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

MARCH 25, 2019

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

March 25, 2019

Suranjan De, MS, MBA
Deputy Director
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# Session 1: FAERS II and E2B R3 Up Versioning Plans

# PLAN & TIMELINE

# 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**

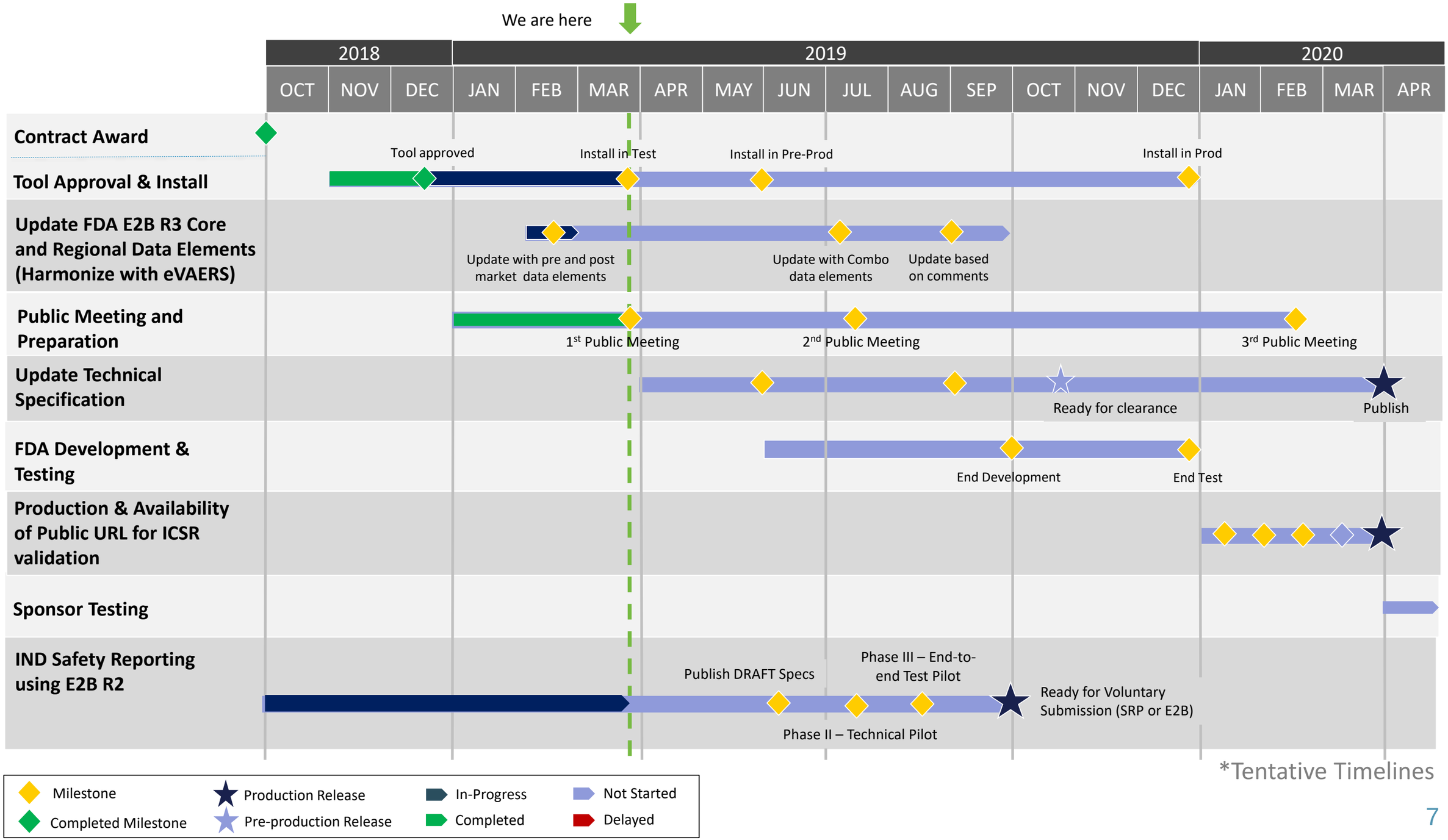
# FAERS II - Scope

- 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

# Testing Plan and Method

- No compliance date has been set for R3 submission
- Sponsors can start testing anytime 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 (explained in later slides)
- 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

# FDA E2B R3 Core and Regional Data Elements

| Field Identification | | | | ICH Business rules | | | | |
|---|---|---|---|---|---|---|---|---|
| SOURCE | HEADER ELEMENT | DATA ELEMENT NUMBER | DATA ELEMENT NAME | MAX LENGTH | DATA TYPE | VALUE ALLOWED | CONFORMANCE | ICH BUSINESS RULE |

| Post-Market | | IND | | Combo | |
|---|---|---|---|---|---|
| CONFORMANCE | FAERS Business Rule | CONFORMANCE | IND Business Rule | CONFORMANCE | Combo Business Rule |

| NullFlavor Applicable | | | | | | | | Field OIDs |
|---|---|---|---|---|---|---|---|---|
| NI | MSK | UNK | NA | ASKU | NASK | NINF | PINF | Code system OID |

| Xpath | | | |
|---|---|---|---|
| HL7 Data Type | HL7 Data Type (sub component) | Value | Null |

# Questions

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

March 25, 2019

Meredith K. Chuk, M.D.
Acting Associate Director for Safety
Office of Hematology and Oncology Products/OND/CDER/FDA

# Session 2: Electronic Submission of

## IND Safety Reports

# BACKGROUND, IMPLEMENTATION PLANS, STANDARDS, CASE SCENARIOS

# Outline

- Background
- Implementation plans
  - Description of new process
  - Pilot
  - Requirements and timelines for 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

# IND Safety Reports

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

| **Current Process:**<br><br>**PDFs in eCTD format** | **New Process:**<br><br>**ICH E2B XML files to FAERS** |
|---|---|
| • Inefficient and labor intensive review<br><br>• Lack of universal tracking system | • Allows for use of data visualization and analytic tools for review and tracking<br><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) |

# Process Pilot

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

# 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 October 2019
  - Date to be published on FAERS website 30 days prior

[1] Those that contain individual patient data

# Communication Plan

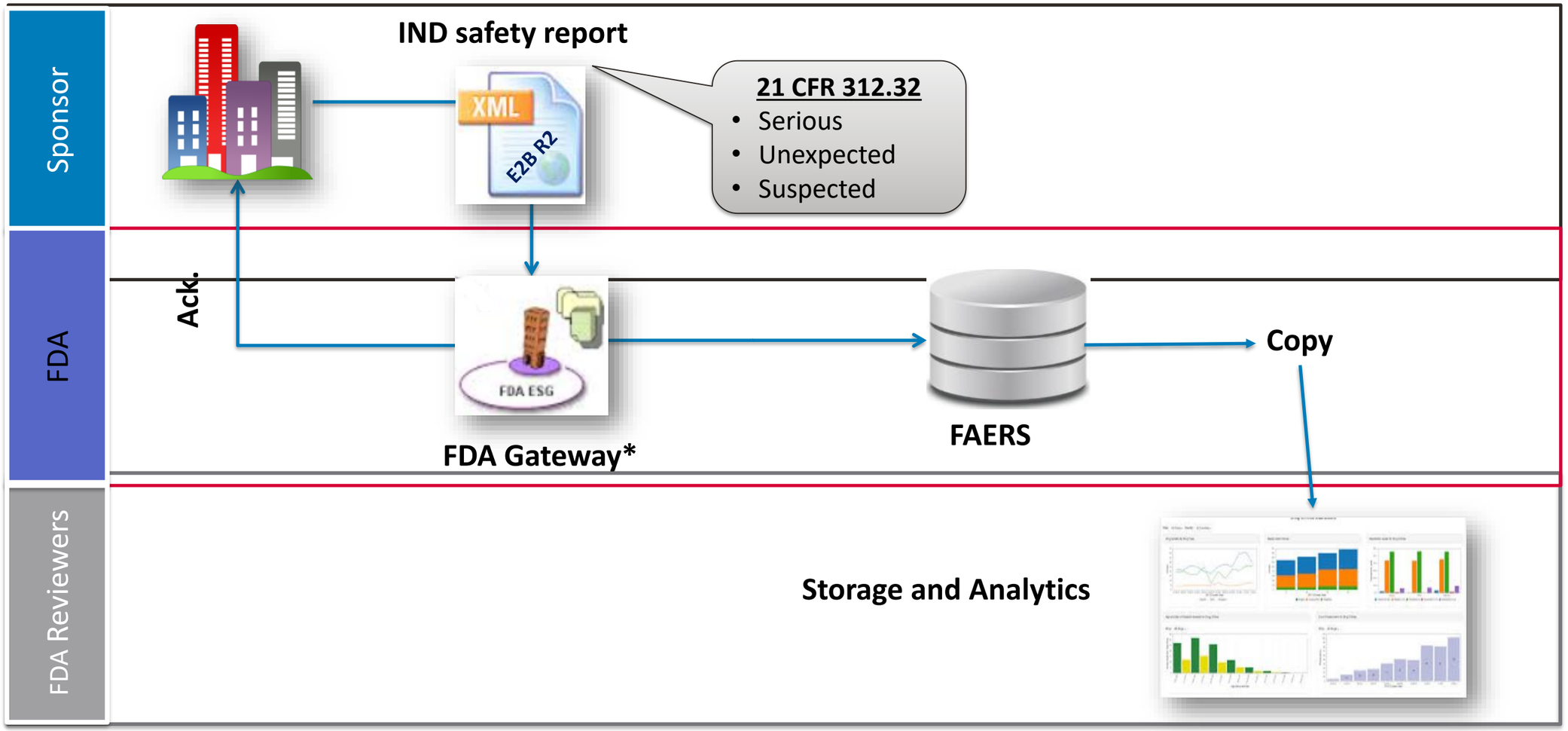
- Draft Guidance with technical conformance guide (TCG) and updated technical specifications to be published together ahead of October 2019

- Updated FAERS website with link to page with information specific to IND safety reports
  - Guidance, TCG, tech specs, use cases, FAQs

- SBIA Webinar

- Other FDA communications

# IND Safety Report Data Flow



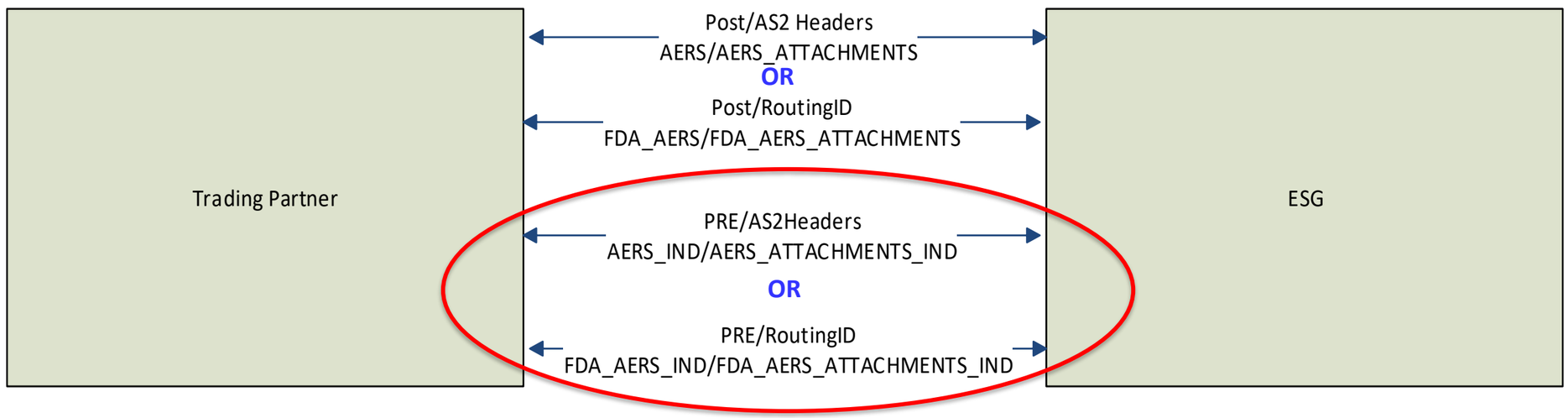

Ack= Acknowledgement
FAERS= FDA Adverse Event Reporting System
*= separate submission path for IND safety reports

**Goal to begin accepting E2B(R2) reports = October 2019**

# Separate Submission Paths for IND and Postmarket Safety Reports

- FDA has defined new header attributes and routing IDs for IND safety reports and attachments

- 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<br>(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<br>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.<br>(21 CFR 312.32(c)(1)(i)(C) | X | |
| Findings from other studies<br>(21 CFR 312.32(c)(1)(ii)) | | X |
| Findings from animal or in vitro testing<br>(21 CFR 312.32(c)(1)(iii)) | | X |
| Increased rate of occurrence of serious suspected adverse reactions<br>(21 CFR 312.32(c)(1)(iv)) | | X |

