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

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October 11, 2019

Pre-Requisite for today's Webinar

- March 25, 2019 Meeting
  - Presentation Slides (https://www.fda.gov/media/129211/download)
  - Webcast
    - https://youtu.be/14HddDViXqM?list=PLey4Qe-UxcxYQJSF_XlqzmBlZH63_ZOv0
- July 17, 2019 Meeting
  - Presentation Slides (https://www.fda.gov/media/129211/download)
  - Webcast
    - https://collaboration.fda.gov/ppkmmrbuk7x6/
    - https://collaboration.fda.gov/pdlq0643grry/
    - https://collaboration.fda.gov/pkrygx4qq3zk/
    - https://collaboration.fda.gov/puej5e4vj9ev/

Agenda

- FAERS II and E2B R3 Up Versioning Plans
  - Describe the objective, scope and timeline of E2B R3 regional implementation
- E2B(R3) Regional Elements
- Updates on electronic submission routing mechanisms
  - Describe the different routing mechanisms to submit via ESG or Safety Reporting Portal
- Testing ICH E2B (R3) Regional XML files
  - Describe the methods to test ICH E2B (R3) regional XMLs

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FAERS II AND E2B R3 UP VERSIONING PLANS

FAERS II - Objectives

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

HHS has designated FAERS II as a Modernization Priority

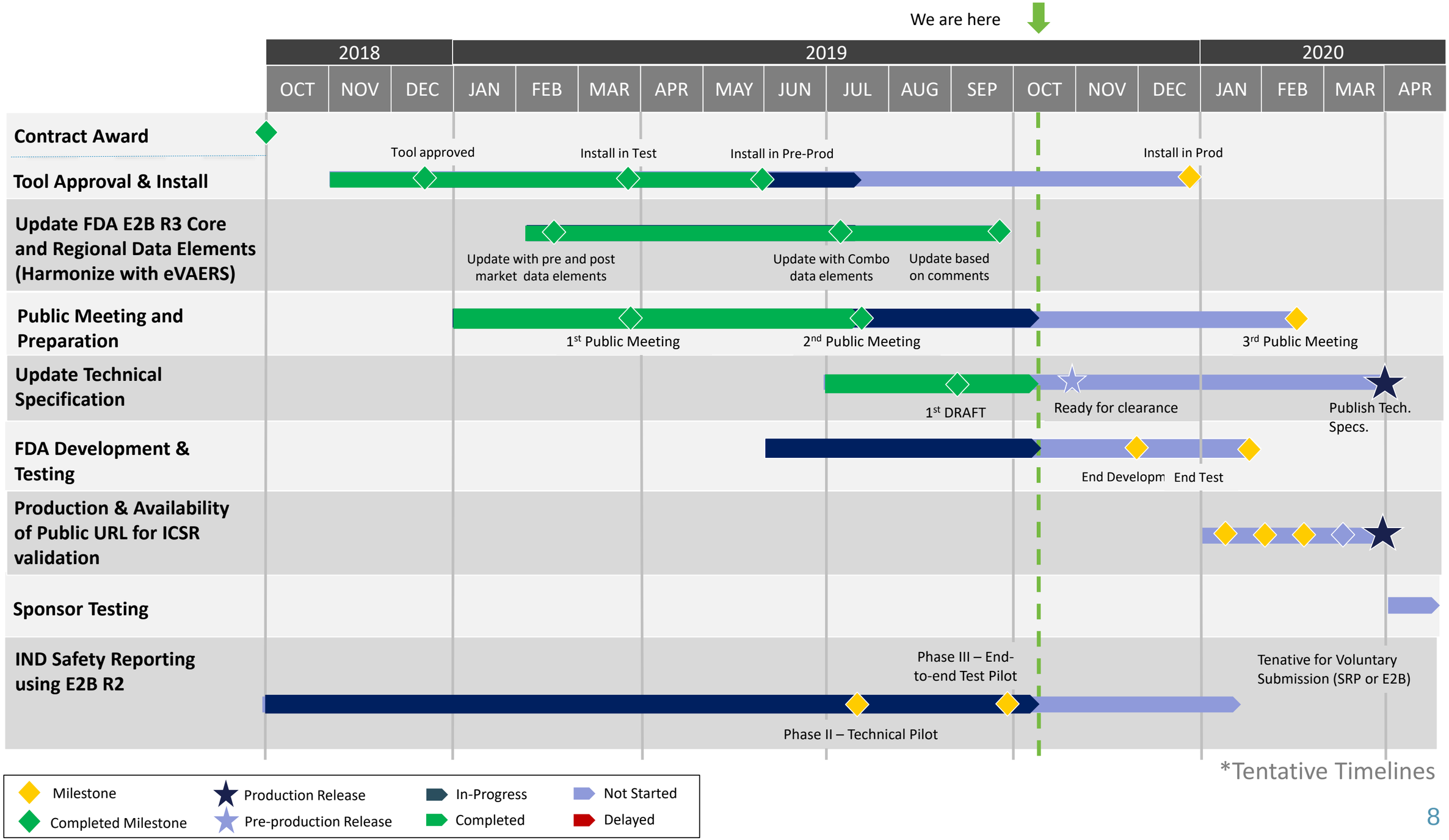
FAERS II - Scope

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

FAERS II Tools

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

FAERS II - E2B R3 Roadmap*



*Tentative Timelines

IND Requirements and Timelines

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

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

- Goal to begin voluntary submissions in Q1 2020

[1] Those that contain individual patient data

Meeting I Summary

- Session 1: FAERS II and E2B R3 Up Versioning Plans
  - Communicated FDA's plans on FAERS II and E2B R3 up versioning
  - FDA's current planned E2B R3 production date is March 2020
  - Currently no compliance timelines have set for E2B R3 by FDA
  - Discussed Testing Plan and Method
- Session 2: Electronic submission of IND safety reporting
  - Introduction to IND safety reporting to FAERS at the FDA
  - Provided information on the implementation plans, regional requirements using E2B R2 & R3, and use case examples
  - Discussed the regional data elements in R2 and R3 for IND safety reporting and IDMP
- Session 3: Electronic submission of Post-market safety reporting
