasets should be organized into a specific file directory structure and a specific headings and hierarchy structure



References:
FDA Study Data Technical Conformance Guide (Appendix E; Version 4.2, October 2018)
ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files

Additional Details for Error 1734

❖ **Full ts.xpt**

Sponsors should submit a dataset named 'ts.xpt' following published CDISC Standard and FDA Study Data Technical Conformance Guide

❖ **Simplified ts.xpt**

Sponsors should submit a dataset named 'ts.xpt' with four variables: STUDYID, TSPARMCD, TSVAL, AND TSVALNF)

Example of ts.xpt Datasets

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	• Left blank when study start date is provided in TSVAL • Exception code as specified in the ISO 21090 Standard when study start date is not available

References:
FDA Study Data Technical Conformance Guide (Appendices F & G; Version 4.2, October 2018)
FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Study Data Requirements for Submissions

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; 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, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	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; 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	

Reference: FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Emphasis on Errors 1735 and Inclusion of 1789

- Each submission typically contains many studies, an STF file is necessary to process study files into their corresponding studies; Accepting a submission where CDER cannot process the study tagging file will result in the reviewer seeing a list of files for which they do no not know the study they belong to

- If a study data file (e.g. define.xml) is not properly tagged in the STF file, it cannot be identified and located, resulting in Error 1736 being reported

Error	Description	Severity Level
1789	STF Files must be submitted in a study section. STF s are not required for required sections*	**High**
1735	Correct STF file-tags must be used for all standardized datasets and corresponding define.xml files in required sections*	**High**

** Refer to the latest Technical Rejection Criteria for Study Data*

Reference: FDA Study Data Technical Rejection Criteria (Revised Jan. 2019)

Tools for Industry

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

www.fda.gov

Gateway

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 Jan. 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

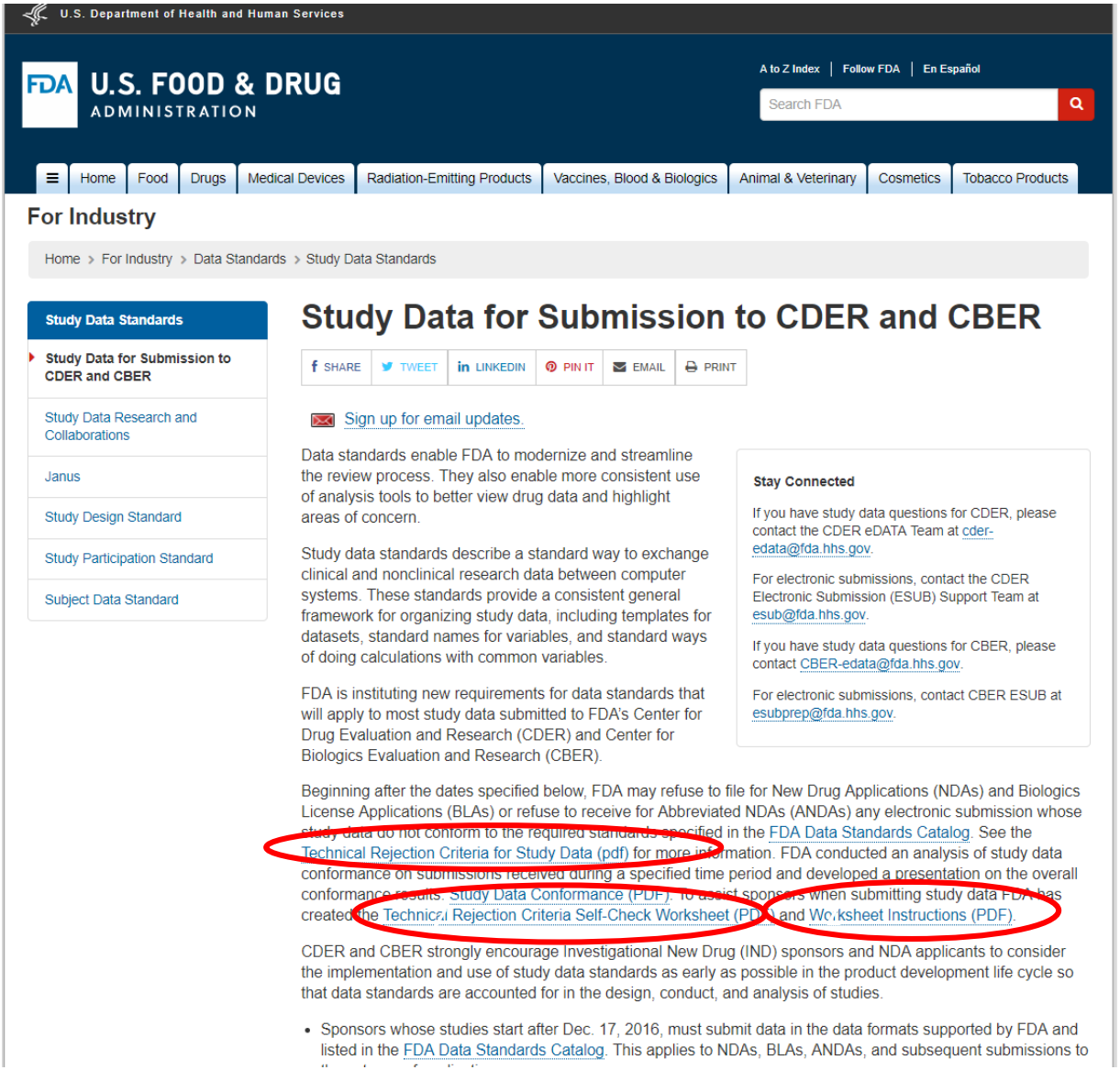
2. TRC Self-Check Worksheet & Instruction

