ICH
harmonisation for better health

ICH E2B(R3) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs)
Module III of III

January 2026

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

E2B Training Module III

Target audience:	Regulatory authorities, pharmaceutical companies, clinical trial sponsors, IT system vendors and other interested parties with a background in IT, regulatory and/or safety reporting
Learning outcomes:	At the end of this Module you should be able to: − Understand the relationship between ISO ICSR, HL7 ICSR message and ICH E2B(R3) message − Understand Regulatory Agency implementation examples and considerations − Understand Industry implementation examples and considerations
Further information:	ICH E2B training modules I and II ICH E2B(R3) Implementation Guide Package HL7 **ICH Information Paper for OIDs and UUIDs**
Note:	This set of ICH E2B training modules is progressive, i.e., high-level information is presented in earlier slides and more technical and detailed information is presented in subsequent modules

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Introduction (1/2)

- ICH E2B(R3) was published in 2013 and supersedes ICH E2B(R2).
- The background of ICH E2B specifications, the main principles and concepts in ICH E2B reporting and high-level differences between the versions ICH E2B(R2) and ICH E2B(R3) are discussed in Training Modules I and II.
- Module III focuses on technical and practical implementation of ICH E2B(R3) specification.
- Industry and regulator perspectives are taken into account, including different levels of experience with ICH E2B implementations.

Introduction (2/2)

ICH E2B(R3) implementation is dependent on:

- Role of the implementer, e.g., regulator or pharmaceutical company.
- Required functionalities for creating, editing, sending and receiving electronic ICSR and Acknowledgement (ACK) messages.
- The need to act in a local or global regulatory environment.
- Backwards forwards compatibility (BFC) aspects:
  - Whether transitioning from ICH E2B(R2) to ICH E2B(R3) is necessary.
  - Whether ICH E2B(R2) and ICH E2B(R3) need to be supported simultaneously.

Whereas needs of implementers can vary, regional Implementation Guides (IGs) and BFC aspects play an important role in implementation strategies.

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Regional Implementation Guides

- The ICH E2B(R3) IG was developed through international harmonisation using a consensus approach.
- Majority of the requirements of the ICH regions were incorporated into the ICH E2B(R3) IG, however some requirements due to differences in regional legislation could not be covered.
- The ICH E2B(R3) IG makes provisions for this fact, and it is expected that regulators in each ICH region will produce its own regional IG based on the core set of the ICH document.
- Implementers from pharmaceutical companies and clinical trial sponsors need to consider the regional IGs as applicable.
- The intention is that each region's IG will not conflict with each other.

Regional IG - Electronic Data Interchange (EDI)

Regional IGs should describe the procedures concerning the Electronic Data Interchange (EDI) of ICSRs and ACKs.

The procedures should ensure:

- Protection of ICSR and ACKs against the risks of unauthorised access, disclosure, alteration, delay, destruction or loss, ensuring the verification of integrity, the nonrepudiation of origin and receipt and ensuring the confidentiality of ICSRs and ACKs.
- Successful transmission and receipt of encrypted and digitally signed ICSRs and ACKs.

Source: EU ICSR Implementation Guide, March 2021

Regional Implementation Guides

Regional IGs specify regional technical requirements, compatibility between versions and the process for transmitting ICSRs and ACK messages and describe the obligations of stakeholders in ensuring successful electronic communication.

A regional IG typically describes:

- EDI, electronic gateway and additional methods of submission.
- Business continuity aspects.
- Region-specific data elements, value sets and business rules.
- Forwards compatibility, if transitioning from ICH E2B(R2) to ICH E2B(R3).

Regional IG - Electronic Gateway (1/2)

- **A Gateway:**
  - Is a link between two computer programs or systems.
  - Acts as a portal between two programs allowing them to share information by communicating using protocols on a computer or between dissimilar computers.*
  - Uses a combination of public/private key encryption to secure transmission of safety messages.
  - Should follow the ICH M2 Recommendation 'Electronic Standards for the Transfer of Regulatory Information (ESTRI) General Recommendation – ESTRI Gateway'.

*https://en.wikipedia.org/wiki/Gateway_(computer program)

Regional IG - Electronic Gateway (2/2)

- **The regional IG should:**
  - Specify the process for establishing a trading partner relationship and specify the types of encryption keys required (e.g., self-signed or managed).
  - Fully describe the testing procedure for establishing a Gateway connection.
  - Fully describe the testing protocol for verifying submitted messages meet business requirements.
  - Specify the hours of support for technology related issues.
  - Specify the supported protocols (e.g., web (AS2), email (AS1), etc.).

Source: EU ICSR Implementation Guide, March 2021

Regional IG - Additional methods of submission

In addition to an electronic Gateway, some regions provide additional methods for submitting ICSRs:

- **Web Trader**
  - An alternative solution to the use of a local Gateway to support the electronic transmission of ICSRs and ACKs.
  - Allows registered EDI Partners to exchange EDI Messages.
- **Web Based Portal**
  - Allows registered EDI Partners to generate fully ICH E2B(R3) compliant ICSRs and ACKs and to electronically upload these messages securely.
  - May allow registered EDI Partners to view the date of the transmission of all EDI Messages that have been sent and received.

Source: EU ICSR Implementation Guide, March 2021

Regional IG - Business Continuity

System failures may occur at either the sender or receiver location.

Examples include:

- Failure to generate safety messages.
- Transmission failure by sender gateway.
- Failure of message receipt.
- Processing failure at recipient's database.

The regional IG should specify the procedures to be followed in each failure scenario.

Source: EU ICSR Implementation Guide, March 2021

Regional IG – region specific Business Rules

Technical details for composing a valid ICSR should include:

- Information required by the message header such as XML character set information.
- Location of XML schemas used to validate safety messages.
- Information on receiver identifiers used for Gateway routing or internal message routing.
- Information on how to submit attachments and the allowable file formats, media types, representation, or compression.
- Information on the use of local language in safety messages.
- Specific guidance on regional requirements for specific data elements and values – if applicable.
- Information on data elements that are mandatory for a particular region.

Regional IG – Business Rule spreadsheet

- Regulators are advised to present regional data elements, business rules and/or value sets (when applicable) consistently in the 'ICH E2B(R3) Core Data Elements and Business Rules template' available in the ICH E2B(R3) IG package.

Field Identification				Business rules									
SOURCE	HEADER ELEMENT	DATA ELEMENT NUMBER	DATA ELEMENT NAME	MAX LENGTH	DATA TYPE	VALUE ALLOWED	CONFORMANCE	ICH BUSINESS RULE	REGIONAL BUSINESS RULE	Q&A	NI	MSK	UNK
ICH	C.1	C.1.1	Sender's (case) Safety Report Unique Identifier	100	AN	Free text (country code-company or regulator name-report number)	Mandatory	A two character country code will be used in all instances for the country component of the Unique Identifier. The country code EU exists in the ISO 3166 country code list as an exceptional reservation code to support any application that needs to represent the name European Union. In this case, 'EU' will be accepted as the country code. The format of C.1.1 ensures a unique report identifier for the sender of particular ICSR. The use of a '-' (dash/hyphen) should be avoided in the 'company or regulator name'. Both the "Sender's (case) Safety Report Unique Identifier" (C.1.1) and the "Worldwide Unique Case Identification Number" (C.1.8.1) data elements are mapped to the repeatable XML attribute<id> in the 'investigationEvent' entity in the HL7 ICSR model (See Appendix I (D) the Reference Instances).ICH uses two value– "2.16.840.1.113883.3.989.2.1.3.1" and "2.16.840.1.113883.3.989.2.1.3.2"– in the root portion of the investigationEvent.id to distinguish C.1.1 and C.1.8.1. The following notation will be used to represent C.1.1: <id extension="country code-company name-report no" root="2.16.840.1.113883.3.989.2.1.3.1"/> The following notation will be used to represent C.1.8.1. <id extension="country code-company name-report no" root="2.16.840.1.113883.3.989.2.1.3.2"/>		4.1 (009)	No	No	No
ICH	C.1	C.1.3	Type of Report	1	N	1=Spontaneous Report 2=Report from study 3= other 4= Not available to sender (unknown)	Mandatory			4.2 (014)	No	No	No
ICH	C.1	C.1.4	Date Report Was First Received from Source	-	Date/Time	See Appendix II for further information.	Mandatory	Minimum precision required is the day (i.e. "CCYYMMDD"). The date specified cannot refer to a future date.		4.3 (015)	No	No	No
ICH	C.1	C.1.5	Date of Most Recent Information for This Report	-	Date/Time	See Appendix II for further information.	Mandatory	Minimum precision required is the day (i.e. "CCYYMMDD"). The date specified cannot refer to a future date.		4.3 (015)	No	No	No

Regional IG – region specific Business Rules

- To properly assign regional data elements, it is necessary to have a basic understanding of the International Organisation for Standardisation (ISO) / the Health Level Seven (HL7) ICSR as this is the basis for the ICH E2B(R3) ICSR message specification.
- For region specific value sets it may be necessary to specify an OID (Object Identifier Code).
- See section 4 of this Training Module for more information.

Source: EU ICSR Implementation Guide, March 2021

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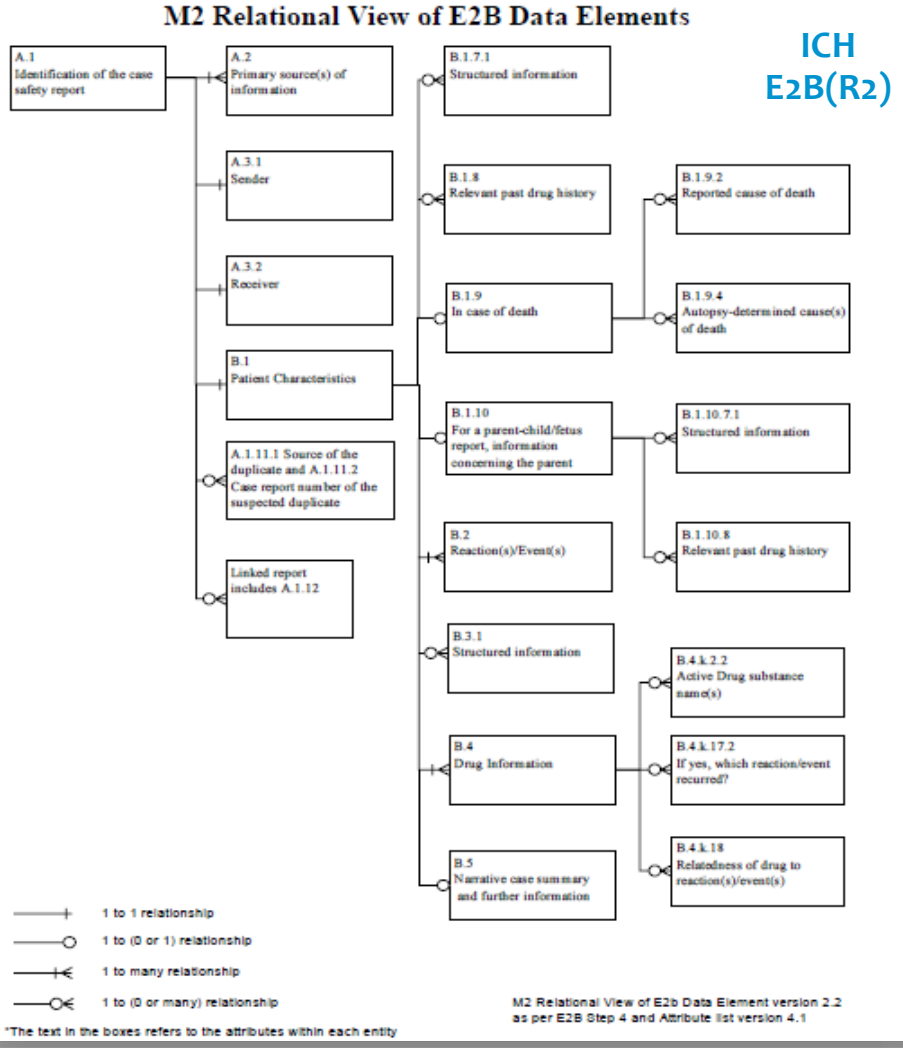
Considerations for planning transition from ICH E2B(R2) to ICH E2B(R3)

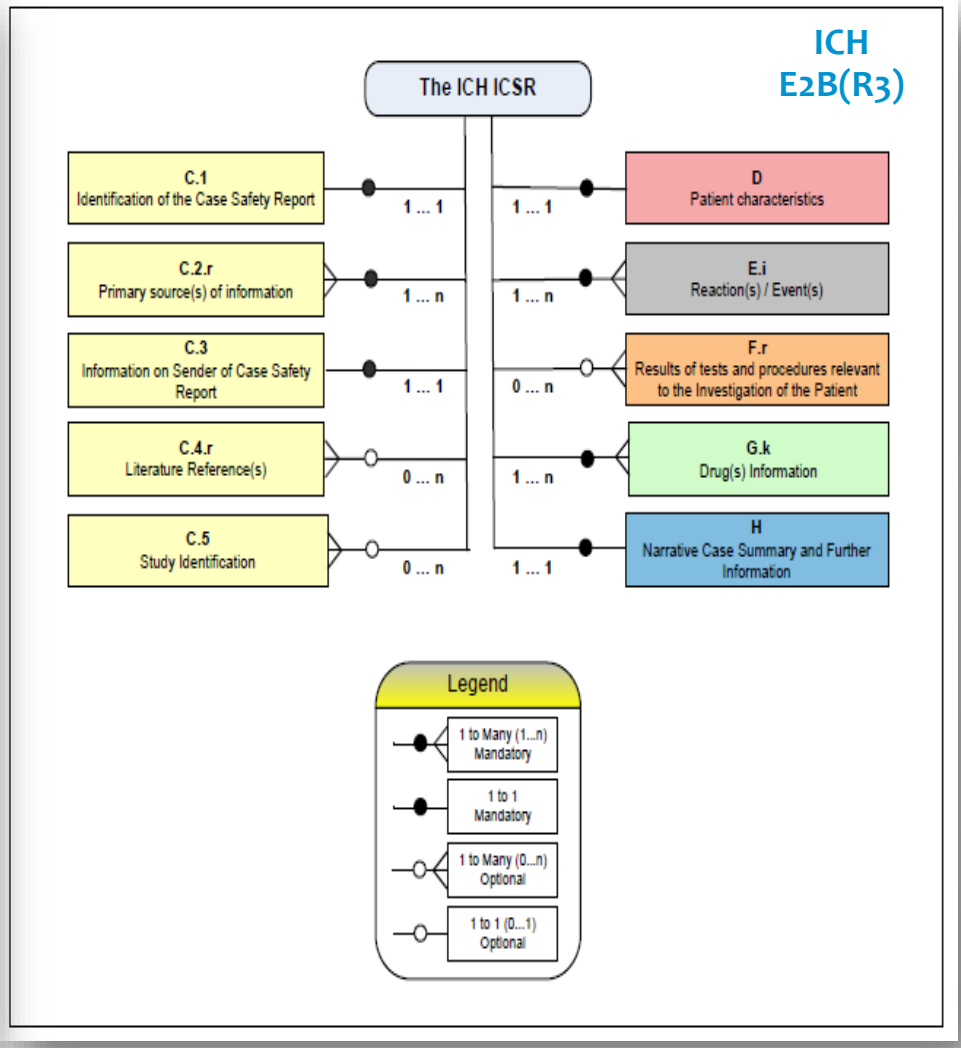
- It is expected that ICH E2B(R2) will be phased out at some point in time, however:
  - Global companies will need to be prepared to exchange messages using both ICH E2B(R2) and ICH E2B(R3).
  - Regulatory authorities need to consider a transitional phase during which both versions are accepted.
- The backwards/forwards compatibility (BFC) documentation published by ICH in the ICH E2B(R3) IG package provides a starting point for analysing incompatibilities.
- Conversion tools are available for use with major commercial safety database products.
  - Note that conversions have implications on data quality and impacts data analysis.

ICH E2B(R2) comparison with ICH E2B(R3)

ICH E2B(R2)



ICH E2B(R3)



Transitioning from ICH E2B(R2) to ICH E2B(R3)

A General Approach for Analysis

Review each ICH E2B(R3) data element section by section.

Map each ICH E2B(R2) and ICH E2B(R3) Data Element to fields in your safety database. Identify any gaps.

Decide how to handle ICH E2B(R3) data elements that do not currently exist in your safety dataset.

Do you need to add any new fields? Are any conversions required? Have you defined all the necessary business rules?

Identify data changes that may impact business processing. For example, does your database support seriousness at the event level?

Forwards Compatibility of Regional Data Element

Forwards compatibility refers to the mapping between ICH E2B(R2) and ICH E2B(R3) data elements and rules for conversion.

- **For the Regulator**
  - If a new regional data element was added for the first time in ICH E2B(R3), then no forward compatibility is required.
  - If an existing ICH E2B(R2) regional data element was added in ICH E2B(R3), then provide the mapping and the rules for conversion.
- **For the Company**
  - Follow the forward compatibility rules provided by the regulators.

Differences between ICH E2B(R2) and ICH E2B(R3)

The following 7 slides provide a non-exhaustive set of examples of some of the most-important changes between the ICH E2B(R2) and ICH E2B(R3) structures.

For a full list of the changes, see the BFC documentation published by ICH in the ICH E2B(R3) IG package.

