agencia española de medicamentos y productos sanitarios

Bundesamt für Sicherheit im Gesundheitswesen
BASG

UNICOM

Up-scaling the global univocal identification of medicines

FHIR 4 NCAs:
Track Changes on medicinal product variations
Friday 13th of October 2023

Speakers: Noel Diamant (AGES), Gianluca Risi (AEMPS)
Work package lead: Georg Neuwirther (AGES)

This project has received funding from the European Union's
Horizon 2020 research and innovation programme under grant agreement No 875299

Disclaimer

The information provided represents the knowledge and status at the time of its preparation. It does not necessarily represent the view of the regulatory authority to which the presenter belongs. Do not use this information for decision making, but instead always refer to official documents, relevant regulations, regulatory guidelines and SPOR guidance material

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Agenda

- ***Georg Neuwirther***
  UNICOM WP3 Lead, Austrian Medicines Agency
- ***Noel Diamant***
  Product Co-Owner for eAF, Austrian Medicines Agency
- ***Gianluca Risi***
  Senior Software Engineer, AEMPS

1 **Introduction, Motivation**
10:00 – 10:20
- *Georg Neuwirther*

2 **References – Where to start?**
10:20 – 10:25
- *Noel Diamant*

3 **Introduction to Variation Changes**
Types of provenances in Present/Proposed
10:25 – 10:45
- *Noel Diamant*

4 **Examples of Variation Changes**
Examples of different types of changes
10:45 – 11:15
- *Gianluca Risi, Noel Diamant*

5 **National FHIR Survey outcome**
eAF import at different NCAs
11:15 – 11:20
- *Noel Diamant*

7 **Closing / Q&A**
11:20 – 11:45
- *Georg Neuwirther*

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Motivation

1. **Data availability in regulator systems (HMA/EMA)** becomes more essential
   - ➢ see also HMA/EMA strategy to 2025 and EMA/HMA announcements.

1. The **"technical new" application forms (PLM Portal/DADI)** will provide improved opportunities **to import application and medicinal product data into our IT system**

2. A pan-European project **"UNICOM"** and **EMA** are working on the implementation of new data standards called **ISO – IDMP**
   - ➢ **This will help us to represent and store medicinal product data in a common approach – like eCTD standards to structure dossiers!**

unicom-project.eu

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Data on medicines (ISO IDMP standards): Overview

The European Medicines Agency (EMA) is in the process of implementing the standards developed by the International Organization for Standardization (ISO) for the identification of medicinal products (IDMP).

Source: EMA - High-quality data to empowerdata-drivenmedicines regulation in the European Union | European Medicines Agency (europa.eu)

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Let's use this meeting to understand the new opportunities and get technical info on how I can use them

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What is UNICOM?

…. This innovation action is expected to support two goals:

(i) the cross-border mobility of European patients by offering safer eDispensations across borders,

(ii) the implementation of the IDMP standards in Member States drug databases (including a possible linkage to the EU SPOR - Substance, Product, Organisation and Referential master data database) allowing the identification of locally available medicinal products which are equivalent to the one identified in a foreign prescription. …"

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• Further detail can be found here: https://unicom-project.eu/ or on LinkedIn

• Focus for EMRN - **is objective ii)**, ".. to foster the implementation of IDMP in Europe. .."

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Introducing ISO IDMP compliant application forms

- Applying for authorisations for medicinal products and managing their life cycles is a regulated process supported by electronic application forms and supporting electronic tools.

- **At the moment neither application forms nor the tools for initial authorisations, variations and renewals are compliant to the ISO IDMP standards. Thus, it is currently not possible to start, automate and feed regulatory processes with IDMP compliant/structured data and easily re-use the data in EU-wide eHealth services.**

The aim of this UNICOM work package is to adapt the application forms and required tools towards the ISO IDMP standards and to increase the usage of EMA's SPOR.
It will therefore *deliver web-based application forms compatible with IDMP standards*

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Introducing ISO IDMP compliant application forms

- **7 National competent authorities** are working together in this topic in the UNICOM project
  - Spain (Development of the PDF representation – Implementation of the variation FHIR profiles)
  - Austria (Product Owner PLM Product Owner together with a Product Owner from EMA)
  - Contribution of Expertise, Knowledge, Testing, Communication, etc. of the Netherlands, Germany, Ireland, Sweden, Norway

- **EMA is developing the core IT service Product Lifecycle Management Portal**
  - EMA is not an UNICOM partner!

https://plm-portal.ema.europa.eu/

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AS-IS: Electronic Application Forms for Medicinal Products

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WP 3

PDF-based forms including a PDF-proprietary Data Exchange Format

Applicants

Initial Applications

Lifecycle Management

Regulators

Substance Terms, Organisations, Controlled Dictionary (EMA, providing master data from EUTCT, RMS, OMS)

Regulatory IT-Systems

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TO-BE and status of development

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WP 3

UAT partly achieved, **first Variation Application From release in production since 04/11/2022**

In progress

pending

Web Tool supporting IDMP/FHIR compatible application dataset formats

DADI

Variation Application

Initial Application

Renewal Application

Initial Applications

Lifecycle Management

Regulators

New Retrieving master d

New IDMP/FHIR format

Substance Terms, Organisation data, Referentials
EMA, providing controlled dictionaries)

Medicinal Products
(PMS, providing master data for medicinal products)

Regulatory IT-Systems

See also collaboration with UNICOM WP4

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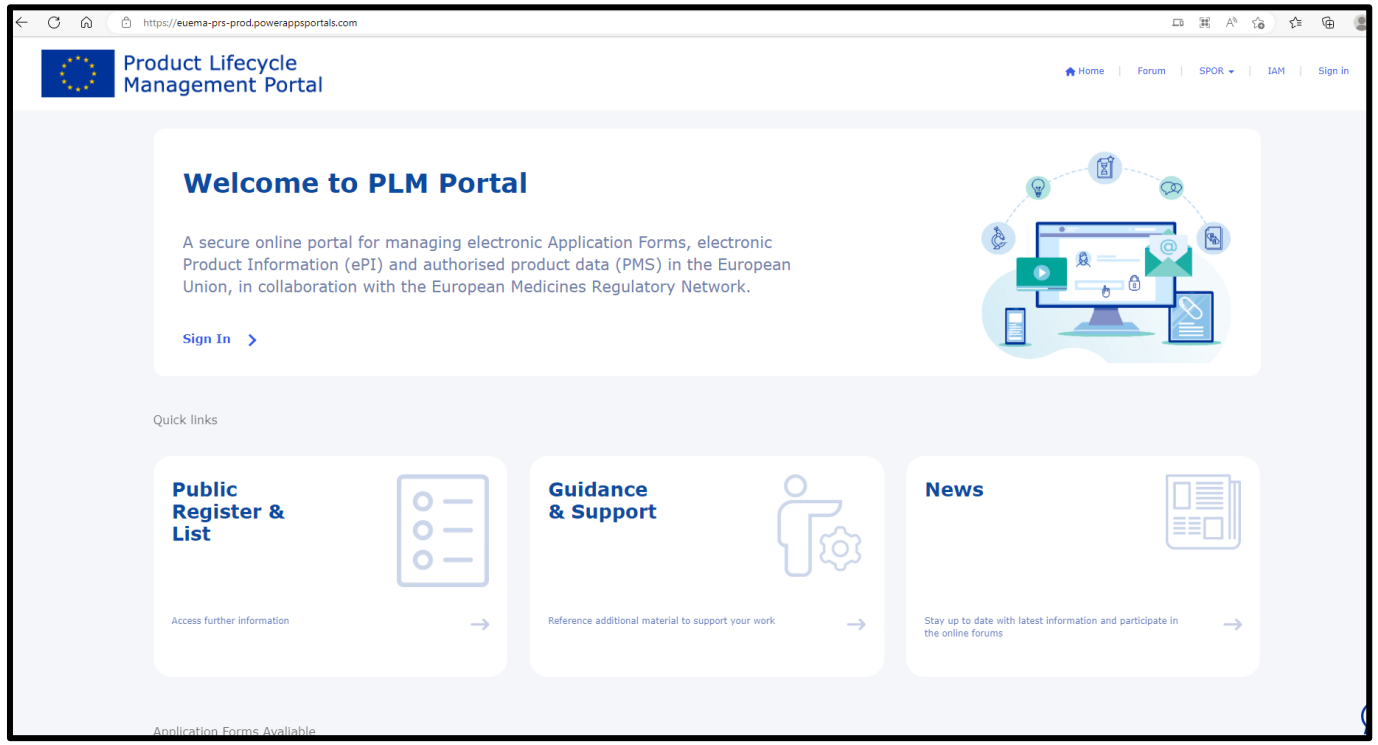
First Go-Live Release

WP 3

- The first release of Variation Application Forms is successfully online since 04.11.2022
  - This version covers variations of centrally authorised medicinal products
  - Link: **Home · PLM (powerappsportals.com)**



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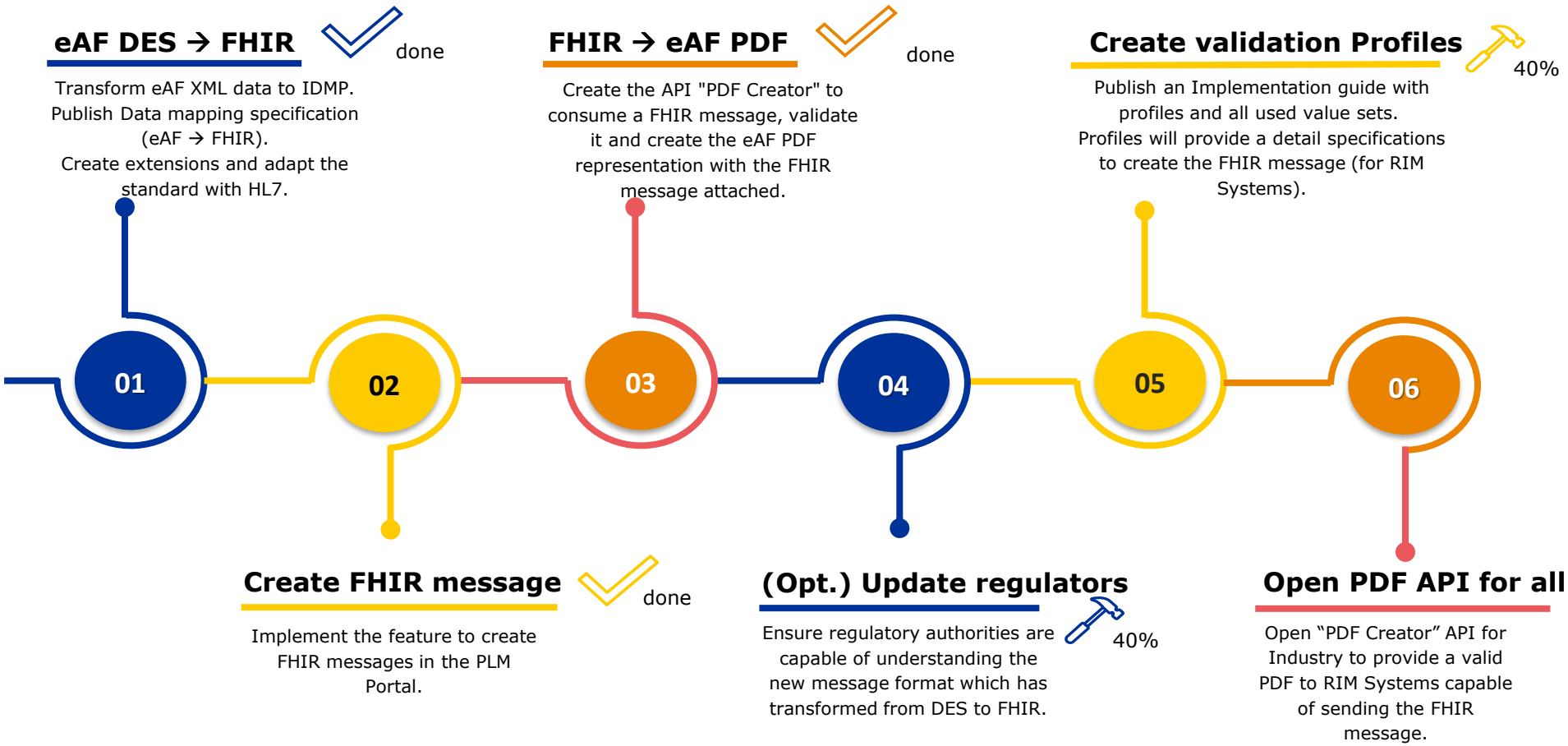
References – Where to start?

eAF variation API Milestone plan



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How to get involved?