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

Published Technical Rejection Criteria for Study Data & Self-Check Worksheet



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For Industry

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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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Sign up for email updates.

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"
https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm630740.pdf"

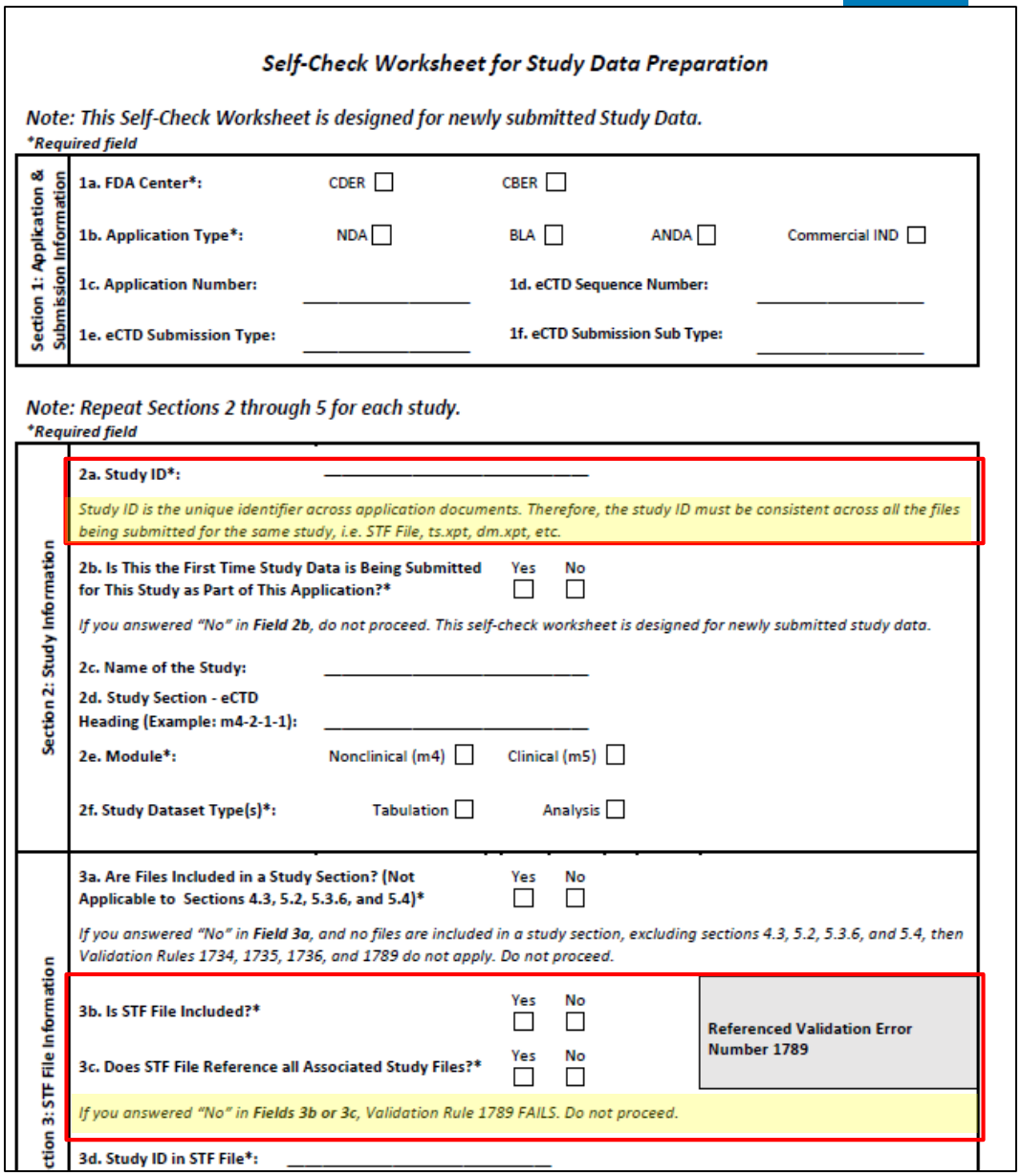
"Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf

