

DELIVERABLE 1.3

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Revision History

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Abstract (for dissemination)	This deliverable's goal is to present a multi standards framework that underpins solutions to identified issues in epSOS: the EU cross-border health data exchange specifications and its pilot results. In particular the identification of medicinal products and the attention to factors related to multiple contexts are addressed creating an infostructure, based on a multi standards framework.
Keywords	Unambiguous identification of medicinal products, standards framework, standards identified

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise, in particular through references to earlier work.

Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

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Executive Summary D1.3

openMedicine has the ambition to better enable cross-border healthcare delivery, particularly the exchange of electronic prescriptions and safe dispensation of prescribed medicinal products. The project advances the unambiguous identification of medicinal products and thereby patient safety in cross-border settings. Such cross-border health data exchange is underpinned by the European Directive 2011/24/EU.

This deliverable's goal is to present a multi standards framework that underpins solutions to identified issues in epSOS: the EU cross-border health data exchange specifications and its pilot results. In particular, the identification of medicinal products and the attention to factors related to multiple contexts are addressed here. With the multiple contexts is meant that the various issues are not only around ambiguity of identification of medicinal products, but additional layers that came forward when using identifiers from the regulatory domain at the clinical level, but also topics that need to be addressed at higher levels, for instance the level of communication, communication partners, electronic systems, differences in legal regulations around prescription, substitution and so on. The task is to create an infostructure that is based on a standards framework. The standards framework should also allow the exploration in a systematic manner of these contextual parameters that epSOS identified. This deliverable follows D 1.1 in which the epSOS project and the perceived issues are described in detail, and D 1.2 that specifies the epSOS ePrescription use cases.

The methodology to create this infostructure is loosely based on Checkland's systems thinking so that a comprehensive layer (framework) of systems (standards) and subsystems (additional standards) can be presented. The work is based on desk research and discussions with stakeholders, project team members and external experts. The resulting overall infostructure can be used to determine useful and feasible solutions. An overall standards framework illustrates the relationships between the various standards both at the level of the unambiguous identifiers for medicinal products, for descriptive attributes of medicinal products, and for the various contexts at the level of continuity of care, health IT architectures, EHR systems, messages and so on, some of which were identified in a set of use cases. Next, the Medicinal and Pharmaceutical Products Related Standards are discussed, in particular the set of five international standards for the Identification of Medicinal Products (IDMP) because these are mandatory internationally in the regulatory domain and provide the appropriate identifiers and descriptive attributes for clinical use missing in epSOS. Next, various health informatics standards that provide formats for the electronic exchange of medication data are introduced, such as electronic messages and implementation profiles. It explains how the development of systems can be based on the health care business and how, through a specification process, this leads to implementable systems that are able to handle the unambiguous identification for medicinal products. To achieve a situation in which each medicinal product gets an unambiguous identifier, the actual terminological systems that provide concepts, terms, and codes for concrete medicinal products are presented. This points to the medicinal product dictionary systems and terminology systems where to find a unique identifier for each regulated medicinal product. A very detailed model for the medicinal product, which can be used by most stakeholders and their applications, is included. That is a draft identifying pertinent data elements for

medicinal product identifications, and the associated terminologies for each data element. This work will be completed in D 2.3.

Various standards define the context for the electronic exchange of medication related data. It presents the health care business standards such as systems of concepts for continuity of care, the architecture for health information systems, the logical electronic health record that defines a life time record per individual subject, functional requirements for electronic health records and ongoing work in this area.

This deliverable presents the multi standards framework that underpins solutions to identified issues in epSOS for the ePrescription for cross-border health data exchange in the EU. Specific recommendations following from the above outline of standards include:

- The multidimensional approach, based on the generic component model assists in getting a good overview of the matters and to identify relationships at the right levels.
- To allow proper dispensation of the right medicines to patients anywhere in Europe, the IDMP identifiers and descriptive attributes should be used in the epSOS CDA exchange format, and any future exchange format. There is ongoing debate on the level of precision that is required.
- To support these identifiers, and their application in systems and data exchange, a series of terminologies, classifications and medicinal product dictionaries is necessary.
- It is clear that despite wide coverage, not every relevant product attribute, or required information classes can be identified with OIDs (unique identifier system) and unique class codes per product / information item. This is an area for future work.
- The Detailed Clinical Model that specifies every class and each class's code and codes system, identifies the requirements and assists in specifying the appropriate OIDs, codes and value sets.
- Standards work is a moving target, and openMedicine needs to make adjustments. In particular Deliverables 2.1, 2.2 and 2.3 are asked to address the following parts :
 - How are medicines currently identified in various standards?
 - How can the IDMP implementation guides be referred to in the work of WP2?
 - For D 2.3, how can the DCM for the Medicinal Product be finalized and published?
 - How can the currently missing codes per information class / data element be obtained and included?
 - Is it possible to add the additional value sets that are required for the medicinal product?
 - How can we achieve to obtain proper OIDs for all identifiers and all code systems?
 - Is it possible to complete the representations in UML and XML, in particular in HL7 v3 CDA for epSOS?
- Using standardization on every level, a flexible cross-domain approach becomes possible, as is illustrated in the ISO TS 19256 Medicinal Product Dictionary where both the clinical and the regulation domains around medicines are depicted and use the same IDMP identifications. This example can be further used in openMedicine.
- Future Deliverables for openMedicine can depict the application of the IDMP in epSOS in examples of such contexts, offering help in the cross-border situations on several levels of processes and organization that have not yet been addressed.

1 Aim and Scope of the Document

Directive 2011/24/EU of the European parliament and of the council of 9 March 2011 sets the scene for the application of patients' rights in cross-border healthcare, including the required exchange of information to accompany this, e.g. between medical records, and the support of eHealth¹. Article 11 discusses the cross-border recognition of prescriptions. This directive underpins the epSOS project in particular and this standards framework in general.

The European project epSOS tested a first set of specifications, based on the Health Level Seven version 3 (HL7 v3) Clinical Document Architecture (CDA) for both a patient summary and for an ePrescription. Although in general the pilots were successful, the problems identified in the epSOS project with cross border prescriptions and their follow up with a dispense in another country than where the prescription was issued are twofold: a) the medicines cannot be identified properly and b) questions arise such as who is allowed to prescribe, so a context issue. Regulations, organizational and clinical contexts do vary significantly too and have impact on cross border ePrescription. Both issues of identification and context factors need to be addressed for future cross border care. The identification of medicinal products in epSOS was based on existing standards, such as the HL7 CDA guidelines, but did not yet include reference to the ISO series for Identification of Medicinal Products (IDMP).

Hence, the goal of D1.3 is twofold: Most important goal is to propose an starting point for an infostructure to identify and describe medicinal products at various levels (including Package, Medicinal Product, Pharmaceutical Product and Substance) to support unambiguous identification of medicines across borders and cultures of practice, for the purpose of prescribing and dispensing and clinical record keeping. Secondary goal is to identify standards that allow the identification of various contextual aspects, such as regulations, logistics, and workflows that have to support interoperable communication of e-Prescription.

This deliverable D 1.3 follows D 1.1 in which the epSOS project is described in detail, and D 1.2 that specifies the ePrescription use cases. For D 1.3, 'an infostructure' is defined by the SemanticHealthNetwork project as "a formal process for the governance of interoperability resources". It is the infrastructure to manage "information resources" around medicinal products. This infostructure addresses both the actual issue of identifying (regulated) medicinal products, following the IDMP standards, but at the same time placing it in various additional standards that play a role in the cross-border electronic prescription.

Chapters 2 & 3 offer references and terms and abbreviations respectively.

Chapter 4 describes the methodology applied to prepare deliverable 1.3.

Chapter 5 explains the infostructure framework, using the Generic Component Model (GCM).

Chapter 6 presents use cases for the cross-border ePrescription scenario .

Chapter 7 specifies IDMP and related standards for the identification of medicinal products.

¹ DIRECTIVE 2011/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 9 March 2011 on the application of patients' rights in cross-border healthcare. Official Journal of the European Union, 4-4-2011 L 88/45-L88/65.

Chapter 8 adds the actual systems that provide the concepts, terms, codes and specifications for concrete medicinal products.

Chapter 9 addresses additional terminologies that can be part of an ePrescription,

Chapter 10 describes the various health informatics standards that provide formats for the electronic exchange of medication data, such as electronic messages and implementation profiles that cover the dynamics of ePrescriptions.

Chapter 11 presents various standards that define the context for the electronic exchange of medication related data such as the health care business standards and the architecture for health information systems, and functional requirements for electronic health records. .

Chapter 12 presents a list of required data elements from the IDMP standards and lists which are required for ePrescription and Dispense as underpinning for a draft Detailed Clinical Model for the medicinal product which can be used by most stakeholders and their applications.

Chapter 13 presents a synthesis of the various standards for the initial infostructure.

Chapter 14 discusses how this work relates to some national health strategies in order to get a first impression of how this could work in practice and feeding the openMedicine roadmap.

The final chapter presents a discussion, conclusion and recommendations.

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3 Terms and Definitions

In the document the following terms and definitions were included.

3.1 Terms/Acronyms

API	Active Pharmaceutical Ingredient
CEM	Clinical Element Model
CIMI	Clinical Information Modelling Initiative
Contsys	System of concepts for continuity of care. ISO 13940
DCM	Detailed Clinical Model. ISO TS 13972
EC	European Commission
EMA	European Medicines Agency
epSOS	Smart Open Services for European Patients - Open eHealth Initiative for European Large Scale Pilot of Patient Summary and Electronic Prescription
EU	European Union
FHIR	Fast Health Interoperable Resources
FMD	Falsified Medicine Directive
GCM	Generic Component Model as published by Blobel, 2010
GS1	Name of a standards developing organisation.
HCER	Health Care Encounter Report
HL7	Health Level 7 standards developing organization
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
INN	International Non-proprietary Names
OTC	Over The Counter, that is not requiring a prescription
OWL	Web Ontology Language
RDF	Resource Description Framework
RM-ODP	Reference Model of Open Distributed Processing
SDO's	standards developing organizations
SSM	Soft Systems Methodology (Checkland, 1984)
TOGAF	The Open Group Architectural Framework
UML	Unified Modelling Language
WHO	World Health Organisation.

WONCA World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians

XML eXtensible Markup Language

3.2 Use of Terms and Definitions

Active Pharmaceutical Ingredient Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings

[Reference: WHO]

ePrescription a medicinal prescription, as defined by Article 1(19) of Directive 2001/3/EC, issued and transmitted electronically

[Reference: openMedicine Dictionary]

Health Care Encounter Report (HCER) a synthetic document, based on the Patient Summary, generated after an encounter abroad, returned to the country of affiliation, which contains findings and the Medication Summary of medicinal products prescribed while abroad

[Reference: epSOS]

Medication Related Overview a subset of the Patient Summary including information a pharmacist might need, to safely dispense a medicinal product (e.g. Medication Summary, allergies...), not having access to the full Patient Summary

[Reference: epSOS]

Medicinal product any substance or combination of substances that may be administered to human beings (or animals) for treating or preventing disease, with the view to making a medical diagnosis or to restore, correct or modify physiological functions

[Reference: ISO 11615:2012]

Patient Summary a dataset of essential and understandable health information that is made available at the point of care to deliver safe patient care during unscheduled care and planned care with its maximal impact in the unscheduled care

[Reference: epSOS]

Pharmaceutical product a qualitative and quantitative composition of a medicinal product in the dose form approved for administration in line with the regulated product information

[Reference: ISO 11615:2012]

4 Methodology

For the development of the infostructure for openMedicine a so called multi-method approach is required. This is for the following reasons: to come to a comprehensive overview for the infostructure, a combination of analytical methods, requirements setting approaches, information modelling and architectural design is the best way to go (Blobel, 2010). However, there is a baseline approach underpinning this multi-methods approach: the infostructure should help solve problems in the real world of exchanging information about medicinal products and their use. However, to achieve this, the infostructure needs to come up with an improved situation: fewer errors and less missing data. Hence, the improved situation will be modelled as an ideal situation (vision) against which the implementation in the real world can be discussed and planned. This approach is often called systems design. Since the problems in health care are often ill structured (Checkland, 1984, Checkland and Scholes, 1990), a soft approach, taking into account human factors is appropriate. Soft Systems Methodology (SSM) implies a methodology to analyse reality, design the improvements via models, and compare the models with reality again. Checkland (1984) suggests adding a cultural stream to SSM in order to achieve the desired and feasible changes for all stakeholders (Checkland, 1984). This approach has also been tested in healthcare (Checkland and Scholes, 1990).

The vision statement guiding this SSM approach is the following: To achieve an infostructure to describe medicinal products at various levels (including Package, MPID, PhPID and Substance), to have the definitional standards available to populate both the structural components and to populate each descriptive component with unambiguous identifications derived from well-maintained terminology and code systems, and to support interoperable communication across borders and cultures of practice in a multi-level framework that facilitates various contextual aspects, such as legislations and workflows. In SSM terms this can be seen as the root definition.

Altogether the approach for openMedicine deals with drawing a general architectural framework from the analysis and requirements that have been expressed in the epSOS inheritance. In order to have this architectural framework approved, feedback and discussion rounds are held among the WP1 membership. During these feedback rounds, additional requirement setting and analysis took place. In particular, a concrete set of use cases has been proposed to aid the requirements setting for the unambiguous identifiers for medicinal products. These actual requirements specification and the determination of the solution is not part of this deliverable that merely functions as the inventory, but will be handled in D 2.1, D 2.2 and D 2.3. However, the inventory of standards identified for the framework will support the cross border interoperability later in the project via harmonizing the information model and the terminology model intersections for the unambiguous description of medicinal products.

For analysing, designing and implementing the openMedicine architecture, the Generic Component Model (GCM) framework and its data and its process representations will be used as the overall modelling approach. Unified Modelling Language (UML) is applied for specifying data structures, processes and interactions. The conventions as deployed in various standards developing organizations (SDO's) are taken into account.

The GCM framework enables analysis, modelling and implementation of systems combining the architecture of systems, systems theory, ontological applications, and the Reference Model – Open Distributed Processing (RM-ODP) (Blobe, 2010).

The core technologies used to create epSOS include Health Level 7 (HL7) version 3 Clinical Document Architecture (CDA). The CDA consists of an HL7 specific Unified Modelling Language (UML) logical model, and computable CDA eXtensible Mark-up Language (XML) specifications for the actual implementation. This is accompanied by reference sets of data elements, data types, unique code bindings to for instance EDQM or ATC, and value set specifications, to allow structured data to be included in the CDA and exchanged electronically. Specific clinical content, e.g. the medical diagnosis or the prescribed medications are further specified in HL7 v3 XML templates.

The following steps are taken in this multi-method approach for the infostructure:

Create a draft architectural framework for the required standards and solicit feedback on this approach from experts in the field, and manage this feedback in updated versions of the deliverable. This follows up on D 1.1 epSOS inheritance and D 1.2 use cases from openMedicine.

Analyse, specify and model EHR / PHR / Pharmacy Information Systems requirements (from HL7 /ISO EHR-S FM / FP) pertaining to the medication identification and exchange. Data models were drawn up for the medication identification from IDMP using HL7 pharmacy specifications, in particular the detailed data specifications for the medication identification. Next, the detailed specification of the terminologies and value sets were included in the modelling. For the context, based on the GCM, additional standards were identified and included. The GCM is used to place each of the standards in this generic framework.

From this input, specifically the review of the data elements from the IDMP standards, a draft Detailed Clinical Model for the Medicinal Product has been derived, however input from stakeholders has been and will be solicited in the next phase of openMedicine. The intention is to include a completed version in Deliverable 2.3. D 2.3 will include the required descriptive and definitional components that are identified in D1.3, D 2.3 will work further based on the use cases as specified in Annex A. Also the relationships with Deliverables 2.1 and 2.2 are part of D 2.3.

Using the SSM approach (Checkland, 1984), we support the analysis and resolution of the problems. We do not really enter the synthesis of the solution. So proposing a solution (and as for instance in the DCM medicinal product) facilitates discussing it for correctness, feasibility and desirability and is more or less the endpoint of this deliverable 1.3. It is the endpoint of systems thinking and in SSM positioned before actually moving into the solution. The solution is part of D 2.3.

5 Conceptual Standards Framework

Healthcare is a very simple process: one human being has an illness and another human being treats the illness and cares for the sick person. This process goes back several tens of thousands of years in our history. However, despite its simplicity, which is still true, this depiction is in our age no longer sufficient to deal with illnesses, diseases, treatments and medicinal products. Human kind has developed significantly, in particular in health, medicine and pharmacy on one hand and in information management and technology on the other. Healthcare transformed into a multi layered organization with multi millions working in it on different levels, a proliferation of specialist domains, increasing knowledge of human function, in particular to the detailed level of individual genes, and to a complete industry searching and testing ever new medicinal products. Also, information management has moved significantly in the past centuries, starting with medical statistics or epidemiology some centuries ago, with current information technology bringing data processing powers that never existed before.

5.1 Infostructure as multi-layered cubical framework

This complexity of our modern age can be illustrated by the generic component model (Blobel, 2010), which describes in a cubic the relationships between different levels of the organization of healthcare, the interactions between various domains, and the interaction with the information system development process. Such a complex view is important as the baseline for the openMedicine infostructure, since the exchange of information on medicinal products involves many stakeholders, processes, jurisdictions, and principal and practical issues to solve. The details of the epSOS ePrescription have been discussed in D 1.1. extensively, this deliverable D 1.3 builds upon that. Additionally, derived from D 1.1, the set of use cases has been drawn up in D 1.2, which is used for additional requirements setting.

Figure 1 represents the generic component model (GCM) in a cube form, representing the mathematical axis x , y and z (Blobel, 2010). The z axis addresses various domains interacting with each other, for instance medicine (disease and treatment), pharmacy (active ingredients that cure) and legislation (marketing authorization for medicinal products). The y axis deals with the hierarchy in healthcare, from the overall business (e.g. the medication process), through relations networks (the actors patients, doctors, pharmacies interacting with each other for medicinal treatment), through aggregations (such as the epSOS HL7v3 message) to the details (the identified medicinal products, the data elements required for that and the terminologies and codes). Blobel (2010) assumes that one should compare, interact, exchange at equal levels in this structure, and each cell in the cube can be represented by one or more ontologies that describe the reality in that particular component. Finally, the x axis deals with the information system development starting with a business view (e.g., medicine, pharmacology and regulation), including an information and computational view independent of technology and ending with engineering a running technical application.

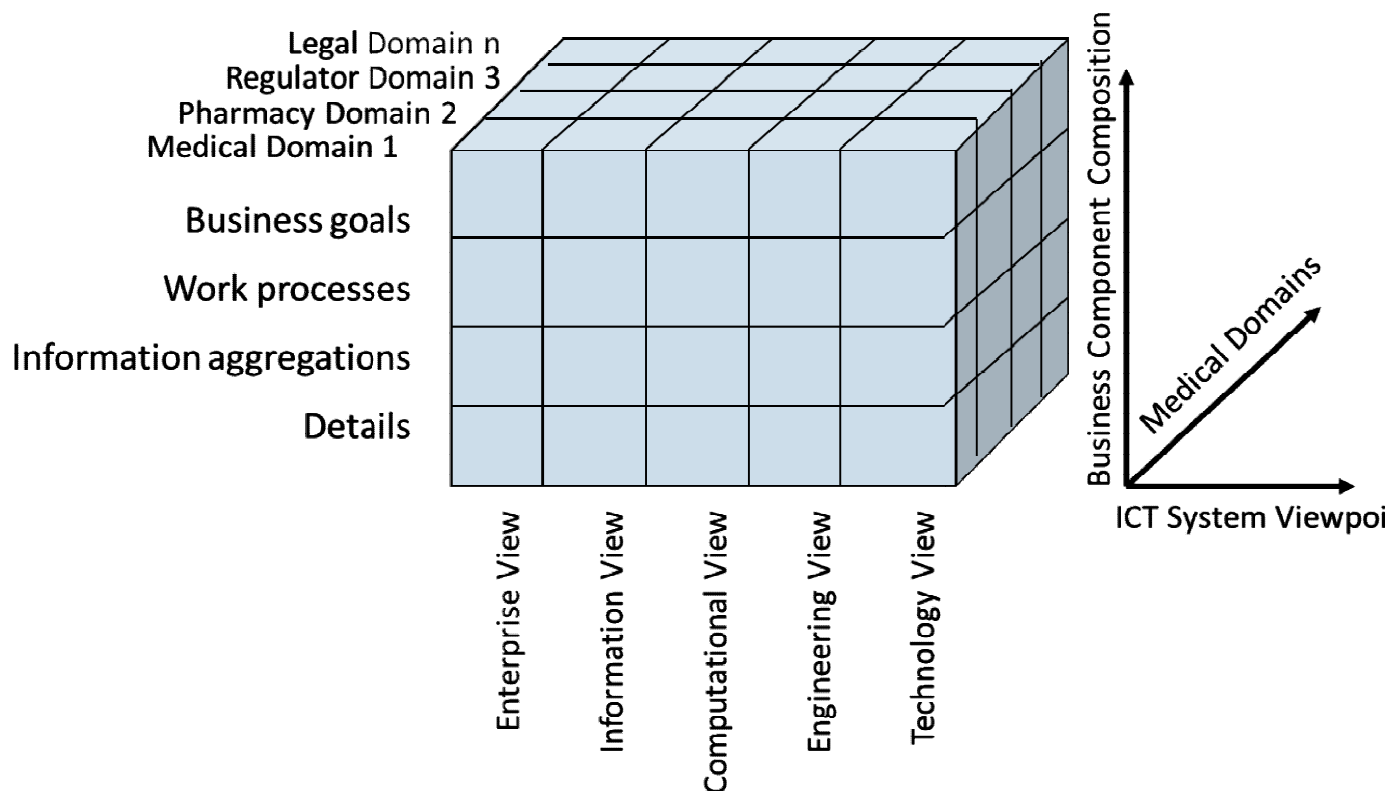


Figure 1. Generic Component Model or GCM, adjusted for medicinal product (Blobel, 2010).

5.2 Standards for Identifying Medicinal Products

The following chapters describe various healthcare informatics standards from different standardization organizations. It will start with the lower levels of the GCM axis, i.e. the details of the Medicinal Product Identifiers as used IDMP, and other standards, specifically relevant for use in epSOS. From there the infrastructure description moves bottom up to the health care systems view (the y axis in the GCM) that describe the various contexts for epSOS, and then also discuss the other axes. However, it is not the intention of this deliverable to be exhaustive in addressing every possible standard, but to limit ourselves to those that are considered relevant for openMedicine, as these are based on the requirements identified in D 1.1 and the use cases from D 1.2 and ongoing work in openMedicine as depicted in the next chapter.

6 Use cases

openMedicine is driven by use cases. In particular, the cross border clinical application of medicinal products and their identifiers is the core use case. And, this is largely (but not only) driven by patient safety issues. Specifically, the identification in the scenario of cross-border prescription is a reference use case, since it is expected to cover a significant set of requirements (see D1.1 and D 1.2). However, as D1.1 shows, the different aspects indicate a need for a further breakdown in concrete use cases. That set is provided in section 6.2 below. Nevertheless, there are other use cases where proper identification of medicinal products is needed. openMedicine D 1.2 presents these and describes them in detail. For reason of hand over to D 1.3 the total set of use cases is presented here below, keeping the original D 1.2 numbering for reference:

- 5 Definitions of complementary and/or alternative use-cases
 - 5.1 *Recording medication history*
 - 5.1.1 Patient safety
 - 5.1.2 Reconciling medication list
 - 5.2 *Unique EU level Medicinal product registration*
 - 5.3 *Reimbursement eligibility purposes*
 - 5.4 *Adverse drug events and pharmacovigilance*
 - 5.5 *Unintended use of unidentified medicinal products*
 - 5.6 *Product traceability*
 - 5.6.1 Ordering and supply
 - 5.6.2 Product recall
 - 5.6.3 Product authentication against counterfeiting
 - 5.6.4 Clinical trials
 - 5.6.5 Clinical research
 - 5.6.6 Waste management

6.1 Patient Safety

Since ‘to Err is Human’ was published, the reduction of medication errors has permeated the whole clinical and pharmacy specialties around the world (IOM, 1999). The mere fact that about 100.000 Americans would die annually due to errors in the prescription, dispense and administration of medicines was a shocking message leading to other countries coming up with similar calculations and tons of measures to check and control the handling of medications. Specifically, where medication errors and adverse drug events are preventable, measures were required and possible, and have become daily practice. The now widespread CPOE (Computerized Physician Order Entry) approach resulted from these initial findings and found their way into many national regulations. In the follow up report “Crossing the Quality Chasm” (IOM, 2001) recommendations were given for the use of electronic medication ordering, with computer- and internet-based information systems to support clinical decisions of prescribing clinicians.