Changes/Differences ICH E2B(R2) and ICH E2B(R3)

Differences between versions

Concept	ICH E2B(R2)	ICH E2B(R3)
Amendment Reports	N/A	Reports may be nullified or amended
Attachments	Provided separately from the message	Embedded in the ICSR
Seriousness Criteria	Case Level	Event Level
Medical Confirmation	Case Level	Event Level
Country of Occurrence	Case Level	Event Level
Null Flavors	N/A	Used to indicate why information may be missing
IDMP – Identification of Medicinal Products	N/A	Ability to use controlled vocabularies when available

Additional Key Differences (1/5)

New, Changed and Expanded Data Elements

ICH E2B(R3) ID	Description	Change
C.1.6.1.r.1	Documents Held by Sender	Expanded from 100 to 2,000 characters
C.1.9.1.r.1	Source(s) of the Case Identifier	Expanded from 50 to 100 characters
C.1.11.2	Reason for Nullification / Amendment*	Expanded from 200 to 2,000 characters

**Amendments are new in E2B(R3). E2B(R2) only allowed Nullification*

Additional Key Differences (2/5)

New, Changed and Expanded Data Elements

Section C.5 – Study Identification

ICH E2B(R3) ID	Description	Change
C.5.2	Study Name	Expanded from 100 to 2,000 characters
C.5.3	Sponsor Study Number	Expanded from 35 to 50 characters

Section E.i – Reaction(s)/Event(s) (Repeat as necessary)

ICH E2B(R3) ID	Description	Change
E.i.1.1a	Reaction / Event as Reported by the Primary Source in Native Language	Expanded from 200 to 250 characters
E.i.1.2	Reaction / Event as Reported by the Primary Source for Translation	New in ICH E2B(R3)

Additional Key Differences (3/5)

New, Changed and Expanded Data Elements

Section H – Narrative Case Summary and Further Information

ICH E2B(R3) ID	Description	Change
H.2	Reporter's Comments	Expanded from 500 to 20,000 characters
H.4	Sender's Comments	Expanded from 2,000 to 20,000 characters
H.5.r.1a	Case Summary and Reporter's Comments Text	New field in ICH E2B(R3) for local language requirements

Additional Key Differences (4/5)

New, Changed Expanded and Deleted Data Elements

Section G.k Drug(s) Information (Repeat as necessary)

ICH E2B(R3) ID	Description	Change
G.k.2.2	Medicinal Product Name as Reported by the Primary Source	Expanded from 70 to 250 characters
G.k.2.3.r.1	Substance / Specified Substance Name	Expanded from 100 to 250 characters
G.k.7.r	Indication for Use in Case (repeat as necessary)	More than one indication can be provided
G.k.11	Additional Information on Drug (free text)	Expanded from 100 to 2,000 characters

ICH E2B(R2) ID	Description	Change
B.4.k.5.3	Drug separate dosage number	Deleted
B.4.k.5.4	Number of units in the interval	Retained, but ICH E2B(R3) use altered
B.4.k.5.5	Definition of the time interval unit	Retained

Additional Key Differences (5/5)

New, Changed and Expanded Data Elements

- Acceptable data type, data length and values allowed are also different.

Example. G.k.5b (B.4.k.5.7) Cumulative Dose to First Reaction (unit)

Concept	ICH E2B(R2)	ICH E2B(R3)
Data Type	3N	50AN
Value Allowed	32 codes	Constrained UCUM codes and {DF}

Mapping Between ICH E2B(R2) and ICH E2B(R3)

Most of ICH E2B(R2) data elements are mapped to ICH E2B(R3) data elements

ICH E2B(R2)		ICH E2B(R3)	
Element ID	Element Name	Element ID	Element Name
B.1	Patient Characteristics (header / entity)	D	Patient Characteristics
B.1.1	Patient	D.1	Patient (name or initials)
		D.1.1	Patient Medical Record Number(s) and Source(s) of the Record Number (if allowable)
B.1.1.1a	Patient Medical Record Number(s) and Source(s) of the Record Number (GP Medical Record Number)	D.1.1.1	Patient Medical Record Number(s) and Source(s) of the Record Number (GP Medical Record Number)
B.1.1.1b	Patient Medical Record Number(s) and Source(s) of the Record Number (Specialist Record Number)	D.1.1.2	Patient Medical Record Number(s) and Source(s) of the Record Number (Specialist Record Number)
B.1.1.1c	Patient Medical Record Number(s) and Source(s) of the Record Number (Hospital Record Number)	D.1.1.3	Patient Medical Record Number(s) and Source(s) of the Record Number (Hospital Record Number)
B.1.1.1d	Patient Medical Record Number(s) and Source(s) of the Record Number (Investigation Number)	D.1.1.4	Patient Medical Record Number(s) and Source(s) of the Record Number (Investigation Number)
B.1.2	Age Information (header)	D.2	Age Information
B.1.2.1a	Date of Birth (date format)		
B.1.2.1b	Date of Birth	D.2.1	Date of Birth

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Regulatory authorities should consider

- Development of Regional Implementation Guideline and other technical materials
  - Consider existing regional requirements of other ICH regulators.
- Methods of submission
- Testing with stakeholders
  - Conduct large-scale pilot testing(s) with stakeholders and IT system vendors to identify issues to be resolved.
  - ICH regulators are recommended to perform cross-regional testing if regional data elements are defined.*
- Transition timeline
  - Consider a feasible timeline by which all stakeholders can begin ICH E2B(R3) reporting.
  - Consider a feasible time to phase out ICH E2B(R2) reporting (if applicable).
- Stakeholder involvement
  - Including WHO Programme for International Drug Monitoring.
- The impact of ICH E2B(R3) on any downstream systems, e.g., analytics tools

*https://www.ich.org/page/contact-form

Methods of submission

- Consider the necessity of multiple electronic ICSR submission methods based on the capabilities of stakeholders who will be required to submit ICH E2B(R3) messages.
  - ESTRI Gateway.
  - EDI.*
  - Other (e.g., web based portal).

*Electronic data interchange. Wikipedia. Available from: https://en.wikipedia.org/wiki/Electronic_data_interchange (Page Version: 3 January 2026)

Provide ICSR submission support resources

- Consider the necessity of providing ICSR submission support resources for stakeholders that do not have the means.
  - Data entry resource.
    - To support ICSR file creation and validation based on the ICH E2B(R3) guideline and regional guideline.
  - ICSR submission resource with digital signature for Gateway submission.
    - To prevent spoofing.
    - To detect data manipulation.
    - To encrypt and decrypt ICSR files.
  - Training resources & environment for sender's validation.
    - To simulate ICSR transmission.

Testing

- **Pre-go-live Testing with stakeholders is recommended.**
  - To support submission and receipt validation.
  - As many stakeholders as possible should take part in testing, e.g.:
    - Regulatory authorities.
    - Pharmaceutical companies (from small to medium to large companies).
    - System vendors.
- **Detailed testing plan based on practical use cases and multiple scenarios and viewpoints is useful to ensure a smooth transition.**
  - Multiple rounds of testing would be preferred.
  - Testing exchange of ACK messages should be taken into account.
- **Testing environment should permit continuous testing by stakeholders, e.g., for system upgrades.**

Transition Period

- **Consider the necessity of a transition period from ICH E2B(R2) to ICH E2B(R3).**
  - Adopting ICH E2B(R3) is challenging not only for regulatory authorities but also pharmaceutical companies.
  - Implementing ICH E2B(R3) will likely require upgrades or enhancements to existing systems and processes.
    - Allow enough time for stakeholders to plan their transition.
    - Feasible plan should be prepared with stakeholders' input.
  - Regulators should consider the impact of receiving data simultaneously in ICH E2B(R2) and ICH E2B(R3) on any downstream systems, e.g., analytics tools.

Stakeholder involvement

- Joint planning and collaboration helps ensure successful implementation and transition.
- Provide stakeholders with regular updates on progress.
- Conduct public meetings with stakeholders to:
  - Enable two-way communication for questions and status.
  - Collect feedback from implementers.
  - Resolve challenges and answer questions.

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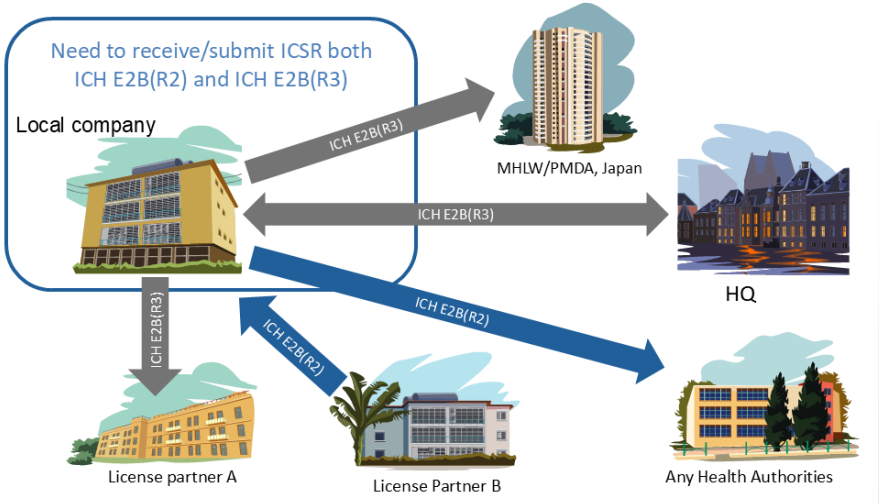
Pharmaceutical companies' considerations (1/2)

A pharmaceutical company implementation strategy largely depends on their geographic coverage:

- Are these regulators still accepting ICH E2B(R2)? ICH E2B(R3) only? Or both ICH E2B(R2) and ICH E2B(R3)? Is there a deadline for accepting only ICH E2B(R3)?
- Which methods of submission are accepted by these regulators?
- Which regulators need to receive ICSRs: only 1 region? or multiple regions?
- Are submission tools provided by regulators (if any) suitable for your needs?

Capability to support both ICH E2B(R2) and ICH E2B(R3)



There are several options to adapt ICH E2B reporting as follows:

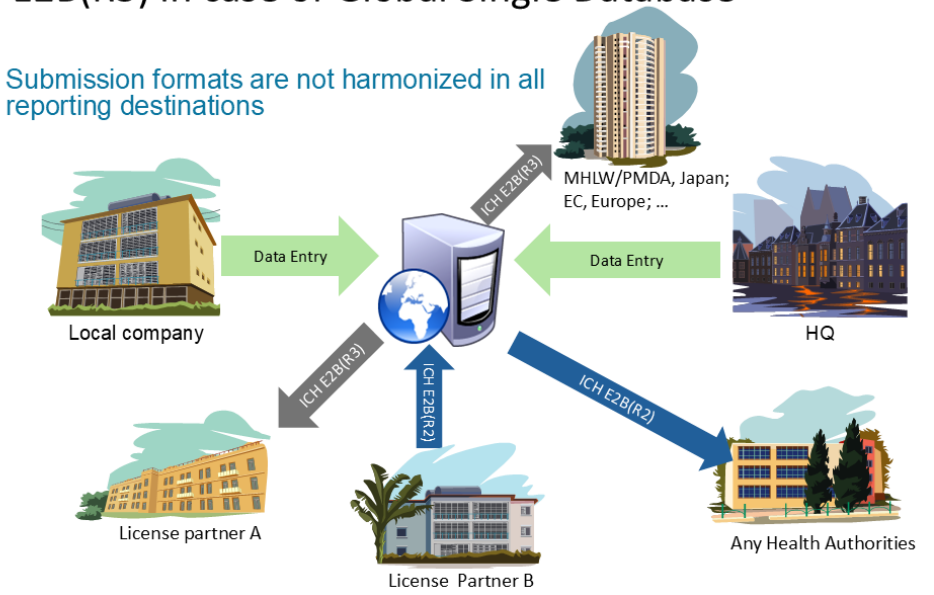
- Direct data entry to regulator's web site.
- Stand-alone tool to generate XML files.
- Regional specific safety database.
- Global single safety database.

Pharmaceutical companies' considerations (2/2)

If the company has implemented a single, global system, the company will have to understand not only the differences between ICH E2B(R2) and ICH E2B(R3), but must also understand each regional requirement.

- Data entry guidelines should consider regional requirements.
- Business rules should take into consideration regional data logic checks and any limitations on file size/file formats in each region.

Capability to support both ICH E2B(R2) and ICH E2B(R3) in case of Global Single Database



Consideration points from company point of view

- There are differences in file size and file formats between ICH E2B(R2) and ICH E2B(R3). These differences must be considered for submissions to different agencies or partners.
- The company needs to ensure field-level mapping for ICH E2B(R2) and ICH E2B(R3) are correct based on the ICH IG and that the mappings also conform with regional requirements.
- The company may decide to create custom business rules and specific logic for populating some fields (e.g., Null Flavor, patient information, etc.).

The changed field from ICH E2B(R2) and ICH E2B(R3) (1/3)

A) ***New fields***

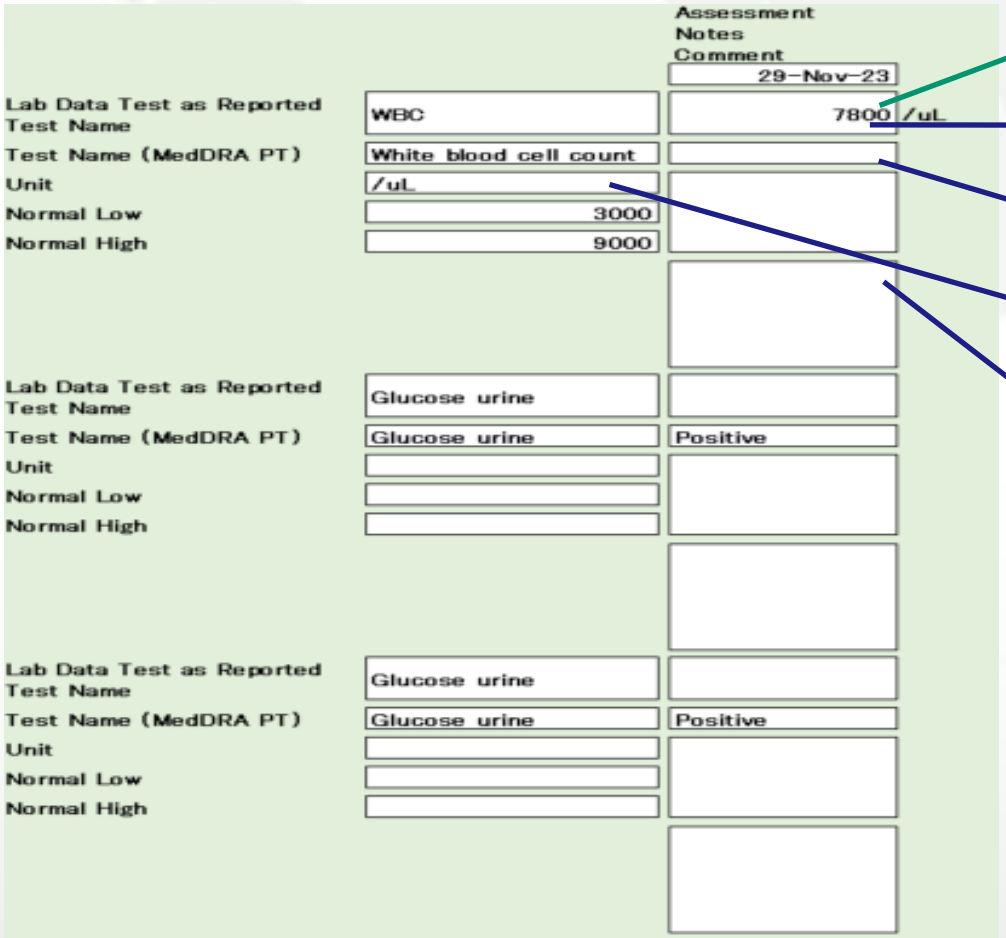
B) ***Deleted fields***

C) ***Structure changes***

D) ***Data length change***

The changed field from ICH E2B(R2) and ICH E2B(R3) (2/3)

Example 1 : Structure change of Lab test result



ICH E2B(R2): B.3.1d Test Result (value/qualifier)

ICH E2B(R3): F.r.3.2 Test Result (value)

ICH E2B(R3): F.r.3.1 Test Result (code)

ICH E2B(R3): F.r.3.3 Test Result (unit)

ICH E2B(R3): F.r.3.4 Result Unstructured Data (free text)

Different mapping would be required from the same filed of database.

- ICH E2B(R2) accept alphanumeric (AN) value for Test result field (B.3.1.d).
- ICH E2B(R3) accept only numeric value for test result field (F.r.3.2).
- If needed, the company would need to export AN values for F.r.3.4.

The changed field from ICH E2B(R2) and ICH E2B(R3) (3/3)

Example2 **: Data length change of Narrative field**

ICH E2B(R2): B.5.1 20,000 AN

ICH E2B(R3): H.1 100,000 AN

The company may want to set the business rule to limit the narrative to the length for ICH E2B(R2) (20,000AN) to avoid truncating the narrative when exporting ICH E2B(R2) messages.

Pharmaceutical companies' considerations (1/2)

- Testing with regulatory authorities
  - The system vendor should test their software with the regulator to ensure compatibility with the regulator's requirements.
  - The company should conduct testing with each regulator to ensure adherence with regulator requirements.
  - The company should also conduct the testing with regulator to ensure the system is accurately implemented.
  - The company should use validation tools provided by regulators (if available).
  - After a system upgrade, the company should check if re-testing is required by the regulator(s).
  - The company should test receipt and processing of ICSRs and ACKs within their Safety database.

Pharmaceutical companies' considerations (2/2)

- Companies should ensure pharmacovigilance staffs are suitable, educated and trained in ICH E2B(R3).
- The company should consider the impact of ICH E2B(R3) on downstream systems such as analytics tools, process for producing aggregate report summary tables, and other systems and processes.

Adapting E2B Submissions in company

Consider which strategies are appropriate in each region:

- Database for ICH E2B(R3)
  - A) Build a new ICH E2B(R3) database separately from the existing ICH E2B(R2) database.
  - B) Integrate with the existing ICH E2B(R2) database to build single database.

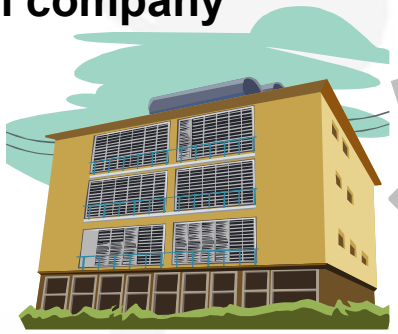
- ICSR reception system for ICH E2B(R3)
  - A) Build a new ICH E2B(R3) ICSR reception system separately from the existing ICH E2B(R2) ICSR reception system.
  - B) Integrate with the existing ICH E2B(R2) ICSR reception system to build single ICSR reception system.

