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

Project acronym: UNICOM
Project full title: Up-scaling the global univocal identification of medicines in the context of Digital Single Market strategy
Call identifier: H2020-SC1-DTH-2019

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

Version:	1.0
Status:	Final
Dissemination Level[a]:	PU
Due date of deliverable:	30.11.2021
Actual submission date:	30.11.2021
Work Package:	WP9: Medicinal Product Dictionaries and Clinical System Software
Lead partner for this deliverable:	IHD
Partner(s) contributing:	SNOMED; ZINDEX; VIDAL; IDMP1
Deliverable type[b]:	R

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[a] Dissemination level: PU: Public; CO: Confidential, only for members of the consortium (including the Commission Services); EU-RES: Classified Information: RESTREINT UE (Commission Decision 2005/444/EC); EU-CON: Classified Information: CONFIDENTIEL UE (Commission Decision 2005/444/EC); EU-SEC Classified Information: SECRET UE (Commission Decision 2005/444/EC)

[b] Type of the deliverable: R: Document, report; DEM: Demonstrator, pilot, prototype; DEC: Websites, patent fillings, videos, etc.; OTHER; ETHICS: Ethics requirement; ORDP: Open Research Data Pilot

Resource consumption estimate:	Person months
I~HD	2.5
IDMP1	0.5
ZINDEX	0.5
SNOMED	0.5
VIDAL	0.5

Revision history

Version	Date	Changes made	Author(s)
0.1	31.01.2021	First draft	JJames IHD
0.2	31.05.2021	Section 6 fully updated with requirements	JJames IHD
0.3	30.09.2021	Sections 7 and 8 fully elucidated	JJames IHD
RC1	02.11.2021	Full document for formal WP review	JJames IHD
RC2	02.11.2021	Full document with updates from the full review	JJames IHD
RC3	18.11.2021	Final version minus Glossary	JJames IHD
Final	23.11.2021	Final version with Glossary	JJames IHD
Final	30.11.2021	Submission	

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

Deliverable abstract

The prescribing, dispensing, and administration systems that are used by clinicians for patients rely on medicinal product dictionaries (MPD) to identify, describe, and provide information about medicines. Currently, MPD must gather content from a variety of sources and structure it in the way that is most useful for the healthcare culture that they serve. A key source for MPD is the information provided by the national medicines authorisation agencies (NCAs) in the Summary of Product Characteristics (SmPC), but these are currently text documents. The Identification of Medicinal Products (IDMP) standards, when implemented by the NCAs, could provide this information in a well-structured manner using standardised terminologies for MPD to then use in the clinical systems of patient care.

This deliverable describes MPD requirements, using the standards for MPD and how MPD are currently modeled and populated with high quality data to meet their business needs. It then describes what will likely be provided by the NCAs through IDMP, and then examines the gaps, uncertainties, challenges and possible mismatches between the requirements and the likely provision. Finally, it offers some insights into the issues and some recommendations for resolution.

Keywords:IDMP – Identification of Medicinal Products; MPD – Medicinal Product Dictionaries; Patient Medication Summaries; Prescribing; Dispensing; Interoperability

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List of abbreviations and definitions

Abbreviation	Complete form
ATC	Anatomical Therapeutic Chemical classification
BoSS	basis of strength substance
CDS	clinical decision support (system)
DCP	decentralised procedure
EBM	evidence based medicine
EDQM	European Directorate for the Quality of Medicines & HealthCare
eP/eD	electronic prescription / electronic dispensation (record)
EHR	electronic health record
eMAR	Electronic medication administration record (system)
FHIR	Fast Healthcare Interoperability Resources
IDMP	Identification of Medicinal Products
ISO	International Organisation for Standardization
MPD	medicinal product dictionary (system)
MPID	medicinal product identifier
MRP	mutual recognition procedure
NCA	national competent authority (national drug authority., national medicines (authorization) agency
OHDSI	Observational Health Data Sciences and Informatics
OTC	over the counter medicine
PAI	precise active ingredient substance
PhPID	pharmaceutical product identifier
PS	patient summary
SmPC	summary of product characteristics
SPOR	Substances, Products, Organisations and Referentials
TS	Technical Specification (from ISO)
WHO-UMC	Uppsala Monitoring Centre

1 Executive summary

The administration of one or more medicines is the commonest intervention used in the care of patients. In order to do this medication administration safely and effectively, especially at any point when care is transitioned across from one provider or organisation or nation to another, the correct identification and accurate description of the medicines is a critical requirement.

In any healthcare system, the identification and accurate description of medicines is the task of a medicinal product dictionary (MPD). MPD must gather information to identify and accurately describe medicinal products from a variety of sources and then they must structure it in the way that is most useful for the healthcare culture that they serve. An important source of information is that provided by the national medicines authorisation agencies (NCAs) in the Summary of Product Characteristics (SmPC), but as these are currently text documents, their content must be extracted and structured by MPD before it can be used in clinical systems. The shared vision of UNICOM is that the Identification of Medicinal Products (IDMP) standards, although developed for use *within* the regulatory domain, when implemented by the NCAs, *could* provide information in a well-structured manner using standardised terminologies so that MPD can use it directly, with all ambiguity removed. This information would be available for the products of their own countries AND from other countries, using the same structures, and thereby allowing systems to „safely understand“ the descriptions of medicines from other countries, supporting safe cross border care.

In order to make this vision a reality, the provision of IDMP data must be analysed against the requirements of MPD for medicines identification data. The use cases and requirements that MPD must fulfil are described with reference to (i) the ISO/TS 19256 (2016) Health informatics — Requirements for medicinal product dictionary systems for health care; (ii) those documented by UNICOM D5.1/eHDSI for cross border care; (iii) ensuring patient safety by the use of clinical decision support and evidence-based medicine.

MPDs fulfil these requirements in a variety of ways. From investigative work undertaken in previous tasks and reported in summary, the different patterns of data flow and business process across eHealth to populate the MPD in use across the Community are described, as are the various ways that MPD function in supporting electronic prescribing in their environment. Despite this variety, just two patterns of MPD exist: the older linear/backbone model and the now more common mirror image model. But whichever model is used, the challenges of populating it with reliably structured identification data are similar, it is here that detail can be of critical importance to patient safety. It is therefore in the accurate and reliable provision of this detailed identification information that IDMP could make a significant contribution to MPD and therefore to patient care.

It is in this detail that there are currently some challenges, uncertainties, gaps and possible mismatches between the requirements of MPD and the provision of IDMP data, as at this time and in the current state of implementation. There are some recommendations on how to develop the implementation of IDMP such that the information provision would be more accurate and reliable; these are both at the standards level and for the practical implementation. The concept of the „pivot“ for medicines identification interoperability, as opposed to attempting global abstract concept identification, is elucidated.

2 Content of the deliverable

This deliverable is a report that describes the analysis of medicinal product identification data provided by NCAs (and SPOR) as that is understood within the UNICOM project at this point and compared with that known to be needed in Medicinal Product Dictionaries (MPD) operating throughout the European Community supporting patient care and secondary uses. In addition to the general sections of Introduction, Aims and Objectives and Methodology, the report contains a large chapter describing the requirements for identification of medicinal products in patient care, the basic requirements that all MPD must meet in order to function as MPD. The following two sections then take these requirements and show how these are implemented, firstly in the patterns of models found in MPD and then secondly in the population of these models to provide the actual information that clinicians and patients need. Having gathered and ordered the requirements, the deliverable then describes, within the understanding available at this time, what IDMP will or may provide and compares that with the requirements, highlighting particular issues and gaps as well as noting how the increased availability of structured information using controlled terminology has the potential to bring considerable benefit to MPD, reducing the need to mine information from unstructured text in document form. Finally, the deliverable offers some recommendations and conclusions to address some of the challenges that have become evident through the analysis in order that the most benefit from IDMP implementation can be garnered for the MPD that serve clinicians and patients throughout the European Community.

2.1 Acknowledgements beyond WP9

This deliverable is the output of the UNICOM partners involved in Work Package 9, but others from within the UNICOM project, most particularly from Work Package 4 and from colleagues from WHO-UMC have contributed significantly to the content through participation in discussion and working with examples.

3 Introduction

The overall vision of the UNICOM project is to „help ensure that any medicine and its contents can be accurately identified anywhere in the world“ as a part of improving patient safety and enabling better healthcare for all. Since the administration of one or more medicines is the commonest intervention used in the care of patients – for example, a prescribed medicine is the most frequent treatment provided for patients in the United Kingdom's National Health Service[1], correctly identifying and then providing an accurate description of these medicines is a critical requirement to support safe and effective patient care, especially at any point when care is transitioned from one provider or organisation to another.

To realise this vision practically, UNICOM focuses on the implementation of the ISO IDMP standards so that trusted structured data used to identify medicinal products can be made available **from** its source – the national medicines regulatory agencies – **to** healthcare professionals and patients. The implementation of the IDMP suite of standards by the national medicines regulatory agencies in the member states of the European Community has the potential to provide authoritative, high quality standardised, machine processable data to support the identification of medicinal products.

The main way that healthcare professionals access medication information and use it in prescribing, dispensing and administration is through the medicinal product dictionary (MPD) present in their clinical system. Therefore in order for this trusted data to be used by those that need it, it must flow into the MPD used by the clinical systems – prescribing and dispensing systems and electronic health record systems. It is then available to be used for direct day to day patient care and for sharing through medication summaries as part of the individual patient summary to support emergency care etc.

The phrase 'medicines are not ordinary items of commerce' is often used[2] to highlight that medicines form a special class of objects whose use and supply are subject to regional, national and supranational legislation and regulation. These, and the cultural and language differences in the practice and delivery of care and the different patterns for reimbursement of medicines costs, means that the MPD(s) that serve these areas will have the necessary content, structured appropriately, to meet all these requirements. An understanding of these patterns of structure, content and maintenance responsibility, in essence a "characterisation" of them, provides the overview in which to place the system which facilitates cross border care of patients involving medication – cross border prescribing and dispensing, and sharing of medication summaries. Indeed, MPD themselves need to understand these things and how they might need to interact with data from other MPD so that the vision of cross-border care can be realised with safe and meaningful interoperability of medication concepts.

There are hundreds of thousands of medicinal products available for use in healthcare across Europe and each medicinal product has many characteristics (attributes), both defining and non-defining. It is therefore critically important to unambiguously identify and describe each product so that safe high-quality patient care can be delivered wherever it is needed. The ISO TS:19256 defines an "MPD system" as something that "establishes a consistent representation of medication concepts (set of identifiers) at various levels of detail and with meaningful relationships between the concepts, in order to support parts of several processes in healthcare in which medication plays a role". The Technical Specification (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 in a variety of other healthcare information systems" [3]. This interoperability is a core area for the UNICOM project as it looks to support cross border care involving medication. In this document, rather than "MPD system", just "MPD" (Medicinal Product Dictionary) is the term that will be used.

4 Aims and Objectives

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 are therefore to provide as much clarity as possible on

- The requirements of MPD for medicinal product identification data, for all their various use cases
- The data flows and business processes of medicinal product identification data within eHealth and patient care (as opposed to within the regulatory domain)
- The structures and the population of these structures in use today in the various MPD across the community, and to document how these meet the requirements for medicinal product identification in patient care in their particular circumstances
- 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 requirements and the provision
- Any recommendations that may help to overcome the challenges and bridge the gaps that are identified in order that IDMP data can most effectively be used by MPD to support patient care across the European Community

These insights will then also be used in the requirements for implementation and mapping guidelines for use of IDMP data with MPD (Task 9.4/Deliverable D9.2).

5 Methodology

In order to undertake an analysis of medicinal product identification data provided by NCAs (and SPOR) compared to that needed in MPD for clinical care and for secondary uses, the following steps were undertaken:

- Requirements gathering:
  - From existing standards in the domain – in particular ISO/TS 19256 (2016) Health informatics — Requirements for medicinal product dictionary systems for health care
  - From within UNICOM for the cross-border care scenarios of ePrescribing/dispensing and describing medication in patient summaries (as available in the autumn of 2021)
    - Informed by the analysis of existing ePrescribing/dispensing systems and their business architecture as implemented across the European Community, undertaken in T9.2
  - From clinical decision support and evidence-based medicine (secondary uses – the main research use cases are covered in UNICOM WP8)
  - From the existing data flow (as researched in T9.1) as medicinal product identification data provided by NCAs as it moves through various organisations to the MPD used by clinicians and patients across the European Community
- Summarisation of the requirements as how these are implemented through MPDs
  - Describing the patterns of models of MPDs and why they are as they are – the ways in which their requirements have shaped them
  - Describing the population of these models, the detail of the domain and the key attributes and values for them, including the known challenges and difficult areas
- Summarisation of what IDMP provides to meet the requirements and challenges
  - Based on what is known at the time of writing, whilst also
  - Describing some of the unknowns of IDMP provision and implementation

From this analysis it was then possible to offer a concluding set of recommendations as to how IDMP provision could be developed to meet the needs of MPD that support the clinicians working day to day to provide healthcare for the patients and citizens of the European Community.

6 Requirements for Identifying and Describing Medicinal Products in Patient Care

Introduction:

This chapter 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.

It also draws in requirements from elsewhere within the UNICOM project, most particularly from those facilitating exchange of medicinal product information to support medication business processes of prescribing and dispensing and information sharing across state borders.

This chapter links closely to the next chapter (7) which shows how these requirements are met by the product identification models of the various MPD currently operating in patient care.

6.1 Standards for Medicinal Product Dictionaries (MPD): ISO/TS 19256 (2016) Health informatics — Requirements for medicinal product dictionary systems for health care

This is a technical specification describing the use cases for an MPD (i.e. the business processes that require an MPD) and the functional requirements, the things that an MPD must do or provide in order to be effective in those business processes. Clinical decision support (CDS) is stated as „out of scope“ for the TS, but it acknowledges the importance of this, and that one or more „knowledgebase systems“ would be associated with an MPD to provide CDS functionality. The requirements for CDS are described in this document in section 6.3.

It states that the goal of an MPD is „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 medicinal product identifiers can be used in a variety of other healthcare information systems“. This is a useful definitional statement for MPD, although the limitation to „available“ medicinal products might be disputed, because providing identification of medicines used in the past is clearly important for patient care, particularly as the prevalence of long term conditions increases, and it is possibly contradicted (or even overridden) by a later statement on the requirements for the MPD to be „comprehensive and exhaustive“ – including all medicinal products in scope. This is in harmony with one of the main *Cimino desiderata*[4], the best practice for healthcare terminology, of „content, content, content“.

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, both of which are extremely relevant to the focus of implementation of IDMP in the UNICOM project:

- the development, supply and use of medicinal products is highly regulated; this directly affects how medicines are named and therefore identified
    - the core premise of UNICOM is that trusted medicines identification information can be sourced from the medicines regulatory agencies/national competent authorities
- 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
    - there is ‚medication abstraction“ in the IDMP standards (the PhPIDs); 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 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, and therefore not everything in them 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 specification then goes on to describe in detail the business processes and use cases for an MPD, which then allows it to provide a set of requirements. These processes are:

6.1.1 Prescribing

The key focus here is that the MPD is able to „***describe medicinal product in sufficient detail that the next action in the process (either dispensing or administration) can identify the correct product to dispense/administer***“, which, depending on the jurisdictional cultural setting of the MPD may require description of:

- a product *in full* – an actual manufactured product (brand named or not) and the relevant pack size;
- a product in *some degree of abstraction*, e.g. an abstraction level that contains elements like active substance, dose form and strength but no brand name
  - the degree of abstraction may be a fixed number of elements and therefore a fixed set of classes, or a varying number of elements depending on the needs of the prescriber

In addition, there should be linkage from the medicinal product concepts to clinical decision support (including for posology) and identifiers suitable for storage in an electronic medication record.

6.1.2 Dispensing (and including reimbursement management)

The MPD is able to „***describe medicinal product in sufficient detail that the dispenser can correctly select the actual product to dispense***“. This requires that the MPD offers „descriptions of all the available medicinal products **at various levels of abstraction from the most detailed form to the very generic**, with appropriate relationships between these levels“; ultimately the medication dispensed must be selected from or be the entirety of a packaged medicinal product. All the necessary supporting data needed to fulfil national or local rules on reimbursement and/or substitution will also be required.

Just as for prescribing, there should be linkage from the medicinal product concepts to clinical decision support (including for posology and possibly automatic labelling instructions) and identifiers suitable for storage in an electronic medication record.

6.1.3 Administration

The recording of medicines administration is usually only undertaken in certain care settings, such as a hospital or a care home providing nursing support; it is not generally undertaken in primary care by patients or carers in any formal system. An administration recording system may be part of a larger system such as an EHR or may be a specialist system such as a closed loop medication system, or in nursing care facilities an (electronic) Medication Administration Recording system (eMAR). The MPD is therefore required to offer to that system medicinal product descriptions in the same way as for dispensing, so that the administered medicine can be correctly selected. In addition, for closed loop medication systems, the „track and trace“ functionality will be supported.

6.1.4 Recording medication history/medication reconciliation

This requires the MPD to „offer descriptions of all the available medicinal products at various levels of abstraction from the most detailed form to the very generic, with appropriate relationships between

these levels“ – and in particular, to offer grouping concepts and relationships to product concepts to support the reconciliation process.

6.1.5 (Electronic) data exchange

The specification recognises that an MPD „shall be useful both for human users, and for various health information systems“ and that as such, human interaction takes place through interfacing which can present different views, both of various identification descriptions of products and their ancillary concepts, to different users in different ways. The specification also highlights the importance of regular updating of information to ensure its currency.

Whilst recognising the importance of the supply chain in getting medicinal products to patients in a safe, reliable and timely manner, including track and trace, that some MPD do engage with these activities, they are not part of the core scope of the UNICOM project, so have not been elaborated here. Similarly, the processes and requirements around analysis, statistics, pharmacoepidemiology, clinical research and pharmacovigilance from this specification are not elaborated here; any requirements coming directly from T8.1 Clinical Applications of IDMP, T8.2 Application of IDMP in big data for science and T8.4 Pharmacovigilance are detailed separately elsewhere in this document.

6.1.6 Functional requirements

In the normative content, the specification gives a set of functional requirements, some of which were introduced in the business processes sections previously described; those specifically related to identification of medicinal products are listed here:

- A listing (inventory or catalogue) of medicinal products concepts (real and related abstract concepts, including packaged medicinal products), authorised products and others (for example, standard extemporaneous products) for use in health, pharmacy and clinical applications, which have
  - Unique identification for each concept, both human readable and machine processable, in applicable language(s) for the target audience and including synonyms
  - Characteristics of these concepts, as separate discrete elements; this includes
    - the „characteristics“ of medicinal products as described in ISO 11615 (although no explicit list is given) and the abstracted concepts such as „pharmaceutical product“ of ISO 11616 and the manufactured item(s) present in the associated packages
    - the „characteristics“ of packaged medicinal products, including container type and container quantity and any device included in the package
  - Relationships between the concepts, including explicitly „products“ and „packaged products“ as present in ISO 11615

- The following information is required for authorised products/packages as appropriate:
  - The marketing authorisation number
  - The authorisation status and applicable status date
  - The marketing authorisation holder
  - The marketing status and applicable status date
  - The legal status of supply
  - If the MPD contains multi-national content, the country to which the above information applies should be stated

The information about status (the individual product lifecycle - the authorisation, marketing, and removal from the market) highlights the requirement for MPD maintenance as time goes on, to maintain currency of information, especially as it relates to product availability. Historical data is also needed for medication records management.

Other data about (for example) manufacturing of an authorised product or package is described in the specification, but since this is not vital for product identification, it is not included here. Similarly there is a set of data here that is extremely useful to have available for a product or package, especially when trying to identify similar products, and as such is listed here, but it is not considered essential for single product identification:

- Additional monitoring and special measure indicators as described in ISO 11615
- One or more classifications (such as ATC)

- Reference or access to SmPC/PIL
- Approved route(s) of administration; an MPD can add data about “off-label“ route(s) of administration if appropriate and sourced from recognised (inter)national guidance
- Approved indications

6.2 European cross border pharmaceutical care (UNICOM D5.1)

The EC Directive 2011/24 covers citizens’ rights to cross-border healthcare; these „rights to healthcare“ include medication services, specifically ePrescription/eDispensation (eP/eD) services and the sharing of medication related information as part of the Patient Summary (PS). The eHealth Digital Service Infrastructure (eHDSI) is working within the UNICOM project, in WP5-7, to develop cross-border eP/eD and PS services,. D5.1 from this group is the „Business requirements for the adoption of IDMP in eHealth Services“ and that document has been examined specifically to gather requirements for medication identification in the cross border setting that can then be included in this analysis.

6.2.1 Comprehensible and unambiguous medicinal product identification

The primary premise for eP/eD is that a patient from Country A should be able to have their prescription, written correctly in Country A, safely dispensed in Country B, and the information about that supply to be returned to Country A. This requires that the prescription information, including description of the medication to be dispensed, be transformed into a format comprehensible within Country B. There is no absolute requirement that any original „medicinal product code“ must be understood across borders, the requirement, expressed in R9 of the D5.1 document, is that „the practitioner in country B will be able to understand (unequivocally) what are characteristics are specified for the product“. This is reiterated in R11 (of D5.1), although confusingly this includes product identifiers (which were excluded in R9). The confusion arises from a desire that there will be, or indeed already are, some translatable „product codes“ (e.g. an MPID for a centrally authorised product [although it may be that even these are not interoperable] a PhPID [if there can be agreement on how these will be defined] or a SNOMED CT code). These requirements are reiterated again in R13 and R14 of D5.1.

D5.1 includes the concept of a „pivot“ which is indeed what is needed for safe and effective cross system (which includes cross border) medication patient care (see section 10.3 of this document). This concept is commonly used in these situations (e.g. in the US with RxNorm, in OHDSI with their mapping, in SNOMED CT with the MP-only and child concepts, in particular the Clinical Drug, and in many of the models of international decision support vendors (see chapter 7). In D5.1 this „pivot“ is primarily composed of „the relevant attributes (substance, dose form and strength)“, although there is a sense that these may not be sufficient for safe and effective cross system (which includes cross border) medication patient care in some cases. This document (D9.1) seeks to explore those cases in more detail, using the experience of the members of WP9, so as to give a more explicit sense of the requirements that will be needed for this and the other use cases in scope.

Following on from the primary premise for eP/eD stated above, there is the requirement that the dispensing information from Country B will be returned to the appropriate healthcare system(s) in Country A in the form of a new clinical document. All the same mechanisms to uniquely and unambiguously describe the medicinal product should apply, as should the sense of describing the groupings/rules under which the dispensing decision was governed.

6.2.2 Medicinal product categorisation and grouping

D5.1 includes both medicinal product categorisation (R8) and grouping (R14&15). Since categorisation is about placing things into groups based on particular characteristics, this document deals with these together. There is a requirement (R8) that category information be „translatable and transportable to another country“. The example given is ATC and indeed this categorisation, designed as it is as a tool for international drug utilisation review (pharmacoepidemiology) with the ultimate aim of improving drug use, is applicable in all countries and contexts. However, at the other extreme, as D5.1 recognises, some categorisations are extremely local and will present significant challenges in being usefully translated. In between are categorisations such as the legal status of supply, which although as a general concept is widely used (and as such is present as an attribute in ISO 11615), will have significant variations of actual categories in the different countries.

The D5.1 acknowledges many of the variety of ways that a medicinal product can be described within a prescription and the effect of local regulation on this and on the dispensing that will follow the prescription (for example, substitution of a branded product for one from another manufacturer). Substitution may itself be governed by „categories“ or „groupings“ that are also required to be comprehensible across borders, so that a in some way the „context“ of categorisation or grouping of the product selected in Country A (e.g. „branded, but substitution expected“, compared to „no substitution“) can be understood in Country B. There is however, some doubt as to whether this can be done „deterministically“ (i.e. based on rules that a computer can operate); in order to facilitate pharmacists‘ professional activity in this, R15 states that a common vocabulary will help in understanding of groupings and practice from one country context into another. It must always be accepted that the law governing dispensing will be that of Country B.

Given the likely challenges that will be encountered with these requirements from D5.1, it is suggested that category and grouping information be visible and shareable and use a common vocabulary where possible, but these are not considered „relevant attributes“ for medication identification.

6.2.3 Cross border patient summaries

As well as dealing with eP/eD, D5.1 also deals with patient medication information as part of the Patient Summary, to support care of a patient from Country A in Country B. As with eP/eD, the core requirement is to “Transcode and Translate” the necessary information, and specifically to provide unambiguous identification of any medicinal products, either as a complete authorised product, as an abstract representation of a product, or through a set of descriptive attributes.

6.2.4 Other use cases

Whilst primarily concerned with cross border eP/eD, D5.1 does mention another use case of relevance, that of patients/citizens being able to access information, in their preferred language, about medicinal products (including those available without prescription) in a country which is not their usual residence. This involves correctly identifying the product concerned and being able to access information about it using a set of concepts that are both interoperable (e.g. comprehensible in all the systems involved) and safely translatable.

6.2.5 UNICOM D5.1 Requirements Summary:

- Understandability is a key requirement – transcoding or look up should cover both **products and attributes** “*For example, if the prescription contains the code 10000034, it is unlikely that this code is understood in country B, but it (is) important to understand that this refers to Fusidic Acid, 250 mg tablets – by expressing the relevant attributes (substance, dose form and strength*”
  Substitution rules must be expressed using common terminology and processing. If country A allows/expects substitution, this should be indicated to country B, and so should the type of substitution
- **Detail must not be lost** By using IDMP identifiers, detail on medication identification should not be lost; for example, if the prescription in Country A uses a brand name and gives a pack size, the transcoding and translation for Country B should not use “only” a PhP type concept without some indication of the brand and pack size
- There must be a way to identify the type of description of the medicinal product (branded, generic, with pack size, without pack size) as well as the actual product to support transcoding and data transfer
- Classifications should be visible and understandable across borders – not just ATC but also business classifications like legal status of supply

Additional extra requirements:

Finally, after the important functional requirements are met with the possibility of transcoding the content between countries, the practical adoption of IDMP services may depend on additional services, for example:

- A lookup service that allows to check the “IDMP expression” of a product, which enables IDMP-centric product search (e.g. for substitution).

- A lookup service for checking a product's characteristics in a different language or specific context (e.g. a patient from Greece can scan the barcode of an OTC (over the counter medicine) in Finland and see the relevant characteristics of the product in their language)

6.3 Clinical decision support and evidence-based medicine

As described already within the UNICOM project in WP8 and in Deliverable D8.1, Report on the link between IDMP and Pharmacotherapeutic Groups and the Need for Medical Data in Pharmacotherapeutic Audit, information about medicines themselves must be able to „cross borders" as easily as possible. Using medicines safely and reducing risks has been and is of continuing concern to individual healthcare professionals, to their employers and related organisations, to national responsible authorities and internationally. Increasing patient safety by improving the safe administration of medicines to patients and increasing the evidence base of medicines use has rightly become a focus in both the provision of healthcare itself and the development of information technology applications to support the provision of that care.

6.3.1 Clinical Decision Support

Medication clinical decision support (CDS), especially as implemented through information technology, is a system whereby the totality of information about a medicine, either on its own or in combination with others, is filtered using inputs from the patient (e.g. their age, weight and clinical conditions) so that appropriate „alerts" can be generated. These alerts interrupt the medication process (prescribing, dispensing or administration) and warn the clinician about the specific pieces of information for that medication that are relevant to that patient's situation and which could be potentially harmful if the medication is administered to that patient. CDS functionality as described in a report by a JAMIA Clinical Decision Support Workgroup[5], includes drug allergy checking, drug interaction checking and other clinical information display (such as contraindication information) in its basic functionality level, moving on to more advanced functionality such as weight-based dose checking for paediatrics, pro-active disease management alerts, and drug-lab alerts.

In order to function effectively, medication CDS needs to understand which medicine is the focus and also the medications that are present in the patient's medication profile, as well as the clinical situation of the patient. To do this, MPD must describe each medication and ensure that there are associations from the identification of the medicine to relevant clinical information *about* the medicine (its contraindications, interactions etc.). Since some clinical information can vary between different presentations of what might appear similar medications (e.g. different contraindications and posology for a liposomal formulation than from a „plain" formulation) these associations must be accurate and exact, which requires that the identification of the medicine itself be of sufficient granularity.

CDS is expensive both in time and expertise to develop and maintain. Information about contraindications, interactions etc. grows and changes as expertise in the use of medicines develops. Whilst initially the primary source of information for MPD and the clinicians they support is from the authorised product literature (the Summary of Product Characteristics), over time this must be augmented by information from primary and secondary literature; CDS can be itself be considered as a tertiary source since it compiles and organises information from primary and secondary sources and because CDS and its accompanying monographs has almost completely replaced the printed compendia that used to provide comprehensive medication information. Although CDS must be applied sensitively within each individual healthcare context in order to avoid inappropriate alerting (often referred to as „noise") much of the basic data is universally applicable (for example, cross sensitivity to a particular set of active substances). Therefore in order to mitigate the time and expense of CDS development and maintenance, CDS information needs to be translatable across countries and borders and applicable to the correct amount of abstraction (for example, some contraindications apply only to a particular strength of a medicine or to a particular route of administration). Therefore CDS and MPD must maintain accurate and exact associations between its information and the medicines and their identification at various levels of abstraction. Note that the relationship of a knowledge base to an MPD is described in TS 22756 Requirements for a knowledge base for clinical decision support systems to be used in medication related processes.

6.3.2 Evidence based medicine

Evidence-based medicine (EBM) is the application of the best available research to the delivery of clinical care. This covers the best use of diagnostic tests and use of therapeutic/preventative interventions and seeks to incorporate the patient experience (preferences, concerns and expectations) in the therapeutic decision-making process. In the context of the use of medicines, EBM aims to have the medications administered to patients based on the best evidence of safety and efficacy in the patient's particular clinical context and in keeping polypharmacy to a minimum. The practice of EBM is usually mediated through the development and application of clinical guidelines which are usually condition based but which will often describe the use of various medicines (e.g. the British Thoracic Society guideline for the management of asthma) but some are applied to specific medications, especially high cost medications.