Currently, medication errors and adverse events are still occurring, see for example a recent study by Nanji, Patel, Shaikh, Seger, and Bates (2015). Nanji et al, (2015), report on a study towards medication errors and adverse drug events during perioperative care. A total of 277 operations were observed with 3,671 medication administrations of which 193 (5.3%; 95% CI, 4.5 to 6.0) involved a medication error and/or adverse drug event. Nanji et al (2015) conclude in their prospective observational study that approximately 1 in 20 perioperative

medication administrations, and every second operation, resulted in a medication error and/or an adverse drug event. More than one third of these errors led to observed patient harm, and the remaining two thirds had the potential for patient harm (Nanji et al, 2015). Of course this is an example to illustrate the issue.

As far as we know there are no figures available about cross border medication errors or adverse events, but given the difficulty in identifying medicinal products and the contextual variables that make cross border prescription a difficult task, one cannot simply assume that it is safer than normal practice. Hence, it is important to identify cross border use cases for medicinal product identification, which will be presented in the next section.

6.2 Use cases for Cross-border product identification

- Use Case 1: Prescription is issued in one country (Country A), must be dispensed in another country (Country B).

The following use cases correspond to the expected variations in product identification, as well as the impacting aspects, most of which are described in D1.1.

- Use Case 1.1: Product identified by the brand name in country A; in country B there is one equivalent
- Use Case 1.2: Product identified by brand name in country A, in country B there are several equivalents
- Use Case 1.3: Product identified by International Non-proprietary Names (INN) in country A, in country B there are several equivalents
- Use Case 1.4: Product identified by INN in country A, several active substances, in country B there are several equivalents
- Use Case 1.5: Product identified by INN in country A, dose form is implicit, in country B there are several dose forms
- Use Case 1.6: Product identified by INN in country A, dose form is implicit but in country B the specified dose form is not existing
- Use Case 1.7: Product identified by brand name in country A, product is NOT existing in country B
- Use Case 1.8: Product identified by a code for a country-specific "cluster" in country A, in country B there are several equivalents
- Use Case 1.9: Product identified by brand name in country A, product exists in country B but is protected substance
- Use Case 1.10: Product identified by brand name of drug containing protected substance in country A, product exists in country B
- Use Case 1.11: Product identified by INN in country A, substance is not authorized in country B.

- Use Case 1.12: Product identified by brand name in country A, product exists in country B but is an OTC
- Use Case 1.13: Product identified by commercial name in country A, using INN, and marking "patient intolerant to lactose". In country B, medication exists with or without lactose
- Use Case 1.14: Product identified by brand name in country A, default dosage form in country A is different from the default in country B
- Use Case 1.15: Product identified by brand name in country A, quantity per pack is implicit, and is different from the available quantity in country B
- Use Case 1.16: Product identified by brand name in country A, administration route in the prescription is different from the default in country A
- Use Case 1.17: Product identified by brand name in country A, administration route in the prescription is different from the default in country B
- Use Case 1.18: Product identified by brand name in country A, commercial product does not contain lactose, and there are several products with or without lactose in country B
- Use Case 1.19: Product identified by brand name in country A, "substitution allowed" in prescription, country B does not allow substitution by default
- Use Case 1.20: Product identified by brand name in country A, "substitution allowed" in prescription, country A has therapeutic substitution, country B has generic substitution
- Use Case 1.21: Prescription of product A contains different attributes for the composition: "1 box of 10 ampoules of 5 ml" or "Teriparatide 20 mcg/dose 28 doses Solution for injection in pre-filled pen".
- Use Case 2: Identification of dispensed products
 - Use Case 2.1: Medication is dispensed, and the outcome of this dispensing is added to the patient record in country A.
 - Use Case 2.2: OTC Medication is dispensed in country B, and in country A it is important for the medication record
 - Use Case 2.3: Medication is being dispensed and this is done in consideration with the Falsified Medicine Directive (FMD).
- Use Case 3 Identification of administered products:
 - Use Case 3.1: Patient wants to report an adverse drug event of a drug they took while on vacation.

- Use Case 4

Use Case 4.1: In a central Database (DB), new medication is authorized by a Member State (by its regulatory entity) and this is to be added to the DB. This medication must be identified in order to be added to an existing group, establishing the appropriate identifier(s) or link(s) for equivalence to the other medications.

6.3 Analysis and requirements

As onset to further analysis of the use cases and requirements setting in openMedicine WP2 and further, the following assumption holds:

- The reference use case is to identify a prescribed medication so that it can be dispensed. The analysis for that use case covers a large set of requirements which will cover most of the other needs. When this is not the case, the other use cases will be analysed as well.
- Scenarios: Prescription must be prepared (upfront or ad hoc) in a manner that can be understood for dispensing. Three approaches are possible for this: 1. prescription is prepared for "cross-border" *ab initio*, or 2. prepared just after prescription, or 3. prepared *ad hoc* at the time of dispense.
 - Independently of the approach taken, there are 3 scenarios for ensuring the correct identification: a) common identifier values, b) matching values of an identifier, or c) a set of identifying attributes.
- The identification of an equivalent product may not always be univocal: for some cases, there is no equivalent, and for some cases, there are several equivalents. There are several options to address this, and these options influence the attributes to choose.
- Besides product characteristics, other attributes may influence the equivalence: the prescription may contain other information which may be helpful in deciding which product can be used as an equivalent, like substitution indication. Or the substitution rules at each country, which enable more flexibility in the equivalence. Some of this information is not available until the prescription is issued. Other influential information may be available in each country. A classification of attributes according to the several sources of information is needed.
- When dispensing, the pharmacist must not only identify the product but also verify the conditions for dispensing.

For any of the scenarios, the requirements can be derived from the use cases. These are characterized as a set of abilities/functionalities, which can later be prioritized into e.g. a MoSCoW-like hierarchy (Must/Should/Could), considering technical, societal or regulatory impact, effort and feasibility - i.e. in many cases a solution for a requirement may not be technical, but some regulatory guidance. For this deliverable, we will continue to work with use cases prescription, dispense and record keeping.

7 Medicinal and Pharmaceutical Products Related Standards

This chapter covers specific standards relevant for the Medications or Pharmaceutical products themselves. This is the core of the standards framework for this deliverable. In the GCM, this part is covering the y-axis for stakeholders, processes, aggregations and details and from the x-axis the enterprise and information viewpoints.

7.1 IDMP series

The Identification of Medicinal Products (IDMP) was developed to facilitate the exchange of information between pharmaceutical companies and regulatory authorities (Telonis, 2014). It was adopted by International Standard Development Organizations (SDOs) in the Joint Initiative project (JIC) and handled through ISO. The scope of the work in ISO was widened to include activities in the health care domain e.g. e-prescription. And according the Vienna agreement between CEN and ISO the IDMP set is also a European standard from CEN.

For openMedicine, the IDMP series form the core of the future required identification for medicinal products. Further in the project, specific guidance to the use of such identifiers will be given. Suffice here to state that the MPID or Medicinal Product Identifier is the unique identifier allocated to a Medicinal Product supplementary to any existing authorization number as ascribed by a Medicines Regulatory Agency in a jurisdiction. The PhPID is the Pharmaceutical Product Identifier, which is referring to the composition of the pharmaceutical product, including one or more active and other ingredients, quantities, and characteristics at generic levels as the pharmaceutical form and the route of administration. The reference to 'Regulated' means that this series deals with those medicines that are formally approved by the European Medicines Agency and have a marketing authorization. Regulated implies usually approved for a national jurisdiction. This implies that non-authorized or locally created medicinal products will not get an IDMP based identification, issued by EMA.

Currently, the EN ISO Identification of Medicinal Products (IDMP) package was completed in 2012 and comprises the following five standards:

- EN ISO 11615:2012(E), Health Informatics, Identification of Medicinal Products (IDMP) standard Data elements and structures for unique identification and exchange of regulated medicinal product information
- EN ISO 11616:2012(E), Health Informatics, Identification of Medicinal Products (IDMP) standard Data elements and structures for unique identification and exchange of regulated pharmaceutical product information
- EN ISO 11238:2012(E), Health Informatics, Identification of Medicinal Products (IDMP) standard Data elements and structures for unique identification and exchange of regulated information on substances
- EN ISO 11239:2012(E), Health Informatics, Identification of Medicinal Products (IDMP) standard Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging

- EN ISO 11240:2012(E), Health Informatics, Identification of Medicinal Products (IDMP) standard Data elements and structures for unique identification and exchange of units of measurement.

These five parts are linked together in the following way (figure 2):

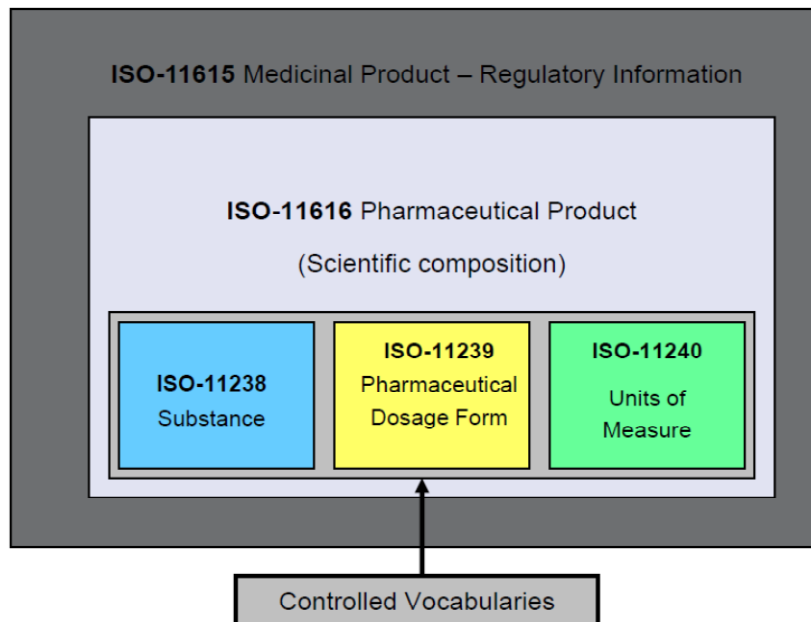


Figure 2. Relationships between the IDMP standards (Telonis, 2014).

Implementation Guides for ISO IDMP standards are currently under development as prCEN/ISO Technical Specifications (TS).

Since the electronic handling of terminologies, for instance as value sets for pull down menu's, and the storage of data elements in databases, where the value from a value set can be inserted, there is a fundamental discourse on what needs to go into the terminology model and what needs to be handled in the information model. After over 50 years this is not solved and probably never will. We only can make pragmatic choices and handle the inconsistencies, for example the reader is referred to the HL7 Terminology work that gives guidance on the information model choices and the terminology model choices, and their intersection. In epSOS the choices were made to solve significant issues at the information model and communication standard level and not in the terminology model. The example is presented in chapter 10, section 1.

In table 1 below an indication is given at which different levels identifiers / identifying characteristics from IDMP should be taken. However, it is not in the scope of the framework to redo the IDMP set in detail. However, it becomes clear from the examples that appropriate terminologies are required, clarifying that we need more than one terminology.

Table 1				
Simplified illustration of where information model and terminology model meet				
Topic	IDMP	Information Model example	Terminology model example	To do
Overall structure	IDMP class model	Each identifier and descriptor gets its own class	Each class would need its own terminology to identify the class itself and to populate the class	Create terminology system, its OID and next an actual name/code for each class; e.g. to identify a class that represents the PhPID concept. Concrete "IDMP terminology", OID "123.456.789.0" Code "PhPID" as mnemonic code and "987654" as instance code.
Pharmaceutical product	PhPID CEN ISO 11616	IDMP / DCM / HL7 Common Product Model	RX-Norm	Create the PhPID identification generator on international level. derived => globally unique
Regulated Medicinal Product	MPID CEN ISO 11615	IDMP / DCM / HL7 Common Product Model	regulated regional identifiers.	multiple identifiers possible for different jurisdictions
Dose	doseform CEN ISO 11239		EDQM European Directorate for the Quality of Medicine	pharmaceutical dose form
Substance	CEN ISO 11238		G-SRS & SMS Global Substance Registration System	
Strength	CEN ISO 11240		UCUM	
Packaging	CEN ISO TS 16791		Requirements for international machine-readable coding of medicinal product package identifiers PCID. medicinal product package identifier GTIN Global Trade Item Number (from GS1)	

7.2 Implementation Guides for ISO IDMP series

In the second year of the openMedicine project, deliverable 2.3 will go deeper into the IDMP implementation guides, currently under development.

7.3 Medicinal Product Package Identifiers

ISO TS 16791 Health informatics — Requirements for international machine-readable coding of medicinal product package identifiers discusses how the identifiers for packages are handled. This is a more logistical processes oriented technical specification. The scope of TS 16791 is to provide guidance on identification and labelling of medicinal products through the whole logistics from the point of manufacture of packaged medicinal product to the point of dispensing the product. It does outline best practice for AIDC bar-coding solutions for applications (AIDC is Automatic Identification and Data Capture). Where required, it does consider the coding interoperability requirements for other AIDC technologies such as Radio Frequency Identification (RFID). This standard refers to PCID, the medicinal product package identifier and the GTIN Global Trade Item Number (from GS1).

The relationship with MPID and PhPID are illustrated in figure 3.

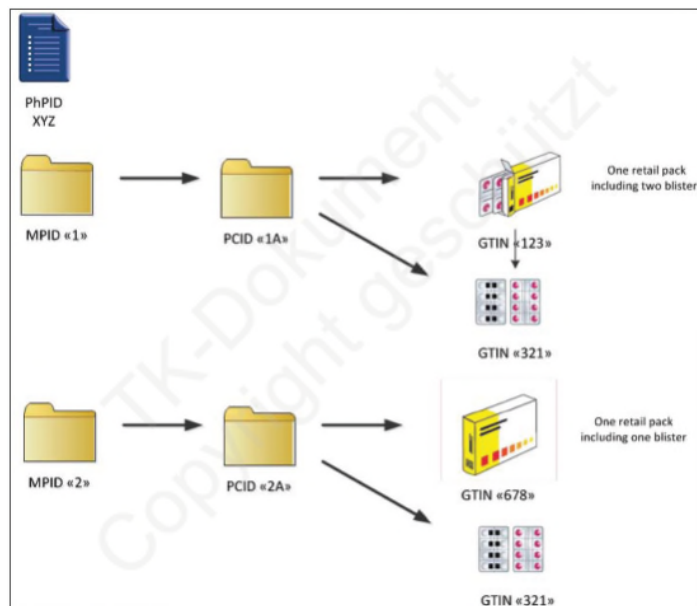


Figure 3 shows the relationship between various identifications of medicinal products.

7.4 GS1

GS1 is a standard development organisation, dedicated to supply chain efficiencies; since its origin in 1974 – focussing at that time to consumer goods – GS1 has expanded its members to over 20 domains, including Healthcare. GS1 develops and maintains a system of standards, which is addressing identification needs in the open supply chain. The system of standards is based on a common semantic (e.g. defining a “trade item”), a set of data carriers (bar codes and RFID tags) and number of business processes (electronic catalogues, traceability, etc.).

The GS1 Global Trade Item Number (GTIN) is widely used to identify medicinal product packaging (EN ISO 11615, § 3.1.52) sold for instance in retail pharmacies. When associated with attributes, such as batch/lot number, expiry date, the GTIN is usually carried in a GS1 Data Matrix and enables traceability by lot. In the context of the EU Falsified Medicine Directive, medicinal product packages have to be uniquely identified, that unique

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identification being carried in a 2-dimensional bar code (Data Matrix) as the delegated act will specify. It is expected the GS1 Data Matrix, including GTIN, batch/log, expiry date and serial number to fulfil the requirements from the delegated act with the easiest market penetration in the countries where the medicinal product packaging are already identified with a GTIN².

GTIN are not only used to identify retail packages, but as well for the identification of larger items (a carton containing several retail packs) or smaller items (an ampoule in a retail pack containing several ampoules). They are therefore useful for capturing traceability information along the supply chain, as well as verifying that the right medicinal product is going to be administered to the right patient.

7.5 Relevance of IDMP and identifiers for infostructure

The IDMP series of standards, including the related implementation guides form the heart of the openMedicine recommendations for identifying and describing medicinal products. These are the base for the infostructure and should be placed on the lowest level of the CGM cube, whereas the IDMP standards themselves are one level up, the data aggregations or groupings.

² Ireland, United Kingdom, Netherlands, Czech Republic, Poland, Finland, Estonia, Lithuania, Leetonia, Slovakia, Slovenia, Croatia, Rumania, Bulgaria; Spain, France, Austria, Iceland, Denmark, Sweden, Norway, Switzerland, Greece, Turkey

8 Dictionaries, Terminologies and Codes for Medicinal Products

This chapter contains actual terminological and coding systems, and their databases or dictionaries that specify and uniquely code concrete medicinal products. We need medicinal product terminology to populate our prescribing and dispensing communication information models and standards which needs to be used in a distributed and non-heterogeneous enterprise. This therefore requires a significant degree of multi-layer integration. In the GCM, this chapter covers the Y axis the data aggregations and the details level and from the X axis the information and to some extend computational viewpoints.

8.1 Medicinal Product Dictionary Systems

The EN ISO TS 19256 specifies what the goal is for a Medicinal Product Dictionary System (MPD-system), how it should look like and which use cases around medicinal products such a MPD-system should support. In particular, the focus is offering medicinal product data for use in prescription, dispensing and administration on the clinical care side. But it also covers logistics, maintenance and linkage to regulations for the authorized medicinal products and to pharmacovigilance. The MPD follows carefully the IDMP standards series, in particular for the proper identification of the medicinal products, and the descriptive attributes. The MPD system fits in the situations depicted in Figure 4.

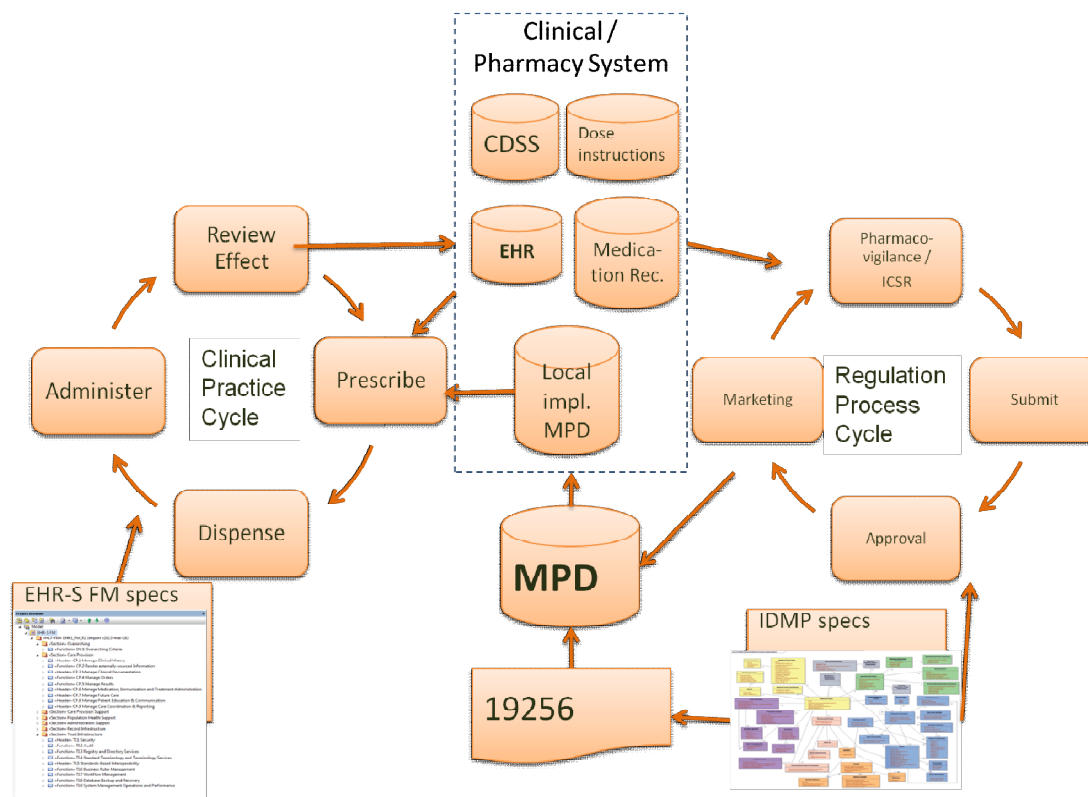


Figure 4: position of the Medicinal Product Dictionary System between healthcare processes and regulating processes. © EN ISO TS 19256.

8.2 Snomed CT

Snomed CT® stands for 'Systematized Nomenclature of Medicine – Clinical Terms'. Ownership and management of Snomed CT is currently with IHTSDO, International Health Terminology Standards Development Organization. Terminology can be seen as a structured collection of terms, organized in a systematic and logical manner, and carefully governed and maintained. Snomed CT a clinical terminology, consisting of terms that are used in health care. Snomed CT is a multi-hierarchical terminology that meets the requirements laid out by Cimino (1998) in the desiderata for controlled clinical terminologies, including concept and unique code permanence, poly hierarchies, exclusion of not otherwise specified and other criteria. Each of the nineteen Snomed CT hierarchies is organized on concept level, which allows to include several terms per concept (so it includes synonyms), and on relationships between concepts, such as genus - species relationships (mother - child, or 'x' is a 'w' relationship). Each concept in Snomed CT has a unique and never changing code, guaranteeing uniqueness. The relations between concepts are hierarchical within their base category. However, Snomed CT allows post-coordination of concepts between defined hierarchies (not all options are allowed). The hierarchies include more than 300.000 active concepts (IHTSDO, 2015):

- Clinical finding (finding, disease)
- Procedure
- Observable entity
- Body structure (Morphologically abnormal structure)
- Organism
- Substance
- Pharmaceutical/biologic product
- Specimen
- Qualifier value
- Record artifact
- Physical object
- Physical force
- Events
- Environments/geographical locations
- Social context
- Situation with explicit content
- Staging and scales
- Linkage concept (link assertion, attributes)
- Special concept.

IHTSDO has started several years ago with a group of pharmacists and other scientists to review the pharmaceutical / biological product axis. Although that group has had some meetings and conference calls in the beginning period, not concrete results have been made available. More recently IHTSDO restarted work on this, but for this deliverable of openMedicine it is too early to give concrete results. It is important however that the Snomed CT concepts for pharmaceutical products do match with the ISO IDMP series and with the ISO TS MPD 19256. We have solicited such content from IHTSDO, but there is no formal IHTSDO reports on this available, therefore we directly inquired with IHTSDO. We did get the following formal responses from IHTSDO.

Response 1. Snomed CT work on drug standards in progress (Green, 2015). This is included verbatim in this section: "The IHTSDO currently is aware of the increased profile of drug standards internationally. The IHTSDO also recognises the value of drug vocabularies such

as RxNorm, dm+d, ATC, and supporting standards such as MedDRA, IDNP, UCUM. SNOMED CT aims to provide a terminology interface in this space to support interoperability. Within the SNOMED CT International release, this will be undertaken by providing drug information to the level of Medicinal Entity and Medicinal Form. This will be enhanced at a national level by additional concept modelling to support nationally driven use cases, such as GTiN.

