



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

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- ▶ 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



- ▶ 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



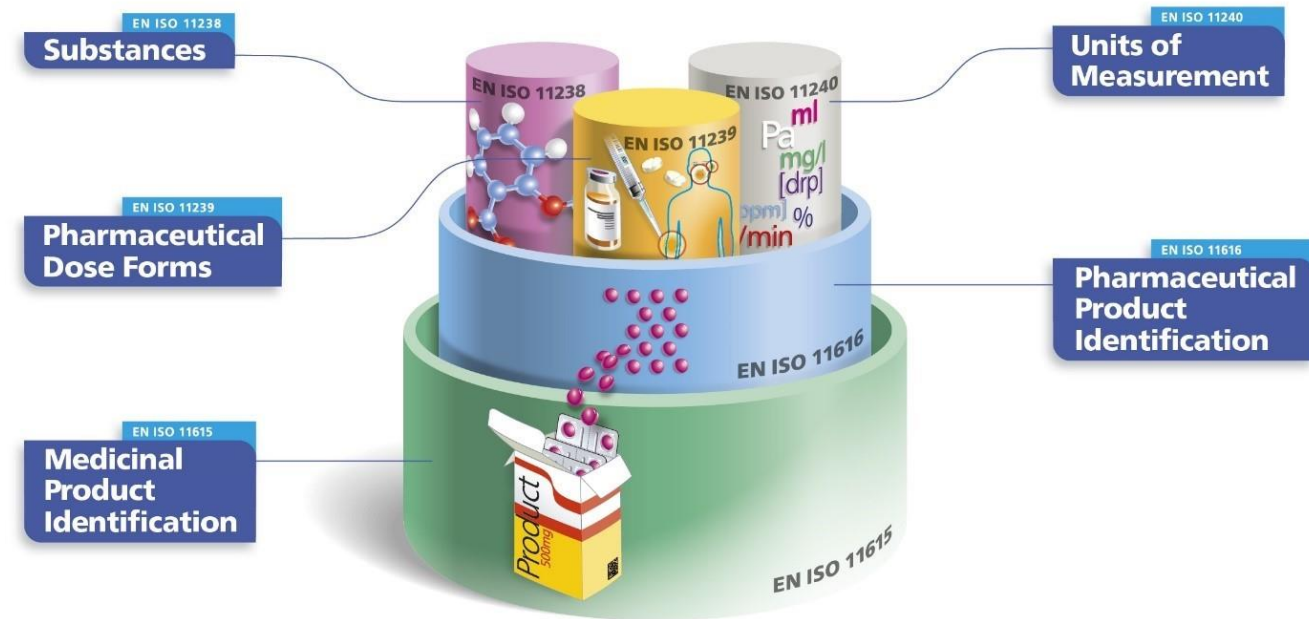
# A few words about UNICOM Project

UN  COM

## ► What if

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

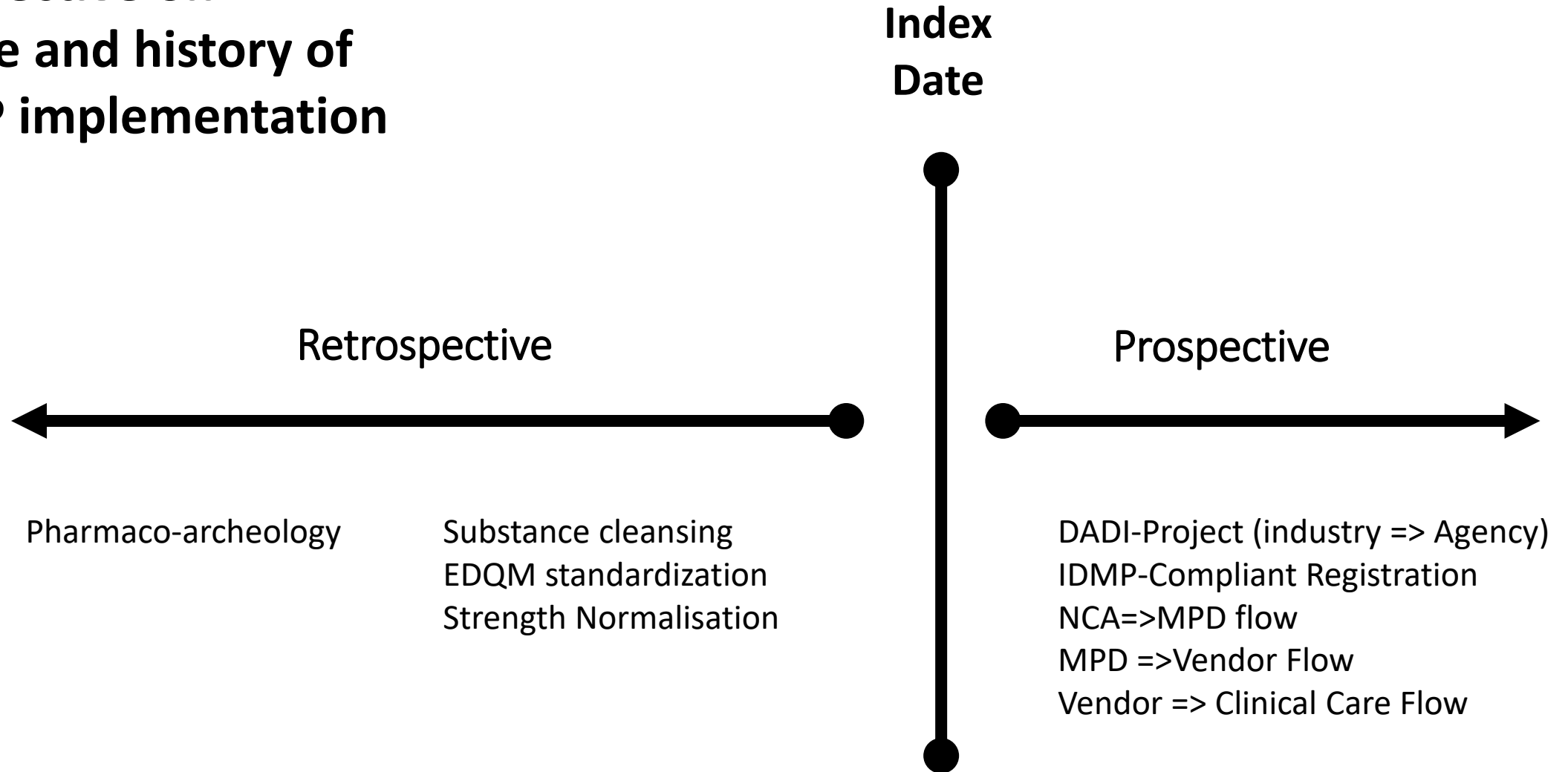
**That is the ambition of the 5 SO/CEN Standards**



- ▶ 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>
  
- ▶ 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



## ▶ 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





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

- simvastatin
- enalapril
- omeprazole
- diclofenac
- cefuroxime
- salbutamol
- amoxicillin
- clavulanate
- insulin glargine
- teriparatide
- drospirenone
- ethinylestradiol
- glyceryl trinitrate

- calcium carbonate
- ergocalciferol
- paracetamol
- diazepam
- morphine
- enoxaparin
- hydrocortisone
- lidocaine
- trastuzumab
- chloroquine
- clomipramine
- carbamazepine

- metformin
- amlodipine
- perindopril
- tramadol
- ciclosporine
- itraconazole
- goserelin
- clotrimazole
- varenicline
- ibuprofen
- tafluprost

- ▶ This list is mostly on chemical substances
- ▶ The list contains (almost) no combination products  
(except : amoxiclav and a fixed combination contraceptive)
- ▶ 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

