WP-1 / 24th community of expertise
Global alignment on substances based on the ISO IDMP and the SRS software

15 September 2023

Moderation:

Christian Hay, NICTIZ/UNICOM WP 1, ISO TC 215 WG 6, GS1
Robert Stegwee, NICTIZ/UNICOM WP 1, CEN TC 251

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

SOME RULES FOR THE VIRTUAL MEETINGS

UNICOM

- ✓**Everybody is on mute**
- ✓**You post your question in the Q&A facility**
- ✓**When you speak, please keep concise**
- ✓**You may show your approval !**

After (and during) the introduction presentations, any UNICOM related question / comment may be shared with Q&A

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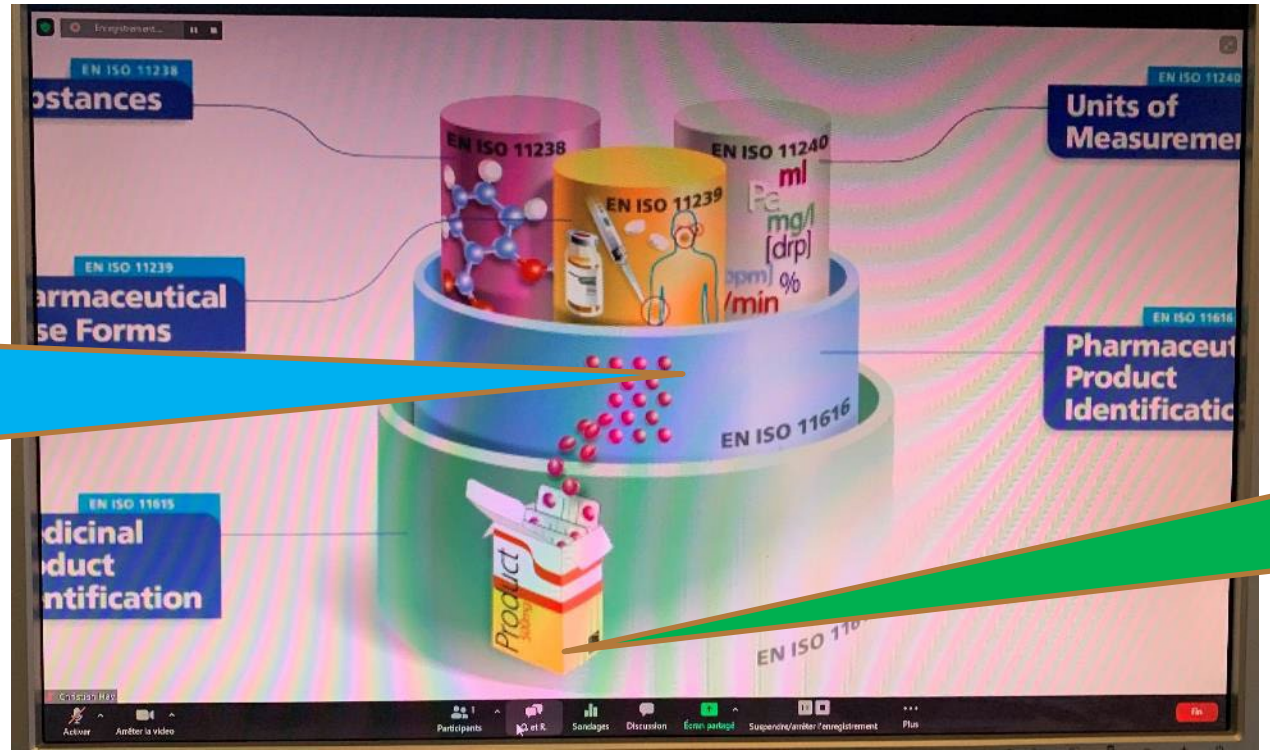
Asking a question or making a comment: please use the Q&A facility

1. Move the mouse on the screen to have the options bar appearing



2. You then select «Q&A» and write your question

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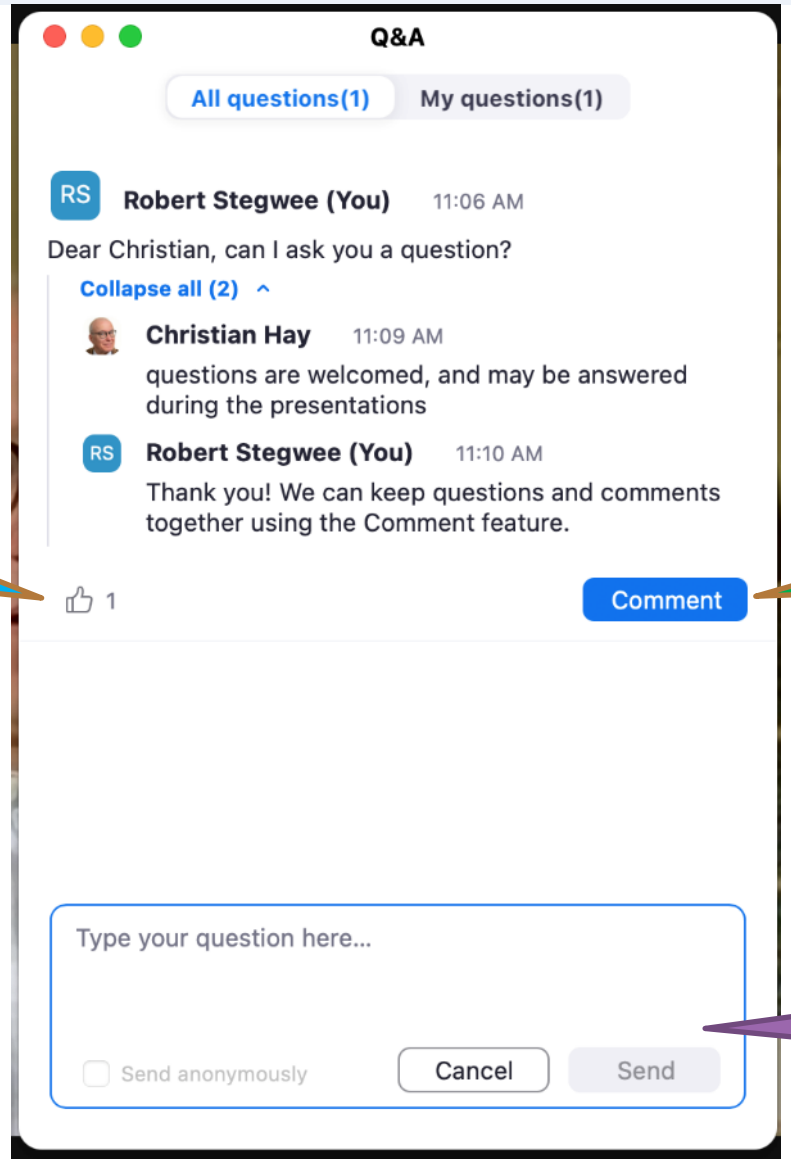
Showing support and providing a comment on a question or answer

You can support a question by clicking the «thumbs up» which moves it up on the list for the presenters



You can comment on a question or answer to engage in a conversation

Typing and sending a new question does not retain the context of your comment

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Security

- Security is our priority
- This session is password protected

Recording of this session is made available on UNICOM's youtube channel
https://https://www.youtube.com/c/UNICOM-IDMP

At the end of the virtual session, a questionnaire will be sent to the participants, to help us understand participant's reactions and needs

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Global alignment on substances based on the ISO IDMP and the SRS software

Olof Lagerlund, Magnus Wallberg (WHO-UMC)
Annet Rozema (or colleague) (EU-SRS team at CBG/MEB)
Norman Schmuff (FDA)

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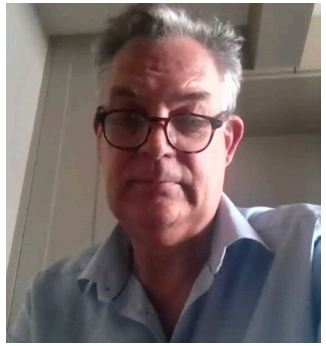
Introductions to our esteemed colleagues and today's speakers…

Olof Lagerlund

Magnus Wallberg

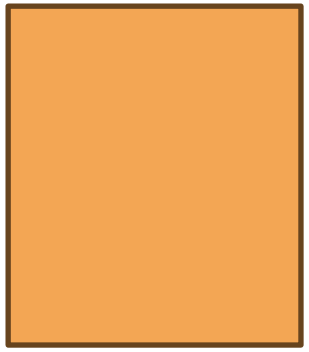
Annet Rozema

…and pannelist



Robert vander Stichele

Monica Harry



Norman Schmuff

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Questions, comments

- Please use the Q&A facility !

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EU-SRS

Community of Expertise – 15/Sept/2023

EU-SRS

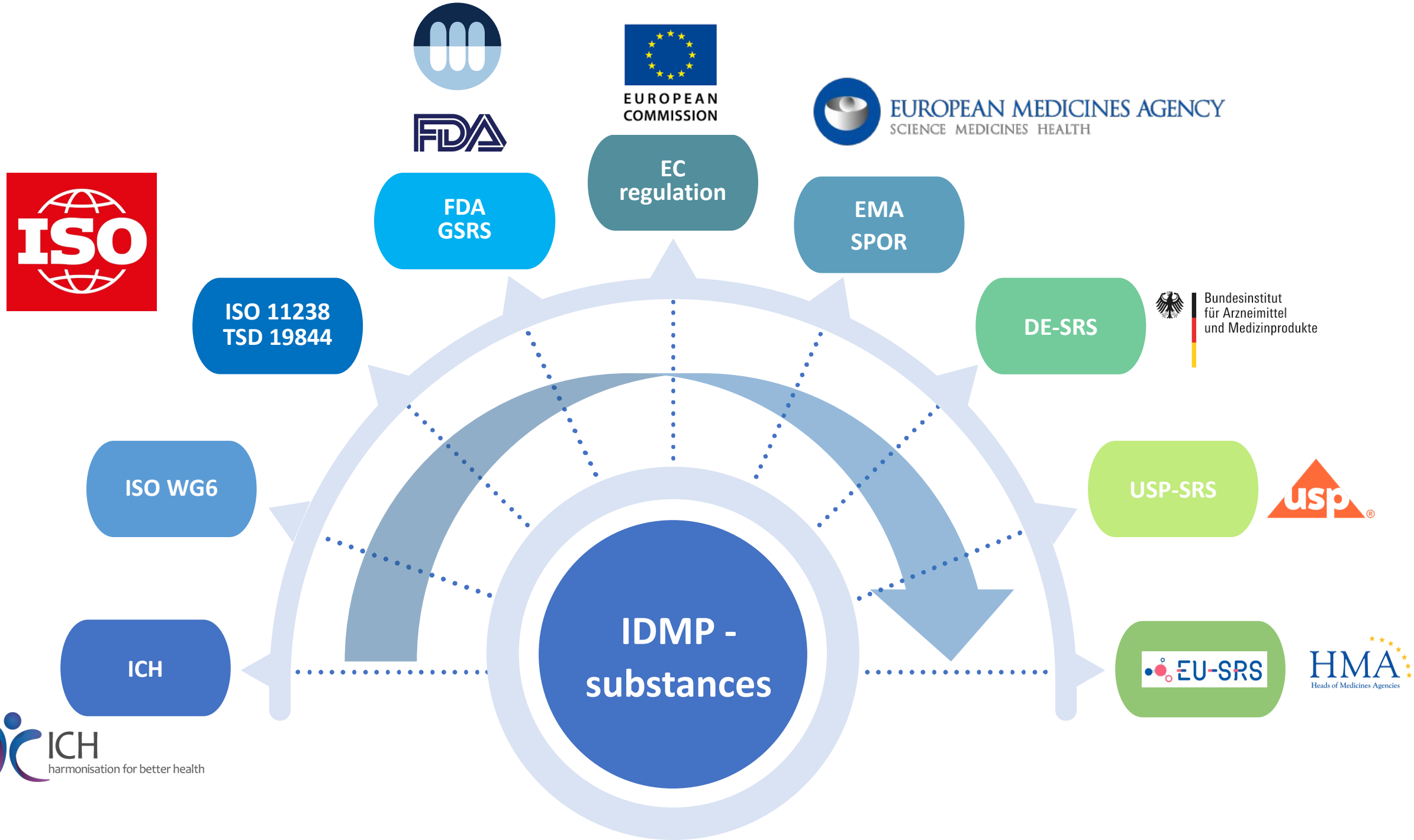
THE EUROPEAN SUBSTANCE REGISTRATION SYSTEM

