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Deliverable D9.2: Implementation Guidance for Identification of Medicinal Products (IDMP) in Medicinal Product Dictionaries

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Deliverable abstract

This document provides implementation and mapping guidelines for use of Identification of Medicinal Product (IDMP) data within Medicinal Product Dictionaries (MPD). It includes different scenarios of implementation depending on the structure of the MPD. It gives an overview on the controlled vocabularies/terminology from Substances, Products, Organisations and Referentials (SPOR) from the European Medicines Agency (EMA).

It will help MPD providers to use IDMP data for prescribing and for dispensing, nationally and for cross-border care.

Involved partners: IDMP1, IHD, ZINDEX, VIDAL, IEDOH, SNOMED, DWIZ

Keywords: Controlled Medical Terminology, Vocabulary, ISO Standards, SPOR, PMS, IDMP, Medicinal Product Dictionary, Mapping Controlled Vocabularies, Extraction Transformation Loading Process.

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List of abbreviations

Abbreviation	Complete form
ATC	anatomical therapeutic chemical classification
BoSS	basis of strength substance
CDS	clinical decision support
CoE	Community of Expertise
DADI	Digital Application Dataset Integration Project
eD	eDispensation
EDQM	European Directorate for the Quality of Medicines & HealthCare
EHR	electronic health record
EMA	European Medicines Agency
eP	ePrescription
ePI	Electronic Product Information
ETL	Extraction Transformation Loading
EU	Europe
EU IG	EU IDMP Implementation Guide
FHIR	fast healthcare interoperability resources
IDMP	identification of medicinal products
IG	implementation guide
ISO	International Organisation for Standardization
MAH	marketing authorisation holder
MPD	medicinal product dictionary system
NCA	national competent authority
OHDSI	observational health data sciences and informatics
PAI	precise active ingredient substance
PhPID	pharmaceutical product identifier
PS	patient summary
SNOMED CT	SNOMED clinical terms
SPC, SmPC	summary of product characteristics
SPOR	substances, products, organisations and referentials

TS	technical specification
WHO-UMC	Uppsala Monitoring Centre
XEVMPD	extended EudraVigilance medicinal product dictionary

1 Executive summary

UNICOM is a European Commission supported Innovation Action that focuses on improving patient safety and healthcare by facilitating the flow of standardised “trusted data” about medicines from the regulatory agencies through to clinicians’ desktops and to patients via apps.

It does this by focusing on the implementation of the International Organization for Standardization (ISO) suite of IDMP (Identification of Medicinal Products) standards in national competent authorities and then use of that data in patient care.

The IDMP suite of standards is about the accurate identification of medicines and UNICOM’s goal is to have them widely implemented.

The European Medicines Agency (EMA) has implemented the ISO Standard of Implementation of Medicinal Products (IDMP) into regulatory processes and thus also National Competent Authorities are required to adapt their product data to the IDMP Standard.

This Implementation Guide for Medicinal Product Dictionary Provider (MPD) gives guidance on how to interact with trusted National Competent Authorities´ (NCA) data as a single source of truth for description of the medicinal products.

The IDMP common data model and the EMA PMS Implementation Guide have been used as a core element in this initiative for harmonising the terminologies used as well as facilitating the cross-border ePrescription in the EU.

The interoperability in ePrescription is a focal area for the UNICOM project as it looks to support cross border care involving medication.

This implementation guide provides insights into how the implementation of IDMP could be managed such that it most effectively supports the flow of medicinal product identification data from the “trusted source” of the NCAs to clinicians and patients through the MPD that operate in the patient care systems throughout the European Community.

2 Content of the deliverable

2.1 Contents of the deliverable

This deliverable is an IDMP implementation and mapping guide for MPD providers. It reflects the status of IDMP as of 31.5.2022 (the submission date for this deliverable).

This IG will explain how to implement IDMP data into an drug dictionary, using the IDMP drug model. After describing the controlled vocabularies of SPOR and the IDMP data model for drugs, this IG will explore different implementation approaches including mapping to the IDMP PMS data and creating an IDMP drug extension data directly from national drug regulatory information. Lastly, this IG will consider the benefits and challenges of each approach, and how using the IDMP product model and SPOR attributes values supports this ambitious interoperability goal.

2.2 Objective and scope

MPDs in eHealth systems demand very consistent and very high data quality to describe medicinal products and provide their additional functionalities such as clinical decision support.

To get good data quality, the data providers need to understand IDMP as well as possible and they need help to do this. IDMP standards are complex, and examples are still fragmentary.

The aim of this deliverable is to provide insights into if and how the implementation of IDMP could be managed such that it most effectively supports the flow of medicinal product identification data from the “trusted source” of the NCAs to clinicians and patients through the MPD that operate in the patient care systems throughout the European Community.

The objectives of this delivery D9.2 is to provide as much clarity as possible on

- The structured Extraction, Transformation, and Loading process (ETL) to implement IDMP data
- The appropriate mapping process to map MPDs data to IDMP data based on the MPD structure
- Any recommendations that may help to achieve the implementation and the mapping of IDMP data to the MPD data

Other deliverables in UNICOM look at other aspects of implementing IDMP into MPD – for example "D9.1 IDMP versus NCAs IDMP data gap analysis"

REFERENCE TO UNICOM DELIVERABLE D9.1: AN ANALYSIS OF THE IDMP MEDICINAL PRODUCT IDENTIFICATION DATA PROVIDED BY NCAS (AND SPOR) COMPARED TO THAT NEEDED IN MPD FOR CLINICAL CARE AND FOR SECONDARY USES

D9.1 is focused on the following core points

- The requirements of MPD for medicinal product identification data, for the use case of identifying medicinal products in a cross-border patient care and ePrescription

- The data flows of medicinal product identification data from NCAs (and SPOR) to MPDs

- An understanding of what is likely to be provided by the NCAs (and SPOR) and what the structured format of that data is likely to be

- The congruence, challenges, and gaps between the existing MPDs´ data and the IDMP data

- Equivalence and interchangeability in patient care and ePrescription

Equivalence and interchangeability are themselves qualitative concepts that depend on their use case; this document focuses on how to best Implement IDMP to MPD for cross-border product identification in patient care.

Other deliverables in UNICOM look at other use cases – for example in pharmacovigilance "D8.7 IDMP Coding Principles and Guidance for ICSRs".

Reference to

D8.7 IDMP Coding Principles and Guidance for ICSRs

One of the biggest challenges in developing this implementation guide is to achieving clarity on what it is that IDMP will provide. The following is based on what is known and understood regarding IDMP and its implementation from the various standards documents and implementation guidance as of May 2022. The implementation of ISO 11615 and IDMP PMS data discussed here is that put forward by the EMA in its Implementation Guide V2.0 (version 2021-02) using the Fast Health Interoperability Resources (FHIR).

3 Methods

3.1 Summary of approach

To undertake an analysis of how the implementation of IDMP could be managed effectively in MPD, the following steps were undertaken:

- Listing the data elements that are needed to precisely identify a medicinal product via IDMP data in a medication lists in a cross-border patient care
- Describing how to make a gap analysis of these IDMP product identifiers compared to the MPDs´ congruent data elements
- Describing the patterns of models of MPDs and depending on it – the ways how to best implement and map IDMP data
- Analysing similar mapping projects in standard terminologies such as SNOMED CT
- Defining step by step IDMP data integration as a structured process of Extraction, Transformation and Loading (ETL)
- Giving best practice tips based on what is known at the time of writing (May 2022), whilst also
- Describing some of the unknowns of IDMP provision and implementation
- Working with a pool of substances and products which could be used for testing purposes
- Organising a CoE on "Draft Implementation Guide of IDMP into MPD" to understand the pain points of MPD providers in IDMP to implement those into this IG as far as possible

From this analysis it was then possible to offer a set of recommendations as to how IDMP implementation into MPDs could be managed to meet the needs of MPD to precisely identify medicinal products in a cross-border ePrescription based on IDMP product data.

Reference to the CoE " Unicom – Pilot Product List ", November 2020 link to all CoE

3.2 Community of Expertise for MPD provider

Reference to the CoE 25.2.2022, "Draft Implementation Guide of IDMP in MPD" Link to all CoE

For a better understanding of what MPD provider will need to implement IDMP into their MPDs, we organised a CoE on "Draft Implementation Guide of IDMP into MPD". With question-and-answer sessions via MentiMeter we got feedback on what the pain points of MPD provider in IDMP are.

3.2.1 Feedback on type of support needed

During the CoE on IDMP implementation for MPD, we started a MentiMeter analysis on the question "What type of support would you need to start an ETL Process on implementing IDMP into your MPD?" In the graphic below you can see the result. We put in green the points covered by this IG. In black and red those points which are not part of this document.

What do you wish as help for your IDMP implementation?	Answer type(s)
Lots of examples of products, especially tricky products.	examples
Not directly involved in this work (therefore, no pain points) ;-).	
Political committment of stakeholders	
A good cookbook	step by step guideline
Examles	examples
A public list of pitfalls and solutions	pitfalls and solutions
mapping this and harmonize this with my country referenced vocabulary (WHO ATC)	step by step guideline
Guideline for implementation in personal health record	step by stepguideline
Depends on implementation date	
process to Dose form EDQM. A methodology to perform a first gap analysis	step by step guideline for gap analysis and training
Examples and trainings	examples and training
A business case outlining the profits of moving to idmp for a local mpd from a cost benefits persperctive	use cases (based on that you can make a business case yourself, cannot be done centrally)
Use cases	use cases
A guideline for implementation in pharmacovigilance	step by step guideline
Multiple mapping grids_ open format	
Access to example data (we'd like to see SMS and PMS up and running)	examples
A SNOMED-IDMP cross-map would really facilitate this, as we are already fully mapped to SNOMED (and local version: dm+d)	cross-maps
Gap analysis, use cases, guidelines to implementation	use case/step by step guideline for gap analysis and mapping
Single source of truth	
Pharmacovigilance	
Dispensing Traceability Interoperability	
Regulatory complianceStructure internal databaseMore efficient decision making	
Interoperabilty	
Track and trace in the world wide	
Cross border	
Is there a use case involved in patient's sign-off from hospitals > general practice (and/or home)? I.e., especially if the way drugs are dispensed in hospitals is not the same way in which they are available to the patient post-release.)	use case
Step by step guideline is appreciated	step by step guideline for mapping

Figure 1 - MentiMeter: How to support you in implementing IDMP?

3.2.2 Approach to these wishes for support

This table gives all the comments from the attendees of the Community of Expertise webinar; responses are given where possible and for those that are not the main focus of this deliverable (e.g. the response about pharmacovigilance and ICSR) BUT it is not possible, within the scope of this project, to provide positive responses for all.

Table 3-1 Where to find Answers

WISHES FOR TYPE OF SUPPORT	WHERE TO FIND IN THIS IG OR IN UNICOM
A business case outlining the profits of moving to IDMP for a local MPD from a cost benefits perspective	UNICOM is not currently able to provide this specifically for MPD

A good cookbook; Step by step guideline is appreciated	"IDMP Implementation Guidance"
A public list of pitfalls and solutions	Chapter "Challenges in Implementation"
A SNOMED-IDMP cross-map would really facilitate this, as we are already fully mapped to SNOMED (and local version: dm+d)	Chapter "IDMP and SNOMED CT"
Access to example data (requested most often in this CoE) especially tricky products	UNICOM has some example data in its "Pilot Product List" but this is currently for use within the UNICOM project unfortunately
Cross border product identification	D9.1 AN ANALYSIS OF THE IDMP MEDICINAL PRODUCT IDENTIFICATION DATA PROVIDED BY NCAS (AND SPOR) COMPARED TO THAT NEEDED IN MPD FOR CLINICAL CARE AND FOR SECONDARY USES
Gap analysis to implementation	Chapter 4.1.2 First gap analysis from MPD to IDMP data
Guideline for implementation in personal health record	Probably, this is through an MPD. An app will use the data of an MPD. An app builder will not use IDMP. So this point is covered by the guidelines for an MPD.
Improved wording: IDMP tends to confuse organizations (EDQM), systems (PMS, SMS) vs. code systems and value sets.	We improved the wording in this document
Political commitment of stakeholders	"IDMP and MPDs legal Background"
Mapping and harmonizing this with my country referenced vocabulary (WHO ATC)	See chapter concerning ATC code
Structure internal database	Chapter Implementation depending on the MPD model
Training sessions by international experts for the standardization process to Dose form EDQM.	This would be a request to EDQM, this is not part of this IG.
Use cases	Chapter 4.1.4 Use Cases for IDMP in MPDs for product identification
A guideline for implementation in pharmacovigilance	D8.7 IDMP Coding Principles and Guidance for ICSRs

3.2.3 Statistics on structured standardisation process versus EDQM dose forms

The EDQM Pharmaceutical Dose Form terminology is one of the foundation terminologies that is used in the identification of medicinal products. Therefore, during the CoE on IDMP implementation for MPD, we started a MentiMeter analysis on the question "Has your organisation already started an EDQM

standardisation process?" to have a sense of how organisations are progressing with their IDMP implementation. In the graphic below you can see the result.

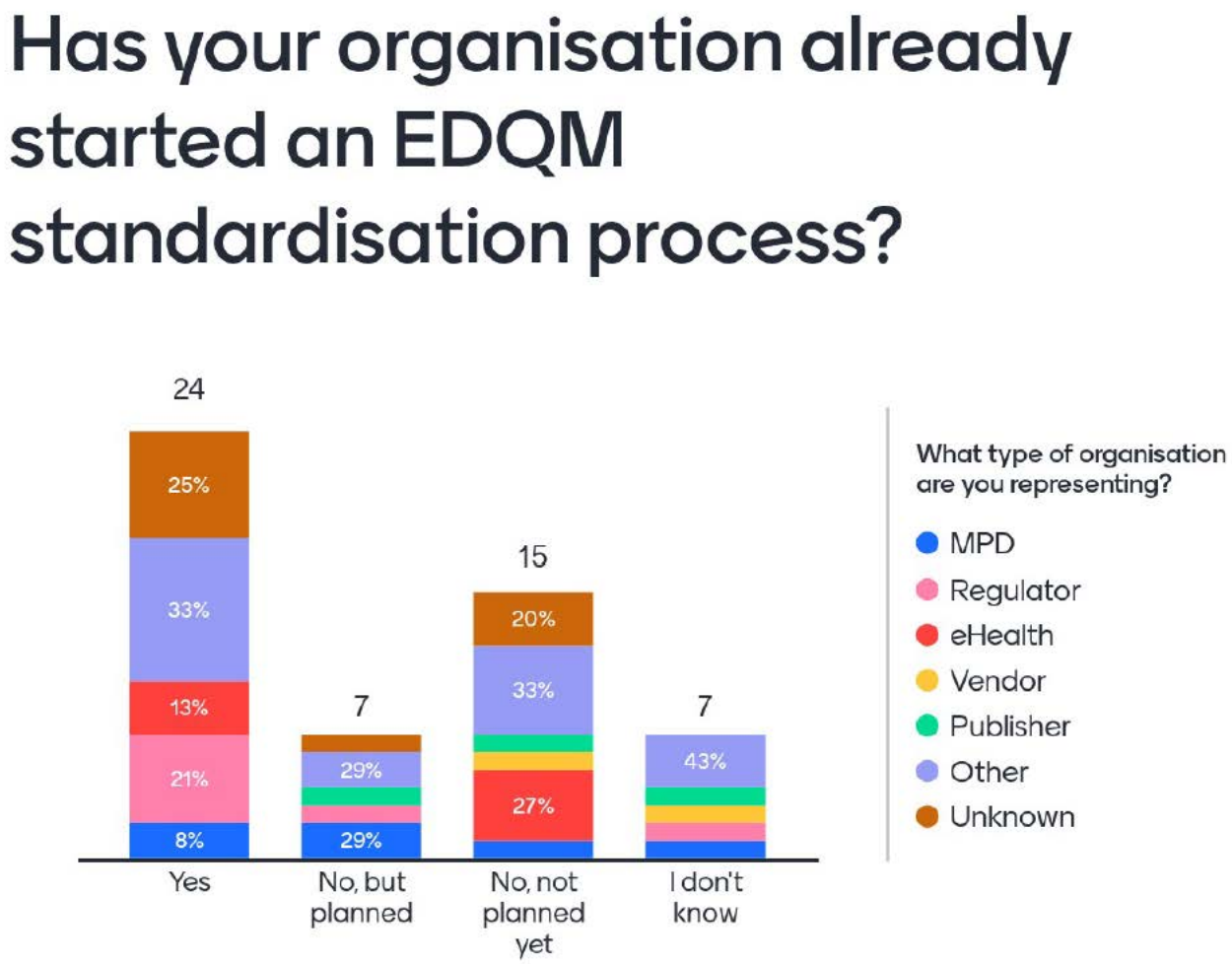


Figure 2 - Organisation with an EDQM standardisation process analytic

The majority of organisations of all types had indeed started their mapping process, with others having the mapping planned, but a significant number have not started, including both eHealth and MPD organisations, indicating that guidance is definitely required.

Reference to the CoE 25.2.2022, "Draft Implementation Guide of IDMP in MPD"

https://unicom-project.eu/all-community-of-expertise-webinars-in-a-nutshell/

Source (retrieved 13.1.2022):

Mapping Guidance for EDQM to SNOMED CT Pharmaceutical Dose Form Mapping

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

4 Context of IDMP and MPDs

REFERENCE TO UNICOM DELIVERABLE D9.1: AN ANALYSIS OF THE IDMP MEDICINAL PRODUCT IDENTIFICATION DATA PROVIDED BY NCAS (AND SPOR) COMPARED TO THAT NEEDED IN MPD FOR CLINICAL CARE AND FOR SECONDARY USES

The document D9.1 provides requirements for the identification and description of medicinal products in patient care by examining existing medicinal product dictionaries that are used in patient care and particularly by examining the standards that govern them, the use cases that they support, and the challenges they face and overcome. It draws on investigative work undertaken in two previous tasks in Work Package 9; T9.1 - a characterisation of the MPD (commercial/national) that operate in EU member states and T9.2, which characterises the community prescribing and dispensing software systems that that operate in EU member states facilitating the main community-based care medication business processes of prescribing and dispensing.

The document D9.1 is about the gap between IDMP data needed for regulatory purposes and IDMP data needed for clinical care and secundary use in MPDs.

4.1.1 The Identification of Medicinal Products (IDMP)

Reference to Technical Specifications (TS) 16791 https://www.iso.org/standard/75312.html

Reference to Technical Requirements (TR) 14872 https://www.iso.org/standard/65714.html

Recognising the technical challenges of identifying medicinal products across disparate regions, ISO designed the IDMP Standard as a mechanism to standardize the structure, content, and semantics of product data and to make it possible to identify them globally.

The IDMP Standards are a set of 5 ISO international standards that has been developed in response to a worldwide demand for internationally harmonised specifications for identification and description of medicinal products. IDMP provides the basis for the unique identification of medicinal products, which facilitates the activities of medicines regulatory agencies worldwide by jurisdiction for a variety of regulatory activities (development, registration and life cycle management of medicinal products, pharmacovigilance, and risk management).

In IDMP Standards messaging specifications are included as an integral part of the standards. They describe and protect the integrity of the interactions for the submission of regulated medicinal product information in the context of the unique product identification; they include acknowledgement of receipt including the validation of transmitted information. Health Level Seven (HL7) FHIR Message Exchange are normative within the IDMP Standards.

IDMP Standards are completed with Implementation Guides, as well as with:

- Technical Specifications (TS) 16791 (provides guidance for the identification of medicinal products by using international supply chain Standards, securing traceability, safe supply chain and other market requirements)
- Technical Requirements (TR) 14872 (Requirements for the implementation of the Standards for the identification of medicinal products for the exchange of regulated medicinal product Information)

The ISO IDMP standards have been designed to cover many aspects of information about medicinal products not purely identification, to support a broad range of regulatory contexts. An overview of the data elements contained in the ISO IDMP standard is shown (for illustration purposes only) in the figure below.

Source (retrieved 8.12.2021):

https://www.ema.europa.eu/en/documents/other/introduction-iso-identification-medicinal-products-spor-programme_en.pdf

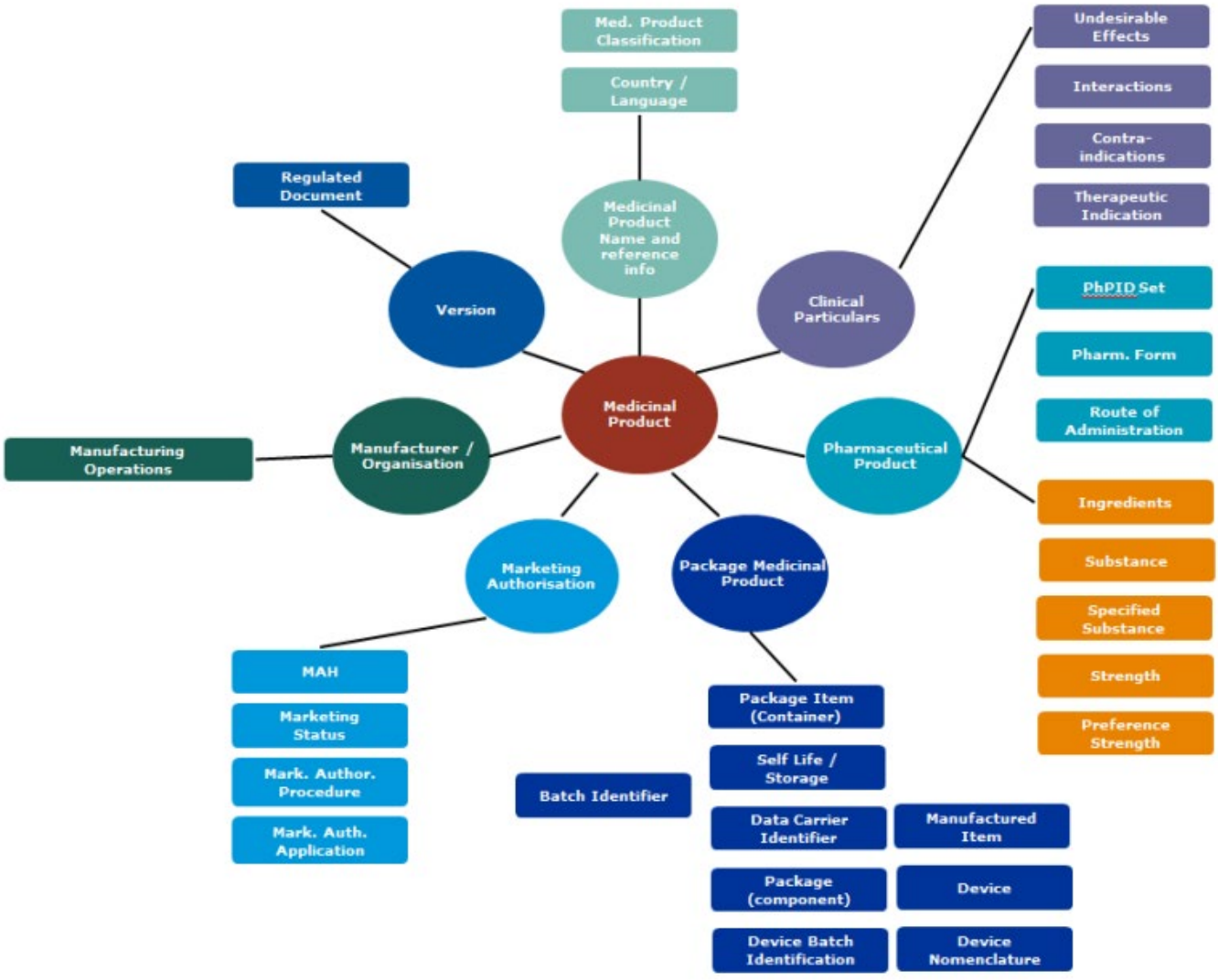


Figure 3 - Overview of ISO IDMP data elements - for illustration purposes only

4.1.2 The Medicinal Product Dictionary

The medicinal product dictionary plays a central role in storing and disseminating information about medicinal products for prescription and dispensation in a country.

The MPD is sourced with different types of information from NCAs´ marketing authorisation process, from regulated text files such as the SmPCs, and from other scientific documentation.

The MPD provides a structured repository of information from these sources and makes them available to multiple types of users such as clinicians (via supporting software and systems), patients (via online queries or apps), e-Health authorities and others. MPD focusses on marketed and available medicinal products.

In this the IDMP product data provide a complete and accurate structured information on medicinal products, provided by a single source of trust, the NCA.

Reference to the Community of Expertise webinars in a nutshell

CoE " IDMP and Medical products dictionaries", April 2021

CoE " IDMP Implementation Guide for Medical products dictionaries", February 2022

Link to All CoE

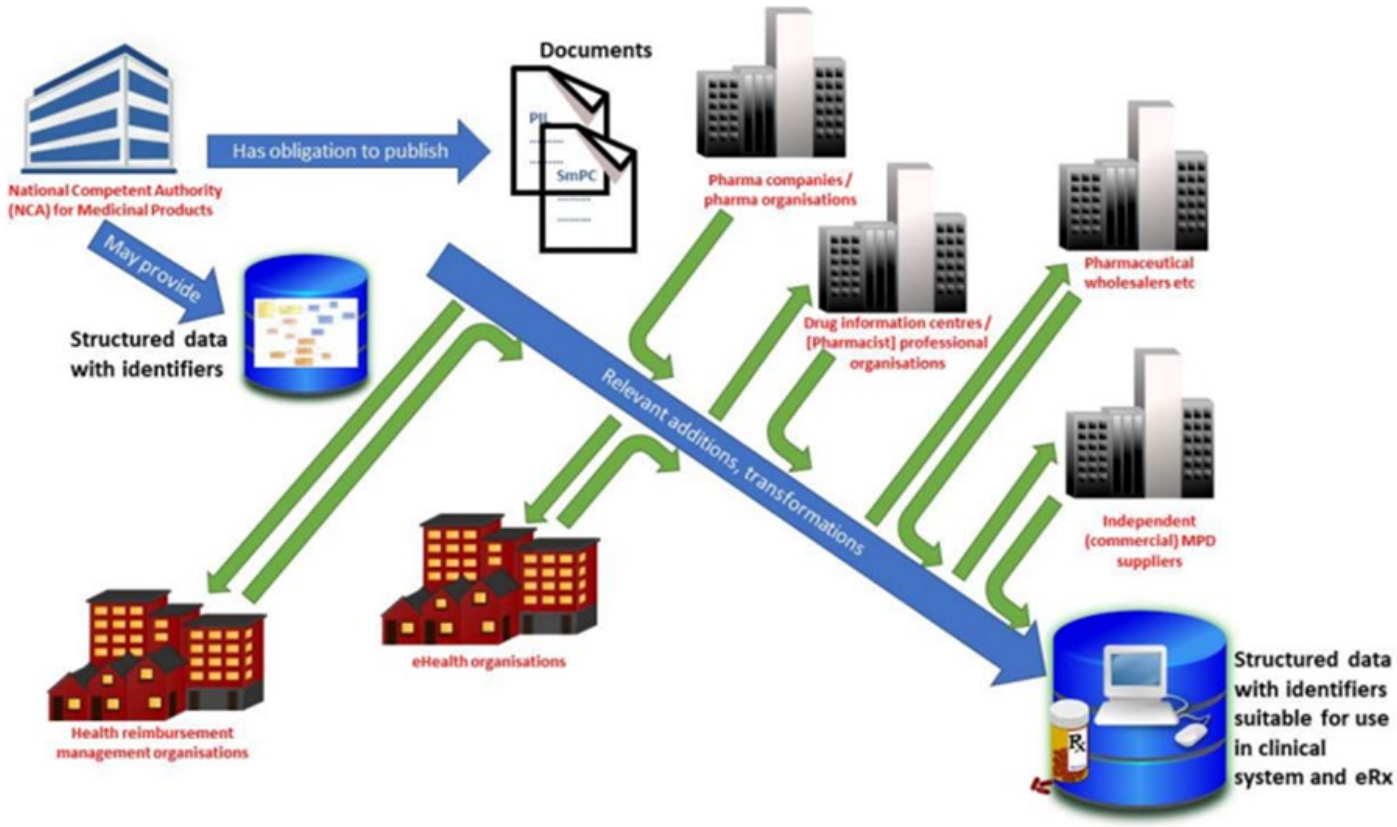
4.1.3 The Journey from authorized Product Data to ePrescription (eRx)

Everywhere in healthcare, across the world, within hospitals and private practices, regulatory agencies, medicinal product dictionary providers and medical product manufacturers, insurance companies and at the heart of every patient interaction, there is a common challenge: how do we identify products?

Why? The journey of product data from the NCAs to eRx to the patient is an arduous one. In fact, there is no single notion of "product data," nor is there a singular notion of "medication". Views and requirements of a product can be very different.

One important aspect to be considered for MPD data is knowing the source(s) of their information, and therefore how various types of information flow into them. The primary source of information about medicines for MPDs is the Summary of Product Characteristics – the SmPC. The SmPC provides the regulated, scientifically validated information that assists healthcare professionals in prescribing and dispensing. This source data needs to be extracted from in some instances, free text, or structured text, and it will be augmented with other information (e.g. clinical and reimbursement information) before the MPD is fit for purpose within a healthcare domain. The diagram below and the description of the discussion following, examines the process to produce an MPD for ePrescription and clinical use.

Figure 4 Data flow of trusted NCA´s product data via MPD suppliers to eRx



REFERENCE TO UNICOM DELIVERABLE D9.1: AN ANALYSIS OF THE IDMP MEDICINAL PRODUCT IDENTIFICATION DATA PROVIDED BY NCAS (AND SPOR) COMPARED TO THAT NEEDED IN MPD FOR CLINICAL CARE AND FOR SECONDARY USES, CHAPTER 6.5.1.2. STRUCTURED PRODUCT INFORMATION FROM NCAS

NCAs from twelve countries provide structured data and identification and description of medicinal product concepts – either at the product or package level or both. These countries are CZE, DNK, POL, PRT, AUT, BEL, HRV, EST, FIN, SWE, NOR and ESP.

The characterisation of MPD according to the provision of medication concepts, descriptions and identifiers needed to support the business processes of patient care yielded two clear patterns– those with a "full set" of real and abstract product and package concepts versus those that have primarily actual package concepts. D9.1 analysis these two major patterns for the structure of an MPD, and a small number of variations in the flow of data from source at the NCA to MPDs.

EMA website for information on centrally authorised products (CAP):

https://www.ema.europa.eu/en/medicines

HMA website for products authorised by the Mutual Recognition or Decentralised procedures:

https://www.hma.eu/mriproductindex.html

4.1.4 Use Cases for IDMP in MPDs for product identification

REFERENCE TO:

INTERNATIONAL ORGANIZATION FOR STANDARDS. ISO/TS 19256:2016 HEALTH INFORMATICS: REQUIREMENTS FOR MEDICINAL PRODUCT DICTIONARY SYSTEMS FOR HEALTH CARE

The ISO TS:19256 defines an "MPD system" as something that "stablishes a consistent representation of medication concepts (set of identifiers) at various levels of detail and with meaningful relationships between the concepts, to support parts of several processes in healthcare in which medication plays a role". The TS also provides a goal or raison d'être for an MPD system in terms of interoperability: "to offer various parties in healthcare a complete overview of available medicinal products in such a way the (elements of the) concepts and the descriptions and identifiers can be used interoperable in a variety of other healthcare information systems.

The specification contains a section ("Relation with ISO IDMP standards") which describes how its content relates to the ISO IDMP standards. One of the aims of this is to facilitate "accuracy and consistency of the use of concepts and terms according to the ISO IDMP standards" but it also acknowledges and highlights two important considerations:

1.) the development, supply and use of medicinal products is highly regulated; this directly affects how medicines are named and therefore identified

2.) cultural differences in the practice and delivery of care and national legislation and remuneration practices require MPD meet specific local, regional and/or national needs; this directly affects the specific collection of 'medication abstractions' which must be identified, defined and related to each other within an MPD

The specification suggests that information structures should be "consistent and appropriate" according to the ISO IDMP Standards"; however the reason for this and a sense of how much consistency and appropriateness is possible or desirable is not detailed.

It acknowledges that the IDMP standards are primarily designed for the medicines regulatory process rather than patient care. Therefore not everything in the IDMP standard is required to be supported in an MPD. But it makes a clear and explicit statement that it expects that, at some point in the future – and indeed there is a section on "Migration" to acknowledge this journey, MPD "will be created and maintained in accordance with the IDMP series". The specification also explicitly states that when MPD use ancillary concepts in identification of medicinal products (substances, dose forms and routes of administration etc.) the same concepts and their identifiers be as used in IDMP and in the regulatory domain, although it acknowledges that "different views" may be needed and suggests that this may require "mapping".

The IDMP standards as used by EMA and the NCAs are primarily designed for the medicines regulatory processes rather than patient care and ePrescription. And even in this regulatory area the differentiation of IDMP data depending on the specific regulatory use case such as PMS, DADI, Falsified Medicines, pharmacovigilance, and clinical studies was still a work in progress at the time of writing this document.

Supply of medicines is highly regulated, and different from country to country.

For example:

- "Variquel 0.2 mg/ml, solution for injection" (UK)
- "Terlipressin Acetate 1 mg solution for injection" (Sweden)

These are equivalent products, although their name and description are different, because they both contain 0.2mg/mL of terlipressin acetate.

So, each country needs to express their medicinal products in the way that fits with their national regulation and their healthcare culture and practice.

There is a medical product abstraction in the IDMP standards (the PhPs); however, at this point in the UNICOM project it remains unclear as to a) how those abstractions are fully defined and b) which use case(s) they are designed to meet.

The bridge between national MPD data and IDMP data allows us to identify generic products even if they are described differently in different countries. IDMP allows us to interchange information even though we cannot use the same concepts and data models.

Use cases related to eRX which are relevant to MPD provider and in the scope of this document are:

- Identifying medicinal products in patient medication lists (including cross-border care)
- Facilitate international interoperability of medication concepts
- Provide compatibility with the IDMP model for identification of medicinal products cross-border
- Electronic data exchange of medicinal products identifier compatible with the IDMP standard

Statistic on use cases for implementing IDMP data

During the CoE on IDMP implementation for MPD, we started a MentiMeter analysis on the question "Use cases for implementing IDMP data?". In the graphic below you can see the result.

Keyword: what are three use cases for implementing IDMP data?

