WP-1 / community of expertise

October 2021
Interactive session and Community of Expertise: Perspectives on substance and strength in IDMP

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Jeffrey Martin, SMPA

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
✓ 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.
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
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.
Security

- Security is our priority
- This session is password protected

Recording of this session will be made available on UNICOM’s youtube channel.

At the end of the virtual session, a questionnaire will be sent to the participants, to help us understand participant’s reactions and needs.
Introductions to our esteemed colleagues and today's speakers

Isabel Chicharo  
Petra Kristic  
Jeff Martin

...and our panellist

Malin Fladvad  
Julie James  
Annet Rozema  
Jean-Gonzague Fontaine
Questions in the Q & A facility, please
For feedback, please go to:
https://forms.gle/fqCozyWtoGiPbxj26

Thanks for your time
Implementing Substance cleansing results in SMS
Background
Business goals

- Use Human and Veterinary (H&V) Substance data during regulatory procedures e.g. approving a Clinical Trial, approving a Marketing Authorisation.
- Use H&V Substance data throughout Product lifecycle and Regulatory procedures e.g. what Procedures this Substance has been involved with.
- Use H&V Substance data to connect the scientific details with regulatory context e.g. a particular signal for a class of substances or with a particular structure.

Drive better regulatory decisions
History – Substance data in EU

- **xEVMPD**
  - H Substances only
  - Created by Industry

- **EUTCT**
  - H Substances
  - Created by Industry
  - V Substances
  - Created by Industry
  - **EUTCT ID, mapping to EV codes**
  - Available for browsing/export to NCAs
  - Available for browsing only to Industry

- **SMS**
  - Centralised registration of new/updated H & V substances
  - Mixed cleansed/uncleansed Substance data
  - **SMS ID = EUTCT ID!**, mapping to EV codes
  - Available only via consuming systems
  - In use by most EU telematics systems

- **EU-SRS**
  - Cleansed H & V substances
  - Scientifically correct and enriched substance data
  - Substance Target Operating Model
  - **SMS ID = EUTCT ID!**, mapping to EV codes, UNII etc
  - Available for browsing/export to NCAs & Industry

Impact on mappings required to support implementation/integrations
Low trust for use in regulatory processes
Substance dataflow - Vision

Consumers / users of SOR data
Industry (NCAs, EMA)

- Use SOR data for preparing regulatory applications

New/updated Substance

Substance Requests

Industry RIMS

SPOR Portal or IRIS

Substance Management

EMA Data Stewards

- Broker of substance requests and substance data to Telematics systems
- "Simplified" view of substance data that supports selection in regulatory processes

EU Substance List

SMS

SMS and EU-SRS data is aligned
There is only one EU Substance list although there are 2 views of the same EU substance list

Substance Validation Group

- Enabler of scientifically sound management of substances data
- "Detailed" view of substance data that supports scientific identification of substances

Use of substance data

Consuming Telematics & EMA Systems:
EUTCT, EudraCT, eAF, xEVMED, EudraGMDP, IRIS, SIAMED

- Use Substance data during regulatory procedures e.g. approving a Clinical Trial

Consumers / users of SOR data
(Industry), NCAs, EMA

- Use Substance data to connect the Product lifecycle with Regulatory context e.g. what procedures this Substance has been involved with

- Use Substance data to connect the scientific details with regulatory context e.g. a particular signal for a class of substances or with a particular structure
Approach/roadmap

**Improve Substance Data Quality**

1. **Improve existing Substance Data quality**:
   - Consider Legal drivers & urgent timelines > start with Vet substances
   - Focus on classes/substances used on biggest number of products

2. **Enrich substance data** to enable critical relationship/support further analysis > Vaccines

**Integrate Substance data**

1. **Integrate substance data in Products**
   - Ensure Products use (cleansed &) correct Substance data
   - Generate PHPID

2. **Integrate Substance data in regulatory processes**
   - Clinical Trials (EudraCT, CTIS), Marketing Authorisations (eAF, IRIS), Inspections EudraGMDP), Pharmacovigilance (xEVMDP)

3. **Align Substance & Product data Globally**
   - Integrate Substance data with WHO/UMC/FDA
   - Align PHPID
   - support PhVig and/or global use cases

**Harness the power of Substance data**

1. Develop Analytics/reporting capabilities
   - Substances in products,
   - substances in procedures
   - substances/products/procedures over time
   - ...

   **Use Substance data to connect the Product lifecycle and Regulatory context**

2. Use Substance scientific data (substance class, chemical structure, etc) impurities to aggregate or refine results e.g. a particular signal for a class of substances or with a particular structure

   **Use Substance data to connect the scientific details with regulatory context and drive regulatory decisions**
### System

