Electronic Submission of Adverse Event Reports to FDA Adverse Event Reporting System (FAERS) using International Council for Harmonisation (ICH) E2B(R3) Standards

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FAERS II Update

PLAN & TIMELINE

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
- Decommission old tools vulnerable to security risks

HHS has designated FAERS II as a Modernization Priority

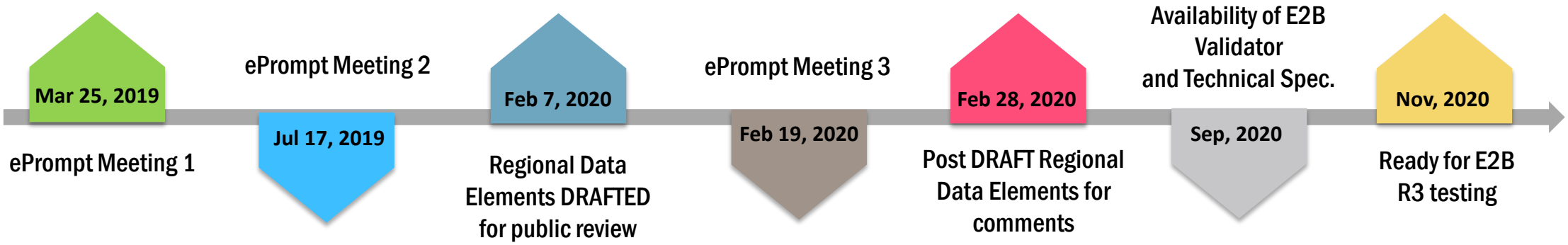
FAERS II - Scope

- Implementation and maintenance of COTS pharmacovigilance software for
  - submission and case processing platform for pre-market and post-market safety reports along with product quality defect reports
  - data analytics and signal management lifecycle
- Operations and maintenance of implemented COTS tool
  - includes activities from initiation through deployment
  - any required enhancements, maintenance and support to meet the objectives
- Decommission of Oracle AERS, FBIS, Tracktor, DQRS

FAERS II Tools

- Data Analytics and Signal Management
  - RxLogix PV Signal & PV Reports
- Case processing
  - Aris Global LifeSphere

FAERS II - E2B R3 Roadmap*



*Tentative Timelines

Testing Plan and Method

- No compliance date defined for R3 submission
- Sponsors can start testing after Sept 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 in R3 format
  - Use both routing mechanism (explained in later slides)
- Sponsor's must notify FDA when ready for first production submission to FDA in R3 format
- All question during testing must be sent to eprompt@fda.hhs.gov

FDA E2B R3 Core and Regional Data Elements Spreadsheet

Field Identification			
SOURCE	HEADER Element	DATA ELEMENT NUMBER	DATA ELEMENT NAME

Field Type		
MAX LENGTH	DATA TYPE	VALUES ALLOWED

ICH	
CONFORMANCE	ICH Business Rules

FDA E2B R3 Core and Regional Data Elements Spreadsheet

Post-Market	
CONFORMANCE	Post-Market Business Rule

Pre-Market	
CONFORMANCE	Pre-Market Business Rule

Type of Change	Notes	Null Flag Applicable							
		NI	MSK	UNK	NA	ASKU	NASK	NINF	PINF	OTH

Field OIDs	HL7 Data Type	
Code system OID	HL7 Data Type	HL7 Data Type (sub component)

E2B R3 Regional Requirements

PRE-MARKET & POST-MARKET

Regional Requirement

- FDA's technical approach for submitting ICSRs, for incorporating its regionally controlled terminology and for adding regional data elements that are not addressed in the ICH E2B (R3) Implementation Guideline (IG) for the following FDA-regulated products:
  - Drug products marketed for human use with approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs)
  - Drug and biologic products for human use under an Investigational New Drug (IND) or BA or BE studies that are exempt from the IND requirement
  - Prescription drug products marketed for human use without an approved application
  - Nonprescription (over-the-counter human drug products marketed without an approved application)
  - Biological products marketed for human use with approved biologic license applications (BLAs).

Regional Requirement

- “FDA Regional Implementation Specifications for ICH E2B(R3) Implementation: Postmarket Submission of Individual Case Safety Reports (ICSRs) for Drugs and Biologics, Excluding Vaccines” posted on June 23, 2016
- Follow core ICH E2B R3 with a few regional requirements
- Regional Elements (next slides)

Regional Requirement

Data Element Conformance

- FDA supports the ICH E2B(R3) data element conformance categories (e.g., required or optional) described in the ICH E2B(R3) IG
- FDA data element conformance may vary due to regional regulatory specifications not addressed in the ICH E2B(R3) IG
- These exceptions are noted in the next few slides

Regional Requirement

Terminology

- FDA supports Medical Dictionary for Regulatory Activities (MedDRA) for coding of clinical and laboratory terms.
  - Use the Lowest Level Term (LLT) and record the LLT as the MedDRA numeric code rather than the LLT name
  - e.g., the LLT name is Rash; the MedDRA numeric code for LLT Rash is 10378444)
  - Stakeholders should refer to the ICH E2B(R3) IG for data elements that specify the use of MedDRA coding.

Regional Requirement

Terminology

- FDA supports the use of constrained Unified Codes for Units of Measurement (UCUM) for coding units of measure (e.g., medication dosing units).
- FDA regional terminology supports the controlled terminology of the U.S. National Cancer Institute (NCI), the EVS, and the FDA's Global Substance Registration System (GSRS).
- FDA supports the use of EDQM Dosage Form and Route of Administration

Regional Requirement

- **N.1.3 Batch Sender Identifier**
  - Post-Market and Pre-Market
    - Business Rule: Senders should use the **Data Universal Numbering System (DUNS) number** for N.1.3 using the Dun and Bradstreet (D&B) Object Identifier 1.3.6.1.4.1.519.1. The DUNS number for Business Entity Identifiers is used to validate business entities in various FDA information systems
- **N.1.4 Batch Receiver Identifier**
  - Post-Market
    - Business Rule: Use value ZZFDA for production. Use value ZZFDATST for pre-production
  - Pre-Market
    - Business Rule: Use value ZZFDA_PREMKT for production. Use value ZZFDATST_PREMKT for pre-production
- **N.2.r.2 Message Sender Identifier**
  - Post-Market
    - Business Rule: Senders must receive FDA approval of their Batch Sender Identifier before beginning FAERS Submissions. The Message Sender Identifier can be the DUNS ID (9 Digit Identifier and DUNS OID 1.3.6.1.4.1.519.1) or other Identifier with FDA approval. ICSR batches with non-approved sender identifiers will be rejected.
  - Pre-Market
    - Business Rule: Senders must receive FDA approval of their Batch Sender Identifier before beginning FAERS Submissions. The Message Sender Identifier can be the DUNS ID (9 Digit Identifier and DUNS OID 1.3.6.1.4.1.519.1) or other Identifier with FDA approval. ICSR batches with non-approved sender identifiers will be rejected.

Regional Requirement

- **N.2.r.3 Message Receiver Identifier**
  - Post-Market
    - Business Rule: FDA requires that these identifiers correspond to the FDA ESG connection (e.g., WebTrader or AS2 B2B) used to send the ICSR submission to FAERS.
      - For ICSR Submissions: CDER
  - Pre-Market
    - Business Rule: FDA requires that these identifiers correspond to the FDA ESG connection (e.g., WebTrader or AS2 B2B) used to send the ICSR submission to FAERS. Though all reports will come to FAERS but this information will be used to route the report to the appropriate Center.
      - CDER IND ICSR: CDER_PREMKT
      - CBER IND ICSR: CBER_PREMKT

Regional Requirement

- **C.1.1 Sender's (case) Safety Report Unique Identifier**
  - Post-Market and Pre-Market
    - Business Rule: Use the MCN Number for the previously submitted paper report. Required for FDA to review, process and archive (21 CFR 312.32)
- **C.1.3 Type of Report**
  - Pre-Market
    - Business Rule: For pre-market ICSR use 2=Report from Study
- **C.1.6.1.r.2 Included Documents**
  - Post-Market and Pre-Market
    - Data Type: B64
    - Business Rule: Compression is not used for US reporting and encoding is limited to B64

Regional Requirement

- **C.1.7 Does this Case Fulfill the Local Criteria for an Expedited Report?**
  - Post-Market and Pre-Market
    - Business Rule: FDA does not support use of the HL7 nullFlavor NI in initial submissions. Initial submissions with nullFlavor NI will be rejected. For FDA reporting, if C.1.7 is populated with a “false” value, the ICSR is considered a non-expedited report
- **FDA.C.1.7.1 Local Criteria Report Type**
  - Post-Market and Pre-Market
    - Max Length: 1
    - Data Type: N
    - Values Allowed: 1=15-Day; 2=Periodic; 4=5-Day; 5=30-Day; 6=7-Day
    - Conformance: Mandatory
    - Business Rule: Use element values 1 for 15-Day Expedited and 2 for Periodic Non-expedited. Use element values 4 for remedial action to prevent an unreasonable risk of substantial harm to the public health. Use element values 5 for malfunction with no associated adverse event.
      C.1.7 must be true if FDA.C.1.7.1 is 1 or 4 or 6
      C.1.7 must be false if FDA.C.1.7.1 is 2 or 5
    - Code System OID : 2.16.840.1.113883.3.989.5.1.2.1.1.1