It is even more expensive both in time and expertise to both undertake the studies that underpin the practice of evidence-based medicine and to then translate this into useful clinical guidelines than it is to develop clinical decision support. This knowledge (information translated into contextual action), which is often developed in individual and/or specialised academic medical centres, must be able to be re-used in various different healthcare cultures. To do this it must be accurately applied to the relevant medicinal products in that culture. Being able to identify the different medications involved in any guideline accurately is a prerequisite to this type of information sharing and is essential to ongoing sustainability of these developments.

6.4 Medicinal Products in an international standard Patient Care Terminology: SNOMED CT

The regulatory processes that govern the authorisation of medicines and indeed their use in patient care mean that it is very challenging to produce and maintain a medicinal product dictionary that is appropriate for use in several nations; to have something that is globally useful and appropriate is even more challenging. Within the European Union, even for those medicinal products authorised at a supranational level, such as those authorised centrally under the auspices of the European Medicines Agency and given a community-wide authorisation, there may be differences in how the individual member states describe the centrally authorised product. For products authorised by a shared authorisation process such as exist across the European Union (the Mutual Recognition procedure (MRP) and Decentralised procedure (DCP)), although these both result in a „mutually recognised product", each „concerned member state" in that process will issue their own marketing authorisation for the product and therefore potentially have differences in the product description, and that is before any differences in language are considered.

It is of course this challenge that the IDMP suite of standards confronts „head on" – but it does so primarily within the regulatory domain, with an initial focus on pharmacovigilance and a secondary focus on management of the authorisation application process, which at least puts some limits on the requirements to be considered. And within the pharmacovigilance domain, there is already the WHODrug Global[6] which is used primarily to identify concomitant medications for Individual Case Safety Reports (ICSRs) in pharmacovigilance, both in clinical trials and in post authorisation surveillance. It is available in English and Chinese. In addition, there is the ATC classification[7], but since this is a classification of medicinal products rather than a terminology, it is not further described here.

6.4.1 SNOMED CT International Edition Medicinal Product Content

However, this analysis is concerned with clinical (patient) care and associated secondary uses such as harmacoepidemiology. There is one international non-commercial terminology product that contains internationally relevant medicinal product content: SNOMED CT[8]. SNOMED CT is the most comprehensive clinical terminology in use around the world to record the process of patient care. Its use in electronic health records improves communication between the different healthcare professionals caring for a patient, increasing the availability of relevant and critical clinical information. SNOMED CT is a multilingual terminology, helping to remove language barriers in patient care; this is a key concern for cross border care, as was highlighted in the requirements of section 6.2 above. Member nations are responsible for translation; entire or partial translations are available in at least 7 different languages.

When clinical information is stored in a way that allows meaning-based retrieval, the benefits are greatly increased:

- for individual patients and those caring for them, for example in facilitating real time decision support and advice systems including guideline implementation and monitoring and analysis/retrieval of patients needing follow-up or treatment alteration
- for populations, enabling more accurate retrospective reporting for research, data analytics, precision medicine and management – for example facilitating early identification of emerging health issues, monitoring of population health and agile response to changing clinical practices

SNOMED International produces the international release of SNOMED CT, containing the domains of health record content (for example, body structures, procedures, clinical findings/disorders, medicinal products) that are relevant and understandable globally in healthcare systems. This common understanding is necessary for international conformance and interoperability. In addition, member nations and organisations may develop their own extension editions, allowing them to have content authored and configured 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 Release Medicinal Product hierarchy[9] is comprised of abstract concepts with international applicability that represent varying levels of specificity (e.g. active ingredient, active ingredient + intended site, basis of strength substance + precise active ingredient + strength + pharmaceutical dose form). It also includes groupers based on chemical structure of active ingredient, mechanism of action of active ingredient, 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.

Because of the challenges of managing an international medicinal product dictionary in a way that is useful, there needs to be some limitation on the use cases that it serves, as noted above for the WHO Drug Global in pharmacovigilance and indeed for IDMP itself. The primary use cases for the SNOMED CT International Release Medicinal Product hierarchy include:

- To provide consistently modeled 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].

6.5 Characterising MPD used in Member States (from T9.1)

T9.1 in the UNICOM project was to undertake a characterisation of the MPD (Medicinal Product Dictionaries) that operate in EU member states, with particular reference to electronic prescribing and dispensing of medicines to patients. Knowing what currently is used and why it exists is a method of gathering requirements that can be used in this analysis of what is needed against what IDMP implementation can or will provide. The characterisation was undertaken using an on-line survey to

gather initial information from participants within the UNICOM project and beyond[c], followed up by one or more detailed interviews of experts in the domain, with the notes from the interview being shared with the expert(s) for their verification. All participants were gratefully thanked for their generous giving of time and expertise.

The characterisation has then been undertaken on two axes:

- The data and its flow from the original source (NCA) through other data sources to the distribution to MPD as used in clinician systems
- The medication concepts present in the MPD used in clinician systems and how these relate together

Although there was observation of MPD offering clinical information (indications, contraindications, drug interactions etc.) and/or clinical decision support (offering clinical information actively in the medication process by means of rules and alerts), the characterisation concentrated on the identification of medicinal products and their packages both as real/actual objects and as more generic or abstract objects.

6.5.1 MPD Data Sources and Data Flow

One aspect of characterisation of MPD is to examine the source(s) of their information, and therefore how various types of information flow into them. The primary source of information about medicines for clinicians is the Summary of Product Characteristics – the SmPC. The SmPC provides the "regulated, scientifically validated information that assists healthcare professionals in prescribing and dispensing" whereas the PIL informs "patients and consumers about their medicine and its safe use"[11]. This is always the starting point for all MPD, but information may need to be structured or added to before the MPD is fit for purpose within a healthcare culture. The diagram below and the description of the discussion following examines the process to produce an MPD for clinical use.

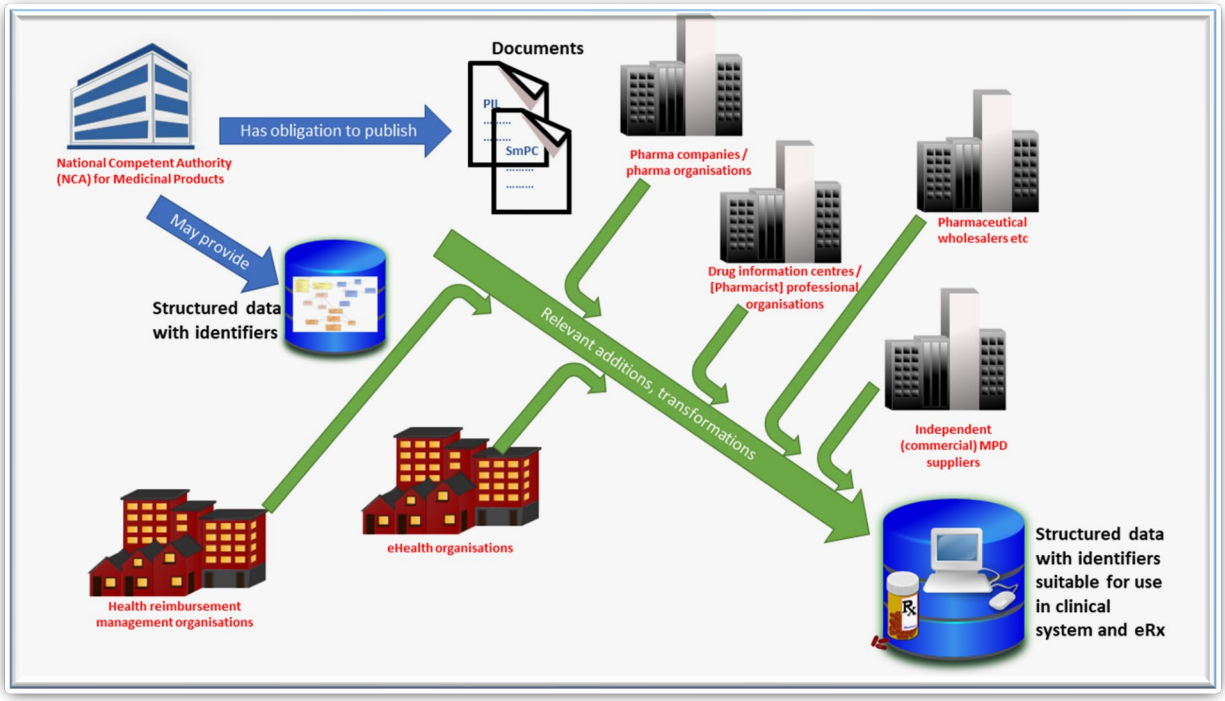


Figure 1: Medicinal Product data flow diagram from NCA to MPD on clinician's system

[c] All the member states of the European Union were potential subjects for this characterisation, plus those in the European Economic Area and the United Kingdom. However, to date, no information has been obtained for Bulgaria, Cyprus, Hungary, Iceland, Latvia, Liechtenstein (specifically, although this could be taken to follow the patterns for Austria), Lithuania, Luxembourg, Malta, Romania, Slovakia, or Slovenia

6.5.1.1. Product Information Documents from NCAs

Each member country has a National Competent Authority (NCA) that undertakes, on behalf of their government, the authorisation of medicinal products for sale or supply to patients. NCAs have a responsibility to publish product information: at a minimum the Summary of Product Characteristics SmPC and Patient Information Leaflet PIL; some also publish the assessment report (EPAR).

All NCAs publish this product information as text documents, usually as pdfs, occasionally

- A small number outsource this publication task (e.g. ITA)
- Some publish product information for only their nationally authorised products and then provide link to the EMA website for information on centrally authorised products (CAP) (https://www.ema.europa.eu/en/medicines)
    - A few also refer to the HMA website for products authorised by the Mutual Recognition or Decentralised procedures, rather than provide the data directly (https://www.hma.eu/mriproductindex.html)

For those countries where structured product information is not provided by the NCA, these text documents, sometimes supplemented by a listing (e.g. in a spreadsheet) of the authorised products, provide the main sources of data for any of the other agencies (for example, eHealth agencies, reimbursement agencies, wholesalers etc.) listed in the section below to use to provide an MPD (nationally mandated or otherwise) for use in patient care. Eight countries in the survey follow this pattern (FRA, DEU, GRE, Ireland, NLD, and GBR; ITA and CHE have been included in this section as the structured data/MPD provided is via a commercial organisation and its MPD).

6.5.1.2. Structured Product Information from NCAs

NCAs from twelve countries in the survey provide structured data and identification and description of medicinal product concepts – either at the product or package level or both. This may be available through a search facility with results for individual medicinal products being provided for download, or the information for all medicines in scope (usually all current authorised medicines) is downloadable either directly or via a partner organisation.

In five countries, data – and most particularly the identifiers and descriptions of medicinal products – can be and are used in patient care systems directly (CZE, DNK, POL, PRT and ESP), even if commercial MPD suppliers provide alternative sources of the data that system vendors could use, that has been enriched (e.g. with the addition of clinical information). In the other seven countries (AUT, BEL, HRV, EST, FIN, SWE and NOR) medicinal product data from the NCA is enriched by another agency or agencies providing additional identification and descriptive content (e.g. for package identification, providing reimbursement groups or building full product names from discrete data items) by:

- pharmaceutical wholesalers, adding availability data and increasing the scope of information including other products needed in community care (medical devices, nutritional supplements etc.) (AUT, NOR)
- an organisation responsible for managing health insurance and medicines reimbursement (often as part of or closely linked to the main eHealth organisation) making sure patients have access to cost effective medicine for their care (HRV, EST, SWE)
- pharmaceutical companies or their representative organisation, to add pack size information (if not present in the NCA data), price and availability data etc. (HRV, SWE)
- drug information centres, adding structure and health insurance information to support reimbursement to increase the usability of the data (BEL)

In these seven countries, commercial MPD suppliers may also take the standard data provided above and add value to it for use in clinical systems, but the identifiers used in patient care will be those from these agencies.

6.5.1.3. Distribution of Data

Of the countries where the NCA does not currently provide structured descriptive data and product identifiers, but a national MPD for use in ePrescribing and dispensing is in place, its distribution to the

clinical systems is from the author of the MPD – an eHealth agency (GBR and GRE – although the latter is not an MPD, instead it is a reimbursement list of medicinal product packages), professional pharmacy association (NLD) or commercial supplier (CHE, ITA).

For the twelve countries where the NCA provides the basic structured data and identification and description of medicinal product concepts, four NCAs are also responsible for the distribution of the data (CZE, DNK, ESP, PRT) and in four distribution is via the eHealth agency platform (EST, FIN, POL, SWE). For two countries, the distribution is via the wholesaler/pharmacy association, who have worked in partnership with the NCA (AUT, NOR), in one it is via the reimbursement agency (HRV) and for one it is via the consortium (consisting of the NCA, the independent drug information centre, the Health Insurance Institute and the eHEALTH authorities) that produces the full MPD (BEL).

6.5.2 MPD Characterisation

As described above in section 6.1, ISO TS 19256 refers to the various ways in which an MPD should provide the medication concepts, descriptions and identifiers needed to support

- clinical care of patients (prescribing, dispensing, administration, recording and reconciling a medication profile)
- managing the supply chain for medicines, including their reimbursement
- research and analytics, including pharmacovigilance

ISO TS 19256 does not provide an information model for the medication concepts, descriptions and identifiers but notes that the ISO IDMP (11615/11616) medication concepts are required, but also that additional information such as synonyms are useful. It also discusses scope, noting that IDMP is concerned with authorised medicines (even if some of these are authorised for investigation only) whereas an MPD is likely to need a wider range of content, including unlicensed medicines, medicines no longer available/authorised (e.g. for historic record purposes) and practically, information about products that are not medicinal products but that are prescribed or dispensed (healthcare devices, nutritional supplements etc.). IDMP also covers *all* authorised medicines and their packages, whereas MPD will publish for use *only* those medicines and packages that are actually marketed and placed into the supply chain to be available for use in patient care.

The following is a simplified diagram of the main medication concepts and relationships, with reference to how these relate to the ISO IDMP main concepts, to then be able to provide a characterisation of the content of various MPD in use. It is a simplification of what is actually somewhat complex; it does not provide the level of detail, recursion of classes and cardinality of relationships that are needed – and which exist in IDMP – to support description of products containing more than one type of manufactured item, or the recursion needed to fully describe products which are described clinically both with a concentration strength and a presentations strength. It also does not give any detail as to how „product abstraction“ is managed in order to meet the requirements of different national prescription and dispensing regulation and practice; that is discussed further on in Section 7 of this document.

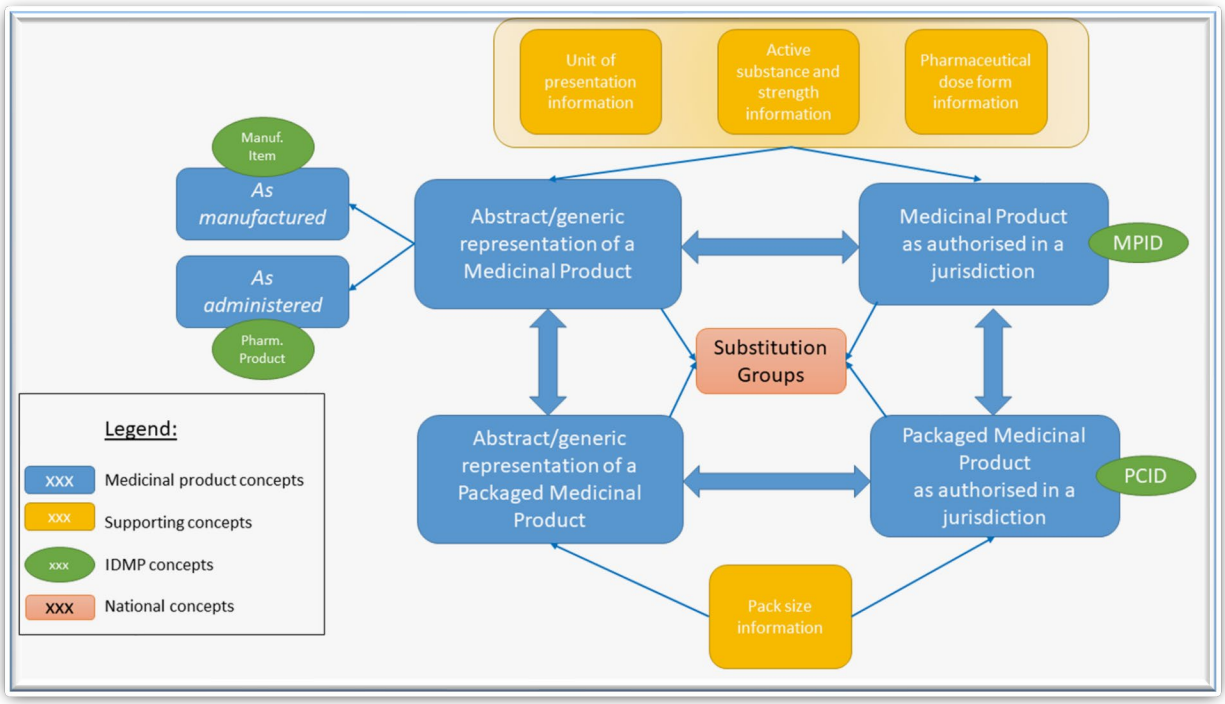


Figure 2: Simplified diagram of medication objects for MPD characterisation

The characterisation process found that the MPD used in clinical systems for prescribing and dispensing could be categorised into two broad groups:

- those providing identifiers and descriptions for the real or actual medicinal product packages (only), with or without the addition of local substitution groups (but usually with)
- those providing a "full set" of the four medication concepts shown in the diagram above, for products and packages of the real or actual objects themselves as authorised and abstract or generic representations of them, with or without data about the supporting concepts

Note that although all authorised medicinal products are assigned a marketing authorisation "number", this survey found that this is never used as an identifier for the medicinal product in any MPD in clinical care.

Five countries have nationally provided MPD that deliver a full set of medication concepts that is has some level of mandate for use in digital prescribing and dispensing systems; in two countries this is delivered by the NCA (ESP, PRT) and in one by the NCA and a consortium of all stakeholders (BEL). In the other two cases, the MPD is provided by the eHealth agency in one country (GBR) and by the pharmacists' professional organisation in the other (NLD). In one country (NOR) there is some generic representation of medicinal products (not packs) but this does not currently include most parenteral products, so in this characterisation is not considered to have a full set of medication concepts.

Three other countries have commercial MPD that could be considered "full"; one is authored by a pharmacists' professional organisation (IRE), another authored on behalf of a consortium of commercial MPD suppliers (FRA) and the third (more of a tree structure than the mirrored authorised/generic product/pack pattern) by a commercial MPD supplier (CHE). But in all three of these countries there is currently no single national MPD and currently no national ePrescribing system, so the identifiers and descriptions provided do not (yet) function as a unified national MPD for patient care.

The other eleven countries in the survey primarily described real packaged medicinal products only. However, to maximise cost efficiency, these countries that rely on identification of packaged medicinal products for both prescribing and dispensing usually also have information about substitution, either based on rules or product groupings or both, published through a variety of media. The MPD of each country provide these groupings and/or implementations of the rules in an electronic format together

with the list of packaged medicinal products that they relate to, thereby providing “relationships” between packages as well as just a list of packaged medicine representation.

6.5.3 Conclusions from Characterising MPD used in Member States (from T9.1)

There is no one single pattern of data flow for medicinal product identification and description data to go from its source in the NCA of a country to its final destination(s) – the clinical systems used for patient care for prescribing, dispensing and medication records. There are a small set of similar flow patterns, from that where the NCA is the only agency involved to that where a whole consortium of national organisations is involved. But it is a small set of patterns and a small set of agencies which collaborate together, those organisations being (government) reimbursement agencies, pharmaceutical wholesalers and pharmacists’ professional organisations including drug information centres, pharmaceutical companies or their representative national organisation, and commercial MPD and knowledge suppliers. Understanding this small set of flows and the organisations involved enables those charged with the implementation of IDMP to identify who is liable to be impacted, either positively or negatively, by any changes in provision of data or data structures and to communicate/negotiate with them, especially in cases where there is not currently a close partnership in the data flow. These patterns also inform those responsible for architecting cross border care, to select where in the data flow process would be most suitable for blending in information about data from other countries’ MPDs, both directly for individual queries to national contact points and indirectly to source the data for national contact points. This will be particularly pertinent for the handful of countries that currently do not have a single national MPD providing medicinal product identifiers for patient care from any source.

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. There was an almost even split between the two patterns. It is unsurprising to find MPD providing only actual medicinal product package concepts; these are the real-world things manufactured by pharmaceutical companies, released into the supply chain, that are dispensed to patients and from which patients administer their medication.

In contrast to the more traditional top-down approach to clinical terminology and ontology (have a thing and make its description ever more granular by the addition of attributes), MPD must be constructed bottom-up; the real authorised packaged medicinal products are what exists, but abstractions of these can be made by removing attributes and making the descriptions of concepts less granular or precise. In this way, MPD ensure that abstract classes are all supported by real products and no unnecessary or misleading concepts are authored. But abstract concepts require rules and patterns to give consistency in their production and maintenance. These concepts and their rules must be developed to meet the business needs of the domain, which may sometimes be conflicting, especially for different types of products. The rules must also cater for the rarer patterns and so can become somewhat complex and challenging to design, maintain and implement.

The characterisation of the main MPD available for use in European countries for primary use in patient care, specifically prescribing and dispensing, has yielded a landscape with just 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 clinician desktop.

6.6 Characterising the business architectures for ePrescribing in EU member states

T9.2 in the UNICOM project was to undertake a characterisation of community prescribing and dispensing software system suppliers that operate in EU member states, because having some understanding of these systems – their providers, their usage etc. - in the various member states will be helpful to correctly target the implementation guidance for IDMP with MPD that will be produced later in the UNICOM project. The characterisation of the systems included a characterisation of the different business architectures that ePrescribing and dispensing operate within; this is described here because having an understanding of these architectures, it is possible to anticipate how any changes due to the availability of IDMP data either through the existing MPD used by the systems or through a national

centre of some sort might be implemented. The patterns for the architectures described below were developed within the Pharmacy Workgroup of Health Level 7, to support the implementation of the prescribing and dispensing message flows in its international V3 Pharmacy specifications. It was clear that the establishment of ePrescribing and dispensing solutions, particularly in a community pharmacy context, is significantly impacted by legislative and business dynamics in an implementing setting. These dynamics, in turn, drive substantial variations in implementation architectures.

6.6.1 Repository-based Architectures

These are characterised by prescription messages being sent to the repository by clinical systems that support the prescribing process. For dispensing to take place, the dispensing system must obtain the prescription information from the repository. The dispensing system may request the prescription using the patient identifier (for example, a national health card) or prescription identifier (for example one- or two-dimensional bar codes). As well as the usual response of sending the prescription, either in response to a query message or a direct request message, there will be a variety of other responses (e.g. prescription already filled, with another pharmacy etc.).

In all of the following diagrams, these are the system roles:

Table 1: System roles for electronic prescribing architectures

Prescribing System	A system intended to support a clinician with prescribing authority.
Dispensing System	A system intended to support a clinician with dispensing authority.
Administering System	A system intended to support a clinician in the recording or updating of medication administrations.

6.6.1.1. Central repository

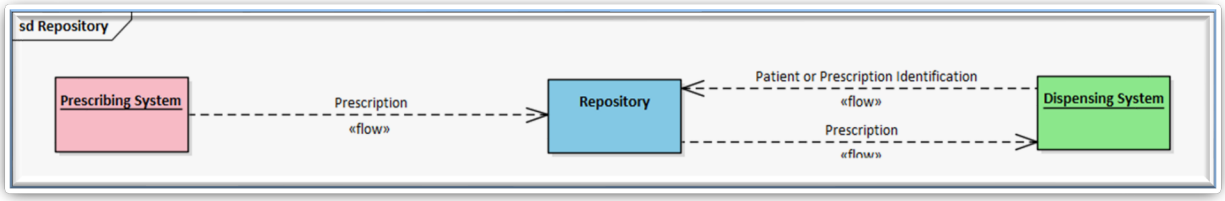


Figure 3: System architecture for ePrescribing with a central repository

The central repository has little functionality other than as a repository for prescriptions and to respond to requests for prescription information. This architecture can support a “nominated or designated pharmacy” if that functionality is allowed within the country and the information is included in the prescription at the point of prescribing, or if the patient is given access to functionality within the repository to forward their prescriptions to a particular pharmacy directly.

This is the most common architecture for community electronic transfer of prescriptions (“e-Prescribing”) and is the standard architecture in almost all European countries that have an e-Prescribing system.

6.6.1.2. Controlling Hub and Repository

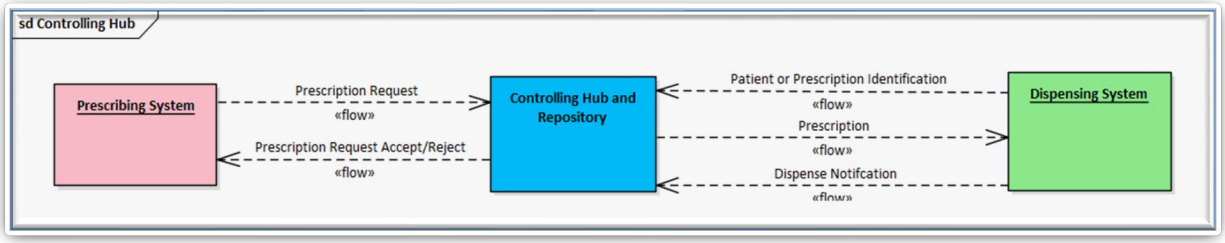


Figure 4: System architecture for ePrescribing with a controlling hub and repository

In this architecture, the repository acts as a hub and exercises control over the process. The prescribing system sends a "request to prescribe" to the hub, which undertakes checks on it, both clinical and administrative. If those checks are passed, accepts/makes "active" the prescription request and issues an identifier for the prescription. The prescribing system may also query the hub prior to the prescription process for information about the patient's current medication. The dispensing system queries the hub for active prescriptions for a patient (usually based on patient ID), receives all active prescriptions, then chooses which will be dispensed based on patient request. It may then notify the hub of the dispense (and in some cases, also the prescription collection).

This architecture is not common and is not used in Europe; it has been implemented in Canada in the CeRx system.

6.6.1.3. Index Repository (Federated System)

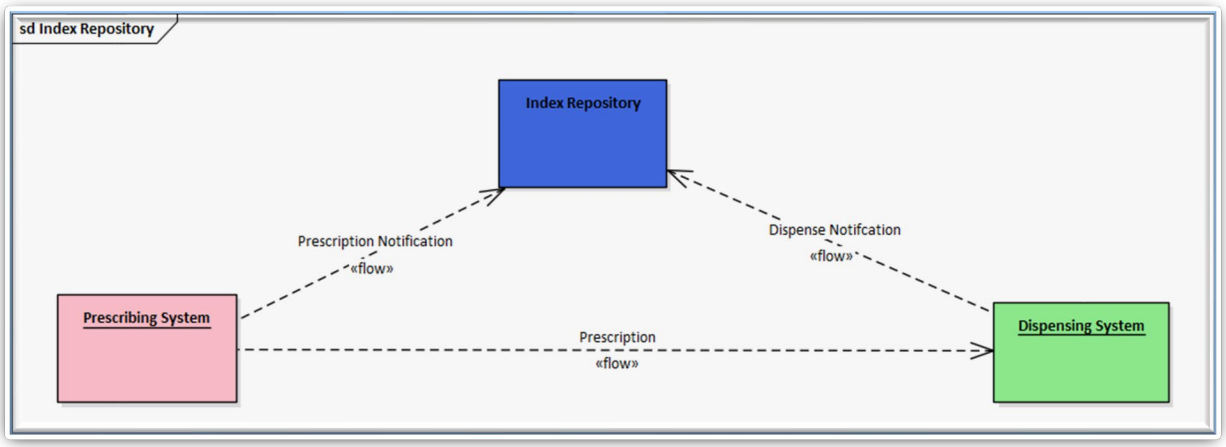


Figure 5: System architecture for ePrescribing with an index repository

In this architecture, there is a registry, but it holds only information about the identity of events (prescriptions and dispensations). The actual electronic prescribing process occurs on a "push" model; the prescription is pushed to the pharmacy of the patient's choice at the time of prescribing. Both prescribers and dispensers may query the Index repository for information about previous events and may then query the initiating system for the data about those events (flows not shown).

This architecture has the advantage that information is always stored at the system that initiated it. However, it is not widely used. The only implementation of this architecture in Europe is in the Netherlands.

6.6.2 Directed (point-to-point) Architectures

These are primarily found in institutional settings but are included here for completeness and because they could be implemented in a community setting if a direct “push” model were used without any repository.

6.6.2.1. Standard Institutional

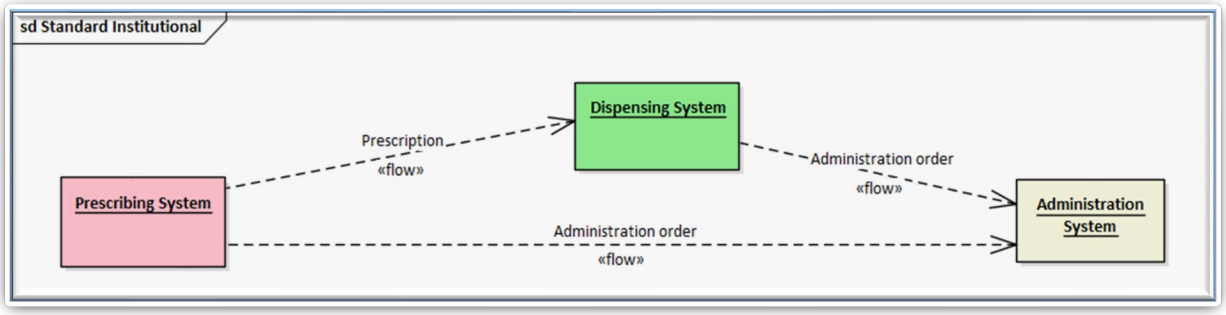


Figure 6: System architecture for directed ePrescribing within an institution

The prescription information is sent directly from the prescribing system to the dispensing system. In an institutional setting, an “administration” message might (also) be sent to a nursing system, from either the prescribing system or the dispensing system.