AGENDA

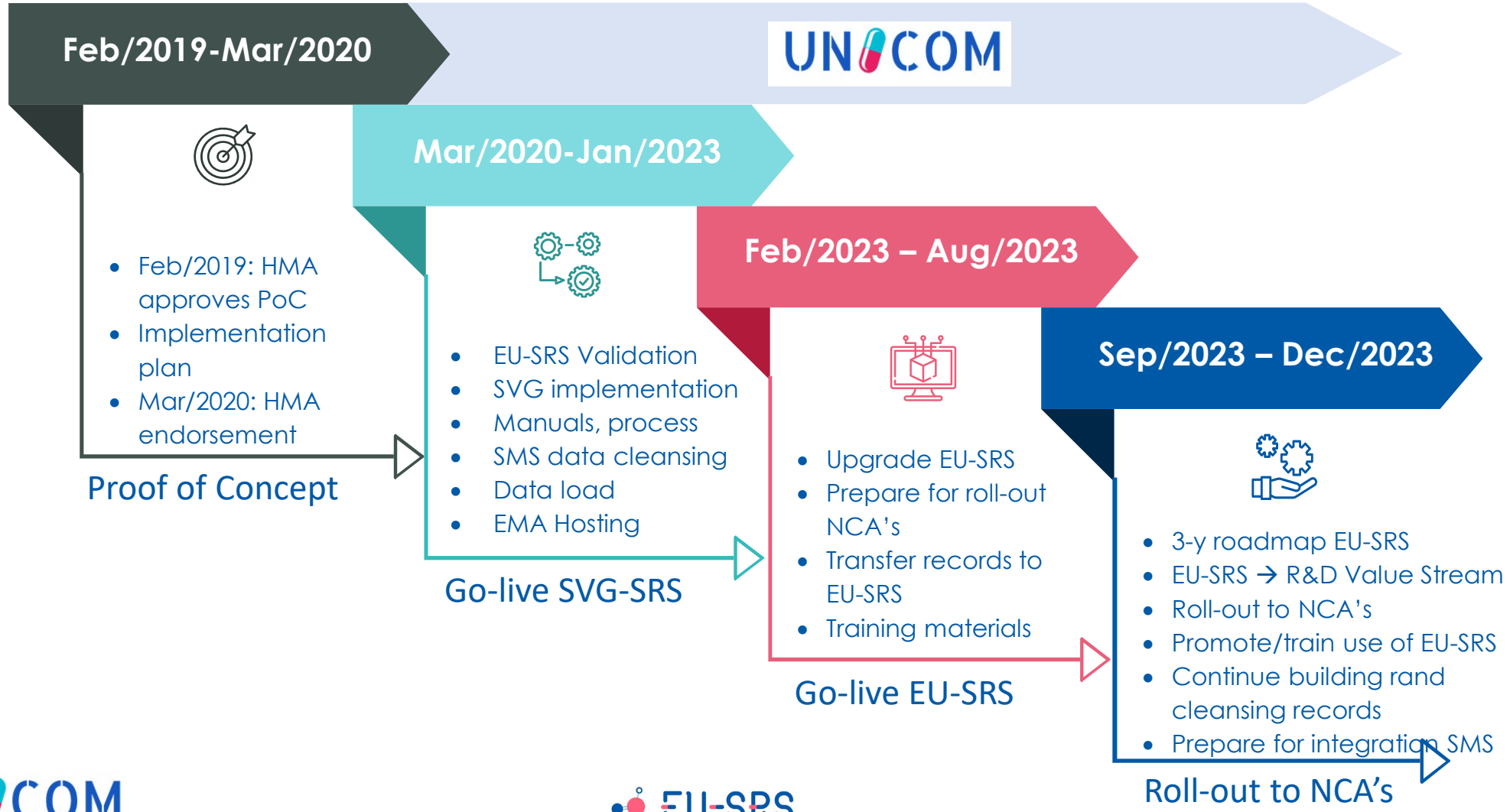
1. Background & status EU-SRS
2. Current benefits of EU-SRS
3. Next steps

1. BACKGROUND & STATUS EU-SRS

EU-SRS
THE EUROPEAN SUBSTANCE REGISTRATION SYSTEM


FDA
EUROPEAN COMMISSION
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
ISO
FDA GSRS
EC regulation
EMA SPOR
ISO 11238
TSD 19844
DE-SRS
Bundesinstitut
für Arzneimittel
und Medizinprodukte
ISO WG6
USP-SRS
usp
IDMP - substances
ICH
EU-SRS
HMA
Heads of Medicines Agencies
ICH
harmonisation for better health

EU-SRS IMPLEMENTATION PATH



EU-SRS
Ver. 3.0.3

Menu | Browse Substances | Search | Search Substances

Quick Links

Substances

- Browse Substances
- Structure Search
- Sequence Search
- Advanced Search

Register

- Chemical
- Protein
- Polymer
- Nucleic Acid
- Structurally Diverse
- Concept

European Substance Registration System – EU-SRS

EU-SRS is the European Substance Registration System. The system is used by the Substances Validation Group (SVG) to capture scientific data on substances used in medicinal products.The database is making use of the open-source software from FDA/NCATS, called GSRS. EU-SRS allows the SVG ensure consistent definitions of substances, consistent with the ISO 11238 standard.The EU-SRS system is hosted and maintained by EMA. The substance data is maintained by the national substance experts of the SVG.

Search Substances

Browse Substances | Structure Search | Sequence Search | Bulk Search

Total substances: 17,683

Chemicals	17,405	Polymers	0	Structurally Diverse	197
Proteins	79	Nucleic Acids	0	Concepts	0

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EU-SRS

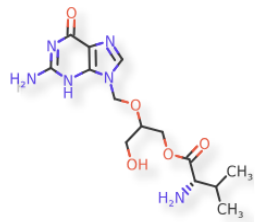
There is one exact (name, standardized name or code) match for "Valganciclovir"

Show All Records Matching Search

Valganciclovir

100000089025

EPIMERIC



Names: Valganciclovir ✓
(2RS)-2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]-3-hydroxypropyl L-valinate

Codes:

SMSID : 100000089025

SVGID : 001649

xEVMPD : SUB00007MIG

FDA UNII : GCU97FKN3R

CAS : 175865-60-8

INN : 7650

PUBCHEM : 135413535

RMS : 100000075670 , 100000000012

Less

Relationships: 1

Mol. Weight: 354.36

Formula: $C_{14}H_{22}N_6O_5$

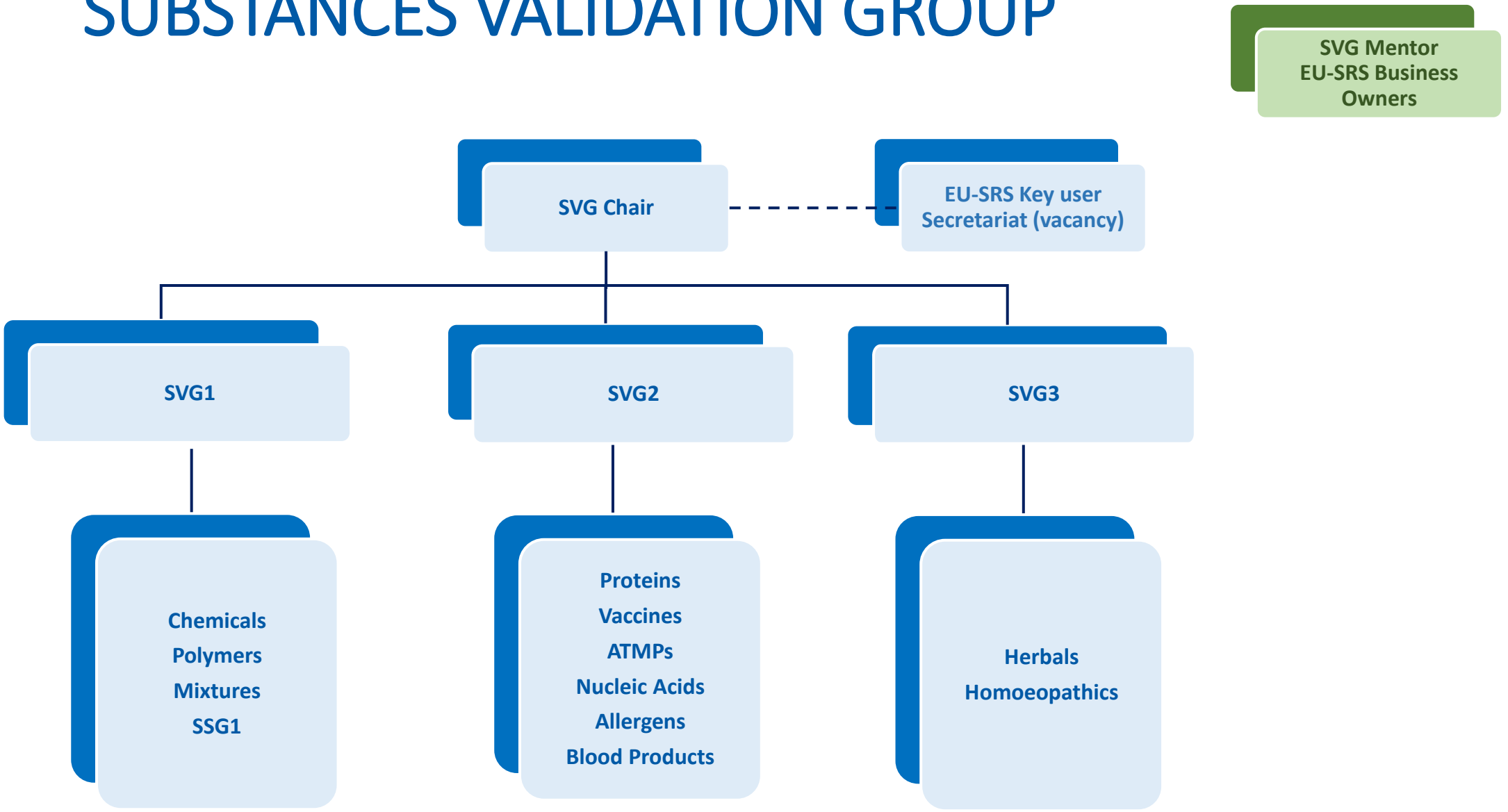
Substance Hierarchy

Valganciclovir	100000089025
Valganciclovir hydrochloride	100000091375 *{SALT/SOLVATE}*

