Regulatory Submissions, Information, and Document Management Forum

February 10-12 2020 | North Bethesda, MD

FDA: Digital IND Safety Reporting

Ginny Hussong, CBER (Chair)

FDA's Implementation of Digital IND Safety

Meredith K. Chuk, M.D., Acting Associate Director for Safety, OOD/OND/CDER

FAERS II Status Update for IND Safety

Suranjan De, M.S., MBA, Deputy Director, RSS/OND/CDER

Safety Reporting Portal Update

Vali M. Tschirgi, Project Manager, Office of the Director, CBER

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Digital IND Safety Reporting Program

FDA's Implementation of Digital IND Safety

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Acting Associate Director for Safety, OOD/OND/CDER

Drug Information Association (DIA)
FEBRUARY 11, 2020

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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)

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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)

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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

FDA will announce when the voluntary submission process will begin

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

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- *Providing Regulatory Submissions in Electronic Format: IND Safety Reports - Draft Guidance for Industry (October 2019)*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

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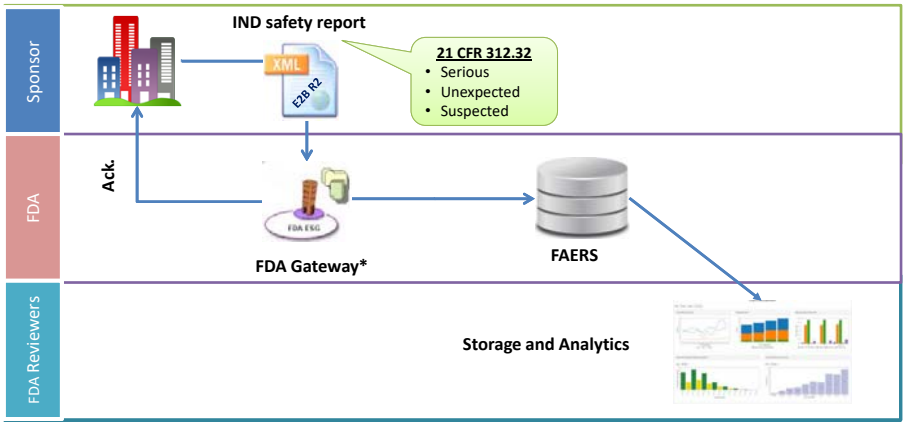
IND Safety Report Data Flow



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

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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

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Technical Specifications

- *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* has been updated with information for IND reporting
- ICH E2B(R2) elements specific to IND safety reporting
  - IND numbers
  - Cross-reporting
  - Reports from aggregate analysis

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Technical specifications

- **IND numbers**
  - Data elements for IND number(s) = A.2.3.2
  - IND number where the event occurred (A.2.3.2), or "parent" IND if report is from an aggregate analysis or from other source
  - *Required for processing and routing to appropriate FDA review division*

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Technical Specifications

- **Cross-reporting**
  - As per 2012 guidance, *Safety Reporting Requirements for INDs and BA/BE Studies*, sponsors should submit IND safety reports to all INDs where they are evaluating the drug
    - To avoid duplicate reports submitted to FAERS, all relevant IND numbers should be listed in a single report
  - Only ONE IND safety report should be submitted per event
  - IND number(s) for cross-reported IND(s) placed in repeated block A.2
    - Repeat block A.2, only A.2.3.2 and A.2.3.3, as many times as needed for cross-reported INDs

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Technical Specifications

- **Reports from aggregate analysis**
  - Required as per (21 CFR 312.32(c)(1)(i)(C) or (21 CFR 312.32(c)(1)(i)(B) where several events are included
  - Submit one report describing event and drug information and link individual cases that made up the aggregate analysis with data element A.1.12

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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

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Digital IND Safety Reporting Program

FAERS II Status Update for IND Safety

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Drug Information Association (DIA)
FEBRUARY 11, 2020

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Agenda

- Routing Mechanism
- E2B R2 Data Elements
- E2B R3 Data Elements
- E2B R2 -> E2B R3 Forward Compatibility

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Routing Mechanism - Process

- Capture the IND# by using the study ID field - support triage of ICSRs
- Two separate "Routes" for submission
- Senders will send pre- and post-market ICSRs to separate routes
  - Sponsors will be responsible for sending the ISCR to the correct destination based on whether it is a pre- or post-market ICSR
- The pre-market (IND) ICSR submission would include the study name and the study number

