Relevance of EU-SRS to global IDMP implementation and the UNICOM clinical Pilots

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Overview

► My Background

► UNICOM
  ▶ The UNICOM Project
  ▶ The pilots in UNICOM
  ▶ The UNICOM Pilot Product List of 35 substances

► Hierarchy of substance
  ▶ Type of substances, grouper of substances, grouper of medicinal products
  ▶ Ontology of substance
  ▶ Experiences from early work on standardization to IDMP
  ▶ Requests to the EU-SRS Working Party
  ▶ The role of substance in virtual drug models
My Background

► Work Package leader of WP8 (IDMP and Clinical Care)

► GP and Clinical Pharmacologist
  ▶ Practice and research experience
  ▶ Training experience in medicine and pharmacy

► Project manager of the Belgian Independent Drug Information Centre
  ▶ Web information for health professionals
  ▶ The Authentic source of medicines (SAM Database)
  ▶ The Belgian ICT-Implementation of INN Prescribing

► Drug Utilisation Researcher
  ▶ ESAC project (European Surveillance of Antibiotic Consumption)
  ▶ Guidelines for Cross National Comparison of Drug Exposure

► Doctoral Thesis on drug information for patients
A few words about UNICOM Project
The UNICOM Project

► What if

We would be able to recognise any medicinal product from anywhere in the world anywhere in the world.

That is the ambition of the 5 SO/CEN Standards
UNICOM Project (2)

- a large action program, from the EU Horizon programme,
- with a 20 MEURO Budget,
- 44 participating organizations,
- among which 11 National Competent Agency for marketing authorization of Medicinal Products and a number of eHealth Institutions
  - [https://unicom-project.eu](https://unicom-project.eu)

- Testimony of large institutional support for IDMP implementation
  - Supported by ICH (International Council of Harmonisation)
  - Supported by EMA, FDA
  - Supported by a global Working Group (bringing together FDA, EMA, WHO_Uppsala Monitoring Centre for Pharmacovigilance)
Perspective on future and history of IDMP implementation

Retrospective
- Pharmaco-archeology
- Substance cleansing
- EDQM standardization
- Strength Normalisation

Prospective
- DADI-Project (industry => Agency)
- IDMP-Compliant Registration
- NCA=>MPD flow
- MPD =>Vendor Flow
- Vendor => Clinical Care Flow
The Pilots in UNICOM

The cross-border services of eHealth
- ePrescribing;
- eDispensing;
- ePatient Summary
  in Finland, Estonia, Spain, Portugal, Norway, Ireland, Austria, Sweden
  (Wave 6 starting last trimester of 2024)

The clinical pilots in WP8

- **Task 8.1**
  Facilitate International Decision Support Systems to be implemented in national EHR-systems

- **Task 8.2**
  Comparing national therapeutic arsenals

- **Task 8.3**
  Creating patient-facing apps from Greece, Italy and US
Limitations of this presentation on Substances:

For this presentation we will focus on:

- Substances with the role of active ingredient
  (not the excipientia or ingredients with clinical relevance)
- Chemical Substances
  Which have a moiety
  and (often but not always) a modifier
- 35 substances of the UNICOM Pilot Product List
  - frequently used older chemicals
  - Priority list of eHEALTH
  - Exemplary substances with special issues
The Unicom Pilot Product List

List of 35 substances

<table>
<thead>
<tr>
<th>Substances</th>
<th>Substances</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>simvastatin</td>
<td>calcium carbonate</td>
<td>metformin</td>
</tr>
<tr>
<td>enalapril</td>
<td>ergocalciferol</td>
<td>amlodipine</td>
</tr>
<tr>
<td>omeprazole</td>
<td>paracetamol</td>
<td>perindopril</td>
</tr>
<tr>
<td>diclofenac</td>
<td>diazepam</td>
<td>tramadol</td>
</tr>
<tr>
<td>cefuroxime</td>
<td>morphine</td>
<td>ciclosporine</td>
</tr>
<tr>
<td>salbutamol</td>
<td>enoxaparin</td>
<td>itraconazole</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>hydrocortisone</td>
<td>goserelin</td>
</tr>
<tr>
<td>clavulanate</td>
<td>lidocaine</td>
<td>clotrimazole</td>
</tr>
<tr>
<td>insulin glargine</td>
<td>trastuzumab</td>
<td>varenicline</td>
</tr>
<tr>
<td>teriparatide</td>
<td>chloroquine</td>
<td>ibuprofen</td>
</tr>
<tr>
<td>drospirenone</td>
<td>clomipramine</td>
<td>tafluprost</td>
</tr>
<tr>
<td>ethinylestradiol</td>
<td>carbamazepine</td>
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</tr>
<tr>
<td>glyceryl trinitrate</td>
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</tbody>
</table>
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 875299