6.6.2.2. (Dispensing) Service Centric

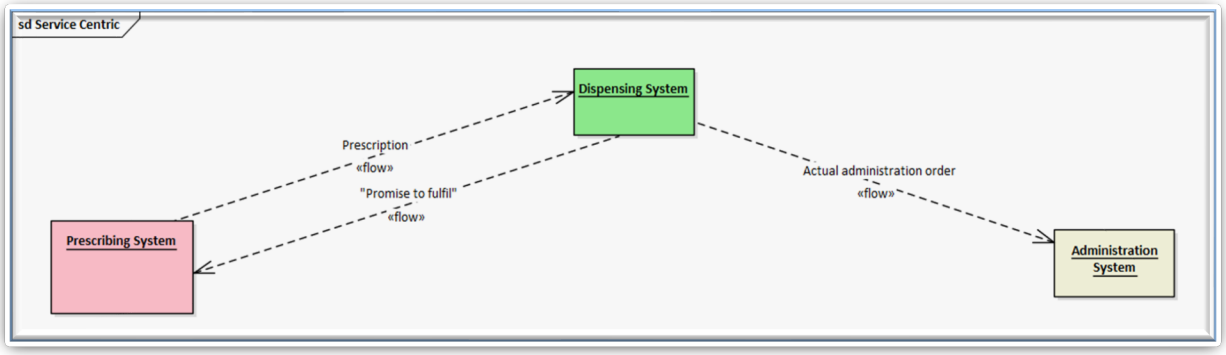


Figure 7: System architecture for directed ePrescribing with a dispensing service

As in the standard institutional architecture, the prescription information is sent directly from the prescribing system to the dispensing system, but the dispensing system has a responsibility to check the prescription and ‘transform’ it (if required) before fulfilling it and sending the administration order to the administration system. The ‘transformation’ is to take an abstract prescription (e.g. “warfarin oral 4mg daily”) and provide an administrable order (e.g. “warfarin 1mg oral tablet daily plus warfarin 3mg oral tablet daily”) and the medication to fulfil it, and communicate that both to the administration system and “back” to the prescribing system as a “promise to fulfil” the abstract prescription. In many institutional cases, the dispensing system is co-ordinated with an automated supply system or a unit dose supply system.

6.6.3 Conclusions from ePrescribing business architectures patterning

The homogeneity of the business architecture used for ePrescribing and dispensing in the “central repository” implementation pattern provides a clear opportunity for this central repository to play an active part in managing the use of IDMP data particularly for cross border care, although how that might

interact with the MPD that are actually used in the prescribing and dispensing systems of the country would need to be elucidated.

7 MPD Models

Since a fundamental axiom of a medicinal product dictionary is that it **can** identify the medicinal products whose descriptions it contains, another view into „requirements“ is to study how existing systems are designed and modelled in order to meet their requirements and function successfully in their environment.

It would seem that there are two clear patterns for medicinal product dictionaries, and for ease of reference these are here named by reference to the overall shape pattern of their classes: the linear (backbone) pattern and the mirror image pattern. There is also a third pattern which could be considered a hybrid of the two approaches. Each pattern is described, accompanied, when appropriate by the „definitional attributes“ – the set of properties that are used to uniquely identify objects that would be present within each class. For the classes „authorised products“ and „authorised package products“, the content is compatible with the IDMP „medicinal product“ and „packaged medicinal product“ respectively, although most MPD would not hold the „full set“ of IDMP data for either. Indeed, task T9.4 in UNICOM is investigating the subset of data items from IDMP (in particular ISO 11615) that is most appropriate for MPD supporting patient care.

7.1 The linear/backbone model MPD

The linear or „backbone“ model for an MPD consists of a set (usually 5) of classes of objects related together in a line which can be traversed in either direction. Here the line is given horizontally and can be traversed from left to right or right to left.

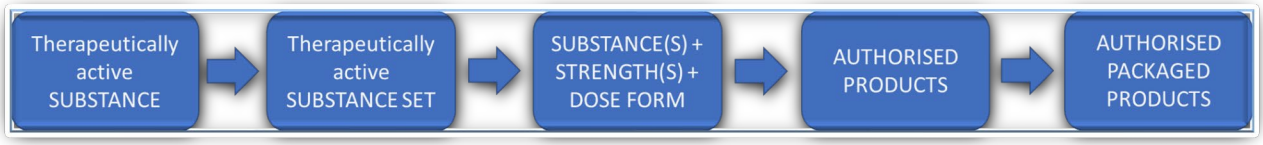


Figure 8:The linear/backbone model for an MPD

Starting from the left, the linear model has a class of therapeutically single active Substances; substances may be described in various granularities, including their base molecule, modification (salt, ester etc.) and sometimes also including hydration/solvation. There may be a hierarchy within this class (e.g. „amlodipine besilate may be a child concept of an „amlodipine“ concept“) but this is not mandatory. The next class groups these substances into sets as found in authorised products. The class in the middle adds the appropriate strength(s) and a dose form to give **an abstract representation of an authorised product**. The fourth class from the left contains the authorised products, usually described using a brand name, and finally the fifth class contains packaged products.

Example:

Figure 9: Example of a multiple active ingredient product in the linear/backbone model for an MPD

Although this model „works“ from left to right, its management must be from right to left, because a therapeutically active substance, substance set and substance set + strength(s) + dose form will not be present unless there is or has been an authorised product with that combination of components. For example, there could be no object that is „simvastatin 20mg + ezetimibe 10mg solution for injection“ as there are no authorised products that are parenteral preparations of either of these therapeutic substances.

The structure of this linear model is hierarchical, flowing from active moiety substance to authorised medicinal product and package. It is not a strict „is a“ subsumption structure, because the classes of objects are not of the same type; a product *is not* „a substance set“, a package *is not* „a product“, but the model does have a parent-child structure, and every child must have a single parent. Since it is hierarchical, although it tends to be viewed as linear, it actually forms a tree structure, as shown in the example below: (note – the example is for a single ingredient substance, so the Substance Set class is not shown and the authorised packaged product has been omitted due to space – if present it would have shown even more leaf objects).

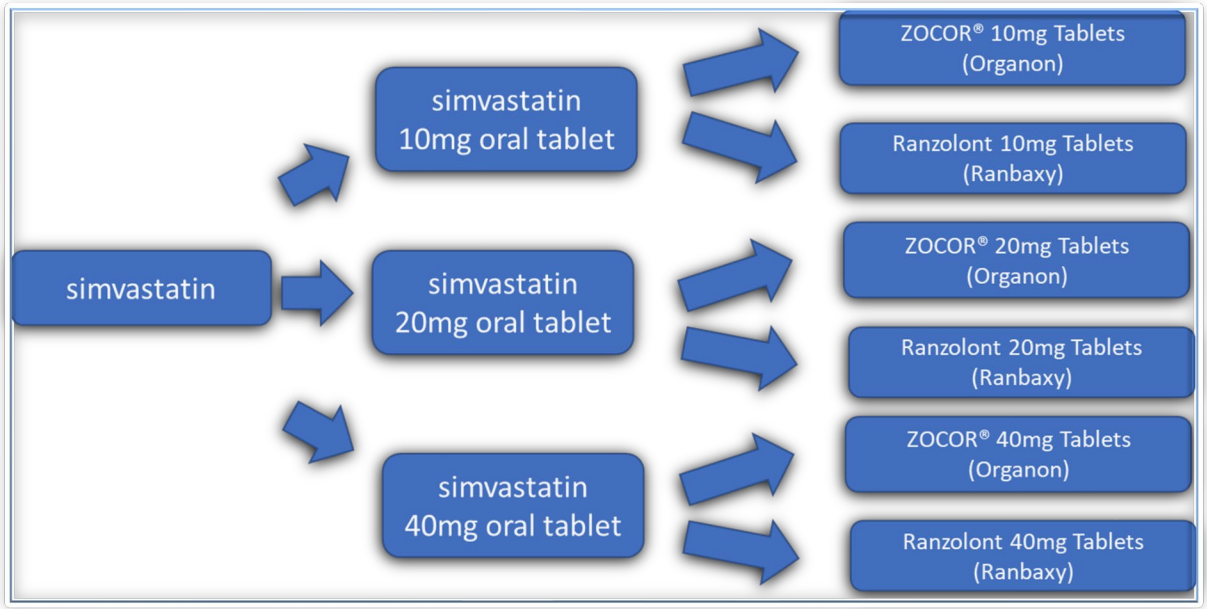


Figure 10: Example of a single active ingredient product in the linear/backbone model for an MPD showing the progression from active substance to real product

The linear model MPD is the basis for some of the oldest MPD, and it is still used by some, particularly in the United States. It was possibly first publicly described by the Health Informatics Group of First Databank Inc. in the late 1990s[12], and continues to be used by First Databank as the foundation for their MedKnowledge product[13], with the Substance class being the „HIC“ – the Hierarchical Ingredient Code (HIC) and the middle class being the Generic Code Number (GCN) sequence number. The authorised product and its packages are identified by National Drug Code (NDC) issued by the Food and Drugs Administration (FDA). Also in the US, the Medispan drug database uses this model, with the central class being their GPI – Generic Product Identifier[14] and then also using the FDA's NDC codes for authorised products and packages.

In Europe, the G-Standaard as distributed by Z-Index[15] to serve the Netherlands uses a linear structure, here shown vertically rather than horizontally. Instead of a Substance Set class, there are two classes of objects, the SSK and the SPK, where the route of administration is included. The GPK class is the central class, and again there is an intermediate abstract class, (the PRK, introduced to support generic prescribing) that introduces some more detail of unit of presentation and size, before the HPK which is the authorised product and the ZI number which is identifies the authorised packaged product.

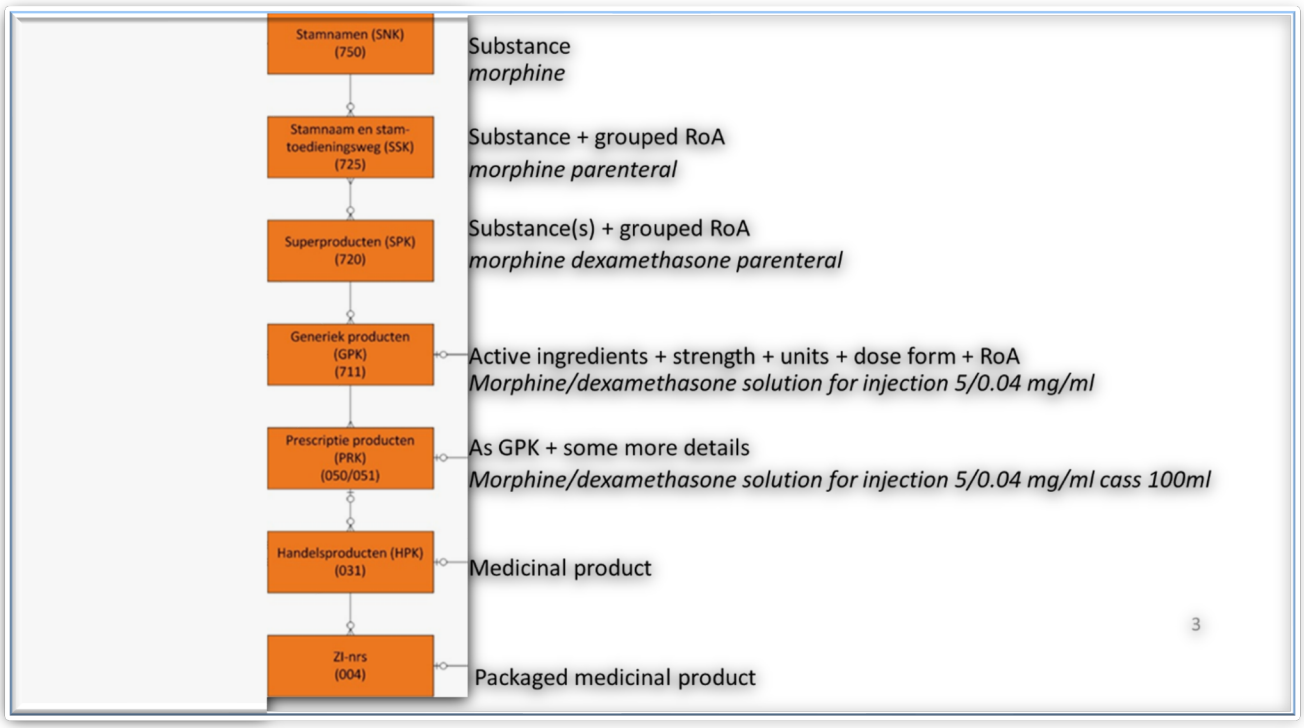


Figure 11: Diagram of the Z-Index linear modelled MPD

The hierarchical structure of the linear or „backbone“ model for an MPD is considered to be very useful when coupling an MPD with the provision of clinical decision support for safer medicines use. This allows for clinical information such as drug interactions or contraindications of use to be linked to an appropriate level (for instance, drug interactions to Substance Set + „route“) and then „inherited down“ to the products that are associated with that. This is both efficient for information maintenance and also comprehensive; all products that should have that information inherit it automatically. All three of the organisations above that are mentioned as using this model are organisations that provide clinical decision support alongside their medicinal product dictionary.

The linear model can also be truncated, either two just two and sometimes even only one class:

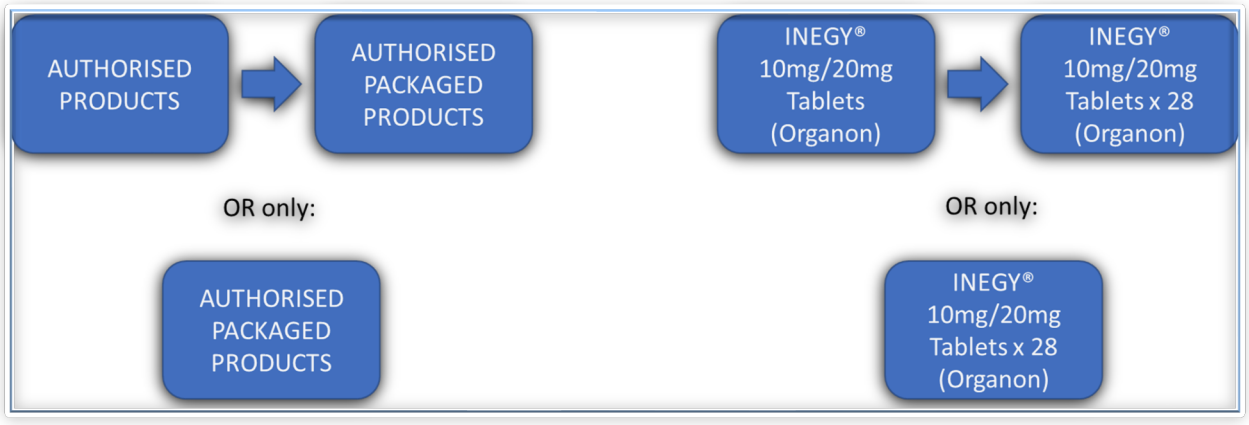


Figure 12: Truncated linear MPD model with an example

This is the model currently used in the majority of member states, as found in the T9.1 MPD characterisation.

7.2 The mirror image model MPD

The „mirror image“ model for an MPD consists of four of classes of objects related together in a symmetrical arrangement which can be traversed both up and down and across the axes of symmetry. In this model, only medicinal products and their packages are represented, therapeutically active substances considered as supporting information (along with dose form and unit of presentation) and are therefore not a class of the model itself.

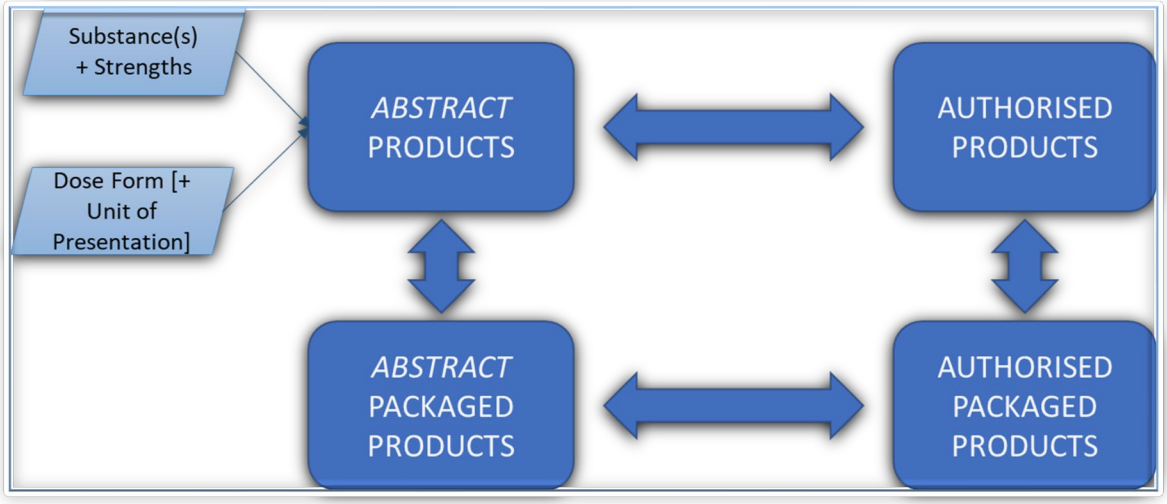


Figure 13: Mirror image model for an MPD

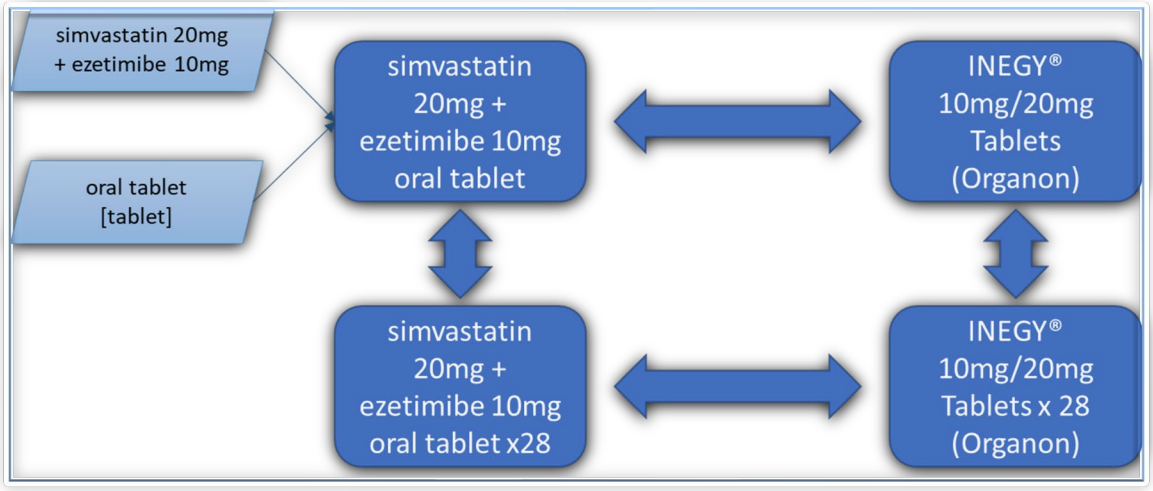


Figure 14: Example of a multiple active ingredient product in the mirror image model for an MPD

The relationships between the classes in the „mirror image“ model are not strictly hierarchical. The vertical relationship between the authorised product and its package(s) is the same as that in between the two classes in the linear model, and the mirror image relationship of abstract product to abstract package is similar. The relationship between the abstract product and the authorised products and their equivalent packages is sometimes considered a subsumption (is a) relationship, but strictly is an association whereby the authorised product is a real instantiation of the abstract (it cannot be a „realisation“ as this has a restricted meaning in modeling terms and is about one class implementing the *behaviour* of a class).

The original use cases for this pattern of MPD model are to support national prescribing and dispensing, particularly in primary care, in a healthcare culture where generic prescribing was required. Clinical decision support was expected to work ***with*** the model, but was not the use case for it. Prescribers use

the abstract product (or package) concept for the prescription, with a reference price given to an abstract package; dispensers then select a package (or content from a package) to dispense from the associated authorised products and packages.

The model is generally populated from right to left (the „bottom up“ approach) whereby when a product and its package(s) are authorised, they are entered into the MPD and associated with their appropriate abstract representations, if already existing, and if not, the abstract objects are also created.

7.2.1 Variations

There are three variations of the „mirror image“ model, one with three classes, one with five classes and one with six.

The three class model does not have the abstract package class; since the primary use case for this is to provide a reference price for reimbursement, in those healthcare cultures where a single reference price is not appropriate, the abstract package class may have little value and is not present.

The five class model has an additional more abstract class „above“ the abstract product:

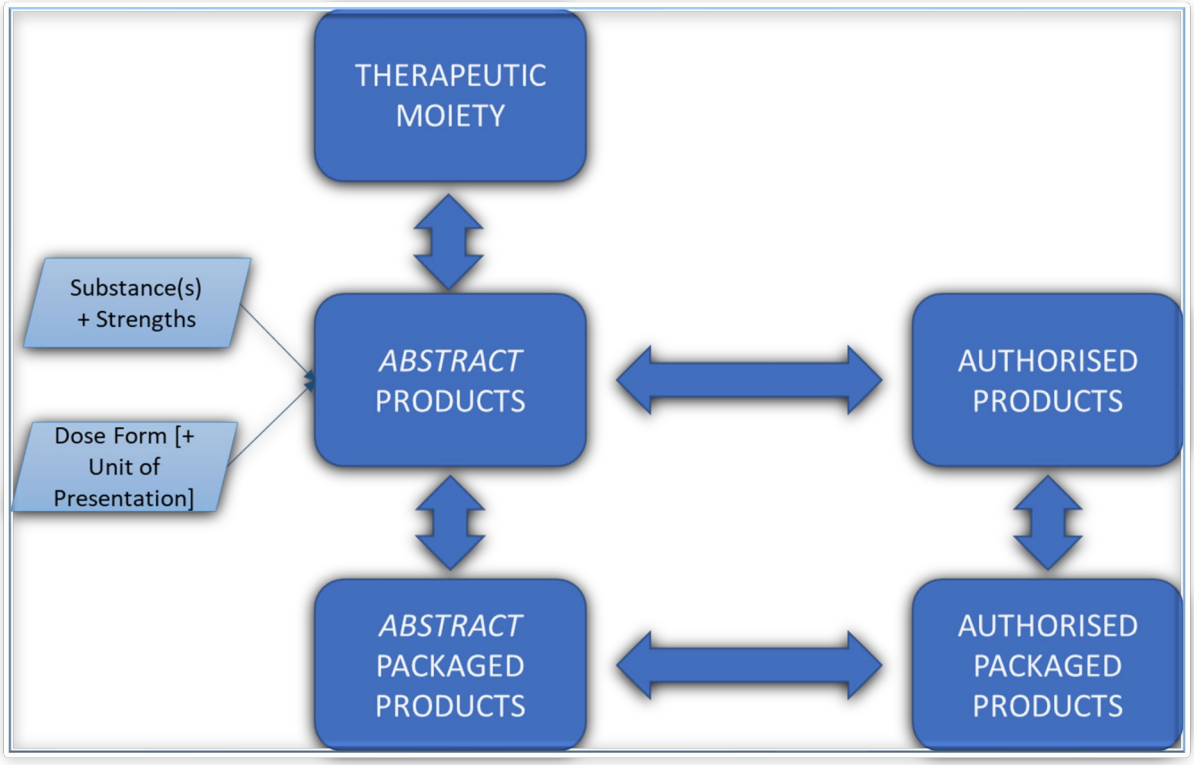


Figure 15: The 5 class variation of the mirror image model for an MPD

The Therapeutic Moiety class describes medicinal products without any reference to strength or dose form and supports the „abstract prescribing“ use case often found in secondary care whereby the prescriber specifies the moiety set and a dose quantity to be administered rather than a product strength and a route of administration rather than a dose form. The selection of the product to administer is then made separately, either by the pharmacist or nurse, or automatically by a pharmacy/administration system, which may do this either directly or by offering a choice of product based on rules. The difference between the Therapeutic Moiety of the mirror-image model and the Substance Set of the linear model is that the Therapeutic Moiety is often more abstract than the substance(s) of a Substance Set (for example „amoxicillin“ rather than „amoxicillin (as amoxicillin trihydrate)“ and „clavulanic acid“ rather than „clavulanic acid (as potassium clavulanate)“.

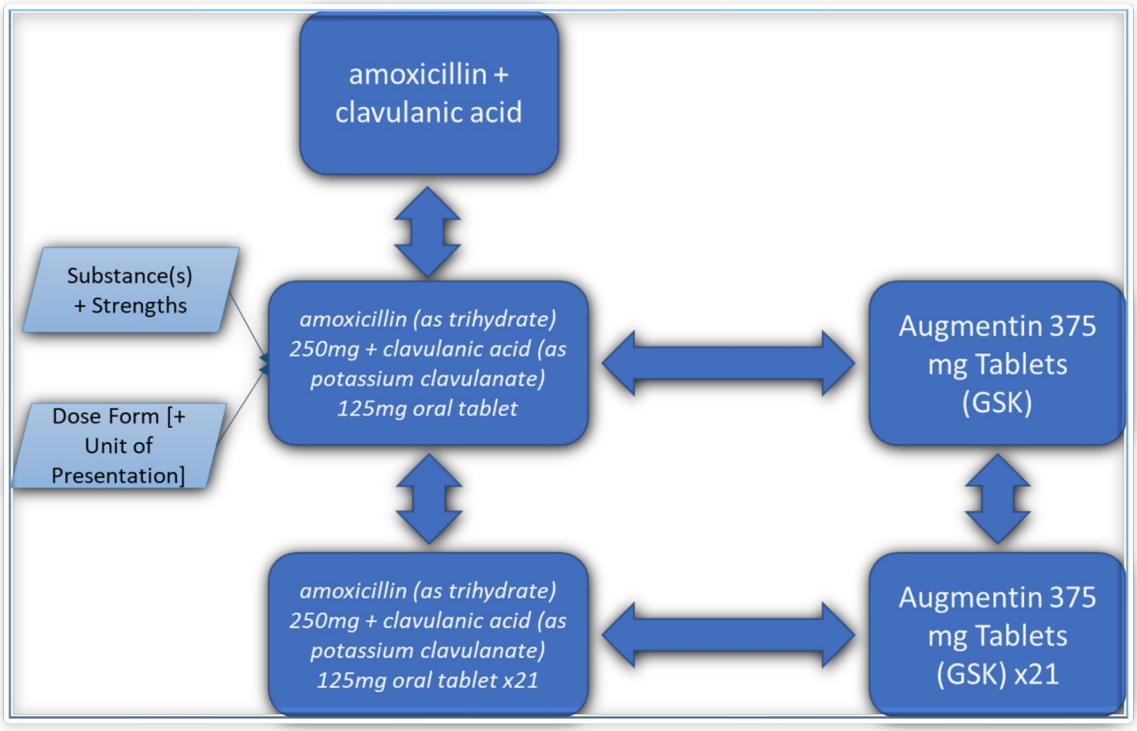


Figure 16: Example of a multiple active ingredient product in the 5 class variation of the mirror image model for an MPD

The six class variation of the mirror-image model has an abstract authorised product class, the Product Family, which has a brand name associated with a single Therapeutic Moiety but similarly no dose form or strength. The main use case for this is for protocol patient management, when a patient needs to change to a different strength of a particular product, for example in terminal care pain management to step up to a more higher strength product with the same dose form release characteristics.

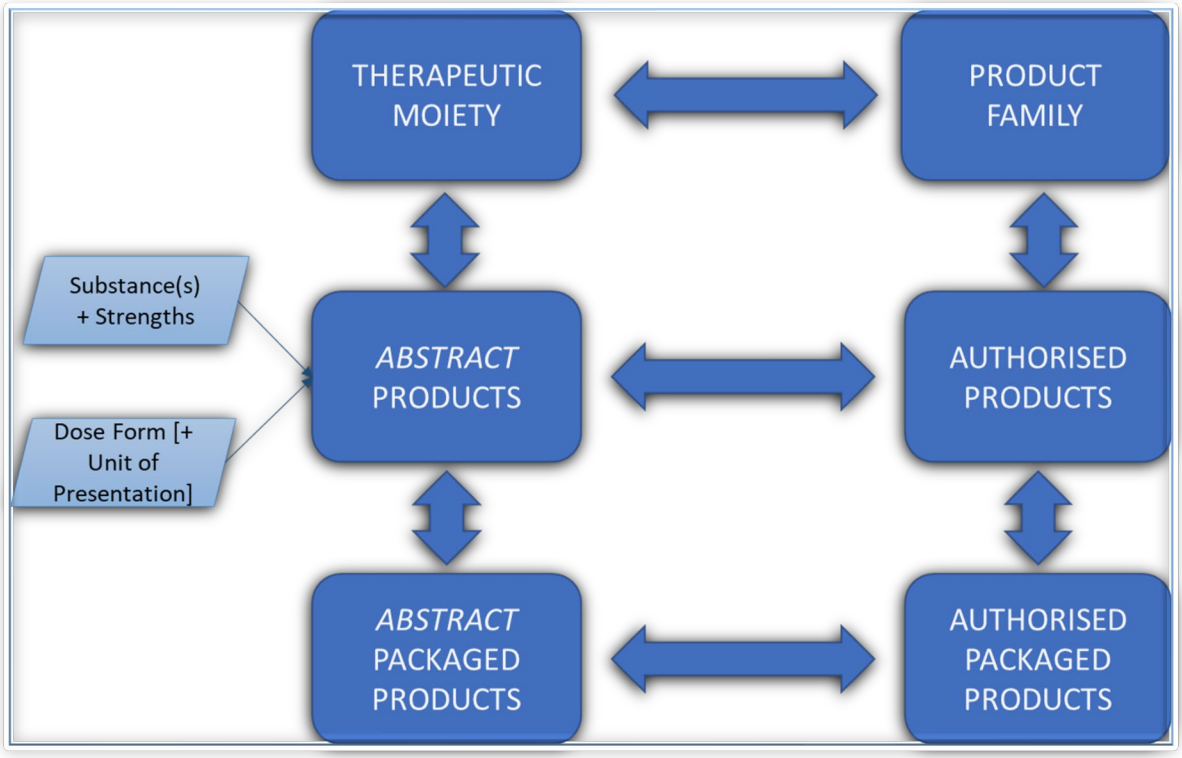


Figure 17: The 6 class variation of the mirror image model for an MPD

Not all authorised products are suitable for abstraction to a Product Family class; product brand name ranges where the same name is used for different therapeutic moieties should not have this abstracted class.

