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Working Paper: Application of IDMP in Drug Labelling and Drug Information, in Clinical Decision Support and in Quality Assurance of Clinical Data

This is a UNICOM working paper developed under Grant Agreement No 875299 of the EU Horizon 2020 programme.It has been made available in the public domain to ensure early dissemination of core UNICOM results of wider interest and to collect supplementary feed-back from the public.

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Statement of originality

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Document abstract

In this working paper we discuss the final results of task T8.1 on IDMP and Clinical care.

We explore what IDMP can mean for quality of care in pharmacotherapy, and how it can be integrated in clinical decision support systems.

First, we discuss the grouping of active substances and medicinal products into pharmaco-therapeutic groups, with the ATC classification, SNOMED-CT and RxNorm, Classifications of international Medicinal product Dictionaries, the Standardised Drug Groups of the Uppsala Monitoring Centre, and a classification for medical education and patient information.

Then, we describe a methodology for linking International Drug Classifications to National Medicinal Products, from national medicinal product packs to global pharmaceutical product, to the ATC level V class, and to Clinical Classifications.

In a next chapter, we describe the initiatives to produce meaningful sets of medicinal products, standardised to IDMP, such as the UNICOM Pilot Product List, the UFIS Database, the T6.1 UNICOM FHIR Server, and the Minimal Data Set, containing all medicinal products for 4 substances from 10 countries. The objective of this description is to illustrate the importance of having IDMP-compliant data for demonstration purposes.

Finally, the use of this Minimal Data Set in the Patient Facing APP and in decision support systems is discussed.

This work concludes by stating that the implementation of the ISO/CEN standards will bring precision and robustness to the application of decision rules, expressed in general drug class statements, in the national Medicinal Product Dictionaries, allowing decision support systems to cross the borders of the member states in Europe in a feasible way.

Commented [LN1]: Should it not be «in» instead of to ?

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Working paper review

	Internal reviewer: Luc Nicolas (ETHEL)			External reviewer:		
	Answer	Comments	Type*	Answer	Comments	Type*
Is the working paper in accordance with						
the Description of Action?	☒ Yes ☐ No	The document refers clearly to the tasks and sub-tasks of the DoA	☐ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
the international State of the Art?	☒ Yes ☐ No	Make sure to provide external links when referring to external sources.	☐ M ☒ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
Is the quality of the working paper in a status						
that allows it to be sent to European Commission?	☐ Yes ☒ No	A number of clarifications need to be made; please also check carefully all editing proposed. Some sections need additions.	☐ M ☒ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
that needs improvement of the writing by the originator of the working paper?	☒ Yes ☐ No	Aside from comments and editing, please also make sure that all abbreviations are listed and ae exported from the glossary	☐ M ☒ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
that needs further work by the Partners responsible for the working paper?	☒ Yes ☐ No	The annexes cannot be provided "as is" and need to be reformatted so that included in the document (with a possible open link to the full resource)	☒ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
Is the structure and contents of the working paper						
structured, logical and easy to understand?	☒ Yes ☐ No	The document is well structured and to the point but wording is sometimes a bit fuzzy.	☐ M ☒ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
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Is in** conformance with UNICOM working paper template?	☒ Yes ☐ No		☐ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a

* Type of comments: M = Major comment; m = minor comment; a = advice

List of abbreviations

Abbreviation	Complete form
AMP	Actual Medicinal Product
AMPP	Actual Medicinal Product Pack
API	Application Programming Interface
ATC	Anatomical therapeutic Chemical Classification
ATM	Actual Therapeutic Moiety
BCFI	Belgian Centre for Pharmaco-therapeutic Information
CAP	Centralised Authorisation Procedure
CAS	Chemical Abstract Service
CD	Clinical Drug
CDF	Complex Dose Form
CEF	Connecting Europe Facility
CEN	European Standards Commission / Comité Européen de Normalisation
CMT	Combined Term
DCP	Decentralised Procedure
DDD	Defined Daily Dose
DPP	Defined Daily Dose per Package
EDQM	European Directorate for the Quality of Medicines
eHDSI	EHealth Digital Services Infrastructure
EMA	European Medicines Agency
EPC	Established Pharmaceutical Classes
ePI	Electronic Product Information
EU	European Union
FMD	Falsified Medicines Directive
FDA	Food and Drug Administration
FHIR	Fast Healthcare Interoperability Resources
GTIN	Global Trade Item Number
EHDS	European Health Data Space
EHR	Electronic Health Record
HL7	Health Level 7
IDMP	Identification of Medicinal Products

INN	International Non-Proprietary Name
IPS	International Patient Summary
ISO	International Standards Organisation
MPD	Medicinal Product Dictionary
MPID	Medicinal Product Identifier
NCA	National Competent Agency
NOMA	Norwegian Medical Product Agency
OMS	Organisation Management System
PAI	Precise active ingredient
PCID	Pack Identifier
PDF	Pharmaceutical Dose Form
PhPID	Pharmaceutical Product Identifier
PMS	Product Management System
RMS	Reference Management System
SDG	Standardised Drug Groups
SDO	Standards Developing Organisation
SmPC	Summary of Product Characteristics
SMS	Substance Management System
SPOR	Substance, Product, Organisation, Reference System
UFIS	Unicom FHIR Server
UL	User Leaflet
UMC	Uppsala Monitoring Centre
UNII	Unique Ingredient Identifier
USP	United States Pharmacopeia
VMP	Virtual Medicinal Product
VMPGroup	Virtual Medicinal Product Group
VTM	Virtual Therapeutic Moiety
WHO CC DSM	WHO Collaborating Centre for Drug Statistics Methodology

1 Executive summary

Include an executive summary of 1 page maximum. It should contain an adequate description of the contents of the document, for the reader who does not have the time to read the whole document.

In this working paper we discuss the final results of task T8.1 on IDMP and Clinical care.

We explore what IDMP can mean for quality of care in pharmacotherapy, and how it can be integrated in clinical decision support systems.

First, we discuss the grouping of active substances and medicinal products into pharmaco-therapeutic groups, with the ATC classification, SNOMED-CT and RxNorm, Classifications of international Medicinal product Dictionaries, the Standardised Drug Groups of the Uppsala Monitoring Centre, and a classification for medical education and patient information.

Then, we describe a methodology for linking International Drug Classifications to National Medicinal Products, from national medicinal product packs to global pharmaceutical product, to the ATC level V class, and to Clinical Classifications.

In a next chapter, we describe the initiatives to produce meaningful sets of medicinal products, standardised to IDMP, such as the UNICOM Pilot Product List, the UFIS Database, The T6.1 UNICOM FHIR Server, and the Minimal Data Set, containing all medicinal products for 4 substances from 10 countries.

Finally, the use of this Minimal Data Set in the Patient Facing APP and in decision support systems is discussed.

IDMP was developed as a standard with regulatory marketing authorisation and pharmacovigilance as use cases. However, the ambition was to expand its application over the whole spectrum of domains for medicinal products, from prescribing and dispensing, to supply chain management, Public Health Monitoring, Drug utilisation research, and pharmaco-epidemiological outcome assessment (for side-effects and comparative effectiveness research.

The implementation of IDMP in the databases of the regulatory authorities of the member states is progressing but remains far from complete. By creating electronic application forms (eAFs), compliant with IDMP, EMA is setting the stage for handling all future new medicines. But the legacy conversion of the more than 400.000 older medicinal products in the different member states is a formidable task and might take longer. Because of lack of concrete progress in IDMP implementation some elements from the Description of Work could not be elaborated. .

In this project we needed to create a minimum of data to be made available dealing with all medicinal product packs relevant to 4 substances (amlodipine, carbamazepine, ibuprofen, and simvastatin) for at least 3 countries (Greece, Italy, USA).

This Minimal Data Set was used to demonstrate multilingual access to drug information, with explicit links to pharmacotherapeutic classes and decision support systems.

From this piloting work we can conclude that the implementation of the ISO/CEN standards will bring precision and robustness to the application of decision rules, expressed in general drug class statements, to the national Medicinal Product Dictionaries, allowing decision support systems to cross the borders of the member states in Europe in a feasible way.

2 Content of the working paper

2.1 Contents of the working paper

In the Description of Action of the UNICOM project, the following general description of the task T8.1 is given; Results of this task are reported in the present working paper D8.2 and in the previous working paper D8.1, submitted in 2022:

General desciption of Task T8.1 in Workpackage 8 : IDMP and Clinical Care, as given in the Description of Action

This task will improve Patient Safety in eDispensation through multilingual management of drug class terminology in interpreting drug labelling/leaflets and supporting medication information in pharmacies and patient apps. The aim is to provide the methodology to link national medicinal products to international drug classifications, making optimal use of IDMP, through concrete creation of PhPIDs for the medicinal products pertaining to the 35 selected substances from the UNICOM FHIR IDMP Server.

It will create a repository of the draft PhPIDs, incorporating the 3 constituent elements (substance, dose form, strength) and the links to national medicinal products and international classification.

The use of this repository will be demonstrated in the application of decision support systems across Europe, and in the tools for patients navigate drug class names in product labelling.

It will progress through five linked activities.

(i) This task will first analyse and consolidate the drug class names that are currently expressed differently and to different levels of granularity across a rich diversity of sources, including: major pharmacology handbooks and drug dictionaries, explicit criteria of (potentially) inappropriate prescribing, decision rules for pharmacodynamics and pharmacokinetic interactions, Summaries of Products Characteristics, the WHO ATC, RxNORM and the SNOMED International Virtual Product Model. From these, a consolidated fit-for-purpose nomenclature and hierarchy of drugs and classes will be developed, for education and training of pharmacists and physicians, and for drug information to patients. These will be stored in a standardized multilingual terminological resource (compliant with ISO- 16642 Terminological Markup Framework), and be linked to the relevant PhPIDs, for application in countries participating in the eDispensation Cross Border pilots.

(ii) The task will then develop a methodology to analyse the quality of medical data in EHRs and patient summaries, based on the information in the medication lists. The rule bases of well-validated lists of explicit criteria of potentially inappropriate prescribing (EU7-PIM list, START-STOPP list, Beers' list, LaRoche List etc.) will be analysed for their components in terms of clinical data (diagnoses, contra-indications, renal and kidney function). The clinical elements required for these rules will be transformed into correlation and safety criteria for clinical information, triggered by the presence of specific medications in the medication list.

(iii) This activity will apply IDMP via the above fit-for-purpose classification to cross-referencing pharmacotherapeutic groups in drug labelling and drug information by pharmacists. Functional specifications will be developed for a demonstrator user interface and FHIR APIs to enable patients to interpret drug group names in patient information leaflets from major medicinal products, and to relate this to the other medicinal products on their medication list, as a standalone app and/or a web service for pharmacists. To support cross-border care, these specifications will include medicinal products that are not licenced within one country, but are available in other countries (UMLs), with the possibility to retrieve the SmPC and User Package Leaflet from these products, in the languages of the countries where these products are available.

(iv) This activity will apply IDMP via the above fit-for-purpose classification to the cross-border implementation of European clinical decision support systems (CDSS). It will compile an inventory of European CDSS and assess the potential impact of a more consistent and accurate classification on the CDSS in at least in four countries. A survey among commercial and academic CDSS knowledge producers will establish the extent and approach to planned IDMP implementations, and their appreciation of the added value of the use of IDMP in their system, in terms of feasibility, operational costs, and improved outcomes from their products. Guidance will be produced to promote and support this adoption.

(v) This activity will apply the above classifications and clinical data correlation rules to conduct an audit of the quality of medical data in EHRs and Patient Summaries that are part of cross-border ePrescriptions. In four countries, a test of semantic operability of the transfer of 100 medication lists between different EHR interoperability models (CEN/EN17269, CEN/TS17288, openEHR, HL7 CDA, ISO EN13606) will be performed in different health care settings by comparing the results of computerized audit of prescribing quality on sending and received data. This audit will serve as a demonstrator and promoter of the value of IDMP to improve clinical data quality. An overview will be made of the extent and quality of the implementation of IDMP in the certification procedures of EHRs in Europe and Patient Summary validations in Europe, based on the effective deployment of the envisioned EHRxF format.

In this working paper each of these five linked activities will be described in a separate chapter, with a variety of results presented in annexes.

The process of selecting 35 substances for the UNICOM Pilot Product List will be described.

The approach to create a repository of draft PhPIDs for all medicinal products of 4 of these 35 selected substances in the UNICOM Pilot Product List will be explained. The repository includes medicinal products from 3 countries, involved in the creating of patient facing apps (T8.3) namely Italy, Greece and the USA. In addition, the Medicinal products for the same 4 substances in Belgium, Norway, Ecuador, and Tunisia have been added. This repository exists as an online SQL database for scientific analysis, but its content is also transferrable fo the UNICOM IDMP FHIR SERVER.

The methodology to link national medicinal products to international classifications was developed with the support of an “in-house” ontology of dose forms. This made possible the creation of a database linking all the PhPIDs from the repository to the ATC classification which illustrates the results.

An application of this approach to decision support will be illustrated and incorporated in the patient facing apps in 3 countries (ITA, GRC, and USA). Finally, the application of the methodology in navigating drug class names in product labelling will be presented.

2.2 Authorship and responsibilities

The Project Coordinator submits the working papers in accordance with the timing and conditions set out in the DoA.

The leader of the Work Package, I-HD (Dipak Kalra), to which the working paper is assigned reports to the Project Coordinator about the progress and completion of the output and the document, and ensure that it has the required quality.

The lead beneficiary of this working paper I-HD (Robert Vander Stichele) has edited the document. All authors who have made significant contributions to the working paper are listed in the table contained in the second page of the template.

3 Methodology to describe Pharmacotherapeutic Drug Classes

3.1 Overview of drug classifications

Drug information on medicinal products in official labelling such as the Summary of Product Characteristics (SmPC) and User Leaflet, can be ordered in class-specific information and substance-specific information.

Often these information carriers refer to drug classes (e.g. *if you are an elderly person, and you are on ACE-inhibitors and diuretics, you should not take a non-steroidal anti-inflammatory agent, because of the risk of renal insufficiency*).

For alerting the patient on potential interactions between his/her medication and a drug class, a prerequisite is that the medication list of the patient is coded and identified with global identifiers, linked to a code in the ATC classification, and linked to one or more relevant drug class names.[1] Many countries now maintain a register of the link between their national identifiers and the ATC classification from the World Health Organisation.[2] Attributing an ATC code to new drugs has become standard practice in regulatory affairs.

Another prerequisite is that the relevant drug classes are expressed as ATC classes, and that the ATC classes are linked to a national compendium.[3]

Drug Classes can be grouped along several axes:

- Anatomical region
- Chemical structure
- Therapeutic indication
- Mechanism of action
- Molecular Target

3.1.1 Examples of high level international classifications

The ATC classification is a rigid 5 level taxonomy, based on anatomical region, chemical structure, and therapeutic indication. Its primary purpose is to conduct drug utilisation research and to quantify drug exposure in populations. Therefore, this classification may not replace more clinically relevant classification.

Handbooks of clinical pharmacology and big national compendia have tables of contents to classify active ingredients and medicinal products. These uni-dimensional hierarchies will reflect to some extent different editorial choices, different medical cultures, and may have different levels of depth and granularity. This is obvious when comparing the table of contents of the British National Formulary, the established pharmacologic Classes (EPCs) of the Food and Drug Agency, the Belgian BCFI (Belgian Center for Pharmacotheraputic Information), the French ViDAL, and the German Rote Liste, the Goodman and Gilman handbook. The implicit classifications are constantly evolving, as new drugs and drug classes are developed.

For the creation and maintenance of drug classes a more ontology-oriented approach enables multi-hierarchical classification, with numerous scientific and clinical applications. Examples are SNOMED-CT drug model,

[1] EURO-MED STAT Group. EURO-MED-STAT: monitoring expenditure and utilization of medicinal products in the European Union countries: a public health approach. Eur J Public Health. 2003 Sep;13(3 Suppl):95-100.

[2] Rønning M, Litleskare I, Addis A, Batel-Marques F, Carvajal A, Sainz M, Folino-Gallo P, Jansen P, Santiago L, Vander Stichele R, on behalf of the EURO-MED-STAT Group. Recommendations for national registers of medicinal products with validated ATC codes and DDD values. Ital J Pub Health, 2006;3(1):30-35.

[3] Rønning M, Blix HS, Strøm H, Skovlund E, Andersen M, Stichele RV. Problems in collecting comparable national drug use data in Europe: the example of antibacterials. Eur J Clin Pharmacol. 2003 Apr;58(12):843-9.