The UNICOM Pilot Product List of 35 substances

- This list is mostly on chemical substances
- The list contains (almost) no combination products (except: amoxiclav and a fixed combination anticonceptive)
- For each substance all possible modifiers are identified (0, 1, 2 or more)
- For each substance, all codes from 5 coding systems are given for moiety and moiety+modifier
- For each substance, we would like to have the molecular mass of moiety and modifier

This selection of 35 substances leads to:

- 100-120 pharmaceutical products
- 300-400 Medicinal Products
- 600-1200 Medicinal Product Packages
  Depending on the country
Hierarchy of substance
Substance is a key element that determines, together with dose form, the normalisation of strength expression of medicinal products.

Note: Substance with dose form and strength determine the effect of the medication.
### Type of Substances

#### Active moiety
- Amlodipine
- Carbamazepine

#### Moiety + Modifier
- Amlodipine besylate
- Amlodipine mesylate
- Amlodipine maleate

No modifier for carbamazepine

For moiety and for moiety+modifier, data on molecular mass are available.

### Codes available in

<table>
<thead>
<tr>
<th>EU-SRS</th>
<th>WHODRUG</th>
<th>UNII</th>
<th>CAS</th>
<th>Snomed-CT</th>
</tr>
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<tbody>
<tr>
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</tr>
</tbody>
</table>

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 875299.
<table>
<thead>
<tr>
<th>Type of Substances</th>
<th>Attribute of substance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active moiety</strong></td>
<td><strong>Substance with the role of Precise Active Ingredient</strong></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td><strong>Moiety + Modifier</strong></td>
<td><strong>Moiety + Modifier</strong></td>
</tr>
<tr>
<td>Amlodipine besylate</td>
<td>Amlodipine besylate</td>
</tr>
</tbody>
</table>

This attribute is not self-evident nor deducible from the codes for moiety.
Principle in IDMP for Substance identification

► To represent the substance in the Medicinal Product at the level of the Pharmaceutical product the (chemical) substance must be specified with the modifier, in case there is a modifier.

▷ In the case of amlodipine, one needs to specify the modifier (besylate, mesylate, or maleate)

▷ In the case of carbamazepine, there is no modifier

In many legacy systems inside the agencies, the modifier is often not specified.
In the case of the Belgian Drug Database

1100 of the 4000 medicinal products have a blank space in the column of the modifier

It is estimated that

- In one third, no modifier is to be specified
- In one third, the substance has only one possible modifier and hence can be filled automatically
- In one third, the substance has 2 or more modifiers and hence, one needs to go back to the original file of the product to determine which modifier is the right one
Principle in IDMP for Substance identification

- For the abstract, exact representation of a national medicinal product as a global pharmaceutical product, it is necessary to determine for the chemical substances, which is the substance with the role of PAI.

  i.c. Carbamazepine
  i.c. Amlodipine besylate, or amlodipine mesylate, or amlodipine maleate

The question is:

  Can EU-SRS provide this crucial information?
  for each moiety:
    Is a modifier needed?
    If yes, what is the finite list of possible modifiers?
    Determine the attribute PAI?
For most of the medicinal products, the strength printed on the box is the strength of the moiety.

- “Strength” in IDMP is the strength of the “reference substance” (= the moiety)
- “Reference strength” in IDMP is the strength of the moiety+modifier

The latter is not clinically relevant but requested by IDMP to be specified (to check the basis of strength; to inform production processes).

