Electronic Submission of IND Safety Reports to FDA Adverse Event Reporting System (FAERS)

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Agenda

- Background
- Implementation plans
  - Description of new process, including requirements and implementation
  - Data flow
  - Types of IND safety reports to be sent to FAERS
  - Data elements for IND safety reports using ICH E2B(R2)
- Case examples
- Routing Mechanism

IND Safety Reports

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

Current Process: **PDFs in eCTD format**	**New Process:** **ICH E2B XML files to FAERS**
• Inefficient and labor intensive review • Lack of universal tracking system	• Allows for use of data visualization and analytic tools for review and tracking • Leverages existing processes in use for postmarket safety reporting (ICH E2B data standards & FDA gateway) • Complies with existing federal regulations 21 CFR 312.32(c)(1)(v)

Process Pilot

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

Requirements and Timelines

- **Required change in format under 745A(a) of FD&C Act**
  - Sponsors of commercial INDs will be required to submit certain IND safety reports* to FAERS by one of two methods:
    - Electronic Submissions Gateway (ESG)

      or
    - Safety Reporting Portal (SRP)
  - Requirement effective 24 months after publication of final guidance; voluntary submissions from all sponsors will be accepted and encouraged prior to requirement

<u>FDA will announce when the voluntary submission process will begin</u>

*Serious and unexpected suspected adverse reactions that contain individual patient data

Communication Plan

- *Providing Regulatory Submissions in Electronic Format: IND Safety Reports - Draft Guidance for Industry (October 2019)*

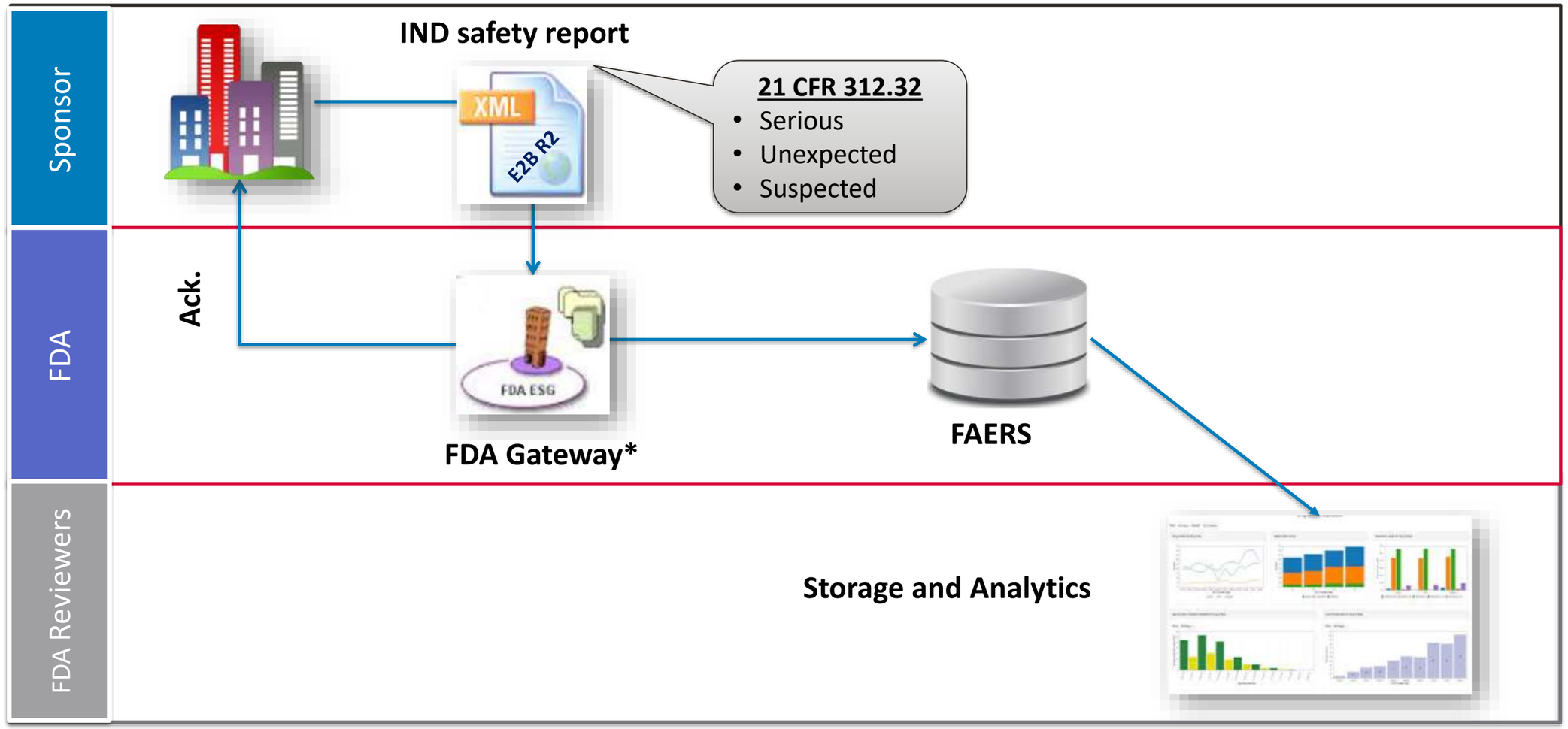
- *Electronic Submission of IND Safety Reports - Technical Conformance Guide (October 2019)*

