Reporting premarket and postmarket safety reports to FDA using ICH E2B(R3) standards

JANUARY 13, 2023

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Outline

- Background
- FDA Regional Implementation of E2B(R3)
- Submission Methods & Mechanism
- IND Safety Reporting
- IND-exempt BA/BE Study Safety Reporting
- Testing and Implementation

Background

- Initial plan: Use E2B R2 for IND and IND-exempt BA/BE safety reporting
- Implement E2B R3 for both premarket and postmarket safety report at the same time - based on the complexity and suggestions from industry
- Change in direction pushed implementation timeline. Dependency includes:
  - Update and clearance to final guidance
  - Update to technical specifications
  - Vendor timelines
- New date for voluntary reporting will be communicated on FAERS Electronic Submission web page

FDA Regional Implementation of E2B(R3)

- Standard supported
  - Premarket: Only R3 standard
  - Postmarket: Currently R2 and will move to R3 standards. Date to retire R2 TBD
- Information about E2B(R3) testing and implementation will be made available on the FAERS Electronic Submissions web page
- Regional Extensions: Refers to FDA data elements and terminologies supported in the ICSR file in addition to the ICH E2B (R3) data elements
- Recommends the use of the XML data element "displayName" to facilitate human and computer system identification and understanding

```
<subjectOf2 typeCode="SBJ">
<observation classCode="OBS" moodCode="EVN">
<code code="C16564" displayName="Ethnic Group" codeSystem="2.16.840.1.113883.3.26.1.1"/>
```

FDA Regional Implementation of E2B(R3)

- Acknowledgement – Two (2) acknowledgements
  - ACK1: FDA Message Delivery Notification (MDN)
  - ACK2: FAERS Review Acceptance/Rejection
    - *ACK.B.r.7: Error / Warning Message or Comment* – Max length updated to 2000
- Refer to FDA E2B(R3) Core and Regional Data Elements and Business Rules document for all core ICH and regional extension to create ICSR files
- FDA data element conformance may vary from the ICH ICSR IG due to regional regulatory specifications
  - variations are noted in the FDA E2B(R3) Core and Regional Data Elements and Business Rules document

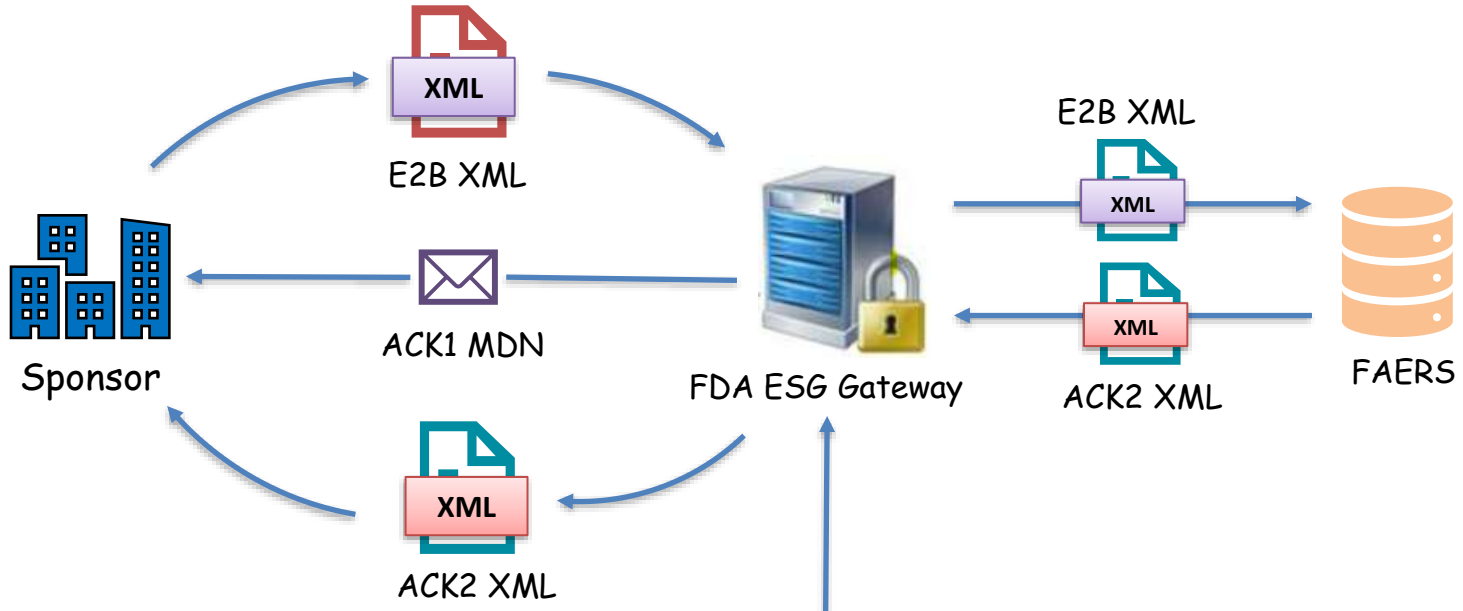
FDA Regional Implementation of E2B(R3)