Regional Requirement

- **C.1.9.1.r.1 Source(s) of the Case Identifier**
  - Post-Market
    - Business Rule: FDA will provide a warning (and not reject) if C.1.9.1 (Other Case Identifiers in Previous Transmissions) = true and C.1.9.1.r.1 is not provided
- **C.1.9.1.r.2 Case Identifier(s)**
  - Post-Market
    - Business Rule: FDA will provide a warning (and not reject) if C.1.9.1 (Other Case Identifiers in Previous Transmissions) = true and C.1.9.1.r.1 is not provided.
- **C.1.10.r Identification Number of the Report Which Is Linked to This Report**
  - Pre-Market
    - Use to link all Sender's (case) Safety Report Unique Identifier that make up an Aggregate Analysis as per 312.32(c)(1)(i)(C).
- **FDA.C.1.12 Combination Product Report Indicator**
  - Post-Market
    - Data Type: Boolean
    - Values Allowed: false, true, nullFlavor: NI
    - Conformance: Mandatory
    - Code System OID : 2.16.840.1.113883.3.989.5.1.2.1.3

Regional Requirement

- **FDA.C.2.r.2.8 Reporter's Email**
  - Pre-Market and Post-Market
    - Max Length: 100
    - Data Type: AN
    - Conformance: Optional
- **C.5.2 Study Name**
  - Pre-Market
    - Business Rule: Concatenate **Study ID$Abbreviated Trial Name**. The Study ID should be the same value used in the Study Tagging file format of the eCTD submission.
- **FDA.C.5.4a FDA Other Study Type Where Reaction(s) / Event(s) Were Observed**
  - Pre-Market
    - Max Length: 1
    - Data Type: N
    - Values Allowed: 1=Aggregate
    - Conformance: Conditional-Mandatory
    - Business Rule: Required for Aggregate Report. Use value 1=Aggregate and C.1.3=2 (Report from study).
    - Null Flavor Applicable: -
    - Code System OID: 2.16.840.1.113883.3.989.2.1.1.9

Regional Requirement

- **FDA.C.5.5a IND Number where AE Occurred**
  - Pre-Market and Post-Market
    - Max Length: 10
    - Data Type: N
    - Conformance: Conditional-Mandatory
    - Business Rule: Required if Element Value for C.1.3 is 2=Report from study, and FDA.C.5.5b is not populated. The format must be "123456". For IND safety reports submitted from an aggregate analysis (FDA.C.5.4a = 1 (Aggregate)) from trials conducted under more than one IND, use the “Parent” IND number. For postmarket study report, this data element should be left blank with nullFlavor = NA.
    - Null Flavor Applicable: NA
- **FDA.C.5.5b Pre-ANDA Number where AE Occurred**
  - Pre-Market
    - Max Length: 10
    - Data Type: N
    - Conformance: Conditional-Mandatory
    - Business Rule: Required if Element Value for C.1.3 is 2=Report from study and FDA.C.5.5a is not populated. The format must be "234567" for BA/BE study. For postmarket study report, this data element should be left blank with nullFlavor = NA.
    - Null Flavor Applicable: NA

Regional Requirement

- **FDA.C.5.r.6 IND number of cross reported IND**
  - Pre-Market
    - Max Length: 10
    - Data Type: N
    - Conformance: Conditional-Mandatory
    - Business Rule: Required, if element value for FDA.C.5.5a is populated. This data element should be left blank with nullFlavor = NA, if there are no other cross reported IND
    - Null Flavor Applicable: NA
- **D.1 Patient (name or initial)**

  Business Rule:
  - If the patient is not the primary source reporter and other available data elements (e.g., age, date of birth, or sex) are unknown, then the HL7 null flavor codes NI or ASKU (Asked But Unknown) can be used
  - When the patient information is not provided due to regional privacy restrictions (e.g., foreign reports), FDA supports the use of the HL7 null flavor code MSK (Masked)
  - Post-Market: Use nullFlavor NA where no patient is involved. (e.g. Medication error, Compounding). For combination product, if a single report is reported for a malfunction without an adverse event, the element value should be “NONE”. For combination product, if there are multiple malfunction reports with no adverse event, then the element value should be “SUMMARY”.
  - Pre-Market: For Aggregate Report, the element value must be “AGGREGATE”

Regional Requirement

- **D.9.1 Date of Death**
  - Pre-Market
    - Conformance: Conditional-Mandatory
    - Business Rule: If Outcomes attributed to adverse event is Death, then Death Date is required.
- **FDA.D.11.r.1 Patient Race Code**
  - Pre-Market and Post-Market
    - Max Length: 10
    - Data Type: AN
    - Values Allowed: <Observation><code>= C17049.
      - C16352=African American
      - C41259=American Indian or Alaska Native
      - C41260=Asian
      - C41219=Native Hawaiian or Other Pacific Islander
      - C41261=White
    - Conformance: Mandatory
    - Business Rule: For post-market ICSR, if Patient (name or initials) (D.1) is "NONE" or "SUMMARY" then use nullFlavor: NA. For pre-market ICSR, if FDA.C.5.4a = 1 (Aggregate), then use nullFlavor: NA
    - Null Flavor Applicable: UNK, MSK, OTH, NA

Regional Requirement

- **FDA.D.12 Patient Ethnicity Code**
  - Pre-Market and Post-Market
    - Max Length: 10
    - Data Type: AN
    - Values Allowed: <Observation><code>= C16564
      - C17459=Hispanic or Latino
      - C41222=Non Hispanic or Latino
    - Conformance: Mandatory
    - Business Rule: For post-market ICSR, if Patient (name or initials) (D.1) is "NONE" or "SUMMARY" then use nullFlavor: NA. For pre-market ICSR, if if FDA.C.5.4a = 1 (Aggregate), then use nullFlavor: NA
    - Null Flavor Applicable: UNK, MSK, OTH, NA

Regional Requirement

- **FDA.E.i.3.2h Required Intervention**
  - Pre-Market and Post-Market
    - Max Length: 10
    - Data Type: Boolean
    - Values Allowed: true, nullFlavor: NI
    - Conformance: Mandatory
    - Business Rule: This is an outcome for device reporting or medication error reporting
    - Null Flavor Applicable: NI
    - Code System OID: 2.16.840.1.113883.3.989.2.1.1.19

- **G.k.1 Characterisation of Drug Role**
  - Pre-Market
    - Business Rule: Characterization of product role is mandatory to identify Suspect and Concomitant products. Only the following values are allowed for pre-market ICSR 1=Suspect 2=Concomitant 3=Interacting
  - Post-Market
    - Business Rule: Use 4=Drug Not Administered, if FDA.G.k.1a (FDA Other Characterisation of Drug Role) = 1 (Similar Device)

Regional Requirement

- **FDA.G.k.1a FDA Other Characterisation of Drug Role**
  - Post-Market
    - Max Length: 1
    - Data Type: N
    - Values Allowed: 1=Similar Device
    - Conformance: Mandatory
    - Business Rule: Use 1=Similar when reporting for Similar combination products under 21 CFR 4.102(c) and 803.50. Since each ICSR must contain at least one 'Suspect', 'Interacting', or 'Drug Not Administered, for reporting a similar device G.k.1 (Characterisation of Drug Role) must be 4=Drug Not Administered. If 1=Similar Device is reported then Malfunction (FDA.G.k.12.r.1) must be true.
    - Code System OID: 2.16.840.1.113883.3.989.5.1.2.1.1.8

Regional Requirement

- **G.k.2.2 Medicinal Product Name as Reported by the Primary Source**
  - Post-Market
    - Business Rule:
      - FDA validates medicinal product names for products licensed in the United States against the available Structured Product Labeling (SPL)
      - When the product has an SPL file, use the same naming convention in the ICSR as the name appears in the SPL file
      - If the Medicinal Product Name is not provided but the active substance name is known, provide the active substance as it appears in the FDA's Global Substance Registration System (GSRS) using the free text element G.k.2.3.r.1 Substance/Specified Substance Name
      - If the Medicinal Product Name as Reported by the Primary Source is a foreign product trade name, provide the foreign product trade name using the free text element G.k.2.2 Medicinal Product Name as Reported by the Primary Source and active substance name as it appears in the FDA's GSRS using the free text element G.k.2.3.r.1 Substance/Specified Substance Name.

