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

APRIL 4, 2023

# Discloser

- We have no financial relationships to disclose
- We will not discuss any off-label or investigational use

# Session Overview

## Description

- This session will review 1) requirements for submitting safety reports for INDs, IND-exempt BA/BE studies, and approved drug and therapeutic biologic products (excluding vaccine) using the ICH E2B(R3) format; 2) submission method and mechanism; 3) highlight regional extensions; and 4) Implementation plan

## Objectives

- Recognize that FDA will require reporting of IND and postmarket safety reports to be submitted in the ICH E2B (R3) format to FAERS via the FDA Gateway or the Safety Reporting Portal
- Understand in detail regional data elements that are key for postmarket, IND, and IND-exempt BA/BE safety reporting

# Speakers

- **Reporting of postmarket safety reports to FDA using ICH E2B(R3) standards**

Suranjan De, M.S., M.B.A.
Deputy Director, Regulatory Science Staff
Office of Surveillance and Epidemiology, CDER, U.S. FDA

- **Reporting of INDs safety reports to FDA using ICH E2B(R3) standards**

Y. Veronica Pei, M.D., M.Ed., M.P.H.
Lieutenant Commander, U.S. Public Health Service
Associate Director of Biomedical Informatics
Office of New Drug, CDER, U.S. FDA

- **Reporting of IND-exempt BA/BE safety reports to FDA using ICH E2B(R3) standards**

Jung Lee, R.Ph., MPH
Safety Officer, Division of Clinical Safety and Surveillance
Office of Safety and Clinical Evaluation
Office of Generic Drug, CDER, U.S. FDA

# Outline

| | | | | | |
|---|---|---|---|---|---|
| **Background** | Regional Implementation of E2B(R3) | Submission Methods & Mechanism | BREAK | E2B(R3) Implementation Package | |
| Common Regional Extensions | BREAK | Postmarket Safety Reporting | IND Safety Reporting | BA/BE Study Safety Reporting for Generic Drugs | |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | R2 -> R3 Regional Forward Compatibility | Summary | |

# Background

- **Initial plan**:  Use E2B R2 for IND and IND-exempt BA/BE safety reporting
- Implement E2B R3 submission 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

*Premarket – refers to both IND and IND-exempt BA/BE safety reports

# Outline

| | | | | | |
|---|---|---|---|---|---|
| Background | **Regional Implementation of E2B(R3)** | Submission Methods & Mechanism | BREAK | E2B(R3) Implementation Package | |
| Common Regional Extensions | BREAK | Postmarket Safety Reporting | IND Safety Reporting | BA/BE Study Safety Reporting for Generic Drugs | |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | R2 -> R3 Regional Forward Compatibility | Summary | |

# 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

Periodic Adverse Event Drug Experience Report (PADER)