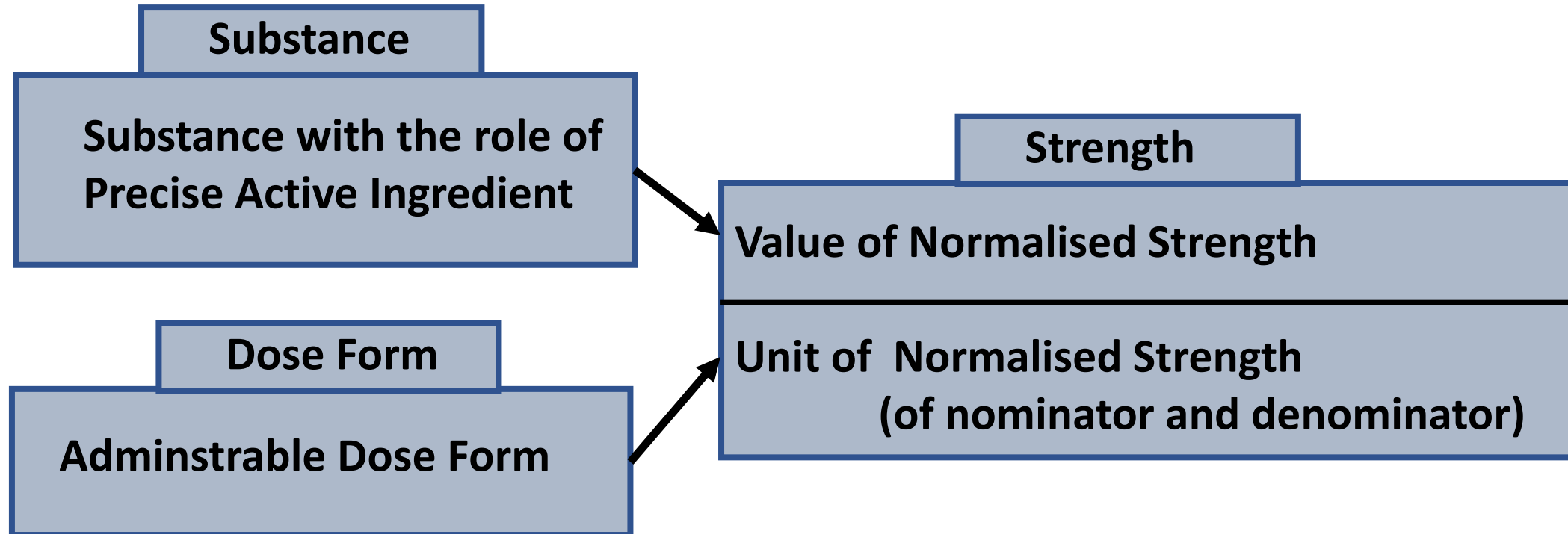
This selection of 35 substances leads to :

- ▷ 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

## Codes available in

### Active moiety

Amlodipine

Carbamazepine

### Moiety + Modifier

Amlodipine besylate

Amlodipine mesylate

Amlodipine maleate

No modifier for carbamazepine

EU-SRS	WHODRUG	UNII	CAS	Snomed-CT

EU-SRS	WHODRUG	UNII	CAS	Snomed-CT

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



## Type of Substances

### Active moiety

Amlodipine  
Carbamazepine

### Moiety + Modifier

Amlodipine besylate

## Attribute of substance

### Substance with the role of Precise Active Ingredient

Carbamazepine

Amlodipine besylate

This attribute is not self-evident nor deducible from the codes for moiety



- ▶ 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



- 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+ Modifer  
 And Moiety  
 without a Modifier

All with the role of  
 Precise Active  
 Ingredient (PAI)

	SMS
(Modified) substances with the attribute of Precise Active Ingredient	
diclofenac (ionized)	100000092798
diclofenac sodium	100000092272
diclofenac potassium	100000092368
diclofenac diethylamine	100000091074
diclofenac epolamine	100000085789
amoxicillin sodium	100000090113
amoxicillin trihydrate	100000092629
carbamazepine	100000092127
amlodipine besilate	100000090079
amlodipine mesilate	100000089571
amlodipine benzoate	Not existing
amlodipine maleate	100000089370
simvastatine	100000091786
enalapril maleate	100000091343
enalaprilat	100000153305"
Enalapril sodium	100000153305"
omeprazole sodium	100000090186
omeprazole magnesium	100000085918
cefuroxime sodium	100000091436
cefuroxime axetil	100000093039
salbutamol sulfate	100000090564
Potassium clavinalate	100000093061
insulin glargine	100000085460
teriparatide acetate	100000084795
calcium carbonate	100000091518
ergocalciferol	100000090229
paracetamol	100000090270
diazepam	100000092362
morphine hydrochloride	100000090494
morphine sulfate	100000076239
morphine tartrate	100000076257
morphine liposomal (sulfate)	not present
enoxaparin sodium	100000090152
hydrocortisone sodium succinate	100000092550
hydrocortisone valerate	100000086711
hydrocortisone acetate	100000092260
hydrocortisone butyrate	100000085172
hydrocortisone aceponate	100000084215
hydrocortisone probutate	100000085172
hydrocortisone cypionate	100000086187
hydrocortisone sodium phosphate	100000086691
lidocaine hydrochloride	100000139489
trastuzumab emtansine	100000128434
trastuzumab deruxtecan	100000174462
imatinib mesilate	missing
clomipramine hydrochloride	100000090503
metformin hydrochloride	100000091366
metformin pamoate	100000091840
perindopril arginine	100000088816
perindopril erbumine	100000091602
perindopril erbumine monohydrate	100000130680
perindopril tosilate	100000141420
tramadol hydrochloride	100000093275
ciclosporine	100000092121
itraconazole	100000091697
goserelin acetate	100000086673
glyceryl trinitrate	missing
chloroquine phosphate	100000092628
chloroquine sulfate	100000090551
chloroquine hydrochloride	100000084735
chloroquine diphosphate	100000129152
clotrimazole	100000092074
varenciline tartrate	00109205001
varenciline dihydrochloride	00109202063
ibuprofen sodium	100000085009
ibuprofen lysine	100000090111
ibuprofen sodium dihydrate	
ibuprofen D,L-lysinate	100000133453
ibuprofen 1-(4-sulfonylphenyl)-2-methyl-ethanone	100000079980
ibuprofen arginine	100000092228
ibuprofen (sodium salt)	100000175414
tafluprost	100000115886