The IHTSDO will be undertaking the development of a customer driven drug concept model that will support the standard representation of drugs at a national level, but will not make an effort to populate the model internationally, due to the high variability of drug products in different realms.

IHTSDO will also collaborate with the GinAS initiative, and have begun analysing where there are gaps in the drug areas provided by other vocabularies. This activity has been undertaken in consultation with our customers, and is being used to inform our content development in this area going forward.” (Green, 2015).

Response 2. SNOMED CT substances update (Adelöf, 2015) is also included verbatim:

“Changes for January 2016 SNOMED CT International Release

- Concepts referring to “therapeutic intention and use” will be retired - these are not always true because feedback has identified these are not always true about a substance/drug
- Aim of the change is to improve the quality of the hierarchy, while minimizing impact to current ongoing content projects as well as to current implementations

These changes amount to 120 concept retirements. These changes are focused on grouper concepts, and are being done due to quality issues related to the allergy work and in support of the drugs project. This represents a small number of the proposed changes related to the much larger Substance Redesign project. The substance redesign work scheduled for the July 2016, will be focused on content referenced by the ‘Drug and medicament’ hierarchy and will be done so with full consultation with stakeholders.

The substance redesign work that is scheduled for 2017 and beyond. In view of the drivers for this piece of work and the urgency with which it is required, we have not undertaken a technology preview, as the size and impact of the work is relatively small. In the schedule for early 2017 there is a technology preview of the substances work, which will give the opportunity for IHTSDO Members and key stakeholders to feedback, which will be important as it relates to the redesign of the substances hierarchy in its entirety rather than a small number of concepts. We hope that colleagues making decisions about the future of substances in Europe would wish to engage with use on this work.” (Adelöf, 2015).

As part of openMedicine there is continuous interest in the development and use of Snomed CT. However, it are mixed messages that we get. EMA and the national medicines agencies are currently not expecting to use Snomed CT for the medicinal product. On the other hand, the openMedicine workshop in Spain revealed that Spain has created a National extension to Snomed CT in which the pharmaceutical data that require controlled terminologies where

developed and unique codes assigned. It is beyond the scope of openMedicine to give more particulars on what the various standards organizations, regulators or countries decide.

8.3 WHO DD

The WHO Drug Dictionary is an international classification of medicines created by the WHO Programme for International Drug Monitoring and managed by the Uppsala Monitoring Centre (Lindquist, 2008). The WHO Drug Dictionary contains data from 1968 onwards (Wallberg, 2009). Since 2005 there have been major changes that led to the WHO Drug Dictionary Enhanced, available via a web browser (UCM, 2015). WHO DDE is the most comprehensive and actively-used drug reference work in the world (UCM, 2015). For many stakeholders it is an indispensable source of medicinal product information for drug development and safety surveillance.

WHO DD(E) is an online database with information about medicinal products from all over the world (Wallberg, 2009). It does contain data about medicinal products and information related to them in a relational database system. WHO DD includes a Drug/Medicinal Product classification with a structure to allow easy and flexible data retrieval and analysis. It has classifications of chemicals and of indications, hierarchically ordered to allow different levels of precision and to facilitate navigation and aggregation. Substance names are included according to International Non Proprietary Names (INN) and drugs are classified according to the Anatomical-Therapeutic-Chemical (ATC) classifications system (Wallberg, 2009). Further it holds information on companies and reference sources, in particular proprietary names for both single-ingredient and multiple-ingredient medicinal products and the same goes for nonproprietary/generic names. Codes and IDs are offered for each entry. Linkages between products with the same ingredients (generics and brands) and Linkages between products containing the same base ingredient, but different salt/esters (Wallberg, 2009). No entries are deleted even though they are withdrawn from the market, since old case reports might be coded with these products (Wallberg, 2009). Withdrawn products are marked as OLD FORM.

8.4 Anatomical Therapeutic Chemical Classification

In the Anatomical Therapeutic Chemical (ATC) classification system, the active therapeutic substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties (WHO, 2015). The goal of ATC is to support pharmacoepidemiology. It is not intended for use in clinical practice, but we do see many clinical practice uses of ATC codes, such as in HL7 v3 prescription and dispense messages.

The WHO ATC classifies drugs at five different levels.

- On level 1, the drugs are divided into fourteen main groups representing the anatomical main groups. For instance, dermatological drugs.
- On level 2, the pharmacological/therapeutic subgroups are placed. For instance, diuretics.
- The 3rd level contains pharmacological subgroups, such as e.g. blood glucose lowering drugs, excl. Insulins.
- The 4th level defines chemical - therapeutic subgroups. For example, sulfonamides.

- Finally, level 5 is the chemical substance, e.g. metformin

The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups. ATC is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOC), and was first published in 1976 (WHO, 2015). (www.whocc.no/)

Each bottom-level ATC code stands for a pharmaceutically used substance, or a combination of substances, in a single therapeutic area (or use). Exceptionally, some drugs can have more than one code, in case substantial differences in dose or route of administration lead to different indications. Acetylsalicylic acid (aspirin), for example, has A01AD05 as a drug for local oral treatment, B01AC06 as platelet aggregation inhibitors, and N02BA01 as an analgesic and antipyretic. The ATC classification is used to group several different brands sharing the same active substance and indications under one code. Hence; it is not intended for specific identification of specific Medicinal Products (named entities).

8.5 Dose forms and other materials (EDQM)

The European Medicines Agency (EMA) provides detailed guidance on data submission formats for authorization process for medicines. The website of EMA (EMA, 2015) lists a substantive set of guidance documents, related to data submission for authorised medicines³. This would include the legal notice, detailed guidance documents and controlled vocabularies for the Extended EudraVigilance Product Report Message (XEVPRM) schema.

The controlled vocabularies of the European Directorate of Quality of Medicines (EDQM) provide standard translations for standard terms of basic descriptors of medicinal products (e.g. route of administration, pharmaceutical forms). Harmonisation work needs to be done with similar value sets of EpsOS, SNOMED CT, and the international harmonisation efforts between Europe, US, and Japan.

One example is the specification of dose forms for medicines. D 1.1 from openMedicine specifies in more detail the relevance of this part (section 3.4.4). This is the set of internal controlled vocabularies for pharmaceutical dose forms, which includes basic dose forms, intended site, administration methods, among others. All terms used have a unique code and a definition, rendering the EDQM an important vocabulary for medicinal products.

8.6 Unified Code for Units of Measure (UCUM)

To express units of measurement in health information technology, developers and implementers often refer to the UCUM system: Unified Code for Units of Measure (Shadow, McDonald, 1999a). According to the website, UCUM supports an unambiguous electronic communication of quantities together with their units (Shadow and McDonald, 1999a). The Unified Code for Units of Measure (UCUM) is referenced for units of measure because it is a code system intended to include all units of measures being contemporarily used in international science, engineering, and business. The focus for UCUM is on electronic communication between systems, in contrast to human to human communication. The typical

³ <https://standardterms.edqm.eu>

applications of the UCUM are its use in electronic data exchanges, such as based on Health Level 7 messages and documents. The Unified Code for Units of Measure is hosted on the website: <http://unitsofmeasure.org/> and currently maintained by the Riegenstrieff institute.

For openMedicine it is important to know that medication strength expressed as a measurable / physical quantity (type PQ) is exchanged using UCUM. And also when pertinent data for medication use are exchanged, and have a physical quantity measure, this is also expressed with UCUM. For instance, where an HL7 v3 Observation / value is a physical quantity, the unit of measure shall be expressed using a valid UCUM expression. UCUM has a unique OID that specifies its use in messages: `<element key="UCUM" value="2.16.840.1.113883.6.8"/>`.

The following table shows a few example values from UCUM (Table 2):

Table 2. UCUM example.	
UCUM	Descriptive Name
kg/m2	KiloGramsPerSquareMeter
mm2	SquareMilliMeter
mmHG	MilliMetersOfMercury
10*3	Thousand
[ft_i]	Feet
Cel	DegreesCelsius

How this is used in a template is specified in Table 3.

Table 3 Example Unit Of Body Weight from an ad random HL7 CDA guide		
Value Set: Unit Of Body Weight 2.16.840.1.113883.11.20.11.17		
Code	Code System	Print Name
kg	UCUM	kg
[lb_av]	UCUM	lb

Figure 5 shows this in an XML representation as excerpt from HL7 v3.

```
And the equivalence in HL7 XML
<code code="3141-9" codeSystem="2.16.840.1.113883.6.1"
  codeSystemName="LOINC" displayName="Weight Measured"/>
<statusCode code="completed"/>
<effectiveTime value="20150527"/>
<!-- SHALL with unit (not value) constrained to ucum valueset of kg/pounds -->
<value xsi:type="PQ" value="67" unit="kg"/>
```

Figure 5. XML presentation of UCUM unit of measures.

8.7 UNique Ingredient Identifier (UNII)

The United States Pharmacopeia (USP) and the Substance Registration System (SRS) of the Food and Drug Administration (FDA) are linked to the UNique Ingredient Identifier (UNII). UNII is a non-proprietary, unique, unambiguous, non-semantic, alphanumeric and free identifier linked to a substance's molecular structure or descriptive information. The format for UNII is ten alphanumeric characters long. It is randomly generated and does not contain any inherent information on the type of substance.

The SRS generates permanent and unique identifiers for substances in regulated products. These do include ingredients in drugs and in biologic products and are based on the molecular structures and where required additional descriptive information that defines a substance. The SRS generates the UNII for each substance.

8.8 Terminology for multilingual substance descriptions

The controlled vocabularies of the European Directorate of Quality of Medicines (EDQM) have been described in a previous section, as is the required harmonisation work among value sets internationally. Chemical substances are named entities which can be named at the chemical level or the therapeutic level (in gradual levels from abstractions (e.g. amlodipine for the collection of pharmaceutical products containing the base “amlodipine”, regardless of the esters used (e.g. “amlodipine besilate” and amlodipine “mesilate” as the specific names for specific combinations of base and ester). These substances can be coded and identified in different coding systems (CAS, ATC, PubCHEM, CHeBI, IUPHAR, etc.) or named with standardized vocabularies (UIPAC, International NonProprietary Nomenclature (INN), SNOMED CT). INN is multi-lingual, so is Snomed CT.

In the European system for periodic updates of safety reports (PSUR) a list is maintained (EURD-List). The EURD list includes the active substances and combinations of active substances contained in medicines subject to different marketing authorisations and authorised in more than one Member State. It is a list of abstracted names of therapeutic

substances (and their marketed combinations) for which one single safety report is maintained⁴ (EMA, 2015).

A national drug database used for searching a medicinal product is obviously available in that country's national language(s). The openMedicine PhPID, to be used in cross border identification is language independent. If used in both country of prescription and country of dispensing, there is no need of translation anymore. In all other cases a translation is required, as in epSOS.

Efforts are made for a standardized approach to the translation of international reference terminologies such as ATC, ICD, and subsets of SNOMED CT. For SNOMED CT translations, international governance has been installed. For other terminologies, an emerging expert center is the French Health Terminology/Ontology Portal (HeTOP), located in Rouen, France (see SHN Deliverable 3.3 Annex 3)⁵. Within SHN, a web-based, collaborative approach to maintenance of such multilingual translations of classifications or value sets has been proposed (see SHN Deliverable 3.3 Annex 2 and 5).

Beyond the identification of medicinal products, there is also regulated terminology regarding rational use and drug safety (contra-indications, indications, adverse drug reactions). For instance, the terminology of adverse drug reaction reporting is highly linked to systems such as MEDDRA and WHO-ART. MedDRA is (to be) used in the registration / authorization and in the pharmacovigilance track. MedDRA is licensed for use as an adverse event reporting terminology. It is probably not used for prescribing dispensing or clinical medication purposes. MedDRA is not to be considered as a medicinal product identifying attribute. If it would be used for contra-indications, it would need rewriting and extending its scope (see ongoing discussions in ISO IDMP work). Also SNOMED CT lists a number of these clinical terms. Probably interface terminologies to these reference terminologies need to be build. The approach to build such an interface terminology was outlined in a pilot project around Heart failure (Cardillo, Warnier, Roumier et al, 2013). With the advent of regulated patient drug information in patient package inserts, the European commission has supported multi-terminological efforts around glossaries for patient terms (see Annex 1 of SHN Deliverable D3.3).

For the identification of medications, for safe interchangeability, and for efficient risk/benefit communication to physicians and patients, it is important to control to some extent the creation of drug groups. The tables of content of important international drug information sources such as the British National Formula, or the Dutch Farmacotherapeutisch Kompas are mono-hierarchic classifications of brands, active substances into groups. There is a big variety in classifying drug groups, sometimes reflecting diverging clinical medical cultures. These groups and/or classifications are important in cross border substitution of medicinal products in case no match is found in the country of dispensing. Of course we consider for granted that the "grouping" meets regulatory and marketing requirements applicable in the

⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000361.jsp&, (last assessed on August 28, 2015)

⁵ <http://www.semantichealthnet.eu/index.cfm/deliverables/>. Last assessed on August, 28, 2015

country of dispensing. Efforts have been made to adopt a systematic, multi-hierarchical approach to classifying drugs according to chemical structure, therapeutic intent, working mechanism, etc. (Hanna et al, 2013). Drug Classes are important because the members of these classes may or may not share common effects and side-effects. Belonging to a drug class is a fundamental aspect of a medicinal product. Many of the items in drug information (e.g. in drug-drug interactions) refer to cross-referencing of information between drug classes (Furberg, 2000, Garcia-Serna & Mestres, 2010, Smith, Harrison and Morgan, 2011, Soares & Carneiro, 2002).

8.9 RxNorm

An example standard, out of scope for this deliverable, but so often referred to is RxNorm. RxNorm is a standard for the over the counter and/or prescribed drugs in the United States. The National Library of Medicine (NLM) created and maintains RxNorm (NLM, 2015). RxNorm is a normalized naming system for both generic and branded drugs. To prevent confusion, in particular when exchanging electronic drug information, RxNorm provides normalized names and unique identifiers for medicines and drugs. Further, RxNorm is also a tool supporting semantic interoperation between drug terminologies and pharmacy knowledge base systems. The latter for instance to detect drug-drug interactions.

8.10 Controlled Terminologies relevance for infostructure

For the infostructure a robust set of controlled vocabularies / terminologies are relevant. For various descriptive attributes of a medicinal product these are required, such as EDQM for dose forms and UCUM for units that already have been determined. However, ongoing work will come up with future decisions which controlled terminology will be used for the other data elements. In the overall infostructure controlled terminologies should be placed on the lowest level of the y axis. They are relevant in particular for both the openMedicine clinical use cases of prescription, dispense and record keeping and therefore can be taken from the IDMP standards, which originally are created for regulation use cases. However, some recommendations apply: structure determines what terminology will fit (IDMP is the base structure here). And Purpose determines the structure. Hence, the use case and goal oriented approach in openMedicine.

9 Other terminological standards relevant for epSOS ePrescription

This chapter contains actual terminological and coding systems that specify and uniquely code additional data that can be relevant in epSOS ePrescription, such as the reason for prescribing. In the GCM, this chapter covers the Z axis such that it bridges the medical and the pharmacy domains, on the Y axis the data aggregations and the details level and from the X axis the information and to some extent computational viewpoints.

9.1 International Classification of Diseases (ICD)

The International Classification of Diseases (ICD) from the World Health Organization (WHO, 2015) is the standard statistical tool for reporting epidemiology, in particular mortality and morbidity incidence and prevalence data. In the past decades this statistical classification has increasingly been used for health management, in particular reimbursement, and is used more and more for clinical purposes to document medical diagnoses in electronic health records, and decision support. ICD applications include the analysis of the general health situation of populations, and it is used all over the world. The main goal of ICD, its current version is 10 is to promote international comparability in the collection, processing, classification, and presentation of vital health statistics about diseases in populations. The ICD is published and maintained by the World Health Organization, it is implemented by all the European Union Member States. It is used by Eurostat as a standard code list for the classification of diseases (Joinup, 2015). The ICD has been used since the 1900s with ICD-1 until now with ICD-10. ICD-11 should be operational by 2017 (WHO, 2015). ICD 10 includes a chapter on allergies against substances / medications. This is Z88 Personal history of allergy to drugs, medicaments and biological substances (Figure 6).

Z88	Personal history of allergy to drugs, medicaments and biological substances
Z88.0	Personal history of allergy to penicillin
Z88.1	Personal history of allergy to other antibiotic agents
Z88.2	Personal history of allergy to sulfonamides
Z88.3	Personal history of allergy to other anti-infective agents
Z88.4	Personal history of allergy to anaesthetic agent
Z88.5	Personal history of allergy to narcotic agent
Z88.6	Personal history of allergy to analgesic agent
Z88.7	Personal history of allergy to serum and vaccine
Z88.8	Personal history of allergy to other drugs, medicaments and biological substances
Z88.9	Personal history of allergy to unspecified drugs, medicaments and biological substances

Figure 6. The ICD 10 chapter on allergies.

For epSOS it is an important resource to accompany data on medicinal products in electronic health records and electronic messages, in particular the Patient Summary. It helps to identify the reason why a given medicinal product was prescribed. In general, it is not included in the ePrescription. However, in some jurisdictions privacy ruling might prohibit to include the medical diagnoses for reading of the patient summary by some professionals.

In epSOS allergies are managed differently from ICD 10. Allergies to drugs are identified by ATC. Allergies to substances are identified by SNOMED-CT. In both case, the severity is expressed with SNOMED-CT terms. Currently, the ICD 10 Zxx codes are excluded from epSOS Valuesets.

9.2 International Classification for Primary Care (ICPC)

The International Classification of Primary Care (ICPC) was published in 1987 by WONCA (*World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians*). It is part of the WHO family of classifications and information of version 2 is published on the WHO site: <http://www.who.int/classifications/icd/adaptations/icpc2/en/>. The ICPC is available on CD-ROM in some languages, and more recently also online: <http://icpc.who-fic.nl/browser.aspx>.

According the WHO, the ICPC-2 classifies patient data and clinical activity in the domains of General/Family Practice and primary care. The classification is partly based on the frequency distribution of problems seen in these domains. This way the patient's reason for encounter (RFE), the problems/diagnosis managed, interventions can be classified, and ordered in an episode of care structure in a medical record (both paper and electronic).

ICPC is not included among epSOS Patient Summary code systems/valuesets. However some Member States (e.g. Portugal) have to map it into ICD-10 Illness & Disorders Value Set to be transferred abroad.

9.3 MedDRA®

The Medical Dictionary for Regulatory Activities (MedDRA®) is an international highly specific and standardised medical terminology. MedDRA® is used to facilitate sharing of regulatory information internationally for medical products that are used by humans. In particular, it is used by regulatory authorities in the pharmaceutical industry during the regulatory process. In addition, it is the adverse event classification dictionary endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA is used to classify adverse event data from clinical trials; from spontaneous adverse event reports by health care professionals, patients and others; and from other sources of adverse event data (MedDRA, 2015).

MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® trademark is owned by IFPMA on behalf of ICH.

MedDRA® is organized in five levels of categories and codes. The top level starts with System Organ Class (SOC), such as aetiology, infection, surgical procedure, which then is divided into High-Level Group Terms (HLGT), High-Level Terms (HLT) include anatomy, pathology, physiology, aetiology or function descriptors. Preferred Terms (PT) which are distinct descriptors (single medical concepts) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic. Finally, the lowest level includes about 70.000 Lowest Level Terms (LLT), describing the clinical observations (MedDRA, 2015). MedDRA® includes openMedicine_deliverable_T1 3_InfostructureStandardsFramework-v1.1PostReview Page 40 of 99 31/05/2016

Standardized MedDRA Queries (SMQs) to facilitate retrieval of MedDRA® coded data. SMQs are groupings of terms that relate to a defined medical condition for example anaphylactic reactions.

For data entry for Individual cases the data are coded at the most specific (LLT) level, and outputs of counts at the PT level. The higher levels (HLT, HLGT and SOC) and the SMQ are used for searching and subtotalling reports (MedDRA, 2015).

In accordance with Article 57(2) of Regulation 726/2004, marketing authorisation holders (MAHs) are obliged to electronically submit information on all medicinal products authorised for human use in the European Union (EMA, 2015). As part of the electronic submission of information for authorised medicinal products, the authorised therapeutic indications should be provided using the MedDRA® dictionary for coding (EMA, 2015). According EMA (2015), the MedDRA® codification of an indication should be provided in the form of the most suitable low level term (LLTs).

9.4 Additional Terminologies relevance for infostructure

For the infostructure additional clinical controlled terminologies that support use cases as for prescription are relevant. In particular, the reason for prescription can be taken from e.g. ICPC or ICD 10, and/or Snomed CT. On the other hand, MedDRA is important for the pharmaceutical industry, and has no clinical relevance. In the overall infostructure also the clinical oriented controlled terminologies and the industry oriented vocabularies should be placed on the lowest level of the y axis. However, here it is important to link it to the top level, which stakeholders will apply what terminology, in order to prevent errors in its application. The medicinal product dictionary is the key health IT application that will bring the information from the EU and national regulators to the hands of a clinician or pharmacist to deliver good quality health care through medications.

Important for this deliverable is that the terminologies form a crucial part of the infostructure, however, their identification, development/selection is work that is ongoing at both ISO and FDA/EMA level. It is beyond the scope of this deliverable to come up with a final listing.

10 Information and communication standards

This chapter presents various standards that are relevant for the electronic exchange of medication data. These would require and implement the medicinal product identifiers. In the GCM, this chapter covers the y-axis for (communication) processes, data aggregations and details and from the x-axis the information and computational viewpoints. HL7 (i.e., epSOS) addresses the information / computational view and IHE the process viewpoints such as the workflows and interactions.

10.1 epSOS specifications

The epSOS Large Scale Pilot specified, implemented and operated the cross border services of ePrescription / eDispensation. A citizen, while abroad (Country B), needs to retrieve an ePrescription generated in his Country of Affiliation (Country A). The Pharmacist from the Country of Treatment (Country B) can request the List of Valid Prescriptions, select with the citizen which one has to be dispensed, receive the selected prescription (transcoded and translated), and dispense all (or part) of the prescribed medications. If needed and allowed, the pharmacist can perform a generic substitution. One or more eDispensation documents are returned to Country A, to allow the (partial) fulfilment of the ePrescription.

Spain, Italy, Sweden, Finland, Denmark and Greece piloted ePrescription / eDispensation with real patients, Hungary and Croatia activated the service with test patients only.

In scope of epSOS were:

- Electronic Prescriptions
- Medicinal products for human use
- Community pharmacies
- Substitution of commercial packaging

Out of epSOS scope were:

- Narcotics/Magisterial preparations/Treatment/procedure/clinical test prescription
- Reimbursement management
- Specific and complicated topics like narcotics and sealed prescriptions
- Hospital pharmacies and drug administration

In the Country of Affiliation, the ePrescription is generated to DESCRIBE the prescribed Pharmaceutical Product. In special cases (e.g. when substitution is not allowed) the Medicinal Product is identified. In the Country of Treatment, the ePrescription is translated into the local language, to allow to the Pharmacist to IDENTIFY the Medicinal Product to be dispensed. eDispensation created to describe and identify the dispensed medicinal product.

It is left to the Country of Affiliation to decide which prescriptions are valid at the time of request (i.e. they can be dispensed) and which one can be safely transmitted abroad, avoiding patient safety risks (e.g. because of lack of structured/coded information). It is left to

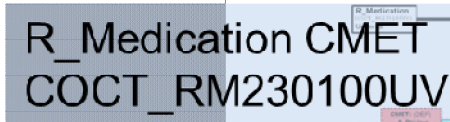
the pharmacist to decide on what can be dispensed, applying the Country of Treatment legislation.