- Controlled Terminology
  - NCI Enterprise Vocabulary Services (EVS)
  - MedDRA
  - Unified Codes for Units of Measurement (UCUM)
  - European Directorate for the Quality of Medicines (EDQM)
  - Device Product Code (“ProCode”)
  - FDA Global Substance Registration System (GSRS) Unique Ingredient Identifiers (UNII)
  - Structured Product Labeling (SPL)
- ICH elements that use FDA-controlled terminologies are noted and defined in the relevant sections of technical specification

SUBMISSION METHODS & MECHANISM

Submission Methods

Option A
via Database-to-Database Transmission



Option B
via Safety Reporting Portal (SRP)

SRP requires Sponsors to register and receive login credentials

Submission Methods

- ICSR Option A: Database-to-Database Transmission (“E2B”)
  - Submitters who have database-to-database transmission capability may directly submit ICSRs in the XML format via the Electronic Submissions Gateway (ESG)

- ICSR Option B: Safety Reporting Portal (SRP)
  - Requires registration and receive login credentials
  - Submitters enter the ICSR information manually into a web-based form and submit
  - Submitted ICSR uploaded into the FAERS database

Safety Reporting Portal (SRP)

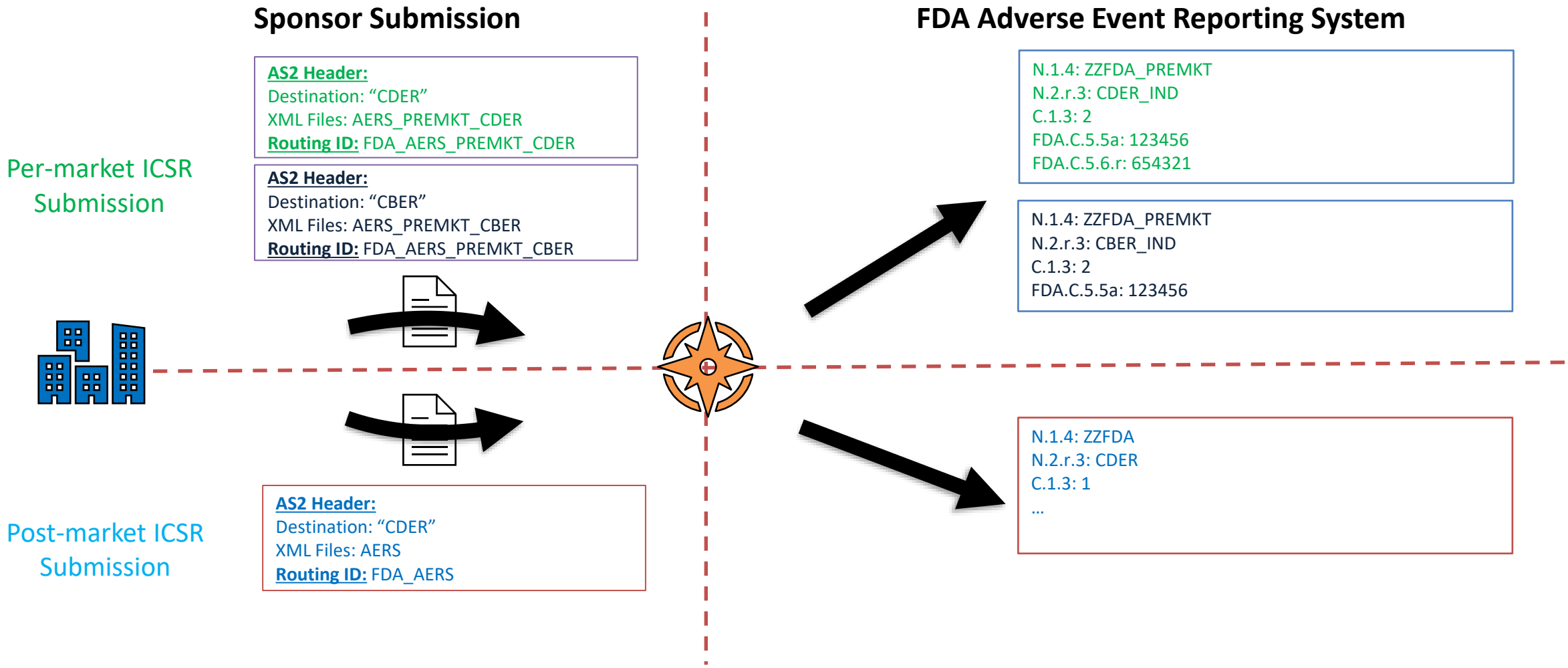
- **SRP Intended for**
  - Sponsors and CROs without infrastructure for direct ESG (gateway-to-gateway) submission
  - Individual reports only; no batch reporting via SRP
  - Can be used for both commercial and research INDs safety reporting
- **If CRO**
  - Separate account needed for each sponsor/license holder
- **Post-market and premarket reporting**
  - Maintained separately—select up front, can navigate between them
  - Complete an on-line form
- **“Free” (no added cost to use)**
- Contact FAERSESUB@fda.hhs.gov to request an SRP account