RxNorm, and the USP Drug Classification (https://www.usp.org/health-quality-safety/usp-drug-classification-system).[4]

Classifications have been mapped among each other: WHODrug to ATC, RxNorm to ATC, SNOMED-CT to ATC, RxNorm to SNOMED-CT, Established pharmacologic classes from the FDA to SNOMED-CT[5]

3.1.2 Multilingual examples

Multilingual examples of drug class classifications are rather scarce. The Belgian Centre for Pharmaco-Therapeutic Information publishes and maintains its drug classification in Dutch and French (www.bcfi.be/nl/chapters and www.cbip.be/fr/chapters). SNOMED-CT and MEDDRA have multilingual extensions, which may not yet be completed for drug class concepts.

In the Multilingual Glossary of Technical and Popular Medical Terms, drug class names mentioned in drug labelling (Summary of Product Characteristics -SmPC) were collected, standardized as technical and popular terms, and translated in 11 languages of the EU. [6]

3.1.3 A classification for medical education and patient product information

Selected lists of drug classes for specific purposes, such as drug information, medical education and computerized decision support have been created.

In the Netherlands, a selected list of drug names was created to support an electronic platform (https://www.pscribe.nl/en-GB/Entrance/Home/Index)[7] for pharmacotherapy teaching, according to WHO standards of rational prescribing. On this platform, clinical cases are created by and shared among teachers in pharmacology to medical students and pharmacy students.[8] The clinical cases are limited to frequent and important clinical issues in primary care. In the list of educational objectives of the curriculum this list of clinical problems in primary care is explicitly mentioned[9]. For each clinical problem on the list a fixed list of drug classes suitable for treatment has been selected, and within each drug class, a limited number of active substances (connected to the available national product list) are selected, to be known in graduate medical education.

The selected drug classes are ordered in a hierarchy of 5 levels, which contains 19 general chapters, 103 second level terms, 196 third level terms, and 58 fourth level terms (see Annex 1). Hence, this classification contains 386 grouping concepts (9 terms used more than one time) in maximum 4 levels of hierarchy, leading to 1600 active substances, still a formidable challenge for medical students and students in pharmacy to master.

At the fifth level, the level of the active substance, ATC codes Level V were listed 1620 times in this classification, covering almost all Medicinal Products on the market of the Netherlands and Belgium. Of these ATC Codes, 1563 were unique (hence 57 listed more than one time in the classification). In 265 occurrences, there was more than one ATC code for the active substance, or a different Route of administration for the same substance.

[4] https://www.usp.org/health-quality-safety/usp-drug-classification-system

[5] Nelson SD, Parker J, Lario R, Winnenburg R, Erlbaum MS, Lincoln MJ, Bodenreider O. Interoperability of medication Classification Systems: Lessons Learned Mapping Established Pharmacologic Classes (EPCs) to SNOMED CT. Stud Health Technol Inform. 2017;245:920-924.

[6] https://searchworks.stanford.edu/view/4079735

[7] Keijsers CJ, Segers WS, de Wildt DJ, Brouwers JR, Keijsers L, Jansen PA. Implementation of the WHO-6-step method in the medical curriculum to improve pharmacology knowledge and pharmacotherapy skills. Br J Clin Pharmacol. 2015 Jun;79(6):896-906

[8] Van Doorn ABD, den Otter AR, Janssen GJA, Middel LJ, Bijl GK, Bijl PP, de Waard-Siebinga I, Vander Stichele R, de Vries ThPGM, Henning RH. Pscribe: a Pharmacotherapy E-learning Web-application enabling registration and mapping of the rational drug-choice process of students and experts, Clinical Therapeutics, 2015:37(8) Suppl: e46

[9] Urushibara-Miyachi Y, Kikukawa M, Ikusaka M, Otaki J, Nishigori H. Lists of potential diagnoses that final-year medical students need to consider: a modified Delphi study. BMC Med Educ. 2021 Apr 23;21(1):234.

In this simple taxonomy, suitable for medical education and for navigation in drug information, the number of hierarchical levels is the same than in the ATC classification, but more clinically oriented, with multiple (more than one) entries possible for some lower-level terms, and many second and third level terms that are not further specified.

The Drug Class entries in this classification have been translated in English, Greek and Italian for the purpose of the work on Patient Facing Apps in Task T8.3. These entries are transferrable to a Terminological Markup Framework Multilingual Technology (ISO/CEN Terminological Markup Format, ISO 16642).[10]

3.1.4 Other examples

Finally, examples exist where complicated drug classes have been formally expressed as listings of corresponding ATC codes at the fifth level of the ATC (the level of the substance).

One example is the class of anticholinergic drugs, with examples in many therapeutic indications, either deliberately used for their anticholinergic effect, or related to anticholinergic side-effects. One such example is the international Duran List, labelling a thorough selection of 100 anticholinergic substances (50 with strong and 50 with weak effect)[11]

Another example is the operationalization of validated international lists of explicit criteria for (in)appropriate prescribing based on Beers List, STOPP/START and EU-7 PIM list. The substances and drug classes mentioned in these lists were all defined in terms of ATC V codes or combination of codes. (See Annex 2).

Recently, a systematic analysis of drug brand names in FAERS was conducted, with linking to the active ingredient and to the ATC classification.[12]

3.1.5 Standardized drug groups (SDGs)

Finally, the WHO collaborating Centre for Pharmacovigilance, the Uppsala Monitoring Centre (UMC) has produced the Standardized Drug Groups (SDGs),[13] defined as any grouping of medicines having one or several properties in common. These Groups are defined in standardized WHO Drug terminology for substances (linked to the variants), and in terms of ATC level V codes.

[10] Federica Vezzani, Giorgio Maria Di Nunzio. Multilingual digital terminology: Introduction to the special issue. Digital Scholarship in the Humanities, Volume 38, Issue Supplement_1, June 2023, Pages i1–i5, https://doi.org/10.1093/llc/fqad028

[11] Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. Eur J Clin Pharmacol. 2013 Jul;69(7):1485-96.

[12] Fusaroli M, Giunchi V, Battini V, Puligheddu S, Khouri C, Carnovale C, Raschi E, Poluzzi E. Enhancing Transparency in Defining Studied Drugs: The Open-Source Living DiAna Dictionary for Standardizing Drug Names in the FAERS. Drug Saf. 2024 Mar;47(3):271-284.

[13] Lagerlund O, Strese S, Fladvad M, Lindquist M. WHODrug: A Global, Validated and Updated Dictionary for Medicinal Information. Ther Innov Regul Sci. 2020 Sep;54(5):1116-1122..

Standardised Drug Groups in WHODrug Terminology	
1. Analgesia producing opoids	24. Drugs interacting with CYP2C19
2. Antiangiogenic drugs	25. Drugs interacting with CYP2C8
3. Antiarrhythmics	26. Drugs interacting with CYP2C9
4. Antidepressants	27. Drugs interacting with CYP2D6
5. Antiemetics and antinauseants	28. Drugs interacting with CYP2E1
6. Antihaemorrhagic drugs	29. Drugs interacting with CYP3A
7. Antihistamines	30. Drugs interacting with OATP
8. Antihypertensives	31. Drugs interacting with P-glycoprotein (P-gp)
9. Antithrombotic drugs	32. Drugs interacting with UGT
10. Benzodiazepines	33. Drugs used in diabetes
11. Blood and related drugs	34. Drugs used in pain therapies
12. Corticosteroids	35. Essential fatty acids
13. Disease-modifying antirheumatic drugs (DMARDs)	36. Hormone replacement therapy
14. Diuretics	37. Immunomodulators
15. Drugs acting on gonadotropin-releasing hormone (GnRH) receptors	38. Monoclonal antibodies
16. Drugs acting on NMDA receptors	39. Nonsteroidal anti-inflammatory drugs (NSAIDs)
17. Drugs for gastric acid related disorders	40. Phosphodiesterase (PDE) inhibitors
18. Drugs for obstructive airway diseases	41. Psychoanaleptics
19. Drugs for ulcerative colitis	42. Radiopharmaceuticals
20. Drugs interacting with BCRP	43. Statins
21. Drugs interacting with CYP1A2	44. Systemic anti-infectives
22. Drugs interacting with CYP2A6	45. Vaccines
23. Drugs interacting with CYP2B6	

Figure 1. WHO Standardised Drug Groups (SDGs)

All these different approaches to drug grouping can be connected to the ATC classification, and from there to National Drug Dictionaries, who very often code all their medicinal products using this classification. This link to the medicinal products is a crude link, based on substance, and does not take into account granular dose form and strength, although for a number of substances, the ATC Classification assigns more than one Route of Administration, with sometimes different ATC codes. IDMP is expected to be instrumental to add more precision and robustness to this linking.

Linked Activity 1: Drug Classifications

3.2 Methodology for linking International Drug Classifications to National Medicinal Products

3.2.1 From national medicinal product pack to global pharmaceutical product

Discussion on the concept of Medicinal Product Pack

In most developed countries, medicinal products are distributed in discrete packs (outer package), containing an inner package, enclosing the manufactured item, and the written drug information as a folded leaflet. This is in contrast with bulk dispensing where medicinal products are present in the pharmacies in large containers and dispensed to the patient in a white paper bag or orange plastic bottle, with a written posology instruction (e.g.to be taken twice a day).

In 2002, the European Union, including the United Kingdom, moved from bulk dispensing (pills in large containers shipped to the pharmacy and then dispensed in white paper bags) fto unit-of-use distribution (with an outer package, containing an inner package, the manufactured items, and a User Leaflet in the

package. The requirement of a user leaflet in understandable language for the public is an example of a legal obligation for an industry to communicate with the customer in an understandable way.

In most countries with unit-of-use distribution of medicinal products, each package has its own number (as such and/or represented by a barcode). This number can originate from the distribution sector, from the marketing research sector, or from the regulatory authorities. It is to be distinguished from the GTIN number, which is a number given by the industry, and related to the specific combination of inner package and manufactured Item. There is also the batch number, from the industry, allowing back tracing to the production process. In addition, there can also be serialisation numbers (unique number per pack as 2D barcodes, to check against Falsified Medicinal Products.

Most Medicinal Product Dictionaries, whether maintained by the regulatory authorities, the pharmacists unions, the software vendors, independent drug information centres, the industry, or private publishers will list the National Drug Code, identifying each individual pack. The number is unique and identifies the company marketing the product, the substances (combinations of active and inactive ingredients), the dose form, the type of pack, the pack size. There are national rules which need to be applied when a National Drug Code needs to change when variations of any of these elements occur.

In some less developed countries, it could occur that the national drug code from the distribution sector is not be known by the regulator or by the Medicinal Product Dictionary publisher, because of a lack of communication between systems.

In the drug models, explained in WP9 (D9.1), this lowest concept of identification is named the Actual Medicinal Product Package (AMPP). There may be subtle differences in the delineation of this concept in each country depending on whether differences in pack type or manufactured items are taken into consideration. It is at this level that the IDMP ontology provides the PCID, to be constructed and maintained by rules that are common to all countries. The lifecycle and rules that govern the updating of these concepts may show subtle differences.

Commented [LN2]: First time mentioned thus full name

In some countries, this concept is defined by the mathematical pack size (number of tablets in a pack in case of presentation strength or total volume of a syrup in case of concentration strength). In other countries, the type of package will also be taken into account and then the NDC will differ for a pack with 5 blisters of 6 tablets, and a pack of 6 blisters of 5 tablets, both with a pack size of 30), In the USA, the NDC will even differ when the same medicinal product is allowed to be marketed with two different manufactured items (e.g. grey oval tablets or white round tablets, coming from two different generic bulk manufactures), a situation that will not or seldom occur in Europe.

Commented [LN3]: Full name please

For the description of the pack, which is the level of the record in a database, it is important to have a unique ID (a primary key). However, the nature of this primary key can differ country by county (taking into account or not taking into account small differences in pack type or manufactured item).

For comparison between countries, it is therefore important to precisely identify a comparable concept for pack (AMPP) that is based solely on the mathematical pack size, ignoring differences in pack type. The issue of pack type is not an issue of great clinical relevance and does not or very seldomly play a role in the drug choice process of the physician.

Discussion on the concept of Medicinal Product

A Medicinal Product is a concept which aims at the aggregation of medicinal product packs, with the same marketing company, the same substance(s), the same dose form, and the same strength, within the jurisdiction of a national marketing authorisation authority.

In IDMP the substance must be specified if a modifier is present. The dose form must be termed from the value set of the granular EDQM dose form terminology. The strength must be normalised according to agreed business rules (e.g. a choice to be made between a gel of 3%;100 ml gel with 3 grams substance; or a gel of 30 mg/ml). These business rules for normalisation of the expression of strength are complicated, depending on the pattern of dose form, and still debated with the partners of the GIDWG (Global IDMP Working Group), under the leadership of the WHO.

In the Drug Models this concept would be called the Actual Medicinal Product concept (AMP). In IDMP ontology the concept is the Medicinal Product, with again universal rules to build and maintain the Medicinal Product ID (MPID).

The labelling of the different packages aggregated under this concept may or may not be the same for all packages. Sometimes small packages with a low strength may have different indications and different labelling.

Determining the characteristics of a company is not always easy, as there are many differences: multinational company, regional subsidiary, national company, manufacturer, distributer, re-packager, etc. One can focus on the national marketing authorization holder. These names are not always standardised. For example in the US database RxNorm, where the information is entered by the company at the moment of an application for a new National Drug Code, the company name may be misspelled and this will be propagated throughout the concept tree, and may hamper the correct creation of the concept of medicinal product. In Europe, with the provision of centralised SPOR Terminology Services for organisations (the Organisation Management System OMS) this problem can be minimised.

Discussion on the concept of Actual Therapeutic Moiety

An actual therapeutic moiety is an aggregation of medicinal products, marketed by the same company and with the same substance(s).

The label in the country is usually a phantasy brand name without the company name (e.g. Tenormin®) or with the company name (e.g. Norvasc® Pfizer®). In case of generics, the label consists of the generic substance name + the company name (e.g. simvastatin TEVA® or amlodipine Sandoz®).

Linguistic similarity between these brand name labels in different countries do not necessarily mean that the products in these countries are identical.

The marketing authorisation and the link to the official label can be on this level, but also be more specific on lower levels, depending on the medicinal product.

Discussion on the concept of Pharmaceutical Product

Description of the concept

In the IDMP architecture the Pharmaceutical Product is a concept subordinated to Medicinal Product.

It is the global representation of the elements in a Medicinal Product that are not country-specific or company-specific.

The Pharmaceutical Product Set is the combination of 3 elements.

- Substance (with modifier if any)
- Administrable dose form (granular value set of EDQM)
- Strength (normalised by business rules)

As such it is a concept that groups all medicinal products from different countries that carry these 3 elements, and will be identified by a global Identifier: the PhPID.

Four levels are distinguished for different combinations between these 3 elements:

- PhPID Level IV : Substance + dose form + strength
- PhPID Level III : Substance + dose form
- PhPID Level II : Substance + strength
- PhPID Level I : Substance

PhPID Level I is a concept that binds all actual therapeutic moieties with the same substance (+ modifier if any) from any country.

PhPID Level IV is the full global representation of the essence of any national medicinal product from any country.

Figure 2 provides a summary of the concepts and their relationships.

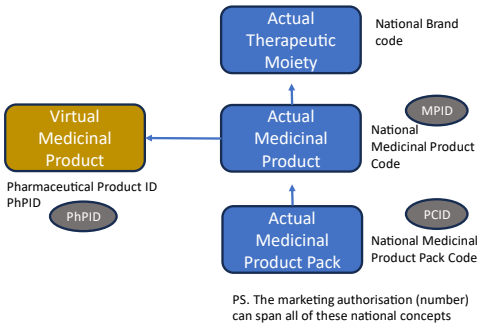

Figure 2. Actual and Virtual concepts

In figure 3, this is illustrated by a concrete medicinal product:

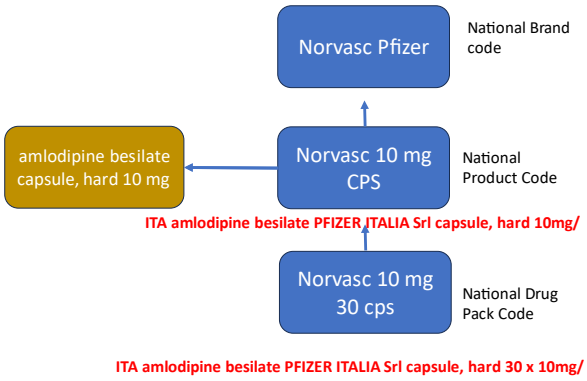

Figure 3. Example of a Medicinal Product

Creation of the global identifier

The debate is still raging on the level of granularity that is needed for the creation of the PhPID.