<table>
<thead>
<tr>
<th>System</th>
<th>Domain</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>EudraCT &amp; CTIS*</td>
<td>H</td>
<td>Phase 1-4 Trials</td>
</tr>
<tr>
<td>IRIS</td>
<td>H&amp;V – CAPs only</td>
<td>Scientific Advice + Orphan Designation + ITF + Marketing Status + Inspections + Parallel Distribution</td>
</tr>
<tr>
<td>eAF &amp; DADI*</td>
<td>H&amp;V</td>
<td>Submission MAA, Variations, Renewal</td>
</tr>
<tr>
<td>SIAMED</td>
<td>H&amp;V – CAPs only</td>
<td>ATMP certification + PRIME + Eligibility + Review + Approval &amp; lifecycle mgt + MRL + Art 58</td>
</tr>
<tr>
<td>UPD*</td>
<td>V</td>
<td>Approval &amp; lifecycle mgt</td>
</tr>
<tr>
<td>EudraGMDP</td>
<td>H&amp;V</td>
<td>Inspections &amp; GxP certificates + Manufacturing Import Authorisation + Wholesale Distribution Authorisation</td>
</tr>
<tr>
<td>EudraVigilance (xEVMPD/Art 57 &amp; ICSR)</td>
<td>H</td>
<td>Safety reporting, Approval &amp; lifecycle mgt</td>
</tr>
</tbody>
</table>
Improve Substance Data Quality
(Substance data cleansing)
• There is a close collaboration with EMA, NCA’s, FDA/NCATS, and WHO-UMC

• The 22 SVG members come from a variety of NCA’s. They are assessors and/or substance experts
# Veterinary substance cleansing

**Activity prioritized in EU-SRS project/SVG throughout 2020 to support UPD**

<table>
<thead>
<tr>
<th>Substance Class</th>
<th># unique EUTCT/SMS Ids*</th>
<th>SVG cleansing</th>
<th>SMS implementation</th>
<th>EU-SRS building records</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterinary substances</td>
<td>5.049</td>
<td>De-duplication complete - 5K records <strong>(79%)</strong> invalid</td>
<td>Completed (Jun 20). Also includes all chemical substances, which were cleansed and re-inserted as “Human”</td>
<td>N/A</td>
</tr>
<tr>
<td>Veterinary substances - Valid</td>
<td>1.036 (974 vaccines)</td>
<td>Completed (Apr 21)</td>
<td>Completed (Apr 21)</td>
<td>Load script + some manual work. Preparation in finalization stage Vet vaccines will be loaded (basic data) and then records are completed and hierarchy is added in EU-SRS.</td>
</tr>
</tbody>
</table>
| Mapping of Vet NCA product/substances | ~26,496 NCA records | NA | •22 NCAs requested until now, all substances mapped  
•Creation of ~ 300 missing substances in accordance with SVG rules | Load script + some manual work. |

- **Final outcome of cleansing implemented in SMS**
- **SMS data available in UPD (veterinary product database)**
- **Vet NCA substance data mapped to SMS**
## Human substance cleansing

### Activity prioritised in EU-SRS project/SVG throughout 2021-2022 to support all systems/processes who consume Substance data and PMS implementation

<table>
<thead>
<tr>
<th>Substance Class</th>
<th># unique EUTCT/ SMS Ids*</th>
<th>SVG cleansing</th>
<th>SMS implementation</th>
<th>EU-SRS building records</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemicals</td>
<td>17.000</td>
<td>Almost completed (end Oct 21)</td>
<td>Ongoing Aim to complete 93% end 2021</td>
<td>Load into EU-SRS with script. Testing ongoing</td>
</tr>
<tr>
<td>Human vaccines</td>
<td>1.030</td>
<td>Ongoing, per organism type Bordetella, Influenza</td>
<td>Ongoing</td>
<td>Ongoing per organism type 5 / 55 organism groups built in EU-SRS</td>
</tr>
<tr>
<td>Proteins</td>
<td>2.000</td>
<td>Insulins already cleansed Ongoing, current focus on MAB</td>
<td>Not yet started</td>
<td>Started, on hold. Current focus is on documenting the cleansing approach</td>
</tr>
<tr>
<td>Polymers</td>
<td>1.465</td>
<td>Kick-off scheduled</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>SSG1</td>
<td>&gt;17.000</td>
<td>Current focus on homeopathics naming (n=13k)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mixtures</td>
<td>1.856</td>
<td>To start in 2022</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Number of substances changing due to cleansing of subst class, merges/splits, etc

- With the cleansing of Chemicals 71% of substances used in products are of good data quality
- As cleansing is implemented in SMS, consuming systems/processes benefit from improved Substance data quality
Human Substances

Total Human substances

Type | # subs | % subs | % referenced in Human Approved Products
--- | --- | --- | ---
Chemical | 19463 | 37.5% | 71.3%
Polymer | 1114 | 2.1% | 21.4%
SSGx | 3389 | 6.5% | 2.4%
Flavours/coatings | 2772 | 5.3% | 1.4%
Herbal & Extracts | 5787 | 11.1% | 1.2%
Mixture | 958 | 1.8% | 1.1%
Vaccine | 1031 | 2.0% | 0.3%
Homoeopathic | 13238 | 25.5% | 0.3%
Protein | 1992 | 3.8% | 0.2%
Remaining | 2181 | 4.2% | 0.6%
Total | 51925 | 100.0% | 100.0%

Data from 2020. Data from 2021 not yet available

*Number of substances/class changing due to cleansing of subst class, merges/splits, etc

Conclusions:

- **Planned work (Chem, Prot and Vac)** correspond to **72%** in approved products
- **Poly** correspond to **21%** in products. Not prioritised yet since most are excipients – next type to be cleansed
- After **Chem, Prot, Vac and Poly**, **93%** subs used in approved products will be cleansed!
- **Homeopathics** are **26%** subs but only **0.3%** in products