- ICSR submission system for ICH E2B(R3) ICSRs
  - A) Set up new ICH E2B(R3) ICSR submission system separately from the existing ICH E2B(R2) ICSR submission system
  - B) Integrate with the existing ICH E2B(R2) ICSR submission system

Capability to support both ICH E2B(R2) and ICH E2B(R3)

Assess the need to support both ICH E2B(R2) and ICH E2B(R3)

Local company



ICH E2B(R3)

MHLW/PMDA, Japan

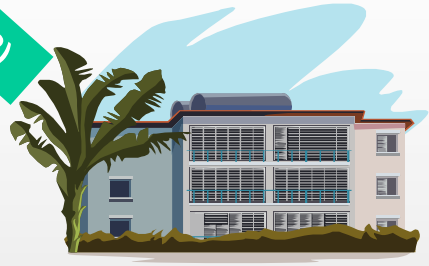
ICH E2B(R3)

HQ

ICH E2B(R3)

License partner A

ICH E2B(R2)



License Partner B

ICH E2B(R2)

Any Health Authorities

Capability to support both ICH E2B(R2) and ICH E2B(R3) in case of Global Single Database

It is the sender's responsibility to monitor completeness of messages being successfully acknowledged (reconcile).

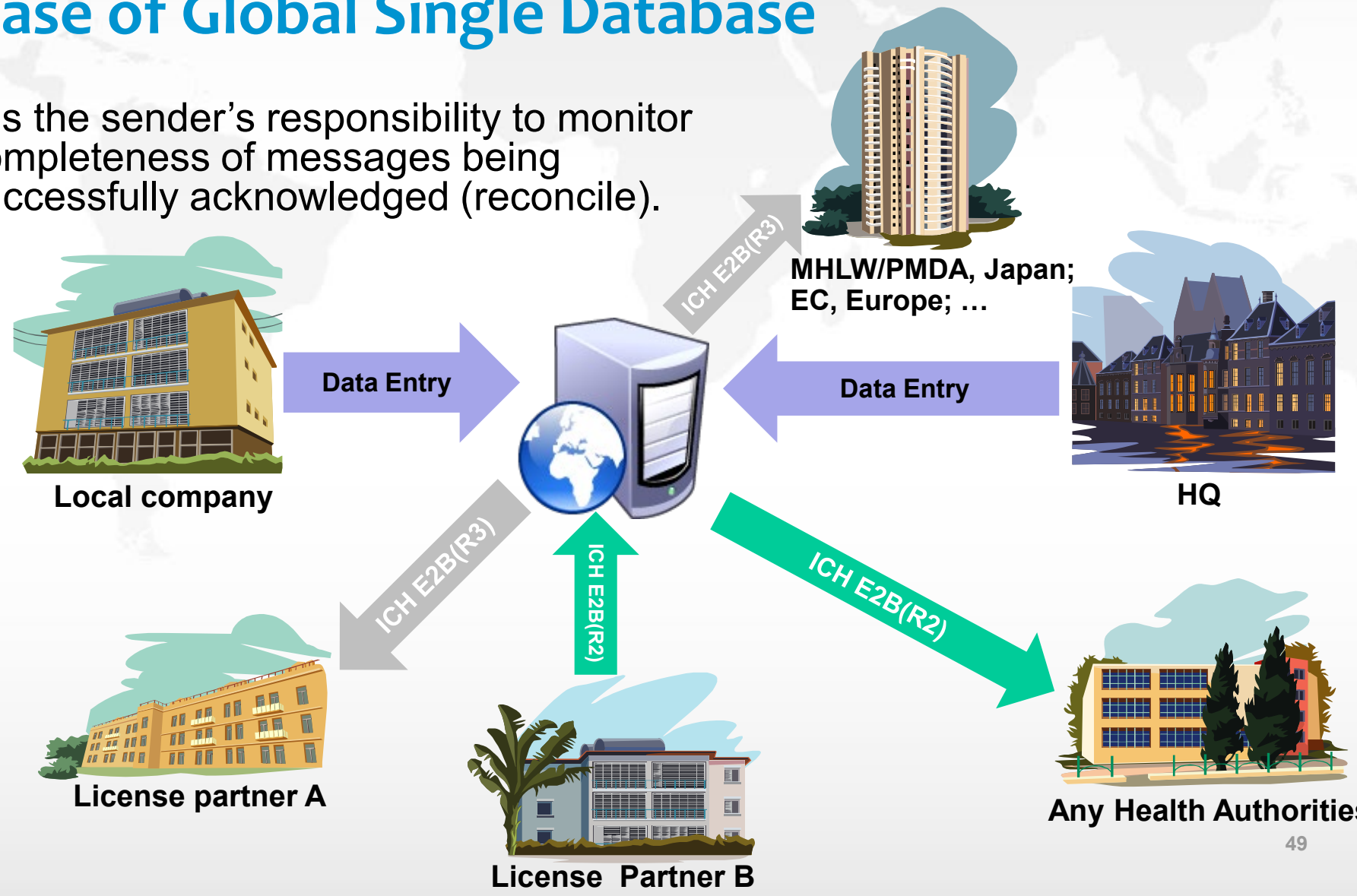


Table of Contents

ISO/HL7 27953_2 standard (1/4)

This section explains

- how to utilize the ISO package and ICH E2B(R3) Implementation Package to learn and
- understand the HL7 ICSR Refined Message Information Models (RMIMs) and ICH E2B(R3) message

- Basic understanding of HL7 ICSR RMIM is necessary to interpret ICH E2B(R3) message and to assign additional regional data elements properly

ISO/HL7 27953_2 standard (2/4)

- The ICH E2B(R3) ICSR message standard was developed through a collaborative relationship between the ICH and the *Joint Initiative Council* (JIC)
  - The JIC is a partnership of ISO, HL7, the *European Committee for Standardisation* (CEN), the *Clinical Data Interchange Standards Consortium* (CDISC), SNOMED International (formerly known as IHTSDO), and GS1.
- The ICSR standard named '*ISO / HL7 27953-2: 2011 Health informatics -- Individual case safety reports (ICSRs) in pharmacovigilance -- Part 2: Human pharmaceutical reporting requirements for ICSR*' is available at the ISO website*.

*https://www.iso.org/iso/store.html

ISO/HL7 27953_2 standard (3/4)

- ISO/HL7 27953_2 was created for regulatory reporting for human pharmaceuticals
- ISO /HL7 27953-2 message is based on HL7 Version 3 (v3) Standards

```
- <PORR_IN049016UV>
      <!--N.2.r.1: Message Identifier-->
    <id root="2.16.840.1.113883.3.989.2.1.3.1" extension="GB-EMA-1905JPN003641JAA"/>
      <!--N.2.r.4: Date of Message Creation-->
    <creationTime value="20200408093927"/>
    <interactionId root="2.16.840.1.113883.1.6" extension="PORR_IN049016UV"/>
    <processingCode code="P"/>
    <processingModeCode code="T"/>
    <acceptAckCode code="AL"/>
      <!--N.2.r.3: Message Receiver Identifier-->
  - <receiver typeCode="RCV">
    - <device determinerCode="INSTANCE" classCode="DEV">
        <id root="2.16.840.1.113883.3.989.2.1.3.12" extension="EMA"/>
      </device>
    </receiver>
      <!--N.2.r.2: Message Sender Identifier-->
  - <sender typeCode="SND">
    - <device determinerCode="INSTANCE" classCode="DEV">
        <id root="2.16.840.1.113883.3.989.2.1.3.11" extension="ABC"/>
      </device>
    </sender>
  - <controlActProcess classCode="CACT" moodCode="EVN">
      <code code="PORR_TE049016UV" codeSystem="2.16.840.1.113883.1.18"/>
        <!--C.1.2: Date of Creation-->
      <effectiveTime value="20200408093927"/>
    - <subject typeCode="SUBJ">
      - <investigationEvent classCode="INVSTG" moodCode="EVN">
            <!--C.1.1: Sender's (case) Safety Report Unique Identifier -->
          <id root="2.16.840.1.113883.3.989.2.1.3.1" extension="GB-EMA-1905JPN003641JAA"/>
            <!--C.1.8.1: Worldwide Unique Case Identification Number -->
          <id root="2.16.840.1.113883.3.989.2.1.3.2" extension="GB-EMA-M2019-14223"/>
```

Introduce New Regional Data Elements (1/3)

- New data elements most likely will be introduced by a regulator.
- Define the new data element. This includes:
  - Name of the data element.
  - Description for the data element.
  - Are Observation values required?
  - Data type and Data length.
  - Data Conformance (e.g., required, optional, conditional-required).
  - Data Rules.
  - Appropriate Null Flavor, if data element required and not available.
- Identify the class for the new data element in the HL7 model.
  - HL7 Observation Class and CE Data Type,
  - HL7 Act Class and Instance Identifier Data Type,
- HL7 model will help to define the xPath.

Introduce New Regional Data Elements (2/3)

- If Observation values are required:
  - Identify the standards to be used and the appropriate OID.
  - If standard not available, then request the appropriate SDO for creation of the terminology (including the concept and definition, all its associated term options and term definitions).
  - If SDO does not recommend but is still needed, then prepare regional OID.

- ICH Arc: 2.16.840.1.113883.3.989.5.1.2
{joint-iso-itu-t(2) country(16) us(840) organization(1) hl7(113883) externalUseRoots(3) ich-estri(989) regional-specialised(5) sub-reg(1) fda(2)}

1 – FAERS 2.16.840.1.113883.3.989.5.1.2.1
{joint-iso-itu-t(2) country(16) us(840) organization(1) hl7(113883) externalUseRoots(3) ich-estri(989) regional-specialised(5) sub-reg(1) fda(2) FAERS(1)}

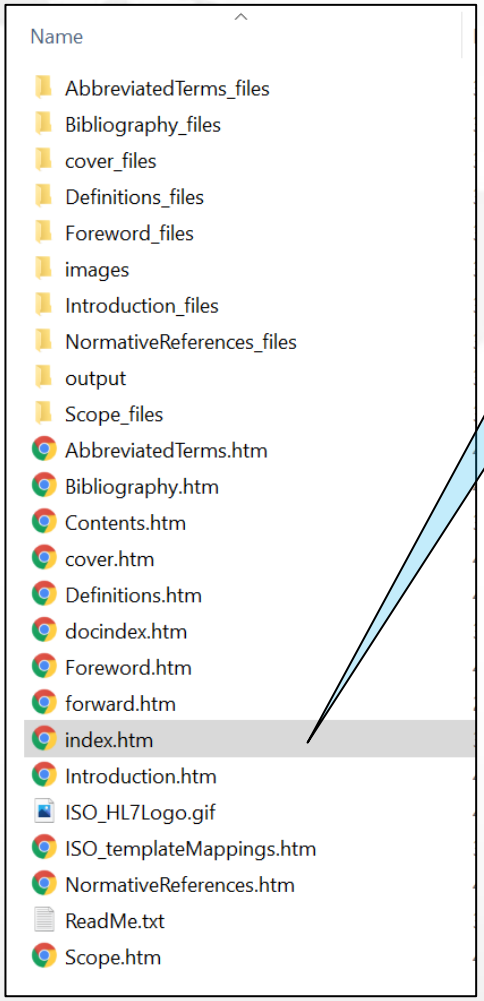
Introduce New Regional Data Elements (3/3)

- Regional OIDs use

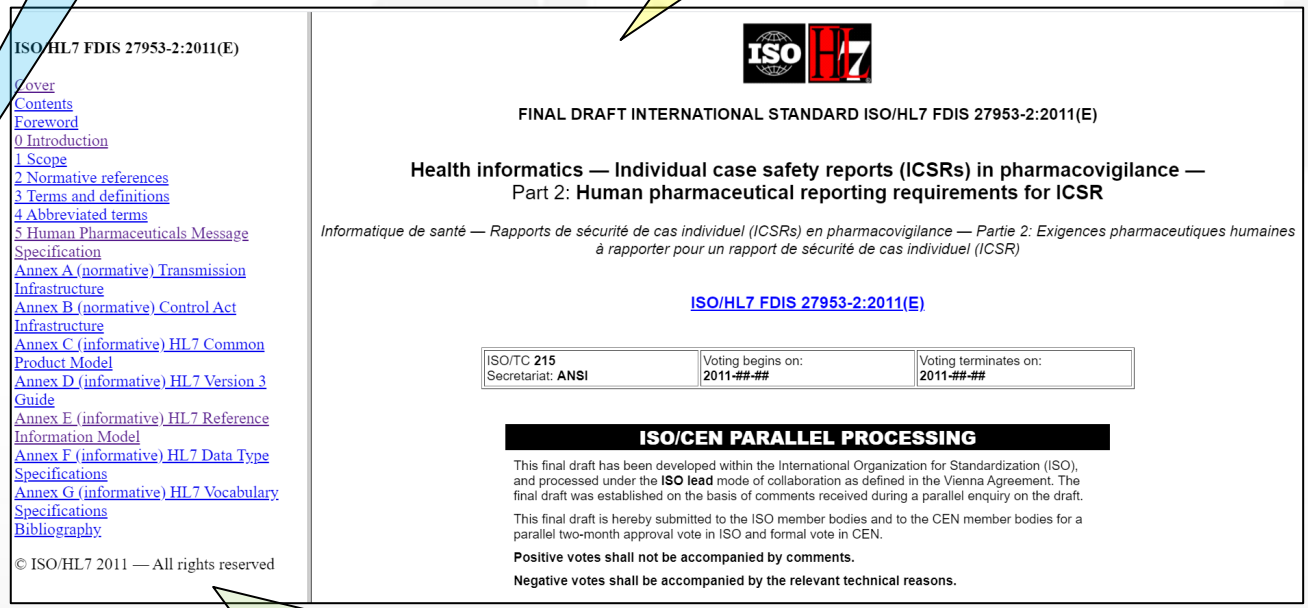
  {joint-iso-itu-t(2) country(16) us(840) organization(1) hl7(113883) externalUseRoots(3) ich-estri(989) regional-specialised(5) sub-reg(1) fda(2) FAERS(1)}

  - 1 - Code List: 2.16.840.1.113883.3.989.5.1.2.1.1
  - 2 – namespace: 2.16.840.1.113883.3.989.5.1.2.1.2
  - 3 – observationCode: 2.16.840.1.113883.3.989.5.1.2.1.3

ISO/HL7 27953_2 standard (4/4)



With ISO package unzipped, click on the ***Index.htm*** file to open ***HL7 ICSR Cover page.***



ISO/HL7 FDIS 27953-2:2011(E)

Cover
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Foreword
0 Introduction
1 Scope
2 Normative references
3 Terms and definitions
4 Abbreviated terms
5 Human Pharmaceuticals Message Specification
Annex A (normative) Transmission Infrastructure
Annex B (normative) Control Act Infrastructure
Annex C (informative) HL7 Common Product Model
Annex D (informative) HL7 Version 3 Guide
Annex E (informative) HL7 Reference Information Model
Annex F (informative) HL7 Data Type Specifications
Annex G (informative) HL7 Vocabulary Specifications
Bibliography

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FINAL DRAFT INTERNATIONAL STANDARD ISO/HL7 FDIS 27953-2:2011(E)

Health informatics — Individual case safety reports (ICSRs) in pharmacovigilance —
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ISO/HL7 FDIS 27953-2:2011(E)

ISO/TC **215** Secretariat: **ANSI**	Voting begins on: **2011-##-##**	Voting terminates on: **2011-##-##**

ISO/CEN PARALLEL PROCESSING

This final draft has been developed within the International Organization for Standardization (ISO), and processed under the **ISO lead** mode of collaboration as defined in the Vienna Agreement. The final draft was established on the basis of comments received during a parallel enquiry on the draft.

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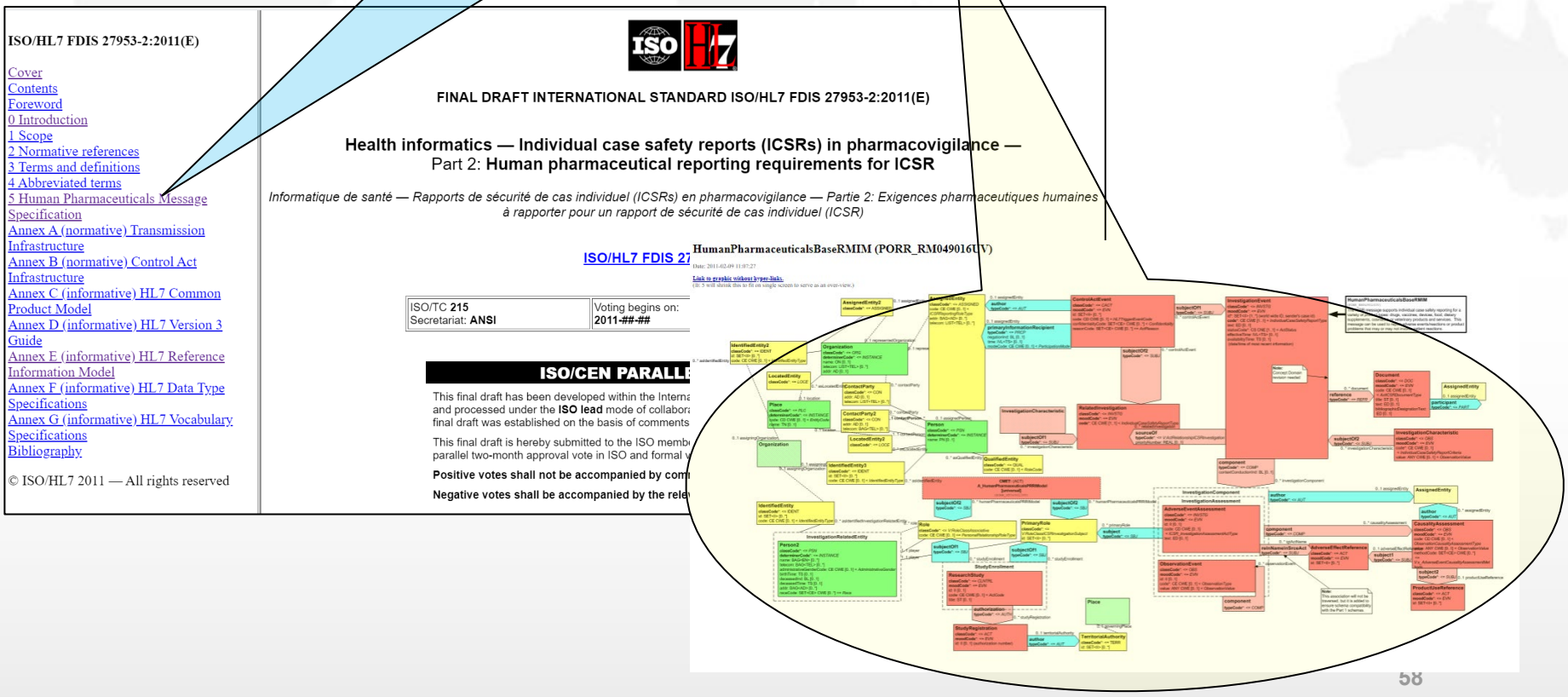
Positive votes shall not be accompanied by comments.