Previous Trainings

The following training will focus on specific elements of the medicinal product part of the variation message.

Previous trainings were given to

- Get an overview of the full product:

FHIR Training: The **Medicinal Product part of FHIR**
--> (recording) <--

- Get an overview of the variation message:

FHIR Training: **FHIR on Variations**
--> (recording) <--

- Top 10 most wanted IDMP fields

FHIR Training: Top 10 IDMP fields through XPath
--> (recording) <--

How to contribute

Business Focus

- Give your input to the:
  - PMS SMEs and Network PO
  - eAF SMEs and Network PO
- Get in contact with Vet colleagues and:
  Learn from the upload to UPD and give feedback

Standardisation Focus

- Be part of the Connecthatons "Vulcan stream" at HL7
- "BR & R group" at HL7 also handles the medicinal product

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Cost-free References – Where to start?

ISO IDMP EU IG v2.1.1
Start by looking at the ISO diagram in the EU IG Chapter 2 Page 30
Link to EU IG

FHIR Documentation
Get familiar with the basics in FHIR or attend a training
Getting started: http://build.fhir.org/documentation.html
Product in Version 4.6: https://hl7.org/fhir/2021May/medicinalproductdefinition.html

Data models and Mappings (eAF & DES to FHIR)
Link to be added

Training materials and Examples
Link to be added

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Scope of today

- **Track changes...**

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Variation Changes

Present / Proposed values for variations and medicinal products

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Concepts to represent changes to master data

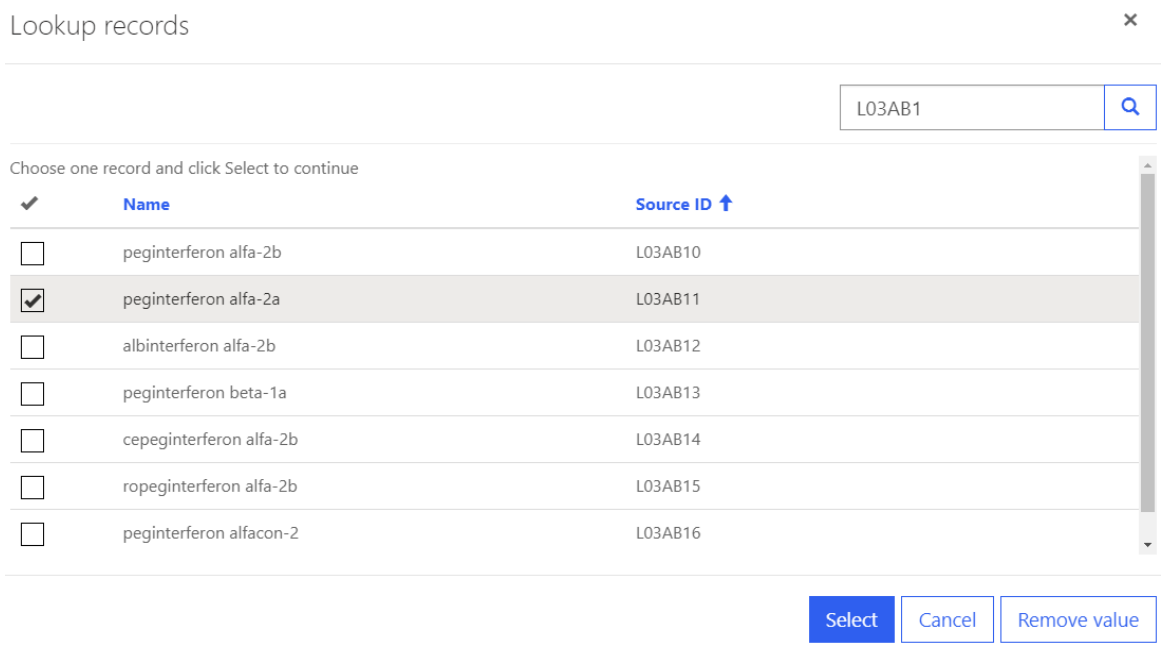
Present & Proposed

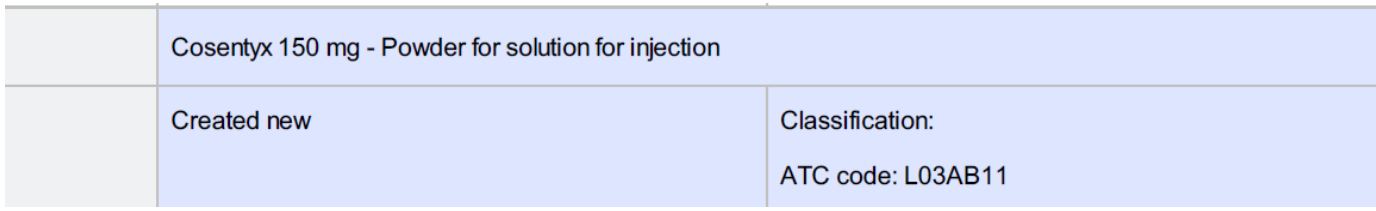
The future variation application form minimises free text changes and enables applicants to directly propose changes in structured data elements.

The proposed changes are automatica lly logged and made visible in the PDF form.

Behind the scenes they are not text but references to data elements in order for national IT systems to consume them.

So called "FHIR Provenances" can be used to import this "Change Log"






```
<extension url="http://ema.europa.eu/fhir/extension/targetElement">
  <extension url="http://ema.europa.eu/fhir/extension/targetActivity">
    <valueCoding>
      <system value="http://terminology.hl7.org/CodeSystem/v3-DataOperation" />
      <code value="CREATE" />
    </valueCoding>
  </extension>
  <extension url="url">
    <valueUrl value="#13889352-c13a-4f0f-8649-00dab76976e5" />
  </extension>
</extension>
<reference value="MedicinalProductDefinition/UAT600000000986" />
```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Resource for "Track changes"

What is a provenance?

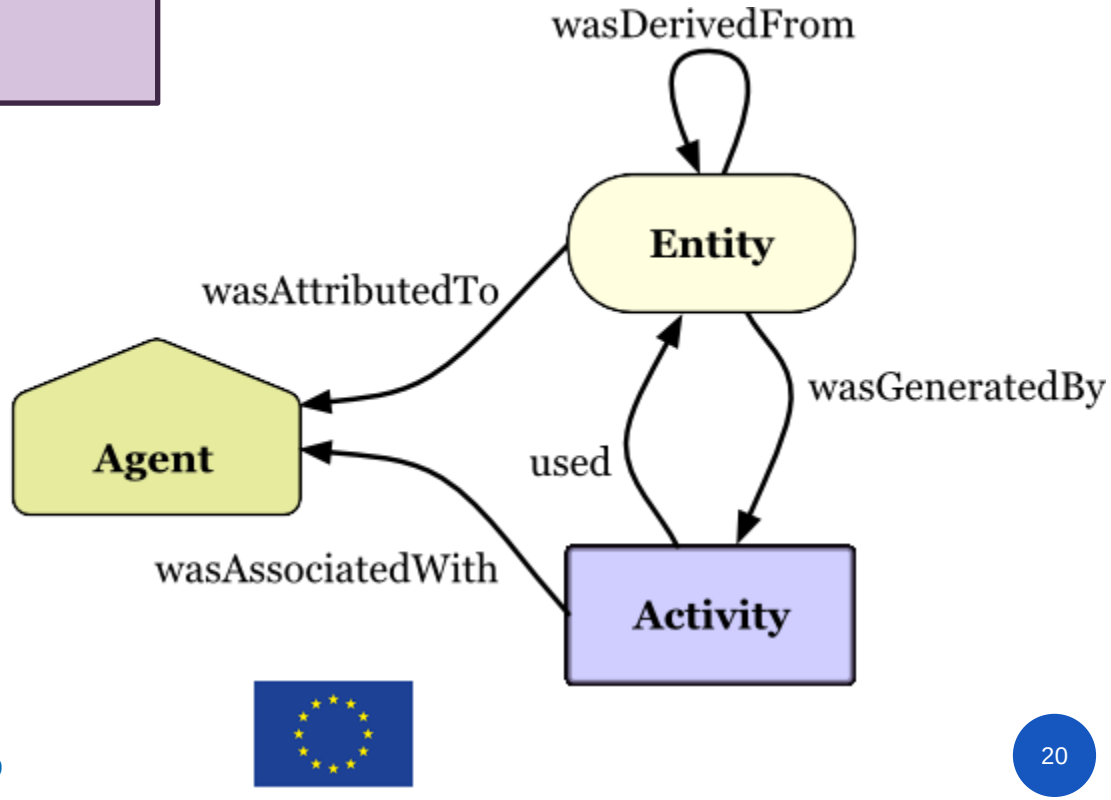
Provenance of a resource is a record that describes entities and processes involved in producing and delivering or otherwise influencing that resource.
Provenance provides a critical foundation for assessing authenticity, enabling trust, and allowing reproducibility. […]

Definition from http://build.fhir.org/provenance.html

Who did it?

What was done?

What is affected?