Notes:
- Flavours/coatings and homeopathics are presented separately
- Remaining SSG1/SSG3/SSG3 are presented together in “SSGx”
- Herbs and Herbal extracts are presented together
- Blood derived, Allergen, Nucleic acid, ATMP, Other are presented together in “Remaining”
- Vet substances are not presented since all types are being cleansed and currently no products are linked
### Chemicals cleansing implementation in SMS

**By end of 2021, it is expected to have at least 93%* of chemicals cleansed in SMS**

*Exact percentage depends on the number of substances that are possible to nullify in 2021 (considering products/ICSRs links)*

<table>
<thead>
<tr>
<th># substances</th>
<th>September 2021</th>
<th>October 2021</th>
<th>November 2021</th>
<th>December 2021</th>
<th>2022 (month TBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>~11.300</td>
<td>Adjust substance type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>~90 - 1% new</td>
<td>Create</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>~680 – 4% duplicates</td>
<td>Analyse Duplicate/merge</td>
<td>Nullify “Duplicate/merge” w/o Prod/ICSR</td>
<td>Nullify “Duplicate/merge” w/o Prod/ICSR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>~300 - 3% invalid</td>
<td>Analyse Invalid</td>
<td>Nullify “Invalid” w/o Prod/ICSR</td>
<td>Nullify “Invalid” w/o Prod/ICSR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>~11.200 - 68% unchanged</td>
<td></td>
<td>Confirm No action required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>~4.120 - 25% updated</td>
<td>Analyse Update</td>
<td>Update</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other substance types

Proteins
- Insulins already cleansed by the SVG in May 2020
  - Many suggested nullifications with major impact on products/ICSRs recoding expected
  - To be implemented in SMS after Chemicals
- Current focus on monoclonal antibodies used in approved products (i.e. already with INN)
  - Cleansing started in 2021 and ongoing, still in early stages
  - Limited changes in PT expected (since there is an INN)
  - Limited impact in EMA systems expected

Vaccines
- SVG cleansing started end 2020, ongoing and still in early stages, by microorganism group and most used in products
- Industry involvement in cleansing and completing information for vaccines
- Final cleansing approach to be confirmed by end November
- Major changes in PT expected
- Major impact on products/ICSRs recoding
Other substance types

**Polymers**
- Kick-off scheduled
- Major changes in PT expected
- Limited impact in products/ICSRs recoding expected since they are mostly excipients

**Homeophetics**
- Discussions in initial stage
- Major changes in PT expected
- Major impact on products/ICSRs recoding expected
  - Implementation timelines depended on DADI: it must be possible to search for aliases in the new eAF before implementation can be assured, otherwise MAH will not be able to find their own substances

**Mixtures**
- To start in 2022
- Not major changes in PT expected
- Limited impact in products/ICSRs recoding expected
Substance data cleansing - impact & benefits

Cleansing

- New substances created (usually more granular)
- Substance is updated – new preferred term or alias
  - Substance is “invalid” and should be nullified

Impacts

- MAH should review their products composition to ensure they are referring to the correct/granular substance
  - Any products in xEVMPD linked to “invalid” substances must be relinked to replacement substance before substance nullification can happen.

Benefits

- With the cleansing of Chemicals, 71% of substances used in approved products are of good data quality.
- All consuming systems/processes benefit from improved Substance data quality.
Substance Data Mgt in 2021

**Consumers/users of SOR data**
- Industry (NCAs, EMA)

**Substance Management**
- EMA Data Stewards
  - Broker of substance requests and substance data to Telematics systems
  - "Simplified" view of substance data that supports selection in regulatory processes

**Use of substance data**
- Users can benefit from Substance data cleansed by SVG through SMS

**Consuming Telematics & EMA Systems:**
- EUTCT, EudraCT, eAF, xEVMoD, EudraGMDP, IRIS, SIAMED

**TO NOTE:**
- Users cannot identify cleansed/uncleansed Substance data
  - Flag/identification of cleansed records in SMS by Q4 21
- **NCA users** can access SMS data via SMS API
- Industry users cannot access SMS API nor export substance data from SPOR Portal
  - Industry & NCAs to be able to export a list of substances, including cleansed flag, by Q1 22

**Consumers/users of SOR data**
- Industry, NCAs, EMA

**EMA Service Desk**
- New/updated Substance
- Manual Sync
- SMS API

**SMS**
- EMA Data Stewards
- Substance Validation Group

**EU-SRS**
- Enabler of scientifically sound management of substances data
  - "Detailed" view of substance data that supports scientific identification of substances
Key messages

- Joint cleansing enabling release to stakeholders and timely mapping to support V- and H- use cases:
  - **Vet NCA data mapped to high-quality Vet Substance data in support of UPD implementation**
    - Vet Subst cleansing throughout 2020, completed by SVG and implemented in SMS by April 2021
    - Vet NCA substance data mapped to SMS
  - **With the cleansing of Chemicals 71% of substances used in products are of good data quality. All consuming systems/processes benefit from improved Substance data quality.**
    - Human substance cleansing by SVG throughout 2021-2022
    - Priority setting based on impact (analysis-based)
    - Human Chemicals cleansing complete by SVG in Oct 21, 93% implemented in SMS by Dec 21
  - **Cleansed substance data is identifiable and available for users to consume from SMS**
    - Flag/identification of cleansed records in SMS by Q4 21
    - Export/List of cleansed records by Q1 22
Questions in the Q & A facility, please
For feedback, please go to:
https://forms.gle/fqCozyWtoGiPbxj26