  - Discussed the regional data elements in R3 for Post-market safety reporting
- Session 4: Updates on electronic submission routing mechanisms
  - Electronic submission routing mechanisms for pre-market and post-market
  - Mechanisms for industry to validate E2B R3 regional files

Meeting II Summary

- Session 1: Synopsys from previous meeting
  - Communicated E2B R3 Roadmap
- Session 2: E2B R3 Regional Requirement for Premarket Safety Reporting
  - Discussed the regional data elements
- Session 3: Generic Drugs – BA/BE trials safety reporting
  - Discussed the regional for safety reporting
- Session 4: E2B R3 Regional Requirements for Combo Product safety reporting
  - Discussed the background and rule
  - Discussed the regional data elements
- Session 5: CBER's Update on Electronic Safety reporting for Vaccine
  - Discussed the regional data elements
- Session 6: E2B R3 implementation – Industry experience with Regulators

Question 1

What are the methods for submitting ICSRs to FAERS by sponsors?

A. Electronic Submission Gateway
B. Safety Reporting Portal
C. MedWatch Online
D. A and B

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E2B(R3) REGIONAL ELEMENTS

E2B R3 Elements

- E2B R3 Regional Elements – New
  - These are new regional elements added
  - 24 elements
- E2B R3 ICH Elements – Update
  - These are core ICH elements that slightly differ in business rules
  - 20 elements

E2B R3 Regional Elements – New

- **Identification of the Case Safety Report (C.1)**
  - Local Criteria Report Type (FDA.C.1.7.1)
  - Combination Product Flag (FDA.C.1.12) (Only for Post-market)
- **Primary Source(s) of Information (C.r.2)**
  - Reporter's Email (FDA.C.2.r.2.8)
- **Study Identification (C.5)**
  - IND Number where AE Occurred (FDA.C.5.5a)
  - IND number of cross reported IND (FDA.C.5.r.6)
  - Pre-ANDA Number where AE Occurred (FDA.C.5.5b)

E2B R3 Regional Elements - New

- **Patient Characteristics (D.)**
  - Patient Race Code (FDA.D.11.r.1)
  - Patient Ethnicity Code (FDA.D.12)
- **Reaction/Event as Reported by the Primary Source (E.i)**
  - Required Intervention (FDA.E.i.3.2h)

E2B R3 Regional Elements - New

- **Device Information (repeat as necessary) (FDA.G.k.12.r)**
  - Malfunction (FDA.G.k.12.r.1)
  - If follow-up, what type? (FDA.G.k.12.r.2.r.1)
  - Device Problem Code (FDA.G.k.12.r.3.r.2)
  - Device Brand Name (FDA.G.k.12.r.4)
  - Common Device Name (FDA.G.k.12.r.5)
  - Device Product Code (FDA.G.k.12.r.6)