Regional Requirement

- **G.k.3.1 Authorisation/Application Number**
  - Post-Market
    - Business Rule: FDA requires the use of a prefix to determine the application type associated with suspect products. For example, for human drug products, include the acronym “NDA” or “ANDA” immediately followed by the application number with no spaces; for example, NDA012345, ANDA012345

Product Type	FDA Application Type	Recommended Format
Human drug products	NDA or ANDA	NDA123456 or ANDA012345
Biologics License Application	BLA	BLA123456
Prescription drug products marketed without an approved application	Rx No Application	000000
Non-prescription drug product marketed without an approved application	Non-Rx No Application	999999
Compounded products marketed	Compounded Products	COMP99

Regional Requirement

- **G.k.9.i.2.r.1 Source of Assessment**
  - Pre-Market
    - Conformance: Conditional-Mandatory
    - Business Rule: Required if element value for C.1.3 is 2=Report from study. Use the value “Sponsor” for reporting Sponsor's assessment and “Investigator” to report reporter's or investigators assessment. At a minimum the assessment for the Sponsor must be reported.
- **G.k.9.i.2.r.2 Method of Assessment**
  - Pre-Market
    - Conformance: Conditional-Mandatory
    - Business Rule: Required if Element Value for C.1.3 is 2=Report from study. Default to value “FDA”.
- **G.k.9.i.2.r.3 Result of Assessment**
  - Pre-Market
    - Conformance: Conditional-Mandatory
    - Business Rule: Required if Element Value for C.1.3 is 2=Report from study. For premarket Safety Reports, at least one suspect product should have relatedness of drug to reaction/ event. Use the value "Suspected" or "Not Suspected"

Regional Requirement

- **FDA.G.k.10.r.1 FDA Specialized Product Category**
  - Post-Market
    - Max Length: 10
    - Data Type: AN
    - Values Allowed:
      - C102834=Type 1: Convenience Kit of Co-Package
      - C102835=Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)
      - C102836=Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)
      - C102837=Type 4: Device Coated/Impregnated/Otherwise Combined with Drug
      - C102838=Type 5: Device Coated or Otherwise Combined with Biologic
      - C102839=Type 6: Drug/Biologic Combination
      - C102840=Type 7: Separate Products Requiring Cross Labeling
      - C102841=Type 8: Possible Combination Based on Cross Labeling of Separate Products (Temporary Type)
      - C102842=Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)
    - Conformance: Optional
    - Code System OID: 2.16.840.1.113883.3.26.1.1

Regional Requirement

- **FDA.G.k.13 Pre-ANDA Drug Role**
  - Pre-Market
    - Max Length: 1
    - Data Type: N
    - Values Allowed: 1=Test drug; 2=Reference drug; 3=Placebo; 4=Vehicle
    - Conformance: Conditional-Mandatory
    - Business Rule: Required only when FDA.C.5.5b (Pre-ANDA Number where AE Occurred) has a value other than nullFlavor
    - Code System OID: 2.16.840.1.113883.3.989.5.1.2.1.1.7
- **FDA.G.k.12.r.1 Malfunction**
  - Post-Market
    - Data Type: Boolean
    - Values Allowed: <Observation><code>= C54026. true, false
    - Conformance: Conditional-Mandatory
    - Business Rule: This field must be set to true for at least one G.k.1 = 1 (Suspect) or G.k.1 = 4 (Drug not Administered) per ICSR, when FDA.C.1.7.1 (Local Criteria Report Type) = 5 (30-Day)

Regional Requirement

- **FDA.G.k.12.r.2.r.1 If follow-up, what type?**
  - Post-Market
    - Max Length: 1
    - Data Type: N
    - Values Allowed: 1=Correction; 2=Additional Information; 3=Response to FDA Request; 4= Device Evaluation
    - Conformance: Optional
    - Business Rule: Classification of the type of follow-up ICSR. Use the same manufacturer control number (to ensure the report is not misidentified in FAERS as an initial report). One or more codes can be provided.
    - Code System OID: 2.16.840.1.113883.3.989.5.1.2.1.1.5
- **FDA.G.k.12.r.3.r.2 Device Problem Code**
  - Post-Market
    - Max Length: 6
    - Data Type: AN
    - Values Allowed: <Observation><code>= C54451. FDA Device Problem Codelist
    - Conformance: Conditional-Mandatory
    - Business Rule: This field is required when FDA.G.k.12.r.1 (Malfunction) = true. FDA will only validate format. One or more codes can be provided.

Regional Requirement

- **FDA.G.k.12.r.4 Device Brand Name**
  - Post-Market
    - Max Length: 80
    - Data Type: AN
    - Values Allowed: Free Text
    - Conformance: Conditional-Mandatory
    - Business Rule: At least one of the 3 must be reported with a non null value: FDA.G.k.12.r.4 (Device Brand Name) or FDA.G.k.12.r.5 (Common Device Name) or FDA.G.k.12.r.6 (Device Product Code) for the device constituent part when FDA.C.1.12 (Combination Product Report Indicator) is true. There will always be two elements present – the first being the brand name, and the second being the common device name. Either can be null however, if both are null a value for FDA.G.k.12.r.6 (Device Product Code) is required.
- **FDA.G.k.12.r.5 Common Device Name**
  - Post-Market
    - Max Length: 80
    - Data Type: AN
    - Values Allowed: Free Text
    - Conformance: Conditional-Mandatory
    - Business Rule: At least one of the 3 must be reported with a non null value: FDA.G.k.12.r.4 (Device Brand Name) or FDA.G.k.12.r.5 (Common Device Name) or FDA.G.k.12.r.6 (Device Product Code) for the device constituent part when FDA.C.1.12 (Combination Product Report Indicator) is true. There will always be two elements present – the first being the brand name, and the second being the common device name. Either can be null however, if both are null a value for FDA.G.k.12.r.6 (Device Product Code) is required.

Regional Requirement

- **FDA.G.k.12.r.6 Device Product Code**
  - Post-Market
    - Max Length: 10
    - Data Type: AN
    - Values Allowed: FDA Device Component Code
    - Conformance: Conditional-Mandatory
    - Business Rule: At least one of the 3 must be reported with a non null value: FDA.G.k.12.r.4 (Device Brand Name) or FDA.G.k.12.r.5 (Common Device Name) or FDA.G.k.12.r.6 (Device Product Code) for the device constituent part when FDA.C.1.12 (Combination Product Report Indicator) is true. There will always be two elements present – the first being the brand name, and the second being the common device name. Either can be null however, if both are null a value for FDA.G.k.12.r.6 (Device Product Code) is required.
    - Code System OID: 2.16.840.1.113883.3.26.1.1

- **FDA.G.k.12.r.7.1a Device Manufacturer Name**
  - Post-Market
    - Max Length: 100
    - Data Type: AN
    - Values Allowed: Free Text
    - Conformance: Optional

Regional Requirement

- **FDA.G.k.12.r.7.1b Device Manufacturer Address**
  - Post-Market
    - Max Length: 100
    - Data Type: AN
    - Values Allowed: Free Text
    - Conformance: Optional
- **FDA.G.k.12.r.7.1c Device Manufacturer City**
  - Post-Market
    - Max Length: 35
    - Data Type: AN
    - Values Allowed: Free Text
    - Conformance: Optional
- **FDA.G.k.12.r.7.1d Device Manufacturer State**
  - Post-Market
    - Max Length: 35
    - Data Type: AN
    - Values Allowed: Free Text
    - Conformance: Optional
- **FDA.G.k.12.r.7.1e Device Manufacturer Country**
  - Post-Market
    - Max Length: 2
    - Data Type: AN
    - Values Allowed: ISO 3166-1 alpha-2, EU
    - Conformance: Optional

Regional Requirement

- **FDA.G.k.12.r.8 Device Usage**
  - Post-Market
    - Max Length: 1
    - Data Type: N
    - Values Allowed: 1=Initial Use of Device; 2=Reuse; 3=Unknown
    - Conformance: Optional
    - OID: 2.16.840.1.113883.3.989.5.1.2.2.1.1.4

- **FDA.G.k.12.r.9 Device Lot Number**
  - Post-Market
    - Max Length: 100
    - Data Type: AN
    - Values Allowed: Free Text
    - Conformance: Optional
    - Business Rule: UDI PI, the lot or batch number within which a device was manufactured

Regional Requirement

- **FDA.G.k.12.r.10 Operator of the Device**
  - Post-Market
    - Max Length: 1
    - Data Type: N
    - Values Allowed: 1= Health Professional; 2= Lay User/Patient; 3 = Other
    - Conformance: Optional
    - Business Rule: Use '1' or '2' to describe the operator, If none applicable, then Specify value '3'.
    - OID: 2.16.840.1.113883.3.989.5.1.2.1.1.6

- **FDA.G.k.12.r.11.r.1 Remedial Action Initiated**
  - Post-Market
    - Max Length: 100
    - Data Type: AN
    - Values Allowed: 1-Recall; 2-Repair; 3-Replacement; 4-Relabeling; 5-Notification; 6-Inspection; 7-Patient Monitoring; 8-Modification or Adjustment; 9-Other
    - Conformance: Conditional-Mandatory
    - Business Rule: This field is required when Malfunction = true , C.1.7 = Yes and Local Criteria for Report = 5-day. One or more codes can be provided.
    - OID: 2.16.840.1.113883.3.989.5.1.2.1.1.3