Thanks for your time
Strength

(presentation vs concentration)

29th of October 2021

Petra Kristic
Agenda

01 Pharmaceutical product
02 Dose form and unit of presentation
03 Strength Presentation and concentration
04 (Reference strength)
0 1 Pharmaceutical Product and manufactured item
What describes a Pharmaceutical product

According to ISO_TS 20451, a PhPID is based on

1. Active substance(s)/Specified substances
2. Strength(s), Strength units (units of measurement and/or unit of presentation)
3. Reference strength(s), Reference substance(s)
4. Administrable dose form
5. Medical device

**pharmaceutical product** - qualitative and quantitative composition of a medicinal product in the dose form authorized for administration by a regulatory authority, and as represented with any corresponding regulated product information
According to ISO_TS 20451, a PhPID is based on:

**Active substances**
- Actives
- Adjuvants

**Specified substances**
- SG1 (elements used to describe solvents, specific markers, physical form of substance..)
- SG2 (capture manufacturer of either substance or specified substance with min. manufacturing information – production system type, method type, production system)
- SG3 (capture grade of material (pharm.))
- SG4 (includes critical manufacturing process, specifications..)

**Reference strength (s) / reference substance (s)**
A reference strength is an expression of the strength in terms of a reference substance and a reference specified substance – e.g. Metoprolol succinate (190 mg) equivalent to 100 mg metoprolol.

**Strength, strength units**
- The strength of the substance or specified substance shall be specified as a quantity of the substance/specified substance present in a given pharmaceutical product. A numerator value and numerator unit as well as a denominator value and denominator unit shall be specified (strength units).
- If pharmaceutical products has undergone transformation - strength resulting from transformation should be used.
- Strength can be expressed in two ways:
  - strength (presentation) – quantity in the dose form, unit of presentation or in the volume – e.g. 10mg/5ml, 20 mg/tablet
  - strength (concentration) – quantity present per unit of volume/mass – e.g. 2mg/ml

**Administrable dose form**
After it has undergone any necessary reconstitution, where applicable.

e.g. two manufactured items are described as “powder for solution for injection” and “solvent for solution for injection” which after transformation corresponds to the administrable dose form “solution for injection”.

**Medical device**
- A pharmaceutical product may refer to a drug that is associated with a medical device. In this instance, the device term and term ID (unique device identifier) shall be displayed with the substance(s) and specified substance(s) terms for the product at all applicable PhPID levels.
Manufactured item

• Describes the product as it is authorized and, where applicable, before transformation into the administrable pharmaceutical form (referred to as the manufactured item, as contained in the packaged medicinal product).

• A Medicinal Product may contain, in the packaging, one or more manufactured items and corresponding to one or more pharmaceutical products:
  • “Film-coated tablet” - single manufactured item and single pharmaceutical product
  • Powder for solution for injection and Solvent for Solution for injection - multiple manufactured items and single pharmaceutical products
  • “Oral Capsule” & “External Cream” - multiple manufactured items and multiple pharmaceutical products
Dose Form and unit of presentation
Dose form and unit of presentation

**Manufactured dose form**

The manufactured dose form described with the authorized pharmaceutical form(s) in section 3. Pharmaceutical Form of the SmPC or other regulatory document (description prior to any transformation into the final form administered to the patient) shall be specified as a term ID.

**Administrable dose form**

The administrable dose form corresponds with the dose form intended for administration to the patient, after any necessary transformation of the manufactured dose form has been carried out. This information shall be provided in line with the information indicated in Section 3. Pharmaceutical form of the corresponding SmPC. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list.
Dose form and unit of presentation

**Manufactured Dose Form:** Powder for solution for injection  
**Unit of presentation:** Vial

**Administrable Dose Form:** Solution for injection  
**Unit of presentation:** Syringe
Dose form and unit of presentation

Unit of presentation – If Manufactured and Pharmaceutical item differ

Manufactured item
Unit of Presentation: Tablet

Pharmaceutical item
Unit of Presentation: Portion

Section 8.1.2.2 Unit of presentation (ISO_TS 20451)

from the dissolution of the tablet in water, an activity of reconstitution. Thus, the pharmaceutical product’s administrable dose form should be specified as “solution” for oral route, and the ingredients would be specified on the basis of volume of such solution. If the reconstitution instructions are inexact or cannot be fully specified (because of “quantity sufficient ...” clauses in the reconstitution specifications), so that the final volume and concentration of the ingredients are not known, then the administrable dose form shall be considered a “portion” of unknown volume, i.e. in the case of the dissolvable tablet, it would be the “portion of solution resulting from dissolving one tablet”. Then the ingredients and administration instructions can be specified based on this countable portion.
Dose form and unit of presentation
Product Berocca – Effervescent tablet

Unit of presentation in the data model when Manufactured item and Pharmaceutical product differ

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This product is a multivitamin preparation with high dosed B-complex vitamins and vitamin C as well as calcium, magnesium and zinc. This product is a multivitamin and mineral preparation, containing 9 vitamins and 3 minerals.