# Technical Specifications

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

- Data elements for IND number(s)
  - IND number where the event occurred (A.2.3.2)
    - Required to be a valid IND number for processing and routing
  - IND number(s) for cross-referenced IND(s)
    - Repeat only A.2.3.2 and A.2.3.3 as many times as needed for other relevant INDs

*https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM601820.pdf

# Technical Specifications

- E2B(R2) variables for premarket reporting
  - IND number where event occurred
  - Repeat as needed for cross-referenced IND numbers

| Data Element | DTD Descriptor 2.1 | Title | Field Length | Element Values for DTD 2.1 | Notes |
|---|---|---|---|---|---|
| A.2.3.2 | <sponsorstudynumb> | Sponsor Study Number | 35AN | IND Number Under Which the Clinical Trial where the Event Occurred is Conducted<br><br>For 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[1] | Include the Acronym "IND" Followed by a Space and then the IND number for the Application (e.g. IND 123456)<br>Do not populate the Data Element B.4.k.4.1<drugauthorizationnumb> for IND Safety Reports |
| A.2.3.3 | <observestudytype> | Study Type in Which the Reaction(s)/ Event(s) were Observed | 1N | 1= Clinical Trials<br>2= Individual Patient Use (*e.g. ‘Compassionate Use’ or ‘Named Patient Basis’*)<br>3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*)<br>4= Report from Aggregate Analysis 312.32©(1)(i)(C)<br>5= cross-referenced INDs | Required if Element Value for A.1.4 is 2=Report from Study<br><br>If Element Value 4 is Chosen, A.1.9 Should = 1. |

# Technical Specifications

- E2B(R2) variables for premarket reporting
  - Type of report
    - Report from study
  - Expedited criteria
    - New regional data element values (7 and 15 day)
  - Clinical trial identification
    - eCTD study tag name and abbreviated trial name

| 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<br>2=Report from Study<br>3=Other<br>4=Not Available to Sender (unknown) | Use 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<br>2=No<br>4=5-Day<br>5=30-Day<br>6=7-Day | Use Element Values 1 for 15-Day Expedited<br><br>Use Element Values 6 for 7-Day Expedited |
| A.2.3.1 | <studyname> | Study Name | 100AN | Study ID Associated with eCTD, Study Tagging File (STF) As Used in eCTD Submissions Concatenated using "#" with Abbreviated Trial Name | Use the Format eCTD study ID# Abbreviated Trial Name |

# Technical Specifications

- Causality assessment
  - At least one product should be a suspect product
  - Default to sponsor assessment
  - Include investigator assessment in B.5.2
  - Recommend binary response (suspected/not suspected)

| 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 | <drugreactionassesmeddra version> | 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 | | Default to Sponsor and Include Investigator Assessment in B.5.2 |
| B.4.k.18.3 | <drugassessmentmethod> | Method of Assessment | 35AN | | |
| B.4.k.18.4 | <drugresult> | Result | 35AN | 1= Suspected<br>2= Not suspected | |

# Technical Specifications

- Narrative fields
  - Construct narratives that fit within character limitations
  - Rationale for sponsor assessment should be in B.5.4

| Data Element | DTD Descriptor 2.1 | Title | Field Length | Notes |
|---|---|---|---|---|
| B.5.1 | <narrativeincludeclinical> | Case Narrative Including Clinical Course, Therapeutic Measure, Outcome and Additional Relevant Information | 20,000 AN | ICSR Attachments can be Submitted with additional Information that exceeds the character limitations of 20,000 AN though FDA strongly encourages sponsors to construct narratives that fit within E2B character limitations.<br><br>Sponsors should not submit attachments for narratives instead of using this field. |
| B.5.4 | <sendercomment> | Sender's comments | 2000 AN | Rationale for Sponsor's causality assessment should be in this field |

# Technical Specifications

- Investigational product identification
  - Active substance, product information

| Data Element | DTD Descriptor 2.1 | Title | Field Length | Notes |
|---|---|---|---|---|
| B.4.k.2.1 | <medicinalproduct> | Proprietary Medicinal Product Name | 70AN | 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 Name | 100AN | |

# Technical Specifications

- Reports from aggregate analysis
  - One ‘index’ report with individual ICSRs linked to this report
  - Use ‘parent IND’ number as primary IND
  - New regional data values for study type
  - Patient identifier is ‘aggregate’

| Data Element | DTD Descriptor 2.1 | Title | Field Length | Element Values for DTD 2.1 | Notes |
|---|---|---|---|---|---|
| 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) |
| A.2.3.2 | <sponsorstudynumb> | Sponsor Study Number | 35AN | IND Number Under Which the Clinical Trial where the Event Occurred is Conducted<br><br>For 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 | Include the Acronym "IND" Followed by a Space and then the IND number for the Application (e.g. IND 123456)<br>Do not populate the Data Element B.4.k.4.1<drugauthorizationnumb> for IND Safety Reports |
| A.2.3.3 | <observestudytype> | Study Type in Which the Reaction(s)/ Event(s) were Observed | 1N | 1= Clinical Trials<br>2= Individual Patient Use (*e.g. ‘Compassionate Use’ or ‘Named Patient Basis’*)<br>3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*)<br>4= Report from Aggregate Analysis 312.32(c)(1)(i)(C) | Required if Element Value for A.1.4 is 2=Report from Study<br><br>If Element Value 4 is Chosen, A.1.9 Should = 1. |
| B.1.1 | <patientinitial> | Patient Identifier | 10AN | | For a Report from an Aggregate Analysis, The Element Value Should Be “AGGREGATE” |

# Benefits to Industry

- Efficiency gains in processing and submission
  - Direct electronic submission to FDA from PV
    - no 1571 or cover letter
  - Ability to automate submission compliance and tracking within safety database
  - Eliminates need to send duplicate reports

- More comprehensive and structured formatting 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 | Field Length | Element Values for DTD 2.1 | Notes |
|---|---|---|---|---|---|
| A.2.3.2 | <sponsorstudynumb> | Sponsor Study Number | 35AN | IND Number Under Which the Clinical Trial where the Event Occurred is Conducted | 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<br>2= Individual Patient Use (*e.g. 'Compassionate Use' or 'Named Patient Basis'*)<br>3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*)<br>4= Report from Aggregate Analysis 312.32(c)(1)(i)(C)<br>5=Cross-referenced IND safety report | Required if Element Value for A.1.4 is 2=Report from Study<br><br>If Element Value 4 is Chosen, A.1.9 Should = 1. |

- Block A.2 is repeatable
  - Use first block to designate IND where event occurred
    - 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-referenced IND

# Case Scenario 2

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

| Data Element | DTD Descriptor | Suspect drug is drug A only | Suspect drug is drug B or C only and report meets IND safety reporting requirements (21 CFR 312.32) | Suspect drug is drug B and C and report meets IND safety reporting requirements (21 CFR 312.32) |
|---|---|---|---|---|
| B.4.k.2.1 | <medicinalproduct> | Company code<br><br>OR<br><br>Proprietary medicinal product name for drug A | Proprietary medicinal product name for drug B or C | Field should be populated twice as follows:<br>Proprietary medicinal product name for drug B and C |
| B.4.k.2.2 | <activesubstancename> | Active drug substance name for drug A | Active drug substance name for drug B or C | Field should be populated twice as follows:<br>Active drug substance name for drug B and/or C |
| A.2.3.2. | <sponsorstudynumb> | IND number under which the clinical trial where the event occurred is conducted | | |

# Case Scenarios 3

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

| Data Element | DTD Descriptor | Suspect drug is drug A only | Suspect drug is drug B and/or C only and report meets IND safety reporting requirements (21 CFR 312.32) | Suspect drug is all 3 drugs and meets IND safety reporting requirements (21 CFR 312.32) for drugs B and C |
|---|---|---|---|---|
| B.4.k.2.1 | <medicinalproduct> | Company code<br><br>OR<br><br>Proprietary medicinal product name for drug A | Field may be repeated twice as follows:<br>Proprietary medicinal product name for drug B and/or C | Field should be repeated three times as follows:<br>Company code or Proprietary medicinal product name for drug A and Proprietary medicinal product name for drugs B and C |
| B.4.k.2.2 | <activesubstancename> | Active drug substance name for drug A | Field may be repeated twice as follows: Active drug substance name for drug B and/or C | Field should be repeated three times as follows:<br>Active drug substance name for drug A, B and C |
| A.2.3.2. | <sponsorstudynumb> | IND number under which the clinical trial where the event occurred is conducted | | |

# Case Scenarios 4

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

| Data Field | DTD Descriptor | Suspect drug is drug A only | Suspect drug is drug B and report meets IND safety reporting requirements (21 CFR 312.32) | Suspect drug is A and drug B and report meets IND safety reporting requirements for drug B (21 CFR 312.32) |
|---|---|---|---|---|
| B.4.k.2.1 | <medicinalproduct> | Proprietary medicinal product name for drug A | Proprietary medicinal product name for drug B | Field should be repeated twice as follows:<br>Proprietary medicinal product name for drug A and B |
| B.4.k.2.2 | <activesubstancename> | Active drug substance name for drug A | Active drug substance name for drug B | Field should be repeated twice as follows:<br>Active drug substance name for drug A and B |
| A.2.3.2. | <sponsorstudynumb> | IND number under which the clinical trial where the event occurred is conducted | | |

# Questions

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

March 25, 2019

TJ Chen

Project Manager

# 15 min Break

## Session 2: Up versioning to ICH E2B R3 Regional requirements

# ICH E2B UP VERSIONING

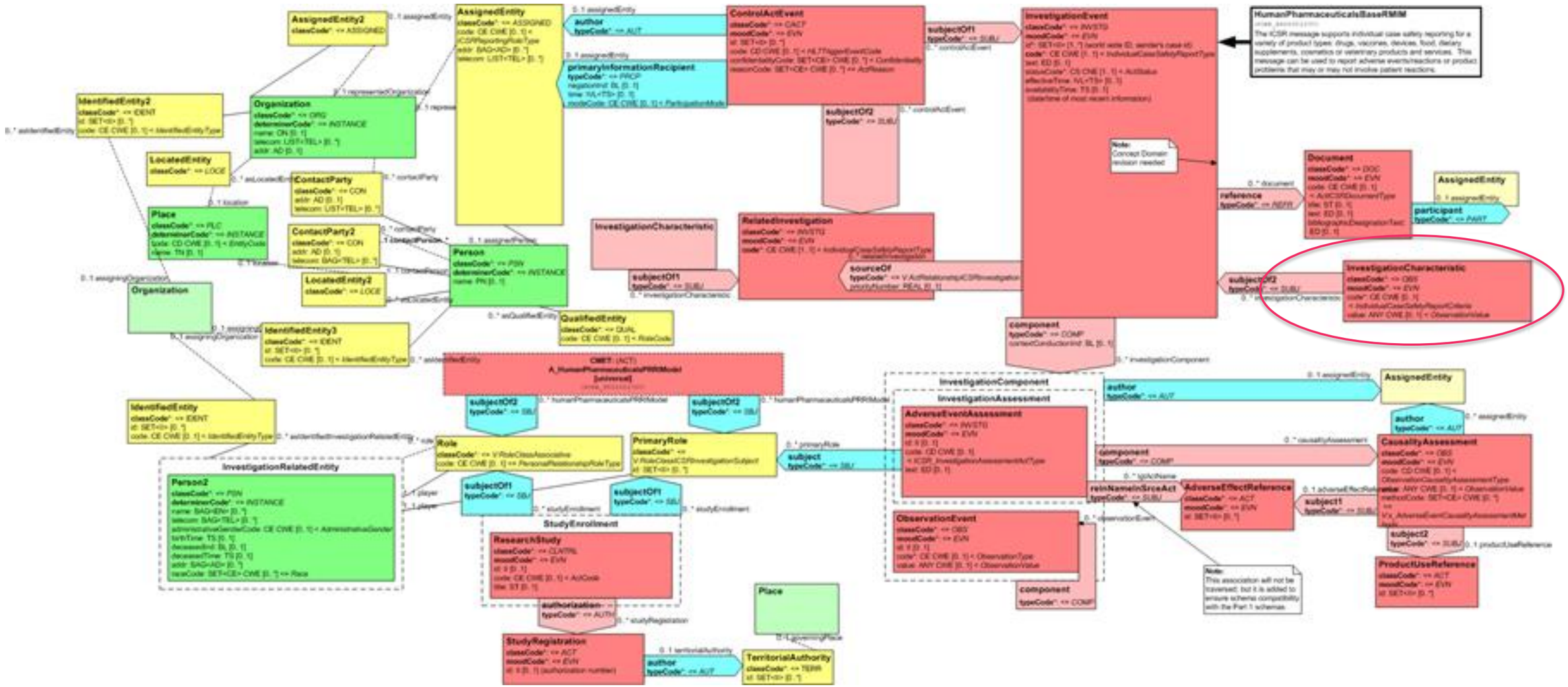
# ICH E2B Up Versioning Resource

- ICH E2B(R3) IG Package
  - http://estri.ich.org/e2br3/E2B(R3)_IG_Complete_Package_v1_07.zip
  - Appendix I (B) ICH ICSR Backwards and Forwards Compatibility (BFC) Recommendations
  - Appendix I (H) ICH ICSR BFC conversion