The most strict and granular definition is the one mentioned above: substance (with modifier if any); granular EDQM dose form; strength (normalised according to business rules).

But several alternatives have been proposed, based on relaxing the obligation to explicitly name the modifier for the substance, if any, and considering less granular value sets for the dose forms.

The argument is that for regions outside Europe the attribution of the granular administrable EDQM dose formis too difficult, too cumbersome, and too error prone. An aggregation is proposed based on the unique combinations of 4 characteristics of the administrable dose form (basic dose form, method of administration, release-characteristics, intended site).

This proposal has been explored in depth in an analysis of the EDQM terminology and the results of this analysis have been published[14]. In the conclusions of this research, it was clearly stated that the mechanical grouping based on unique combinations of these characteristics was not always creating distinct, clinically relevant groups. Many groups needed to be concatenated or split. The level of granularity proves to become similar to the granularity of RxNorm, but insufficient for clear distinction.

Within the context of the work in the GIDWG working group, however, this proposal is still sufficient, under impulse of the FDA and the non-European Regions of the WHO.

For the normalisation of strength, a global solution seems however to be in the making, based on business rules for strength expression according to patterns of dose form. These business rules provide guidance on which dose forms must be expressed in presentation strength and which dose forms in concentration strength. In addition, the rules indicate the right choice for various ways to express concentration in percentage, as weight over volume (125 mg/5ml), or as a true concentration (25mg/ml).

In figure 4, it is indicated how the expression 50 units/ml is transformed in codes to be fed into the algoritm, creating the PhPID.

[14] 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

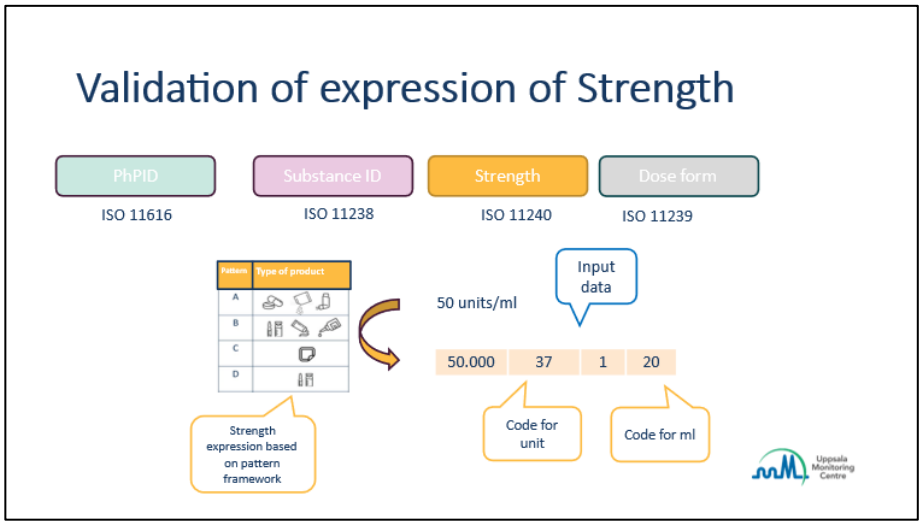

Figure 4. Expression of strength and patterns of dose form

The choices made for the granularity in the representation of those 3 elements (substance, dose form, strength) has of course a direct impact on the resulting global identifier.

	Substance	Dose form	Normalized Strength*
Method 1	Moiety+modifier	Granular EDQM ADF	GIDWG
Method 2	Moiety+modifier	Unique Combinations EDQM Characteristics	GIDWG
Method 3	Moiety	Granular EDQM ADF	GIDWG
Method 4	Moiety	Unique Combinations EDQM Characteristics	GIDWG

*Normalized strength according to the business rules elaborated by the GIDWG (EMA, FDA, WHO_UMC, ...)

Figure 5. Methods for PhPID Definition

The decision to opt for one of these methods has a direct impact on the workload related to the legacy conversion of older medicinal products to IDMP and on the maintenance of the identification process. But it has also important consequences in terms of granularity and precision.

It can be argued that if IDMP wants to make a difference as a system for medicinal Product Identification, the emphasis should be on precision, and hence the first method should be preferred.

This method of producing PhPID with a high level of granularity and precision creates the rock-solid foundation for precision in medicinal product identification and for the solid building of higher levels of aggregation that might be more clinically relevant.

Coding issues

Substances are currently coded in Europe through the EU-SRS, with output to the NCAs through the SMS SPOR services. The cleansing of this database has been a tremendous work, conducted in collaboration with the US Food and Drug Administration, and with the vision to promote a Global Substance Identifier (GSID), both for the moiety and for the moiety+modifier.

For the dose form, based on EDQM terminology, there are codes proper to EDQM, but the SPOR Services create a new coding system for each value in the EDQM value sets, with an automatic mapping between both.

This SPOR code is available to NCAs through the EMA portal but may be more difficult to access by other stakeholders. Mapping lists between the term labels and the two coding systems can be easily provided. However, a decision is to be made on which of the two codes will be fed into the PhPID creating algorithm.

On a global scale, in the GIDWG, the tendency is to work with the original EDQM Code. EMA is more inclined to work with the equivalent SPOR code.

Again, this choice of code systems to be fed in the algoritm for creation of PhPIDs can lead to different numbers, depending on the choice made.

Governance

It is obvious that the creation and maintenance of a coding system such as PhPID will require a lot of coordination. The WHO CC for Pharmaco-vigilance Uppsala Monitoring Centre (UMC) has volunteered to take up the role of keeping a repository of PhPIDs and coordinate the consistency and maintenance rules for this endeavour.

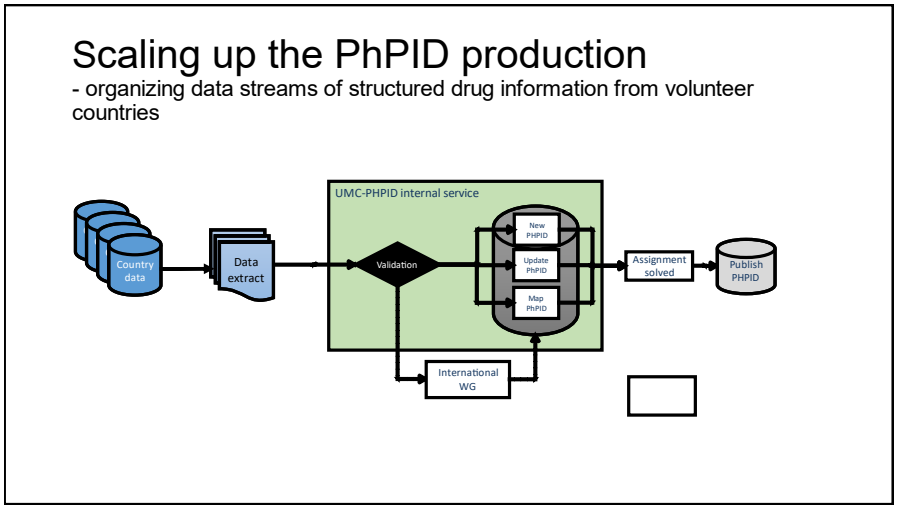

Figure 6. Proposed WHO/UMC/PhPID Repository

However, some National Competent Authorities in Europe claim that the rules for the production of PhPID can be formulated in a simple way, and that the responsibility for producing PhPIDs can be kept at the national level, with consistent results, and possibly with some international curating method.

Discussion on the advantages of granularity in IDMP in defining the Pharmaceutical Product

For the creation of substitution rules in cross-border exchange of ePrescriptions and the medication lists in the International Patient Summary, the granular description of the administrable dose form and the naming of the modifier for the active ingredient of a medicinal product provides a more solid basis to decide by which national medicinal product a medicinal product from another EU country can be substituted.

The same is true for conducting cross-national comparisons of the extent and variability of national medicinal product dictionaries, and for conducting detailed price comparisons and comparisons of the reimbursement rules, which can vary by substance modifier, dose form, and pack size.

For pharmaco-epidemiology research, it is important that the information on drug exposure can be interpreted at a granular level. Safety profiles of products can be influenced by subtle differences in dose form or modifiers of active ingredients. In D8.4 of UNICOM, a protocol is described for a study comparing the cardiovascular side effects of diclofenac sodium with diclofenac potassium.

Finally, for clinical reasons, the details on the granularity of dose forms or the modifier of active substance may not always be of relevance. However, to build in a robust way clinical meaningful aggregation concepts for prescribing by international non-proprietary name (INN prescribing) it is necessary to start from a precise and global description of the national medicinal products, made possible by the implementation of IDMP standards.

IDMP implementation for new and older medicinal products

For new medicinal products evaluated by EMA in the Centralized Authorisation Procedure (CAP), IDMP compliance will be guaranteed thanks to the introduction of the Product Management Service (PMS) and the creation of the electronic application form (eAF). Currently this is still work in progress, as only variations are considered by now.

By contrast, for the older medicinal products, and for Decentralized Procedures (DCP) the national NCAs face the formidable task to convert the description of these products to the new IDMP standards. National medicinal Dictionaries contain easily between 8.000 to 15.000 Medicinal product packs per country. And there are 27 Member States.

Hence, this legacy conversion is a formidable task. For very old medicinal products, the existing labelling may lack some of the essential information such as the nature of a salt or ester (modifier) of the active ingredient (moiety). Digging up such information has been labelled with the term „pharmaco-archaeology“.

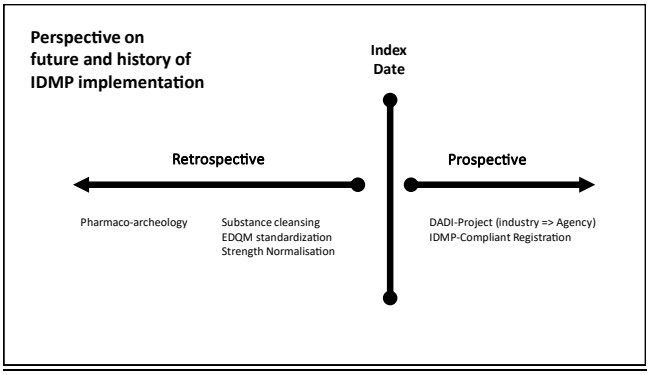

Figure 7. Legacy conversion versus prospective implementation

Discussion on the relationship with other virtual drug schemes

In this project, we have explored the relationship between IDMP Pharmaceutical Product concept and the virtual drug models of RxNorm and SNOMED CT.[15]

In the US, RxNorm, produced by the National Library of Medicine, the concept that is most closely related to the PhPID is the concept “Clinical Drug“. However, this concept is built upon the active moiety of the molecule with therapeutic effect, without the modifier (salt of ester). Although this information is present in the RxNorm system, it is not used for the construction of the concept of “Clinical Drug“. In addition, for dose form, another building block of the concept, the terminology of dose form from RxNorm is used, which is much less granular then the EDQM dose forms, and without the formalized definitions, descriptors, and characteristics. The expression of strength might be decided by companies during the application for a National Drug Code, and might not always be normalised between companies.

[15] 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.

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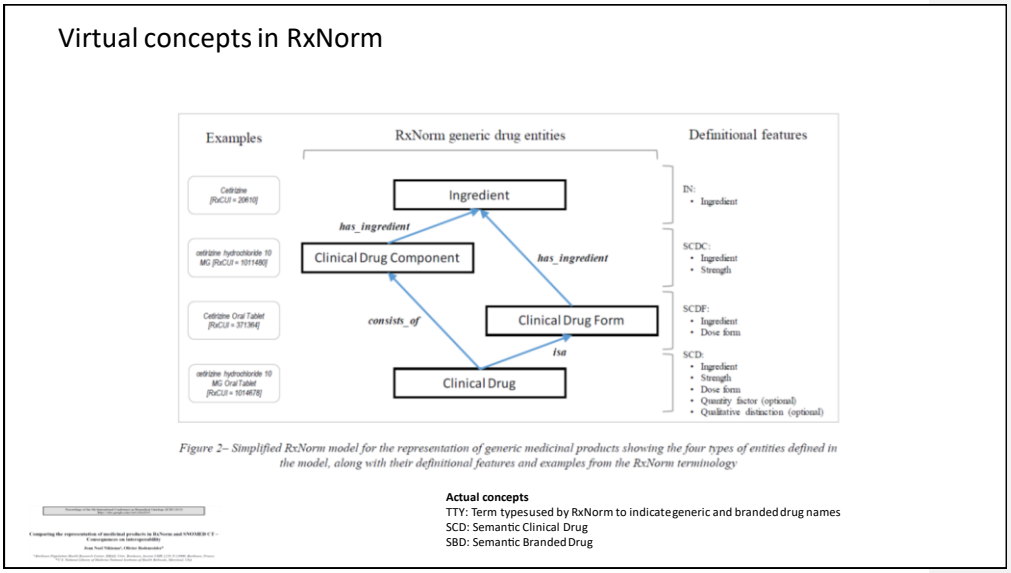

Figure 8. RxNorm Virtual drug concepts

For the virtual drug model of SNOMED-CT, there is a concept that is very close to the concept of Pharmaceutical Product in IDMP, also named „Clinical Drug“. Here the substance with the role of Precise Active Ingredient (PAI) is explicitly used (hence, moiety+modifier, if any). So, that is very similar to IDMP PhPID. For the dose form, a value set for pharmaceutical dose forms is used. This value set is a bit smaller and slightly different (more pragmatic ?) than the value set of EDQM pharmaceutical dose forms. To define the concept SNOMED-CT uses the manufactured dose form, which describe the product before it is transformed in an administrable dose form (e.g. powder for oral solution“, transformed to „oral solution“). In IDMP, as a rule, the PhPID should be constructed based on the administrable dose form (hence, after transformation of the product, if any transformation occurs).

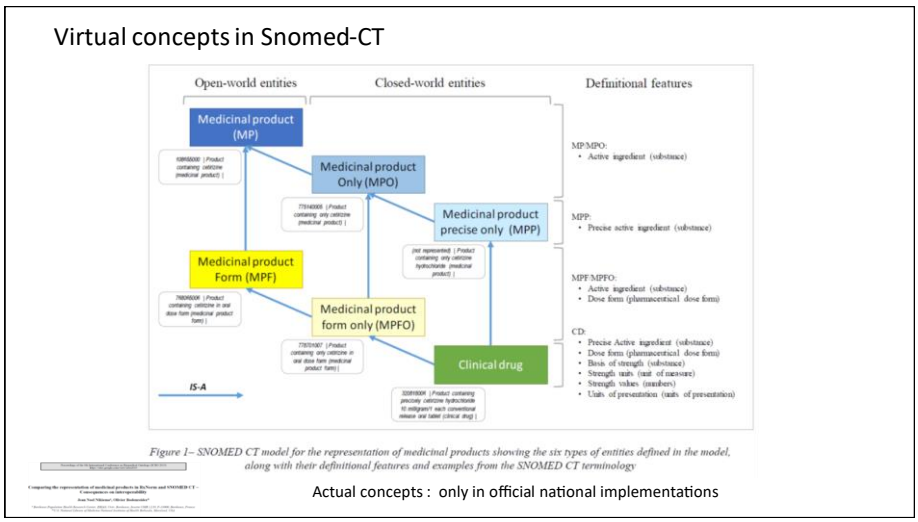

Figure 9. SNOMED-CT virtual concepts

The two latter illustrations were taken from a comparison between the virtual models of RxNorm and SNOMED CT.[16] Note, that the SNOMED-CT concept “Medicinal Product” (similar to the concept “Virtual Therapeutic Moiety in Dm+D) has a different meaning than the IDMP concept of “Medicinal Product” (similar to the concept “Actual Medicinal Product” in Dm+d and Belgian SAM database).

In the Belgian Authentic Source of Medicines (SAM database - an open source Medicinal Product Dictionary commonly constructed by several public Partners)17 and in the UK „Dictionary of Medicines and Devices“ (DM+D)18 the concept of Virtual Medicinal Product has the closest correspondence with the IDMP Pharmaceutical Product, but without EU-SMS coding of the substances, and with the use of national value sets of dose form.

3.2.2 From global pharmaceutical product to the ATC level V class

As mentioned above, the WHO Collaborating Centre for Pharmacovigilance (Uppsala Monitoring Centre UMC) is planning the production and maintenance of Pharmaceutical Product identifiers (PhPIDs).