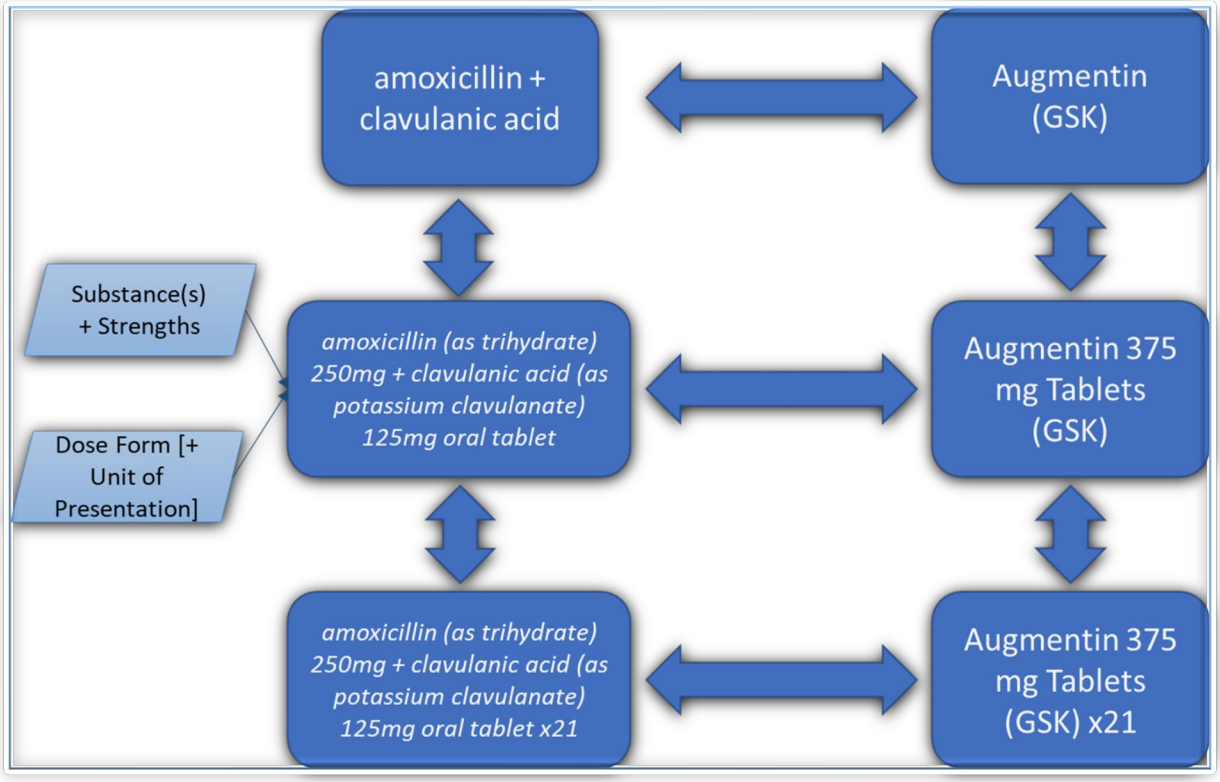


Figure 18: Example of a multiple active ingredient product in the 6 class variation of the mirror image model for an MPD

There are various examples of the mirror-image model MPD in use; these include the NHS Dictionary of Medicines and Devices[16] (NHS dm+d), the Belgian Authentic Source on Medicines[17] (SAM) database, the Spanish Nomenclator for Prescription[18], the Canadian Clinical Drug Dataset[19] (CCDD), the Australian Medicines Terminology[20] (AMT), the New Zealand Universal List of Medicines[21] (NZULM) and the Uruguay Dictionary of Medicines and prescribable products[22] (DNMA).

Below is a picture of the NHS dm+d browser showing the implementation of the „five class“ variation of the mirror image model, and following that a diagram from the Belgian SAM model guidance showing the „six class“ variation:

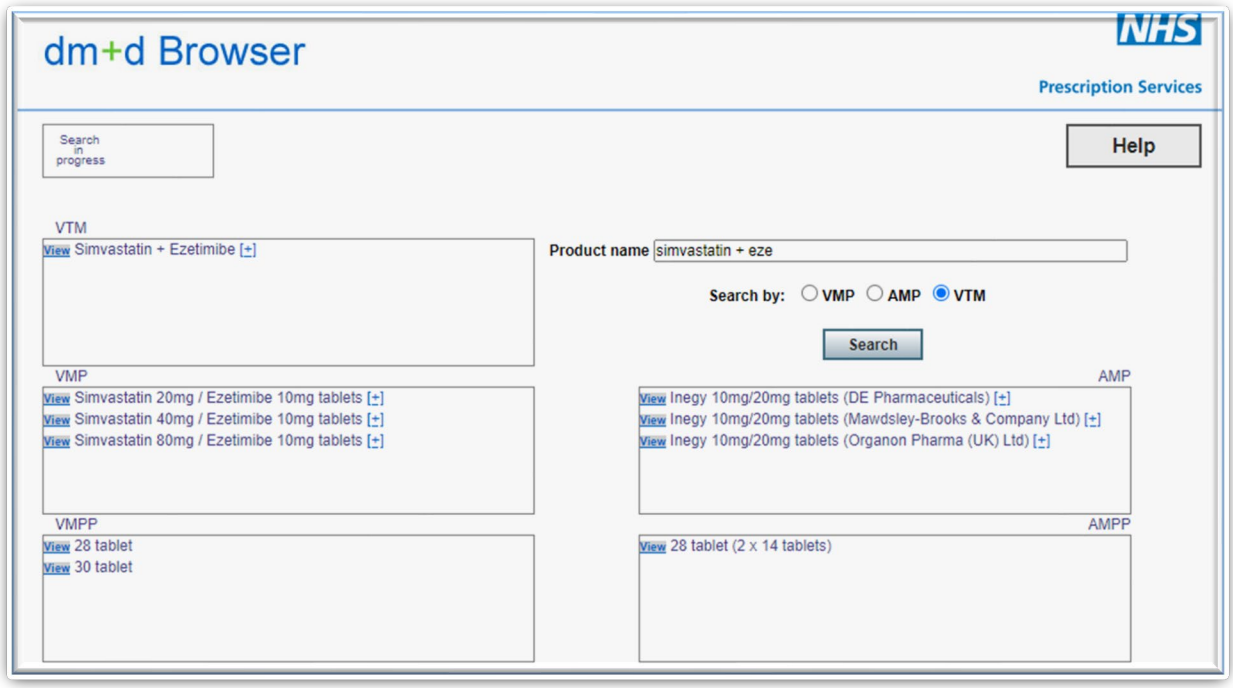


Figure 19: Screen shot of the NHS dm+d – a 5 class mirror image modelled MPD

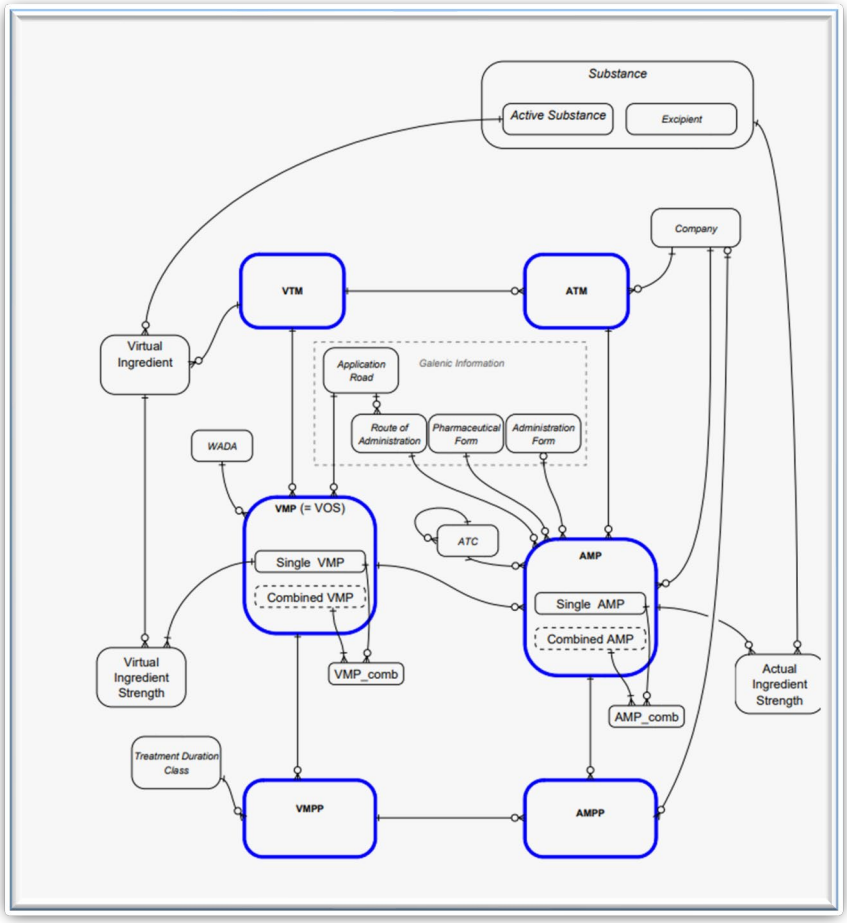


Figure 20: Diagram of the Belgian SAMS – a 6 class mirror image modelled MPD

7.3 The Hybrid model – RxNorm

This model is exemplified by RxNorm, used in the United States. This was developed not as a medicinal product dictionary, but as a metathesaurus based on the principles of the Unified Medical Language System (UMLS) of the US National Library of Medicine, to be a „vocabulary database“ that mapped together concepts from other (commercial) MPD. It was developed in the mid 2000s to provide a „standardised nomenclature of clinical drugs“ (where the „semantic clinical drug“ (SCD) is described as „a pharmaceutical product given to (or taken by) a patient with a therapeutic or diagnostic intent“). It is characterised by normalised names, combining the active ingredient substance(s), their strength(s) and dose form, and these elements also formed the core relationships of the RxNorm model. The set of dose forms used was originally fairly small but has expanded over the years as more use cases have come forward; however it is still much smaller than an equivalent European set (as authored by EDQM). For example, there are no „infusion“ dose forms, most parenteral dose forms are „injection“.

The drawing below shows both the „linear“ nature of the model, shown here as starting at the bottom right with the active substance, flowing up to the „Substance+Strength Set and Dose form“ (the „Clinical Drug“) and then down again to bottom left where the authorised product is described and the „mirror image“ shown here with the bidirectional arrow between the Clinical Drug and the Branded Product.

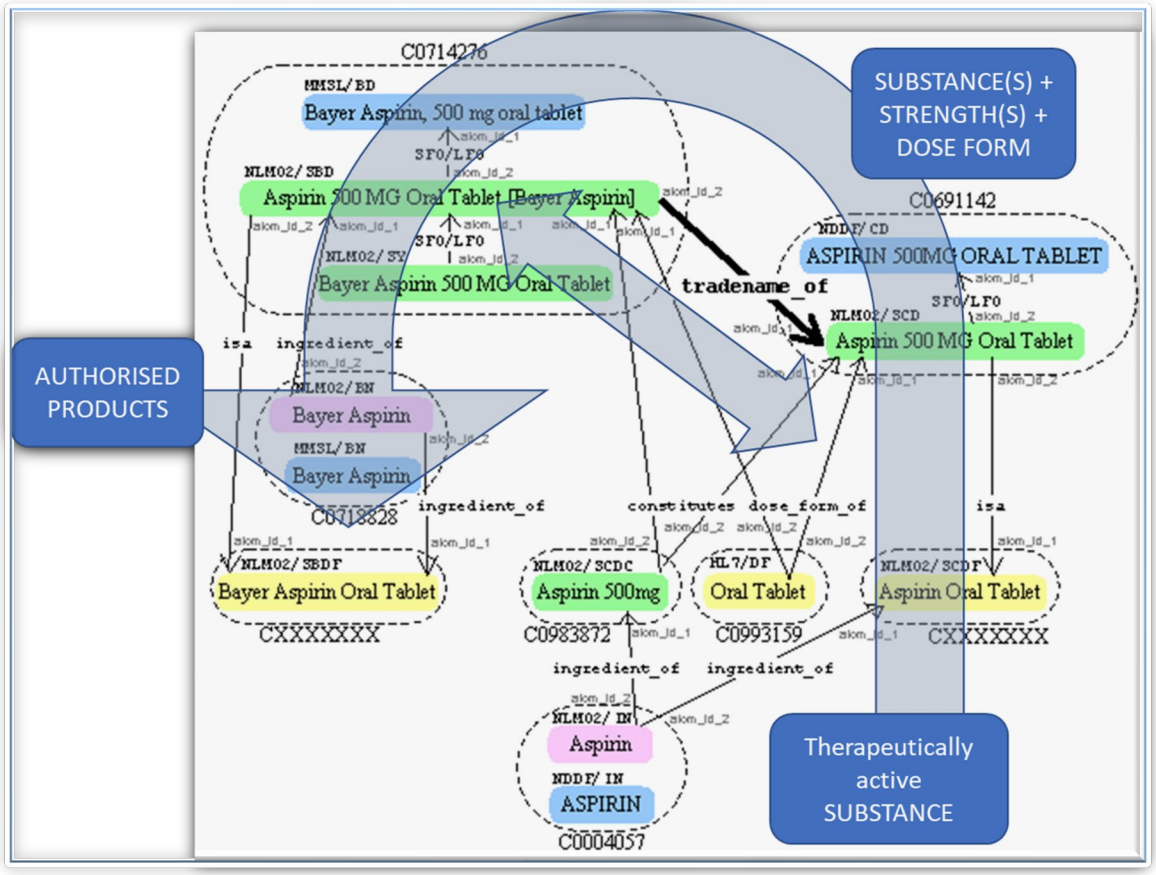


Figure 21: Diagram of the US RxNorm metathesaurus – a hybrid model

Originally there was no reference to unit of presentation or pack size in the model, because its use case was to act as a pivot for concepts from other MPD, with mappings to both the abstract clinical drug objects and the real authorised products. However, in the last 5+ years this has changed, motivated considerably by the U.S. Department of Health and Human Services' (HHS) Office of the National Coordinator for Health Information Technology (ONC) drive for digital health services for citizens. The digital health services have needed a standardised MPD to support information for all aspects of patient care, including electronic prescribing and sharing of medication information (including pharmacy benefits information); so RxNorm has evolved to meet this need, adding in these key concepts of unit of presentation and pack size – particularly to support prescribing, dispensing and reimbursement.

The RxNorm model and its mapping principles are also used by the Observational Health Data Sciences and Informatics (OHDSI) project for mapping medicinal product information of varying levels of granularity of description together in a way that can be used for clinical research.

8 Populating MPD models – the editorial policy challenge

After the challenge of designing or choosing the appropriate model with which to build an MPD, the second and possibly greater challenge is to populate that model with the necessary data in a consistent and reproducible manner such that the information it provides can be used meaningfully in patient care at different times and in different contexts. This is the „editorial policy“ challenge for maintenance of MPD.

This section takes various editorial challenges that are known to exist in MPD and discusses the various strategies that can be adopted to overcome them to resolve issues, and how the same challenge can be overcome in different ways depending on the use case(s) that the MPD must support.

8.1 Scope

For ISO TS 19256, the scope was clear („available medicinal products“) and, as discussed in section 6.1 of this document, even this provides challenges, because MPD need to support recording of historic information about products that were previously available and also support look up of information about these products. Any secondary use in analytics would also require information about products used in the past; for example inclusion/exclusion criteria for clinical trials can state things like „any product from <<group>> currently taken or taken at any point in the last x years“.

But beyond that, MPD need to serve their users by providing identification and information for **all** the products that their users need to reference, either in the prescribing/dispensing process and/or recording in the patient record. Therefore, many MPD contain identification of and information about a range of products: medicinal products as well as medical devices, homeopathic products, nutritional products and cosmetic products. Defining and describing the scope of a typical MPD's product coverage is therefore not easy; challenges include:

- Describing and managing products that were in times past authorised as medicinal products but which are now
  - authorised as medical devices rather than as medicinal products due to change in legislation;
    - examples include bladder irrigation products (containing saline or similar), ocular lubricants and joint lubricants and some head lice treatments (containing hyaluronic acid and derivatives)
  - no longer authorised for sale and supply in a particular jurisdiction, or in any jurisdiction. The authorisation may have been
    - withdrawn usually due to safety concerns (e.g. cerivastatin, thioridizine)
    - allowed to lapse (that is – not been renewed by the company at the end of the authorisation period) usually because of economic issues (either the market is now too small to justify the authorisation costs, or the product has been superceded by cheaper and/or more effective products) (e.g. pivampicillin, Pondocillin®.
    - Limited supplies of such products may even still be available for use in particular patients where no other treatment is suitable
- Describing and managing products that are authorised in a jurisdiction *other than that which the MPD is operating in*. These may be used for
  - direct patient care, where the patient is prescribed a product under various regulations – „compassionate use“, „named-patient“, „special order“, etc.
    - This is especially relevant in countries with small populations where companies can feel that it is uneconomic to undertake a full authorisation process with the regulatory agency for that country, yet patients need access to these medicines and information on their identification and use must be present in MPD. Often MPD find it hard to source reliable information when they receive requests to make additions to their scope – for example from a product name that appears in a wholesaler list, or a product name in a letter from a specialist unit to a general practitioner
    - It is also used when there are product shortages in one country and products must be imported more quickly than would be possible using normal importation processes. For example, in France, the national medicines agency can request

MPD to reference such products using the „ATU nominative“ or „accès précoce“; these products are described in the MPD but with very limited clinical or administrative information (sometimes even no package size information)
    - cross border care, whereby there is a need to match the description of a medicinal product used by a patient „from country A“ in „country B“ to provide emergency care safely for that patient
- Describing and managing products that are still in their investigational phases prior to obtaining a marketing authorisation. Many MPD exclude investigational products from their scope because
    - It is difficult to obtain accurate information about them
    - The records of their use are (unfortunately) almost always kept separately from the main medication recording system(s) in use. This is often because of the „blinding“ of the investigation
- Supporting the activity of 'prescribing', which is the process of a healthcare professional making an order for supply and use of a „product“ for a patient, and that „product“ could be a medicinal product, a medical device or a nutritional product
    - Additionally and increasingly in some healthcare cultures, activities (or „services“) can be prescribed as well as products, for example supervised exercise classes or mindfulness therapy
- For those MPD that also provide clinical decision support, some naturopathic medicines and nutritional supplements can have important clinical effects (e.g. hypericum, calcium supplements) and so recording use of these in the patient record is important, if the information can be obtained reliably

Consequently, patient care MPD have to determine their own scope, covering various different types of „products“ beyond simply medicinal products authorised within their own jurisdiction and, occasionally, also including the description of „services“ or „activities“.

8.2 Definitional attributes

In this section, the „definitional attributes“ that are most commonly used to describe the abstract classes of medicinal product objects in the main MPD models from section 7 (linear or mirror image) are discussed in turn, along with examples of some of the particular challenges that these offer. These definitional attributes are:

- Substance and strength – all of the models had these as critical data items, as all medicinal products contain substances
- Dose form – again, all the models included this, as all medicinal products must be formulated into a dose form in order to be supplied into patient care and presented to the patient for administration
- Unit of presentation – most clearly present in the „mirror image“ model

8.2.1 Substance and strength: Composition

ISO 11238 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances defines a substance as „matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical“. This definition is accompanied by a note that describes different important groups of substances – single substances, mixture substances or what it terms „specified substances“. It lists five types of single substances: chemical, protein, nucleic acid, polymer and structurally diverse substances. It notes that substances may be „salts, solvates, free acids, free bases or mixtures of related compounds that are either isolated or synthesized together“. A further note explains „discrete existence“ as referring to the „ability of a substance to exist independently of any other substance“.

In ISO 11615, the strength (or „quantitative composition“) of a medicinal product is the „amount of substance expressed using a ratio scale“. For therapeutically active substances in medicines, the strength is an expression of potency – giving a sense of measurement or or calculation of the therapeutic activity of the medicine – a way to describe the amount of medicine required to produce a therapeutic effect of given intensity. Consequently, clear, accurate and unambiguous expression of strength is a critical safety issue when describing medicinal products. Strength is a ratio concept, whereby the amount of substance must be expressed in terms of an amount of something else – so having the numerator and denominator quantities. For medicinal products, the strength is "*the amount of (active)*

substance in one instance of "a whole" of medicinal product"; for some products, that "whole" is very easy to define – and relates directly to the unit of presentation for the product and hence why unit of presentation is considered a definitional attribute in some of the medicinal product models described above. For other products, that "whole" is harder to identify, and that will be discussed further below.

Therefore, substances, with their strength when appropriate. are what form the composition of a medicinal product:

- the qualitative composition of a medicine features the substance(s) in their role of being therapeutically active or as excipient
- the quantitative composition of a medicine describes the amount of substance(s) present – the strength

Different substances are present in medicinal products in different roles. Generally, when identifying abstract medicinal products, the active ingredient substance roles are the ones that are focused on, whereas the inactive or excipient roles (flavour, colour, preservative etc.) are applicable only to real authorised medicinal products.

8.2.1.1. Excipient substances

Excipient substance information is very important for patients to avoid allergic reactions or intolerance symptoms and many MPD do carry detailed excipient information for authorised products, to the extent that it is available, including any quantitative information especially for substances known to cause intolerances such as lactose, or those known to be problematic in particular conditions, such as aspartame in phenylketonuria. The European Medicines Agency publishes various guidelines regarding „Excipients of Concern"[23] which support marketing authorisation holders to provide the necessary information and which assist MPD in assessing and using it.

In addition to substances causing allergy or intolerance, some medicinal products, either directly or indirectly, contain quantities of sodium which can be clinically significant for patients with renal failure or similar conditions. This too is highlighted in the published information and is used by MPD to help to keep these susceptible patients safe.

Excipient substances can only be declared for authorised products; it is usually inappropriate to consider excipient substances for abstract product representations. The exception to this might be if there were additional attributes declaring „absence" – so, for example, ophthalmic preparations that are „preservative free". However, defining anything by „absence" is challenging, and few MPD offer these types of abstract concepts. It can be more appropriate to action decision support at the stage of selection of an authorised product for dispensing/administration to ensure the required absence of particular excipient substances.

8.2.1.2. Adjuvant substances

Adjuvant substances are substances present in vaccine medicinal products specifically to potentiate the immune response to the antigen(s) present in the product and/or to modulate towards the desired immune response. Knowing whether a vaccine medicinal product is adjuvanted or not is therefore important in assessing the likely immune status of a patient and therefore, when describing vaccine medicinal products at an abstract level, the presence or otherwise of one or more adjuvanting substances, in addition of the specific antigen(s) is important.

8.2.1.3. Therapeutically active substances

Most abstractions of a medicinal product are defined only by the composition of the **active** ingredient substances, but within that there are various facets that must be considered:

- the active ingredient substance that is present at an appropriate level of granularity; this can be termed the „precise ingredient substance"
- the substance against which the strength is measured and quoted (the „basis of strength substance, or BoSS), especially in the product labelling and in clinical use of the product for statement of dose quantity
    - this may be the exact same substance as the precise ingredient substance, or

- it may be the base substance if the precise ingredient substance has a modification (e.g. salt or ester), or
- it may be a different modification of the base substance

Precise active ingredient substance

The precise active ingredient substance is the active substance that is actually present in the medicinal product as it is presented into the supply chain (i.e. before any transformation to an administrable dose form, should this be required) described with as much detail as possible. The precise active ingredient substance may sometimes be identified in product information by the use of „as“.

For example:

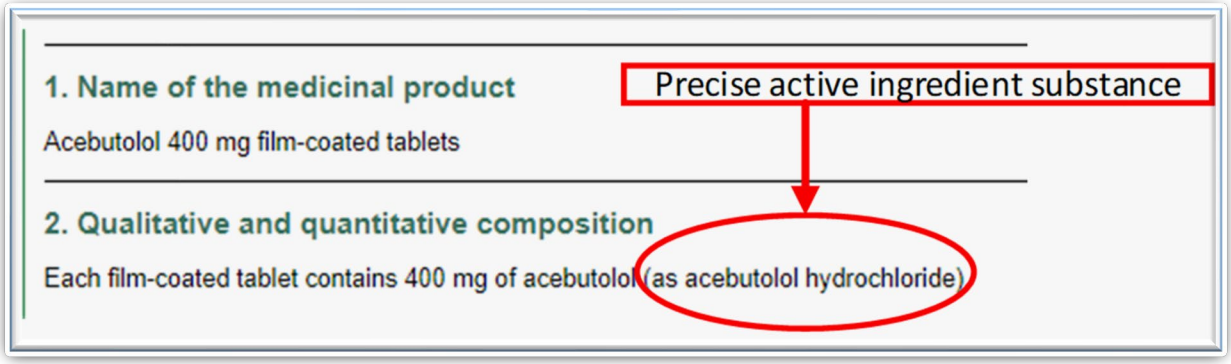


Figure 22: SmPC extract – UK - showing precise active ingredient substance

The precise active ingredient substance present in this product is acebutolol hydrochloride.

Although the precise active ingredient substance should be stated with as much granularity as possible, even this can present challenges, especially for data that is presented as text. The challenge of substances being described differently in different languages is well known and can be managed by a good multi-lingual substance terminology. In the example of a similar product described in French, the precise active ingredient substance is „chlorhydrate d’acébutolol“

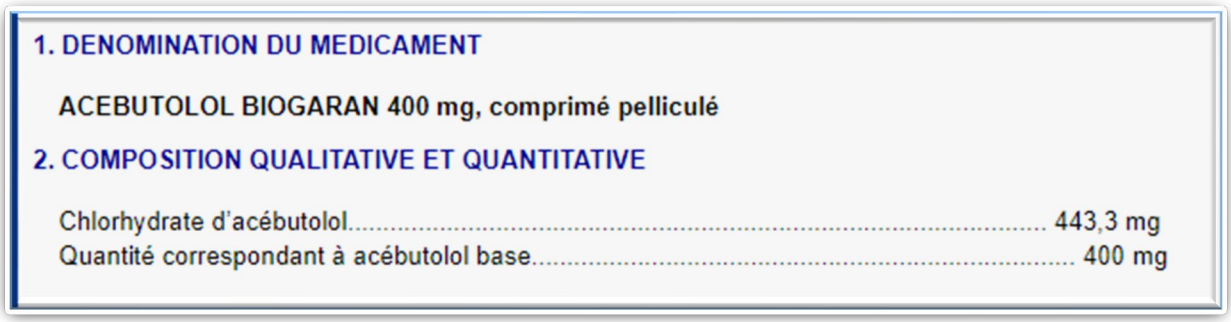


Figure 23: SmPC extract - FR - showing precise active ingredient substance

However, some substances have what are in effect „synonymous terms“ but it is very difficult to identify that they are indeed synonymous, both within a particular jurisdiction, and even more so across jurisdictions. Consider the following two products and their labelled composition information:

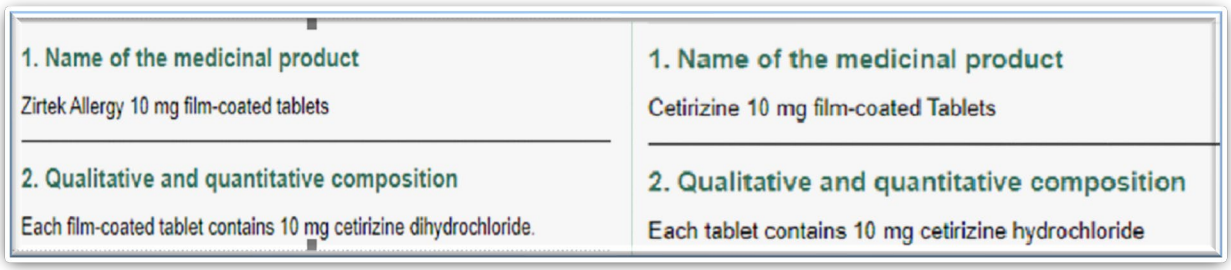


Figure 24: SmPC extracts for two products using different descriptions for the same precise active ingredient substance

At first sight, these would appear to contain different precise active ingredient substances – cetirizine hydrochloride and cetirizine dihydrochloride, since normally „hydrochloride“ is used when the modification consists of a single hydrochloride (monohydrochloride). However, when consulting a substance reference terminology such as G-SRS (as currently access to EU-SRS is not available), it is clear that the terms cetirizine hydrochloride and cetirizine dihydrochloride are synonymous and both refer to the dihydrochloride. The only truly reliable descriptions are the molecular structure diagram and also the molecular formula ($C_{21}H_{25}ClN_2O_3.2ClH$) where the two hydrochloride salt modifiers can also be seen

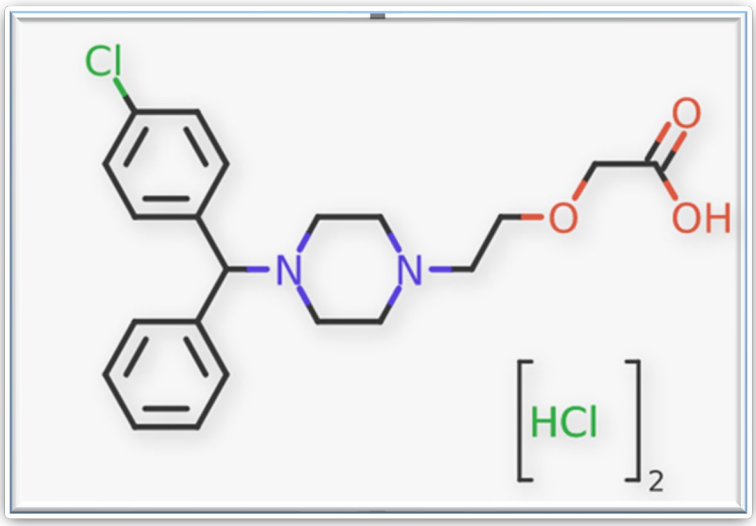


Figure 25: Structure of cetirizine (di)hydrochloride, showing the two hydrochlorides

In order to present clinicians with accurate data, as although clinicians rarely want to be delving into this detail of chemistry, they do want to be able to prescribe and dispense accurately, MPDs have to examine product data carefully and sometimes further investigate beyond the product data presented in order to represent composition correctly and allow correct grouping of products in abstract classes.