Figure 5 - Word cloud on answers concerning use cases for implementing IDMP data

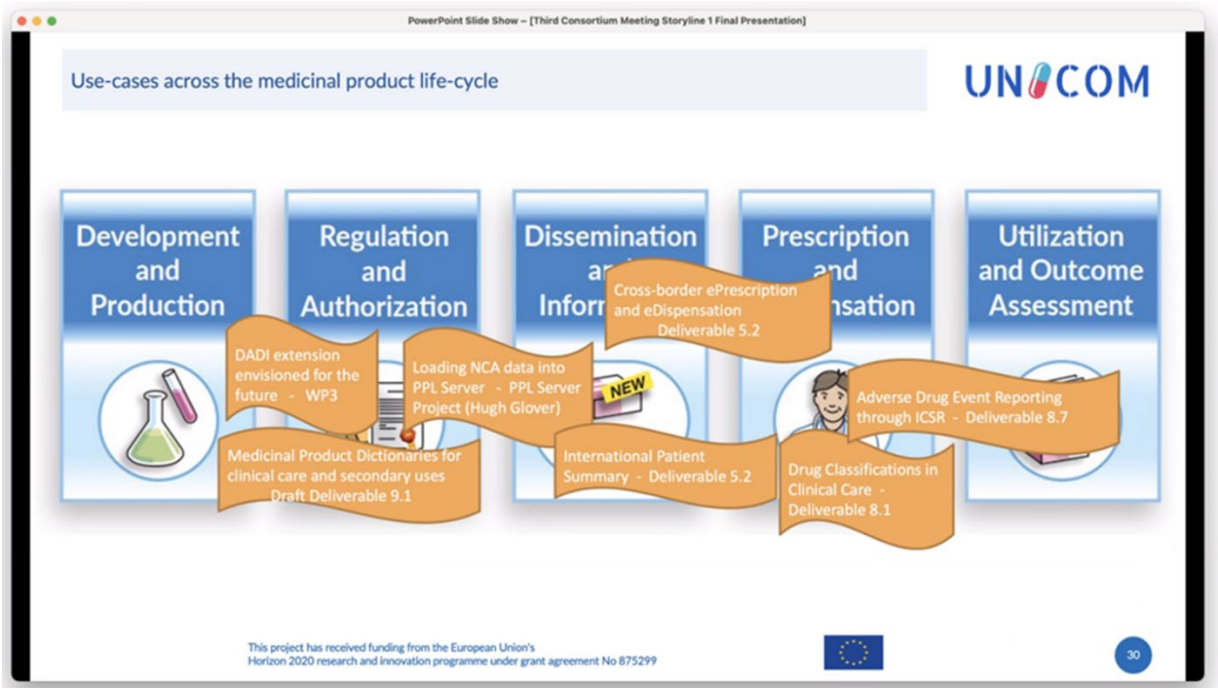


Figure 6 - Use-cases across the medicinal life-cycle

4.1.5 IDMP documentation

Data on medicines (ISO IDMP standards): Overview from EMA website:

https://www.ema.europa.eu/en/human-regulatory/overview/data-medicines-iso-idmp-standards-overview

4.1.6 IDMP and MPDs legal Background

There are no legal requirements for MPDs to use IDMP data yet. There are even no legal requirements for NCAs to publish their structured product data in form of IDMP data yet.

The only legal requirement is (as of today) EMA´s timeline for making the upload of IDMP based regulatory data from industry to NCAs mandatory in the DADI Project (see chapter 4.1.9). The implementation of these new IDMP based forms supports the EU requirement to integrate ISO IDMP standards for human medicines. The PMS data model will link to DADI. It is planned to go life at the end of 2022 for new products in the central procedure evaluated by EMA.

5 SPOR Standardised Vocabularies

Reference to EMA SPOR Portal

The SPOR Portal contains the following contents:

SPOR documents and other content, a Database with organisation data which refers to a dictionary of Organisations and their locations details and Referential data which refers to Lists and Terms of IDMP ontology.

https://spor.ema.europa.eu/sporwi/

5.1 Substance, product, organisation and referential (SPOR) data of EMA

The European Medicines Agency (EMA) is in the process of implementing the standards developed by the International Organization for Standardization (ISO) for the identification of medicinal products (IDMP).

EMA is implementing the standards in a phased programme based on the four domains of master data in pharmaceutical regulatory processes: substance, product, organisation and referential (SPOR) master data.

The ISO IDMP standards specify the use of standardised definitions for the identification and description of medicinal products for human use.

Their purpose is to facilitate the reliable exchange of medicinal product information in a robust and consistent manner.

They help to ensure wide interoperability across global regulatory and healthcare communities, which is critical in ensuring accurate analysis and unambiguous communication across jurisdictions.

Commission Implementing Regulation (EU) No 520/2012 (articles 25 and 26) obliges European Union (EU) Member States, marketing authorisation holders and EMA to make use of the ISO IDMP standards. This will impact on many areas of the pharmaceutical regulatory environment, both in the EU and other regions.

Four domains of master data and management

The four SPOR services cover the four domains of SPOR master data:

- Substance Management Service (SMS) - harmonised data and definitions to uniquely identify the ingredients and materials that constitute a medicinal product.
- Product Management Service (PMS) - harmonised data and definitions to uniquely identify a medicinal product based on regulated information (e.g. marketing authorisation, packaging and medicinal information).
- Organisation Management Service (OMS)- data comprising organisation name and location address, for organisations such as marketing authorisation holders, sponsors, regulatory authorities and manufacturers.
- Referential Management Service (RMS)- lists of terms (controlled vocabularies) to describe attributes of products, e.g., lists of dosage forms, units of measurement and routes of administration.

While the ISO IDMP standards relate to human medicinal products, SPOR applies to both human and veterinary domains. Human and veterinary medicines will use the same SMS, OMS and RMS services in terms of data, format, and processes for submitting and maintaining master data.

The EMA together with the European Commission, European Union (EU) Network Data Board and EU ISO IDMP Task Force have endorsed a phased implementation of the ISO IDMP standards. This will allow lessons learnt during each phase to be applied to subsequent phases, processes, and systems to mature over time and stakeholders to gain an understanding prior to the full roll out.

The first phase of SPOR implementation focuses on delivering the RMS, SMS and OMS, which lay the data foundations for the subsequent delivery of PMS.

OMS and RMS are operational and enable organisation and referential data to be entered once and reused many times in MPDs and other business processes and related regulatory procedures.

The submission and maintenance of data on authorised human medicines is already mandatory since July 2012. This is based on a format called Extended EudraVigilance Product Report Message (xEVPRM), which will be replaced by the ISO IDMP compatible format.

RMS contains 152 lists (and growing) comprising 125K+ terms from different maintenance organisations such as EDQM standard terms (dosage forms, routes of administration); WHO (ATC Human, ATC Vet); and MSSO (MedDRA).

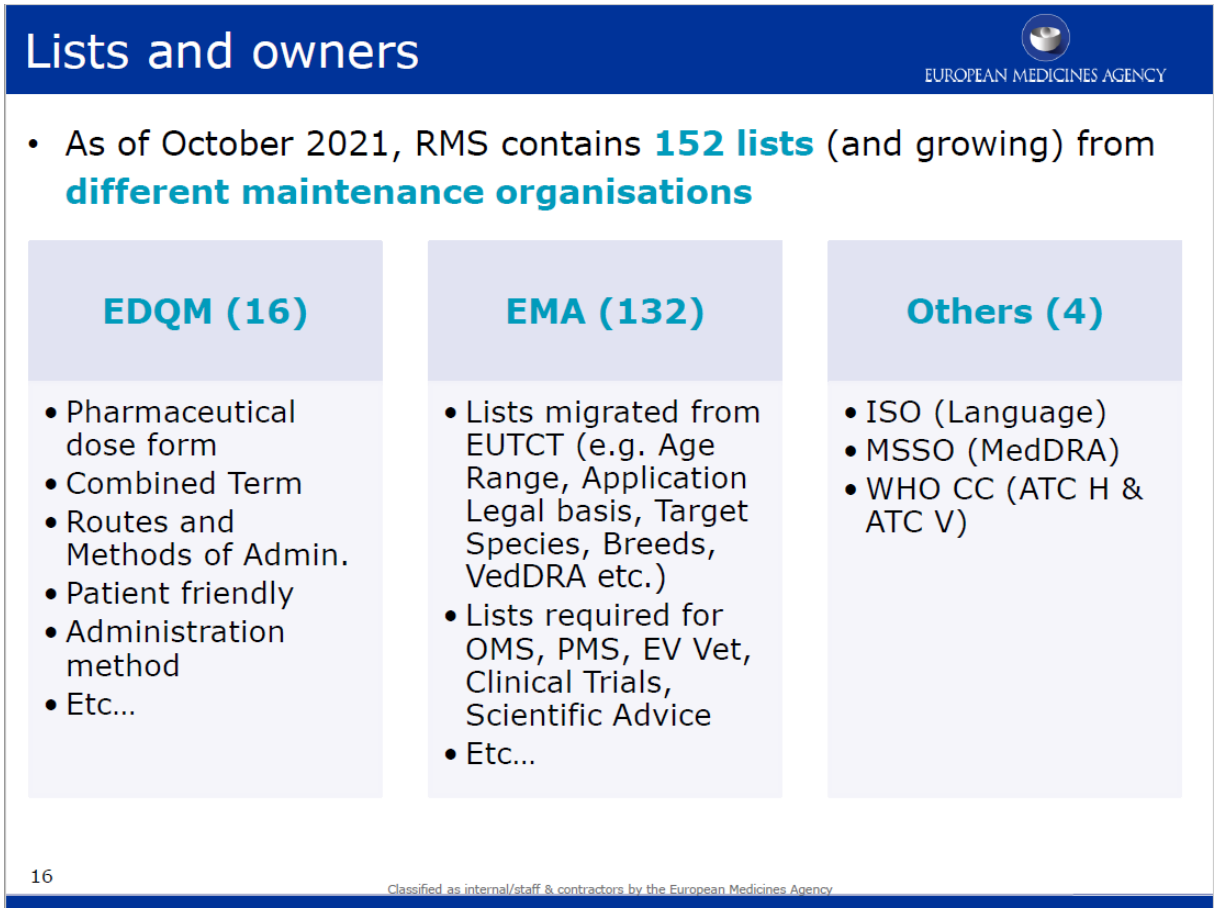


Figure 7 - RMS lists and owners

5.2 Access to the SPOR Referentials

5.2.1 EMA SPOR Portal

EMA´s Industry Webinar - Introduction to RMS services and activities (Nov. 2021) *https://youtu.be/VLrFcwQbsVw*

Manuals, documents, technical guidance to SPOR - How to search, view, export data and web user manual in RMS web portal:

https://spor.ema.europa.eu/rmswi/#/viewDocuments

You will find the EMA SPOR Portal homepage here:

https://spor.ema.europa.eu/rmswi/

The SPOR Portal is a public website. Anyone with access to the internet automatically possesses 'read-only' guest user access. Users registered for any EMA application, and after they log in, will also have some level of download access which is relevant for MPD provider.

Link to create a new EMA account:

https://register.ema.europa.eu/identityiq/home.html

The help file on how to register is here:

https://register.ema.europa.eu/identityiq/help/selfregister.html

RMS All these lists will be held in RMS:

(Source RMS web user manual version 1.0, retrieved 8.12.2021)

		RMS All these lists will be held in RMS				
		RMS/EUTCT	EDQM	Bfarm/ UCUM*	WHO	MSSO
		- Country/Language - Target species, Vet lists - EudraCT lists, TIGes lists, etc - VedDRA	- Dosage Forms - Routes of Administration - Containers/packaging - Units of Presentation	- Units of measurement * Done by EMA in the first phase	- ATC Human - ATC Vet - INN	- MedDRA
		Lists in RMS to which stakeholders have access				
NCAs	Download/access lists via RMS	Yes	Yes	Yes	**Yes**	Yes
NCAs	Requests changes to lists/terms via RMS	Yes Mostly for legacy Unlikely in other cases, Industry should have done it in advance	Yes Mostly for legacy Unlikely in other cases, Industry should have done it in advance	Yes Mostly for legacy Unlikely in other cases, Industry should have done it in advance	**Request to WHO first and then to EMA**	No, request to MSSO Only available in EMA via updates from MSO
NCAs	Add/amend translations via RMS	Yes	No, through EDQM only	Yes	**Yes**	No
INDUSTRY	Download/access lists via RMS	Yes	Yes	Yes	No Browse only Access through WHO	No Browse only Access through MSSO
INDUSTRY	Requests changes to lists/terms via RMS	Yes	Yes	Yes	**Request to WHO first and then to EMA**	No, request to MSSO Only available in EMA via updates from MSO
INDUSTRY	Add/amend translations via RMS	No	No	No	No	No

Figure 8 - RMS lists and stakeholder access

5.3 Using the SPOR Referential

In addition to the ISO IDMP Standards, additional, more detailed specifications and guidance are required to understand the implementation of ISO IDMP by the EMA. These are outlined in here.

Table 5-1 - IDMP Implementation Guides

Specification/Guide	Description	Responsible organisation
ISO IDMP Standards	▶ Define the required data elements and their structure ▶ Provide 'business-level' description of IDMP	ISO TC 215 Working Group 6
ISO IDMP Implementation Guides (Technical Standards)	▶ Define the technical details on how to implement the standards ▶ Include field formats, business rules etc.	ISO TC 215 Working Group 6
HL7 Messaging Specifications	▶ Define the messages that will be used to exchange IDMP information ▶ Based on existing HL7 'Common Product Model' standard (similar to FDA's SPL)	HL7

Regional Implementation Guides	▶ Interpretation of fields specifically for the regional regulatory environment ▶ Guidance on processes of submitting and updating data	Regional regulators
EMA PMS Implementation Guide	▶ Interpretation of fields specifically for the European regulatory environment ▶ Guidance on processes of submitting and updating data	EMA

Regional implementation guides define details of implementation that are specific to a jurisdiction. This includes both how specific fields should be interpreted as well as the processes mandated by the regulator to provide the data.

5.3.1 RMS functionalities

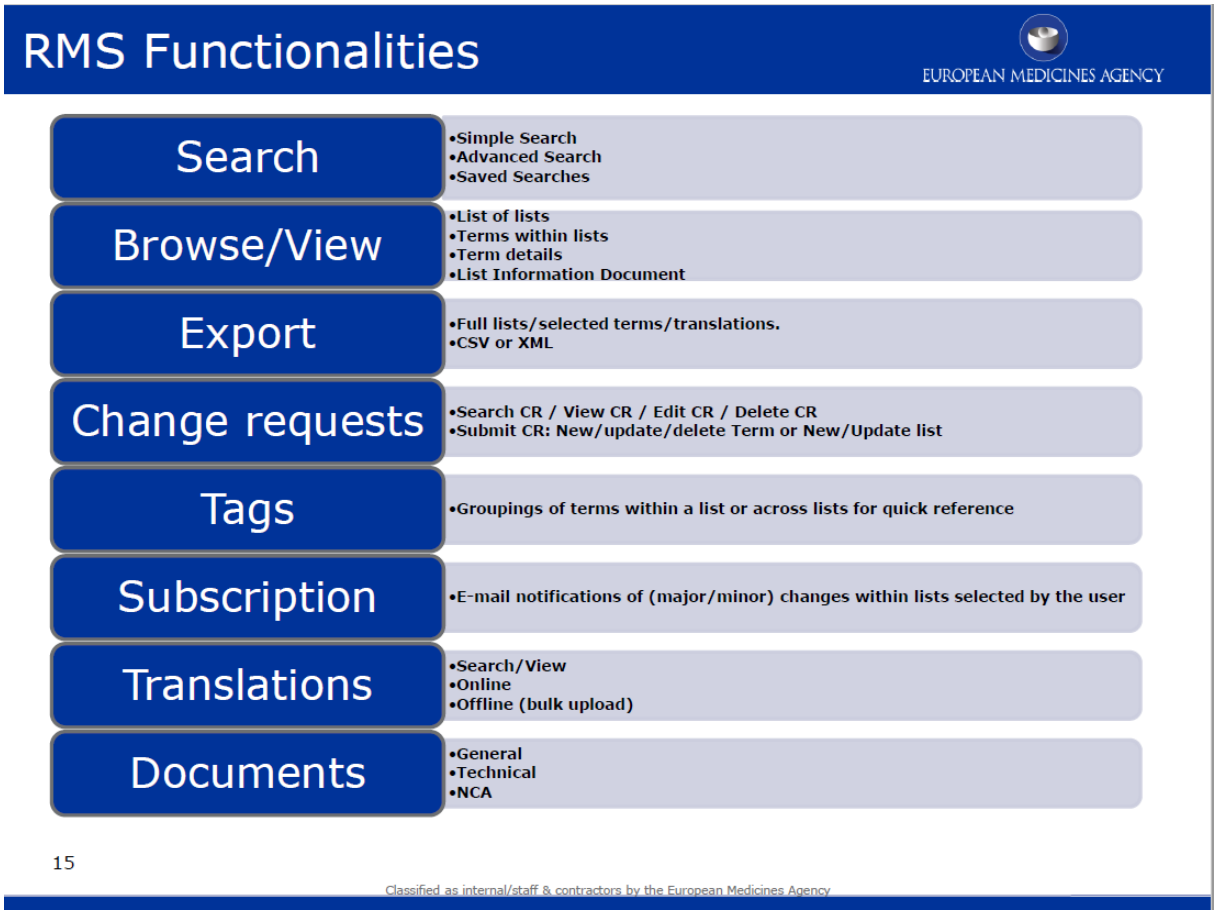


Figure 9 - RMS functionalities

5.4 Structure of SPOR Lists and Terms

Source https://spor.ema.europa.eu/rmswi/ help file "Technical Documents", retrieved 8.12.2021

5.4.1 RMS Data Model - Documentation

You will find the RMS Conceptual Model, the Logical Data Model and documentation (created by the SAP PowerDesigner) in the help files of the SPOR Portal of EMA.

(Source https://spor.ema.europa.eu/rmswi/ help file "Technical Documents", retrieved 8.12.2021)

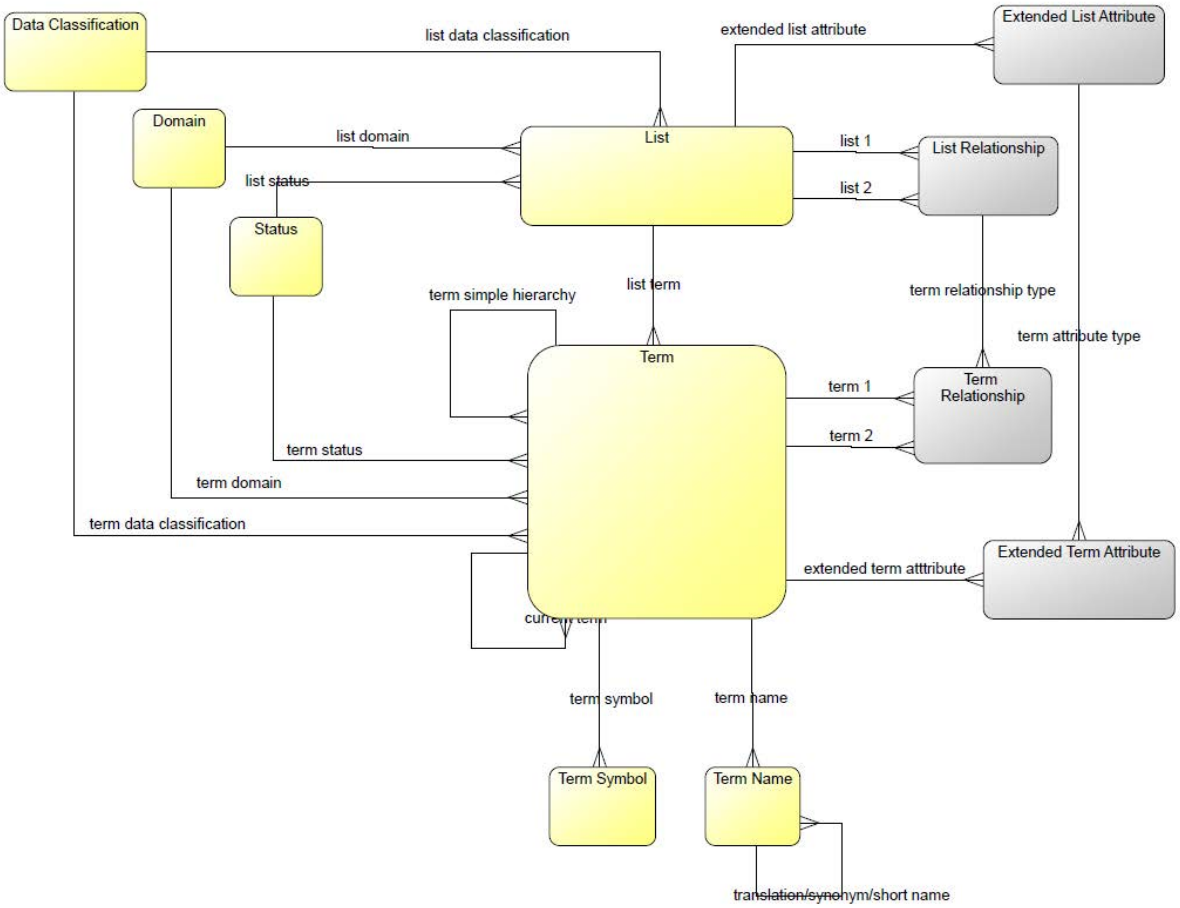


Figure 10 - RMS Conceptual Data Model

5.4.2 Identifier

Each term and each list has its unique identifier.

Source: document A1 - RMS Introduction - Webinar 21 October 2021 (EMA SPOR Portal9, retrieved 8.12.2021)