The adopted exchange format is HL7 CDA v2 Level 3 (the so called epSOS Pivot CDA document, supported by the original signed ePrescription in pdf, embedded in a CDA v2 Level 1⁶).

- The ePrescription document has 1..1 Prescription Section (1.3.6.1.4.1.12559.11.10.1.3.1.2.1) [derived from the CCD 3.9 (2.16.840.1.113883.10.20.1.8)].
- The prescription section has 1..N entries conformant with the Prescription Item template (1.3.6.1.4.1.12559.11.10.1.3.1.3.2)
- The Prescription Item includes 1..1 consumable.manufacturedProduct element conformant with the Medicine Content Entry template (1.3.6.1.4.1.12559.11.10.1.3.1.3.1) [with epSOS CDA extensions]
- CDA classes Manufactured Product and Material have been enhanced with attributes and relationships of the Medication and Medicine classes from the R_Medication CMET (COCT_RM230100UV).

Figure 7 provides a schematic picture of the adopted model. It is unreadable, for the details the reader is referred to the actual materials. Figure 7 specifies in different classes the various levels of identification of medicinal products. For instance, at the bottom the substance, one level up the medicinal product, and above that again the package identifier (the green coloured classes). Each class has specific attributes that help to specify details. However, this model is quite complex and has many relationships identified. Therefore, epSOS summarised the core data elements that must be present in the ePrescription. Figure 8 illustrates the current representation of the medicinal product in epSOS, indicating which elements are compulsory and which other are optional, together with the adopted coding systems (Table 4).

⁶ The detailed implementation guide of epSOS ePrescription is provided in epSOS D9.1 “epSOS Pilot System Component Specification”; “Appendix B1/B2: Implementation v1.4 (http://www.epsos.eu/uploads/tx_epsosfileshare/D3.9.1_Appendix_B1_B2_Implementation_v1.4_20110725_01.pdf).



class Conceptual_1

```
classDiagram
    class ePrescription {
        +Active ingredient [1..N]
        +Country A Cross-border/regional/national medicinal product code [0..1]
        +Medicinal product package
        +Pharmaceutical dose form
        +Brand name of the medicinal product prescribed in country A [0..1]
        +Strength of the medicinal product [1..N]
        +Instructions to patient [0..1]
    }
```

ePrescription::Medicinal Product

- + Active ingredient [1..N]
- + Country A Cross-border/regional/national medicinal product code [0..1]
- + Medicinal product package
- + Pharmaceutical dose form
- + Brand name of the medicinal product prescribed in country A [0..1]
- + Strength of the medicinal product [1..N]
- + Instructions to patient [0..1]

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Table 4 required code systems in epSOS

Required	Optional
Active ingredient (WHO ATC)	Country A Cross-border/regional/national medicinal product code
Strength of the medicinal product (UCUM)	Brand name of the medicinal product prescribed in country A
Medicinal product package (EDQM, UCUM)	Route of Administration (EDQM)
Pharmaceutical dose form (EDQM)	

openMedicine D1.1 “epSOS identification/description problems” analyses epSOS Use Cases and specifications. In particular Chapter 3: “Issues/showstoppers and proposed workaround” list the issues encountered during the pilot and the solutions implemented or just proposed.

In summary the main issues to identify medicinal products were:

- epSOS Member States agreed to adopt WHO ATC to describe active ingredient, being the only code systems common to all, knowing in advance it was not adequate to describe complex Active Ingredients
- In most of the Member States, structured and coded data to describe the complex and special pharmaceutical product characteristics, were not available
- The adopted model was not adequate to cover all products, especially complex multiproduct packages

So there is no common medicinal product identifier, medicines are currently described by a set of structured attributes.

10.2 IHE profile on exchange of prescriptions

IHE (Integrating the Healthcare Enterprise) is focused on the dynamic model of communication about medicines. IHE produces profiles for the clinical workflow. Also a proposal was brought to ISO to report that format. IHE, specifically the IHE Pharmacy domain, produces and updates a technical framework for the medication workflows. The IHE technical framework references other standards (like HL7 and LOINC) and profiles them to establish consistent healthcare information exchange. IHE work is relevant for the contextual requirements for D 1.3, in particular to better track and trace the workflow and communication about medications and the corresponding data exchange.

The IHE Pharmacy Technical Framework⁷ presents mechanisms for ordering, dispensing and administration of medicinal products in community settings and hospital settings.

⁷ http://ihe.net/Technical_Frameworks/#pharmacy

For community settings, IHE profiles the use of CDA documents. The CDA content in the relevant IHE templates (Prescription and Pharmaceutical Advice) was designed in alignment with epSOS. Recent evolutions in the specification of both epSOS and IHE Pharmacy have introduced some divergence⁸.

The information model in IHE is summarized as follows (Figure 9):

- **Actors** represent a defined functionality or component of an interoperable solution. It refers to a technical component, not to a human being / health professional. The IHE Pharmacy actors currently relevant for OpenMedicine are
- **Prescription Placer and Pharmaceutical Advisor** – The actors are responsible for creating and changing orders for treatments
- **Dispenser** – Actor responsible for retrieving prescriptions, dispensing, and reporting the outcome of the dispensing
- **Transactions** are the information objects created and consulted between actors. The IHE Pharmacy transactions currently relevant for OpenMedicine are the **Prescription** (and **Pharmaceutical Advice**), and, to lesser extent, the **Dispense**.
- There is a **separation between the transactions and the workflow**. The management of prescription workflows (e.g. determining whether a prescription can be dispensed, etc.) is separate and not contained in the transactions. The transactions only contain the metadata needed for this (e.g. if the prescription is validated).

In IHE Pharmacy, prescriptions are sent to (and then retrieved from) a repository using standard IHE XDS transactions. The continuity of treatment and workflow are ensured by an actor called Pharmacy Manager, which determines whether a prescription can (still) be dispensed, and keeps track of any eventual changes to the prescription.

For IHE, both the Community Pharmacy Manager and the Treatment Manager are common, to ensure the technical interoperability between prescribers and dispensers. This is appropriate for intra-border prescription and dispense. In cross-border dispensing, the repositories may be shared but the role of Community Pharmacy Manager may not be existing or not central.

⁸ This divergence between epSOS and IHE (and other standards) will be revisited in deliverable D2.2

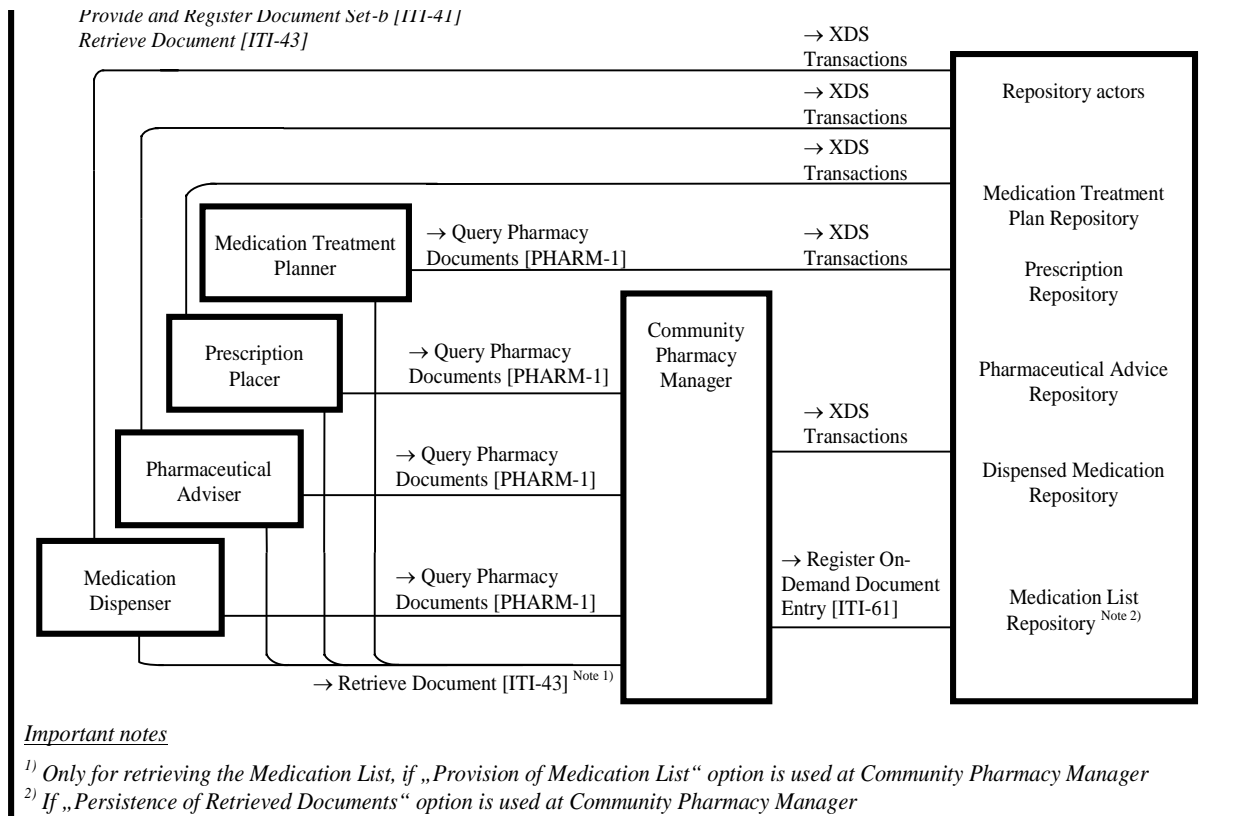


Figure 9. IHE representation of the medication process.

In the Technical Framework, IHE Pharmacy includes the data necessary to identify the medicinal product, as well as conditions for dispense. This includes "generic name" or "brand name", quantity, etc.

In terms of data available and needed, some important considerations in IHE Pharmacy:

- The identification of the product between different systems is assumed by means of providing common codes and vocabularies. IHE Pharmacy specifications do not contain a solution for the challenge in OpenMedicine.
- The treatment may be updated during its lifecycle. A "prescription" document is not changing (due to auditability reasons) but the treatment changes are captured in documents.
- In the several actions in the workflow - e.g. dispensing - the participants must consult the "currently valid" treatment. This is "produced" based on the prescription, the changes, etc.
- The decision to dispense may require checking previous dispenses from the repository. This is one of the data attributes described in the deliverable D2.2⁹.

The analysis of the data elements in D2.2 and its comparison with the standards provides an overview of these data elements and how they exist in other standards.

⁹ openMedicine D2.2 Comprehensive set of openMedicine identifying and descriptive attributes of medicinal products and the available standards

10.3 Individual Case Safety Report (ICSR)

ISO 27953-1:2011 seeks to establish an international framework for data exchange and information sharing by providing a common messaging format for transmission of ICSRs for adverse drug reactions (ADR), adverse events (AE), product problems and consumer complaints that can occur upon the administration or use of one or more products.

The messaging format for ICSR is based upon the HL7 Reference Information Model (RIM) and can be extended or constrained to accommodate a variety of reporting use cases. ISO 27953-1:2011 will be harmonized over time with other HL7 public health and patient safety reporting standards to help ensure that messaging constructs and vocabulary are harmonized in the HL7 Public Health and Regulatory Reporting domains.

The data elements used in ISO 27953-1:2011 were identified as consistent across many of the use cases and can be applied to a variety of reporting scenarios. Specific reporting requirements within organizations or regions might vary.

ISO 27953-2:2011 seeks to create a standardized framework for international regulatory reporting and information sharing by providing a common set of data elements and a messaging format for transmission of ICSRs for adverse drug reactions (ADR), adverse events (AE), infections, and incidents that can occur upon the administration of one or more human pharmaceutical products to a patient, regardless of source and destination.

10.4 ICSR Implementation Guide for Europe

During the development and following the marketing authorization of medicinal products in the European Economic Area (EEA), requirements apply for electronic reporting and evaluating suspected adverse reactions (EMA, 2013). Regulation (EC) No 726/2004, Directive 2001/83/EC as amended and Directive 2001/20/EC outline these requirements to EudraVigilance, the data processing network and management system of the European Medicines Agency (EMA).

EudraVigilance was developed by the Agency in full compliance with the specifications of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (EMA, 2013). ICH agreed to use the International Organization for Standardization (ISO) Individual Case Safety Report (ICSR) standard ISO EN 27953 - 2 to meet the reporting requirements for E2B(R3): EN ISO 27953 - 2:2011 Health Informatics, Individual case safety reports (ICSRs) in pharmacovigilance — Part 2: Human pharmaceutical reporting requirements for ICSR (ISO 27953-2:2011).

ICSRs shall be used for reporting to the EudraVigilance database suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time [IR Art 27] (EMA, 2013). The EudraVigilance database should contain all cases of suspected adverse reactions that are reportable and be based on the highest internationally recognized data quality standards.

To achieve these objectives, all stakeholders should adhere to:

- The electronic reporting requirements as defined in EU legislation;

- The concepts of data structuring, coding and reporting in line with the EU legislation, guidelines, standards and principles (EMA, 2013).

The implementation guides specify in detail the interactions between stakeholders, and the data elements, their coding, and their XML representation.

This guide is, similar to epSOS, using HL7 v3 messaging for the exchange of data. Relevant for openMedicine is that it already gives guidance on the XML representation of the MPID from ISO 11615, and with more details on substances and on the PhPID from ISO 11616 (Table 5 and figures 10 and 11. Albeit, some OIDs are still missing, pending the completion of ISO implementation guides for this.

Table 5 - Medicinal Product Identifier (MPID) data element (from ICSR) (G.k.2.1.1b, D.8.r.2b, D.10.8.r.3b)¹⁰

User Guidance	This data element captures the Medicinal Product Identifier (MPID)
Conformance	Optional
Data Type	250AN
OID	To be confirmed after ISO IDMP IGs are made available
Value Allowed	Free Text
Business Rule(s)	Mandatory if D.8.r.2a, D.10.8.r.2a, G.k.2.1.1a is populated

XML Snippet for the MPID

```
<code code="4" codeSystem="2.16.840.1.113883.3.989.2.1.1.20" displayName="drugInformation"/>
<component typeCode="COMP">
  <substanceAdministration classCode="SBADM" moodCode="EVN">
    <id root="3c91b4d5-e039-4a7a-9c30-67671b0ef9e4"/>
    <consumable typeCode="CSM">
      <instanceOfKind classCode="INST">
        <kindOfProduct classCode="MMAT" determinerCode="KIND">
          <code code="GB-XYZ Pharma-13456" codeSystem="EU.OID.MPID"11 codeSystemVersion="1"/>
          <name>Fastaction FlexPen 100 IU/ml Solution for injection</name>
```

Figure 10. XML Snippet for the MPID

¹⁰ The codes have the following meaning in the ICSR: in the ICSR medicinal product is captured in three different contexts: The first is the drug(s) the patient is taking at the time of experiencing an adverse drug reaction (G.k.2.1.1b), the second is the patient's medical drug history. This is capture other drugs the patient has taken in the past but are unlikely to still be in the patient's body at the time of the adverse event (D.8.r.2b). The final section relates parent-child reports where a child is exposed to a drug taken by a parent, typically via a transplacental or transmammary route, this section captures the parent's drug history rather than the patient's (child) (D.10.8.r.3b) drug history.

¹¹ This is a placeholder for the actual OID from the organisation that gives the instance identifications for MPID.

XML Snippet for PhPID

```
<code code="4" codeSystem="2.16.840.1.113883.3.989.2.1.1.20" displayName="drugInformation"/>
  <component typeCode="COMP">
    <substanceAdministration classCode="SBADM" moodCode="EVN">
      <id root="3c91b4d5-e039-4a7a-9c30-67671b0ef9e4"/>
      <consumable typeCode="CSM">
        <instanceOfKind classCode="INST">
          <kindOfProduct classCode="MMAT" determinerCode="KIND">
            <code code="13456" codeSystem="EU.OID.PHPID"12 codeSystemVersion="1"/>
            <name>Fastaction FlexPen 100 IU/ml Solution for injection</name>
```

Figure 11 - XML Snippet for PhPID

The implementation in HL7 v3 is published in the normative edition and ballots as Draft Standard for Trial Use (DSTU) in the Regulated Reporting domain as Safety Report Management Topic, and uses the HL7 v3 Product Model PORR_RM049011UV (HL7, 2015).

10.5 Electronic Prescription Requirements

ISO/DIS 17523 Health informatics — Requirements for electronic prescriptions is a work in progress that provides the basic set of requirements that is needed to define which information is minimally required to accompany electronic prescriptions in order to have exactly the required medicine dispensed to the patient. This includes all relevant information with regard to its correct and safe use. Hence, it specifies generic principles that are considered important for all electronic prescriptions. Furthermore, it specifies a list of elements that can be considered core elements that are essential for all electronic prescriptions or for electronic prescriptions in certain jurisdictions, or in different clinical settings (primary health care, hospital, etc.).

The scope of DIS 17523 is constrained to the content of the prescription electronic prescription itself, the digital document which is issued by a prescribing health professional and received by a dispensing health professional. The prescribed product is to be dispensed directly or through an appointed authorized health professional with the aim to be administered to a human patient. DIS 17523 does not indicate any mandatory data elements, but if a data element specified in DIS 17523 is used, it should meet the requirements.

A comparison between ISO DIS 17523 and epSOS implementation guide will be provided in future deliverable 2.3¹³, after finalization of the ISO ballot for 17523.

10.6 HL7 v3 Common Product Model

The Pharmacy domain in HL7, specifies the domain message information model (D-MIM) for pharmacy, from which all concrete messages are derived in the form of Refined Message Information Models (R-MIMs). The HL7 Pharmacy domain deals with messaging to support the prescription, dispensing, and administration of medications and Medication Knowledge Base Queries in both a Community and an Institutional setting (HL7, 2015). Ongoing work

¹² This is a placeholder for the actual OID from the organisation that gives the instance identifications for PhPID.

¹³ openMedicine D2.3 openMedicine final identifying and descriptive attributes

harmonizes the use of the core components such as the `AdministerableMedication` for use in both messages and clinical documents (CDA's).

The base model for the medicinal product in most HL7 v3 specifications are based on a so called Common Message Element Type (CMET) represented as a logical constrainable model in HL7 UML, and from this model a proper HL7 v3 XML template is derived. In the previous section on epSOS examples of the used templates identified with an OID and expressed in HL7 v3 XML were presented. That template would ideally be the Common Product Model, which is currently in ballot at HL7 international June – July 2015. The Common Product Model in HL7 v3 is used to align between different representations of (medicinal) products used within the payload of HL7 Version 3 messages (HL7, 2015a). According the HL7 ballot, one goal of this effort is to make it possible to achieve a single representation, which can be used as a CMET across the models of different domains in HL7. One of the users of the Common Product Model is the HL7 Pharmacy Workgroup who contributed to its creation in a co-production with other HL7 workgroups.

Due to the use of Common Product Models, CMETs and the HL7 templating mechanism, increasingly such base materials can be used in overall structures as messages or Clinical Documents (CDA).

Another group using these base materials for Common Product Model includes the Regulated Products domain. The Regulated Product domain currently contains specifications addressing Regulated Product Submission, and Structured Product Labeling or SPL (HL7, 2015b). The topics in this domain support approval of regulated products that includes, but is not limited to, medical devices, drugs, biologics, veterinary medicine, and food and feed additives. Due to the nature of HL7 v3 developments, for each application a domain specific guideline must be created, such as which was the case for epSOS.

Currently, SPL 7 only describes the document data structures specification. Throughout various releases 2-6 of SPL, harmonization was undertaken. Originally SPL 2 consisted of 3 parts: (1) document data structures, (2) data structures describing the product, and (3) data structures describing the clinical use of the product. The "Product Instance" was added in release 4 supporting listing of devices and biologics, among others. Since SPL R5, the SPL product data elements specification has become the HL7 Common Product Model (CPM). Now, SPL simply makes normative reference to the CPM. According HL7, all of the SPL product data elements are now defined in the CPM. Therefore, for the use within epSOS and Patient Summaries, the CPM should be considered, as was done above.

10.7 Antelope Project

eHealth Interoperability is a major policy topic in Europe, critical for the development of Member States' national or regional eHealth services. Current policies address services that rely on the availability of reliable and interpretable data exchanged between healthcare systems used by patients and health professionals. Several recent cross-border projects such as epSOS¹⁴, Calliope¹⁵ and its governance roadmap, HITCH¹⁶ for interoperability

¹⁴ <http://epsos.eu/>

¹⁵ <http://www.calliope-network.eu/>

testing recommendations and roadmap, the eHealth European Interoperability Framework (eEIF) for the definition of the standards adoption process, use cases and identification of business use cases and EHR-QTN17 with a roadmap for functional quality assessment of EHR systems asked for clarity on policies and standards for eHealth interoperability (Antilope D 7.3, 2015).

According to Antilope (2015), a good level of (semantic) interoperability could be the result of converging actions and investments if they are understood and positioned in a consistent enabling framework. Thus, the Thematic Network Antilope was set up to support the dissemination and adoption of such an Interoperability Framework. Antilope built further on recommendations, roadmaps, national/regional and local Interoperability projects. Between 2013 and 2015, the Antilope project was focused on the dissemination and adoption of the eHealth European Interoperability Framework (eEIF) as defined by the eEIF study published in July 2013. Antilope developed guidelines and recommendations that support the eEIF. Antilope developed a consistent framework that help projects or implementers to deploy their own interoperable solutions. Antilope consists of several interrelated components that support different stages of a project, e.g. specifications, implementations and testing processes.

The Antilope comprehensive and usable framework enables the development of a unified market and improves the quality of the projects and solutions in eHealth and consists of the following four results:

- The refined eEIF in version 1: The Antilope framework offers tools to solve interoperability problems with respect of consistency over Europe. It proposes a level scheme that lists the multiple aspects of interoperability that projects need to take care of. In addition, a set of use cases, profiles and their implementation guidance are described for underlying standards for a concrete and interoperable implementation.
- The Quality Management System for Interoperability Testing: The Quality Management System (QMS) for interoperability testing offers customizable descriptions and a set of templates for interoperability testing.
- A coherent set of Testing tools: a portfolio of testing tools for testing the recognized use cases and profiles from the eEIF. Further, it offers an inventory of recommended open source testing tools available.
- Quality label and certification processes: Antilope finally provides organizational models, examples and guidance to preserve consistency at each level of organization, country and EU.

The Antilope results are available for (EU) projects already in progress, and for future projects to implement and deploy. Figure 12 shows how Antilope results can be taken up by projects and initiatives. It is not exhaustive, as Antilope results might be used in other projects as well.

¹⁶ <http://www.hitch-project.eu/>

¹⁷ Thematic Network on Quality Labelling And Certification of EHR Systems: http://ec.europa.eu/information_society/apps/projects/factsheet/index.cfm?project_ref=238912

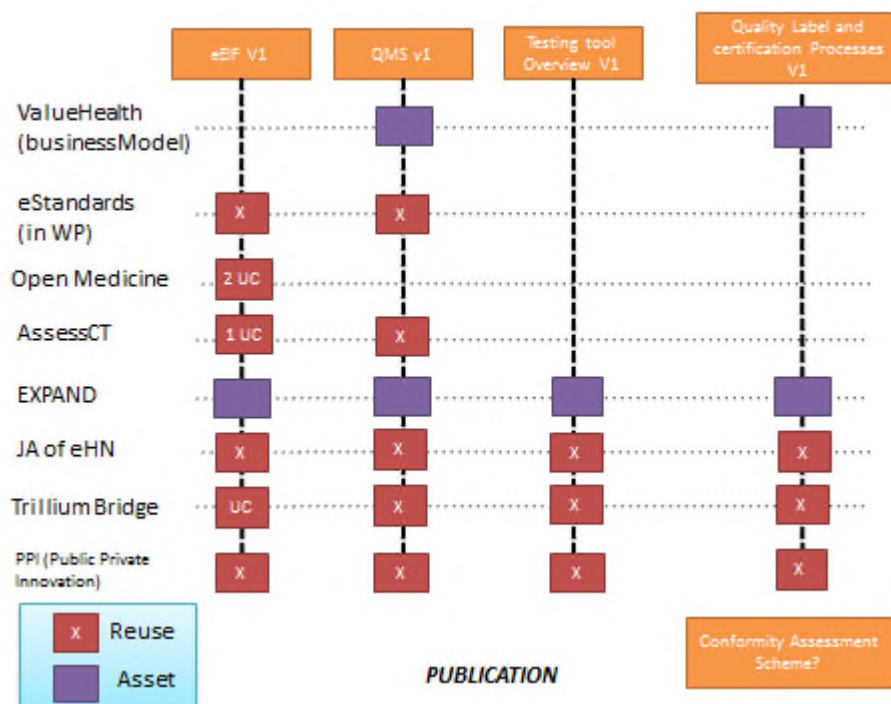


Figure 12: Re-use of Antilope assets in other EU projects and initiatives

The Assets (in purple) serve as input and references for the projects Health Value, EXPAND and Joint Action of eHN. These projects will provide feedback and suggest improvements of the assets. It is unknown if such a formal process for the governance of this process is established.