Negative votes shall be accompanied by the relevant technical reasons.

Left panel provides good training/reading material to understand HL7 V3 standard.

HL7 ICSR RMIM (1/3)

- Click on "5 Human Pharmaceuticals Message Specification" and scroll down to section 5.5.1 for the HumanPharmaceuticalsBaseRMIM, click on the diagram to open a large model for study.



ISO/HL7 FDIS 27953-2:2011(E)

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ISO/HL7 FDIS 27

ISO/TC **215** Secretariat: **ANSI**	Voting begins on: **2011-##-##**

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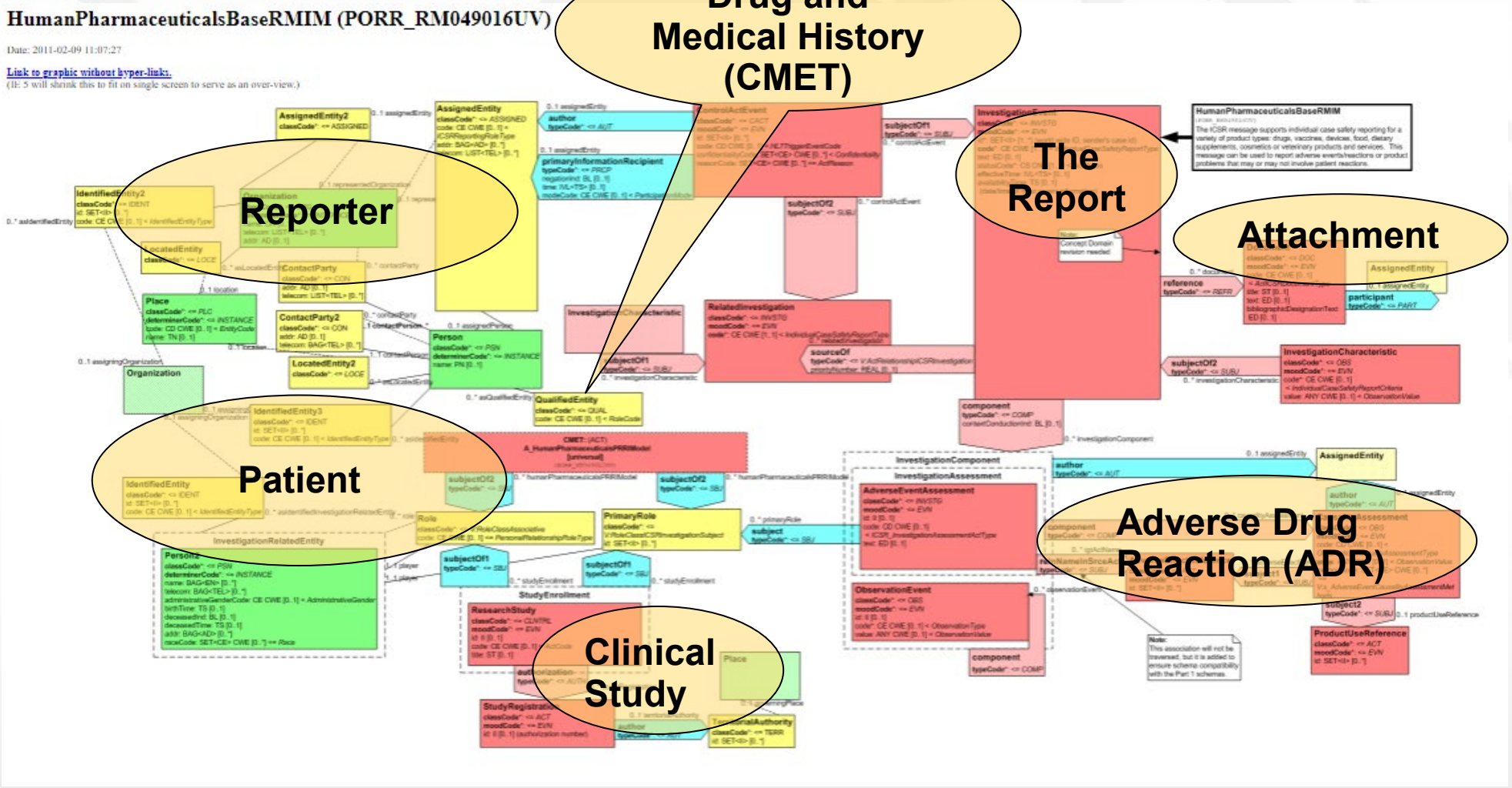
HumanPharmaceuticalsBaseRMIM (PORR_RM049016UV)

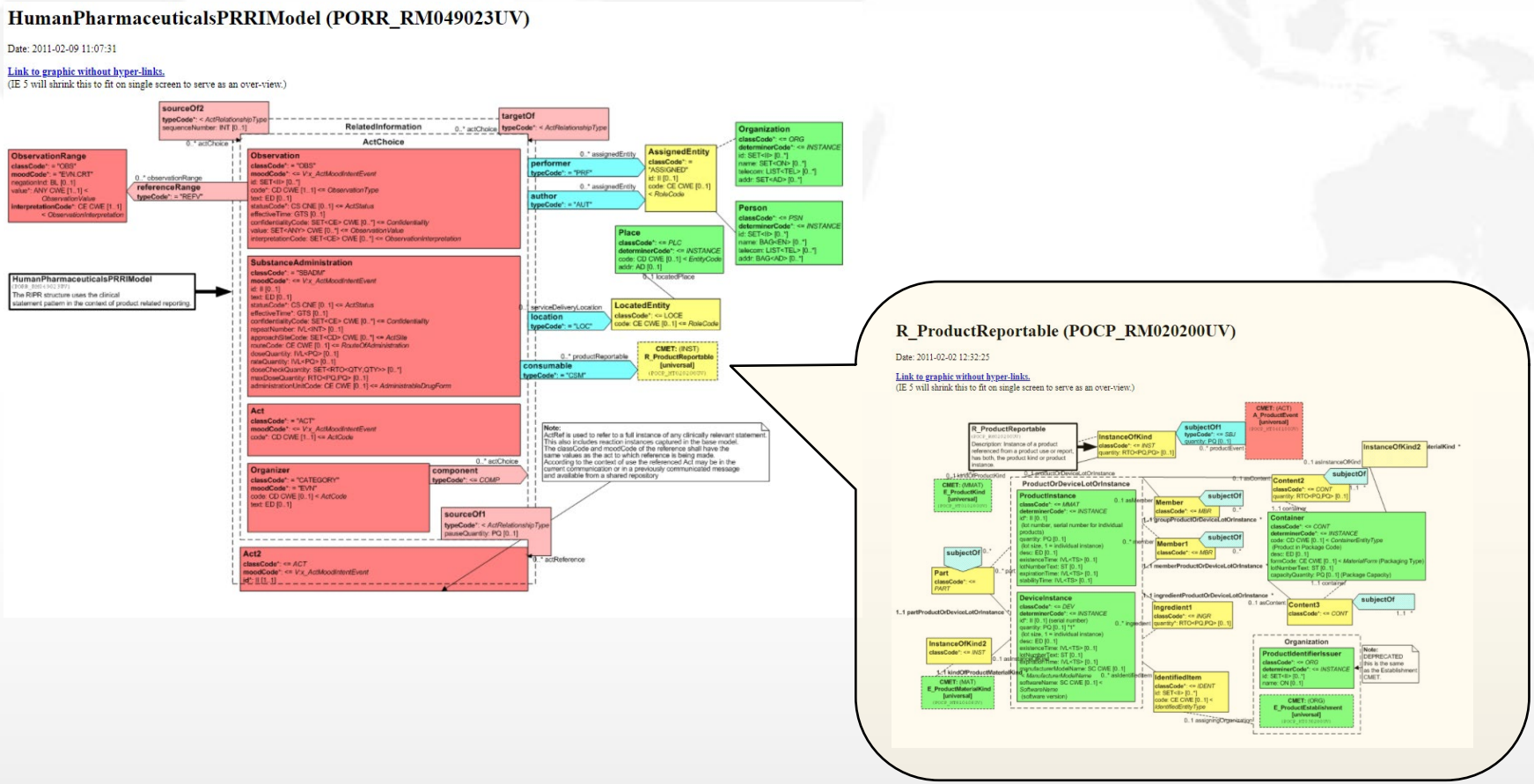
HL7 ICSR RMIM (2/3)

High-level grouping



HL7 ICSR RMIM (3/3)

- From the base diagram, click on boxes noted as “CMET” to open linked modules/diagrams.



Use ICH E2B(R3) Reference Instance to learn the model

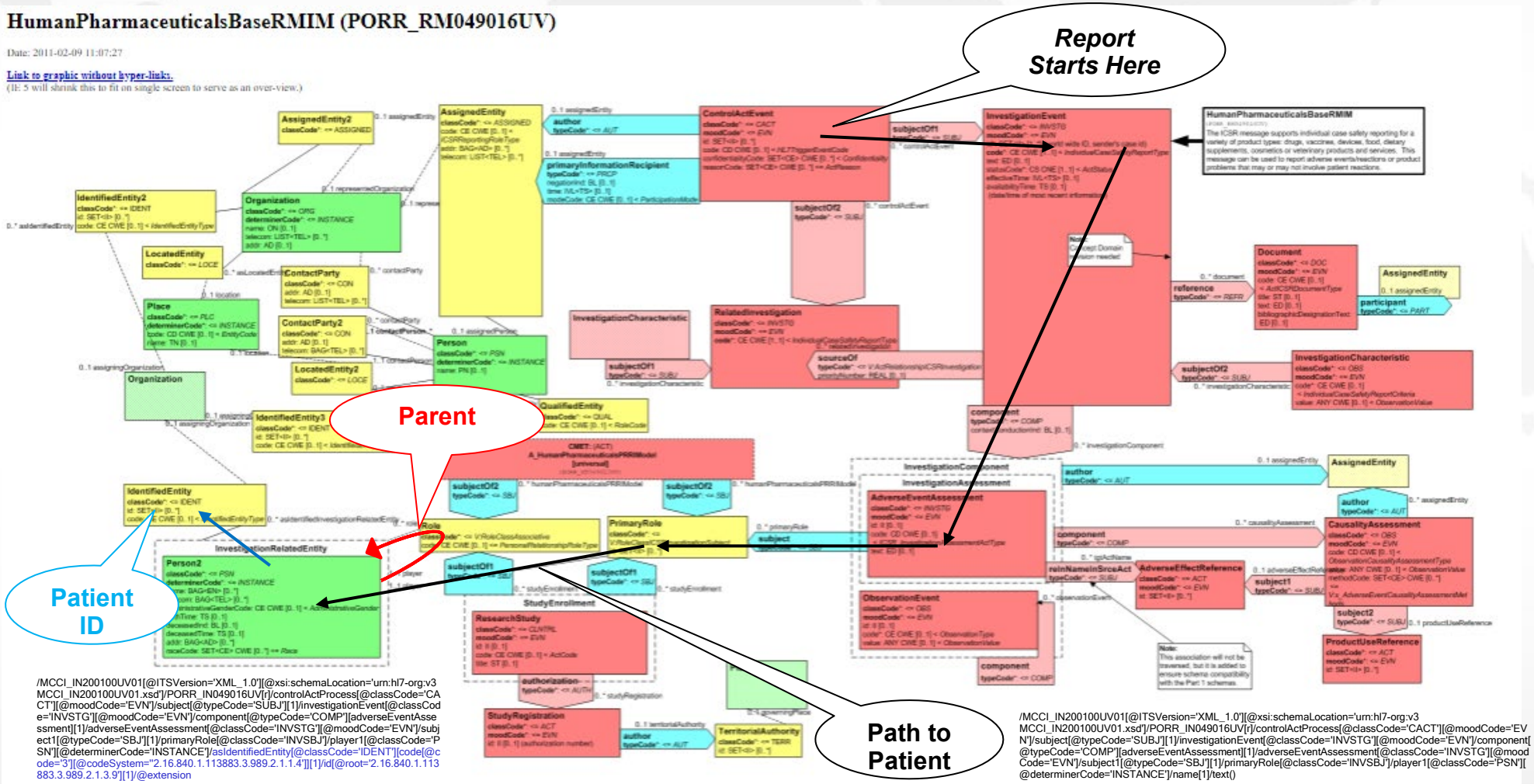
```
<investigationEvent classCode="INVSTG" moodCode="EVN">
        <id extension="C.1.1" root="2.16.840.1.113883.3.989.2.1.3.1"/>
        <!-- C.1.1: Sender's (case) Safety Report Unique Identifier -->
                .
                .
        <component typeCode="COMP">
                <adverseEventAssessment classCode="INVSTG" moodCode="EVN">
                        <subject1 typeCode="SBJ">
                                <primaryRole classCode="INVSBJ">
                                        <player1 classCode="PSN" determinerCode="INSTANCE">
                                                <name>D.1</name>
                                                <!-- D.1: Patient (name or initials) -->
                                                <administrativeGenderCode code="D.5" codeSystem="1.0.5218"/>
                                                <!-- D.5 Sex -->
                                                <birthTime value="20090101"/>
                                                <!-- D.2.1: Date of Birth -->
                                                <deceasedTime value="20090101"/>
                                                <!-- D.9.1: Date of Death -->
                                                <asIdentifiedEntity classCode="IDENT">
                                                        <id extension="D.1.1.1" root="2.16.840.1.113883.3.989.2.1.3.7"/>
                                                        <!-- D.1.1.1: Patient Medical Record Number(s) and Source(s) of the Record Number (GP Medical Record Number) -->
                                                        <code code="1" codeSystem="2.16.840.1.113883.3.989.2.1.1.4" codeSystemVersion="1.0" displayName="GP"/>
                                                </asIdentifiedEntity>
                                                <asIdentifiedEntity classCode="IDENT">
                                                        <id extension="D.1.1.2" root="2.16.840.1.113883.3.989.2.1.3.8"/>
                                                        <!-- D.1.1.2: Patient Medical Record Number(s) and Source(s) of the Record Number (Specialist Record Number) -->
                                                        <code code="2" codeSystem="2.16.840.1.113883.3.989.2.1.1.4" codeSystemVersion="1.0" displayName="Specialist"/>
                                                </asIdentifiedEntity>
                                                <asIdentifiedEntity classCode="IDENT">
                                                        <id extension="D.1.1.3" root="2.16.840.1.113883.3.989.2.1.3.9"/>
                                                        <!-- D.1.1.3: Patient Medical Record Number(s) and Source(s) of the Record Number (Hospital Record Number) -->
                                                        <code code="3" codeSystem="2.16.840.1.113883.3.989.2.1.1.4" codeSystemVersion="1.0" displayName="Hospital Record"/>
                                                </asIdentifiedEntity>
                                                <asIdentifiedEntity classCode="IDENT">
                                                        <id extension="D.1.1.4" root="2.16.840.1.113883.3.989.2.1.3.10"/>
                                                        <!-- D.1.1.4: Patient Medical Record Number(s) and Source(s) of the Record Number (Investigation Number) -->
                                                        <code code="4" codeSystem="2.16.840.1.113883.3.989.2.1.1.4" codeSystemVersion="1.0" displayName="Investigation"/>
                                                </asIdentifiedEntity>
                                                <role classCode="PRS">
                                                        <code code="PRN" codeSystem="2.16.840.1.113883.5.111"/>
                                                        <associatedPerson classCode="PSN" determinerCode="INSTANCE">
                                                                <name>D.10.1</name>
                                                                <!-- D.10.1: Parent Identification -->
                                                                <administrativeGenderCode code="D.10.6" codeSystem="1.0.5218"/>
                                                                <!-- D.10.6: Sex of Parent -->
                                                                <birthTime value="20090101"/>
                                                                <!-- D.10.2.1: Date of Birth of Parent -->
                                                        </associatedPerson>
```

Patient

Patient ID(s)

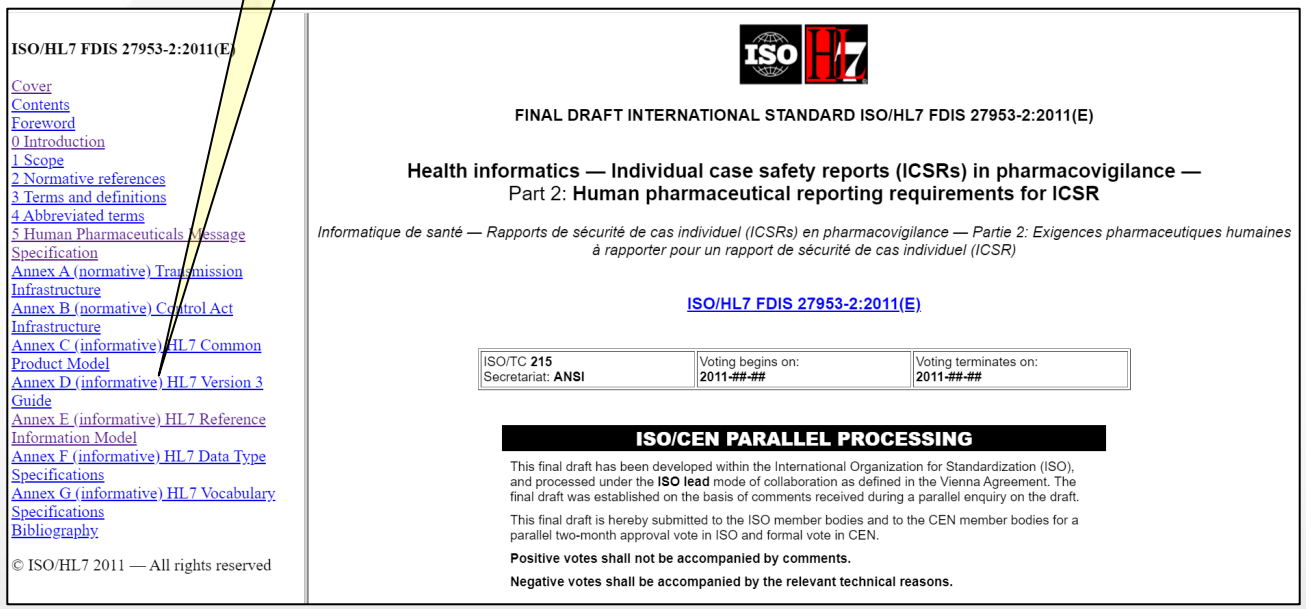
Parent

Use Reference Instance to traverse the RMIM



HL7 ICSR V3

- The ISO/HL7 ICSR is based on HL7 Reference Information Model (RIM) Release 2 and is bound to HL7 Abstract Data Types Release 1.
- Click on Annex D to learn the HL7 V3 standard.
  - RIM, D-MIM, and R-MIM.
  - Classes, Relationships, and Attributes.
  - Data Types.