- descriptive portion must be submitted using eCTD
- E2B R3 ICSRs to FAERS

```
<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
  - FAERS will accept country code 'EU'

# FDA Regional Implementation of E2B(R3)

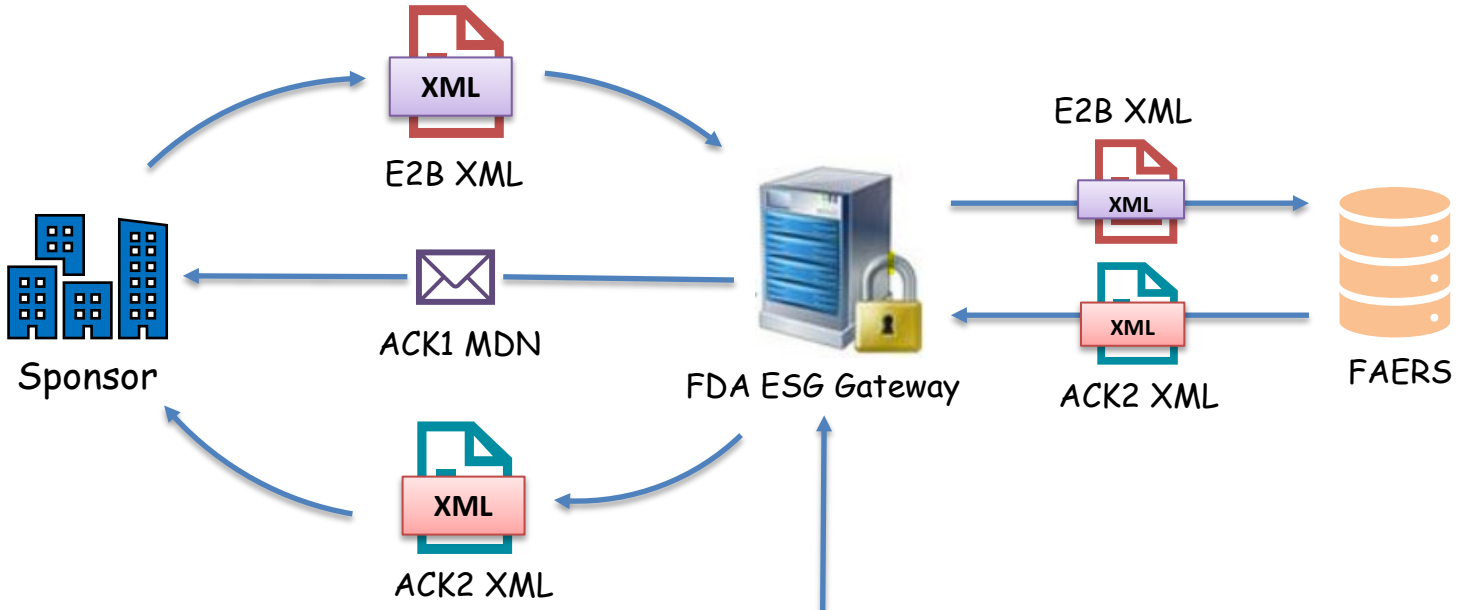
- Controlled Terminology
  - NCI Enterprise Vocabulary Services (EVS)
  - MedDRA
  - Unified Codes for Units of Measurement (UCUM)
  - European Directorate for the Quality of Medicines (EDQM)
  - Device Product Code (“ProCode”)
  - FDA Global Substance Registration System (GSRS) Unique Ingredient Identifiers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

# Outline

| | | | | |
|---|---|---|---|---|
| Background | Regional Implementation of E2B(R3) | **Submission Methods & Mechanism** | BREAK | E2B(R3) Implementation Package |
| Common Regional Extensions | BREAK | Postmarket Safety Reporting | IND Safety Reporting | BA/BE Study Safety Reporting for Generic Drugs |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | R2 -> R3 Regional Forward Compatibility | Summary |

# Submission Methods

Option A:
via Database-to-Database Transmission




OR

Option B:
via Safety Reporting Portal (SRP)


SRP requires Sponsors to register and receive login credentials

# Submission Methods

**Option A**
**via Database-to-Database Transmission**

- Submitters who have database-to-database transmission capability may directly submit ICSRs in the XML format via the Electronic Submissions Gateway (ESG)

**Option B**
**via 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

Do not submit ICSRs via both options. Always stick to one option.

# 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
  - Not available for vaccine 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
  - Do not upload E2B R3 XML via SRP
  - Emails acknowledgement on submission – keep for records

# Safety Reporting Portal (SRP)

- **Changes to SRP**
  - Based on MedWatch 3500A
  - Performed updates to include premarket questionnaire
  - Current postmarket questionnaire updated to accommodate E2B R3 structure
- **“Free” (no added cost to use)**
- **Availability**
  - Both SRP and E2B R3 via ESG for premarket submission will be available at the same time
  - No additional action required by existing SRP users for postmarket reporting
- Contact FAERSESUB@fda.hhs.gov to request an SRP account

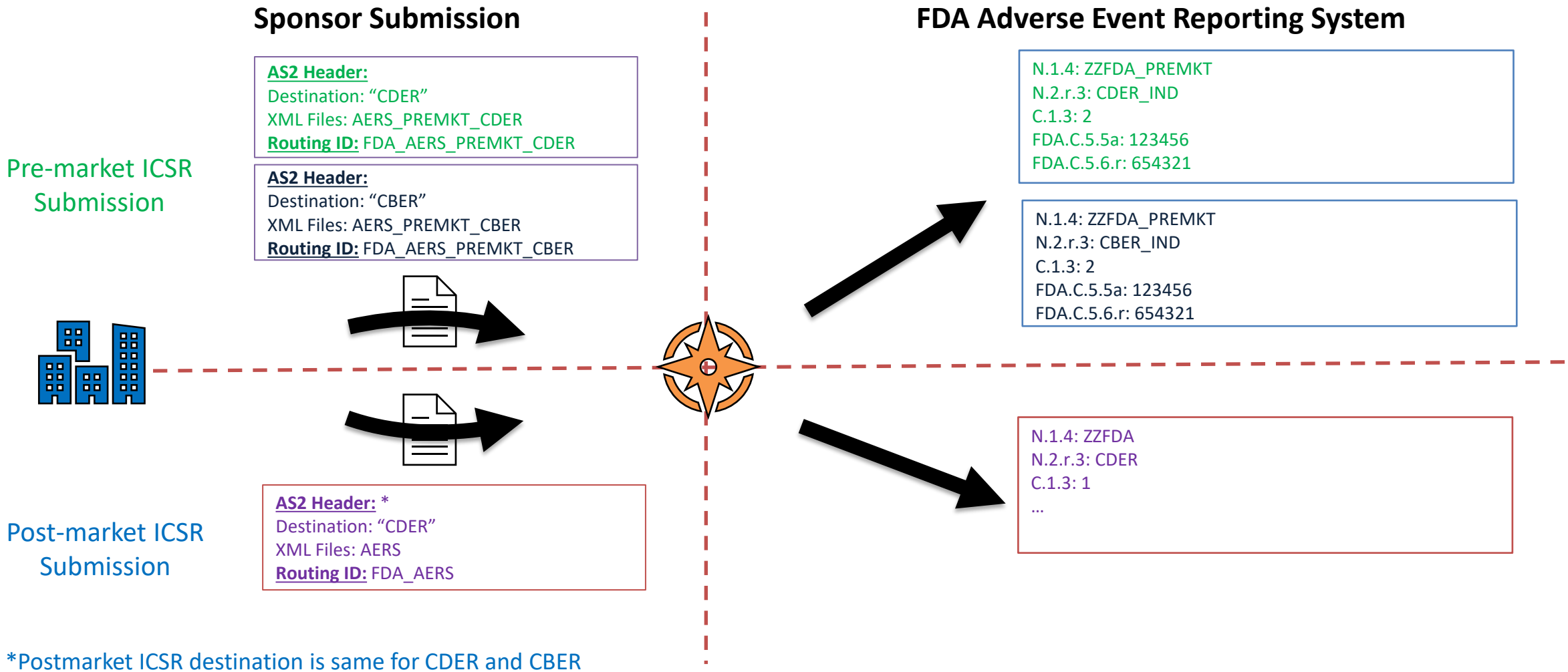
# Separate ESG Submission Paths

| AS2 Headers/ Routing IDs | Postmarketing reports | Premarketing reports for CDER | Premarketing reports for CBER |
|---|---|---|---|
| **AS2 Headers** | Destination: "CDER"<br><br>XML files: AERS | Destination: "CDER"<br><br>XML files: AERS_PREMKT_CDER | Destination: "CBER"<br><br>XML files: AERS_PREMKT_CBER |
| **Routing IDs** | XML files: FDA_AERS<br><br>WebTrader Accounts: CDER AERS<br><br>AS2 Accounts: FDA_AERS | XML files: FDA_AERS_PREMKT_ CDER | XML files: FDA_AERS_PREMKT_ CBER |

- Defined **new header attributes and routing IDs** for premarket safety reports
- Two pathways allow **separation of premarket from postmarket reports**
- **Rejection** will occur if:
  - Premarket report incorrectly submitted to postmarket pathway
  - Postmarket report incorrectly submitted to premarket pathway
- Premarket reports will NOT be published publicly

**ESG Appendix J: AS2 Routing IDs**
https://www.fda.gov/industry/about-esg/esg-appendix-j-as2-routing-ids

# Approach to Triage of ICSRs via ESG




*Postmarket ICSR destination is same for CDER and CBER (excluding vaccine)

# Separate Submission Path Business Rules

- Section N.1: ICH ICSR 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"<br>XML Files: AERS_PREMKT_CDER | XML Files:<br>FDA_AERS_PREMKT_CDER | ZZFDA_PREMKT | CDER_IND |
| | CBER IND ICSR | Destination: "CBER"<br>XML Files: AERS_PREMKT_CBER | XML Files:<br>FDA_AERS_PREMKT_CBER | ZZFDA_PREMKT | CBER_IND |
| | CDER IND-exempt BA/BE ICSR | Destination: "CDER"<br>XML Files: AERS_PREMKT_CDER | XML Files:<br>FDA_AERS_PREMKT_CDER | ZZFDA_PREMKT | CDER_IND_EXEMPT_BA_BE |
| Postmarket | Postmarket ICSR | Destination: "CDER"<br>XML Files: AERS | XML Files: FDA_AERS | ZZFDA | CDER |

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

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

# BREAK (10:15AM – 10:30AM)

# Outline

| | | | | | |
|---|---|---|---|---|---|
| Background | | Regional Implementation of E2B(R3) | | Submission Methods & Mechanism | **E2B(R3) Implementation Package** |
| Common Regional Extensions | BREAK | Postmarket Safety Reporting | | IND Safety Reporting | BA/BE Study Safety Reporting for Generic Drugs |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | | R2 -> R3 Regional Forward Compatibility | Summary |

# E2B (R3) FDA Implementation Package

| | |
|---|---|
| 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<br>• 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 |

| | |
|---|---|
| Filename: | FDA E2B(R3) Core and Regional Data Elements and Business Rules – Version 1.3.xlsx (January 2023) |
| Content: | • Provides a comprehensive list of core ICH and FDA regional data elements, data element attributes, conformance, business rules, XPaths and acknowledgement attributes<br>• Some of the regional data elements in this document are detailed in the FDA Regional Implementation Technical Specification for E2B(R3) |

# E2B (R3) FDA Implementation Package

| | |
|---|---|
| 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<br>• Mostly applicable to postmarket safety reporting |

| | |
|---|---|
| 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<br>• The zip file has a Read Me.txt file describing the different scenarios |

# Outline

| | | | | |
|---|---|---|---|---|
| Background | Regional Implementation of E2B(R3) | Submission Methods & Mechanism | BREAK | E2B(R3) Implementation Package |
| **Common Regional Extensions** | BREAK | Postmarket Safety Reporting | IND Safety Reporting | BA/BE Study Safety Reporting for Generic Drugs |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | R2 -> R3 Regional Forward Compatibility | Summary |

# Common Regional Extensions

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

## Element Name: Sender's (case) Safety Report Unique Identifier (C.1.1)

- Business Rule
  - Use the same Sender's (case) Safety Report Unique Identifier (C.1.1) for all previously submitted reports.
  - Always use the same identifier for data element C.1.1 that was assigned to the initial ICSR when submitting follow-up reports for the lifecycle of a case

## Element Name: Type of Report (C.1.3)

- Business Rule
  - If Batch Receiver Identifier (N.1.4) = ZZFDA_PREMKT then Type of Report (C.1.3) must be 2=Report from Study

# Common Regional Extensions

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

**Element Name:** **Local Criteria Report Type (FDA.C.1.7.1)**

- Max Length: 1
- Data Type: Numeric (N)
- Conformance: Required
- Values Allowed: <Observation><code>= C54588
  - 1=15-Day
  - 2=Non-Expedited AE
  - 4=5-Day
  - 5=30-Day
  - 6=7-Day
- Business Rule: Refer to the FDA E2B(R3) Core and Regional Data Elements and Business Rules document for the business rules

# Common Regional Extensions

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

**Element Name:** **Local Criteria Report Type (FDA.C.1.7.1)**

- N
- D
- C
- V
- E ment f

| |
|---|
| **For postmarket ICSRs**<br>If Combination Product Report Indicator (FDA.C.1.12) = True and Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7) = True, Observation Code: (Value allowed: 1, 4) |
| If Combination Product Report Indicator (FDA.C.1.12) = True and Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7) = False or NI, Observation Code: (Value allowed: 2, 5) |