The results (in red) will be reused for the purpose of the respective project: selection of use cases, QMS for implementation, testing tools and quality label testing processes. In this way, the results from the Antilope deliverables will be actively used and live on in the projects. For openMedicine and hence epSOS, Antilope is relevant because it may influence how requirements are documented so that they can be properly tested.

10.8 Other projects

Of course, such a document is limited to the scope to look into relevant standards for epSOS ePrescription. It covers the European region. However, we must be aware that other projects and standards can be of relevance. One will be briefly discussed here as example.

The EU Trillium Bridge support action extends the European Patient Summaries (epSOS) and the US' Meaningful Use II, Transitions of Care in the United States (TrilliumBridge, 2015). The main goal of the project is to establish a semantic interoperability bridge for EU and US citizens alike. Both jurisdictions use an HL7 v3 CDA based patient summary, covering many of the same concepts, but using differences in operationalisation. The ultimate goal is advancing eHealth innovation and contributing to quality care, sustainability and economic growth on both sides of the wire.

10.9 Information standards role in the infostructure

For the infostructure the information standards focus on two levels from the GCM: processes and aggregations. IHE in particular creates profiles for specific processes, supporting specific use cases identified at the top level of the architecture. IHE profiles for ePrescription, eDispense and Record keeping and exchanging summaries form the core for the openMedicine infostructure. Once the process is identified and described, the appropriate information standard can be identified. This is in case of epSOS the HL7 v3 CDA, and in case of ICSR, it is a v3 message. However, of more interest for the infostructure is perhaps that these information standards help us bridge the health care world, such as clinical, pharmaceutical and more to the health IT systems world and facilitate the creation and use of well maintainable systems. The Antelope project, and in addition other EU funded projects helps to use and reuse existing materials, so that new projects can move beyond what was already established.

11 Contexts Standards for Exchange of Medicinal Product Identifiers

These standards including the architectural approach provide the abstract requirements to identify stakeholders for cross border data exchange, to focus on continuity of cross border pharmaceutical care that must be met in order to fulfil the use cases of cross border prescribing and dispensing of medicinal products.

This set of standards discusses the framework context for epSOS. Since epSOS concerns the exchange of data between various clinical systems, it is imperative to discuss the criteria for such systems in order to be able to meet the requirements for cross border exchange. In the GCM, this chapter covers mainly the y-axis for business concepts and from the x-axis the RM-ODP viewpoints, starting with enterprise viewpoints. Also, it covers the z-axis of linking multiple domains in healthcare together. However, of course, HISA moves with the x-axis and covers also information and computational viewpoints. RM-ODP of course spans the whole x-axis. Finally, 13606-2 and 13606-3 and the Detailed Clinical Model are best placed on the detail level of the y-axis and the enterprise and information viewpoint of the x-axis, also crossing many domains on the z-axis.

11.1 Top layer: Contsys

In order to manage complexity rationally, a layered approach of models is required. Following the GCM as defined as the guiding principle, we can identify various standards at different levels that help to keep an overview of the whole and at the same time allow zooming in at a detailed component. Such way forward helps to get the required precision at the most detailed level, while at the same time understanding how such a little detail fits in the overall structure and complexity of health care and the applied standards in health care.

The top level standard to be addressed here is the conceptual representation of healthcare and healthcare services as laid out in the Contsys standard (2015). The general aim for the ISO EN 13940 standard for systems of concepts for continuity of care (Contsys) is to provide a comprehensive, conceptual basis for content and context in healthcare services. Contsys should be the foundation for interoperability at all levels in healthcare organizations and for development of information systems in healthcare (Oughtibridge, 2014). Contsys relates to other standards in particular at the conceptual level it links to for instance Snomed CT medical terminology in which concepts and relationships are defined and organized. Contsys and terminologies will normally be used in logical reference (information) models that are abstract models holding the logics. Specific details are expressed in logical information models or detailed clinical models or DCM (Goossen, 2014). DCM allow clinical concept representations to be modelled independent of a specific implementation technology, facilitating standardization at detailed level and reuse in various physical or computational platforms. (Figure 13).

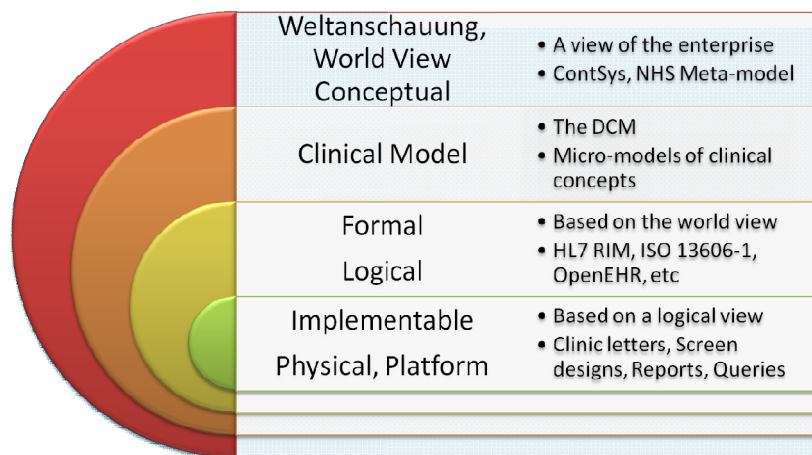


Figure 13. The relationship between Contsys and other levels of standards and models (Oughtibridge, 2014).

Contsys specifies the actors in the healthcare system, handling of health issues, the core processes and their time dimensions, activities, linkages to knowledge sources and data management in continuity of care. The latter is core for openMedicine because openMedicine tries to establish continuity in the use of medicinal products cross borders, where many health care information can be mapped to Contsys, allowing not only on the individual product to achieve understanding and interoperability, but also to allow from a specific jurisdiction to map actors, goals, rulings to equivalent components defined and grouped in Contsys.

11.2 Architecture for the standards framework

A generic architectural framework consists in general of four distinct layers: the business layer, the process layer, the information layer and the information and communication systems layer. This approach is largely influenced by the generic framework from The Open Group, or TOGAF¹⁸. It can be seen as the breakdown of the GCM y axis top level, via the y axis lower level to the x axis of system development, representing the enterprise view, informational view and computational views.

11.2.1 Health Informatics Service Architecture (HISA)

HISA is a three part CEN/ISO standard: EN/ISO 12967 Health Information Service Architecture. HISA provides guidance for the description, planning, development and integration of health information systems. HISA can be used both within one healthcare facility and across different healthcare organizations. The CEN/ISO standard describes an open and modular architecture integrating the common data and business logic into a specific architectural layer, and stays distinct from individual applications.

Architecture standards usually outline a layered framework which can be used in the development and integration of consistent, coherent health applications, such as Electronic Health Systems, databases and workstations. This is done through the definition construction

¹⁸ <https://www.opengroup.org/togaf/>

requirements and outlining of protocols for communications, within one healthcare organization, and for data exchange across healthcare organizations. It is in this respect that this three part standard is relevant for openMedicine.

EN/ISO 12967 consists of the following three parts: Enterprise Viewpoint; Information Viewpoint; and Computational Viewpoint. Each part handles a specific aspect of the health information service architecture such that it supports openness and vendor-independence. Each part will be described briefly.

11.2.2 Part One: Enterprise Viewpoint

Part 1, the Enterprise Viewpoint component, assumes that business, processes and information can be made accessible throughout the whole organization information ecosystem, for instance through services. It defines normalized interfaces for EHR-system applications and services. It makes use of the viewpoints as presented by ISO Reference Model Open Distributed Processing (ODP) standard: Enterprise, Information and Computational viewpoints, whereas the, sometimes separated layer of processes is included in the Enterprise part. The HISA standard provides a formal standard for a service-oriented architecture (SOA), specific for the requirements of health services. This part of the standard in particular sets forth the common enterprise-level requirements such as stakeholders, workflows, and authorizations that must be supported through the HISA.

11.2.3 Part Two: Information Viewpoint

ISO 12967-2:2009 specifies the fundamental characteristics of the information model to be implemented by the information ecosystem to provide a comprehensive and integrated management of the organization's data and to support the fundamental business processes of the healthcare organization, as defined in ISO 12967-1. This specification does not represent a fixed, complete, specification of all possible data that can be necessary in healthcare organizations. However, it does specify a set of characteristics, organization of individual information objects that are identified as fundamental and common to all healthcare organizations. The specifications were designed to be universally relevant, whilst being sufficiently specific to allow implementers to derive an efficient design of the information management for their organization.

11.2.4 Part Three: Computational Viewpoint

ISO 12967-3:2009 specifies the fundamental characteristics of the computational model to be implemented by a specific architectural layer of the information system. This part assumes implementation, via for instance a middleware environment, and provides a comprehensive and integrated interface to the common enterprise information systems. It supports the business processes of the healthcare organization, as defined in ISO 12967-1. It is designed to be universally relevant, whilst still being specific enough for implementers to derive an efficient design of the system for their organization. There is no explicit or implicit assumption about the physical technologies, tools or solutions to be adopted for its physical implementation.

11.3 RM ODP

The Reference Model of Open Distributed Processing (RM-ODP) serves as a coordinating framework for system development. RM-ODP comprises five components including the enterprise viewpoint, information viewpoint, computational viewpoint, engineering viewpoint and finally technical viewpoint.

- The enterprise viewpoint focuses on the purpose, scope and policies for the system. It describes the business requirements and how to meet them.
- The information viewpoint focuses on the semantics of the information and the information processing performed. It describes the information managed by the system and the structure and content type of the supporting data.
- The computational viewpoint enables distribution through functional decomposition on the system into objects which interact at interfaces. It describes the functionality provided by the system and its functional decomposition.
- The engineering viewpoint focuses on the mechanisms and functions required to support distributed interactions between objects in the system. It describes the distribution of processing performed by the system to manage the information and provide the functionality.
- The technology viewpoint, which focuses on the choice of technology of the system. It describes the technologies chosen to provide the processing, functionality and presentation of information.

RM-ODP assumes that in the enterprise viewpoint the requirements analysis is carried out and next, through a structured specification process, the technical system is created. This is the baseline in the generic component model as depicted in chapter 4. Of course, the RM ODP as a whole places itself on the x-axis of the GCM.

Due to the technology choices made in the past for epSOS ePrescription, i.e. the HL7 v3 CDA, we also need to reverse engineer from the technology viewpoint back to the information and enterprise viewpoints to see what can be improved. In particular, since a principle piece of information is missing: the medicinal product identifier, and the context of exchanging the prescription is hampered to specific contextual parameters at the enterprise level: different legislations cross border that are not attuned at the enterprise level.

11.4 Content of Electronic Health Records and Pharmacy Systems

Next level of standards, bridging the axis y, axis x and axis z from the GCM include those that define criteria for Electronic Health Records (systems) (EHR). For openMedicine, the EHR is important because it will hold the prescription and administration data, applying the specified identifiers and the appropriate terminology and coding, and data relevant for individual case safety reporting.

11.4.1 ISO 18308

ISO 18308 specifies the overall architecture of Electronic Health Records. It needs carefully distinction from the HL7 / ISO standard for the Electronic Health Record – System Functional

Model and Profiles (ISO/HL7 10781)). The primary distinction lies in the word System attached to the latter, but also the overall build up and scope for both differ.

ISO 18308 envisions an Electronic Health Record (EHR) in principle as a logical view on health data collected by professionals during a patient's life time. In other words, the 18308 looks at a consistent organization of data on behalf of an individual during many episodes of care, and combining the records of many professionals, even in different organizations. This is in contrast with the most currently used EHR-systems. Most systems are developed or at least configured to support one clinical domain (such as diabetes record system) or one professional (such as the GP EHR-system). ISO 18308 specifies health system objectives and several categories of requirements for EHR architecture. These include:

1. Requirements for the representation of clinical information. This includes data, health record entries, the contextual information and intra-record linkages, data specification, retrieval and views, workflow support. It implies for openMedicine that data structures around medicinal products, their identifiers and their position in overall models and processes is made explicit.
2. Communication and interoperability requirements. This includes applying interoperability standards in order to exchange data from one EHR-system to another, or to other healthcare IT applications. It implies for openMedicine to deploy interoperability standards, which is done through the epSOS specifications.
3. Ethical and legal requirements. This includes requirements as: health record provenance, record is for one subject of care only, proper identification, authorization and attestation for EHR data entry, locations, date time and version management. It implies for openMedicine that such requirements are met in the specifications and can be exchanged from one EHR and or pharmacy system to another.
4. Fair information principles should be applied. This includes accountability, purpose orientation, consent, limiting the reuse of data, access policies, access by subject, and audit ability. For openMedicine it implies that such fair information principles are used both at sending and receiving systems, facilities and professional levels.

11.4.2 HL7 EHR-S FM

The Electronic Health Record System Functional Model (ISO/HL7 10781), further EHR-S FM specifies the concrete functional requirements and conformance statements for EHR systems. Various Functional Profiles (FP's) are derived from this EHR-S FM, such as for public health, cardiology, child care, meaningful use testing, and others (ISO/HL7 10781). The EHR-S FM function list is defined from the user perspective to enable consistent expression of system functionality (ISO/HL7 10781). The HL7 EHR-S Functional Model defines a standardized model of the functions that may be present in EHR Systems (ISO/HL7 10781).

The EHR-S Functional Model does not address whether the EHR-S is a system-of-systems or a single system providing the functions required by the users (ISO/HL7 10781), but within the normative sections of the Functional Model, the term "system" is used generically to cover the continuum of implementation options. Interoperability is in the EHR-S FM considered both from semantic (clear, consistent and persistent communication of meaning)

and technical (format, syntax and physical connectivity) viewpoints (ISO/HL7 10781). This EHR-S FM does not address or endorse specific implementations or technology, nor does it include the data content of the electronic health record. Finally, the EHR-S Functional Model supports research needs by ensuring that the data available to researchers follow the required protocols for privacy, confidentiality, and security (ISO/HL7 10781).

Currently the functions are specified in 7 sections (Figure 14):

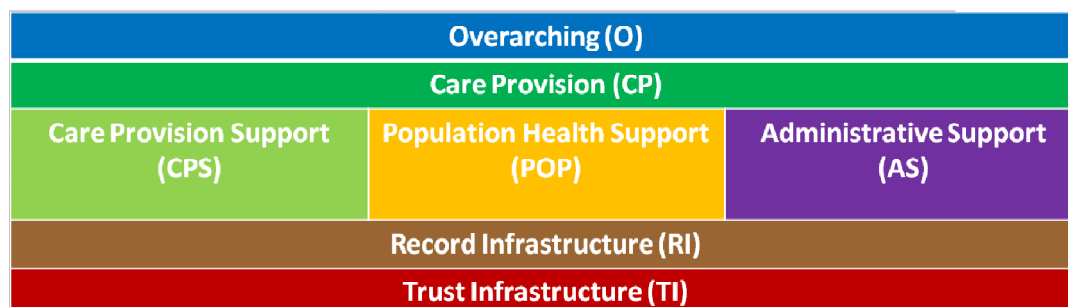


Figure 14. Sections of the Electronic Health Record System Functional Model (ISO/HL7 10781).

11.4.3 Pharmacy ISO / HL7 EHR-S Functional Profile

ISO – HL7 Electronic Health Record System Functional Model (EHR-S FM) release 1 has a specified profile for medication. A Functional Profile is a specification which uses the Functional Model to indicate which functions are required, desired or implemented for certain EHR systems, healthcare delivery settings, or for other purposes. This Pharmacist/Pharmacy Provider Functional Profile will facilitate EHR systems capturing clinical medication related data at the point of contact or point of care. The Pharmacist/Pharmacy Provider Functional Profile specifies the functional requirements needed to support messaging among prescribers, pharmacist/pharmacy providers and other healthcare entities needing medication related information.

The Pharmacist/Pharmacy Provider Functional Profile is derived from the HL7 EHR-S FM Release 1.1 dated June, 2009. An update to a release 2 Pharmacist/Pharmacy Provider Functional Profile based on the EHR-S FM Release 2, March 2014, is under way. This document provides significant functional and descriptive requirements that are relevant to D1.3's framework.

11.5 EN ISO 13606 Series

One particular ISO standard set of importance to the openMedicine work is the 13606 series on electronic health record communication. In order to get a patient summary filled with the proper clinical content, this content must first be entered and stored in an EHR. The 13606 series is a so called multipart standard, consisting of 5 distinct but closely related contents. Part one specifies a reference model, part two a specification language for archetypes, part two example archetypes, part four security settings for record content, and part five exchange technology specifications. This set of standards is currently undergoing a revision.

- ISO 13606 Electronic health record communication - Part 1: Reference model

The challenge for continuity of care is called EHR interoperability. This requires a generalized approach to represent every type of health record data structure *in a consistent way*. This includes records arising from any profession, specialty or health service. It must be able to address all kinds of the clinical data sets, value sets, templates, etc. that are required by different healthcare domains. This is normally quite diverse, complex and it will change frequently as clinical practice and medical knowledge advance. The 13606 series supports the widely acknowledged health informatics challenge of *semantic interoperability*. ISO 13606-1 can be seen as an information viewpoint specification as it is defined in ISO/IEC 10746-1. It is not intended to specify the internal architecture or database design of EHR systems.

The approach adopted by ISO 13606 distinguishes between generic properties of health record information expressed in the Reference Model and archetypes that specify detailed clinical content. The reference model is specified in part 1. The Reference Model represents the general characteristics of health record components, how they are organized and aggregated, and the context information required to meet ethical, legal and provenance requirements. This 13606 reference model defines the classes that form generic building blocks of the EHR. It reflects the characteristics of electronic health records that remain stable over time. ISO 13606-1:2008 specifies the communication of part or all of the electronic health record (EHR) of a single identified subject of care between EHR systems, or between EHR systems and a centralized EHR data repository, for continuity of care or with systems for secondary data use. 13606-1 may also be used for EHR communication between an EHR system or repository and other clinical applications such as decision support systems, or with middleware components, e.g. to store patient records in clinical data ware houses. Principle is that the process needs to access or provide EHR data, or represent EHR data within a distributed (federated) record system. It predominantly supports the direct care given to identifiable individuals, or to some extent support population monitoring systems such as disease registries and public health surveillance where individual cases must remain recognizable e.g. through pseudonymisation.

Use of health records for other purposes such as teaching, clinical audit, administration and reporting, service management, research and epidemiology, which often require anonymisation or aggregation of individual records, are not the focus of ISO 13606-1:2008 but such secondary uses might also find this document useful.

- ISO 13606 Part 2: Archetype specification

The subject of the EHR or EHR extract to be communicated is an individual person, and the scope of the communication is predominantly with respect to that person's continuous care. This second part of ISO 13606 defines an archetype model to be used to represent archetypes - small models for clinical data specification. Archetypes are used to specify clinical content in the context of the Reference Model. It defines a serialized representation of data elements, which may be used as an exchange format for communicating. An archetype is a formal and computable expression of a distinct, *domain-level concept*, expressed in the form of constraints on data whose instances conform to the Reference Model. Consys and 13606 are aligning the overall picture of continuity of care with the details that should be expressed in archetypes. E.g. Consys identifies the stakeholders and their processes, where 13606-2 specifies the medication archetype with the various characteristics.

According to ISO 13606-2: “For an EHR Extract, as defined in this part of ISO 13606, an archetype instance specifies (and effectively constrains) a particular hierarchy of RECORD_COMPONENT sub-classes, defining or constraining their names and other relevant attribute values, optionality and multiplicity at any point in the hierarchy, the data types and value ranges that ELEMENT data values may take, and other constraints.” The use of archetypes is supported, but not made mandatory, by this part of ISO 13606. A specification for archetypes is defined in this part: the archetype definition language or ADL.

- ISO 13606 Part 3: Reference archetypes

Part three of ISO 13606 is for the communication of part or all of the electronic health record (EHR) of a single identified subject of care, and defines term lists that each specify the set of values that particular attributes of the Reference Model defined in ISO 13606-1 may take. It also defines informative reference archetypes that correspond to ENTRY-level data structures within the Reference Models of for instance *openEHR* and HL7 Version 3. This enables those instances to be represented within a consistent data structure when data is communicated between EHRs and/or other systems. If applied for medication prescription and / or dispense, the EHR would need to have medication sections, and accommodate archetypes handling the prescription, the dispense, the medicinal product, the pharmaceutical product and such.

- ISO/TS 13606 Part 4: Security

Part of ISO 13606 describes a methodology for specifying the privileges to get access to EHR data. The methodology addresses the requirements that uniquely pertain to EHR communications and to represent and communicate EHR-specific information that will inform decisions within the system to allow access. General security requirements that apply to EHR communications are not included, but are referred to. ISO 13606-4 points at technical solutions and standards that specify details on services meeting these security needs. In particular role based access policies for the different layers in the reference model from ISO 13606-1 are addressed, allowing details.

- ISO 13606 Part 5: Interface specification

This part of ISO 13606 specifies the information architecture required for interoperable communications between systems and services that provide EHR data or that need them for continuity of care or secondary data use. This part of ISO 13606 does not specify the internal architecture or database design of such systems.

ISO 13606-5 defines a set of interfaces to request (query) and provide (response): an EHR_EXTRACT for a given subject of care as defined in ISO 13606 part one; one or more ARCHETYPE(s) as defined in ISO 13606 part two; an EHR_AUDIT_LOG_EXTRACT for a given subject of care as defined in ISO/TS 13606 part four.

This part of ISO 13606 defines the set of interactions for requesting each of these artefacts, and for providing the data to the requesting party or declining the request. This part five of ISO 13606 defines the Computational Viewpoint for each interface, but it does not specify or restrict particular engineering approaches to implement these as data exports, services or messages. This part of ISO 13606 effectively defines the payload to be communicated at each interface.

11.6 Context standards role in the infostructure

For the infostructure the context standards try to combine the little pieces into a broad perspective. Again, depending where one is looking from, various contexts can be identified and analysed. HISA identifies the core levels of an architecture. Contsys gives a thorough set of concepts and describes the main processes in health care, linking them to the overarching business, and linking them to details as in aggregations and details of data elements. The other standards in this chapter focus on requirements for Electronic Health Record systems that would have to support the health business, the processes, the data aggregations, and finally the single data elements. The requirements standards facilitate creating of health IT in order to enable e-health strategies come true, and such a process can systematically be supported with RM-ODP, following the x-axis of the GCM.