Regional Requirement

- *Linking Initial and Follow-up ICSRs*
  - If the initial ICSR was submitted on paper but its follow-up ICSR will be submitted electronically, include the C.1.1 Sender's (case) Safety Report Unique Identifier from the initial report in both C.1.1 and in C.1.8.1 Worldwide Unique Case Identification in the follow-up electronic submission
  - Always use the same identifier for C.1.8.1 that was assigned to the initial ICSR when submitting follow-up reports for the lifecycle of a case

E2B R3 Regional Requirements

FDA SPECIFIC OBJECT IDENTIFIERS (OIDS)

FDA Specific Object Identifiers (OIDs)

02/19/2020

Ta-Jen (TJ) Chen

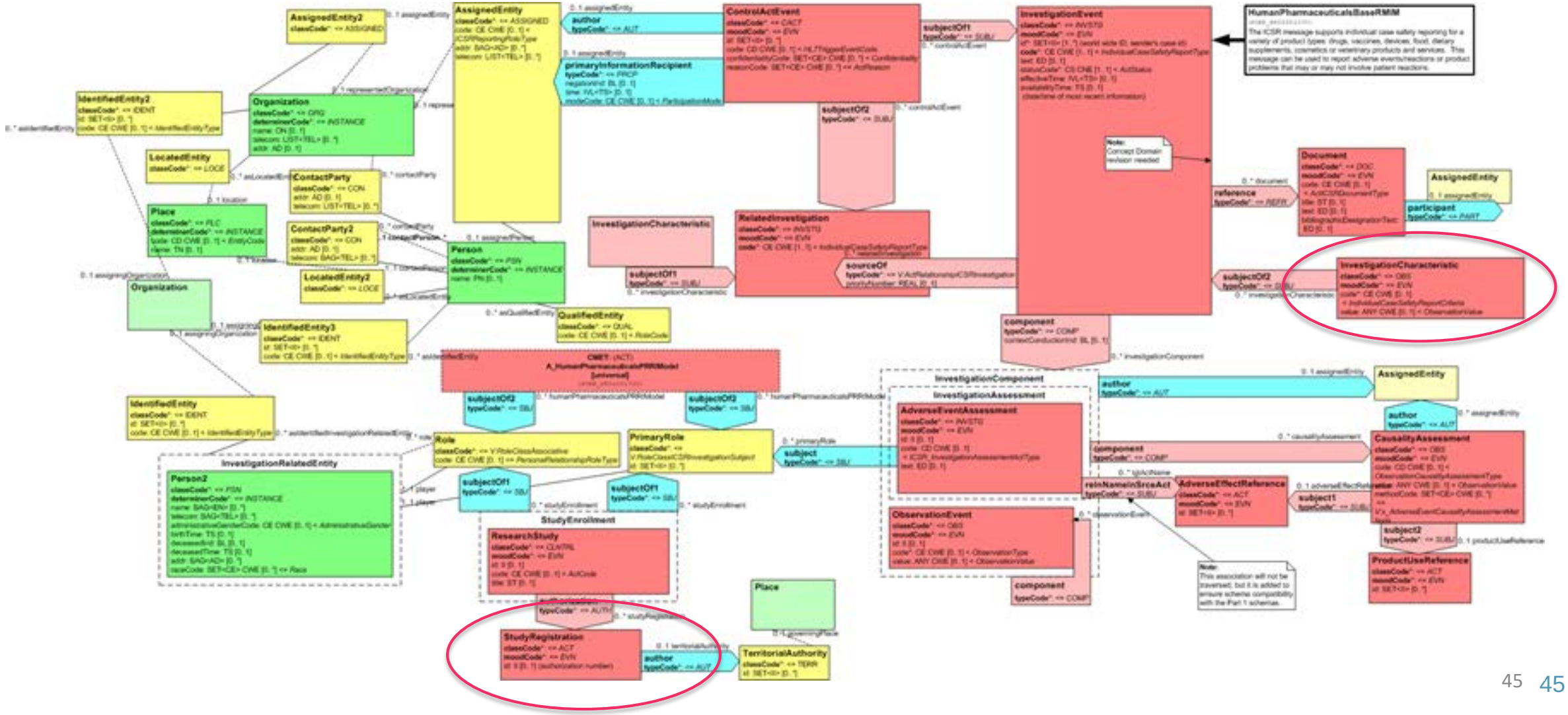
Office of Strategic Programs

U.S. Food and Drug Administration

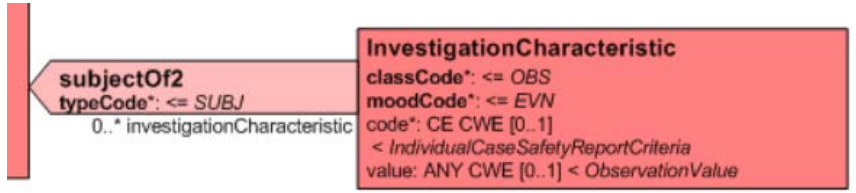
Object Identifier (OID)

- An *Object Identifier* (OID) is a sequence of numbers to uniquely identify an object.
- Each OID corresponds to a node in the "OID tree" or hierarchy, which is formally defined using the International Telecommunications Union's (ITU) OID standard, X.660. The root of the tree contains the following three arcs:
  - 0: ITU-T
  - 1: ISO
  - 2: Joint-ISO-ITU-T
- These numbers are written either as a string of digits separated by dots or as a list of named 'branches.'
  - MedDRA dictionary of terms is identified by the OID 2.16.840.1.113883.6.163 which also represents the branch 'joint-iso-itu-t.country.us.organisation.hl7.external-code-system.MedDRA'.

HL7 HumanPharmaceuticalsBaseRMIM



HL7 Observation Class and CE Data Type



InvestigationCharacteristic

- HL7 V3 Observation Class
- Attributes
  - Code - determines what kind of observation
    - data type CE
  - Value - result of the observation
    - data type ANY
    - Use CE for this instance

Coded With Equivalents (**CE**)

- code ST
- codeSystem UID
- codeSystemName ST
- codeSystemVersion ST
- displayName ST
- originalText ED
- translation SET<CV>

C.1.3 Type of Report -

- code="1" codeSystem="2.16.840.1.113883.3.989.2.1.1.23" displayName="ichReportType"
- value xsi:type="CE" code="n" codeSystem="2.16.840.1.113883.3.989.2.1.1.2"

FDA.C.1.7.1 Local Criteria Report Type

- code="1" codeSystem="2.16.840.1.113883.3.989.2.1.1.23" displayName="ichReportType"
- value xsi:type="CE" code="n" codeSystem=" ***2.16.840.1.113883.3.989.5.1.2.1.1.1***"

HL7 Act Class and II Data Type

StudyRegistration

- HL7 V3 Act Class
- Attributes
  - Id – for authorization number
    - data type II
    - Repurpose for IND number

Instance Identifier (**II**)

- extension ST
- UID root UIT
- assigningAuthorityName ST
- displayable BL

C.5.1.r.1 Study Registration Number: 2.16.840.1.113883.3.989.2.1.3.6

- extension="NL-CCMO-CC12345.001.002"
- root="2.16.840.1.113883.3.989.2.1.3.6"

FDA FAERS OID(s)

FDA OID from ICH

ICH Arc: 2.16.840.1.113883.3.989.5.1.2

- {joint-iso-itu-t(2) country(16) us(840) organization(1) hl7(113883) externalUseRoots(3) ich-estri(989) regional-specialised(5) sub-reg(1) fda(2)}

- **1 – FAERS *2.16.840.1.113883.3.989.5.1.2.1***
  - {joint-iso-itu-t(2) country(16) us(840) organization(1) hl7(113883) externalUseRoots(3) ich-estri(989) regional-specialised(5) sub-reg(1) fda(2) FAERS(1)}
- **2 – eCTD *2.16.840.1.113883.3.989.5.1.2.2***
  - {joint-iso-itu-t(2) country(16) us(840) organization(1) hl7(113883) externalUseRoots(3) ich-estri(989) regional-specialised(5) sub-reg(1) fda(2) eCTD(2)}

FDA FAERS OID(s)

FDA FAERS OIDs

- ***ICH Arc: 2.16.840.1.113883.3.989.5.1.2.1***
  - {joint-iso-itu-t(2) country(16) us(840) organization(1) hl7(113883) externalUseRoots(3) ich-estri(989) regional-specialised(5) sub-reg(1) fda(2) FAERS(1)}
- **1** - Code List*: 2.16.840.1.113883.3.989.5.1.2.1.1*
  - 1 – Local Criteria Report Type (*2.16.840.1.113883.3.989.5.1.2.1.1.1*)
  - *6 – Operator of the device ((2.16.840.1.113883.3.989.5.1.2.1.1.2)*
- **2** - namespace: *2.16.840.1.113883.3.989.5.1.2.1.2*
  - 1 – Primary IND (*2.16.840.1.113883.3.989.5.1.2.1.2.1*)
  - 2 – Primary Pre-ANDA (*2.16.840.1.113883.3.989.5.1.2.1.2.2*)
- **3** - observationCode: *2.16.840.1.113883.3.989.5.1.2.1.3*
  - 1 – Combination Product Flag *(2.16.840.1.113883.3.989.5.1.2.1.3.1)*
  - 2 – Single Use Device (*2.16.840.1.113883.3.989.5.1.2.1.3.2*)
  - 3 – Remedial Action