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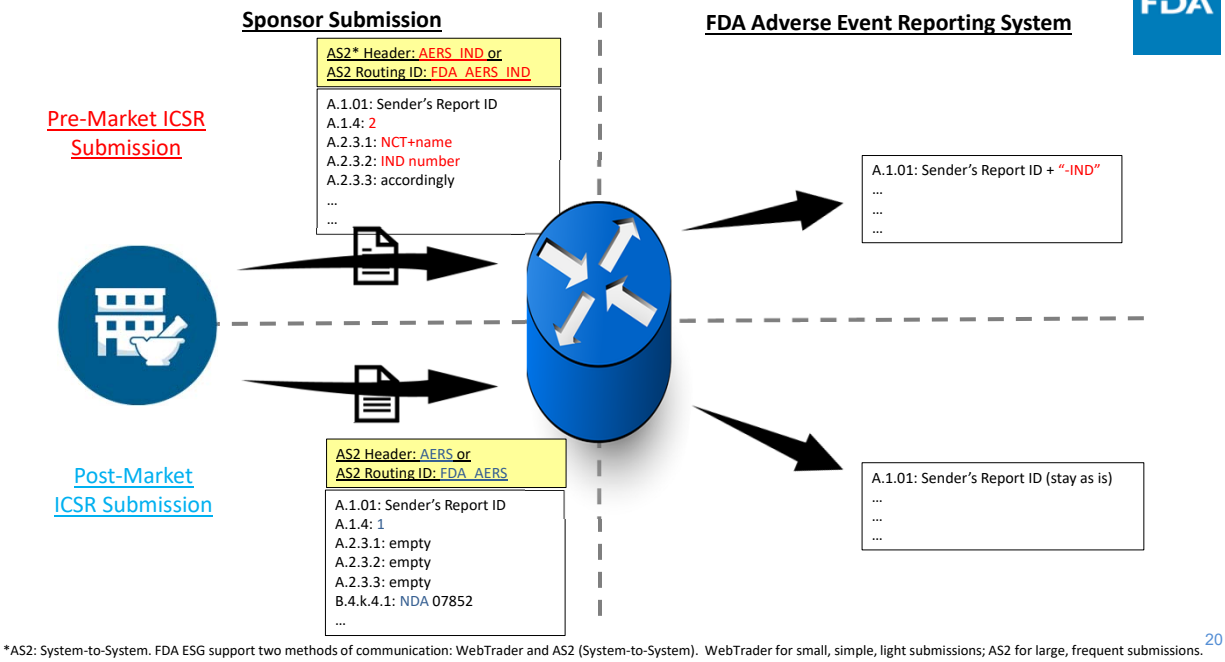
Routing Mechanism - Triage of ICSRs



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

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Routing Mechanism - Methods

- Two separate "Routes" for submission of safety reports (used for both pre or post market ICSRs)
  - Method 1: AS2 Header Attributes, or
  - Method 2: AS2 Routing IDs
- E2B Data Elements are re-purposed and designated specifically for pre-market

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Routing Mechanism - Method 1

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

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

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Routing Mechanism - Method 2

- **AS2 Routing ID's** – using unique routing ID's
  - Current State: Post market reports (does not apply to pre-market)
    - Routing ID's: "**FDA_AERS**" for XML's and "**FDA_AERS_ATTACHMENTS**" for PDF's
  - Future State: For IND reports, new Routing ID's would need to be setup and corresponding configuration changes required (would apply to pre market ICSRs).
    - Routing ID's: "**FDA_AERS_IND**" for XML's and "**FDA_AERS_ATTACHMENTS_IND**" for PDF's

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

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Agenda

- Routing Mechanism
- **E2B R2 Data Elements**
- E2B R3 Data Elements
- E2B R2 -> E2B R3 Forward Compatibility

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E2B R2 Specific Premarket Data Elements

Data Element	DTD Descriptor 2.1	Title	Field Length	Element Values for DTD 2.1	Notes
A.1.4	<reporttype>	Type of Report	1N	1=Spontaneous 2=Report from Study 3=Other 4=Not Available to Sender (unknown)	Element value= 2 for Report from Study
A.1.9	<fulfillexpeditecriteria>	Does this case fulfill the local criteria for an expedited report?	1N	1=Yes 2=No 4=5-Day 5=30-Day 6=7-Day	Element value=1 for 15-Day Expedited Element value= 6 for 7-Day Expedited
A.1.12	<linkreportnumb>	Identification Number of the report which is linked to this report	100AN		Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per (312.32(c)(1)(i)(B)) when a Narrative Summary Report is provided, this field should be populated in the IND Safety Report that contains the Narrative Summary Report.