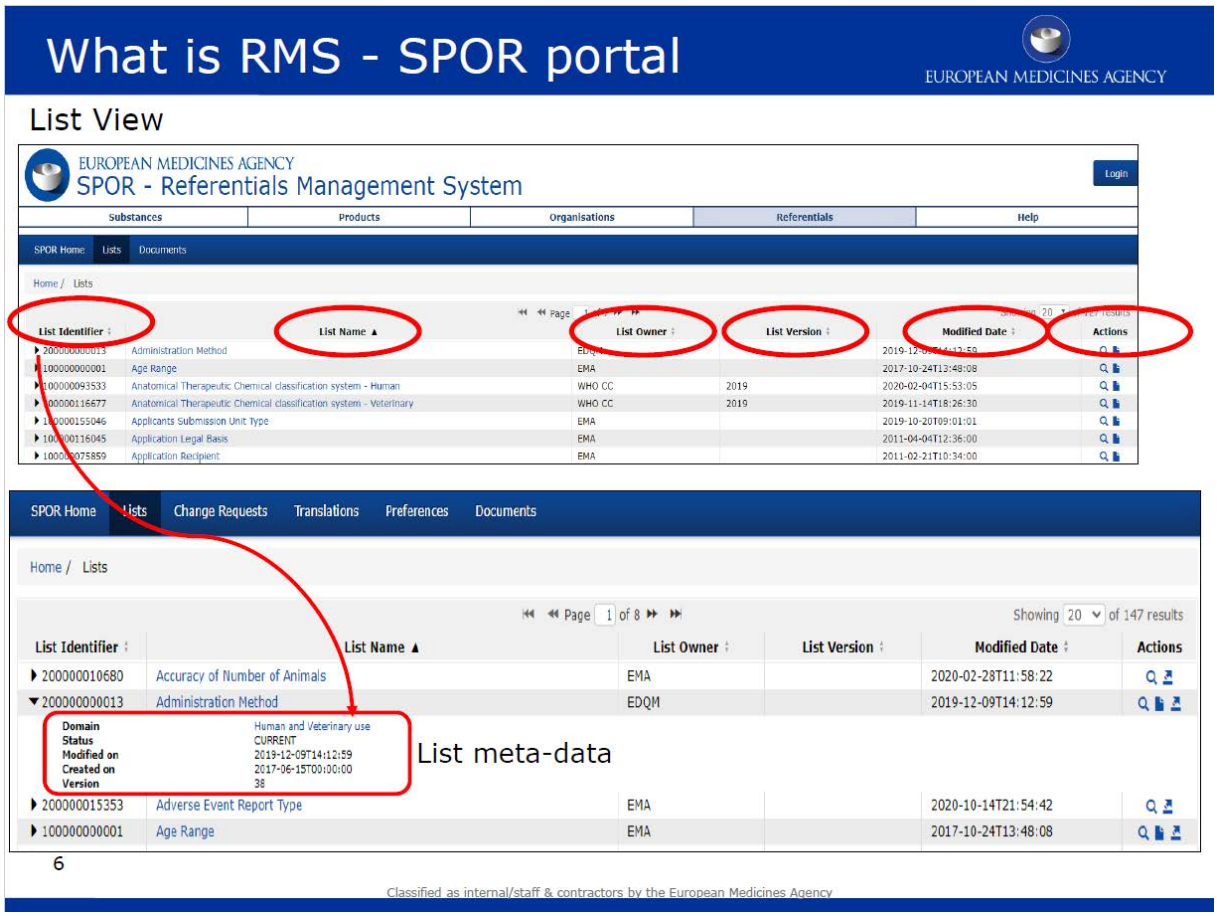


Figure 11 - SPOR list identifiers

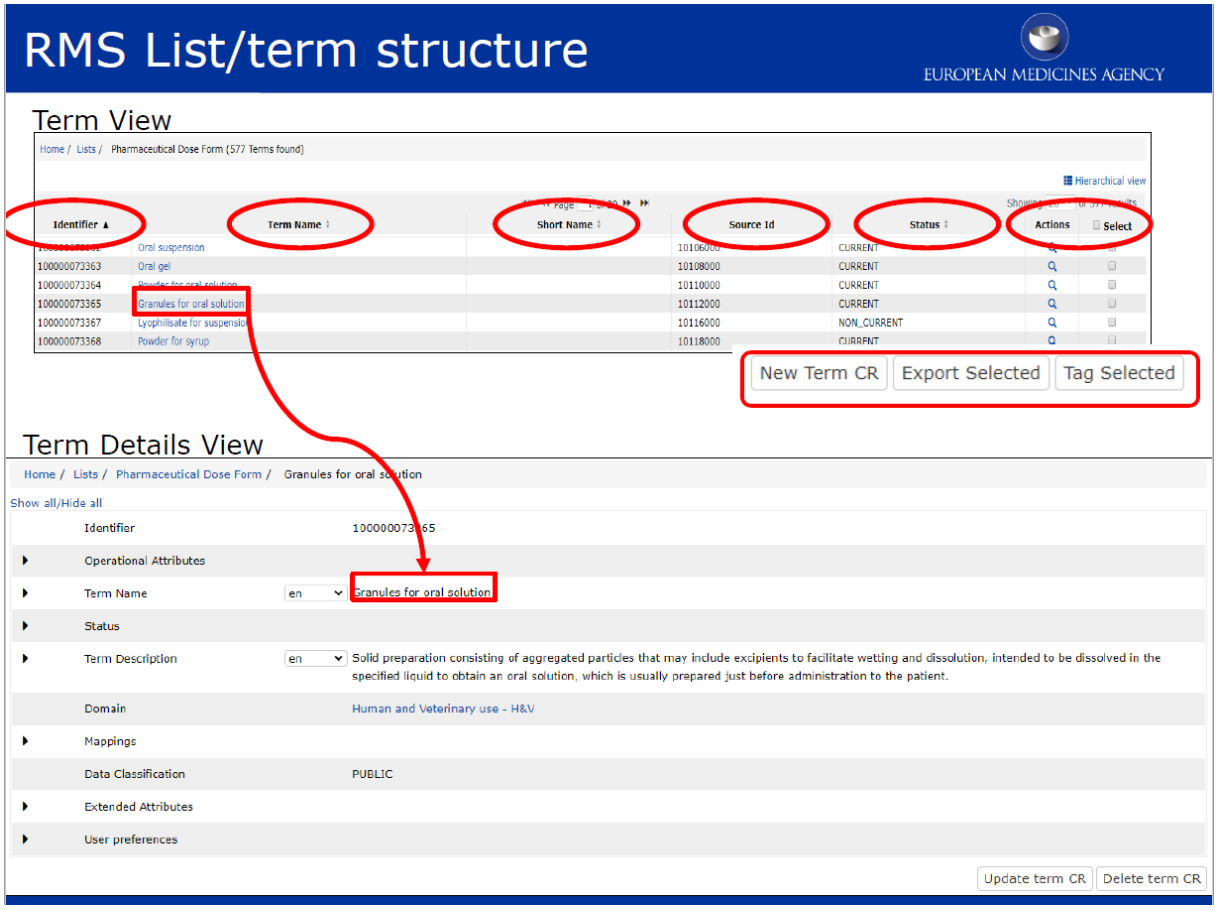


Figure 12 - SPOR term identifier

5.4.3 Term details

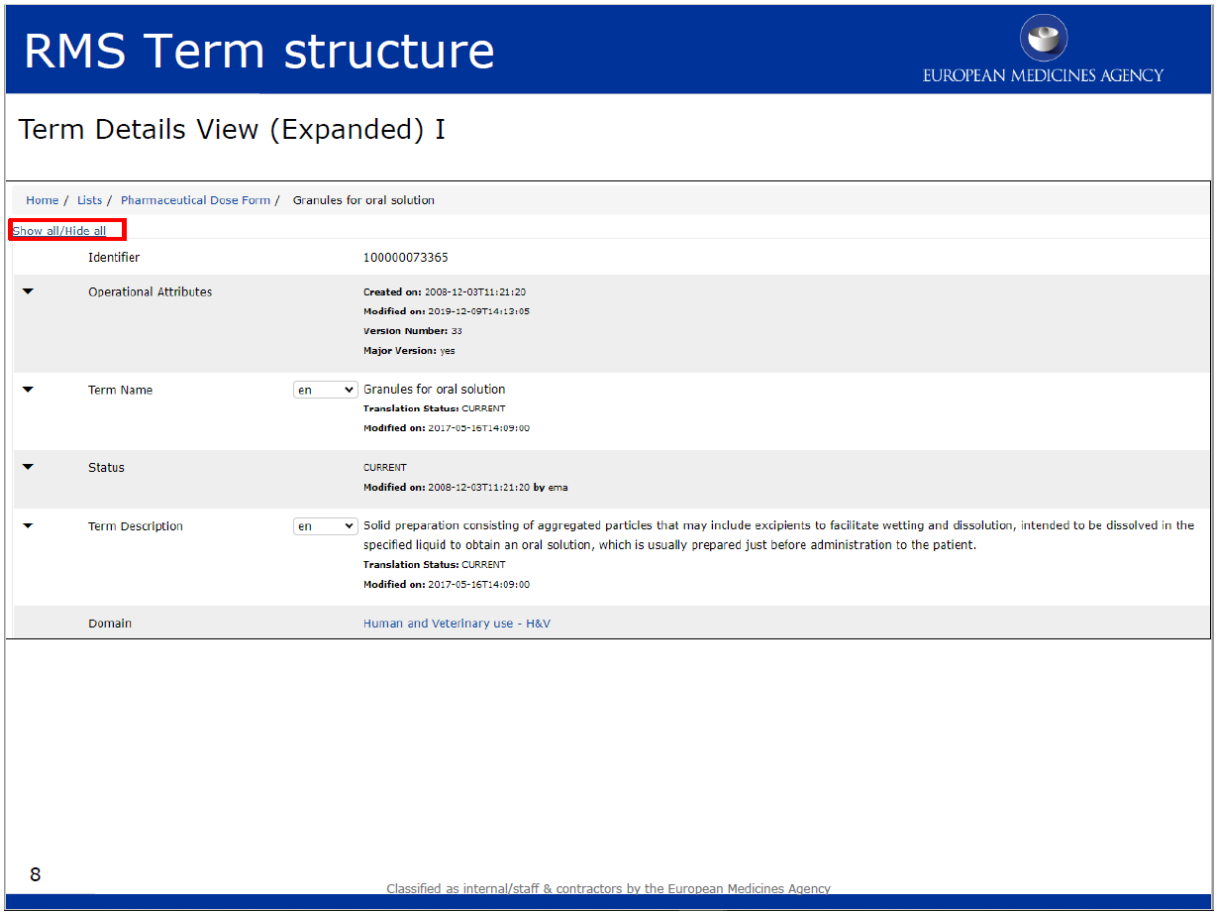


Figure 13 - Term details

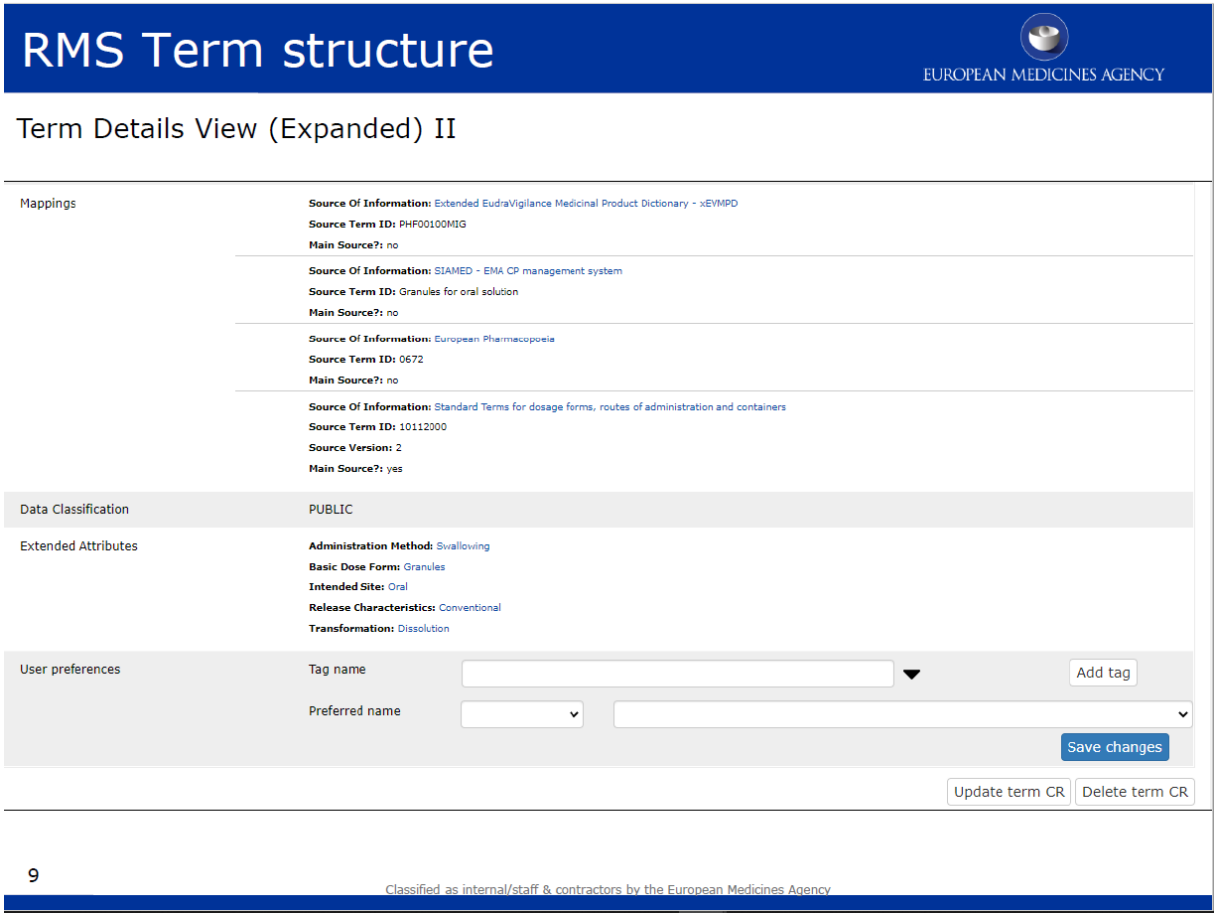


Figure 14 - Term details extended

5.4.4 Term attributes

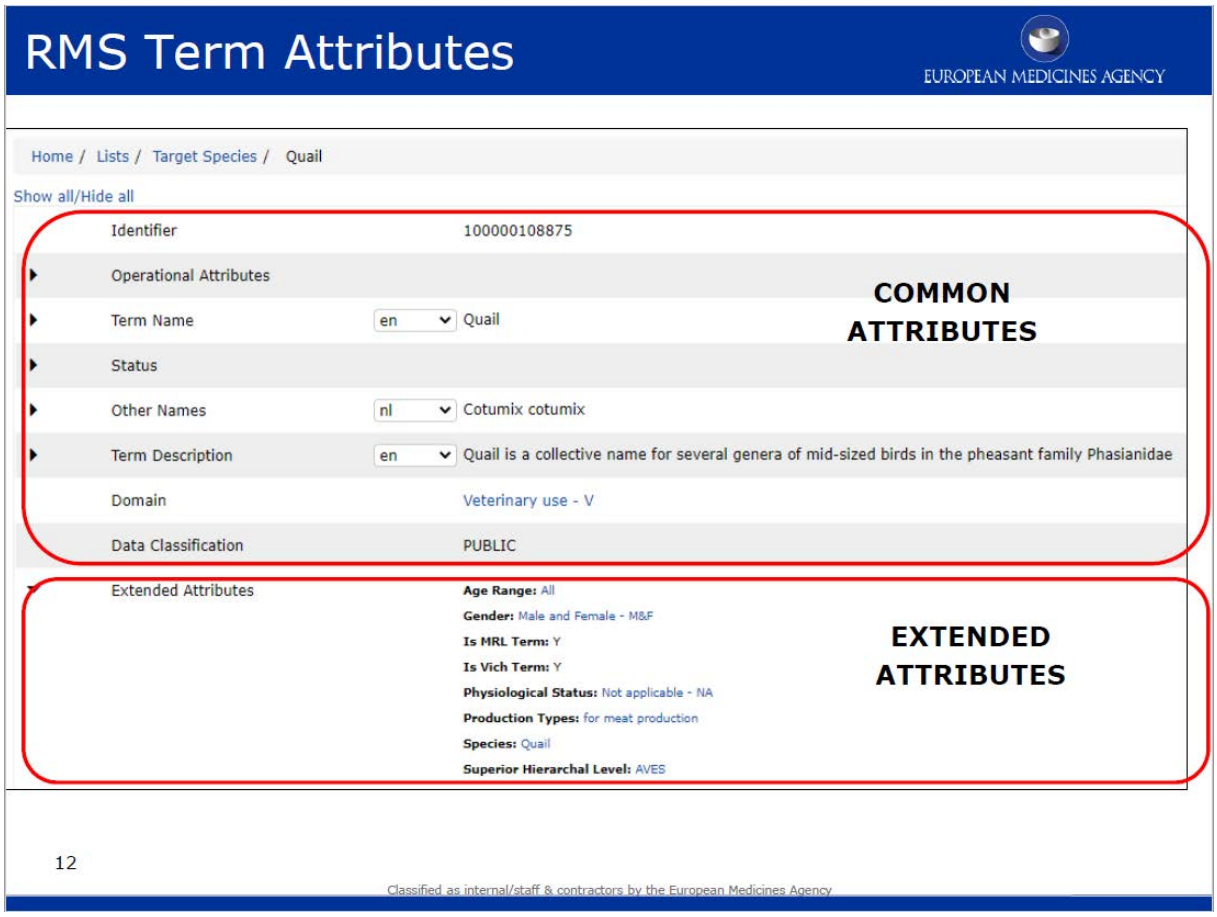


Figure 15 - Term attributes

5.4.5 List information document

Figure 16 - RMS list information document

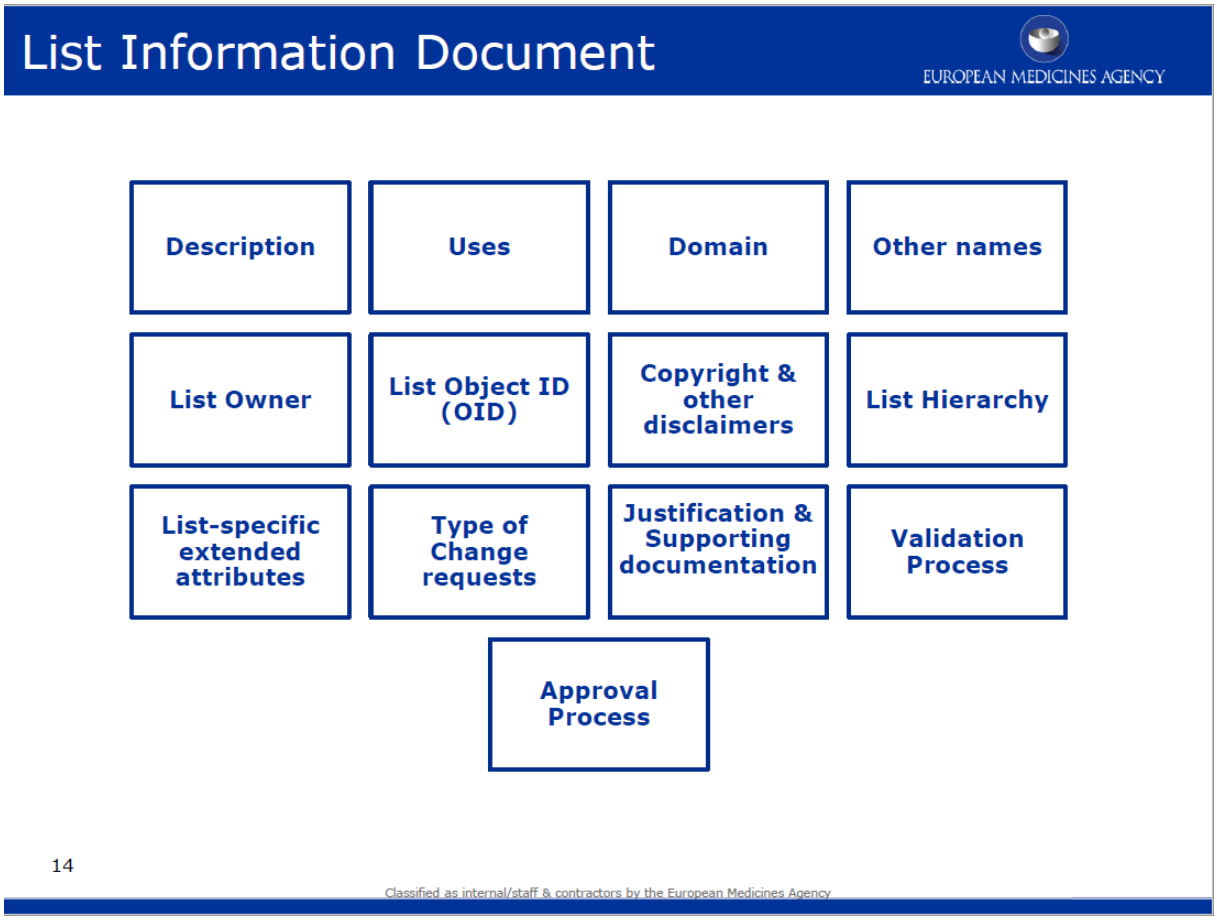


Figure 17 - Content of the list information document

5.4.6 Hierarchy

There is a hierarchical view and a flat view on the terms.

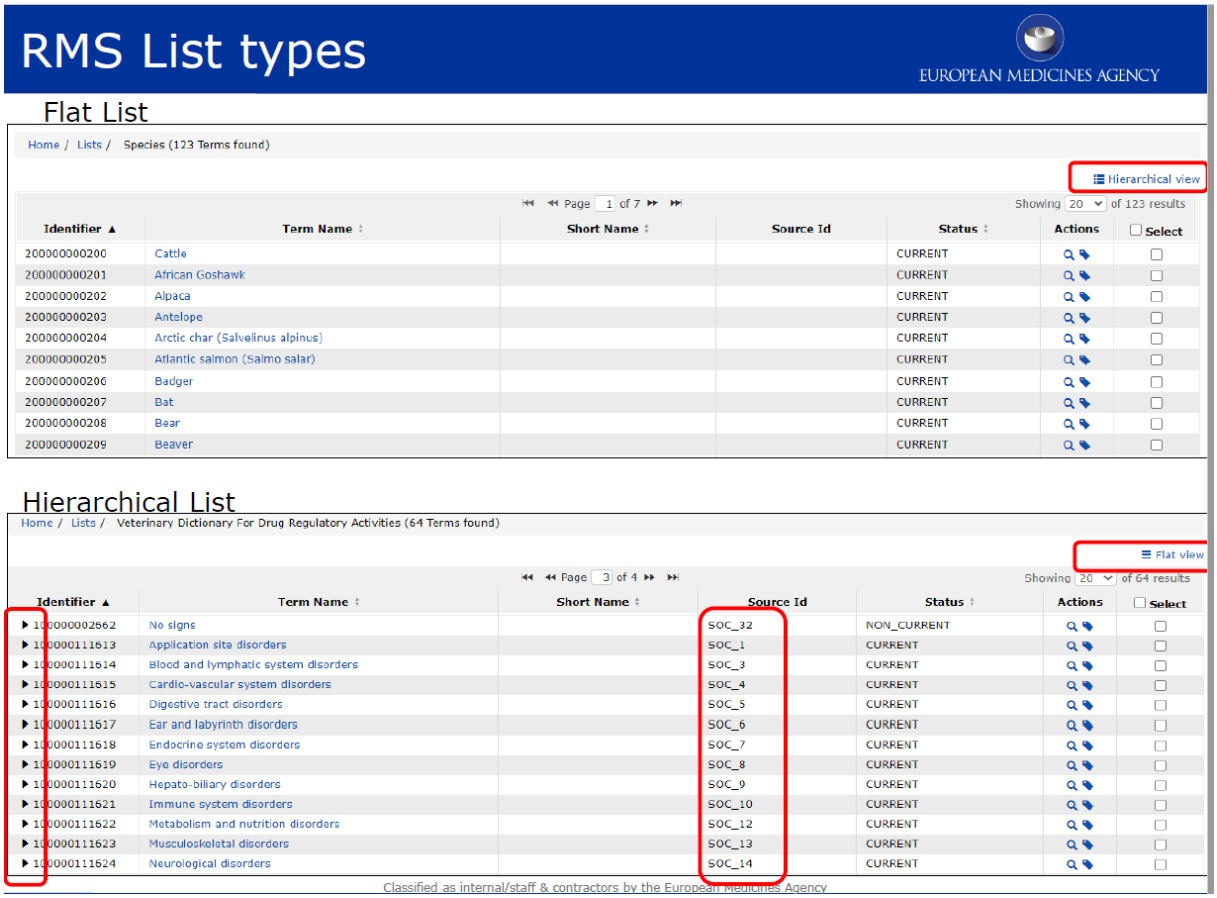


Figure 18 - Hierarchical view of terms

5.5 IDMP Product Data

5.5.1 EMA PMS

Source (retrieved 14.1.2022)

https://www.ema.europa.eu/en/documents/other/introduction-iso-identification-medicinal-products-spor-programme_en.pdf (page 8, 21.10.2021)

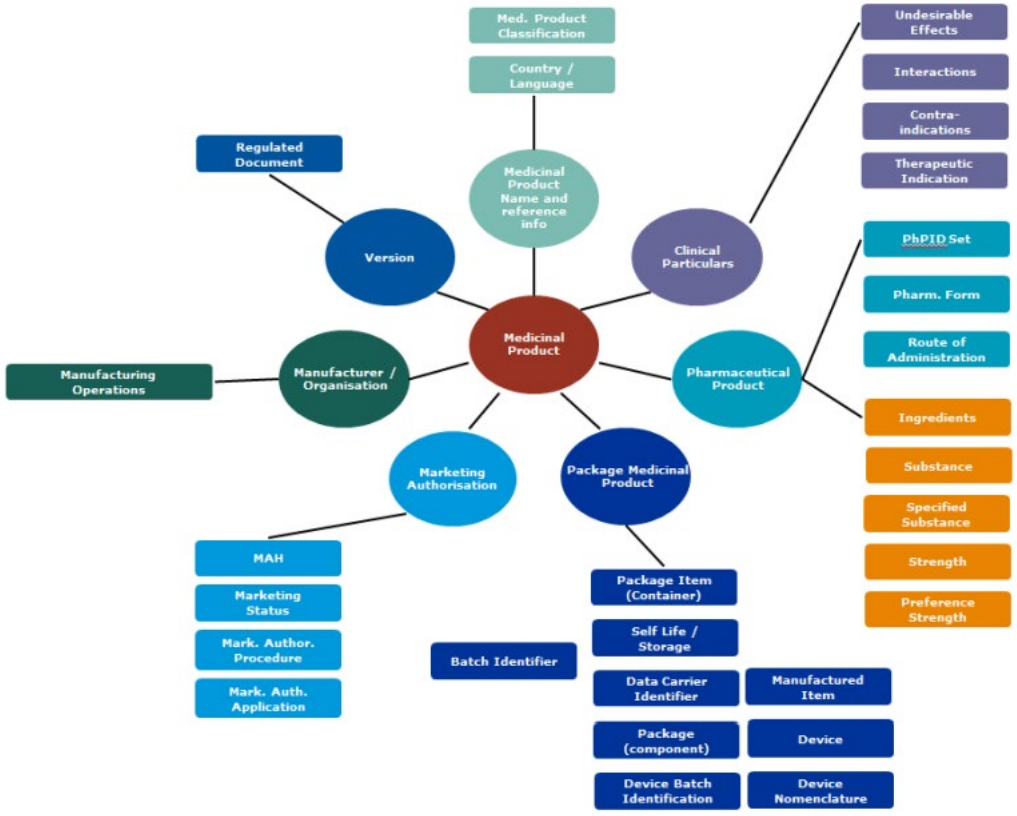


Figure 19 - Identifying medicinal products via the ISO IDMP format

Central to the IDMP model is the Medicinal Product. This object gathers all the product characteristics that are necessary to describe and uniquely identify regulated products, and is composed of the following elements:

- Medicinal Product Name.
- Pharmaceutical Product, which describes the scientific properties of the medicine itself. This includes the ingredients, which are one or more Substances (see below for further information on Substances), the pharmaceutical form, the route of administration and the strength;
- Clinical Particulars (e.g., indication, contraindications);
- Packaged Medicinal Product, which includes information on the products package, any included devices and the manufacturing batch;
- Marketing Authorisation details;
- Manufacturer;

5.5.2 EMA´s PMS Implementation Guide

Source (retrieved 14.1.2022)

Products Management Services (PMS) - Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe - Chapter 7 : XEVMPD - PMS Migration guide
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/products-management-services-pms-implementation-international-organization-standardization-iso_en-0.pdf

The Article 57 data are the predecessor of the IDMP data. The EMA gives guidance on how to migrate the data held in the eXtended Eudravigilance Medicinal Product Dictionary (XEVMPD) and submitted by marketing authorisation holders (MAHs) under the Art.57 (2) legal obligations since 2012, into the ISO IDMP-compliant data format and terminologies.

This is quite an interesting document for MPD provider as mostly the source for MPD product data is actually the SmPC content evolving via the regulatory process of the product´s authorisation. It is a part of the EMA PMS IG as Chapter 7 : XEVMPD - PMS Migration guide.

6 First gap analysis from MPD to IDMP data

To get an overview on the work ahead, a first gap analysis of the target MPD data and the IDMP data is crucial. It might even be useful to involve external IDMP expertise for this first gap analysis. The outcome of this gap analysis will help you plan how to proceed with the implementation of IDMP in your MPD.

The best starting point to get an overview on the IDMP data elements is the EMA PMS Implementation Guide.

Referral to EMA IG online (retrieved the 26.1.2022, under development): https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/product-management-services-pms-implementation-international-organization-standardization-iso_en-0.pdf

Product Management Service (PMS) - Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe

Chapter 2: Data elements for the electronic submission of information on medicinal products for human use

Referral to the CoE March 2021 on "EMA Implementation guide (EU IG v2.0)" link to the page all CoE

Referral to the ISO TS 19256 MPD, which is the base for the EMA IG.

Based on EMA PMS Implementation Guide V2.0 (version 2021-02) we have identified a list of nearly 70 IDMP data elements relevant to MPD. You will find this list as Excel file attachment to this document. The list is based on the IDMP logical model and colour coded in the same way.

Figure 20 - Legend for Authorised Medicinal Product Colours

Marked in yellow are the IDMP tables which have been checked in the following gap analysis.

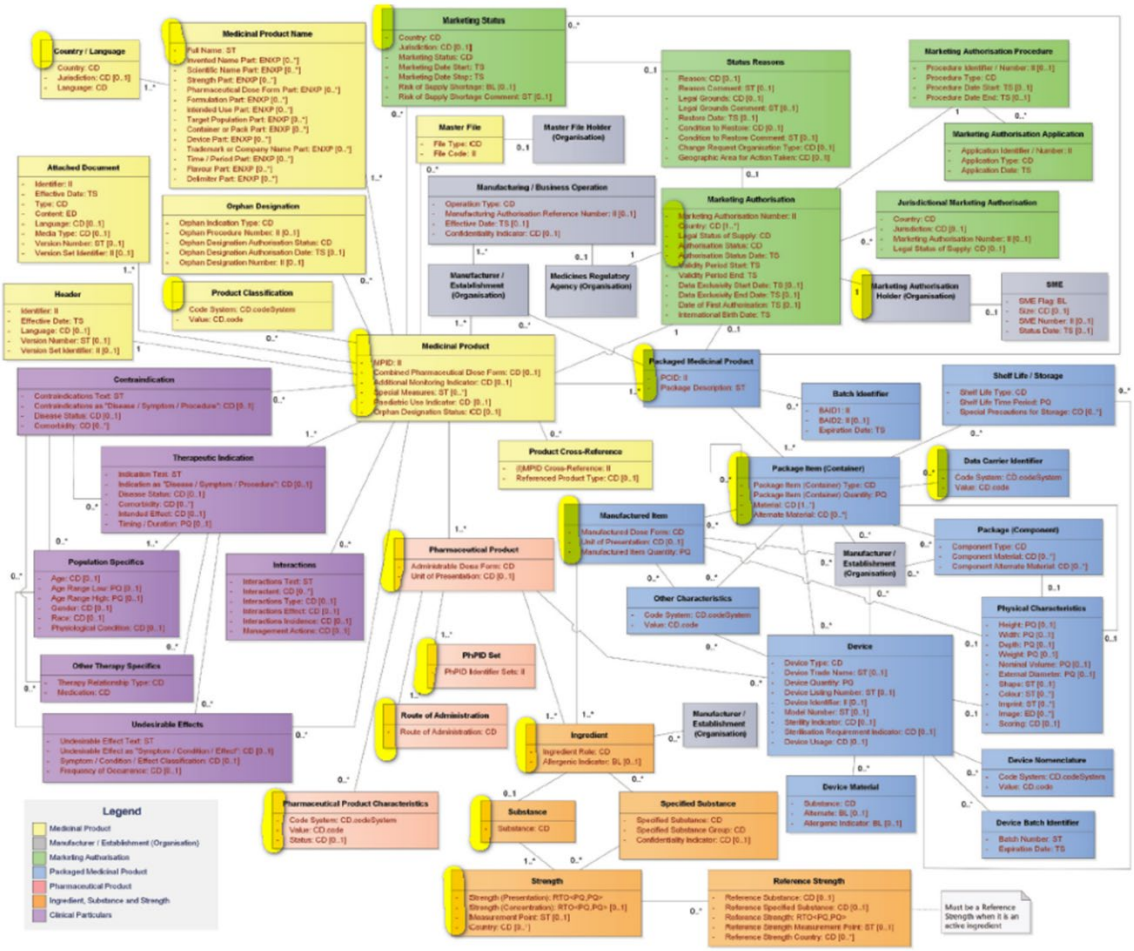


Figure 21 - Legend for Authorised Medicinal Product Tables probably relevant to MPDs

For 5 different national product dictionaries, we made a rough analysis of which fields would be valuable for this special MPD and how the IDMP data could be used.

Table 6-1 - Legend IDMP Data Elements Classification

Classification	MPD data	Example	Rationale
1	add to MPD as new data element	PMS ID	New data element because it has never existed before
2	update MPD data with IDMP data	Additional monitoring indicator	Use the IDMP data because it will be more accurate
3	to be defined individually per MPD	Marketing status and date	IDMP may not have this information or not in the granularity as expected by the MPD
4	others	not classifiable, to be checked when more	

		information is available, e.g., paediatric age range birth-14 or birth-18 or other granularity.	
5	not defined as IDMP data field	No occurrence	
6	ignore	Not usable for MPD	
7	filter	Vet / human domain	For filtering out special groups of products

6.1 Medicinal Product

The medicinal product elements are the core elements of IDMP and represent the top level of the data elements. Most MPD providers indicate that they will add the PMS ID as new data element to their MPD - see 1 in their columns in the table below.

G	I	J	K	L	Y	Z	AA	AB	AC	AD
EMA Implementation Guide Section V2.0 (versio 2021-0	Category	Sub-Category	Sub-Sub-Category	Sub-Sub-sub-Category	Classification Dm+D (UK)	Classification Zindex (NL)	Classification NHPC (IR)	Classification SAM(BE)	Classification ABDA (DE)	Classification Vidal (FR)
1.1	Product Management Service Identifier (PMS ID)				1	1	1		1	1
1.2	Medicinal product identifier (MPID)				1	1	1		1	1
1.4	Type				7	4	1		1	1
1.5	(Authorised) pharmaceutical form				1	2	2		1	1
1.6	Combined pharmaceutical dose form				2	2?	2		1	1

Figure 22 - Data analysis Medicinal Product

6.2 Pharmaceutical Product - Administrable Dose Form

The administrable dose form concept is a new concept for all the MPDs in this group. Up to now most MPDs have been working on the basis of the manufactured dose form. In case of granularity mismatches in mapping the pharmaceutical dose forms, it may be good to also consider using attributes of the administrable dose form. FDA has presented this draft concept for mapping FDA´s data in their presentation in the 02-2020 ISO Meeting.

EMA Implementation Guide Section V2.0 (versic 2021-0	Category	Sub-Category	Sub-Sub-Category	Sub-Sub-sub-Category	Classification Dm+D (UK)	Classification Zindex (NL)	Classification NHPC (IR)	Classification ABDA (DE)	Classification Vidal (FR)	Classification PHARMAWIZARD
6.2	Pharmaceutical product	Administrable Dose Form			7	1?	2	1	1	4
FDA Presentation 02-2020	Pharmaceutical product	Administrable Dose Form	Administration Method (AME)		6	4	1	1	1	4
FDA Presentation 02-2020	Pharmaceutical product	Administrable Dose Form	Intended Site (ISI)		6	2	2	1	1	4
FDA Presentation 02-2020	Pharmaceutical product	Administrable Dose Form	Transformation (TRA)		6	4	1	1	1	4
FDA Presentation 02-2020	Pharmaceutical product	Administrable Dose Form	Release Characteristics (RCA)		6	4	1	1	1	4
FDA Presentation 02-2020	Pharmaceutical product	Administrable Dose Form	Basic Drug Form (BDF)		6	4	1	1	1	4
FDA Presentation 02-2020	Pharmaceutical product	Administrable Dose Form	State of Matter (SOM)		6	4	1	1	1	4

Figure 23 - Data analysis Pharmaceutical Product - Administrable Dose Form

6.3 Ingredient and strength

Since IDMP ingredients and strength data are based on the administrable dose form, data is probably only partially available in MPD data. How to integrate substance and strength data into the MPD will probably best be handled together with how to implement the administrable dose form concept.

EMA Implementation Guide Section V2.0 (versio... 2021-0	Category	Sub-Category	Sub-Sub-Category	Sub-Sub-sub-Category	Classification Dm+D (UK)	Classification Zindex (NL)	Classification NHPC (IR)	Classification ABDA (DE)	Classification Vidal (FR)	Classification PHARMAWIZARD
5.1	Pharmaceutical product	Ingredient	Ingredient role		7	2	1	1	1	2
5.2	Pharmaceutical product	Ingredient	Manufacturer		6	4	1	1	1	4
5.3.1	Pharmaceutical product	Ingredient	Substance	Substance	7	2	1	1	1	2
5.3.2.2.1	Pharmaceutical product	Ingredient	Substance	Strength	7	?	3	1	1	2
5.3.2.2.2	Pharmaceutical product	Ingredient	Substance	Strength	7	4	2	1	1	2

Figure 24 - Data analysis Pharmaceutical Product - Ingredient and strength

6.4 Packaged Medicinal Product

For Packaged Medicinal Product, IDMP introduces a quite complex data model. The packages are a key element for MPDs and in eHealth activities. The packages are using mostly nationally defined package identifiers. The field "Data Carrier Identifier" is therefore most relevant to MPD provider. As of today, it is not quite clear, if the Data Carrier Identifier will be available to NCAs, the moment product data will be published.

EMA Implementation Guide Section V2.0 (version 2021-02)	Category	Sub-Category	Sub-Sub-Category	Sub-Sub-sub-Category	Classification Dm+D (UK)	Classification Zindex (NL)	Classification NHPC (IR)	Classification ABDA (DE)	Classification Vidal (FR)
4.1	Packaged medicinal product	Packaged Medicinal Product Identifier PCID			1	1	1	1	1
4.2	Packaged medicinal product	Package description			6	2?	1	1	1
4.2.1	Packaged medicinal product	Package description	Language		6	4	1	1	1
4.3	Packaged medicinal product	Pack size			2	4	3	1	1
4.7.1	Packaged medicinal product	Package item (container)	Package item (container) type		1	1.2	3	1	1
4.7.2	Packaged medicinal product	Package item (container)	Package item reference(s)		1	4	1	1	1
4.7.3	Packaged medicinal product	Package item (container)	Manufactured item reference(s)		1	4	1	1	1
4.7.5	Packaged medicinal product	Package item (container)	Package item (container) quantity		2	2?	1	1	1
4.7.6	Packaged medicinal product	Package item (container)	Data carrier identifier		1	4	1	1	1
4.7.7	Packaged medicinal product	Package item (container)	Material		6	4	1	1	1

Figure 25 - Data analysis Packaged Medicinal Product

6.5 Conclusion

After this first analysis of IDMP data and granularity it became clear, that the process of implementing IDMP data into a MPD is different for many reasons not the least of which is the fact that all MPDs are structured differently within different national extensions as regards granularities and specialities. There is no “one-size-fits-all” solution. To conduct a reliable gap analysis expertise in both data content and structure, and technical expertise in data storage will be needed for both data models, one expert on the MPD data and one expert on the IDMP data. Mobilise inhouse expertise, if needed supported by external consultants.

7 Mapping Guidelines

7.1 Formal Mapping Guidelines

Mapping is the process of defining a set of maps.

A map is an association between a particular code/concept/term in one code system, and code/concept/term in another code system that have the same (or similar) meaning.

Maps are developed in accordance with a documented rationale, for a given purpose, and as a result there may be different maps between the same pair of code systems to meet different use cases.

- Simple map is a 1:1 relationship between a source terminology to a selected target concept of another terminology ie. between concepts with similar meaning, E.g., SNOMED CT to ICD-O.
- Complex map is regarded as a rule-based map in that it includes multiple map groups and map advice, E.g., SNOMED CT to ICD-10.

7.1.1 Prerequisites

Prior to embarking on the process of creating a map, the following are key considerations not to be overlooked. Some of these points listed below also include the distribution of the mapping to other stakeholders.

- Agreed scope based on agreed use cases
- Methodology to be used e.g., dual independent review vs. mapper-reviewer workflow
- Creation of a map requires a documented mapping process outlining a clear workflow tied to a methodology
- Requirement for local or national modifications
- Establishing a robust Quality Assurance process
- Resource planning: agreement of required competencies and skill sets for mappers
- Education and training:
- - Source and target terminologies
- - Understand and explain the purpose of the map
- - Understand the chosen methodology
- - Understand the way in which the map will be utilised (end user experience)
- - Understand and be able to apply the structure, content and relationships for the source and target terminology
- - Tooling: understand the process to develop, maintain and publish the map
- End-user feedback methodology
- Clinical validation
- Technical validation
- Governance and ongoing maintenance agreement
- Agreed format for publication and distribution
- Agreed timelines for publication and distribution including future
- Funding - ongoing
- Tooling: map tooling environment (for example the Mapping Tool developed by SNOMED CT International) or will it be a spreadsheet exercise?

7.1.2 General mapping principles/Conventions

Given the many and various rules to consider to produce accurate, consistent and reproducible maps, there needs to be clearly worded, documented mapping conventions (rules) focused on ensuring a consistent approach resulting in a stable quality product that is fit for purpose.

Key principles:

- Source and target of the map must be identified.
- Bi-directional maps must be managed as two separate artefacts and created separately.
- Create pilot map as proof of concept.
- Checking the hierarchical placement to determine if the concepts/terms are equivalent. Flagging any concepts/terms that are not an Exact Match as unmappable; identifies relevant concepts in either terminology that might be missing and are required to provide a more complete mapping.

- Established agreement on the addition of any new content

7.2 Mapping Scenarios for IDMP

There are different solutions and best practices for different scenarios with advantages and disadvantages:

- Mapping all IDMP data elements (which proved to be the most challenging as mostly granularity between existing product data and IDMP data where different)
- Mapping only IDMP data elements relevant to product identification, such as mapping the PhPID, MPID, PCID to the corresponding ID's in the MPD. This proved to be the most efficient solution the moment an MPD is already existing and is using its individual controlled vocabularies and product structure. This form will also help in keeping the mapping updated according to the terminologies evolving.
- When starting the creation of a MPD from scratch, genuine IDMP data formats, referential, and models should be used.

Match on datafields (1)

Level	Local MPD	IDMP
Substance	Omeprazol magnesium (76384) Omeprazol (as magnesium salt) (76392)	Omeprazole magnesium (100000085918) Omeprazole (100000092047)
PhP	Omeprazole magnesium (76384) 20,6 mg (229) Omeprazol (as magnesium salt) (76392) 20,0 mg (229) Gastro-resistant tablet (250)	Omeprazole magnesium (100000085918) 20,6 mg (100000110655) Omeprazole (100000092047) 20,0 mg (100000110655) Gastro-resistant tablet (100000073667)
MPID	Losec Control 20 mg gastro-resistant tablet (xxx) Corden Pharma (xxx) etc	Losec Control 20 mg gastro-resistant tablet (xxx) Corden Pharma (LOC-100021459) Etc
PCID	1 Blister (37) 7 'each' [tablets] (245) etc	1 Blister (100000073496) 7 tablets (200000002152) etc

Date

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

1

Figure 26 - Example mapping all IDMP data elements (CoE, 25.2.2022, Leonora Grandia Z-Index)

7.2.1 MPD Structure

The mapping strategy also depends on the MPD structure if it is a mirror MPD or a flat MPD.