12 openMedicine and Clinical Modelling

The epSOS specifications have been looking at two kinds of clinical modelling: HL7 v3 templating against the CDA and to some extent archetypes against the EN ISO 13606-2. Some of the problems epSOS experienced are probably caused by taking a too technology driven approach. That is that not the quality of the model drove the implementation, but implementation specifications as HL7 version 3 CDA XML and ADL version 1.4 were taken for granted to fit the clinical content into. These technical or physical representations have their limitations for exchange of semantics, in particular for cross-border purposes, where context determines what can or must be exchanged and what can be interpreted. For instance, ADL 1.4 does not have a clear code binding from a data element to a unique code such as from Snomed CT, rendering it too difficult to follow up on the IDMP standards in particular where IDMP expects a controlled vocabulary. In this chapter we will list the specific identifiers and descriptive attributes that IDMP expects and these will be cross checked against the use cases ePrescription, dispense and record keeping.

12.1 Two-level Modelling

Since the invention of two-level modelling for electronic health records (Rector et al, 1993) many collections of Detailed Clinical Models (DCM) have been established that can be used and reused. Review of six clinical modelling approaches revealed both commonalities and differences between existing approaches (Goossen et al, 2010, Goossen and Goossen-Baremans, 2010). Interestingly, the differences concern the abstract modelling layers, while the single data elements are often equivalent. The DCM approaches reviewed include ISO 13606 archetypes, OpenEHR archetypes, HL7 templates for v3 Care Record message and for v3 CDA, Intermountain Health Care Clinical Element Models (CEM), Korean Clinical Contents Models and finally the Detailed Clinical Models based on Unified Modeling Language (UML) practiced by HL7 International and in the Netherlands.

However, since 2010 three additional initiatives evolved (Goossen, 2015b):

1. Clinical Information Modeling Initiative (CIMI). CIMI uses the archetype definition language (ADL), but upgraded this to version 2.0 (and ongoing work to higher versions) which overcomes many of the limitations of older archetypes. ADL 2.0 now includes code bindings for instance so that the linkage between information modelling and terminology can better be realised.
2. Fast Health Interoperable Resources (FHIR)[®] from HL7. Instead of the earlier v3 approach, FHIR standardizes 80% and leaves 20% open for local extensions and uses Restful interfaces and JSON, supporting apps and mobile devices world. An issue for openMedicine can be that FHIR allows non standardized content, hence hampering interoperability, in particular cross border. FHIR looks to be totally on the Info model side.
3. Semantic Health Net deploys ontology based modelling, using the Web Ontology Language (OWL) and Resource Description Framework (RDF) representations in which the triplets are the core (Martínez-Costa et al, 2015). RDF triples can support the information model / terminology model intersection, but to date this has not been implemented in EHR or pharmacy systems.

Sorting out if models specified in one physical implementation specification can be transformed into another technical format is supported using a differentiation approach between conceptual, logical and physical models (ISO TR 11179, Cuggia, 2009, Goossen and Goossen-Baremans, 2010). Another approach to the analysis is the place of DCM in multidimensional health systems architectures, for instance the Generic Component Model (Blobel, 2010). Blobel et al (2014) also suggest linking DCMs in any technical format to the various ontologies in health care (Blobel et al, 2014). None of the current DCM approaches is meeting all requirements against architectures and ontologies in full.

For epSOS the implication is clear: it is not sufficient to map the data elements from country to country or from country to the reference technical representation in HL7 v3 XML, but it is important to also position the whole process in the multi-layered health care business, the ICT development process and to check for cross domain consistency. As stated before, this is relevant for legislation, for workflow, for the reason for prescription and additional factors identified in D 1.1. And in particular, this must be consistent between prescription and dispensing levels, and it must be consistent between the terminology used, and the informational structures in the EHRs and pharmacy systems and communication specifications. With respect to the architectural aspects, DCMs, and also their technical representations, would position on the lowest level of specification in the y axis of the Generic Component Model, i.e. the most granular detail of health information management: the single data elements and the relevant code system where appropriate. This lowest level of data element specification and terminology binding is the most commonly addressed in any DCM specification, and is independent of the technology used (Goossen et al, 2010).

Most DCM developments do follow this architecture line top down. But all requirements and solutions have to be analysed and defined top down and bottom up recursively. Develop, implement and then test with explicit examples. The implication most often emerging from a single top down approach is that all materials specified on a lower level inherit some characteristics from a higher level. In the example of epSOS, this is illustrated through the use of the architectural approach in the HL7 Clinical Document Architecture, which has three levels: 1 document information describing the stakeholders and business goal (i.e. exchange of data), 2 document structure including the actual clinical goal (such as ePrescription for a given subject) and 3 detailed clinical data entries, (such as the prescribed medication, the dose, the route of administration and more).. All subsequent data element specification such as diagnoses, context, medication prescription and dispense data, and concrete values are fitted in. That does have some advantages in the information technology approach, which is why CDA is popular with some implementers. The CDA approach itself does not cause the problems, however, the top down approach might not sufficiently address the required details. For that, a more bottom up approach is important: the precise analysis of the details, in the case of epSOS the details of medicinal product identifiers that address the substance, the pharmaceutical product, the medicinal product and the package identifiers, and in addition the describing attributes. In contrast to this “top down fit all in a CDA” approach to clinical modelling, which is mimicked in the ISO 13606-1 reference model, Goossen and Goossen (2010), following some of the recommendations by Guccia et al (2009), specified a bottom up approach along the GCM. The main advantage of the bottom up approach is that the core of the data is analysed and specified, without being bothered by the top down requirements that are addressed better on other levels in the GCM.

The main advantage of two level modelling for this is the reuse of models in many different contexts, or as Blobel et al (2014) argue, in various ontologies. This would position DCMs to the lowest level in a specific approach, such as EN ISO 13606, HL7 v3 CDA or epSOS. However, some reuse options across domains, across use cases, and across technologies are hampered by only using the top down approach. In particular, only top down limits the flexibility of DCMs for multi-compositionality in the health systems architectures. For example, when it is clear that a medicinal product has four layers of data specifications (substance, pharmaceutical product, regulated medicinal product and package) we can specify all relevant data elements that need to be exchanged. When the DCM is finalized for the medicinal product, and the interests of different use cases are further made explicit in D 2.3 (See openMedicine D 1.2 for the various use cases for identification of medicinal products, and chapter 6 for the actual use cases for D 1.3), it becomes clear that both clinical processes as prescription, dispense, and administration and logistic processes as ordering, delivery and billing, and regulation processes as marketing authorization, inclusion in medicinal product dictionaries can all be supported by the same clinical model. From the detailed specification that covers the conceptual and logical level, it is quite a simple step to various implementation specifications. However, each use case will add additional requirements to the data and hence to the model, e.g. who is the prescriber, how should the medicinal product be used, how often and under which circumstances. These use cases require different models, at a higher level of abstraction, and indeed are compositions of multiple detailed clinical models. For this deliverable, we have selected the first set of use cases only to create the initial DCM. This will be explained in the next part.

This becomes even clearer when we look at the x-axis of the Generic Component Model: the coordinating framework of the Reference Model of Open Distributed Processing (RM-ODP). This framework comprises the following five components: the enterprise viewpoint, information viewpoint, computational viewpoint, engineering viewpoint and finally technical viewpoint. In this framework, the DCMs are useful in the enterprise, information and computation viewpoints. Hence, this is loosely following the conceptual, logical and physical model layers of ISO TR 11179.

Blobel et al, (2014) suggest that DCM work needs to be completed with (multiple) ontologies. However, Blobel et al (2014) accept multiple ontologies in the multidimensional space of GCM; ontologies of health care systems, ontologies of information technological systems, and the ontologies of the various (clinical) domains. DCMs have their specific position in each of the three axis of the Generic Component Model. And in the domain axis (z) this is to support reuse of models in adjacent domains. That is in particular relevant for the clinical domain around medicines, the logistic domain of medicines and the regulating domain of medicines. If the model is created well, it can serve all three domains and hence support proper identification and usability in the various practices, while at the same time preserving overall consistency for clinical, logistical and regulation purposes, also cross border.

12.2 Detailed Clinical Models

Technical Specification CEN / ISO TS 13972 describes requirements and recommended methods against which clinicians / stakeholders can gather, analyse and, specify the clinical context, content, and structure of Detailed Clinical Models, and govern them. Detailed Clinical Models (DCMs) are logical models of clinical concepts useful for defining and

structuring clinical data elements. A well-formed DCM includes: 1) medical content and medical contexts, 2) specification of data elements, relationships, and attributes, 3) code bindings to medical terminologies, 4) meta-data and versioning, and 5) governance of DCMs. The TS further defines how to achieve logical model accuracy, and DCM development and the methodology principles supporting the production and governance of quality DCMs to minimize risk and ensure patient safety. DCMs offer maximal detail and precision, without specifying these details in one specific computer programming language such as archetype definition language or eXtended Markup Language.

Figure 15 specifies the five key parts of any DCM

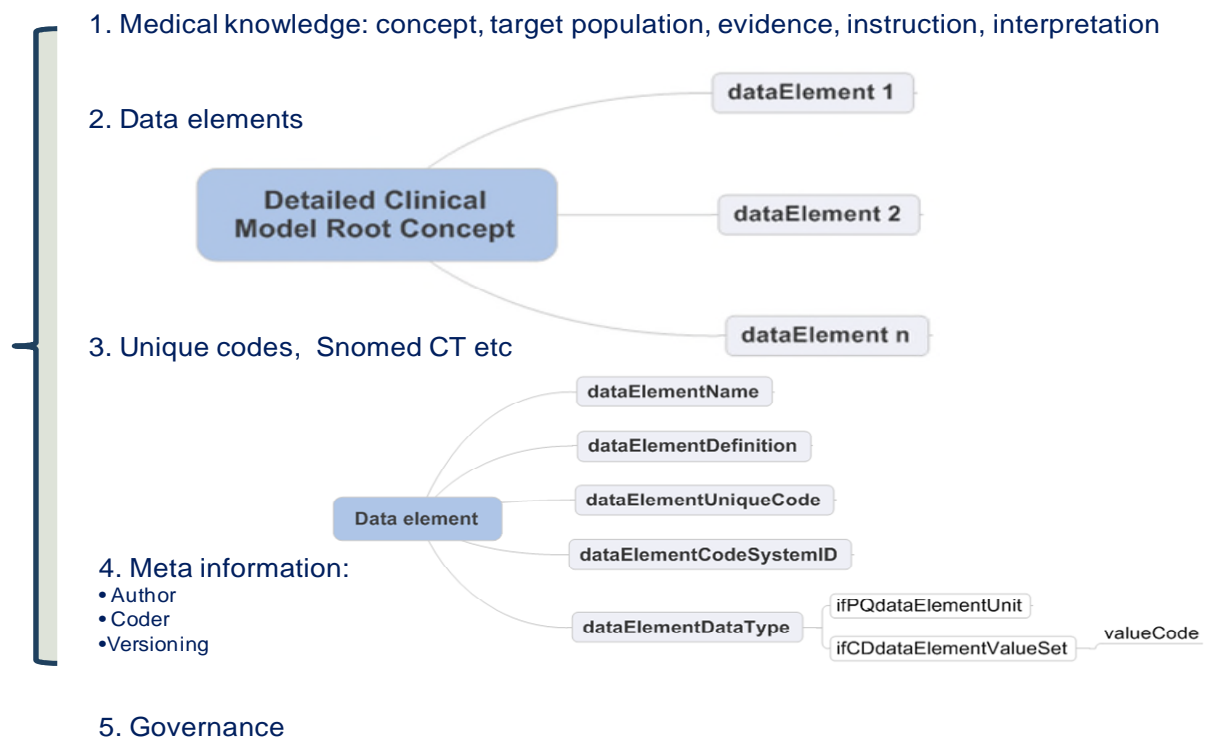


Figure 15. Five key parts of a Detailed Clinical Model: 1 medical knowledge, 2 data elements starting with root concept, 3 unique codes, 4 meta information and 5 governance.

12.3 IDMP data elements relevant for ePrescription

We decided to start a systematic review of all data elements that are specified in the IDMP standards against their usefulness for the ePrescription use cases. Because underlying work for several use cases is still underway in openMedicine we focus in particular on “basic” Use Cases for ePrescription, dispense and record keeping 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.13, 1.14, 1.15, 1.16, 1.17, 1.18 and 2.1. The others deal with either topic that will be addressed later in openMedicine such as drugs, clusters and substitution, or are out of scope for the ePrescription, dispense and record keeping.

The data elements are identified from the IDMP implementation guides that facilitate the implementation of IDMP and that are exactly what openMedicine tries to achieve. However, the IDMP implementation guides carefully follow the IDMP standards, so there will be no

gaps. The order is pragmatically chosen, starting with the substance, via pharmaceutical product to medicinal product and finally the package identifiers.

Given the policy decision for openMedicine that the missing identification of medicinal products in ePrescription will be selected from the IDMP series, four core data elements form the basis. These are the substance identifier (ISO 11238), the pharmaceutical product identifier or PhPID (ISO 11616), the Medicinal Product Identifier (MPID), and finally the Packaged Medicinal Product Identifier (PCID). These four form the core for openMedicine, because these will in near future be issued worldwide by the various regulators and allow mapping from one level of specification (e.g. substance id), to another level (e.g. the package identifier PCID). Hence, these four form the core of the cross border identification of medicinal products. These are therefore the base of the DCM and are listed in Table 12.1 and depicted in Figure 16.

Table 6. Core data elements from IDMP for all use cases for all domains.

Source	Data element	Use case Xborder ePrescription / Dispense / Record keeping	Include/ exclude in DCM	Motivation
ISO 11238	Substance ID	Include	include	Every substance will be identified by this mandatory ID.
ISO 11616	Pharmaceutical Product Identifier PhPID	Include	include	Every pharmaceutical product will be identified by this mandatory ID.
ISO 11615	Medicinal Product Identifier MPID	Include	include	Every (regulated) medicinal product will be identified by this mandatory ID.
ISO 11615	Packaged Medicinal Product Identifier (PCID)	Include	include	Every packaged product will be identified by this mandatory ID.

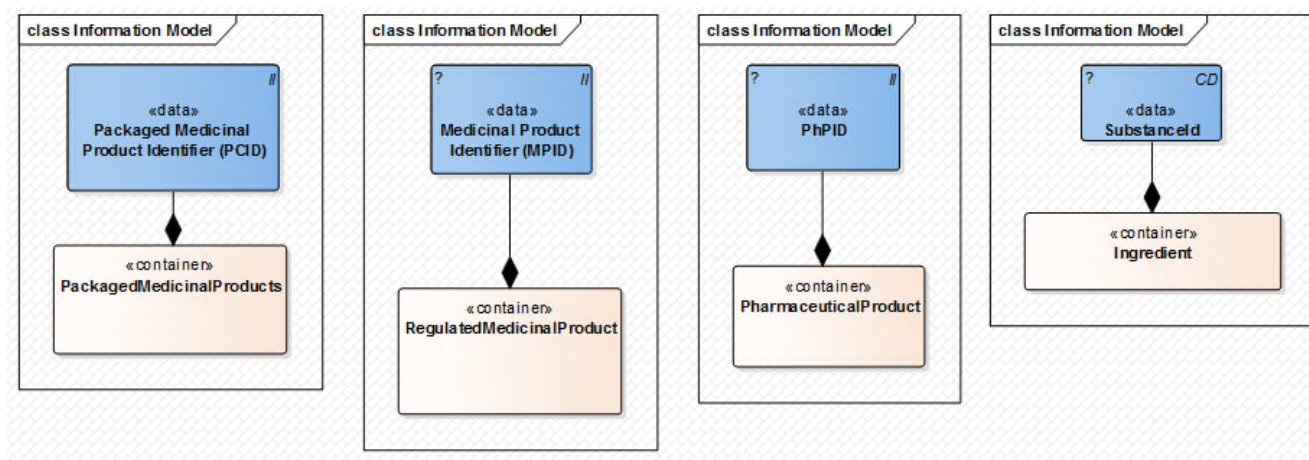


Figure 16. The core of a DCM for medicinal products: the four data elements for IDMP identifiers, each represented by a UML information class.

To continue the creation of the DCM, the various IDMP standards, and their implementation guides have been screened for the single data elements. Each has been listed from the regulator perspective (M for mandatory, indicated with 'Shall' in the statement, C for conditional (indicated as such), O for Optional, indicated with "Should", or "May"). Next, the relevance for the three use cases prescription, dispense and clinical record keeping have been identified via include or exclude. Finally, the decision is made whether or not to include the data element with a class representation in the DCM medicinal product. The latter is also done via include (class will go into the model) or exclude (class will be excluded from the DCM). However, it needs to be stressed that this is a different approach compared to normal development of DCM's or clinical models as archetypes of HL7 models, in which mostly all possible use cases are taken into account and lead to a maximal, or better optimal data set for the clinical model in order to support the use and reuse for various use cases.

On the other hand, the medicinal product is quite a complex model. And for ease of understanding and facilitate application for the three selected use cases, this is already a challenge. Hence, a less comprehensive DCM, which can be build further when additional use cases move to implementation, can be a good starting point, and via versioning further be developed in the future.

In Table 7 the mandatory data elements as specified in ISO 11238 and ISO TS 19844, for the substance ID and descriptive attributes are listed. Figure 17 presents the data elements from Table 7 that were selected to be included, or optional in the DCM fragment for ingredients. The question marks in a class point to yet unknown or not specified controlled vocabulary.

Table 7. Data elements from the substance standard.

Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/ exclude	Motivation
EN ISO 11238	Substances	Holds various data elements that will not be used in clinical practice / e-prescription. A selection is made which elements can be of use in cross border exchange			
ISO TS 19844	Implementation guide for 11238	Holds implementation specifications, in particular in HL7 v3 format (CPM) of the data elements in 11238 that will not be used in clinical practice / e-prescription. A selection is made which elements can be of use in cross border exchange.			
ISO TS 19844	Ingredient	M	include	include	Core concept for the ingredient level of data elements. A substance is any matter that has a discrete existence, irrespective of origin, which may be biological or chemical.
ISO TS 19844	4.1. Specified_Substance	M	include	include optional	This one is normally not used in clinical practice, and hence not yet included in the DCM. However, included optional based on expert input.
ISO TS 19844	4.1. Specified_SubstanceGroup	M	include	exclude	Valueset 4 categories. Normally not used in clinical practice, could be considered for an extension later.

ISO TS 19844	4.2. Substance_ID	M	include	include	Every substance will be identified by an ID. Once a substance has been defined, a unique identifier that is permanently associated with that substance will be assigned.
ISO TS 19844	4.2.1 Substance type	M	include	include	To distinguish specific substances from each other.
ISO TS 19844	4.3. Substance_Name	M	include	include	Name for the core concept. A substance is any matter that has a discrete existence, irrespective of origin, which may be biological or chemical.
ISO TS 19844	4.3.2. Substance_Name_Type	M	exclude	exclude	Every name shall have one and only one name type. Official names are typically non-proprietary names used in a given jurisdiction and domain to refer to a specific substance. For use in substance database.
ISO TS 19844	4.3.3. Language	M	exclude	exclude	This is more appropriately found in substance catalogues and manufacturer documentation.
ISO TS 19844	Substance name synonym	M	exclude	include optional	Official names are typically non-proprietary names used in a given jurisdiction and domain to refer to a specific substance. Can be described in various systems or formats such as official and systematic, based on expert input.
ISO TS 19844	Single_Substance or Mixture_Substance	M	exclude	exclude	The distinction is relevant for clinical practice, e.g. in case of allergies for an adjuvant substance but is included in specified_substance
EN ISO 11616	Role	M	include	include	It is important for each substance to know its role, active ingredient, expedient or adjuvant.
ISO TS 19844	4.4. Reference Sources	C	exclude	exclude	This is more appropriately found in substance catalogues and manufacturer documentation
ISO TS 19844	4.5. Reference source document	C	exclude	exclude	This is more appropriately found in substance catalogues and manufacturer documentation
ISO TS 19844	4.6. Substance_Code	C	exclude	exclude	This is more appropriately found in substance catalogues and manufacturer documentation
ISO TS 19844	4.7. Reference_Informat	S	exclude	exclude	This is more appropriately found in substance

	ion				catalogues and manufacturer documentation
ISO TS 19844	4.8. Structure	C	exclude	include optional	Structural information is an essential element for all chemical substances and for other types of substances that have structurally definable elements or modifications. Option to determine exact substance (e.g molecular weight, herbal origin, type of acid in protein).
ISO TS 19844	4.9 Amount	C	exclude	include optional	Optional to include amount to provide the quantitative or qualitative values that are associated with a substance, e.g. molecular weight.
ISO TS 19844	4.10 Source Material	C	exclude	exclude	This is more appropriately found in substance catalogues and manufacturer documentation
ISO TS 19844	4.11 Modification	C	exclude	exclude	This is more appropriately found in substance catalogues and manufacturer documentation
ISO TS 19844	4.12 Property	C	exclude	exclude	This is more appropriately found in substance catalogues and manufacturer documentation
ISO TS 19844	4.13 Version	M	exclude	exclude	This is more appropriately found in substance catalogues and manufacturer documentation
ISO TS 19844	5. Various types of substance	M	exclude	exclude	This is more appropriately found in substance catalogues and manufacturer documentation. Chemical substances shall be defined on the basis of their complete covalent molecular structure; the presence of a salt and/or solvates is also captured.

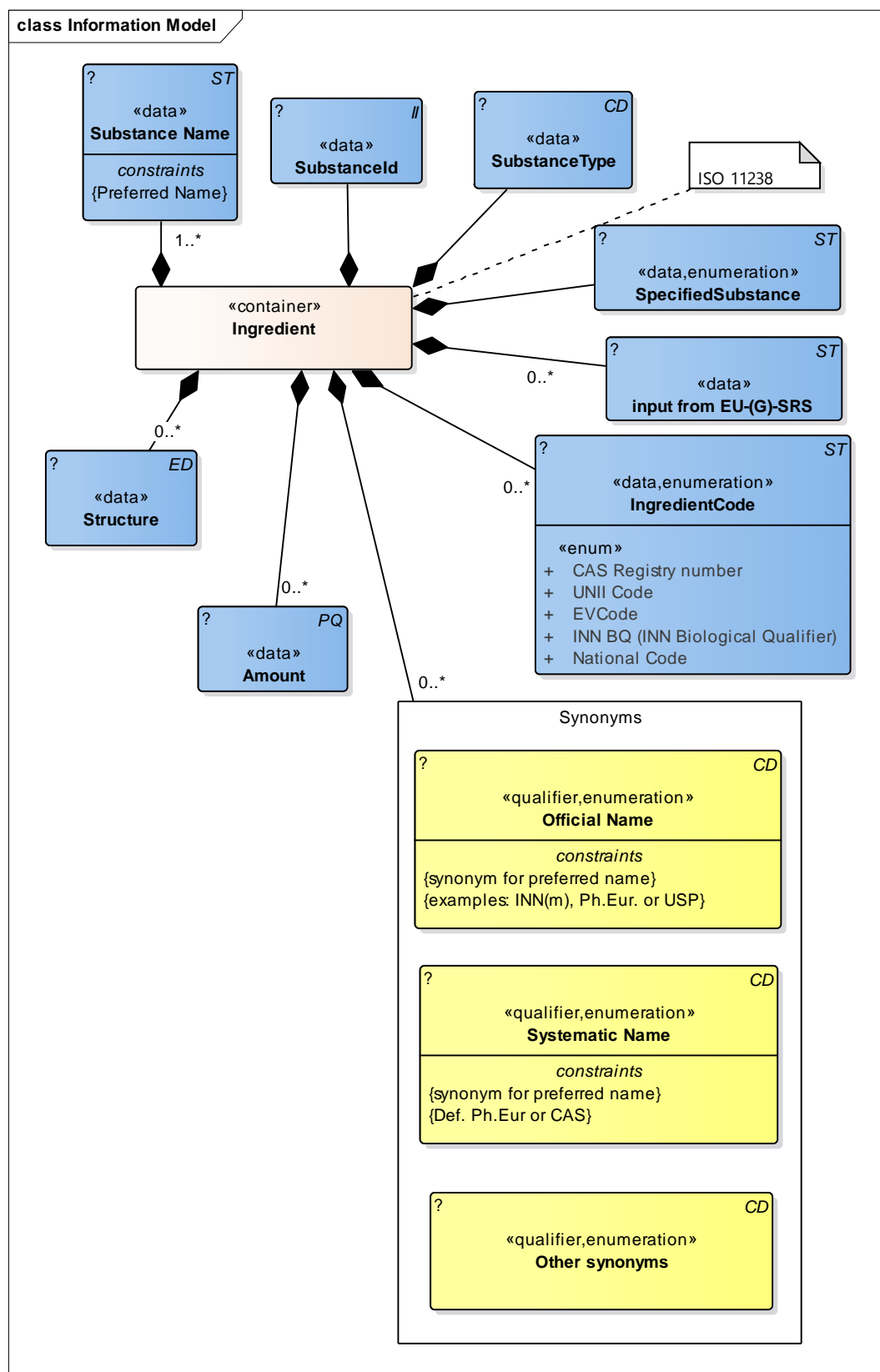


Figure 17 DCM data elements for substances, some are optional, indicated with 0..*.