| If Combination Product Report Indicator (FDA.C.1.12) = False or NI and Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7) = True, Observation Code: (Value allowed: 1) |
| If Combination Product Report Indicator (FDA.C.1.12) = False or NI and Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7) = False or NI, Observation Code: (Value allowed: 2) |
| **For premarket ICSRs**<br>For 15-Day or 7-Day Expedited report, if Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7) = True and Type of Report (C.1.3) = 2 (Report from Study) then Observation Code: (Value allowed: 1, 6) respectively. |

# Common Regional Extensions

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

| Element Name: | **Does This Case Fulfil the Local Criteria for an Expedited Report? (C.1.7)** |
|---|---|

- Guidance
  - specify whether the case fulfills regional specifications for expedited reporting
  - Local Criteria Report Type (FDA.C.1.7.1) = 7-day, 15-day or 5-day are considered expedited reports, then C.1.7 must be “true”
  - Local Criteria Report Type (FDA.C.1.7.1) = non-expedited AE or 30-day are considered non-expedited reports, then C.1.7 must be “false”
- Business Rule
  - Initial submissions with nullFlavor “NI” will be rejected

# Common Regional Extensions

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

**Element Name:** **Combination Product Report Indicator (FDA.C.1.12)**

- Max Length: N/A
- Data Type: Boolean
- Conformance: Required
- Values Allowed: <Observation><code>= C156384
  - false
  - true
  - nullFlavor: NI
- Business Rule: Required per Postmarketing Safety Reporting for Combination Products - Guidance for Industry and FDA Staff

# Common Regional Extensions

- Section C.2.r: Primary Source(s) of Information (repeat as necessary)

**Element Name:** **Reporter's Email (FDA.C.2.r.2.8)**

- Max Length: 100
- Data Type: Alpha Numeric (AN)
- Conformance: Required
- Values Allowed: <Observation><code>
  - nullFlavor: NASK
- Business Rule
  - When submitting a nullFlavor response also include the telecom prefix within the value attribute to correctly reference the related telecom type, as shown in examples:

    <telecom value="mailto:email@address.com"/>

    <telecom nullflavor="NASK" value="mailto"/>

# Common Regional Extensions

- Section C.3.3: Information on Sender of Case Safety Report

| Data Element Conformance changed to Required | |
|---|---|
| Sender's Department (C.3.3.1) | Sender's State or Province (C.3.4.3) |
| Sender's Title (C.3.3.2) | Sender's Postcode (C.3.4.4) |
| Sender's Given Name (C.3.3.3) | Sender's Country Code (C.3.4.5) |
| Sender's Family Name (C.3.3.5) | Sender's Telephone (C.3.4.6) |
| Sender's Street Address (C.3.4.1) | Sender's Fax (C.3.4.7) |
| Sender's City (C.3.4.2) | Sender's E-mail Address (C.3.4.8) |

# Common Regional Extensions

- Section D: Patient Characteristics

## Element Name: **Patient (name or initial) (D.1)**

- Business Rule
  - No patient involved on a compounding product report or medication error report use nullFlavor: NA
  - For combination product report having malfunction with no AE use nullFlavor: NA
  - For combination product report having malfunction on a batch of combination products with no AE use value “SUMMARY”
  - For Aggregate report use value “AGGREGRATE”
  - If *Type of Report (C.1.3) is 2 (=Report from study)* and *IND Number where AE Occurred (FDA.C.5.5a)* is provided and *Identification Number of the Report Which Is Linked to This Report (C.1.10.r )* is populated then *Patient (name or initials) (D.1)* must have the value 'AGGREGATE'

# Common Regional Extensions

- Section D: Patient Characteristics

**Element Name:** **Patient Race Code (FDA.D.11.r.1)**

- Max Length: 10
- Data Type: Alpha Numeric (AN)
- Conformance: Required
- 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
  - nullFlavor: UNK, MSK, OTH, NA
- Business Rule
  - Must be provided as nullFlavor: NA when Patient (name or initial) (D.1) is provided as nullFlavor: NA or "SUMMARY" or "AGGREGRATE"

# Common Regional Extensions

- Section D: Patient Characteristics

**Element Name:** **Patient Ethnicity Code (FDA.D.12)**

- Max Length: 10
- Data Type: Alpha Numeric (AN)
- Conformance: Required
- Values Allowed: <Observation><code>= C16564
  - C17459=Hispanic or Latino
  - C41222=Non Hispanic or Latino
  - nullFlavor: UNK, MSK, NI, NA
- Business Rule
  - Must be provided as nullFlavor: NA when Patient (name or initial) (D.1) is provided as nullFlavor: NA or "SUMMARY" or "AGGREGRATE"

# Common Regional Extensions

- Section G.k: Drug(s) Information (repeat as necessary)

## Element Name: Characterisation of Drug Role (G.k.1)

- Business Rule
  - **For postmarket ICSRs**
    - The first product (under section G) should have this data element answered as ‘1’ (=Suspect) or ‘3’ (=Interacting), unless the product has at least once device constituent part where Malfunction (FDA.G.k.12.r.1) is “true”, in which case the Observation Code: (Value allowed: 1, 3, 4)
    - At least one product must be reported with Observation Code: (Value allowed: 1, 3, 4)
  - **For premarket ICSRs**
    - For IND ICSRs, Only use Observation Code: (Value allowed: 1, 2, 3) and at least one product must be reported with Observation Code: (Value allowed: 1, 3)
    - For IND-exempt BA/BE ICSRs, Use Observation Code: (Value allowed: 1, 2, 3, 4) and at least one product must be reported with Observation Code: (Value allowed: 1, 3, 4)

# Common Regional Extensions

- Section G.k: Drug(s) Information (repeat as necessary)

| Element Name: | **FDA Other Characterisation of Drug Role (FDA.G.k.1.a)** |
|---|---|

- Max Length: 1
- Data Type: Numeric (N)
- Conformance: Conditional-Required
- Values Allowed:
  - 1=Similar Device
- Business Rule
  - For Similar Device, Observation Code: (Value allowed: 1) must be provided if *Combination Product Report Indicator (FDA.C.1.12)* is 'true', *Malfunction (FDA.G.k.12.r.1)* is 'true' and *Characterisation of Drug Role (G.k.1)* = '4' (Drug Not Administered) under 21 CFR 4.102(c) and 803.50

# Common Regional Extensions

- Section G.k: Drug(s) Information (repeat as necessary)
  - **G.K.2.1.1b: Medicinal Product Identifier (MPID)**
    - The FDA National Drug Code (NDC), when known, should be used as the regional MPID
    - Use either only the first two segments of the NDC or the full NDC as regional MPID in ICSR
  - **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 foreign product trade name
  - **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
    - If foreign product, provide the active substance name as it appears in the FDA's GSRS
    - FDA UNII codes are updated monthly and may be obtained from the FDA's GSRS UNII list

# Common Regional Extensions

- Section G.k: Drug(s) Information (repeat as necessary)

## Element Name: Authorisation/Application Number (G.k.3.1)

| 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.

# Common Regional Extensions

- Section G.k: Drug(s) Information (repeat as necessary)

**Element Name:** **Pharmaceutical Dose Form TermID (G.k.4.r.9.2b)**

- Guidance
  - Use <Observation><code> = C54456, if not available use EDQM code

**Element Name:** **Route of Administration TermID (G.k.4.r.10.2b)**

- Guidance
  - Use <Observation><code> = C54456, if not available use EDQM code

# Common Regional Extensions

- Section G.k: Drug(s) Information (repeat as necessary)

**Element Name:** **FDA Additional Information on Drug (coded) (repeat as necessary) (FDA.G.k.10a.r)**

Used to provide characteristics associated with a product

- Max Length: 2
- Data Type: Numeric (N)
- Conformance: Conditional-Required
- Values Allowed:
  - 1=Test
  - 2=Reference
  - 3=Bulk ingredient
  - 4=Bulk Ingredient For Human Prescription Compounding
  - 5=Unapproved Drug Product Manufactured Exclusively for Private Label Distributer