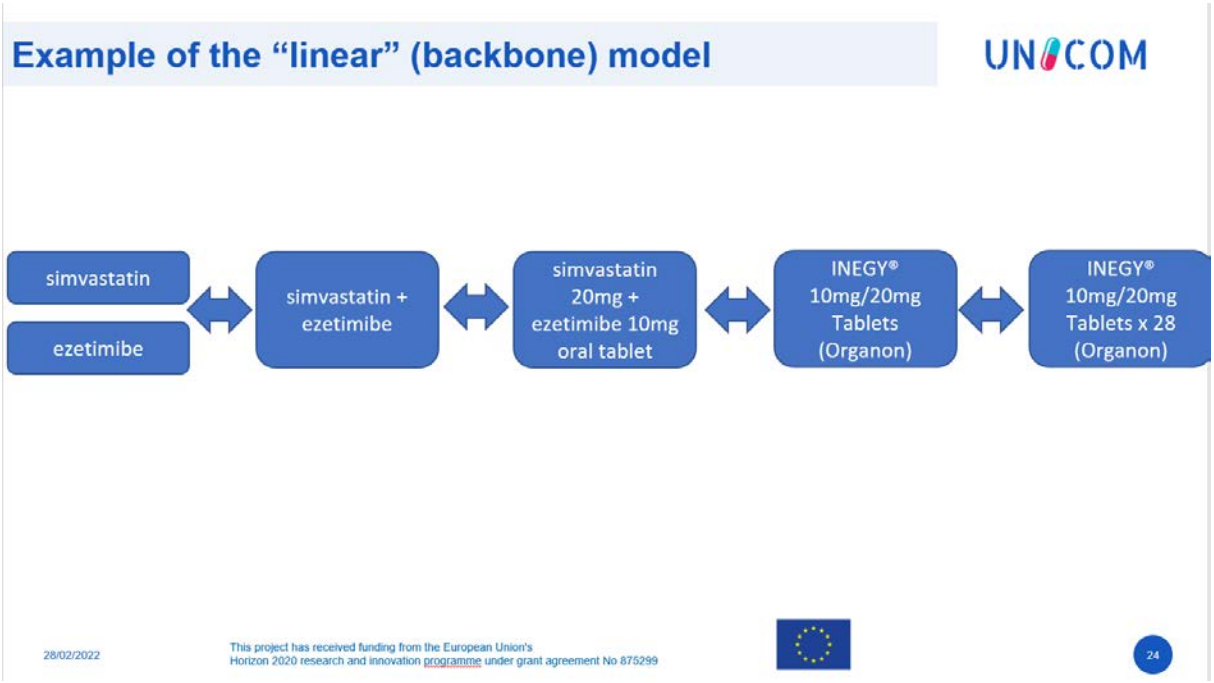


Figure 27 - Example of the "linear" MPD model

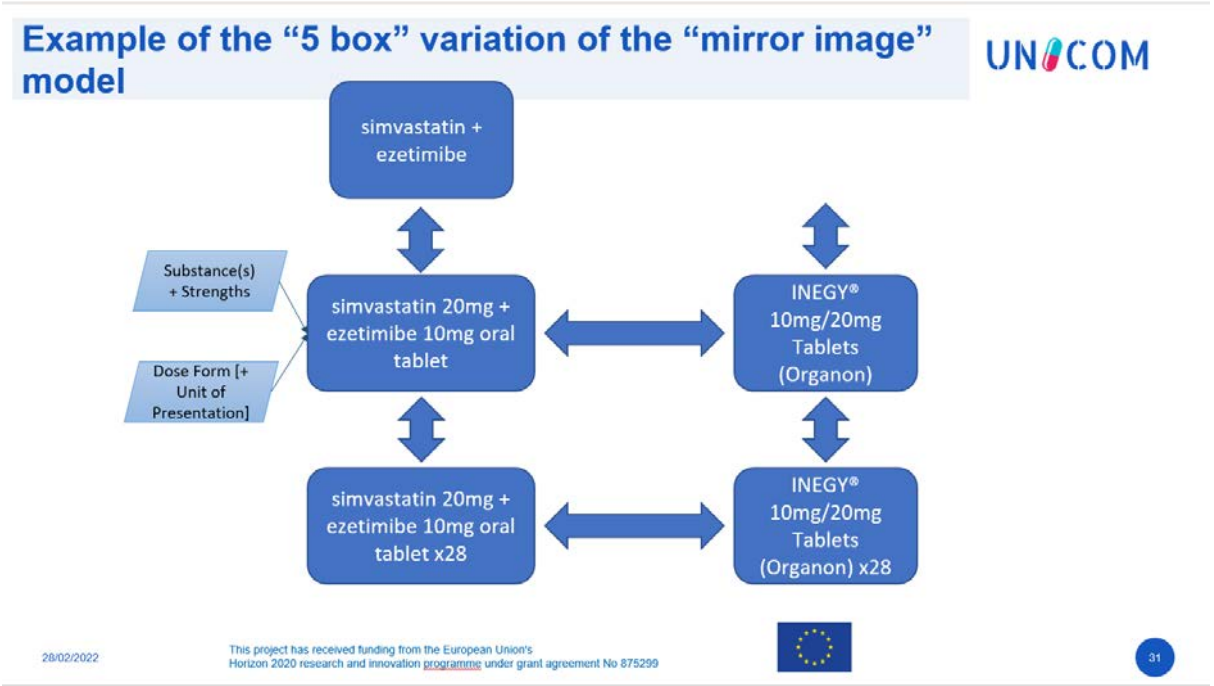


Figure 28 - Example of the "5 box" variation of the "mirror image" MPD model

7.2.2 How does the IDMP model fit?

The IDMP model is more “linear” than “mirror image. But the philosophy is different as the central/starting concept is the Medicinal Product.

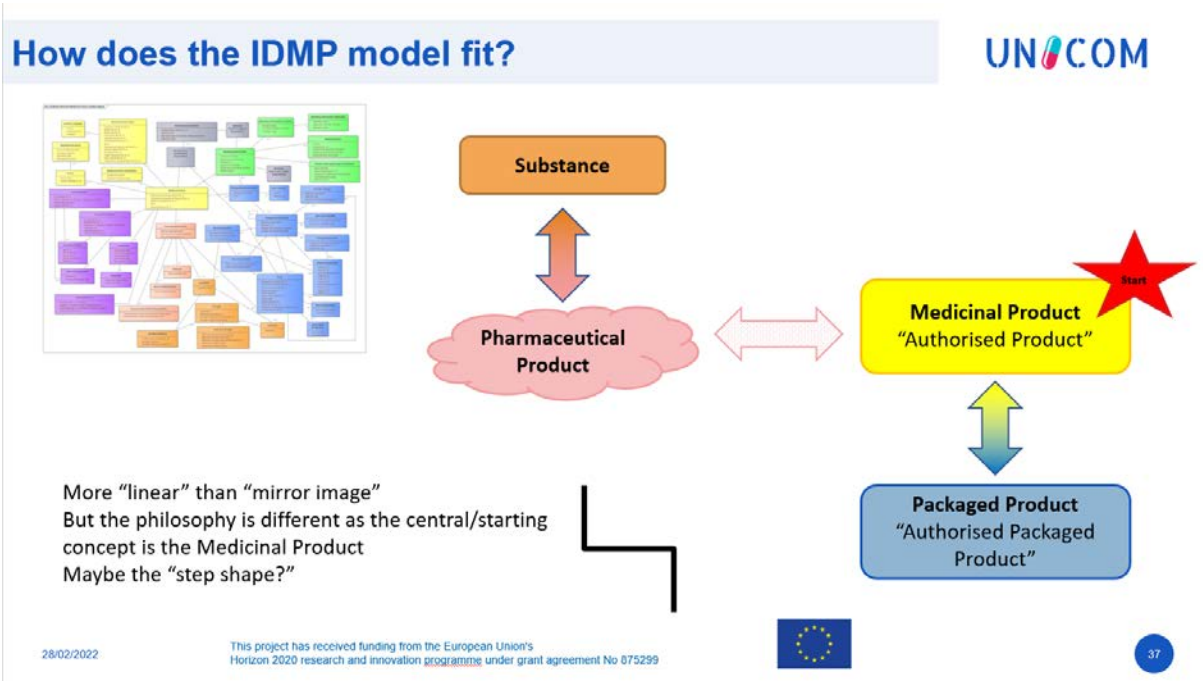


Figure 29 - IDMP model is more "linear" than "mirror"

Reference to the Community of Expertise 25.2.2022, "Draft Implementation Guide of IDMP in Medicinal Product Dictionaries" for all the content of this chapter.

https://unicom-project.eu/all-community-of-expertise-webinars-in-a-nutshell/

The mapping strategy also depends on the MPD structure if it is a mirror MPD or a flat MPD. For more information, please refer to the following document:

Implementing an Interoperable National Drug Dictionary using SNOMED CT

http://confluence.ihtsdotools.org/download/attachments/115870807/1b.%20SNOMED%20CT%20Drug%20Model%20for%20supporting%20National%20Extension%20V1.0.pdf?api=v2

7.3 SPOR and mappings

The current EMA IDMP implementation requires use of the SPOR terminologies, even to the extent of „recoding" externally sourced content such as ATC and EDQM´s pharmaceutical dose forms controlled vocabulary. This means that organisations external to the regulatory domain, including eHealth organisations and MPD, will have to manage a mapping to the terminologies as they use them. Even if that mapping is 1:1, all mapping introduces risk and additional resource demand.

There is a tendency to look globally not at a direct mapping, but to try to use attributes rather than SPOR identifiers. The danger is also, that in different stages in the life cycle of a product, different terminologies are used (e.g., MedDRA in regulatory and SNOMED in eHealth and ePrescription).

Additionally mapping work will be challenging in terms of maintaining an updating in line with the version of the terminologies as they evolve. So perhaps it may be best practice to map your local and internal MPD identifiers directly to the IDMP PHPID.

One-to-one mapping may not be possible, it is context/use case dependent as in:

- MedDRA´s clinical terms to SNOMED CT and SNOMED CT to MedDRA
- EDQM´s dose forms choices for manufactured and / or administrable dose form
- EDQM to SNOMED CT for dose forms

The result is data at the end of the life cycle of product data, different from the data you have started with.

For example: the product may originally have been described as a "capsule" but after the implementation of IDMP and the use of standard EDQM dose forms, the product must be described as having a "hard capsule" pharmaceutical dose form.

Having a standardised map facilitates the movement of information in a standardised way and facilitates consistent retrieval. It is essential that processes are in place for maintenance and updating. Consideration must be given to maintaining data history.

Once a globally unique identifier exists in IDMP, it will be possible to navigate to the undisputed source of the actual attributes that you need for your use-case.

Source (retrieved 14.1.2022)

IDMP1 Tool for matching your data with IDMP controlled terms, The Identification for Medicinal Products (IDMP) translating and converting tool for healthcare professionals.

https://www.idmp1.com/wiki/spor-data-mapping-activities/

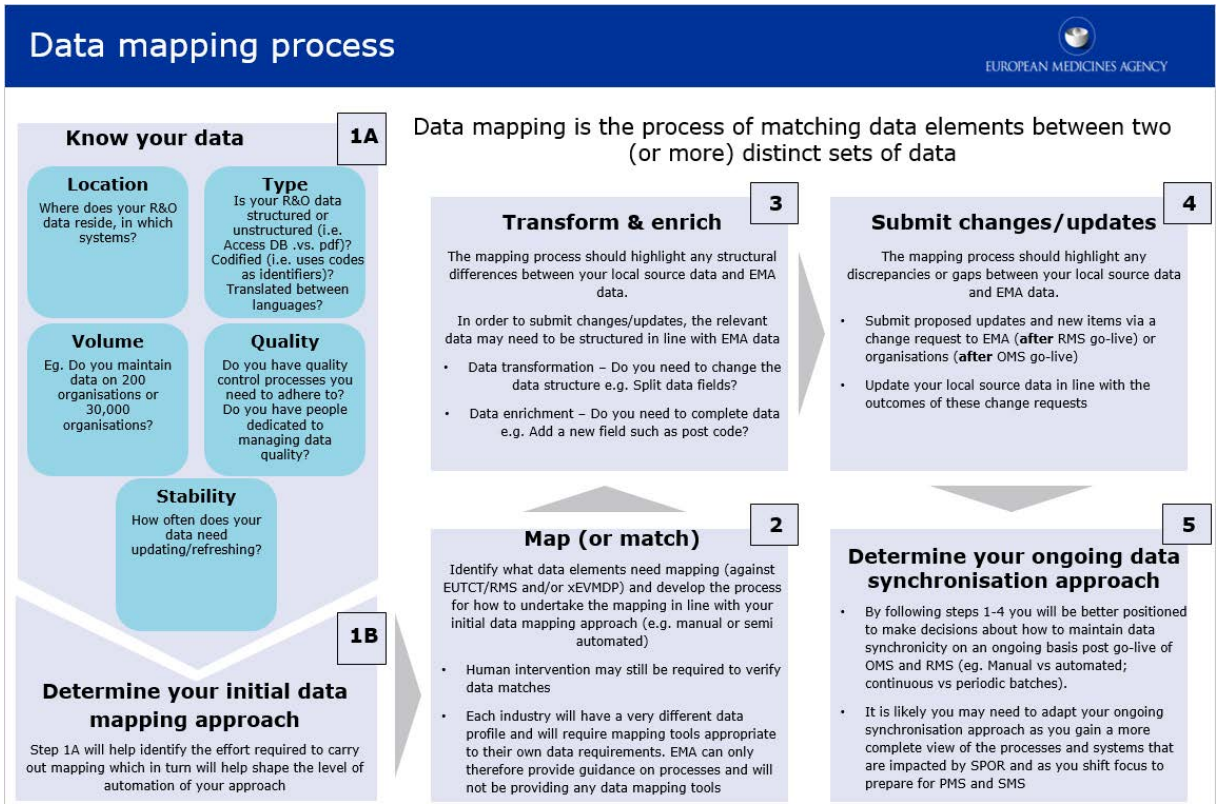


Figure 30 - Data mapping process

Some tricky aspects to pay attention to:

- Case sensitive / insensitive
- Plural / singular
- Avoid mapping to NULLIFIED - fix data instead
- Exclude "use" in ROA (or make sure that certain standard additions or deletions from the terms does disturb the mapping process)
- Map directly to SPOR ID for the EDQM pharmaceutical dose forms
- How to track the versioning of the mappings

7.4 Summary for the Mapping Process

Here summarised the mentioned steps of mapping in form of a Recipe as 'cook book', as it was asked during our CoE.

1a. Know your data

1b Determine your initial data mapping approach

2. Map or match

3. Transform and enrich

4. Check on changes / updates needed in your MPD data

5. Determine your ongoing data synchronisation approach

5. plan much more time than estimated for the process

6. start the work…

7.5 Maintaining the Map

Decide on the update process and update rhythm of the map between the MPD data and the IDMP data.

	Manual mapping	Automated mapping	Substitution
Description	• Manual download/upload of the RMS – deltas only? • Maintain a manual mapping of "internal" & RMS lists	• Consuming Static URLs/ Services – deltas only or full set of terms • Automate the mapping of "internal" & RMS lists	• Consuming Static URLs/ Services – deltas only or full set of terms • Replace "internal" list with RMSlist
PROS	• Easier to implement	• Only one mapping required • Easier to maintain – can be automated	• Only one mapping required • Easiest to maintain
CONS	• Harder to maintain – needs manual intervention • No assurance that all parties perform a consistent mapping	• Harder to implement • May still need some manual intervention • May require reclassification of records	• Hardest to implement • May require huge system changes
Requirements	• Human resources availability • Adherence to process – mapping, change requests or pre-registration of terms	• Investment in coding of mapping logic • Ideally automation of change requests or enforcement of pre-registration in RMS	• Requires coding of mapping logic
Frequency	• Daily?? Weekly? • Before any exchange of data?	• Daily? • Before any exchange of data?	• Continuously?? • Before any exchange of data?

Figure 31 - Maintaining the Map

Major challenges in this synchronisation process:

- Term in local language has changed
- Term in a different language has changed
- A completely irrelevant change has triggered a new version
- The term status was changed (e.g., non-current)
- In special cases national terms might have priority

7.6 Mapping PMS ID

Example of Losec Control 20 mg

Referral to CoE on "IDMP Implementation Guide for MPDs", 25.2.2022, link to all CoE

Level	Local MPD	IDMP
Substance	Omeprazol magnesium (76384) Omeprazol (as magnesium salt) (76392)	Omeprazole magnesium (100000085918) Omeprazole (100000092047)
PhP	Omeprazole magnesium (76384) 20,6 mg (229) Omeprazol (as magnesium salt) (76392) 20 mg (229) Gastro-resistant tablet (250)	Omeprazole magnesium (100000085918) 20,6 mg (100000110655) Omeprazole (100000092047) 20,6 mg (100000110655) Gastro-resistant tablet (100000073776)
MPID	Losec Control 20 mg gastro-resistant tablet (xxx) Corden Pharma (xxx) etc	Losec Control 20 mg gastro-resistant tablet (xxx) Corden Pharma (LOC-100021459) etc
PCID	1 Blister (37) 7 'each' [tablets] (245) etc	1 Blister (100000073496) 7 tablets (200000002152) etc

Figure 32 - Mapping Substance, MPID, PCID

8 Challenges in Implementation

8.1 Substance Hierarchy in products´ strength

Codes for collections of products and codes for collections of substances, entail two different domains, with different governance and use cases. The use case of CAS for example describing chemical molecules is different from the more pharmacological approach of EUTCT SMS and IDMP SPOR.

EUTCT SMS has supported the need for a substance hierarchy and a grouper, but always linked to the use case of describing medicinal products active ingredients and strength. The idea of a grouper is currently not worked out in EUTCT SMS, but it was recognised that this could become a working item, and discussions were still under way (as of May 2022).

https://unicom-project.eu/all-community-of-expertise-webinars-in-a-nutshell/

Unicom page on the CoE "Perspectives on substance and strength in IDMP" (November 2021) Link to all CoE

8.2 PHPIDs data elements

Reference to:

D9.1 Pivot section. " MPD will have their own "PhP" - how they interact with the IDMP PhPID will depend on their structure, their use cases and how PhPIDs evolve"

The brochure "IDMP in a capsule" describes how PHPIDs elements relate to MPDs. You find this on https://bit.ly/IDMP_in_a_capsule. The purpose of that document is to provide an overview about the medicinal product life cycle and how this is supported by the IDMP set of ISO standards. That includes description on how PHPIDs are created.

https://bit.ly/IDMP_in_a_capsule

The PhPID globally represents the substances, strength, and pharmaceutical dose form of a medicinal product, regardless of where it is prescribed, dispensed or used.

Unicom page on the CoE "PhPID – calculating a globally unique identification as defined by IDMP" (September 2020) Link to all CoE

Unicom page on the CoE "PhPID in – Vaccine challenges – cleansing, confidentiality and vaccine naming" (January 2022) Link to all CoE

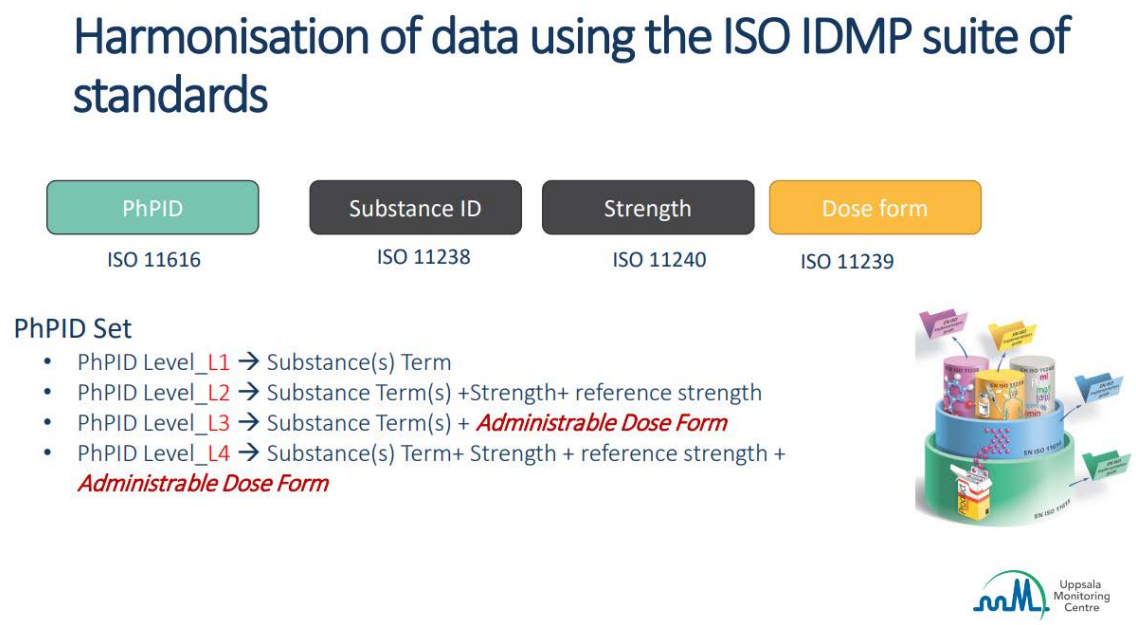


Figure 33 - Harmonisation of data using the ISO IDMP suite of standards (Uppsala Monitoring Centre)

8.3 Pharmaceutical Dose Form and Unit of Presentation

EDQM and SPOR Ids and Rhythm of update

MPD products have often been mapped to the EDQM Dose Forms. The EDQM Dose Forms are also used in IDMP. But IDMP SPOR comes with its own pharmaceutical dose form identifier. So, a mapping from the EDQM identifier to the corresponding SPOR identifier will be needed.

Note: For those MPDs which already use the EDQM Pharmaceutical Dose Form Code, it might be important to check on the maintenance of this code. The Update rhythm between EDQM publication and SPOR PHF Code publication may be different. Also, most MPDs are using the concept of the manufactured pharmaceutical dose form to express substance and strength. IDMP product data, including substance and strength data is based on the administrable dose form concept.

Reference to D9.1 Chapter 8.2 Definitional attributes

Both manufactured dose forms and administrable dose forms are a type of pharmaceutical dose forms. For a significant proportion of pharmaceutical dose forms, no transformation is required prior to their administration to the patient. However, for those that do require a transformation, representing that, and representing the transformed product, can be challenging for MPD.

Generally, MPD use the manufactured dose form representation, rather than the administrable dose form. For example, a parenteral product supplied as a powder for solution for injection will be described using that dose form and the product strength will be given as a mass amount „per unit of presentation" (vial or ampoule). This makes it difficult, even if a specific solvent is supplied, to be sure of the volume used to transform the powder into a solution for administration. And on top the strength as liquid concentration strength (or indeed presentation strength) must be safely provided.

The exception are oral liquids, usually antibiotic preparations. Although the product is supplied as (for example) a „powder for oral suspension", an exact volume of solvent must be added and this transformation is undertaken prior to dispensing the product to a patient. Therefore, the clinically relevant dose form is the administrable dose form (for example oral solution or oral suspension) and the strength will be described as if it is already the liquid that will be administered rather than the powder, for example, as 125mg/5mL. This reflects the standard dosing measure of a 5mL medicine spoon or occasionally as a concentration strength with a unitary denominator of „per 1ml" (25mg/1ml).

The representation of the medicinal product will probably use the administrable dose form and the strength description that matches this rather than the manufactured dose form.

For those oral liquids that are supplied as powders and undergo transformation for administration, the unit of presentation for the supply (the powder in the bottle) may be different from the unit of presentation of the administration (the 5mL spoonful).

So, for many types of MPDs, the denominator part of the strength ratio is „the unit of presentation ". But this may differ from MPD to MPD.

8.4 Concentration versus presentation strength

CoE " Perspectives on substance and strength in IDMP", November 2021 link to all CoE

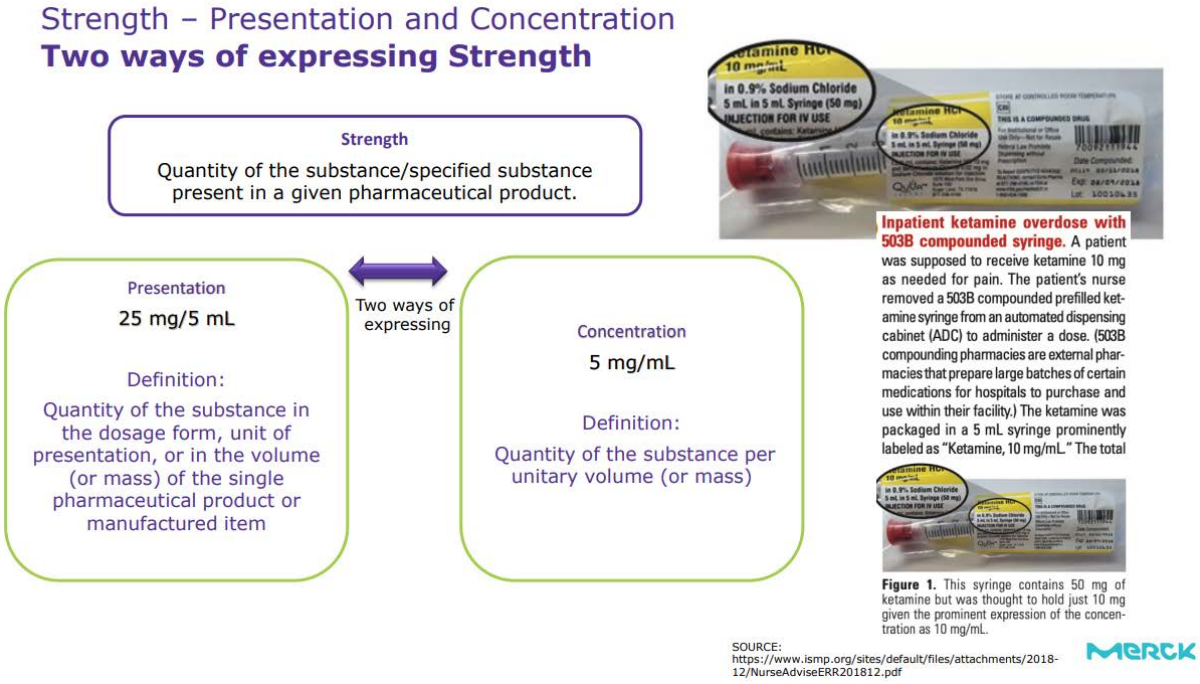


Figure 34 - Strength - Presentation and Concentration

There are different practise and way of expressing the strength when it comes to labelling. When expressing the strength following should be considered:

- SmPC is to be used as a main reference (examples given in Ch.8 of IDMP IG)
- Either presentation or concentration strength to be used (*if both present in SmPC MAH can add these on optional basis)
- In case of difference between Ch. 8 and SmPC – information in SmPC is the leading one
- Reference table should give a high-level guidance when it comes to expressing the strength – nevertheless decisions on how to express the strength might deviate and should be decided case-by case

You will find a set of patterns which are included to the EMA IG. They have been developed to give structure to the examples used. The patterns show how the Manufactured Item (MI) and the Pharmaceutical Product (PhP) should be expressed for a particular type of product. Products can then be matched to the appropriate pattern which then shows how the MI and PhP should look, for which the strength is mandatory.

Pattern	Type of product	Examples	Manufac. Item Unit of Present.	Pharm. Prod. unit of Present	Strength by Presentation	Strength by Concentration
1a	Solid, countable	Tablets, capsules, suppositories	Basic dose form related to the pharmaceutical form of the MI (tablet, capsule, etc.)	Basic dose form related to the pharmaceutical form of the Pharm Prod (tablet, capsule etc.)	Mandatory	Empty
1b	Solid dose forms in "container"	Powder or granules in sachet, ampoules, vials, Spincap, Rotocap – the whole content of the capsule is delivered to the patient via one or more actuations	Container (vial, sachet, etc.)	Container (vial, sachet, etc…) – not always informative depending on the dosing instructions	Mandatory	Empty
1c	Metered dose delivered by a metered actuation - dose cannot be adjusted	Dry-powder inhalers (DPI) pressurised metered-dose inhalers (pMDI), nasal sprays	Actuation (inhaler)	Actuation (inhaler, etc.)	Mandatory	Empty
2a	Products enclosed in a "presentation", where the total amount per presentation is clinically relevant	Unit dose solutions, parenteral liquid, unit dose nebuliser solutions NOT partial use preparations	Container (vial, etc.)	Container (vial, etc.)	Mandatory Expressed per total volume of the presentation (not per unit of presentation). This makes calculations easier	Mandatory (QRD)

Product Management Service (PMS) - Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe
EMA/285849/2020
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Figure 35 - Patterns for expression of strength (part 1)

Pattern	Type of product	Examples	Manufac. Item Unit of Present.	Pharm. Prod. unit of Present	Strength by Presentation	Strength by Concentration
2b	Products enclosed in a "presentation", where the concentration is clinically relevant rather than the total amount in the presentation	Multi-dose syringe, Partial dose syringe, infusion bags	Container (bottle, etc.)	N/A since it is the concentration that is relevant	Optional	Mandatory
3a	Continuous presentation (dosing is individual/not accurate and the total volume in the container is of less importance for dosing purposes)	Bulk powders/granules, semi-solids "bulk" liquids (e.g. eye drops)	Not useful clinically	N/A since it is the concentration that is relevant	Optional – usually not interesting	Mandatory
3b	Products enclosed in a "presentation", where the dose has a delivery rate	Transdermal patches	Patch	N/A since it is the concentration that is relevant	Optional	Mandatory – as a delivery rate over time

Figure 36 - Patterns for expression of strength (part 2)

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/product-management-service-pms-implementation-international-organization-standardization-iso_en.pdf

See page 32 + 33 + 34 + 35 of PMS IG

8.5 IDMP logical model

Reference to Unicom Deliverable 1.2 Requirements for a new ISO logical model [platform independent] PDF

CoE " How will a common logical model for IDMP help you?", February 2021 link All CoE

Actually (as of May 2022) there is no official IDMP logical model in existing standards. In ISO WG6 it is planned to have an IDMP logical model drafted by March 2023. So, this is still work in progress.

Of course, this is challenging work, as each logical model is always based on the business process it is created for.

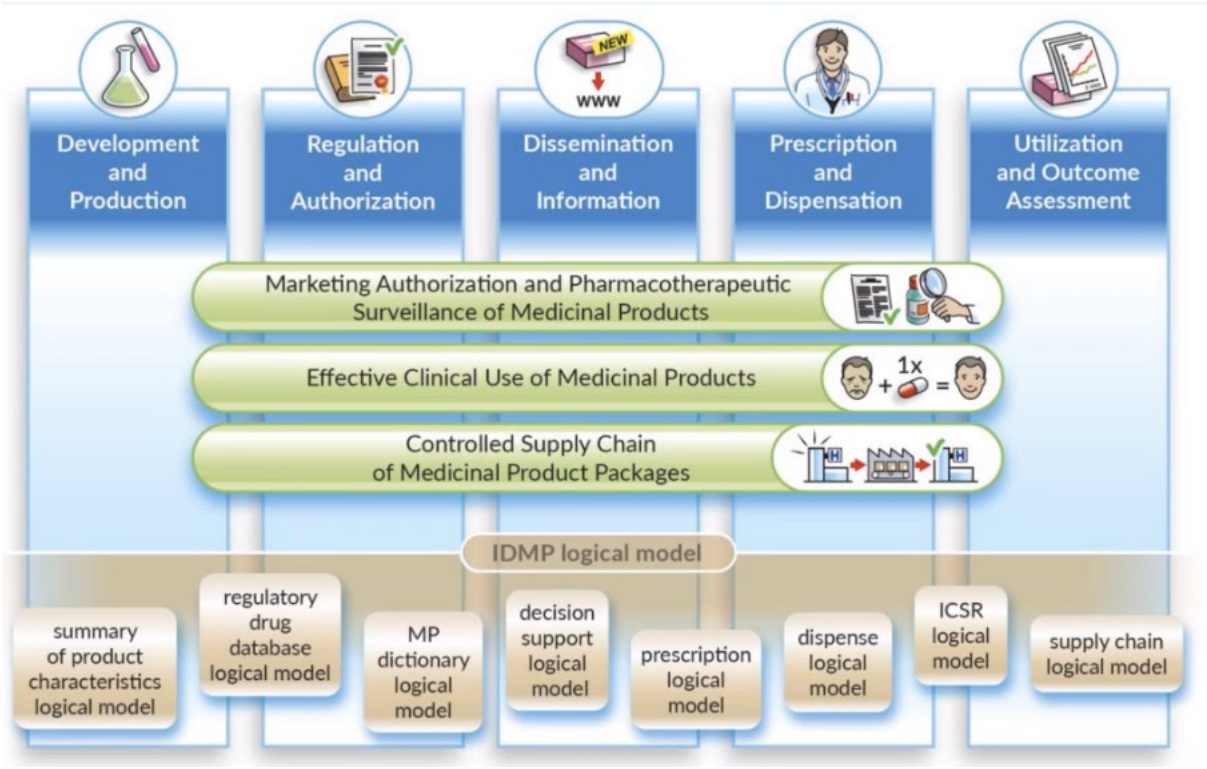

Figure 37 - Unicom IDMP logical models and business requirements

The biggest barrier to the unambiguous and fair identification of medicinal products is to overcome:

- Diverging implementation of IDMP
- Inconsistencies of interpretation
- The need for semantic alignment between regulatory implementations
- Essential governance of the IDMP standards and implementations is not assigned to a specific overarching governing body

8.6 IDMP in clinical applications

Reference to the Community of Expertise on clinical applications 4.2.2022 YouTube video

Presenters: Robert Vander Stichele (I~HD, UNICOM WP1 and WP8) Mohammad Nouri Sharikabad (WHO Collaborating Centre for Drug Statistics Methodology, Oslo and UNICOM WP1) Malin Fladvad (WHO-UMC, UNICOM WP1)

Reference to Deliverable D8.1: Report on the link between IDMP and Pharmacotherapeutic Groups and the Need for Medical Data in Pharmacotherapeutic Audit PDF

9 ETL Process

To get from your MPD data into the IDMP Common Data Model (CDM) you need to design and develop an Extraction Transformation Loading (ETL) process.

This process should restructure either the MPD data to the IDMP CDM or the other way round and add mappings from or to the IDMP Standardised Vocabularies. Typically, it is implemented as a set of automated scripts, for example SQL scripts. It is important that this ETL process is repeatable, so that it can be rerun whenever the source data is refreshed.

Creating an ETL is usually a large undertaking. Best practice requires four major steps:

- Data experts and IDMP experts together design the ETL.
- People with medical knowledge create the code mappings.
- A technical person implements the ETL.
- All are involved in quality control.

In this chapter we will discuss each of these steps in detail. Several tools are being developed at the time of the creation of this document to support some of these steps, and these will be discussed as well. We close this chapter with a discussion of IDMP and ETL maintenance.

Source of the figure from OMOP ETL process (retrieved 26.1.2022) under

https://ohdsi.github.io/TheBookOfOhdsi/ExtractTransformLoad.html

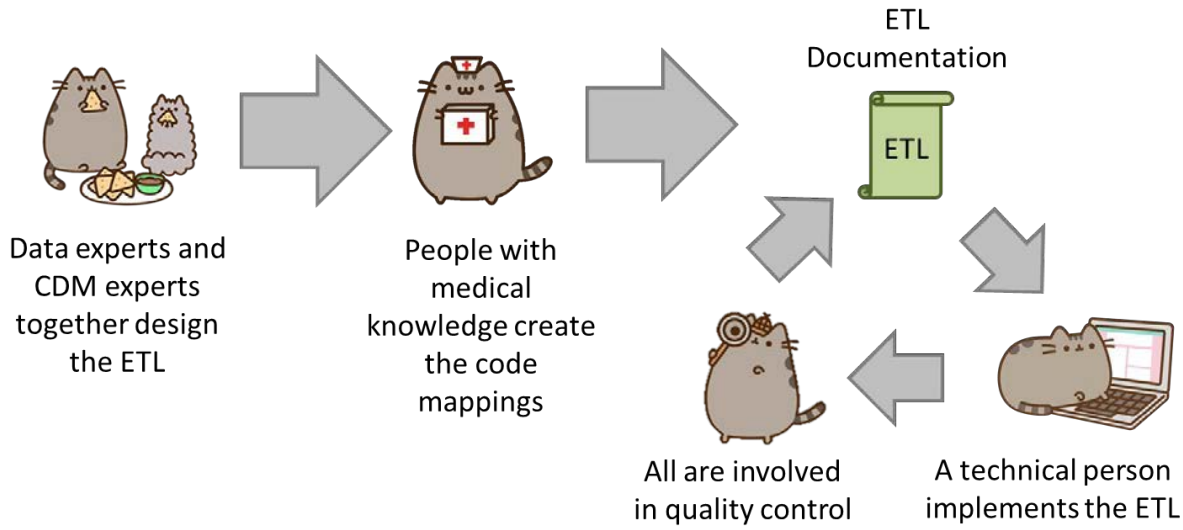

Figure 38 - ETL process from MPD to IDMP

9.1 ETL Step 1: Design the ETL

The goal of this step 1 is to learn about IDMP to help with designing an extract, transform, & load process to take or to map your database from your internal data model to the IDMP Common Data Model.