National Medicinal Products Dictionaries, once standardised to IDMP, can link to this International Register and check the correctness of their choice of the 3 main constituents of the Pharmaceutical Product and the corresponding code (PhPID).

On the other hand, most National Medicinal Product Registers are also linked to the ATC classification, often with attribution to each medicinal product of an ATC-Code Level V (the level of substance or combination of substances), the ATC Route of Administration, the choice of the Defined Daily Dose

[16] Noel Nikiema J, Bodenreider O. Comparing the representation of medicinal products in RxNorm and SNOMED CT - Consequences on interoperability. CEUR Workshop Proc. 2019 Aug;2931:F1-F6.

[17] https://www.samportal.be/fr/sam

[18] https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/dictionary-medicines-and-devices-dmd

(DDD). For each Medicinal Product Pack a calculation of the number “Defined Daily Doses per Package (DPP)” may be available for purposes of Drug Utilisation Research.

Linkage from ATC to other Systems

Links between ATC classification have been realised since long with the US RxNorm system[19,20] and Medical Subject Headings (MeSH)[21], and the British National Formulary.[22]

There is no formal map between ATC and SNOMED CT yet but this can be constructed using indirect methods.[23]

The WHO Collaborating Centre for Drug Statistics Methodology in Oslo has recently started a project aiming at universal access to the ATC classification with API methodology. The API has 6-7 so called endpoints. During the current year the centre will manage to make available at least one and at best 3 of these API end points. The first one will be the alterations from the previous year[24].

Linkage from ATC to IDMP

The principle is to create a link between the ATC Level V codes of the 14 chapters of the ATC classification and the PhPID repository. Both Source and Target are maintained by two independent organisations related to the World Health Organisation.

The creation and the maintenance of a mapping between ATC and PhPID could be performed by an international Consortium and facilitated by making use of the structural power of IDMP, the cleansed databases for substance, and EDQM.

[19] Bodenreider O, Rodriguez LM. Analyzing U.S. prescription lists with RxNorm and the ATC/DDD Index. AMIA Annu Symp Proc. 2014 Nov 14;2014:297-306.

[20] Ostropolets A, Talapova P, De Wilde M, Abedtash H, Rijnbeek P, Reich CG. A High-Fidelity Combined ATC-Rxnorm Drug Hierarchy for Large-Scale Observational Research. Stud Health Technol Inform. 2024 Jan 25;310:53-57

[21] https://ceur-ws.org/Vol-1061/Paper5_vdos2013.pdf

[22] https://assets.researchsquare.com/files/rs-1858694/v1_covered.pdf?c=1658259381

[23] https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=87d565031a39e8f9aa4ff83ea018ae9673de0b88

[24] Personal Communication from Mohammad Nouri Sharikabad, director of WHO CC DSM, Oslo, Norway

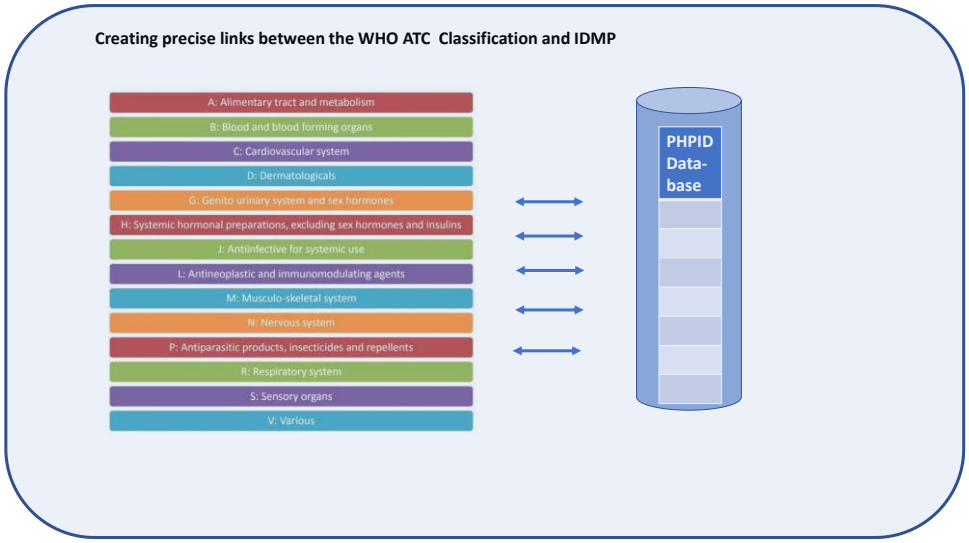

Figure 10. Linking ATC to PhPID

The corner stones for such a linking effort will be an ontology of substances, an ontology of dose forms, and the normalisation of strength.

These 3 elements will first be discussed briefly, as they provide crucial steps in the gradual aggregation of the granular PhPID (defined by substance with the role of the Precise active ingredient (PAI), granular administrable dose form, and normalised strength to the high-level concept of the ATC Classification Level V (the level of medicinal products with the same active moiety, regardless of their dose form and strength).

Note: The ATC classification assigns for some substances a different ATC code depending on Route of Administrationor strength.

In the next chapter, the creation of an ontology for dose form will be discussed more extensively.

The need for an ontology of substances

There has been a global effort to cleanse the substance databases from the EU (SMS) and the US (FDA), and to produce a global Substance identifier for both Moiety and moiety+modifier, if any. This has extensively been reported in the published working papers of Unicom WP2.

Hence it becomes possible to create a simple hierarchy of substances, clearly separating three concepts:

1. The active moiety of a substance
   e.g. amlodipine[-]
2. The substance with the role of Precise Active Ingredient (PAI) (moiety modifier, if any)
   e.g. amlodipine besilate
3. The grouper of substances with the same active moiety
   e.g. amlodipine (a name for the collection of the substances with the role of precise active ingredient: amlodipine besilate, amlodipine mesilate, amlodipine maleate).

Note: for the first two levels, a different code for each of these concepts is available in the existing coding systems (WHODRUG, SMS, UNII, CAS, SNOMED-CT).

	WHODrug	SMS	UNII	CAS	SNOMED-CT
amlodipine[-]	00972401001	100000085259	1J444QC288	88150-42-9	386864001
amlodipine besilate	00972402001	100000090079	864V2Q084H	111470-99-6	84976003

Figure 11. Moiety and moiety+modifier codes

For the concept of *grouper of substances* with the same active moiety there is currently no international coding system, a situation which should be remediated. This concept could include groupers of combinations of substances with the same active moiety.

The intention to include this element of hierarchy in the structure of the EU-SMS database and in its output through the SMS SPOR services has been repeatedly expressed during the UNICOM project. Furthermore, we stressed the importance to make the resource available to external parties. Some progress has been made in this respect but there are not yet clear milestones for both the alignment with SPOR and availability for third parties.

It has been estimated that one third of the chemical substances has no modifier, and on third only exists with one modifier. The remaining substances can either exist as a moiety with a moiety, and have one or more possible modifiers, or have two or more modifiers, whose presence is mandatory. In this latter remaining group of substances, specific inquiries must be undertaken to decide which of the modifier needs to be chosen for a specific medicinal product. For older products this information may not be present in the labelling, and to get that information will require considerable research in the archives of either the regulatory agency or the original manufacturer (if still existing). It is an element that potentially can put a lot of burden on the legacy conversion process, and some may doubt the clinical relevance of this effort, which is nevertheless needed for the sake of consistency of the IDMP implementation process. Assistance from the industry taking advantage of the new electronic and IDMP compliant variation application process could be crucial for solving this issue. Agencies could require a variation (change of the labelling) in case this information is missing.

Commented [LN4]: ??

Note : In IDMP the PhPID Level 1 could serve as a *grouper of medicinal products* (not substances) with the same substance with the role of PAI (PhPID L1 amlodipine besilate: the global representation of all products with amlodipine besilate).

Currently there is in IDMP no *grouper of medicinal products* with the same active moiety (e.g. amlodipine), representing all medicinal products with amlodipine as active moiety. This role is partly taken up by the ATC classification, but with some limitations regarding products with

combinations of substances. A solution for this limitation should thus be found in an elaboration of the concept of Virtual Therapeutic Moiety (VMP).

The need for an ontology of Dose Form

In each country, the medicinal product dictionary uses a national value set of dose forms (often including information on split ability).

Implementation of IDMP requires standardisation of these national value sets to the EDQM standard terms for dose form. This standardized value set can then replace, but most probably be added to the national value set.

This crucial process of standardisation will be discussed in the next chapter.

IDMP requires to provide for every national medicinal product the granular administrable dose form.

At supranational level, it was decided that EDQM should be used for this by the International Council of Harmonisation, grouping the regulatory agencies of Europe, the USA, and Japan.[25]

Commented [LN5]: How to explain the different position of FDA in GDWIG then ? Context of use ?

Very often in the regulatory domain, the drug labelling uses the terminology of the manufactured dose form. That is the dose form associated to the medicinal product delivered by the producing company to the pharmacy. In some cases, that manufactured dose form needs to be transformed by the pharmacist (or the patient) to an administrable dose form. A simple example would be “powder for syrup, transformed to “syrup“. A more complicated example is “powder for a concentrate for dispersion for injection (Cominraty Pfizer/Biontech : the first Covid-19 vaccine), transformed in two steps to “dispersion for injection.“

Once the granular administrable dose form for a specific national medicinal product has been determined by choosing the right EDQM label and code (and subsequently the right EU-SPOR code from the Refererntials Management system (RMS), additional inherent information becomes available from the EDQM databases.

Besides a formal definition of each value in the EDQM dataset, there are 2 descriptors (Basic Dose Form, State of Matter) and 4 characteristics (Transformation Method, Release Characteristics, Method of Administration, and Intended Site), proper to each dose form.

Currently there are 3 types of pharmaceutical forms:

PDF: Pharmaceutical Dose Forms

443 current values (all of them can be manufactured dose forms, and 305 are administrable, as such or after transformation)

CDF: Combined Pharmaceutical Dose Form

66 values (all of which include 2 or more manufactured dose forms to be transformed to an administrable form)

CMT: Combined terms

73 values (65 pharmaceutical dose forms (60 administrable) and 8 combined pharmaceutical dose forms, each in combination with a container or administration device)

[25] https://www.ema.europa.eu/en/documents/other/mandatory-use-iso-icsrich-e2br3-and-edqm-terminology-dosage-forms-df-and-routes-administration-roa_en.pdf

SNOMED-CT works with pharmaceutical dose forms and the value set is slightly less than 400. The same apparatus of descriptors and characteristics is present in the system, albeit with slightly different value sets. This should come as no surprise because EDQM dose terms and SNOMED CT dose terms both follow the logic of the ISO/CEN standard EN ISO 11239 on Pharmaceutical Dose Forms.

RxNorm has a much lower level of granularity with a value set of dose forms not exceeding 200; no distinction between manufactured dose form and administrable dose form is made, and there is a limited aggregation in dose form groups.

There is a formal mapping from SNOMED-CT dose forms to EDQM dose forms, initiated in the UNICOM project[26]. The mapping of EDQM Dose Forms to SNOMED CT is based on March 2023 EDQM version and January 2023 International Edition of SNOMED CT. Individual mapping from EDQM to SNOMED terms were classified as "Equivalent", "Narrower than", or "Broader than". The successful mapping rate was estimated to be 60%.

There was no mapping attempt in the opposite direction, from SNOMED-CT to EDQM dose form terms.

RxNorm has been connected to the SNOMED virtual Drug model, including for dose forms. It has however been acknowledged that more work is needed to align the dose forms of RxNorm and SNOMED-CT.[27]

An attempt was made during the UNICOM project to align the EDQM dose forms with RxNorm dose forms, illustrating the less precise value set of RxNorm.[28] The preceding development of the ontology of EDQM dose forms (which is detailed in the next chapter) was crucial for this alignment process.

A similar attempt could be made to align also with the dose forms of SNOMED-CT.

Four limitations of the EDQM terminology were observed during this work.

- EDQM (and IDMP) does not work with the property of “splitability” for several solid oral dose forms, such as tablets or capsules that can be split in two (divules). Hence, standardisation leads here to some loss of information, illustrating the continued need for national information, added by the National Agency or the National Medicinal Product Dictionary.
- The notion of systemic effect of the dose form is not acknowledged. While this may be an attribute to be given at the level of the medicinal product (e.g. nasal sprays with local effect, and nasal sprays with systemic effects), it is probably possible to assign to most of the dose forms the notion of “systemic effect“, “local effect“, leaving a few dose forms without the label ”unclear effect“.
- The issue of splitable, crushable, and mixable dose forms is not considered by EDQM, as this may be properties that vary at the product level. However, these issues can be important for drug safety[29]. Maintenance of this information is currently at the national level, either in medicinal product dictionaries or in hospital pharmacy systems.
- In the EDQM system, for each Pharmaceutical Dose form that can (or must) be transformed, the nature of the transformation process is described in a characteristic (transformation). The result of that process, the administrable dose form, is not formally described. Although this is often obvious it is not always the case.
  The EDQM organisation reacted positively to this remark and prepared a formal file where for all Pharmaceutical Dose form the administrable dose form, resulting from a transformation process is given. A first draft was recently updated, with the intention to continue the updating process (see Annex 3).

[26] https://confluence.ihtsdotools.org/display/USRG/Mapping+Guidance+for+EDQM+to+SNOMED+CT+Pharmaceutical+Dose+Form+Mapping

[27] Nikiema J, Bodenreider O. Comparing the representation of medicinal products in RxNorm and SNOMED CT - Consequences on interoperability. CEUR Workshop Proc. 2019 Aug;2931:F1-F6.

[28] 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.

[29] Senger C, Seidling HM, Quinzler R, Leser U, Haefeli WE. Design and evaluation of an ontology-based drug application database. Methods Inf Med. 2011;50(3):273-84.

The value set of the Intended Site (characteristic) is rather small (N=27, with some combinations possible), and may be insufficient for the construction of an INN prescribing instruction with substance, a dose form, and strength section. The precision of the EDQM dose forms (N=443) may be, on the one hand, very instrumental for a precise global identification, but, on the other hand, too elaborated for clinical purposes, such as INN prescribing.

Value Set of EDQM Intended Site Characteristic	
Auricular	Nasal
Buccal	Ocular
Cutaneous	Oculonasal
Dental	Oral
Endocervical	Oromucosal
Environmental	Parenteral
Extracorporeal	Pulmonary
Gastric	Rectal
Gastroenteral	Sublingual
Intestinal	Transdermal
Intramammary	Unknown/Miscellaneous
Intraperitoneal	Urethral
Intrauterine	Vaginal
Intravesical	

Figure 12. Value Set of EDQM ISI characteristic

Note: the values "cutaneous/transdermal" and "intravesical/urethral" were split to the separate values - resp. cutaneous and transdermal, and intravesical and urethral - following discussions initiated in UNICOM. Also note the differentiation between oral, buccal, oromucosal, and sublingual.

Finally, we identified a need to create an intermediate level of aggregation for the EDQM dose forms, for the use cases of INN prescribing and the alignment with RxNorm Dose forms.

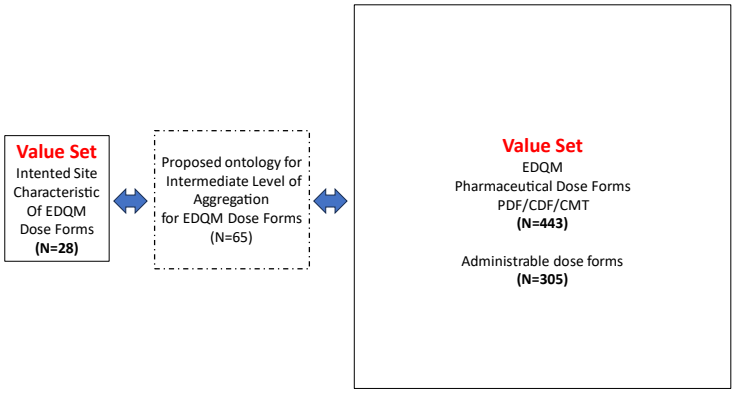

Figure 13. Dose form aggregation

Hence, a draft proposal for such a dose form ontology was elaborated within WP8, based on a thorough analysis of the unique combinations of the characteristics of the dose forms, with their formal definitions (more details in the next chapter).

The result of this work was published as a simple ontology of dose forms in WebProtégé.[30]

This ontology was used for an alignment of EDQM dose forms with RxNorm.[31]

A final validation round with experts within UNICOM is currently under way.