  - nullFlavor: NA
- Business Rule
  - If *Pre-ANDA Number where AE Occurred (FDA.C.5.5b)* is present, then the Observation Code: (Value allowed: 1, 2) must be used to describe the drug's role in the IND-Exempt BA/BE study. Use nullFlavor: NA for all other drugs or if information is not available.

# Common Regional Extensions

- Section G.k: Drug(s) Information (repeat as necessary)

Element Name: **FDA Specialized Product Category (FDA.G.k.13.r)**

Used to provide characteristics associated with a combination product

- Max Length: 10
- Data Type: Alpha Numeric (AN)
- Conformance: Optional
- Values Allowed: <Observation><code>= C94031
  - 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)

# Common Regional Extensions

- 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.

# BREAK (11:45AM – 12:30PM)

# Outline

| | | | | | |
|---|---|---|---|---|---|
| Background | | Regional Implementation of E2B(R3) | | Submission Methods & Mechanism | BREAK |
| Common Regional Extensions | BREAK | **Postmarket Safety Reporting** | | IND Safety Reporting | |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | | R2 -> R3 Regional Forward Compatibility | |

| | |
|---|---|
| E2B(R3) Implementation Package | |
| BA/BE Study Safety Reporting for Generic Drugs | |
| Summary | |

# POSTMARKET SAFETY REPORTING

# Postmarket 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"<br>XML Files: AERS_PREMKT_CDER | XML Files:<br>FDA_AERS_PREMKT_CDER | ZZFDA_PREMKT | CDER_IND |
| | CBER IND ICSR | Destination: "CBER"<br>XML Files: AERS_PREMKT_CBER | XML Files:<br>FDA_AERS_PREMKT_CBER | ZZFDA_PREMKT | CBER_IND |
| | CDER IND-exempt BA/BE ICSR | Destination: "CDER"<br>XML Files: AERS_PREMKT_CDER | XML Files:<br>FDA_AERS_PREMKT_CDER | ZZFDA_PREMKT | CDER_IND_EXEMPT_BA_BE |
| **Postmarket** | **Postmarket ICSR** | **Destination: "CDER"<br>XML Files: AERS** | **XML Files: FDA_AERS** | **ZZFDA** | **CDER** |

# Postmarket Safety Reporting

- Section E.i: Reaction/Event as Reported by the Primary Source

## Element Name: **Required Intervention (FDA.E.i.3.2h)**

- Max Length: N/A
- Data Type: Boolean
- Conformance: Required
- Values Allowed:
  - true
  - nullFlavor: NI
- Guidance
  - For Pre-Market safety reports the value of the data element must always be nullFlavor: NI

# Postmarket Safety Reporting

- Section G.k: Drug(s) Information (repeat as necessary)

## Element Name: Device Information (repeat as necessary) (FDA.G.k.12.r)

| Data Element | Max Length | Data Type | Values Allowed | Conformance | Business Rule |
|---|---|---|---|---|---|
| Malfunction (FDA.G.k.12.r.1) | N/A | Boolean | <Observation><code>= C54026<br>true, false | Conditional-Required | If *Local Criteria Report Type (FDA.C.1.7.1)* = 5, then *Malfunction (FDA.G.k.12.r.1)* must be 'true' for at least one suspect product |
| If follow-up, what type? (FDA.G.k.12.r.2.r) | 1 | N | <Observation><code>= C54592<br>1=Correction<br>2=Additional Information<br>3=Response to FDA Request<br>4=Device Evaluation | Optional | OID: 2.16.840.1.113883.3.989.5.1.2.1.1.5 |
| Device Problem Code (FDA.G.k.12.r.3.r) | 7 | AN | <Observation><code>= C54451<br>FDA Device Problem Codelist (https://www.fda.gov/media/146825/download) | Conditional-Required | Required, if *Malfunction (FDA.G.k.12.r.1)* is 'true'. FDA will only validate format. One or more codes can be provided |
| Device Brand Name (FDA.G.k.12.r.4) | 80 | AN | Free Text<br>nullFlavor: NI | Conditional-Required | If *Combination Product Report Indicator (FDA.C.1.12)* is true, then provide the device brand name and the common device name. Either can be null however, if both are null a value for *Device Product Code (FDA.G.k.12.r.6)* is required |
| Common Device Name (FDA.G.k.12.r.5) | 80 | AN | Free Text<br>nullFlavor: NI | Conditional-Required | If *Combination Product Report Indicator (FDA.C.1.12)* is true, then provide the device brand name and the common device name. Either can be null however, if both are null a value for *Device Product Code (FDA.G.k.12.r.6)* is required |

# Postmarket Safety Reporting

- Section G.k: Drug(s) Information (repeat as necessary)

## Element Name: Device Information (repeat as necessary) (FDA.G.k.12.r)

| Data Element | Max Length | Data Type | Values Allowed | Conformance | Business Rule |
|---|---|---|---|---|---|
| Device Product Code (FDA.G.k.12.r.6) | 10 | AN | FDA Device Component Code (https://www.fda.gov/media/146826/download) | Conditional-Required | If both Device Brand Name (FDA.G.k.12.r.4) and Common Device Name (FDA.G.k.12.r.5) are null, then the value for Device Product Code (FDA.G.k.12.r.6) is required |
| Device Manufacturer Name (FDA.G.k.12.r.7.1a) | 100 | AN | Free Text | Optional | |
| Device Manufacturer Address (FDA.G.k.12.r.7.1b) | 100 | AN | Free Text | Optional | |
| Device Manufacturer City (FDA.G.k.12.r.7.1c) | 35 | AN | Free Text | Optional | |
| Device Manufacturer State (FDA.G.k.12.r.7.1d) | 40 | AN | Free Text | Optional | |
| Device Manufacturer Country (FDA.G.k.12.r.7.1e) | 2 | AN | ISO 3166-1 alpha-2, EU | Optional | |
| Device Usage (FDA.G.k.12.r.8) | 1 | N | <Observation><code>= C54595<br>1=Initial Use of Device<br>2=Reuse<br>3=Unknown | Optional | OID:2.16.840.1.113883.3.989.5.1.2.1.1.4 |
| Device Lot Number (FDA.G.k.12.r.9) | 100 | AN | Free Text | Optional | |

# Outline

| | | | | |
|---|---|---|---|---|
| Background | Regional Implementation of E2B(R3) | Submission Methods & Mechanism | BREAK | E2B(R3) Implementation Package |
| Common Regional Extensions | BREAK | Postmarket Safety Reporting | **IND Safety Reporting** | BA/BE Study Safety Reporting for Generic Drugs |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | R2 -> R3 Regional Forward Compatibility | Summary |

# Reporting of IND safety reports to FDA using ICH E2B(R3) standards

Y. Veronica Pei, M.D., M.Ed., M.P.H.
Lieutenant Commander, U.S. Public Health Service
Associate Director of Biomedical Informatics
Office of New Drug
Center for Drug Evaluation and Research
Food and Drug Administration

# 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**<br>**PDFs in eCTD format** | **New Process**<br>**ICH E2B XML files to FAERS** |
|---|---|
| • Inefficient and labor-intensive review<br>• Does not allow use of data visualization and analytics tools for review<br>• Lack of universal tracking system | • Allows for use of visualization and analytics tools for review and tracking<br>• In addition:<br>  • Leverages existing processes in use for postmarket safety reporting (ICH E2B data standards & FDA gateway)<br>  • 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[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 end of this year
  - Date to be published on FAERS website 30 days prior

[1] Those that contain individual patient data

# 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.

*FDA Adverse Event Reporting System (FAERS) Electronic Submissions | FDA

# IND Safety Report - 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"<br>XML Files: AERS_PREMKT_CDER** | **XML Files:<br>FDA_AERS_PREMKT_CDER** | **ZZFDA_PREMKT** | **CDER_IND** |
| | **CBER IND ICSR** | **Destination: "CBER"<br>XML Files: AERS_PREMKT_CBER** | **XML Files:<br>FDA_AERS_PREMKT_CBER** | **ZZFDA_PREMKT** | **CBER_IND** |
| | CDER IND-exempt BA/BE ICSR | Destination: "CDER"<br>XML Files: AERS_PREMKT_CDER | XML Files:<br>FDA_AERS_PREMKT_CDER | ZZFDA_PREMKT | CDER_IND_EXEMPT_BA_BE |
| Postmarket | Postmarket ICSR | Destination: "CDER"<br>XML Files: AERS | XML Files: FDA_AERS | ZZFDA | CDER |

# Submission for Different 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 |

# How will the new process benefit the Sponsors?

No need to submit  1571 or cover letter for IND safety reports