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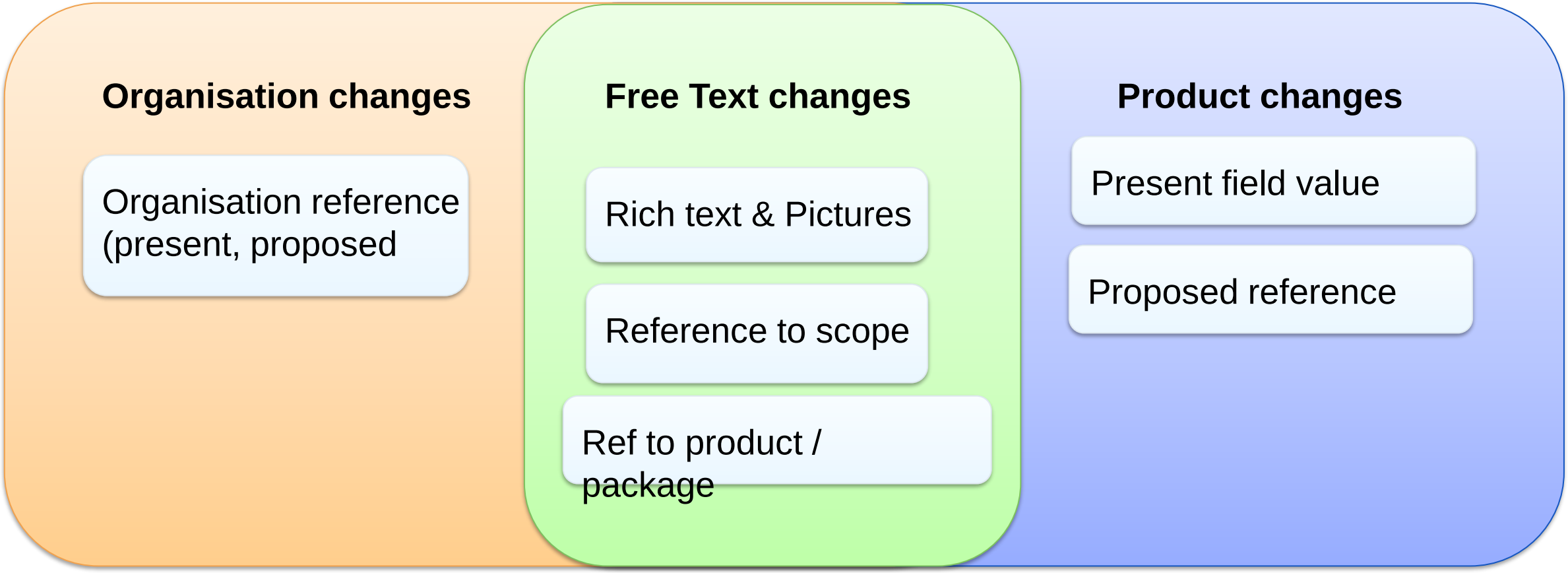
Types of changes

- Every proposed change on master data will know its relation to the **Scope**, **Product** and **package**
- There are 3 types of changes. Free text is always included:



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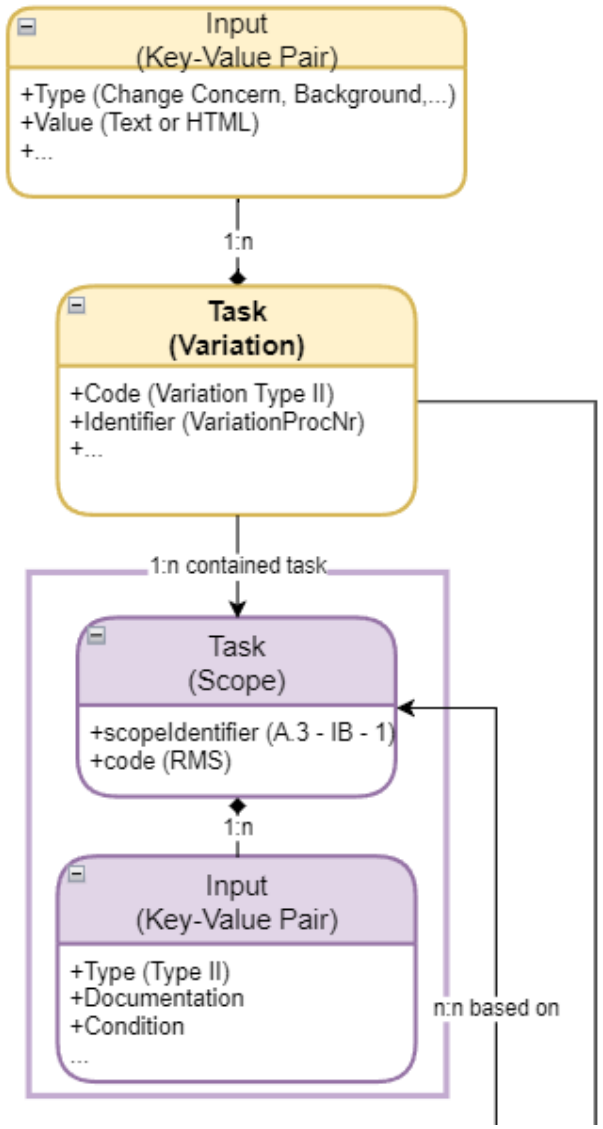
Variation and its Scopes - Relevant attributes



A Task (variation and contained task (scope) resource for each variation classification

- Task (Variation)
  - ✓ Identifier: Variation Procedure Nr
  - ✓ Code: Procedure type (MAA, Variation, Renewal)
- (contained) Task (Scope)
  - ✓ Identifer: Scope as known from the variation regulation + Type + ID
  - ✓ Code: Scope RMS Id
  - ✓ Input key value pairs for Type, Documentation and Conditions

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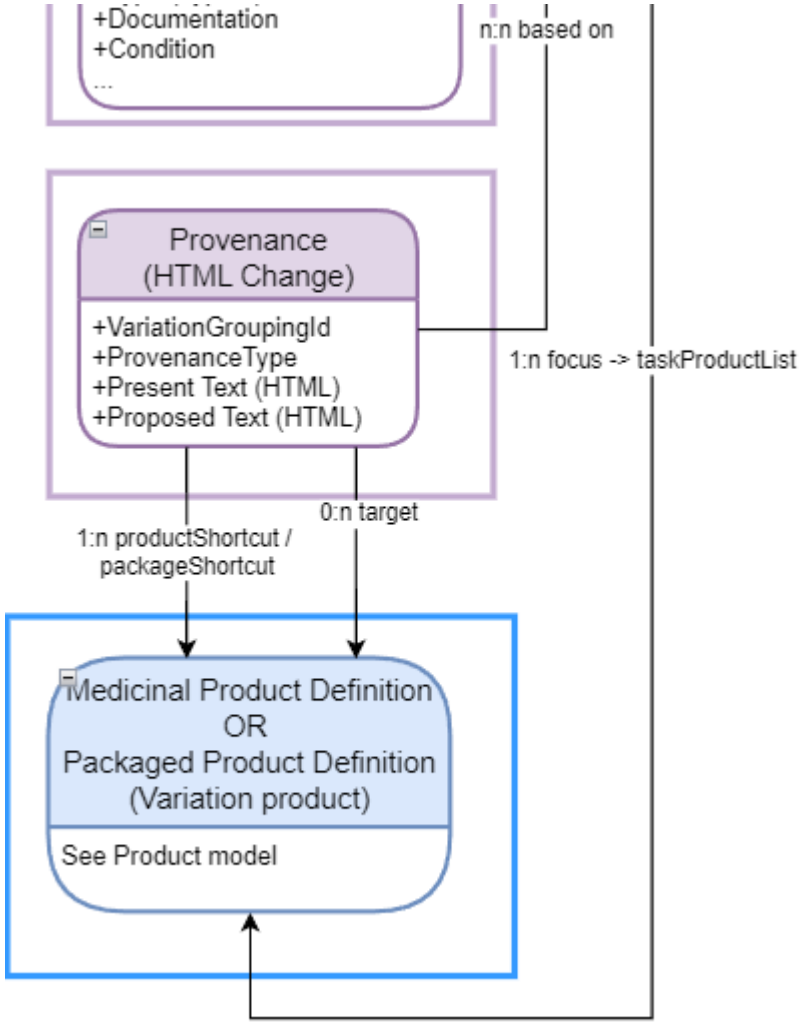
Free text change - Relevant attributes



A free text change with old (current) and new (proposed) texts

- Provenance
  - ✓ type – fixed value equal to 90000000997
  - ✓ Variation grouping Id: not used for free text change
  - ✓ Present and proposed text in html form – may contain images and rich text
  - ✓ Present and proposed ASMF number
  - ✓ Agent: the org making the change

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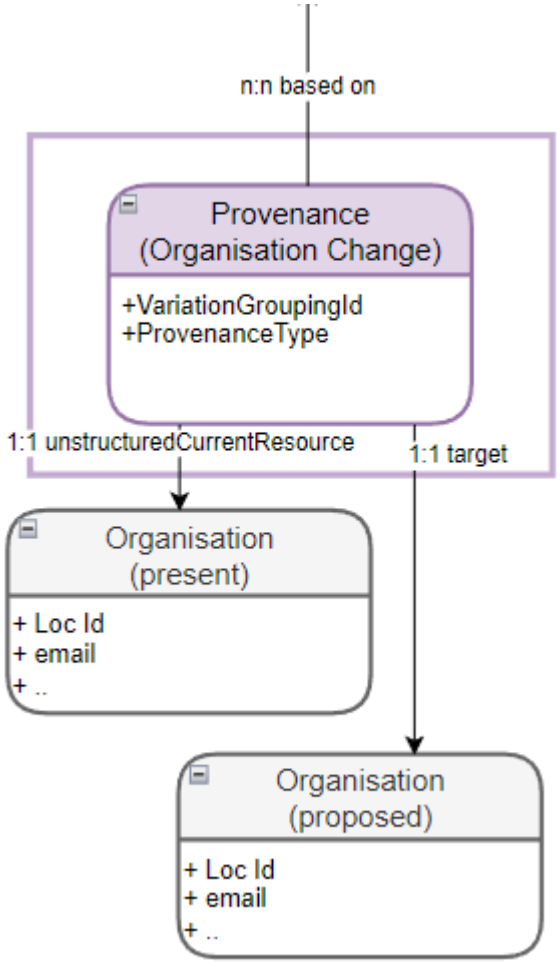
Organisation change - Relevant attributes



A change of an organisation with old (current) and new (proposed) organisations

- Provenance
  - ✓ type – fixed value equal to 90000000998
  - ✓ Variation grouping Id: to group free text and different organisation changes (they share affected products/packages and scope(s))
  - ✓ Present and proposed organisations: two references to organisation resources included in the bundle
  - ✓ Agent: the org making the change

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Product change - Relevant attributes

- Target the resource(s) affected by the change (Note: not always a MedicianlProductDefinition or a PackagedProductDefinition resource)
  - Target element the element of the resource affected by the change (CREATE and UPDATE changes). Note: not always a MedicianlProductDefinition or a PackagedProductDefinition
  - Target activity type of the modification made to the element of the re source (all changes)
  - Target path contains information about the element being deleted (only DELETE changes)
    - ✓ Target parent reference to the resource whose element is being deleted
    - ✓ Path the path in the parent element where the element being deleted was (FhirPath – segments separated by ".")
    - ✓ Current value element being deleted

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- **Target the resource(s) affected by the change (Note: not always a MedicianlProductDefinition or a PackagedProductDefinition resource)**
  - **Target element the element of the resource affected by the change (CREATE and UPDATE changes). Note: not always a MedicianlProductDefinition or a PackagedProductDefinition**
  - **Target activity type of the modification made to the element of the resource (all changes)**
  - **Target path contains information about the element being deleted (only DELETE changes)**
    - ✓ **Target parent reference to the resource whose element is being deleted**
    - ✓ **Path the path in the parent element where the element being deleted was (FhirPath – segments separated by ".")**
    - ✓ **Current value element being deleted**