Separate Submission Paths

- Defined new header attributes and routing IDs for premarket safety reports
- Two pathways allow separation of premarket from postmarket reports
- Premarket reports will NOT be published publicly

AS2 Headers/ Routing IDs	Postmarketing reports	Premarketing reports for CDER	Premarketing reports for CBER
AS2 Headers	Destination: "CDER" XML files: AERS	Destination: "CDER" XML files: AERS_PREMKT_CDER	Destination: "CBER" XML files: AERS_PREMKT_CBER
Routing IDs	XML files: FDA_AERS WebTrader Accounts: CDER AERS AS2 Accounts: FDA_AERS	XML files: FDA_AERS_PREMKT_ CDER	XML files: FDA_AERS_PREMKT_ CBER

Approach to Triage of ICSRs via ESG



Separate Submission Path Business Rules

- Section N.1: ICH CSR Transmission Identification
  - **Batch Receiver Identifier (N.1.4) and Message Receiver Identifier (N.2.r.3)**

		AS2 Header	Routing ID	N.1.4 Value	N.2.r.3 Value
Premarket	CDER IND ICSR	Destination: "CDER" XML Files: AERS_PREMKT_CDER	XML Files: FDA_AERS_PREMKT_CDER	ZZFDA_PREMKT	CDER_IND
	CBER IND ICSR	Destination: "CBER" XML Files: AERS_PREMKT_CBER	XML Files: FDA_AERS_PREMKT_CBER	ZZFDA_PREMKT	CBER_IND
	CDER IND-exempt BA/BE ICSR	Destination: "CDER" XML Files: AERS_PREMKT_CDER	XML Files: FDA_AERS_PREMKT_CDER	ZZFDA_PREMKT	CDER_IND_EXEMPT_BA_BE
Postmarket	Postmarket ICSR	Destination: "CDER" XML Files: AERS	XML Files: FDA_AERS	ZZFDA	CDER

For all *Message Receiver Identifier (data element N.2.r.3)* = CDER, the *Batch Receiver Identifier (data element N.1.4)* must be "ZZFDA".

For all *Message Receiver Identifier (data element N.2.r.3)* = CDER_IND or CBER_IND or CDER_IND_EXEMPT_BA_BE, the *Batch Receiver Identifier (data element N.1.4)* must be "ZZFDA_PREMKT"

FDA Regional Implementation of E2B(R3)

- Section C.1: Identification of a Case Safety Report

  This data element indicates within how many days the ICSR was submitted.

  - **Element Name: Local Criteria Report Type**
  - Element ID: FDA.C.1.7.1
  - Max Length: 1
  - Data Type: Numeric
  - Conformance: Required
  - Business Rules: Refer to the FDA E2B(R3) Core and Regional Data Elements and Business Rules document for the business rules

FDA Regional Implementation of E2B(R3)

- Section C.1: Identification of a Case Safety Report
  - **C.1.7: Does this Case Fulfill the Local Criteria for an Expedited Report?**
    - specify whether the case fulfills regional specifications for expedited reporting
    - *Local Criteria Report Type (FDA.C.1.7.1)* = 7-day reports, 15-day reports or 5-day reports are considered expedited reports, then *C.1.7* must be “true”
    - *Local Criteria Report Type (FDA.C.1.7.1)* = non-expedited reports or 30-day reports are considered non-expedited reports, then *C.1.7* must be “false”
  - **Linking Initial and Follow-Up ICSRs**
    - always use the same identifier for data element *Sender’s (case) Safety Report Unique Identifier (C.1.1)* that was assigned to the initial ICSR when submitting follow-up reports for the lifecycle of a case.
  - **FDA.C.5.5a: IND Number Where AE Occurred**
  - **FDA.C.5.5b: Pre-ANDA Number Where AE Occurred**
  - **FDA.C.5.r.6: IND Number of Cross-Reported IND**

Data elements explained later under IND and IND-exempt BA/BE safety reporting

FDA Regional Implementation of E2B(R3)

- Section D: Patient Characteristics
  - **D.1: Patient (Name or Initials)**

	Condition	Value
Postmarket	No patient involved on a compounding product report or medication error report	nullFlavor: NA
	Combination product malfunction ICSR with no AE	nullFlavor: NA
	Malfunction on a batch of combination products with no AE	SUMMARY
Premarket	Aggregate report	AGGREGATE