CURRENT ACCESS / ROLL-OUT STRATEGY

- Roll-out **wave 1:**
  - Colleagues of agencies involved in the SVG
  - Current number of users in EU-SRS: n= 26
  - Timing: August/September 2023
- Roll-out **wave 2**:
  - EU NCA colleagues, not limited to those involved in the SVG
  - Targeted roll out, so use case-driven
    - Chemical assessors
    - Substance experts
    - Pharmacovigilance
    - IT-experts
  - Timing: October – December 2023

SUBSTANCES VALIDATION GROUP



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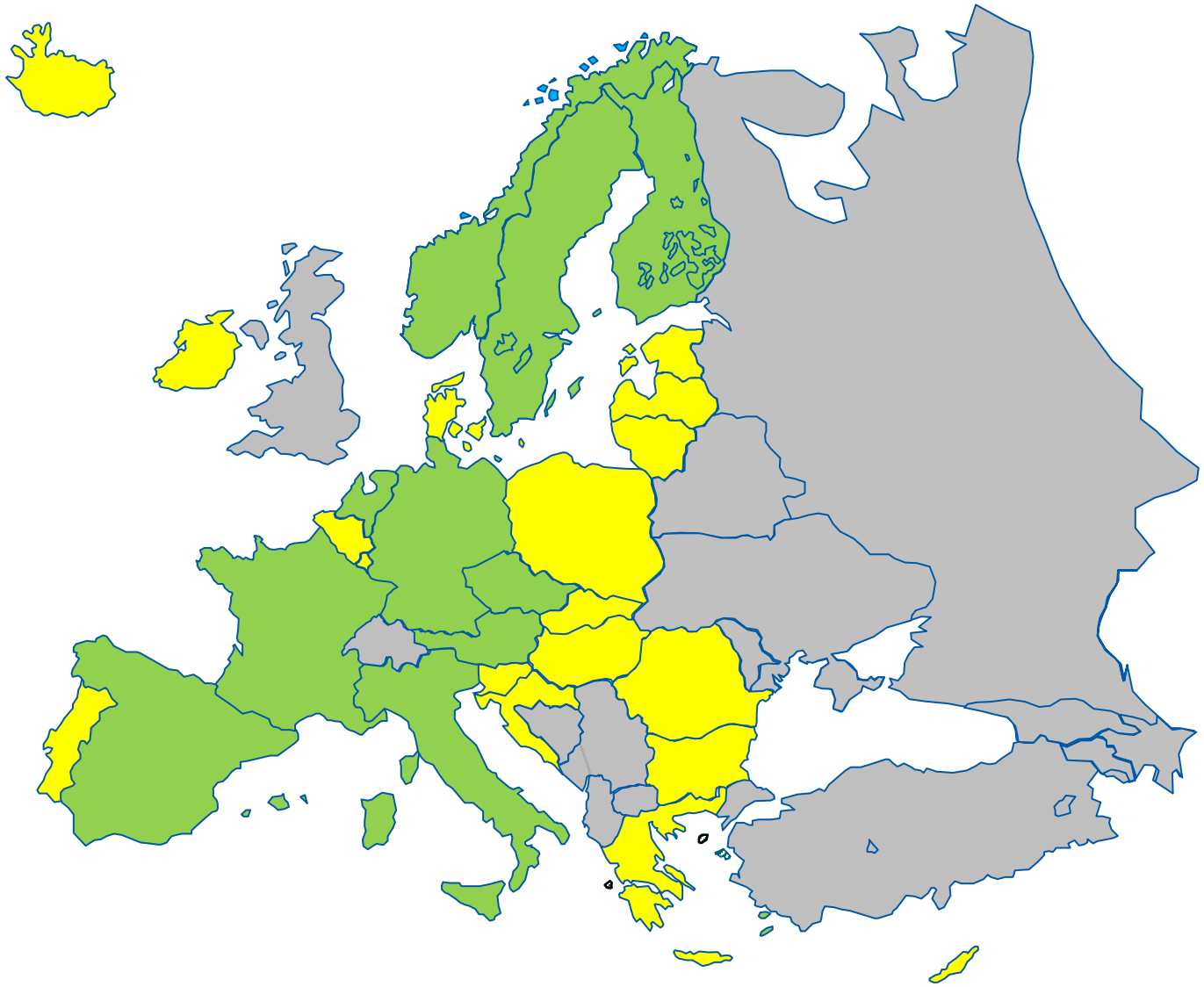
EU-SRS

MANY NCA'S PARTICIPATE IN THE SVG



EEA member involved in SVG

EEA member not yet involved in SVG

- Close collaboration with EMA, NCA's, FDA/NCATS, and WHO-UMC
- The >20 SVG members come from a variety of NCA's. They are assessors and/or substance experts

RESPONSIBILITIES EU-SRS

EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Hosting

Maintenance EU-SRS

Collaboration with NCATS on software development

SVG

HMA
Heads of Medicines Agencies

Content EU-SRS

Data management standards & agreements

Collaboration with stakeholders, e.g. ISO

In-kind contribution NCA's

https://www.hma.eu/about-hma/working-groups/hma/hma-substances-validation-group.html

2. CURRENT BENEFITS

EU-SRS
THE EUROPEAN SUBSTANCE REGISTRATION SYSTEM

CURRENT BENEFITS FROM EU-SRS

- One-stop shop to feed national databases
  - Efficiency increase nationally
  - High quality data
- Feed data to SMS
- Flag SMS data issues
- Direct access for assessors to high quality substance information, e.g. structure information
- Enabling structured data submission

INTERNATIONAL COLLABORATION

Use of GSRS software is expanding

- FDA/NCATS
- USP
- DE-SRS (BfArM)
- EU-SRS
- UMC-SRS

Interest in joining (global) management of substance data:

- Kew Gardens
- Industry
- UMC
- Swissmedic

Use of GSRS software is enabler of global substance management!

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EU-SRS

3. NEXT STEPS

EU-SRS
THE EUROPEAN SUBSTANCE REGISTRATION SYSTEM

EU-SRS NEXT PHASE

2024/2025 –Wave 1 (t.b.c.)

- Process improvements / efficiency SVG
- Upgrade to GSRS 3.1/3.x, e.g. staging area
- Interface SMS/SRS
- Improve accessibility EU-SRS
- Substances backlog, prio 1
- **Globalization, incl GSID**
- Support NCAs/EMA with using EU-SRS

2026 and further – Wave 2 (t.b.c.)

- Substances backlog, prio 2
  SSG2 (i.r.t. SPOR OMS)
  SSG3
- Software upgrades GSRS
- Public EU-SRS
- Product module
- **Global substance management**

FUTURE DIRECTION: GLOBALIZATION

- GIDWG *(see next topic)*
- GSRS
- Industry

GSRS software

- FDA-SRS
- NCATS-SRS
- USP-SRS
- DE-SRS
- EU-SRS
- UMC-SRS
- Industry-SRS
- ….

IDMP data submission

- Same dataset, multiple agencies
- Efficiency increase
- Preventing errors

Global alignment on substances based on the ISO IDMP and the SRS software

Olof Lagerlund and Magnus Wallberg CoE, September 15th

Uppsala Monitoring Centre

Agenda

Introduction

GSID

PhPID

FHIR

IDMP implementation is a *collaborative* project

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Where we are

ISO IDMP
1st ISO publication of the standards.

GSRS
ISO 11238

EU-UNICOM
ISO IDMP

EMA-FDA collaboration on IDMP
Signed project charter: 2019

Global PhPID Pilot
ISO 11239 - ISO/TS 20440

Vaccines initiative
ISO 11238 - ISO/TS 19844

Global IDMP WG

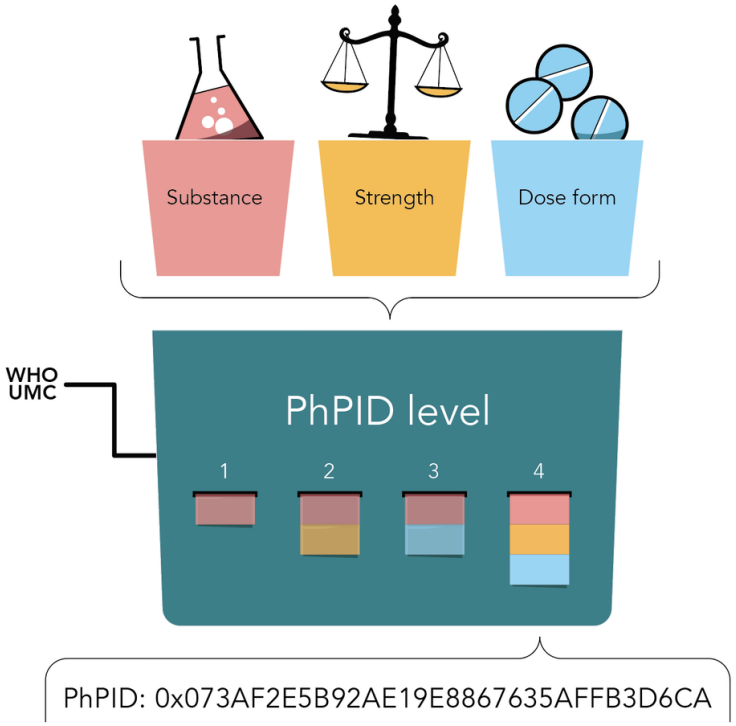
ISO IDMP
1st ISO publication of the standards.