One effervescent tablet contains:
Ascorbic acid 500 mg

6.5 Nature and contents of container

Packages: 10, 15, 2x10, 2x15, 3x15, 4x15 (the effervescent tablets are wrapped in aluminium foil before packing into PP plastic tablet containers and aluminium tablet containers, LDPE plastic caps containing a desiccant.

Desiccator capsule:
Pure silica gel (white gel) with a molecular sieve.

Aluminium foil strip packs of 1 tablet (with desiccant).
0 3  
Strength – Presentation and Concentration
Strength – Presentation and Concentration

Description diagram Substance and Strength

- Strength relations to (Specified) Substance
- ‘Strength (Presentation) and ‘Strength (Concentration) are attributes of the object ‘Strength’

Figure 3 — Ingredients, substance and strength section detailed description diagram
Strength – Presentation and Concentration
Two ways of expressing Strength

Strength
Quantity of the substance/specified substance present in a given pharmaceutical product.

Presentation
25 mg/5 mL

Definition:
Quantity of the substance in the dosage form, unit of presentation, or in the volume (or mass) of the single pharmaceutical product or manufactured item

Concentration
5 mg/mL

Definition:
Quantity of the substance per unitary volume (or mass)

Inpatient ketamine overdose with 503B compounded syringe. A patient was supposed to receive ketamine 10 mg as needed for pain. The patient’s nurse removed a 503B compounded prefilled ketamine syringe from an automated dispensing cabinet (ADC) to administer a dose. (503B compounding pharmacies are external pharmacies that prepare large batches of certain medications for hospitals to purchase and use within their facility.) The ketamine was packaged in a 5 mL syringe prominently labeled as “Ketamine, 10 mg/mL.” The total

Figure 1. This syringe contains 50 mg of ketamine but was thought to hold just 10 mg given the prominent expression of the concentration as 10 mg/mL.

SOURCE:
# Reference table for expression of strength

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Type of product</th>
<th>Examples</th>
<th>MI Unit of Present.</th>
<th>PP Unit of Present.</th>
<th>Strength by Presentation</th>
<th>Strength by Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Solid, countable Tablets, capsules, suppositories</td>
<td>Tablets, capsules, suppositories</td>
<td>Basic dose form related to the pharmaceutical form of the MI (tablet, capsule, etc.)</td>
<td>Basic dose form related to the pharmaceutical form of the Pharm Prod (tablet, capsule etc.)</td>
<td>M</td>
<td>E</td>
</tr>
<tr>
<td>1b</td>
<td>Solid dose forms in &quot;container&quot;</td>
<td>Powder or granules in sachet, ampoules, vials, Spincap, Rotocap – the whole content of the capsule is delivered to the patient via one or more actuations</td>
<td>Container (vial, sachet, etc.)</td>
<td>Container (vial, sachet, etc...) – not always informative depending on the dosing instructions</td>
<td>M</td>
<td>E</td>
</tr>
</tbody>
</table>

**MI** – Manufactured Item  
**PP** – Pharmaceutical product  
**M** – Mandatory  
**E** – Empty  
**O** – Optional
## Reference table for expression of strength

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</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>Metered dose delivered by a metered actuation - dose cannot be adjusted</td>
<td>Dry-powder inhalers (DPI) pressurised metered-dose inhalers (pMDI), nasal sprays</td>
<td>Actuation (inhaler)</td>
<td>Actuation (inhaler, etc.)</td>
<td>M</td>
<td>E</td>
</tr>
<tr>
<td>2a</td>
<td>Products enclosed in a &quot;presentation &quot;, where the total amount per presentation is clinically relevant</td>
<td>Unit dose solutions, parenteral liquid, unit dose nebuliser solutions NOT partial use preparations</td>
<td>Container (vial, sachet, etc.)</td>
<td>Container (vial, sachet, etc...)</td>
<td>M - Expressed per total volume of the presentation (not per unit of presentation). This makes calculations easier</td>
<td>M</td>
</tr>
</tbody>
</table>

**MI** – Manufactured Item  
**PP** – Pharmaceutical product  
**M** – Mandatory  
**E** – Empty  
**O** – Optional
### Reference table for expression of strength

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Type of product</th>
<th>Examples</th>
<th>MI Unit of Present.</th>
<th>PP Unit of Present.</th>
<th>Strength by Presentation</th>
<th>Strength by Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>Products enclosed in a &quot;presentation&quot;, where the concentration is clinically relevant rather than the total amount in the presentation</td>
<td>Multi-dose syringe, Partial dose syringe, infusion bags</td>
<td>Container (bottle, etc.)</td>
<td>N/A since it is the concentration that is relevant</td>
<td>O</td>
<td>M</td>
</tr>
<tr>
<td>3a</td>
<td>Continuous presentation (dosing is individual/not accurate and the total volume in the container is of less importance for dosing purposes)</td>
<td>Bulk powders/granules, semisolids &quot;bulk&quot; liquids (e.g. eye drops)</td>
<td>Not useful clinically</td>
<td>N/A since it is the concentration that is relevant</td>
<td>O</td>
<td>M</td>
</tr>
</tbody>
</table>