  - **FDA.D.11.r: Patient Race Code**
    - senders may submit multiple observation codes for patient race (see FDA E2B(R3) Core and Regional Data Elements and Business Rules document for element details)
  - **FDA.D.12: Patient Ethnicity Code**
    - senders may submit only one observation code for patient ethnic group (see FDA E2B(R3) Core and Regional Data Elements and Business Rules document for element details)

FDA Regional Implementation of E2B(R3)

- Section G.k: Drug(s) Information
  - **G.K.2.1.1b: Medicinal Product Identifier (MPID)**
    - The FDA National Drug Code (NDC), when known, should be used as the regional MPID
  - **G.k.2.2: Medicinal Product Name as Reported by the Primary Source**
    - FDA validates Medicinal Product Names for products marketed in the United States against the available Structured Product Labeling (SPL)
    - If the Medicinal Product Name is not provided but the active substance name is known, provide the active substance name as it appears in the FDA's GSRS
    - If foreign product trade name, provide the active substance name as it appears in the FDA's GSRS
  - **G.k.2.3.r.2b: Substance/Specified Substance TermID**
    - Always populate data element *G.k.2.3.r.1, Substance/Specified Substance Name* and populate *G.k.2.3.r.2b: Substance/Specified Substance TermID* if available, using FDA's GSRS UNII
    - FDA UNII codes are updated monthly and may be obtained from the FDA's GSRS UNII list

FDA Regional Implementation of E2B(R3)

- Section G.k: Drug(s) Information
  - **G.k.3.1: Authorisation/Application Number**

Product Type	FDA Application Type*	Recommended Format
Human drug/biologic product	NDA/ANDA/BA/BN	NDA123456 or ANDA012345 or BA123456 or BN123456
Biological product	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 product marketed	Compounded Product	COMP99

* For IND and IND exempt BA/BE safety reports that are reporting on marketed drug products and biologic al product s being evaluated under an IND or IND-exempt BA/BE, do not place the IND or pre-ANDA number in this field, respectively. Use data element ***FDA.C.5.5a: IND Number Where AE Occurred*** and ***FDA.C.5.5b: Pre-ANDA Number Where AE Occurred*** for IND and IND-exempt BA/BE, respectively.

FDA Regional Implementation of E2B(R3)

- Section G.k: Drug(s) Information
  - **FDA.G.k.10a.r: FDA Additional Information on Drug**
    - used to provide characteristics associated with product information
    - codes comprise the product exposure in an IND-exempt BA/BE study and about compounding products
    - see FDA E2B(R3) Core and Regional Data Elements and Business Rules for details
  - **FDA.G.k.13.r: FDA Specialized Product Category**
    - used to provide characteristics associated with combination product
    - see FDA E2B(R3) Core and Regional Data Elements and Business Rules for details

FDA Regional Implementation of E2B(R3)

- Section G.k: Drug(s) Information
  - **FDA.G.k.12.r: Device Information (repeat as necessary)**
    - FDA has provided regional extensions to accommodate reports for Combination Products as required by 21 CFR Part 4, Subpart B, which was added by the “Postmarketing Safety Reporting for Combination Products” rule
    - see FDA E2B(R3) Core and Regional Data Elements and Business Rules for element details

- Section E.i: Reaction/Event as Reported by the Primary Source
  - For combination products, enter MedDRA reaction/event terms instead of Patient Problem Codes
  - For a malfunction-only combination product reports, enter a MedDRA code associated with a relevant product quality issue or the MedDRA LLT code “No adverse event” for data element *E.i.2.1b, Reaction / Event (MedDRA code)*
  - **FDA.E.i.3.2h: Required Intervention**
    - Required data element
    - If not known, use nullFlavor: NI

FDA Regional Implementation of E2B(R3)

- Submission Rules
  - Define conditions resulting in a negative acknowledgement and not be accepted by FAERS, if not met.
  - E2B(R3) Core and Regional Data Elements and Business Rules defines the conformance and the business rules for each data element.
  - The tab “Rejection and Warning Rules” lists the rejection rules that will result in a negative acknowledgement, and the warning rules that will notify a warning but result in positive acknowledgement
- Forward Compatibility
  - Defines the rules to migrate existing regional E2B(R2) data elements to the regional E2B R3 data elements
  - FDA E2B(R3) Forward Compatible Rules lists the data elements and the rules to be applied
  - Appendix I (B) to the ICH E2B(R3) ICSRs Implementation Guide — Backwards and Forwards Compatibility (April 2022) should be referenced for data elements whose ”Source” is ICH.