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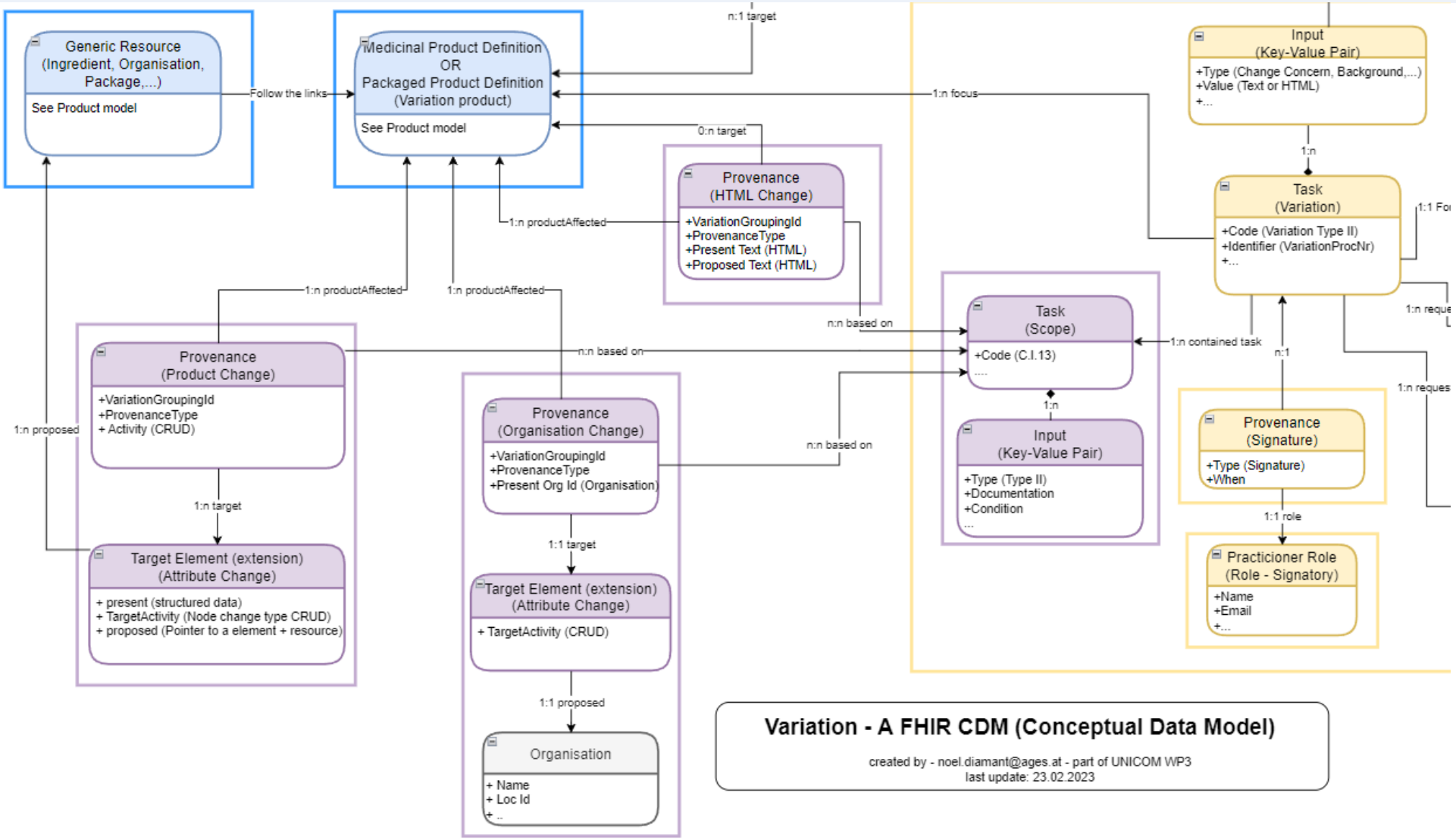
Provenance Conceptual Model



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Concepts to represent master data

PDF

Model

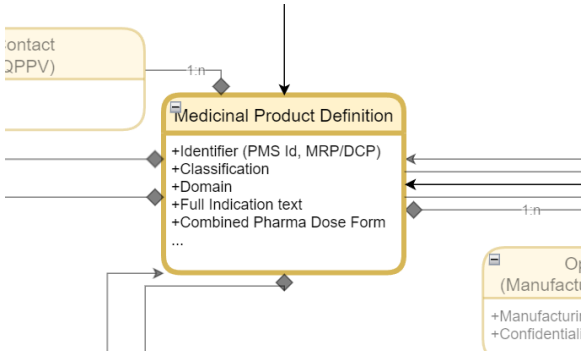
FHIR Structure

Business & Domain Experts

2. PRODUCTS CONCERNED BY THIS APPLICATION

Active Substance
Ceftazidime

MA Number(s) [8]	Full name [21]	MA Holder name	Member state	Pharmaceutical Form [22]
BE168122UAT	Glazidim 1 g Pulver zur Herstellung einer Injektions-oder Infusionslösung	UAT ORG (ORG-200036101) LOC	Belgium	Powder for solution for injection/infusion



Name	Flags	Card.	Type	Description & Constraints
Identifier	Σ N		Element	An identifier intended for computation Elements defined in Ancestors: id, extension
use	?! Σ	0..1	code	usual | official | temp | secondary | old (If known) IdentifierUse (Required)
type	Σ	0..1	CodeableConcept	Description of identifier IdentifierType (Extensible)
system	Σ	0..1	uri	The namespace for the identifier value
value	Σ	0..1	string	The value that is unique
period	Σ	0..1	Period	Time period when id is/was valid for use
assigner	Σ	0..1	Reference(Organization)	Organization that issued id (may be just text)

XML Representation

XPath

Handover to IT Experts

```
<identifier>
  <system value="http://ema.europa.eu/fhir/pmsId" />
  <value value="UAT600010787360" />
</identifier>
```

Element/Collection	Xpath	Description
$product	1. $allProducts[1] 2. $allProducts[f:identifier[f:system/@value = $identifierSystem_pmsId and f:value/@value = 'xyz']]	Get a concrete producto by some criteria: 1. The first producto of the list of affected products 2. Product whose PmsId is "xyz"

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Free text change - Business context

Product Lifecycle Management Portal

Full Name	Authorised Dose Form	Active Substance	Authorisation Country	MA Holder	MA Nr.	MRP / CP Nr.	PMS ID
Qwerty 30 mg - Gastro-resistant capsule, hard	Gastro-resistant capsule, hard	MERQWERTYAMINE BITARTRATE	European Union	UAT ORG (ORG-200036099)	EU/9/13/777UAT	EMEA/H/C/902777UAT	UAT900000000777
Zwerty 30 mg - Gastro-resistant capsule, hard	Gastro-resistant capsule, hard	MERZWERTYAMINE BITARTRATE	Germany	UAT ORG (ORG-200036099)	PA1077/027/888UAT		UAT00007888

eAF Variation PDF

2. PRODUCTS CONCERNED BY THIS APPLICATION

Active Substance
Mercaptamine

MA Number(s) [8]	Full name [21]	MA Holder name	Member state	Pharmaceutical Form [22]
EU/9/13/777UAT	Qwerty 30 mg - Gastro-resistant capsule, hard	UAT ORG (ORG-200036099)	European Union	Gastro-resistant capsule, hard
PA1077/027/888UAT	Zwerty 30 mg - Gastro-resistant capsule, hard	UAT ORG (ORG-200036099)	Germany	Gastro-resistant capsule, hard

HL7® FHIR®

name	Σ	1..*	BackboneElement
productName	Σ	1..1	string
type	Σ	0..1	CodeableConcept
namePart	Σ	0..*	BackboneElement
part	Σ	1..1	string
type	Σ	1..1	CodeableConcept
countryLanguage	Σ	0..*	BackboneElement
country	Σ	1..1	CodeableConcept
jurisdiction	Σ	0..1	CodeableConcept
language	Σ	1..1	CodeableConcept

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Free text change provenance - Basics

- **Purpose:** model a free text change with old (current) and new (proposed) texts
- **Relevant attributes**
  - **Provenance type** – fixed value equal to **90000000997**
  - **Variation grouping Id**: to group all the provenances belonging to the same "UI change" (they share affected products/packages and scope(s))

  - **Present and proposed text** in html form – may contain images and rich text
  - **Present and proposed ASMF number**

  - **Agent:** the org making the change
  - **Scope:** variation type (e.g.: *"A.3 Change in name of the active substance or of an excipient"*)

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XPath basic rules

- All elements belong to a namespace. FHIR one is **http://hl7.org/fhir**
- Nodes are targeted by their name
- Location paths are defined using the **/** symbol between node names in the path
- Attributes are targeted by their attribute name prefixed by the @ symbol
- Predicates (filters) can be defined using the **[…]** sintaxis
- Support for functions (e.g.: **trim()**, **local-name()**…)
- Several versions of the specification

- **Tip:** use variables! (to store intermediate results)

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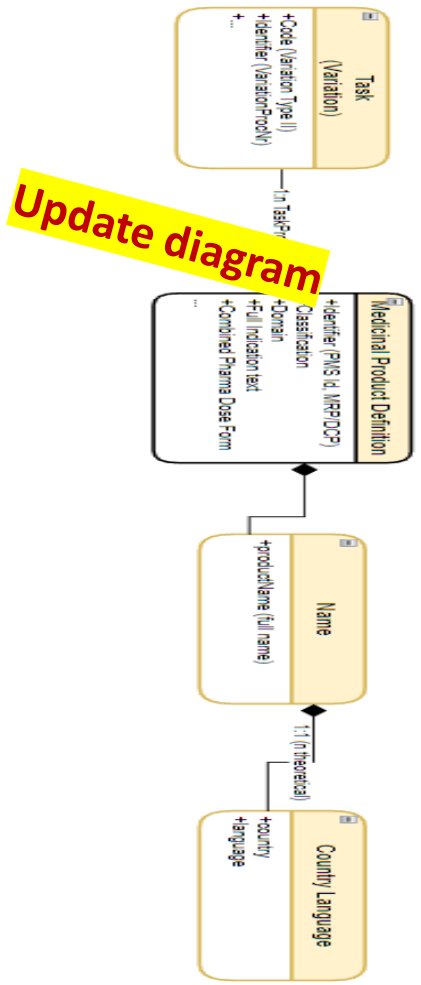
Free text change - XML context

Steps to query text change provenances and their data



Element/Collection	XPath	Description
$allProvenances	`/f:Bundle/f:entry/f:resource/f:Provenance`	All the provenances contained in the bundle
$changeProvenances	`$allProvenances[f:activity/f:coding/f:code/@value != $const_activityCodeAttest]`	All the change provenances (the signature one is excluded)
$provenancesInGroup	`$changeProvenances[f:extension[@url = $extension_variationGroupingId]/f:valueId/@value = $groupingId]`	All the changes provenances belonging to the same group, given its id value in **$groupingid**
$orgProvenances	`$provenancesInGroup[f:extension[@url = $extension_provenanceType]/f:valueCoding[f:system/@value = $rmsList_provenanceType]/f:code/@value = $rmsId_provenanceType_htmlChange]`	The (only one) text provenance contained in the group
$presentText	`string(f:extension[@url = $extension_unstructuredCurrentValue]/f:valueString/@value)`	The present text (current value) **Note:** text is html-encoded
$proposedText	`string(f:extension[@url = $extension_unstructuredProposedValue]/f:valueString/@value)`	The proposed text (proposed value) **Note:** text is html-encoded

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Free text change – XML context

Present text

```
string(f:extension[@url
= $extension_unstructuredCurrentValue][$currPos]/f:valueString/@valu
```

Proposed text

```
string(f:extension[@url = $extension_unstructuredProposedValue][$cur
@value)
```

Returned values is:

- <div data-wrapper="true" style="font-family:'Segoe UI','Helvetica Neue',sans-serif; font-size:9pt">
<div>j</div>…

Once decoded:

- j

HTML special characters must be unescaped!!