**MI** – Manufactured Item  
**PP** – Pharmaceutical product  
**M** – Mandatory  
**E** – Empty  
**O** – Optional
# Reference table for expression of strength

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Type of product</th>
<th>Examples</th>
<th>MI Unit of Present.</th>
<th>PP Unit of Present.</th>
<th>Strength by Presentation</th>
<th>Strength by Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>Products enclosed in a &quot;presentation&quot;, where the dose has a delivery rate</td>
<td>Transdermal patches</td>
<td>Patch</td>
<td>N/A since it is the concentration that is relevant</td>
<td>O</td>
<td>M - as a delivery rate over time</td>
</tr>
</tbody>
</table>

MI – Manufactured Item  
PP – Pharmaceutical product  
M – Mandatory  
E – Empty  
O - Optional
There are different practies and way of expressing the strength when it comes to labelling

When expressing the strenght following shoud be considered:
- SmPC to be used as a main reference (examples given in Ch.8 of IDMP IG)
- Either presentation or concetration strength to be used (*if both present in SmPC MAH can add these on optional basis)
- In case of difference between Ch. 8 and SmPC – information in SmPC is the leading one

Reference table should give a high-level guidance when it comes to expressing the strength – nevertheless decisions on how to express the strength might deviate and should be decided case-by-case
Points of attention for this example:

- This example fits with the Pattern 1a (Solid, countable). In this case, only the Presentation Strength is required for both manufactured Item and Pharmaceutical Products.
- The strength(s) of all the ingredients are always expressed using the Numerator and Denominator. For this example, the Presentation Strength is expressed in [milligram(s)] per [tablet].
- If there is no reference substance that differs from the ingredient actually in the product, active substance and its strength must be repeated in the data object « Reference Strength »
- On the graphical representation some entities and links are missing, and other boxes have been replicated for human readability purposes.
- Manufactured Item quantity – please refer to the section Alignment of Manufactured Item Quantity, Unit of Presentation and Pack Size for more guidance.
Points of attention for this example:

- This example fits with the Pattern 3a (Continuous Presentation):
  - Concentration Strength is mandatory.
  - MI – Presentation Strength is Optional.
  - pHp – Presentation Strength is unknown, and therefore empty.

- Strength(s) must be expressed as per SmPC.
  - If two expressions of the concentration are available ("2% w/w" and "20mg/gram"), the "mg per gram" should be prioritized.
  - No computation – if the presentation strength is not mentioned as-is in the SmPC, it shouldn’t be provided even if it can be computed based on the quantity & concentration.

- If there is no reference substance that differs from the ingredient actually in the product, active substance and its strength must be repeated in the data object « Reference Strength »

**Manufactured Item quantity** – please refer to the section 4.10.2 for more guidance.
0 4 Reference strength
Reference strength

- Reference strength represents the strength (quantitative composition) of the active moiety of the active substance or of another substance used to express the strength of the product.

- For example, if an active substance is in the form of a salt or hydrate, the reference strength shall be expressed in terms of the mass [or biological activity in International (or other) units where appropriate] of the active moiety (base, acid or anhydrous material). The reference substance and reference strength can be found in section 2. Qualitative and Quantitative Composition of the corresponding SmPC.

- If there is no reference substance, active substance and its strength must be repeated in the data object Reference Strength.
Questions in the Q & A facility, please
For feedback, please go to :
https://forms.gle/fqCozyWtoGiPbxj26

Thanks for your time
Data Patterns for IDMP-based Medicinal Product Information

Dr Jeff Martin
Business and Information Architect
IT Department
Swedish Medical Products Agency
2021-10-18
At EMA, there is a medicinal product dictionary provided for under Art 57 in EC 726/2004, primarily for Pharmacovigilance (human medicines)

- often called the “Art 57-database”
- format: xEVMPD – extended EudraVigilance Medicinal Product Dictionary
  - based on early drafts of IDMP (pre-2012)

EMA is building the next generation of this MPD – Product Management Services (PMS)

- based on IDMP with a few extensions and not with all attributes

Data will need to be converted from xEVMPD format to IDMP format

- EMA will do first conversion and Marketing Authorisation Holders (MAHs) are expected to enrich the data
The Issue - Data Quality (1)

- In the xEVMPD medicines dictionary, there are more than 600,000 products delivered from more than 4,000 data providers – from MAH

- Ambition to use the MPD data for more than Pharmacovigilance
  - prescription support
    - including cross-border
  - generic prescriptions and generic substitution
  - regulatory efficiency improvement
  - Demands very consistent and very high data quality – close to 100% correct

- If your data is not used in the health care system, then you do not have the ultimate quality control check!
The Issue - Data Quality (2)

► Highly unlikely that anybody’s data is 100 % correct
   ➢ The SE MPA is looking over its veterinary data and we are finding errors even though we have been publishing vet data for e-prescriptions for almost 20 years
   ➢ Regulatory problems
     ✓ e.g. Paracox-5 vet Suspension till oral suspension (approved 2000) is actually a combined dose form since it is co-packed with a spray solution but it was approved as a conventional Pharm Dose Form
       • called ”Solvent for spray-on-chickens” in the UK
     ✓ Comirnaty has different Pharm Dose forms in the EU and Canada/US
   ➢ Inconsistent or incorrect input to databases
     ✓ Had two products, a 2 % and a 10 %
       • one: x mg/g
       • other: x g/kg
   ➢ Inconsistent data for similar products from different companies
The Issue - Data Quality (3)