To be augmented  
 With all the languages  
 From the SPOR-SMS  
 dataset

## Three meanings of a substance term

	<b>Amlodipine (1)</b>
	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.
	<b>Amlodipine (2)</b>
	Term for the collection of modified substances (amlodipine besilate, mesilate and maleate), which all contain amlodipine (1)
	<b>Amlodipine (3)</b>
	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.

## Two meanings of a modified substance term

	<b>Amlodipine besylate (1)</b>
	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
	<b>Amlodipine besylate (2)</b>
	Term for the collection of medicinal products containing this specific modified substance



## 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)

## Group 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

## Group 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



## Example of aggregated representation of medicinal products at work

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

C08CA01 amlodipine

#### Virtual Medicinal Product Group

amlodipine oral 10 mg

amlodipine oral 5 mg

#### Pharmaceutical Product

amlodipine besilate capsule, hard 10 mg

amlodipine besilate tablet 10 mg

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

amlodipine besilate capsule, hard 5 mg

amlodipine besilate tablet 5 mg

#### Medicinal Product (Belgium)

amlodipine besilate capsule, hard 10 mg

Amlor harde caps. 10 mg Upjohn

amlodipine besilate tablet 10 mg

Amlodipine EG (PIP) tabl. (deelb.) Besilate 10 mg PI-Pharma

Amlodipine EG tabl. (deelb.) Besilate 10 mg EG

Amlodipine Mylan tabl. (deelb.) Besilate 10 mg Mylan

Amlodipine Teva tabl. (deelb.) 10 mg Teva

Amlodipin Sandoz (Impexeco) tabl. (deelb.) Besilaat 10 mg Impexeco

Amlodipin Sandoz tabl. (deelb.) Besilaat 10 mg Sandoz

Amlobemed tabl. (deelb.) 10 mg 3DDD

Amlodipin AB tabl. 10 mg Aurobindo

Amlodipin Sandoz tabl. (deelb.) Besilaat 10 mg Sandoz





## What if

a Greek patient shows up on 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