Make a gap analysis of the data elements you will get from IDMP product data to your internal product data elements.

It is important to clearly separate the design of the ETL from the implementation of the ETL. Designing the ETL requires extensive knowledge of both the source data as well as the IDMP CDM. Implementing the ETL on the other hand typically relies mostly on technical expertise on how to make the ETL computationally efficient. If you try to do both at once, you are likely to get stuck in detail, while you should be focusing on the overall picture.

To initiate an ETL process on a database you need to understand your data, including the tables, fields, and content. On the other hand you need to understand the IDMP data structure, content and data elements. Matching those data elements to your tables, fields and content will be part of the ETL design.

9.2 ETL Step 2: Create the Code Mappings

IDMP comes with controlled vocabularies on all attributes needed for identifying medicinal products. This means that the coding systems in your MPD data need to be aligned with or mapped to IDMP coding systems. If using the approach to make a mapping to all elements, check the IDMP data elements list relevant to the MPD, to determine which controlled vocabularies need to be implemented in your ETL process. If you make a mapping just on PhPID, MPID and PCID, you may not need a mapping to the coding elements.

Unfortunately, sometimes the MPD data uses coding systems that are not in the IDMP vocabularies or in another granularity. In this case, an enrichment of data may be needed from the MPD coding system to the IDMP coding system. Code mapping can be a daunting task, especially when there are many codes in the MPD coding system. There are several things that can be done to make the task easier:

- Focus on the most frequently used codes. A code that is never used or infrequently used is not worth the effort of mapping.
- Make use of existing information whenever possible. For example, MPD products have often been mapped to ATC. Although ATC is not detailed enough for many purposes, the relationships between ATC and IDMP can be used to make good guesses of what the right IDMP codes are. The ATC codes (with ROA) can be used to group similar products for subtasks in the work (cutting the elephant to pieces).
- Each mapping requires exact definition of its use case.

9.3 ETL Step 3: Implement the ETL

Once the design and code mappings are completed, the ETL process can be implemented in a piece of software. When the ETL was being designed we recommended that people who are knowledgeable about the source and IDMP work together on the task. Similarly, when the ETL is being implemented it is preferred to use people who have experience with working with data (particularly large data) and experience with implementing ETLs. This may mean working with individuals outside of your immediate group or hiring technical consultants to execute the implementation. It is also important to note that this is not a one-time expense. Moving forward it would be good to have someone or a team who spends at least some dedicated time to maintaining and running the ETL. Doing ETL for legacy conversion will be a once-in-a-lifetime operation and dissipate when the legacy conversion is finished and PMS takes over.

Implementation usually varies site to site, and it largely depends on many factors including infrastructure, size of the database, the complexity of the ETL, and the technical expertise available. Because it depends on many factors, we cannot make a formal recommendation on how best to implement an ETL.

9.4 ETL Step 4: Quality Control

For the extract, transform, load process, quality control is iterative. The typical pattern is to write logic -> implement logic -> test logic -> fix/write logic. There are many ways to go about testing an ETL but here are some high-level ways to approach quality control from an ETL standpoint.

- Review of the ETL design document, computer code, and code mappings. Any one person can make mistakes, so always at least one other person should review what was done.
- Manually compare all information on a sample of medicinal products in the source and target data. Use for this e.g., one group of products with one common active ingredient and pharmaceutical dose form.
- Compare overall counts in the source and target data.
- Create unit tests meant to replicate a pattern in the source data that should be addressed in the ETL. For example, if your ETL specifies that products for vet use only should be dropped, create a unit test of a product for vet use only and assess how the builder handles it.

9.4.1 ETL Maintenance

It is no small effort to design the ETL, create the mappings, implement the ETL, and build out quality control measures. Unfortunately, the effort does not stop there. There is a cycle of ETL maintenance that is a continuous process after the first Common Data Model (CDM) is built. Some common triggers that require maintenance are changes in the source data, a bug in the ETL, a new IDMP Vocabulary is released, or the CDM itself has changed or updated. If one of these triggers occur the following might need updating: the ETL documentation, the software programming running the ETL, and test cases and quality controls.

Often a healthcare data source is forever changing. New data might be available (e.g. a new column in the data might exist). Also technical changes in the IDMP data such as the update to a new FHIR resource version may change. Not all changes in the source data may trigger a change in the ETL processing of it, however at a bare minimum the changes that break the ETL processing will need to be addressed.

The IDMP data are also ever changing just as your source data may be. In fact, the IDMP data can have multiple releases as MPD vocabularies update. Each CDM is run on a specific version of a Vocabulary and running on a newer improved Vocabulary could result in changes in how sources codes get mapped to in the standardised vocabularies. Often differences between Vocabularies are minor, so building a new CDM every time a new Vocabulary is released is not necessary. However, it is good practice to adopt a new Vocabulary once or twice a year which would require reprocessing the CDM again. It is rare that changes in a new version of a Vocabulary would require the ETL code itself to be updated.

The final trigger that could require CDM or ETL maintenance is when the IDMP common data model itself updates. As the use of IDMP grows and new business processes and with-it new data requirements are found this may lead to additional data being stored in the IDMP CDM. This might mean data that you previously were not storing in the CDM might have a location in a new CDM version. Less frequently are changes to existing CDM structure, however it is a possibility. For example, the EMA has announced to migrate to the newest FHIR resource version which could cause an error in ETL processing.

Data Download

The EMA SPOR Portal is delivering data management services for substances, products, organisations and referential (SPOR) for download. SMS and PMS are not currently activated. SMS EUTCT will probably become the IDMP Substance Coding System for SMS (discussion is still ongoing as of 7.2.2022).

Figure 39 - The four SPOR data management services

SPOR Download data *EUTCT (will probably become the IDMP Substance Coding System)* *https://spor.ema.europa.eu/eutct/lists* *EMA SPOR*

https://spor.ema.europa.eu/sporwi/

Data Integrity and Migration

At the time of the migration and transformation of the IDMP product data into the MPD´s product master data all data based on the controlled vocabularies (CVs) will be mapped and recoded against the terminology available in RMS, OMS and SMS respectively and as applicable.

To maintain data integrity, the following load order must be maintained when loading to the Master Data Management (MDM):

a. Reference data;

b. Organisation data;

c. Substance data;

d. Product data;

e. Deprecation (Substance, Product, Organisation or Reference data transaction).

The table below highlights the relationship between each domain (columns) and its dependencies (rows):

	S	P	O	R
S		X		
P				
O		X		
R	X	X	X	

Figure 40 Dependencies between PMS and its referential

EMA IG (chapter7)

EMA IG V2 CHAPTER 7 / AS reference!

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/products-management-services-pms-implementation-international-organization-standardization-iso_en-0.pdf

9.5 Mapping Tools

There are several mapping tools in the process of being developed for mapping to or from IDMP. Please find 2 as examples as placeholder in the following chapters.

9.5.1 IDMP1-Matching Tools

Source (retrieved 7.2.2022)

Homepage: https://www.idpm1.com

The IDMP1 Matching Tools helps healthcare professionals matching their data with IDMP controlled terms. These Identification for Medicinal Products (IDMP) translating and converting tools include at the same time global international drug standards such as IDMP, SNOMED, ICD10, RxNORM, WHO ATC etc..

The user interface of the IDMP Matching Tool is usable for free (www.idmp1.com), the API version is based on a Software a Service (SAS) subscription.

Based on the IDMP1 Matching API there are several helpful solutions:

- IDMP Term Browser
- IDMP Drug Dictionary
- Active Ingredients Dictionary
- MAH Drug Dictionaries

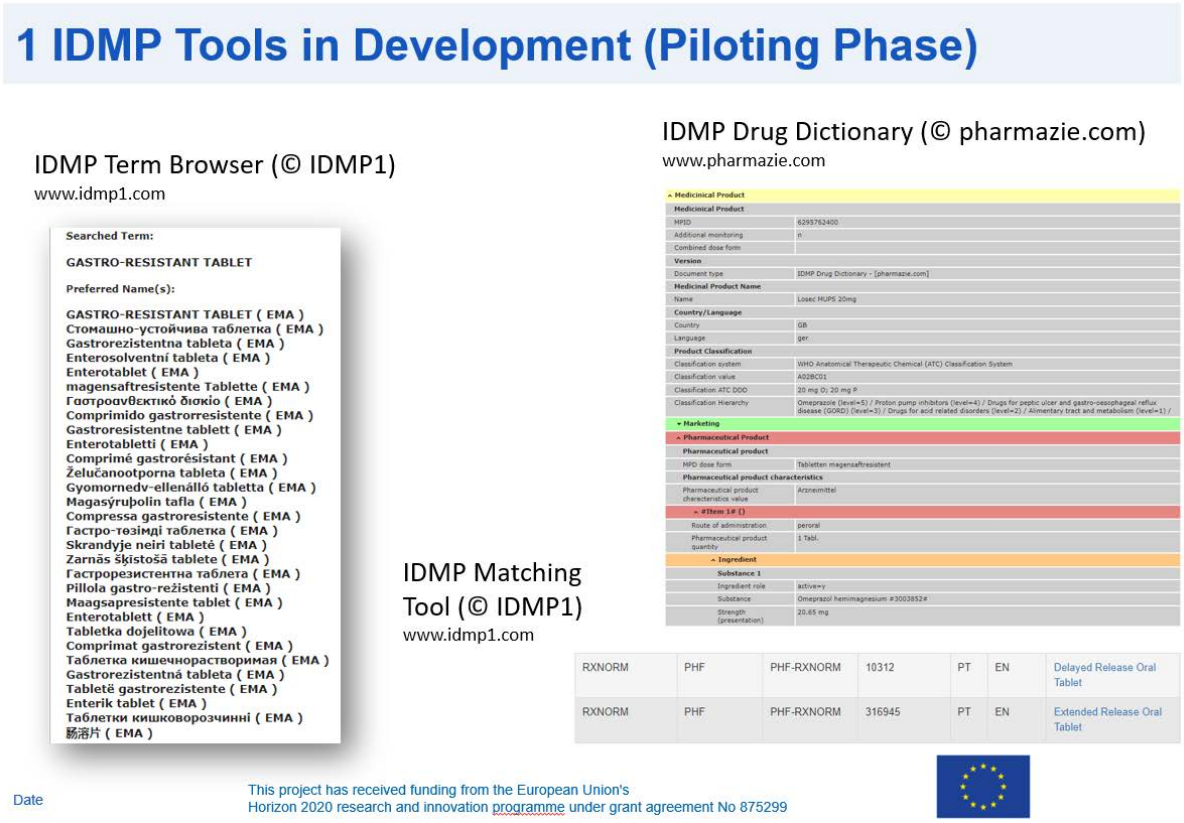

Figure 41 - IDMP Tools in Development (Piloting Phase)

9.5.2 Sporify

Source (retrieved 14.1.2022)

Homepage: https://www.sporify.eu/

Sporify is a tool to match, maintain, synchronise & integrate SPOR Data.

It is a single solution to match, maintain, synchronise and integrate SPOR Data. It is a product of the CorrIT Ltd located in Ireland and based on a SAS subscription.

9.6 Final thoughts on the ETL

The ETL process is different for many reasons, not the least of which is the fact that you are all processing unique source data, making it hard to create a “one-size-fits-all” solution. However, here some best practice advice.

- The 80/20 rule. If you can avoid it do not spend too much time manually mapping source codes to concepts sets. Ideally, map the source codes that cover most of your data. This should be enough to get you started and you can address any remaining codes in the future based on use cases.
- It’s ok if you lose data that is not of the required quality. Often these are the records that would be discarded before starting an analysis, anyway, just remove them during the ETL process instead.
- A CDM requires maintenance. Just because you complete an ETL does not mean you do not need to touch it ever again. Your raw data might change, there might be a bug in the code, there may be

new vocabulary or an update to the CDM. Plan to allocate resources for these changes so your ETL is always up to date.

- Plan the versioning of the ETL data.
- Be aware, that your ETL process should always be based on your concrete use case(s).

10 Mapping for SNOMED Users

Reference to "Implementing an Interoperable National Drug Dictionary using SNOMED CT" (© SNOMED International)

It is available here on YouTube: https://www.youtube.com/watch?v=b354WzHv2Qw

Interlinking IDMP with SNOMED CT is kind of related to implementing an interoperable national drug dictionary using SNOMED CT. The mapping strategy also depends on the MPD structure if it is a mirror MPD or a flat MPD. The above mentioned video gives a very good introduction to interested parties on how to implement a national MPD.

10.1 IDMP and SNOMED CT

Reference to SNOMED CT Drug Model for supporting National Extension V1.0 including IDMP compatibility

https://confluence.ihtsdotools.org/download/attachments/115870807/1b.%20SNOMED%20CT%20Drug%20Model%20for%20supporting%20National%20Extension%20V1.0.pdf?api=v2

SNOMED CT is the most comprehensive, multi-lingual clinical terminology in use around the world in electronic health records. By facilitating consistent, accurate, representation of relevant clinical information in the shared electronic health record, communication between the various healthcare professionals involved in managing patient care, is improved.

Mapped as it is to other international standards, SNOMED CT is helping to remove language barriers in patient care; member nations are responsible for translation; entire or partial translations are available in at least 7 different languages.

SNOMED CT has an International Edition, containing content covering various domains, (e.g., body structures, procedures, clinical findings/disorders, medicinal products) used and understood in more than one national healthcare system. This shared understanding is necessary for international conformance and interoperability.

In addition, member nations and organisations may develop their own extension editions containing content to support a wide range of national, local, institution, vendor, discipline, or specialty specific requirements. This core/extension mechanism is especially important for the identification and description of medicinal products and packages in the SNOMED CT ecosystem.

The SNOMED CT International Medicinal Product hierarchy is composed of abstract concepts with international applicability that represent varying levels of specificity (e.g., active ingredient, active ingredient + intended site of administration, basis of strength substance + precise active ingredient + strength + pharmaceutical dose form). It also includes groupers based on chemical structure of active ingredient substance, mechanism of action of active ingredient substance, or therapeutic role of product. The real or actual products, as authorised by medicines regulatory agencies within specific jurisdictions, are not within scope for the International Release; that level of specificity would exist in a national extension.

The primary use cases for the SNOMED CT International Release Medicinal Product hierarchy include:

- To provide consistently modelled and usable concepts that can serve as a foundation for the creation of national extensions to allow member countries to create additional concepts suitable for their own healthcare culture and practice, or to which existing terminology can be mapped if required.
- To facilitate international interoperability of medicinal product concepts (e.g., for patient summaries or cross-border care).
- To provide compatibility with the IDMP model or other external standards, where appropriate, for identification of medicinal products.
- To provide components and structure that can support development of medication-related decision support.
- To support analysis of medicinal product-related information in healthcare data for pharmacovigilance or research purposes.

- To provide medicinal product concepts required to sufficiently define concepts in other SNOMED CT hierarchies.

Note that the content in the SNOMED CT International Release Medicinal Product hierarchy is not intended to support prescribing use cases but may be sufficient to do so for some implementations; support for prescribing use cases would generally be expected at the national extension level.

10.1.1 SNOMED CT Medicinal Product Content

Medicinal products are described in the International Edition of SNOMED CT in five different levels of abstraction:

Medicinal Product "containing"

An abstract representation of a medicinal product based on description of active ingredient substance(s) that it contains. It means that the medicinal product must contain the active ingredient(s) specified in the FSN but may also contain additional active ingredient(s).

Medicinal Product "containing only"

An abstract representation of a medicinal product based on description of active ingredient substance(s) that it contains. It means that the medicinal product must contain only the active ingredient(s) specified in the FSN.

Medicinal Product Form "containing"

An abstract representation of a medicinal product based on description of active ingredient substance(s) that it contains and on the generalised intended site of administration. It means that the medicinal product must contain the active ingredient(s) specified in the FSN but may also contain additional active ingredient(s).

Medicinal Product Form "containing only"

An abstract representation of a medicinal product based on description of active ingredient substance(s) that it contains and on the generalised intended site administration. It means that the medicinal product must contain only the active ingredient(s) specified in the FSN.

Clinical Drug "containing precisely"

An abstract representation of a medicinal product based on description of the Specified substance with the role of Precise active ingredient, basis of strength substance (BoSS), strength, manufactured dose form, and unit of presentation of a drug product. It implies that the drug product must contain only the precise active ingredient(s) specified in the FSN.

The model in the International Edition of SNOMED CT provides support for National Extensions to describe the actual products authorised and marketed in their own jurisdiction and to author intermediate concepts as required by the local culture.

10.1.2 SNOMED CT Medicinal Product content and IDMP Content

IDMP standards and the SNOMED CT Medicinal Product hierarchy are designed to support different domains with differing use cases, the former the regulatory domain, the latter the patient care domain. However, there is significant harmony and synergy between them. The diagram below shows how the classes of concepts in the Medicinal Product terminology present in SNOMED CT and classes to identify medicinal product concepts in the IDMP suite can be related to each other based on the current understanding of the PhPID concepts in IDMP; the numbered relationship lines are given further detail in the table below.

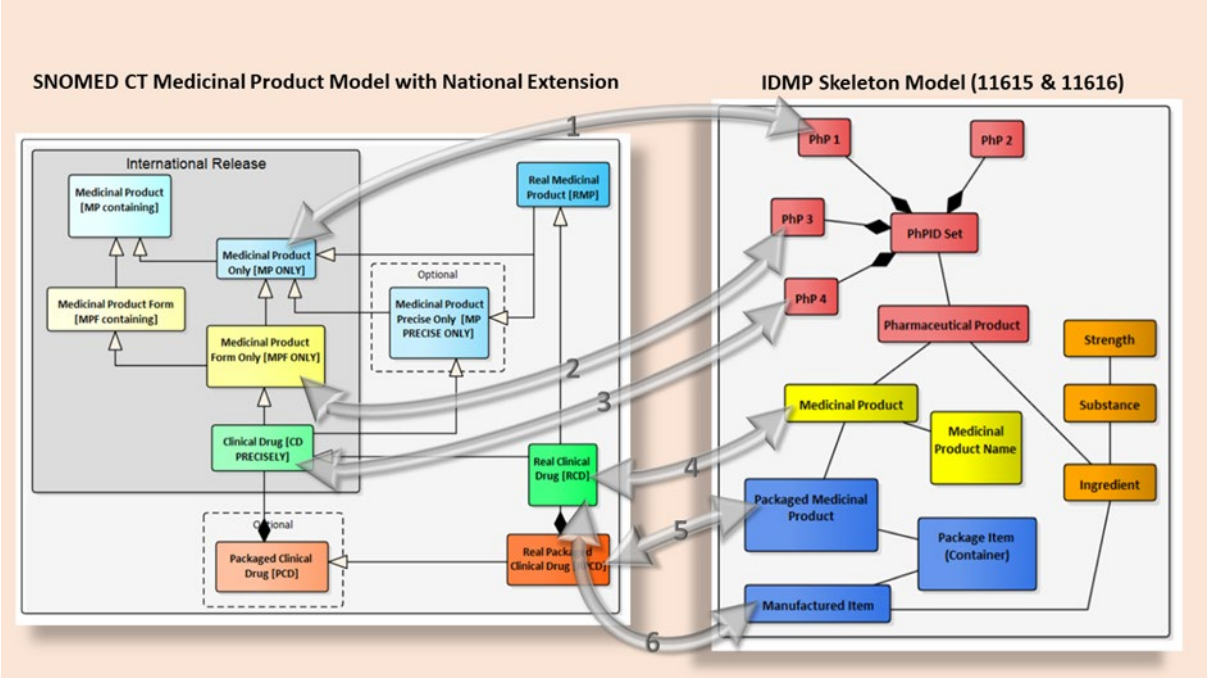

Figure 42 - SNOMED Product Model relation to IDMP Skeleton Model

The table below provides further detail to that diagram by comparing the classes of each medicinal product identification system together.

Table 10-1 - SNOMED concept in relation to IDMP concept

Line in diagram	SNOMED CT CT CT		IDMP	
	Concept	Definition	Concept	Definition
NA	Medicinal Product "containing"	An abstract representation of a medicinal product based on description of active ingredient substance(s) that it contains. It means that the medicinal product must contain the active ingredient(s) specified in the FSN but may also contain additional active ingredient(s). Examples: 108600003 |Product containing atorvastatin (medicinal product)| 409411009 |Product containing amlodipine and atorvastatin (medicinal product)|	No similar equivalent	Not applicable
1	Medicinal Product "containing only"	An abstract representation of a medicinal product based on description of active ingredient substance(s) that it contains. It means that the medicinal product	PhP Level 1 (from ISO 11616)	Active Substance(s)*

		must contain only the active ingredient(s) specified in the FSN. Examples: 773455007 |Product containing only atorvastatin (medicinal product)| 773457004 |Product containing only amlodipine and atorvastatin (medicinal product)|		
NA	Medicinal Product Form "containing"	An abstract representation of a medicinal product based on description of active ingredient substance(s) that it contains and on the generalised intended site of administration. It means that the medicinal product must contain the active ingredient(s) specified in the FSN but may also contain additional active ingredient(s). Examples: 437876006 |Product containing paracetamol in oral dose form (medicinal product form)| 767783007 |Product containing codeine and paracetamol in oral dose form (medicinal product form)|	No similar equivalent	
2	Medicinal Product Form "containing only"	An abstract representation of a medicinal product based on description of active ingredient substance(s) that it contains and on the generalised intended site of administration. It means that the medicinal product must contain only the active ingredient(s) specified in the FSN. Examples: 780128004 |Product containing only paracetamol in oral dose form (medicinal product form)| 778848002 |Product containing only codeine and paracetamol in oral dose form (medicinal product form)|	PhP Level 3 (from ISO 11616)	Active Substance(s)* + Administrable Dose Form

NA	No similar equivalent	No clinical use case has been identified to support inclusion of this concept class.	PhP Level 2 (from ISO 11616)	Active Substance(s)* + Strength + Reference Strength
3	Clinical Drug "containing precisely"	An abstract representation of a medicinal product based on description of the precise active ingredient substance(s), basis of strength substance (BoSS), strength, manufactured dose form, and unit of presentation of a drug product. It implies that the drug product must contain only the precise active ingredient(s) specified in the FSN. Examples: 322236009 |Product containing precisely paracetamol 500 milligram/1 each conventional release oral tablet (clinical drug)| 765548006 |Product containing precisely doxazosin (as doxazosin mesilate) 4 milligram/1 each prolonged-release oral tablet (clinical drug)| 443620003 |Product containing precisely aliskiren 300 milligram and valsartan 320 milligram/1 each conventional release oral tablet (clinical drug)| 322238005 |Product containing precisely paracetamol 24 milligram/1 millilitre conventional release oral solution (clinical drug)|	PhP Level 4 (from ISO 11616))	PhP4: Active Substance(s)* + Strength + Reference Strength + Administrable Dose Form
	Real Medicinal Product [National Extension]	The representation of a medicinal product marketed by a single organisation (supplier) in a single jurisdiction under a single name (which may be a trade or brand name) and which contains the same set of active ingredient substances, regardless of any modification of those active ingredient substances. It is a subtype of and real-world equivalent to the Medicinal Product Only (MP only) class in the International Edition of SNOMED CT	No similar equivalent	

		Examples: Inlyta product Pfizer Limited (real medicinal product)		
4 and 6	Real Clinical Drug [National Extension]	The representation of a medicinal product marketed by a single organisation (supplier) in a single jurisdiction under a single name (which may be a trade or brand name) and which contains the same set of precise active ingredient substances and strengths in a single manufactured dose form. It is a subtype of and real-world equivalent to the Clinical Drug (CD precisely) class in the International Edition of SNOMED CT Examples: Inlyta 3 mg tablet Pfizer Limited (real clinical drug)	Medicinal Product (MPID) (from ISO 11615) and /or Manufactured Item (not an identified class) (from ISO 11615)	any pharmaceutical product or combination of pharmaceutical products that may be administered to human beings (or animals) for treating or preventing disease, with the aim/purpose of making a medical diagnosis or to restore, correct or modify physiological functions Manufactured Item: Qualitative and quantitative composition of a product as contained in the packaging of the Medicinal Product as put on the market or Investigational Medicinal Product as used in a clinical trial
5	Real Packaged Clinical Drug [National Extension]	A representation of a medicinal product as it is supplied in a package by a by a single organisation (manufacturer or supplier) in a single jurisdiction under a single name (which may be a trade or brand name) for placement into the supply chain Examples: Package containing 28 tablets Inlyta 3 mg tablet Pfizer Limited (real packaged clinical drug)	Packaged Product (PCID) (from ISO 11615)	Medicinal Product in a container being part of a package, representing the entirety that has been packaged for sale or supply

10.1.3 Routes of administration

The SNOMED CT value set is more granular than that in EDQM / IDMP. For example, where EDQM uses “oromucosal” SNOMED CT uses the more granular sites that are reflected in the concept names; therefore “buccal tablet” will have an ISI of “buccal” in SCT not “oromucosal”, although with the ontology relationships in SNOMED CT, the buccal intended site is a child of the oromucosal intended site, so grouping is machine processable.

10.1.4 Specified Substances

SNOMED CT does not have specified substances. Specified substances are important to the regulatory use cases and are often proprietary, so would not be appropriate for SNOMED CT or indeed MPD use. The domain definition for SNOMED CT substances excludes specified substances.

10.1.5 Manufactured Dose Forms

The administrable dose form definition does not exist in SNOMED, hence there is no completely equal SNOMED level to the PHPID level IV. SNOMED, specifically addresses the patient care use cases, which require manufactured dose form in preference to the administrable dose form. However, for oral antibiotic liquids, the administrable dose form is used because this is the most clinically relevant for the SNOMED CT use cases. The Editorial Policy of SNOMED describes this in detail.

Because of the ontological nature of SNOMED CT, you get the basic dose form automatically for each and every Clinical Drug because of the concept definition.

10.2 Mapping EDQM / IDMP dose forms to SNOMED

There is a pilot project in progress at SNOMED International in cooperation with EDQM as part of the work ongoing at the Drug Extension User Support Group. This is a draft map from EDQM pharmaceutical dose forms to SNOMED CT pharmaceutical dose forms and whilst IDMP compliant, it is not a map from IDMP directly.

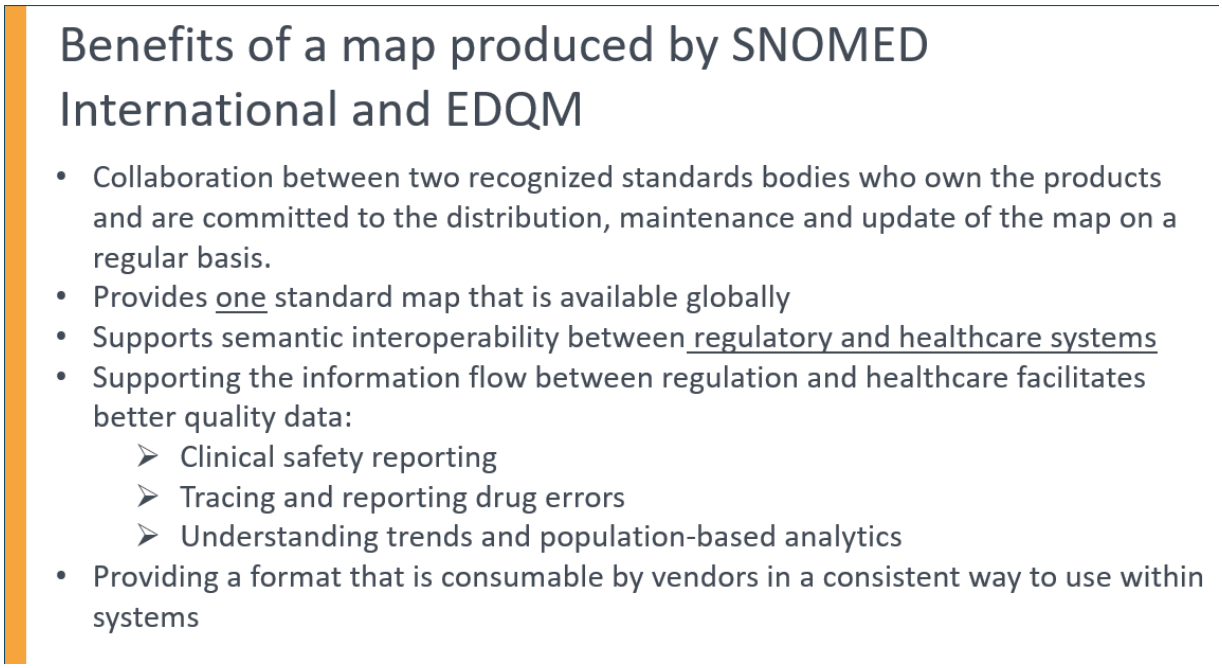

Figure 43 - Benefits of a map SNOMED EDQM

10.3 Snap-2-SNOMED Project

Source (retrieved 14.1.2022)

Snap-2 SNOMED is a hosted tool for SNOMED International Members to collaboratively create and maintain simple maps to SNOMED CT (work in progress). This application is hosted by SNOMED International for use by the community. To log in you need a SNOMED International account.

This tool is aimed at SNOMED members and their stakeholders to collaboratively create and maintain simple maps to SNOMED CT.

Source (retrieved 14.1.2022)

https://confluence.ihtsdotools.org/download/attachments/123901441/MTUG%20meeting%20%2823%20March%202021%29.pptx?api=v2

https://snap.snomedtools.org/ and user guide http://snomed.org/s2sug

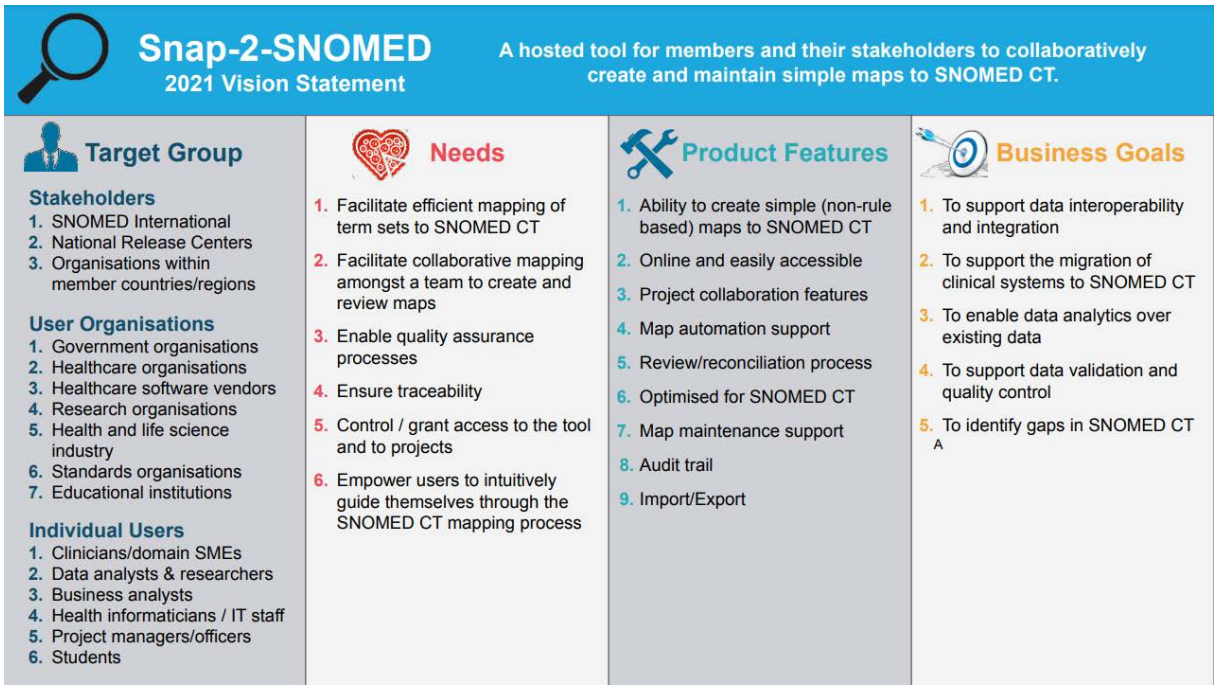

Figure 44 - Snap-2-SNOMED 2021 Vision Statement

11 Activities related to IDMP

11.1 ePI for Medicinal Products in the EU

Electronic product information for human medicines in the EU is a joint EMA–HMA–EC collaboration which has started in March 2017. The development of this ePI project will be relevant for MPD providers as MPDs are the link between regulatory data and e-Prescription. ePI data will also use IDMP SPOR data.

It states that the regulator will provide PMS structured data, SmPC, Leaflet and the package label. To which extend PMS data will be part of the ePI is still work in progress.

Source (retrieved 13.1.2022)

Electronic product information for human medicines in the EU: key principles

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/electronic-product-information-human-medicines-european-union-key-principles_en.pdf

(retrieved 8.3.2022)

Report on public consultation on EU ePI Common Standard Summary of comments received and next steps (as of 22.2.2022)

https://www.ema.europa.eu/en/documents/report/report-public-consultation-eu-common-standard-electronic-product-information-epi-summary-comments_en.pdf

The key principals in this ePI projects are:

The regulator should hold ePI data, as a trustworthy source for reliable medicines information. The NCA in each country will store and handle ePI in their jurisdiction. In addition, it is envisaged that a pan-European medicines web portal could provide a central point for access of ePI for all centrally and nationally authorised medicines.

Implication: In the future, it is envisaged that the EMA and all NCAs will be able to use ePI from the point of submission, and ePI will be made available through EMA and NCA websites.

ePI will interface and interact with many ongoing and foreseen eHealth initiatives. eHealth and related services should work together, within and across organisations or domains. ePI interoperability with cross-border prescription, electronic health records, the future European medicines web portal, pharmacovigilance systems, SPOR data management services, future ePI for veterinary medicines, a future European common data model, current electronic application procedures and national ePI systems must be considered in the design of EU ePI.

Use of ePI in both an EU and global context should also be considered.