Normalisation of strength

Although the expression of strength may seem to be the least problematic one for constructing a global PhPID, there are several tricky issues which need to be dealt with in IDMP.

National medicinal Products have a strength printed on the outer package. That is the strength expression as authorised by the National Regulatory Authority. For most medicinal products this reference strength is the strength of the moiety (not considering the molecular weight of the salt/ester (modifier)). However, this is not always the case within one specific country and this may differ also between countries. Medical departments of pharmaceutical companies may also have different strategies in this regard, now or in the past.

Hence, IDMP requires to determine the strength of the moiety and the strength of the moiety+modifier. To know the second strength when one strength is known, requires the knowledge of the molecular weight of both instances. One also needs to know to which of the two instances of the molecule the authorized strength refers. And that is often also part of the “pharmaco-archaeology“ process.

Moreover, for each product a choice must be made between a presentation strength and a concentration strength.

For products with presentation strength, only the value and the unit of the numerator need to be known for a specific unit of presentation (that needs to be determined in EDQM terminology). The pack size will in that case refer to the number of units of presentation in the medicinal product pack.

For products with a concentration strength, a numerator value and unit need to be determined and a denominator value and unit The denominator value will be default 1 and not mentioned (e.g. 5mg/ml). Here the numerical pack size will be the total volume or weight of the product e.g. 80ml syrup or 30g dermal gel).

A 3% dermal gel can be expressed as 3 gr per 100ml or 30mg/ml. It is not acceptable to represent these different strengths in different PhPIDs as they are essentially the same.

There is thus a strict need to normalize different expressions of the same strength in a global way.

This is not an easy task and has been the focus of long and intense technical debate on how to express the strength in function of different patterns of dose forms. This debate has been held in the GIDWG (Global IDMP Working Group), with WHO UMC, EU, FDA, with an intense contribution of the Norwegian Agency NOMA, and other stakeholders. Several versions of what is called „business rules for strength expression“ have been edited, and circulated internally, but no official draft has yet been published.

Issues with multi-dose and uni-dose vials, issues with inhalers, dermal products remain to be solved.

It is possible but not guaranteed that a first draft will be made public by the end of the UNICOM project in May 2024.

[30] 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

[31] 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.

Controlling the expression of strength will be one important aspect of the governance role of WHO UMC when establishing the Repository of PhPIDs.

Linking the PhPID to ATC Levvel V through the Virtual Medicinal Product Group

With these 3 elements (specified substance, granular administrable dose form and 2 ontologies) a clinical meaningful stepping stone can be established to link the global representation of national medicinal products (PhPID) to the ATC Classification Level V. Two ontologies can govern a higher level of aggregation: an ontology of substance can aggregate the substance with the role of PAI to the grouper of substances with the same moiety (to be labelled with the INN terminologiy). The EDQM administrable dose form can be aggregated to the value set of the Intended Site Characteristic. The strength expression can remain unchanged in this effort. These 3 aggregated elements will together establish the concept of the Virtual Medicinal Product Group (VMPGroup). And this concept can be linked to the ATC classification Level V, almost always on a one to one badis. We suggest this to be a international academic collaborative effort, in close cooperation with the WHO CC for Drug Statistics in Oslo (global governor of the ATC Classification), and with the WHO CC for Pharmacovigilance (Uppsala Monitoring Centre UMC) (global governor of the PhPID Repository).

Commented [LN6]: Are the 2 ontologies an element ? Maybe components is better

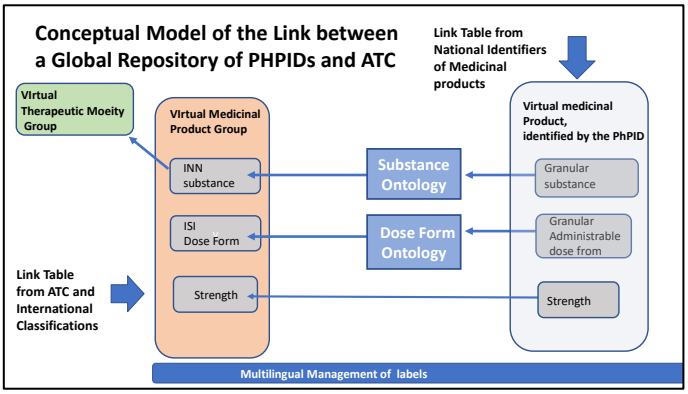

Figure 14. Link from PhPID to ATC

3.2.3 From ATC Level V to Clinical Classifications

When Medicinal Products are linked to the ATC level V they are automatically linked to 4 higher hierarchical classes of this Classification, widely used for Drug Utilisation research.

A	Alimentary tract and metabolism
	(1st level, anatomical main group)
A10	Drugs used in diabetes
	(2nd level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excl. insulins
	(3rd level, pharmacological subgroup)
A10BA	Biguanides
	(4th level, chemical subgroup)
A10BA02	Metformin
	(5th level, chemical substance)

Figure 15. The 5 connected levels of the ATC Classification

In the previous chapter we discussed the link between several international pharmacotherapeutic classifications and the ATC Level V code.

3.2.4 Closing the loop from medicinal product pack to pharmacotherapeutic drug classes

Medicinal product packs in almost all countries bear bear a distinctive national identification code known as the National Drug Code (NDC). This code is unique to each package available in the market and serves to identify authorized packages and distribution units within the supply chain. Functioning as a primary key in the medicinal product dictionary, this code is linked to the medicinal product but may vary depending on the pack size, such as small, larger, or the largest package available. In the United States, the NDC code may vary for each medicinal product, particularly if there are multiple manufacturing options available, for instance, white round pills from an Indian generic provider or oval grey pills from a Chinese provider, both containing the same substance and strength. The regulations governing the life cycle of such a code, such as updating when there is a change of ingredients, may differ in each country.

For clinicians, distinguishing between a pack of 5 blisters with 6 tablets or a package of 6 blisters with 5 tablets may not be relevant, nor the material of the blister, whether it be aluminum or plastic. What matters is the numerical pack size, indicating the quantity of tablets in a package. Moreover, information on pack type is not consistently available from all countries and may only be presented as a text string.

IDMP has a whole set of rules for creating and maintaining PCIDs (Pack control identifiers), which could potentially replace or complement National Drug Codes. However, only a few countries have made significant progress in implementing IDMP to generate PCIDs for all their medicinal product packs.

In this project, we introduced the concept of “medicinal product pack“, defined by the country ISO-3 country code, the marketing authorisation holder, the specified substance, the granular EDQM administrable dose form, the strength (presentation of concentration strength), and, finally, the numerical pack size. This concept facilitates the comparison of the occurrences of this concept across different countries.

Furthermore, we devised the concept of "Medicinal Product," which encompasses the aforementioned elements excluding the numerical packsize. This enables a comparison of the variety of different medicinal products across various countries. It was imperative to rectify company names in the US due to subtle spelling variations that were initially entered during the NDC application process and subsequently propagated in the RxNorm system.

Subsequently, we formulated the concept of "Pharmaceutical Product," defined by the specified substance, the granular EDQM code, and the strength, omitting the company and country, as it represents a global concept.

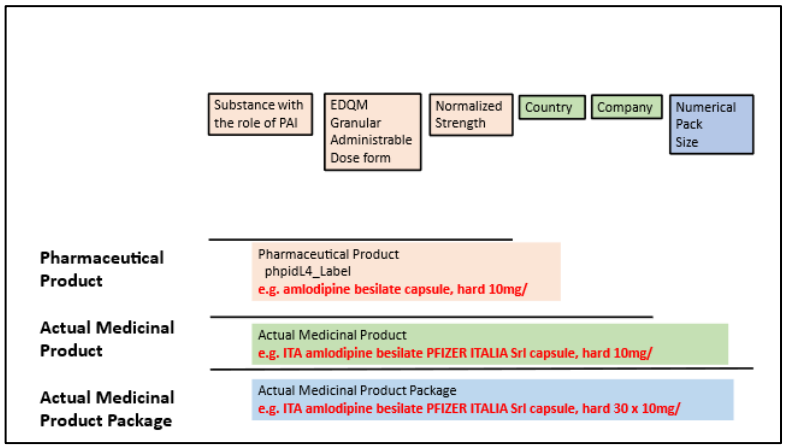

Figure 16. Construction of concepts

We finally introduced the concept of „Virtual Medicinal Product Group (VMPGroup), delineated by the moiety, the value of the Intended Site characteristic of the dose form, and the strength. For instance, the label for the example depicted in the figure is „amlodipine oral 10 mg," with the ATC-Code Level V identified as C08CA01.

No numerical identifiers were utilized, as the string of values within the concepts uniquely defines the concept.

In the subsequent sections, we will elucidate how this methodology was applied to analyze a subset of the therapeutic arsenal comprising medicinal products across various countries. The method of linking a medicinal product pack to the ATC level V code and subsequently to any pharmacotherapeutic class in multiple international drug classifications is best exemplified in the forthcoming figure.

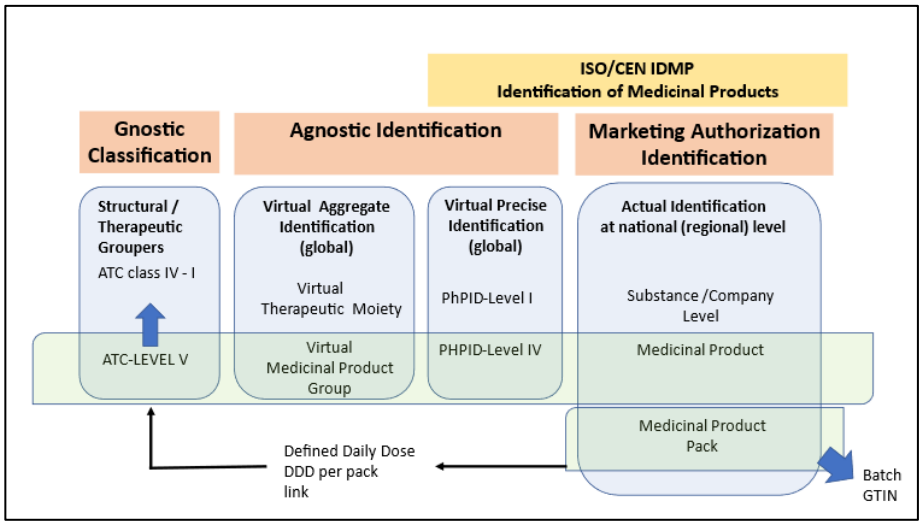

Figure 17. Double loop towards the ATC

ISO/CEN IDMP standards govern the national Marketing authorisation identification from pack to product at the national level. In addition, it provides a global identifier for the medicinal products which remains neutral regarding their therapeutic categorization. The intermediate layer of the Virtual Medicinal Product Group provides further aggregation of substance and dose form based on substance and dose form but remains detached from therapeutic classification. The connection to the Anatomical Therapeutic Chemical (ATC) classification is crucial for situating products within a clinical context. This typically involves a one-to-one relationship, although there are exceptions, such as aspirin tablets 100mg, which can be used as both a preventive cardiovascular drug and a pediatric pain reliever, resulting in two distinct ATC codes..

In many countries, there exists a registry of medicinal product packs, which connects the pack identifier to the ATC level V code, its ATC route of administration, the Defined Daily Dose (DDD), and calculates the number of DDDs per package (DPP). This registry serves as a critical component within administrative and scientific databases' ICT systems for conducting drug utilization research.

Upon the completion of IDMP implementation, this will establish a dual linkage between medicinal product packs and ATC level V, presenting numerous opportunities for enhancing the quality assurance of the registry.

4 Attempts to produce complete samples of medicinal products, standardised to IDMP, for a limited number of substances.

Several tasks outlined in Work Packages 5 to 8 were designed to operate with complete data sets on IDMP standardised sets of medicinal products It quickly became evident that this would pose a significant challenge for many National Competent Authorities (NCAs) involved in the project, particularly given the emergence of the COVID-19 pandemic, which diverted the agencies' attention elsewhere.

Hence, the leadership of UNICOM, and the work packages 1,6,7,8 and 9 have proposed to focus on a pilot product list of a limited number of substances.

4.1 The UNICOM Pilot Product List

4.1.1 Rationale

- The objective of this endavour was to choose a set of substances to focus on for generating IDMP-compliant descriptions of medicinal products across various countries.
- Ideally, this selection would encompass a range of substances that present challenges in medicinal product identification information and cross-border prescribing.

4.1.2 Methodology

The following criteria were selected:

- Frequently used substances
- Substances that exemplify challenges in product identification.
- Substances from the Connecting Europe Facility (CEF) eHealth Digital Service Infrastructure (eHDSI) Critical Test Data (the list of medicinal products for the cross border pilots)
- Focus on chemical substances, and a limited number of combinations (amoxiclav and an anti-conceptive combination (drospirone+ethinylestradiol))

For all selected substances, a working group of experts from WP9, WP8 and WP2 determined all available modifiers for each substance-if any- and collected the codes for active moiety and for moiety+modifier-if any- in the following coding systems:

- EU-SRS
- WHODrug
- UNII
- CAS
- SNOMED-CT

This list was also shared with the WHO CC Centre of OSLO, with the request to add available ACT-codes (sometimes more than one per substance).

Based on this list of ATC codes, several countries were asked to provide a list of available medicinal products in their country.

4.1.3 Results

A list of 35 substances was established (37 when combinations are split)

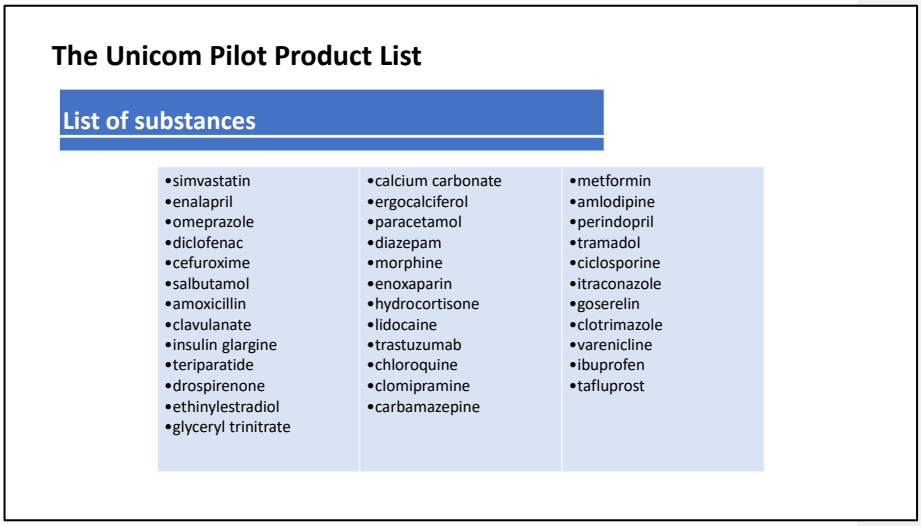

Figure 18. UNICOM Pilot Product List

The coding of these substances and their modifiers -if any- was completed by a group of UNICOM experts,[32] resulting in a list of these substances and their codes in EU-SRS, WHODrug, UNII, CAS, and SNOMED-CT (see Annex 4)

The list of relevant ATC-codes for the UNICOM Pilot Product List was provided by the WHO CC for Drugs Statistics Methodology (DMS) (see Annex 5).[33]

The list of medicinal products corresponding to these ATC codes was compiled for Belgium, Greece, Italy, Norway, and Finland.

For the pilot with Patient Facing App (T8.3), full collections of medicinal products for a least some substances in Greece, Italy and the United States of America were needed. Four substances were selected from the minimal dataset of 35 substances, namely amlodipine, carbamazepine, ibuprofen, simvastatin. This selection was based on frequency, and suitability for demonstrating decision support applications.

4.2 UFIS and the UNICOM T6.1 FHIR SERVER

From that point the work around this Pilot Product List split up.

WP9 focussed on describing for each substance one or a few medicinal product completely in IDMP, and to store that information in the UFIS database (a FHIR server, following the guidance of the Biomedical Research and Regulation Working Group[34]).

[32] In collaboration with Ursula Tschorn, Julie James, Annet Rozema, Leonora Grandia, Robert Vander Stichele
[33] Courtesy of Mohammad Nouri Sharikabad, director of WHO CC DSM in Oslo, Norway
[34] https://www.hl7.org/Special/committees/rcrim/index.cfm

Another group established the UNICOM FHIR Server D6.1, following the guidance of the HL7 FHIR Pharmacy Working Group).[35]

Ultimately, some 300 Medicinal Products, mainly from Sweden and Estonia, were transferred to UFIS. When this database was terminated by the NCAs, the data were transferred to the UNICOM T6.1 FHIR Server.

