EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Session 3 – ISO ICSR Implementation Technical Aspects - Part 2

HL7 V3 messaging

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Data Standardisation and Analytics

Usage of nullflavor flags

- The HL7/ISO ICSR schema requires that mandatory data elements must always be part of the ICSR message. In some situations mandatory data elements might be empty of content for specific reasons for an ICSR that is still considered valid.
- In HL7 messaging the issue of empty elements is handled through the use of a nullFlavor flags. These flags prevent a field being empty and provides the receiver of the ICSR with a reason for the lack of data.
- Valid messages can be created containing mandatory elements without transmitting content. The reason for a blank element is referred to as the 'flavor' of the null value.

Nullflavor Types

- 15 Types of null found in the HL7 V3 specifications
  - 8 are used in the E2B(R3) Implementation

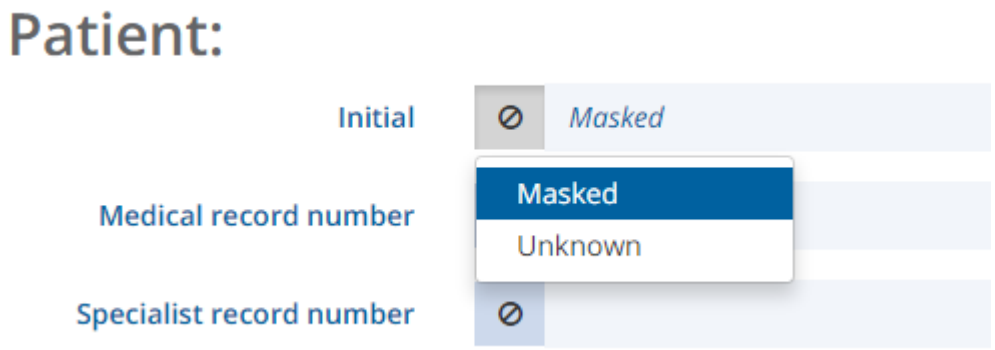
NI	No Information
NA	Not Applicable
UNK	Unknown
NINF	Negative Infinity
PINF	Positive Infinity
MSK	Masked
ASKU	Asked but unknown
NASK	Not asked

Storing Nullflavors

- The E2B(R3) might have a field described as Yes/No/Unknown, in the HL7 message the element might have a Boolean datatype along with a Nullflavor "UNK"
  - Do you store the Nullflavor in a separate column of the database?
  - Do you store as a coded field 1-Yes, 2-No & 3-UNK rather than as a Boolean?
  - How do you display Nulls to the user?

Storing/Viewing Nullflavors

- The new EudraVigilance online tool will incorporate nullflavors as an additional drop down list available for each field that supports it



UUIDs - Universally Unique Identifier

- Used in the ICSR message for cross-referencing, this allows many to many relationships within the XML such as drug-reaction assessments
  - xxxxxxxx-xxxx-**4**xxx-xxxx-xxxxxxxxxxxx
- There are 5 versions of the standard
  - Which version should you implement?
    - The ICH documentation does not specify a version or a preferred version
  - Version 4 - Random numbers will be implemented for EudraVigilance

UUIDs - Universally Unique Identifier

- **Questions**
  - Should you store the UUID used in received or sent messages?
  - Should you re-use the same UUID in follow-ups?
  - What will other organisations you exchange data with do?

- There is no specific ICH guidance on this
- EudraVigilance will generate UUIDs at the time of XML file creation

UCUM - PQ data type

- The Unified Code for Units of Measure is a code system intended to include all units of measures
- The single units of UCUM can be combined in many ways as long as the follow the correct syntax rules

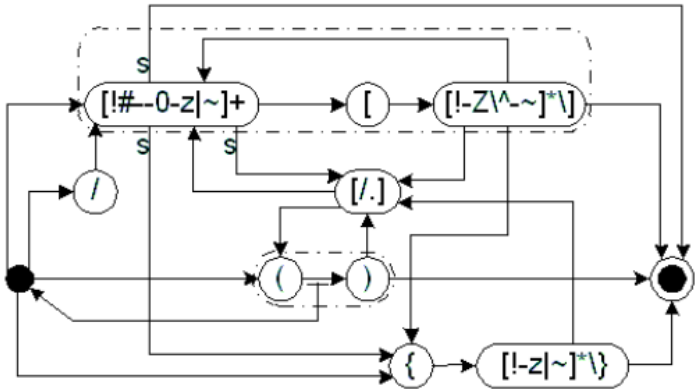


Figure 1: Pushdown-state automaton describing the syntax.