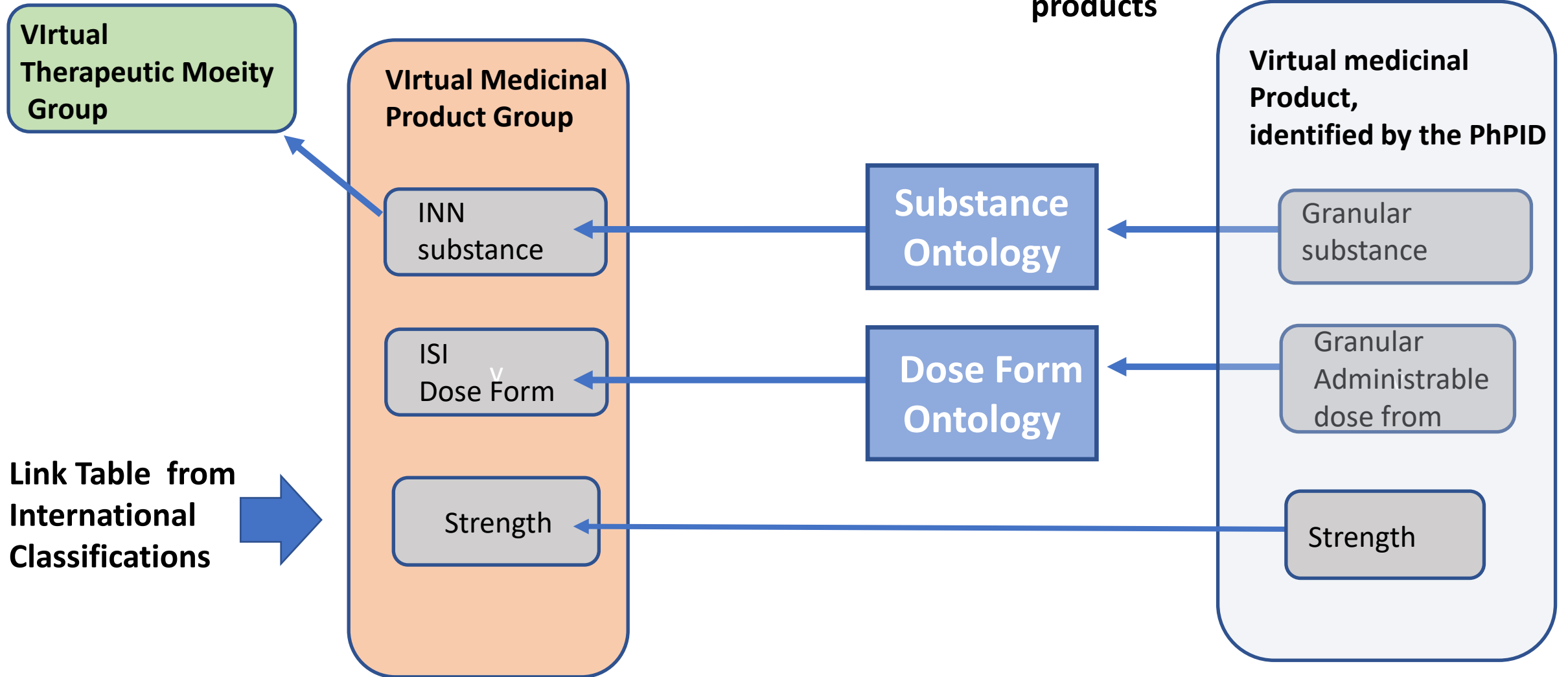
**amlodipine oral 10 mg,**

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



Multilingual Management of labels

**ISO/CEN IDMP**  
**Identification of Medicinal Products**

**Gnostic Classification**

**Agnostic Identification**

**Marketing Authorization Identification**

**Structural / Therapeutic Groupers**  
ATC class IV - I

↑

ATC-LEVEL V

**Virtual Aggregate Identification (global)**

Virtual Therapeutic Moiety

Virtual Medicinal Product Group

**Virtual Precise Identification (global)**

PhPID-Level I

PHPID-Level IV

**Actual Identification at national (regional) level**

Substance /Company Level

Medicinal Product

Medicinal Product Pack



Defined Daily Dose  
DDD per pack  
link



Batch  
GTIN

**Thank you for your attention.  
Time for questions ?**

**UN  COM**

## UNICOM PUBLICATIONS

### References

1. Vander Stichele RH, Hay C, Fladvad M, Sturkenboom MCJM, Chen RT. How to ensure we can track and trace global use of COVID-19 vaccines? *Vaccine*. 2021 Jan 8;39(2):176-179. doi: 10.1016/j.vaccine.2020.11.055
2. Vander Stichele R, Kalra D. Aggregations of Substance in Virtual Drug Models Based on ISO/CEN Standards for Identification of Medicinal Products (IDMP). *Stud Health Technol Inform*. 2022 May 25;294:377-381. doi: 10.3233/SHTI220478.
3. Vander Stichele, R.H.; Roumier, J.; van Nimwegen, D. How Granular Can a Dose Form Be Described? Considering EDQM Standard Terms for a Global Terminology. *Appl. Sci*. 2022, 12, 4337. <https://doi.org/10.3390/app12094337>
4. Karapetian N, Vander Stichele R, Quintana Y. Alignment of two standard terminologies for dosage form: RxNorm from the National Library of Medicine for the United States and EDQM from the European Directorate for the Quality in Medicines and Healthcare for Europe. *Int J Med Inform*. 2022 Sep;165:104826. doi: 10.1016/j.ijmedinf.2022.104826.