4.3 The minimal data set on 4 substances, based on "data as is", created in Work Package 8

After two years within UNICOM, it became evident that the WHO Collaborating Centre for Pharmacovigilance, Upsala Monitoring Centre (UMC), would undertake the responsibility of maintaining a repository of PhPIDs once consensus was reached regarding the principles of applying the ISO/CEN IDMP standards for this purpose.

Only a few National Competent Authorities, namely those of Sweden, Estonia, and Portugal, had generated IDMP-compliant data for approximately 300 medicinal products, selected to exemplify substances listed in the UNICOM Pilot Project List. Examples included combination products such as amoxiclav, and also complex products with more than one manufactured item (e.g. the three-phasic contraceptive oestrogen/progestogen pill), products for Helicobacter treatment with several manufactured items, parenterals with medical devices.

A FHIR server was built to harbour those IDMP-compliant data, and they were later transferred to the UNICOM FHIR SERVER (database T6.1).

For this approach, the NCA participating in the provision of data needed to comply to IDMP-internally, and to provide the data in FHIR format, according to the EU IDMP Implementation Guide.

While this approach was very useful for the participating NCAs to test and demonstrate their internal IDMP-compliant systems, the collection of medicinal products did not serve the needs of the pilots and tasks of Work Package 8, nor the needs for testing the substitution component, as envisioned in T6.2.

For that, it was imperative to have complete samples of all available medicinal product packs for each active substance. Moreover, complete samples of medicinal product packs for one substance, needed to be also available in at least one, and in preferably more countries. This was necessary to facilitate testing of a substitution module in cross-border services and to conduct experiments involving patients traveling to foreign countries with a patient-facing app containing their personal list of national medications.

4.3.1 Motivation for the initial decision to create a minimal data set.

By the third year of UNICOM, it became clear that such samples would not be provided by the participating National Competent Authorities (NCAs); it was then decided to start a parallel data collection of "data AS IS", meaning that a request would be made to a national data provider to provide complete samples of medicinal product packs for a limited, predefined list of substances. It was not necessary for the data to have undergone prior attempts at standardization to IDMP. The local descriptions of the products would suffice.

4.3.2 Constraints of this work

Several constraints were agreed to limit the amount of work to a feasible extent:

- First, medicinal products for only 4 substances (amlodipine, carabamazepine, ibuprofen, simvastatin were requested.
- The request was solely for the provision of national identifiers and descriptors, which were required to encompass information on active substances (with the role of Precise Active Ingredient), dose form and strength (as stated on the national package), the marketing authorization holder, pack size, national drug code for the pack, and, optionally, pack description

[35] https://www.hl7.org/Special/committees/medication/index.cfm

(unstructured if necessary) and pill description (if available). The countries that already had some of these data supplemented with IDMP requirements were invited to provide this information, but in the end the request was directed to countries that did not yet had such standardized data. .

- Only data on single medicinal products (containing only one active ingredient) were collected.
- The data collection focussed on medicinal products that were authorized and currently on the market (with a grace period of one year).
- The onus of standardisation to IDMP would rely upon an internal team of WP8 (a clinical pharmacologist, a drug database expert, and a semantic expert in dose form ontologies) and the result of this work would be returned to the data provider, and validated in a number of feedback cycles.

4.3.3 Countries involved

As especially in the initial phases this internal standardisation was expected to be quite laborious, the effort was limited to 4 substances (amlodipine, carbamazepine, ibuprofen, simvastatin) and to 10 countries.

The three countries were the countries that were involved in the pilots for the Patient Facing App of T8.3, namely Italy, Greece, and USA.

Data were also retrieved from Norway, Belgium, and Finland.

In a later phase, data from France, Spain, Tunisia (Africa), and Ecuador (Latin-America) were added.

The latter countries were added because they volunteered for the effort and to serve the needs of the cross-national comparison of national pharmacotherapeutic arsenals, envisioned in T8.2.

4.3.4 Sources per country

For this project, data could be sourced not only from National Competent Authorities but also from national Medicinal Product Dictionaries or drug databases supported by pharmacy or Electronic Health Record (EHR) vendors.

For Belgium, Ecuador, and Tunisia data were provided by independent drug information centres.

For Norway, the National Competent Agency, NOMA, provided the data.

For Greece, Italy, Finland, Spain, France, eHealth agencies participated.

Commented [LN7]: This is the NCA which provided the data !

For the USA, data were retrieved from the RxNorm System, in collaboration with the National Library of Medicine.

4.3.5 Methodology of the data collection process and central standardisation

Only countries expressing interest in this pragmatic approach were invited to take part.

A protocol detailing the scope of the requested data was dispatched.

Data sets in Excel of the different countries were sent to the WP8 team, and examined in a first round of feedback to see whether the constraints were respected (only single products, only currently marketed products), and to see whether crucial information was missing.

Data from the different countries were transferred to one big worksheet in Excel, to perform the standardisation to EDQM where needed, and to check the consistency of the data.

IDMP standardisation was limited to:

- the substance information (moiety and moiety+modifier in SMS code)
- the dose form information (manufactured dose form, administrable dose form in EDQM code)
- the expression of strength (presentation strength, concentration strength, reference strength)

- the unit of presentation (in case of presentation strength) in EDQM code
- the route(s) of administration in EDQM code
- numerical pack size (with unit if concentration strength)
- ATC-code verification

These are basically the variables of the Minimum Attribute List for the cross-border services (as determined in WP5). Pack description, even if available, was not included in the standardisation effort.

In the initial phase of the project, data sets were collected from a variety of national data providers in Excel files.

The data were subsequently transferred to a comprehensive Excel worksheet, acting as a repository for both the original local data and the progressive incorporation of IDMP data into the national dataset.

Once the IDMP transformation of the minimal data set of 4 substances for one country was finished, the data were exported to the UNICOM FHIR SERVER, and available in FHIR format there, for experiments with the substitution module and the patient facing app.

4.3.6 Further development of the data collection process

As experience was gained with the procedure, the data request was refined to be more precise, incorporating the following details:

- optional local variables (e.g. URL to official labelling)
- mandatory local variables
- variables needed in the standardisation process to be filled with IDMP compliant data
- variables in IDMP that could be constructed automatically based on the mandatory variables.

The latter variables were mainly concatenated labels for the construction of:

- medicinal product pack
- medicinal product
- Pharmaceutical product
- Virtual Medicinal Product Group (INN prescription)

All data were migrated to an online SQL database optimized for content quality control, for streamlined export to the UNICOM FHIR SERVER, and for conducing to cross-national analyses of therapeutic arsenals. .

4.3.7 Overview of the Minimal data sets per substance and per country

For the 4 selected substances the number of medicinal product packs ranged from 50 to 200 per country, with an outlier for the USA of more than 5.000 medicinal product packs.

A detailed analysis of these samples will be provided in Working paper D8.4

The data from Italy, Greece and USA have been successfully used for the demonstrations of the Patient Facing App (T8.3) and for the development of the substitution module (T6.2).

5 Demonstrate the use of this repository in the application of decision support systems across Europe, and in the tools for patients to navigate drug class names in product labelling

Including the discussion of linked activities (ii), (iii), (iv) and (v)

To be able to demonstrate the application of IDMP-Compliant Pharmaceutical Products in decision support systems, the following prerequisites are needed:

First, complete sets of medicinal product packages (including the global Pharmaceutical Identifier) pertaining to a specific active substance needed to be available for several European countries.

Secondly, a repository of Global Identifiers (Pharmaceutical Product Identifiers of PhPIDs) needed to be maintained. This aspect was supposed to be taken up by the WHO Upsala Monitoring Centre for Pharmacovigilance and elaborated under the governance of the GIDWIG (Global IDMP Working Group), involving EMA and FDA and other stakeholders. As the discussion on the precise algoritms and coding systems for this PHPID creation, it was decided to work with an identifying label rather than with a coded identifier. We used a concatenated string of the label of the substance with the role of PAI, the administrable EDQM dose form and the strength expression to create the unique label for each Pharmaceucal Poduct.

Thirdly, a link needed to be created between this repository of PhPIDs and the fifth level of the ATC-classification, the pivot for expressing pharmacotherapeutic groups.

The methodological approach for creating this link was presented to the Pistoia-IDMP-Ontology group (a consortium of IDMP experts in the pharmaceutical Industry) on August 1, 2023 (see Annex 6) , and to the WHO Collaborating Centre for Drug Statistics Methodology on October 3, 2023 (see Annex 7).

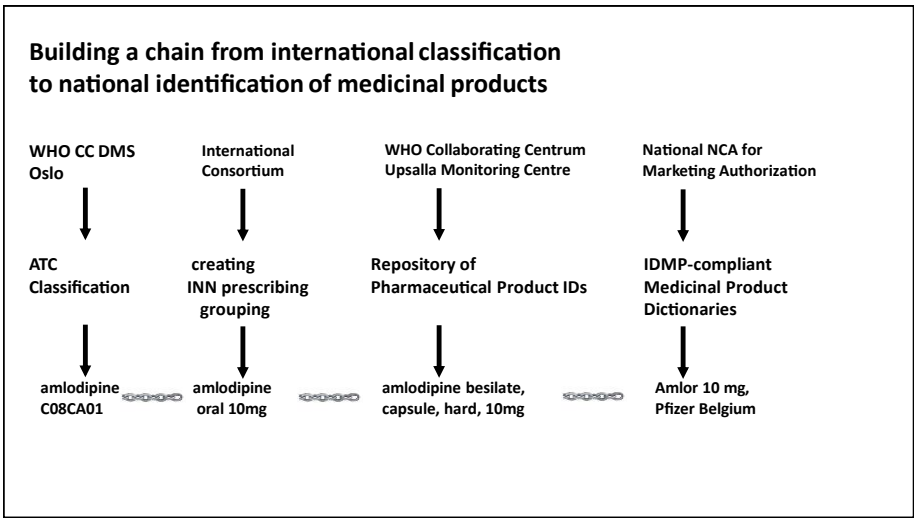

Figure 19. A chain of concepts

Decision rules to guide rational pharmacotherapy are mostly expressed in terms of high-level ATC-codes.

However, these decision rules must be linked to different national Medicinal Product Dictionaries (MPDs) in different countries in different languages (24 official languages).

The European Union counts 27 EU Member States, while the UK, Norway, and other affiliated countries have close relationships with the EU. Each country usually host several databases on medicinal products. Decision support systems and drug information systems originating in Europe, tailored to a specific country, language, and drug database, face challenges in expanding into other countries. The need for translations and adaptation to local drug databases hampers the market penetration of these resources, despite their high level of expertise.

The full implementation of IDMP across all Member States and in all medicinal product dictionaries will significantly enhance the commercialization of academic expertise in pharmacotherapy.

In the forthcoming chapters, we will demonstrate the efficacy of decision support in pharmacotherapy with the implementation of such a chain of concepts.

5.1 IDMP and Drug information

Supplying information on pharmacotherapy represents one approach to decision support.

For medicinal products, this information is very regulated and must be in accordance with the official labelling, edited during the marketing authorisation process, and constantly updated, if new information arises from the pharmacovigilance system.

All the information from companies -including advertising- must comply with that labelling.

In European countries, the labeling text is accessible in paper format, presented in a patient-friendly version, and is also publicly available for healthcare professionals in the Summary of Product Characteristics.

This information is highly structured, as the template for list redaction is strictly regulated.

Over the past few years, frustration has mounted over the antiquated distribution method of providing this information on paper resembling biblical scrolls enclosed within medicinal product packages..

5.1.1 Electronic Product information (ePI)

EMA and a group of EU National Competent Authorities are testing the use of ePI in a one-year pilot project started in July 2023.

ePI refers to the authorised, statutory product information for medicines (including the summary of product characteristics, package leaflet and labelling) adapted for handling in electronic format and dissemination via the web, e-platforms and in print.

Transitioning to ePI offers advantages such as improved accessibility, searchability and multilingual capabilities.

ePI can also integrate with electronic healthcare systems, enabling healthcare professionals and patients to access accurate and up-to-date product information more conveniently.[36]

IMI-projects such as Gravitate-Health[37] explore the possibilities of these new information carriers, in collaboration between industry, regulatory authorities, scientists, health care providers and patient organisations.

Electronic Applications will make it possible to better navigate the information, in function of the interest of the reader.

The implementation of IDMP will enhance these innovations, and allow multilingual extensions, and links to additional evidence-based information.

Of particular interest will be the cross linking of specific information on a particular medicinal product to pharmacotherapeutic classes, either classes that contain similar medicinal products, or classes that may cause safety issues when used in conjunction with the particular product.

In the Unicom Project, only 4 drug classes -each with one substance- could be explored:

Calcium-antagonists:	amlodipine
Anti-epileptics with narrow therapeutic window:	carbamazepine
Non-steroidal anti-inflammatory agents:	ibuprofen
Statins:	simvastatin

[36] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/product-information-requirements/electronic-product-information-epi

[37] https://www.gravitatehealth.eu/

This was not sufficient for practical experiments with cross linking between products and pharmacotherapeutic classes on a large scale as requested in Linked Activity (ii) (see **Error! Reference source not found.**). Prerequisite for this will be the full implementation of IDMP for all medicinal products in a country, and preferably in a few countries.

In the UNICOM Patient Facing App Demonstrator (D8.5) a few specific examples were elaborated based on the Minimal Data Set featuring the substances mentioned above..

5.2 Drug Information Centres

In several countries, independent Drug Information Centres provide services to prescribing physicians and dentists, and dispensing pharmacists, through the publication of Medicinal Product Dictionaries (MPD) and web sites, sometimes supported by the regulatory authorities.

IDMP will support international cooperation between these drug bulletins.

5.3 IDMP and Guidelines

Guidelines play an increasingly pivotal role in shaping the daily practices of healthcare providers. Typically, these guidelines are tailored to address specific diseases for particular healthcare professions. However, they can also be designed to address multimorbidity with a multidisciplinary approach.

Guidelines can be translated in specific practice recommendations, gathered in evidence-based point-of-care information summaries[38].[39] These guidelines contain a lot of references to pharmacotherapy.

Examples of such point of care summaries with international penetration is EBM-Guidelines®, from Finland, distributed in several European Countries in several languages.[40] Linking such resources to the national Medicinal Product Dictionaries will be greatly facilitated by the implementation of IMDP in the 27 Member States of the European Union. Also, the internationalisation of MPDs such as BNF in the UK, ZN-Index in the Netherlands and Vidal in France may be fostered by IDMP. Similar argumentation can be developed for producers of care pathways.

Commented [LN8]: A link maybe ?

Tools to evaluate the quality of these point-of-care resources have been developed.[41]

Lately, FHIR resources have been created to support Evidence-based Medicine, with the aim to represent evidence from clinical trials (the cornerstone for the assessment of efficacy of medicines, and for real world data, instrumental for pharmacovigilance and pharmacoepidemiology).[42]

An important consideration here is the specificity, which can vary across different levels: the level of individual medicinal products, the level of pharmaceutical products (comprising all medicinal products with the same substance, dose form, and strength), and the level of pharmacotherapeutic class. For

[39] Banzi R, Liberati A, Moschetti I, Tagliabue L, Moja L. A review of online evidence-based practice point-of-care information summary providers. J Med Internet Res. 2010 Jul 7;12(3):e26.

[40] https://www.duodecim.fi/english

[41] Lenaerts G, Bekkering GE, Goossens M, De Coninck L, Delvaux N, Cordyn S, Adriaenssens J, Aertgeerts B, Vankrunkelsven P. A Tool to Assess the Trustworthiness of Evidence-Based Point-of-Care Information for Health Care Professionals (CAPOCI): Design and Validation Study. J Med Internet Res. 2021 Oct 5;23(10):e27174

[42] Vorisek CN, Lehne M, Klopfenstein SAI, Mayer PJ, Bartschke A, Haese T, Thun S. Fast Healthcare Interoperability Resources (FHIR) for Interoperability in Health Research: Systematic Review JMIR Med Inform 2022;10(7):e35724

clarity and conciseness, it's crucial to manage and differentiate these distinct levels effectively.