No separate submission for cross-reported IND

Immediate acknowledgement of your ICSR submission

Additional Benefits

- Submit ICSR directly from your safety database
- Eliminates need to send ICSRs to your Regulatory Affairs

# Scenario 1 – Safety 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 (FDA.C.5.5a)

- Max Length: 10
- Data Type: Numeric (N) (The format must be “123456“)
- Conformance: Conditional-Required
  - 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.
- Business Rule:
  - 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

# Scenario 2 – Cross-reporting

Other sponsor INDs evaluating the same suspect product (cross-referenced INDs) should be listed in the same report as below

Element Name: **IND number of cross reported IND (FDA.C.5.6.r)**

- Max Length: 10
- Data Type: Numeric (N) (The format must be “123456“)
- Conformance: Conditional-Required
  - 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

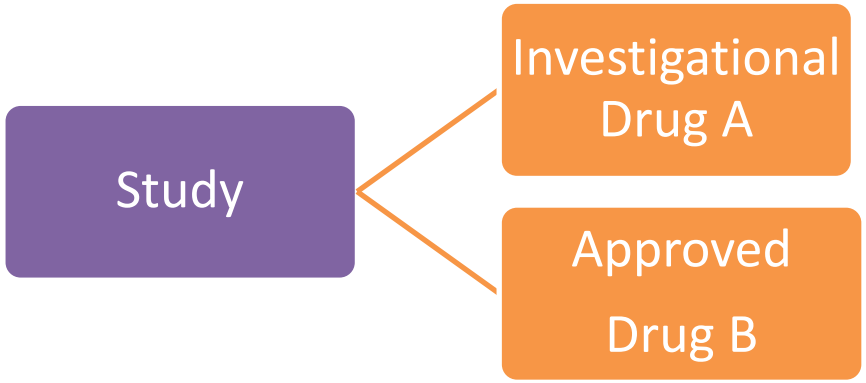
# Scenario 3 – Reports from aggregate analyses

- 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) |

# Scenario 4 – Investigational and approved drugs

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

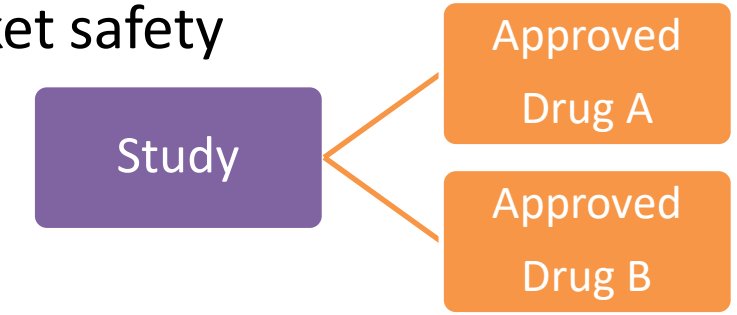



| Element Name | Element ID | Suspect drug is drug A | Suspect drug is drug B and report meets IND safety reporting requirements (21 CFR 312.32) |
|---|---|---|---|
| Medicinal Product Name as Reported by the Primary Source | G.k.2.2 | Company code<br>OR<br>Established name (e.g., INN, USAN) for drug A<br>OR<br>Proprietary medicinal product name for **drug A** | Proprietary medicinal product name for **drug 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** |
| IND Number where AE Occurred | FDA.C.5.5a | IND number under which the clinical trial where the event occurred is conducted | |

# Scenario 5 – Approved drug under an IND

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

- Submit 2 reports to FARES if report meets IND and postmarket safety reporting requirements:
  1. IND
  2. Postmarket




| | | AS2 Header | Routing ID | N.1.4 Value | N.2.r.3 Value |
|---|---|---|---|---|---|
| Premarket | CDER IND ICSR | Destination: "CDER"<br>XML Files: AERS_PREMKT_CDER | XML Files:<br>FDA_AERS_PREMKT_CDER | ZZFDA_PREMKT | CDER_IND |
| | CBER IND ICSR | Destination: "CBER"<br>XML Files: AERS_PREMKT_CBER | XML Files:<br>FDA_AERS_PREMKT_CBER | ZZFDA_PREMKT | CBER_IND |
| Postmarket | Postmarket ICSR | Destination: "CDER"<br>XML Files: AERS | XML Files: FDA_AERS | ZZFDA | CDER |

# Scenario 6 – 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<br>• 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. *Note: This value has no specific significance but to just differentiate assessment from other regions*<br>• 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<br>• For Result of Assessment (G.k.9.i.2.r.3) use the value "**Suspected**" or "**Not Suspected**"<br>• 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 |

# Other IND Regional Extensions

- Section C.5: Study Identification

## Element Name: Study Name (C.5.2)

- Business Rule:
  - 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 *Study Name (C.5.2)* should be in the format Study ID$Abbreviated Trial Name
  - The  Study ID should be the same value used in the Study Tagging file format of the eCTD submission.

## Element Name: Study Type Where Reaction(s) / Event(s) Were Observed (C.5.4)

- Business Rule:
  - If *Patient (name or initials) (D.1)* = AGGREGRATE, then Observation Code: (Value allowed: 1) for *Study Type Where Reaction(s) / Event(s) Were Observed (C.5.4)*

# Other IND Regional Extensions

- Section C.5: Study Identification

**Element Name:** **Date of Death (D.9.1)**

- Conformance: Conditional Required
  - If *Results in Death (E.i.3.2a)* is true then *Date of Death (D.9.1)* is required.

# Outline

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Background | | Regional Implementation of E2B(R3) | | Submission Methods & Mechanism | BREAK | E2B(R3) Implementation Package | |
| Common Regional Extensions | BREAK | Postmarket Safety Reporting | | IND Safety Reporting | | **BA/BE Study Safety Reporting for Generic Drugs** | |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | | R2 -> R3 Regional Forward Compatibility | | Summary | |

# BA/BE Study Safety Reporting for Generic Drugs

Jung Lee, RPh, MPH
Division of Clinical Safety and Surveillance
Office of Safety and Clinical Evaluation
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

# Objectives

- Generic drug pharmacovigilance overview
- Bioavailability/Bioequivalence (BA/BE) Studies and Safety Reporting Requirements & Processes
- Electronic Premarket Safety Reports from BA/BE Studies

# Generic Drug Pharmacovigilance: a Collaborative Process

**Across FDA Centers:**

- Center for Drug Evaluation and Research (CDER)
- Center for Devices and Radiological Health (CDRH)

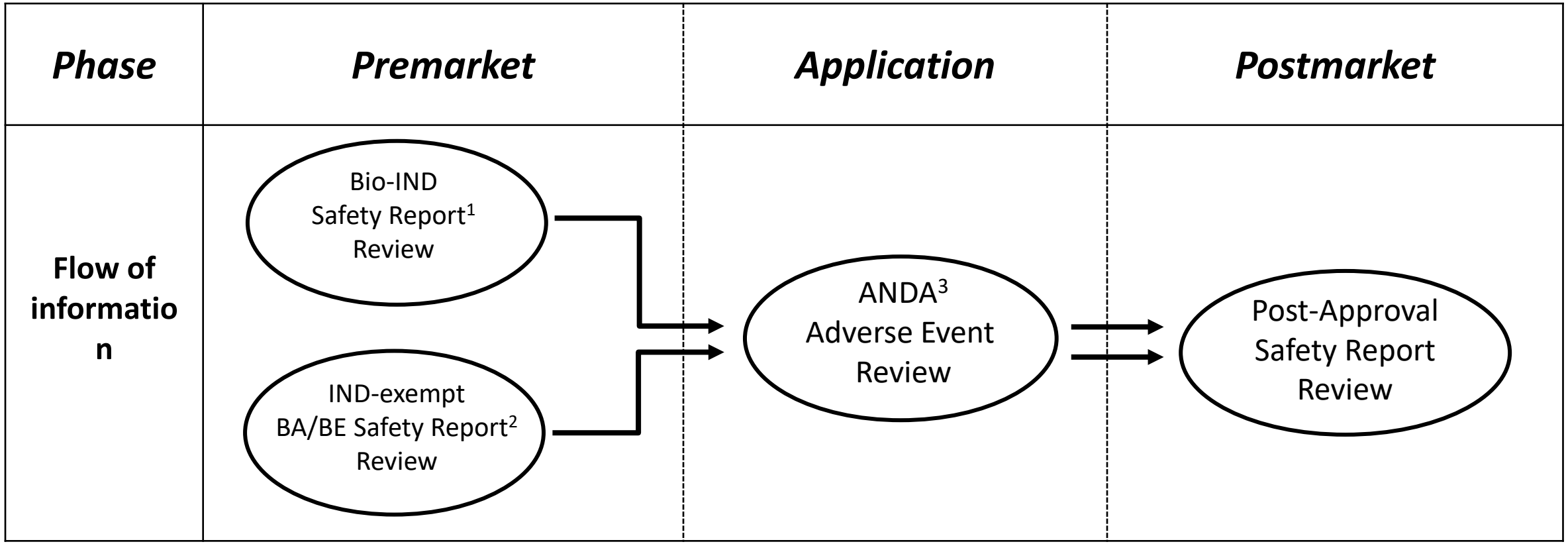
**Across CDER Offices:**

- Office of Generic Drugs (OGD)
- Office of Surveillance and Epidemiology (OSE)
- Office of New Drugs (OND)
- Office of Pharmaceutical Quality (OPQ)
- Office of Compliance (OC)

**Across OGD Offices:**

- Office of Safety and Clinical Evaluation (OSCE)
- Office of Bioequivalence (OB)
- Office of Research and Standards (ORS)
- Office of Generic Drug Policy (OGDP)
- Office of Regulatory Operations (ORO)

# Generic Drug Pharmacovigilance




[1]**Bio-IND Safety Report** = A safety report submitted from a **BA/BE study conducted under an Investigational New Drug application (IND)**. Refer to MAPP 5210.5 rev. 3. (https://www.fda.gov/media/72562/download).

[2]**IND-exempt BA/BE Safety Report** = A safety report submitted from a **BA/BE study not conducted under an IND**.

[3]ANDA=Abbreviated New Drug Application

# BA/BE Study Safety Reporting Requirements

**BA/BE study conducted under an IND**

- Studies must meet safety reporting requirements under 21 CFR 320.31 and 312.32
- Sponsors are required to submit an IND safety report(s) for an event that meet the following conditions: 1) serious, 2) unexpected and 3) suspected adverse reaction(s) => SUSARs
- Includes individual case safety report and aggregate reports

**BA/BE study NOT conducted under an IND**

- Meets IND exemption under 21 CFR 320.31
- Must meet expedited safety reporting requirements under 21 CFR 320.31(d)(3)-
  The person conducting a BA or BE study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event [SAE] observed during conduct of the study, **regardless of whether the event** is considered drug related, as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence.

# Current Generic Drug Premarket vs. Postmarket Safety Report Submission & Review

| Report Type | | Premarket | | Postmarket Safety Reports |
|---|---|---|---|---|
| | | **Bio-IND Safety Reports** | **IND-exempt BA/BE Safety Reports** | |
| **Submission** | Source | Sponsors *conducting* ***BA/BE studies conducted under an IND*** | Drug companies or CROs conducting ***BA/BE studies Not conducted under an IND*** | Drug companies, healthcare professionals, consumers, etc. |
| | Format | Form FDA 3500A | Form FDA 3500A | E2B |
| | Route | via eCTD | • via OGD Premarket email inbox, which is manually entered into the Panorama project tracking system. Initial and Follow-up also linked manually. | via database-to-database (D2D) transmission electronically or Safety Reporting Portal to the FDA Adverse Event Reporting System (FAERS) |
| **Review** | | OGD/OSCE/DCSS reviews SUSARs. | OGD/OSCE/DCSS reviews SAEs. When ANDA is submitted, SAE reviews are linked to ANDA. | OGD/OSCE/DCSS analyzes and reviews safety reports in FAERS and Drug Quality Reporting System (DQRS). |