UCUM challenges

- Kilograms can be expressed as 1000.g or 10*3.g or kg
- Coding Test result units may require regular expressions in order to validate that correct UCUM values have been provided.
- Biological units expressed within {} brackets may require additional agreement between organisations
- {} brackets also used for BFC rules to transfer non-UCUM codes from E2B(R2) XML file into an E2B(R3) file

UCUM – BFC R2 → R3 – Note for caution

- The BFC rule tries to map Units from R2 lists to UCUM units
- If it can not find a mapping the curly brackets will be used {..} to transfer the data
- This will cause an issue for test result units which don't have a published R2 list

UCUM – Next steps

- BfArM – Has expressed an interest in being the service provider for publishing lists of UCUM units to be used in the pharmaceuticals domain
- Unit list would be published free to use by all organisations

Object Identifiers (OIDs)

- OIDs are used in E2B(R3) messages to identify the coding system being used. E.g. MedDRA
- The OIDs to use are published in the ICH IG and the EU specific OIDs are published in the EU IG

http://www.oid-info.com/

http://oid-info.com/get/2.16.840.1.113883.6.163

Code systems & OIDs

```
<code code="29" codeSystem="2.16.840.1.113883.3.989.2.1.1.19" codeSystemVersion="2.0" displayName="reaction"/>

<value xsi:type="CE" code="D.10.8.r.7b" codeSystem="2.16.840.1.113883.6.163" codeSystemVersion="D.10.8.r.7a"/>
```

- Code & value elements are where code systems and OIDs will be usually found. value will also have an xsi:type to indicate the value is coded rather than free text
- code – The code from the controlled vocabulary
- codeSystem – The OID that identifies which controlled
- codeSystemVersion – Identifies the version of controlled vocabulary
- displayName – Provides the human readable text version of the code

Display name

- It is an optional attribute that can be used with coded elements
- Advice - Use it everywhere!
- Once you become more familiar with the E2B(R3) message it really helps with reviewing and debugging the XML
- It can also be used for generating human readable versions of the XML by using XSLTs

<organizer> elements

```
<organizer classCode="CATEGORY" moodCode="EVN">
  <code code="2" codeSystem="2.16.840.1.113883.3.989.2.1.1.20" codeSystemVersion="2.0" displayName="drugHistory"/>
  <component typeCode="COMP">  - #1 – drug history no. 1
  <component typeCode="COMP"> - #2 – drug history no. 2
 <component typeCode="COMP">  - #n - drug history no. n
</organizer>
```

XSLT/Schematron rule if count > 1 then send parsing error ack

```
count(//PORR_IN049016UV/controlActProcess/subject/investigationEvent/component/adverseEventAssessment/subject1/primaryRole/subjectOf2/organizer/code[@codeSystem='2.16.840.1.113883.3.989.2.1.1.20' and @code='2']) > 1
```

XSLT/Schematron rules

- The business rules and schema do not stop sections being repeated that according to the implementation guide (logical model) are expected only once
  - For example patient weight could be repeated (Note: the same code and code system is used for both patient and parent sections)

```
<subjectOf2 typeCode="SBJ">
  <observation classCode="OBS" moodCode="EVN">
    <code code="7" codeSystem="2.16.840.1.113883.3.989.2.1.1.19" codeSystemVersion="2.0" displayName="bodyWeight"/>
    <value xsi:type="PQ" value="50" unit="kg"/>
  </observation>
</subjectOf2>
```

- How will your system react if it was repeated?
- Pre-processing rules could be used after schema check and before loading and business rules validation