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

Overview of the Self-Check Worksheet

- **Designed to walk sponsors through each step of TRC validation process**
- **Dynamically guides sponsors through study data requirements based on study information entered**
- **Designed to help the sponsors when they prepare study data to submit to the FDA for the first time**

Reference: "Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf
"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf



Self-Check Worksheet for Study Data Preparation

Note: This Self-Check Worksheet is designed for newly submitted Study Data.
**Required field*

Section 1: Application & Submission Information

1a. FDA Center*: CDER ☐ CBER ☐

1b. Application Type*: NDA ☐ BLA ☐ ANDA ☐ Commercial IND ☐

1c. Application Number: _____ **1d. eCTD Sequence Number:** _____

1e. eCTD Submission Type: _____ **1f. eCTD Submission Sub Type:** _____

Note: Repeat Sections 2 through 5 for each study.
**Required field*

Section 2: Study Information

2a. Study ID*: _____

Study ID is the unique identifier across application documents. Therefore, the study ID must be consistent across all the files being submitted for the same study, i.e. STF File, ts.xpt, dm.xpt, etc.

2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?* Yes ☐ No ☐

*If you answered "No" in **Field 2b**, do not proceed. This self-check worksheet is designed for newly submitted study data.*

2c. Name of the Study: _____

2d. Study Section - eCTD Heading (Example: m4-2-1-1): _____

2e. Module*: Nonclinical (m4) ☐ Clinical (m5) ☐

2f. Study Dataset Type(s)*: Tabulation ☐ Analysis ☐

Section 3: STF File Information

3a. Are Files Included in a Study Section? (Not Applicable to Sections 4.3, 5.2, 5.3.6, and 5.4)* Yes ☐ No ☐

*If you answered "No" in **Field 3a**, and no files are included in a study section, excluding sections 4.3, 5.2, 5.3.6, and 5.4, then Validation Rules 1734, 1735, 1736, and 1789 do not apply. Do not proceed.*

3b. Is STF File Included?* Yes ☐ No ☐

3c. Does STF File Reference all Associated Study Files?* Yes ☐ No ☐

Referenced Validation Error Number 1789

*If you answered "No" in **Fields 3b or 3c**, Validation Rule 1789 FAILS. Do not proceed.*