**FAERS II Enhancements will bring opportunities for electronic submission of adverse events from premarket BA/BE studies for generic drugs!**

# Electronic IND Safety Reporting Requirement

- IND safety reports as Individual Case Safety Reports (ICSRs) under 745A(a) of the Federal Food Drug and Cosmetic (FD&C) Act
  - October 2019: Draft Guidance for Industry- *Providing Regulatory Submissions in Electronic Format: IND Safety Reports*
  - Sponsors of commercial INDs are required to submit specified IND safety reports by FAERS using one or two options:
    - Electronic Submissions Gateway (D2D Transmission)
    - Safety Reporting Portal
  - Begin voluntary submissions in E2B(R3) format - date to be published on FAERS website prior to launch
  - Requirement 24 months after **Final** Guidance publishes

- Bio-IND Safety Reports (from **BA/BE studies conducted under an IND**) must meet the electronic ICSR reporting requirement under 745A(a) of the FD&C Act.

# IND-exempt BA/BE Safety Reporting

## A. Options for submission:

1. Currently Form FDA 3500A email to OGD-PremarketSafetyReports@fda.hhs.gov.

2. Once FAERS II enhancement for premarket is available:
   - E2B format is an acceptable form of notification to the FDA for an SAE(s) **required** under 21 CFR 320.31(d)(3).

   - Options for submitting IND-exempt BA/BE Safety Reports as ICSRs in E2B(R3) format
     - **Electronic Submission Gateway (D2D Transmission)** **<- Today's Focus**
     - Safety Reporting Portal

# Voluntary Electronic Submission of IND-exempt BA/BE Safety Reports

## B. Electronic Submission Gateway (D2D Transmission) Option:

### 1. Understand requirements[4,5]

- *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products Guidance for Industry Technical Specifications Document* (hereafter referred as Technical Specifications Document)
- ***Draft*** *Guidance for Industry*: *Electronic Submission of Expedited Safety Reports from IND-exempt BA/BE studies*

***Additional resources***:

- *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments*
- *E2B(R3) Electronic Transmission of Individual Case Safety Reports (ICSRs) Implementation Guide –Data Elements and Message Specification*
- *FDA E2B(R3) Core and Regional Data Elements and Business Rules*

[4] Search for FDA Guidance Documents (https://www.fda.gov/regulatory-information/search-fda-guidance-documents).

[5] FAERS Electronic Submissions (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions).

# Voluntary Electronic Submission of IND-exempt BA/BE Safety Reports

## 2. Prepare IT system

- FAERS II will accept **premarket ICSRs in E2B (R3) format.**
- Learn the **specifications for preparing and submitting electronic submission** of ICSRs.
- Need an account with FDA to submit ICSRs electronically.
- Notify the FAERS electronic submission coordinator at faersesub@fda.hhs.gov to create an account.

## 3. Obtain pre-assigned ANDA number ('Pre-ANDA')[6,7]

- Request using CDER NextGen Portal prior to:

-> Submitting an SAE(s) from the BA/BE study **or**

-> Starting subject recruitment for the BA/BE study

[6] Requesting a Pre-Assigned Application number (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number).

[7] CDER NextGen Portal (https://cdernextgenportal.fda.gov/Login_CDER?ec=302&startURL=%2Fs%2F).

# Voluntary Electronic Submission of IND-exempt BA/BE Safety Reports

## 4. Identify ICSRs from IND-exempt BA/BE studies

a. Include submission path business rules

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

Message receiver identifier: N.2.r.3 & Batch receiver Identifier: N.1.4

b. Choose element value=2 for 'Report from study' as the 'Type of Report' in Data Element C.1.3

| Data element | Title | Element value |
|---|---|---|
| **C.1.3** | **Type of Report** | **2=Report from study** |

# Voluntary Electronic Submission of IND-exempt BA/BE Safety Reports

## 4. Identify ICSRs from IND-exempt BA/BE studies

c. Submit Pre-assigned ANDA ('Pre-ANDA')[8] number

| Data element | Title | Element values |
|---|---|---|
| **FDA.C.5.5b** | **Pre-ANDA Number where AE Occurred** | **Numeric** |

- Max Length: 10
- Data Type: Numeric (N) (For example, "234567")
- **Conformance: Conditional-Required**
- Business Rule:
  - 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.5.5b)* is required.
  - Required to be a valid Pre-ANDA number for processing and routing

[8]Although these are pre-assigned ANDA numbers and the term 'Pre-ANDA' is being used with these numbers, each submission may or may not be associated with the Office of Generic Drug's Pre-ANDA Program (https://www.fda.gov/drugs/generic-drugs/pre-anda-program) for complex drug products .

# Voluntary Electronic Submission of IND-exempt BA/BE Safety Reports

## 5. Identify drug substance

| Data element | Title | Element values |
|---|---|---|
| G.k.2.2 | Medicinal Product Name as Reported by the Primary Source | Medicinal product name (free text) |
| G.k.2.3.r.1 | Substance/Specified Substance Name | Drug substance name (free text) |

- Report drug substance name in data element G.k.2.3.r.1
- Report medicinal product name (proprietary name) using data element G.k.2.2 if available.
- Report only drug substance name if medicinal product name (proprietary name) is not available.

## 6. Characterize drug's role

| Data element | Title | Element values |
|---|---|---|
| G.k.1 | Characterization of Drug Role | 1 = Suspect<br>2 = Concomitant<br>3 = Interacting<br>4 = Drug not administered |

# Voluntary Electronic Submission of IND-exempt BA/BE Safety Reports

## 7. Inform Test vs. Reference* Unique to generic drugs

| Data element | Title | Element values |
|---|---|---|
| **FDA.G.k.10.a.r** | **FDA Additional Information on Drug** | **1 = Test**<br>**2 = Reference**<br>**nullFlavor=NA** |

- Max Length: 2
- Data Type: Numeric (N)
- **Conformance: Conditional-Required**
- Business Rule:
  - If *Pre-ANDA Number where AE Occurred (FDA.C.5.5b) is present, then the Observation Code: (Value allowed: 1, 2) must be used to describe the drug's role in the IND-Exempt BA/BE study.*
  - *Use nullFlavor: NA for all other drugs or if information is not available.*

# Voluntary Electronic Submission of IND-exempt BA/BE Safety Reports

8. **Other considerations**
   - Refer to the Technical Specifications Document for information on:
     - ICH E2B data elements
     - Regional specifications of the ICH E2B data elements

9. **Check examples if needed**
   - Look for FDA ICSR XML instances with Read Me descriptions
   - Available at FAERS electronic submission web page[9]

10. **Look for FDA Notification of Receipt**
    - Review Acknowledgements & Notifications indicating the status of submission, successful acceptance or rejection with reason for rejection after submission.
    - Contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov if the acknowledgements or notifications are not received.

[9] FAERS Electronic Submissions (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions).

# Voluntary Electronic Submission of IND-exempt BA/BE Safety Reports

## C. Advantages:

### 1. Non-public space

- FAERS II will use specific data fields (such as E2B data element FDA.C.5.5b for IND-exempt BA/BE Safety Reports) to identify pre-market reports and sequester them from postmarket reports that are available in the public portal.

### 2. Increased efficiencies

- One submission method
    1) IND-exempt BA/BE safety reports
    2) Bio-IND safety reports
    3) Postmarket safety reports
- Automated confirmation of receipt

### 3. Support generic drug pharmacovigilance

- Improved generic drug signal detection
- Enhanced data management & analytics

# Acknowledgements


- Howard Chazin, OGD/OSCE/DCSS Director
- Debra Catterson, OGD/OSCE/DCSS Deputy Director