1 – 15 Day
2 – Periodic
4 – 5 Day
5 – 30 Day
6 – 7 Day

1 – Health Professional
2 – Lay User/Patient
3 - Other

E2B R3 Regional Requirements

R2 -> R3 REGIONAL FORWARD COMPATIBILITY

R2 -> R3 Forward Compatibility

Rule	Regional Field(R2)	Description(R2)	R2	Regional Field(R3)	Description(R3)	R3	Comment
FDA-01	A.1.9	Does this case fulfill the local criteria for an expedited report?	1=15-Day 2=Periodic 4=5-Day 5=30-Day 6=7-Day	FDA.C.1.7.1	Local Criteria Report Type	1=15-Day 2=Periodic 4=5-Day 5=30-Day 6=7-Day	Mapping 1, 2, 4, 5 and 6 to 1, 2, 4, 5 and 6.
FDA-02	A.1.FDA.15	Combination Product Report Flag	- Yes - No - <not set>	FDA.C.1.12	Combination Product Flag	- true - false - nullFlavor: NI	Mapping yes-true and no-false If not set in R2, use nullFlavor: NI in R3
FDA-03	A.2.3.3	Study Type Where Reaction(s) / Event(s) Were Observed	1= Clinical Trials 2= Individual Patient Use 3= Other Studies 4= Report from Aggregate Analysis or for Several Events Submitted if a Narrative Summary Report is Provided 5= Cross-Reported IND Safety Report	C.5.4	Study Type Where Reaction(s) / Event(s) Were Observed	1= Clinical Trials 2= Individual Patient Use 3= Other Studies	- Mapping 1, 2 and 3 to 1, 2 and 3. - If value is 4, then set: • the value of D.1 (Patient (name or initials)) to "AGGREGATE“ • FDA.C.5.4a (FDA Other Study Type Where Reaction(s) / Event(s) Were Observed) to 1=Aggregate - If value is 5, then copy only the numeric part of A.2.3.2 (Sponsor Study Number) records to FDA.C.5.r.6 (IND number of cross reported IND)
FDA-04	A.2.3.2	Sponsor Study Number	IND 123456	FDA.C.5.5a	IND Number where AE Occurred	123456	If A.2.3.3 (Study Type Where Reaction(s) / Event(s) Were Observed) is not equal to 5, then copy only the numeric part of A.2.3.2 (Sponsor Study Number) to FDA.C.5.5a (IND Number where AE Occurred)
FDA-05	A.2.3.2	Sponsor Study Number	IND 123456	FDA.C.5.r.6	IND number of cross reported IND	123456	If A.2.3.3 (Study Type Where Reaction(s) / Event(s) Were Observed) is equal to 5, then copy only the numeric part of A.2.3.2 (Sponsor Study Number) to FDA.C.5.r.6 (IND number of cross reported IND)

R2 -> R3 Forward Compatibility

Rule	Regional Field(R2)	Description(R2)	R2	Regional Field(R3)	Description(R3)	R3	Comment
FDA-06	B.4.k.20.FDA.17	Malfunction	- Yes - No - <not set>	FDA.G.k.12.r.1	Malfunction	- true - false	Mapping yes-true and no-false If not set in R2, set field to value "false" in R3
FDA-07	B.4.k.20.FDA.18.1a	Correction	- Yes - No - <not set>	FDA.G.k.12.r.2.r.1	If follow-up, what type?	1=correction 2=additional information 3=response to FDA request 4= device evaluation	If B.4.k.20.FDA.18.1a is Yes, then FDA.G.k.12.r.2.r.1=1. If B.4.k.20.FDA.18.1b is Yes, then FDA.G.k.12.r.2.r.1=2 If B.4.k.20.FDA.18.1c is Yes, then FDA.G.k.12.r.2.r.1=3 If B.4.k.20.FDA.18.1d is Yes, then FDA.G.k.12.r.2.r.1=4 Since this is a repeating entity there could be multiple values Each R2 tag value is setup as a repeatable value with in the R3 entity. If the values of the R2 fields is No or <no set> then don't include them.
	B.4.k.20.FDA.18.1b	Additional Information	- Yes - No - <not set>				
	B.4.k.20.FDA.18.1c	Response to FDA Request	- Yes - No - <not set>				
	B.4.k.20.FDA.18.1d	Device Evaluation	- Yes - No - <not set>				

R2 -> R3 Forward Compatibility

Rule	Regional Field(R2)	Description(R2)	R2	Regional Field(R3)	Description(R3)	R3	Comment
FDA-08	B.4.k.20.FDA.14.1a	Recall	- Yes - No - <not set>	FDA.G.k.12.r.11.r	Remedial Action Initiated	1=Recall 2=Repair 3=Replacement 4=Relabeling 5=Notification 6=Inspection 7=Patient Monitoring 8=Modification or Adjustment 9=Other	Since this is a repeating entity there could be multiple values. Each R2 tag value is setup as a repeatable value with in the R3 entity. If the values of the R2 fields is No or <no set> then don't include them.
	B.4.k.20.FDA.14.1b	Repair	- Yes - No - <not set>				
	B.4.k.20.FDA.14.1c	Replace	- Yes - No - <not set>				
	B.4.k.20.FDA.14.1d	Relabeling	- Yes - No - <not set>				
	B.4.k.20.FDA.14.1e	Notification	- Yes - No - <not set>				
	B.4.k.20.FDA.14.1f	Inspection	- Yes - No - <not set>				
	B.4.k.20.FDA.14.1g	Patient Monitoring	- Yes - No - <not set>				
	B.4.k.20.FDA.14.1h	Modification/Adjustment	- Yes - No - <not set>				
FDA-09	B.4.k.20.FDA.14.1i	Other	Free Text	FDA.G.k.12.r.11.r	Remedial Action Initiated	9=Other	If value present in R2 then include 9=Other in R3 for the tag FDA.G.k.12.r.11.r (Remedial Action Initiated). Do not include the R2 value.
FDA-10	B.4.k.20.FDA.19.1b	Evaluation Value		FDA.G.k.12.r.3.r.2	Device Problem Code		Copy Evaluation Value to Device Problem Code, where the R2 tag B.4.k.20.FDA.19.1a (Evaluation Type) is 01=Device Problem.

R2 -> R3 Forward Compatibility

Rule	Regional Field(R2)	Description(R2)	R2	Regional Field(R3)	Description(R3)	R3	Comment
FDA-11	B.4.k.20.FDA.1	Brand Name	Free Text	FDA.G.k.12.r.4	Device Brand Name	Free Text	Copy R2 value as is to R3.
	B.4.k.20.FDA.2	Common Device Name	Free Text	FDA.G.k.12.r.5	Common Device Name	Free Text	
	B.4.k.20.FDA.3	Product Code	FDA Device Component Code	FDA.G.k.12.r.6	Device Product Code	FDA Device Component Code	
FDA-12	B.4.k.20.FDA.4a	Device Manufacturer Name	Free Text	FDA.G.k.12.r.7.1a	Device Manufacturer Name	Free Text	Copy R2 value to R3 as is.
	B.4.k.20.FDA.4b	Manufacturer Address	Free Text	FDA.G.k.12.r.7.1b	Manufacturer Address	Free Text	
	B.4.k.20.FDA.4c	Manufacturer City	Free Text	FDA.G.k.12.r.7.1c	Device Manufacturer City	Free Text	
	B.4.k.20.FDA.4d	Manufacturer State	Free Text	FDA.G.k.12.r.7.1d	Device Manufacturer State	Free Text	
	B.4.k.20.FDA.4e	Manufacturer Country	ISO3166	FDA.G.k.12.r.7.1e	Device Manufacturer Country	ISO3166	
FDA-13	B.4.k.20.FDA.15	Device Usage	1=Initial Use of Device 2=Reuse 3=Unknown <not set>	FDA.G.k.12.r.8	Device Usage	1=Initial Use of Device 2=Reuse 3=Unknown <not set>	Copy R2 value to R3 as is.
FDA-14	B.4.k.20.FDA.16	Device Lot Number	Free Text	FDA.G.k.12.r.9	Device Lot Number	Free Text	Copy R2 value to R3 as is.
FDA-15	B.4.k.20.FDA.20	Operator of the Device	Free Text	FDA.G.k.12.r.10a	Operator of the Device	1= Health Professional 2= Lay User/Patient 3 = Other	Map R2 value of “Health Professional” to 1 in R3; “Lay User/Patient” to 2 in R3. If the R2 value is not “Health Professional” or “Lay User/Patient” then set R3 value to 3.