E2B (R3) FDA Implementation Package

1

Filename: [FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products.pdf](#) (August 2022)

Content:

- Purpose of this technical specifications document is to assist submitters transmitting electronic ICSRs with attachments to the (FAERS) database
- Describes FDA's technical approach for submitting ICSRs, for incorporating its regionally controlled terminology, and for implementing regional extensions that are not in ICH ICSR IG

2

Filename: [FDA E2B(R3) Core and Regional Data Elements and Business Rules – Version 1.3.xlsx](#) (August 2022)

Content:

- Provides a comprehensive list of core ICH and FDA regional data elements, data element attributes, conformance, business rules, XPaths and acknowledgement attributes
- Some to the regional data elements in this document are detailed in the FDA Regional Implementation Technical Specification for E2B(R3)

E2B (R3) FDA Implementation Package

3

Filename: FDA E2B(R3) Forward Compatible Rules.xlsx (April 2022)

Content:

- Assist reporters and recipients in implementing systems with special focus on the recommended rules for conversion of data from regional E2B R2 and regional E2B R3
- Mostly applicable to postmarket safety reporting

4

Filename: FDA ICSR XML Instances.zip (August 2022)

Content:

- This document lists the scenarios provided as FDA ICSR XML Instance and acknowledgement examples based on FDA ICH E2B(R3) Technical Specifications Document
- The zip file has a Read Me.txt file that describes the different scenarios

IND SAFETY REPORTING

IND Safety Reports – Current and New Process

- 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)

IND Safety Reports - Requirements and Timelines

- **Required change in format under 745A(a) of FD&C Act**
  - Sponsors of commercial INDs must submit specified 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 end of this year
  - Date to be published on FAERS website 30 days prior

IND Safety Reports - Communication Plan

- Updated FAERS website with link to:
  - Draft Guidance
  - Technical Conformance Guide
  - Technical Specifications
  - Regional and Code Data Elements and Business Rules
  - XML instances
- ePrompt Meeting
- Other communications like DIA

Premarketing Safety Reporting

In preparation for the electronic transmission of premarketing safety reports in the International Council for Harmonisation (ICH) E2B(R3) format, FDA has posted the following documents regarding the electronic submission of ICSRs for certain investigational new drug application (IND) safety reports for drug and biological products and IND-exempt bioavailability/bioequivalence (BA/BE) safety reports to FAERS. These documents are posted to help sponsors prepare their systems for electronic submission of IND safety reports in the E2B(R3) format.

1. Providing Regulatory Submissions in Electronic Format: IND Safety Reports - Draft Guidance for Industry (October 2019)
2. Electronic Submission of IND Safety Reports - Technical Conformance Guide (April 2022)
3. Technical Specifications Document - FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products (August 2022)
4. Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies - Draft Guidance for Industry (August 2022)
5. FDA E2B(R3) Core and Regional Data Elements and Business Rules (Excel file August 2022)
6. FDA ICSR XML Instances (zip file August 2022)

Please note, FDA is not currently accepting the submission of premarket ICSRs in the E2B(R3) format. Please continue to submit IND safety reports using eCTD format and IND-exempt BA/BE safety reports on Form FDA 3500A. FDA will update this web page when final guidance for IND safety reporting is published, and when FDA will accept IND and IND-exempt BA/BE safety reports in E2B(R3) format on a voluntary basis. FDA will also update this web page to communicate when submission of safety reports in E2B(R3) format is required for certain INDs after the period of voluntary submission.

IND Safety Report - Separate Submission Path Business Rules

- **Batch Receiver Identifier (N.1.4) and Message Receiver Identifier (N.2.r.3)**

		AS2 Header	Routing ID	N.1.4 Value	N.2.r.3 Value
Premarket	**CDER IND ICSR**	**Destination: "CDER" XML Files: AERS_PREMKT_CDER**	**XML Files: FDA_AERS_PREMKT_CDER**	**ZZFDA_PREMKT**	**CDER_IND**
	CBER IND ICSR	**Destination: "CBER" XML Files: AERS_PREMKT_CBER**	**XML Files: FDA_AERS_PREMKT_CBER**	**ZZFDA_PREMKT**	**CBER_IND**
	CDER IND-exempt BA/BE ICSR	Destination: "CDER" XML Files: AERS_PREMKT_CDER	XML Files: FDA_AERS_PREMKT_CDER	ZZFDA_PREMKT	CDER_IND_EXEMPT_BA_BE
Postmarket	Postmarket ICSR	Destination: "CDER" XML Files: AERS	XML Files: FDA_AERS	ZZFDA	CDER

Case Study 1 – Types of IND Safety Reports

- Not all IND safety reports will go to FAERS

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

Case Study 1 – Discussion

- No 1571 or cover letter for IND safety reports sent to FAERS
- How will processes/interactions between PV/Safety teams and Regulatory Affairs change?
- Questions?