3d. Study ID in STF File*: _____

Sections of the Study Data Self-Check Worksheet

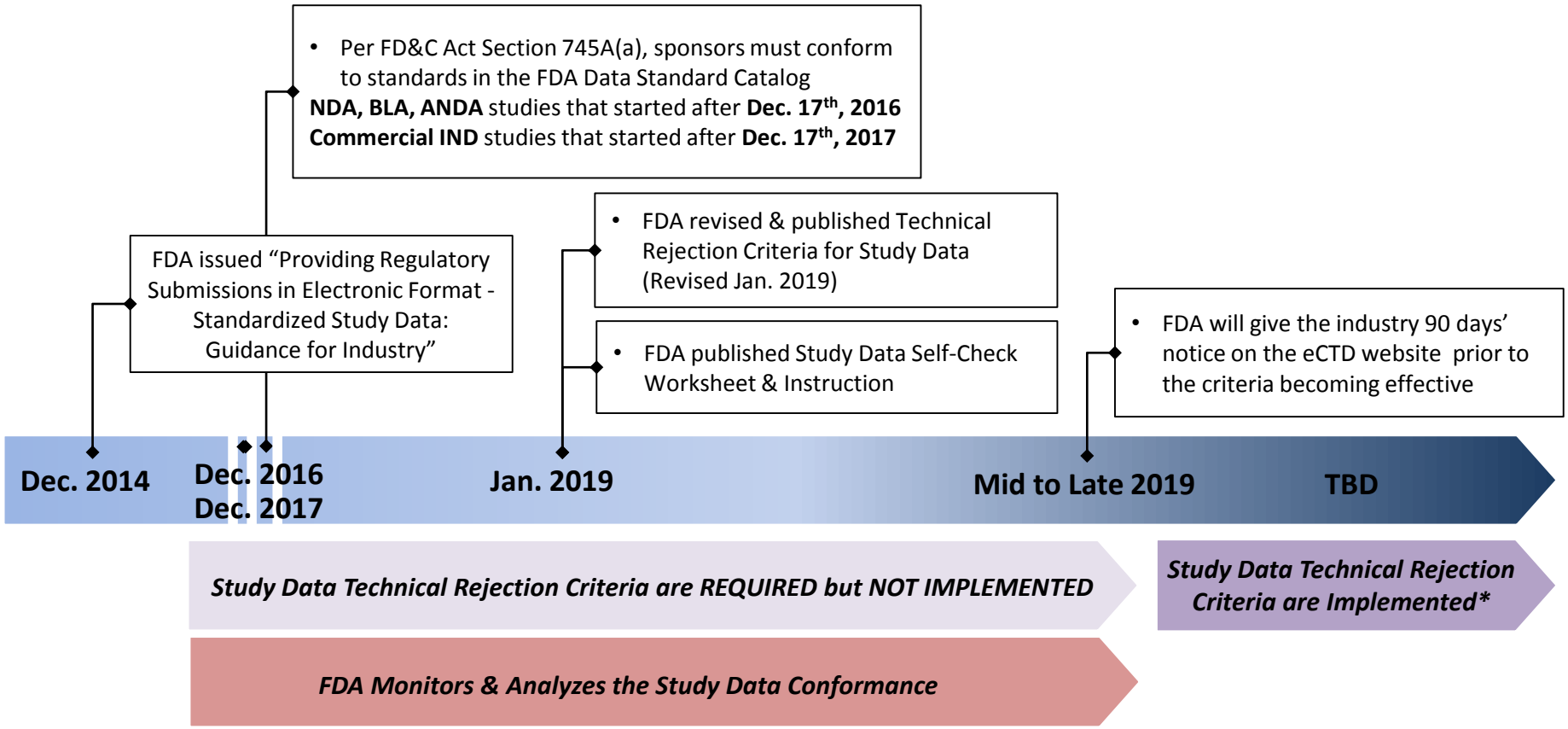
Section	Contents	Example(s)
1	**Application & Submission Information** • Provides high level information about the application and submission	1a. FDA Center*: CDER ☐ CBER ☐
2	**Study Information** • Provides more detailed information about the specific study	2a. Study ID*: 2f. Study Dataset Type(s)*: Tabulation ☐ Analysis ☐
3	**STF File Information** (1789 Validation Error) • Provide information about STF file	3b. Is STF File Included?* Yes ☐ No ☐ 3c. Does STF File Reference all Associated Study Files?* Yes ☐ No ☐
4	**TS File Information** (1734 Validation Error) • Provide information about ts.xpt file with study start date	4c. Study ID in TS File*: _____ 4d. Does Study ID in STF & TS Files Match?* Yes ☐ No ☐
5	**Standardized Dataset Information** (1735 & 1736 Validation Error) • Provide information about SEND or STDM and/or ADaM dataset and define.xml • Provide information about STF File-tags	5f. Is DM File Included?* Yes ☐ No ☐ 5g. Is Define File Included?* Yes ☐ No ☐

Note: Sections 2 through 5 are repeated for each study.

Reference: "Technical Rejection Criteria Self-Check Worksheet"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630732.pdf
"Technical Rejection Criteria Self-Check Worksheet Instructions"
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM630733.pdf

Implementation Timeline

FDA published Revised Study Data Technical Rejection Criteria (Revised Jan. 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

- Based on the revised TRC, about 21.6% all submissions were received with non-critical errors for 1734 and 1736.
- FDA published Study Data Self-Check Worksheet to help sponsors to follow the revised TRC
- 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.

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/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM630740.PDF
- **"Study Data Technical Conformance Guide"**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM624939.PDF
- **"FDA Data Standards Catalog"**
  HTTPS://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/DEFAULT.HTM
- **"Technical Rejection Criteria Self-Check Worksheet"**
  HTTPS://WWW.FDA.GOV/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM630732.PDF

  "Technical Rejection Criteria Self-Check Worksheet Instructions"
  HTTPS://WWW.FDA.GOV/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM630733.PDF

Recommended Readings:

- **For FDA instruction of Study Data submission, see the FDA "Study Data for Submission to CDER and CBER" page at:**
  HTTPS://WWW.FDA.GOV/DRUGS/DEVELOPMENTAPPROVALPROCESS/FORMSSUBMISSIONREQUIREMENTS/ELECTRONICSUBMISSIONS/UCM248635.HTM

- **For the full list of Study Data standards, see the FDA "Study Data Standards Resources" page at:**
  HTTP://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS

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