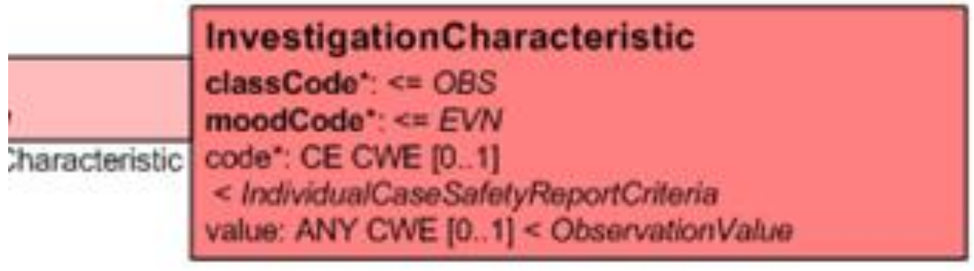
# Administrative and Identification Elements

| R2 Element | R2 Element Name | Data Type | Element Values for DTD 2.1 | R3 Element | R3 Element Name | Data Type | Element Values |
|---|---|---|---|---|---|---|---|
| A.1.9 | Does This Case Fulfill the Local Criteria for an Expedited Report? | 1N | 1=yes (expedited)<br>2=no (non-expedited)<br>4=5-Day<br>5=30-Day | C.1.7 | Does This Case Fulfil the Local Criteria for an Expedited Report? | Boolean | False, True, NI |
| | | | | FDA.C.1.7.1 | FDA Report Type (MedWatch G.7) | 1N | 1=15-Day<br>2=Periodic<br>4=5-Day<br>5=30-Day<br>6=7-day |
| A.1.0.1 | Sender's (case) Safety Report Unique Identifier (safety report identifier) | 100AN | Manufacturer Control Number (MCN) | C.1.1 | Sender's (case) Safety Report Unique Identifier | 100AN | |
| A.1.10.1 | Regulatory Authority's Case Report Number | 100AN | | C.1.8.1 | Worldwide Unique Case Identification Number | 100AN | |
| A.1.10.2 | Other Sender's Case Report Number | 100AN | | C.1.8.2 | First Sender of This Case | 1N | 1=Regulator<br>2=Other |
| A.3.1.2 | Sender Identifier (sender organization) | 60AN | | C.3.2 | Sender's Organisation | 100AN | |

# FDA Report Type and Combination Product Flag



# HL7 Observation Class and CE Data Type



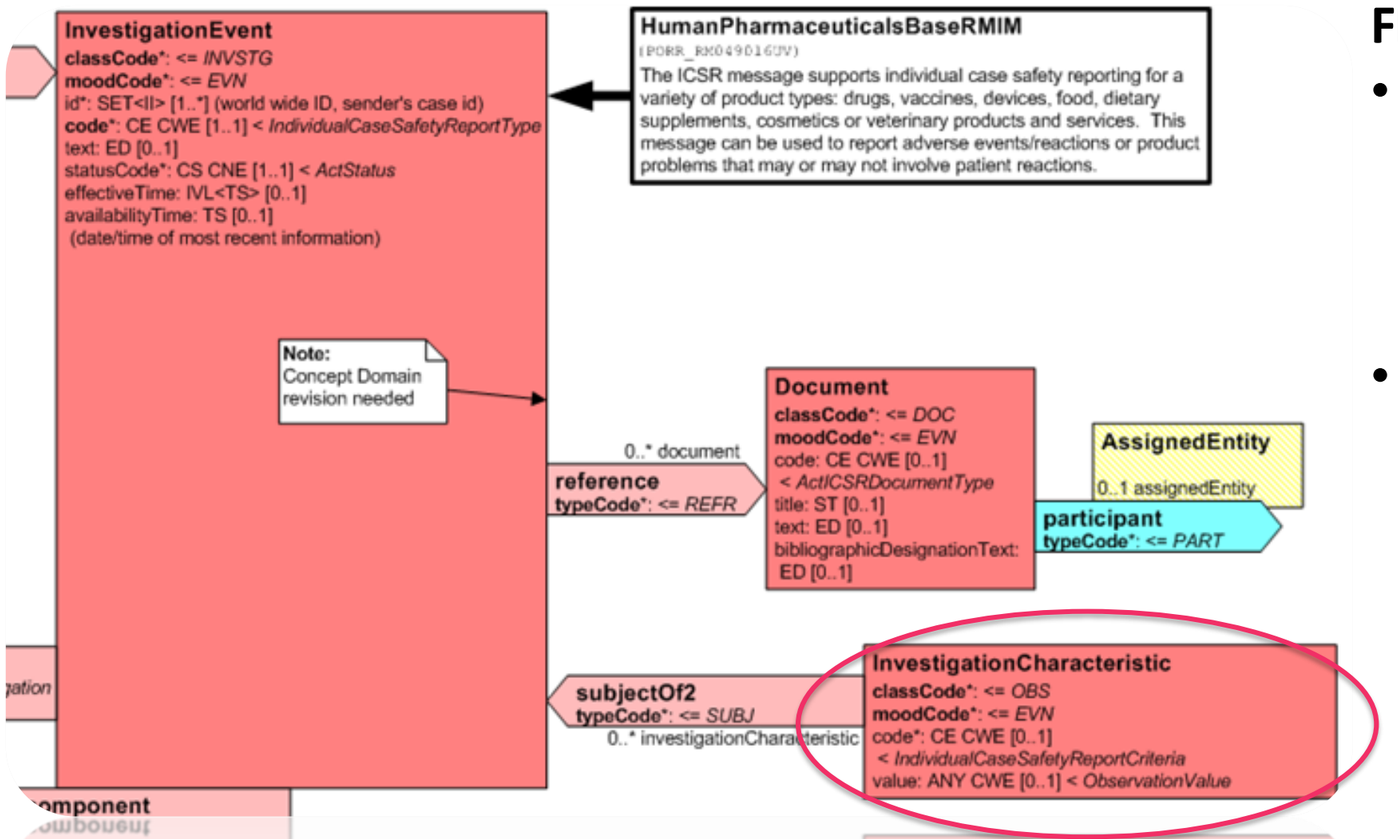

InvestigationCharacteristic

- 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>

# FDA Report Type Data Elements

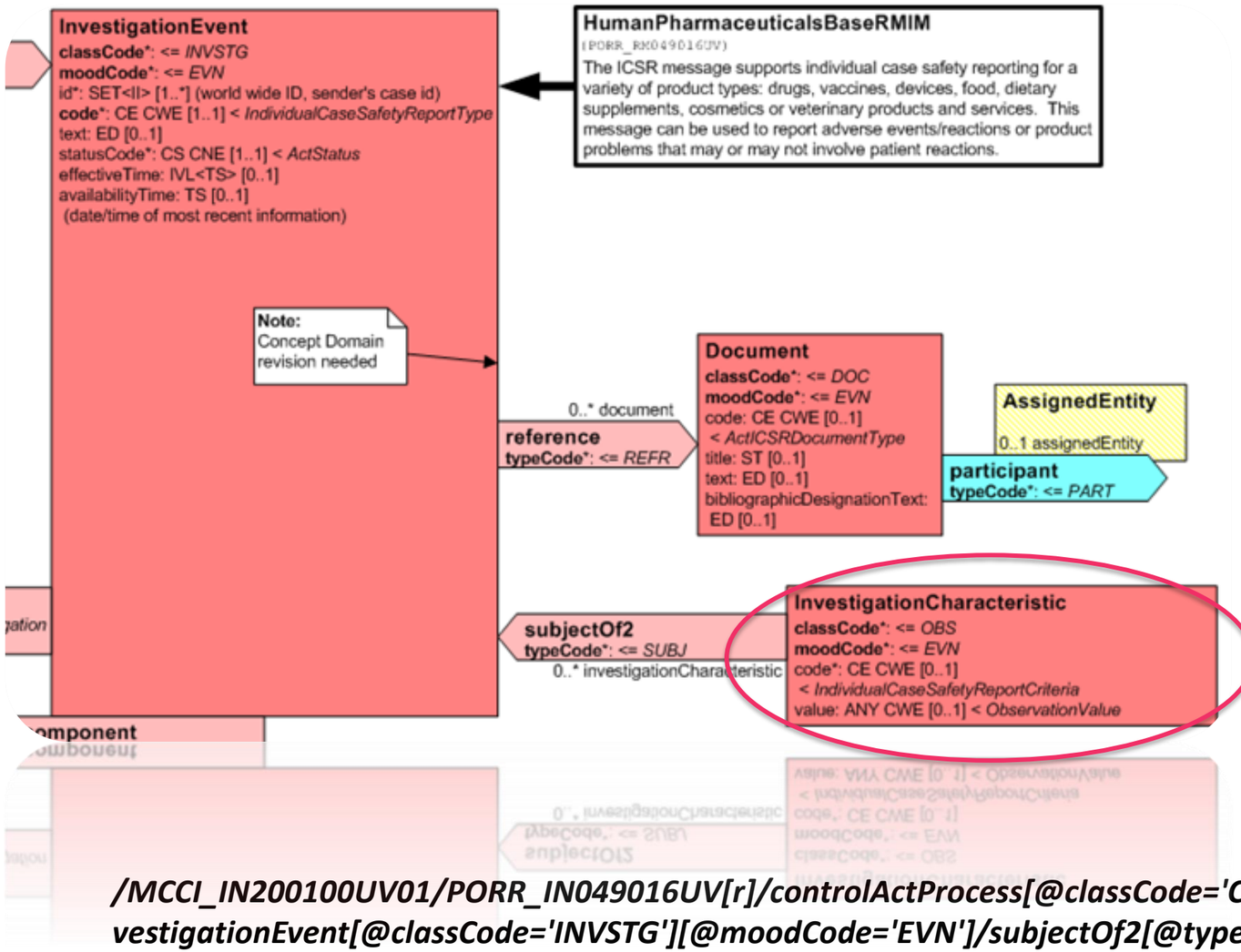



**FDA.C.1.71.1**

- InvestigationCharacteristic.code (CE)
  - codeSystem=2.16.840.1.113883.3.989.5.1.2 (FDA OID)
  - code=n1 (FDA Report Type)
- InvestigationCharacteristic.value (CE)
  - codeSystem=2.16.840.1.113883.3.989.5.1.2.n1 (FDA Report Type)
  - Code
    - 1=15-Day
    - 2=Periodic
    - 4=5-Day
    - 5=30-Day
    - 6=7-day

***/MCCI_IN200100UV01/PORR_IN049016UV[r]/controlActProcess[@classCode='CACT'][@moodCode='EVN']/subject[@typeCode='SUBJ'][1]/investigationEvent[@classCode='INVSTG'][@moodCode='EVN']/subjectOf2[@typeCode='SUBJ'][investigationCharacteristic/code[@code='n'][@codeSystem='2.16.840.1.113883.3.989.5.1.2']][1]/investigationCharacteristic[@classCode='OBS'][@moodCode='EVN']/value[@xsi:type='CE'][@codeSystem=2.16.840.1.113883.3.989.5.1.2.n']/@code***