Escaped secuence	Character
<	<
>	>
"	"
…	…

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Organisation change provenance - Basics

- **Purpose:** model a change of an organisation with old (current) and new (proposed) organisations
- **Relevant attributes**
  - **Provenance type** – fixed value equal to **90000000998**
  - **Variation grouping Id**: to group all the provenances belonging to the same "UI change" (they share affected products/packages and scope(s))
  - **Present and proposed orgs** two references to organisation resources included in the bundle
  - **Agent:** the org making the change
  - **Scope:** variation type (e.g.: *"A.3 Change in name of the active substance or of an excipient"*)

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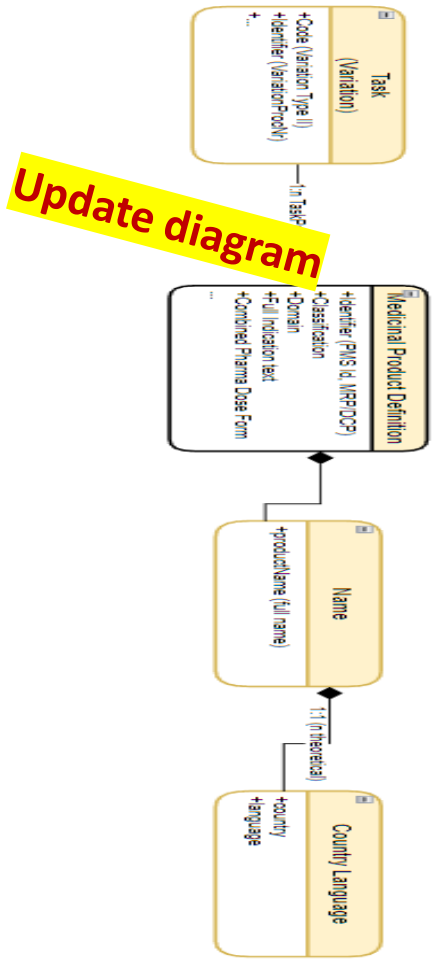
Organisation change - XML context

Steps to query organisation change provenances and their data



Element/Collection	XPath	Description
$provenancesInGroup	`$changeProvenances[f:extension[@url = $extension_variationGroupingId]/f:valueId/@value = $groupingId]`	All the changes provenances belonging to the same group, given its id value in **$groupingid**
$orgProvenances	`$provenancesInGroup[f:extension[@url = $extension_provenanceType]/f:valueCoding[f:system/@value = $rmsList_provenanceType]/f:code/@value = $rmsId_provenanceType_organizationChange]`	All the organisation change provenances contained in the group (there can be many)
$presentOrgId	`substring-after(f:extension[@url = $extension_unstructuredCurrentResource]/f:valueReference/f:reference/@value, '/')`	Id of the current organisation resource
$proposedOrgId	`substring-after(f:target/f:reference/@value, '/')`	Id of the proposed organisation resource
$presentOrg	`$allOrganizations[f:id/@value = $presentOrgId]`	Present organisation resource
$proposedOrg	`$allOrganizations[f:id/@value = $proposedOrgId]`	Proposed organisation resource

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Organisation change – XML context

Present organisation Id

```
substring-after(f:extension[@url
= $extension_unstructuredCurrentResource]/f:valueReference/f:referenc
e/@value, '/')
```

Returned values is:

- **869e1c434882b7e3f8d69a30addf073a**

Proposed organisation id

```
substring-after(f:target/f:reference/@value, '/')
```

Returned values is:

- **632e1c1b3a2a37adf8d69a30addf073a**

Organisation details

```
$allOrganizations[f:id/@value = $proposedOrgId]/f:name/@value
```

Returned values is:

- **1 0 1 Carefarm GmbH**

```
<entry>
  <resource>
    <Provenance>
      <id value="7eee6fb8bd8dc0edf8d69a30ce653a8a" />
      <extension url="http://ema.europa.eu/fhir/extension/variationGroupingId">
      <extension url="http://ema.europa.eu/fhir/extension/provenanceType">
      <extension url="http://ema.europa.eu/fhir/extension/unstructuredCurrentResource">
        <valueReference>
          <reference value="Organization/869e1c434882b7e3f8d69a30addf073a" />
        </valueReference>
      </extension>
      <extension url="http://ema.europa.eu/fhir/extension/productShortcut">
      <target>
        <reference value="Organization/632e1c1b3a2a37adf8d69a30addf073a" />
      </target>
      <recorded value="2022-11-14T13:32:03+00:00" />
      <activity>
      <basedOn>
      <agent>
    </Provenance>
  </resource>
</entry>
```

```
<entry>
  <resource>
    <Organization>
      <id value="632e1c1b3a2a37adf8d69a30addf073a" />
      <identifier>
        <system value="https://spor.ema.europa.eu/v1/locations" />
        <value value="LOC-100019286" />
      </identifier>
      <identifier>
        <system value="http://ema.europa.eu/fhir/organizationAccountNumber" />
        <value value="0000500611" />
      </identifier>
      <name value="1 0 1 Carefarm GmbH" />
      <address>
        <line value="Fixheider Straße 4" />
        <line value="Quettingen" />
        <city value="Leverkusen" />
        <state value="North Rhine-Westphalia" />
        <postalCode value="51381" />
        <country value="Germany">
      </address>
      <partOf>
    </Organization>
  </resource>
</entry>
```


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Product change provenance - Basics

Diagram on this page

- **Purpose:** model a change on some attribute of a product
- **Relevant attributes**
  - **Provenance type** – fixed value equal to **90000000999**
  - **Variation grouping Id**: to group all the provenances belonging to the same "UI change" (they share affected products/packages and scope(s))

  - **See next slide**

  - **Agent:** the org making the change
  - **Scope:** variation type (e.g.: *"A.3 Change in name of the active substance or of an excipient"*)

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Product change provenance - Basics (cont.)

Diagram on this page

- **Target** the resource(s) affected by the change (Note: not always a MedicianlProductDefinition or a PackagedProductDefinition resource)
  - **Target element** the element of the resource affected by the change (CREATE and UPDATE changes). Note: not always a MedicianlProductDefinition or a PackagedProductDefinition
  - **Target activity** type of the modification made to the element of the resource (all changes)
  - **Target path** contains information about the element being deleted (only DELETE changes)
    - **Target parent** reference to the resource whose element is being deleted
    - **Path** the path in the parent element where the element being deleted was (FhirPath – segments separated by ".")
    - **Current value** element being deleted

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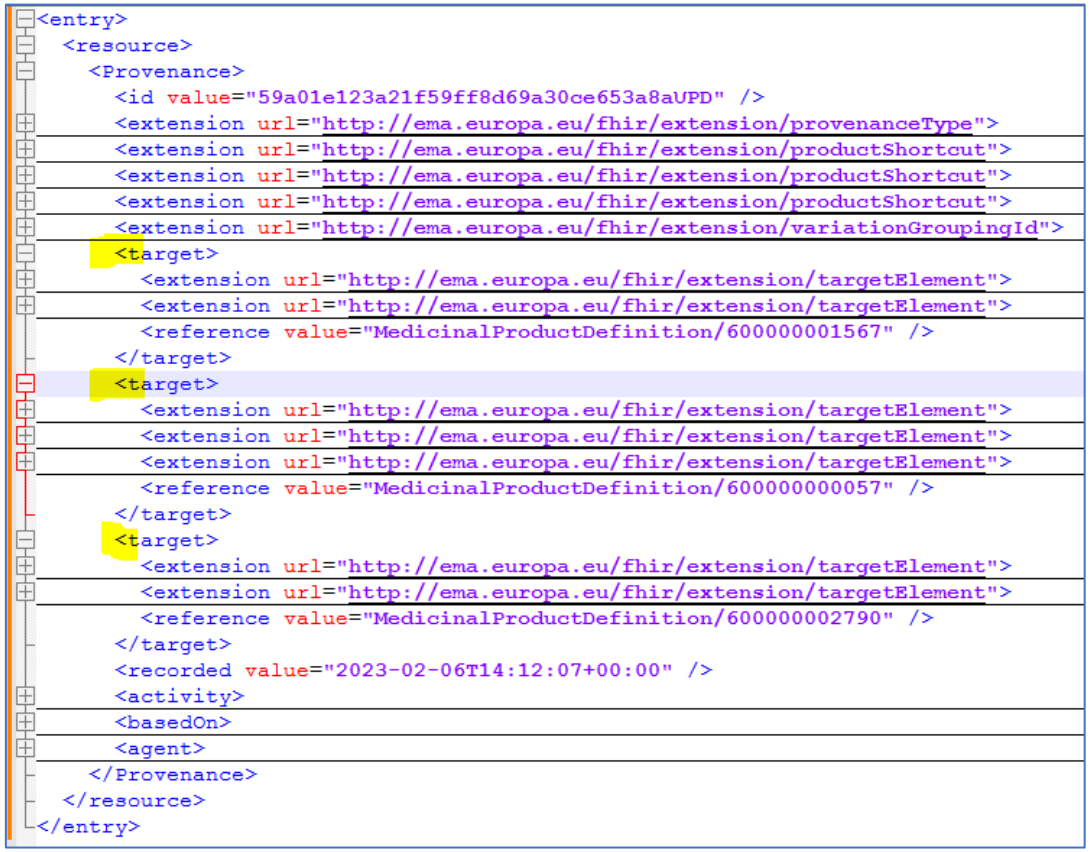
Structured change – XML context

- The change affects three products (the provenance has three targets)
  - First product has two changes (two targetElements extensions)
  - Second product has three changes
  - Third product has two changes

- "Helper" links to:
  - The products affected, in the **productShortcut** extensions
  - The packages affected, in the **selectedPackage** extensions



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Structured change – XML context – CREATE change

Create change

- The second change of the product with id **600000000057** is a **CREATE** change having:
  - The created element with id **09bc5b0f-9bbd-4859-8f8d-c149e2d7b12d**

```
<target>
  <extension url="http://ema.europa.eu/fhir/extension/targetElement">
  <extension url="http://ema.europa.eu/fhir/extension/targetElement">
    <extension url="http://ema.europa.eu/fhir/extension/targetActivity">
      <valueCoding>
        <system value="http://terminology.hl7.org/CodeSystem/v3-DataOperation" />
        <code value="CREATE" />
      </valueCoding>
    </extension>
    <extension url="url">
      <valueUrl value="#09bc5b0f-9bbd-4859-8f8d-c149e2d7b12d" />
    </extension>
  </extension>
  <extension url="http://ema.europa.eu/fhir/extension/targetElement">
  <reference value="MedicinalProductDefinition/600000000057" />
</target>
```