- To get good data quality, we need the data providers to understand IDMP as well as possible and they need help to do this.
- IDMP standards are complex and examples are fragmentary.
- The EU Implementation Guide, chapter 8, includes a number of examples for different product types.
The Answer – Systematise the Products

- Complexity mainly around the composition and packaging (excluding the Clinical Particulars)
- Find patterns for different product types and describe how the data should be provided for these patterns
- First version of patterns added to v 2.0 of Chapter 8 – Practical Examples of the EU IG
Pattern 1a – example: Losec

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Examples</th>
<th>Manufactured Item</th>
<th>Pharmaceutical Product</th>
<th>Strength – Unit of Presentation</th>
<th>Strength – Unit of Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid, countable</td>
<td>Tablets</td>
<td>Tablets</td>
<td>Basic dose form related to the pharmaceutical form of the Man Item</td>
<td>Basic dose form related to the pharmaceutical form of the Pharm Item</td>
<td>Mandatory Empty</td>
</tr>
<tr>
<td></td>
<td>Capsules</td>
<td>Capsules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suppositories</td>
<td>Suppositories</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Medicinal Product:** Losec 10 mg gastro-resistant tablet

**Packaged Medicinal Product**
- 10 tablets each in of 5 blisters in a box
- Description: Blister, 50 tablets

**Manufactured Item**
- Unit of Presentation: Tablet
- Manufactured Dose Form: Gastro-resistant tablet
- Manufactured Item Quantity: 10 units
- Ingredient/substance/strength:
  - Presentation: omeprazole magnesium 10,3 mg/1 unit
  - Concentration: N/A

**With ten tablets in the blister card as the manufactured item**

**Reference strength/substance**
- Presentation: omeprazole 10 mg/1 unit
- Concentration: N/A

**Pharmaceutical product**
- Administerable Dose Form: Gastro-resistant tablet
- Route of Administration: Oral use
- Unit of Presentation: Tablet
- Ingredient/substance/strength:
  - Presentation: omeprazole 10 mg/1 unit
  - Concentration: N/A

**Package Item (Container) – recursive**
- Package Item (Container) – outer
  - Package Item Type: Box
  - Package Item Quantity: 1
  - Inside the outer package:
    - Reference strength/substance:
      - Presentation: omeprazole magnesium 10,3 mg/1 unit
      - Concentration: N/A
    - Ingredient/substance/strength:
      - Presentation: omeprazole 10 mg/1 unit
      - Concentration: N/A

- Package Item (Container) – inner
  - Package Item Type: Blister
  - Package Item Quantity: 5
  - Inside the inner package:
    - Reference strength/substance:
      - Presentation: omeprazole magnesium 10,3 mg/1 unit
      - Concentration: N/A
    - Ingredient/substance/strength:
      - Presentation: omeprazole 10 mg/1 unit
      - Concentration: N/A
Pattern 1b – example: Laktulos Meda

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Examples</th>
<th>Manufactured Item</th>
<th>Pharmaceutical Product</th>
<th>Strength – Presentation</th>
<th>Strength – Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid dose forms in &quot;container&quot;</td>
<td>Powder or granules in sachet, ampoules, vials, Spincap, Rotacap – the whole contents of the capsule is delivered to the patient via one or more actuations</td>
<td>Container (vial, sachet, etc)</td>
<td>Container/Portion (vial, sachet, etc) Note – not always informative depending on the dosing instructions</td>
<td>Mandatory</td>
<td>Empty</td>
</tr>
</tbody>
</table>

Medicinal Product: Laktulos Meda 10 g Oral powder in sachet

Packaged Medicinal Product
4 boxes of 100 sachets
Description: Sachets, 4 x 100

Manufactured Item
Manufactured Dose Form: Oral powder
Manufactured Item Quantity: 100 units
Unit of Presentation: Sachet

Ingredient/substance/strength
Presentation: lactulose 10 g/1 unit
Concentration: N/A

Reference strength/substance
Presentation: lactulose 10 g/1 unit
Concentration: N/A

Reference strength/substance
Presentation: lactulose 10 g/1 unit
Concentration: N/A

Ingredient/substance/strength
Presentation: lactulose 10 g/1 unit
Concentration: N/A

Reference strength/substance
Presentation: lactulose 10 g/1 unit
Concentration: N/A

Ingredient/substance/strength
Presentation: lactulose 10 g/1 unit
Concentration: N/A

Pharmaceutical product
Administrable Dose Form: Oral solution
Route of Administration: Oral use
Unit of Presentation: Portion

Package Item (Container) – recursive
Package Item Type: Box
Package Item Quantity: 1

Package Item (Container) – outer
Package Item Type: Box
Package Item Quantity: 4

Package Item (Container) – inner
Package Item Type: Box
Package Item Quantity: 4
### Pattern 2a – example: IntronA