# Combination Product Flag




**FDA.C.1.71.12**

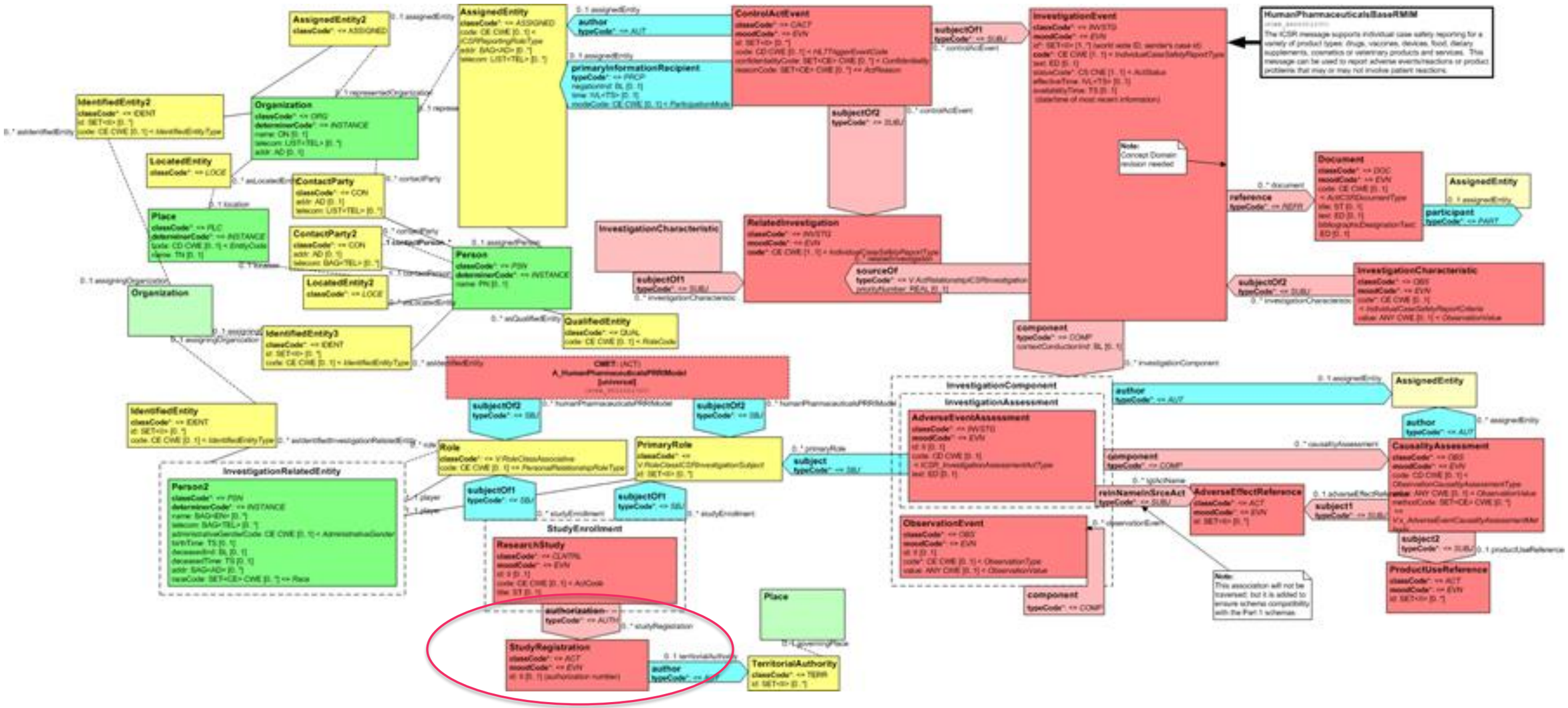
- InvestigationCharacteristic.code (CE)
  - codeSystem=2.16.840.1.11388 3.3.989.5.1.2 (FDA OID)
  - code=n2 (Combination Product Flag)
- InvestigationCharacteristic.value (Boolean)
  - True
  - false

***/MCCI_IN200100UV01/PORR_IN049016UV[r]/controlActProcess[@classCode='CACT'][@moodCode='EVN']/subject[@typeCode='SUBJ'][1]/investigationEvent[@classCode='INVSTG'][@moodCode='EVN']/subjectOf2[@typeCode='SUBJ'][investigationCharacteristic/code[@code='n'][@codeSystem='2.16.840.1.113883.3.989.5.1.2']][1]/investigationCharacteristic[@classCode='OBS'][@moodCode='EVN']/value[@xsi:type='BL']/@value***

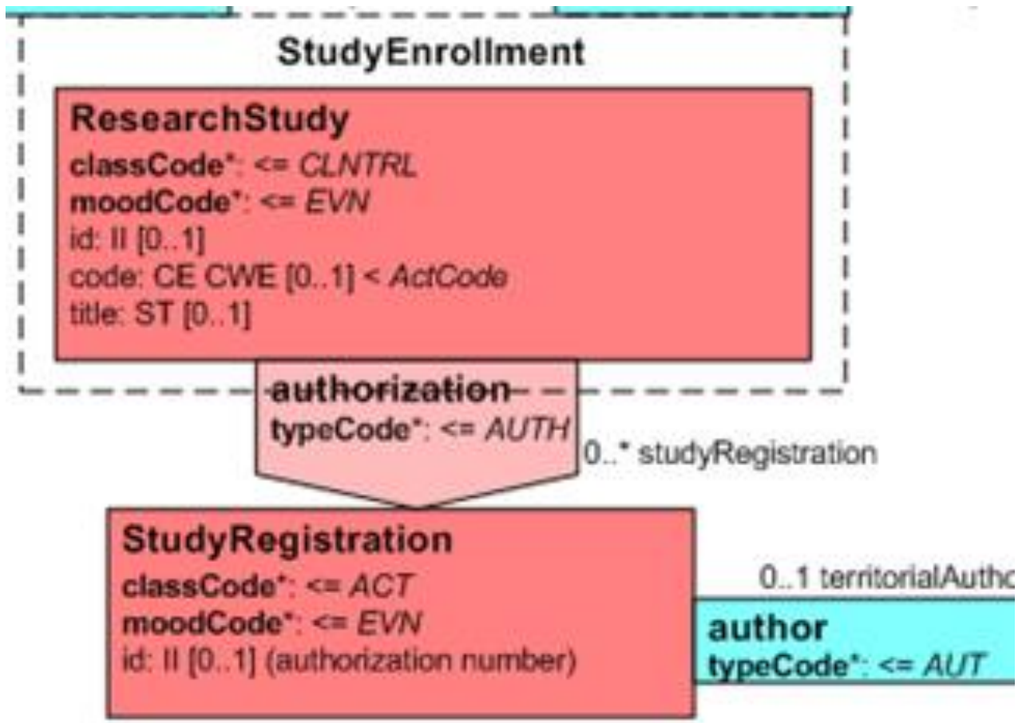
# Administrative and Identification Elements for IND Safety Report

| R2 Element | R2 Element Name | Data Type | Element Values for DTD 2.1 | R3 Element | R3 Element Name | Data Type | Values |
|---|---|---|---|---|---|---|---|
| A.1.4 | Type of report | 1N | 1=Spontaneous<br>2=Report from study<br>3=Other<br>4=Not available to sender (unknown) | C.1.7 | Type of report | 1N | 1=Spontaneous<br>2=Report from study<br>3=Other<br>4=Not available to sender (unknown) |
| A.2.3.1 | Study name | 100AN | | C.5.2 | Study name | 2000AN | Study ID Associated with eCTD, study tagging file (STF) concatenated with abbreviated trial name using "#" |
| A.2.3.3 | Study type in which the reaction(s)/event (s) were observed | 1N | | C.5.4 | Study type where reaction(s)/event(s) were observed | 1N | 1=Clinical trials<br>2=Individual patient use(e.g. 'compassionate use' or 'named patient basis')<br>3=Other studies (e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring)<br>Required if Element Value for A.1.4 is 2=Report from study |
| A.2.3.2 | Sponsor study number | 35AN | IND number under which the clinical trial where the event occurred is conducted | FDA.C.5.5 | IND or PANDA # where AE Occurred | 10AN | IND number under which the clinical trial where the event occurred is conducted |
| | | | | FDA.c.5.r.6 | IND # for other INDs with same suspect product | 10AN | Repeatable |

# IND Number


AssignedEntity2
AssignedEntity
author
primaryInformationRecipient
ControlActEvent
subjectOf1
InvestigationEvent
HumanPharmaceuticalsBaseRMIM
IdentifiedEntity2
Organization
LocatedEntity
ContactParty
Place
ContactParty2
Person
LocatedEntity2
Organization
IdentifiedEntity3
QualifiedEntity
subjectOf2
InvestigationCharacteristic
RelatedInvestigation
sourceOf
Note:
Concept Domain
revision needed
Document
reference
participant
AssignedEntity
component
InvestigationComponent
InvestigationAssessment
AdverseEventAssessment
ObservationEvent
CausalityAssessment
AdverseEffectReference
ProductUseReference
reinNamelnSrceAct
Note:
This association will not be
traversed, but it is added to
ensure schema compatibility
with the Part 1 schemas.
IdentifiedEntity
InvestigationRelatedEntity
Person2
Role
PrimaryRole
subject
StudyEnrollment
ResearchStudy
authorization
StudyRegistration
Place
TerritorialAuthority

# HL7 Act Class and II Data Type



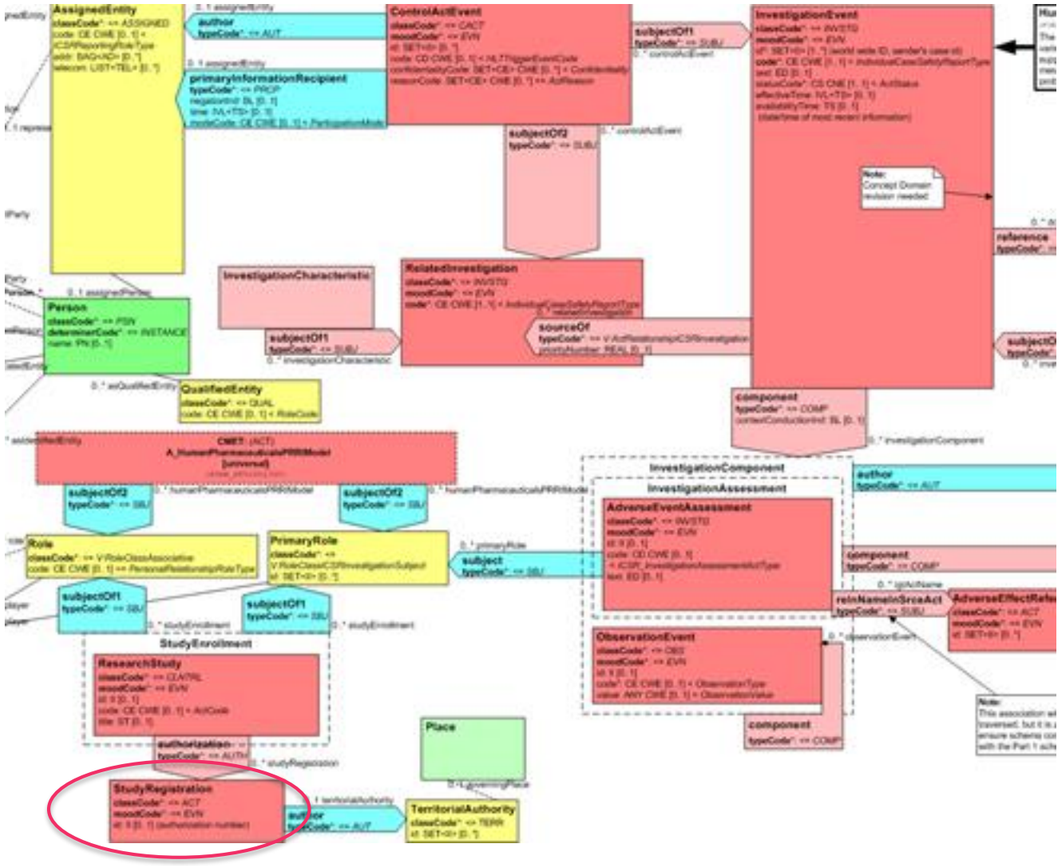

StudyRegistration

- 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

# IND Numbers Data Elements




**FDA.C.5.5 IND or PANDA # where AE Occurred**

- observationEvent.id (II)
  - root=2.16.840.1.113883.3.989.5.1.2.m1 (IND where AE Occurred)
  - extension=IND or PANDA # (where AE Occurred)

**FDA.C.5.6r IND # for INDs with same suspect product**

- observationEvent.id (II)
  - root= 2.16.840.1.113883.3.989.5.1.2.m2 (FDA-OID for IND where AE Occurred)
  - extension=IND # (other INDs)
- repeatable

***/MCCI_IN200100UV01/PORR_IN049016UV[r]/controlActProcess[@classCode='CACT'][@moodCode='EVN']/subject[@typeCode='SUBJ'][1]/investigationEvent[@classCode='INVSTG'][@moodCode='EVN']/component[@typeCode='COMP'][adverseEventAssessment][1]/adverseEventAssessment[@classCode='INVSTG'][@moodCode='EVN']/subject1[@typeCode='SBJ'][1]/primaryRole[@classCode='INVSBJ']/subjectOf1[@typeCode='SBJ'][1]/researchStudy[@classCode='CLNTRL'][@moodCode='EVN']/authorization[@typeCode='AUTH'][r]/studyRegistration[@classCode='ACT'][@moodCode='EVN']/id[@root= 2.16.840.1.113883.3.989.5.1.2.m2 ]/@extension***