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E2B R2 Specific Premarket Data Elements

Data Element	DTD Descriptor 2.1	Title	Field Length	Element Values for DTD 2.1	Notes
A.2.3.1	<studyname>	Study Name	100AN	Study ID_$Abbreviated Trial Name	The Study ID should be the same value used in the study tagging file format of the eCTD submission.
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	35AN	IND number under which the clinical trial where the event occurred is conducted Use the "Parent" IND number* for reports submitted from an Aggregate Analysis as per (312.32(c)(1)(i)(C)) or for several events submitted as per (312.32(c)(1)(i)(B)), from trials conducted under more than one IND	Populate this field with the Primary IND in the first block and repeat block A.2 with elements A.2.3.2 and A.2.3.3.as noted below with element value= 5 for sponsor's other INDs evaluating suspect product (where applicable) Include the acronym "IND" followed by a space and then the IND number for the application (e.g. IND 123456)
A.2.3.3	<observestudytype>	Study type in which the Reaction(s)/ Event(s) were observed	1N	1= Clinical Trials 2= Individual Patient Use 3= Other Studies 4= Report from Aggregate Analysis 5= Cross-reported IND Safety Report	Required if element value for A.1.4 is 2=Report from Study Repeat this field as needed with element value= 5 for each Cross-reported IND. The first block of this element in the report must not be 5. If element value 4 is chosen, then A.1.9= 1.

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E2B R2 Specific Premarket Data Elements

Data Element	DTD Descriptor 2.1	Title	Field Length	Element Values for DTD 2.1	Notes
B.1.1	<patientinitial>	Patient Identifier	10AN		For a report from an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is provided, the element value should be "AGGREGATE"
B.4.k.2.1	<medicinalproduct>	Proprietary Medicinal Product Name	70AN		For investigational drug and biological products without an established name (i.e. INN or USAN name), prior to submitting IND safety reports to FAERS, the sponsor should submit a clinical information amendment to the IND, listing the names of the active drug substance/s and the medicinal product as they will be reported in E2B file submissions. The names should fit within the established E2B character length limits. Use company product code if no established name, for multi-ingredient products, or if name exceeds character length
B.4.k.2.2	<activesubstancename>	Active Drug Substance Names	100AN		
B.5.4	<sendercomment>	Sender's Comments	2000AN		Identification and analysis of previously submitted events (as required by 312.32(c)(1)) should be reported in this field.

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E2B R2 Specific Premarket Data Elements

Data Element	DTD Descriptor 2.1	Title	Field Length	Element Values for DTD 2.1	Notes
B.4.k.18	<drugreactionrelatedness>	Relatedness of Drug to Reaction/ Event			For IND Safety Reports, at least one suspect product should have relatedness of drug to reaction/ event
B.4.k.18.1a	<drugreactionassesmeddraversion>	MedDRA Version for Reaction Assessed	8AN		
B.4.k.18.1b	<drugreactionasses>	Reaction Assessed	250AN		
B.4.k.18.2	<drugassessmentsource>	Source of Assessment	60AN		Use the value "Sponsor" or "Investigator". Include sponsor and investigator assessment in separate blocks
B.4.k.18.3	<drugassessmentmethod>	Method of Assessment	35AN	FDA Method	Use the value "FDA Method".
B.4.k.18.4	<drugresult>	Result	35AN	1=Suspected 2=Not suspected	For IND Safety Reports, at least one suspect product should have relatedness of drug to reaction/ event

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E2B R2 Specific Premarket Data Elements

Data Element	DTD Descriptor 2.1	Title	Field Length	Element Values for DTD 2.1	Notes
B.5.1	<narrativeincludeclinical>	Case Narrative Including Clinical Course, Therapeutic Measures, Outcome, and Additional Relevant Information	20,000AN		FDA strongly encourages sponsors to construct narratives that fit within the ICH E2B character limit of 20,000 AN. If your narrative exceeds this limit, sponsors should include as much of the narrative as possible in this field and submit an ICSR attachment for any text that exceeds the character limit. Sponsors should not submit an ICSR attachment containing the entire narrative and leave the case narrative field empty. For reports from Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) where PDF is attached, put "see attached Narrative Summary Report" in this field.
B.5.4	<sendercomment>	Sender's Comments	2000AN		Identification and analysis of previously submitted events (as required by 312.32(c)(1)) should be reported in this field.