Case Study 2 – Reporting on Primary IND

- For reports to FAERS, only one IND safety report will be submitted to the IND where the event occurred (primary IND)
  - **Element Name: IND Number where AE Occurred**
  - Element ID: FDA.C.5.5a
  - Max Length: 10
  - Data Type: Numeric
  - Conformance: Conditional-Required
  - Business Rules:
    - If Type of Report (C.1.3) is 2=Report from study and Message Receiver Identifier (N.2.r.3) = 'CDER_IND' or 'CBER_IND' then IND Number where AE Occurred (FDA.C.5.5a) is required. The format must be "123456".
    - For IND safety 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
    - Required to be a valid IND number for processing and routing

Case Study 3 – IND safety reports “cross-reporting”

- What process changes will be required to accommodate new process for “cross-reporting”?
- Other sponsor INDs evaluating the same suspect product will be listed in the same report as below.
  - **Element Name: IND number of cross reported IND**
  - Element ID: FDA.C.5.6.r
  - Max Length: 10
  - Data Type: Numeric
  - Conformance: Conditional-Required
  - Business Rules:
    - If IND Number where AE Occurred (FDA.C.5.5a) is populated, then
      - IND number of cross reported IND (FDA.C.5.6.r) is required.
      - Use nullFlavor=NA if there are no other cross reported IND

Case Study 4 – Reports from aggregate analyses

- Required as per 21 CFR 312.32(c)(1)(i)(C)
- Use “parent” IND number for primary IND
- What process changes will be required for this new process?
  - To identify the “parent” IND
  - Linking of reports associated with the analysis

Element Name	Element ID	Data Value and Rules
Sender’s (case) Safety Report Unique Identifier	C.1.1	Reports from aggregate analyses must have its own Sender’s (case) Safety Report Unique Identifier. For all follow-ups use the same value.
IND Number where AE Occurred	FDA.C.5.5a	For IND safety 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
Patient (name or initials)	D.1	For Aggregate Report, the element value must be “AGGREGATE”
Identification Number of the Report Which Is Linked to This Report	C.1.10.r	If *Patient (name or initials) (D.1)* = AGGREGRATE, then *Identification Number of the Report Which Is Linked to This Report (C.1.10.r)* must be provided for all *Sender’s (case) Safety Report Unique Identifier (C.1.1)* that makes up an Aggregate Analysis as per 312.32(c)(1)(i)(C)

Case Study 5 – Investigational and approved drugs

- Two arm trial: Investigational drug A compared to approved drugs B and/or C

Element Name	Element ID	Suspect drug is drug A only	Suspect drug is drug B or C only and report meets IND safety reporting requirements (21 CFR 312.32)	Suspect drug is drug B and C only and report meets IND safety reporting requirements (21 CFR 312.32)
Medicinal Product Name as Reported by the Primary Source	G.k.2.2	Company code OR Proprietary medicinal product name for drug A	Proprietary medicinal product name for drug B or C	Field should be populated twice as follows: Proprietary medicinal product name for drug B and C
Substance / Specified Substance Name	G.k.2.3.r.1	Active drug substance name for drug A	Active drug substance name for drug B or C	Field should be populated twice as follows: Active drug substance name for drug B and C
IND Number where AE Occurred	FDA.C.5.5a	IND number under which the clinical trial where the event occurred is conducted		

Case Study 6 – Add-on therapies

- Two arm trial: Investigational drug A plus approved drugs B and C compared to approved drugs B and C

Element Name	Element ID	Suspect drug is drug A only	Suspect drug is drug B and/or C only and report meets IND safety reporting requirements (21 CFR 312.32)	Suspect drug is all 3 drugs and IND safety reporting requirements (21 CFR 312.32) for drugs B and C
Medicinal Product Name as Reported by the Primary Source	G.k.2.2	Company code OR Proprietary medicinal product name for drug A	Field should be populated as follows: Proprietary medicinal product name for drug B and/or C	Field should be populated as follows: Company code or Proprietary medicinal product name for drug A and Proprietary medicinal product name for drug B and C
Substance / Specified Substance Name	G.k.2.3.r.1	Active drug substance name for drug A	Field should be populated as follows: Active drug substance name for drug B and/or C	Field should be populated as follows: Active drug substance name for drug A, B and C
IND Number where AE Occurred	FDA.C.5.5a	IND number under which the clinical trial where the event occurred is conducted		

Case Study 7 – Approved drug under an IND

- Two arm trial (Approved drugs conducted under an IND to support a new indication for approved drug A): Approved drug A plus approved drug B compared to approved drug B

Element Name	Element ID	Suspect drug is drug A only	Suspect drug is drug B and report meets IND safety reporting requirements (21 CFR 312.32)	Suspect drug is drug A and drug B and report meets IND safety reporting requirements (21 CFR 312.32) for drug B
Medicinal Product Name as Reported by the Primary Source	G.k.2.2	Proprietary medicinal product name for drug A	Proprietary medicinal product name for drug B	Field should be populated twice as follows: Proprietary medicinal product name for drug A and B
Substance / Specified Substance Name	G.k.2.3.r.1	Active drug substance name for drug A	Active drug substance name for drug B	Field should be populated twice as follows: Active drug substance name for drug A and B
IND Number where AE Occurred	FDA.C.5.5a	IND number under which the clinical trial where the event occurred is conducted		