E2B R3 Regional Elements - New

- **Device Information (repeat as necessary) (FDA.G.k.12.r)**
  - Device Manufacturer (FDA.G.k.12.r.7)
    - Details on next slide
  - Device Usage (FDA.G.k.12.r.8)
  - Device Lot Number (FDA.G.k.12.r.9)
  - Operator of the Device (FDA.G.k.12.r.10.a)
  - Remedial Action Initiated (FDA.G.k.12.r.11.r)

E2B R3 Regional Elements - New

- **Device Manufacturer (FDA.G.k.12.r.7)**
  - Device Manufacturer Name (FDA.G.k.12.r.7.1a)
  - Manufacturer Address (FDA.G.k.12.r.7.1b)
  - Device Manufacturer City (FDA.G.k.12.r.7.1c)
  - Device Manufacturer State (FDA.G.k.12.r.7.1d)
  - Device Manufacturer Country (FDA.G.k.12.r.7.1e)

E2B R3 ICH Elements - Update

Batch Sender Identifier N.1.3

Senders should use the **Data Universal Numbering System (DUNS) number** for N.1.3 using the Dun and Bradstreet (D&B) Object Identifier 1.3.6.1.4.1.519.1. The DUNS number for Business Entity Identifiers is used to validate business entities in various FDA information systems.

E2B R3 ICH Elements - Update

Batch Receiver Identifier N.1.4

FDA uses two different message receiver identifiers for test and production submissions. These identifiers are:

- Postmarket
  - For Test ICSR Submissions: ZZFDATST
  - For Production ICSR Submissions: ZZFDA
- Premarket
  - For Test ICSR Submissions: ZZFDATST_PREMKT
  - For Production ICSR Submissions: ZZFDA_PREMKT

E2B R3 ICH Elements - Update

Message Receiver Identifier N.2.r.3

- Postmarket
  - CDER
- Premarket
  - CDER IND use CDER_PREMKT
  - CBER IND use CBER_PREMKT

E2B R3 ICH Elements - Update

Section C: Identification of the Case Safety Report

Does this Case Fulfill the Local Criteria for an Expedited Report? C.1.7

- FDA *does not* support use of the HL7 nullFlavor NI in initial submissions
- Initial submissions with nullFlavor NI will be rejected
- For FDA reporting, if C.1.7 is populated with a “false” value, the ICSR is considered a non-expedited report

Linking Initial and Follow-up ICSRs

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

E2B R3 ICH Elements - Update

Section C: Identification of the Case Safety Report

Type of Report C.1.3

- For pre-market ICSRs use 2=Report from Study

Included Documents C.1.6.r.2

- Compression is not used for US reporting and encoding is limited to B64

Source(s) of the Case Identifier C.1.9.1.r.1

- FDA will provide a warning (and not reject) if C.1.9.1 = true and C.1.9.1.r.1 is not provided.

Case Identifier(s) C.1.9.1.r.1

- FDA will provide a warning (and not reject) if C.1.9.1 = true and C.1.9.1.r.1 is not provided.

E2B R3 ICH Elements - Update

Section C: Identification of the Case Safety Report

Person Responsible for Sending Report C.3.3

- Element under C.3.3 are Mandatory

Section D: Patient Characteristics

Patient (name or initial) D.1

- Use nullFlavor NA where no patient is involved. (e.g. Medication error, Compounding)
- For combination product, if a single report is reported for a malfunction without an adverse event, the element value should be “NONE”.
- For combination product, if there are multiple malfunction reports with no adverse event, then the element value should be “SUMMARY”.
- For Aggregate IND Safety Report, the element value must be “AGGREGATE”

E2B R3 ICH Elements - Update

Section D: Patient Characteristics

Date of Death D.9.1

- Conditional-Mandatory
- If Outcomes attributed to adverse event is Death then Death Date is required.

E2B R3 ICH Elements - Update

Section G.k: Drug(s) Information

Medicinal Product Name as Reported by the Primary Source G.k.2.2

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

E2B R3 ICH Elements - Update

Section G.k: Drug(s) Information

Characterisation of Drug Role G.k.1

- For pre-market ICSRs valid values are 1=Suspect 2=Concomitant

Pharmaceutical Dose Form TermID G.k.4.r.9.2b & Route of Administration TermID G.k.4.r.10.2b

- *For post-market*
  - *R2 - FDA accepts the European Medicines Agency (EMA) dosage codes or text.*
  - *R3 - EDQM code or free text*
- *For pre-market*
  - *CDISC Dosage Form codelist*