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Agenda

- Routing Mechanism
- E2B R2 Data Elements
- **E2B R3 Data Elements**
- E2B R2 -> E2B R3 Forward Compatibility

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E2B R3 Specific Premarket Data Elements

Data Element	Data Element Name	Field Length	Conformance	Notes
FDA.C.1.7.1	Local Criteria Report Type	1N	Mandatory	Use element values 1 for 15-Day Expedited and 6 for 7-Day Expedited.
C.1.10.r	Identification Number of the Report Which Is Linked to This Report	100AN	Optional	Use to link all Sender's (case) Safety Report Unique Identifier that make up an Aggregate Analysis as per 312.32(c)(1)(i)(C)
C.5.2	Study Name	2000AN	Optional	Study ID$Abbreviated Trial Name The Study ID should be the same value used in the Study Tagging file format of the eCTD submission.
C.5.4	Study Type Where Reaction(s) / Event(s) Were Observed	1N	Conditional-Mandatory	Optional, but required if C.1.3=2(Report from study). For Aggregate Report, use value 4=Aggregate with the new OID
FDA.C.5.5a	IND Number where AE Occurred	10N	Conditional-Mandatory	Required if C.1.3 =2 (Report from study), and FDA.C.5.5b is not populated. The format must be "123456". For IND safety reports submitted from an aggregate analysis (312.32(c)(1)(i)(C)) from trials conducted under more than one IND, use the "Parent" IND number

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E2B R3 Specific Premarket Data Elements

Data Element	Data Element Name	Field Length	Conformance	Notes
FDA.C.5.5b	Pre-ANDA Number where AE Occurred	10N	Conditional-Mandatory	Required if C.1.3=2 (Report from study) and FDA.C.5.5a is not populated. The format must be "234567" for BA/BE study
FDA.C.5.r.6	IND number of cross reported IND	10N	Mandatory	Required if element value for FDA.C.5.5a is populated. Use nullFlavor=NA if there are no other cross reported IND
D.1	Patient (name or initials)	60AN	Mandatory	For Aggregate Report, the element value must be "AGGREGATE"
FDA.D.11.r.1	Patient Race Code	10AN	Mandatory	If Patient (name or initials) (D.1) is "AGGREGATE" then use nullFlavor: NA
FDA.C.5.5a	Patient Ethnicity Code	10AN	Mandatory	If Patient (name or initials) (D.1) is "AGGREGATE" then use nullFlavor: NA
G.k.9.i.2.r.1	Source of Assessment	60AN	Conditional-Mandatory	Required if Element Value for C.1.3 is 2=Report from study Default to "Sponsor" and Include Investigator Assessment in H.1 (R2 B.5.1)
G.k.9.i.2.r.2	Method of Assessment	60AN	Conditional-Mandatory	Required if Element Value for C.1.3 is 2=Report from study Default to value "FDA Method".
G.k.9.i.2.r.3	Result of Assessment	60AN	Conditional-Mandatory	Required if Element Value for C.1.3 is 2=Report from study For IND Safety Reports, at least one suspect product should have relatedness of drug to reaction/ event. Use the value "Suspected" or "Not Suspected"

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Agenda

- Routing Mechanism
- E2B R2 Data Elements
- E2B R3 Data Elements
- **E2B R2 -> E2B R3 Forward Compatibility**

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E2B R2 -> E2B R3 Forward Compatibility

Element	Regional R2			Regional R3			Rule	Conversion R2->R3
Study Type Where Reaction(s) / Event(s) Were Observed	A.2.3.3	0..1	1N	C.5.4	0..1	1N	FDA-03	Copy values 1, 2 and 3 as is. If value is 4, then set D.1 (Patient (name or initials) to "AGGREGATE" If value is 5, then copy only the numeric part of A.2.3.2 (Sponsor Study Number) to FDA.C.5.r.6 (IND number of cross reported IND)
Sponsor Study Number	A.2.3.2	0..1	35AN	FDA.C.5.5a	0..1	10N	FDA-04	Copy only the numeric part of A.2.3.2 (Sponsor Study Number) to FDA.C.5.5a (IND Number where AE Occurred) where A.2.3.3 (Study Type Where Reaction(s) / Event(s) Were Observed) is not equal to 5
				FDA.C.5.r.6	0..N	10N	FDA-05	Copy only the numeric part of A.2.3.2 (Sponsor Study Number) to FDA.C.5.r.6 (IND number of cross reported IND) where A.2.3.3 (Study Type Where Reaction(s) / Event(s) Were Observed) is equal to 5

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Digital IND Safety Reporting Program

Safety Reporting Portal

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FEBRUARY 11, 2020

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Safety Reporting Portal (SRP)

- No-cost, web-based questionnaire for submitting individual safety reports to FDA
- Guides user through data entry for initial and follow-up reports
- Creates the electronic Individual Case Safety Report (ICSR) and submits to FAERS via the Electronic Submission Gateway (ESG)

https://www.safetyreporting.hhs.gov

Note: There are several report types that can be submitted via SRP.