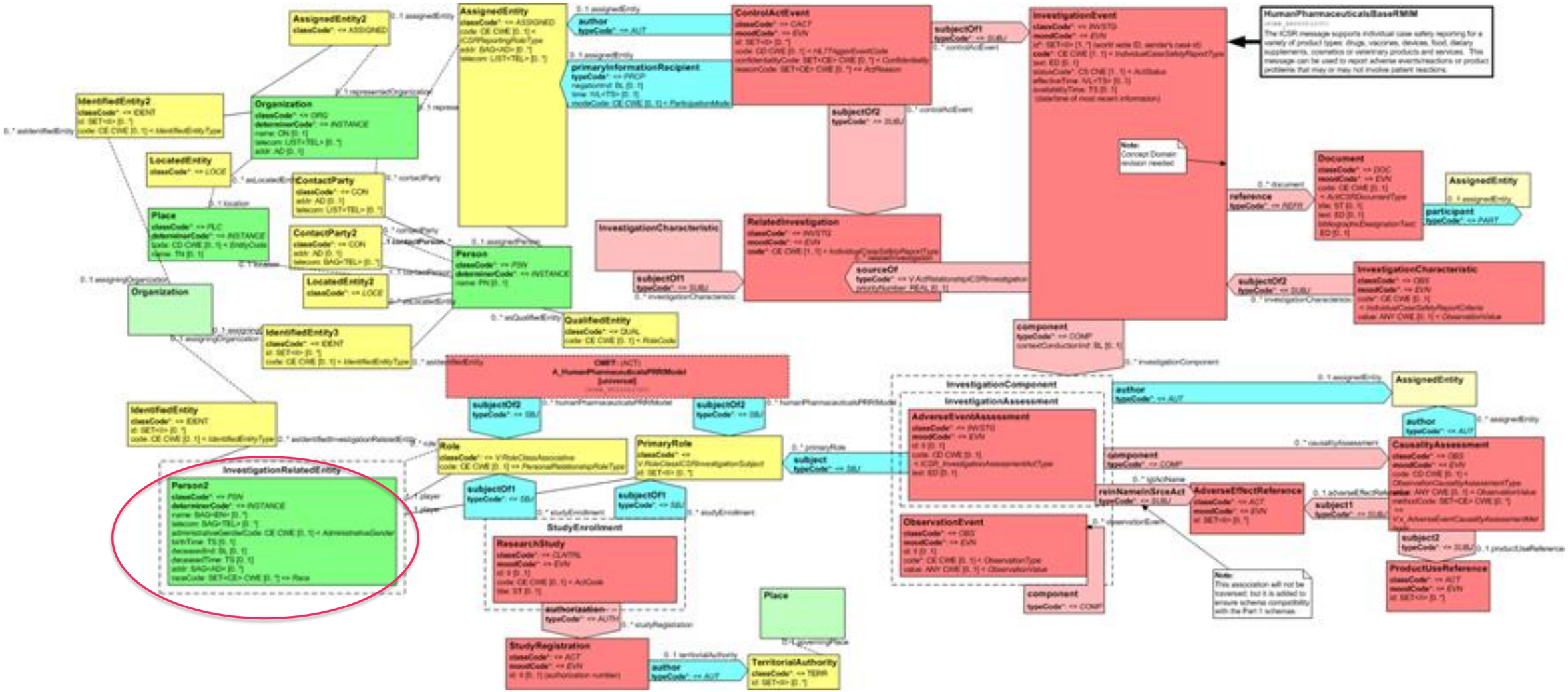
# Street Address 2 & Email

- Street Address Line 2 (Reporter, Sender)
  - HL7 Postal Address (AD)
    - Specializes LIST<ADXP>

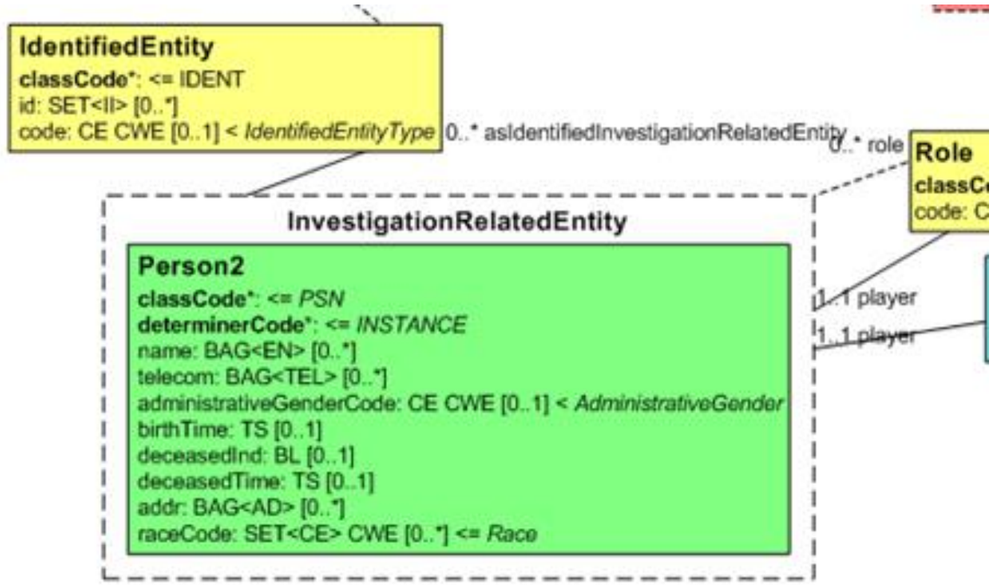
<addr>
<streetAddressLine>10903 New Hampshire Avenue</streetAddressLine>
<streetAddressLine >White Oak Building 1</streetAddressLine>
<city>Silver Spring</city>
<state>MD</state>
<postalCode>20993</postalCode>
</addr>

- Reporter's Email
  - HL7 Telecommunication Address (TEL)
    - Specializes URL
  - Same construct as C.3.4.8: Sender's E-Mail Address
    - <telecom value="**mailto:xxx@xxxxx.gc.ca**"/>

# Patient Race



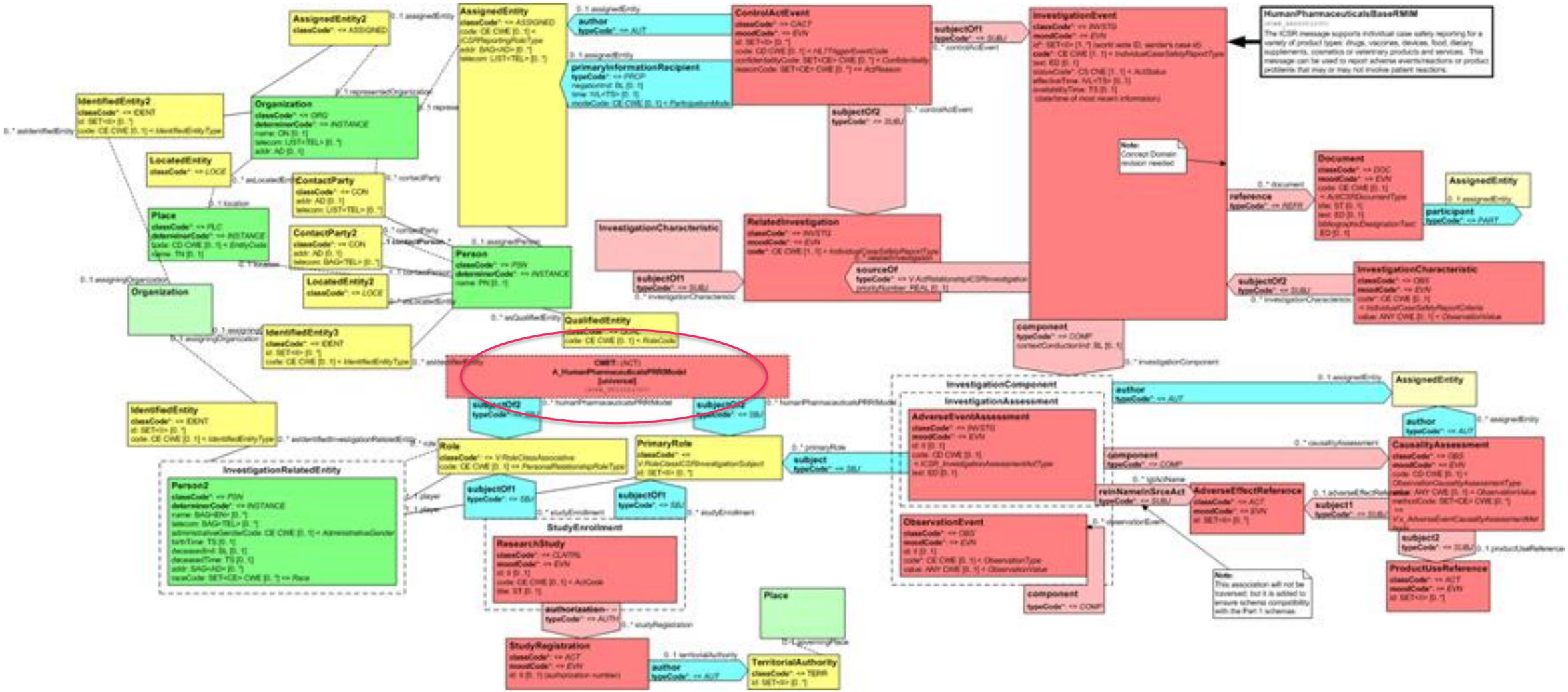
# Patient Race Code



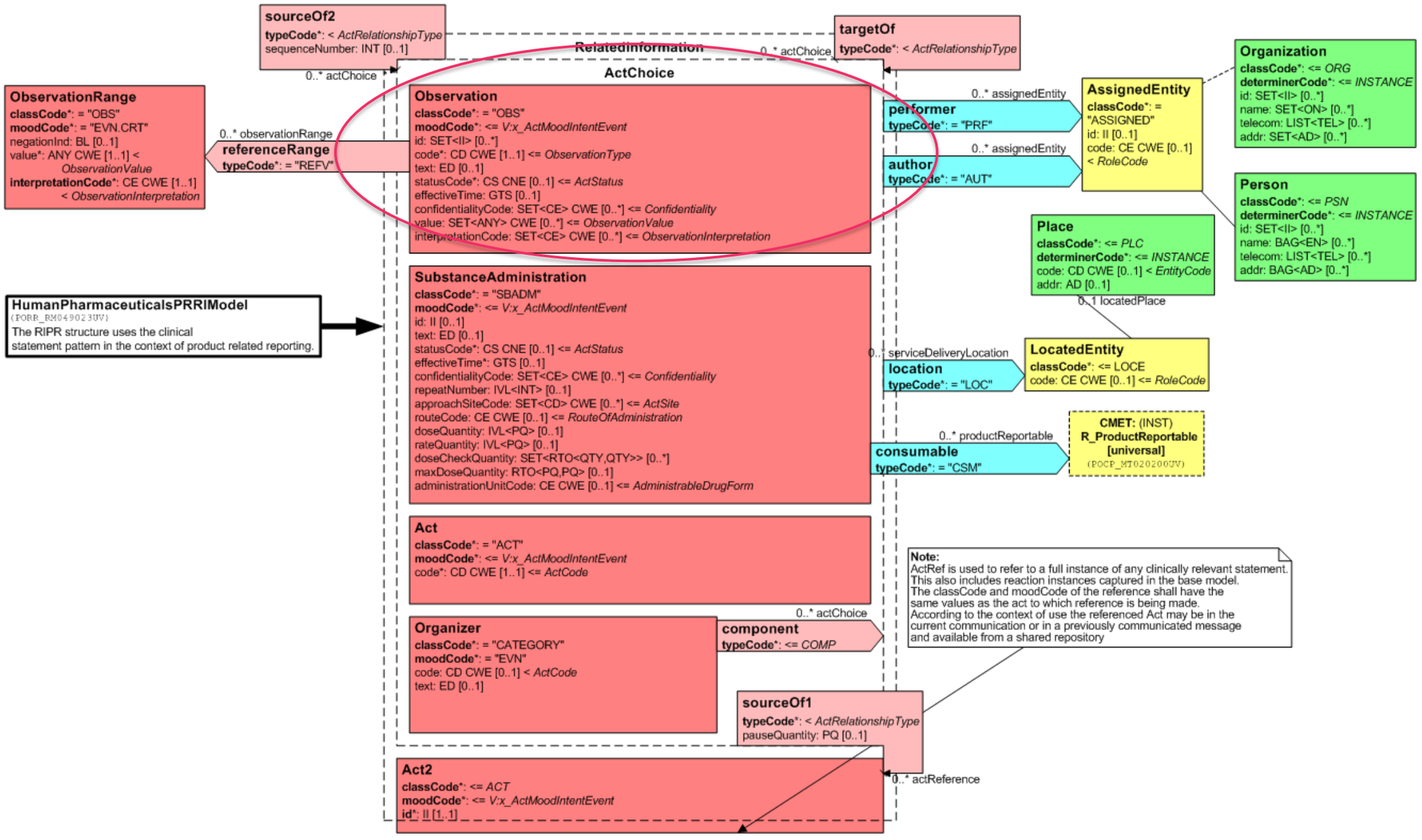

- raceCode exist in the RIMM
  - SET <CE>
- NCI Thesaurus (2.16.840.1.113883.3.26.1.1)
  - C16352 = African American
  - C41259 = American Indian or Alaska Native
  - C1260 = Asian
  - C1219 = Native Hawaiian or Other Pacific Islander
  - C41261 = White