ISO/HL7 FDIS 27953-2:2011(E)

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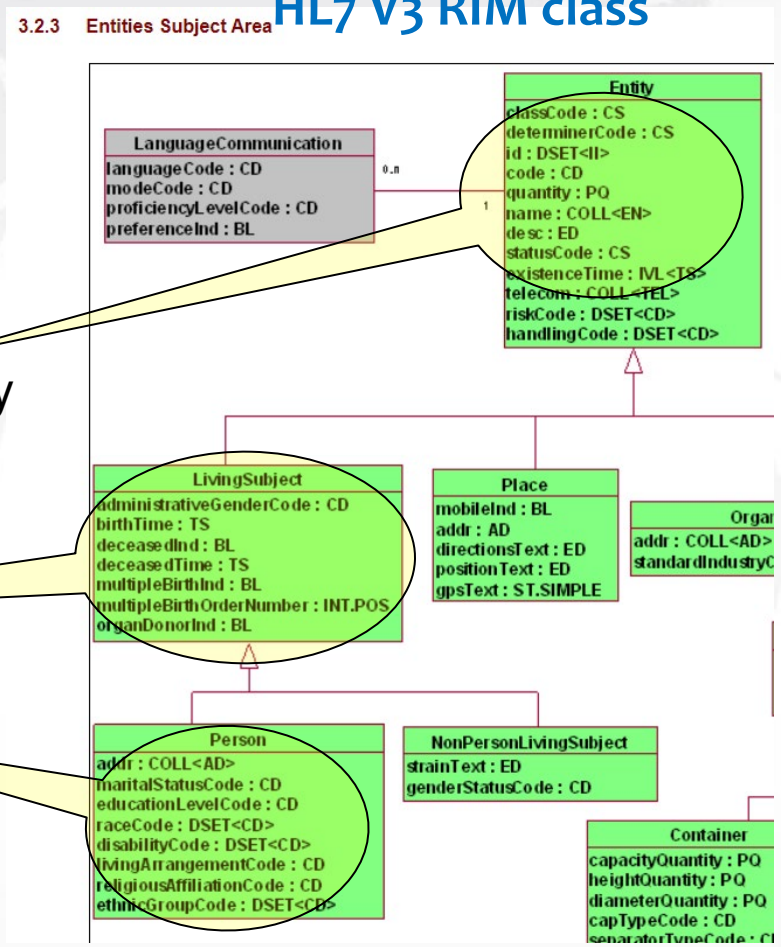
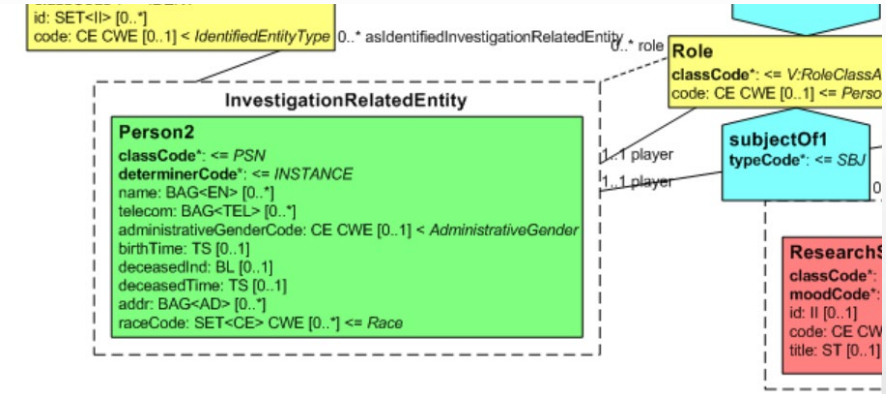
Focus on ISO/HL7 ICSR for assigning regional data elements

- RMIM/DMIM is based on a subset of cloned classes from RIM.
- The cloned classes contain a subset of attributes from RIM classes.
- Example – Person2 attributes
  - Name & telecom attributes inherits form Entity class
  - AdministrativeGenderCode, birthtime, deceasedInd & deceasedTime attributes inherits from LivingSubject class
  - addr & raceCode attributes inherits from Person class

HL7 V3 RIM class



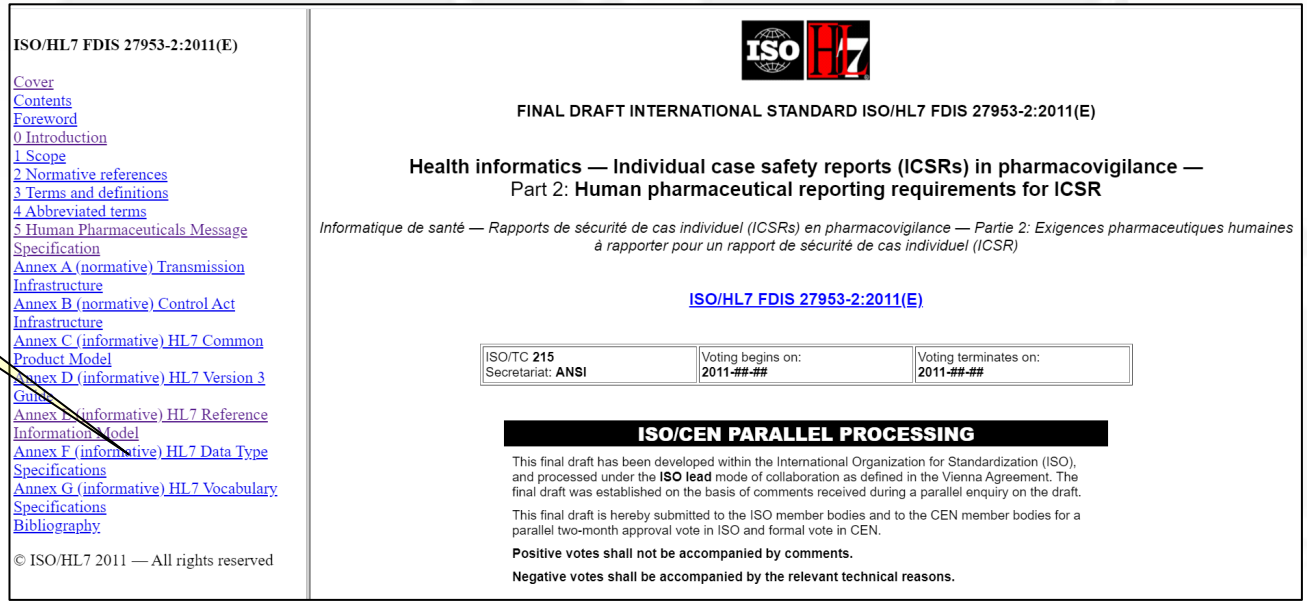
ICSR RMIM class



Any Classes or Attributes not in ISO/HL7 ICSR RMIM will not be validated against the ICSR schema

HL7 V3 Data Type

Click on Annex F for Hl7 Data Type Specifications



ISO/HL7 FDIS 27953-2:2011(E)

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- **Data types**
  - Are **specifications** for the value domain of an attribute.
- **Data types have components, except “Primitive Data Type”**
- **Each component is assigned a data type**
- **Data types have hierarchies**

Focus on ISO/HL7 ICSR for assigning regional data elements

HL7 Coded Data Types (such as Concept Descriptor (CD), Coded With Equivalents (CE), Concept Role (CR), Coded Simple Value (CS), and Coded Value (CV)) utilize "codeSystem" for interpretation / validation of the code

Data Type for the codeSystem is Unique Identifier String (UID).

UID is a character string that uniquely identify an object globally.

The form of UID can be an OID, a Universally Unique Identifier (UUID) or a Real User Identifier (RUID).

UID is associated with one vocabulary domain:

- HL7 defined domain.
- HL7 recognized external coding scheme : ICD-10, ISO 3166, LOINC, MedDRA, UCUM.
- Locally-defined codes.

- Extensibility
  - CNE: coded no extensions.
  - CWE: coded with extensions.

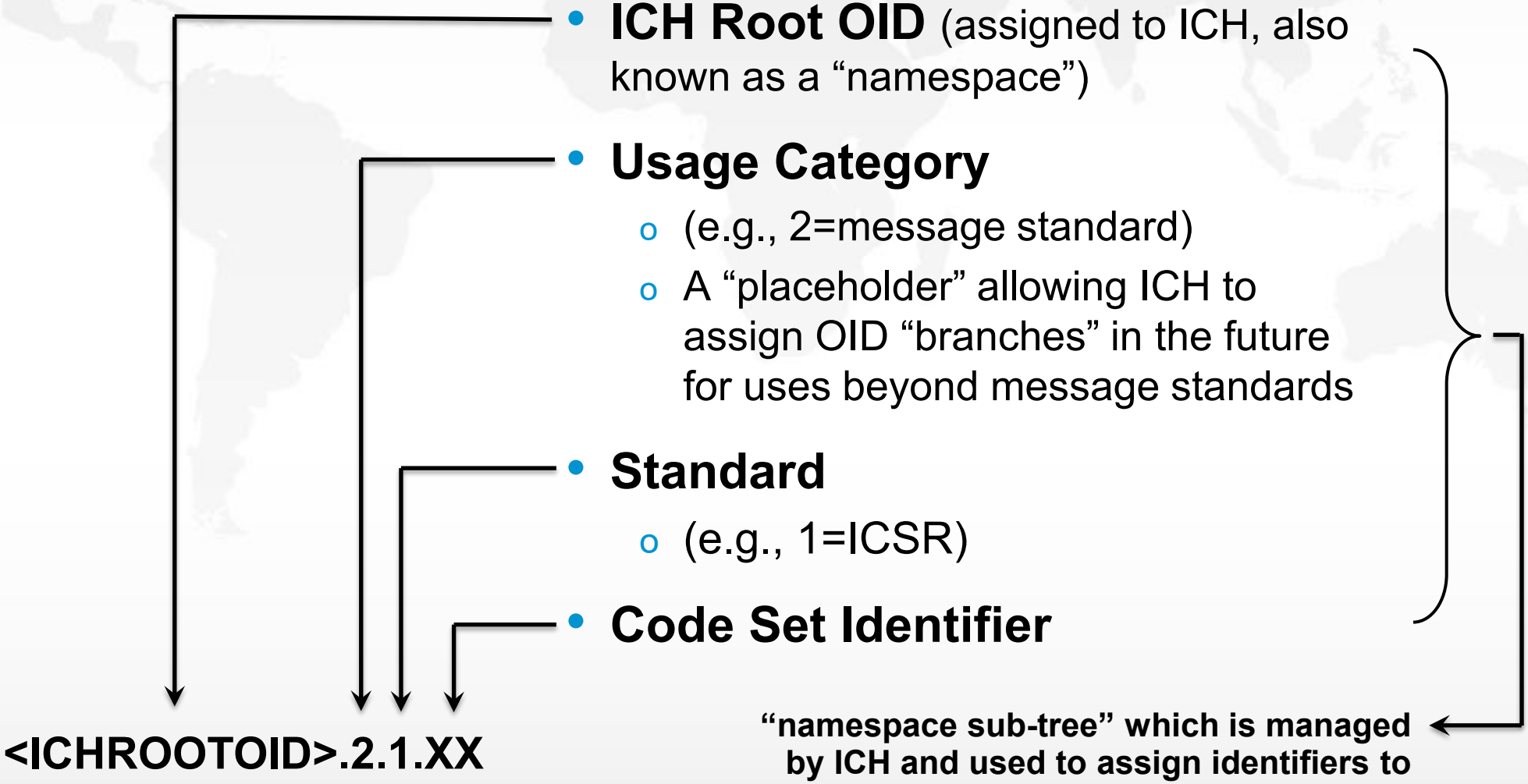
Object Identifier (OID)

- **An OID is a sequence of numbers to uniquely identify an object.**
- **These numbers are written either as a string of digits separated by dots or as a list of named 'branches.'**
  - ICH - 2.16.840.1.113883.3.989
  - {joint-iso-itu-t.country.us.organization.hl7.externalUseRoots.ich-estri}
- **An organization with a registered OID can create and assign child OIDs from the registered OID.**
- **Please refer to ICH M2 Information Paper for detail information on OID - https://admin.ich.org/sites/default/files/inline-files/OID_Information_Paper_1.pdf.**

ICH OID assignment framework (1/2)

- ICH is a Registration Authority under the arc of HL7 with responsibility to assign its own OIDs.
  - 2.16.840.1.113883.3.989 {joint-iso-itu-t.country.us.organization.hl7.externalUseRoots.ich-estri}.
- ICH M2 EWG acts on behalf of ICH to assign and maintain OID values in partnership with the particular relevant ICH EWG developing a standard that may require code lists or namespaces.
- Code list versions will be managed and indicated on ESTRI website but OID values will not change as versions change.

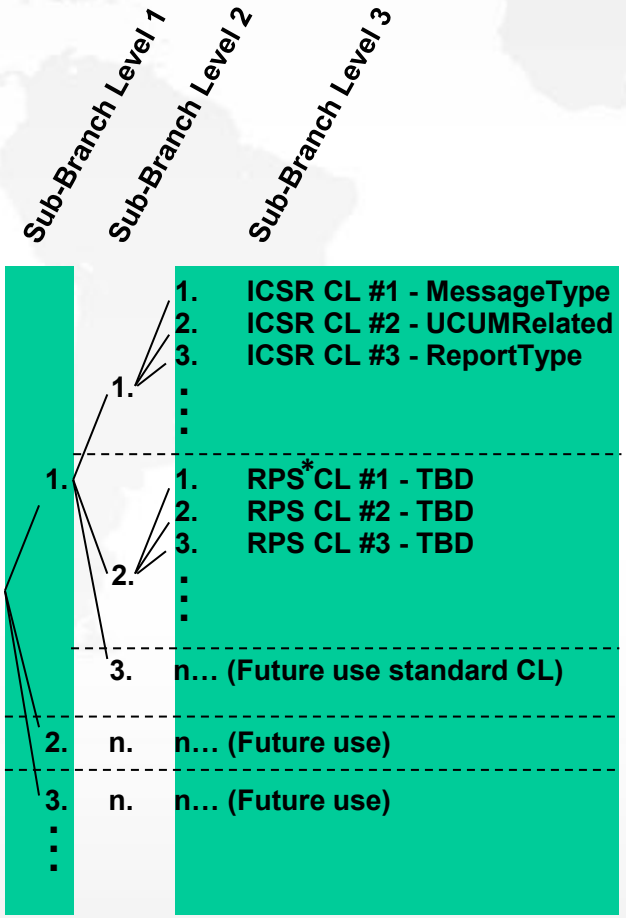
ICH OID assignment framework (2/2)



ICH OID assignment framework for ICH E2B

- **ich-estri** 2.16.840.1.113883.3.989
  - ich-estri-msg-stds 2.16.840.1.113883.3.989.2
    - ich-estri-msg-stds-e2b-icsr 2.16.840.1.113883.3.989.2.1
      - ich-estri-msg-stds-e2b-icsr-code-lists 2.16.840.1.113883.3.989.2.1.1
      - ich-estri-msg-stds-e2b-icsr-documents 2.16.840.1.113883.3.989.2.1.2
      - ich-estri-msg-stds-e2b-icsr-other-namespaces 2.16.840.1.113883.3.989.2.1.3
  - ich-estri-regional-specialized.sub-reg 2.16.840.1.113883.3.989.5.1
    - ich-estri-regional-specialized.sub-reg.eu 2.16.840.1.113883.3.989.5.1.1
    - ich-estri-regional-specialized.sub-reg.fda 2.16.840.1.113883.3.989.5.1.2
    - ich-estri-regional-specialized.sub-reg.smc 2.16.840.1.113883.3.989.5.1.5