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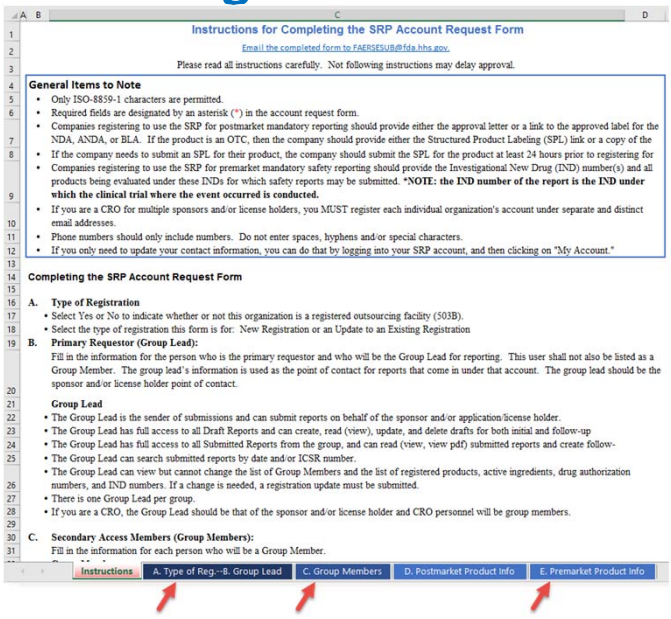
SRP Account Registration

- Email FAERSESUB@fda.hhs.gov to advise FDA of your intent to begin submitting via the SRP
- MS Excel Registration Form (used for pre- and/or post-market reporting)
- Complete worksheets A/B, C, and E for premarket reporting
- Specify:
  - Access to individuals
  - Products and INDs for reporting



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SRP Data Entry / Information

- Report Identifying Information
- Sender Information
- Reporter Information
- Patient Information
- Suspect Product Information
- Adverse Event Details
- Concomitant Product Information
- Cross-reported INDs
- Aggregate Analysis
- Attached Files

Information captured and reported via SRP matches FDA requirements

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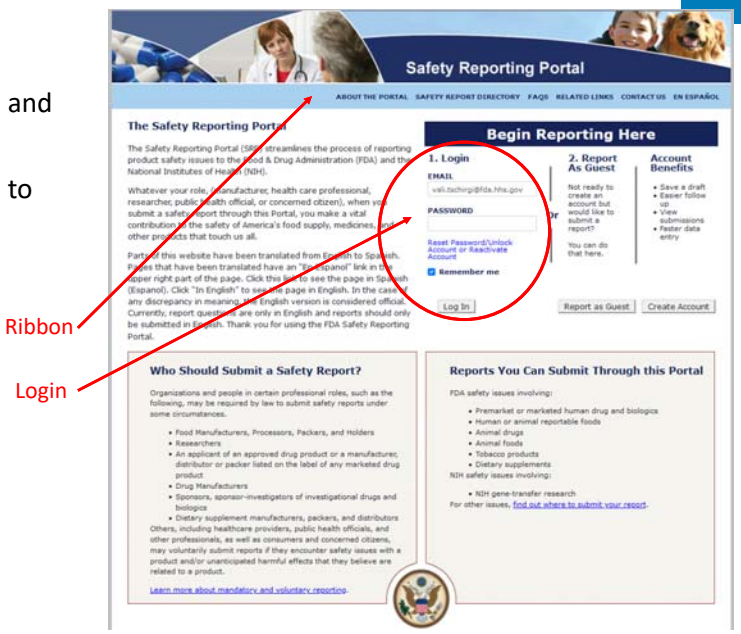
SRP Home Screen

- SRP Home screen
  - Provides general information and User Login
  - Light blue ribbon with access to FAQs, Related Links, Contact information, Help, and the Spanish version are always available



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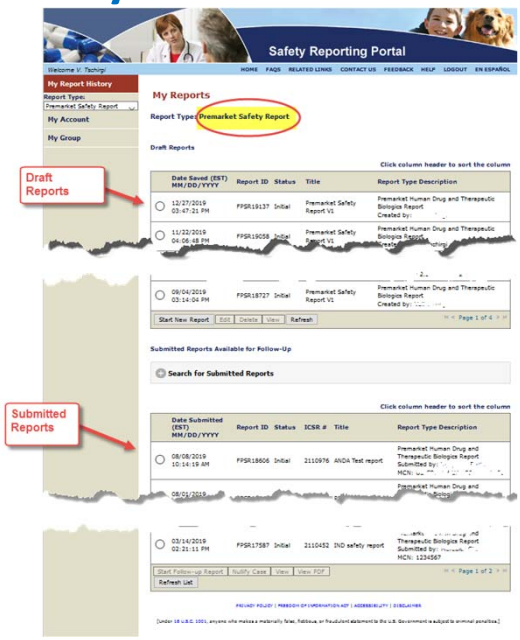
"My Report History" Screen