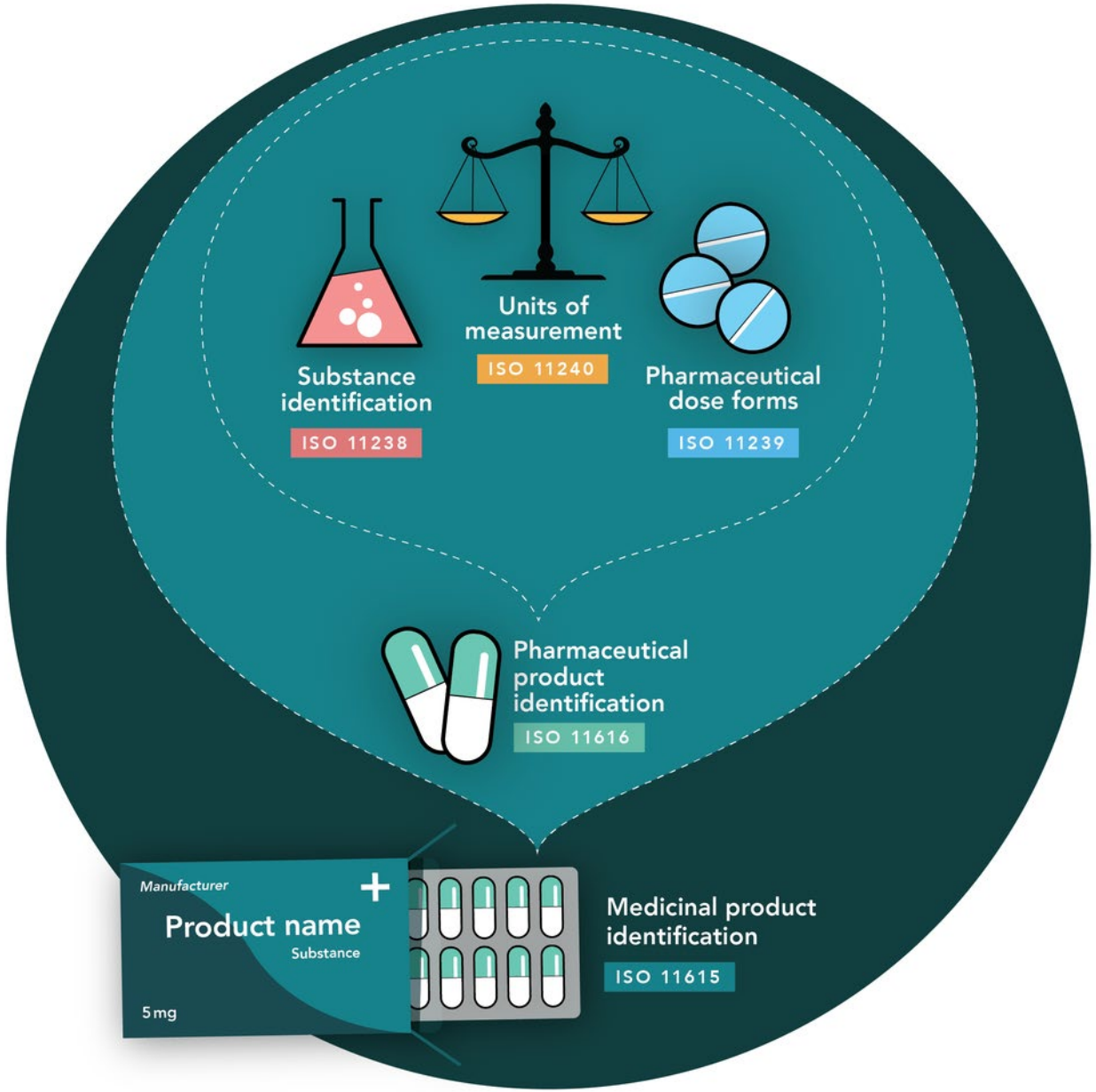
SPOR
OMS-RMS-SMS

EU-SRS
ISO 11238 - ISO/TS 19844

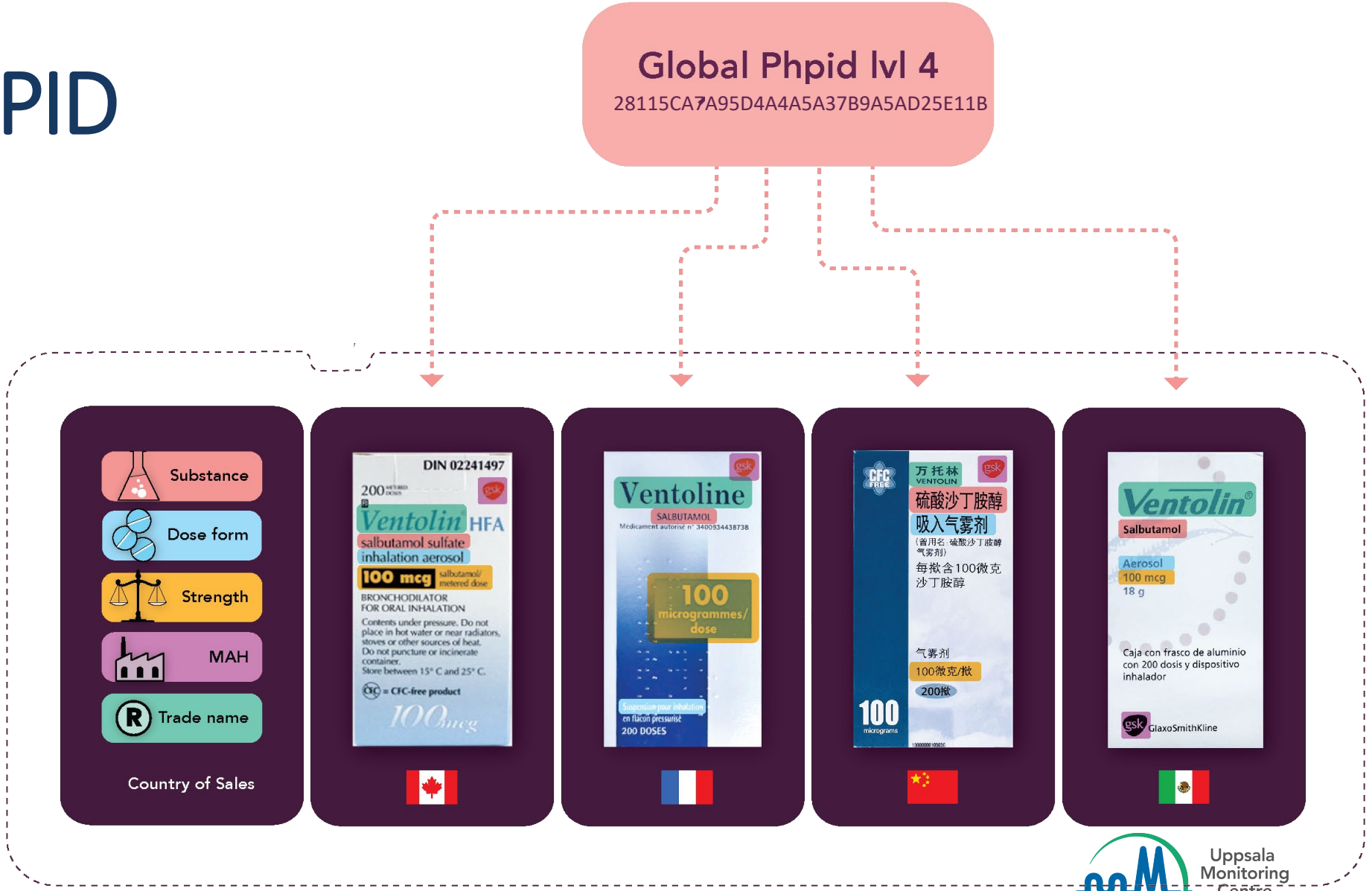
EMA-FDA collaboration on IDMP
Signed project charter: 2019

Global PhPID





Global PhPID



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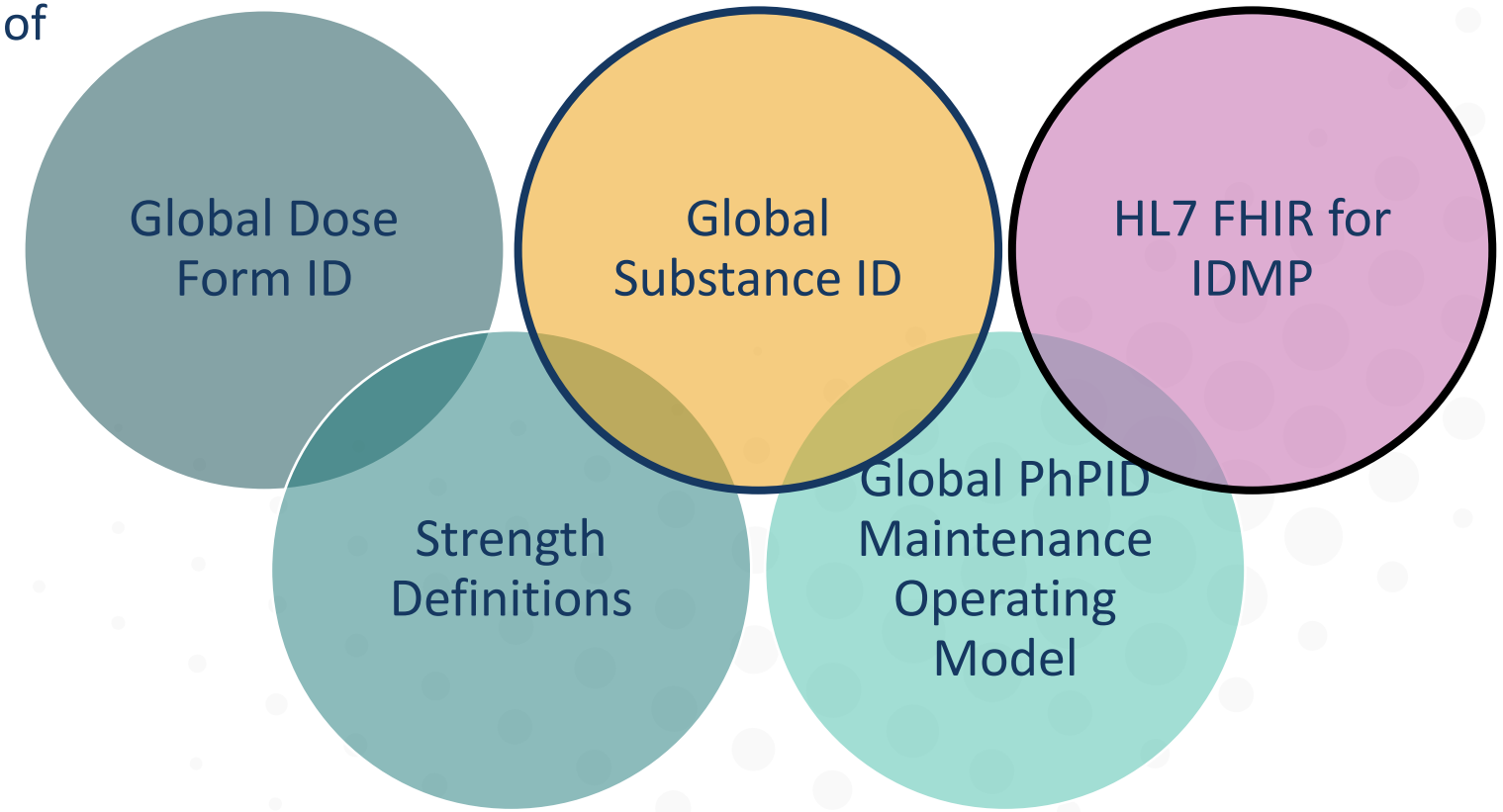
GIDWG projects