<https://unicom-project.eu/wp->

[content/uploads/2022/01/UNICOM\\_D8.1\\_IDMP\\_and\\_DrugClassification.pdf](https://unicom-project.eu/wp-content/uploads/2022/01/UNICOM_D8.1_IDMP_and_DrugClassification.pdf)

# Virtual Drug Models

In

IDMPM

Snomed-Ct

RxNorm

Dm+d/SAM

## Concepts in drug identification at the national level for concrete products

IDMP	SNOMED-CT	Dm+d/SAM	RxNorm
	Real Medicinal Product	Actual Therapeutic Moiety	Brand name
Medicinal Product	Real Clinical Drug	Actual Medicinal Product	Semantic Branded Drug
Packaged Medicinal Product	Real Packaged Clinical Drug	Actual Medicinal Product Package	Brand Name Pack

Medicinal Products

## Concepts in drug identification for abstract but granular representation of medicinal products

IDMP	SNOMED-CT	Dm+d/SAM	RxNorm
PhPID Level 1 <i>(precise active ingredient group)</i>	Medicinal Drug Precisely	Virtual Therapeutic Moiety	
PhPID Level 4 <i>(Pharmaceutical Product Group)</i>	Clinical Drug Precisely	Virtual Medicinal Product	Semantic Clinical Drug <i>(not precise ingredient)</i>
	Packaged Clinical Drug Precisely	Virtual Medicinal Product Package	Generic Pack

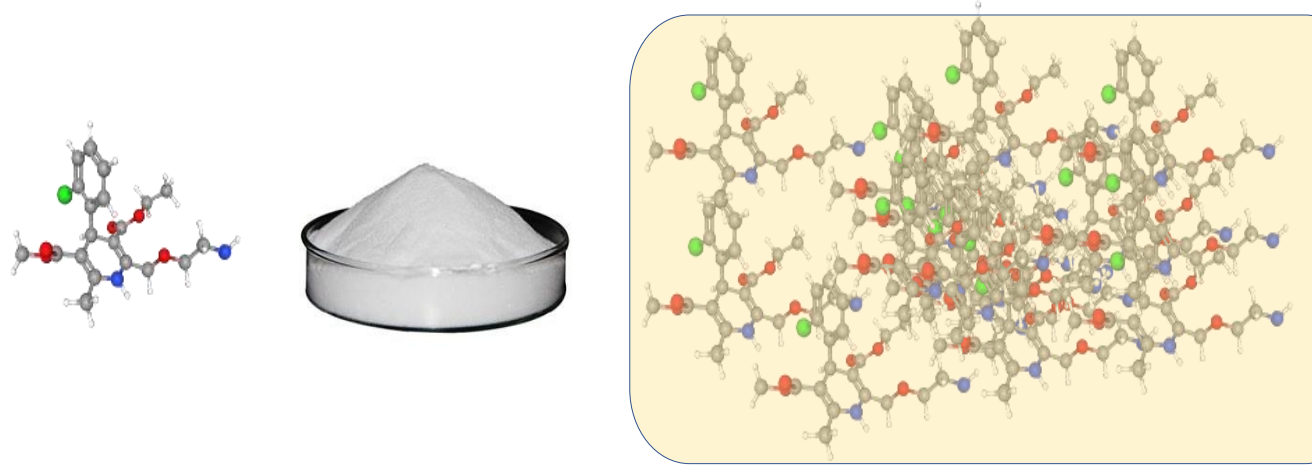
“Exact” abstract representation

## Concepts in drug identification for higher levels of abstraction in representation of medicinal products

IDMP	SNOMED-CT	Dm+d/SAM	RxNorm	UNICOM-PPL
	Medical Product Only			Virtual Therapeutic Moiety Group
	Medicinal Product Form Only + Strength	Virtual Medicinal Product Group	Semantic Clinical Drug <i>Not high level dose form</i>	Virtual Medicinal Product Group
	Real Packaged Clinical Drug			

Higher level aggregation

# The distinction between active ingredient as a molecule or as an aggregate (Drug Ontology, 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)

)

Hanna J, Bian J, Hogan WR. An accurate and precise representation of drug ingredients. *J Biomed Semantics*. 2016 Apr 19;7:7.

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**

			Strength	Molecular mass of the moiety	Molecular Mass of the Modified Substance	Weight of the scattered aggregate of the modified substance in the tablet	Reference strength
<b>Amlodipine besylate</b>			5 mg	409 g/mol	567 g/mol	6,9315 mg	
<b>Amlodipine mesylate</b>			5 mg	409 g/mol	505 g/mol	6,1736 mg	
<b>Amlodipine maleate</b>			5 mg	409 g/mol	530 g/mol	6,4792 mg	



# Haiku on what binds and separates almost similar things



*Cherry blossoms are cherry blossoms and not hedge bindweeds  
They are pink, delicate and blossom in the spring  
Yet, every cherry blossom is unique*