- Separated by Report Type (Premarket vs. Post-market)
- Table of Draft Reports
  - Select to continue editing, view, or delete the draft report
  - Start new report
- Table of Submitted Reports
  - Select to view report or create a follow-up report
  - Option to nullify entire case
  - Search option – e.g., if list is long
  - Save a .pdf of your original submitted report before submitting a follow-up report; only latest submitted report kept



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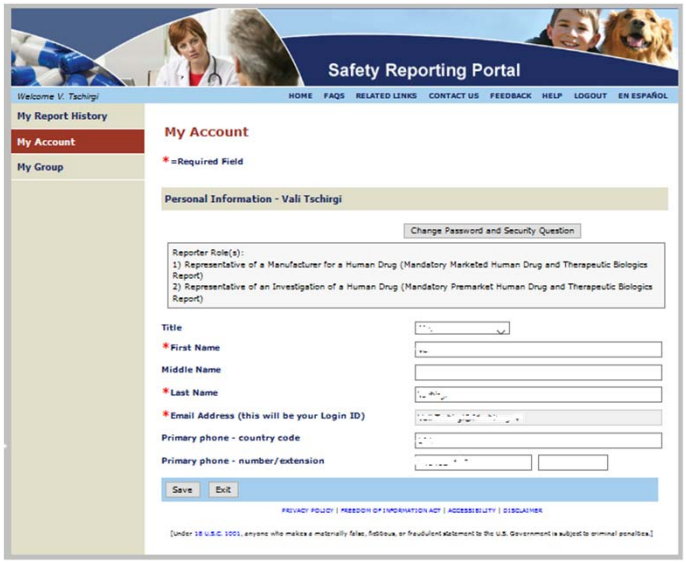
"My Account" Screen

- Displays editable contact information (name and phone number)
- Displays non-editable email address (used as Login ID)
- Submit updated registration form to add accounts or modify email address
- Option to change password and/or security question



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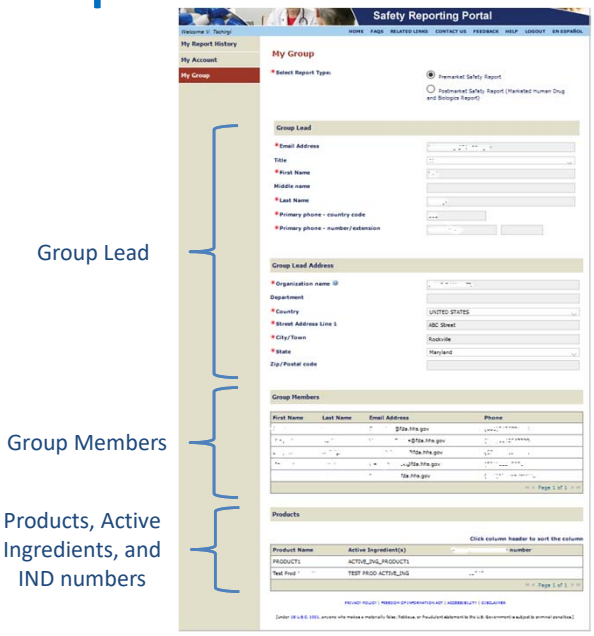
"My Group" Screen

- **Group Lead** name and address from registration form Tab A/B
- **Group Members** from registration form Tab C
- **Products**, **active ingredients** and **IND numbers** from registration form Tab E
- Submit updated registration form to add or change information



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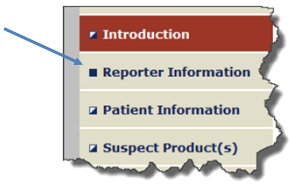
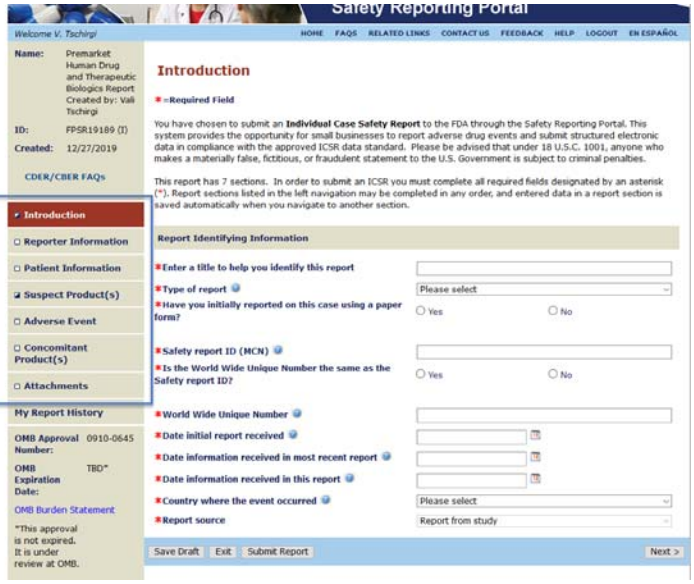
Safety Report Data Entry