Electronic product information for human medicines in the EU: key principles

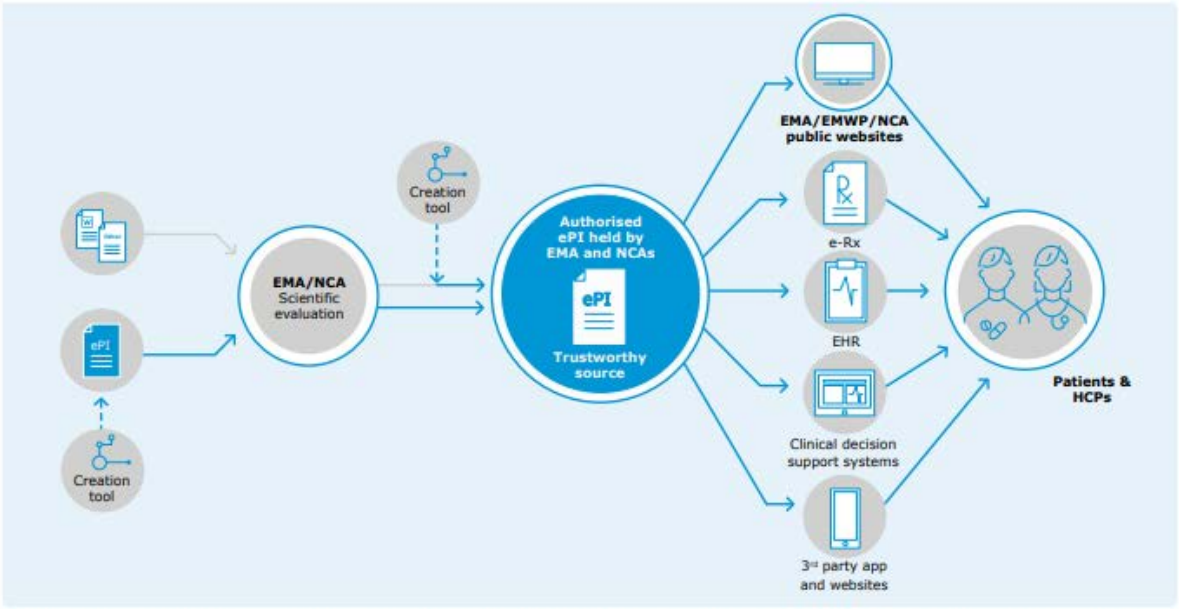

Figure 1. Proposed model for ePI process (subject to change following feasibility analysis once ePI project is started). A free, validated ePI creation tool is provided by the regulator. The tool could be used by the MAH to create ePI for submission in an application or to create ePI once an evaluation is complete. ePI for both nationally and centrally authorised products can be accessed from the European medicines web portal (EMWP) and NCA public websites. ePI can be used with systems for e-prescribing (e-Rx) and electronic health records (EHR). Data can be accessed by third-parties for example, for use in websites and patient / consumer apps.

Figure 45 - Model for ePI process

11.1.1 Gravitate-Health

The Gravitate Health is a public – private partnership with 39 members from Europe and the US, co-led by University of Oslo (coordinator) and Pfizer (industry lead), funded by the Innovative Medicines Initiative (IMI) – a joint undertaking of the European Commission, the European Federation of Pharmaceutical Industries and Associations (EFPIA), IMI2 Associated Partners.

The current objective of this project is to create a new digital platform that gives patients a more accessible way of acquiring trusted medicinal product Information. This will be done by combining information from the International Patient Summary (IPS) document, a selected list of medication list with ePIs for each medication and the associated medication product definition resources.

Source (retrieved 14.1.2022)

https://www.gravitatehealth.eu/

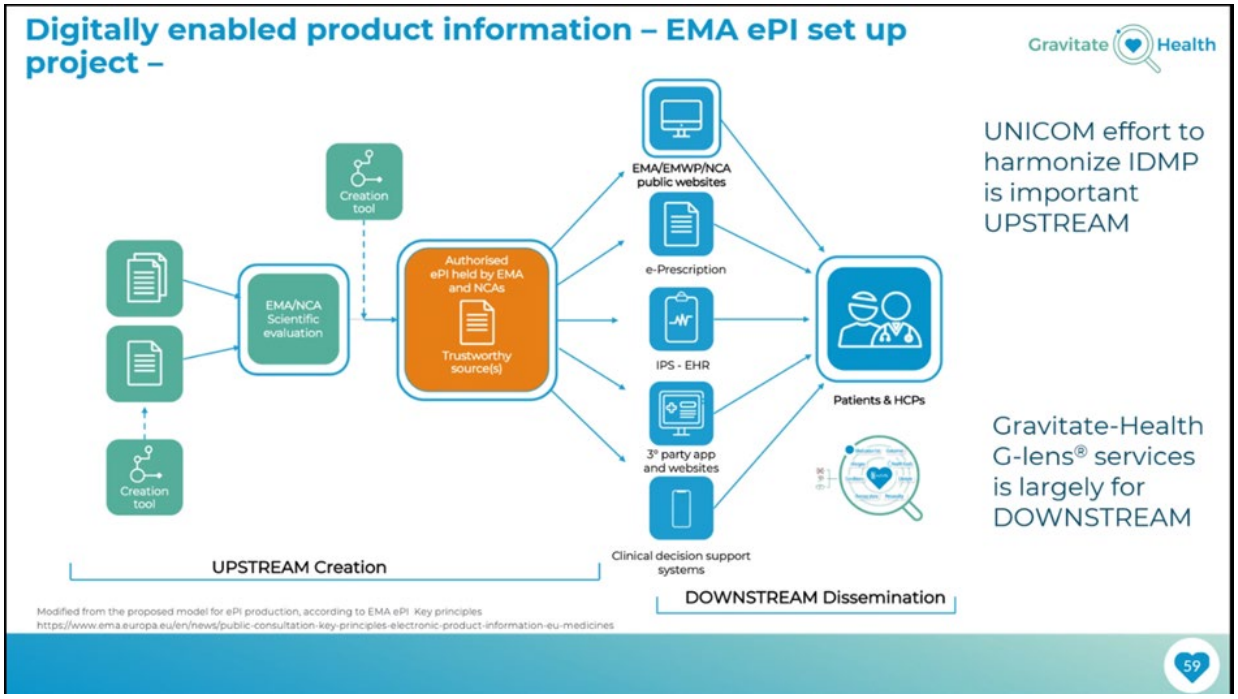

Figure 46 - Gravitate-Health G-lens(R) services

11.2 Digital Application Dataset Integration (DADI)

The Digital Application Dataset Integration (DADI) project of EMA will replace PDF electronic application forms (eAF) used for regulatory submissions with online forms, making the future form-filling and submission-handling process more efficient.

The implementation of these new forms supports the EU requirement to integrate ISO IDMP (Identification of Medicinal Products) standards for human medicines. The PMS data model will link to DADI and vice versa.

It is planned to go life at the end of 2022. The output of this DADI project will feed into the PMS product data.

Source EMA retrieved 7.2.2022, 25.1.2022 presentation on DADI - FHIR and DATA

Introducing DADI – The Digital Application Dataset Integration Network Project to replace electronic application forms, 18 January 2022, Webinar

https://www.ema.europa.eu/en/documents/presentation/presentation-introducing-dadi-digital-application-dataset-integration-network-project-replace_en.pdf

DADI is lead by the EMA and will replace all the eForms in regulatory.

Introducing DADI | Objectives

EUROPEAN MEDICINES AGENCY

Project Objectives

1. Replace the **current PDF-format application forms** for marketing authorisation applications, variations and renewals for human and veterinary medicinal products **with web-based application forms** compatible with ISO IDMP and FHIR standards and the EU Implementation Guide for human medicine
2. Provide a **structured data format (FHIR standard based)** which can be **imported** into PMS services and reused in other submission related tasks to support the PMS target operating model
3. Provide a **human readable PDF output** in line with the Notice to Applicants requirements
4. Use an **out of the box solution for the interface**

How is PMS linked to eAF

EUROPEAN MEDICINES AGENCY

PMS

eAF

Key concepts

- The **variation** form uses data from PMS by;
  - Product selection from
  - Display of structured data elements that can be changed in scope of the variation
- PMS and eAF data structures adhere to the **ISO IDMP** (for human CAPs and NAPs); Veterinary products will follow in a similar fashion (UPD)
- Not all PMS data elements are in scope of **MAA/variation/Renewal** forms
  - Data/Process **Out of scope**: MA transfer, Update of QPPV, PSMF location, PhV contacts, marketing status and authorisation status
- The DADI project does **not** define the new business processes, but is focusing on providing the basis for data to be exchanged: A **common FHIR message** format for medicinal products
- Examples of processes that can be built based on the same FHIR message:
  - Feeding approved data **back to PMS**
  - The submission of **Art 57(2)** data elements
  - as well as **data cleansing/enrichment**

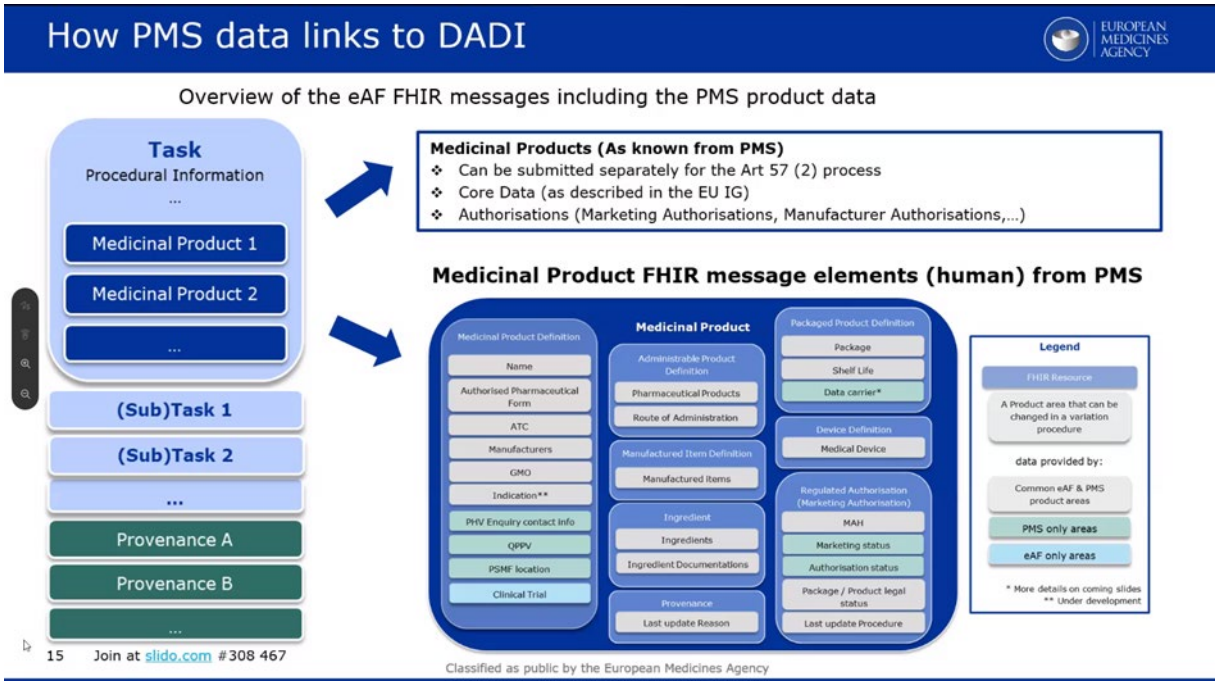

Figure 47 - How PMS data links to DADI (Source EMA as of 25.1.2022)

Project Question and Answers Version 2 (as of December 2021) PDF

This document is for information only and is based on insights available at the time of its release. It will be updated regularly by EMA.

12 Call to action

The implementation of ISO IDMP/SPOR turns out to be a moving target requiring significant investment. Work on a global scale is essential and crucial in this fast-developing eHealth world, but even more important is to monitor the jurisdictional requirements in parallel. The implementation of ISO IDMP/SPOR must be based on more than one business case to be able to explore the full power of harmonised high-quality data.

For an MPD provider it is also crucial to monitor the future developments of ePI and DADI (see chapter 4.1.8 and 4.1.9 this document).

ePI will interface and interact with many ongoing and foreseen eHealth initiatives such as cross-border prescription and electronic health records. The SPOR data management services, and a future European common data model, must be considered in the design of EU and global MPD application systems.

To realise the benefits for all stakeholders, pharmaceutical companies, regulators and MPD providers shall act to fully implement IDMP standards for medicinal products.

IDMP standards-enabled information shall then be collected and stored in medicinal product dictionaries for easy access by doctors and pharmacists.

With the link between IDMP standards and the MPD, IT solution providers shall integrate this medicinal product information in their solutions. Only then, will healthcare providers be able to safely prescribe and dispense the right medicinal products to the right patients, regardless of where they are.

Public health organisations can more easily and quickly aggregate worldwide information to address ADEs, recalls and important public health initiatives to ensure the world is a safer place for everyone.

13 Appendices

13.1 Gap Analysis Belgium MPD SAM - IDMP

*Reference to the **Gap Analysis SAM - ISO IDMP** (see Annex)*

"The Belgian Agency (FAGG/AFMPS) commissioned DIGILE for the IDMP/SAM Gap Analysis in the scope of UNICOM. The result of the Belgian MPD SAM-2-IDMP gap analysis, is part of D9.2 delivery with official permission of the FAGG - AMPS (the Belgian NCA).

The 3 big challenges in the Belgian gap analysis between SAM as Belgian MPD and IDMP where:

- Finding and mapping the SAM substances to the IDMP Substances
- Checking the already existing relation of the SAM to the EDQM dose form
- Normalisation of the product strength

Please find the outcome of this analysis as an additional PDF file attachment to this document.

Two examples to find in this document as result of the gap analysis:

	only used	terms		items
current EDQM terms	277	94%	585	80%
deprecated EDQM terms	3	1%	24	3%
rejected EDQM terms	2	1%	4	1%
not found as EDQM term	13	4%	118	16%
total number of terms	**295**	100%	**731**	100%

Figure 48 - Gap analysis between SAM and EDQM pharmaceutical dose forms

In SAM, 12 out of 303 units of measure do not validate as UCUM units:

unit	validation	remark
kcaL	kcaL is not a valid UCUM unit.	kcaL is not a valid UCUM code. No alternatives were found.
kcaL/(8.h)	kcaL/(8.h) is not a valid UCUM unit.	kcaL is not a valid UCUM code. No alternatives were found.
kcaL/d	kcaL/d is not a valid UCUM unit.	kcaL is not a valid UCUM code. No alternatives were found.
kcaL/h	kcaL/h is not a valid UCUM unit.	kcaL is not a valid UCUM code. No alternatives were found.
k{unit}/mL	k{unit}/mL is not a valid UCUM unit.	k is not a valid unit expression, but [k] is. Did you mean [k] (Boltzmann constant)?
Lm/m2	Lm/m2 is not a valid UCUM unit.	Lm is not a valid UCUM code. No alternatives were found.
mg I/mL	mg I/mL is not a valid UCUM unit.	mg I/mL is not a valid unit. Blank spaces are not allowed in unit expressions.
		I is not a valid UCUM code. We found possible units that might be what was meant: [mi_i], mile, standard unit used in the US and internationally [cr_i], cord, unit of measure of dry volume used to measure firewood equal 128 ft3 [cml_i], circular mil,
[ppm] mol	[ppm] mol is not a valid UCUM unit.	[ppm] mol is not a valid unit. Blank spaces are not allowed in unit expressions.
		[ppm]mol is not a valid UCUM code. No alternatives were found.
[ppm] mol/mol	[ppm] mol/mol is not a valid UCUM unit.	[ppm] mol/mol is not a valid unit. Blank spaces are not allowed in unit expressions.
		[ppm]mol is not a valid UCUM code. No alternatives were found.
% v/v	% v/v is not a valid UCUM unit.	% v/v is not a valid unit. Blank spaces are not allowed in unit expressions.

Figure 49 - Gap analysis between SAM and UCUM units of measure

Gap analysis
SAM - ISO IDMP

Annex to D9.2 Implementation Guidance for IDMP in MPD´s

This analysis has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No. 875299

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Funded by the European Union

Funded by the European Union

1. Introduction

1.1. Goal

This report aims to give a concise and accessible overview of the findings of a **high-level gap analysis** between the data elements in the Belgian authentic source of medicines **SAM** and the data elements in the **ISO IDMP** standards.

Such a high-level analysis can be seen as a first step of an ISO IDMP internal readiness assessment. This analysis is not meant to be exhaustive, but has the ambition to map out the main differences and points for attention concerning data elements which can then be further elaborated upon in further analyses.

It is important to stress that further efforts in analysing the data readiness will have to be complemented with analyses from the perspectives of people, processes and technologies as well. Moreover, the precise role of the EMA in the context of the SPOR project under development, the additional requirements of the EMA on top of the ISO IDMP standards and the division of responsibilities between the national competent authority, i.e. the FAGG/AFMPS, and EMA will need to be considered when remedying the gaps.

Digile is certainly willing to do further analyses and to further assist the FAGG/AMFPS.

1.2. Context

The ISO IDMP standards

The ISO IDMP[1] standards were initially developed in response to the need to standardize the definition of a medicinal product to facilitate pharmacovigilance activities, but were extended to much broader uses in the regulation of medicinal products for human use by providing complete and accurate data about these medicinal products throughout their life cycles.

Adopting these standards should, amongst others, lead to minimizing confusion and errors about the identification of medicinal products and allowing for the accurate analysis and unambiguous communication across jurisdictions.

The scope of the standards supports various regulatory activities, such as clinical trials and inspections, and healthcare practices, such as the prescription and

[1] International Organisation for Standardisation, Identification of Medicinal Products

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dispensation of medicines, and covers the entire product lifecycle: products in development, investigational products, products under evaluation and authorised products.

ISO IDMP comprises five separate standards that establish definitions and concepts and describe data elements and their structural relationships.

The EMA SPOR programme and EU requirements

The EMA[2] is implementing the ISO IDMP standards for the identification of medicinal products in a programme called SPOR, based on the four domains of master data in pharmaceutical regulatory processes: substance, product, organisation and referential data.

The EMA implements ISO IDMP standards in phases and will develop ISO IDMP compliant business services for the central management of data in each of the four SPOR domains. The EMA will first deliver the organisations and referential management services, which in turn will lay the foundations for the subsequent delivery of substance and product management services.

The submission and maintenance of data regarding authorized human medicines in the EU and the European Economic Area (EAA has been mandatory since July 2012 and was based on a format called xEVPRM Extended EudraVigilance Product Report Message). The xEVPRM format will be replaced by the ISO IDMP format that includes all information currently available in the xEVPRM format[3].

In fact, EU Member States, marketing authorization holders and the European Medicines Agency (EMA are mandated to use ISO IDMP standards for the exchange and communication of information on medicinal products. The use of ISO IDMP is a regulatory requirement[4]. According to the regulation: "*The use of internationally agreed terminology, format and standards should facilitate the interoperability of systems used for the performance of pharmacovigilance activities and avoids the duplication of encoding activities concerning the same information. It should also allow for an easier information exchange between regulatory authorities on an international level.*"

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[2] European Medicines Agency

[3] It needs to be emphasized, however, that some conceptual differences are introduced which will need to be taken into account when performing the data migration.

[4] according to the Commission Implementing Regulation (EU No 520/2012 (articles 25 and 26 which mandates the use of ISO IDMP for the exchange of information on medicinal products across the European Union

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The Belgian authentic source of medicines (SAM), a joint initiative of the competent authorities for medicinal products in Belgium, was initially developed as a reference database supporting the electronic procedure to request the refund of so-called "chapter IV" medicines. It has since been considerably extended to support, amongst others, the electronic prescription of medicines. From 2020, the use of SAM for ambulant prescription of medicines is required by Belgian law.

Currently, SAM contains public information about (mainly[5]) **authorized medicines** and a broadening of its scope and applications is still being explored.

The core of the SAM data model consists of three parts:

- a medicinal product definition part, that is subdivided into two parts, a virtual part containing medicinal products on a generic level and an actual part containing branded medicinal products,
- a reimbursement law definition part consisting of legislation content and modeling and
- a reimbursement part consisting of information such as prices and copayment amounts.

The reimbursement law definition part and the reimbursement part concern pricing and reimbursement elements that are very specific to the Belgian context and out of scope for the ISO IDMP standards. In the remainder of the analysis, only the **medicinal product definition part** of the SAM data model will therefore be taken into consideration.

Several organizations provide the SAM database with contents. The main suppliers of data for the medicinal product definition part are:

- the **FAGG / AFMPS**, the national competent authority or NCA in Belgium for medicines, and
- the **BCFI / CBIP**, a non-profit organization recognized by Belgian law responsible for independent pharmacotherapeutic information in Belgium.

Whereas the BCFI/CBIP only supplies information for products that are commercialized on the Belgian market (mainly in the virtual medicinal product part), the FAGG/AFMPS supplies information for all authorized products including products that have been authorized in the past but have been suspended or revoked (mainly in the actual medicinal product part).

[5] medicines for which the authorization has been suspended or revoked are present as well, and for some non-medicinal products and compounds limited information

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It is important to mention that the ISO IDMP standards concern authorized as well as **investigational medicinal products**. As the activities prior to approval of the first marketing authorization for a medicinal product[6] are not covered by SAM, **this gap analysis will be limited to the authorized medicinal products**. Therefore, from the restrictive point of view of SAM, everything that concerns investigational products in the ISO IDMP standards could be seen as a gap.

In fact, a medicinal product's journey can be summarized in five steps:

1. development and production,
2. regulation and authorization,
3. dissemination and information,
4. prescription and dispensation, and
5. utilization and outcome assessment.

The first step in this journey, development and production, falls out of the scope of SAM. The last step, outcome assessment, is only partially in scope: data elements such as batch numbers, expiry dates and serial numbers of medicinal products are not managed in SAM.

1.3. Overview

We first focus on the data elements that belong to **reference concepts**: the Pharmaceutical forms, Routes of administration, Units of measurements, Substances, Packaging and Organizations.

Next, the data elements of the **core ISO IDMP concepts** are covered: Pharmaceutical Products, Medicinal Products and Medicinal Product Packages and their relations with the reference concepts.

For each concept, our findings are divided into five sections:

- **General**: an introduction and some general remarks concerning the concept in the ISO IDMP standards and SAM
- **Missing or different in SAM model** ISO IDMP elements that are structurally missing (or different) in the current SAM datamodel
- **Content missing in SAM**: ISO IDMP elements that are structurally present in the SAM datamodel, but for which content expected by ISO IDMP is missing in SAM
- **Content present in SAM but incomplete or not always in accordance**: content expected by ISO IDMP that is is largely present in SAM, but not complete or fully compliant with the requirements

[6] in Belgium called the pre-authorization phase

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- **Questions and / or remarks** (optional): some remarks and/or questions that do not fit in one of the sections above

More detailed material is included in the Appendix.

Overview of the main ISO IDMP concepts (source: EMA SPOR documentation)

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2. Reference concepts

2.1. Pharmaceutical forms

General

- The reference list of pharmaceutical forms[7] in SAM is an amended list of EDQM pharmaceutical dose forms, combined dose forms and combined terms.

- The EDQM standard is ISO IDMP compliant[8] in the sense that it meets the specifications in the ISO IDMP standard concerning pharmaceutical dose forms.

- It should be mentioned, however, that there is currently no global agreement on the use of a central vocabulary, such as EDQM, for pharmaceutical dose forms in IDMP[9].

Missing or different in SAM model

- The **relationship between medicinal products and pharmaceutical forms** in SAM is many-to-many[10], while ISO IDMP prescribes a many-to-one relationship. According to ISO IDMP, instead of linking a product to multiple pharmaceutical form terms, the product should be linked to a combination term (provided for by the EDQM standard).

  For example, both terms "*Oogdruppels, suspensie*" and "*Oordruppels, suspensie*" are linked to the product *Terra Cortril* (SAM viewer), while the

[7] the pharmaceutical reference concept in the actual part of SAM, not the virtual form reference concept in the virtual part

[8] the EDQM documentation states explicitly: "*The [EDQM Standard Terms database is built in compliance with ISO 11239:2012, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging and ISO/TS 20440:2016, Health informatics — Identification of medicinal products — Implementation guide for ISO 11239 data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging.*"

[9] "*The original ISO 11239:2012 standard, Regulated Information on Pharmaceutical Dose Forms, Units of Presentation, Routes of Administration and Packaging, was based on the use of a single controlled vocabulary (i.e., EDQM that regions could use to communicate with each other. Further, the technical specification, TS 20440:2016 guide for ISO 11239:2012, assumes the use of a single controlled vocabulary or a mapping to it. However, there is currently no agreement on such a central vocabulary, in particular, for pharmaceutical dose forms.*"

[10] more precisely, an AMPC in SAM can be (and is sometimes) linked to multiple pharmaceutical forms

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combined dose form term "*Ear/eye drops, suspension*" should be linked instead.

For a complete list of cases where multiple terms are linked to one product, see 6.4. AMPPs with multiple Pharmaceutical forms.

- More information concerning combined dose forms taken from EDQM
  - *The **combined pharmaceutical dose form** is used to combine two or more pharmaceutical dose forms into a single term, in order to describe a medicinal product that consists of two or more manufactured items that are intended to be combined to produce a single pharmaceutical product for administration to the patient.*
  - *It is not used to combine pharmaceutical dose forms with other classes of term such as containers or administration devices, see instead combined terms: A **combined term** is used to combine one or more pharmaceutical dose forms and one or more items of packaging (usually a container or an administration device) into a single term.*
  - *It is not used to combine pharmaceutical dose forms that are packaged together but administered separately rather than being combined to produce a single pharmaceutical product, see instead combination packs: A **combination pack** is used to combine two or more pharmaceutical dose forms (or combined pharmaceutical dose forms, or combined terms) to describe products that are packaged together but are administered separately as independent pharmaceutical products.*

Content missing in SAM

- Mostly **EDQM terms** for pharmaceutical forms are used in SAM but the EDQM id itself is missing and should preferably be added. The SAM data model allows for this by means of the "Standard Form" concept, representing encodings of the pharmaceutical forms.

Content present in SAM but incomplete or not always in accordance

- A small minority of 6 % of the pharmaceutical forms linked to products in SAM are **not valid EDQM terms**. Around 20 % of the terms present in the reference table in SAM are not valid EDQM terms. Either those terms are flagged as rejected or deprecated by EDQM or they aren't found as an EDQM dose form altogether. A complete summary of the results and a list of problematic terms can be found in the Appendix 6.1. Validation pharmaceutical forms.

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- In the SAM documentation[11], it is stated that if no EDQM standard term is available for a pharmaceutical form, it is created by the FAGG/AFMPS. Indeed, some pharmaceutical forms found in SAM are not EDQM terms. Using non-standard terms will complicate interoperability and should be avoided as much as possible. Such terms should, at the very least, comply with the ISO IDMP standard for pharmaceutical forms. Moreover, if such new terms seem necessary, change requests should be submitted to EDQM in which the addition of the new terms to the EDQM standard is motivated. More information can be found on the EDQM standard terms website. As a national competent authority, the FAGG/AFMPS can submit suggestions to EDQM. It should be mentioned, however, that EDQM tends to avoid highly specific terms: "*To avoid a proliferation of over-complicated terms, complete information cannot always be included in a Standard Term, and should instead appear elsewhere [...]*" In some cases, it might therefore be preferable to use a more general term and reflect on putting more specific information in other data elements.

- EDQM terms are in some cases used improperly in SAM. The intended site(s) of a pharmaceutical form should be uniquely deducible and is mentioned in the definition of an EDQM term. An EDQM term with a specific intended site is sometimes used in SAM in the context of an intended site for which it was not meant to be used, for example:
  - The term *"gel"* implies cutaneous use, but is also used in SAM for urethral use (e.g. *Instillagel*) or dental use (e.g. *Elmex Medical Gel*).
  - The term *"granulate"* implies oral use, but is also used in SAM for cutaneous use (e.g. *Simcobyl*).
  - The term *"tablet"* implies oral use, but is also used in SAM for cutaneous + extracorporeal + vaginal use (e.g. *Chloramine Pura*) and oral + sublingual use (e.g. *Cedocard*).

Questions and/or remarks

- none

2.2. Routes of administration

General

- The reference list of routes of administration in SAM is an amended list of EDQM routes of administration.

[11] Conceptual Data Dossier (https://samportal.be/sam/SAM%20v2%20CDD.pdf)

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- The EDQM standard is ISO IDMP compliant[12] in the sense that it meets the specifications in the ISO IDMP standard concerning routes of administration.

- It should be mentioned, however, that there is currently no global agreement on the use of a central vocabulary, such as EDQM, for routes of administration in IDMP[13].

Missing or different in SAM model

- *none*

Content missing in SAM

- Mostly **EDQM terms** for routes of administration are used in SAM but the EDQM id itself is missing and should preferably be added. The SAM data model allows for this by means of the "Standard Form" concept, representing encodings of the pharmaceutical forms.

Content present in SAM but incomplete or not always in accordance

- Four routes of administration out of 85 in the reference table in SAM **aren't found as EDQM terms**:
  - *Parenteral use*
  - *Intraventricular use*
  - *Local use* (though never linked to a product)
  - *To determinate* (though never linked to a product)

- In the SAM documentation[14], it is stated that if no EDQM standard term is available for a route of administration, it is created by the FAGG/AFMPS. Indeed, some pharmaceutical forms found in SAM are not EDQM terms. Using

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[12] the EDQM documentation states explicitly: "*The [EDQM] Standard Terms database is built in compliance with ISO 11239:2012, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging and ISO/TS 20440:2016, Health informatics — Identification of medicinal products — Implementation guide for ISO 11239 data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging.*"

[13] "*The original ISO 11239:2012 standard, Regulated Information on Pharmaceutical Dose Forms, Units of Presentation, Routes of Administration and Packaging, was based on the use of a single controlled vocabulary (i.e., EDQM) that regions could use to communicate with each other. Further, the technical specification, TS 20440:2016 guide for ISO 11239:2012, assumes the use of a single controlled vocabulary or a mapping to it. However, there is currently no agreement on such a central vocabulary, in particular, for pharmaceutical dose forms.*"

[14] Conceptual Data Dossier (https://samportal.be/sam/SAM%20v2%20CDD.pdf)

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non-standard terms will complicate interoperability and should be avoided as much as possible. Such terms should, at the very least, comply with the ISO IDMP standard for pharmaceutical forms. Moreover, if such new terms seem necessary, change requests should be submitted to EDQM in which the addition of the new terms to the EDQM standard is motivated. More information can be found on the EDQM standard terms website. As a national competent authority, the FAGG/AFMPS can submit suggestions to EDQM. It should be mentioned, however, that EDQM tends to avoid highly specific terms: "*To avoid a proliferation of over-complicated terms, complete information cannot always be included in a Standard Term, and should instead appear elsewhere [...]*" In some cases, it might therefore be preferable to use a more general term and reflect on putting more specific information in other data elements.

Questions and/or remarks

- *none*

2.3. Units of measurement

General

- The units of measurement in SAM are encoded in the UCUM code system as required by the ISO IDMP standards: *the reference vocabulary shall be the UCUM code system and UCUM shall be used in the messages to communicate electronically between such applications*.

Missing or different in SAM model

- *none*

Content missing in SAM

- *none*

Content present in SAM but incomplete or not always in accordance

- In the SAM reference table with units, 12 out of 303 units **do not validate as a UCUM unit**. For an overview of these problematic units, see Appendix 6.3. Validation units of measure.

Questions and/or remarks

- The definition of a particular **arbitrary reference quantity** generally is not included in the definition of the arbitrary unit code. The unit code [IU□, for example, relates the quantity value to a particular substance-specific WHO international unit, where the exact reference is to be provided in the definition of the related substance given in context, i.e. as defined in ISO 11238.

  Therefore, conformant structures and vocabularies for communication shall be able to provide the required reference information explicitly or implicitly in the context of the quantity value. This is a requirement for the vocabularies for substances and methods and is outside the scope for the ISO IDMP International Standard.

2.4. Substances

General

- There is currently no global agreement on the use of a central vocabulary, such as UNII[15] of the FDA or WHODrug[16], for substances in IDMP. It is clear however, that in order to be able to centrally assign a PhPID (see further) such an agreement will be necessary.

- In SAM, if available, the International Nonproprietary Name (INN□ or its translation is used for the name of a substance. In the SAM documentation, it is stated that this is a universal concept for which the information is retrieved and provided by FAMHP from currently available international or European databases. However, the use of the INN name only implies that a standardized version of the name is used, not that a substance in SAM is encoded by assigning an international ID to identify the substance. The IDs used in SAM are internal IDs that are not internationally agreed upon.

Missing or different in SAM model

- The SAM data model does not capture **the relationships between substances**. For example, the relations between a specific salt or ester (e.g. *perindopril tert-butylamine)* and its free base (e.g. *perindopril*) or between a hydrated substance and its anhydrous counterpart are missing.

[15] Unique Ingredient Identifier, https://fdasis.nlm.nih.gov/srs/jsp/srs/uniiListDownload.jsp
[16] https://www.who-umc.org/whodrug/access-tools/download-area/

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These relationships are essential to the description of medicinal products, the basis of strength and the classification of substances[17]. Neither is the substance type such as free base, salt, ester, etc. indicated in SAM. The lack of such relationships and information combined with the way in which strengths and ingredients are encoded makes deriving the role[18] of ingredients as prescribed by ISO IDMP impossible.

For example, if a substance A is linked to a medicinal product in SAM to express its strength and a substance B is linked to the product because it is the real ingredient of the product, no distinction can be made between the ISO IDMP role ACTIM (active ingredient, where the active moiety is the basis of strength[19]) or ACTIR (active ingredient, where another reference substance is the basis of strength[20]). Based on the information in SAM, one cannot derive whether substance B is e.g. a salt of substance A □ISO IDMP role ACTIM□ or is a different reference substance (ISO IDMP role ACTIR□.