A further challenge to the accuracy of precise active ingredient substance information for medicinal products is solvation, of which hydration is the most common example. Solvation is described in ISO 11238 and its implementation guidance in TS 19844 as a particular type of co-crystals. The presence of co-crystals can alter the physico-chemical properties of a substance, for example by increasing the speed of solublisation. Therefore, in ISO 11238, solvated substances are considered to be separate substances and as such are candidates for use as a precise active ingredient substance in for product composition and indeed, there are products where the precise active ingredient substance is described with its full solvation:

Although co-crystals are widely used in the pharmaceutical industry and are sometimes specifically designed into the substance to achieve certain properties in the *formulation* of the product; for example to increase the stability of the final product or to alter the manufacturing behaviour of either the final or an interim product (improving compaction, flowability, filterability etc.), they do not appear to have any

effect on the *therapeutics* of the product. Therefore, a product whose precise active ingredient substance has solvation is extremely unlikely to exhibit any different therapeutic effect to one whose precise active ingredient substance is not solvated; similarly, differences in amount of solvation can be discounted. For example, a product whose precise active ingredient substance is azithromycin monohydrate will have no therapeutic difference from one whose precise active ingredient substance is azithromycin dihydrate. However, the presence of a co-crystal may significantly affect the molecular weight of a substance, and as such has an influence on strength measurement, which is a key part of the quantitative composition of the product and therefore in knowing which products can be grouped together by their strength. This is discussed further in the BoSS section below.

Description of various nanoparticulate substances can also sometimes be challenging, particularly since transforming a basic therapeutic substance into a nanoparticle can alter its biodistribution profile, usually enhancing the therapeutic index as against the unmodified substance. It may also provide targeted administration for potentially toxic medications to particular tissues, thereby decreasing the total overall dose quantity of the medication needing to be administered to the patient to achieve the therapeutic effect.

Liposomes are nanoparticles that are closed vesicles that are composed of one or more lipid bi-layers consisting of specific proportions of amphiphilic (possessing both hydrophilic (water-loving, polar) and lipophilic (fat-loving) properties) substances such as phospholipids and cholesterol; these arrange themselves into one or more concentric bilayer membranes when hydrated in aqueous solutions. The therapeutically active substance, if it is hydrophilic, will be in an aqueous solution „encapsulated“ inside the liposome or nanoparticle; if it is lipophilic, it will tend to intercalate itself into the lipidic layered structure. The active substance is not “bonded” inside the liposome as it must diffuse out of the layered structure in vivo in order to have its therapeutic effect. When liposomal technology was first applied to medicinal products, some MPD considered the liposome to be part of the dose form, but as time has passed and understanding grown, liposomes are considered to be associated directly with the active substance, as a „mixture substance“ in 11238. This is because they modify the physico-chemical properties of the active substance, thereby modifying its biopharmaceutical profile (diffusion, dissolution, absorbtion, excretion etc.) and therefore there are usually considerable clinical differences between medicinal products containing a liposomal substance and those containing the plain substance, although the expression of strength is usually still against the plain substance.

Pegylated substances are those whereby a substance (often a protein) is “coated” or “wrapped” polyethylene glycol (PEG) or similar long chain polymer. Like liposomal encapsulation, pegylation improves the pharmacokinetics of the original substance (usually increasing its half-life) and also decreasing its immunogenicity. Since the PEG is covalently attached to the therapeutic substance it is considered as a totally separate substance and usually has its own international non-proprietary name (INN).

8.2.1.4. Basis of strength substance (BoSS)

The basis of strength substance is a particularly important substance role. This is the substance that the product strength refers to for the labelling, and as such is usually related to the dose quantity for clinical use. As well as the examples below, a well known clinical challenge involving basis of strength substance is phenytoin, where the oral capsules have phenytoin sodium as basis of strength substance but the oral suspension uses phenytoin base, meaning that switching between formulation (for example, post-operatively if a patient has difficulty swallowing) must be carefully calculated using the appropriate basis of strength substances and their conversion values. It is therefore essential that MPD can describe BoSS accurately, and if supporting dose calculation, have conversion values available.

BoSS = PAI

In some cases, this is the same as the precise active ingredient substance, especially for those products where the therapeutically active substance has no modification, as shown below with digoxin:

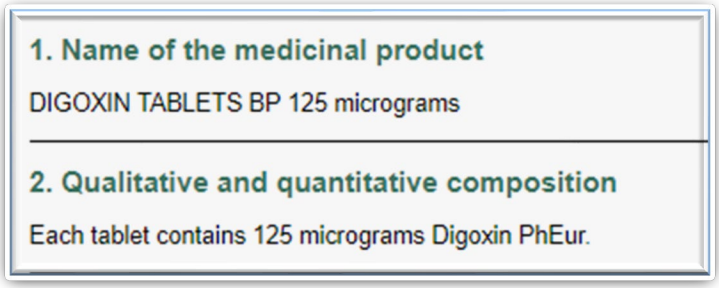


Figure 26: SmPC extract where the precise active ingredient substance is the same as the BoSS

Both the precise active ingredient substance and the basis of strength substance is „digoxin“.

BoSS = unmodified substance (substance (base))

But in other products, the basis of strength substance is not the same as the precise active ingredient substance; often it is the substance without any modification, as shown in the example below:

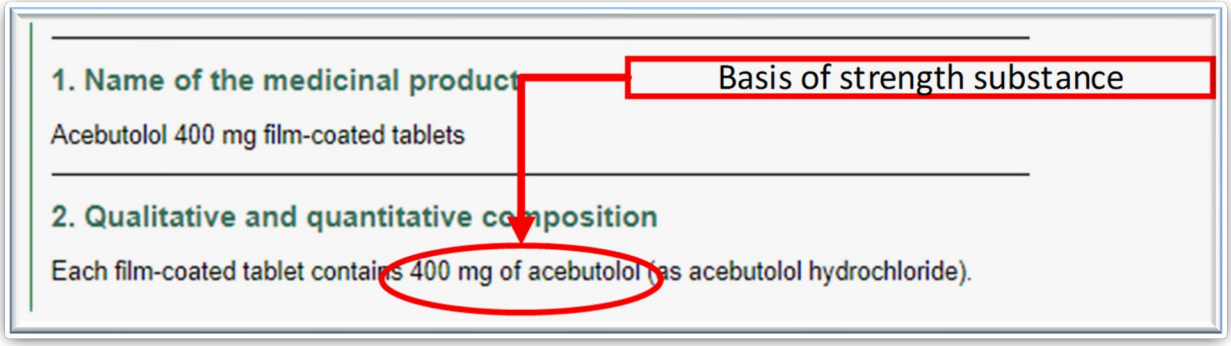


Figure 27: SmPC extract where the precise active ingredient substance *not* the same as the BoSS

The basis of strength substance is „acebutolol“ as there are 400mg of acebutolol (base) in each tablet.

In cases where the basis of strength substance is an unmodified substance (which is sometimes terms the „active moiety“ – the portion of the precise active ingredient substance that is therapeutically active), it is possible to group what in some healthcare cultures will be considered clinically (therapeutically) equivalent products by this, thereby disregarding the precise active ingredient substance. For example:

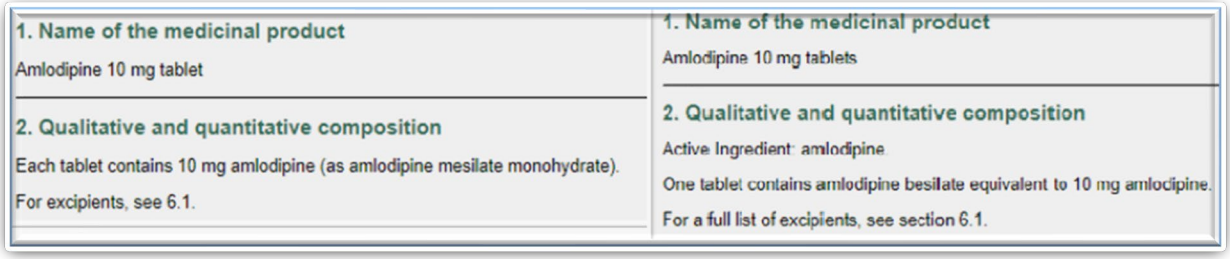


Figure 28: SmPC extracts for two products with different precise active ingredient substances but the same BoSS

Here there are two products, each containing 10mg of amlodipine (base), so with the same basis of strength, but with different ester modifications as their precise active ingredient substance, one with the mesilate (from methanesulfonic acid (CH_3SO_3H)) and one with the besilate (from benzenesulfonic acid ($C_6H_5SO_3H$)). Some MPD may wish to group these two products (and the many others like them) in a single object of „amlodipine 10mg oral tablet“.

BUT, particularly when supporting semantic interoperability use cases, it is very important to understand the rules/editorial policy that governs the creation of abstract objects in an MPD. In the following example, what might at first sight be considered two therapeutically equivalent products actually have a therapeutic substance strength difference, with Product B being over 13% more „potent“ than Product A:

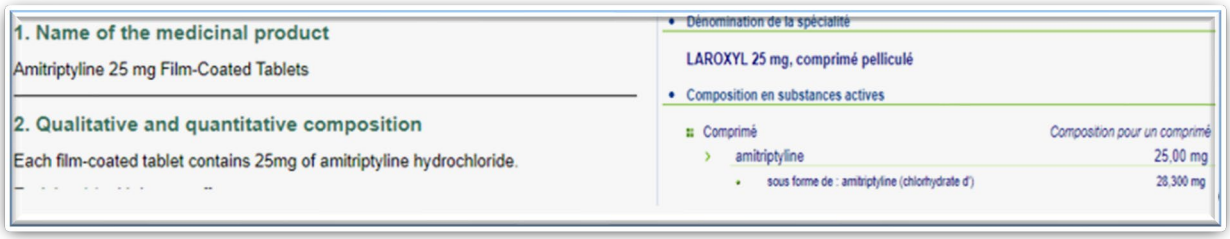


Figure 29: SmPC extracts for two products with the same precise active ingredient substances but *different* BoSS

Table 2: Two different products with the same precise active ingredient substance but different BoSS

	Product A	**Product B**
Precise active ingredient substance	amitriptyline hydrochloride	amitriptyline hydrochloride
Basis of strength substance	amitriptyline hydrochloride	amitriptyline (base)
Strength	25.0mg	25.0mg

BoSS = Reference substance

Another pattern is where the basis of strength substance is not the same as the active ingredient substance nor is it the base (unmodified) substance; instead the BoSS is a reference substance, which may or may not be related to the precise active ingredient substance. Though rare, this pattern does occur and can have significant clinical consequences. In the example below, the clinically labelled strength of the product is 8mg/2mL:

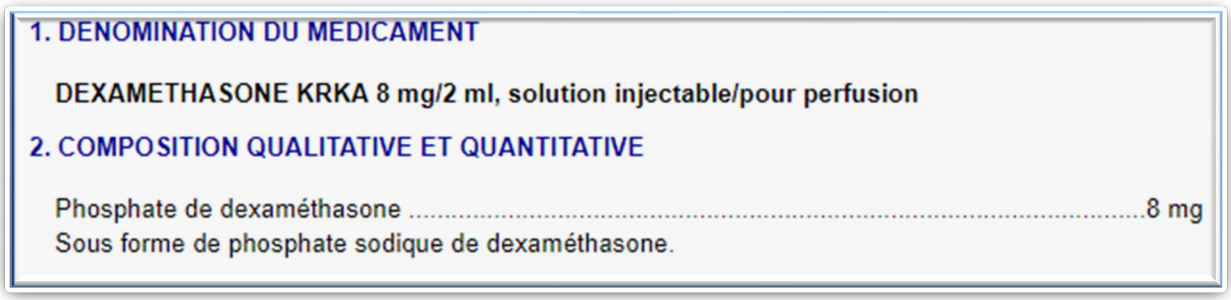
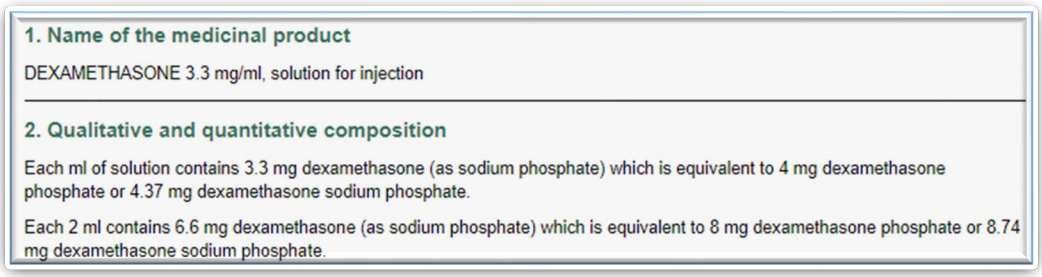


Figure 30: SmPC extract for Dexamethasone solution injectable - FR

Precise active ingredient substance: dexamethasone sodium phosphate (phosphate sodique de dexaméthasone),

Basis of strength substance: dexamethasone phosphate – a „reference substance“ that is neither the unmodified substance (dexamethasone) nor the substance actually present in the manufactured product

In some countries, the labelling of similar products has changed such that the basis of strength substance is the unmodified substance – as shown below - but this risks making information less consistent across borders and more challenging for safe sharing of medicinal product information.



1. Name of the medicinal product

DEXAMETHASONE 3.3 mg/ml, solution for injection

2. Qualitative and quantitative composition

Each ml of solution contains 3.3 mg dexamethasone (as sodium phosphate) which is equivalent to 4 mg dexamethasone phosphate or 4.37 mg dexamethasone sodium phosphate.

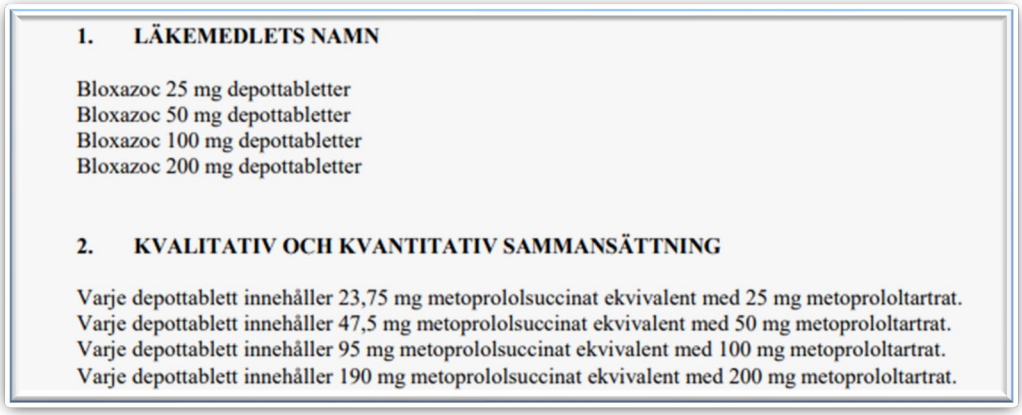
Each 2 ml contains 6.6 mg dexamethasone (as sodium phosphate) which is equivalent to 8 mg dexamethasone phosphate or 8.74 mg dexamethasone sodium phosphate.

Figure 31: SmPC extract for Dexamethasone solution for injection – UK

For the dexamethasone product:

- Precise active ingredient substance: dexamethasone sodium phosphate
- Basis of strength substance: dexamethasone (base) – Strength 3.3mg/mL (or 6.6mg/2mL)
- Alternative reference substance and strength: dexamethasone phosphate Strength: 8mg/2mL.

Another example that shows this particular substance challenge is metoprolol; below is a Swedish product:



1. LÄKEMEDLETS NAMN

Bloxazoc 25 mg depottabletter
Bloxazoc 50 mg depottabletter
Bloxazoc 100 mg depottabletter
Bloxazoc 200 mg depottabletter

2. KVALITATIV OCH KVANTITATIV SAMMANSÄTTNING

Varje depottablett innehåller 23,75 mg metoprololsuccinat ekvivalent med 25 mg metoprololtartrat.
Varje depottablett innehåller 47,5 mg metoprololsuccinat ekvivalent med 50 mg metoprololtartrat.
Varje depottablett innehåller 95 mg metoprololsuccinat ekvivalent med 100 mg metoprololtartrat.
Varje depottablett innehåller 190 mg metoprololsuccinat ekvivalent med 200 mg metoprololtartrat.

Figure 32: SmPC extract for Bloxazoc - SWE

For the Bloxazoc 50mg product:

- Precise active ingredient substance: metoprolol succinate
- Basis of strength substance: metoprolol tartrate Strength: 50mg per tablet

One further example, showing that this issue is widespread, this time from France:

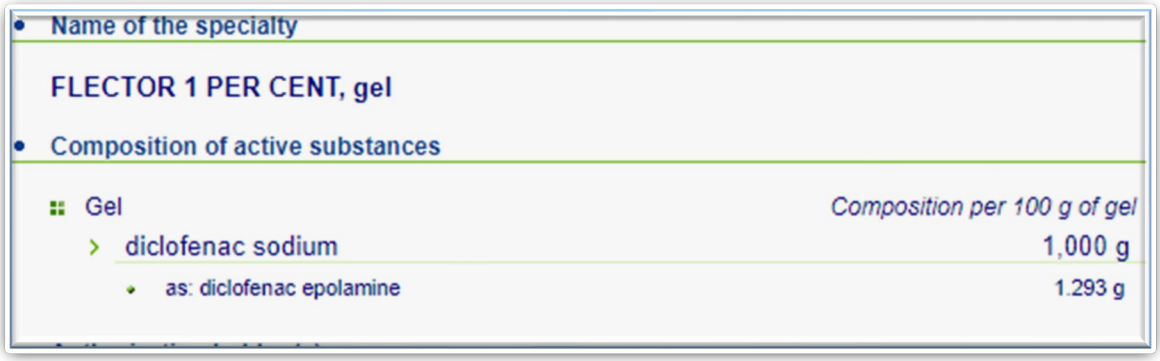


Figure 33: SmPC extract for Flector – FR

For the Flector product:

- Precise active ingredient substance: diclofenac epolamine
- Basis of strength substance: diclofenac sodium Strength: 1% (10mg/1g)

BoSS = Solvated substance

Solvated substances can also be basis of strength substances. Whilst a solvated substance as the precise active ingredient substance is unlikely to have clinical significance, a solvated substance as a basis of strength substance is important to consider, because it affects molecular weight and therefore the amount of substance present.

For example, this irinotecan product:

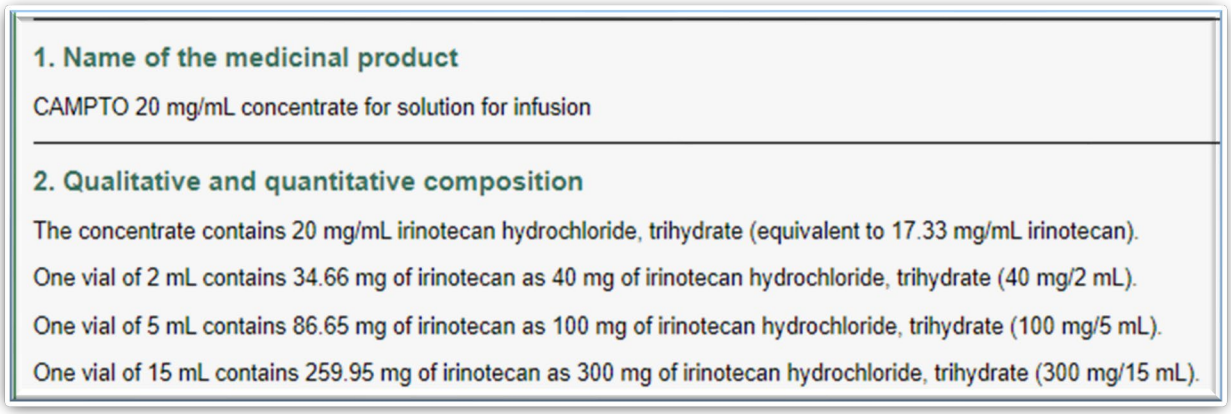
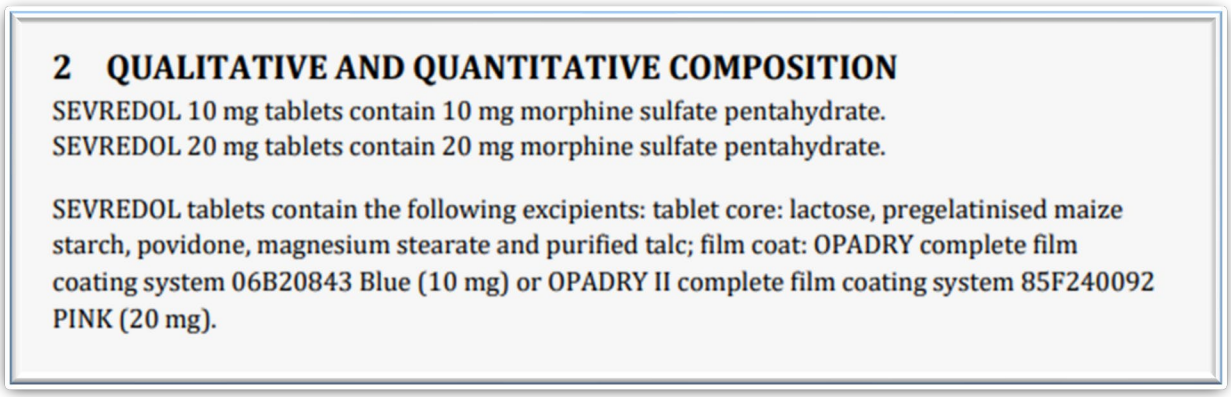


Figure 34: SmPC extract for Campto - UK

Here, the BoSS is irinotecan hydrochloride trihydrate, even though the strength of the unmodified substance is stated. In the Posology section of the SmPC, the dose quantity calculation is stated in terms of the irinotecan hydrochloride trihydrate and must be calculated on a per square metre of body surface area.

However, not all cultures describe a solvated substance in its full granularity, even when it is the basis of strength substance, which is a particular issue for interoperability. The following example shows a morphine product with the same brand name from the same global pharmaceutical organisation (albeit registered with different names in the different countries) as authorised in two different countries (both English speaking to make the comparison easier). The headline label strength is the same in both, but the quantitative composition is clearly different, with the first showing that the BoSS is „morphine sulfate pentahydrate“ but the second showing only „morphine sulfate“.

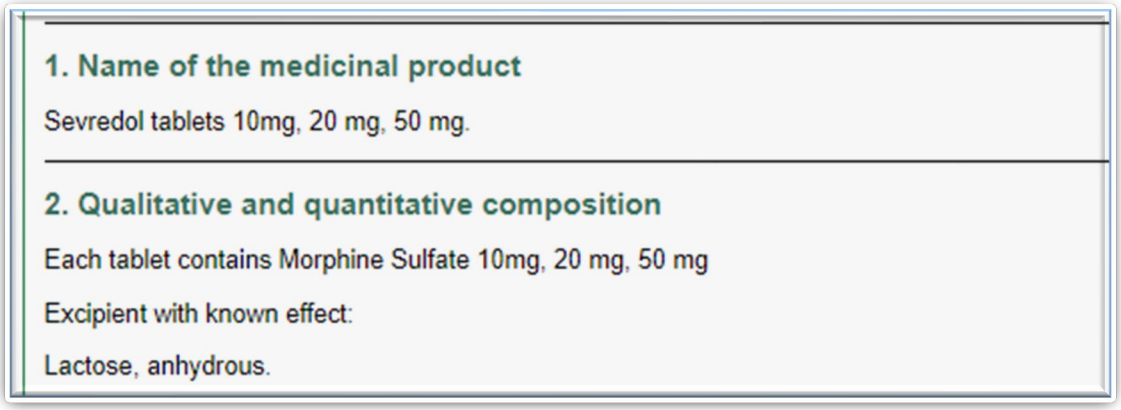


2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SEVREDOL 10 mg tablets contain 10 mg morphine sulfate pentahydrate.
SEVREDOL 20 mg tablets contain 20 mg morphine sulfate pentahydrate.

SEVREDOL tablets contain the following excipients: tablet core: lactose, pregelatinised maize starch, povidone, magnesium stearate and purified talc; film coat: OPADRY complete film coating system 06B20843 Blue (10 mg) or OPADRY II complete film coating system 85F240092 PINK (20 mg).

Figure 35: SmPC extract for Sevredol - AUS



1. Name of the medicinal product

Sevredol tablets 10mg, 20 mg, 50 mg.

2. Qualitative and quantitative composition

Each tablet contains Morphine Sulfate 10mg, 20 mg, 50 mg

Excipient with known effect:

Lactose, anhydrous.

Figure 36: SmPC extract for Sevredol - UK

Given this „authorised“ information about the BoSS, MPDs in the two countries will describe the products differently, making processable interoperability very difficult or impossible:

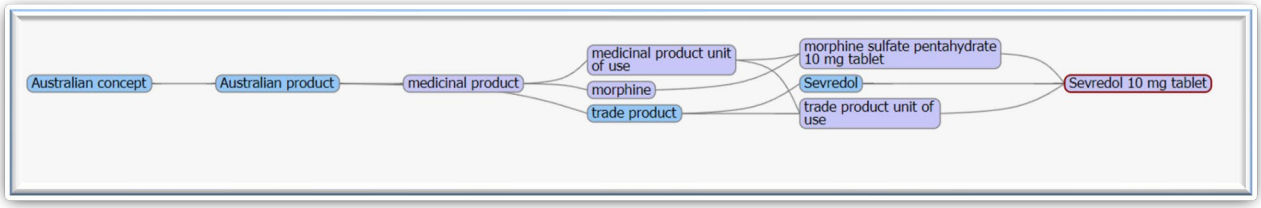


Figure 37: AMT (Shrimp browser) showing Sevredol with morphine sulfate pentahydrate as BoSS

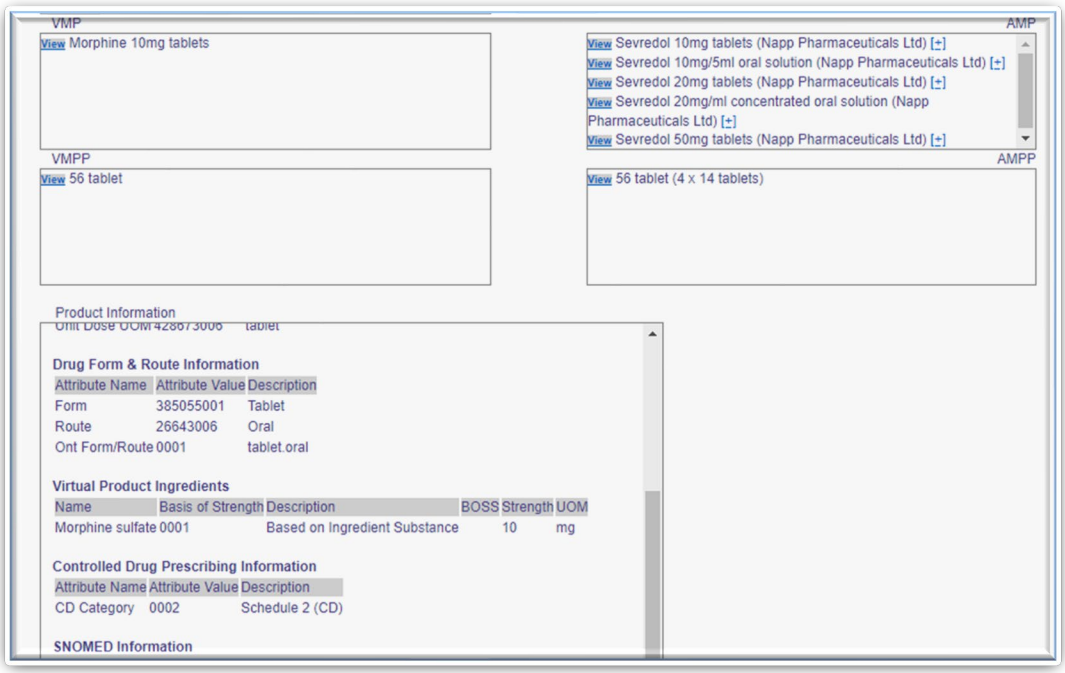


Figure 38: NHS dm+d showing Sevredol with morphine sulfate as BoSS

8.2.1.5. Alternative strength Units

Medicinal products may have alternative units as well as alternative substances with which to describe strength – these are usually either mass units (grams, milligrams, micrograms etc.) or international units. International units (IU) are a unit used to describe the biological activity of a variety of biologically active medicinal substances, particularly vitamins, hormones, some vaccines and blood products.