- New Premarket Report
  - Data entry sections
  - Filled box indicates met minimum required data entry for submission



- Follow-up Report
  - Same data entry screens
  - Last submitted report is starting point for editing



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Frequently Asked Questions (FAQs)

- **How long does it take to register?**
  - Your account will be activated in about 7 to 10 business days.
  - You will be notified via email with the subject line "SRP Account Activation" that will include the web link to the SRP portal along with account information.
  - After receiving this email, your account will be considered active and you may begin submitting reports.

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Frequently Asked Questions (FAQs) (cont.)

- **I already submit via ESG, may I use SRP as a back-up?**
  - No. Only Sponsors/Applicants who do not have database-to-database capability may submit electronic ICSRs using the SRP. Gateway partners cannot use the SRP. Gateway partners are those companies that submit electronically via the Electronic Submission Gateway.

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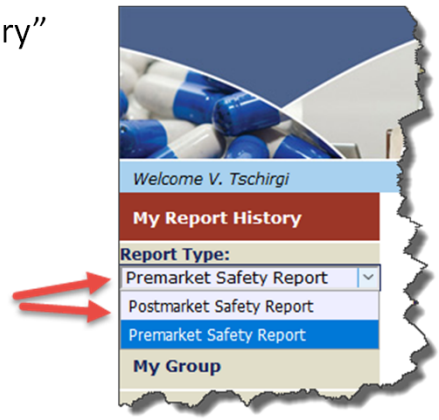
Frequently Asked Questions (FAQs) (cont.)

- **How do I enter premarket vs. post-market reports?**
  - Select the report type in "My Report History"
  - Post-market and premarket reports are grouped and tracked separately
  - If a given safety event needs both a premarket and post-market report to FDA, the reports are entered separately in SRP



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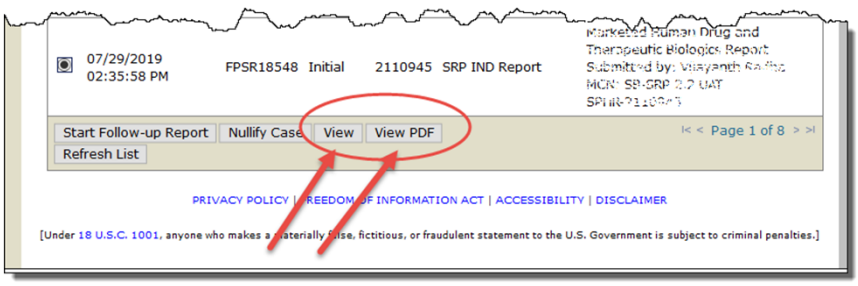
Frequently Asked Questions (FAQs) (cont.)

- **What reports are available in SRP?**
  - On-line views of draft and submitted reports
  - PDF view of submitted reports



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Frequently Asked Questions (FAQs) (cont.)

- **Can I query reports in SRP?**
  - You can query submitted reports by the date submitted, ICSR number, and/or Title

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Frequently Asked Questions (FAQs) (cont.)

- **Are records of my reports kept?**
  - SRP stores in-process drafts and only the most recent submitted report (or nullify) for each event
  - Keep your own PDF of each report submitted
  - Reports are not accessible after SRP account is deactivated

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Findings from the Pilot

- Logically designed, easy to use
- Ensures XML is formatted per FDA's technical specifications; sponsor does not have to learn XML and AS2
- Confirmation emails are sent to the person who submitted the report per email in registration form. If multiple individuals submit reports, make sure working as expected
- Data entry can be labor-intensive as there is no tool for uploading (e.g., from spreadsheet)
- May not match internal process currently in place (e.g., for collecting data from investigators) – could add time

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Summary

- **SRP Intended for**
  - Sponsors and CROs without infrastructure for direct ESG (gateway-to-gateway) submission
  - Individual reports only; no batch reporting via SRP
- **If CRO**
  - Separate account needed for each sponsor/license holder
- **Post-market and premarket reporting**
  - Maintained separately—select up front, can navigate between them
  - Cannot copy/paste or transfer data; manually enter
- **"Free" (no added cost to use)**
- Contact FAERSESUB@fda.hhs.gov to request an SRP account

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Reference:

SRP ACCOUNT REGISTRATION FORM

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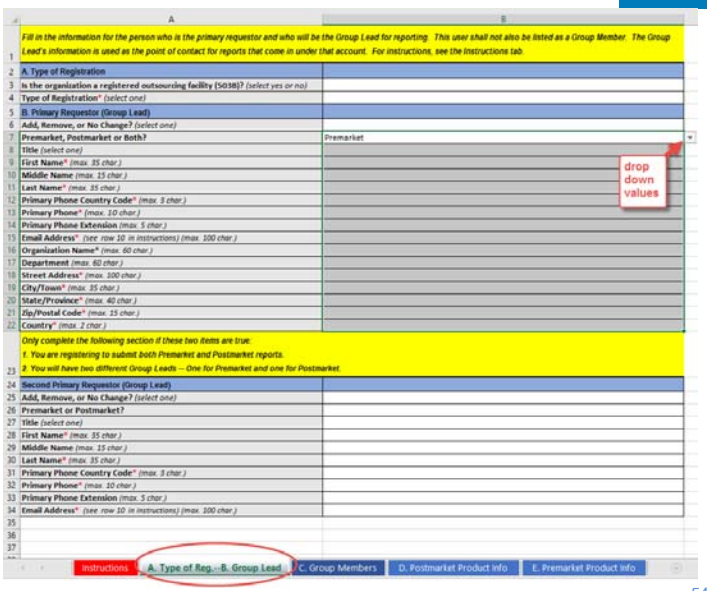
Registration for SRP Account: Tab "A/B"

- Contact information for primary and secondary sender of reports (Sponsor/ License Holder)
- Drop-down values for some fields



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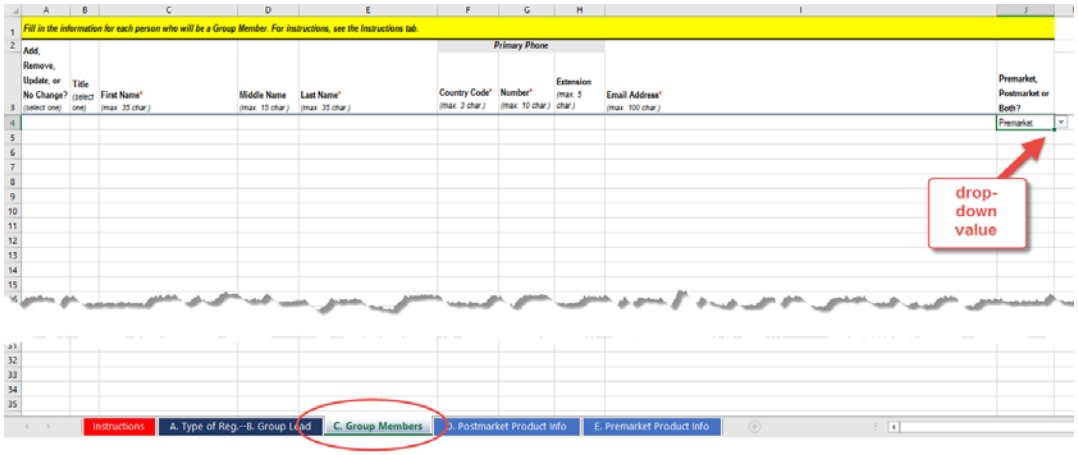
Registration for SRP Account: Tab "C"



Contact information for additional individuals (e.g., CRO) allowed to submit premarket, post-market, or both reports

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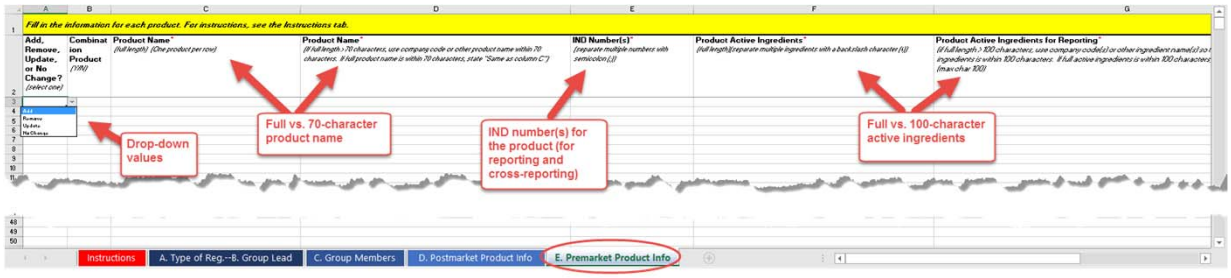
Registration for SRP Account: Tab "E"



- Product and active ingredient information (full and limited character length)
- IND #(s) for reporting and cross-reporting
- Can be an approved/licensed product studied under IND(s)

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