- The element pointed by the change is a **classification** element representing an ATC code

```
<classification id="09bc5b0f-9bbd-4859-8f8d-c149e2d7b12d">
  <coding>
    <extension url="http://ema.europa.eu/fhir/extension/codeSystemName">
      <valueString value="Anatomical Therapeutic Chemical classification system - Human" />
    </extension>
    <extension url="http://ema.europa.eu/fhir/extension/atcPending">
      <valueString value="false" />
    </extension>
    <system value="https://spor.ema.europa.eu/v1/lists/100000093533" />
    <code value="100000094017" />
    <display value="A10AD05" />
  </coding>
</classification>
```


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Structured change – XML context – UPDATE change

Update change

- The first change of the product with id **600000000057** is an **UPDATE** change having:
  - The current (old) value with the boolean value **false**
  - The changed element with id **d70f60e4-f74e-4352-97c8-92abfff18004**

```
<target>
  <extension url="http://ema.europa.eu/fhir/extension/targetElement">
    <extension url="http://ema.europa.eu/fhir/extension/targetActivity">
      <valueCoding>
        <system value="http://terminology.hl7.org/CodeSystem/v3-DataOperation" />
        <code value="UPDATE" />
      </valueCoding>
    </extension>
    <extension url="http://ema.europa.eu/fhir/extension/currentValue">
      <valueBoolean value="false" />
    </extension>
    <extension url="url">
      <valueUrl value="#d70f60e4-f74e-4352-97c8-92abfff18004" />
    </extension>
  </extension>
  <extension url="http://ema.europa.eu/fhir/extension/targetElement">
  <extension url="http://ema.europa.eu/fhir/extension/targetElement">
    <reference value="MedicinalProductDefinition/600000000057" />
</target>
```

- (Hyper)jumping to the proposed element, using its id, an extension inside an ATC classification element is found
  - It has a **valueBoolean** inner element
  - Its new (proposed) value is **true**

```
<classification>
  <coding>
    <extension url="http://ema.europa.eu/fhir/extension/codeSystemName">
      <valueString value="Anatomical Therapeutic Chemical classification system - Human" />
    </extension>
    <extension url="http://ema.europa.eu/fhir/extension/atcPending">
      <valueBoolean value="true" id="d70f60e4-f74e-4352-97c8-92abfff18004" />
    </extension>
    <system value="https://spor.ema.europa.eu/v1/lists/100000093533" />
    <code value="100000094421" />
    <display value="B03XA01" />
  </coding>
</classification>
```


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Structured change – XML context – DELETE change

DELETE change

- The third change of the product with id **UAT600000001010** is a **DELETE** change having:
  - The deleted element with path **"classification"** starting from the (targetParent) MedicinalProductDefinition resource with Id of **UAT600000001010**
  - The element being deleted being a **codeableConcept** element representing an ATC code

```
<target>
  <extension url="http://ema.europa.eu/fhir/extension/targetElement">
  <extension url="http://ema.europa.eu/fhir/extension/targetElement">
  <extension url="http://ema.europa.eu/fhir/extension/targetPath">
    <extension url="path">
      <valueString value="classification" />
    </extension>
    <extension url="http://ema.europa.eu/fhir/extension/targetActivity">
      <valueCoding>
        <system value="http://terminology.hl7.org/CodeSystem/v3-DataOperation" />
        <code value="DELETE" />
      </valueCoding>
    </extension>
    <extension url="http://ema.europa.eu/fhir/extension/targetParent">
      <valueUrl value="MedicinalProductDefinition/UAT600000001010" />
    </extension>
    <extension url="http://ema.europa.eu/fhir/extension/currentValue">
      <valueCodeableConcept>
        <coding>
          <extension url="http://ema.europa.eu/fhir/extension/codeSystemName">
            <valueString value="Anatomical Therapeutic Chemical classification system - Human" />
          </extension>
          <extension url="http://ema.europa.eu/fhir/extension/atcPending">
            <valueString value="false" />
          </extension>
          <system value="https://spor.ema.europa.eu/v1/lists/100000093533" />
          <code value="100000097115" />
          <display value="zoledronic acid" />
        </coding>
      </valueCodeableConcept>
    </extension>
  </extension>
  <reference value="MedicinalProductDefinition/UAT600000001010" />
</target>
```


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Product change example #1

- **Change of ATC code on several products**
- **CREATE and UPDATE changes**
- **Three products involved:**
  - **600000001567 - NovoMix 100 U/ml - Suspension for injection**
  - **600000000057 - Abseamed 3000 IU/0.3 ml - Solution for injection in pre-filled syringe**
  - **600000002790 - Sifrol 0.26 mg - Prolonged-release tablet**

- **Changes are**

Product	Changes
600000001567 - NovoMix	• **CREATE** ATC code **B03XA01** • **CREATE** ATC code **N04BC05**
600000000057 - Abseamed	• **UPDATE** ATC code **A10AD05** "ATC pending" attribute from **false** to **true** • **CREATE** ATC code **B03XA01** • **CREATE** ATC code **N04BC05**
600000002790 - Sifrol	• **CREATE** ATC code **B03XA01** • **CREATE** ATC code **N04BC05**

To be shown in the demo

WHO ATC codes
B03XA01 is **erythropoietin**
N04BC05 is **pramipexole**
A10AD05 is **insulin aspart**

Disclaimer:
This is not a real example!!

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Product change example #2

- **Change of ATC code on several products**
- **CREATE and UPDATE changes**
- **Three products involved:**
  - **UAT1234000 - Abacus Control gastro-resistant tablets 66 mg**
  - **UAT5678000 - Finacea 150 mg/g Gel**
  - **UAT9999000- Aclasta 5 mg/100 ml - Solution for infusion**

- **Changes are**

Product	Changes
UAT1234000 - Abacus	• **CREATE** ATC code **A01AD06** • **CREATE** ATC code **M05BA08**
UAT5678000 - Finacea	• **CREATE** ATC code **A01AD06** • **CREATE** ATC code **M05BA08**
UAT9999000 - Aclasta	• **CREATE** ATC code **A01AD06** • **CREATE** ATC code **M05BA08** • **DELETE** ATC code **A01AD02**

To be shown in the demo

WHO ATC codes
A01AD06 is **adrenalone**
M05BA08 is **zoledronic acid**
A01AD02 is **benzydamine**

Disclaimer:
This is not a real example!!

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Live inspection of the FHIR XML

From example #1:

- Show an **UPDATE** change
- Show a **CREATE** change

From example #2:

- Show a **DELETE** change

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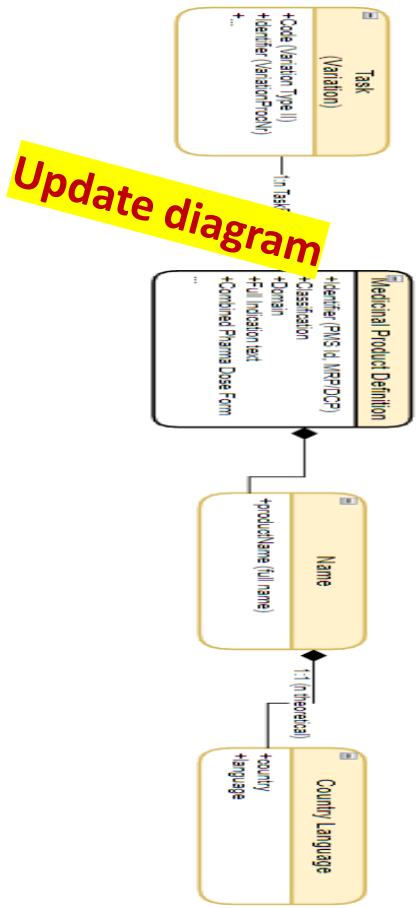
Structured change - XML context

Steps to query structured change provenances and their data



Element/Collection	XPath	Description
$structuredChangeProvenances	`$provenancesInGroup[f:extension[@url = $extension_provenanceType]/f:valueCoding[f:system/@value = $rmsList_provenanceType]/f:code/@value = $rmsId_provenanceType_productChange]`	All the product change provenances contained in the group (there can be many)
$changeTargets	`$structuredChangeProvenances[1]/f:target`	All the target resources of the first product change provenance (there can be many)
$targetResourceActivity	`$structuredChangeProvenances[1]/f:activity/f:coding/f:code/@value`	Type of change made on the resources (CREATE, UPDATE or DELETE) Same for all the target resources
$targetResourceId	`Substring-after($changeTargets[1]/f:reference/@value, '/')`	The resource id of the first target resource in the change provenance
$targetElements	`$changeTargets[1]/f:extension[@url = $extension_targetElement]`	All the target elements of the first target resource (there can be many)
$targetElementActivity	`$targetElements[1]/f:extension[@url = $extension_targetActivity]/f:valueCoding/f:code/@value`	Type of the change made on the first element (CREATE, UPDATE or DELETE) **Note:** in case of DELETE, the targetElement is the parent of the element being deleted

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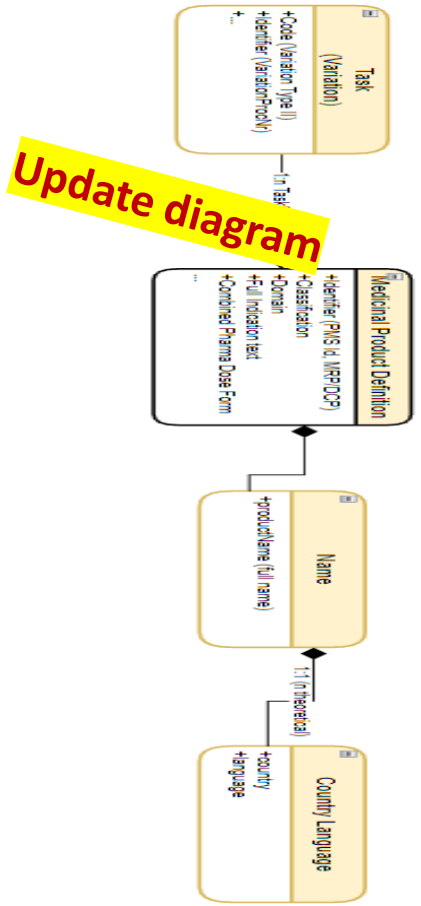
Structured change - XML context (Cont.)

Steps to query structured change provenances and their data



Element/Collection	XPath	Description
$targetElementCurrentValue	`$targetElements[1]/f:extension[@url = $extension_currentValue]/child::*[1]`	Current value of the first target element. It is the first child of the currentValue extension. Its type varies in each case **It is a FHIR value[x] element**
$targetElementProposedElemId	`substring-after($targetElements[1]/f:extension[@url = 'url']/f:valueUrl/@value, '#')`	Proposed value element id inside the first target element **It can point to any node (element) in the bundle**
$targetElementProposedValue	`//child::*[@id = $targetElementProposedElemId]`	Proposed value of the first target element. It can be any element inside the target resource.