- *Revised Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments (September 2019)*

- FAERS website recently updated with links the Guidance and technical specification documents specific to IND safety reports

- Other FDA communications when voluntary submissions begin

IND Safety Report Data Flow



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

Separate Submission Paths for IND and Postmarket Safety Reports

- FDA has defined new header attributes and routing IDs for IND safety reports and attachments
  - AS2 Headers
    - Destination: CDER
    - XML files: AERS_PREMKT
    - PDFs: AERS_ATTACHMENTS_PREMKT
  - Routing IDs
    - XML files: FDA_AERS_PREMKT
    - PDFs: FDA_AERS_ATTACHMENTS_PREMKT

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

Where to Submit IND Safety Reports

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

Technical Specifications

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

- Data elements for IND number(s)
  - IND number where the event occurred (A.2.3.2)
    - Required for processing and routing to appropriate FDA review division
  - IND number(s) for cross-reported IND(s)
    - Repeat block A.2, only A.2.3.2 and A.2.3.3, as many times as needed for cross-reported INDs

Technical Specifications for IND Safety Reporting – IND Number

Data Element	DTD Descriptor 2.1	Title	Element values (notes)
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	**IND 123456** **(IND number where event occurred)**
A.2.3.3	<observestudytype>	Study Type	1=Clinical Trials 2=Individual Patient use 3=Other Studies 4=Report from Aggregate analysis 5=Cross-reported IND safety report

Technical Specifications for IND Safety Reporting

Data Element	DTD Descriptor 2.1	Title	Element values (notes)
A.1.4	<reporttype>	Type of Report	1=Spontaneous **2=Report from Study** 3=Other 4=Not Available to Sender
A.2.3.1	<studyname>	Study Name	Study ID_$Abbreviated Trial name (study ID is from study tagging file in eCTD)
A.2.3.3	<fulfillexpeditedcriteria>	Does this case fulfill local criteria for an expedited report	1=Yes (use for 15 day reports) 6=7-day

Technical Specifications for IND Safety Reporting – Drug Information

Data Element	DTD Descriptor 2.1	Title	Element values (notes)
B.4.k.2.1	<medicinalproduct>	Medicinal Product name	(Use INN or USAN name, if applicable. Use company code if no established name, with multi-ingredient products, or if name exceeds character length.) (Submit E2B naming conventions if no INN or USAN name)
B.4.k.2.2	<activesubstancename>	Active drug substance name	

Technical Specifications for IND Safety Reporting – Causality Assessment

Data Element	DTD Descriptor 2.1	Title	Element values (notes)
B.4.k.18	<drugreactionrelatedness>	Relatedness of drug to reaction/event	(at least one suspect product should be related to an event)
B.4.k.18.1b	<drugreactionassess>	Reaction assessed	
B.4.k.18.2	<drugassessmentsource>	Source of assessment	(sponsor assessment is required, repeat block for investigator assessment)
B.4.k.18.4	<drugresult>	Result	1=suspected 2=not suspected

Technical Specifications for IND Safety Reporting - Narratives

Data Element	DTD Descriptor 2.1	Title	Element values (notes)
B.5.1	<narrativeincludeclinical>	Case narrative	(Construct narratives that fit within 20,000 AN E2B(R2) field length limit)
B.5.4	<sendercomment>	Sender's comments	(Include analysis of similar events in this field)

Benefits to Industry

- Efficiency gains in processing and submission
  - Direct electronic submission to FDA from PV
    - no 1571 or cover letter
  - Eliminates need to send duplicate reports
- More comprehensive and structured format than Medwatch form
- Consistent with format for NDA/BLA and ex-US submissions

Case Scenario 1

For any IND safety report where the sponsor is evaluating the investigational drug under more than one IND

Data Element	DTD Descriptor 2.1	Title	Element values (notes)
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	IND 123456
A.2.3.3	<observestudytype>	Study Type	1 = Clinical Trials 2 = Individual Patient use 3 = Other Studies 4 = Report from Aggregate analysis 5 = Cross-reported IND safety report

- Block A.2 is repeatable
  - Use first block to designate IND where event occurred = primary IND
    - A.2.3.2 = primary IND
    - A.2.3.3 = data values 1, 2, 3, or 4
  - Repeat block A.2 with only A.2.3.2 = IND number and A.2.3.3 data value = 5 as many times as needed for each cross-reported IND