Case Study 8 – Reporting of Causality

- Reporting of causality for IND safety report

Element Name	Element ID	Conformance	Business Rule
Source of Assessment	G.k.9.i.2.r.1	Conditional-Required	• Default Source of Assessment (G.k.9.i.2.r.1) to "**Sponsor**" and Include Investigator Assessment in H.1 • Required, if Element Value for Type of Report (C.1.3) is 2 (=Report from study) and IND Number where AE Occurred (FDA.C.5.5a) is provided
Method of Assessment	G.k.9.i.2.r.2	Conditional-Required	• Default Method of Assessment (G.k.9.i.2.r.2) to "**FDA**" to differentiate from other assessment methods. • Required, if Element Value for Type of Report (C.1.3) is 2 (=Report from study) and IND Number where AE Occurred (FDA.C.5.5a) is provided
Result of Assessment	G.k.9.i.2.r.3	Conditional-Required	• For IND Safety Reports, at least one suspect product should have relatedness of drug to reaction/event • For Result of Assessment (G.k.9.i.2.r.3) use the value "**Suspected**" or "**Not Suspected**" • Required, if Element Value for Type of Report (C.1.3) is 2 (=Report from study) and IND Number where AE Occurred (FDA.C.5.5a) is provided

IND-EXEMPT BIO-AVAILIBILITY (BA) / BIO-EQUIVALENT (BE) STUDY SAFETY REPORTING

IND-exempt BA/BE Safety Reporting

- In the Federal Register of September 29, 2010, FDA published a final rule that revised the IND (including Bio-IND) safety reporting requirements for human drug and biological products under 21 CFR part 312.
- Added safety reporting requirements for persons conducting IND-exempt BA/BE studies under 21 CFR 320.31
- This regulation outlines when BA and BE studies are exempt from the IND requirements

IND-Exempt BA/BE Safety Report - Separate Submission Path Business Rules

- **Batch Receiver Identifier (N.1.4) and Message Receiver Identifier (N.2.r.3)**

		AS2 Header	Routing ID	N.1.4 Value	N.2.r.3 Value
Premarket	CDER IND ICSR	Destination: "CDER" XML Files: AERS_PREMKT_CDER	XML Files: FDA_AERS_PREMKT_CDER	ZZFDA_PREMKT	CDER_IND
	CBER IND ICSR	Destination: "CBER" XML Files: AERS_PREMKT_CBER	XML Files: FDA_AERS_PREMKT_CBER	ZZFDA_PREMKT	CBER_IND
	CDER IND-exempt BA/BE ICSR	**Destination: "CDER" XML Files: AERS_PREMKT_CDER**	**XML Files: FDA_AERS_PREMKT_CDER**	**ZZFDA_PREMKT**	**CDER_IND_EXEMPT_BA_BE**
Postmarket	Postmarket ICSR	Destination: "CDER" XML Files: AERS	XML Files: FDA_AERS	ZZFDA	CDER

IND-exempt BA/BE Safety Report – Reporting on Pre-ANDA

- For reports to FAERS, only one safety report will be submitted to the IND-exempt BA/BE Study where the event occurred (Pre-ANDA)
  - **Element Name: Pre-ANDA Number where AE Occurred**
  - Element ID: FDA.C.5.5b
  - Max Length: 10
  - Data Type: Numeric
  - Conformance: Conditional-Required
  - Business Rules:
    - If *Type of Report (C.1.3)* is 2=Report from study and *Message Receiver Identifier (N.2.r.3)* = CDER_IND_EXEMPT_BA_BE' then Pre-ANDA Number where AE Occurred (FDA.C.5.5a) is required. The format must be “234567".
    - Required to be a valid Pre-ANDA number for processing and routing