Illustrated Node Hierarchy



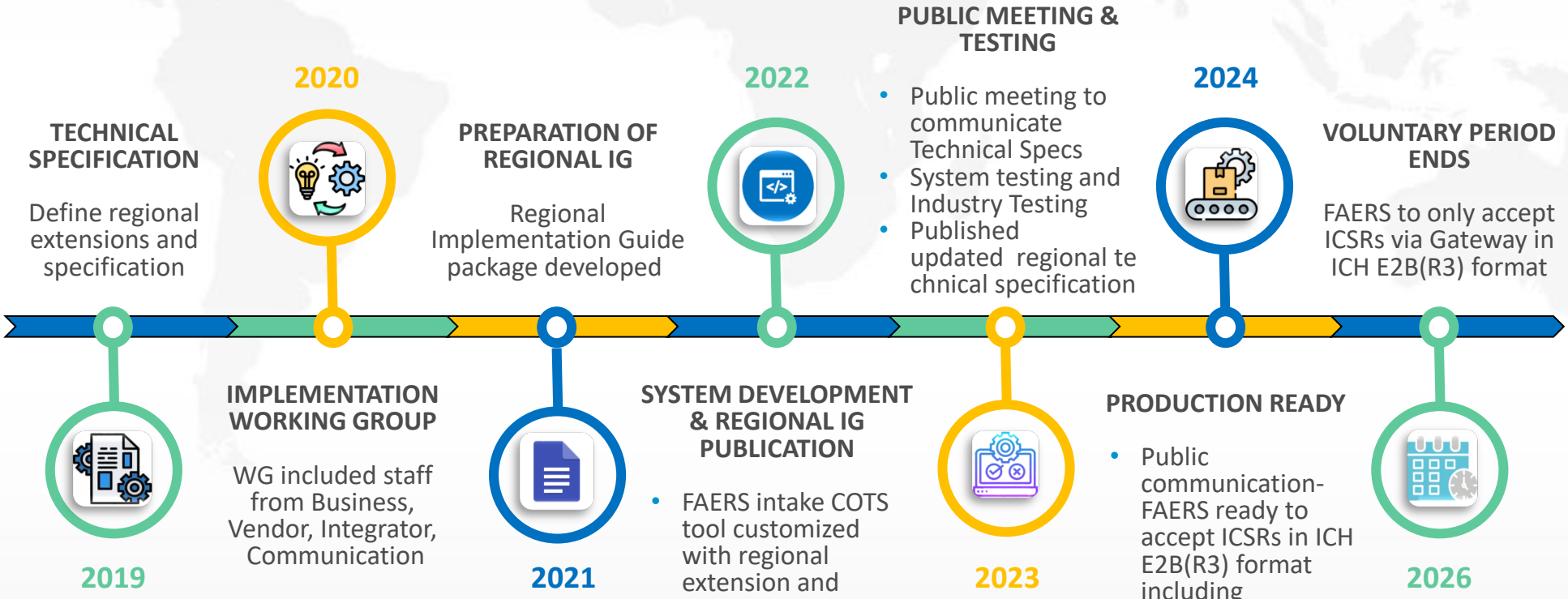
- **Versioning**
  - Versions of the code list will be tracked by ICH internally; however, the OID will not change for a new version.
  - Decision: no sub-branch or new OID for versions.
- **Common Code Lists**
  - Over time, some code lists may be applicable to multiple standards. In such cases, subsequent uses would reference the originally assigned code list OID. For example, it is acceptable for RPS to use a code list that has a value of "1" at sub-branch level 2.

NOTE: consideration was given to removing sub-branch level 2 in the "code systems" branch, however, this has been retained for the time being.

*RPS: Regulated Product Submission

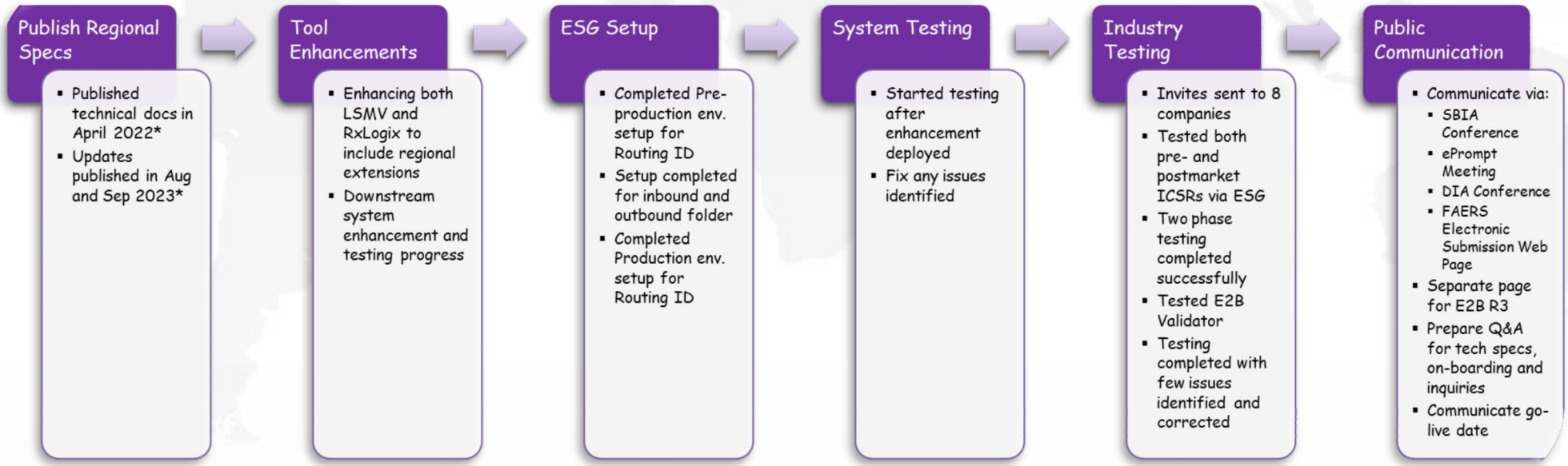
Table of Contents

E2B(R3) Implementation Milestones in FDA, United States
in the case of FAERS



Note: FDA, Unites States Vaccine Adverse Event Reporting System (VAERS) electronic submission per ICH E2B(R3) format has been in operation since 2015.

Implementation Activities in FDA, United States



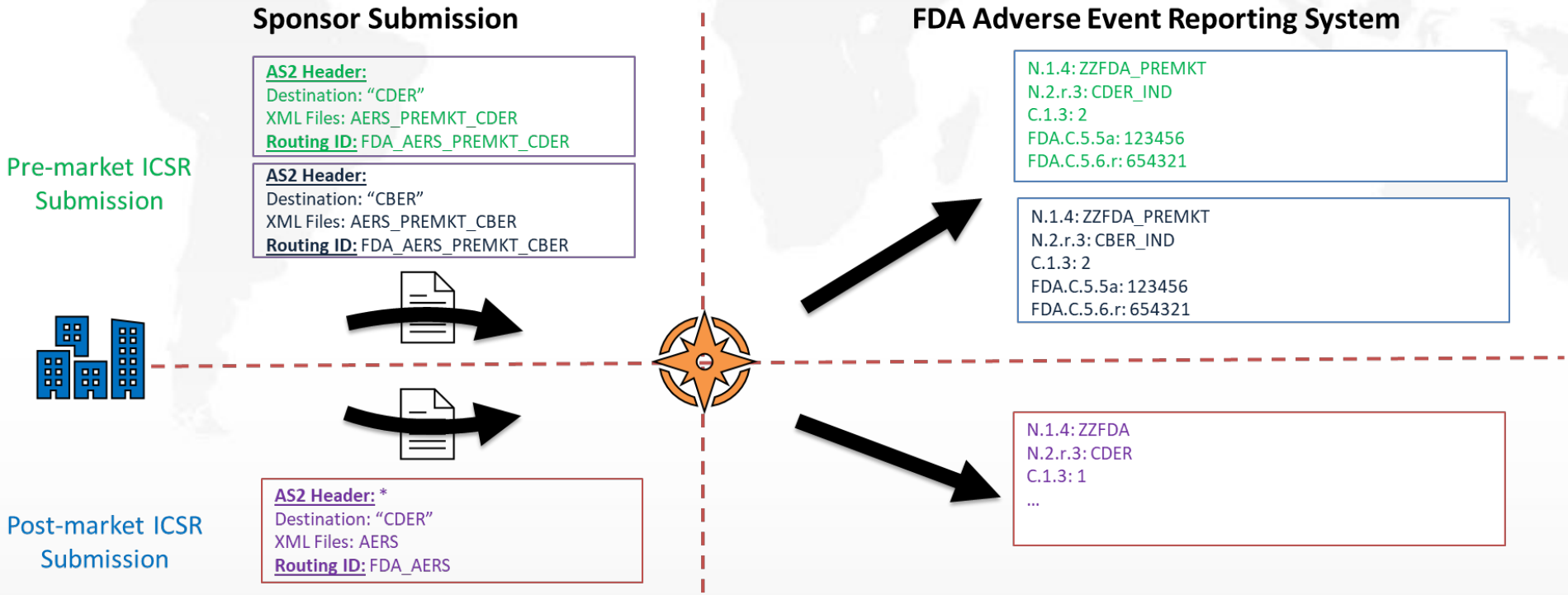
Regional Consideration in FDA, United States

- Introduce New Regional Data Elements.
- Publish Regional Technical Specification.
- Publish Consolidated list of core ICH and Regional data elements with business rules.
- Publish Forward compatibility rules for the regional elements.
- Provide ICH E2B(R3) validator tool that accounts for regional data elements and regional rules.
- Downstream systems impact considerations and reconciliation opportunities.

ICH E2B(R3) Validator in FDA, United States

- FDA, United States ICH E2B(R3) Validator helps to facilitate the validation of the ICH E2B(R3) XML files generated from companies' safety database during the testing phase.
- Provides a web-based interface that enables submitter to select an ICH E2B(R3) XML file and validate.
- The validation status and results are displayed to the user immediately.

Approach to Triage of ICSRs via ESG in FDA, United States



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

Triaging protects nonpublic information

FDA, United States' Regional IG Package

Document / Web Page	Accessible At
FDA, United States Adverse Event Reporting System (FAERS) Electronic Submissions –Web page	https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions
FDA, United States Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products (Aug 2022)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-regional-implementation-guide-e2br3-electronic-transmission-individual-case-safety-reports-drug
FDA, United States ICH E2B(R3) Core and Regional Data Elements and Business Rules v1.5 (Oct 2023)	https://www.fda.gov/media/157982/download
FDA, United States ICH E2B(R3) Forward Compatible Rules (Apr 2022)	https://www.fda.gov/media/157993/download
FDA, United States ICH ICSR XML Instances (Sep 2023)	https://www.fda.gov/media/157983/download
Electronic Submission of IND Safety Reports - Technical Conformance Guide (Apr 2022)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-ind-safety-reports-technical-conformance-guide
Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies - Draft Guidance for Industry (Aug 2022)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-expedited-safety-reports-ind-exempt-babe-studies-guidance-industry
FAERS ICH E2B(R3)Validator	https://faers2-validator.preprod.fda.gov/LSMV/Validator

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Introduction to EudraVigilance

- EudraVigilance (EV) is the centralised European database of suspected adverse reactions to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA).
  - The database is managed by EMA, on behalf of the European National Competent Authorities (NCAs).
  - EEA NCAs, marketing authorisation holders (MAHs) and clinical trial sponsors submit ICSRs to EudraVigilance.
  - EudraVigilance was implemented in December 2001 using ICH E2B(R2).
  - Electronic reporting (ICH E2B(R2) format) was made legally mandatory in 2005
  - A new version of the EudraVigilance system supporting ICH E2B(R3) went live in November 2017.
    - Initially exchange of both ICH E2B(R2) and ICH E2B(R3) messages was supported.
    - As from June 2022 onwards only ICH E2B(R3) is supported (as per EU legislation).

EudraVigilance upgrade to ICH E2B(R3): EC, Europe Technical Planning

- Before development started at EC, Europe the following documents were prepared:
  - EudraVigilance system business requirements.
    - Creation of system use cases.
  - Technical design documentation.
    - Logical model including mappings to the ISO ICSR messaging model (XSD) and Implementation Guides.
    - Physical model including mapping to the ICH E2B(R2) logical model.
      - Development of data migration scripts.
- It took 6 months for this type of work to be completed.
- Knowledge of HL7 V3 messaging helps with this technical design work.

Key milestones ICH E2B(R3) Implementation in EU

Dec 2014

TECHNICAL SPECIFICATION

Publication of EU implementation Guide

Q2 2016

INITIAL STAKEHOLDER TESTING WITH NEW EV SYSTEM

Scope to provide opportunity to selected 's to test the new functionalities implemented in the EV system

Q4 2016

OPEN TESTING

New test environment became available to all stakeholders for testing

Q1 2017

TRAINING PROGRAMME LAUNCHED

- Training with new ICH E2B(R3) format EVWEB launched for all stakeholders
- Video Training published for existing stakeholders for conversion from ICH E2B(R2) to ICH E2B(R3)

Jul 2017

GO-LIVE WITH ICH E2B(R3) MESSAGE EXCHANGE

- Initial go-live in external testing system
- All stakeholders free to use system to test their implementation

Nov 2017

PRODUCTION READY

- 22 Nov 2017 Production system goes live with ICH E2B(R3) message exchange

Jun 2022

MANDATORY USE OF ICH E2B(R3) & EDQM FOR DOSE & ROA

- Date chosen based on stakeholder readiness survey from 2019
- Mandatory use of EDQM terminology for dose & Routes of Administration forced mandatory ICH E2B(R3)

Relationship ISO ICSR standard, ICH E2B(R3) & the EU ICSR IGs

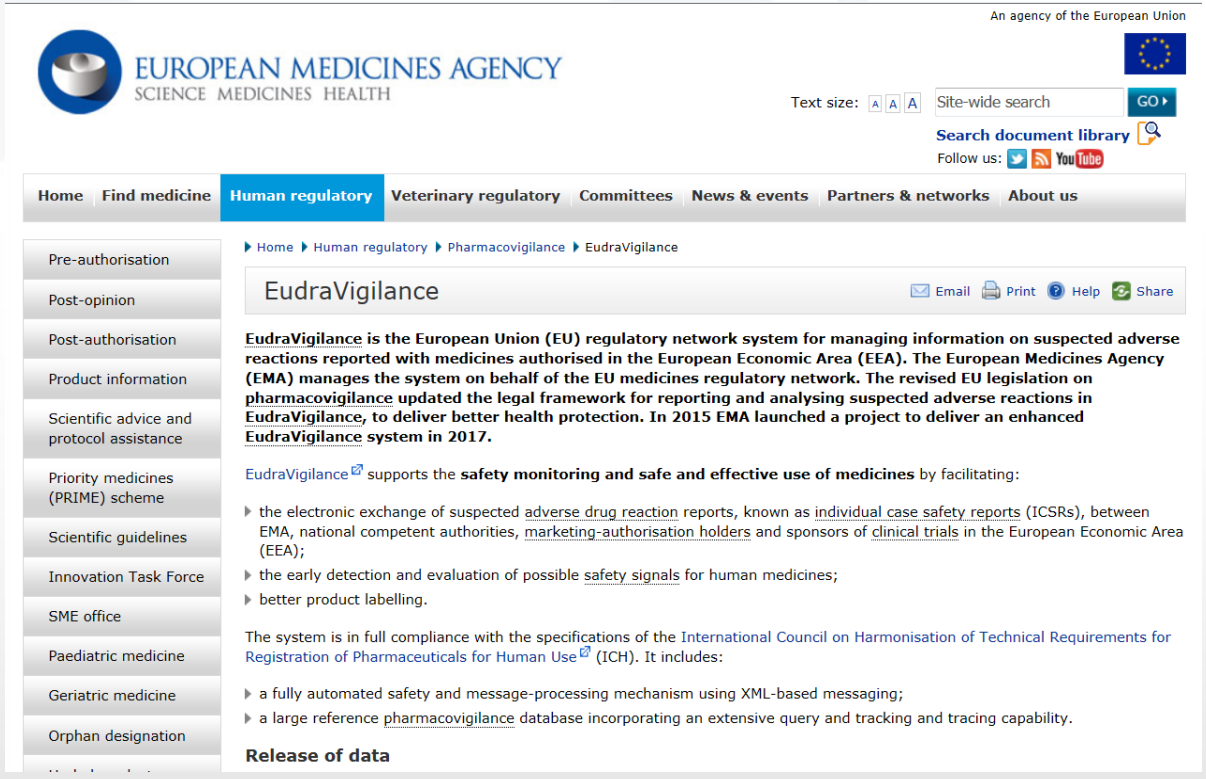
- The ISO standard provides the schema files (technical structure) to be used to create ICSR messages.
- The ICH E2B(R3) (IG) provides the core set of requirements for the contents of messages (ICSRs and ACKs).
- The EU ICSR IG supplements the ICH E2B(R3) IG with additional EU specific requirements:
  - Additional Data elements to the ICH IG.
  - Controlled vocabularies specific to the EU.
  - Business rules (some optional fields in ICH are mandatory in the EU).
- It is emphasized that EU Implementers should not read ICH documentation in isolation, but in conjunction with EU technical documents.

Publication of additional EU Technical Documents (1/2)

- **Documents supporting technical implementation of ICH E2B(R3) in EU:**
  - EU ICSR Implementation Guide (1st published in December 2014).
  - EU ICSR Implementation Guide Business rules spreadsheet.
  - EU Backwards Forwards Conversion (BFC) Element Mapping spreadsheet.
  - EU Backwards Forwards Conversion Tool – Based on the ICH BFC tool it includes the addition EU specific data fields.
  - EU ICH E2B(R3) Code Lists – Provides the list of codes for EU specific data fields.
  - EU Reference Instance – An amended ICH reference instance that includes the EU specific data fields.
  - EU Example Instances – Additional example instances that should be used for testing ICH E2B(R3) transmission to the EudraVigilance system.