R2 -> R3 Forward Compatibility

Rule	Regional Field(R2)	Description(R2)	R2	Regional Field(R3)	Description(R3)	R3	Comment
FDA-16				FDA.D.11.r.1	Patient Race Code	C16352=African American C41259=American Indian or Alaska Native C41260=Asian C41219=Native Hawaiian or Other Pacific Islander C41261=White nullFlavor: UNK, MSK, OTH, NA	Since R2 does not have Patient Race Code data element, to convert from R2 to R3 use nullFlavor: UNK
FDA-17				FDA.D.12	Patient Ethnicity Code	C17459=Hispanic or Latino C41222=Non Hispanic or Latino nullFlavor: UNK, MSK, NI, NA	Since R2 does not have Patient Ethnicity Code data element, to convert from R2 to R3 use nullFlavor: UNK
FDA-18				FDA.E.i.3.2h	Required Intervention	true, nullFlavor: NI	Since R2 does not have Required Intervention data element, to convert from R2 to R3 use nullFlavor: NI
FDA-19	B.4.k.1	Characterization of drug role	1=Suspect 2=Interacting 3=Concomitant 4=Similar Device	FDA.G.k.1a	FDA Other Characterisation of Drug Role	1=Similar Device	Map R2 value of Similar Device to 1 in R3 and since G.k.1 is required, set the value to 4=Drug not Administered.

Updates on electronic submission routing mechanisms and validation

ROUTING MECHANISM

Routing Mechanism

Proposed options for sponsors to submit ICSRs

1. Two separate "Routes" for submission of safety reports are proposed (either may be used for pre or post market ICSRs)
   - **Method 1:** AS2 Header Attributes, or
   - **Method 2:** AS2 Routing IDs
2. Submit pre-market and/or post-market safety reports using appropriate attributes or routing IDs for both E2B R2 and R3
3. E2B Data Element "IND where adverse event occurred" be designated specifically for pre-market to route reports

Routing Mechanism - Method 1

- **AS2 Header Attributes**
  - Current State: Post market reports (does not apply to pre-market)
    - Destination: “CDER” or “CBER”
    - Attribute values: “**AERS**” for XML’s and “**AERS_ATTACHMENTS**” for PDF’s
  - Proposed Future State: For IND reports, new header attributes need to be setup/configured to route the files into the new folders (would apply to pre market ICSRs)
    - Destination remains the same (“CDER” or “CBER)
    - Attribute values: “**AERS_PREMKT**” for XML’s and “**AERS_ATTACHMENTS_PREMKT**” for PDF’s

Note: Attribute value for PDF’s is applicable only for E2B (R2) submissions. For E2B (R3) documents are embedded

Routing Mechanism - Method 2

- **AS2 Routing ID's** – The Electronic Submission Gateway (ESG) would also provide an alternative method to submit files to ESG using unique routing ID's
  - Current State: Post market reports (does not apply to pre-market)
    - Routing ID's: "**FDA_AERS**" for XML's and "**FDA_AERS_ATTACHMENTS**" for PDF's
  - Proposed Future State: For IND reports, new Routing ID's would need to be setup and corresponding configuration changes required (would apply to pre market ICSRs).
    - Routing ID's: "**FDA_AERS_PREMKT**" for XML's and "**FDA_AERS_ATTACHMENTS_PREMKT**" for PDF's

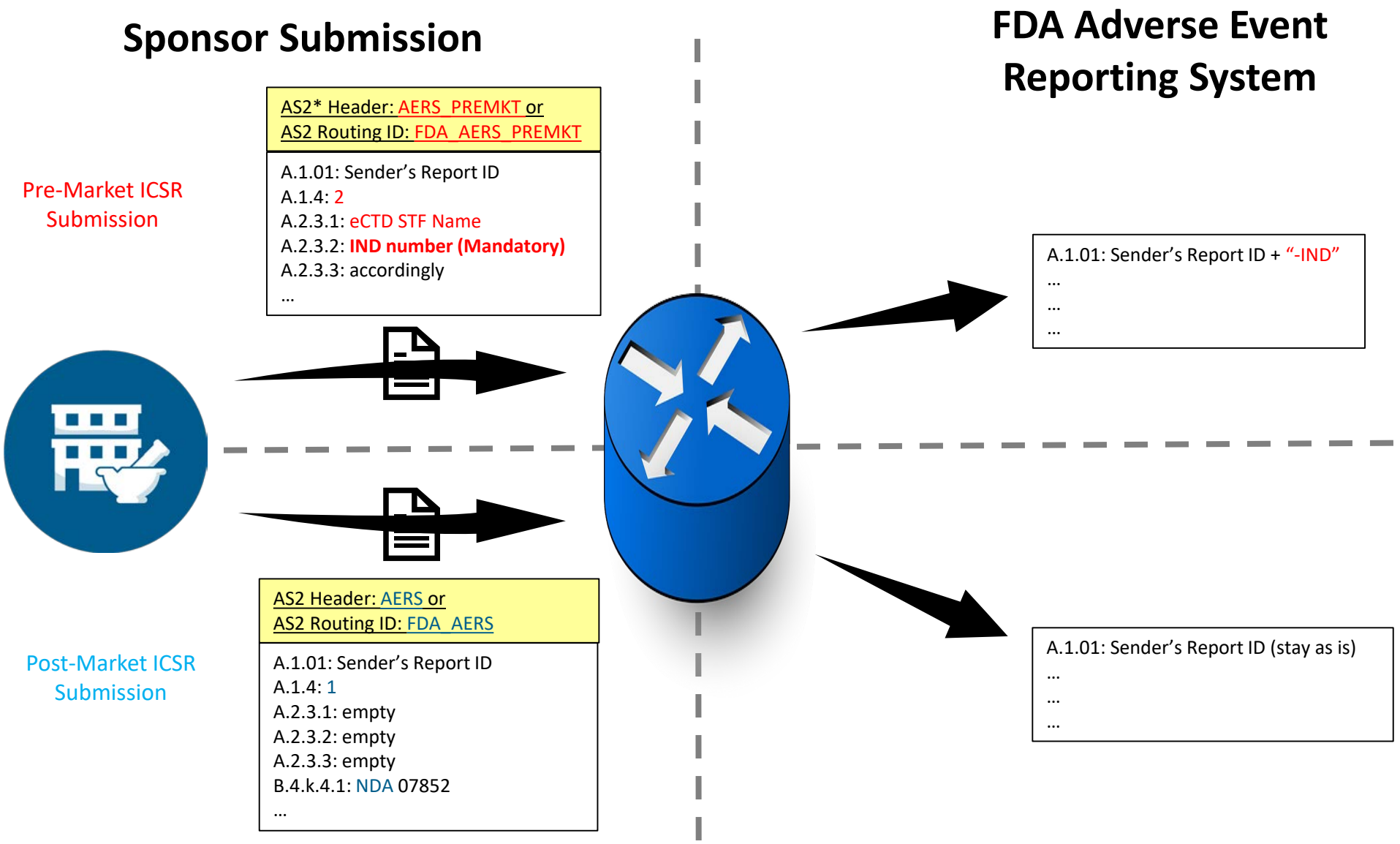
Note: Routing ID's for PDF's is applicable only for E2B (R2) submissions. For E2B (R3) documents are embedded

How Pre & Post Market Safety Reports would be Segregated within FDA

- Safety reports submitted to FDA via different “routes” are stored in different folders
- Acknowledgement will be sent with the original Safety Report Unique Identification
- FAERS checks the E2B pre-market data elements to safeguard pre-market reports are identified
- All pre-market reports will be treated different from the post market reports

Note: Sponsors must submit pre and post market ICSRs via the appropriate route.

Proposed Approach for Future Triage of ICSRs



*AS2: System-to-System. FDA ESG support two methods of communication: WebTrader and AS2 (System-to-System). WebTrader for small, simple, light submissions; AS2 for large, frequent submissions.

Routing Mechanism

Set up Routing Controls

- There are two ways to set up routing controls dictating where a document is sent:
  - Add the custom header attributes to the header of the message to indicate the type of submission (e.g., an IND) and destination (e.g., CBER). Reference ***Appendix G., AS2 Header Attributes***, for information on header attributes content and format. OR
  - Use a unique routing ID to identify the types of submissions and destination. The selection of the routing ID can be automated in the Cyclone/Axway products through the back-end integration pick-up as described in ***Appendix K., AS2 Routing IDs***.