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Examples</th>
<th>Manufactured Item</th>
<th>Pharmaceutical Product</th>
<th>Strength – Presentation</th>
<th>Strength - Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid products enclosed in a &quot;presentation&quot;, where the total amount per presentation is clinically relevant</td>
<td>Liquid preparations: <strong>Unit dose</strong> solutions, parenteral liquid, <strong>unit dose</strong> nebuliser solutions, <strong>single-dose</strong> pre-filled syringe <strong>NOT</strong> partial use preparations</td>
<td>Container (vial, etc)</td>
<td>Container (vial, etc)</td>
<td>Mandatory expressed per total volume of the presentation (not per unit of presentation)</td>
<td>Mandatory (QRD)</td>
</tr>
</tbody>
</table>

**Liquid preparations:**
- Unit dose solutions
- Parenteral liquid
- Unit dose nebuliser solutions
- Single-dose pre-filled syringe

**NOT** partial use preparations

**Container (vial, etc):**
- Mandatory expressed per total volume of the presentation (not per unit of presentation)

**Reference strength/substance:**
- Presentation: interferon alfa-2b 3 MIU/0.5 ml
- Concentration: interferon alfa-2b 6 MIU/ml

**Ingredient/substance/strength:**
- Presentation: interferon alfa-2b 3 MIU/0.5 ml
- Concentration: interferon alfa-2b 6 MIU/ml

**Packaged Medicinal Product:**
- IntronA 3 mill IU solution for injection
- 12 x 0.5 ml vials in a box
- Description: Vial, 12 x 0.5 ml

**Manufactured Item:**
- Manufactured Dose Form: Solution for injection
- Manufactured Item Quantity: 0.5 ml
- Unit of Presentation: Vial

**Pharmaceutical product:**
- Administrable Dose Form: Solution for injection
- Route of Administration: Subcutaneous use
- Unit of Presentation: Vial

**Manufactured Item (Container):**
- Recursive
- Container (vial, etc)

**Package Item (Container):**
- Outer
- Package Item Type: Box
- Package Item Quantity: 1

**Package Item (Container):**
- Inner
- Package Item Type: Vial
- Package Item Quantity: 12
### Pattern 2b – example: Hevicain Spinal Tung

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Examples</th>
<th>Manufactured Item</th>
<th>Pharmaceutical Product</th>
<th>Strength – Presentation</th>
<th>Strength - Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid products enclosed in a &quot;presentation&quot;, where the concentration is clinically relevant rather than the total amount in the presentation</td>
<td>Liquid preparations: <strong>Multi-dose</strong> syringe, <strong>Partial dose</strong> syringe, infusion bags, <strong>multi-dose</strong> vials</td>
<td>Container (bottle, etc)</td>
<td>N/A since it is the concentration that is relevant</td>
<td>optional</td>
<td>Mandatory</td>
</tr>
</tbody>
</table>

**Medicinal Product:** Hevicain Spinal Tung 5mg / ml solution for injection

**Packaged Medicinal Product:**
- **5 x 4 ml ampoules**
  - Description: Ampoule, 5 x 4 ml

**Reference strength/substance:**
- Presentation: bupivacaine hydrochloride, anhydrous 20 mg/ 1 unit (optional)
  - Concentration: bupivacaine hydrochloride, anhydrous 5 mg/ml

**Reference strength/substance:**
- Presentation: bupivacaine 17.8 mg/ 1 unit (optional)
  - Concentration: bupivacaine 4.44 mg/ml

**Manufactured Item**
- **Manufactured Dose Form:** Solution for injection
- **Manufactured Item Quantity:** 4 ml
- **Unit of Presentation:** Ampoule

**Ingredient/substance/strength**
- Presentation: bupivacaine hydrochloride (monohydrate) 21.2 mg / 1 unit (optional)
  - Concentration: bupivacaine hydrochloride (monohydrate) 5.28 mg/ml

**Pharmaceutical product**
- **Administrable Dose Form:** Solution for injection
- **Route of Administration:** Intrathecal use
- **Unit of Presentation:** N/A

**Ingredient/substance/strength**
- Same as for manufactured item
Patterns sometimes need to be combined

When a product falls into several patterns, e.g. Clexane 4000 IU (40 mg)/0.4 ml Solution for injection in pre-filled syringe

- Clexane is often given as a complete syringe (2a) but sometimes on a mg/kg basis (2b) – patterns 2a and 2b
Future work (1)

► So far, we have a total of 7 patterns
  ➢ More are probably needed
  ➢ Attributes in the patterns (so far) are
    ✓ Manufactured Item – Unit of Presentation
    ✓ Pharmaceutical Product – Unit of Presentation
    ✓ Strength Presentation and Strength Concentration – Mandatory or Optional
  ➢ They should be expanded to include more attributes (e.g. Manufactured Item Quantity) that can be included in the patterns

► Very useful to look at pictures of the packaging
  – Google is your friend!
Future work (2)

► Relate the patterns to PhPID work
► Relate to the FHIR work
  ➢ via the Pilot Product List (PPL) WP4 & WP9
► Match against the EU Quality Review of Documents document: “QRD Recommendations on the Expression Of Strength in the Name of Centrally Authorised Human Medicinal Products” from 2009
Thanks to:
Julie James – Blue Wave Informatics
Malin Fladvad – WHO Uppsala Monitoring Centre
Martha Schei Hynne – formerly Norwegian Medicines Agency, NoMA
Questions in the Q & A facility, please
For feedback, please go to :
https://forms.gle/MBXJAabcoJ1SreBT56

Thanks for your time