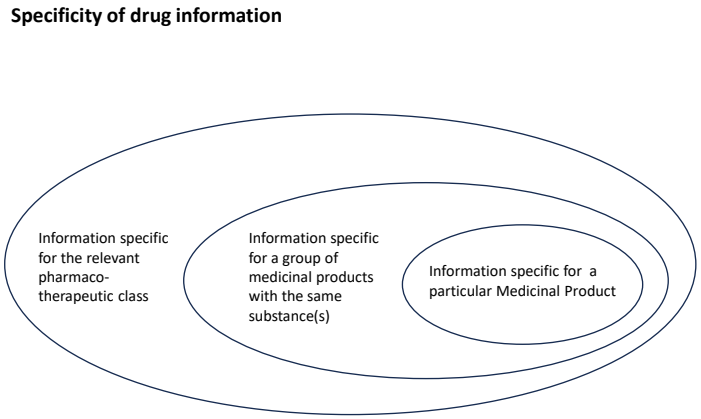

Figure 20. Levels of specificity in drug information

5.4 IDMP and Computerized Decision Support (CDSS)

Computerized Decision Support has been introduced decades ago, from the beginning of the introduction of Electronic Health Records.[43] It was often hailed as a motive for using computers in medical documentation of clinical practice. However, user satisfactions and acceptance could not be taken for granted, as alert fatigue was a phenomenon that quickly kicked in.[44,45]

All over the world many CDSS have been developed for numerous subjects:

- Pharmaco-kinetic interactions
- Pharmaco-dynamic interactions
- Indications
- Contra-indications
- Lactation and pregnancy
- Ability to drive and work machines,
- Allergies
- Posology support
- Detection of cascade therapy (prescriptions for alleviating side-effects of medicinal products)

For pharmaco-kinetic interactions, systems abound, also directed at patients, and accessible by internet, The consistency of these systems is however limited, and there is little consensus on what are clinically relevant alerts.

Commented [LN9]: Missing word here

[43] Beeler PE, Bates DW, Hug BL. Clinical In decision support systems. Swiss Med Wkly. 2014 Dec 23;144:w14073.

[44] McCoy AB, Thomas EJ, Krousel-Wood M, Sittig DF. Clinical decision support alert appropriateness: a review and proposal for improvement. Ochsner J. 2014 Summer;14(2):195-202.

[45] Carli D, Fahrni G, Bonnabry P, Lovis C. Quality of Decision Support in Computerized Provider Order Entry: Systematic Literature Review. JMIR Med Inform. 2018 Jan 24;6(1):e3.

Pharmaco-dynamic interactions are complex to assess, especially in older adults and residents in nursing homes with long lists of medication. Their frequency and impact on quality of life could be more important.

For example, the determination of anti-cholinergic load to which a poly-medicated patient is exposed is a difficult and time-consuming work. There are many anticholinergic scales, some of them integrating this information in a review of scales[46], and some transformed in an automated assessment tool.[47,48]

The Duran List of anticholinergics is a global list of 100 weak and strong anticholinergics, provided with the corresponding ATC codes (see annex 8). Full implementation of IDMP would make the complex connection to all the relevant medicinal products easier, for one country, and certainly also for multiple countries. It would also allow to consider the dose form and strength more easily.

Decision support has also been developed to combine computerized assessment of appropriateness of prescribing with interprofessional evaluation in the context of Long-Term Care Facilities (Nursing homes). Electronic platforms allow nurses, pharmacists, and physicians to cooperate and evaluate automatically generated suggestions for correcting inappropriate prescribing and for deprescribing.[49]

Within UNICOM, in Task T8.5, for the first time the impact of pharmaco-genetics on CDSS has been explored (see D8.5 and D8.10).

One example of complex pharmacodynamic interaction was elaborated in the pilot of the Patient Facing Apps around ibuprofen, to illustrate automatically generated alerts for nephrotoxicity, induced by the concomitant use of Non-Steroidal Anti-inflammatory Agents, ACE-inhibitors and diuretics.

[46] Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. Eur J Clin Pharmacol. 2013 Jul;69(7):1485-96.

[47] Wauters M, Klamer T, Elseviers M, Vaes B, Dalleur O, Degryse J, Durán C, Christiaens T, Azermai M, Vander Stichele R. Anticholinergic Exposure in a Cohort of Adults Aged 80 years and Over: Associations of the MARANTE Scale with Mortality and Hospitalization. Basic Clin Pharmacol Toxicol. 2017 Jun;120(6):591-600.

[48] Wehran T, Eidam A, Czock D, Kopitz J, Plaschke K, Mattern M, Haefeli WE, Bauer JM, Seidling HM. Development and Pilot Testing of an Algorithm-Based Approach to Anticholinergic Deprescribing in Older Patients. Drugs Aging. 2024 Feb;41(2):153-164.

[49] Wauters M, Elseviers M, Vander Stichele R, Dilles T, Thienpont G, Christiaens T. Efficacy, feasibility and acceptability of the OptiMEDs tool for multidisciplinary medication review in nursing homes. Arch Gerontol Geriatr. 2021 Jul-Aug;95:104391.

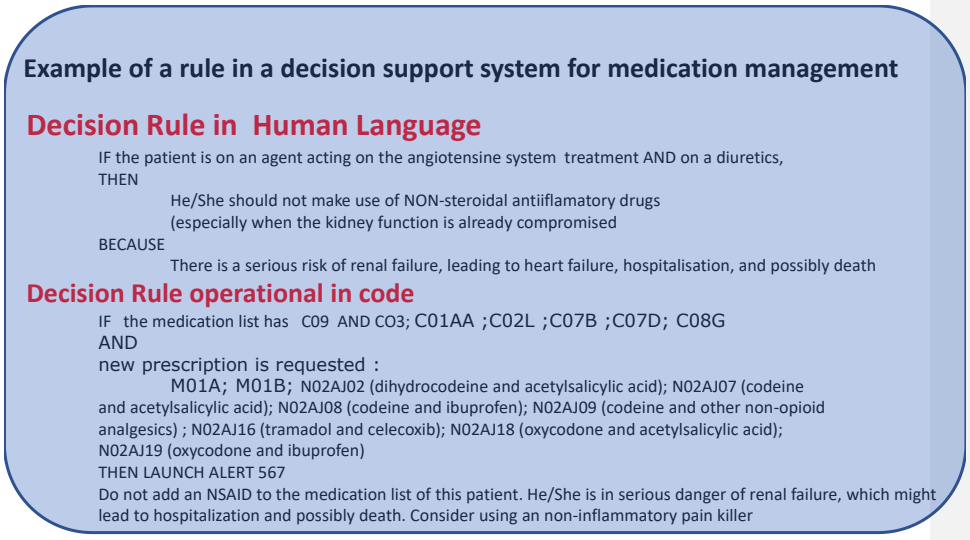

Figure 21. An example of pharmacodynamic nephrotoxic interaction

This illustrates the complexity to express decision rules in broad pharmacotherapeutic classes, to precise ATC code collections, and from there to PhPIDs and national Medicinal Products.

In Europe the penetration and commercial success of such tools is hampered by the barriers of language (24 official languages), differences in national regulations (27 Member States), and by the almost impossible effort to connect to the sheer number of ever evolving Medicinal Product Dictionaries (on average 5 per country). Hence full implementation of IDMP in Europe will contribute to cross the border also for evidence-based drug information and decision support, and not only for ePrescriptions.

5.5 IDMP and substitution rules and INN prescribing

During the UNICOM project, information was collected on the national regulations for substitution and for prescribing by International Non-Proprietary Name.

The initial plan, as outlined in Linked Activity (iii), was to evaluate the impact of these rules on the initial experiments for Cross-Border ePrescription and eDispensation. However, neither the eHSDI test environment nor the implementation of IDMP had progressed sufficiently to allow for the planning and execution of such tests.

Nevertheless, it was possible to use the UNICOM Patient Facing App test environment (D8.5) to simulate testing of semantic interoperability of cross border transfer of medication lists. The 3 patient facing apps involved were:

- HealthPass from Gnomon in Greece:
- PharmaWizard from DataWizard in Italy
- InfoSage from Beth Israel Deaconess Medical Center in the USA.

The medication lists used for the test would have to be limited to the 4 substances, for which all Medicinal Products Packs were standardised to IDMP in the Minimal Data (instrumental to tasks T8.1, T8.2, and T8.3)

For that purpose, 236, 220, and 5167 medicinal product packs from Greece, Italy, and the USA were centrally standardised to IDMP by a small team (a clinical pharmacologist, a terminological expert, and a drug database expert).

The standardisation of the medicinal products was implemented for the variables of the Minimum Attribute List, developed in UNICOM D5.7, listing the variables that are needed for cross-border ePrescriptions, in eHDSI (except for the variables describing Pack Type).

This standardization of IDMP variables was supplemented with the construction of the following concatenated labels:

- pharmaceuticalProductLabel: Specified Substance + granular EDQM dose form + normalised strength
- virtualMedicinalProductGroupLabel: Substance + EDQM characteristic Intended Side + normalised strength.

To provide a global label to each national medicinal product the following labels were constructed:

- medicinalProductLabel: Country + Specified Substance + Company + granular EDQM dose form + normalised strength
- medicinalProductPackLabel: Country + Specified Substance + Company + granular EDQM dose form + normalised strength

As the EDQM Code for granular Administrable dose form was present in the Minimal Data Set, all other characteristics of the dose form (including the Intended Site characteristic) could be added automatically.

This not only allowed to test different algorithms to create the PhPID (see figure 5), but also made the testing of cross border substitution possible in the patient facing apps, a private environment, outside the realm of the eHDSI infrastructure.

In addition, a substitution module was developed in T6.2 to be demonstrated in Patient Facing Apps in 3 countries (see UNICOM D8.5).

Based on the results of the survey of Substitution rules and INN Prescribing, the following 3 levels of substitution were identified:

- Brand substitution: the medicinal product of the ePrescription in sending Country A can only be delivered as an eDispensation by the pharmacist (without confirmation by a physician), in case an identical medicinal product from the same company is marketed in country B

- Pharmaceutical Product substitution: the medicinal product of the ePrescription in sending Country A can be delivered as an eDispensation by the pharmacist (without confirmation by a physician), by picking from a list of medicinal products with the same Pharmaceutical Product (specified substance, granular EDQM administrable dose, normalised Strength)
- INN prescribing: the medicinal product of the ePrescription in sending Country A can be delivered as an eDispensation by the pharmacist (without confirmation by a physician), by picking a suitable candidate from a list with medicinal products (marketed in the country) within the same Virtual Medicinal Product Group (same substance, same EDQM Intended dose form, same normalised strength) in country B.

Based on the results of a survey among UNICOM NCAs on Substitution rules and INN prescribing it beame possible to determine what the possibilities were in the different countries for choosing a replacement for an ePrescription of country A for an eDispensation in country B.

Fig 1. Differences in limitations for finding equivalents for crossborder ePrescriptions in EU countries

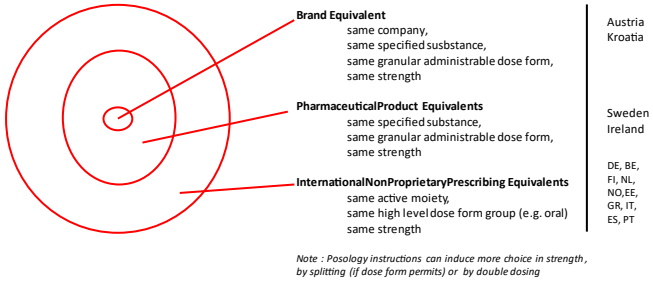

Figure 22. Diversity in rules for substition and INN Prescribing in UNICOM EU member States

To illustrate this approach, we can provide an example.

Let's imagine an Italian Patient with a prescription of the Italian Medical Product NORVASC*14 cpr 10 mg (with the national Drug Code 27428022) traveling to Greece, and requesting an eDispensation in Greece.

The global label of this medicinal product is:

ITA amlodipine besylate PFIZER ITALIA Srl tablet 14 x 10mg/

This is an IDMP standardized label, informing the Greek healthcare provider that this is an Italian medicinal product, containing amlodipine besylate as active substance, licenced by Pfizer, with "tablet" as dose form, in a strength of 10 mg and containing 14 tablets.

Each of these elements is coded, and stored separately so that the selection processes can be applied.

First option

In this example the first option for brand substitution is not available as Pfizer no longer markets amlodipine in Greece.

Second option

The second option is to go for exact substitution based on the Pharmaceutical Product:

amlodipine besylate tablet 10mg/

The substitution module will then generate a list of medicinal product packs:

4516	AMLIBON TAB 10MG/TAB BTx30 (BLISTER)	GRC amlodipine besylate SANDOZ GMBH, KUNDL, AUSTRIA tablet 30 x 10mg/
4320	NORMODIN TAB 10MG/TAB BTx14	GRC amlodipine besylate GENEPHARM AE tablet 14 x 10mg/
6180	AMLIBON BES TAB 10MG/TAB BT x 30 σε BLISTERS	GRC amlodipine besylate SANDOZ GMBH, KUNDL, AUSTRIA tablet 30 x 10mg/
7813	NORDEX/MEDICAL PHARMAQUALITY TAB 10MG/TAB BTx14 (1 BL,x 14)	GRC amlodipine besylate MEDICAL PHARMAQUALITY AE tablet 14 x 10mg/
7732	AMLODIPINE BESILATE/TEVA TAB 10MG/TAB BT x 30 (3x10)	GRC amlodipine besylate TEVA PHARMA B.V., Haarlem, THE NETHERLANDS tablet 30 x 10mg/
8817	AMLODIPINE/MYLAN GENERICS TAB 10MG/TAB BTx30	GRC amlodipine besylate GENERICS PHARMA HELLAS ΕΠΕ tablet 30 x 10mg/
5976	NORVAGEN TAB 10MG/TAB BT x 30 (σε BLIST)	GRC amlodipine besylate STARGEN Ε.Π.Ε. tablet 30 x 10mg/
9063	NORMODIN TAB 10MG/TAB BTx28	GRC amlodipine besylate GENEPHARM AE tablet 28 x 10mg/

Third option: INN substitution

The third option is based on the elements constituting the Virtual Medicinal Product group :

This leads in this case to a much more extended list and more choice for the eDispensation.