Case Scenario 2

Report from aggregate analysis as per 312.32(c)(1)(i)(C) or 312.32(c)(1)(i)(B)

Data Element	DTD Descriptor 2.1	Title	Element values (notes)
A.1.12	<linkedreportnumber>	Identification number of reports linked to this report	(Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis)
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	(Use the “parent” IND number)
A.2.3.3	<observestudytype>	Study Type	1 = clinical trials 2 = individual patient use 3 = other studies 4 = Report from aggregate analysis
B.1.1	<patientinitial>	Patient identifier	Aggregate

Case Scenarios

- See additional information and other case scenarios in appendix of *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments*

Challenge Question #1

Which of the following are required elements for submission of IND safety reports to FAERS?

A. Suspect product
B. IND number
C. Form 1571
D. Both A and B

Challenge Question #2

True or False: FDA is currently accepting IND safety reports to FAERS.

A. True

B. False

Challenge Question #3

What types of IND safety reports will not be submitted to FAERS?

A. 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)

B. 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)

C. 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)

D. Findings from animal or in vitro testing (21 CFR 312.32(c)(1)(iii))

Submit Your Questions

and we will get to them after we hear from

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Routing Mechanism

Setting up routing controls dictating where a document is sent

- Two options :
  - Add the custom header attributes to the header of the message to indicate the type of submission (e.g. an IND) and destination (e.g. CDER). Reference ***Appendix F., AS2 Header Attributes***, for information on header attributes content and format.

OR

  - Use a unique routing ID to identify the types of submissions and destination. The selection of the routing ID can be automated in the Cyclone/Axway products through the back-end integration pick-up as described in ***Appendix J., AS2 Routing IDs***.

Routing Mechanism

Trading Partner Changes

- **AS2 <u>Header Attributes</u>**

  - For current post market reports
    - Destination: “CDER”
    - Attribute values: “**AERS**” for XMLs and “**AERS_ATTACHMENTS**” for PDFs

  - For IND safety reports, new header attributes need to be configured to route the files into the new folders.
    - Destination remains the same
    - Attribute values: “**AERS_PREMKT**” for XMLs and “**AERS_ATTACHMENTS_PREMKT**” for PDFs

Routing Mechanism

Trading Partner Changes

- **AS2 <u>Routing IDs</u>** - ESG also provides alternate method to submit the files using unique routing IDs

  – For current post market reports
    - Routing IDs: "**FDA_AERS**" for XMLs and "**FDA_AERS_ATTACHMENTS**" for PDFs

  – For IND safety reports, new Routing IDs need to be setup and corresponding configuration changes are required
    - Routing IDs: "**FDA_AERS_PREMKT**" for XMLs and "**FDA_AERS_ATTACHMENTS_PREMKT**" for PDFs

Triage of ICSRs

Sponsor Submission

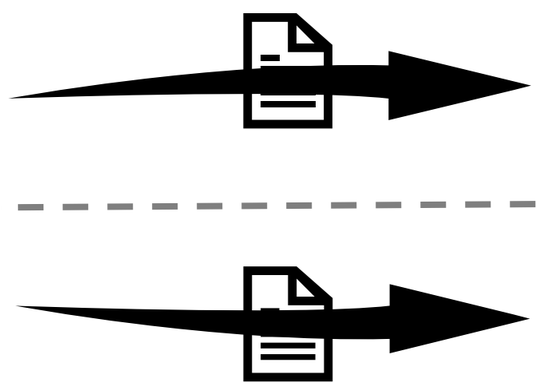
FDA Adverse Event Reporting System

Pre-Market ICSR Submission

AS2* Header: AERS_PREMKT or
AS2 Routing ID: FDA_AERS_PREMKT

A.1.01: Sender's Report ID
A.1.4: 2
A.2.3.1: eCTD STF Name
A.2.3.2: **IND number (Mandatory)**
A.2.3.3: accordingly
…

A.1.01: Sender's Report ID + "-IND"
…
…
…



Post-Market ICSR Submission

AS2 Header: AERS or
AS2 Routing ID: FDA_AERS

A.1.01: Sender's Report ID
A.1.4: 1
A.2.3.1: empty
A.2.3.2: empty
A.2.3.3: empty
B.4.k.4.1: NDA 07852
…

A.1.01: Sender's Report ID (stay as is)
…
…
…

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

Summary

- FDA draft guidance and technical specification documents recently published regarding submission of IND safety reports to FAERS
- **<u>FDA is NOT currently accepting IND safety reports to FAERS</u>**
  - FDA will announce when the voluntary submission process will begin
- Requirement will be in effect 2 years after the final guidance
- IND-specific E2B data elements are <u>critical</u> to ensure regulatory requirements are met

We will take a short break to review your questions and will be right back with answers