E2B R3 ICH Elements - Update

Section G.k: Drug(s) Information

Authorisation/Application Number G.k.3.1

- FDA requires the use of a prefix to determine the application type associated with suspect products
- For example, for human drug products, include the acronym “NDA” or “ANDA” immediately followed by the application number with no spaces; for example, NDA012345, ANDA012345

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

E2B R3 ICH Elements - Update

Section G.k: Drug(s) Information

Source of Assessment G.k.9.i.2.r.1

- Conditional-Mandatory
- Required if Element Value for C.1.3 is 2=Report from study
- Sponsor is required

Method of Assessment G.k.9.i.2.r.2

- Conditional-Mandatory
- Required if Element Value for C.1.3 is 2=Report from study

Result of Assessment G.k.9.i.2.r.3

- Conditional-Mandatory
- Required if Element Value for C.1.3 is 2=Report from study

E2B R3 ICH Elements - Update

Section G.k: Drug(s) Information

a. Additional Information on Drug G.k.10.r

- FDA regionally controlled terminology for FDA Specialized Product Categories is used to provide characteristics associated with product information
- These codes comprise the combination product types and the compound products

Pre-market
12=Test drug
13=Reference drug
14=Placebo
15=Vehicle

Combination
16=Type 1: Convenience Kit or Co-Package
17=Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)
18=Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)
19=Type 4: Device Coated/Impregnated/Otherwise Combined with Drug
20=Type 5: Device Coated or Otherwise Combined with Biologic
21=Type 6: Drug/Biologic Combination
22=Type 7: Separate Products Requiring Cross Labelling
23=Type 8: Possible Combination Based on Cross Labelling of Separate Products (Temporary Type)
24=Type 9: Other Type of Part 3 Combination Product (e.g. Drug/Device/Biological Product)

Compounding
25=Bulk ingredient
26=Bulk Ingredient For Human Prescription Compounding
27=Unapproved Drug Product Manufactured Exclusively for Private Label Distributer

E2B R3 ICH Elements - Update

ACK.B: ICH ICSR Message Acknowledgement

a. ACK.B.r.4: ICSR Message ACK Sender

- For Pre-market
  - Production: ZZFDA_PREMKT
  - Test: ZZFDATST_PREMKT
- Post-market
  - Production: ZZFDA
  - Test: ZZFDATST

Question 2

All regional elements are identified by the prefix “FDA”.

A. True

B. False

Question 3

Compression is used for US reporting and encoding is limited to B64.

A. True

B. False

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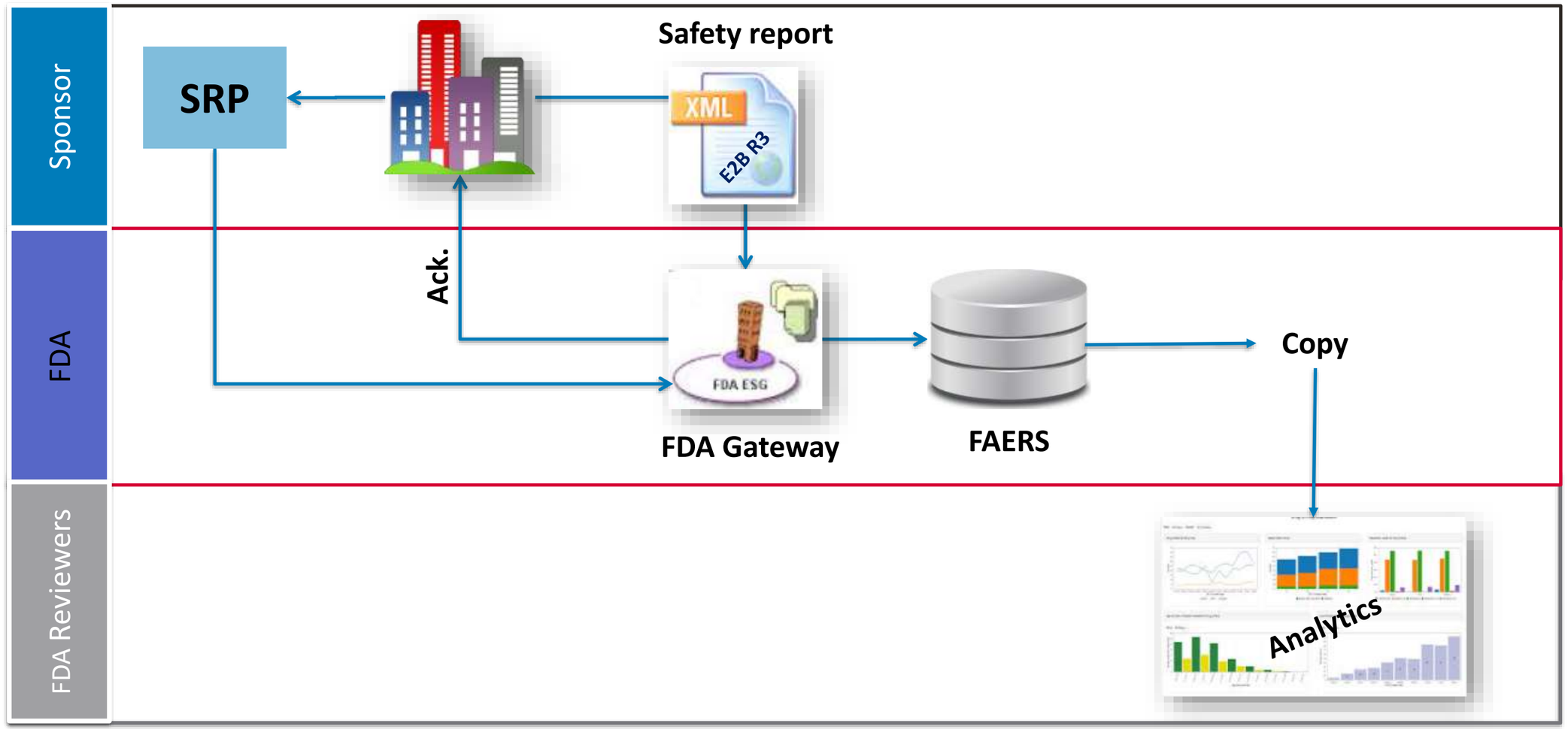
ROUTING MECHANISM