Aim to identify and develop consensus on processes, best practices and operating model for maintenance of global identifiers for marketed medicinal products



www.gidwg.org

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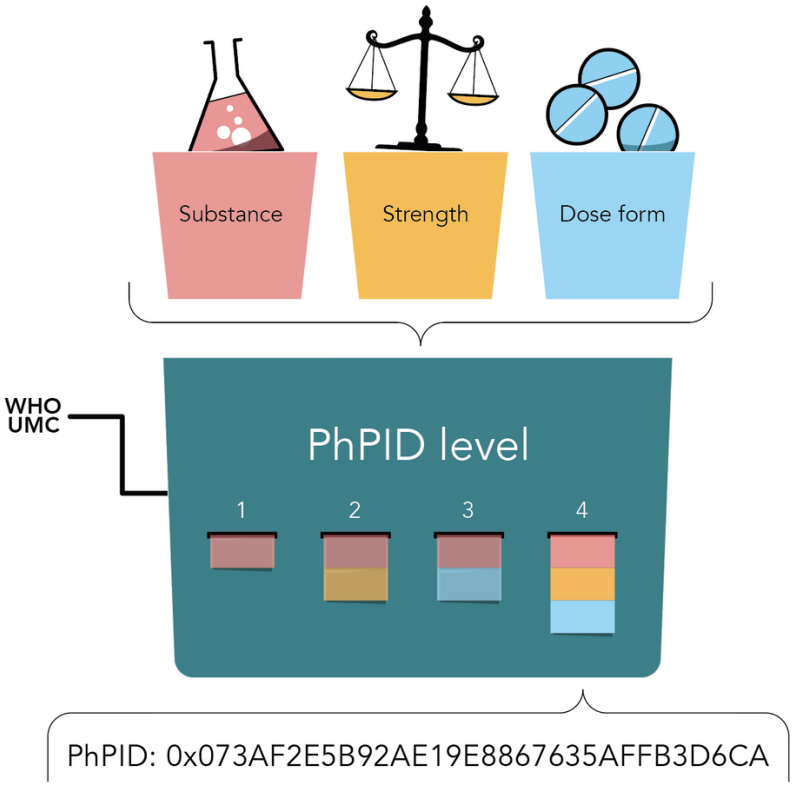
Why a Global substance identifier (GSID) ?

- International naming organizations
  - INN, USAN, JAN…
- Pharmacopeias
  - Ph Eur, Korea, Brazil…
- Other identifiers/codes
  - UNII, SMS-ID, Ijoken…



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Construction of GSID used in the GIDWG pilots

A unique and consistent code following the ISO/IEC 15459 - Part 3 (Ref ISO/IEC 15459). The code consists of 17 characters long text buildup of a Qualifier , Unique text, and Check character.

GSID9ST5UC24F36TN

- The first 4 characters is the qualifier and will always be the text GSID.
- The middle 12 characters are a unique text buildup of random digits and letters.
- The last character is a check character which is used as a redundancy check used for error detection on identification numbers

The order for how substance combination are expressed in PhPID algorithm is: Order by GSID (not by substance name) where numbers precedes letters i.e. 9 before A.

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GSID and PhPID - Business rules in the GIDWG pilot

GSID

- The **GSID** assignment is based on the **ISO 11238:2018** and **ISO/TS 19844.**
- The GSID business rules should clarify the standards when needed.

PhPID

- The **PhPID** assignment is based on the **ISO 11616:2017**
- The PhPID business rules ensures using the appropriate GSID, when generating a PhPID, in a consistent manner.

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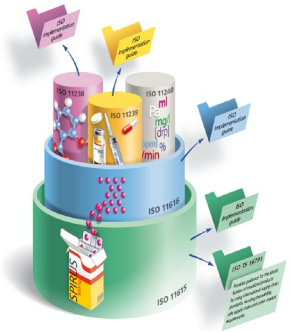
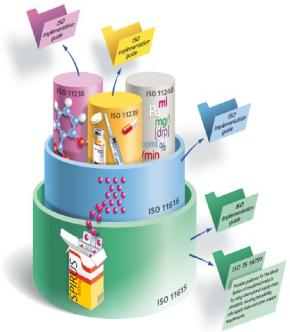
How to deal with challenges in creating global substance ID?

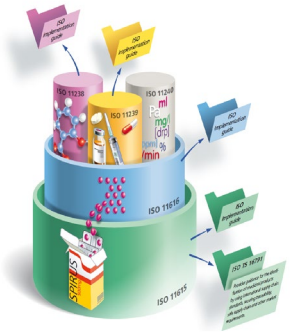


How to deal with challenges in creating global substance ID?



Collaboration

How to deal with challenges in creating global substance ID?

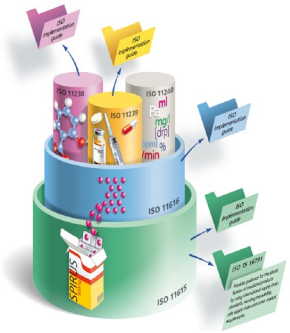


Collaboration

We need a common view of the implementation of the substance standard.

1. Follow the standard
2. Global process for alignment when the standard is not clear

How to deal with challenges in creating global substance ID?

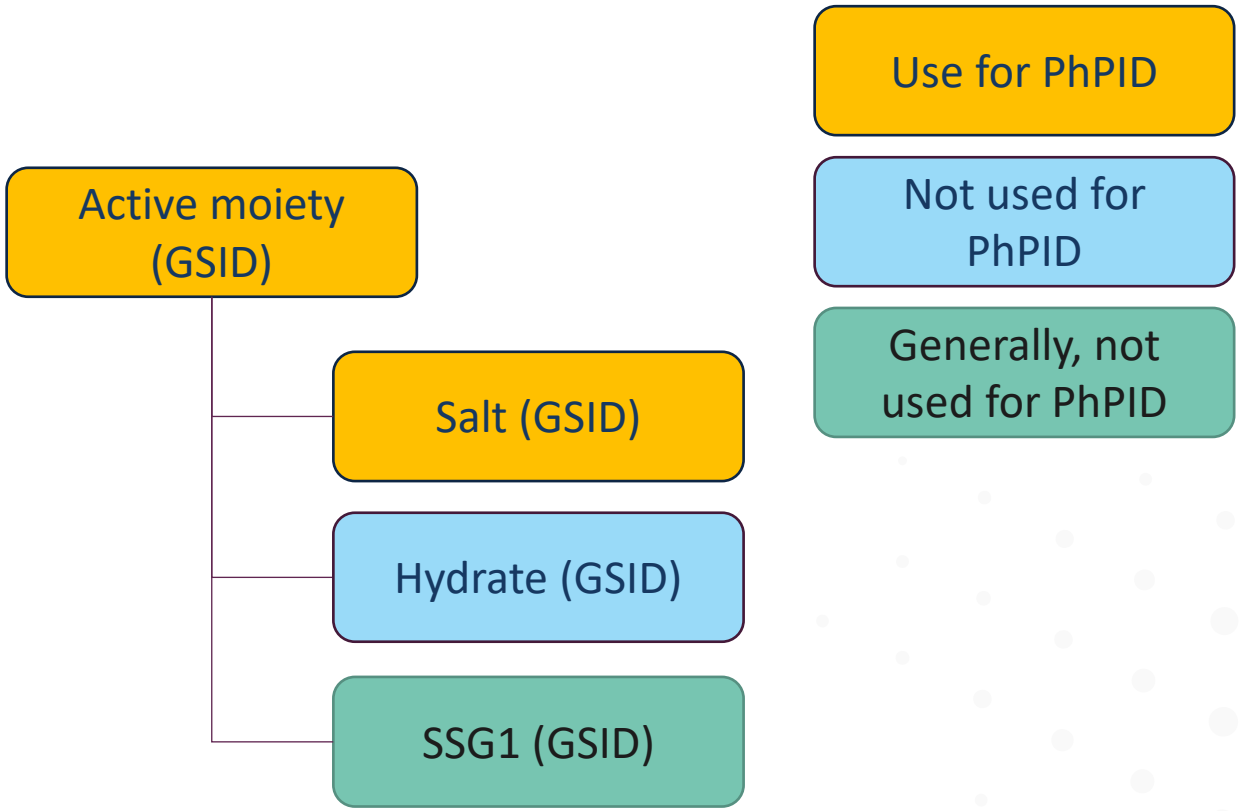


Collaboration

We need a common view of the implementation of the substance standard.

1. Follow the standard
2. Global process for alignment when the standard is not clear
3. Common SRS guide for substance registration
4. Common controlled vocabulary and relationships

PhPID GSID - GIDWG pilot Business rules



GSID can be assigned on the substance and SSG1 level.

For PhPID generation the GSID of the active ingredient, disregarding hydrates, is used.
The SSG1-level is generally not used for PhPID generation.

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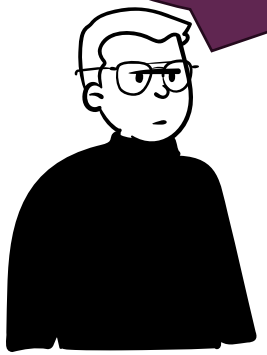
How to deal with challenges using GSID in PhPID generation?

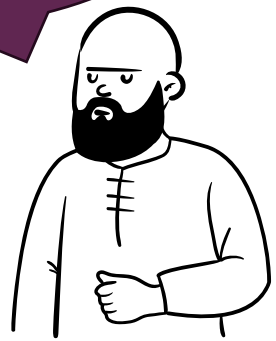
Which substance should be used as active ingredient?

Do you generate an additional PhPID for the active moiety if that product is not marketed?

How to deal with liposomal products?



Have you done anything on structurally diverse?



How to deal with challenges using GSID in PhPID generation?