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Only changes are shown

A variation only includes the product resources that are actually changed

- Rule Nr 1: No half measures!
  If a resource is included because 1 attribute has changed, the entire resource is included;

- Rule Nr 2: Know your neighbors!
  If a resource has a link to a resource that is not being changed, the link is included. The resource that is being linked to, will not be there. This is to be able to compare resources and confirm that something/nothing has changed

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Resources used in Variation

https://hl7.org/fhir/2021May/resourcelist.html

Procedure Management

- Task
  - Task is the main entry point of the procedure. It contains most details as a key value pair on input type & value
  - A task can be the subject of regulated authorisations (e.g. orphan, paediatric applications) and payment details
  - A task has a subtask for every scope in a variation
- Provenance
  - Each of the 3 types of changes are depicted in a provenance of type HTML change, Organisation change or Product Change
  - Provenances are bundled in scopes
  - Each change creates a new provenance
  - A provenance can link any resource depending on what was changed
  - A provenance can also be a signature
- PaymentNotice
  - Payment details within the procedure

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Resources used in PMS

https://hl7.org/fhir/2021May/resourcelist.html

- MedicinalProductDefinition
  - The entry point for the PMS product
- PackagedProductDefinition
  - Packages in a product
- AdministrableProductDefinition
  - Pharmaceutical Product with links to ingredients
- ManufacturedItemDefinition
  - Manufactured Items with links to ingredients
- Ingredient
  - Each Ingredient has a substance link and represents a part of the composition
- RegulatedAuthorization
  - Any kind of authorisation (e.g. Marketing Authorisation, Manufacturing Authorisation,…)
- SubstanceDefinition
  - Contains the substance name and link to SMS
- ActivityDefinition
  - The „operation“ of a manufacturer
- DeviceDefinition
  - Medical Device that is part of the product
- DocumentReference
  - Numbers of documents – no actual document or link
- ClinicalUseIssue
  - Indications of the product
- Organization
  - Contains the link to OMS and a copy of the organisation details
- PracticionerRole
  - A person (not part of any master data)

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Exception: Some resources are mandatory

Some resources will always be included:

- Medicinal ProductDefinition
- IngredientDefinition
  - Reason: Substance Name
  - *implicit: Link to medicinal product (extension) - not Admin product link*
  - Role = Active
- RegulatedAuthorization - **for selected packages and med products** (Type=Marketing Authorization)
- PackagedProductDefinition - ONLY IF SELECTED IN THE UI
- All Orphan Resources
- Orphan RAs, GMP RAs, Paediatric RAs, Market Exclusivity and Market Protection RAs
- Organization (type=MA Holder and Regulator - linked to the RegulatedAuthorization)

- PackagedProductDefinition - ONLY IF SELECTED IN THE UI
- All Orphan Resources
- All parallel resources (MedicinalProductDefinition + RA)
- Substances
- PaymentNotices

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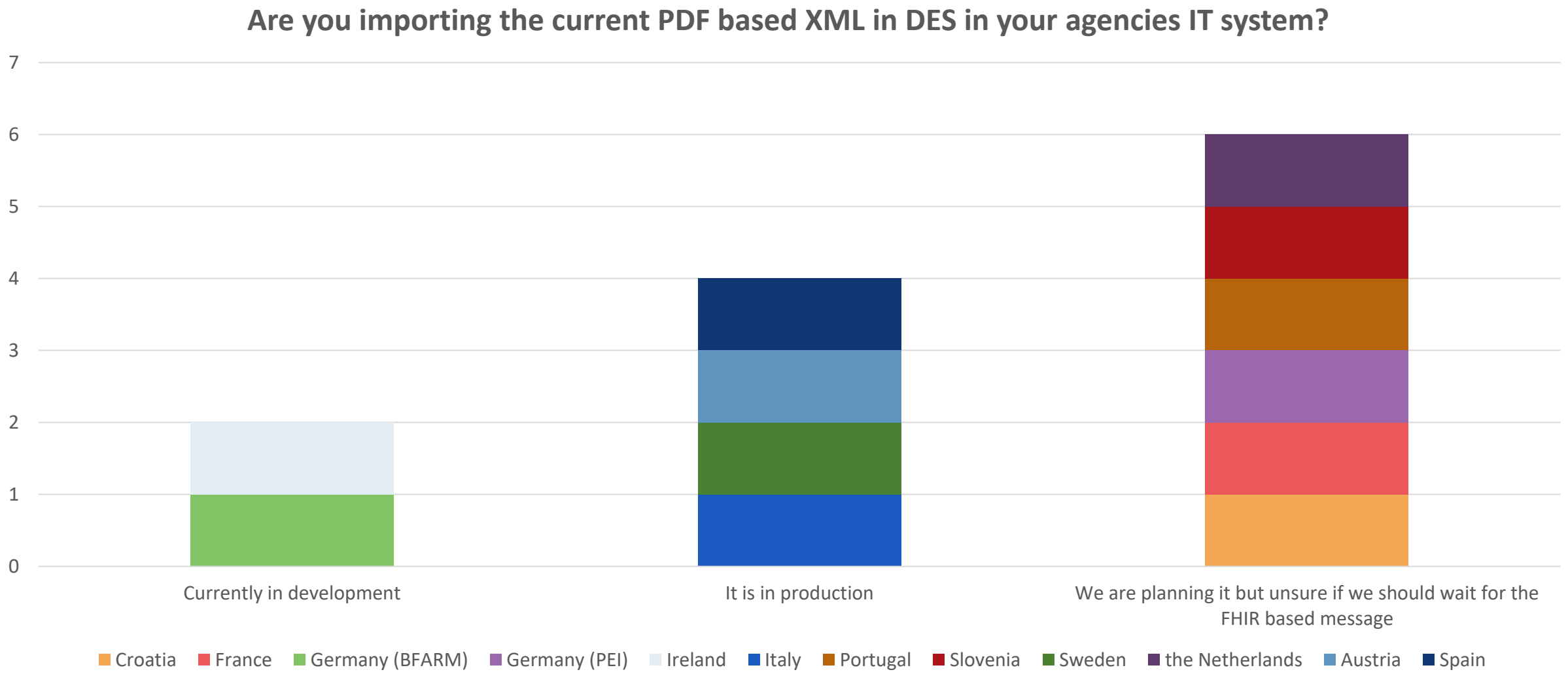
Member States implementing FHIR

Current DES XML



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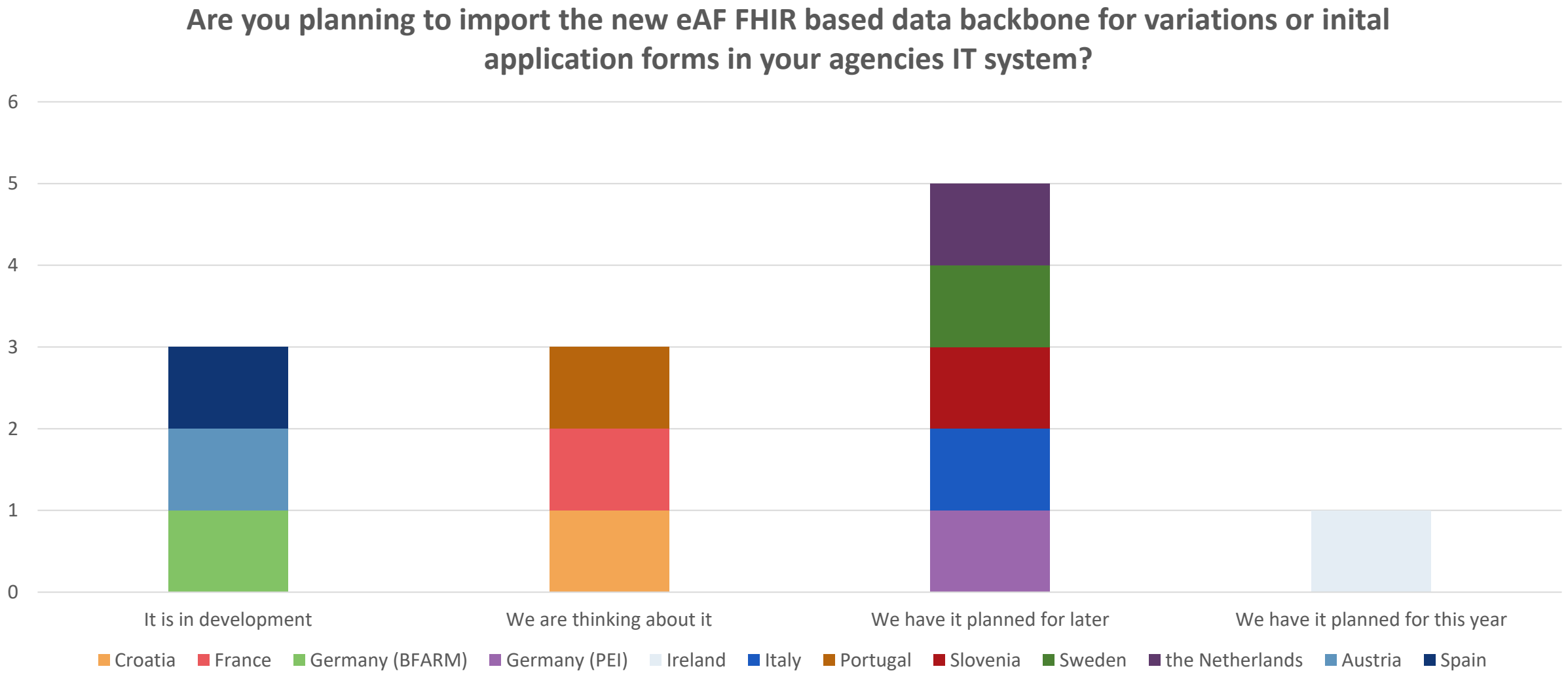
Future FHIR XML



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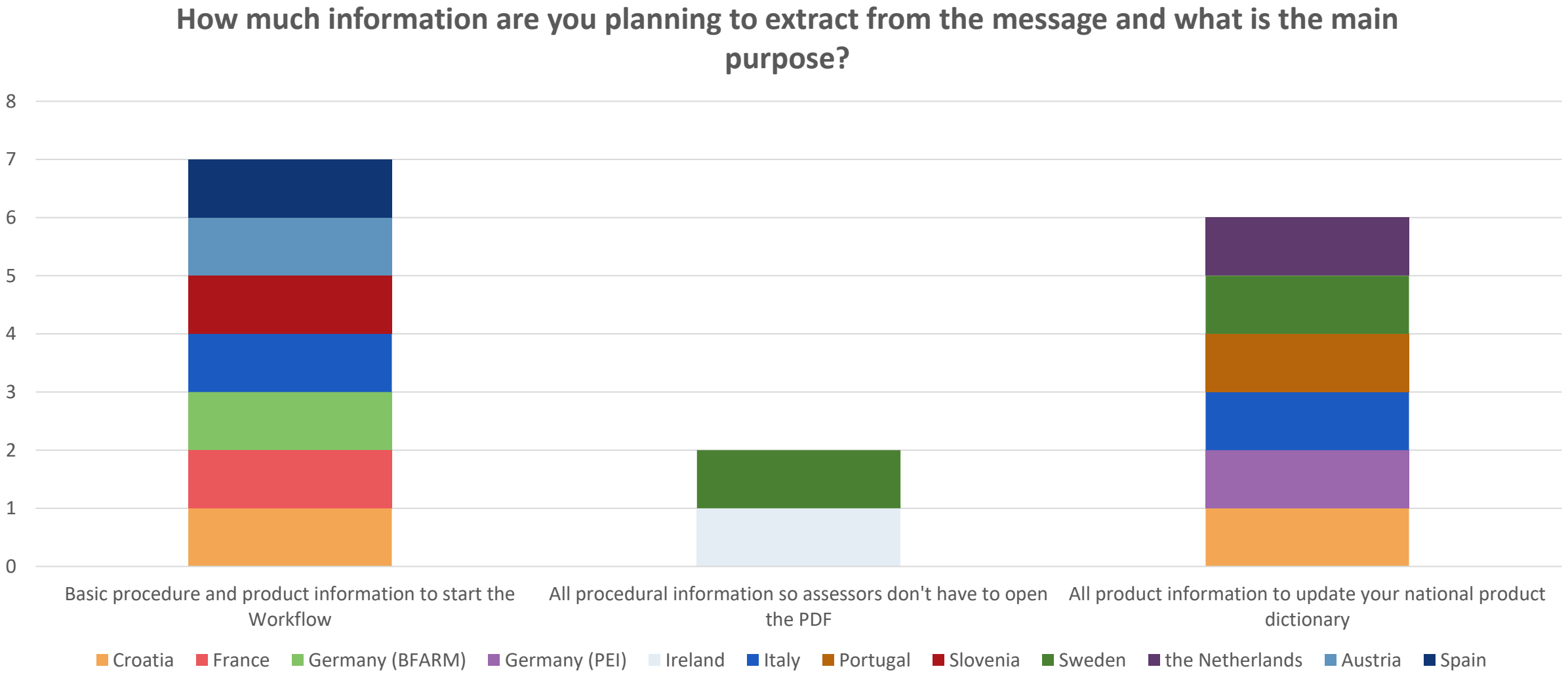
Information extracted (multichoice)