The question is:

Can EU-SRS provide this crucial information?
For each substance with the one or more modifiers
What is the molecular mass of the moiety?
What is the molecular mass of moiety+modifier?
Value Set
For only SMS codes
For Moiety+ Modifier
And Moiety
without a Modifier

All with the role of Precise Active Ingredient (PAI)
### Three meanings of a substance term

<table>
<thead>
<tr>
<th>Amlodipine (1)</th>
<th>Term for the physical reality of chemical molecule, which constitutes the active part of an ingredient with therapeutic role. This molecule has a chemical structure, molecular mass, a code in the CAS-system, and a mechanism of action.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine (2)</td>
<td>Term for the collection of modified substances (amlodipine besilate, mesilate and maleate), which all contain amlodipine (1)</td>
</tr>
<tr>
<td>Amlodipine (3)</td>
<td>Term for the collection of medicinal products that contain any one of the 3 modified substances (named with amlodipine (2)), and no other ingredients with an active role. A medicinal product can be entered in the collection even if the modifier is unknown.</td>
</tr>
</tbody>
</table>

### Two meanings of a modified substance term

<table>
<thead>
<tr>
<th>Amlodipine besylate (1)</th>
<th>Term for the physical reality of a chemical molecule, consisting of the active part and the salt. This molecule has a chemical structure, molecular mass, a code in the CAS-system, and a mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine besylate (2)</td>
<td>Term for the collection of medicinal products containing this specific modified substance</td>
</tr>
</tbody>
</table>
Substance: terms, concepts and coding systems

Code systems for material substances (EU-SMS, UNII, WHODrug, CAS, Snomed-CT)
  Moiety
  Moiety + modifier

Code Systems for grouper of substances
  Currently no coding system existing this concept
    e.g.- “amlodipine” as the name for the collection of substances
    with the same moiety but different modifiers (or no modifiers)

Code systems for grouper of medicinal products
  Grouper of medicinal products sharing the same substance with the role of PAI
    Will be the Level 1 of Pharmaceutical Product in IDMP (PhPID)
    e.g. “amlodipine besylate (GR)”
  Grouper of medicinal products sharing the same (grouper of substance with) active moiety
    Will be usefull for the aggregation of several pharmaceutical products into a higher level
    for INN (or generic) Prescribing
    No global coding system currently existing
Substance with the role of PAI

Coded in EU-SRS in the EU
Coded in UNII in the US
Maybe coded with a global identifier in the future (e.g. WHODurg)

Grouper of medicinal products with the same substance with the role of PAI

PHPID Level 1
Coding system yet to be decided
Could be global system
Would solve EU-Global dilemma for substance in the EU IDMP IG

Grouper of medicinal products with the same moiety

Would bring together the Pharmaceutical Products that share the same moiety
Coding system similar to ATC, but with more sophisticated handling of combinations
Would provide the basis for a sound ontology of substance
Real world example

Example of aggregated representation of medicinal products at work

**Group of Medicinal Products with the same active moiety of substance**

<table>
<thead>
<tr>
<th>C08CA01</th>
<th>amlodipine</th>
</tr>
</thead>
</table>

**Virtual Medicinal Product Group**

- amlodipine oral 10 mg
- amlodipine oral 5 mg

**Pharmaceutical Product**

<table>
<thead>
<tr>
<th>amlodipine besilate</th>
<th>capsule, hard</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>amlodipine besilate</td>
<td>tablet</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

*(note: amlodipine maleate film-coated tablet 10 mg recently disappeared from the Belgian market)*

<table>
<thead>
<tr>
<th>amlodipine besilate</th>
<th>capsule, hard</th>
<th>5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>amlodipine besilate</td>
<td>tablet</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