Three examples of medicinal products in SAM where different ISO IDMP ingredient roles (ACTIM, ACTIB and ACTIR□ should be attributed that cannot be derived from the information that is present in SAM:

- *Amlodipine Belisate Mylan 5 mg tabl. 100* = **ACTIM**
  - real actual ingredient (SAM□: *amlodipinebesilaat quantum satis*
  - real actual ingredient equivalent (SAM□: *amlodipine 5 mg*
- *Perindopril Teva 2,5 mg filmomh. tabl. 30* = **ACTIB**
  - real actual ingredient (SAM□: *perindopriltosylaat 2,5 mg*
  - real actual ingredient equivalent (SAM□: *perindopril 1,704 mg*
- *Metoprolol Retard Mylan 190 mg tabl. verl. afgifte 100* = **ACTIR**
  - real actual ingredient (SAM□: *metoprololsuccinaat 190 mg*
  - real actual ingredient equivalent (SAM□: *metoprololtartraat 200 mg*

[17] *"Relationships between substances such as the relationship between a salt form and its active moiety or parent substance should be captured. These relationships are often essential to the description of medicinal products, the basis of strength and the classification of substances. These relationships are often obvious and rules will be developed for specifying substances involved in each type of relationship. For example, the active moiety of all sodium salts would be the free acid, conversely the active moiety of a hydrochloride salt would be a free base."*

[18] the ingredient roles ACTI, ACTIM, ACTIB, ACTIR or ADJV

[19] e.g. amlodipine 5 mg in Amlor 5 mg containing amlodipine besylate

[20] e.g. iodine 300 mg/ml in Telebrix Gastro 300 mg I/ml containing meglumine ioxitalamate

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Content missing in SAM

- All **excipients**, an important data element for a Medicinal Product (see further) are missing, even for the antibiotics and antimycotics.

- **Adjuvants**, considered as a specific type of excipients by ISO IDMP and necessary for the attribution of PhPIDs (see further), are missing. See for example the vaccine Fendrix (SAM viewer) where the adjuvant is missing as an ingredient.

- ISO IDMP differentiates between substances and **specified substances**. Specified substances shall capture detailed characteristics of single substances or the composition of material that contains multiple substances or multiple physical forms. In SAM the concept of specified substance is not present.

    - Simeticon, for example, should be a specified substance and not a substance according to the ISO IDMP standard, as it is in fact a combination of two substances.
    - The extraction procedure of herbal extracts should be specified at the specified substances level instead of the substance level, for example Thymoseptine syrup containing *Thymus vulgaris* L., herb extracted in ethanol 22% V/V.

  Next to salts, esters and other complexes that belong to the Substance concept in ISO IDMP, other specifications related to e.g. the manufacturing process, biological origin and pharmaceutical grade are captured in the ISO IDMP standards in a related Specified Substance concept that is linked to Pharmaceutical and Medicinal Products. An in-depth modeling of such specific information about substances is provided, resulting in a significant amount of data elements and relationships. As these elements warrant a detailed study on their own and are not (yet) present in SAM, we consider these specific elements to be outside the scope of the current high-level analysis.

  Nevertheless, we draw some general conclusions:

    - Substances of biological or vegetable origin should be described in sufficient detail.
        - ***Specified Substance Group 1.*** *Elements shall be used to describe material that contains multiple substances, solvents used in the preparation of herbal or allergenic extracts, specific marker or signature substances present in plant or animal derived materials,*

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the physical form of a substance, when relevant, and any properties essential to the description of the material. The element groups used to define a Specified Substance Group 1 shall include constituents, physical form and property.

- ***Specified Substance Group 2.*** *Group 2 elements shall be used to capture the manufacturer of either a substance or Specified Substance Group 1 along with minimal manufacturing information. The minimal manufacturing information shall include the overall production method type (i.e. synthetic, extractive, recombinant), production system type, (i.e. cell line, plant or animal tissue), production system (specific cell line).*
- ***Specified Substance Group 3.*** *Group 3 elements shall capture the grade of the material along with the source that defines the given grade.*
  Group 3 elements shall be used to distinguish specific pharmacopoeia grades and technical grades of material. The grade for each pharmacopoeia shall be a separate substance if a pharmacopoeia monograph related to a substance is not harmonised.
- ***Specified Substance Group 4.*** *Group 4 elements shall contain the most detailed information on a substance. This information shall include critical manufacturing processes, specifications (e.g. impurities and related substance limits would be captured using constituents), unitage, reference material and analytical methods used for potency determination.*

- The relationships between substances should be modeled and the substance type (general, specified group 1-4 should be indicated. As the substance master data is an important part of the EMA SPOR project that will be elaborated, it is important to refer to this project.

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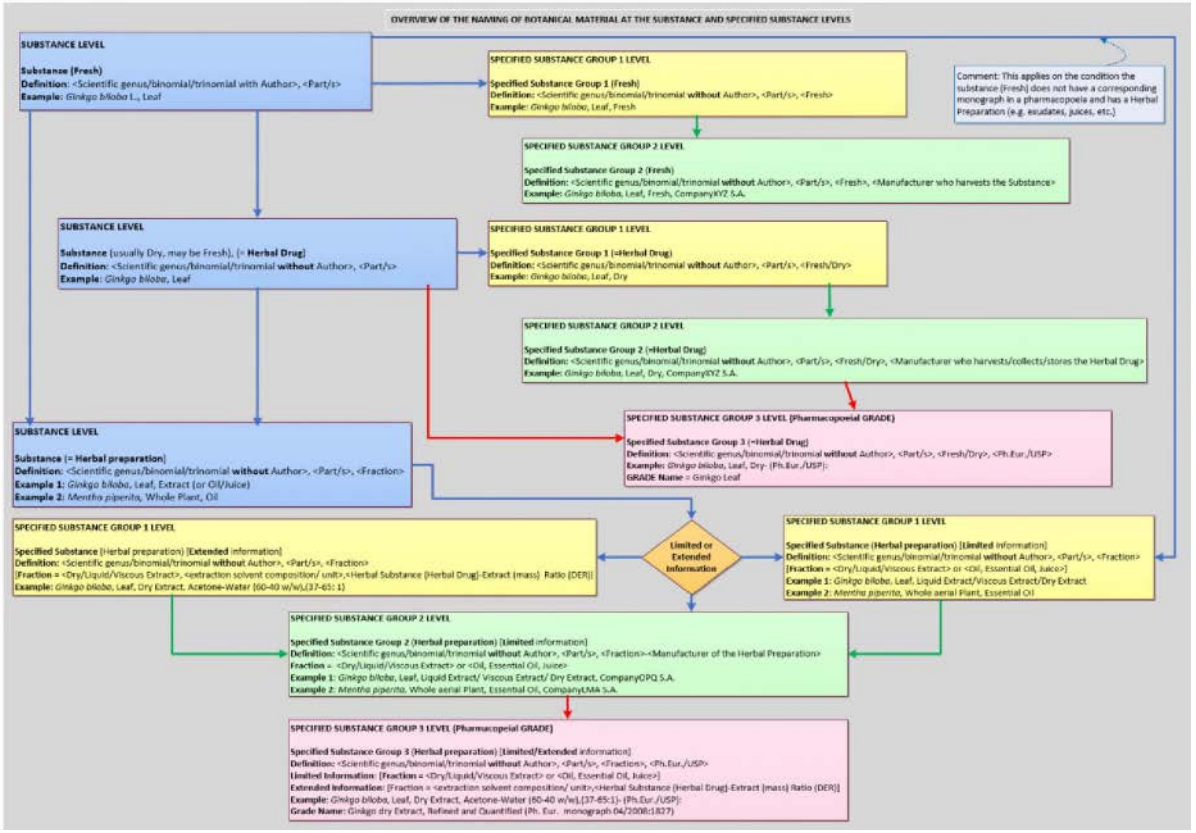

Source: ISO IDMP documentation (Data elements and structures for the unique identification and exchange of regulated information on substances, pg. 365

Content present in SAM but incomplete or not always in accordance

- *none*

Questions and/or remarks

- In accordance with ISO IDMP, **placebo** ingredients are encoded in SAM using a separate substance “Placebo”.

- According to ISO IDMP, the (optional) **classification code** of a substance shall be part of an internationally recognized classification system. The Standard Substance concept in SAM allows for the encoding in multiple classification systems. Currently, the SNOMED CT codes and CAS numbers are present for the substances that are linked to commercialized virtual products by the BCFI/CBIP, thus only for commercialised substances. At the moment, the maintenance of the SNOMED CT codes in SAM is not systematic. Digile is willing to assist in periodic updates and support in encoding.

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2.5. Packaging

General

- The reference list of packaging terms in SAM is an amended list of EDQM packaging terms.
- The EDQM standard is ISO IDMP compliant[21] in the sense that it meets the specifications in the ISO IDMP standard concerning packaging terms.
- It should be mentioned, however, that there is currently no global agreement on the use of a central vocabulary, such as EDQM, for packaging terms in IDMP.

Missing or different in SAM model

- *none*

Content missing

- *none*

Content present in SAM but incomplete or not always in accordance

- Around 25 % of the packaging terms to products in SAM are **not valid EDQM terms**. Around 56 % of the terms present in the reference table in SAM are not valid EDQM terms. Either those terms are flagged as rejected or deprecated by EDQM or they aren't found as an EDQM dose form altogether. A complete summary of the results and a list of problematic terms can be found in the Appendix Validation packaging terms.

Questions and/or remarks

- *none*

[21] the EDQM documentation states explicitly: "*The [EDQM Standard Terms database is built in compliance with ISO 11239:2012, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging and ISO/TS 20440:2016, Health informatics — Identification of medicinal products — Implementation guide for ISO 11239 data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging.*"

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2.6. Organizations

General

- Organizations occur in ISO IDMP and SAM as market authorization holders and as distributors.

Missing or different in SAM model

- The data element (optional) containing the **geographical location**, i.e. latitude and longitude, according to ISO 6709 is missing.

- The **role of the location** within the organization in the context of the Medicinal Product being described should be specified. Unfortunately ISO IDMP doesn't define what the role of the location exactly means.)

Content missing in SAM

- *none*

Content present in SAM but incomplete or not always in accordance

- *none*

Questions and/or remarks

- *none*

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3. Core concepts

3.1. Pharmaceutical Products

General

- According to ISO IDMP, a Pharmaceutical Product is a qualitative and quantitative composition of a Medicinal Product (see further) in the pharmaceutical dose form approved for administration. The following main elements define a Pharmaceutical Product:
    - active substances,
    - strength(s),
    - administrable dose form, after reconstitution or transformation if applicable,
    - medical device if it is a component of a Medicinal Product.

  A Pharmaceutical Product refers to the characteristics of the product after reconstitution.

- A Pharmaceutical Product identifier or PhPID is a globally unique identifier and plays a central role in the regulation and authorization stage. The WHO's Uppsala Monitoring Centre will compute the PhPID on behalf of national competent authority. **The PhPID shall uniquely identify a pharmaceutical product's substances, pharmaceutical (administrable) dose form and strength**. It can be seen as a common denominator from country-to-country, regardless of where the product is prescribed, dispensed and used. Medicinal products with equivalent pharmaceutical properties will be linked to the same PhPID. A PhPID is intended for pharmacovigilance processes as well as other applicable use cases.

- Multiple PhPIDs are attributed to one Pharmaceutical Product:
    - level 1, representing substance(s)
    - level 2, representing substance(s) + strength + reference strength
    - level 3, representing substance(s) + administrable dose form
    - level 4, representing substance(s) + strength + reference strength + administrable dose form

- A separate PhPID to represent the strength concentration, i.e. per unit volume as applicable, will be known as the Pharmaceutical Product Code Concept □PPCC□ as it represents a calculation of the strength presentation of a liquid

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preparation. The PPCC enables comparison of similar liquid medicinal products.

- Another concept, called the Medicinal Product (see 3.2. Medicinal Products) may relate to one or more Pharmaceutical Products, for example as part of a treatment regime. In SAM, such a medicinal product will consist of multiple components (AMPCs and VMPCs). Each component will correspond to a Pharmaceutical Product.

Missing or different in SAM model

- The SAM concept most similar to the Pharmaceutical Product is the VMP or Virtual Medicinal Product. The differences between VMPs and pharmaceutical products are discussed below.

- The **relationship between medicinal products and pharmaceutical forms in SAM is many-to-many**[22], while ISO IDMP prescribes a many-to-one relationship. See 2.1. Pharmaceutical forms for more information.

- When an **adjuvant** is an ingredient of a Medicinal Product, it is a defining element of the corresponding Pharmaceutical Product, similar to the active ingredients and contrary to the excipients. An adjuvant is defined by ISO IDMP as an ingredient that augments or promotes the pharmacological effect of the active ingredient(s) without itself being considered active. The SAM data model allows to specify whether a substance is used as an active ingredient or as an excipient. An indicator that a substance is used as an adjuvant (or that a substance always acts as an adjuvant) is not provided in the SAM data model.

- When a **specific medical device** is a component of a Medicinal Product, it is a defining element of the corresponding Pharmaceutical Product. The type of the device, e.g. inhaler, is present in the AMPPC SAM concept, but its unique device identifier, e.g. "*Precisehaler*", is missing in SAM.

Content missing in SAM

- **Adjuvants**, considered as a specific type of excipients by ISO IDMP and necessary for the attribution of PhPIDs (see further), are not linked to medicinal products. See for example the vaccine Fendrix (SAM viewer).

[22] more precisely, an AMPC in SAM can be (and is sometimes) linked to multiple pharmaceutical forms

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- The strength (presentation) of a Pharmaceutical Product (and a Medicinal Product, see further) is defined using a **unit of presentation** when it has to be described in terms of a countable entity (e.g. a tablet, a bottle, an actuation etc.) rather than a unit of measurement. The unit of presentation is a qualitative term describing the discrete unit in which a pharmaceutical product is presented to describe strength or quantity in cases where a quantitative unit of measurement is not appropriate.
  For items where their quantity is a measured quantity of weight or volume, the "unit of presentation" shall not be given since it is the same as the units of that quantity (that is ml, mg or %). For solid dose forms and other items that are measured by counting integer quantities, the unit for quantity shall be "unit" and the "unit of presentation" shall be the item that is counted.
  It is not always easy[23] to derive the unit of presentation based on the information in SAM such as the pharmaceutical form of an Actual Medicinal Product (AMP) and the container of an Actual Medicinal Product Package Component (AMPP). For example, deriving the unit of presentation "actuation" for inhalers. EDQM states that "*While a unit of presentation will often share the same name as another concept such as a basic dose form or container, it is important that a separate list of terms is maintained for units of presentation. This is because they are used in a different way, and have their own definitions and identifiers.*" Therefore, it is preferable to explicitly provide for a data element for the unit of presentation in SAM.

- In the actual medicinal part of SAM (that contains data from the FAGG/AFMPS) the strength of an ingredient is always expressed as a concentration[24], i.e. per unit volume, in cases where the strength can be expressed as a concentration. This corresponds to what is called strength (concentration) by ISO IDMP.
  To be able to describe the strength (presentation) as prescribed by ISO IDMP, when this **strength (presentation)** is described in terms of a unit of measurement, **the volume per container** is needed as the denominator of the strength expression[25]. It is not always clear how this volume per container can be uniquely derived from SAM data, e.g. in case there are multiple components

[23] For pharmaceutical products whose strength is measured as a quantity of weight or volume, the unit of presentation can be specified as the immediate (lowest level) container. For solid dose forms and other items whose strength is described on the basis of the amount in the unit of presentation, and which are counted in integer quantities, the unit for quantity shall be "1 unit" and the unit of presentation shall be the item that is counted.
[24] i.e. the quantity in the denominator is always one, corresponding to one volume unit
[25] for example 2 ml in case of a vial of 2 ml

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(AMPPCs) or equivalents (AMPPC equivalents). The volume per container is stored at the AMPPC-level in SAM, corresponding to a medicinal product package. As a medicinal product in SAM (AMP) can correspond to multiple medicinal product packages (AMPPs) with theoretically each its own volume per container, in some cases it might be impossible to derive a unique volume for the AMP.

Preferably, the strength of a medicinal product in SAM should be expressed not only as a strength (concentration) but also as a strength (presentation) per container at the AMP level. Further analysis is needed here. In particular, the rules that determine when FAMHP/AFMPS creates an AMP in the case of a liquid medicinal product and the exact role of the volume of the container in these cases should be studied.

- According to ISO IDMP, when the strength of a pharmaceutical product that has undergone a transformation (e.g. reconstitution) is to be specified, it shall be specified using the strength resulting from transformation undertaken exactly in accordance with the regulated product information. E.g. the strength as defined at the AMPPC equivalent container volume of Fluimucil Antibiotic (SAM viewer).

Content present in SAM but incomplete or not always in accordance

- As mentioned in the section about Pharmaceutical forms, a Pharmaceutical Product should have exactly one **administrable dose form**, while in SAM the relation between products and pharmaceutical forms is many-to-many. See the section Pharmaceutical forms for more information.

Questions and/or remarks

- In SAM, the **VMP or Virtual Medicinal Product** concept represents collections of medicinal products having identical properties, e.g. same active substance(s), same (range of) strength(s), same route(s) of administration, same abstract pharmaceutical form(s) etc. The VMP concept is similar to the Pharmaceutical Product concept in ISO IDMP in the sense that it is a generic, brand-independent, concept that groups medicinal products, but there are important differences. The VMP concept is clearly more oriented towards clinical practice and represents clinically equivalent medicinal products, while the Pharmaceutical Product is a concept that has been developed mainly from the perspective of the development of medicinal products and limits to pharmaceutical properties.

- As a result, sometimes a VMP is more specific than a Pharmaceutical Product. Medicinal Products that correspond with the same Pharmaceutical Product can have
  - **different collections of routes of administration**;
    For example, some Medicinal Products containing cefazolin that have otherwise quantitatively and qualitatively identical pharmaceutical properties, are licensed to be administered intraperitoneally while others are not. As this is a clinically relevant distinction, these products will be attributed different VMPs in SAM. In ISO IDMP, such products will be attributed the same Pharmaceutical Product and PhPIDs.
  - **different frequencies of administration**;
    For example, some VMPs are only differing in an administration frequency of once or twice a day, or once or twice a week etc. such as estradiol transdermal patches applied once or twice a week. From a clinical point of view, such products are clearly not equivalent.
  - **different indications**;
    For example, otherwise identical Medicinal Products containing bupropion are licensed for depression while others are licensed for smoking cessation. This distinction is clinically relevant, as the patient leaflets associated with these products differ substantially.
  - **presence or absence of preservatives**;
    For example, the presence or absence of preservatives in eye drops will cause two separate VMPs to be created in SAM. As such preservatives are considered as excipients, in the ISO IDMP standards they are not seen as a defining element of a Pharmaceutical Product.
  - **different manufactured dose forms but identical administrable dose forms**;

- Also, as a result sometimes a Pharmaceutical Product is more specific than a VMP
  - the **specific salt or ester** of a free base will only be a defining element of a VMP when the strength is expressed in function of the specific salt or ester;
    For example, when the strength is expressed in function of the free base as in the Pharmaceutical Products "*amlodipine besylate 10 mg tablet*" and "*amlodipine maleate 10 mg tablet*", a single VMP "*amlodipine 10 mg tablet (or.)*" will correspond.

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- a **specific device** name can be a defining element of a Pharmaceutical Product, but not for a VMP (only a device class, in some cases);
  For example, for the VMP "*formoterol fumaraat 12 µg / 1 dos. poeder (inhal.)*" the difference in devices *Turbohaler* and *Novolizer* will lead to the same VMP.
- an **adjuvant**, for example for vaccines, can be a defining element of a Pharmaceutical Product but not for a VMP;

- Another difference between VMPs and Pharmaceutical Products is that products consisting of **multiple components**, phases or intakes are divided into multiple Pharmaceutical Products. If after reconstitution or transformation the components are mixed to one final administrable product, e.g. the product Revitalose, only a single Pharmaceutical Product will be created according to the ISO IDMP standard, whereas multiple components are encoded in SAM.

- The structured specification of the **strength of an ingredient** is optional and for quite some cases missing in SAM. An example is the specialty Grazax (SAM viewer): no structured strength is specified and only a strength description "quantum satis" is given. The strength (presentation) of a Medicinal and Pharmaceutical Product, however, is mandatory according to ISO IDMP.

- The ISO IDMP documentation[26] states that a **PhPID has one or more active specified substances**, which is then contradicted in other places. It doesn't seem logical that in addition to a substance, at least one specified substance is mandatory.

- In the ISO IDMP documentation[27], it is specified that **a PhPID has one strength** (cardinality relationship: 1..1 based on one to many active substances or specified substances (cardinality relationship: 1..*). In the corresponding UML diagram (see below), however, it is indicated as if there is a single strength per PhPID. If a Pharmaceutical Product has multiple ingredients, however, each ingredient has its own strength and thus there is a one-to-many relationship between a PhPID and the strength of an ingredient.

[26] ISO/TS 20451
[27] ISO/TS 20451

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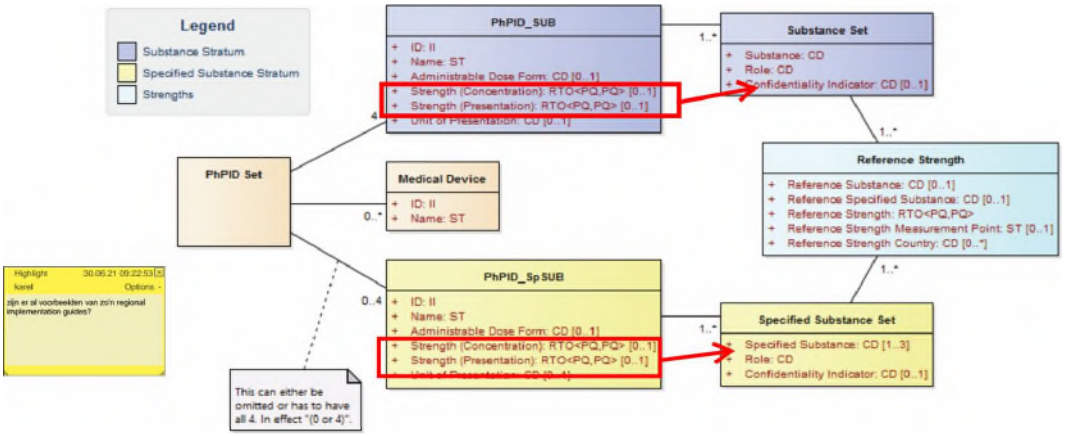

Source: ISO IDMP documentation

- If an EDQM pharmaceutical dose form (see 2.1. Pharmaceutical forms) is used as the pharmaceutical form of a medicinal product, deriving the **administrable dose form** of a Pharmaceutical Product should be possible. The EDQM pharmaceutical dose will often contain the manufactured as well as the administrable dose form. The administrable dose form has to describe the form after it has undergone any necessary reconstitution (if applicable). For example, the manufactured dose forms of two manufactured items are described as the EDQM term “powder for solution for injection” and “solvent for solution for injection” which after transformation corresponds to the administrable dose form “solution for injection”.

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3.2. Medicinal Products

General

- According to ISO IDMP, a **Medicinal Product** is a pharmaceutical product or combination of pharmaceutical products that may be administered to human beings (or animals) for treating or preventing disease, with the aim/purpose of making a medical diagnosis or to restore, correct or modify physiological functions. A Medicinal Product may contain in the packaging one or more manufactured items and one or more pharmaceutical products.

- A Medicinal Product shall be assigned an **MPID** by the Medicines Regulatory Agency, which is the national competent authority or NCA (i.e. the FAGG/AFMPS) for medicines with the decentralized authorization procedure and the EMA for medicines with the centralized authorization procedure. An MPID shall be allocated supplementary to any existing authorisation number. An MPID is assigned for indexing purposes and to contribute to improving patient safety by allowing for the unique identification of Medicinal Products worldwide. MPIDs are going to be linked with the national codes for business continuity purposes (e.g. CNK in Belgium, Z-index in the Netherlands, CIP in France, PZN in Germany).
- A new MPID has to be assigned when one or more of the following elements change[28][29] (some of these elements are missing in SAM, see further):
    - market authorization holder
    - legal status of supply[30]
    - medicinal product name
    - pharmaceutical dose form
    - ingredient substance(s) and their strength
    - medical device(s) presented as part of the MP
    - therapeutic indication(s)
    - excipients[31]

[28] any change to the elements listed is likely to change the significance of the situation when product information about it is shared in the context of pharmacovigilance

[29] it is not required that existing regulatory identifiers change in step with the IDMP requirements for MPID assignment

[30] the legal status of supply is the regional/jurisdictional rule as to whether a Medicinal Product is subject to a medical prescription before it may be supplied to a patient or consumer (what is called delivery modus in SAM)

[31] excipients may cause a unique MPID to be assigned depending on its significance to the qualitative/quantitative composition of the product or any known sensitivities

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- for a seasonal influenza vaccine a new MPID shall be assigned for each given year of formulation

- The medicinal product identifier (MPID) and Medicinal Product Package Identifier (PCID, see further) play a key role in each country in identifying an actually branded medicinal product.

Missing or different in SAM model

- The Medicinal Product Name concept attributes a full name to a Medicinal Product. In addition to this, the **different parts of the name** of a Medicinal Product are tagged by means of name part qualifiers:
  - CON: Container name
  - DEV: Device name
  - FLAV: Flavour name, e.g. “mint”
  - FORMUL: Formulation, e.g. “sugar free”
  - FRM: Form name, e.g. “capsil”
  - POPUL: Target population, e.g. “children’s”
  - SCI: Scientific (generic) name
  - STR: Strength name, e.g. “extra strong”
  - TIME: For the period used in the name, e.g. flu shot for “2016/2017 season”.
  - TMK: Company name in name, e.g. the “Drug Co.” in “Ranitidine Drug Co.”
  - USE: Indication and use, e.g. “pain relief”.

  For example:

```
<name>Amoxan
 <delimiter>(</delimiter>
 <suffix qualifier=“SCI”>Amoxicillin</suffix>
 <suffix qualifier=“STR”>500 mg</suffix>
 <delimiter>and</delimiter>
 <suffix qualifier=“SCI”>Clavulanic acid</suffix>
 <suffix qualifier=“STR”>125 mg</suffix>
 <delimiter>)</delimiter>
 <suffix qualifier=“FRM”>Tablets</suffix>
</name>
```

  These individual name parts are not tagged or stored separately in SAM, so they can’t be extracted.

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- Sometimes the **full medicinal product names** in SAM[32] are impractically long, and/or contain unnecessary repetitions, for example:
  - *Lysomucil 20 % inf. opl. (pdr. + oplosm.)/oordruppels opl. (pdr. + oplosm.)/endotrach.pulm. instill. opl. (pdr. + oplosm.)/inj. opl. (pdr. + oplosm.)/vernevelopl. (pdr. + oplosm.)/neusdruppels opl. (pdr. + oplosm.) flac.* (SAM viewer)
  - *Neobacitracine oogdruppels susp. (pdr. + oplosm.)/neusdruppels susp. (pdr. + oplosm.)/oordruppels susp. (pdr. + oplosm.)/cut. susp. (pdr. + oplosm.) druppelfl. 10 ml* (SAM viewer).

- The structured specification of the **strength of an ingredient** is optional and for quite some cases missing in SAM. An example is the specialty Grazax (SAM viewer): no structured strength is specified and only a strength description "quantum satis" is given. The strength (presentation) of a Pharmaceutical and Medicinal Product, however, is mandatory according to ISO IDMP.

- The structured data elements in the **clinical particular part** (i.e. **Therapeutic Indications, Undesirable Effects, Contraindications and Interactions**) are missing. These clinical particulars linked to Medicinal Products should be in line with the regulated product information (e.g. SmPC). By means of the Commented Classification concept linked to commercialized Virtual Medicinal Products (VMPs) a small subset of this information is textually available in Markdown format, but this does not comply with the far-reaching structuring ISO IDMP prescribes and applies only to commercialised products merely used in primary care (source: BCFI/CBIP).

- An important set of data elements in the ISO IDMP standards concerns the **traceability** of Medicinal Products at different levels of granularity. Traceability shall be enabled by product identification (level one), **production batch and expiry date** (level two), and by **serial number** (level three). Information at level two and three is out of scope and missing in SAM, so tracking or verification on the instance level of a package or a batch of packages based on SAM data is not possible. ISO IDMP distinguishes three important IDs in these levels, which can't be attributed based on information in SAM:
  - a unique Medicinal Product Batch Identifier (**BAID1**) to reliably recognise and trace a manufacturer's batch number, which appears on the outer packaging of the Medicinal Product,

[32] called prescription names and attributed to AMPs and AMPPs

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- a unique Medicinal Product Batch Identifier (**BAID2**) to reliably recognise and trace a batch number on the immediate packaging of the Medicinal Product, where this is not the outer packaging,
- a unique **serial number**, package level identification of a Packaged Medicinal Product (including the particular package configuration); the combination of a product identificator such as the GTIN and a serial number provides the uniqueness required to develop tracking and verification to the 'instance' level of the item for a given level of packaging.

- Information about the **orphan status** of a medicinal product is limited to a flag indicating whether a product has the status of an orphan medicine or not. In ISO IDMP, the orphan designation structure is much richer:
  - *orphan indication type*: the type of intended use of the Medicinal Product, for instance disease prevention, treatment or diagnostic,
  - *orphan procedure number*: the procedure number for the orphan designation authorisation application,
  - *orphan designation authorisation status*: this attribute is for describing the status of the orphan designation authorisation, for instance granted, pending, expired or withdrawn,
  - *orphan designation authorisation date*: the date in which the orphan designation status was granted,
  - *orphan designation number*: to indicate the orphan designation decision number.

- ISO IDMP describes a **paediatric use indicator** for a Medicinal Product. This is a flag that indicates if the Medicinal Product is also authorized for use in children. Such information is not present in the SAM data model.

- Some **data elements concerning marketing authorization** are missing. This concerns information about the marketing authorisation as issued by a Medicines Regulatory Agency, which grants permission to an organisation to place a Medicinal Product on the market in a region.
  - **Marketing Authorisation** data elements missing in SAM
    - Data exclusivity start date[33]
    - Data exclusivity end date
    - Date of first authorisation: we strongly advise to add a field in the current part of SAM (not only in the historical part) referring to

[33] The "data exclusivity period" is a period of time from initial authorisation of the reference product after which valid applications for generic product can be submitted and lead to the granting of a marketing authorisation.

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the first date of authorization similar to the field in the public medicinal product database of FAGG/AFMPS
        - International birth date[34]
    - **Status reason** data elements for Marketing Status and Marketing Authorisation missing:
        - Reason comment
        - Legal grounds
        - Legal grounds comments
        - Restore date
        - Condition to restore[35]
        - Condition to restore comment
        - Change request organisation type[36]
    - **Marketing Authorisation Procedure** data elements are missing:
        - The regulatory procedure applied to grant or amend a marketing authorisation for a Medicinal Product shall be specified. A region may further refine the requirements in relation to the marketing authorisation procedure (and the associated marketing authorisation application) at implementation such that this information is to be specified only if required.
    - **Marketing Authorisation Application** data elements are missing:
        - A marketing authorisation shall be supported by an application(s), which may comprise of a number of submissions (regulatory activities): initial marketing application and subsequent applications for changes to an existing marketing authorisation (e.g. to renew, vary or withdraw).

- All **excipients**, an important data element for a Medicinal Product, are missing, even for the antibiotics and the antimycotics. This is an important shortcoming.

- Data elements to store the **MPIDs** and **PCIDs** are missing (see above), as well as a procedure to assign such IDs. Digile is willing to support the FAGG/AFMPS in further analyses and the implementation.

- The **therapeutic indications** that define the target disease or condition for which the Medicinal Product is authorized are missing. They are a defining

[34] This is the date of first marketing authorisation for a company's new Medicinal Product in any country in the world.
[35] The date when the marketing or the marketing authorisation of the product is anticipated to be restored.
[36] The organisation that triggered the legal action taken on the marketing or on the marketing authorisation.

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element for an MPID[37].

- For some Medicinal Products, strength is measured at a particular point. For example, the strength of the ingredient in some inhalers is measured at a particular distance from the point of aerosolization. In SAM, no data element to store this **measurement point** is present.

- It is important to mention that the **EMA SPOR** documentation adds several data elements on top of the Medicinal Product concept as defined by ISO IDMP, for example "*Full Indication Text*", "*Pharmacovigilance Enquiry Info*" etc. We refer to the EMA Product Management System documentation[38] for more information.

Content missing in SAM

- *none*

Content present in SAM but incomplete or not always in accordance

- The unique identificator of a package (AMPP in SAM, the CTI-extended, is re-used for **seasonal influenza vaccines**. This is not in the spirit of ISO IDMP where a new MPID, and a fortiori PCID, should be assigned for each given year of formulation. Moreover, in SAM the historic names of such seasonal influenza vaccines corresponding to previous years seem to be retroactively overwritten, see e.g. Influvac Tetra 2020, 2021,SAM viewer) carrying the most recent name throughout the full history of the product. This doesn't seem to be intentional and might be a technical issue.

Questions and/or remarks

- The **legal status of supply** is a defining element for an MPID. The legal status of supply is the regional/jurisdictional rule as to whether a Medicinal Product is subject to a medical prescription before it may be supplied to a patient or consumer. Note that in SAM **one AMP may regroup AMPPs with different delivery modes**, e.g. Paracetamol EG 1000 mg filmomh. tabl. 10 and Paracetamol EG 1000 mg filmomh. tabl. 30.

[37] Depending on the regional requirements of a Medicines Regulatory Agency, therapeutic indications such as age, or related therapeutic indications within a given pharmacological class upon where the mechanism of action or clinical significance is identical, may not warrant a different MPID.

[38] Product Management Service (PMS Implementation of International Organization for Standardization (ISO standards for the identification of medicinal products (IDMP in Europe EMA/285848/2020

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3.3. Medicinal Product Package

General

- The description of a **Packaged Medicinal Product** shall describe the entire packaging from the outer layers down through intermediate packaging to one or more items contained within, and then to the actual description of the individual item(s).

- For each Packaged Medicinal Product, a unique Package Identifier (**PCID**) shall be assigned identifying the packaged medicinal product. The PCID shall consist of the MPID for the Medicinal Product, complemented with a package description code segment referring to a unique identifier for each package:
  - packaged item (container/s): the type, quantity (items per package), material(s) and alternate material(s);
  - package component(s): the type, material(s) and alternate material(s);
  - manufactured item(s): the manufactured dose form, unit of presentation, quantity (items per package).

  Any change of the values related to these code segments shall result in the assignment of a new PCID.

Missing or different in SAM model

- ISO IDMP provides far-reaching flexibility in **describing the different layers of packaging**. It supports an arbitrary number of layers of nested packages: each package can in turn consist of several packages with components described in detail such as closures, devices, manufactured items, its own data carrier identifier, various physical characteristics and information regarding shelf life. In the SAM data model, on the other hand, exactly two layers of packaging are provided: the secondary packaging represented by the AMPP concept and which in turn consists of one or more primary packaging represented by the AMPPC concept.