Table 8 presents the various data elements for ISO 11239 (pharmaceutical dose forms) and their exclusion or inclusion in the DCM. Given that the principle of representing the data elements from the table that are included, or optional with a class in the DCM, this is not done again for the other tables. The final DCM is presented at the end.

Table 8. Data elements from the pharmaceutical dose form standards.					
Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/exclude	Motivation
EN ISO 11239	Pharmaceutical Dose Forms	Holds data elements for the dose form, which is mostly important to know how a medicine should be administered and how quickly an effect is expected.			
ISO TS 20440	Implementation guide for 11239	Holds implementation specifications for the data elements in 11239. A selection is made which elements can be of use in cross border exchange.			
EN ISO 11239	Routes of Administration, Units of Presentation and Packaging.				
EN ISO 11239	Pharmaceutical dose form class	M	include	include	Shall be used to describe the pharmaceutical dose form as it is used in describing medicinal products, codedConcept (CD).
EN ISO 11239	Administrable dose form class	C	include	include	Used when a medicinal product consists of two manufactured items that need transformation to create the pharmaceutical product, e.g. dissolution.
EN ISO 11239	Unit of presentation class	M	include	include	Shall be used to specify the attributes that are needed to describe properly the unit of presentation concept (e.g drop, patch), if no quantitative unit is available. E.g. mg per tablet.
EN ISO 11239	Route of administration class	M	include	include	Shall be used to specify the attributes that are needed to define properly the route of administration concept.
EN ISO 11239	Packaging category class	M	exclude	exclude	Shall be used as the high-level grouping category that classes the packaging concept according to the general category of packaging into which it falls, namely: container, closure and administration device. Seems more regulatory and logistically relevant
EN ISO 11239	Packaging class	M	include	include	Shall be used to specify the attributes that are needed to define properly the container, closure, or administration device concept. This has relevance for the dispense.

EN ISO 11239	Data Types used	M	include	include	EN ISO 11239 uses the data types ST (String), CD (Concept Descriptor), TS (Point in Time) and INT (Integer) defined in ISO 21090.
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Table 9 presents the various data elements for ISO 11240 (Units of Measurement) and their exclusion or inclusion in the DCM. In the DCM these are identified in particular in the classes that have a PQ for the data type. The vocabularies are included in the classes that have a CD data type.

Table 9. Data elements from the units of measurement standard.					
Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/exclude	Motivation
EN ISO 11240	Units of Measurement				
EN ISO 11240	Quantity Value	M	include	include	Shall be expressed as a unit of measurement of the quantity and its numerical value in that unit.
EN ISO 11240	Determined reference vocabulary	M	include	include	The reference vocabulary for quantities shall be the UCUM code system, as required for conformance with ISO 21090 and HL7 V3 data exchange standards. The OID for the UCUM code system is 2.16.840.1.113883.6.8.
EN ISO 11240	Units of Measurement Domain Model	M	exclude	exclude	This is for regulatory purposes to determine a unit for a medicinal product, but will not be used in prescription, dispense or record keeping. Does include instructions for conversions and translations
EN ISO 11240	Operational attributes	M	exclude	exclude	This is for regulatory purposes to determine a unit for a medicinal product, but will not be used in prescription, dispense or record keeping

Table 10 presents the various data elements for ISO 11616 (Pharmaceutical Product) and their exclusion or inclusion in the DCM.

Table 10. Data elements from Pharmaceutical Product standards.					
Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/exclude	Motivation
EN ISO 11616	Pharmaceutical product	Holds data elements for the pharmaceutical product, including the PhPID.			
ISO TS 20451	implementation guide for EN ISO 11616	Holds implementation specifications for the data elements in 11616. A selection is made which elements can be of use in cross border exchange.			
EN ISO 11616	3.1 PhPID identifier	M	include	include	Unique identifier for the pharmaceutical product, mandatory using the relevant pharmaceutical product identifiers. This provides a uniform representation of the pharmaceutical product using the active substance(s)/specified substance(s), their (reference) strength(s), the administrable dose form and, where applicable, the integral device and adjuvant.
EN ISO 11616	3.1.1. Active substance	M	include	include	PhPIDs shall be represented within two strata (active substance stratum and specified substance stratum), both of which contain four PhPID identification levels, for each pharmaceutical product contained in a medicinal product.
EN ISO 11616	3.1.1. Specified Substance	M	include	include	As described in ISO 11238, specified substance(s) shall capture detailed characteristics of single substances or the composition of material that contains multiple substances or multiple physical forms.
EN ISO 11616	5.1.2. PharmaceuticalProduct	M	include	include	Name for the pharmaceutical product. A pharmaceutical product shall be described in terms of its qualitative and quantitative composition and the pharmaceutical dose form authorized/approved for administration (administrable dose form) in line with the regulated product information.
EN ISO 11615	10.7 PharmaceuticalProduct	M	include	include	See above, checked for consistency in both standards

Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/ exclude	Motivation
EN ISO 11616	4.2. Ingredient	M	include	include	There shall be one instance of the Ingredient class for each actual ingredient of either the manufactured item or pharmaceutical product, as appropriate.
EN ISO 11616	4.2.1. IngredientRole	M	include	include	The ingredient role of active substance or adjuvants or other roles. The ingredient roles are included in HL7 CPM file in the full upper case letters exactly as specified in the table in ISO TS 20451 clause 4.2.1 Table 4.
EN ISO 11616	4.2.2. Substance	M	include	include	the active substance, if required as specified substance. A Substance can be specified for an ingredient in the role described.
EN ISO 11616	4.2.3. Specified substance	M	include	include	A specified substance can be specified for an ingredient in the role described. See above, checked for consistency in both standards
EN ISO 11616	4.2.4. SpecifiedSubstance group	M	exclude	exclude	Regulator specific information
EN ISO 11616	4.2.5. Confidentiality Indicator	C	exclude	exclude	Regulator specific information, and only in specific circumstances, not regular prescriptions
EN ISO 11616	4.2.6. Strenght	M	include	include	The strength of the substance or specified substance shall be specified as a quantity of the substance/specified substance present in a given in a pharmaceutical product.
EN ISO 11616	4.2.6. Strenght unit	M	include	include	A numerator value and numerator unit as well as a denominator value and denominator unit shall be specified.
EN ISO 11616	4.2.7. Strength Range (Presentation)	M	include	include	The strength range (presentation) shall be specified.
EN ISO 11616	4.2.8. Strength Range (Concentration)	O	include	include	The strength range (concentration) can be specified.
EN ISO 11616	4.2.9. Measurement Point	O	exclude	exclude	There are Medicinal Products in jurisdictions where strength is measured at a particular point.

Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/ exclude	Motivation
EN ISO 11616	4.2.10. Reference Strength	O	include	include	Even when a Reference Strength is not required, one may quantify the active moiety relationship to express the amount of active moiety.
EN ISO 11616	4.2.11. Reference Strength Substance	C	exclude	exclude	Only in very specific conditions and not part of normal prescriptions
EN ISO 11616	4.2.12. Reference Strength Specified Substance		exclude	exclude	Only in very specific conditions and not part of normal prescriptions
EN ISO 11616	4.2.13. Reference Strength Range	M	include	include	The reference strength range shall be specified. A numerator value and numerator unit as well as a denominator value and denominator unit shall be specified.
EN ISO 11616	5.1.3. Administrable dose form	M	include	include	This shall describe the administrable dose form in accordance with the authorized/approved regulated product information.
EN ISO 11616	5.1.4. Unit of Presentation	M	include	include	The unit of presentation is a qualitative term describing the discrete unit in which a pharmaceutical product is presented to describe strength or quantity in cases where a quantitative unit of measurement is not appropriate.
EN ISO 11616	5.1.5. Pharmaceutical Product Quantity	M	include	include	The quantity (or count number) of the pharmaceutical product shall be described. (INT)
EN ISO 11616	5.1.6. Route of Administration	M	include	include	The route of administration is a concept that is used to describe the path by which the pharmaceutical product is taken into or makes contact with the body. It shall be specified according IDMP.
EN ISO 11616	5.1.7. Pharmaceutical Product Characteristics	O	include	include	This class can be used to describe various characteristics of the Pharmaceutical Product, such as its onset of action.
EN ISO 11616	5.1.8. Pharmaceutical Product Characteristics Code System	O	include	include	The code systems for 5.1.7. Note the implementation allows different code systems to be used here, and different valuesets. Specified as attribute of a class with reference to the code system.

Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/ exclude	Motivation
EN ISO 11616	5.1.9. Pharmaceutical Product Characteristics Value	O	include	include	The value sets for the code system for 5.1.7, specified in the class, with reference to the actual value set.
EN ISO 11616	5.1.10. Device (Pharmaceutical Product)	M	include	include	A pharmaceutical product may refer to a drug that is associated with a medical device (e.g. drug/device, biologic/device). In this instance, the device term and term ID (unique device identifier) shall be displayed with the substance(s) and specified substance(s) terms for the product at all applicable PhPID levels.
EN ISO 11616	5.1.11. Device part	O	include	include	The device, if reflected in the Medicinal Product Name, shall be specified as text, where applicable. (ST)
EN ISO 11616	5.1.12. Adjuvants	M	include	include	A pharmaceutical product may refer to a drug that is associated with an adjuvant. In this instance, the adjuvant term and term ID (unique device identifier) shall be displayed with the substance(s) and specified substance(s) terms for the product at all applicable PhPID levels.

Table 11 presents the various data elements for ISO 11615 (Medicinal Product) and their exclusion or inclusion in the DCM.

Table 11. Data elements from Medicinal Product standards.					
Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/exclude	Motivation
EN ISO 11615	Regulated Medicinal Product Information				Holds data elements for the medicinal product, including the MPID and PCID.
DTS 20443	Implementation Guide				Holds implementation specifications for the data elements in 11615. A selection is made which elements can be of use in cross border xchange.
EN ISO 11615	8.2. MPID	M	include	include	Medicinal Product Identifier. Each MPID should be generated with: Country code segment, Marketing Authorization Holder (Organization Identifier) code segment, and Medicinal Product code segment.
EN ISO 11615	10.1. Medicinal Product	M	include	include	as a grouping mechanism, so container.
EN ISO 11615	10.2. Medicinal Product Name	M	include	include	The medicinal product name is one of the defining characteristics of a medicinal product and its MPID. There is only one medicinal product name for a medicinal product relative to a corresponding MPID from a jurisdiction.
EN ISO 11615	Association MPID & PhPID	M	include	include	Association with Pharmaceutical Product Identifiers (PhPIDs).
EN ISO 11615	A.2.7 Product Classification	O	include	include	The medicinal product can be classified according to various classification systems, which may be jurisdictional or international. One or more of these various classifications of the product can be specified in this section. Example ATC
EN ISO 11615	A.2.8.2 Invented Name Part	C	include	include	The invented name (i.e. trade name) of the medicinal product without e.g. the trademark or any other descriptors reflected in the medicinal product name shall be specified as text, where applicable.
EN ISO 11615	A.2.8.3. Scientific Name Part	M	include	include	The scientific or common (i.e. generic) name of the medicinal product without any other descriptors can be specified as text, where applicable.

Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/exclude	Motivation
EN ISO 11615	A. 2.8.4. StrenghtPart	M	no duplicate	no duplicate	See in 11616 above
EN ISO 11615	A.2.8.5 Pharmaceutical Dose Form Part	M	exclude	exclude	See in 11616 above
EN ISO 11615	A.2.8.6 Formulation Part	M	exclude	exclude	The formulation, if reflected in the Medicinal Product Medicinal Product Name, shall be specified as text, where applicable.
EN ISO 11615	A.2.8.7 Intended Use Part	M	include	include	The intended use, if reflected in the Medicinal Product Name, shall be specified as text, where applicable.
EN ISO 11615	A.2.8.8 Target Population Part	M	include	include	The target population, if reflected in the Medicinal Product Medicinal Product Name, shall be specified as text, where applicable.
EN ISO 11615	A.2.8.9 Container or Pack Part	M	include	include	The container or pack, if reflected in the Medicinal Product Medicinal Product Name, shall be specified as text, where applicable.
EN ISO 11615	A.2.8.10 Device Name Part		include	include	See in 11616 above. The device, if reflected in the Medicinal Product Medicinal Product Name, shall be specified as text, where applicable.
EN ISO 11615	A.2.8.11 Trademark or Company Name Part		include	include	The trademark, if reflected in the Medicinal Product Name, should be specified as text, where applicable.
EN ISO 11615	A.2.8.12 Time/Period Part		exclude	exclude	The time/period, if reflected in the Medicinal Product Name, should be specified as text, where applicable.
EN ISO 11615	A.2.8.13 Flavour Part	M	exclude	exclude	The flavour, if reflected in the Medicinal Product Medicinal Product Name, shall be specified as text, where applicable.
EN ISO 11615	A.2.8.14 Country/Language		exclude	exclude	The country and optionally the jurisdiction where the Medicinal Product Name of a Medicinal Product is authorized should be specified in the official language as applicable.

Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/ exclude	Motivation
EN ISO 11615	A.2.8.14.1 Country		exclude	exclude	The country where the Medicinal Product Name is applicable should be described using ISO 3166-1 alpha-2 or alpha-3 codes.
EN ISO 11615	A.2.8.15 Jurisdiction		exclude	exclude	The jurisdiction within the country where the Medicinal Product Name is applicable can be described using an appropriate controlled terminology, if appropriate.
EN ISO 11615	A.2.8.16 Language		exclude	exclude	The ISO 639-2 Language Code of the Medicinal Product Medicinal Product Name as applicable in the specified country and the jurisdiction shall be specified.
EN ISO 11615	10.3. Version	M	exclude	exclude	Specifies the versioning of the core identifiers related to a medicinal product in a jurisdiction, as well as the characteristics associated with the medicinal product and the documentation that supports the versioning. This is typical for regulation purposes.
EN ISO 11615	10.4. Marketing Authorization	M	exclude	exclude	Specifies the information about the marketing authorization as issued by a Medicines Regulatory Agency
EN ISO 11615	B.2.1 Marketing Authorisation Number	M	include	include	The number as assigned to a Medicinal Product by the Regulatory Medicines Agency of a country shall be specified in text.
EN ISO 11615	B.2.3 Legal Status of Supply	M	exclude	exclude	The legal status of supply of the Medicinal Product as classified by the Regulatory Medicines Agency should be specified (e.g. subject to medical prescription or not).
EN ISO 11615	B.2.4 Authorisation Status	M	exclude	exclude	The status of the marketing authorisation changes throughout the lifecycle of a Medicinal Product depending on the regulatory process applicable in a jurisdiction. This shall be specified using an appropriate controlled vocabulary.
EN ISO 11615	B.2.5 Authorisation Status Date	M	exclude	exclude	The date at which the given status has become applicable should be specified.

Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/exclude	Motivation
EN ISO 11615	B.2.6 Validity Period	M	exclude	exclude	The time period, described in terms of a beginning and end date of the Marketing Authorisation for the relevant status shall be specified.
EN ISO 11615	B.2.7 Marketing Authorization Holder	M	exclude	exclude	Details in relation to the Marketing Authorisation Holder to which a Marketing Authorisation in a jurisdiction was granted shall be specified
EN ISO 11615	B.2.8 Medicines Regulatory Agency	M	exclude	exclude	Details in relation to the Medicines Regulatory Agency that granted the Marketing Authorisation for a Medicinal Product shall be specified using an Organisation class
EN ISO 11615	B.2.9 Marketing Authorisation Procedure	M	exclude	exclude	The regulatory procedure applied to grant or amend a Marketing Authorisation for a Medicinal Product shall be specified.
EN ISO 11615	B.2.10 Marketing Status	M	exclude	exclude	The Marketing Status describes the date when a Medicinal Product is actually put on the market or the date as of which it is no longer available. It also indicates the legal status of supply (e.g. prescription only or non prescription).
EN ISO 11615	B.2.11 Periodic Safety Update Report Submission	M	exclude	exclude	Periodic safety update reports and Periodic Benefit-Risk Evaluation Reports refer to a summary and evaluation of the benefit risk profile of the Medicinal Product by the Marketing Authorization Holder
EN ISO 11615	10.5 Manufacturer/Establishment	M	exclude	exclude	specifies the characteristics of the manufacturing process and other associated operations and their authorizations as issued by a Medicines Regulatory Agency
EN ISO 11615	10.8 Clinical Particulars	M	include	include	specifies information about the clinical particulars of the medicinal product as described in line with the regulated product information
EN ISO 11615	11. Investigational MPID (IMPID)	C	exclude	exclude	Investigational Medicinal Product Identifier (IMPID). This is not for normal prescription, dispense and record keeping, hence out of scope.
EN ISO 11615	I. 2. Investigational Medicinal Product		exclude	exclude	

Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/ exclude	Motivation
EN ISO 11615	9. (C 3.1) PCID	M	include	include	Packaged Medicinal Product Identifier. The PCID should use a common segment pattern related to a package of a Medicinal Product, which when each segment is valued, should define a specific PCID concept. The pattern is: MPID for the Medicinal Product plus Package description code segment, which refers to a unique identifier for each package.
EN ISO 11615	10.6 Packaged Medicinal Product	M	include	include	specifies information about the packaging and container(s) of a medicinal product and any associated device(s), which are an integral part or provided in combination with a medicinal product, as supplied by the manufacturer for sale and distribution.
EN ISO 11615	C.3.2. Package Description	M	include	include	A textual description of the Packaged Medicinal Product shall be provided.
EN ISO 11615	C.3.3 Batch Identifier	C	exclude	exclude	The element should be mandatory for traceability of biomedicinal Products
EN ISO 11615	9.3. BAID_1	M	exclude	exclude	Medicinal Product Batch Identifier on the outer packaging. Where applicable, the BAID_1 should use the batch/lot number and the expiration date together with the PCID.
EN ISO 11615	9.4. BAID_2	O	exclude	exclude	Medicinal Product Batch Identifier on immediate packaging, where this is not the outer packaging.
EN ISO 11615	C.3.4 Package Item (Container)	M	exclude	exclude	A Package Item can be either a single item or package of multiple items. Those items can be of the same kind or of different kinds.

Source ISO IDMP	IDMP data elements	IDMP: Mandatory Should Conditional	Xborder use case	DCM include/ exclude	Motivation
EN ISO 11615	more details on packaging not addressed, such as material, alternate material etc.		exclude	exclude	use for regulation and logistics use cases
EN ISO 11615	C.3.4.10.7 Shape	O	exclude	exclude	Where applicable, the Shape can be specified. An appropriate reference terminology shall be used.
EN ISO 11615	C.3.4.10.8 Colour	O	exclude	exclude	Where applicable, the colour can be specified. An appropriate reference terminology should be used.
EN ISO 11615	more details on packaging not addressed		exclude	exclude	use for regulation and logistics use cases
EN ISO 11615	D. Ingredient, Substance and Strength		no duplicate	no duplicate	This section specifies dataelements from ISO 11238, 11239 and 11240. This has been addressed above.
EN ISO 11615	E. Pharmaceutical product and device		no duplicate	no duplicate	This section specifies dataelements from ISO 11616. This has been addressed above.
EN ISO 11615	F.2 Therapeutic Indication	O	include	include	This class should be used to describe the authorized indication(s) for the Medicinal Product in accordance with the regulated product information.
EN ISO 11615	F.3 Contra- Indication	M	include	include	This class shall be used to describe the authorised contra-indication(s) for the Medicinal Product as described in the regulated product information
EN ISO 11615	F.3.2 Undesirable Effects	M	exclude	exclude	This class should be used to describe the undesirable effects of the Medicinal Product as described in the regulated product information
EN ISO 11615	F.3.3 Interactions	C	exclude	exclude	This class should be used to describe the interactions of the Medicinal Product and other forms of interaction as described in the regulated product information.
EN ISO 11615	G.1 Organization	M	exclude	exclude	
EN ISO 11615	H.2. Manufacturer	M	exclude	exclude	

12.4 Detailed Clinical Models & Medicinal Product Example

Using the DCM modelling style, a Medicinal Product model is created in Unified Modelling Language (UML), based on the data elements from IDMP that are relevant for the use cases ePrescription, dispense and record keeping. Where available it will include bindings to the various terminologies to those classes where they apply (Figure 17). A more finalized version of the DCM specification for the Medicinal Product will be added as annex to deliverable D 2.3 in 2016. The current version is not complete, however, as openMedicine is about identification one could limit the model to purely identifying attributes as we have name, code + coding system. In that case a "reduced" DCM may be sufficient for a starting point. But we decided to also include "describing elements" that enable – combined with each other – identifying a medicinal product. In this case we need a comprehensive model and a comprehensive set of databases for the various terminologies and code systems used. The current draft DCM for Medicinal Products is expanding already on the pure identifying elements, but is not yet comprehensive with respect to all describing elements. The integration of the data structures and the terminologies/codes takes place at the individual class level in the DCM.

If we relate the DCM on medicinal product to the context standards, it is residing as follows:

In the GCM it is on the bottom of the healthcare system view and at the start of the ODP RM, and it can cross domains. The cross-domain feature allows to reuse the same DCM specification in order to allow consistency and interoperability.

For ContSys the DCM is on the 2nd layer, for the conceptual representation of clinical details, albeit with some of the logical model expressed in the UML picture. When we move to the precise level in ContSys, the medicinal product (as DCM) is considered a Resource, used in therapeutical activities. So the DCM medicinal product is a Used Resource in ContSys speak.

In HISA the medicinal product DCM is placed in the information layer. For the 13606-2 the medicinal product DCM can be expressed in ADL to move from the logical model in UML to the implementation specification in ADL and for 13606-3 it is seen as one reference archetype. Within the EHR standards, the DCM medicinal product can be seen as the core content specification for any medicinal product and would require a user interface representation, a storage representation, an operations representation and an exchange representation. The latter can then be converted into HL7 v3 and fit the epSOS CDA, and any other HL7 v3 message. Figure 18 shows the draft DCM medicinal product logical UML model.

work might reveal the opposite and render it crucial for every prescription, or more likely, for some specific use cases. Hence, then the DCM can be further completed through extending or specializing for that additional use case.

13 Synthesis for the Initial Infostructure

This Deliverable 1.3 explores how the initial infostructure for openMedicine could look for both the content of ePrescription, dispense and record keeping, and for its context, the cross border exchange. It is presented as a framework bringing together a whole set of relevant standards for the openMedicine domain. As such, it is focussing on the concurrent use of a vast collection of available standards. Although each of these standards might well be known, the way they interact and support each other are rarely addressed.

The openMedicine infostructure has two main components that need to be seen as complementary: the first component is focusing on the context in which ePrescription and dispense takes place deals with an architectural approach to oversee this and where various e-Health standards apply. The other component is about the identification of medicinal products and their defining characteristics for the ePrescription, dispense and record keeping. Again, here we see concurrent use of the IDMP standards with terminologies and specific implementation guides and more.