**Medicinal Product (Belgium)**

<table>
<thead>
<tr>
<th>amlodipine besilate</th>
<th>capsule, hard</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlor harde caps. 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upjohn</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>amlodipine besilate</th>
<th>tablet</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine EG (PIP) tabl. (deelb.) Besilate 10 mg</td>
<td>PI-Pharma</td>
<td></td>
</tr>
<tr>
<td>Amlodipine EG tabl. (deelb.) Besilate 10 mg</td>
<td>EG</td>
<td></td>
</tr>
<tr>
<td>Amlodipine Mylan tabl. (deelb.) Besilate 10 mg</td>
<td>Mylan</td>
<td></td>
</tr>
<tr>
<td>Amlodipine Teva tabl. (deelb.) 10 mg</td>
<td>Teva</td>
<td></td>
</tr>
<tr>
<td>Amlodipin Sandoz (Impexco) tabl. (deelb.) Besilaat 10 mg</td>
<td>Impexco</td>
<td></td>
</tr>
<tr>
<td>Amlodipin Sandoz tabl. (deelb.) Besilaat 10 mg</td>
<td>Sandoz</td>
<td></td>
</tr>
<tr>
<td>Amloemed tabl. (deelb.) 10 mg</td>
<td>3DDD</td>
<td></td>
</tr>
<tr>
<td>Amlodipin AB tabl. 10 mg</td>
<td>Aurobindo</td>
<td></td>
</tr>
<tr>
<td>Amlodipin Sandoz tabl. (deelb.) Besilaat 10 mg</td>
<td>Sandoz</td>
<td></td>
</tr>
</tbody>
</table>
What if a Greek patient shows up in a Belgian Pharmacy and requests a prescription for αμλοδιπίνη

By identifying the IDMP data on the box, the pharmacist realizes that this about

amlodipine,
    and more specifically
amlodipine oral 10 mg,
    and even more specifically:
amlodipine besilate capsule, hard 10mg

In Belgium available as : Amlor 10 mg (Upjohn), and in generics by a number of companies but as tablets
Basis of INN Prescribing and Smart Substitution

Virtual Therapeutic Moiety Group

Virtual Medicinal Product Group

INN substance

ISI Dose Form

Strength

Substance Ontology

Dose Form Ontology

Virtual medicinal Product, identified by the PhPID

Granular substance

Granular Administrable dose from

Strength

Link Table from National Identifiers of Medicinal products

Link Table from International Classifications

Multilingual Management of labels
Thank you for your attention. Time for questions?
References


Virtual Drug Models

In IDMPM

Snomed-Ct

RxNorm

Dm+D/SAM

Medicinal Products

“Exact” abstract representation

Higher level aggregation
The distinction between active ingredient as a molecule or as an scattered aggregate (Drug Ontology, OBO Foundry)

Amlodipine besylate as a molecule

Has a molecular mass

Has a mechanism of action (disposition)
(calcium antagonism)

Amlodipine besylate as a "scattered aggregate" of molecules in a tablet

Has a weight (as part of the tablet weight)
Has a therapeutic role (lowers hypertension and relieves angina pectoris)


Figure 4. Substance as a molecule and substance as a "scattered aggregate"
Table 11. Calculation of the weight of different modified substances for a given reference strength for the moiety amlodipine

<table>
<thead>
<tr>
<th>Substance</th>
<th>Strength</th>
<th>Molecular Mass of the Moiety</th>
<th>Molecular Mass of the Modified Substance</th>
<th>Weight of the Scattered Aggregate of the Modified Substance in the Tablet</th>
<th>Reference Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine besylate</td>
<td>5 mg</td>
<td>409 g/mol</td>
<td>567 g/mol</td>
<td>6,9315 mg</td>
<td></td>
</tr>
<tr>
<td>Amlodipine mesylate</td>
<td>5 mg</td>
<td>409 g/mol</td>
<td>505 g/mol</td>
<td>6,1736 mg</td>
<td></td>
</tr>
<tr>
<td>Amlodipine maleate</td>
<td>5 mg</td>
<td>409 g/mol</td>
<td>530 g/mol</td>
<td>6,4792 mg</td>
<td></td>
</tr>
</tbody>
</table>
Cherry blossoms are cherry blossoms and not hedge bindweeds
They are pink, delicate and blossom in the spring
Yet, every cherry blossom is unique