- James Osterhout, OGD/OSCE/DCSS Data Team Leader
- Suranjan De, Office of Surveillance and Epidemiology/ Regulatory Science Staff/Deputy Director

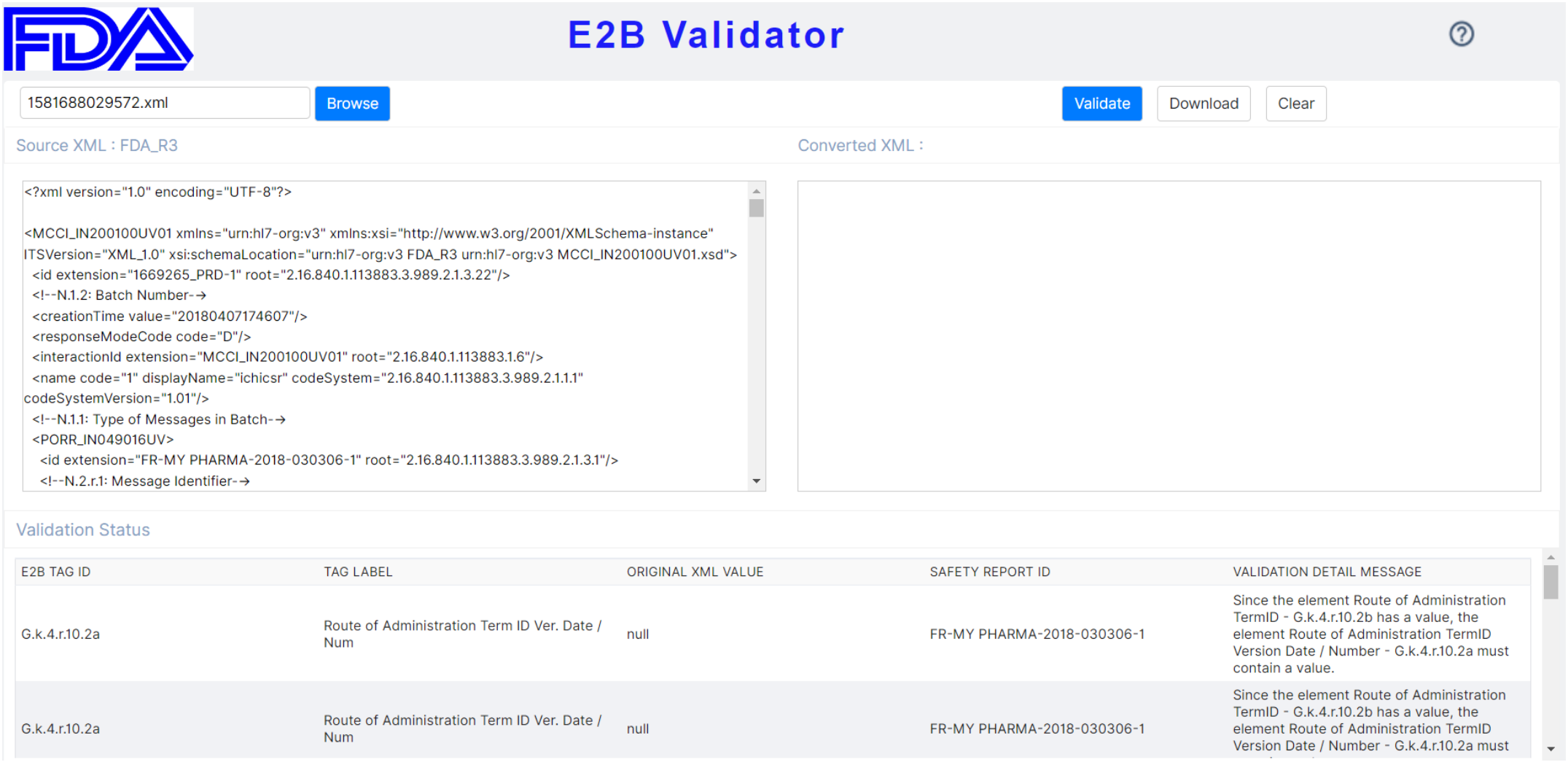
# Outline

| | | | | |
|---|---|---|---|---|
| Background | Regional Implementation of E2B(R3) | Submission Methods & Mechanism | BREAK | E2B(R3) Implementation Package |
| Common Regional Extensions | BREAK | Postmarket Safety Reporting | IND Safety Reporting | BA/BE Study Safety Reporting for Generic Drugs |
| **Validation and Implementation** | BREAK | FDA Specific Object Identifiers (OIDs) | R2 -> R3 Regional Forward Compatibility | Summary |

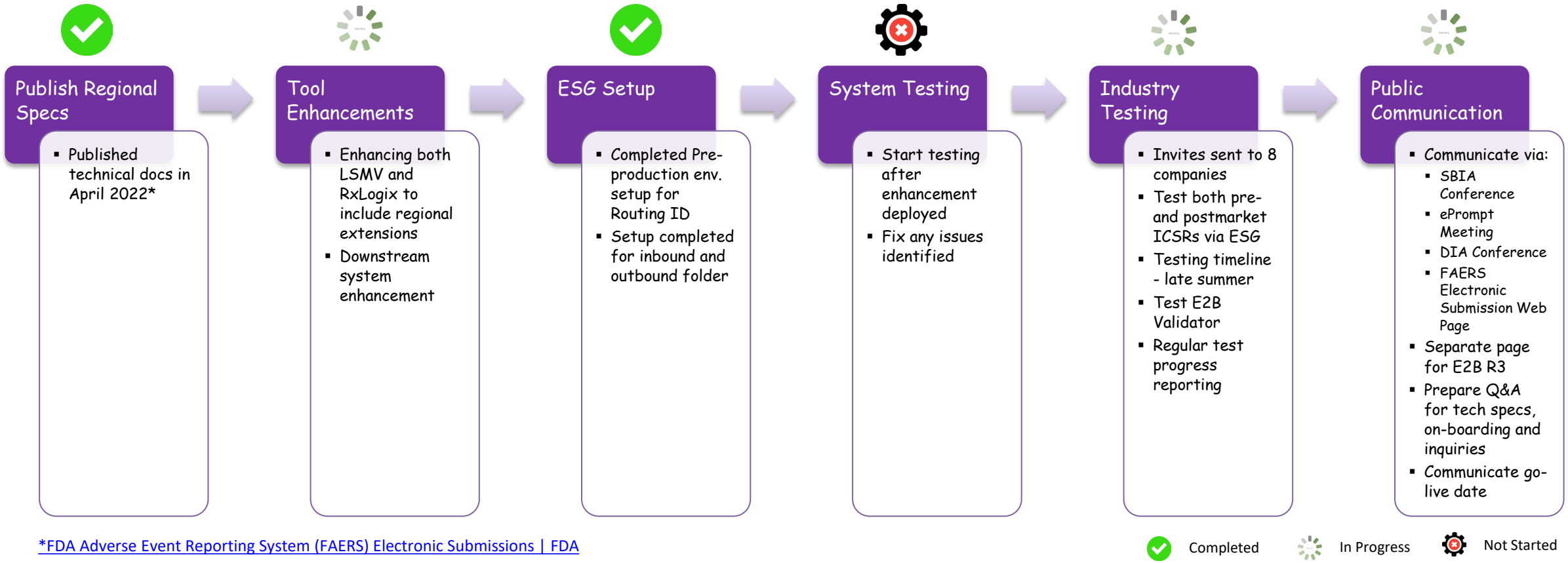
# Mechanism to validate E2B

- Provide a mechanism for industry to validate the regional E2B R3 XML files
- Mechanism can be used to pre-validate prior to 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



# E2B R3 Implementation Plan

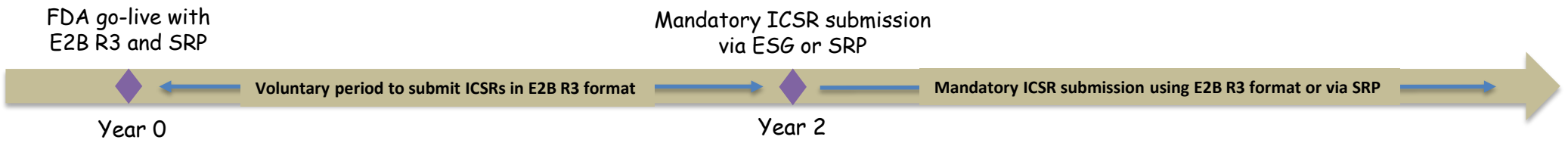



*FDA Adverse Event Reporting System (FAERS) Electronic Submissions | FDA

Sponsors continue to submit premarket ICSRs and postmarket ICSR in eCTD and E2B R2 format respectively until FAERS is ready for R3

# E2B R3 Implementation Plan

- Sponsor's should notify FDA when ready for first production submission to FDA in E2B R3 format
- All question during testing must be sent to faersesub@fda.hhs.gov with subject line "E2B R3 Testing"




During the voluntary submission period for premarket ICSRs:

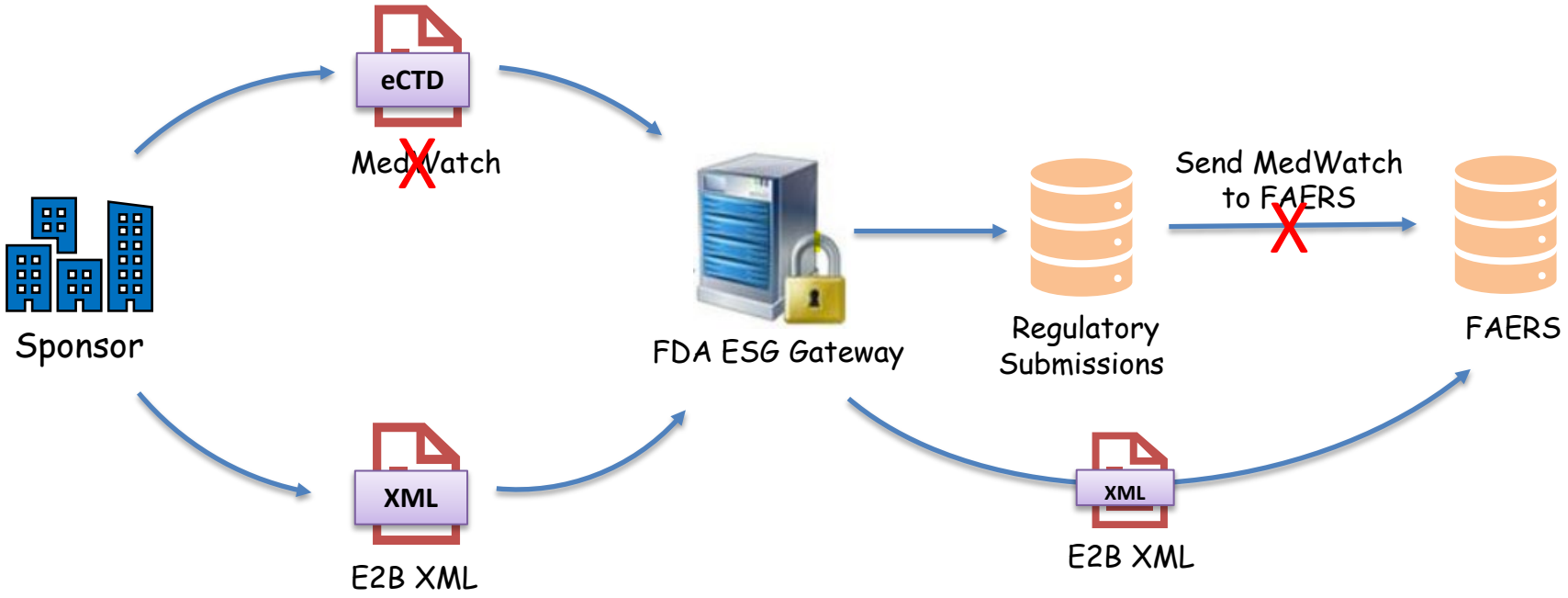
- recommend to use Safety Reporting Portal (SRP) for submission
- submission of 1571 and cover letter not required
- eliminates sending the reports to the company's regulatory affairs

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

- SRP account will be deactivated for premarket safety report

# E2B R3 Implementation Plan

- Data Submission Changes for IND safety reports



# Rejection and Warning

- Do not include >100 ICSRs in a single batch
- All ICSRs in single batch must have same Sender
- All ICSRs batched must be for a common receiver
  - Batching all postmark ICSRs together or all Pre-Markets to CDER together
  - Do not mix premarket ICSRs for CDER with CBER or premarket ICSRs with postmarket reports in a single batch

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

- All ICSRs must coded with latest MedDRA version
- Do not send initial and f/u in same batch…or multiple followups for same case in same batch.

# Rejection and Warning

- Do not submit nullification or amendment ICSR as the initial report
- Other regional specific rejection and warning rules:

| DATA ELEMENT NUMBER | DATA ELEMENT NAME | REJECTION, IF NOT MET | WARNING, IF NOT MET | ERROR DESCRIPTION |
|---|---|---|---|---|
| N.1.4 | Batch Receiver Identifier | ✓ | | ICSR sent to the postmaket route does not have the value "ZZFDA" for N.1.4 |
| | | ✓ | | ICSR sent to the premaket route does not have the value "ZZFDA_PREMKT" for N.1.4 |
| N.2.r.2 | Message Sender Identifier | ✓ | | N.2.r.2 provided is not same for all reports and does not match with N.1.3 |
| N.2.r.3 | Message Receiver Identifier | ✓ | | N.1.4 = "ZZFDA" but N.2.r.3 is not "CDER" |
| | | ✓ | | N.1.4 = "ZZFDA_PREMKT" but N.2.r.3 is not "CDER_IND" or "CBER_IND" or "CDER_IND_EXEMPT_BA_BE" |
| C.1.3 | Type of Report | ✓ | | N.1.4 = "ZZFDA_PREMKT" but C.1.3 is not 2 |
| C.1.6.1.r.1 | Documents Held by Sender | ✓ | | C.1.6.1.r.1 must be provided when C.1.6.1 = true |
| C.1.6.1.r.2 | Included Documents | ✓ | | Compression used for US reporting and encoding is not B64. |
| C.1.7 | Does This Case Fulfil the Local Criteria for an Expedited Report? | ✓ | | nullFlavor 'NI' used for initial report submission |

# Rejection and Warning

- Other regional specific rejection and warning rules:

| DATA ELEMENT NUMBER | DATA ELEMENT NAME | REJECTION, IF NOT MET | WARNING, IF NOT MET | ERROR DESCRIPTION |
|---|---|---|---|---|
| FDA.C.1.7.1 | Local Criteria Report Type | ✓ | | FDA.C.1.7.1 must have Observation Code Value of 1 or 4 when FDA.C.1.12 = true and C.1.7 = true |
| | | ✓ | | FDA.C.1.7.1 must have Observation Code Value of 2 or 5 when FDA.C.1.12 = true and C.1.7 = false or nullFlavor "NI" |
| | | ✓ | | FDA.C.1.7.1 must have Observation Code Value of 1 when FDA.C.1.12 = false or NI and C.1.7 = true |
| | | ✓ | | FDA.C.1.7.1 must have Observation Code Value of 2 when FDA.C.1.12 = false or nullFlavor "NI" and C.1.7 = false or nullFlavor "NI" |
| | | ✓ | | FDA.C.1.7.1 must have Observation Code Value of 1 or 6 when C.1.7 = true and C.1.3 = 2 |
| C.1.10.r | Identification Number of the Report Which Is Linked to This Report | | ✓ | C.1.10.r should be provided when D.1 = "AGGREGRATE" |
| C.5.4 | Study Type Where Reaction(s) / Event(s) Were Observed | | ✓ | C.5.4 should be 1 when D.1 = "AGGREGRATE" |
| FDA.C.5.5a | IND Number where AE Occurred | ✓ | | FDA.C.5.5a must be provided when C.1.3 = 2 and N.2.r.3 = "CDER_IND" or "CBER_IND" |
| FDA.C.5.5b | Pre-ANDA Number where AE Occurred | ✓ | | FDA.C.5.5b must be provided when C.1.3 = 2 and N.2.r.3 = "CDER_IND_EXEMPT_BA_BE" |
| FDA.C.5.6.r | IND number of cross reported IND | ✓ | | FDA.C.5.6.r is not provided or nullFlavor is not 'NA' when FDA.C.5.5a is provided |

# Rejection and Warning

- Other regional specific rejection and warning rules:

| DATA ELEMENT NUMBER | DATA ELEMENT NAME | REJECTION, IF NOT MET | WARNING, IF NOT MET | ERROR DESCRIPTION |
|---|---|---|---|---|
| D.1 | Patient (name or initials) | ✓ | | D.1 must be nullFlavor 'NA' when FDA.C.1.12 = true and FDA.G.k.12.r.1 = true and E.i.2.1b = 10067482 |
| | | ✓ | | D.1 value must be "AGGREGATE" when C.1.10.r is provided |
| D.9.1 | Date of Death | ✓ | | D.9.1 must be provided when C.1.3 = 2 and N.2.r.3 = "CDER_IND" or "CBER_IND" and E.i.3.2a = ture |
| FDA.D.11.r | Patient Race Code | | ✓ | FDA.D.11.r should be provided as nullFlavor "NA" when D.1 is provided as nullFlavor "NA" or "SUMMARY" or "AGGREGRATE" |
| FDA.D.12 | Patient Ethnicity Code | | ✓ | FDA.D.12 should be provided as nullFlavor "NA" when D.1 is provided as nullFlavor "NA" or "SUMMARY" or "AGGREGRATE" |
| G.k.1 | Characterisation of Drug Role | | ✓ | The first product reported does not have G.k.1 with Observation Code Value of 1, 3 or 4. |
| | | ✓ | | G.k.1 must be provided with Observation Code Value of 1, 3 or 4 when C.1.3 = 1 and N.2.r.3 = "CDER" |
| | | ✓ | | G.k.1 must be provided with Observation Code Value of 1 or 3 when C.1.3 = 2 and N.2.r.3 = "CDER_IND" or "CBER_IND" |
| | | ✓ | | G.k.1 must be provided with Observation Code Value of 1, 3 or 4 when C.1.3 = 2 and N.2.r.3 = "CDER_EXEMPT_BA_BE" |
| FDA.G.k.1.a | FDA Other Characterisation of Drug Role | ✓ | | G.k.1.a must be provided when FDA.C.1.12 = true and FDA.G.k.12.r. = true' and G.k.1 = 4 is provided |

# Rejection and Warning

- Other regional specific rejection and warning rules:

| DATA ELEMENT NUMBER | DATA ELEMENT NAME | REJECTION, IF NOT MET | WARNING, IF NOT MET | ERROR DESCRIPTION |
|---|---|---|---|---|
| G.k.9.i.2.r.1 | Source of Assessment | ✓ | | G.k.9.i.2.r.1 must be provided when C.1.3 = 2 and FDA.C.5.5a is provided |
| G.k.9.i.2.r.2 | Method of Assessment | ✓ | | G.k.9.i.2.r.2 must be provided when C.1.3 = 2 and FDA.C.5.5a is provided |
| G.k.9.i.2.r.3 | Result of Assessment | ✓ | | G.k.9.i.2.r.3 must be provided when C.1.3 = 2 and FDA.C.5.5a is provided |
| FDA.G.k.10a.r | FDA Additional Information on Drug (coded) (repeat as necessary) | | ✓ | FDA.G.k.10a.r should be provided with Observation Code value of 1, 2 or nullFlavor "NA" when FDA.C.5.5b is provided |
| FDA.G.k.12.r.1 | Malfunction | ✓ | | FDA.G.k.12.r.1 must be 'true' for at least one suspect product when FDA.C.1.7.1 = 5 |
| FDA.G.k.12.r.3.r | Device Problem Code | ✓ | | FDA.G.k.12.r.3.r must be provided when FDA.G.k.12.r.1 = true |