Publication of additional EU Technical Documents (2/2)

- **Dedicated EudraVigilance webpage at the EC, Europe corporate website:**
  https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance



Change management plan

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 October 2015
EMA/797114/2014
Information Management Division

EudraVigilance stakeholder change management plan

Consultation of Project Maintenance Group 1	15 July 2015
Consultation of Eudravigilance Expert Working Group	23 September 2015
Consultation of Signal Management Review Technical Working Group (SMART WG) – Work Stream 1	7-10 September 2015
Consultation of the Pharmacovigilance Risk Assessment Committee (PRAC)	7-10 September 2015
Implementation Group (IG) for information	14 September 2015
IT Directors for information	22 October 2015
EU Telematic Management Board (EUTMB) for information	15 September 2015
Endorsement by European Risk Management Facilitation Group (ERMS-FG)	12 October 2015
Heads of Medicines Agencies (HMA) for information	22 October 2015

Q4 2015: publication of a change management plan as a starting point for stakeholders to develop their own internal plans up to the go live of ICH E2B(R3) in EU in November 2017:

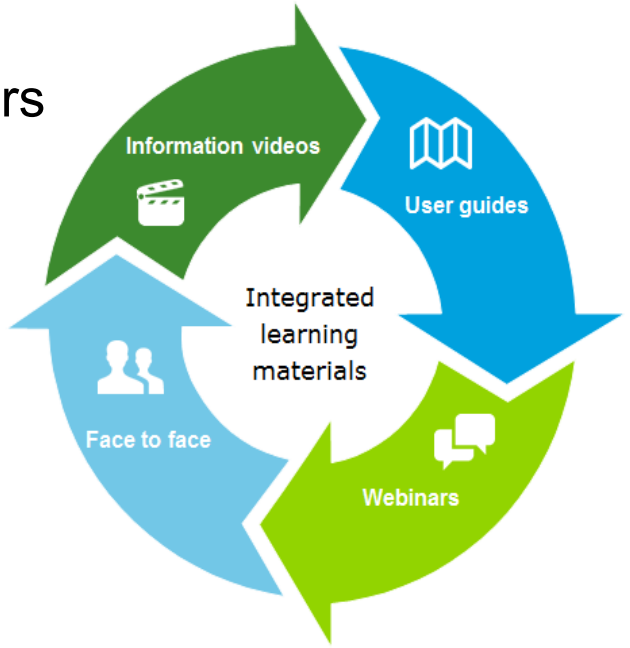
EudraVigilance stakeholder change management plan:
https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/wc500196029_en.pdf

Implementation considerations

- Implementation by stakeholders in EU required a legal basis mandating electronic reporting and format.
  - Since not all stakeholders have the resources/business need to implement advanced electronic systems for ICSR submissions (e.g., small volumes of ICSR to be submitted) EC, Europe has developed an online reporting tool (EVWEB – EudraVigilance Web application) to support these organisations.
- Implementing ICH E2B(R3) in ’s Pharmacovigilance systems:
  s needed to consider implementing a **fully ICH E2B(R3) compliant system or to use a backwards/forwards conversion tool** in order to support the processing of the ICH E2B(R3) format ICSRs and ACKs from EudraVigilance.
- Regardless of using EVWEB or their own systems, all stakeholders need to **understand and apply ICH E2B(R3) principles** (e.g., seriousness at event level, amendment reports, additional drug role characterisation, etc.).

Stakeholder training (flexible training paths)

- s were encouraged to familiarise themselves with the changes in order to be ready for the changed EudraVigilance system.
- Module based online training approach for all users accessible through the EC, Europe website.
- The online learning comprises the use of:
  - Information videos
  - Contextual help in EVWEB.
  - User Manuals.
  - Demo videos.
  - Competency assessments.
- Limited face to face trainings based on a train the trainer approach.



Stakeholder testing with changed EV system (1/4)

Stakeholders were expected to carry out their own development and validation testing activities with EV test system **before requesting quality assurance testing with EC, Europe**. To support this activity a set of test files is available on the EC, Europe website (https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-electronic-reporting)

A. Testing with MAHs

MAHs were requested to complete any testing of their existing systems 3 to 6 months prior to the new EV system going live, to give time for any issues to be addressed

Stakeholder testing with changed EV system (2/4)

B. System testing for Pharmacovigilance database vendors & Contract Research Organisations (CRO)

Vendors & CROs can perform testing for a specific version & build of their system; EC, Europe will confirm if that precise version of the database has passed testing.

- Full testing will NOT be required for individual s using that tested version and configuration

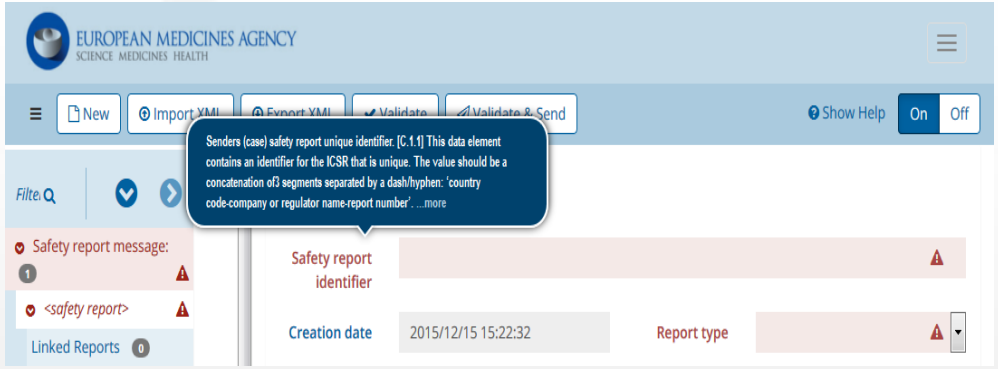
- New/modified versions of the system may require (re-)testing:
  If changes are made to the tested version and its configuration for a specific and if these changes will affect the generation of the XML and/or its contents, the normal testing process with EC, Europe will be required for that MAH

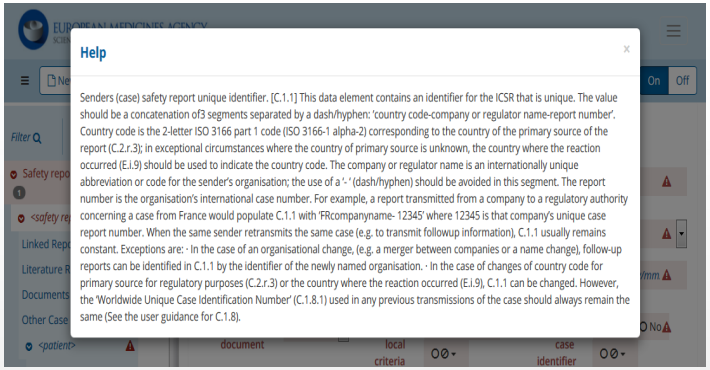
Stakeholder testing with changed EV system (3/4)

C. EVWEB:

A new version of this application was released to support ICH E2B(R3) format ICSRs data entry.

An EV WEB test/training environment was also made available. For organisations using EVWEB no official testing with EC, Europe was required. Instead, they were requested to start training their staff 6 months in advance of the go-live of the new EV system, followed by regular refresher training at least 3 months and 2 weeks before go-live.





Examples of built-in help in EV WEB

Stakeholder testing with changed EV system (4/4)

- **Acknowledgements (ACKs)**
  Implementation and testing activities do not only need to take into account ICSRs, but also ACKs

- **ESTRI Gateway for ICSR transmission:**
  - EC, Europe Gateway software solution remained the same, however some stakeholders needed configuration changes to support ICH E2B(R3) messages (ICSRs and ACKs)
  - As only submissions of ICSRs to EudraVigilance are considered as fulfilling the ’s legal obligations, s should ensure that modifications to their submission systems are configured and tested

Phasing out ICH E2B(R2)

- Converting data from ICH E2B(R2) to ICH E2B(R3) format has implications for data quality.
- To fully benefit from the improved ICH E2B(R3) format, the EU medicines regulatory network agreed on a date for its mandatory use.
- Based on a stakeholder readiness survey done in 2018/2019 it was decided in March 2020 to phase out ICH E2B(R2) messages and only accept ICH E2B(R3) as from June 2022.

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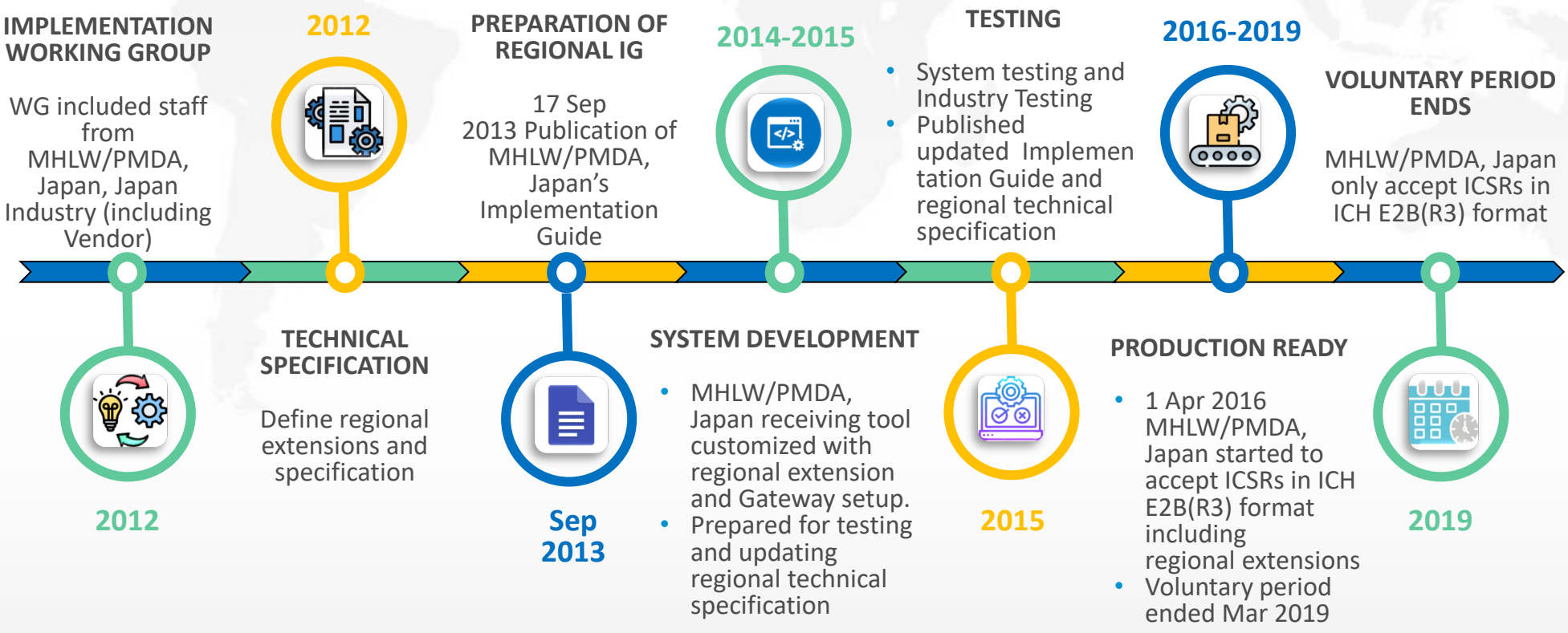
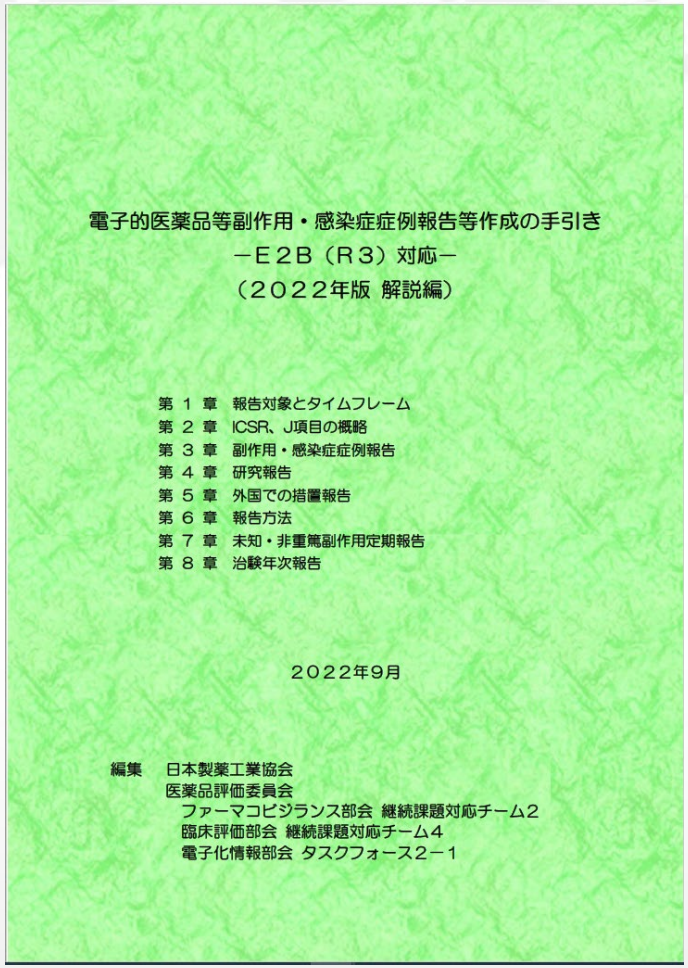
E2B(R3) Implementation Timeline in MHLW/PMDA, Japan



Development of ICH E2B(R3) Guidebook (aka, ICH E2B Green Book)*

- Why “Green Book”?
  - Because its color of the cover is green.
- Developed by JPMA.
  - Approx. 80 members involved in E2B Green Book development.
  - Reviewed by the authority members.
- Referred by not only industry, but also system vendors.



*https://www.jpma.or.jp/information/evaluation/pv_navi/index.html

History of ICH E2B Guidebook (aka, ICH E2B Green Book)

- **Green Book for ICH E2B(R2)**
  - June 2003 : Preliminary version
  - October 2003: 1st edition
  - September 2004: 2nd edition
  - July 2005: Draft of 3rd edition
  - November 2006: 3rd edition
  - April 2012: 4th edition
- **Green Book for ICH E2B(R3)**
  - September 2015: 1st edition
  - June 2018: 2nd edition
  - September 2022: 3rd edition

Main Contents of ICH E2B(R3) Green Book

- Fundamentals on ICSR
  - Definition and its grounds of medicinal product, investigational product, ADR, adverse events (AE) and infections
  - Related laws, ordinaries and notifications
  - Scope of expedited reports and timeframes
- ICH E2B(R3) elements and Japanese regional elements (J elements)
- Detailed explanations and related Q&As to each ICH E2B(R3) element
- Methods and procedure of ICSR reporting

Annex : Case Studies – MHLW/PMDA, Japan

D.1　患者（名前又はイニシャル）

利用の手引き	このデータ項目への入力は重要である。患者を特定できる情報の提示は、国によってはある種の個人情報保護の法規又は規則によって禁止されている場合がある。個人情報保護に抵触しない場合は、この情報を提供する。
適合性	必須
データ型	60AN
OID	なし
許容値	自由記載 nullFlavor：MSK、ASKU、NASK、UNK
記載ルール	
	送信者が患者のイニシャルを知っていても、個人情報保護のためにそれを伝送できない場合、null flavorのMSKを利用してこのデータ項目を空欄のままにする。 情報の欠損や伝送しない情報等を記述するためのnull flavorの使用に関する詳しい手引きについては第2章を参照のこと。

報告分類	市販後				治験			
	国内・感染症	国内・副作用	外国・感染症	外国・副作用	国内・感染症	国内・副作用	外国・感染症	外国・副作用
未完了	◎	◎	◎	◎	◎	◎	◎	◎
完了	◎	◎	◎	◎	◎	◎	◎	◎

1．ローマ字（半角）でイニシャルを記載すること。なお、原則としてローマ字の後にピリオド（半角）「.」をつけること。外国症例の場合、基本的に送信されたイニシャルをそのまま使用して差し支えない。 三部長別添1

Q53：【市販後】【治験】
患者略名の一部が不明・未記載又は全部未記載の場合、「D.1 患者（名前又はイニシャル）」は「X.X.」と記載しても差し支えないか？

A53：【市販後】【治験】
患者略名が不明・未記載等の場合は、「D.1 患者（名前又はイニシャル）」の Null Flavor で記載すること。患者略名を知っているが個人情報保護のため記載しない場合は、Null Flavor の MSK を使用すること。
Null Flavor の使用については E2B(R3)実装ガイド別添１、別添２並びに E2B（R3）ICH Q&A を参照すること。

ICH E2B(R3) IG Japanese translation.

Some MHLW/PMDA, Japan's conformance rules also included additionally to ICH's.

Mandatory/optional for E2B Submission to MHLW/PMDA, Japan.

Related notifications of MHLW/PMDA, Japan.

Q&A from MHLW/PMDA, Japan.

Collaboration between MHLW/PMDA, Japan and Industry

- Starting the public meetings frequently since the *Step 2* of ICH procedure.
- Information sharing with system vendors.
- Negotiating duration of transition time from ICH E2B(R2) to ICH E2B(R3).
- Conducting the large-scale pilot test.
- Providing the questions on the regional guidance from industry and publishing the Q&A notification by MHLW/PMDA, Japan.
- Proposal to set up the structural data in ICH E2B(R3) regional elements instead of narrative description.
  - These are used to be described in narrative section in ICH E2B(R2).
- Request to set up the testing environment.

FPMAJ ICH E2B(R3) Implementation Project

- The Federation of Pharmaceutical Manufacturers' Associations of JAPAN (FPMAJ, "日薬連(NICHI-YAKU-REN)")
  - Japan Pharmaceutical Manufacturers Association, (JPMA, "製薬協（SEI-YAKU-KYO)", an establish member of ICH)
  - Japan Generic Medicines Association (JGA)
  - Japan Self-Medication Industry (JSMI)
- Collaborating with
  - PhRMA in Japan
  - EFPIA in Japan

Methods and Procedure of ICSR Reporting

- MHLW/PMDA, Japan provides 2 electronic methods:
  - EDI tool.
  - Gateway (ICSR reception web site).
    - Both systems provide acknowledgement within some seconds after receipt ICSR files.
- Most of pharmaceutical companies who report ICSR files daily/regularly are using EDI tool.
  - Gateway is usually used by companies for small number of ICSR reports.
  - Or in emergency situation of EDI tools.
- MHLW/PMDA, Japan also accepts to bring ICSR reports in PMDA window directly.
  - MHLW/PMDA, Japan can accept paper form but mandatory simultaneous submission of its ICSR file in general.