Routing Mechanism

Trading Partner Changes

- **AS2 Header Attributes**
  - For current post market reports
    - Destination: “CDER” or “CBER”
    - Attribute values: “**AERS**” for XML’s and “**AERS_ATTACHMENTS**” for PDF’s
  - For new IND reports, new header attributes need to be setup/configure to route the files into the new folders.
    - Destination remains the same
    - Attribute values: “**AERS_PREMKT**” for XML’s and “**AERS_ATTACHMENTS_PREMKT**” for PDF’s

Note: Attribute value for PDF’s is applicable only for E2B (R2) submissions. For E2B (R3) documents are embedded

Routing Mechanism

Trading Partner Changes

- **AS2 Routing ID's** - ESG also provides alternate method to submit the files to ESG using unique routing ID's
  - For current post market reports
    - Routing ID's: "**FDA_AERS**" for XML's and "**FDA_AERS_ATTACHMENTS**" for PDF's
  - For new IND reports, new Routing ID's need to be setup and corresponding configuration changes are required.
    - Routing ID's: "**FDA_AERS_PREMKT**" for XML's and "**FDA_AERS_ATTACHMENTS_PREMKT**" for PDF's

Note: Routing ID's for PDF's is applicable only for E2B (R2) submissions. For E2B (R3) documents are embedded

Updates on electronic submission routing mechanisms and validation

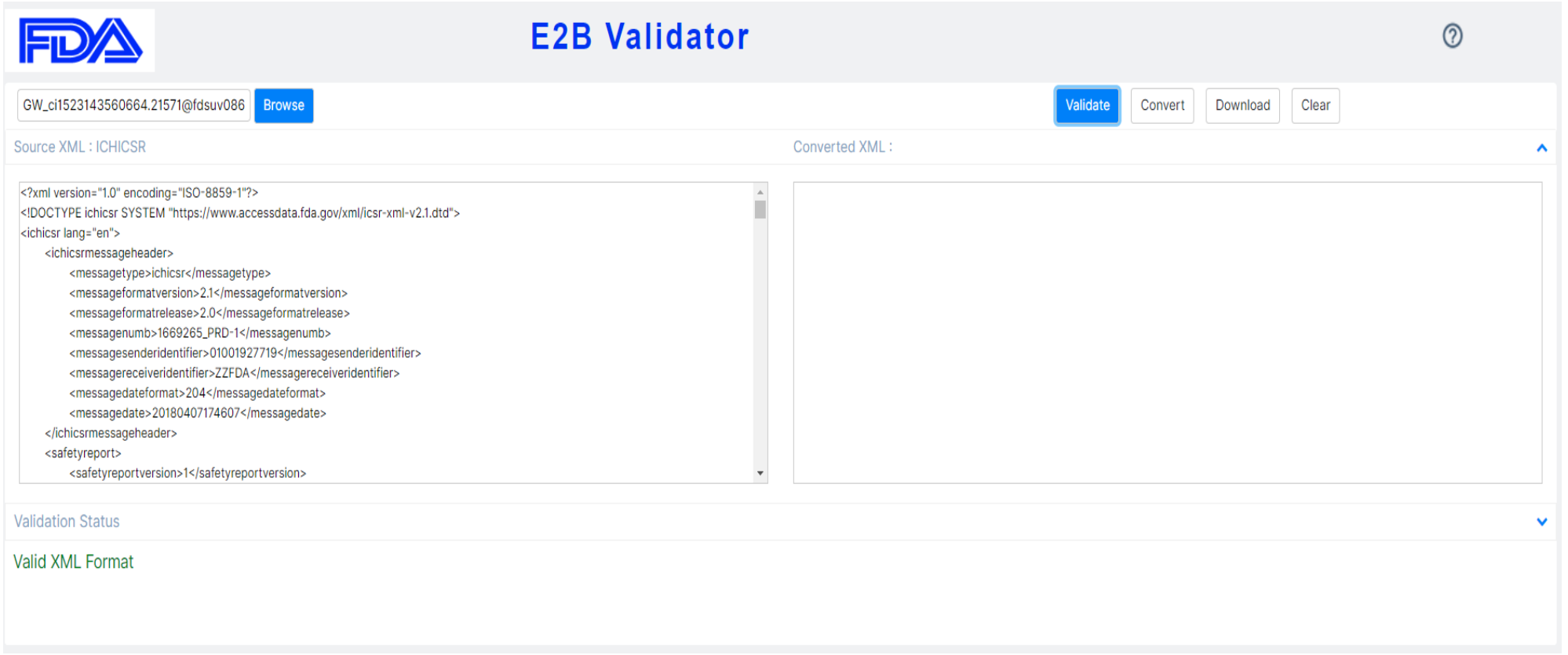
MECHANISM TO VALIDATE E2B

Mechanism to validate E2B

- Provide a mechanism for industry to: i) Validate the regional E2B R2 and regional E2B R3 data files; ii) Convert regional E2B R2 to regional E2B R3 data file
- Mechanism can be used before production submission
- Mechanism available for use via a public URL
- Uploaded file are not stored
- Update FAERS Electronic Submission web page to provide this information