The architecture analyses the situation around medicinal products from four levels, which are:

1. The business level (i.e. cross border service between authorized clinicians), expressed as use cases.
2. The processes level (the ePrescription process and the follow up dispense and record keeping),
3. The data aggregations such as the e-Prescription message and the eDispense record, and the EHR in which record is kept.
4. The detailed data about the medicinal product itself, such as the IDMP series of identifiers and descriptive attributes and the DCM that supports some of the use cases.

The architecture helps to identify stakeholders and address for instance legislation and authorization levels, and identifies the various use cases. From all possible use cases a subset is selected for the initial work. Provided standards as HISA are developed to come up with a solid eHealth architecture on national and even European level. Standards as Consys facilitate in identifying which process is dealt with, and within a process, which resources are used. For instance, in Consys, the medicinal product is a healthcare resource, which can be used in many processes. Mapping national level descriptions to Consys terms, can facilitate the mapping of contexts from one country to another. And according to Blobel, this approach is according to the GCM, important for overall consistency, in particular when crossing borders: we need to ascertain that we talk about the same concept at the same level.

This approach is helping to achieve both a concurrent use of standards, such as each country using its own specifications, but mapping it to another countries specifications. This implies that co-existence of standards is very well possible, so that each country can use it what fits their national e-health developments, while allowing the exchange via mapping or translation services. However, it is beyond this deliverable to specify this more precisely.

Given the choice made to adopt the IDMP series, a clear set of identifiers and attributes is now available and considered the core of the openMedicine infostructure. openMedicine openMedicine_deliverable_T1 3_InfostructureStandardsFramework-v1.1PostReview Page 88 of 99 31/05/2016

suggests to solve the identification problem for the use cases ePrescription and the follow up with a cross border dispense of the medication the patient requires, and its record keeping through the use of the four core identifiers from the ISO IDMP series:

1. Substance identifier,
2. Pharmaceutical product identifier,
3. Regulated medicinal product identifier and
4. Package identifier.

However, these core identifiers from IDMP also concern work in progress. Currently, EMA, FDA and other regulators and stakeholders are working hard on the implementation of these identifiers, including in their own databases (e.g. EMA's article 57 database). One key ongoing action is adding the IDMP identifiers and match all defining attributes. Also, facilitating their distribution to the national regulating bodies is on the agenda. One particular area of work is to give each identifier a unique object identifier (OID) or similar, and to identify each single data element through a unique code, e.g. via HL7 vocabulary, Snomed CT, LOINC, EDMQ, or similar. ISO is currently working on this via the Technical Report 14872. The creation, maintenance, and publication of the actual IDMP identifiers are envisioned by ISO and its partners as a distributed process. Each jurisdiction, for instance for openMedicine Europe's EMA, would establish and maintain the identifiers in its jurisdiction. The ISO Technical Report 14872 describes requirements for maintaining IDMP identifiers within each jurisdiction, and it is foreseen that this will be handled in accordance with this TR.

In addition, for some of the descriptive data of a medicinal product, a controlled vocabulary is required, e.g. for dose forms, colors, and shapes of medicines. Included in ongoing work however, is the determination of exactly which controlled terminology to use for what data element. For instance, the EDQM can be seen as a nearly complete value set for all pharmaceutical dose forms (EDQM, 2014). Also, for the units of all medicinal products, the UCUM standard is adopted worldwide. However, for many other data elements, in particular the identifiers themselves and many of the attributes, there is work in progress, and the overview in chapter 8 illustrates that there is a huge amount of terminologies available, but each requires careful evaluation for fitness for purpose. For the use in Europe, EMA is currently undertaking this evaluation, with a predicted first draft by the end of 2016. It is therefore beyond the scope of D 1.3 in particular but also for openMedicine as a whole to come up with the complete list. But as follow up on the IDMP set of standards, the second recommendation will be to apply the upcoming recommendations from EMA for the controlled terminologies.

The linkage of each (IDMP) data element to specific terms and codes is nevertheless the core of the Detailed Clinical Model, which has been redesigned to some extent, based on a more explicit methodology applied in chapter 12. Because the different countries do not yet use the same identifiers, a mapping tool is required that bridges from e.g. the substance level in country A to the package level in country B, and facilitating that is the main task for the Detailed Clinical Model for the medicinal product. Finally, the DCM facilitates the mapping to specific classes in HL7 Common Product Model, which is to be used in the various implementations of IDMP, in particular for ISO 11615.

Hence, the initial infostructure and standards framework offers models for solutions that facilitate comparing it against various countries' eHealth roadmaps to realize strategic ambitions for ePrescription, eDispense and record keeping. It facilitates discussing the models' correctness, feasibility and desirability in light of the strategic ambitions. The proposed infostructure and framework are thus the endpoint of Checkland's systems thinking and in D 2.3 we will move more into possible solutions for reality. And in this reality we are facing both a concurrent use of various standards at the same time, and in an exceptional situation a coexistence of two standards that can basically do the same, but each is attached to a specific jurisdiction.

Given the various ongoing developments and future decisions to be made by parties external from openMedicine, we can only draw up a well underpinned first draft and guide national e-health strategies with a roadmap. That will be discussed in other deliverables of the project.

14 Impact for national eHealth strategies

Important of a theoretical approach such as taken with both the framework and the Detailed Clinical Model in this infostructure is whether it can be used at the level of the member states. In order to get an **impression** of the practical usability, this initial infostructure has been discussed with representatives from various countries. The selection is done pragmatic and based on work of partners in openMedicine and their home country, and the openMedicine workshop in Madrid May 23, 2016. The first example is chosen given the status of Ireland as being in the beginning phase of the e-health developments, and Mr. Horan participating in this work. Spain has been a strong participant in epSOS and is implementing various aspects of the infostructure required for IDMP, this was presented May 23 and a useful resource for this chapter. The Netherlands has a decade of experience with the use of ePrescription and eDispense messages in HL7 v3 and use of a national Medicinal Product Dictionary, and this work could be discussed based on ongoing work of the author. The choice for the Netherlands is also relevant for this deliverable: the first modelling approach for the DCM in chapter 12 was based on the Dutch ePrescription message and eDispense messages, and the Dutch Medicinal Product Dictionary (G-Standaard), which is in use for several decades now.

Choosing openMedicine membership is very pragmatic and should not be seen as a proper study. It is just a test for the practical relevance of the infostructure and guidance for openMedicine workpackages and deliverables due later. The content is based on a small set of questions pertaining to the uptake of the IDMP, the status of ePrescription and eDispense in the jurisdictions, the transport standards in use or officially selected for this, the existence of an MPD and its readiness for IDMP. Also some impression is asked about the overall architecture of their e-Health strategy and which standards underpin that. The results are presented in this chapter.

14.1 Example 1 Ireland

According mr. Kevin Horan, the director of ICT & Business Services of the Irish Health Products Regulatory Authority (HPRA), Ireland is quite far in preparing for those areas that openMedicine is focusing on. The core of work is based on the IDMP. With that respect openMedicine is really bringing assets to the Irish national developments. On the other hand, the national eHealth strategy has set specific targets, that sometimes require to move faster than openMedicine can do, or that EMA can do on the European level. However, given that all work is based on the same set of standards, whatever will evolve from these parallel works will be consistent with each other. The eHealth strategy for Ireland does include various projects around the use of medicinal products. In particular upgrading the national database of medical products to become ISO IDMP compliant is planned for December 2016. Also the mapping to and implementing European Standard terminologies such as Routes of Administration and Dosage forms is planned for the same time. For mid-2017 the completion of the substance database is foreseen, which will be augmented with identifying and gathering additional product information required by the health system by the end of 2017.

National use of IDMP

As said, the HPRa Database is currently running and is IDMP prepared, it will run on national level by de 2016. The vision is the implementation of a Irish National Drug Catalogue based on the ISO IDMP standard, with data enriched by specialist groups within the health system e.g. for pricing, formularies and such. According to Horan, the goal is to have this implemented in both hospital and community pharmacies and supporting the individual electronic health record based on freely available information. This work has to date been facilitated via creation of a (temporary) national PhPID. Until the European PhPID comes available, this will be used for development and testing. So that specific task of including and maintaining PhPIDs will be redone as part of the development strategy. It is now used for revealing requirements and gaps in the structure, e.g. for clinical indications. Also this holds for the package information. Because the issuing this, the whole can be developed and later on easier dealt with in practice.

Irish National Product Catalogue

A second target for Medication concerns the Irish National Product Catalogue (MPD), it is planned to be finished in about two years from now. This Irish National Product Catalogue should start with medical devices as well, but after the medications are included. The end situation will be to include medical devices information that are used with medicines. For this work, it is difficult to find technical expertise. Ireland would need a blueprint to assist. Again, this is what openMedicine is creating. It would be good if openMedicine creates a workshop approach to enable a member state to take up this nationally. The Irish National Product Catalogue under development has the IDMP as its core and will go live in 2017. The openMedicine project and results help to get this done, it brings together the available knowledge on MPD from EU and international work. For example, this is the case for handling substitution.

ePrescription, eDispense and EHR

At the level of implementation of such information in clinical practice there is more to be done. Ireland currently has no formal (national) approach yet for the ePrescription, eDispensation and electronic health records which would keep such information on individual patient level. There is a new organization 'eHealth Ireland', which just started 2 years ago, and for whom the e-Prescribing is one of the projects. Horan's assumption is that openMedicine is actually helping with that work. Horan has been promoting this work and using the IDMP in this area, but it is perceived as very abstract. So any further aligning the IDMP with openMedicine's supporting information and demonstration materials in order this to become digestible and hence make it possible to be adopted quicker.

With respect to standards which will probably be going to be used, Ireland is looking at HL7 v3 (CDA and/or messaging). CEN 13606 or OpenEHR are not in the picture to support the medicinal product information exchange. Partly this comes from the choice made for the IDMP implementation guides, where the regulators have decided for the HL7 CDA with CPM and SPL (See chapter 10 paragraph 6) for the exchange. The problem for Ireland is that some people 'dabble' in standards (have heard from them talk about them, but have no active implementation knowledge or experience). Hence, there are no implementers that could assist. "Only a few vendors tell by mouth they can do it, but might not implement the standard but their own solution". Nevertheless, the HL7 v3 messaging (such as in the CDA /

SPL) for pharmacy seen as best option for Ireland. Currently, many initiatives are started, but do not lead to concrete results and are stopped before being able to move to the next phase.

In general, there are areas of concern: Ireland does need a knowledge and information plan. This is currently best reflected in the eHealth Strategy for Ireland from the Department of Health (nd). However, this is to set the outline, but not how to actually implement this. Further, it proves to be difficult to influence the strategic decisions, often these focus on short term goals, where a long term approach is required.

14.2 Example 2 Spain

openMedicine partner AEMPS organised an openMedicine workshop May 23 2016 where representatives from the Spanish ministry of Health presented their views on IDMP implementation, including the usefulness of openMedicine materials for their eHealth strategy. From two presentations, the relevance of openMedicine results can be determined and hence, these are summarized here.

eHealth strategy and IDMP

Romero Gutiérrez (2016) discussed the vision of the Spanish Ministry of Health on Digital Health Services for ePrescription and eMedication. This vision assumes sharing Clinical Information Systems content and other clinical information to support eHealth policies. Core applications are the EHR and ePrescription from which the information will be shared within a secure environment, in an accessible and reliable manner. EHRs and ePrescriptions will be locally/regionally supported on different systems, and will share a common architecture for communication of content based on standards, under national and international agreements. Core standards used are the IDMP series and clinical terminologies. For IDMP a full alignment program has been developed, realizing the requirement of concurrent use or coexistence of standards, such as HL7 (used as implementation enabler of IDMP) and clinical terminologies. Spain is carefully monitoring the EU policies, specifically EMA guidances on implementations of IDMP. Once this is clear Spain will align its national policies. According Romero Gutiérrez (2016), terminology is used to communicate clinical information among systems in such a way that no alteration of meaning occurs. Spain is already implementing Snomed CT for clinical information. And given that additional classifications are required, such as ICD 10, mappings will be necessary as well. During the openMedicine workshop in Madrid, May 23 2016, we learned that Spain has created a national extension for Snomed CT which is populated with various terminologies that are required for the medicinal product (Romero Gutiérrez, 2016). Examples of the controlled terminology subsets include substances, doses, and routes of administration. This would be an interesting experience for EMA and hence, is reported here. Romero Gutiérrez (2016) further states that all professionals will be enabled to operate on clinical information according to the requirements of interoperability for clinical data. This will consist of both facilitating professionals with tools and with training how to use them. So the IDMP is seen as one set of key standards for the Spanish eHealth strategy.

ePrescription

With respect to ePrescription, Spain was one of the epSOS implementers. Since then, Spain has further invested in the use of the HL7 CDA for ePrescriptions on the level of the 18 autonomous regions. Fidalgo (2016) presented an overview of the use of ePrescription in Spain. According to Romero Gutiérrez (2016) 2 x 2 regions deploy it currently and 18 x 18 is under development. Fidalgo (2016) gives more details in what is actually in use and further roll out phase. The core components are the security and configuration of the system, the ePrescription and eDispense parts, including secure data storage and exchange, the communication between physicians and pharmacists and patient information based on identification. The objective of the project is to allow electronic prescriptions to be obtained at any pharmacy in the country. The standard used is HL7 v3 with the epSOS specification as basis for implementation. Three difficulties are experienced and current projects work to overcome these. This are difficulties to obtain each ePrescription (the status per region differs from > 99% in one region to < 10% in another). The second is the transcoding and translating. Since EMA has not yet provided the full set of terminologies and value sets, where for the implementation these are required, Spain invested in Snomed CT coding of the relevant concepts for ePrescription. Third difficulty is the electronic identification of patients. Current solution is an unique identification code: the “Health National System Code”. All this is supported by a legal framework. European projects such as EMA and openMedicine are seen as core for exchanges between countries, where a national connection point will facilitate the exchange from country A to country B.

MPD

Fidalgo (2016) also points to the National ID codes for medications, that have unique codes for Branded products, for Generic Name products and for Active Ingredients. As stated before, this is coded with Snomed CT national extension where also the dose, package information and pharmaceutical dose form are coded in. The EMA European Pharmaceutical Database will in the future contain all authorized medicines in the European Union, but that database must be perfectly codified and governed.

14.3 Example 3 the Netherlands

To get an impression on consequences, three key parties in the Netherlands were interviewed: Leonora Grandia, responsible pharmacist for the G-Standard and project lead for the ISO TS 19256 MPD, Michael Tan, program lead for the Dutch ePrescription and eDispense messages at the National Institute for Health Information (NICTIZ), and finally the Dutch regulating authority for medicines (College Beoordeling Geneesmiddelen / Medicines Evaluation Board) in Utrecht. Participants were drs. Anja van Haren, CGB, drs. Joris Kampmeijer, head of department CBG and dr Herman Diederik, expert CBG and EMA. Van Haren participated in the IDMP work and ICSR work, and Diederik is also author on behalf of EMA on various IDMP implementation specifications.

The Netherlands (Nictiz) uses an architectural approach to the national eHealth strategy. This consists of the following levels 1) legal & business, 2) processes, 3) information, 4) application, and 5) ICT-infrastructure (<https://www.nictiz.nl/standaardisatie/overzicht-standaarden/type-standaard>). Most projects and standards are plotted against this overall architectural view.

ePrescription.

On the level of the existing Dutch Health Level 7 version 3 ePrescription and dispense messages, there are few changes expected according Michael Tan. Currently these messages can already hold various identifiers from G-Standaard, but also ATC codes and it is foreseen that IDMP “only adds a few identifiers” to this list, but do not need structural changes. For the national ePrescription it does not change at all, for the eDispensation there are also no changes anticipated. A point of future consideration might become whether the current procedure to have a field in the HL7 v3 message that has all codes together can still be used, or perhaps that the HL7 SPL that specifies each identifier in a separate class, and hence gets a separate XML tag in the v3 message, can be maintained. A cross mapping facility would need to map to equivalent data elements, equivalent vocabulary and equivalent structures.

The Netherlands did not participate in the epSOS pilot. Hence there is no experience with how the use of any identifier would work cross-border. For openMedicine this implies that exactly on the core use case of cross border ePrescription and dispenses and record keeping, there is work ahead. Currently, there is a new approach in a national project initiated by the pharmacists and general practitioners and supported by Nictiz to create so called building blocks in the medication domain. This is ongoing work, building partly upon the Detailed Clinical Model approach, resulting in more specific process descriptions following a health IT architecture, and specific data that are required in steps. In particular, the medical decision making and the logistics will be better sorted out. This would assist in future cross border exchange because content is disentangled from the context. For openMedicine this can imply better determination who is allowed to prescribe what. Tan assumes that for cross border exchange it is important to be able to check roles and authorisations, for instance the certificate of a prescriber. This mapping assures both parties can trust each other. Another use of the IDMP identifiers is foreseen for prevention of falsified medicine.

Medicinal Product Dictionary

From the discussion with Leonora Grandia it becomes clear that the IDMP series is following an architecture that is very similar to the Dutch Medicinal Product Dictionary, the G-Standaard. Within the G-standaard there are unique identification codes for substance, pharmaceutical product (geneeskundig product code GPK), medicinal product (handelsproduct code HPK) and a package code (GS1 barcode). In the MPD these are related, and when entering one code in the MPD, a user can easily look up the equivalent codes on the other levels.

The major impact the IDMP will have for the G-standaard is that in addition to the Dutch codes, there must be separate fields included that represent the IDMP unique identifier for the core four levels. Hence, the main work involved is to create and maintain the mappings between IDMP identifiers as to be issued by EMA and CBG and the existing identification codes in the G-standaard. The need for cross-mapping to use this cross-border is identified, e.g. also related to prescribing on PhPID and the relationship with insurance coverage.

National regulator and IDMP

The CBG is anticipating towards a new role with respect to the responsibility to implement IDMP. In particular how the regulated medicinal products can enter the Dutch market using IDMP identifiers and how to further distribute this information into the G-standaard is a consideration for their work. All this is in an early stage of preparation, with no concrete decisions yet. However, it is viewed from the perspective of a long term history of using unique identifiers for substances, pharmaceutical products, medicinal products, package identifiers and their relationships. Most work is anticipated to complete the regulators database to accommodate the IDMP additional identifiers and the reporting by industry. Another project is foreseen to accommodate the inclusion of these IDMP identifiers into the G-Standaard and the appropriate mapping with the locally existing identifiers.

15 Discussion and Conclusion

The goal of this deliverable 1.3 is to present a multi standards framework that underpins solutions to identified issues in epSOS for the ePrescription for cross-border health data exchange in the EU. These issues include the proper identification of medicinal products and the required attention to multiple contextual factors, such as legislation and workflow. The directions for a solution addresses an infostructure, based on a standards framework, in which both the identification of medicinal products can be handled via the information model for the structural components, and with terminology for the instances of medicinal product identification. Further the standards framework supports contextual factors.

The framework has been based on the three dimensional Generic Component Model (Blobe, 2010). Each dimension: the health system approach, the electronic system development approach, and the cross-domain aspects reveal that beside the actual data and terminology content for the ePrescription, additional layers for processes, business goals, IT specifics and beside the clinical domain, also the legal, organizational, pharmacological, and regulating domains play a role. It has not been the intention to be exhaustive in this, but it does illustrate that such a multiple viewpoint approach systematically organizes the matter. Each chapter's content has been classified along the GCM model, identifying whether something covers more business / enterprise, more process, or more details of information and computation. This classification however, is to facilitate understanding for the reader, and should not be seen as a scientific sound method.

Starting with the actual description of the medicinal product, in particular the CEN ISO IDMP series of standards, it becomes possible to use proper identifications for medicinal products. The IDMP consists of four layers of identification, from bottom to top: substance, pharmaceutical product, regulated medicinal product and finally the package identification. Each level has a specified identifier. Although it is comprehensive, there still will be issues remaining that need future coverage. However, for this moment, the strong recommendation for epSOS and openMedicine is to adopt IDMP identification.

Next, the framework presented moves to the IT environment in which the identified medicinal products will be stored and exchanged. Examples as the epSOS HL7 v3 CDA documents, IHE profiles, and HL7 v3 messages in the medication domain, cover logical and technical representations. Following the RM ODP, these support moving from the pharmaceutical content to the system development cycle, and are hence key for any actual implementation. Some healthcare information system or e-Health application will be used to store information on medications electronically. From such applications dedicated to individual care and treatment, the ePrescription can be derived and exchanged. To allow proper dispensation of the right medicines to patients anywhere in Europe, the IDMP identifiers should be used in the epSOS CDA exchange format, and any future exchange format. There is ongoing debate on the level of precision that is required.

To support these identifiers, and their application in systems and data exchange, a series of terminologies, classifications and medicinal product dictionaries is necessary. These offer the required content for the IDMP specifications, and hence are part of the first epSOS topic: identification. It is clear that despite wide coverage, not every relevant product attribute, or even the required information classes represented can themselves be identified with OIDS

and unique class codes. This is an area for future work, where the Detailed Clinical Model that specifies every class and each class's code and codes system, can be helpful to identify the requirements and to specify the appropriate code and value sets.

However, due to ongoing work on the IDMP implementation guides, only a part of the required content is currently available. Deliverable 2.3 needs to work on exactly those parts that this framework identifies, but cannot address in detail at this moment. During the work on D 1.3 an issue arose which has to be addressed in WP2, and this was discussed with the WP leaders to cover it in upcoming deliverables. Each of the standards in the framework presented here identifies a medication item by using different data elements to "label" and to "structure" the identifying aspects of a medicinal and/or a pharmaceutical product. It is beyond the scope of Deliverable D1.3 to document this aspect for each standard presented. Defining how these elements of standards are used and should be used for cross border identification (and description) of "registered" (authorised) medicinal products is spread over three deliverables in WP2. The following recommendations are given to follow up on this topic.

1. Deliverable D2.1 Regarding identification, how are medicines currently identified in the different standards and/or used for registered products? This can be build upon this framework in D 1.3.
2. Deliverable D2.2 Regarding the complete set of identifying and descriptive attributes that may be useful in cross-border settings. How can the IDMP implementation guides for identification of medicinal products be applied in the work of WP2?
3. Deliverable D2.3 openMedicine sets of identifying attributes for medicines in different scenarios in a cross border setting. How can these attributes be completed in the Detailed Clinical Model?
 - For D 2.3, how can you finalize and publish the DCM for the Medicinal Product, in particular how can the rules that ISO 11616 specifies be used to generate PhPIDs?
 - How can you include the currently missing codes per information class / data element in this DCM?
 - Is it possible to add the additional value sets that are required for the medicinal product?
 - How can we achieve to obtain proper OIDs for all identifiers and all code systems?
 - Is it possible to complete the representations in UML and XML and to populate these with proper terminologies and codes, in particular in HL7 v3 CDA for epSOS cross border ePrescription?

The second area of issues in epSOS concern the various contexts. In order to get a proper overview of the different contextual layers, the Generic Component Model connects the various spaces as represented by the three axes, and within each space, breaks it down in layers (health systems and organisational view, process steps (RM ODP for system development) or relationships (to see where domains connect or even overlap).

Here the ContSys standard helps further to proper define the various health care systems, their stakeholders and processes. HISA supports the further breakdown from organization via processes to information levels. The EHR standards facilitate a proper organisation of the required data, and their exchange can additionally be supported by both the 13606 and the HL7 v3 message and CDA standards.

On the bottom level of this multi context architectural approach, the clinical modelling comes – again – in the picture, facilitating the most detailed specification of clinical background, data elements, terminologies and codes, and logical modelling. From there, the system and exchange formalization and implementation can be done more easily. And due to using standardization on every level, a flexible cross-domain approach also becomes possible, as is illustrated in the MPD where both the clinical domain, and the regulation domain around medicines are depicted and use the same IDMP identifications.

Future Deliverable 2.3 for openMedicine can depict the application of the IDMP in epSOS in examples of such contexts, offering help in the cross-border situations on several levels of processes and organization that have not yet been addressed.