Reference: Upgrade In-house Development ICSR Reception System

While exchanging opinions about ICH E2B(R3) introduction with pharmaceutical companies on a regular basis, a regulatory authority considered strategies on three major points:

A. How to build a database for ICH E2B(R3)

B. How to build a system for receiving ICH E2B(R3) ICSRs

C. How to build submission methods for ICH E2B(R3)

Reference: *A.* How to build a database for ICH E2B(R3)

✓	✗
Combine with existing ICH E2B(R2) database to build one database.	Build a ICH E2B(R3) database separately from existing ICH E2B(R2) database. Reason: Large effort to maintain two (2) databases.

- Considering the maintenance burden of the database, this regulatory authority decided to construct single database.
- However, there were several issues to be resolved regarding data conversion.

Issue: Data conversion from ICH E2B(R2) to ICH E2B(R3).

- Align ICH E2B(R2) data type and length with ICH E2B(R3).
  - Example:
    1. Date data
       - ICH E2B(R2) defines date format in each data element (e.g.,)
         B.1.2.1b: CCYYMMDD
         B.2.i.4b: 102 - Format CCYYMMDD, 203 - Format CCYYMMDDHHMM, 610 - Format CCYYMM, 602 - Format CCYY
       - E2B(R3) defines common date format throughout the guideline,
         i.e. CCYYMMDDhhmmss.UUUU[+/-ZZzz], and minimum precision of date value in each data element e.g.,
         D.2.1: minimum precision is the day (i.e., 'CCYYMMDD')
         E.i.4: minimum precision is the year (i.e., 'CCYY')
    2. Boolean data type
       - ICH E2B(R2) uses numbers, such as 1 = Yes, 2 = No, 3 = Unknown
       - ICH E2B(R3) uses words (true, false) and Null Flavor

- Align ICH E2B(R2) data type and length with ICH E2B(R3)
  - Example

ICH E2B(R2)	ICH E2B(R3)
Date data type • ICH E2B(R2) defines date format in each data element (e.g.,) • B.1.2.1b: CCYYMMDD • B.2.i.4b: ▪ 102 - Format CCYYMMDD ▪ 203 - Format CCYYMMDDHHMM ▪ 610 - Format CCYYMM ▪ 602 - Format CCYY	**Date** data type • ICH E2B(R3) defines common date format throughout the guideline, i.e. CCYYMMDDhhmmss.UUUU[+/-ZZzz], and minimum precision of date value in each data element e.g., • D.2.1: minimum precision is the day (i.e., 'CCYYMMDD') • E.i.4: minimum precision is the year (i.e., 'CCYY')
Boolean data type • ICH E2B(R2) uses numbers, such as 1 = Yes, 2 = No, 3 = Unknown	**Boolean** data type • ICH E2B(R3) uses words (true, false) and Null Flavor

- Example :Drug(s) information (ICH E2B(R2): B.4, ICH E2B(R3): G.k)

ICH E2B(R2)

B.4	
Proprietary medicinal product name	Drug A
Date of start of drug	2010/1/1
Date of last Administration	2010/1/30
Dose	10 mg
Indication for use in the case	Hypertension
Proprietary medicinal product name	Drug A
Date of start of drug	2010/2/1
Date of last Administration	2010/2/20
Dose	20 mg
Indication for use in the case	Hypertension

ICH E2B(R3)

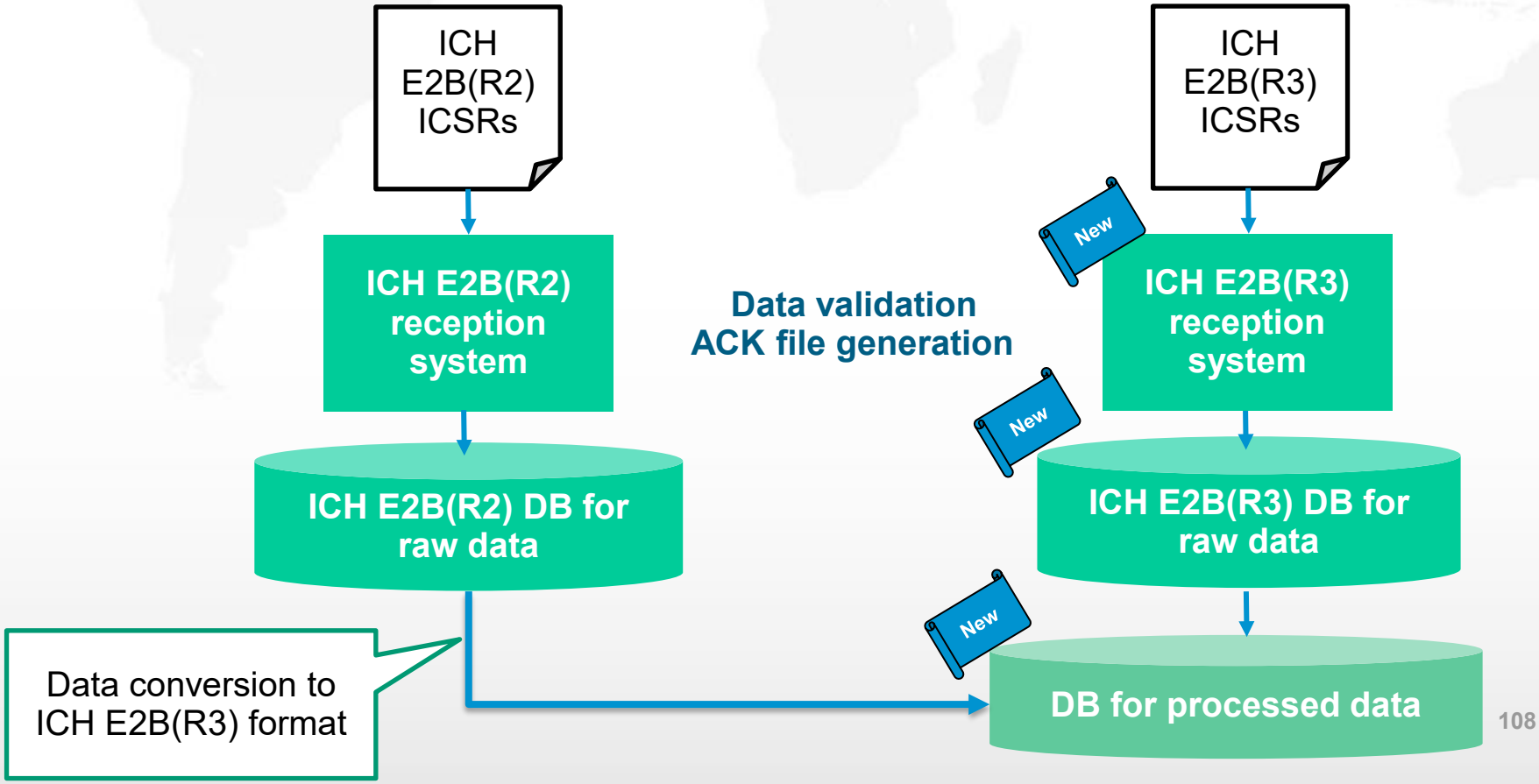
G.k Drug(s) Information	
Medicinal Product Name or Identifier	Drug A

G.k.4.r Dosage Information (repeat as necessary)	
Date and Time of Start of Drug	2010/1/1
Date and Time of Last Administration	2010/1/30
Dose	10 mg
Date and Time of Start of Drug	2010/2/1
Date and Time of Last Administration	2010/2/20
Dose	10 mg

G.k.7.r Indication for Use in Case (repeat as necessary)	
Indication	Hypertension

Solution: Data conversion from ICH E2B(R2) to ICH E2B(R3)

In order to minimize the burden of database maintenance while making it possible to simultaneously search ICH E2B(R2) and ICH E2B(R3) reports, this regulatory authority decided to create another database to store raw data and a database to store processed data.



Reference: *B.* How to build an ICSR reception system for ICH E2B(R3)

✓	✗
Build an ICH E2B(R3) reception system separately from the ICH E2B(R2) reception system	Combine with existing ICH E2B(R2) reception system to build single reception system Reason: It is a lot of load to convert data

Reference: C. How to build Submission methods for ICH E2B(R3)

✓	✗
Build ICH E2B(R3) submission methods separately from existing ICH E2B(R2) submission methods	Combine with existing ICH E2B(R2) submission methods to build one submission method Reason: It is a lot of load to convert data

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ANVISA, Brazil new ICH member and ICH E2B implementation

- Becoming an ICH member in 2018, as part of the commitment, ANVISA, Brazil was expected to align itself with five ICH guidelines within five years, which include ICH E2B.
- Before 2018, Brazil was using two ICSR management systems, Notivisa, by ANVISA, Brazil, and Periweb by the state of São Paulo (80% of local MAH).
- Both systems weren't compatible or adaptable to E2B XML files, so Brazil drove the implementation of ICH E2B with a new system.
- ANVISA, Brazil sought market systems meeting health surveillance product monitoring needs and identified VigiFlow as a feasible solution already aligned with ICH E2B.
- In July 2019, at WG/IG ICH E2B(R3) meeting, ANVISA, Brazil announced the adoption of VigiFlow as the system for receiving and managing ICSRs and implement ICH E2B(R2) and ICH E2B(R3).

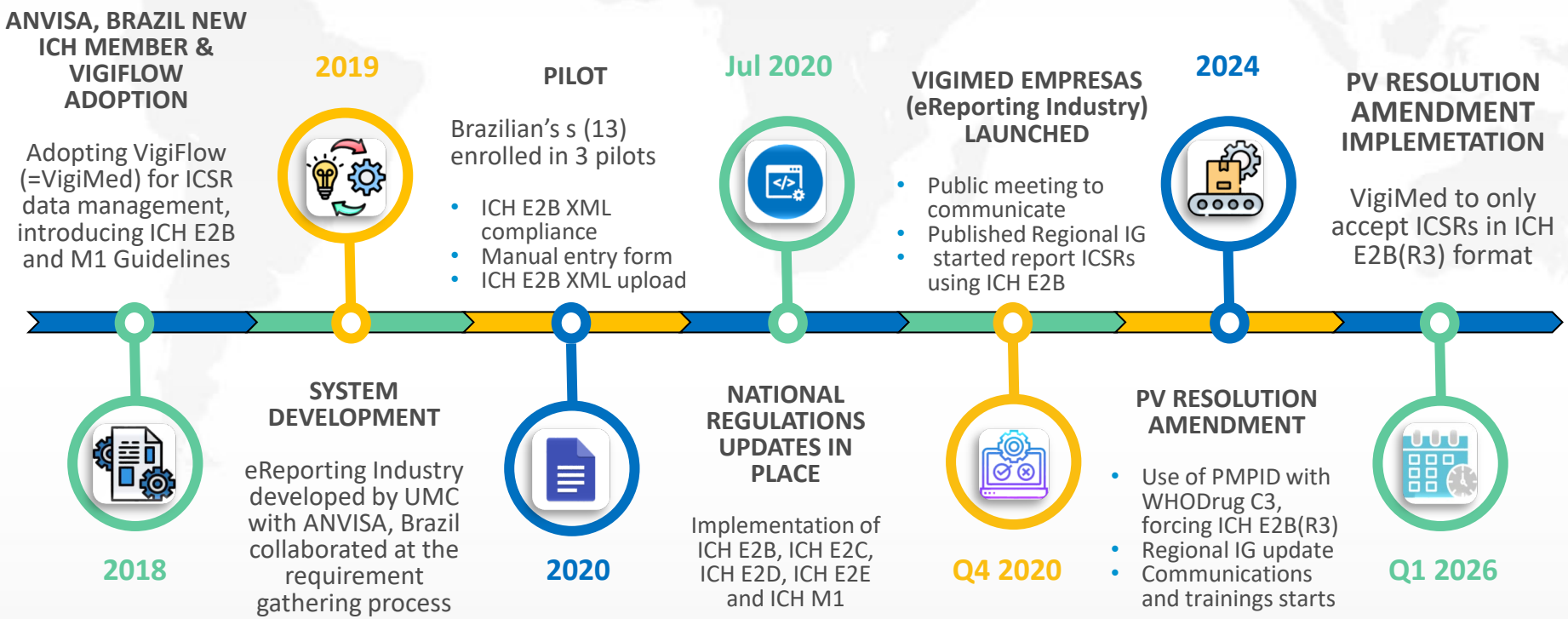
What is VigiFlow?

- VigiFlow is an ICSR management system based on the international ICH E2B(R3) standard.
- Only members of the WHO Programme for International Drug Monitoring are eligible to use VigiFlow, as the system is developed and maintained by the WHO collaborating centre for international drug monitoring, Uppsala Monitoring Centre (UMC).
- Out of the 160 WHO PIDM members, at the beginning of 2025, around 100 national regulatory agencies, NRAs, use VigiFlow for ICSR management.
- VigiFlow cannot offer customer specific configurations but ensures compliance with EU regional requirements for the European NRAs that exchange ICSRs with Eudravigilance.
- The name “VigiMed” is used instead of VigiFlow when referring to its use within the Brazilian regulatory system.

ICH E2B Implementation in Brazil

- In 2018, VigiFlow system already had solutions for patients, healthcare professionals and services, making necessary to let it available in Portuguese for Brazil and improve user registration.
- The solution was development by UMC with ANVISA, Brazil collaboration at the requirement gathering process and the call for MAH to conduct a pilot.
- The eReporting Industry developed by UMC, called in Brazil as VigiMed Empresas, is an add-on module to VigiFlow that allows various actions for the submission and tracking of MAH's ICSRs.
- Off-the-shelf solution with low implementation costs and no installation necessary.

ICH E2B(R3) Implementation Milestones in ANVISA, Brazil



Regional Consideration in ANVISA, Brazil

- MAH's registration by ANVISA, Brazil is required to use VigiMed Empresas.
- MAH can report both using manual data entry or ICH-compliant E2B XML files.
- The manual data entry supporting stakeholders who do not have ICH E2B system:
  - An electronic form is used to submit and save ICRS in ICH E2B XML R3 format.
  - The initial XML needs to be saved to be uploaded when case follow-up is needed, without re-typing.

Regional Consideration in ANVISA, Brazil

- ICH-compliant E2B xml files:
  - Interface to import XML files in ICH E2B(R2) or ICH E2B (R3).
  - ICH E2B(R2) format is converted into ICH E2B(R3) in VigiFlow.
- MAH can initiate annulment, make alterations, and access the system's file acknowledgment messages (ICH E2B(R3)).
- The Gateway is not yet available.

ANVISA, Brazil's Regional IG Package

Dedicated VigiMed Empresas webpage at the ANVISA, Brazil corporate website:
https://www.gov.br/anvisa/pt-br/assuntos/fiscalizacao-e-monitoramento/notificacoes/vigimed/vigimed-empresas

Materiais de suporte ao uso do VigiMed Empresas

Nome/Título da publicação	Versão	Data
Webinar - VigiMed Empresas	-	08/2020
Vídeo de Lançamento do VigiMed Empresas	-	11/2020
Manual de uso do VigiMed Empresas	2ª	03/2025
Instruções para criação de arquivos XML E2B	2ª	03/2025
Como usar o formato C3 do WHODrug para codificação de medicamentos	2ª	02/2025
Orientação técnica para o uso do Whodrug Global em xmls carregados no e-reporting para a indústria para conformidade com E2B(R3)	2ª	09/2024
Perguntas frequentes: Uso do formato WHODrug Global C3 para atender às expectativas regulatórias na região da América Latina	1ª	08/2024

Para acessar a página principal da Farmacovigilância, clique aqui.

Sites de interesse

- Uppsala Monitoring Center (UMC)
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- Medical Dictionary for Regulatory Activities (MedDRA)
- Drug Dictionary WHODrug Global


Agência Nacional de Vigilância Sanitária

VigiMed

AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA - ANVISA
GERÊNCIA DE FARMACOVIGILÂNCIA - GFARM
GERÊNCIA-GERAL DE MONITORAMENTO DE PRODUTOS SUJEITOS À VIGILÂNCIA SANITÁRIA - GGMON
QUINTA DIRETORIA – DIRE5

Instruções para a criação de arquivos

XML ICH E2B

Go-live strategy and phasing out ICH E2B(R2)

In 2024, ANVISA, Brazil amended the Pharmacovigilance Resolution and Regional IG to make the use of MPID and EDQM mandatory, by using WHODrug C3 coding, enforcing the adoption of ICH E2B(R3).

- Since 2022, MAHs have been advised to code medicinal products with WHODrug.
- The new rules will take effect on 21 March 2026, allowing a period for testing and implementation.
- VigiMed Empresas will only accept ICH E2B(R3) files uploads.
- MAHs without ICH E2B(R3) systems will be able to continue using manual entry to submit ICRS in ICH E2B(R3) format.

Stakeholder testing

Testing with MAH supported by ANVISA, Brazil:

- Stakeholders are expected to carry out their own development and validation testing activities and share some samples of XML files with ANVISA, Brazil for testing before going into production.
- Until ANVISA, Brazil approves the ICH E2B upload by the MAH, they can use the manual entry.
- Since April 2025, MAHs will have direct access to the test platform, enabling them to perform validations during development, upgrades, or when required by ANVISA, Brazil as per the terms of the Regional IG Package.

Stakeholder testing

Support for vendors provided by UMC:

- The WHODrug Vendor Programme is available and important support for compliance with regional requirements.
- Two Brazilian vendors had already made tests with UMC and are providing solutions with ICH E2B(R3) and WHODrug.

Stakeholder training and communication strategy

- Stakeholder training is provided by Information videos, User Guides, Webinars and eLearning materials.
- Communications strategy includes:
  - Public consultation for the amendment of PV Resolution.
  - ANVISA, Brazil's official channels for communication.
  - ANVISA, Brazil's webinars.
  - VigiMed Empresas dedicated page.

Contact

- **For any questions, please contact the ICH Secretariat:**

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