Intervals of time

- **TS** – Time stamp (Simple date/time)
- **IVL_TS** – Interval of time start (Simple duration)
  - Start and end date
  - Start OR End date with duration (width)
- **SXPR_TS** –Complex time intervals
  - Mainly used if a start and end date is need with a duration

Time interval - SXPR_TS

```
<effectiveTime xsi:type="SXPR_TS">
  <comp xsi:type="IVL_TS">
    <low value="20090101"/>
    <high value="20101201"/>
  </comp>
  <comp xsi:type="IVL_TS" operator="A">
    <width value="24" unit="E.i.6b"/>
  </comp>
</effectiveTime>
```

operator="A“ is used to denote an intersection, i.e it denotes that the field with this operator must be intersected with the previous time specification.

Drug section - ISO IDMP Implementation

- The reference instance has place holders:
- <code code="G.k.2.1.1b" codeSystem="**TBD-MPID**" codeSystemVersion="G.k.2.1.1a"/>
- These strings do not need to appear in E2B(R3) files until ISO IDMP is implemented
- Before ISO IDMP implementation, you may see use of these code fields when accessing EudraVigilance data. The code and display name will be provided together. In addition the verbatim free text will always be provided alongside

<code code="PIX127347" codeSystem="PIX-code" displayName="Methylphenidate 10 mg"></code>

Drug section – Device components

Note: The logical (business) model representing what is required is different to the representation in the Messaging model

- In the HL7 Message you have two concepts for product, "kind of product" and "instance of kind"
  - kind of product – Describes the type/name of product and properties that are common to all the same product e.g. "Paracetamol 200mg tablets box of 16"
  - instance of kind – Describes the actual box of product taken by the patient – This includes information such as the batch number

Drug section – Device components

- The issue in the model is
  - "Device component ID" would normally sit in the kind of product as it is used to define a product
  - "Device batch no" would sit in the instance of kind to give you the batch number of the device in the box given to the patient.
- The problem is what happens if there is more than one device how do you link the "Device batch no" to the correct "Device component ID"?
  - E.g Syringe with batch no "B34949" and ampule with "C09933"

Drug section – Device components

- In the use case for Device components the requirement for "Device component ID" is for capturing information about the "Device batch no" for advanced therapies,
- It is not being used to identify the product "kind of product"
- The reference instance reflects this

Drug section – Device components

```
<productInstanceInstance classCode="MMAT" determinerCode="INSTANCE">
    <lotNumberText>G.k.4.r.7</lotNumberText>
    <part classCode="PART">
      <partDeviceInstance classCode="DEV">
        <lotNumberText>G.k.2.2.EU.9.r.4</lotNumberText>
        <asInstanceOfKind>
          <kindOfMaterialKind>
            <code code="G.k.2.2.EU.9.r.3" codeSystem="EUOID" codeSystemVersion="G.k.2.2.EU.9.r.2" />
            <name>Enter G.k.2.2.EU.9.r.1</name>
          </kindOfMaterialKind>
        </asInstanceOfKind>
      </partDeviceInstance>
    </part>
  </productInstanceInstance>
```

Drug section – Batch number use of Null

- EU Specific requirement batch number must be provided for biological products
- Requirement for senders to indicate if back number unknown or asked for but not yet provided
- <lotNumberText nullFlavor="ASKU" />

Master Message Type

- The Master message type is EU specific and will need to be processed by MAHs and the NCAs choosing to receive them
- It can be seen when accessing (downloading) data from EudraVigilance, it can not be used for sending data to EudraVigilance
- It will identify duplicate cases that have been received from at least two different organisations
- It is the version of the case that is normally used for signal detection/analysis
- The duplicate numbers section of the ICSR will contain the Worldwide case IDs of all ICSRs that have been identified as a duplicate of the master case

Suggested Reading*

- **ISO/HL7 27953-2:2011 Standard**

  http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=53825

- **HL7 books**
  - HL7 Version 3 Primer Normative Edition version ISBN 3-933819-21-0
  - Principles of Health Interoperability HL7 and SNOMED
  - ISBN: 978-1-44712-800-7

  http://www.hl7.org.uk/marketing/publications.asp

*If you want a more detailed understanding of HL7 V3 messaging