/MCCI_IN200100UV01/PORR_IN049016UV[r]/controlActProcess[@classCode='CACT'][@moodCode='EVN']/subject[@typeCode='SUBJ'][1]/investigationEvent[@classCode='INVSTG'][@moodCode='EVN']/component[@typeCode='COMP'][adverseEventAssessment][1]/adverseEventAssessment[@classCode='INVSTG'][@moodCode='EVN']/subject1[@typeCode='SBJ'][1]/primaryRole[@classCode='INVSBJ']/subjectOf2[@typeCode='SBJ'][observation/code[@code='C17049'][@codeSystem='2.16.840.1.113883.3.26.1.1']][1]/observation[@classCode='OBS'][@moodCode='EVN']/value[@xsi:type='CE'][@codeSystem='2.16.840.1.113883.3.26.1.1'][1]/@code

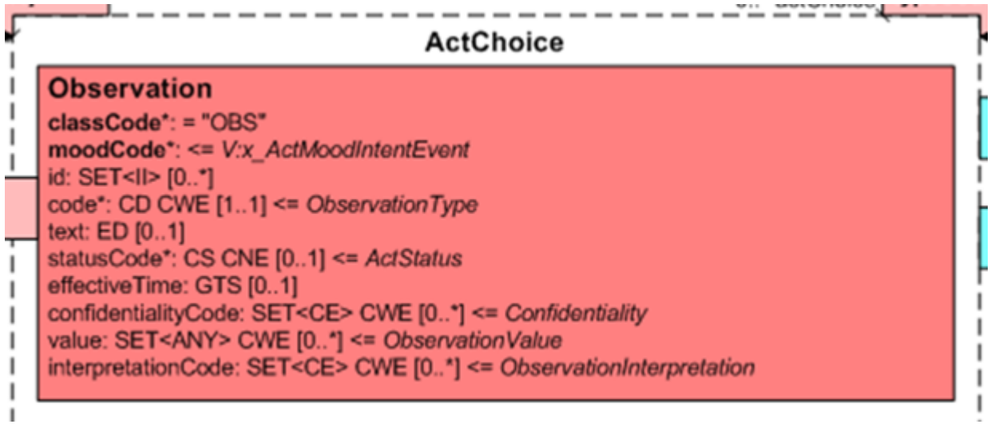
# Patient Ethnicity



# Patient Ethnicity



# Patient Ethnicity Code




- ethnicity not exist in the RIMM
- Use Observation Class
  - Observation.code
    - codeSystem – TBD  (FDA or NCIt)
    - Code – TBD (FDA or NCIt)
  - Observation.value
    - Data type CE
    - codeSystem=2.16.840.1.113883.3.26.1.1 (nCIt)
    - Code -
      - C17459 = Hispanic or Latino
      - C41222 = Non Hispanic or Latino

/MCCI_IN200100UV01/PORR_IN049016UV[r]/controlActProcess[@classCode='CACT'][@moodCode='EVN']/subject[@typeCode='SUBJ'][1]/investigationEvent[@classCode='INVSTG'][@moodCode='EVN']/component[@typeCode='COMP'][adverseEventAssessment][1]/adverseEventAssessment[@classCode='INVSTG'][@moodCode='EVN']/subject1[@typeCode='SBJ'][1]/primaryRole[@classCode='INVSBJ']/subjectOf2[@typeCode='SBJ'][observation/code[@code='C16564'][@codeSystem='2.16.840.1.113883.3.26.1.1']][1]/observation[@classCode='OBS'][@moodCode='EVN']/value[@xsi:type='CE'][@codeSystem='2.16.840.1.113883.3.26.1.1'][1]/@code

# Receiver Information

- E2B(R2) batch level information maps to E2B(R3) N.1.x
- E2B(R2) message Level limited to N.2.r.3 in R3

| R2 Element | Code or Text |
|---|---|
| A.3.2.1 | 2 |
| A.3.2.2a | FDA |
| A.3.2.2b | Office of Surveillance and Epidemiology |
| A.3.2.2d | FAERS |
| A.3.2.3a | 10903 New Hampshire Avenue |
| A.3.2.3b | Silver Spring |
| A.3.2.3c | MD |
| A.3.2.3d | 20993 |
| A.3.2.3e | US |
| A.3.2.3l | faersesub@fda.hhs.gov |

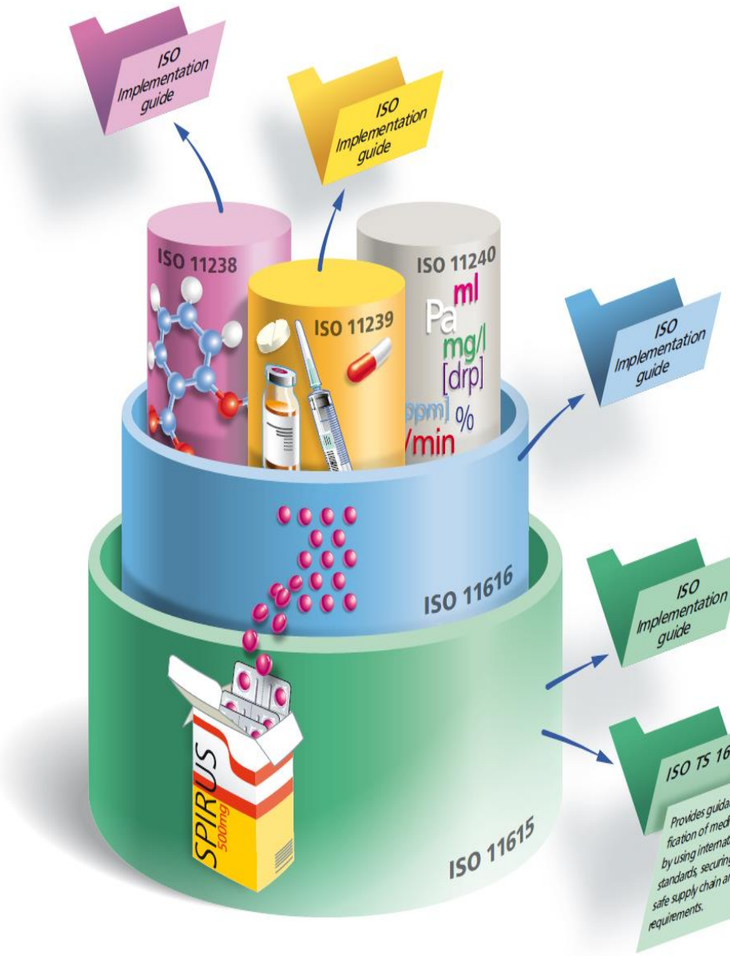
# Object Identifier (OID)

- An *Object Identifier* (OID) is a sequence of numbers to uniquely identify an object.
- The root of the tree contains the following three arcs:
  - 0: ITU-T
  - 1: ISO
  - 2: joint-iso-itu-t
- The numbers represent a hierarchically-assigned namespace.
- These numbers are written either as a string of digits separated by dots or as a list of named ‘branches.’
  - 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)

# What is IDMP?

The Identification of Medicinal Product (IDMP) is a suite of five ISO standards that:

- Defines the data elements and structure to **uniquely** and **unambiguously** identify medicinal product, Pharmaceutical Product, and substance
- Creates **common vocabulary** for improved people communication
- Creates **common messaging** standards for improved IT system communication




- ISO 11615 – Medicinal Product Identification
- ISO 11616 – Pharmaceutical Product Identification
- ISO 11238 – Substance Identification
- ISO 11239 – Pharmaceutical dose forms, units of presentation and routes of administration
- ISO 11240 – Units of measurement

# Medicinal Product Identification

- ISO 11615 - Establishes definitions and concepts and describes data elements and their structural relationships, which are required for the unique identification and the detailed description of Medicinal Products.


- Primary Identification of Medicinal Products
  - **MPID** – Medicinal Product Identifier
    - **Country Code + Marketing Authorization Holder + Product Code**
  - **PCID** – Medicinal Product Package Identifier
    - MPID + **Package Description Code**
  - **BAID_1** – Medicinal Product Batch Identifier (*Outer Packaging*)
    - PCID + **Batch Number + Expiration Date (ISO 8601 date format)**
  - **BAID_2** - Medicinal Product Package Batch Identifier (*Immediate Packaging*)
    - PCID + **Batch Number + Expiration Date (ISO 8601 date format)**

NDC
labeler
product
package

# Pharmaceutical Product Identification

- ISO 11616 - Provides specific levels of information relevant to the identification of a medicinal product or group of (***pharmaceutically equivalent/similar***) medicinal products

- Derived ID based on the following subset of elements:
  - Substance(s)/Specified Substance(s)
  - Strength(s) & Strength units
  - Administrable Dose Form(s)

- PhPID Set
  - ***PhPID_SUB_L1*** *Active Substance(s)*
  - ***PhPID_ SUB _L2*** *Active Substance(s)+Strength*
  - ***PhPID_ SUB _L3*** *Active Substance(s) + Administrable Dose Form*
  - ***PhPID_ SUB _L4*** *Active Substance(s)+ Strength + Administrable Dose Form*

# Linking Medicinal Product



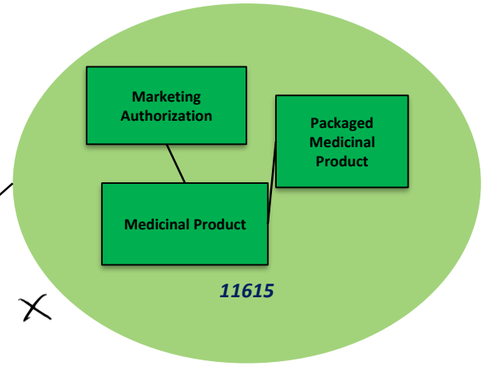


*Acetaminophen = Paracetamol*





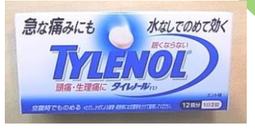






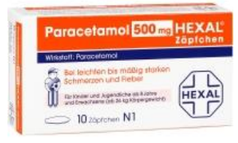












# Break for Lunch

# 60 min

# Session 3: Electronic submission of Post-marketing safety report

# REGIONAL REQUIREMENT

# Regional Requirement

- FDA's technical approach for submitting ICSRs, for incorporating its regionally controlled terminology and for adding regional data elements that are not addressed in the ICH E2B (R3) Implementation Guideline (IG) for the following FDA-regulated products:
  - Drug products marketed for human use with approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs)
  - Investigational drug and biologic products for human use under an Investigational New Drug (IND)
  - Prescription drug products marketed for human use without an approved application
  - Nonprescription (over-the-counter human drug products marketed without an approved application)
  - Biological products marketed for human use with approved biologic license applications (BLAs).

# Regional Requirement

- “FDA Regional Implementation Specifications for ICH E2B(R3) Implementation: Postmarket Submission of Individual Case Safety Reports (ICSRs) for Drugs and Biologics, Excluding Vaccines” posted on June 23, 2016
- Follow core ICH E2B R3 with a few regional requirements
- Regional Elements (next slides)

# Regional Requirement

***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 Identifier1.3.6.1.4.1.519.1. The DUNS number for Business Entity Identifiers is used to validate business entities in various FDA information systems.

# Regional Requirement

***Message Receiver Identifier N.2.r.3***

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_IND
  - For Production ICSR Submissions: ZZFDA_IND

Consideration for Center designation

Premarket

ZZFDA_CDER_IND

ZZFDA_CBER_IND

# Regional Requirement

***Data Element Conformance***

- FDA supports the ICH E2B(R3) data element conformance categories (e.g., required or optional) described in the ICH E2B(R3) IG
- FDA data element conformance may vary due to regional regulatory specifications not addressed in the ICH E2B(R3) IG
- These exceptions are noted in the next few slides

# Regional Requirement

## ***Terminology***

- FDA supports Medical Dictionary for Regulatory Activities (MedDRA) for coding of clinical and laboratory terms.
  - When possible, use the Lowest Level Term (LLT) and record the LLT as the MedDRA numeric code rather than the LLT name
  - e.g., the LLT name is Rash; the MedDRA numeric code for LLT Rash is 10378444)
  - Stakeholders should refer to the ICH E2B(R3) IG for data elements that specify the use of MedDRA coding.