There is no equivalence between international units measurements of different biological substances. For instance, one international unit of vitamin E (tocopherol in its various forms) cannot be equated with one international unit of vitamin A (retinoid acid and its forms) in any way, by mass or by biologic activity or therapeutic efficacy. Although produced by the WHO Expert Committee on Biological Standardization, international units are NOT part of the International System of Units (also known as the SI units, Système international d'unités).

MPD may offer both types of strength units when describing medicines (for example: epoetin alfa 3,000 IU (25.2 micrograms) per 0.3mL in a pre-filled syringe) or they may offer just one strength unit (for example: benzylpenicillin sodium 1200 mg per vial powder for solution for injection OR benzylpenicillin benzathine 1.2 million IU per vial powder for suspension for injection). When calculating dose quantity, either for direct administration or for dose range checking, an MPD may need to undertake a conversion between different units, and therefore will need to have the conversion factor information; for example: 600mg of benzylpenicillin is equivalent to 1 million IU.

8.2.1.6. Substance Relationships

The above sections describe the roles that substances play within medicinal products and expects that the substances that play those roles will be described in the appropriate granularity, based on the implementation of ISO 11238. However, the relationships between substances themselves, regardless of any role that they play is important for MPD.

As described in chapter 7, medicinal products are often grouped together as abstract objects, particularly to support prescribing and reimbursement use cases.

In some groupings, the exact precise active ingredient substance is considered important, in others only the basis of strength substance is important (for example, the higher level product abstractions in the „mirror image“ model). Pharmacoepidemiology and clinical research generally operates at this higher level of abstraction of medication objects, so for example the fifth level of the ATC code is usually

equivalent to this. Detailing the type of relationships between the substances in their roles at the lower levels of abstraction more closely matched to actual products, is key to managing the relationships between the medication objects themselves. For example, if products have different precise active ingredient substances but the same basis of strength substance, it is likely that they reliably be grouped together.

In the provision of clinical decision support, clinical information may be managed at the level of an unmodified substance or may be altered by substance modification. Using relationships between substances associated by modification of a clinically relevant moiety can reduce the maintenance burden of clinical decision support and increase the consistency and accuracy of the alerts provided to clinicians.

8.2.2 Dose Form

„Dose form“ is most explicitly described in the ISO 11239 document from the IDMP suite of standards; this defines several different types of dose form, some of which are highlighted here:

- Administrable dose form – a pharmaceutical dose form for administration to the patient, after any necessary transformation of the manufactured dose form has been carried out
  - Example: solution for injection
  - Note: An administrable dose form is identical to the manufactured dose form in cases where no transformation the manufactured item is necessary (for example, a rectal suppository is both a manufactured dose form and an administered dose form)
- Combined pharmaceutical dose form – a single term to describe two or more (dose forms that correspond to two or more) manufactured items that are intended to be combined in a specific way to produce a single pharmaceutical product; it includes the information on the manufactured dose form of each manufactured item and the administration dose form of the pharmaceutical product
  - Example: powder and solvent for solution for injection
- Manufactured dose form – a pharmaceutical dose form of a manufactured item as manufactured and, where applicable, before transformation into the pharmaceutical product
- Pharmaceutical dose form – the physical manifestation of a product that contains the active ingredient substance(s) and/or inactive ingredient substance(s) that are intended to be delivered to the patient

Therefore, the dose form is the thing that formulates or encapsulates the active and inactive ingredient substance(s) that compose the product (i.e. that are its „composition“). Dose form is a pharmaceutical concept; it is concerned with how medicinal substances are presented to the patient such that they can have their therapeutic effect as safely as possible.

In addition to the dose form concepts described above from the ISO 11239 document, the EDQM Standard Terms overall dose form terminology has two additional classes of dose form concepts:

- Combined term – a single term used to describe a pharmaceutical dose form (or combined pharmaceutical dose form) and an item of packaging, either for the purpose of distinguishing between marketed products that differ only in the container or administration device, or where the item of packaging has special characteristics that are relevant to the use of the medicinal product
  - Example: solution for injection in pre-filled syringe
- Combination pack – a single term used to describe (the dose forms of) two of more medicinal products packaged together and marketed under a single licence, which are intended to be administered independently as separate pharmaceutical products
  - Example: cream + pessary

The different types of dose forms can be related together as shown in the following model diagram, with the red rings showing those types of dose forms that can be used (in Europe) to describe the „authorised dose form“ in section 3 of a product in a Summary of Product Characteristics. In addition, it also shows the various characteristics (intended site of administration, administration method etc.), some of which are described in the ISO 11239 document, that can be used to describe pharmaceutical dose forms.

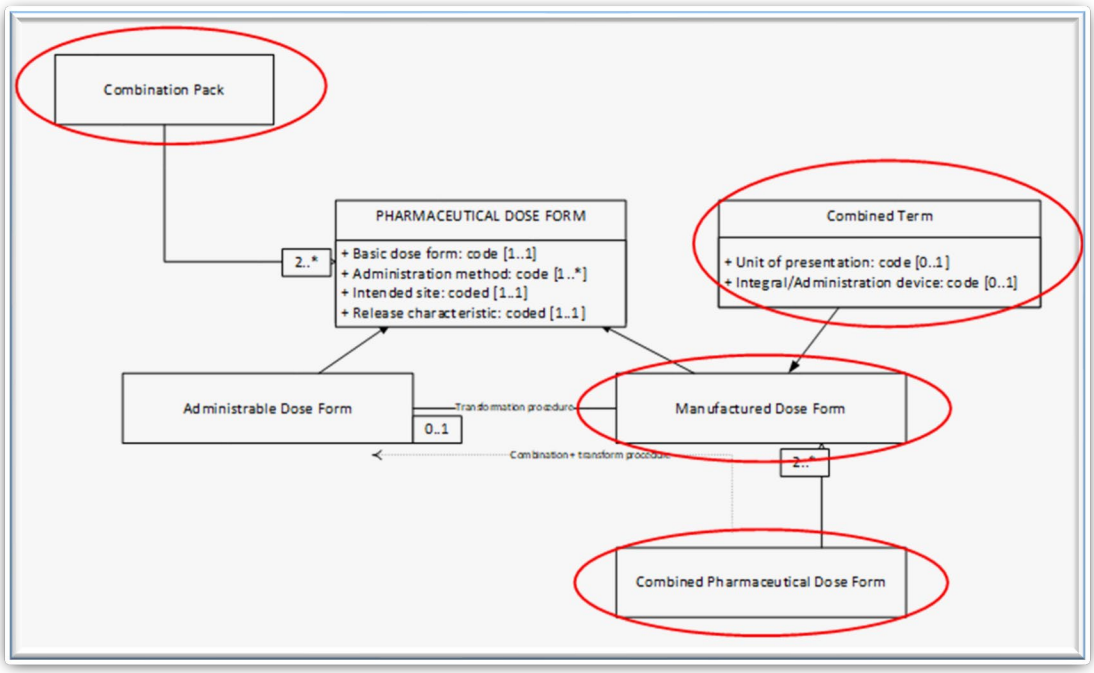


Figure 39: Schematic showing the relationship between dose form types and authorised dose form

For MPD, understanding which type of dose form is being used in which context is important, as is then using the correct type of dose form for each of the medication types of medication concepts that they provide, including the differentiation between the authorised dose form that will be used for authorised products, and the pharmaceutical dose form that is frequently used as the value of the dose form definitional attribute for an abstract medication concept.

Combined terms

Combined term dose form concepts are important for prescribing, especially for parenteral medicinal products that will be used directly by patients in the community. These are frequently presented as pre-filled syringes or pens, often with a large range of strengths of the product being marketed, to reflect the usual range of dose quantities that patients need. The low molecular weight heparins (enoxaparin, dalteparin) and the epoetins are good examples of these types of products. Stating the pharmaceutical dose form (solution for injection) does not provide enough granularity of information to ensure that the patient will receive the exact product that they require – the full combined term (and appropriate description of presentation strength) is required. MPDs therefore need to be able to describe actual medicinal products using combined terms, and, if their healthcare culture requires it, also have abstract representations of these (i.e. based on composition rather than brand name). Similarly, for interoperability, combined terms will convey valuable information about the medication that the pharmaceutical dose form on its own does not provide.

Combination packs

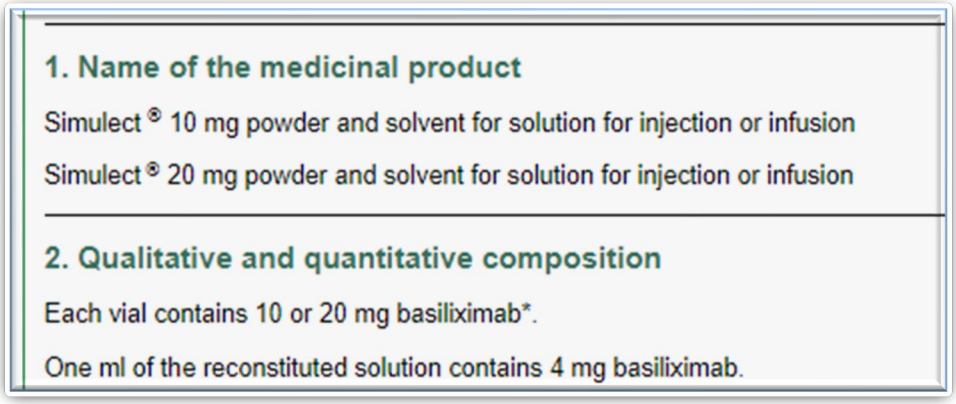
Combination packs are usually authorised for those things that are routinely and usefully administered together, and as such are a convenience for patients in primary care and are less commonly used in secondary care. Primary care prescribers will therefore need to be provided with combination pack information by their MPD, but safety checking (for those MPD or associated software that provides this) is likely to be actioned against the individual items, so the ability to decompose the combination into its component parts is useful.

Combined pharmaceutical dose forms

A combined pharmaceutical dose form will be used when, in order to obtain the administrable product, at least one additional item is needed – for example, a specific diluent/solvent is needed to transform

the product from its manufactured/supplied form to its administrable form. The rules and practice of the healthcare culture will dictate whether it is essential that a combined pharmaceutical dose form is required for prescribing and/or dispensing, and this will affect how any local MPD will use this type of dose form; for example, reimbursement requirements may require full description of all the items necessary for the administration and as such the combined pharmaceutical dose form term may be required.

Combined pharmaceutical dose form terms can be useful to MPD because they indicate products that will undergo a transformation so that the product that is administered should be described differently from the product that is supplied – both in terms of the dose form, but also in terms of the strength. For example,


1. Name of the medicinal product

Simulect ® 10 mg powder and solvent for solution for injection or infusion

Simulect ® 20 mg powder and solvent for solution for injection or infusion

2. Qualitative and quantitative composition

Each vial contains 10 or 20 mg basiliximab*.

One ml of the reconstituted solution contains 4 mg basiliximab.

Figure 40:SmPC extract for Simulect powder and solvent for solution for injection or infusion - UK

The manufactured/supplied product is „basiliximab 10mg/vial powder and solvent for solution for injection“, but, if reconstituted according to the instructions, the administrable (pharmaceutical) product is „„basiliximab 10mg/2.5mL (4mg/mL) solution for injection“. MPD may use this information when supporting administration processes, alerting the administering staff that manipulation/transformation will be required prior to administration. Additionally, MPD may offer one or more objects representing the reconstituted product to support prescribing, since this represents the product *as it can be administered to the patient* and therefore is a clinically relevant description, especially for secondary care.

Pharmaceutical dose form

This is the most familiar, and in a sense most useful of the types of dose form for MPD. It is the pharmaceutical dose form which is used most commonly as the dose form definitional attribute in the abstractions of medicinal products discussed in the models in Chapter 7. By using the schema shown above, if a product has an authorised dose form of a combination pack, a combined term or a combined pharmaceutical dose form, it is possible to use the associations to find the relevant pharmaceutical dose form for each item.

The pharmaceutical dose form is the dose form type that is usually used in the abstract class that includes „dose form“, as it describes the thing that clinicians and patients recognise. For example, a tablet and a capsule are generally well understood concepts, even if articulation of their pharmaceutical differences – such as tablets being distinguished by powder compression into a die-mould – are not necessarily comprehended. An eye drop is clearly distinguishable from a suppository, a cutaneous cream from a solution for injection.

Manufactured and Administrable dose forms

Both manufactured dose forms and administrable dose forms are types 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 in the abstract class that includes dose form, 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 is because it is difficult, even if a specific solvent is supplied, to be sure of the volume used to transform the powder into a solution for administration such that a liquid concentration strength (or indeed presentation strength) could be safely provided. Some MPD may also offer an abstract representation of the administrable product, but this is less common.

There are dose forms that require two transformations prior to administration (the concentrate dose forms, for example: „powder for concentrate and solution for solution for infusion“ where the *powder* is intended to be reconstituted with a specified liquid to obtain a *concentrate* for solution for infusion, which in turn is intended to be diluted with a specified liquid to form a *solution for infusion)*. The final administrable dose form is (probably) „solution for infusion“; most MPD will not describe the intermediate dose form, but it is important to know about it for compounding use cases in secondary care.

The exception to this is 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 in the pharmacy 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, as 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 abstract representation of the medicinal product will therefore use the administrable dose form and the strength description that matches this rather than the manufactured dose form.

„Equivalence“ of dose forms

Since dose form is one of the definitional attributes used to describe the abstract classes of medicinal product objects in the main MPD models from section 7 (linear or mirror image); therefore the boundary between what is and what is not „a different dose form“ defines what is or what is not an equivalent and therefore interchangeable medicinal product. Equivalence and interchangeability are themselves qualitative concepts that depend on their use case; this document focuses on MPD and patient care whereas other deliverables in UNICOM look at other use cases – for example D8.7 and pharmacovigilance.

In supporting patient care, MPD are primarily looking at clinical equivalence – in which case in some healthcare cultures, a conventional release oral tablet may indeed be considered interchangeable with a conventional release oral capsule with the same composition – and – for example, a single indicative price for reimbursement might be set for that group of products. It is therefore the responsibility of each MPD to use dose form information in the way that best meets their own requirements. Some may even define wider hybrid groups, such as a 250mg tablet and a 250mg/5mL oral solution in the same group. Understanding this and differentiations that will be made, including why use of the existing pharmaceutical dose forms is not the complete solution, can contribute to the overall understanding of what should be done to support cross cultural communication of medication information, whether that be for provision of emergency care for individual patients or for amalgamation of information for the wider benefit of the population through clinical research and analysis.

8.2.3 Unit of Presentation

In ISO 11239, unit of presentation is defined as „a qualitative term to describe the discrete countable entity in which a pharmaceutical product or manufactured item is presented, in cases where the strength or quantity is expressed [by] referring to one instance of this countable entity“.

The unit of presentation is possibly the newest addition as a definitional attribute of the models of MPD, and as described in Chapter 7, is most clearly present in the „mirror image“ model. The recognition of the importance of unit of presentation is partly due to the changing nature of the presentation of medicinal products, with more parenteral products presented units such as in pre-filled syringes or pens for self administration so as to allow patients to be cared for in their own homes rather than in hospital. But the concept of unit of presentation has always been implicitly present in MPD, since the strength of a medicinal product must be a ratio concept, and for many types of medicinal product, the denominator part of the strength ratio is „the unit of presentation“.

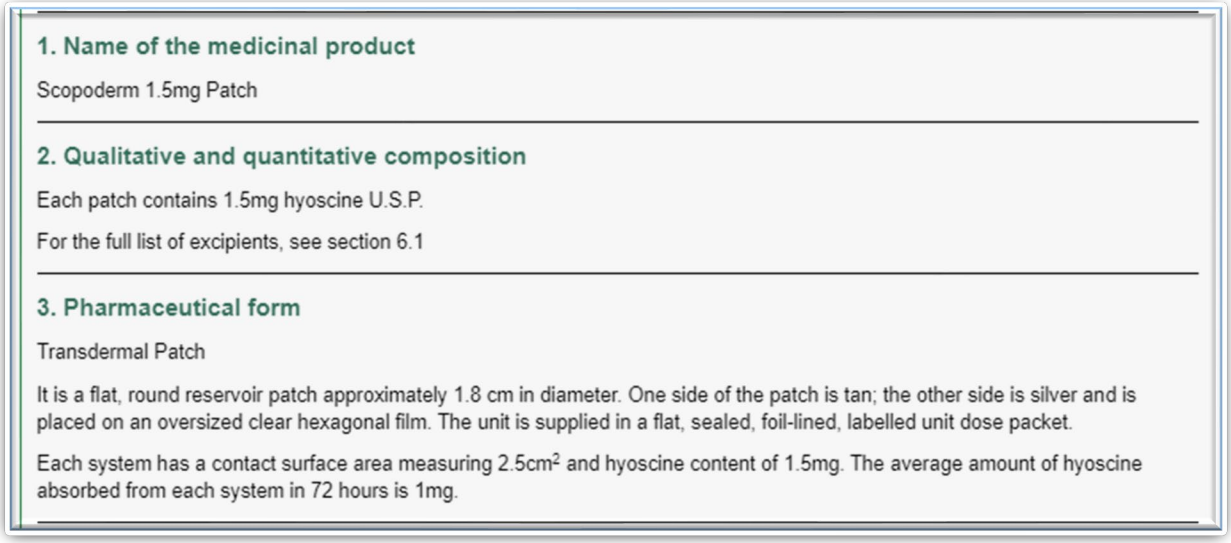
For solid unit dose forms including those that are encapsulated such as capsules and sachets, the unit of presentation usually corresponds to the basic dose form and results in an expression of strength that is a „presentation strength“. For example, the strength of a nifedipine product is expressed as „10mg“ and the 10mg is actually „10mg per unit of presentation“ where the unit of presentation is a „tablet“ – but the pharmaceutical dose form could be a conventional release oral tablet or a prolonged release oral tablet. Then, for the package objects, which many MPD also describe (see Chapter 7) the number of units of presentation per package can be given (often called the pack size).,

For any presentation where the delivery of the product is via a metered dose valve, such as an inhaler, the strength is usually stated as „per actuation“ (of the metered dose valve) and it is this actuation that is the unit of presentation. The dose form may be a solid (a powder spray for example) or a liquid and is often aerosolised as it is administered. As for the solid unit dose forms, the package object describes the number of units of presentation per package (for example, 200 actuations per inhaler).

Continuous presentations, such as the semi-solids like cutaneous creams do not have a unit of presentation unless they are presented with an integral metering device, and as such they will be described using a concentration strength with the denominator unit being an SI unit of weight or volume. The challenge with these presentations for MPD is to find the boundary between the abstract representation of the continuous *product* compared to the package, since the only thing that can be supplied is a package of product (for example, a 30g tube of cream).

Liquid presentations can be particularly challenging to MPD. Oral liquids have the drops/continuous dose form conundrum discussed above, with the attendant challenges to description of strength. Those with a strength given as „per 5 mL“ imply that the unit of presentation is a 5mL medicine spoon, but that is not a standardised unit of presentation, it is normally considered an administration device. Yet to give all oral liquids a concentration (per 1mL) strength description is clinically unhelpful as clinicians expect to see a strength represented in the way that is most appropriate for the dosage schedule, and it ceases to offer any differentiation between those products that are designed for administration by the drops/small volume method from those administered in larger volumes with the spoon. As with the semi-solids, for any oral liquid presentation, unless it is encapsulated in a sachet, the MPD also has to select a boundary for representation of the product and its package – the bottle or similar that it will be supplied in. 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).

„Patch“ products – usually those delivering their active ingredient substance(s) transdermally – have a unit of presentation of „one patch“. Although some products do describe the product strength using a „per patch“, this is not clinically useful, as it is the rate, the amount per hour or the amount per 24 hours that is clinically useful for the strength of the product. Almost all products have now changed to the QRD[24] recommendation of „nominal amount released per unit time“.



1. Name of the medicinal product

Scopoderm 1.5mg Patch

2. Qualitative and quantitative composition

Each patch contains 1.5mg hyoscine U.S.P.

For the full list of excipients, see section 6.1

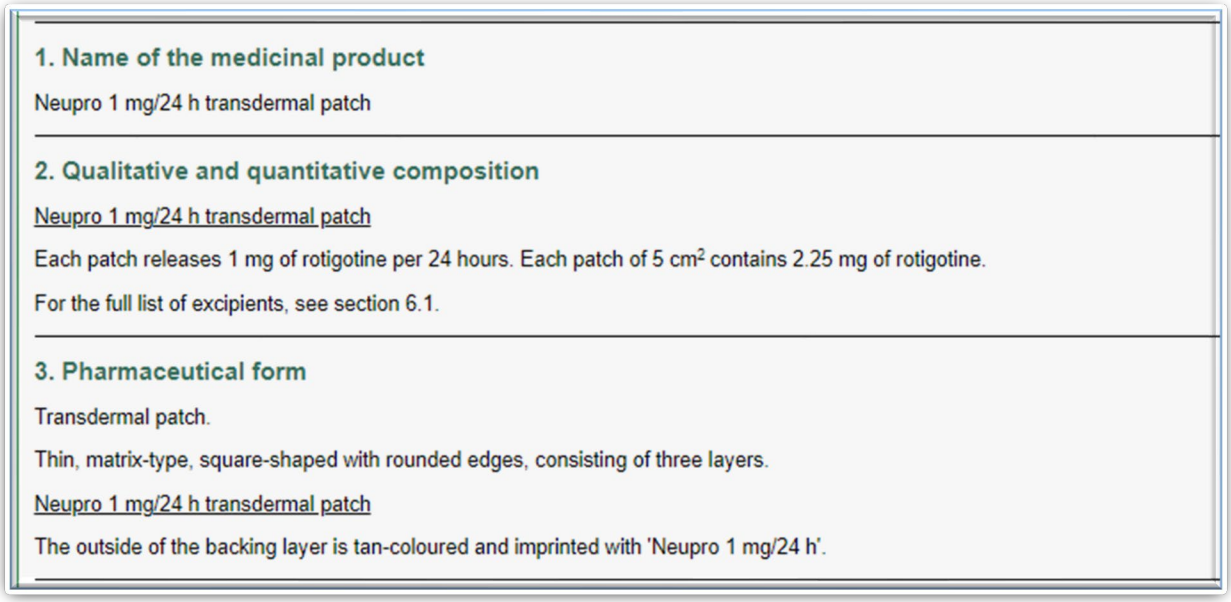
3. Pharmaceutical form

Transdermal Patch

It is a flat, round reservoir patch approximately 1.8 cm in diameter. One side of the patch is tan; the other side is silver and is placed on an oversized clear hexagonal film. The unit is supplied in a flat, sealed, foil-lined, labelled unit dose packet.

Each system has a contact surface area measuring 2.5cm^2 and hyoscine content of 1.5mg. The average amount of hyoscine absorbed from each system in 72 hours is 1mg.

Figure 41:SmPC extract for Scopoderm transdermal patch - UK



1. Name of the medicinal product

Neupro 1 mg/24 h transdermal patch

2. Qualitative and quantitative composition

Neupro 1 mg/24 h transdermal patch

Each patch releases 1 mg of rotigotine per 24 hours. Each patch of 5 cm^2 contains 2.25 mg of rotigotine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Transdermal patch.

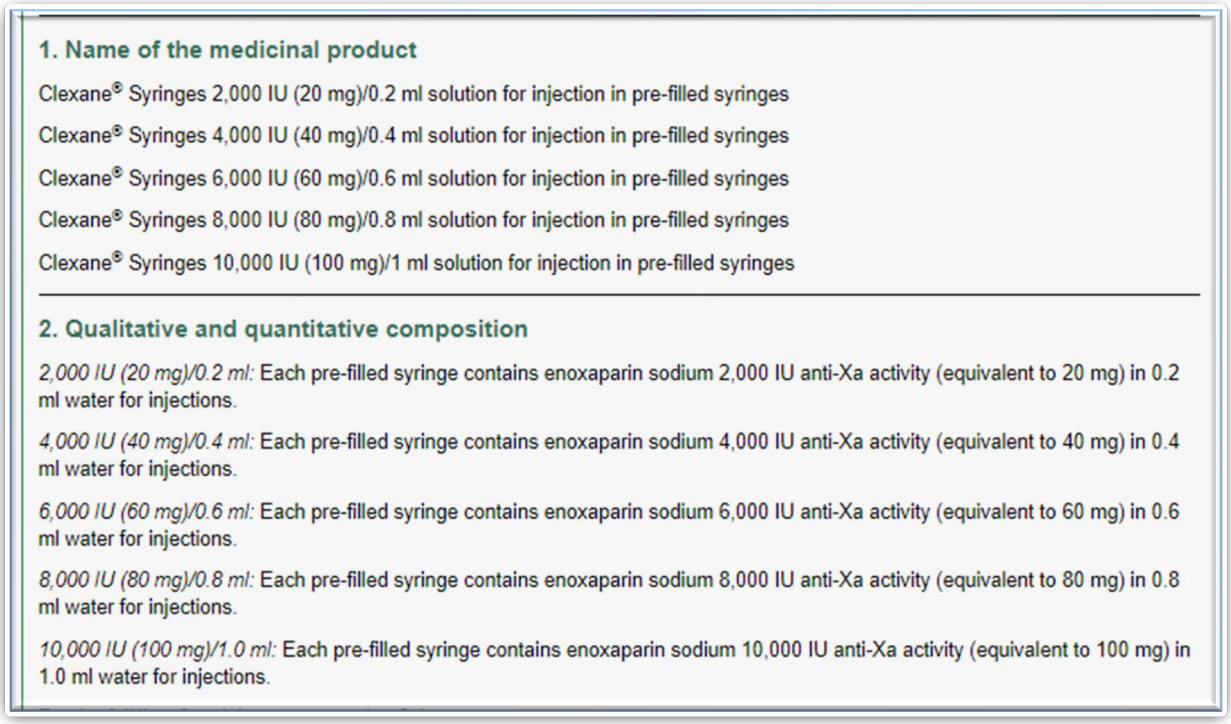
Thin, matrix-type, square-shaped with rounded edges, consisting of three layers.

Neupro 1 mg/24 h transdermal patch

The outside of the backing layer is tan-coloured and imprinted with 'Neupro 1 mg/24 h'.

Figure 42: SmPC extract for Neupro transdermal patch - UK

Parenteral liquids offer yet more challenges. Large volumes (such as infusion fluids) and products needing complex and varying dose calculation (such as the insulins) are usually described using a concentration strength yet the unit of presentation is still important (bag, bottle, vial, cartridge) especially for insulins where the administration device (such as a pen) requires a particular unit of presentation to fit into it. Products where the dose quantity requires all or a large proportion of the volume to be administered are usually described using presentation strength, and indeed this is part of the safety guidance, for example, the EMA states: "It may be necessary in some cases to express the strength as quantity per unit volume and also as the total quantity per total volume. **Reference to the total quantity per total volume should be highlighted**. This is particularly important for injectable products and other medicines available in solution or suspension."[25] MPD therefore need to have individual objects to represent each of the presentation strengths of a product, and each of the different units of presentation (if, for example, the product is present in a 2mL vial and a 2mL ampoule) even though they have the same concentration strength – so the same liquid product inside – as in the enoxaparin product shown below:



1. Name of the medicinal product

Clexane® Syringes 2,000 IU (20 mg)/0.2 ml solution for injection in pre-filled syringes

Clexane® Syringes 4,000 IU (40 mg)/0.4 ml solution for injection in pre-filled syringes

Clexane® Syringes 6,000 IU (60 mg)/0.6 ml solution for injection in pre-filled syringes

Clexane® Syringes 8,000 IU (80 mg)/0.8 ml solution for injection in pre-filled syringes

Clexane® Syringes 10,000 IU (100 mg)/1 ml solution for injection in pre-filled syringes

2. Qualitative and quantitative composition

2,000 IU (20 mg)/0.2 ml: Each pre-filled syringe contains enoxaparin sodium 2,000 IU anti-Xa activity (equivalent to 20 mg) in 0.2 ml water for injections.

4,000 IU (40 mg)/0.4 ml: Each pre-filled syringe contains enoxaparin sodium 4,000 IU anti-Xa activity (equivalent to 40 mg) in 0.4 ml water for injections.

6,000 IU (60 mg)/0.6 ml: Each pre-filled syringe contains enoxaparin sodium 6,000 IU anti-Xa activity (equivalent to 60 mg) in 0.6 ml water for injections.

8,000 IU (80 mg)/0.8 ml: Each pre-filled syringe contains enoxaparin sodium 8,000 IU anti-Xa activity (equivalent to 80 mg) in 0.8 ml water for injections.

10,000 IU (100 mg)/1.0 ml: Each pre-filled syringe contains enoxaparin sodium 10,000 IU anti-Xa activity (equivalent to 100 mg) in 1.0 ml water for injections.

Figure 43:SmPC Extract for Clexane syringes - UK

These individual pre-filled syringe objects are needed for prescribing, so that the exact presentation containing the correct dose quantity can be specified for the patient; they are also needed for correct dispensing and indeed for reimbursement, since the different objects will have different prices. Although recording in a patient record can be done using concentration strength and a dose quantity, particularly when a patient is familiar with using a particular presentation, knowing what that presentation is can be helpful. However, clinical information such as the indications and contraindications are associated with the concentration strength representation – as indicated by all of these presentations being stated in a single Summary of Product Characteristics with its single sections for contraindications and undesirable effects etc.

For parenteral liquids where the unit of presentation is used in the abstract representation of the *product object* in an MPD, the related „packages“ are described in terms of the number of units of presentation provided in the package (for example, 10 vials or 5 syringes in a box). Given this example, it is important to emphasise that the unit of presentation should not be confused with the package of a product, but since the unit of presentation is the „countable unit“, the unit of presentation is often used as *the unit for the pack size quantity;* for example, for a package or „28 tablets“ the pack size quantity value is „28“ and the pack size unit is „tablet“ – which is the unit of presentation.