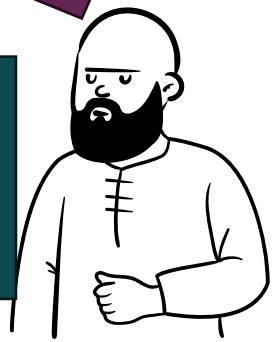
Which substance should be used as active ingredient?

Regulators decides which is to be viewed as active. For PhPID assignment we use GIDWG pilot BR to harmonize.

Do you generate an additional PhPID for the active moiety if that product is not marketed?

See next slide

Have you done anything on structurally diverse?



We started with discussion on vaccines and herbals and have agreed on a basic structure.

How to deal with liposomal products?

The substance level is used for PhPID since the liposomal formulation is treated as an SSG1

PhPID input for active ingredient

Connection between “active moiety” and salt available in WHODrug (with links to products) or SRS (only substances)

Amlodipine (GSID)

Used for PhPID

Amlodipine besilate (GSID)

An additional PhPID for the active moiety can be generated for aggregation and analysis purposes.

PhPID level ? … Input: Amlodipine, 5mg, Tablets

PhPID level 4 … Input: Amlodipine besilate, 5mg, Tablets

Statistics from the GIDWG pilots based on our BR

Between 92 and 99% of all products investigated in the GIDWG pilots can be assigned a PhPID.

- Selected dataset

  Products containing chemicals and proteins

- Three countries

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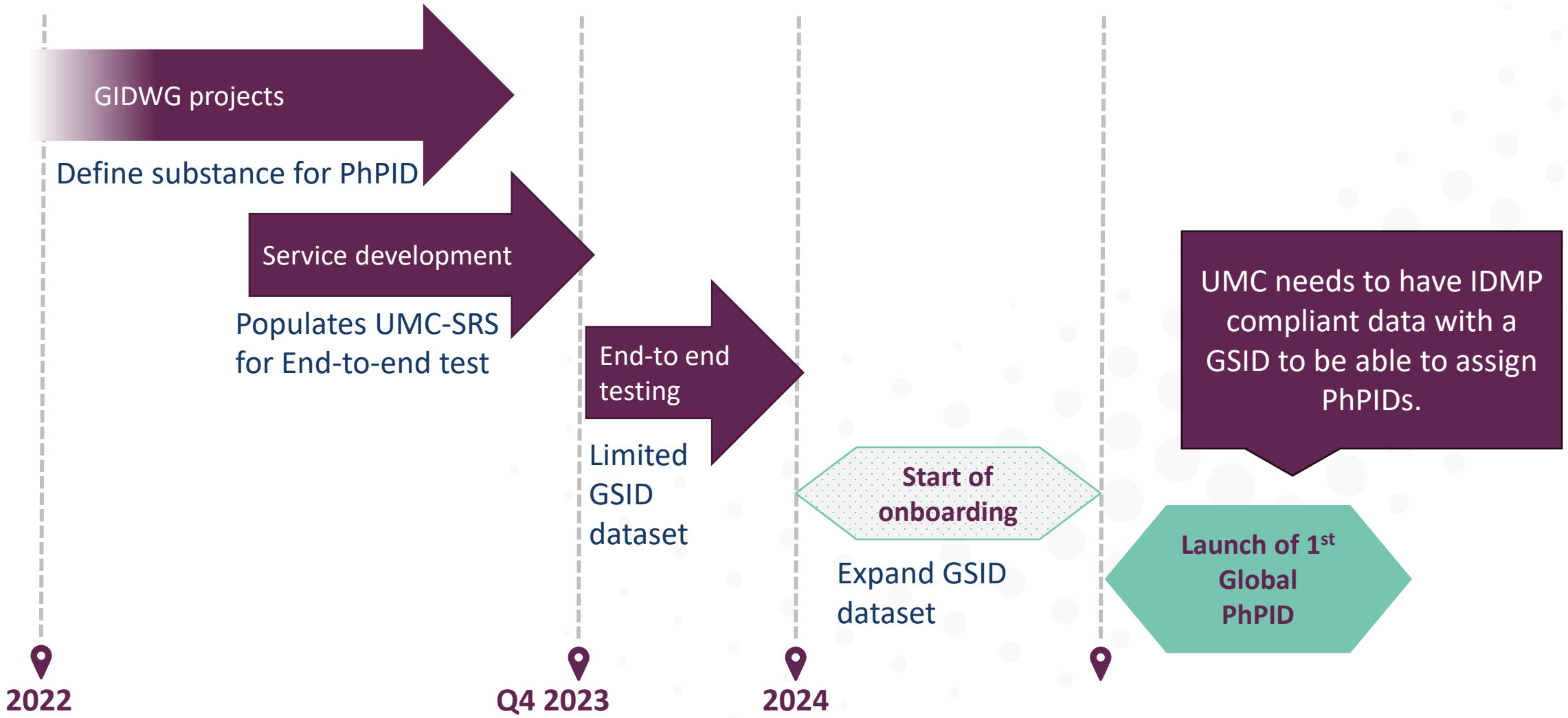
Future perspective – Global Substance ID

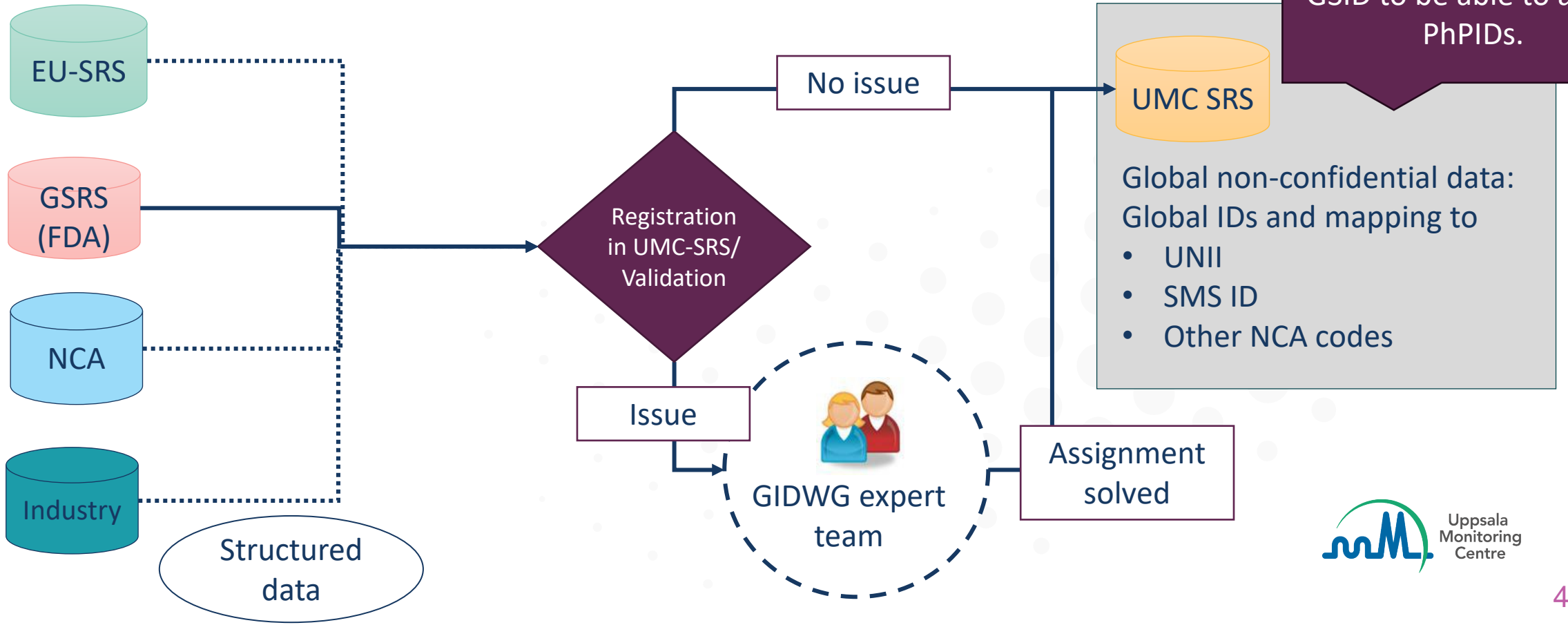


Global substance process in the GIDWG pilots

Substances in marketed products

Non-confidential data export

Assign GSID



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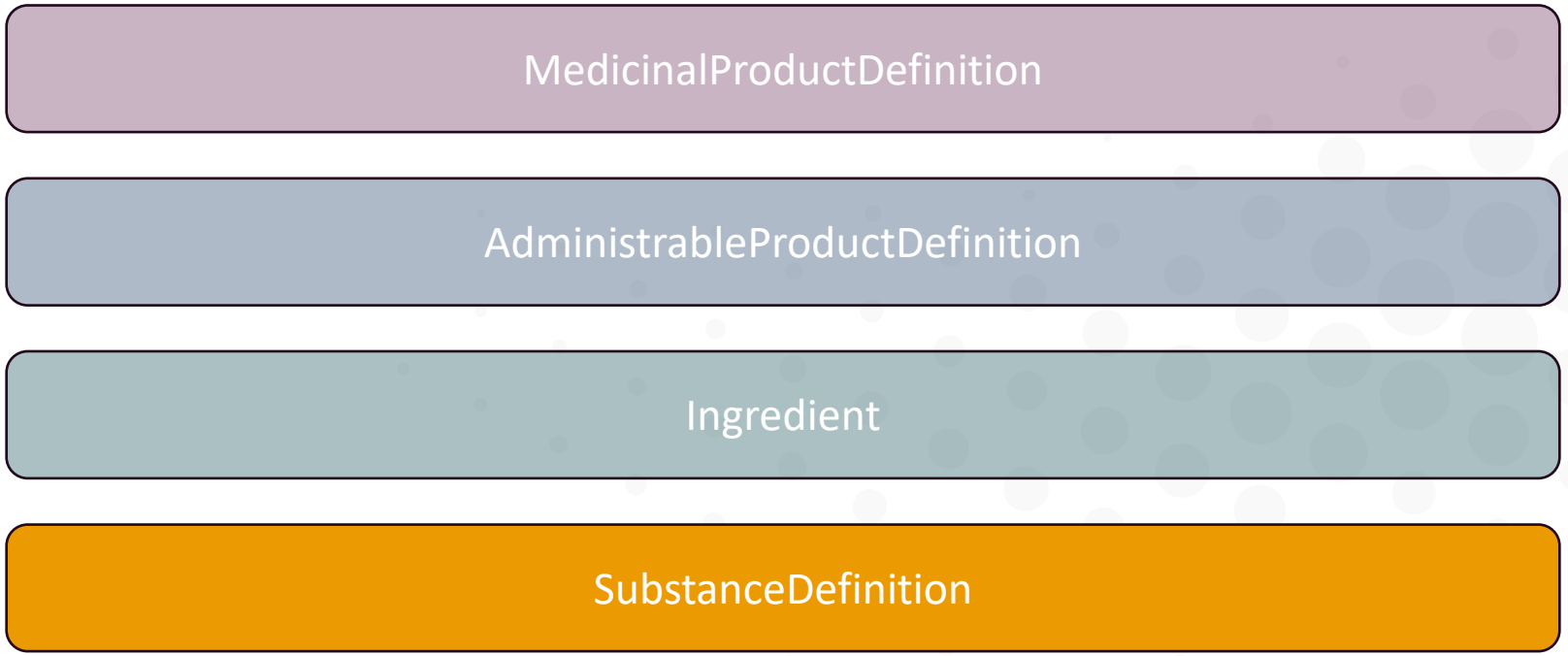
GSID on FHIR