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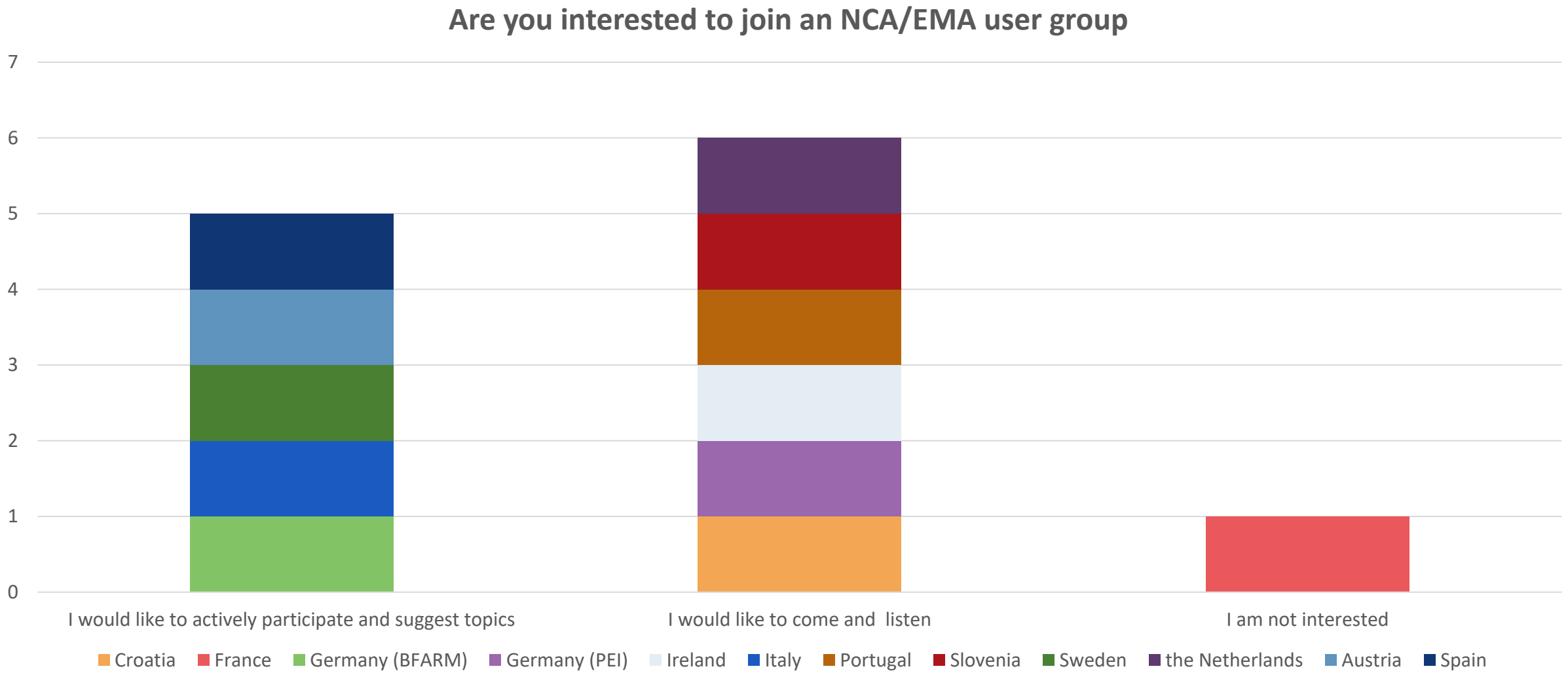
Follow up?



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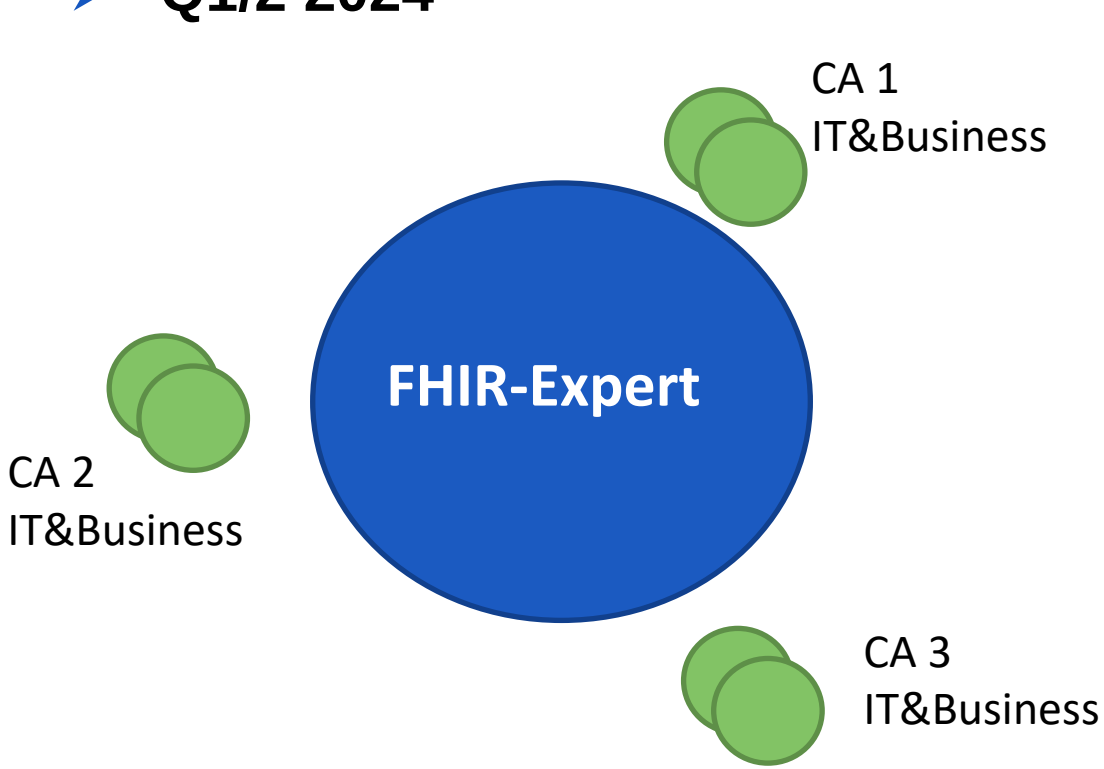
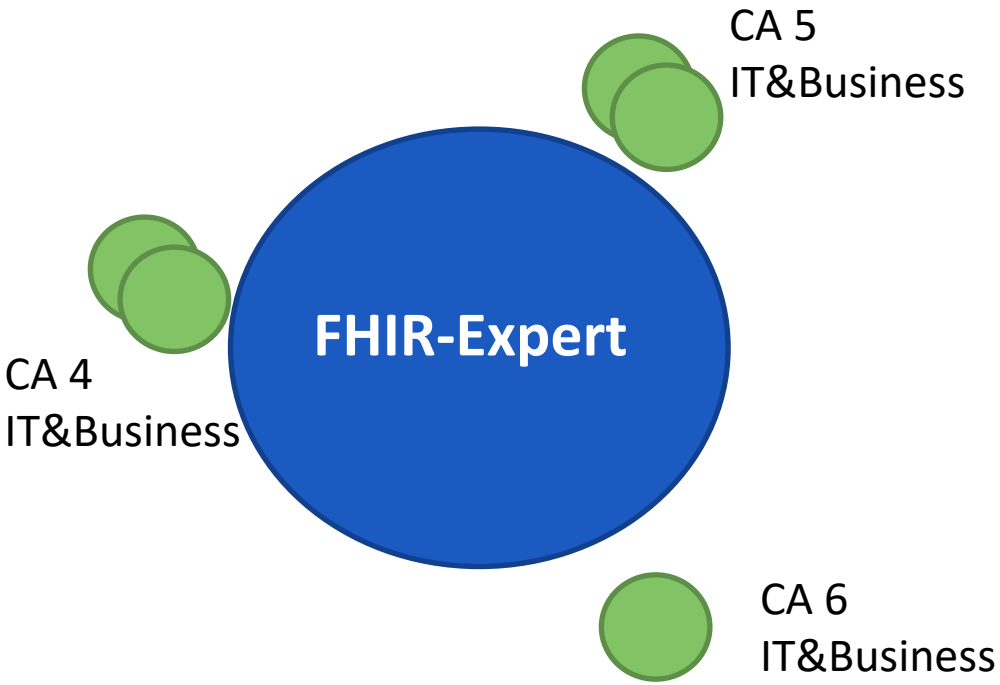
RAthons

- **We would like to organise two RAthons (compare Connectatons)**
  - **Q4/2023**
  - **Q1/2 2024**





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Design

- Bring your own laptop
- On-site meeting to train how to extract data from eAF FHIR messages
- Participants will be trained by FHIR experts
- Participants will be supported trying out practical examples
- Participants will be able to ask and discussion questions
- Participants will be able to transfer knowledge and practical experiences into their agencies
- Business and IT-Experts can learn together

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Next steps

- Agreeing on date and location
- Invitation to (UNICOM) NCA members – first come/first serve
- Identification of table hosts – Noel, Gianluca and on more needed
- Procurement FHIR experts … (agreement with EMA)

- **Proposal:** learning experience on how Connecthaton works in Rennes September at UNICOM test day, Contact Alexander Berler, last day to register 16. June
- First NCA RAthon in UNICOM consortium meeting in Ghent, Nov 27
- Need a stable FHIR variation form and experts from NCAs to participate
- Check list prepared by Noel on what/how for NCAs participation

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The full recording of this webinar will be available on the UNICOM youtube channel accessible from the UNICOM website

On the UNICOM website, under resources, you will also find a number of important documents published as « working papers »

Further Information on UNICOM

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