Note on single and multiple use products: the unit of presentation per se gives no sense as to whether a preparation is for single use or multiple use (whether it contains a single dose quantity or contains enough for two or more doses). The EMA has specified different patterns[26] for strength representation for products that contain a single dose and those that contain multiple doses which utilise the unit of presentation, but that is not to imply that the unit of presentation *itself* signifies this. For example, for single dose quantity nebuliser liquids (solution/suspension/emulsion) the strength should be the presentation strength, so the total amount per unit of presentation – 2.5mg per 1 unit dose vial, where the size of the unit dose vial is 2.5mL, whereas for a multi-dose nebuliser liquid, a concentration strength (amount per unit volume) would be given – 1mg/1mL.

9 Analysis: What IDMP will provide

One of the biggest challenges in undertaking this analysis is achieving clarity at the necessary level of detail for exactly 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 October 2021. The implementation of ISO 11615 discussed here is that put forward by the EMA using the Fast Health Interoperability Resources (FHIR); the possible implementation described by ISO TS 20443, using the HL7 V3 Structured Product Label (SPL) has not been analysed as this appears to not to be relevant and has not been used outside of North America.

9.1 Scope

9.1.1 Authorised medicinal products

The scope of the IDMP standards themselves and the medicinal products that they cover are those that are **authorised for marketing in any jurisdiction**; whether all the products or packages described for those products are actually placed into the supply chain is a different consideration. ISO 11615 does separate the marketing authorisation from the actual marketing activity, but it is clear from discussions to date that NCAs are not always aware of the marketing activity, and if they are, it is often retrospective rather than prospective. There can therefore be a significant amount of information available about products or packages that never have or never will be available for patient care. Devices in scope are only those that are present *within a medicinal product* (such as an oral dropper device, or a prefilled syringe device). In the second part of the standards, there is support for description of those products that are licensed for investigative trials whereby data on safety and efficacy is collected to support the application for an authorisation to market a product. However, whilst the standards can be applied to „all authorised medicinal products“, the *implementation* of the standards with regard to scope is a separate consideration and is being undertaken in different ways by different organisations. The EMA has its SPOR (**S**ubstance, **P**roduct, **O**rganisation and **R**eferentials) system, which is concentrating on centrally authorised products for information supplied directly from authorisation holders in the first instance. National medicines authorities will have their own implementation considerations, both for their own data and for data that they should supply to the EMA.

It is also not currently clear whether IDMP implementation (for example through SPOR) will provide any historical information about previously authorised but no longer marketed medicines. The requirement for MPD to support these is clear, both for medication summaries and profiles and for all secondary uses. Although addressed directly and separately within the UNICOM project, the pharmacovigilance use case clearly needs identification of and information about products that were authorised in the past and indeed that there will be some mechanism whereby IDMP identifiers could be assigned to such products. It would be useful to have more detail of such a mechanism.

The scope of IDMP is generally somewhat smaller than that required by MPD in terms of the products covered, but MPD have always had to source data for unauthorised products, just as they do for products and services beyond medicinal products, so that does not change. One significant benefit to MPD and patient care may be if information on products authorised in other jurisdictions becomes *reliably available and useable* by MPD. As described in section 8.1 above, many MPD, especially in smaller countries, have to describe a significant number of medicinal products that are authorised elsewhere but not in their own country; so if structured information on this type of product became available for their use it would increase the quality and reliability of the data considerably.

9.1.2 Abstract concepts

Within the regulatory domain, for the process of authorisation, there is no requirement for any abstract representation of the medicinal product, such as are seen in the models of MPDs described in section 7 of this document. However for pharmacovigilance including regulatory pharmacovigilance, which was the initial use case for the development of IDMP, there *is* a requirement to be able to group products together using a small set of definitional information either on their own or in combination: the therapeutically active substance(s) and strength and the administrable (not the manufactured) dose form. These abstract grouping concepts are seen in IDMP by the „PhPIDs“ described in ISO 11616 and also represented by the Pharmaceutical Product class in ISO 11615. Detailed discussion of the use of

the Pharmaceutical Product and its identifiers in pharmacovigilance is given in UNICOM D8.7 IDMP Coding Principles and Guidance for ICSRs.

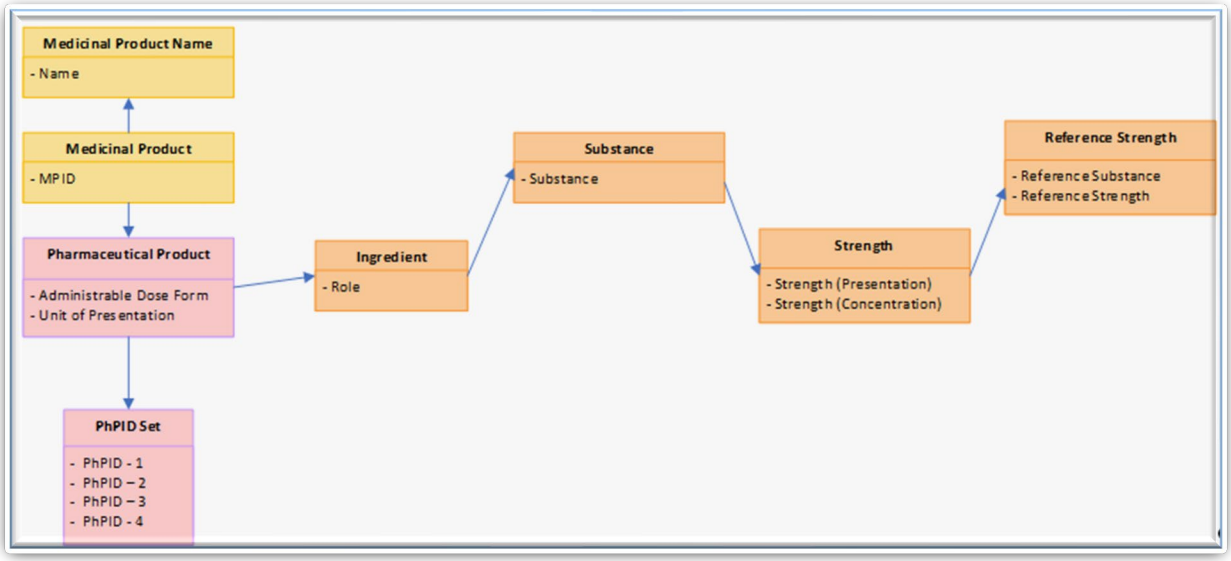


Figure 44: Schematic for Pharmaceutical product and PhPID set relationship

There is some considerable uncertainty as to how the Pharmaceutical Product class will be populated in IDMP implementation, and if by having a Pharmaceutical Product for each Medicinal Product, the Pharmaceutical Product is not actually being managed as either an abstract concept or as a grouping concept; it is a representation of a single medicinal product in its administrable state. This is compounded by uncertainty as to whether or not excipients will be described for the Pharmaceutical Product. If the set PhPIDs are seen as an abstract grouping based on information ***extracted from the Pharmaceutical Product***, then indeed each medicinal product can be related to an abstract set of classes - „the PhPIDs". However, in order for this to be successful, the rules and patterns for how information is placed into these structures must be well documented and well implemented, otherwise the abstractions will not group effectively. In the discussion, some examples of the challenges of those patterns are described in more detail.

Focusing on the PhPIDs as described in ISO 11616, and for substance only (this deliverable has not investigated specified substance at all since there is little known about if/how that will be implemented at this stage), there is the following:

Table 3: PhPID Levels and their definitional attributes

Level	Definitional attribute	Comments/Questions
PhPID 1	(Active) substance(s)	Is this the PAI (?) At what level of granularity? How should this be managed if different manufacturers declare different levels of specificity of a substance?
PhPID 2	(Active) substance(s) + strength + reference strength	Is the strength of the PAI useful? Or will the PhPID2 use only the BoSS and its associated strength? Is a representation of the administrable product strength useful

		for products other than pre-reconsistuted oral antibiotic liquids? Is it possible or even safe to assume a reconstitution volume for transformed products, especially those taken orally „dissolved in a glass of water“?
PhPID 3	(Active) substance(s) + Administrable dose form	Is a representation using administrable dose form (only) useful for products other than pre-reconstituted oral antibiotic liquids?
PhPID 4	(Active) substance(s) + strength + reference strength + Administrable dose form	All the above questions come together here

PhPID 4 and its definitional attributes may appear very similar in nature to the definitional attributes used in the abstract class of medicinal product representation used in MPD. However, as described in section 8, the population of those definitional attributes is well understood and managed by the individual MPD and the various interoperability initiatives that have been undertaken over the years have increased the understanding of these attributes *between* the different MPDs. The different levels of abstraction that different MPD provide also has reasonably good shared understanding. This is in contrast to the implementation guidance for the PhPIDs which is significantly lacking, not least because the business use case(s) that must be supported are less than clear. This means that the levels of abstraction are themselves difficult to clearly understand yet are very „fixed“, with little if any room (as currently described) for flexibility.

9.2 Substance and strength: Composition

The composition of a medicinal product is described in two different places in IDMP ISO 11615

- In the Manufactured Item, where all ingredient substances of whatever role (active, excipient) should be described, with their quantitative composition (strength)
- In the Pharmaceutical Product, where, although not explicitly stated in ISO 11615, but implied by the relationship of the Pharmaceutical Product to the PhPIDs, the focus is on the *active* ingredient substance(s) only
    - However, the EMA implementation guidance (5.1.3) implies that all ingredient roles should be populated for the Pharmaceutical Product and whilst this does not negate the role of the PhPIDs as grouper concepts, it does make it a little more challenging

9.2.1 Substance Relationships

Substances themselves are to be described according to ISO 11238 and its implementation in TS 19833. Both of these focus on the data elements and structures for the unique identification of substances and therefore the provision of unique substance IDs. Neither specification provides very much detail about *the relationship between substances*. There are various types of relationships that are needed:

- Relationships between synonymous terms
    - Common names, as opposed to the systematic (IUPAC) names can be misleading. As noted in 8.2.1.3, unless guidance is given about synonyms both within the substance system itself and in substance description in ISO 11615, it may be difficult for MPD to find certainty as to whether two different „text names“ for substances actually refer to the same thing
- Relationships between substance modifications
    - Relationships between base (unmodified) substances and their salts and/esters
    - Relationships between solvated substances and their anhydrous forms
    - Relationships between substances that are encapsulated (e.g. in nanoparticles such as liposomes) or conjugated with a large polymer (e.g, by pegylation) or oligosaccharide (e.g. cyclodextrin) and their base (unmodified) substances

- Relationships between substances (clinically relevant structural groupings such as „sulfonamide derivatives“)

There is some implicit relationship information in ISO 11238; for example, when describing solvated substances, there is note of how the anhydrous or unsolvated substance is a different substance from any of the solvated substances but there is no sense of how that relationship might be described in any processable way, as it might be in a formal classification or ontology. Nor is there currently any published information about if/how relationships between base (unmodified) substances and their modification might be implemented despite known use cases. It is also not currently clear whether there will be „grouper substances“ that are ontologically different from the base (unmodified) substances; for example „diclofenac“ as a grouper concept that includes diclofenac sodium, diclofenac potassium, diclofenac diethylammonium and unmodified diclofenac base as its children.

As noted in 8.2.1.5, substance relationships are vital for MPD in order to correctly manage abstract classes based on ingredient substances. Other deliverables in UNICOM have detailed the prescribing and pharmacovigilance challenges in this area; as well as these, MPD have to manage substance information to support allergy and intolerance checking, some of which is dependant on the base (unmodified) substance and some on the modifications. Not having a clear sense of what „IDMP will provide“ for substance relationships is therefore somewhat problematic for MPD and their use cases.

9.2.2 Excipient substances

In terms of definitional attributes for abstract medicinal products, MPD focus on the active ingredient substance(s) present, both the precise active ingredient substance and the basis of strength substance and the strength of the latter (or a reference substance). But as described in section 8.2.1.1 above, excipient information, and particularly „Excipients of Concern“[d] are usually managed within MPD as part of the information for the authorised product. To have this information available in a structured format will be very helpful to MPD. It is not yet clear whether the quantitative composition of excipient information will become publicly available, or whether this will be limited to those excipients that are „of concern“. Clearly also, this is most likely to be available for the Manufactured Item(s) and for those things where MPD need to describe the Pharmaceutical Product, some data manipulation will be required.

9.2.3 Substance strength and reference strength

Sections 8.2.1.3 and 8.2.1.4 describe how MPD require precise active ingredient substance and basis of strength substance. Although these terms are not used directly in IDMP or in any of the current implementation guidance, the IDMP implementation *should* be well-placed to provide this information, although it would be reassuring if more detail and examples were given, particularly regarding ingredient roles and if reference strength types were added. For example, currently the ingredient role of „active“ would appear to correspond to „precise ingredient substance“. However, this may not be as „precise“ as precision is usually understood, especially given the challenges of substance synonymy and granularity described above. Guidance currently states the substance should be as in Section 2 of the SmPC, for which further (SmPC) guidance[e] states the „active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant“ – but with no sense of how relevance should be adjudicated. MPD would prefer that the precise active ingredient substance always be stated in its most specific form, with salt or hydrate or both, as it is present, so that there is no room for ambiguity.

The BoSS would benefit from similar disambiguation, especially when this usually relates to the clinically relevant strength. The SmPC guidance for this directs that the BoSS *should* relate to the „active moiety“ in cases where the PAI is a modification; however, this principle has not been uniformly applied over time and care needs to be taken when implementing this for long-standing products; for example, changing the expression of strength of morphine products (as in the example in 8.2.1.4) from morphine sulfate to morphine base would have enormous ramifications across patient care. Indeed, the SmPC guidance accepts and endorses this for „established active substances“ (its example being diltiazem

[d] https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human_en.pdf

[e] https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

hydrochloride). The provision of strength information for a PAI that is not a BoSS is one of the situations where implementation for regulatory requirements can differ from and possibly even diverge from patient care requirements. Regulatory IDMP implementation may require the strength of the PAI to be given if it is taken from sources other than the public SmPC (i.e. the Module 3 of the (e)CTD), whereas patient care does not require this because it is usually clinically irrelevant and unnecessary to share (to avoid confusion). A similar situation exists with overfill and presentation strength; for the regulatory domain this is important information; for patient care it has no importance and indeed could risk being misleading.

For provision of IDMP information to MPD, therefore, it seems most appropriate to implement that the BoSS be explicitly stated, along with the strength as related to the BoSS, then there can be no ambiguity. Currently, the BoSS, if not the PAI, is to be stated as „a reference strength"; this is contrary to how MPD usually understand reference strength, which is as an alternative description for the BoSS and accompanying strength, either in terms of units of measure or in terms of reference substance, or occasionally both.

In the diagram below, for a parenteral dexamethasone product the PAI is dexamethasone sodium phosphate. There is 4.3mg/mL of dexamethasone sodium phosphate present, and sometimes that strength is used clinically; there is 3.3mg/mL of dexamethasone (base) – which for this product as labelled, is the BoSS. But because the „whole number" for dexamethasone products refers to dexamethasone phosphate, the alternative reference strength can be given – 4mg/mL of dexamethasone phosphate – although no dexamethasone phosphate is itself present in the product. It is important to be exact and explicit about which substance any quantitative strength refers to, to ensure accurate dosing. Dexamethasone is used to treat severely ill COVID19 patients in intensive care, where the dose quantity is stated as „6mg per day" [27] meaning explicitly „6mg of dexamethasone (base)"). A misunderstanding here of which strength relates to which substance could lead to something approaching a 10% error in dose quantity calculation which could clearly have significant effects for seriously ill COVID19 patients.

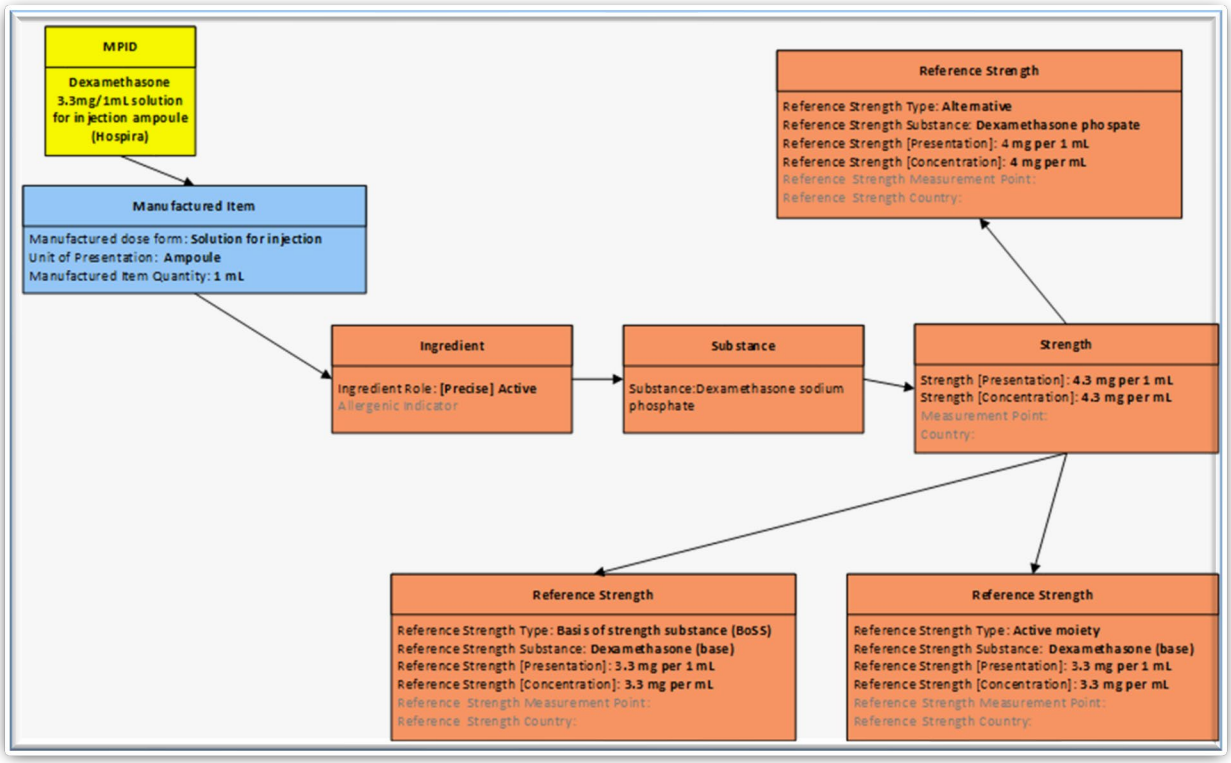


Figure 45:IDMP structure for Composition showing suggested new Reference StrengthType attribute

Introduction of a „Reference Strength Type“ attribute as shown in this diagram could be valuable in helping to make the substance and strength relationship more explicit and therefore safer and clearer to implement, and therefore to provide the most reliable data to MPD.

The reference strength structure can also be used to describe alternative strength units; the BoSS would remain the same but the strength values and units would be different. In order to quickly be able to find this information for dose equivalence calculation, here again a „Reference Strength Type“ attribute would be valuable: maybe „Alternative units“.

9.3 Dose form

IDMP provides dose form information in three places:

- On the **Medicinal Product** – currently in the ISO 11615 standard, the „Combined Dose Form“ to be used when the authorised product contains two or more Manufactured Items, but in the EMA's IDMP Implementation Guidance, this is also the **(Authorised) Dose Form** – the pharmaceutical form as submitted for authorisation and therefore the one present in Section 3 of the SmPC; this can be either a combined pharmaceutical dose form, a combination package, a combined term or a pharmaceutical dose form
- On the **Manufactured Item** – the **Manufactured Dose Form** - which will be of type pharmaceutical dose form but prior to any transformation procedure
- On the **Pharmaceutical Product** – the **Administrable Dose Form** - which will be of type pharmaceutical dose form and which will be after any appropriate transformation procedure

All the concepts that can value these three dose form attributes must be drawn from the EDQM terminology, through the SPOR implementation of it.

Having a very clear structure for where dose form information is available and a known terminology to describe it is extremely valuable for MPD. MPD can take the different types of dose form information provided by IDMP and use them appropriately for their use cases.

However, there are some challenges to using pharmaceutical dose form as the dose form definitional attribute for medicinal product abstraction representations:

Granularity of pharmaceutical dose form description

The granularity of pharmaceutical dose form description is primarily influenced by the set of characteristics – the basic dose form (itself linked to state of matter), the administration method, the administration intended site, the release characteristics and (possibly to a lesser extent, the transformation process). Finding the „Goldilocks granularity“ is challenging, because of the different use cases that must be satisfied. This section describes some of these challenges, and relates directly to the pharmaceutical dose forms as provided by EDQM, since these are the concepts that are used in the implementation of IDMP medicinal product identification in the European context.

„Excessive“ granularity

There are a number of groups of pharmaceutical dose forms where, for patient care MPD, the granularity of dose form description given by the pharmaceutical dose form may be considered excessive, such that it is not *directly* suitable as a definitional attribute for the abstract medication concept needed for the particular healthcare culture and practice. Some of these are discussed below:

The following diagram shows these for two pharmaceutical dose forms, eye drops, solution and eye drops, suspension:

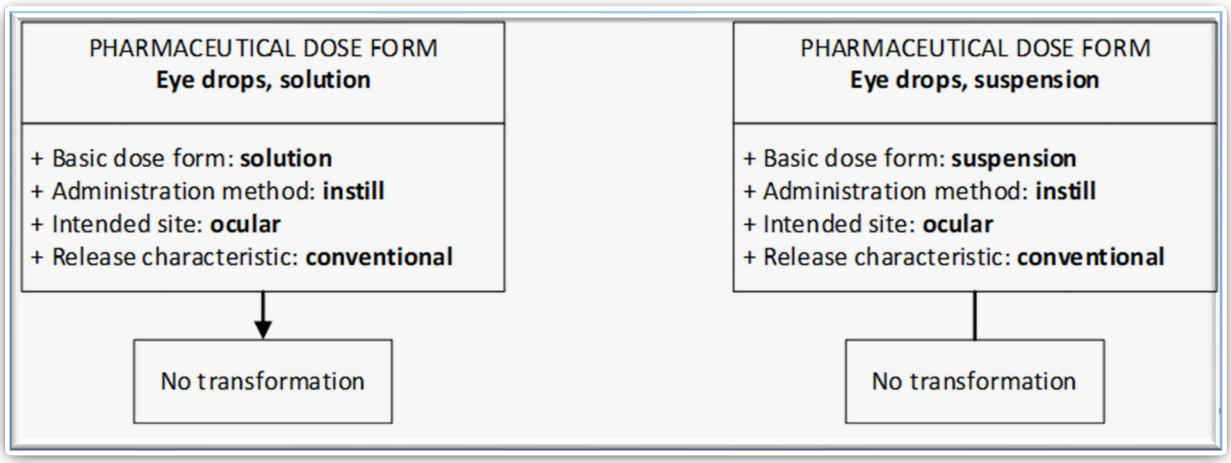


Figure 46:Eye drops, solution and Eye drops, suspension pharmaceutical dose forms

For most clinical use cases, the differentiation between a solution and a suspension for an eye drops preparation is irrelevant – the important choice is for a preparation to be instilled into the eye, as possibly against an eye ointment that will be applied to the eye and eye region. Therefore the granularity of pharmaceutical description is greater than needed by many MPD and some may use only the more general dose form term of „eye drops".

The differentiation, maintained throughout the standard terminology for pharmaceutical dose forms, between „hard" or „soft" capsules is also challenging. Clearly, these **are** different pharmaceutical dose forms, with the former having shell made of two separable parts and the latter being a sealed unit and they must conform to different pharmacopoeial standards. The contents are also likely to be different, with the former containing a dry powder or similar and the latter containing a liquid or semi-solid. However, when viewed in terms of their characteristics, they are „the same".

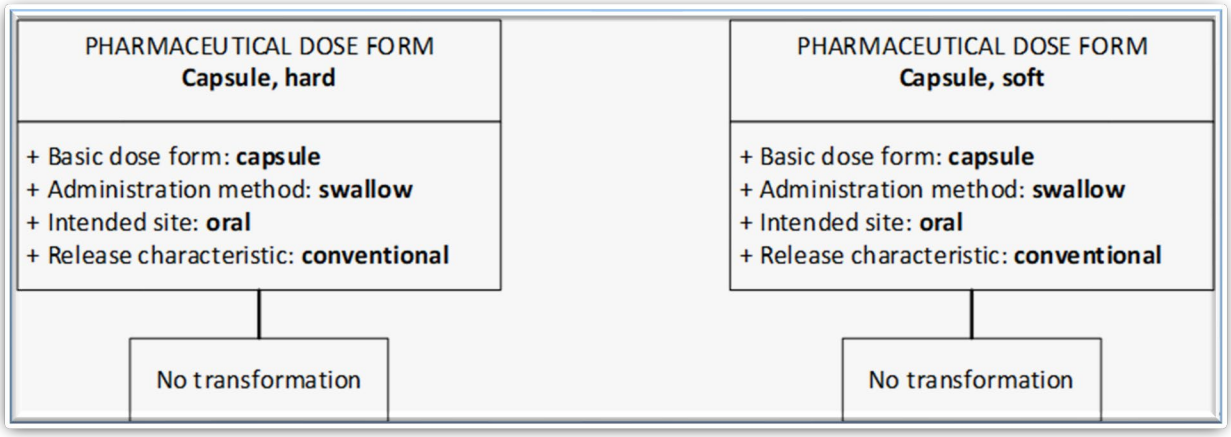


Figure 47:Capsule, hard and Capsule soft pharmaceutical dose forms

Similarly the differentiation between a coated tablet and a film-coated tablet and possibly even a standard uncoated tablet is of little clinical significance; even if the patient may „prefer" a coated tablet as easier to swallow and with less risk of taste issues. But because there is no *clinical* difference in the characteristics of these different dose forms they are often be grouped together by MPD, and particularly for representation of the abstract grouper medication concepts, the definitional dose form attribute may use a more general dose form concept than the pharmaceutical dose form in these situations. This is particularly important for the reimbursement use cases when there is a requirement both to offer choice but also to be clear about cost minimisation.

Note that whilst concepts (in EDQM) such as the „Patient friendly terms" appear to offer these grouping concepts for those use cases where the pharmaceutical dose form is considered excessively granular,

these are not „standard terms“ and nor are there any formal relationships between the pharmaceutical dose forms and the patient friendly terms. Their primary purpose is to offer a term that can be used in space-restricted situations in labelling.

„Sufficient“ granularity

This section describes some of the many groups of pharmaceutical dose forms where, for patient care MPD, the granularity of dose form description given by the pharmaceutical dose form is considered to be sufficient for all use cases, both in regulation and in patient care, including reimbursement.

When describing parenteral products, whether the product is a solution, a suspension or an emulsion may be of critical importance, for example in a critical care situation where the patient must receive a large number of parenteral medications through a limited number of access points, some of which are permanently reserved for medications that must be administered continuously, such as inotropes and sedatives/analgesics. Suspensions and emulsions will be inherently more complex to administer and have increased risk of embolism should something (such as a change in pH due to mixing with another medication) disrupt their stability. So for parenteral products, the granularity of the pharmaceutical dose form, particularly with regard to the basic dose form, is appropriate and is used directly within MPD.

Although description of coated oral pharmaceutical dose forms could be considered excessively granular, the use of „gastro-resistant“, with its associated „delayed“ release characteristic is very useful and of sufficient granularity (without too much detail as to how the gastro-resistance is implemented – external coating, beading etc.) to support the creation of abstract concepts that represent those products with a clearly different clinical profile from those with the conventional release characteristics.

The general differentiation of the semi-solid dose forms, between creams, gels, ointments and foams is also one of sufficient granularity for both patient care and regulation, as is the differentiation between dose forms that offer metered delivery and those that do not (see also below in the Unit of Presentation section).

„Insufficient“ granularity

There are very few cases where the pharmaceutical dose forms do not have enough granularity for patient care MPD. One example concerns prolonged release dose forms. The definition of „prolonged release“ is „release of the [therapeutically active] substance(s) over a longer duration than would be achieved with a conventional-release product [dose form], achieved by a special formulation design and/or manufacturing method“. This is a somewhat qualitative definition, as there is no sense of how much longer a „longer duration“ should be over the conventional release, particularly as there are likely to be pharmacopoeial standards that do give quantitative data on what is considered conventional release for a particular substance. Is „longer“ twice as long or only half as long again? Release prolongation significantly affects dose frequency; there needs to be careful calculation of dosage and product selection when transferring a terminal care patient from a conventional release opiate to a more convenient prolonged release preparation, including consideration of the choice of a 12-hour dose frequency or a 24-hour dose frequency and the products that are appropriate to each. To support this use case, MPD may introduce more granularity to a prolonged release pharmaceutical dose form, understanding that this is not supported by pharmacopoeial standards but that its addition increases the safety of usage of products with these dose forms.

Manufactured and Administrable dose forms

As described in the section above, MPD generally use the manufactured dose form in abstract representations, with the product strength described appropriately for that, with the exception being the oral antibiotic liquids.

This means that for MPD using IDMP information, for the majority of products, the Manufactured Item(s) are the most clinically relevant product descriptions to use, with their attendant dose form and onward description of strength. But for some products, it is the Pharmaceutical Product and its administrable dose form and onward description of strength that is most appropriate, and in certain circumstances some MPD also *separately* represent the reconstituted item with is administrable dose form and liquid strength representation, either as a concentration or as presentation strength or both.

As long as the IDMP implementation presents the dose form information consistently in the relevant places in its structure, MPD can extract either the manufactured dose form or the administrable dose

form or both as they require, and if necessary split or amalgamate authorised dose forms into grouper dose forms as relevant for their use case(s) and culture and practice.

Challenges of interpretation

Some of the pharmaceutical dose form concepts can be challenging to understand and use, especially when they appear to differentiate products by dose form in a way that may not be clinically appropriate. This section gives a set of examples of this.