As part of the HL7 FHIR release 5 there are a number of resources with the aim to support IDMP. Some of those are:



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Name	Flags	Card.	Type	Description & Constraints
SubstanceDefinition	TU		DomainResource	The detailed description of a substance, typically at a level beyond what is used for prescribing Elements defined in Ancestors: id, meta, implicitRules, language, text, contained, extension, modifierExtension
identifier	Σ	0..*	Identifier	Identifier by which this substance is known
version	Σ	0..1	string	A business level version identifier of the substance
status	Σ	0..1	CodeableConcept	Status of substance within the catalogue e.g. active, retired Binding: PublicationStatus (Preferred)
classification	Σ	0..*	CodeableConcept	A categorization, high level e.g. polymer or nucleic acid, or food, chemical, biological, or lower e.g. polymer linear or branch chain, or type of impurity
domain	Σ	0..1	CodeableConcept	If the substance applies to human or veterinary use Binding: Medicinal Product Domain (Example)
grade	Σ	0..*	CodeableConcept	The quality standard, established benchmark, to which substance complies (e.g. USP/NF, BP) Binding: Substance Grade (Example)
description	Σ	0..1	markdown	Textual description of the substance
informationSource	Σ	0..*	Reference(Citation)	Supporting literature
note	Σ	0..*	Annotation	Textual comment about the substance's catalogue or registry record
manufacturer	Σ	0..*	Reference(Organization)	The entity that creates, makes, produces or fabricates the substance
supplier	Σ	0..*	Reference(Organization)	An entity that is the source for the substance. It may be different from the manufacturer
moiety	Σ	0..*	BackboneElement	Moiety, for structural modifications
characterization	Σ	0..*	BackboneElement	General specifications for this substance
property	Σ	0..*	BackboneElement	General specifications for this substance
referenceInformation	Σ	0..1	Reference(SubstanceReferenceInformation)	General information detailing this substance
molecularWeight	Σ	0..*	BackboneElement	The average mass of a molecule of a compound
structure	Σ	0..1	BackboneElement	Structural information
code	Σ	0..*	BackboneElement	Codes associated with the substance
name	Σ	0..*	BackboneElement	Names applicable to this substance
relationship	Σ	0..*	BackboneElement	A link between this substance and another
sourceMaterial	Σ	0..1	BackboneElement	Material or taxonomic/anatomical source

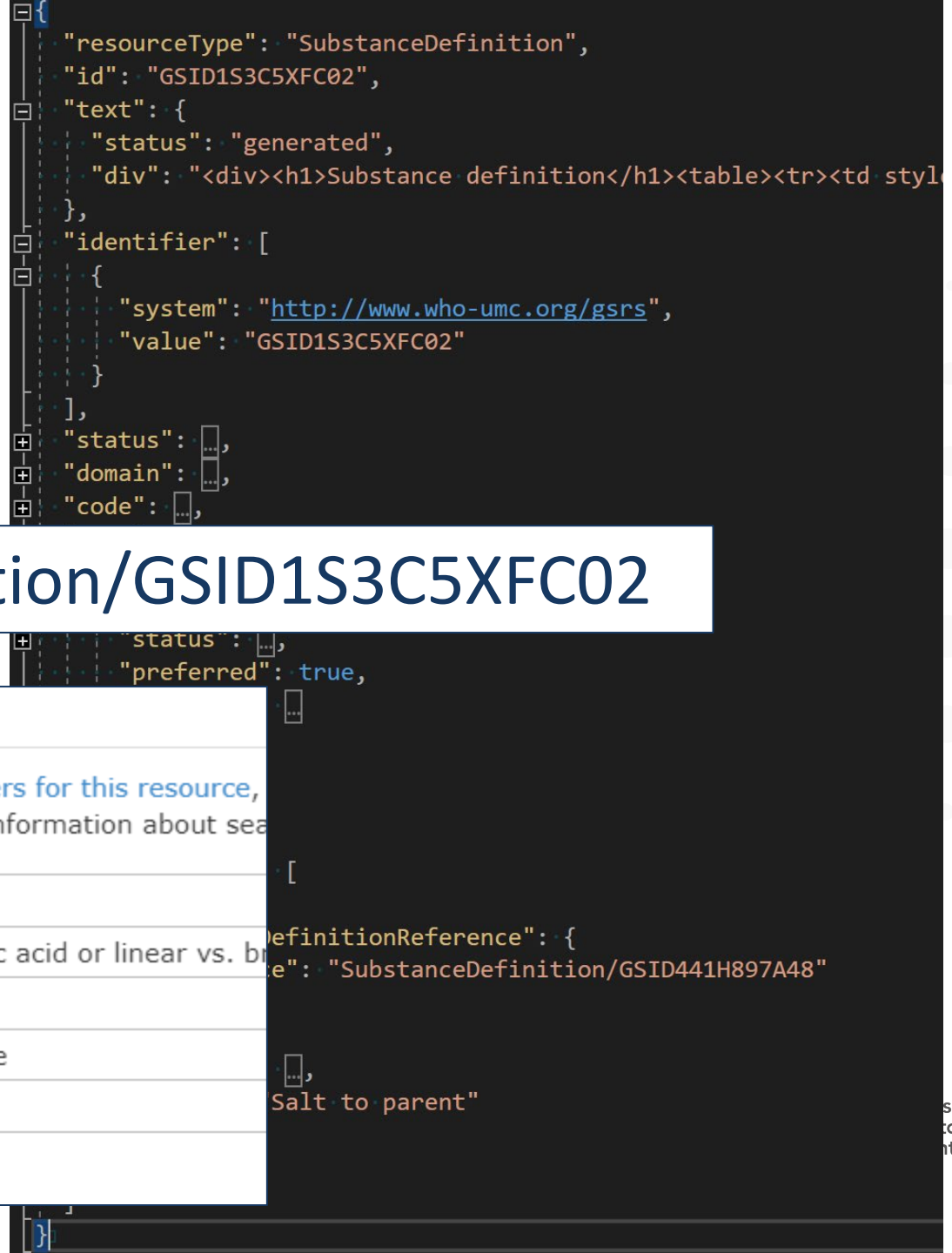
name	Σ	0..*	BackboneElement	Names applicable to this substance
name	Σ	1..1	string	The actual name
type	Σ	0..1	CodeableConcept	Name type e.g. 'systematic', 'scientific, 'brand' Binding: Substance Name Type (Example)
status	Σ	0..1	CodeableConcept	The status of the name e.g. 'current', 'proposed' Binding: PublicationStatus (Preferred)
preferred	Σ	0..1	boolean	If this is the preferred name for this substance
language	Σ	0..*	CodeableConcept	Human language that the name is written in Binding: All Languages (Required) **Additional Bindings** / Purpose Common Languages / Starter Set
domain	Σ	0..*	CodeableConcept	The use context of this name e.g. as an active ingredient or as a food colour additive Binding: Substance Name Domain (Example)
jurisdiction	Σ	0..*	CodeableConcept	The jurisdiction where this name applies Binding: Jurisdiction ValueSet (Example)
synonym	Σ	0..*	see name	A synonym of this particular name, by which the substance is also known
translation	Σ	0..*	see name	A translation for this name into another human language
official	Σ	0..*	BackboneElement	Details of the official nature of this name
authority	Σ	0..1	CodeableConcept	Which authority uses this official name Binding: Substance Name Authority (Preferred)
status	Σ	0..1	CodeableConcept	The status of the official name, for example 'draft', 'active' Binding: PublicationStatus (Preferred)
date	Σ	0..1	dateTime	Date of official name change
source	Σ	0..*	Reference(DocumentReference)	Supporting literature

Example: Goserelin acetate


```
{
  "resourceType": "SubstanceDefinition",
  "id": "GSID1S3C5XFC02",
  "text": {
    "status": "generated",
    "div": "<div><h1>Substance definition</h1><table><tr><td styl
  },
  "identifier": [
    {
      "system": "http://www.who-umc.org/gsrs",
      "value": "GSID1S3C5XFC02"
    }
  ],
  "status": ...,
  "domain": ...,
  "code": ...,
  "name": [
    {
      "name": "Goserelin acetate",
      "status": ...,
      "preferred": true,
      "language": ...
    },
    ...,
    ...
  ],
  "relationship": [
    {
      "substanceDefinitionReference": {
        "reference": "SubstanceDefinition/GSID441H897A48"
      },
      "type": {
        "coding": ...,
        "text": "Salt to parent"
      }
    }
  ]
}
```

Example: Goserelin acetate

http://localhost/SubstanceDefinition/GSID1S3C5XFC02



15.9.4 Search Parameters

Search parameters for this resource. See also the full list of search parameters for this resource, this resource. The common parameters also apply. See Searching for more information about sea

Name	Type	Description
classification	token	High or low level categorization, e.g. polymer vs. nucleic acid or linear vs. br
code	token	The specific code
domain	token	If the substance applies to only human or veterinary use
identifier	token	Identifier by which this substance is known
name	string	The actual name

Requesting a new GSID

Requesting a new GSID is a process that involves human interaction

This is referred to as an **Asynchronous Operation** since the requester will not get an immediate answer to the request

This can be achieved in FHIR by using a special kind of resource - **Task**

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A FHIR Task

A FHIR **Task** is a resource that contains other resources on which some "actions" should be performed.

In our scenario a "draft" **SubstanceDefinition** is sent as **Input** with the purpose of generating a new (or assigning an existing) GSID

If a GSID can be generated or assigned the **Task** is updated with a reference to a SubstanceDefinition with the GSID as **Output**.