amlodipine oral 10mg/

5150	NORVALET CAPS 10MG/CAP BTx30 (BLIST 3x10)	GRC amlodipine besylate INNOVIS HEALTH A.E. capsule, hard 30 x 10mg/
4358	FLODIL CAPS 10MG/CAP BTx30 (BLIST 2x15)	GRC amlodipine besylate MINEPBA ΦΑΡΜΑΚΕΥΤΙΚΗ A.E. capsule, hard 30 x 10mg/
2720	AMLODIN CAPS 10MG/CAP BT x 30(BLIST 3x 10)	GRC amlodipine besylate BENNETT ΦΑΡΜΑΚΕΥΤΙΚΗ A.E. capsule, hard 30 x 10mg/
4516	AMLIBON TAB 10MG/TAB BTx30 (BLISTER)	GRC amlodipine besylate SANDOZ GMBH, KUNDL, AUSTRIA tablet 30 x 10mg/
4303	AMODIPAN CAPS 10MG/CAP BTx30(BLISTER 3x10)	GRC amlodipine besylate SANTA PHARMA A,E, capsule, hard 30 x 10mg/
6237	PIDOLEN (ΓΕΝΟΣΗΜΟ) CAPS 10MG/CAP BTx30 (BLIST 2x15)	GRC amlodipine besylate ΦΑΡΜΕΞ A.E. capsule, hard 30 x 10mg/
4306	AGGOVASK CAPS 10MG/CAP BTx14(BLIST 2x7)	GRC amlodipine besylate PROTON PHARMA ΑΝΩΝΥΜΗ ΦΑΡΜΑΚΕΥΤΙΚΗ ΕΤΑΙΡΕΙΑ capsule, ha
4308	LODIPIN CAPS 10MG/CAP BTx14 (BLIST 1x14)	GRC amlodipine besylate IASIS PHARMA capsule, hard 14 x 10mg/
4309	LODIPIN CAPS 10MG/CAP BTx30 (BLIST 3x10)	GRC amlodipine besylate IASIS PHARMA capsule, hard 30 x 10mg/
4320	NORMODIN TAB 10MG/TAB BTx14	GRC amlodipine besylate GENEPHARM AE tablet 14 x 10mg/
6180	AMLIBON BES TAB 10MG/TAB BT x 30 σε BLISTERS	GRC amlodipine besylate SANDOZ GMBH, KUNDL, AUSTRIA tablet 30 x 10mg/
4269	BARUDEN CAPS 10MG/CAP BTx14 (BLIST 1x14)	GRC amlodipine besylate ΑΝΦΑΡΜ ΕΛΛΑΣ A.E. capsule, hard 14 x 10mg/
4270	BARUDEN CAPS 10MG/CAP BTx28 (BLIST 2x14)	GRC amlodipine besylate ΑΝΦΑΡΜ ΕΛΛΑΣ A.E. capsule, hard 28 x 10mg/
7813	NORDEX/MEDICAL PHARMAQUALITY TAB 10MG/TAB BTx14 (1 BL,x 14)	GRC amlodipine besylate MEDICAL PHARMAQUALITY AE tablet 14 x 10mg/
8145	AMLORETIN CAPS 10MG/CAP BTx28(BLISTER 2x14)	GRC amlodipine besylate NATURALIA A.E. capsule, hard 28 x 10mg/
1913	NORVASC CAPS 10MG/CAP BTX14(BLIST1X14)	GRC amlodipine besylate UPJOHN HELLAS E.Π.E. capsule, hard 14 x 10mg/
5843	ALDOSION CAPS 10MG/CAP BTx30 (BLIST 3x10)	GRC amlodipine besylate ALAPIS ABEE capsule, hard 30 x 10mg/
4576	amlodipine maleate/GENERICS TAB 10MG/TAB BTx14	GRC amlodipine maleate GENERICS PHARMA HELLAS ΕΠΕ tablet 14 x 10mg/
4577	amlodipine maleate/GENERICS TAB 10MG/TAB BTx28	GRC amlodipine maleate GENERICS PHARMA HELLAS ΕΠΕ tablet 28 x 10mg/
4230	AMLOPRESS CAPS 10 MG/CAP BTx 30 (BLIST 3x10)	GRC amlodipine besylate FOS ΦΑΡΜΑΚΕΥΤΙΚΗ ΙΚΕ capsule, hard 30 x 10mg/
4233	AMLODIL CAPS 10MG/CAP BTX14(2BLIST,X7)	GRC amlodipine besylate GAP A.E. capsule, hard 14 x 10mg/
5394	NORFAN CAPS 10MG/CAP BTx28 (BLIST 2x14)	GRC amlodipine besylate VOCATE ΦΑΡΜΑΚΕΥΤΙΚΗ A.E. capsule, hard 28 x 10mg/
5398	AXYPLOT CAPS 10MG/CAP BTx28 (BLIST 4x7)	GRC amlodipine besylate IAMATICA MON. ΕΠΕ capsule, hard 28 x 10mg/
5049	AMLOSILAT CAPS 10 MG/CAP BTx2 BLISTx 14 CAP	GRC amlodipine besylate ALPHA GENERICS THERAPY ΑΕΒΕΦ capsule, hard 28 x 10mg/
4464	DAFOR CAPS 10MG/CAP BTx14 (BLIST 1x14)	GRC amlodipine besylate ΠΝΓ ΓΕΡΟΛΥΜΑΤΟΣ ΜΕΝΤΙΚΑΛ A.E. capsule, hard 14 x 10mg/
4465	DAFOR CAPS 10MG/CAP BTx28 (BLIST 2 x 14)	GRC amlodipine besylate ΠΝΓ ΓΕΡΟΛΥΜΑΤΟΣ ΜΕΝΤΙΚΑΛ A.E. capsule, hard 28 x 10mg/
4472	VASCODIN CAPS 10MG/CAP BT x 14 (BLIST 2x7)	GRC amlodipine besylate HELP ABEE capsule, hard 14 x 10mg/
4473	VASCODIN CAPS 10MG/CAP BT x 30 (BLIST 3x10)	GRC amlodipine besylate HELP ABEE capsule, hard 30 x 10mg/
4477	AMLODIPINE BESILATE/NORMA CAPS 10MG/CAP BTx30 (BLIST 3x10)	GRC amlodipine besylate NOPMA ΕΛΛΑΣ A.E. capsule, hard 30 x 10mg/
4751	EVANGIO CAPS 10MG BTx14 (BLIST 1x14)	GRC amlodipine besylate RAFARM A.E.B.E. capsule, hard 14 x 10mg/
4752	EVANGIO CAPS 10MG BTx30 (BLIST 2x15)	GRC amlodipine besylate RAFARM A.E.B.E. capsule, hard 30 x 10mg/
7732	AMLODIPINE BESILATE/TEVA TAB 10MG/TAB BT x 30 (3x10)	GRC amlodipine besylate TEVA PHARMA B.V., Haarlem, THE NETHERLANDS tablet 30 x 10mg/
4715	NOLVAC TAB 10MG/TAB BTx28 σε BLISTERS	GRC amlodipine maleate ΦΑΡΜΑΤΕΝ ΕΛΛΑΣ ΑΕΒΕ tablet 28 x 10mg/
4716	NOLVAC TAB 10MG/TAB BTx30 σε BLISTERS	GRC amlodipine maleate INNOVIS PHARMA A.E.B.E tablet 30 x 10mg/
5434	ABESYL CAPS 10MG/CAP BTx 30(BLIST 3 x 10)	GRC amlodipine besylate MEDOCHEMIE HELLAS AE capsule, hard 30 x 10mg/
5479	ANGIORETIC CAPS 10MG/CAP BTx 30(BLIST 2x15)	GRC amlodipine besylate MEDARTE ΦΑΡΜΑΚΕΥΤΙΚΗ ABEE capsule, hard 30 x 10mg/
4618	PRECARDIN CAPS 10MG/CAP BTX14(BLIST1X14)	GRC amlodipine besylate FARMEDIA AE capsule, hard 14 x 10mg/
4619	PRECARDIN CAPS 10MG/CAP BTX28(BLIST2X14)	GRC amlodipine besylate FARMEDIA AE capsule, hard 28 x 10mg/
8817	AMLODIPINE/MYLAN GENERICS TAB 10MG/TAB BTx30	GRC amlodipine besylate GENERICS PHARMA HELLAS ΕΠΕ tablet 30 x 10mg/
4824	ROVOXID CAPS 10MG/CAP BTx30 (BLIST 3x10)	GRC amlodipine besylate BIAN A.E. capsule, hard 30 x 10mg/
4690	RAMLET CAPS 10MG/CAP BTx14 (BLIST 1x14)	GRC amlodipine besylate RAFARM A.E.B.E. capsule, hard 14 x 10mg/
4691	RAMLET CAPS 10MG/CAP BTx28 (BLIST 2x14)	GRC amlodipine besylate RAFARM A.E.B.E. capsule, hard 28 x 10mg/
4636	AMLOTENS TAB 10MG/TAB BTx30 (BLISTER 3x10)	GRC amlodipine mesylate monohydrate INNOVIS HEALTH A.E. tablet 30 x 10mg/
5976	NORVAGEN TAB 10MG/TAB BT x 30 (σε BLIST)	GRC amlodipine besylate STARGEN Ε.Π.Ε. tablet 30 x 10mg/
5468	AMILOPID CAPS 10MG/CAP BT x 30(BLIST 3x10)	GRC amlodipine besylate BIANEΞ A.E. capsule, hard 30 x 10mg/
9063	NORMODIN TAB 10MG/TAB BTx28	GRC amlodipine besylate GENEPHARM AE tablet 28 x 10mg/

This approach was implemented for each of the 4 substances and for the 3 countries implicated in Task T8.3, and demonstrated at several events, reported in D8.5. with a pilot in 25 traveling residents, and an evaluation of the concordance of the (e)Prescription and the (e)Dispensation, on private smartphones (and not in the cross-border eHSDI infrastructure)

Hence, we were able to perform the tasks formulated in Linked activity 3: Testing semantic interoperability of cross border transfer of(medication lists

Commented [LN10]: It would be nice to add this kind of conclusions at the end of each chapter so that reviewers can immediately make a link between what was promised and delivered (and if not why).

5.6 IDMP and patient Facing Apps

As described above, the activities around the drug class grouping and decision support were applied in the development of the three Patient Facing Applications in UNICOM

- HealthPass (Greece)
- PharmaWizard (Italy)
- InfoSage (USA)

During the demonstrations, cross linking of drug groups to decision support were tested in the interactions between Italian – Greek residents, Italian - American residents, and Greek – American residents.

For the decision support, the knowledge database of RxNorm was mainly used. To identify the Italian Products, IDMP was used, and to identify the American products outside the Minimal Data Set, the ATC Code was used.

The following examples were used:

- An American resident traveling to Italy dispensed an Italian brand of ibuprofen as a pain killer for an ankle strain. On the medication list of this patient an American diuretic is present, and also an ACE-inhibitor. When integrating the prescription of the Italian product in the medication list, the app generates a safety request to RxNORM, and gets in return an alert for possible renal failure form by concomitant use of 3 nephrotoxic substances. (pharmacodynamic interaction)
- An American resident traveling to Greece, with simvastatin (a statin) on the medication list, gets a prescription in Greece for amlodipine (a calcium anta)agonist for hypertension). Safety request to RxNorm issues a warning of rhabdomyolysis (degradation of muscle) due to a pharmacokinetic interaction, leading to steep increase of the concentration of simvastatin in the blood, and to toxicity. (pharmacokinetic interaction)
- An American resident traveling to Italy, a known poor metabolizer for CYP2C9, receives an OTC prescription for a painful tooth. He receives a warning from RxNorm that it would be better to refrain from taking ibuprofen, or at least half the dose, or take an alternative paracetamol. The risk of toxicity of ibuprofen it too high for this person. (risk of toxicity because of pharmaco-genetic variant)

Hence, we were able to perform tests using the resources developed for linked activity 4: cross linking drug groups and for linked activity 3: testing semantic interoperability of cross border transfer of medication lists.

5.7 IDMP and the quality of clinical data

5.7.1 Using the medication list to improve the quality of medical documentation

Drawing from experience in assessing polypharmacy within nursing homes, it became evident that highly reliable data on medication usage can be obtained from the eMAR systems (electronic Medication Management) utilized by nurses to prepare medication administration rounds. However, in many countries, the quality of medical records in this sector may present challenges. For example, there may be issues such as the absence of a current and comprehensive list of medical problems or indications.

This is particularly a problem for the automatic application of the more complex explicit criteria for (in)appropriate prescribing, as in the international STOPP/START list and the Beers' List. These complex criteria require the presence of interoperable essential clinical data.

A proposal was made to use these criteria, designed for assessment of the quality of prescribing, for the assessment of the completeness of the medical record.

We therefore studied the criteria involving medication (expressed in ATC) and clinical diagnoses.

A list was devised of medications that necessitated clinical data criteria for evaluating their appropriateness. For each medication on the list, the specific nature of the required clinical data was documented.

A program was developed to analyze individual medication lists for the inclusion of such medications. Following an assessment of the presence or absence of specific medical data, questions could be prompted regarding the presence or absence of missing information on particular clinical conditions. Physicians could respond with a simple "yes" or "no" to these questions (anticipated to be limited in number per patient), after which the problem list would be automatically updated in a structured and coded format.

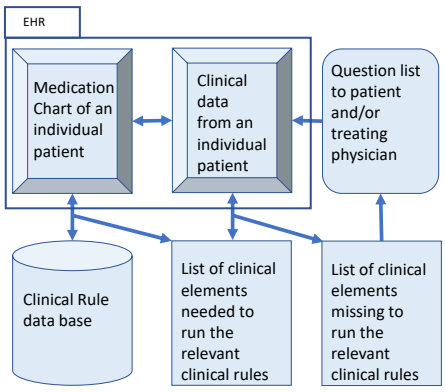

Figure 23. Repairing the quality of medical record through the medication list

This work was developed during the UNICOM project, as a master thesis at Ghent University,[50] resulting in a list of triggering medications with the corresponding inquiry for clinical data (see Annex 9).

- [505050] Bos M. Using Explicit Criteria for potentlially (in)appropriate prescribing to improve medical documentation. [Master Thesis] Ghent University 2023

5.7.2 IDMP and the Patient Summary

The International Patient Summary is an ISO Standard and is expected to become a corner stone of the European Health Data Space.

The FHIR specifications for this resource have been proposed[51] and the eHealth Guidelines related to the Patient Summary indicate the use of IDMP as a terminology for the medication list.[52] IHE profiles have been created for the resource.[53,54]

Applying this resource in actual work on Patient Summaries was hampered by the absence of sufficient material in the cross-border experiments for the international (or European) Patient Summary (IPS).

The practical implementation of IDMP in the variables list of the medication list in the Patient Summary is still under debate.

Finally, the implementation of IDMP in the Medicinal Product Dictionaries in the various countries is progressing but far from completed.

Hence, we have created the resources needed for linked activity 2: Quality Assessment of Clinical Data in patient summaries based on analysis of IDMP medication list, but could not perform actual tests on International Patient Summaries exchanged though the eHSDI cross border infrastructure.

In the EU project SemanticHealthNet, a proposal was put forward for a test to assess the quality of semantic interoperability during the transfer of Electronic Health Care Records content from one vendor to another vendor, either within a country or across borders.

The idea was to work with records from patients with heart failure that were recently updated after an exacerbation with hospitalisation and consultation of the discharge letter.

Such records would then be subjected to an automated examination of the appropriateness of prescribing and produce an evaluation report A. Then the content of the medical record would be transferred to another vendor, within the country or abroad. After the transfer of the electronic record the same analysis would be performed, resulting in a report B.

Comparison of Report A and Report B would confirm or question the semantic interoperability of this transfer.

[51] https://build.fhir.org/ig/HL7/fhir-ips/

[52] eHealth Network. Guideline on the electronic exchange of health data under Cross-Border Directive 2011/24/EU Patient Summary. Release 3.3, June 2023

[53] https://wiki.ihe.net/index.php/International_Patient_Summary_(IPS)

[54] http://www.semantichealthnet.eu/

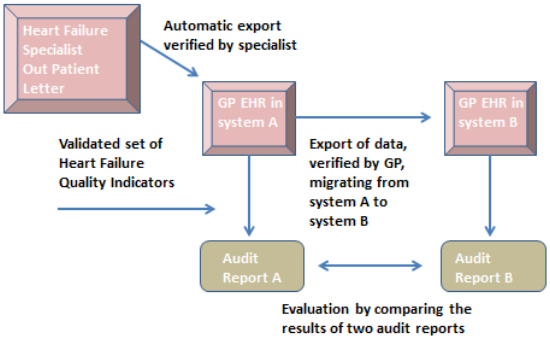

Figure 24. Quality control of semantic interoperability of electronic health records.

In the coming years, when IDMP would be completely integrated in a few countries, and the adaptation of the IPS to IDMP is completed, it will be fascinating to conduct such experiments.

6 Conclusions for IDMP and Clinical Care

IDMP was originally developed as a standard primarily for regulatory marketing authorization and pharmacovigilance purposes. However, the overarching ambition was to broaden its application across various domains related to medicinal products, ranging from prescribing and dispensing to supply chain management, drug utilization research, and pharmaco-epidemiological outcome assessment (including side-effects and comparative effectiveness research).

While the implementation of IDMP in the databases of regulatory authorities across Member States is underway, it remains far from complete. While the European Medicines Agency (EMA) may swiftly adapt IDMP for processing new medicines, the legacy conversion of over 400,000 older medicinal products presents a formidable challenge.

To showcase the practical utility of IDMP in clinical care, this project required the creation of a Minimal Data Set encompassing all Medicinal Product Packs of four substances (amlodipine, carbamazepine, ibuprofen, and simvastatin) across at least three countries (Greece, Italy, USA).

This Minimal Data Set served as a demonstration platform for multilingual access to drug information, along with linking to pharmacotherapeutic classes and decision support systems.

Commented [LN11]: The conclusions are a bit «short» and I miss here a paragraph on
Main achievements and challenges
next possible key steps to progress

7 Annexes

7.1 Annex 1. Drug Classification for Medical Education

7.2 Annex 2. Repository of Potentially Inappropriate Medication (PIM)

7.3 Annex 3. Administrable dose forms in EDQM

7.4 Annex 4. List of Substance Codes for the UNICOM Pilot Product List

7.5 Annex 5. ATC codes pertaining to the UNICOM Pilot Product List

7.6 Annex 6. Presentation to the Pistoia Alliance (August 2023)

7.7 Annex 7. Presentation to the WHO Collaborating Centre (

7.8 Annex 8. The Duran List of Anticholinergics

7.9 Annex 9. Triggers for completing clinical data based on PIM

8 Publications from this work

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.

Manuscripts in preparation

- INN Prescribing and Substitution Rules in Europe
- Validation of a Dose Form Ontology, based on EDQM