There are a number of pharmaceutical dose form concepts that describe „drops“ – two are shown below:

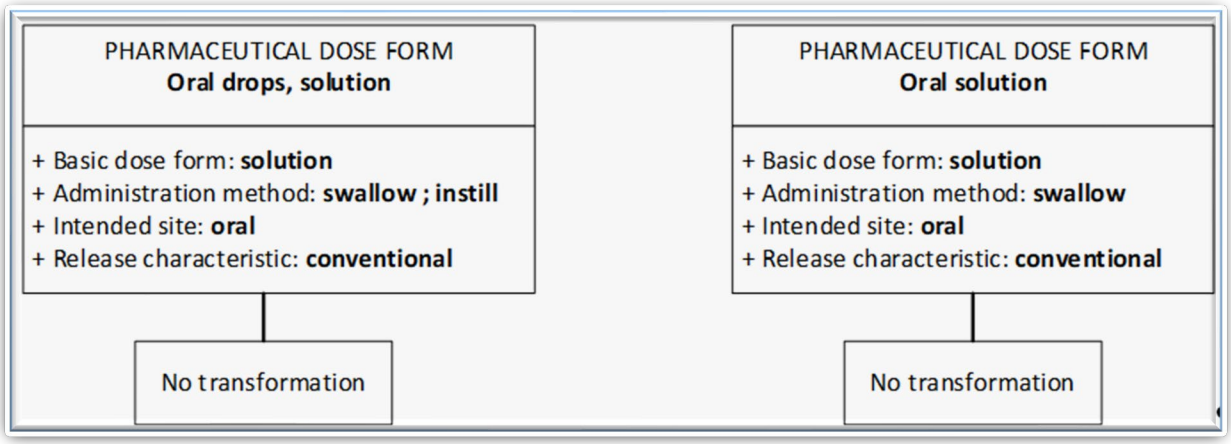


Figure 48:Oral drops, solution and Oral solution pharmaceutical dose forms

For the characteristics, only difference is that the „drops“ dose form has two methods, swallow and instill, whereas the plain solution has only a single method of swallow. In the text definition, the oral solution is stated to have a general use dose quantity of multiples of 5mL whereas the oral drops, solution is „administered in small volumes by means of a suitable measuring device such as a dropper, pipette or oral syringe capable of accurate dosing of the solution“. This difference in dose quantity management is often reflected in a difference in the way the strength of associated products is specified, with a preparation with a drops dose form having a concentration strength – shown here in the first label as a percentage strength (2.4%) and in the second as a presentation strength of 120mg/5mL:.

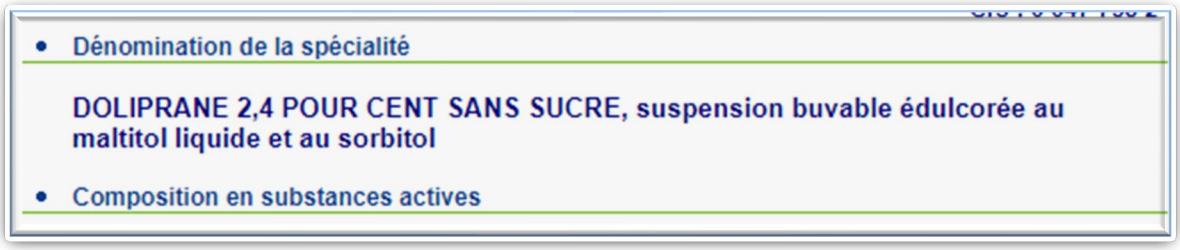


Figure 49: SmPC extract for Doliprane – FR (Paracetamol oral suspension 2.4%)

Figure 50:SmPC extract for Calpol Infant – UK (Paracetamol oral suspension 120mg/5mL)

There is no mention in the dose form characteristics about the administration device, because this is supplied separately to the dose form, not integral to it and, in IDMP, would be described in a different place (the Device class) in the overall product model.

Despite having two different pharmaceutical dose forms, the actual medication is the same „stuff“, and different MPD will make different decisions regarding whether to have a single abstract representation of this or not, depending on their rules and use case(s). This then has implications for interoperability across MPD (and therefore across system borders) because matching using the dose form attribute becomes less reliable than might be considered. This could be overcome by an MPD having more abstract classes than the basic models shown in Chapter 7, using a grouper dose form such as „solution, oral“ (which would have to be different from the current „oral solution“ pharmaceutical dose form and matching using concentration strength.

The introduction of some of the newer pharmaceutical dose forms (such as dispersions and films) also poses some challenges for MPD. Dispersion is usually a general grouping term for any system whereby particles of one material are dispersed in a continuous phase of another material – and therefore would include suspensions and emulsions and possibly also solutions. By having pharmaceutical dose forms that are described as dispersions, MPD are challenged to whether or not to include those with the more established pharmaceutical dose forms or not. Similarly with films – sheets of materials – it can be challenging to determine how clinically different these dose forms are from the more traditional solid dose forms and therefore whether these dose forms should be truly definitional to a product or not.

Differentiating some of the intended sites, particularly those in the mouth, can appear to be overlapping and therefore difficult for MPD to know whether products with different pharmaceutical dose forms are actually comparable or equivalent. The differentiation between an oromucosal film, a buccal film and a sublingual film is made harder by the statement that „Where a preparation is intended for use only at a single specific part of the oral cavity, the appropriate specific term (e.g. Buccal film, Sublingual film) is used instead“; this implies that an oromucosal film is actually a grouping concept, yet it may be used as a pharmaceutical dose form in its own right. Having exclusion criteria in any definition will always pose these sorts of challenges for comprehension and application, particularly when a downstream requirement is to group products together, which is a core part of what MPD do.

„Equivalence“ of dose forms

The EDQM pharmaceutical dose forms have various characteristics, but currently those characteristics are to be considered descriptive rather than definitional; definition can come only from the text provided. Although it is the responsibility of each MPD to manage what it considers to be „equivalent“ dose forms within its healthcare culture and practice, and therefore how it considers dose forms can or cannot be grouped together, interpreting some of the definitions of dose forms and deciding on equivalence would be helped if the characteristics were also able to be considered definitional. The confusion over the dose form assigned to the Comirnaty COVID-19 mRNA Vaccine („concentrate for dispersion for injection“ in the UK, „suspension for injection“ in the USA – when a dispersion is a grouper term for suspensions etc.) is a good example of this problem.

9.4 Unit of Presentation

IDMP provides explicit unit of presentation information available for the Manufactured Item and for the Pharmaceutical Product and in both cases there is the direct association to Ingredient and therefore substance and strength. Its value in both places is that it makes clear how a strength is being described, as in what is the denominator for the strength value so that abstraction and comparison of products can be undertaken more securely.

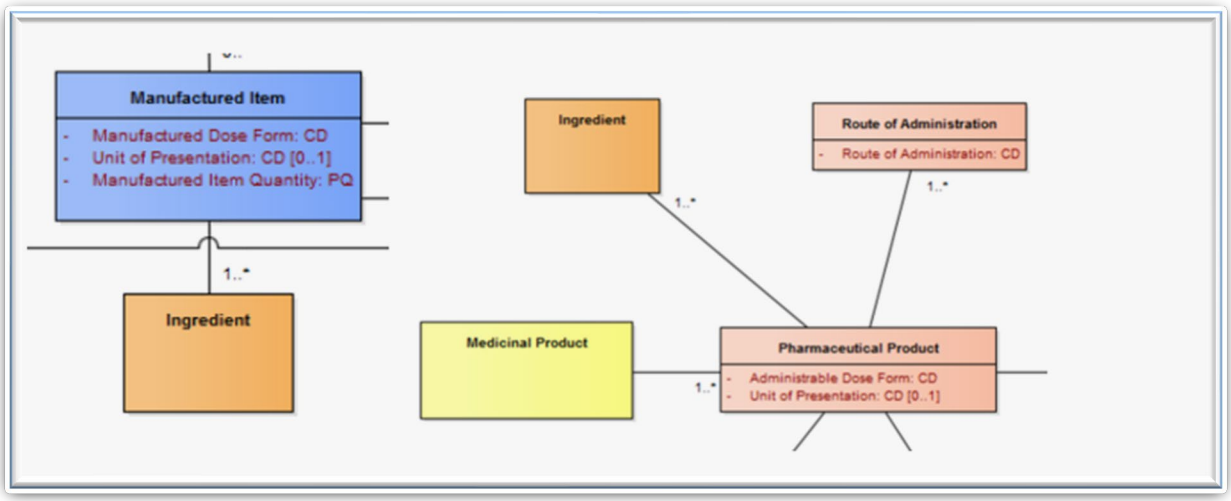


Figure 51: IDMP Structure for Manufactured Item related to Ingredient and Phamaceutical Product related to Ingredient and Medicinal Product

In addition, there is a direct association from Package Item (Container) to the Manufactured Item, so that the number/count of the what is in the package can be made unambiguously in terms of the unit of presentation, which is useful for several use cases, such as to allow comparison between different packs and pack sizes and their prices and for compliance checking.

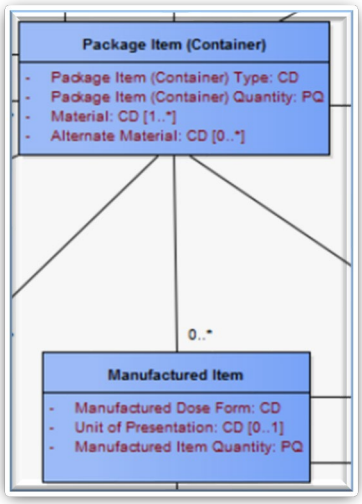
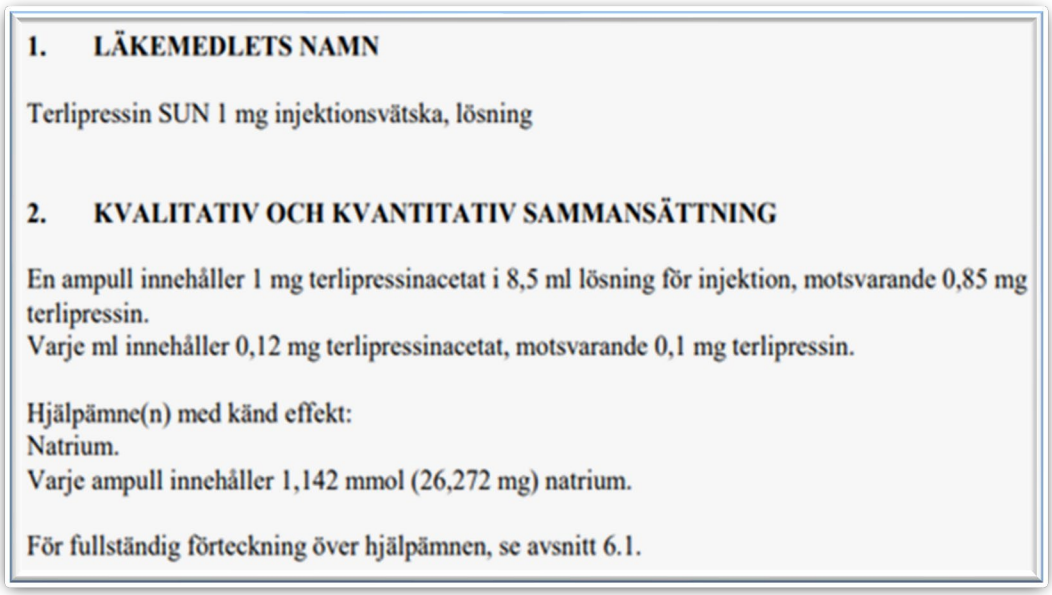


Figure 52: IDMP structure for Manufactured Item related to Packaged Item (Container)

In the example below, two seemingly different products (based on their name) from two different countries can be analysed and considered *therapeutically* equivalent using the unit of presentation information as an anchor for the calculation:



1. LÄKEMEDLETS NAMN

Terlipressin SUN 1 mg injektionsvätska, lösning

2. KVALITATIV OCH KVANTITATIV SAMMANSÄTTNING

En ampull innehåller 1 mg terlipressinacetat i 8,5 ml lösning för injektion, motsvarande 0,85 mg terlipressin.
Varje ml innehåller 0,12 mg terlipressinacetat, motsvarande 0,1 mg terlipressin.

Hjälpämne(n) med känd effekt:
Natrium.
Varje ampull innehåller 1,142 mmol (26,272 mg) natrium.

För fullständig förteckning över hjälpämnen, se avsnitt 6.1.

Figure 53: SmPC extract for Termlipressin SUN 1mg solution for injection – SWE

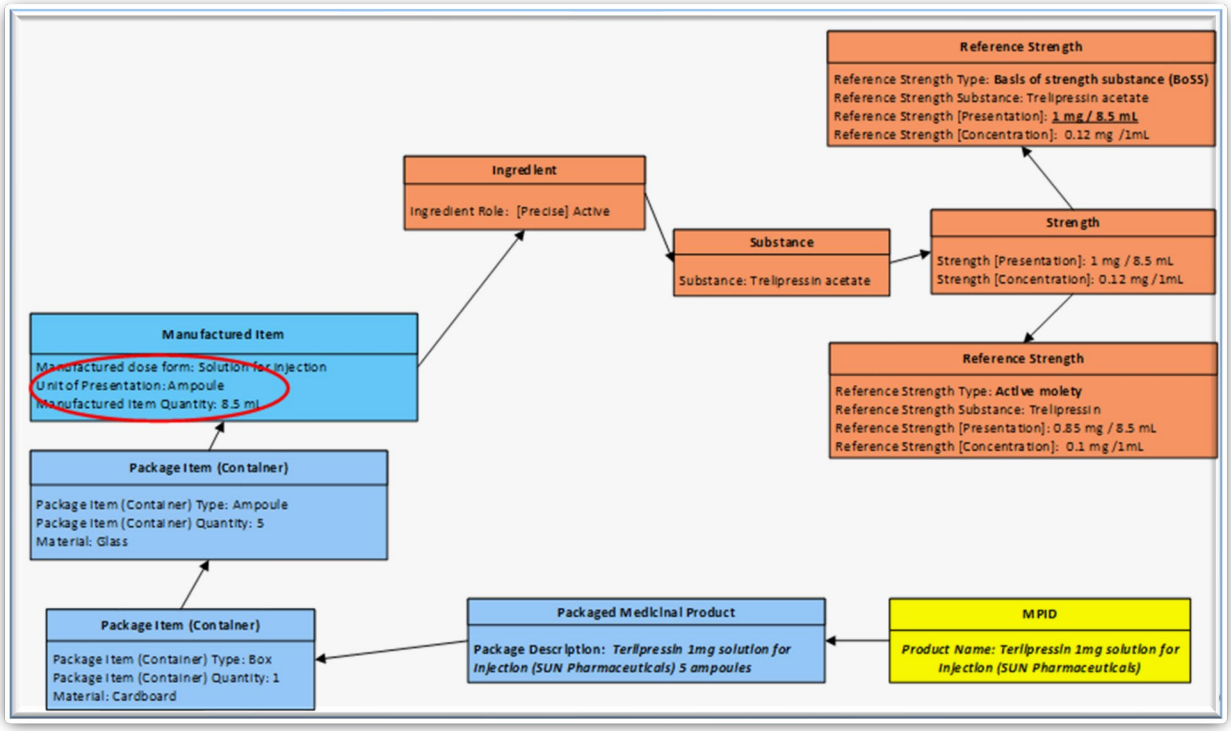
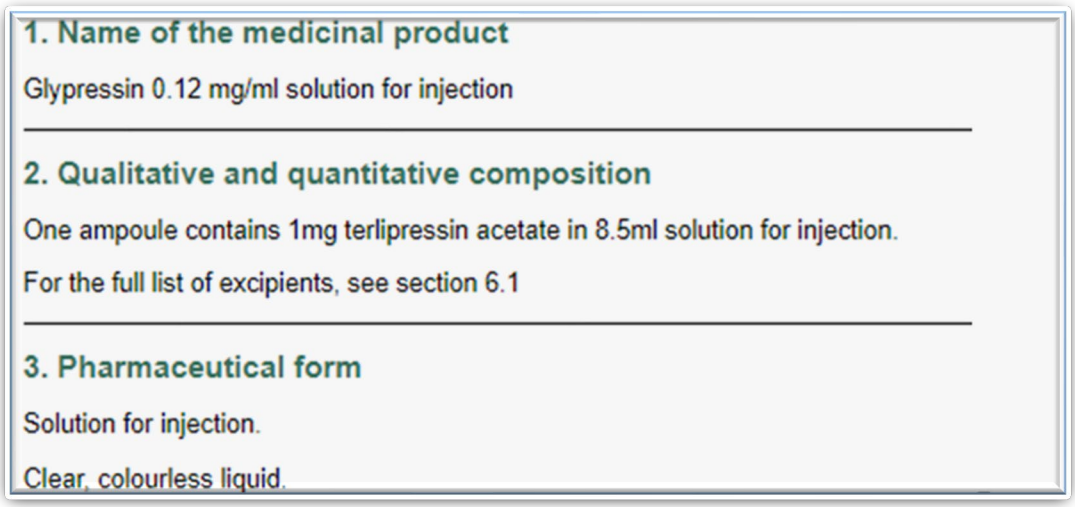


Figure 54: Termlipressin SUN 1mg solution for injection SWE in IDMP structure



1. Name of the medicinal product

Glypressin 0.12 mg/ml solution for injection

2. Qualitative and quantitative composition

One ampoule contains 1mg terlipressin acetate in 8.5ml solution for injection.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Solution for injection.

Clear, colourless liquid.

Figure 55: SmPC extract for Glypressin 0.12mg/mL solution for injection – UK

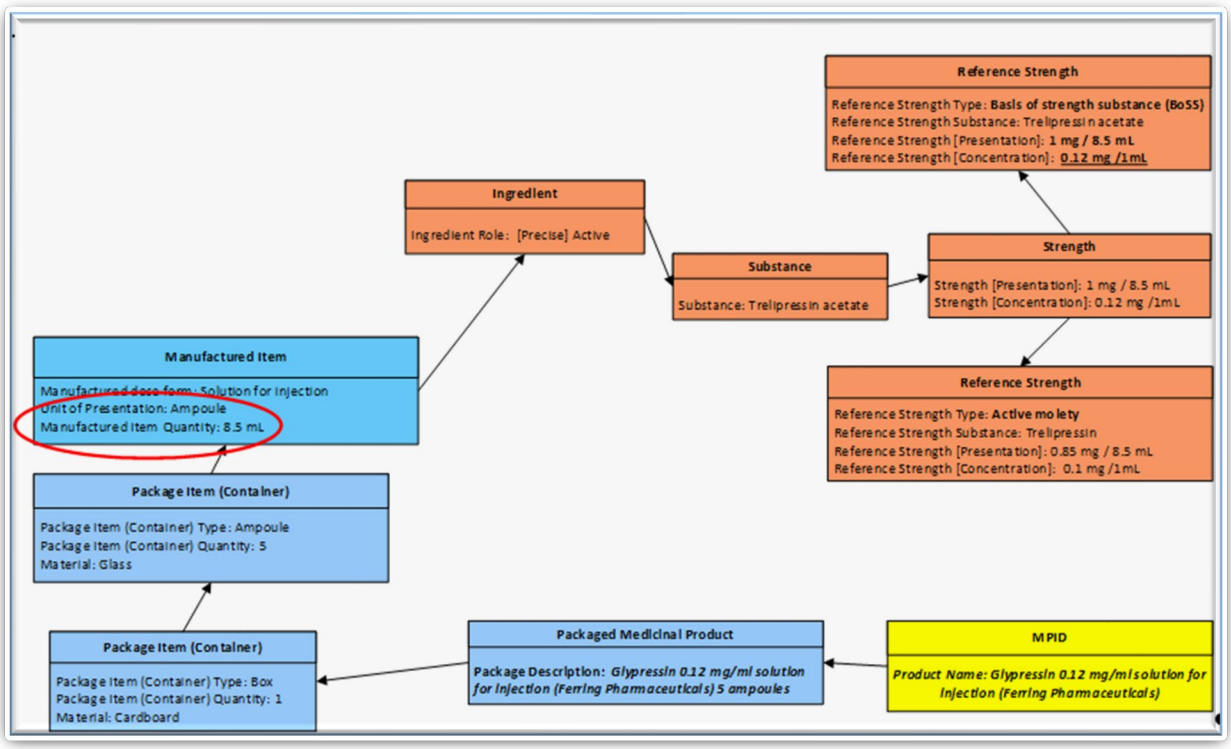


Figure 56: Glypressin 0.12mg/mL solution for injection UK in IDMP structure

Both products are presented in 8.5mL ampoules, so the unit of presentation is an ampoule and the unit of presentation size (fill) is 8.5mL, and both contain terlipressin acetate in that ampoule and use the terlipressin acetate as their basis of strength substance. However, the Swedish product name has given a presentation strength – 1mg of terlipressin acetate in the 8.5mL of solution in the ampoule whereas the UK product name has given a concentration strength – 0.12mg of terlipressin acetate *per mL* of solution present in the ampoule. Knowing that the ampoule contains 8.5mL of solution gives an equivalent presentations strength of 1mg of terlipressin acetate *per unit of presentation*.

The unit of presentation, along with all the definitional attribute information provided in IDMP can therefore be very helpful to MPD, *as long as it is implemented consistently*.

9.5 Implementation technology

Most of this analysis of „what IDMP will provide“ is taken from the ISO IDMP standards directly, with the exception of the dose form information where a standard implementation of a dose form terminology has been provided by EDQM; the unknowns of the substance implementation are also discussed above. However, in Europe at least, the provision of IDMP information will be significantly affected by the implementation technology mandated for use, which for the regulatory domain is HL7's Fast Health Interoperability Resources (FHIR). This is an exchange standard for electronic communication of information using Resources – information constructs – that can be used in xml or JSON. Although a communication technology should not significantly influence the information that it is transmitting, because there has been a move directly from the conceptual ISO standards to an implementable communication specification, some things may necessarily get „decided“ which may not be fully compliant with the standard itself or the requirements of all the stakeholders and some of these (for example strength type) have been discussed in the relevant sections above.

The development of the „IDMP resources“ is focusing on the domain of use of IDMP – the regulatory domain – and not on the onward users of the information – the MPD that then provide information to clinicians and patients. The data flow described in section 6.5 of this document showed how currently, a number of different types of organisations may be involved in the transformation of data as it emerges from the regulatory agencies into the data as it must be presented on clinicians‘ desktops by MPD. The current EMA IDMP implementation does not, as far as it is possible to determine, have the requirements of those organisations in view. For example, the EMA implementation requires use of the SPOR terminologies, even to the extent of „recoding“ externally sourced content such as ATC and EDQM. 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 and even if that mapping is 1:1, all mapping introduces risk and additional resource. It is also not easy for MPD to get access to implementation information, or indeed access to SPOR itself.

There is currently also a separation between the FHIR resources used for IDMP and the FHIR resources used to describe medication for patient care. This is a known issue and despite considerable efforts to try to resolve it, it has been decided within HL7, for the meantime at least, to maintain this separation. There are various reasons for this on both sides, including the significant investment in the clinical resources which means that change to those is not simple and also the requirement of the regulatory domain to meet its own needs in its particular ways.

10 Recommendations and Conclusion

10.1 Scope and domain of implementation

The current focus on the implementation of IDMP is in the national medicines regulatory agencies, following implementation guidance from the EMA and supporting the regulatory process. UNICOM has a clear aim for trusted data to flow from the national medicines regulatory agencies to patient care. But, as shown in sections 6.4 and 6.5 of this document (summarised from T9.1), data flows are heterogenous and only some national medicines regulatory agencies have a data flow into patient care as one of their present or future stated business objectives or obligations. It is not currently clear whether the EMA will be supporting MPD and other stakeholders from outside of the regulatory domain with access into its SPOR system. So although the vision and the aim are extremely laudable and valuable, if not all of the players are able, for whatever reasons, to commit to them, the vision and aim is challenging to realise. This has significant consequences not just for the vision and aim, but for the process of resolution of some or even all of the practical challenges documented in section 9.

It is therefore strongly recommended that the use of IDMP data in patient care once IDMP is implemented, be considered clearly now, in the light of the well known requirements of that different domain, and clarity given as soon as possible ***even if*** medicines regulatory agencies are unable to anything practical about it at this moment. This will allow a „beginning with the end in mind“ mentality when resolving issues and challenges such that patients and clinicians can truly receive the benefits of their MPD having trusted structured data flowing from the medicines regulatory agencies. It is important to so that there are no unfulfilled expectations, particularly for the semantic interoperability use cases.

The scope of the IDMP standards and the products that they can provide information for is smaller than the scope of an MPD in patient care; clarity on the availability and use of information from different member states by MPD, and the availability or otherwise of data on historic products should also be sought.

10.2 Gaps and uncertainties addressed through implementation guidance

The gaps and uncertainties detailed in section 9 must be addressed. This requires detailed and effortful discussion by individuals with the relevant expertise in the domains of interest, authorised to work together to bring at best resolutions, or failing that, a set of options with their advantages and disadvantages documented. General discussion of gaps and uncertainties is rarely productive and can disillusion and demotivate, so it is important that this work is focused, resourced and given authority to achieve. Some of this type of work is already being undertaken and has provided some of the illustrations used in this document.

Engagement with the various standards bodies is important, as some minor adjustments to the main standards would be beneficial (such as the addition of reference strength type to the conceptual model). However, at this point, the main emphasis should be in various levels of implementation guidance. These should have both a technical focus and a business focus. In terms of the technical, FHIR implementation guidance, this should be not just for the information providers (the national medicines regulatory agencies and the EMA) but also for the information receivers. This latter is part of the responsibility for the onward tasks of WP9 within UNICOM. In terms of the business guidance, the patterns of data structures for particular types of products should be (further) developed and shared, again not just in the regulatory domain but also in MPD and patient care, and particularly with those responsible for developing semantic interoperability for medicines identification information.

10.3 Semantic interoperability of medicines information – the pivot concept

This deliverable has described the various levels of abstraction of representation for identification of medicinal products used by MPD, with the requirements that have formed these and compared them to the possible abstract concepts that may be available from IDMP in the PhPIDs. Given that MPD have developed their structures and indeed the terminologies that populate those structures over a number of years in order to provide the best fit for their business requirements, these are unlikely to change, at least in the short term. Therefore, in order to transform information from one MPD into information that is comprehensible in another MPD, in possibly a different healthcare culture and language, rather than

try to develop a globally (or even regionally) appropriately identified abstract concept, such as the PhPIDs, some sort of „pivot“ between different MPDs is needed:

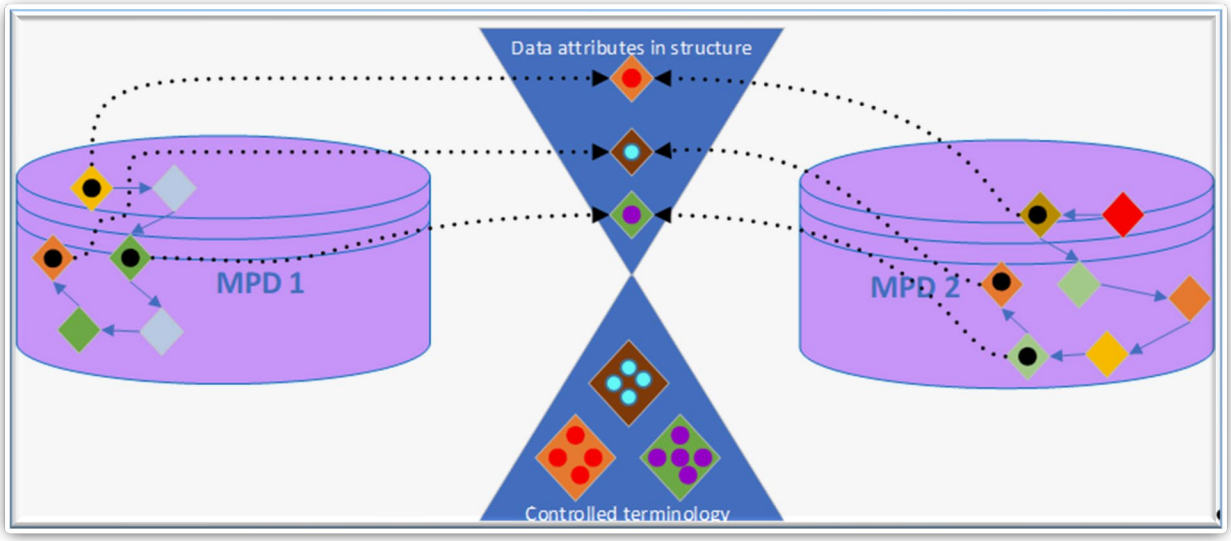


Figure 57: Schematic diagram for a "pivot" for interoperability of medicines identification

This „pivot“ has two main components:

- Data attributes in a structure – the definitional attributes discussed in section 7 and the patterned relationships between them
- Controlled terminology to populate those attributes

IDMP can provide some controlled terminology for those data attributes, such as substances, dose forms and units of presentation, as discussed in section 8. It can also guide the way those data attributes are patterned by providing its data in that structure, so that MPD are familiar with the patterns, can reference them directly and use them when required in the pivoting process. But currently it seems unlikely that IDMP, and in particular PhPID, can directly provide that pivot directly in any reliable way.

10.4 Conclusion

Although at this present time a significant number of challenges remain to be addressed in order to realise the vision of helping to ensure that any medicine and what it contains can be accurately identified anywhere in the world through the implementation of IDMP, that vision remains as a lynch pin of improving medication patient safety and enabling better healthcare for all. To do that, trusted structured data to identify medicinal products must be made available **from** its source – the national medicines regulatory agencies – **to** healthcare professionals and patients who interact with this through their MPD - in a way that understands the business of and therefore fulfils the requirements of both. This deliverable has described the requirements at the patient care end of that data flow – the MPD – and analysed it against what is currently understood to be available from the source – the national medicines regulatory agencies implementing IDMP (and SPOR). It has highlighted the various challenges found and offered some resolutions and provides a foundation from which to undertaken the further work to meet all challenges to deliver on the vision.

11 References

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