Case Study 1 - Reporting subject's drug exposures that occur after enrollment

- Descriptions of E2B Data Elements for Reporting Drug Exposure

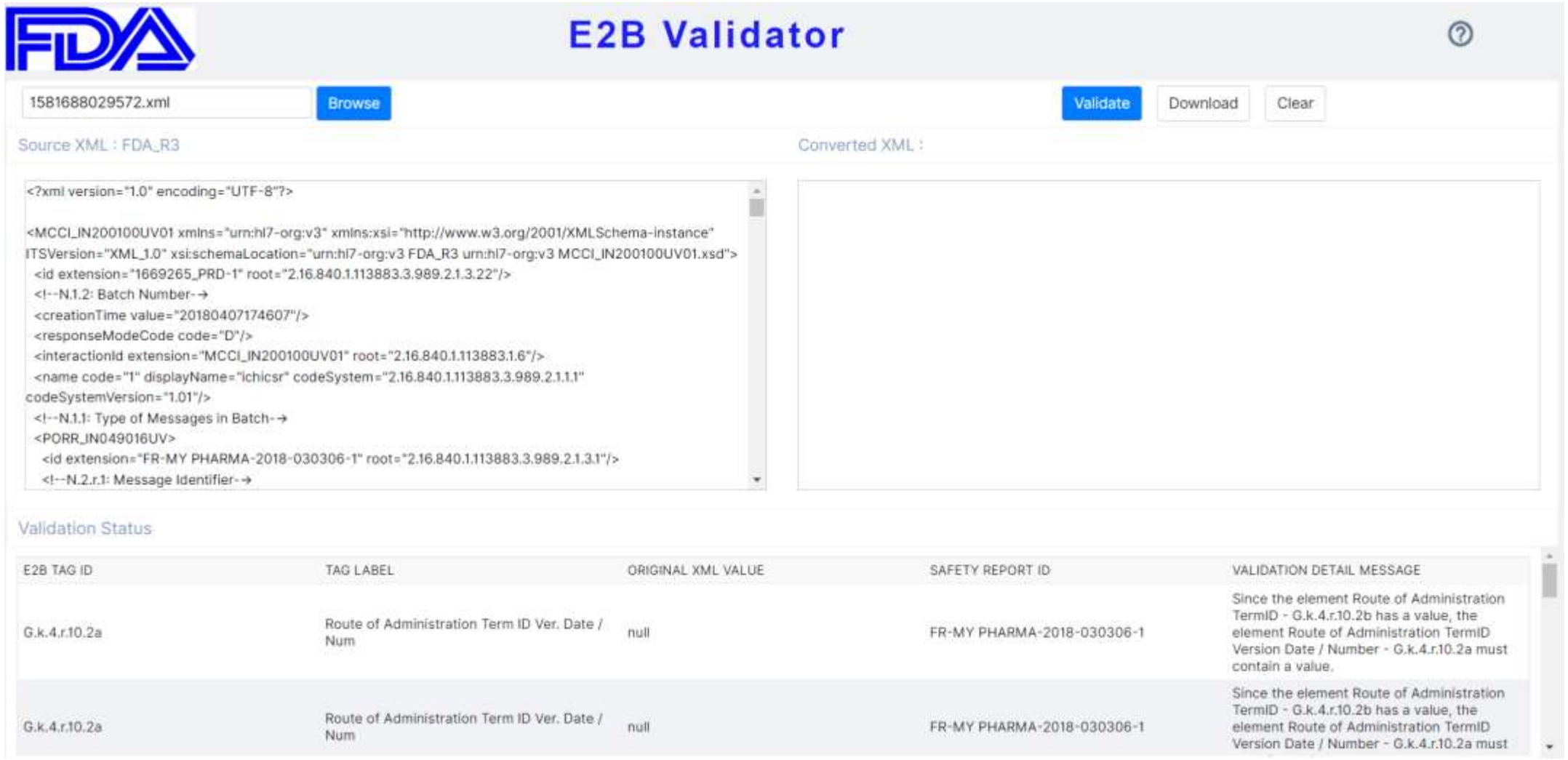
Element Name	Element ID	Element Value
Characterization of Drug Role	G.k.1	1 = Suspect 2 = Concomitant 3 = Interacting 4 = Drug not administered
FDA Additional Information on Drug (coded)	FDA.G.k.10a.r	1 = Test 2 = Reference nullFlavor=NA
Drug identification	G.k.2	(Header – no element value)
Medicinal Product Name as Reported by the Primary Source	G.k.2.2	Medicinal product name (free text)
Substance/Specified Substance Name	G.k.2.3.r.1	Drug substance name (free text)

TESTING AND IMPLEMENTATION

Mechanism to validate E2B

- Provide a mechanism for industry to validate the regional E2B R3 XML files
- Mechanism can be used before production submission
- Mechanism available for use via a public URL
- Uploaded file are not stored
- FAERS Electronic Submission web page will provide this information

Mechanism to validate E2B



Testing and Implementation

- Identify Sponsors who will be ready to test E2B R3 with regional extensions
- Perform testing for both pre and postmarket ICSRs
- Testing timelines will be provided to the indentified Sponsors
- FDA to provide a validator tool to pretest sender's ICSR
  - Validator can be accessed via public URL
- Once validated Sponsor's can submit ICSRs in preproduction environment and receive acks
- Sponsors continue to submit ICSRs in postmarket ICSR in R2 format until ready for R3
- Sponsor's test both premarket and postmarket (including combo product) ICSRs
  - Use the three submission mechanisms (explained in Submission Path slide)

Testing and Implementation

- 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

During the voluntary submission period for premarket ICSRs:

- recommend to use Safety Reporting Portal (SRP) for direct submission
- submission of 1571 and cover letter not required
- eleminates sending the reports to the company's regulatory affairs

Once ready to submit permarket safety report in E2B R3 format via ESG:

- SRP account will be deactivated for permarket safety report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