- ISO IDMP links specific **ingredients** of a medicinal product to the manufactured item, with its own manufactured dose unit and unit of presentation, which in turn is linked to the deepest, primary, packaging layer. In the SAM data model, the specific ingredients associated with a medicinal product are linked to a much more abstract concept: the AMP(C) concept representing one dose (and in that sense corresponds to the manufactured item in ISO IDMP) and is more abstract than the AMPP(C) concept (one AMP can have multiple AMPPs). This reflects the rather clinical approach in SAM in contrast to the more

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pharmaceutical approach in ISO IDMP. The ISO IDMP standard does not specify whether the same manufactured item is linked to multiple packages or whether to each package a separate, duplicated, manufactured item is linked. The first implementation seems most logical and in fact corresponds most to the AMP - C level abstraction in SAM.

- ISO IDMP has **numerous (optional) data elements for packaging-related concepts** that aren't present in the SAM data model. For these elements it may be useful to consider adding (some of) them to SAM as well.
  The following optional data elements (or full concepts) are missing in SAM
  - **Physical Characteristics** - linked to *Package Item (container)*, *Package (component)* and *Device*
    - Height (dimension present as text, but height not structured in SAM
    - Width (dimension present as text, but width not structured in SAM
    - Depth: (dimension present as text, but depth not structured in SAM
    - Weight
    - External Diameter
    - Shape
    - Color
    - Imprint
    - Image
  - **Device**: linked to *Package Item (container)*
    - Device Trade Name
    - Device Listing Number
    - Model Number
    - Sterility Indicator
    - Sterilisation Requirement Indicator
    - Device Usage[39]
  - **Shelf Life and Storage** (completely missing in SAM) linked to *Package Item (Container)* and *Device*
    - Shelf Life Type
    - Shelf Life Time Period
    - Special Precautions for Storage
  - **Manufactured Item**: linked to *Package Item (container)* - deepest level corresponding to the primary packaging
    - Unit of Presentation (see also above)
  - **Device Material** (completely missing in SAM) linked to *Device*

[39] how many times can the device be used

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        - Substance
        - Alternate
        - Allergenic Indicator
    - **Device Batch Identifier** (completely missing in SAM) linked to *Device*
        - Batch Number
        - Expiration Date
    - **Batch Identifier**: linked to *Medicinal Product Package*
        - BAID1
        - BAID2
        - Expiration Date

- In addition to greater flexibility and a richer range of data elements, ISO IDMP sometimes follows a **more extensive structuring of data elements** compared to SAM. In general, a thorough structuring of data elements as prescribed by ISO IDMP is preferable to a textual element merging different elements. For example, the **dimensions** of a patch are decomposed into individual, numerical, data elements for the length and width, while the information regarding the dimensions only in their entirety and as a textual field is present in SAM.

- ISO IDMP supports specifying **alternatives** for some data elements, such as **alternative types of packaging material** that belong to the same packaging item and can be used interchangeably in the field.

Content missing

- *none*

Content present in SAM but incomplete or not always in accordance

- A Packaged Medicinal Product can be accompanied by a **device**. This may be an administration device such as an oral syringe. This device is described using the device class (with type “administration device”). Where a device forms an integrated part of the Packaged Medicinal Product, such as a pre-filled syringe, this is also described using the device class (with type “integrated device”). The specification of a device, necessary for ISO IDMP, is sometimes missing in SAM

- *Foradil 12 µg inhalatiepdr. (harde caps. 60* (SAM viewer)
    - there is only one AMPPC blister with 60 units in SAM and no reference to Aerolizer device included
    - device in ISO IDMP is required even as a defining element of a Pharmaceutical Product

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- *Budesonide Easyhaler 200 µg inhalatiepdr. multidos. cont. 200 doses* (SAM viewer)
  - there is one AMPPC “200 dose multidose container” in SAM
  - container can also contain integrated device, ISO IDMP requires that such integrated device is also described as device (type “integrated device”)

- In ISO IDMP, the **Risk of Supply Shortage** and **Risk of Supply Shortage Comment** data elements are part of the Marketing Status concept that is linked to a Medicinal Product. The definition of the Risk of Supply Shortage data element as “*Indication on whether there is a risk of a product shortage in a region*” seems broader than how the supply problems in SAM are conceived. At the moment, in SAM only materialized supply problems seem to be present and not potential supply problems. While ISO IDMP hints at a proactive measure of risk, this proactive nature does not seem to be present in SAM.

Questions and/or remarks

- The main packaging related concepts and data elements in SAM can be conceptually **mapped** to corresponding basic elements in ISO IDMP quite easily:
  - AMPP ↦ Packaged Medicinal Product + Package Item (Container) [secondary]
  - AMPPC ↦ Package Item (Container) [primary]
    - Packaging Material ↦ Package Item (Container) [primary]: Material
    - Packaging Type ↦ Package Item (Container) [primary]: Type
    - Packaging Closure ↦ Package Item (Container) [primary] 4Package (Component)
    - Device Type ↦ Package Item (Container) [primary] → Device

- According to the ISO IDMP “*Requirements for international machine-readable coding of medicinal product package identifiers*”, the strategy to assign IDs in EU member states seems to be:

  - via the **EMA centralized procedure**
    - a unique PhPID set
    - a unique MA (e.g. EU/1/18/999/003)
    - a unique MPID in EU, IS, NO and LI
    - a unique PCID (e.g. ref to /003 in MA number)
    - 4 EudraVigilance codes (EU, IS, NO or LI)
    - a market specific GTIN

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- a market specific primary packaging identifier

- via **decentralized, national, mutual recognition**
  - a unique PhPID set
  - a market specific MA
  - a market specific MPID
  - a market specific PCID
  - a EudraVigilance code per marketing authorization (i.e. per pack and per country) and per language, e.g. 3 EV codes for BE, one for each language (NL, FR and DE) a market specific GTIN
  - a market specific primary packaging identifier

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4. Conclusion

Generally, the authorized medicines in SAM are already quite well structured. In various areas, the ISO IDMP standards go further and sometimes differ in modeling of the information to varying degrees. Below, we list a selection of actions that could be addressed first.

Above all, data elements that are necessary to be able to centrally assign PhPIDs to Pharmaceutical Products and locally assign MPIDs and PCIDs to Medicinal Products and Medicinal Product Packages deserve special attention. Closing the gap with ISO IDMP for these elements seems definitely doable.

There is currently no global agreement on the use of a central vocabulary for most reference concepts in ISO IDMP. In SAM, the logical choice has been made to use EDQM terms where applicable: they are ISO IDMP compliant and constitute a European standard. Adding the EDQM IDs for these terms to the SAM reference tables would be a quick win. Some cleaning needs to be done in the reference tables, e.g.:

- replacing terms that are not valid EDQM terms by valid terms,
- removing terms that are no longer used[40], also for non-EDQM concepts,
- replace EDQM terms that have been chosen improperly according to their definition.

The choice for UCUM units is logical and in accordance with what the ISO IDMP standards prescribe.

All substances in SAM are not yet encoded in an international standard and are missing some relations and properties. First, the relationships between these substances (such as free base - salt) should be added.
Moreover, awaiting the further development of the EMA SPOR project that should be followed closely, substances and specified substances of varying degrees of specificity should be added to the substance reference table. It must be ensured that specified substances with e.g. vegetable or biological origin are described in sufficient detail as specified by the ISO IDMP standard for substances, and the difference between substances and specified substances should be made.

Adjuvants should be added to the substance reference table, marked as adjuvants and linked to medicinal products. They are necessary for the attribution of PhPIDs (and MPIDs) and thus crucial. Next to the adjuvants, all excipients should be added to the substance reference table, marked as excipients and linked to medicinal products.

[40] for example companies “AAA naam te recupereren” and “2Pharma DELETED” in the reference table in SAM with companies

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Strengths of ingredients should be filled in consistently and descriptions such as "*quantum satis*" instead of numerical values should be avoided as much as possible. Moreover, for the strength (presentation), the unit of presentation and the container volume should be uniquely derivable and should ideally be stored at the same level where the strength resides (AMPC).

It is clear that a SAM AMP is insufficiently granular to completely represent a Medicinal Product as defined in the ISO IDMP standards. Some elements defining whether a new MPID should be attributed, such as therapeutic indications, are even missing on the most detailed level for medicinal products, the AMPP. Preferably, these complementary elements are added to the SAM data model.

For the sake of completeness, we mention that there seem to be quality issues with how changes to FAGG/AFMPS data propagate in the historical part of SAM. Changes such as a new product name, a new marketing authorization holder etc. are retroactively applied to the beginning of the history instead of applied to the moment when the change takes effect. For example, the recent change of the product name "*Penadur LA*" to "*Extencin*" has been retroactively applied to 16/10/1961 SAM viewer). Similar problems are visible for example with the influenza vaccines.

Digile is certainly willing to do further analyses and to further assist the FAGG/AMFPS.

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5. References

- **ISO IDMP standards documentation**
- **SAM documentation**
  - Conceptual Data Dossier
  - PIM document
- **UNICOM documentation**
- **EMA documentation**
  - Introduction to ISO Identification of Medicinal Products, SPOR programme, EMA/732656/2015
  - Product Management Service (PMS) Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe, *Chapter 1 - 8 and Annexes*
- **EDQM documentation**
  - Standard Terms Introduction and Guidance for Use, Version 2.1.3 16 November 2018, EDQM
- Identification of Medicinal Products (IDMP), *Mr. Ta-Jen TJ) Chen, Project Management Officer, FDA/CDER/ Office of Strategic Programs, U.S. Food and Drug Administration*
- IDMP Medicinal Product: How complex could it get?, *Pratyusha Pallavi, Subject Matter Expert - Regulatory Affairs*

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6. Appendices

6.1. Validation pharmaceutical forms

Summary

	only used terms		all terms	
current EDQM terms	277	94%	585	80%
deprecated EDQM terms	3	1%	24	3%
rejected EDQM terms	2	1%	4	1%
not found as EDQM term	13	4%	118	16%
total number of terms	**295**	100%	**731**	100%

Only used terms

Code	Form	EDQM id	
deprecated EDQM terms (3)			
372	Concentrate and diluent for solution for infusion	CDF- 50001500	Deprecated
48	Inhalation gas	PDF- 11118000	Deprecated
148	Oromucosal spray	PDF - 10308000	Deprecated
rejected EDQM terms (2)			
203	Prolonged-release film-coated tablet	PDF- 50055500	Rejected
288	Solution for injection/concentrate for solution for infusion	PDF- 50059000	Rejected
not found as EDQM term (13)			
522	Ear drops, powder and solvent for solution		
318	Ear drops/eye drops, solution		
380	Gastro-resistant prolonged-release granules		
462	Gel, powder and solvent for gel		
477	Nasal drops, powder and solvent for suspension		
292	Periodontal paste		
519	Powder and solvent for cutaneous suspension		
554	Powder and solvent for nasal drops, solution		
530	Powder and solvent for nebulisation solution		
341	Powder for suspension for infusion		
330	Solution for extracorporal circuit		

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291	Sublingual solution		
669	Tablet for use in drinking water		

All terms

Code	Form	EDQM id	
deprecated EDQM terms (24]			
14	Collar	PDF-10526000	Deprecated
435	Concentrate and diluent for solution for infusion	CDF-50001500	Deprecated
36	Concentrate for suspension for infusion	PDF-50014000	Deprecated
46	Cutaneous sponge	PDF-10524000	Deprecated
55	Dental insert	PDF-10404000	Deprecated
66	Dispersion	PDF-12109000	Deprecated
119	Gastro-resistant coated tablet	PDF-50025000	Deprecated
122	Gastro-resistant prolonged-release tablet	PDF-50026250	Deprecated
142	Inhalation gas	PDF-11118000	Deprecated
170	Liquefied gas for dental use	PDF-50034000	Deprecated
175	Lyophilisate for suspension	PDF-10116000	Deprecated
186	Modified-release film-coated tablet	PDF-50035000	Deprecated
429	Oral suspension for use in drinking water	PDF-50070000	Deprecated
458	Oromucosal powder in pouch	CMT-50039300	Deprecated
232	Oromucosal spray	PDF-10308000	Deprecated
652	Pouch	PDF-30047500	Deprecated
261	Powder for solution for nasal spray	PDF-50055000	Deprecated
372	Powder for solution/suspension for injection	PDF-50055150	Deprecated
305	Solution for infusion and oral solution	PDF-50058000	Deprecated
316	Sublingual spray	PDF-10309000	Deprecated
603	Suspension and solvent for suspension for injection	CDF-50062750	Deprecated
320	Suspension for infusion	PDF-50063000	Deprecated
326	Tablet for oral suspension	PDF-50066000	Deprecated
348	Vaginal sponge	PDF-10916000	Deprecated
rejected EDQM terms (4]			
370	Hard capsule with gastro-resistant pellets	PDF-50029600	Rejected
428	Kit for implant	PDF-11303750	Rejected
282	Prolonged-release film-coated tablet	PDF-50055500	Rejected
359	Solution for injection/concentrate for solution for infusion	PDF-50059000	Rejected
not found as EDQM term (118]			
559	Capsule, soft and Tablet		

411 Concentrate for dip solution/spray for external use, solution 567 Concentrate for solution for use in drinking water 734 Concentrate for solution for use in drinking water/milk 589 Concentrate for spray solution		
352 Condom		
530 Cutaneous solution/nasal drops, solution 385 Cutaneous solution/nasal drops, solution/eye drops, solution 533 Cutaneous solution/oral solution 599 Cutaneous suspension/ear drops, suspension 366 Cutaneous/oromucosal/vaginal solution		
717 Cutaneous/vaginal solution		
393 Dental sponge 388 Dental spray 400 Dip solution/cutaneous spray, solution 554 Dispersion for perfusion 587 Ear drops, powder and solvent for solution		
386 Ear drops/eye drops, solution		
383 Ear drops/eye drops, suspension		
528 Ear drops/nasal drops, solution 529 Ear drops/nasal drops, suspension		
568 Eye drops, lyophilisate and solvent for solution		
578 Eye drops, lyophilisate for solution 582 Eye drops, lyophilisate for suspension 97 Eye drops, powder and solution for solution 577 Eye drops, tablet and solvent for solution 526 Eye drops/nasal drops, powder for suspension		
527 Eye drops/nasal drops, solution		
565 Film-coated tablet and chewable tablet 401 Film-coated tablet and effervescent granules 513 Film-coated tablet and effervescent tablet 522 Frozen suspension for nebuliser suspension 190 Gargle/mouth wash 442 Gastro-resistant prolonged-release granules		
519 Gel, powder and solvent for gel		

647	Lyophilisate and solvent for nasal drops, suspension		
424	Lyophilisate and solvent for nasal suspension		
722	Lyophilisate and solvent for oral solution		
721	Lyophilisate and solvent for pour-on solution		
569	Lyophilisate and solvent for suspension for injection/nasal use		
562	Lyophilisate for nebuliser solution		
571	Lyophilisate for nebuliser solution/oculonasal solution		
560	Lyophilisate for nebuliser solution/oculonasal solution/use in drinking water		
514	Lyophilisate for nebuliser suspension		
456	Lyophilisate for nebuliser suspension/oculonasal suspension/use in drinking water		
564	Lyophilisate for oculonasal solution		
583	Lyophilisate for oculonasal suspension/pour-on suspension		
423	Lyophilisate for oral solution		
574	Lyophilisate for pour-on solution		
581	Lyophilisate for pour-on suspension		
553	Lyophilisate for suspension for spray administration		
408	Medicated pellets and solvent for emulsion for injection		
369	Medicated pellets and solvent for suspension for injection		
379	Medicated pellets and solvent for suspension for injection/nasal use		
374	Medicated pellets for nebuliser suspension		
182	Medicated plaster for oromucosal use		
715	Nasal drops, lyophilisate and solvent for solution		
579	Nasal drops, lyophilisate for solution		
588	Nasal drops, medicated pellets and solvent for suspension		
532	Nasal drops, powder and solvent for suspension		
592	Nasal drops, powder for suspension		
576	Nasal drops, tablet and solvent for solution		
364	Nebulisation solution/endotracheopulmonary instillation, powder and solvent for solution		
550	NEW		
561	Oral powder/powder for use in drinking water		
362	Periodontal paste		
380	Pour-on/eye drops/nasal drops, powder for solution		

378	Pour-on/eye drops/nasal drops, suspension		
414	Pour-on/eye drops/nasal drops/oral use, lyophilisate for solution		
714	Pour-on/eye drops/nasal drops/solution for oral use, lyophilisate and solvent for solution		
382	Pour-on/eye drops/nasal drops/solution for oral use, powder for solution		
396	Pour-on/eye drops/nasal drops/solution for oral use, tablet and solvent for solution		
407	Pour-on/eye drops/oral use, lyophilisate for suspension		
403	Powder and pre-admixtures for concentrate for liposomal dispersion for infusion		
584	Powder and solvent for cutaneous suspension		
367	Powder and solvent for cutaneous suspension/eye drops/ear drops/nasal drops		
250	Powder and solvent for instillation solution for intraocular use		
586	Powder and solvent for irrigation solution		
394	Powder and solvent for irrigation solution/cutaneous solution/solution for intravesical use/eye drops/nasal drops		
615	Powder and solvent for nasal drops, solution		
363	Powder and solvent for nasal suspension		
594	Powder and solvent for nebulisation solution		
558	Powder and solvent for oral solution/for solution for injection/infusion		
395	Powder and solvent for oral suspension/eye drops, suspension/nasal drops, suspension		
664	Powder and solvent for prolonged-release suspension for injection in pre-filled syringue		
556	Powder and solvent for solution for injection/infusion/intravesical use		
531	Powder for cutaneous suspension		
597	Powder for nebulisation solution		
371	Powder for nebuliser solution/solution for injection		
389	Powder for oral solution/cutaneous solution/pour-on solution		
391	Powder for oral solution/nebulisation solution/dip solution		
595	Powder for pour-on solution		
485	Powder for solution for cutaneous use		
555	Powder for solution for injection/infusion/intravesical use		
373	Powder for solution/suspension for injection/infusion		
406	Powder for suspension for infusion		
397	Solution for extracorporal circuit		

498 Solution for injection and oral solution		
501 Solution for injection/concentrate for solution for injection		
360 Solution for injection/oral solution 390 Solution for injection/oral solution/sublingual solution		
Solution for injection/solution for infusion/nebulisation solution/endotracheopulmonary instillation/nasal drops/ear drops, 365 powder and solvent for solution		
355 Solution for oropharyngeal use		
525 Solution/suspension for injection 708 Solvent for ...		
748 Solvent for oculonasal suspension		
361 Sublingual solution		
563 Suspension and diluent for suspension for injection		
727 Suspension and solvent for oral spray		
509 Tablet and capsule, soft		
516 Tablet and chewable tablet		
515 Tablet and effervescent granules		
663 Tablet and oral solution		
580 Tablet and solvent for oral solution		
575 Tablet and solvent for pour-on solution		
718 Tablet for cutaneous solution/for use in drinking water 719 Tablet for use in drinking water		
534 To determinate		

6.2. Validation packaging terms

Summary

	only used	terms		all terms
current EDQM terms	38	75%	47	44%
deprecated EDQM terms	0	0%	0	0%
rejected EDQM terms	0	0%	1	1%
not found as EDQM term	13	25%	58	55%
total number of terms	**51**	100%	**106**	100%

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Only used terms

not found as EDQM term		
92 Cartridge in pre-filled pen		
64 Gas cylinder bundle		
80 Gas cylinder bundle with handwheel valve		
98 Gas cylinder bundle with integrated pressure relief valve		
8 Gas cylinder with handwheel valve		
66 Gas cylinder with integrated pressure relief valve		
6 Gas cylinder with pin index valve		
65 Gas cylinder with traditional valve		
94 Gas cylinder with traditional valve/'step down' valve		
12 Generator		
3 n/a		
35 Packaging		
69 Pre-filled syringe with safety device		

All terms

rejected EDQM terms		
77 Calendar package	CON - 3001150 0	Rejected
not found as EDQM term		
72 aaa to recuperate		
75 Ampoule (+ applicator)		
76 Ampoule (blister)		
106 Bag / Sachet		
73 Bag with an integrated infusion set		
38 Blister (+ metering box)		
43 Blister / bottle		
37 Blister + sachet		
93 Blister + strip		
86 Blister + tube		
78 Bottle (+ measuring syringe)		
61 Bottle / barrel		
62 Bottle / jar / barrel		
39 Bottle / pressurised container		

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28	Bottle / sachet		
31	Bottle / tube		
29	Bottle + ampoule		
50	Box / bag		
48	Box / barrel		
49	Box / bottle		
53	Box / jar / strip		
34	Box / sachet		
54	Box / tube		
51	Box / vial		
92	Cartridge in pre-filled pen		
58	Container + bottle		
95	Cup + vial		
9	deprecated		
90	Dropper container / Spray container		
57	Dropper container / vial		
64	Gas cylinder bundle		
80	Gas cylinder bundle with handwheel valve		
98	Gas cylinder bundle with integrated pressure relief valve		
99	Gas cylinder with 'step down' valve		
8	Gas cylinder with handwheel valve		
66	Gas cylinder with integrated pressure relief valve		
6	Gas cylinder with pin index valve		
65	Gas cylinder with traditional valve		
94	Gas cylinder with traditional valve/'step down' valve		
12	Generator		
56	Jar / bag		
55	Jar / barrel		
33	Jar / blister		
44	Jar / sachet		
42	Jar / sachet / bag		
36	Jar / tube		
3	n/a		
35	Packaging		

69 Pre-filled syringe with safety device 47 Tablet container / blister 40 Tube / dredging container 27 Vial + ampoule		
45 Vial + ampoule / pre-filled syringe		
84 Vial + bag 87 Vial + bottle 46 Vial + pre-filled syringe 82 Vial + vial 60 Vial + vial / ampoule		

6.3. Validation units of measure

Summary

In SAM, 12 out of 303 units of measure do not validate as UCUM units:

unit	validation	remark
kcaL	kcaL is not a valid UCUM unit.	kcaL is not a valid UCUM code. No alternatives were found.
kcaL/(8.h)	kcaL/(8.h) is not a valid UCUM unit.	kcaL is not a valid UCUM code. No alternatives were found.
kcaL/d	kcaL/d is not a valid UCUM unit.	kcaL is not a valid UCUM code. No alternatives were found.
kcaL/h	kcaL/h is not a valid UCUM unit.	kcaL is not a valid UCUM code. No alternatives were found.
k{unit}/mL	k{unit}/mL is not a valid UCUM unit.	k is not a valid unit expression, but [k] is. Did you mean [k] (Boltzmann constant)?
Lm/m2	Lm/m2 is not a valid UCUM unit.	Lm is not a valid UCUM code. No alternatives were found.
mg I/mL	mg I/mL is not a valid UCUM unit.	mg I/mL is not a valid unit. Blank spaces are not allowed in unit expressions.
		I is not a valid UCUM code. We found possible units that might be what was meant: [mi_i], mile, standard unit used in the US and internationally [cr_i], cord, unit of measure of dry volume used to measure firewood equal 128 ft3 [cml_i], circular mil,
[ppm] mol	[ppm] mol is not a valid UCUM unit.	[ppm] mol is not a valid unit. Blank spaces are not allowed in unit expressions.
		[ppm]mol is not a valid UCUM code. No alternatives were found.
[ppm] mol/mol	[ppm] mol/mol is not a valid UCUM unit.	[ppm] mol/mol is not a valid unit. Blank spaces are not allowed in unit expressions.
		[ppm]mol is not a valid UCUM code. No alternatives were found.
% v/v	% v/v is not a valid UCUM unit.	% v/v is not a valid unit. Blank spaces are not allowed in unit expressions.

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		%v is not a valid UCUM code. No alternatives were found.; v is not a valid UCUM code. No alternatives were found.
% w/w	% w/w is not a valid UCUM unit.	% w/w is not a valid unit. Blank spaces are not allowed in unit expressions.
		%w is not a valid UCUM code. No alternatives were found.; w is not a valid UCUM code. No alternatives were found.
µg/dose	µg/dose is not a valid UCUM unit.	dose is not a valid UCUM code. We found possible units that might be what was meant: Sv, sievert, SI unit for radiation dose equivalent equal to 1 Joule/kilogram. RAD, radiation absorbed dose, unit of radiation absorbed dose used primarily in the US with base units 100 ergs per gram of material. Also see the SI unit Gray (Gy). REM, radiation equivalent man, unit of equivalent dose which measures the effect of radiation on humans equal to 0.01 sievert. Used primarily in the US. Also see SI unit Sievert (Sv) [CCID_50], 50% cell culture infectious dose, [TCID_50], 50% tissue culture infectious dose, [EID_50], 50% embryo infectious dose,

6.4. AMPPs with multiple Pharmaceutical forms

CTI-ext	Link	Official name	Pharmaceutical forms (NL★
556844-01	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
556844-02	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
556862-01	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
556862-02	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
556853-01	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
556853-02	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
556880-01	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
556880-02	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
556871-01	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
556871-02	viewer	Perisoc	Bewaaroplossing voor organen + Oplossing voor cardioplegie
183355-01	viewer	Piromed Dispers 20 mg	Dispergeerbare tablet + Tablet
570160-01	viewer	Gencebok 10 mg/ml	Drank + Oplossing voor infusie
346893-01	viewer	Peyona 20 mg/ml	Drank + Oplossing voor infusie
376765-01	viewer	Peyona 20 mg/ml	Drank + Oplossing voor infusie
015933-02	viewer	Eau des Carmes Boyer	Drank + Oplossing voor injectie
015933-01	viewer	Eau des Carmes Boyer	Drank + Oplossing voor injectie
112865-01	viewer	Hydroxocobalamine Acetas 5 mg/ml	Drank + Oplossing voor injectie
112865-02	viewer	Hydroxocobalamine Acetas 5 mg/ml	Drank + Oplossing voor injectie
112865-03	viewer	Hydroxocobalamine Acetas 5 mg/ml	Drank + Oplossing voor injectie

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489511-01	viewer	Hydroxocobalamine Acetate Sterop 5 mg/ml	Drank + Oplossing voor injectie
489511-02	viewer	Hydroxocobalamine Acetate Sterop 5 mg/ml	Drank + Oplossing voor injectie
489511-03	viewer	Hydroxocobalamine Acetate Sterop 5 mg/ml	Drank + Oplossing voor injectie
055221-01	viewer	Konakion 10 mg/1 ml	Drank + Oplossing voor injectie
175813-01	viewer	Konakion Paediatric 2 mg/0,2 ml	Drank + Oplossing voor injectie
191633-02	viewer	Lactulose Kela 62 % w/v	Drank + Oplossing voor injectie
191633-01	viewer	Lactulose Kela 62 % w/v	Drank + Oplossing voor injectie
191633-04	viewer	Lactulose Kela 62 % w/v	Drank + Oplossing voor injectie
191633-03	viewer	Lactulose Kela 62 % w/v	Drank + Oplossing voor injectie
058326-01	viewer	Lanoxin 0,05 mg/ml	Drank + Oplossing voor injectie
428653-02	viewer	Vitamine B12 Sterop 1 mg/1 ml	Drank + Oplossing voor injectie
428653-03	viewer	Vitamine B12 Sterop 1 mg/1 ml	Drank + Oplossing voor injectie
428653-04	viewer	Vitamine B12 Sterop 1 mg/1 ml	Drank + Oplossing voor injectie
428653-05	viewer	Vitamine B12 Sterop 1 mg/1 ml	Drank + Oplossing voor injectie
271713-01	viewer	Vitamine B6 Sterop 100 mg/2 ml	Drank + Oplossing voor injectie
271713-02	viewer	Vitamine B6 Sterop 100 mg/2 ml	Drank + Oplossing voor injectie
271713-03	viewer	Vitamine B6 Sterop 100 mg/2 ml	Drank + Oplossing voor injectie
271722-01	viewer	Vitamine B6 Sterop 250 mg/2 ml	Drank + Oplossing voor injectie
271722-03	viewer	Vitamine B6 Sterop 250 mg/2 ml	Drank + Oplossing voor injectie
271722-02	viewer	Vitamine B6 Sterop 250 mg/2 ml	Drank + Oplossing voor injectie
555422-01	viewer	Teicoplanin Bradex 200 mg	Drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie
555422-02	viewer	Teicoplanin Bradex 200 mg	Drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie
555431-02	viewer	Teicoplanin Bradex 200 mg	Drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie
555431-01	viewer	Teicoplanin Bradex 200 mg	Drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie
555440-01	viewer	Teicoplanin Bradex 400 mg	Drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie

555457-02	viewer	Teicoplanin Bradex 400 mg	Drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie
555440-02	viewer	Teicoplanin Bradex 400 mg	Drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie
555457-01	viewer	Teicoplanin Bradex 400 mg	Drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie
027894-01	viewer	Lysomucil 10 %	Endotracheopulmonaire instillatie, poeder en oplosmiddel voor oplossing + Neusdruppels, poeder en oplosmiddel voor oplossing + Oordruppels, poeder en oplosmiddel voor oplossing + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie + Poeder en oplosmiddel voor verneveloplossing
027885-01	viewer	Lysomucil 20 %	Endotracheopulmonaire instillatie, poeder en oplosmiddel voor oplossing + Neusdruppels, poeder en oplosmiddel voor oplossing + Oordruppels, poeder en oplosmiddel voor oplossing + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie + Poeder en oplosmiddel voor verneveloplossing
027912-01	viewer	Fluimucil Antibiotic 405 mg/4 ml	Endotracheopulmonaire instillatie, poeder en oplosmiddel voor oplossing + Poeder en oplosmiddel voor verneveloplossing
027912-02	viewer	Fluimucil Antibiotic 405 mg/4 ml	Endotracheopulmonaire instillatie, poeder en oplosmiddel voor oplossing + Poeder en oplosmiddel voor verneveloplossing
004426-02	viewer	Neobacitracine	Neusdruppels, poeder en oplosmiddel voor suspensie + Oogdruppels, poeder en oplosmiddel voor suspensie + Oordruppels, poeder en oplosmiddel voor suspensie + Poeder en oplosmiddel voor suspensie voor cutaan gebruik
004426-01	viewer	Neobacitracine	Neusdruppels, poeder en oplosmiddel voor suspensie + Oogdruppels, poeder en oplosmiddel voor suspensie + Oordruppels, poeder en oplosmiddel voor suspensie + Poeder en oplosmiddel voor suspensie voor cutaan gebruik
056472-01	viewer	Terra-Cortril + Polymyxine B 5.7 mg/g - 17 mg/g - 11.400 IU/g	Oogdruppels, suspensie + Oordruppels, suspensie
128581-01	viewer	Braunol	Oplossing voor cutaan gebruik + Oplossing voor vaginaal gebruik
128581-02	viewer	Braunol	Oplossing voor cutaan gebruik + Oplossing voor vaginaal gebruik
128581-03	viewer	Braunol	Oplossing voor cutaan gebruik + Oplossing voor vaginaal gebruik
128581-04	viewer	Braunol	Oplossing voor cutaan gebruik + Oplossing voor vaginaal gebruik
128581-05	viewer	Braunol	Oplossing voor cutaan gebruik + Oplossing voor vaginaal gebruik
128581-06	viewer	Braunol	Oplossing voor cutaan gebruik + Oplossing voor vaginaal gebruik
333636-01	viewer	Epirubicine Accord Healthcare 2 mg/ml	Oplossing voor injectie/infusie + Oplossing voor intravesicaal gebruik

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333645-01	viewer	Epirubicine Accord Healthcare 2 mg/ml	Oplossing voor injectie/infusie + Oplossing voor intravesicaal gebruik
333654-01	viewer	Epirubicine Accord Healthcare 2 mg/ml	Oplossing voor injectie/infusie + Oplossing voor intravesicaal gebruik
333663-01	viewer	Epirubicine Accord Healthcare 2 mg/ml	Oplossing voor injectie/infusie + Oplossing voor intravesicaal gebruik
430473-01	viewer	Epirubicine Accord Healthcare 2 mg/ml	Oplossing voor injectie/infusie + Oplossing voor intravesicaal gebruik
146876-01	viewer	Targocid 200 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
146876-03	viewer	Targocid 200 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
146876-02	viewer	Targocid 200 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
146876-04	viewer	Targocid 200 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
147034-02	viewer	Targocid 400 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
147034-01	viewer	Targocid 400 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
147034-04	viewer	Targocid 400 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
147034-03	viewer	Targocid 400 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
481297-01	viewer	Teicoplanin Sandoz 100	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
481297-02	viewer	Teicoplanin Sandoz 100	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
481306-01	viewer	Teicoplanin Sandoz 200 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
481306-02	viewer	Teicoplanin Sandoz 200 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
481315-01	viewer	Teicoplanin Sandoz 400 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie

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481315-02	viewer	Teicoplanin Sandoz 400 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor infusie + Poeder en oplosmiddel voor oplossing voor injectie
533546-01	viewer	Teicoplanine Altan Pharma 200 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie
533555-01	viewer	Teicoplanine Altan Pharma 400 mg	Poeder en oplosmiddel voor drank + Poeder en oplosmiddel voor oplossing voor injectie/infusie
084953-01	viewer	Clonazone 250 mg	Poeder voor gebruik in drinkwater + Poeder voor oplossing voor cutaan gebruik
149791-01	viewer	Pentacarinat 300 mg	Poeder voor oplossing voor injectie + Poeder voor verneveloplossing
489973-02	viewer	Mitomycin Accord Healthcare 10 mg	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
489973-01	viewer	Mitomycin Accord Healthcare 10 mg	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
489964-01	viewer	Mitomycin Accord Healthcare 2 mg	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
489964-03	viewer	Mitomycin Accord Healthcare 2 mg	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
489964-02	viewer	Mitomycin Accord Healthcare 2 mg	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
489982-01	viewer	Mitomycin Accord Healthcare 20 mg	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
489982-02	viewer	Mitomycin Accord Healthcare 20 mg	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506702-02	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506702-01	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506702-03	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506720-01	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506720-03	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506720-02	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506737-02	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506737-01	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506737-03	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506711-01	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik

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506711-03	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
506711-02	viewer	Mitomycin Medac 1 mg/ml	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
456977-01	viewer	Mitomycin Vygoris 20 mg	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
456977-02	viewer	Mitomycin Vygoris 20 mg	Poeder voor oplossing voor injectie/infusie + Poeder voor oplossing voor intravesicaal gebruik
084935-01	viewer	Clonazone 250 mg	Tablet voor gebruik in drinkwater + Tablet voor oplossing voor cutaan gebruik