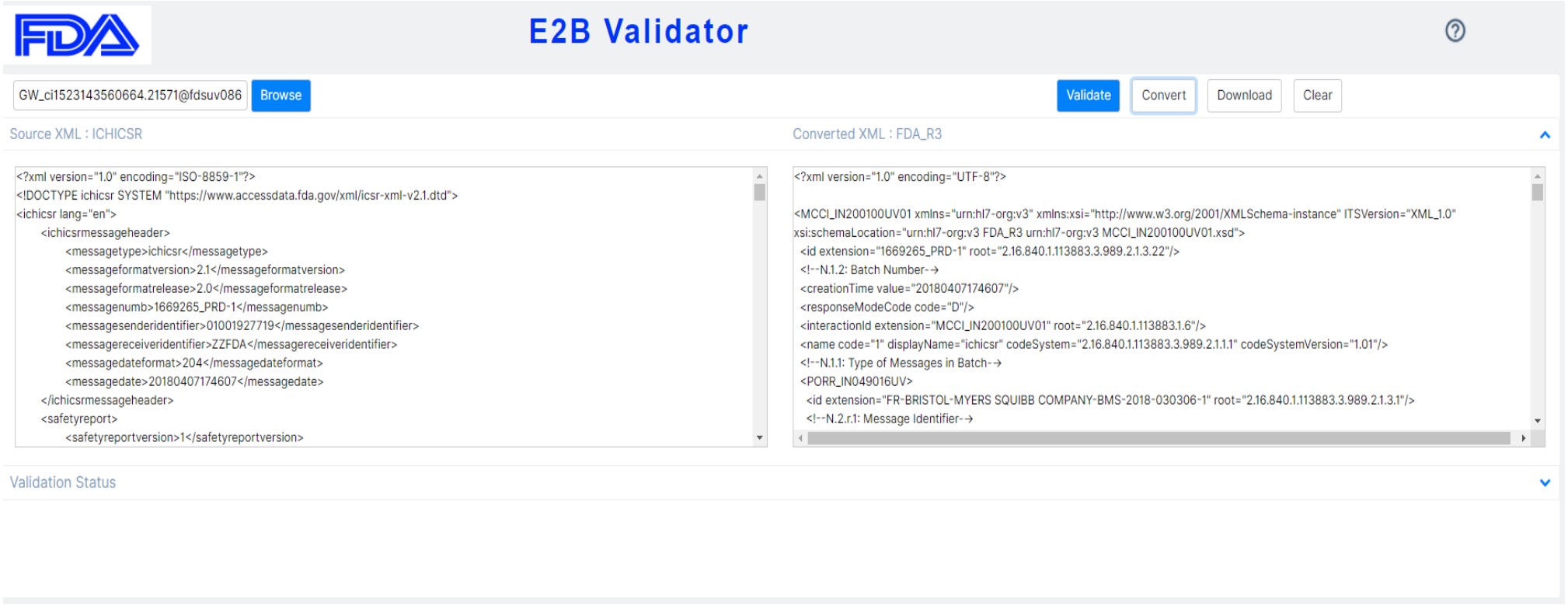
Mechanism to validate E2B

Upload source XML and validate



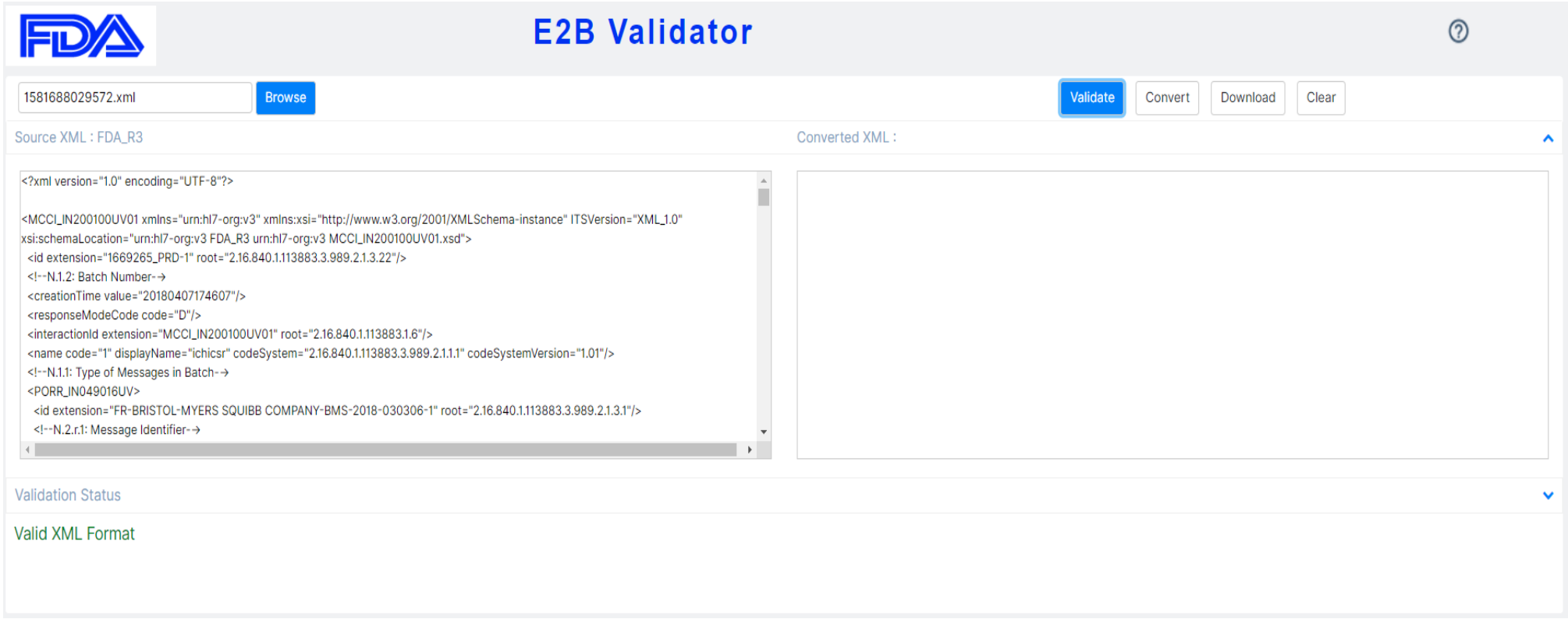
Mechanism to validate E2B

Convert Regional R2 to Regional R3 and download



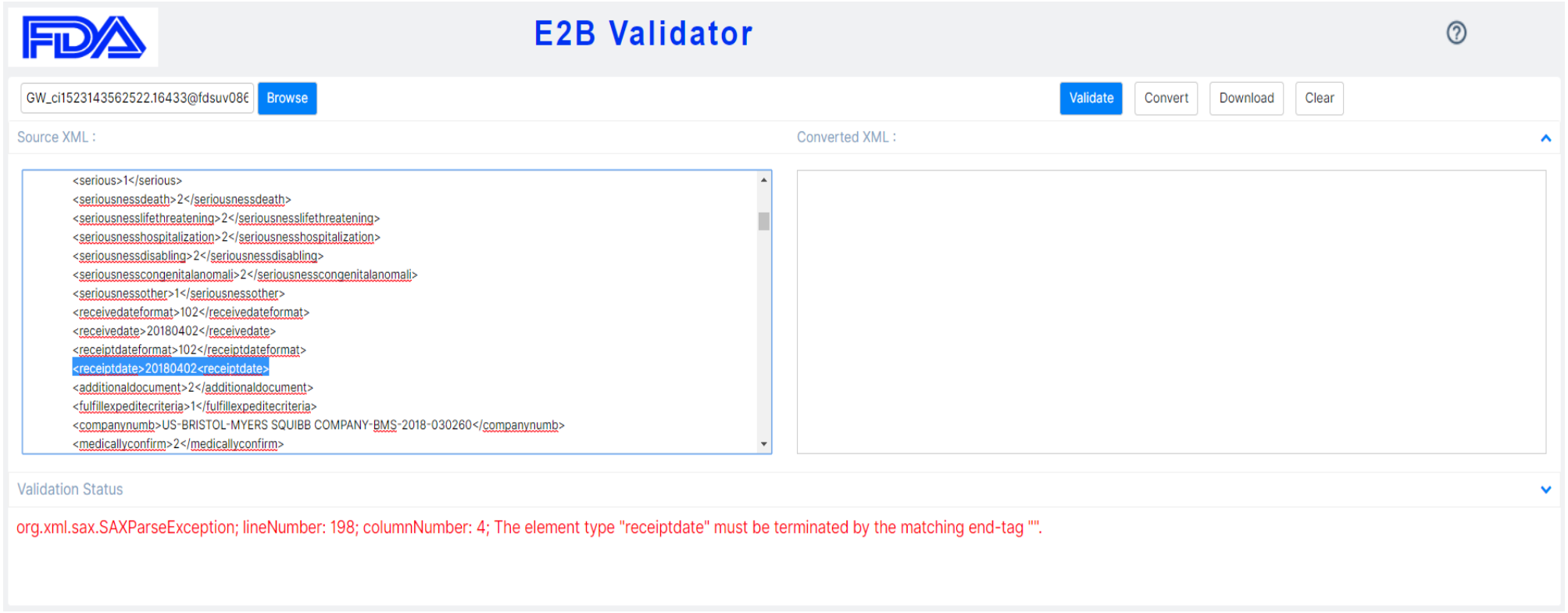
Mechanism to validate E2B

Upload the converted regional R3 and validate



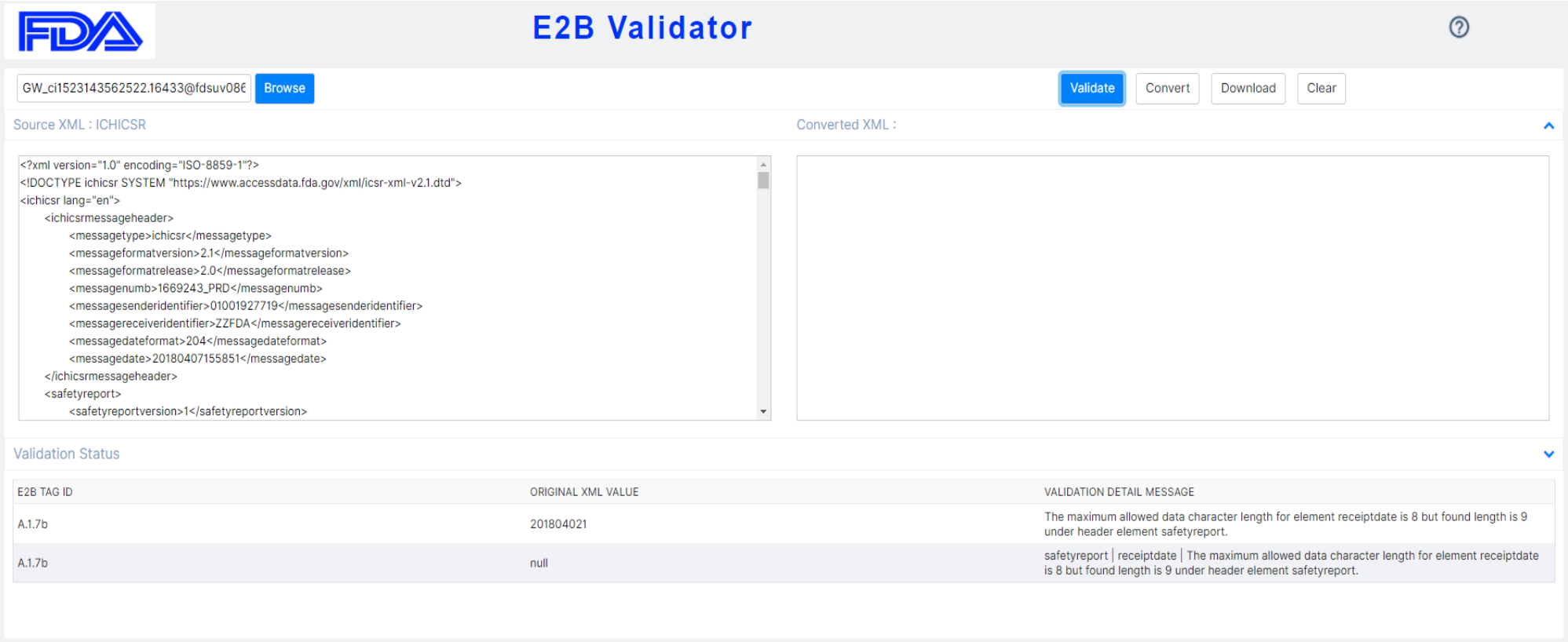
Mechanism to validate E2B

Validation Errors



Mechanism to validate E2B

Validation Errors



Summary & Closing Comments

- FAERS Update
  - Overview of FAERS II
  - Communicated E2B R3 Roadmap
- E2B R3 Regional Requirement
  - Postmarket reginal requirements
  - Premarket regional requirements
- FDA Specific OIDs
  - What is an OID
  - HL7 Observation Class
  - FDA OIDs
- Regional Forward Compatibility
  - Discussed forward compatibility rules
- Submission paths for premarket and postmarket ICSRs
  - Discussed routing mechanism for premarket and postmarket
- Demonstration of E2B Validator

Next Steps

- Today's presentation will be posted on FDA meeting page, including
  - R3 Regional requirement spreadsheet
  - R2 -> R3 Forward Compatibility spreadsheet
- Invite comments via the docket on topics discussed in today's meeting by Mar 20, 2020
- Update specification based on comments received
- Update FDA Regional Implementation Specifications for ICH E2B(R3) Implementation
  - Incorporate comments received via the docket
- Prepare sample regional E2B R3 data files
- Contact: eprompt@fda.hhs.gov after the docket timeframe

Thank You