| | | | ✓ | FDA.G.k.12.r.3.r contain invalid value |
| FDA.G.k.12.r.4 | Device Brand Name | ✓ | | FDA.G.k.12.r.4 and/or FDA.G.k.12.r.5 must be provided when FDA.C.1.12 = true |
| FDA.G.k.12.r.5 | Common Device Name | ✓ | | FDA.G.k.12.r.4 and/or FDA.G.k.12.r.5 must be provided when FDA.C.1.12 = true |
| FDA.G.k.12.r.6 | Device Product Code | ✓ | | FDA.G.k.12.r.6 must be provided when FDA.G.k.12.r.4 and FDA.G.k.12.r.5 are not provided |
| FDA.G.k.12.r.11.r | Remedial Action Initiated | | ✓ | FDA.G.k.12.r.11.r should be provided when FDA.G.k.12.r.1 = true and FDA.C.1.7.1 = 5 |

# BREAK (1:45PM – 2:00PM)

# Outline

| | | | |
|---|---|---|---|
| Background | Regional Implementation of E2B(R3) | Submission Methods & Mechanism | E2B(R3) Implementation Package |
| Common Regional Extensions | Postmarket Safety Reporting | IND Safety Reporting | BA/BE Study Safety Reporting for Generic Drugs |
| Validation and Implementation | **FDA Specific Object Identifiers (OIDs)** | R2 -> R3 Regional Forward Compatibility | Summary |

BREAK

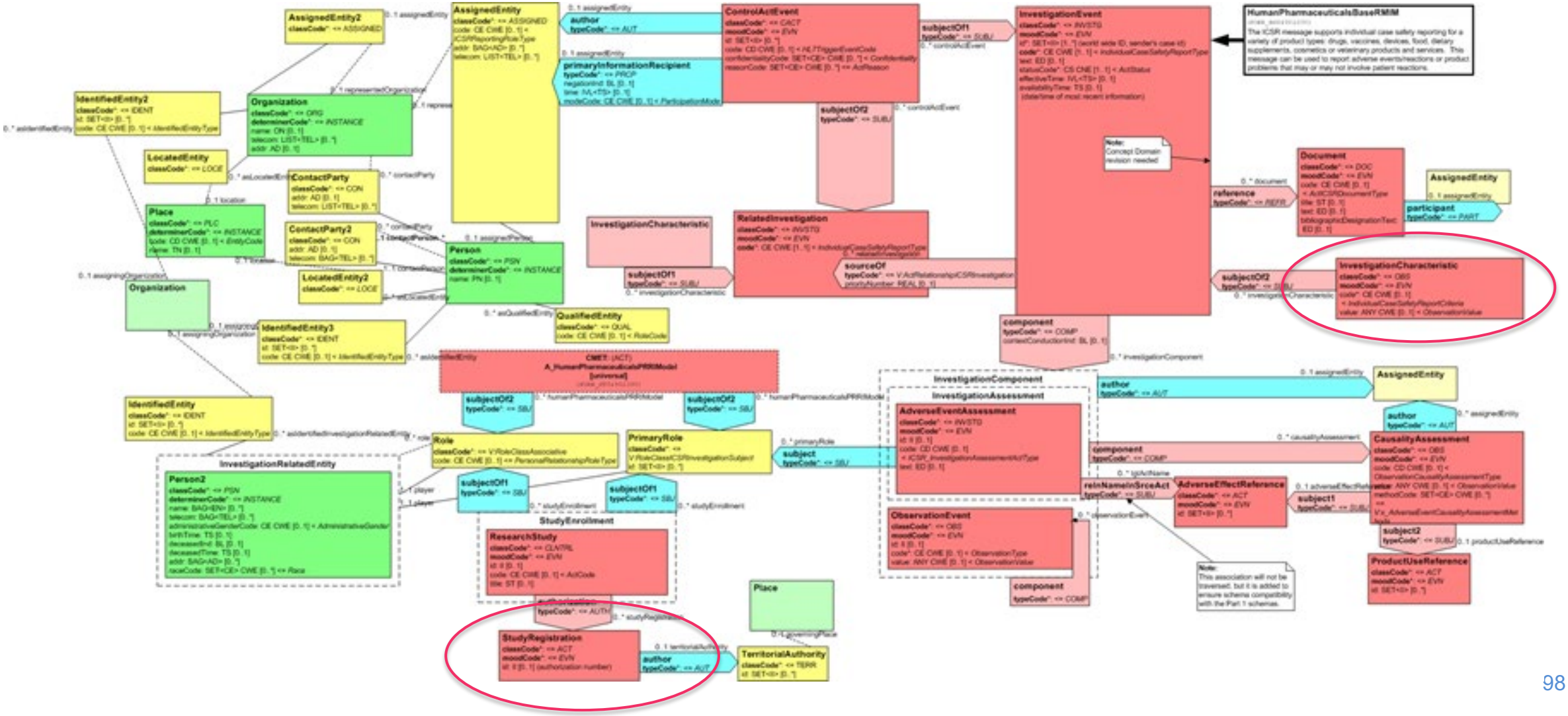
BREAK

BREAK

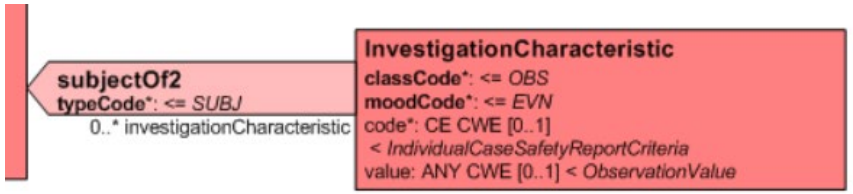
# *Object Identifier (OID)*

- 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 – IND Number where AE Occurred (*2.16.840.1.113883.3.989.5.1.2.1.2.1*)
  - 2 – Pre-ANDA Number where AE Occurred (*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

# Outline

| | | | | |
|---|---|---|---|---|
| Background | Regional Implementation of E2B(R3) | Submission Methods & Mechanism | BREAK | E2B(R3) Implementation Package |
| Common Regional Extensions | BREAK | Postmarket Safety Reporting | IND Safety Reporting | BA/BE Study Safety Reporting for Generic Drugs |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | **R2 -> R3 Regional Forward Compatibility** | Summary |

# 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<br>2=Periodic<br>4=5-Day<br>5=30-Day<br>6=7-Day | FDA.C.1.7.1 | Local Criteria Report Type | 1=15-Day<br>2=Periodic<br>4=5-Day<br>5=30-Day<br>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<br>- No<br>- <not set> | FDA.C.1.12 | Combination Product Flag | - true<br>- false<br>- nullFlavor: NI | Mapping yes-true and no-false<br>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<br>2= Individual Patient Use<br>3= Other Studies | C.5.4 | Study Type Where Reaction(s) / Event(s) Were Observed | 1= Clinical Trials<br>2= Individual Patient Use<br>3= Other Studies | - Mapping 1, 2 and 3 to 1, 2 and 3. |

# 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<br>- No<br>- <not set> | FDA.G.k.12.r.1 | Malfunction | - true<br>- false | Mapping yes-true and no-false<br>If not set in R2, set field to value "false" in R3 |
| FDA-07 | B.4.k.20.FDA.18.1a | Correction | - Yes<br>- No<br>- <not set> | FDA.G.k.12.r.2.r.1 | If follow-up, what type? | 1=correction<br>2=additional information<br>3=response to FDA request<br>4= device evaluation | If B.4.k.20.FDA.18.1a is Yes, then FDA.G.k.12.r.2.r.1=1.<br>If B.4.k.20.FDA.18.1b is Yes, then FDA.G.k.12.r.2.r.1=2<br>If B.4.k.20.FDA.18.1c is Yes, then FDA.G.k.12.r.2.r.1=3<br>If B.4.k.20.FDA.18.1d is Yes, then FDA.G.k.12.r.2.r.1=4<br><br>Since this is a repeating entity there could be multiple values<br><br>Each R2 tag value is setup as a repeatable value with in the R3 entity.<br><br>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<br>- No<br>- <not set> | | | | |
| | B.4.k.20.FDA.18.1c | Response to FDA Request | - Yes<br>- No<br>- <not set> | | | | |
| | B.4.k.20.FDA.18.1d | Device Evaluation | - Yes<br>- No<br>- <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<br>- No<br>- <not set> | FDA.G.k.12.r.11.r | Remedial Action Initiated | 1=Recall<br>2=Repair<br>3=Replacement<br>4=Relabeling<br>5=Notification<br>6=Inspection<br>7=Patient Monitoring<br>8=Modification or Adjustment<br>9=Other | Since this is a repeating entity there could be multiple values.<br><br>Each R2 tag value is setup as a repeatable value with in the R3 entity.<br><br>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<br>- No<br>- <not set> | | | | |
| | B.4.k.20.FDA.14.1c | Replace | - Yes<br>- No<br>- <not set> | | | | |
| | B.4.k.20.FDA.14.1d | Relabeling | - Yes<br>- No<br>- <not set> | | | | |
| | B.4.k.20.FDA.14.1e | Notification | - Yes<br>- No<br>- <not set> | | | | |
| | B.4.k.20.FDA.14.1f | Inspection | - Yes<br>- No<br>- <not set> | | | | |
| | B.4.k.20.FDA.14.1g | Patient Monitoring | - Yes<br>- No<br>- <not set> | | | | |
| | B.4.k.20.FDA.14.1h | Modification/Adjustment | - Yes<br>- No<br>- <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<br>2=Reuse<br>3=Unknown<br><not set> | FDA.G.k.12.r.8 | Device Usage | 1=Initial Use of Device<br>2=Reuse<br>3=Unknown<br><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<br>2= Lay User/Patient<br>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<br>C41259=American Indian or Alaska Native<br>C41260=Asian<br>C41219=Native Hawaiian or Other Pacific Islander<br>C41261=White<br>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<br>C41222=Non Hispanic or Latino<br>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<br>2=Interacting<br>3=Concomitant<br>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. |

# Outline

| | | | | |
|---|---|---|---|---|
| Background | Regional Implementation of E2B(R3) | Submission Methods & Mechanism | BREAK | E2B(R3) Implementation Package |
| Common Regional Extensions | BREAK | Postmarket Safety Reporting | IND Safety Reporting | BA/BE Study Safety Reporting for Generic Drugs |
| Validation and Implementation | BREAK | FDA Specific Object Identifiers (OIDs) | R2 -> R3 Regional Forward Compatibility | **Summary** |

# Summary

- Implement E2B R3 submission for both **premarket and postmarket** safety report **at the same time**
- **New date for voluntary reporting** will be communicated on FAERS Electronic Submission web page
- Refer to **FDA E2B(R3) Core and Regional Data Elements and Business Rules** document for all core ICH and regional extension
- Use of **Controlled Terminology** (e.g., EVS, GSRS etc.)
- **Separate** Submission Path and Business Rules (IND vs IND-exempt BA/BE vs post market)
- **Submission Methods and Mechanisms** based AS2 header and Routing ID
- Discussed **regional extensions** for IND, IND-exempt BA/BE, and postmarket safety reporting
- Plan for **validation and implementation** – E2B validator will be posted on FAERS Electronic Submission web page
- Regional specific **rejection and warning rules**
- Use of **FDA OIDs** in regional extensions
- **R2 to R3 forward compatibility** on regional elements – applicable to postmarket safety reports

# References

| Document / Web Page | Accessible At |
|---|---|
| FDA Adverse Event Reporting System (FAERS) Electronic Submissions –Web page | https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions |
| FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products | https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-regional-implementation-guide-e2br3-electronic-transmission-individual-case-safety-reports-drug |
| FDA E2B(R3) Core and Regional Data Elements and Business Rules | https://www.fda.gov/media/157982/download |
| FDA E2B(R3) Forward Compatible Rules | https://www.fda.gov/media/157993/download |
| FDA ICSR XML Instances | https://www.fda.gov/media/157983/download |
| Electronic Submission of IND Safety Reports - Technical Conformance Guide | https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-ind-safety-reports-technical-conformance-guide |
| Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies - Draft Guidance for Industry | https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-expedited-safety-reports-ind-exempt-babe-studies-guidance-industry |


# Q&A