# Regional Requirement

## *Terminology*

- FDA supports the use of constrained Unified Codes for Units of Measurement (UCUM) for coding units of measure (e.g., medication dosing units).
- FDA regional terminology supports the controlled terminology of the U.S. National Cancer Institute (NCI), the EVS, and the FDA's Global Substance Registration System (GSRS).
- FDA supports the use of EDQM Dosage Form and Route of Administration

# Regional Requirement

***Section C: Identification of the Case Safety Report***

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

- 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

*b. 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

# Regional Requirement

***Section C: Identification of the Case Safety Report***

*c. Correcting an Incorrect Safety Report Identifier*

- In the event that an incorrect safety report ID has been used in a follow-up report, contact the FAERS Electronic Submissions Coordinator at FAERSESUB@fda.hhs.gov

*d. FDA.C.1.7.1: FDA Report Type*

- Identifies the type of reports FDA classifies based on the reporting timelines
- Data length and Type: 1N
- Conformance: Mandatory
- Allowed Values
- New OID

| Post-Market | | IND | | Combo | |
|---|---|---|---|---|---|
| CONFORMANCE | FAERS Business Rule | CONFORMANCE | IND Business Rule | CONFORMANCE | Combo Business Rule |
| Mandatory | 1=15-Day<br>2=Periodic | Mandatory | 1=15-Day<br>6=7-Day | Mandatory | 1=15-Day<br>2=Periodic<br>4=5-Day<br>5=30-Day |

# Regional Requirement

***Section C: Primary Source(s) of Information (repeat as necessary)***

*a. FDA.C.2.r.2.8: Reporter's Email*

- Identifies the email address of the reporter
- Data length and Type: 100AN
- Value Allowed: Free Text
- Conformance: Optional

# Regional Requirement

***Section D: Patient Characteristics***

*a. FDA.D.11.r. : Patient Race Code*

- Identifies the race of the patient and a patient can have one or more race
- Data length and Type: 10AN
- Value Allowed: C16352 = African American, C41259 = American Indian or Alaska Native, C1260 = Asian, C1219 = Native Hawaiian or Other Pacific Islander, C41261 = White
- Conformance: Mandatory
- Business Rule: Must use a valid value or HL7 null flavor. NullFlavors: UNK, MSK, OTH

b. FDA.D.12: Patient Ethnicity Code

- Identifies the ethnicity of the patient
- Data length and Type: 10AN
- Value Allowed: C17459 = Hispanic or Latino,  C41222 = Non Hispanic or Latino
- Conformance: Mandatory
- Business Rule: Must use a valid value or HL7 null flavor

# Regional Requirement

***Section D: Patient Characteristics***

*c. D.1: Patient Information*

- If the patient is not the primary source reporter and other available data elements (e.g., age, date of birth, or sex) are unknown, then the HL7 null flavor codes **NI** or ASKU (Asked But Unknown) can be used
- When the patient information is not provided due to regional privacy restrictions (e.g., foreign reports), FDA supports the use of the HL7 null flavor code MSK (Masked)Identifies the race of the patient and a patient can have one or more race

# Regional Requirement

***Section E: Seriousness Criteria at Event Level***

*a. FDA.E.i.3.2h : Required Intervention*

- Identifies if the seriousness criteria was Required Intervention
- Data length and Type: Boolean
- Value Allowed: true nullFlavor: NI
- Conformance: Mandatory for Post-Market only

# Regional Requirement

***Section G.k: Drug(s) Information***

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

- 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

# Regional Requirement

***Section G.k: Drug(s) Information***

*a. G.k.3.1: Authorisation/Application Number*

- 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 |

# Regional Requirement

***Section G.k: Drug(s) Information***

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

- 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

| FDA Object Identifier: 2.16.840.1.113883.3.26.1.1 | |
|---|---|
| **NCI Concept Identifier** | **Description** |
| Combination Product | |
| C102834 | Type 1: Convenience Kit or 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 Labelling |
| C102841 | Type 8: Possible Combination Based on Cross Labelling of Separate Products (Temporary Type) |
| C102842 | Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product) |
| Compounding Product | |
| C73626 | Bulk ingredient |
| C96793 | Bulk Ingredient For Human Prescription Compounding |
| C95602 | Unapproved Drug Product Manufactured Exclusively for Private Label Distributor |

# Regional Requirement

***ACK.B: ICH ICSR Message Acknowledgement***

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

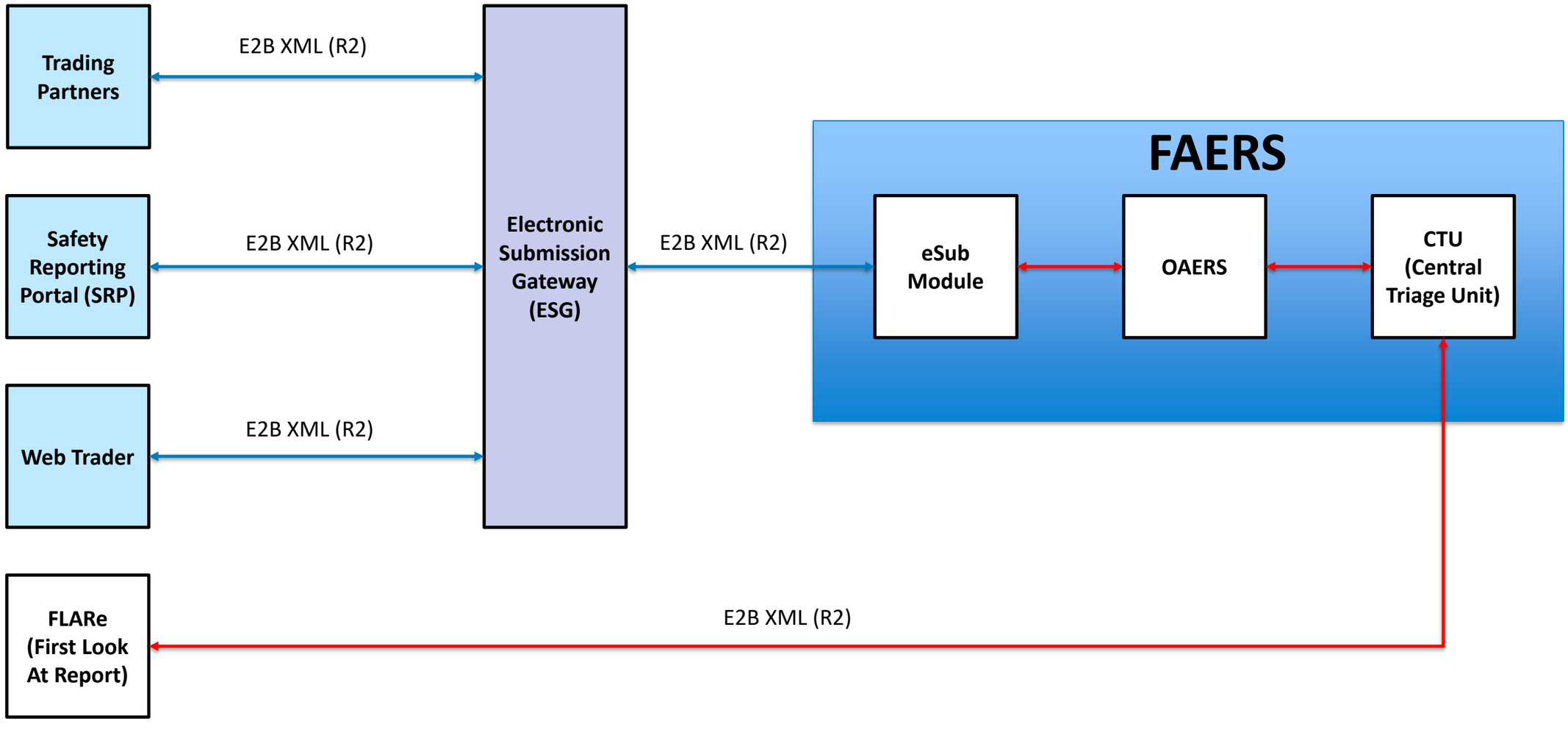
- For Pre-market
  - Production: ZZFDA_IND
  - Test: ZZFDATST_IND
- Post-market
  - Production: ZZFDA
  - Test: ZZFDATST

# Session 4: Updates on electronic submission routing mechanisms and validation

# ROUTING MECHANISM

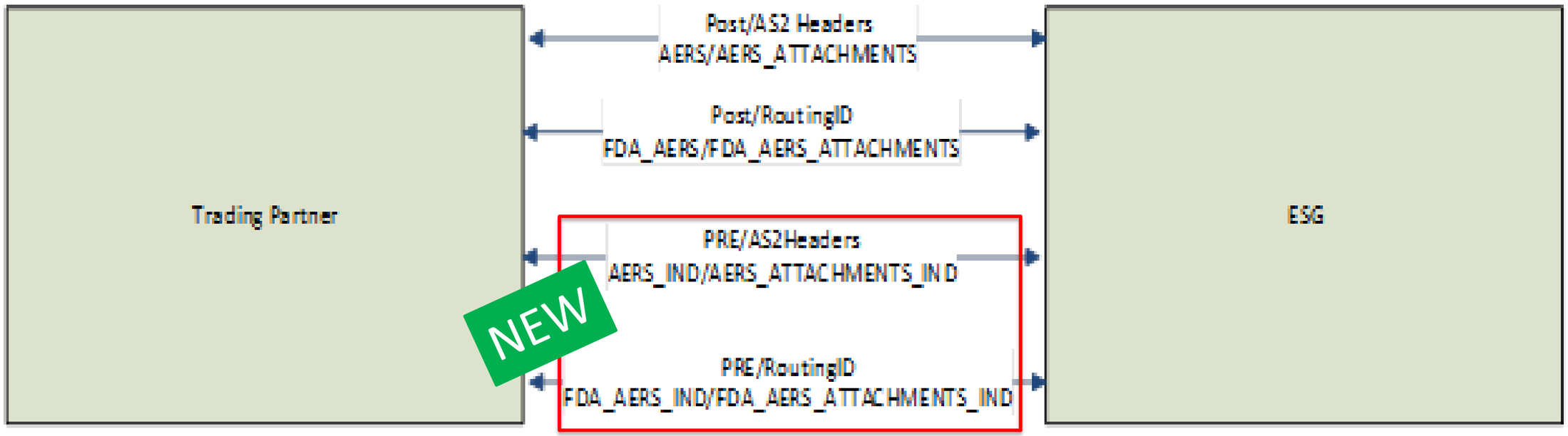
# Routing Mechanism

## Current Flow



# Routing Mechanism

## Trading Partner Changes



# Routing Mechanism

**Proposed options for sponsors to submit ICSRs**

1. Two separate "Routes" for submission of safety reports are proposed (either may be used for pre or post market ICSRs)
   - **Method 1:** AS2 Header Attributes, or
   - **Method 2:** AS2 Routing IDs
2. Submit pre-market and/or post-market safety reports using appropriate attributes or routing IDs for both E2B R2 and R3
3. E2B Data Element "IND where adverse event occurred" be designated specifically for pre-market to route reports

# 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
  - Proposed 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*

# Routing Mechanism - Method 2

- **AS2 Routing ID's** – The Electronic Submission Gateway (ESG) would also provide an alternative method to submit files to ESG 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
  - Proposed 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*

# How Pre & Post Market Safety Reports would be Segregated within FDA

- Safety reports submitted to FDA via different “routes” are stored in different folders
- The FDA Adverse Event Reporting System (FAERS) appends “–IND” to the A.1.0.1 Sender’s (Case) Safety Report Unique Identification data element to all reports in pre-market folder
- Acknowledgement will be sent with the original Safety Report Unique Identification
- FAERS checks the E2B pre-market data elements to safeguard pre-market reports are identified
- All reports with “–IND” postfix will be treated different from the post market reports (without “–IND”)

# Proposed Approach for Future Triage of ICSRs

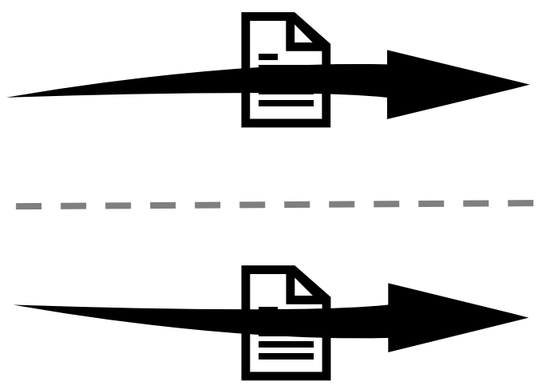
## Sponsor Submission

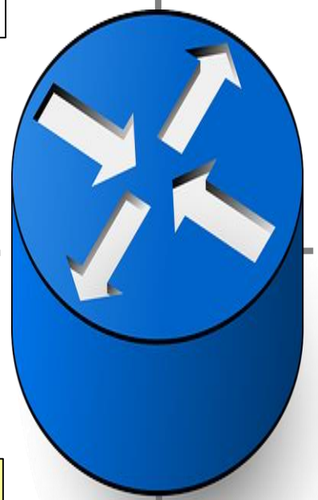
## FDA Adverse Event Reporting System

Pre-Market ICSR Submission

AS2* Header: AERS_IND or
AS2 Routing ID: FDA_AERS_IND

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.

# Routing Mechanism

## Set up Routing Controls

- There are two ways to set up routing controls dictating where a document is sent:
  - 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., CBER). Reference ***Appendix G., 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 K., AS2 Routing IDs***.