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Task	TU		DomainResource	A task to be performed *+ Rule: Task.restriction is only allowed if the Task is seeking fulfillment and a focus is specified.* *+ Rule: Last modified date must be greater than or equal to authored-on date* Elements defined in Ancestors: id, meta, implicitRules, language, text, contained, extension, modifierExtension
identifier		0..*	Identifier	Task Instance Identifier
instantiatesCanonical	Σ	0..1	canonical(ActivityDefinition)	Formal definition of task
instantiatesUri	Σ	0..1	uri	Formal definition of task
basedOn	Σ	0..*	Reference(Any)	Request fulfilled by this task
groupIdentifier	Σ	0..1	Identifier	Requisition or grouper id
partOf	Σ	0..*	Reference(Task)	Composite task
status	?! Σ	1..1	code	draft | requested | received | accepted | + Binding: Task Status (Required)
input		0..*	BackboneElement	Information used to perform task
type		1..1	CodeableConcept	Label for the input Binding: TaskInputParameterType (Example)
value[x]		1..1	*	Content to use in performing the task
output		0..*	BackboneElement	Information produced as part of task
type		1..1	CodeableConcept	Label for output Binding: TaskOutputParameterType (Example)
value[x]		1..1	*	Result of output

Task to request GSID

POST this Task to the Maintenance Organization

*After validating the **Task** using **$validate***

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Response I


{
"resourceType": "Task",
"id": "5b62a4bf-feec-48c7-9ba1-9187173bb208",
"contained": [
{
"resourceType": "SubstanceDefinition",
"id": "597d64f4-c7ff-4c18-9fb0-145b477a496b",
"text": …,
"status": …,
"domain": …,
"name": …
}
],
"status": "received",
"intent": "proposal",
"priority": "routine",
"authoredOn": "2023-09-05",
"lastModified": "2023-09-05",
"requester": …,
"input": …
}

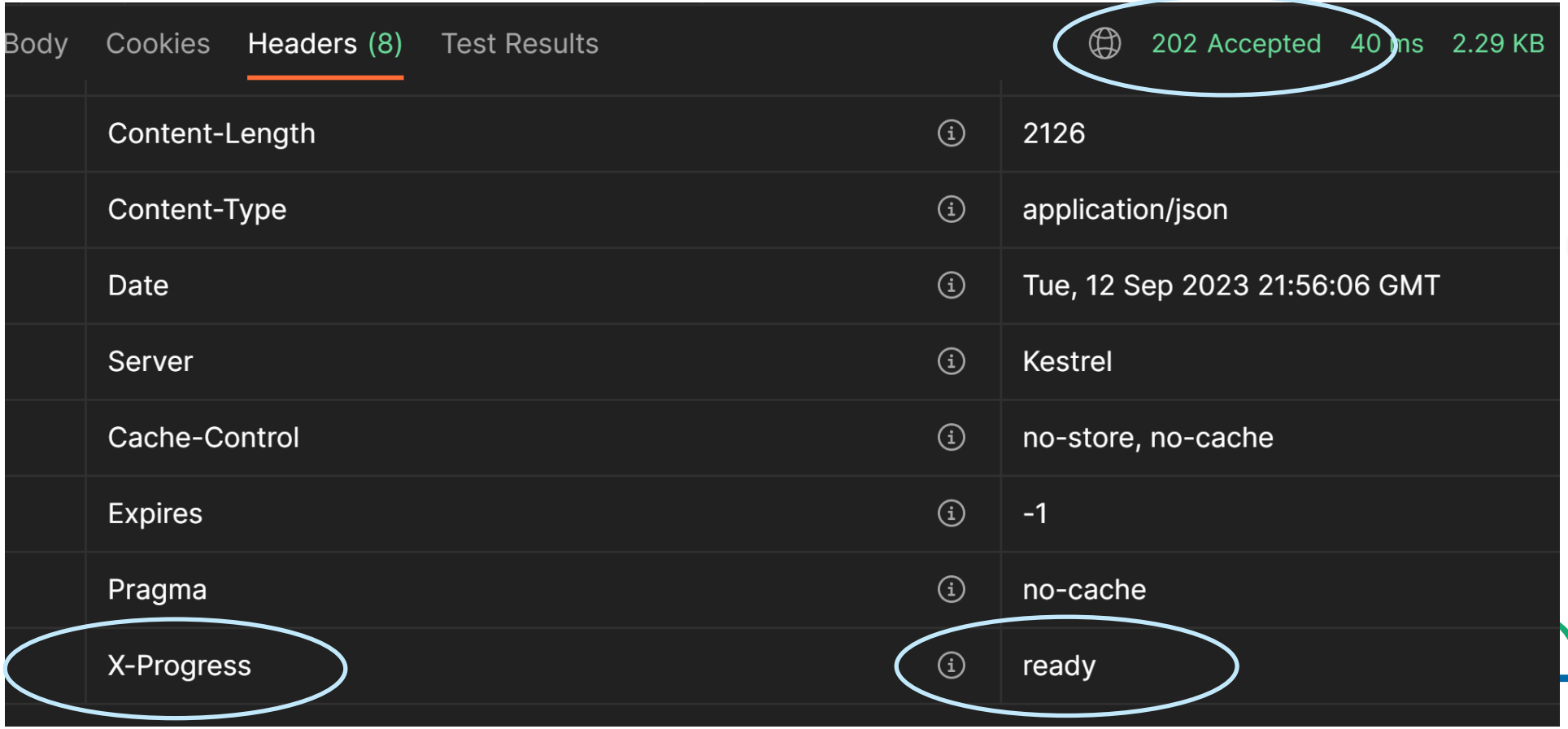
Response II

Body Cookies Headers (8) Test Results 200 OK 446 ms 2.35 KB Save as Example

Key	Value
Content-Length	2129
Content-Type	application/json
Date	Tue, 12 Sep 2023 21:55:52 GMT
Server	Kestrel
Cache-Control	no-store, no-cache
Content-Location	http://localhost:8085/task/5b62a4bf-feec-48c7-9ba1-9187173bb
Expires	-1
Pragma	no-cache

Task status

http://localhost:8085/task/5b62a4bf-feec-48c7-9ba1-9187173bb208



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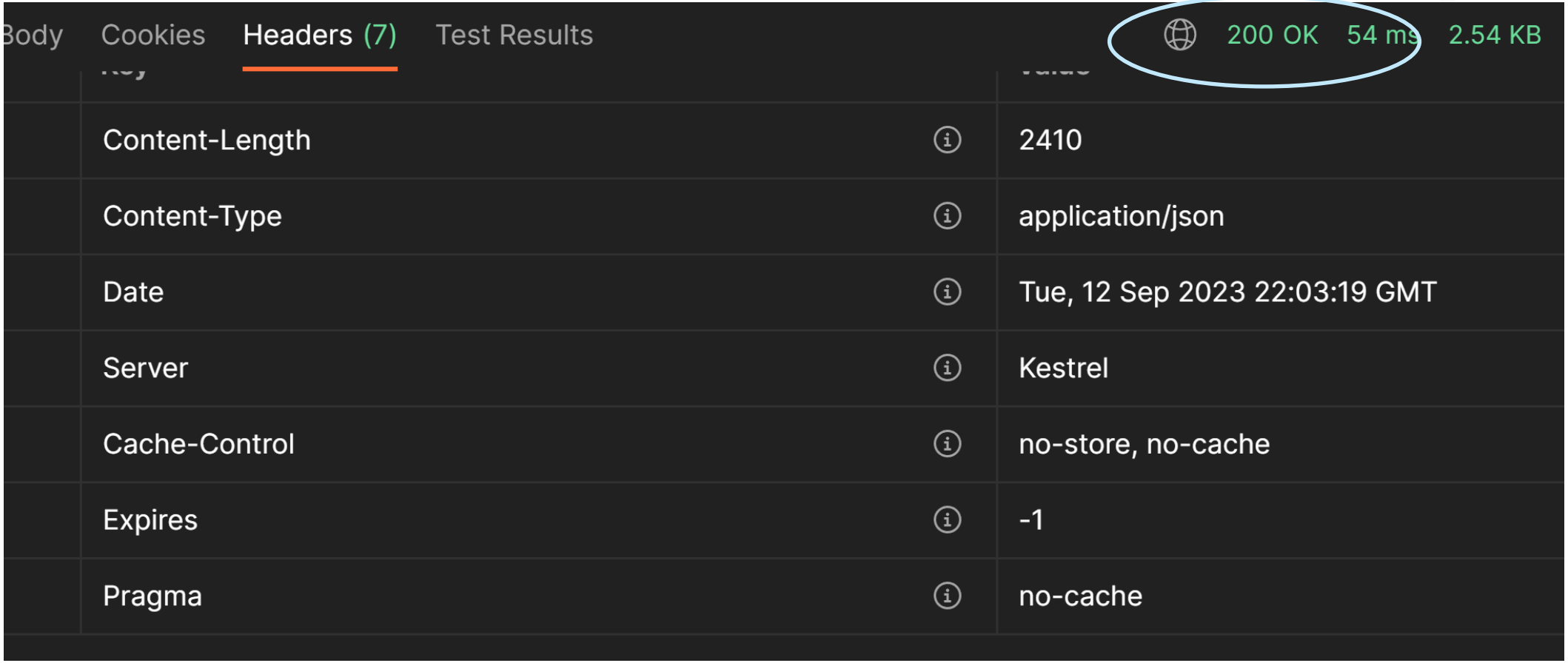
Task status

http://localhost:8085/task/5b62a4bf-feec-48c7-9ba1-9187173bb208



Completed Task


```
{
  "resourceType": "Task",
  "id": "5b62a4bf-feec-48c7-9ba1-9187173bb208",
  "contained": [
    {
      "resourceType": "SubstanceDefinition",
      "id": "597d64f4-c7ff-4c18-9fb0-145b477a496b",
      "text": …,
      "status": …,
      "domain": …,
      "name": …
    }
  ],
  "status": "completed",
  "intent": "proposal",
  "priority": "routine",
  "authoredOn": "2023-09-05",
  "lastModified": "2023-09-05",
  "requester": …,
  "input": …,
  "output": [
    {
      "type": {
        "text": "Generated GSID (SubstanceDefinition)"
      },
      "valueCodeableReference": {
        "reference": {
          "reference": "http://localhost:8085/SubstanceDefinition/GSIDOAOLHNMPEC"
        }
      }
    }
  ]
}
```

Generated SubstaneDefinition

Summary of FHIR Substance Request

1. Create a **SubstanceDefinition** with *"necessary"* information
2. Add the **SubstanceDefinition** to a FHIR **Task**
3. Send (POST) the **Task** to the Maintenance Organization
4. Check for status of **Task** until completed
5. Retrieve the generated **SubstanceDefinition** using the reference in the **Task** output

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Take home message

Collaboration and agreement is the key

Agreement and conformance to global implementation of consisting standards, for example ISO IDMP and HL7 is important

A first process on how to handle issues on a global level developed

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Making medicines **safer for patients**

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Questions in the Q & A facility, please

For feedback, please go to :

https://docs.google.com/forms/d/e/1FAIpQLSfztHb2tch0XyTK_uANl0JUvact00aNd57hM5PweXyAJsMdOg/viewform?usp=pp_url

Thanks for your time