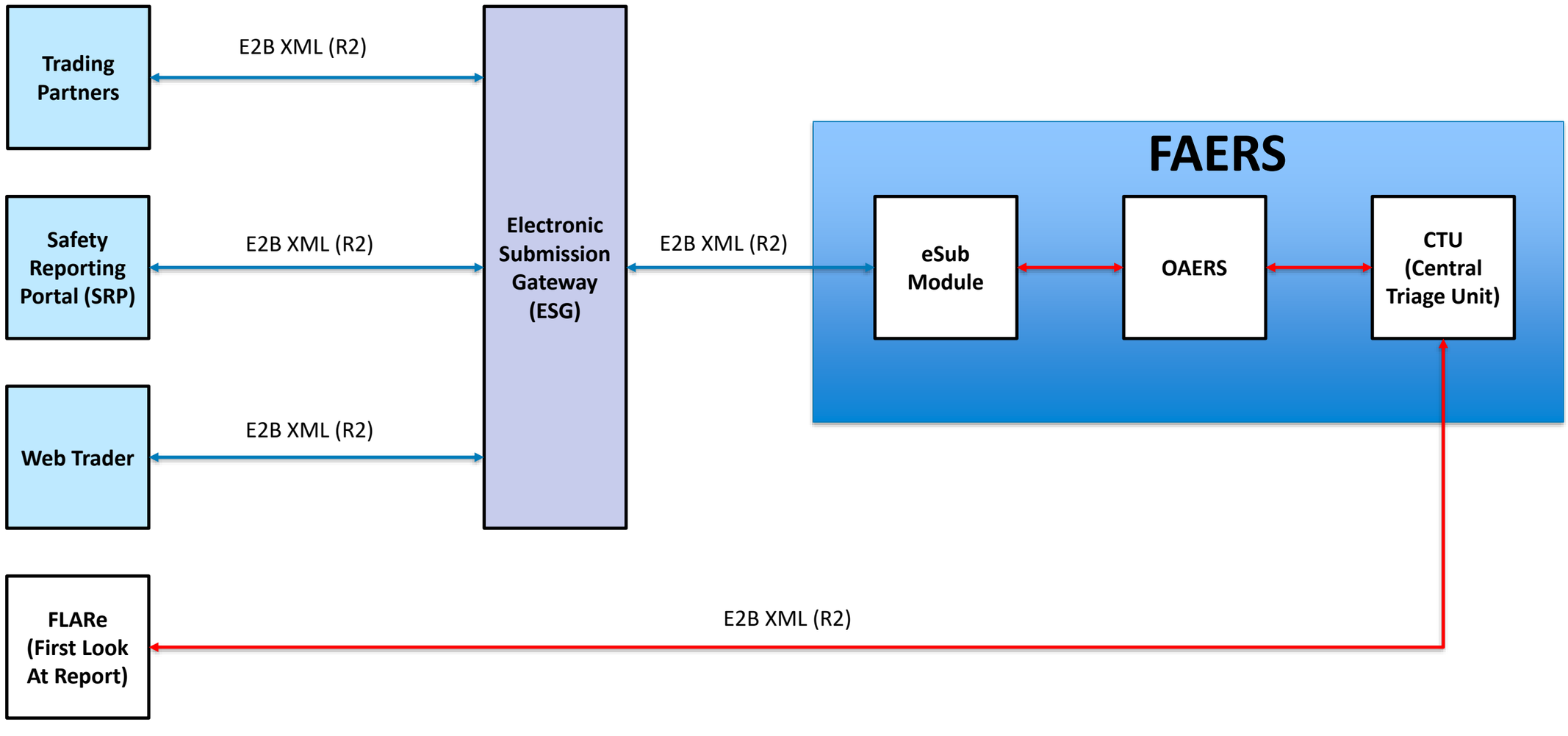
Safety Report Data Flow



Ack= Acknowledgement
FAERS= FDA Adverse Event Reporting System
SRP= Safety Reporting Portal

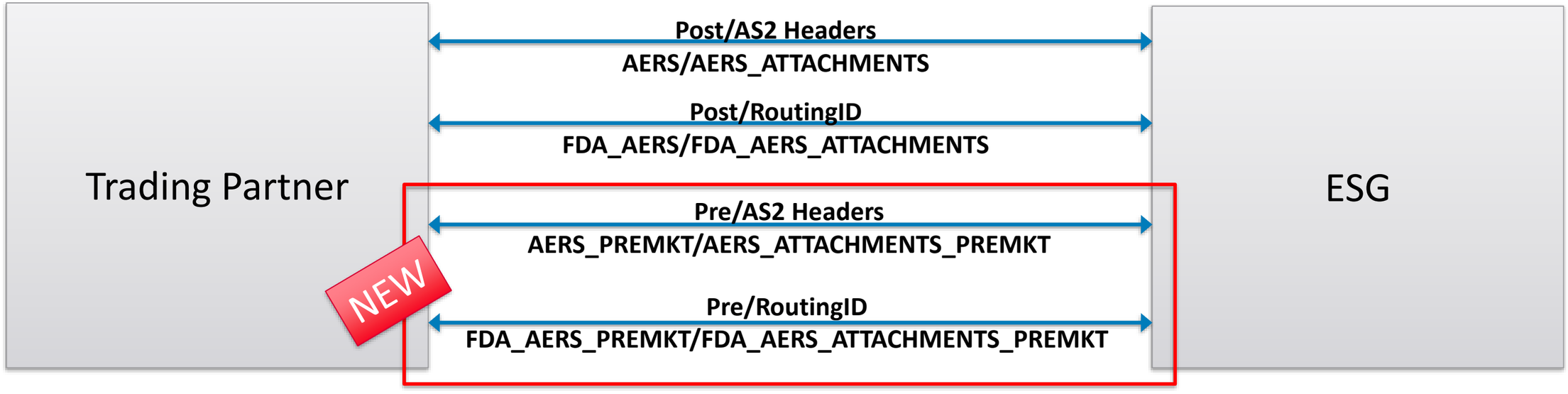
Routing Mechanism

Current Flow



Routing Mechanism

Trading Partner Changes



Question 4

Attachment must be submitted using RoutingId “FDA_AERS_ATTACHMENTS_PREMKT” when moved to E2B R3.

A. True

B. False

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TESTING PLAN

Testing Plan and Method

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

Testing Plan and Method

- Sponsor's must test both premarket and postmarket (including combo product) ICSRs in R3 format
  - Use both routing mechanism
- Sponsor's must notify FDA when ready for first production submission to FDA in R3 format
- In future, FDA plan to conduct cross regional testing
- All question during testing must be sent to eprompt@fda.hhs.gov

Summary of Today's Webinar

- ✓ FAERS II and E2B R3 Up Versioning Plans
  - Described the objective, scope and timeline of E2B R3 regional implementation
- ✓ Described E2B(R3) Regional Elements
- ✓ Communicated the different routing mechanisms to submit via ESG or Safety Reporting Portal
- ✓ Described the methods to test ICH E2B (R3) regional XMLs

Open Q&A begins shortly – type in your questions now

Thank You