# Routing Mechanism

## Trading Partner Changes

- **AS2 Header Attributes**
  - For current post market reports
    - Destination: “CDER” or “CBER”
    - Attribute values: “**AERS**” for XML’s and “**AERS_ATTACHMENTS**” for PDF’s
  - For new IND reports, new header attributes need to be setup/configure to route the files into the new folders.
    - Destination remains the same
    - 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*

# Routing Mechanism

## Trading Partner Changes

- **AS2 Routing ID's** - ESG also provides alternate method to submit the files to ESG using unique routing ID's
  - For current post market reports
    - Routing ID's: "**FDA_AERS**" for XML's and "**FDA_AERS_ATTACHMENTS**" for PDF's
  - For new IND reports, new Routing ID's need to be setup and corresponding configuration changes are required.
    - 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*

## Session 4: Updates on electronic submission routing mechanisms and validation

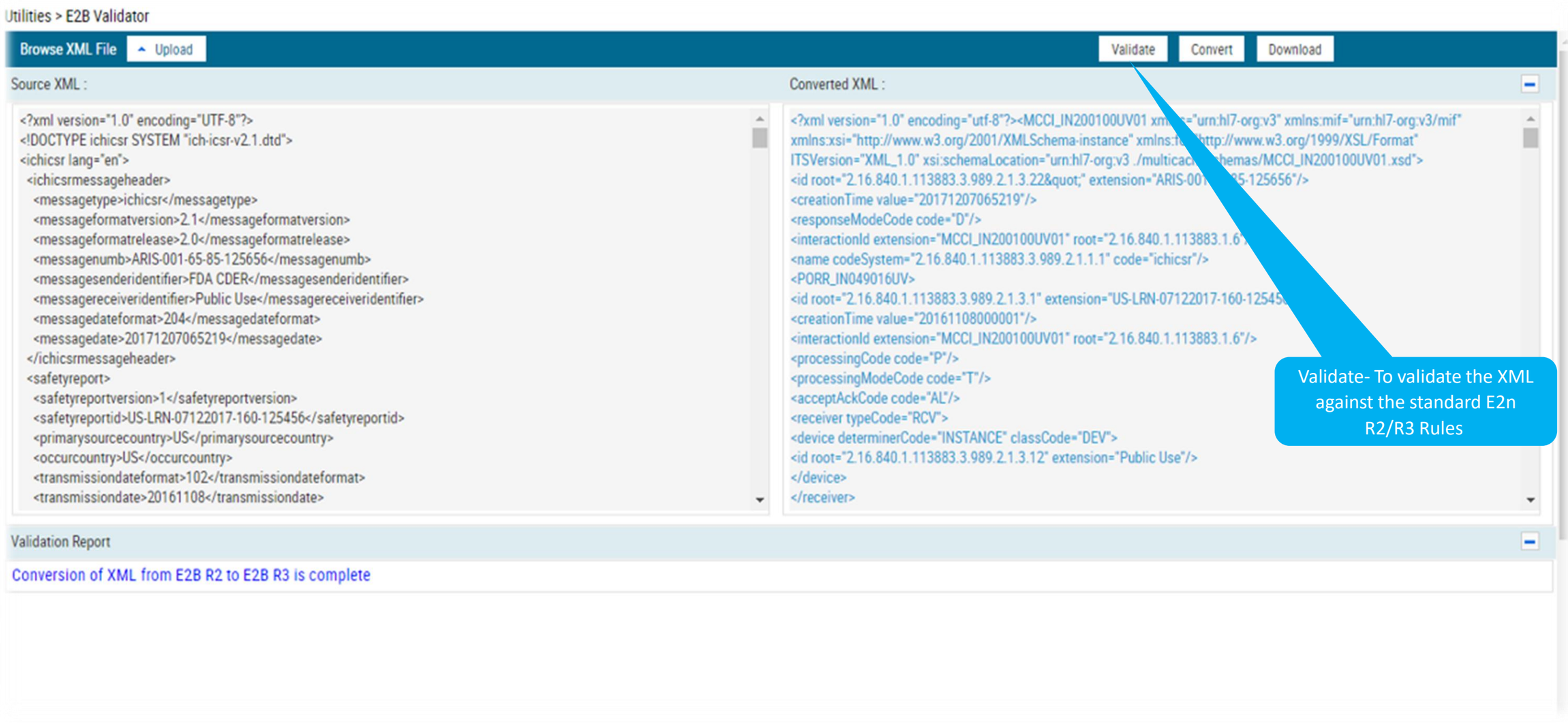
# MECHANISM TO VALIDATE E2B

# Mechanism to validate E2B

- Provide a mechanism for industry to: i) Validate the regional E2B R2 and regional E2B R3 data files; ii)  Convert regional E2B R2 to regional E2B R3 data file
- Mechanism can be used before production submission
- Mechanism available for use via a public URL
- Uploaded file are not stored
- Update FAERS Electronic Submission web page to provide this information

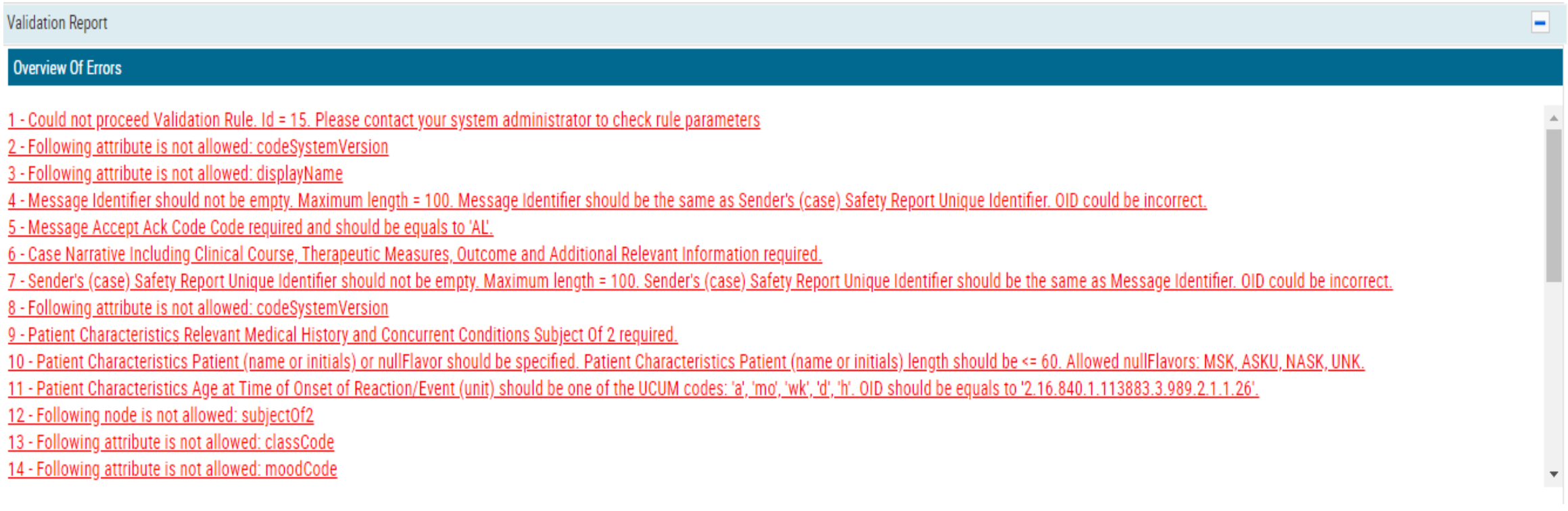
# Mechanism to validate E2B

## 1. Source XML uploaded or pasted on to the window



# Mechanism to validate E2B

## 2. After Uploading a E2B R2/R3 XML validate the file




Validation messages are displayed after validating against the R2/R3 regional specifications

# Mechanism to validate E2B

## 3. The user can correct the XML in the XML View Window

XML View

```
* ERROR : Could not proceed Validation Rule. Id = 15. Please contact your system administrator to check rule parameters [Go To Error 1 ]
1 <?xml version="1.0" encoding="UTF-8"?>
2 <MCCI_IN200100UV01
3       xsi:schemaLocation="urn:hl7-org:v3 http://eudravigilance.ema.europa.eu/XSD/multicacheschemas/MCCI_IN200100UV01.xsd"
4       xmlns="urn:hl7-org:v3" xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" ITSVersion="XML_1.0">
5    <id root="2.16.840.1.113883.3.989.2.1.3.22" extension="ICHICSR-EVHUMAN-20171124150201_5"/>
6    <creationTime value="20171124150201"/>
7    <responseModeCode code="D"/>
8    <interactionId root="2.16.840.1.113883.1.6" extension="MCCI_IN200100UV01"/>
* ERROR : Following attribute is not allowed: displayName [Go To Error 3 ]
* ERROR : Following attribute is not allowed: codeSystemVersion [Go To Error 2 ]
* ERROR : Message Identifier should not be empty. Maximum length = 100. Message Identifier should be the same as Sender's (case) Safety Report Unique Identifier. OID could be incorrect. [Go To Error 4 ]
9    <name code="1" codeSystem="2.16.840.1.113883.3.989.2.1.1.1" codeSystemVersion="2.0" displayName="ICHICSR"/>
10   <PORR_IN049016UV>
11      <id root="2.16.840.1.113883.3.989.2.1.3.1"/>
12      <creationTime value="20171122175452"/>
* ERROR : Message Accept Ack Code Code required and should be equals to 'AL'. [Go To Error 5 ]
13      <interactionId root="2.16.840.1.113883.1.6" extension="PORR_IN049016UV"/>
14      <processingCode code="P"/>
15      <processingModeCode code="T"/>
16      <acceptAckCode code="NE"/>
17      <receiver typeCode="RCV">
18         <device classCode="DEV" determinerCode="INSTANCE">
19            <id root="2.16.840.1.113883.3.989.2.1.3.12" extension="Public Use_12"/>
20         </device>
21      </receiver>
22      <sender typeCode="SND">
```

System points to the XML node where the validation error occurred for user to fix and re-validate

# Mechanism to validate E2B

## 4. E2B XML Conversion

Jtilities > E2B Validator

Browse XML File | Upload | Validate | Convert | Download

Source XML :

```
<?xml version="1.0" encoding="UTF-8"?>
<!DOCTYPE ichicsr SYSTEM "ich-icsr-v2.1.dtd">
<ichicsr lang="en">
 <ichicsrmessageheader>
  <messagetype>ichicsr</messagetype>
  <messageformatversion>2.1</messageformatversion>
  <messageformatrelease>2.0</messageformatrelease>
  <messagenumb>ARIS-001-65-85-125456</messagenumb>
  <messagesenderidentifier>FDA CDER</messagesenderidentifier>
  <messagereceiveridentifier>Public Use</messagereceiveridentifier>
  <messagedateformat>204</messagedateformat>
  <messagedate>20171207065219</messagedate>
 </ichicsrmessageheader>
 <safetyreport>
  <safetyreportversion>1</safetyreportversion>
  <safetyreportid>US-LRN-07122017-160-125456</safetyreportid>
  <primarysourcecountry>US</primarysourcecountry>
  <occurcountry>US</occurcountry>
  <transmissiondateformat>102</transmissiondateformat>
  <transmissiondate>20161108</transmissiondate>
```

Converted XML :

```
<?xml version="1.0" encoding="utf-8"?><MCCI_IN200100UV01 xmlns="urn:hl7-org:v3" xmlns:mif="urn:hl7-org:v3/mif"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xmlns:fo="http://www.w3.org/1999/XSL/Format"
ITSVersion="XML_1.0" xsi:schemaLocation="urn:hl7-org:v3 ./multicacheschemas/MCCI_IN200100UV01.xsd">
<id root="2.16.840.1.113883.3.989.2.1.3.22&amp;quot;" extension="ARIS-001-65-85-125456"/>
<creationTime value="20171207065219"/>
<responseModeCode code="D"/>
<interactionId extension="MCCI_IN200100UV01" root="2.16.840.1.113883.1.6"/>
<name codeSystem="2.16.840.1.113883.3.989.2.1.1.1" code="ichicsr"/>
<PORR_IN049016UV>
<id root="2.16.840.1.113883.3.989.2.1.3.1" extension="US-LRN-07122017-160-125456"/>
<creationTime value="20161108000001"/>
<interactionId extension="MCCI_IN200100UV01" root="2.16.840.1.113883.1.6"/>
<processingCode code="P"/>
<processingModeCode code="T"/>
<acceptAckCode code="AL"/>
<receiver typeCode="RCV">
<device determinerCode="INSTANCE" classCode="DEV">
<id root="2.16.840.1.113883.3.989.2.1.3.12" extension="Public Use"/>
</device>
</receiver>
```

Convert – After Uploading / Copying the E2B R2/R3 XML

Validation Report

Conversion of XML from E2B R2 to E2B R3 is complete

Data converted from E2B R2 to E2B R3

# Summary & Closing Comments

- 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

# Next Steps

- Today's presentation will be posted on FDA meeting page
- Invite comments via the docket on topics discussed in today's meeting by April 25, 2019
- Update schema with regional elements
- Update FDA Regional Implementation Specifications for ICH E2B(R3) Implementation
  - Incorporate comments received via the docket
- Prepare for the next meeting on July 17, 2019
  - Discuss data elements related to combination product
- Prepare sample regional E2B R3 data files
- Contact: eprompt@fda.hhs.gov after the docket timeframe