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Abstract (for dissemination	This document presents some of the conclusions of the openMedicine project. We formulated ten plus two high level recommendations. All these recommendations, except one, address issues related to the identification of a medicine when dispensing in a cross-border context an electronic prescription or when displaying a Patient Summary abroad. One recommendation addresses the issue of "substitution" in the EU. The project endorses the IDMP suite of standards [ISO/EN 11615 and 11616 mainly] and extends the ePrescription and the Patient Summary guideline by including at least one additional identifier: the "generic" Pharmaceutical Product Identifier in the respective data set. Global standards for substances, units of measurement, dosage forms and the (linked) route of administration are becoming available soon. Small differences in usage of these standards between the regulatory and the clinical care context were encountered, not endangering acceptance of these standards. "Tailoring" to these needs is nevertheless recommended. A panel of experts/stakeholders covering the lifecycle of a medicine was involved directly and/or through the Expert Council Meetings (3). The second part of the deliverable builds on the recommendations and presents a roadmap for implementation. The implementation and roll-out of the conclusions of the openMedicine project needs to happen in a very complex legal and social context with an important number of 'interested' parties.
Keywords	Pharmaceutical Product, Pharmaceutical Product Identifier, IDMP, EN/ISO 11615, EN/ISO 11616

Statement of originality

Table of Contents

Executive Summary

The openMedicine project is a Coordination and Support Action, launched as part of the Horizon 2020 PHC 2014 call for proposal.

The CSA call intended mainly to enhance safety and quality of cross-border healthcare.

The epSOS project documented two main issues of concern when validating cross-border ePrescription services. Not all the equivalent medicines available could be identified as such. In other cases correctly identified equivalent medicines could not be dispensed due to local substitution rules.

The epSOS project on the other hand validated its services solely for packaged and branded medicinal products. Substance name based, generic prescriptions, neither magisterial formulas or cluster based prescriptions were considered.

openMedicine validated at first the "medicinal product" data model elaborated by ISO/CEN. The ISO/CEN standards [11615] and [11616] confirms previously defined levels of structuring and/or presentation of "medicinal products" [12610] starting with substances, pharmaceutical products, medicinal products and medicinal product packages.

Each of these representations should have at least a name or a textual descriptive identification and a coded ID for multilingual or cross jurisdiction services. This was – at least for the pharmaceutical product – not the case, until ISO/CEN/FDA as well as the openMedicine team agreed to assign a univocal identifier to each distinct combination of substance, strength, dosage form (and route of administration). That identifier is called the Pharmaceutical Product ID (PhPID)ID). Example of a PhPID : tablet of 400 mg carbamazepine oral usage is in every country the same; independently of the name given to ad medicinal product Tegretol.

Each of the identifiers, when available at the point of prescribing, when dispensing or when producing a Patient Summary, should be integrated into the respective documents.

Twelve Recommendations were formulated, ten of them addressing the ideal long term view, based on the ISO/CEN 11615 and 11616 and a validated IDMP compatible E.M.A. drug database, covering all the regulated medicines and their packages.

Two of the recommendations (3 and 4) are added in order to enable shortly, more specifically during the Phase I of the CEF program, using the Article 57 & 2 EMA database for the implementation of at first the ePrescription services.

Finally the Commission required the consortium to produce an openMedicine Roadmap, covering the identification aspects of a complete medicines lifecycle.

The full roll-out of the ePrescription, eDispensation and Patient Summary services will take several years from now and is not expected to be realised before the early 2020's. This is due to the need (and the will) of EMA to be the authorised data source for all the supranational medicines related information. This requires the actual Article 57 &2 drug database to be complete, validated, translated and structured in a way fully IDMP compatible.

Considering the strong wish expressed by the Member States at the aded and validated Article 57 data *for those countries participating in phase 1 of the CEF.*

A large number of stakeholders will be involved in the implementation of the roadmap but finally, at least during the first period, speed of realisation will highly depend on the progress made in building EMA databases, its validation and maintenance.

The grant agreement specifies that an openMedicine Implementation Roadmap should be agreed on. The consortium preferred to submit a separate document rather than adding a chapter to the Recommendations deliverable.

The full roll-out of the ePrescription, eDispensation and Patient Summary services, as defined in the openMedicine conclusions, will take several years from now and is not expected to be realised before the early 2020's. This is essentially due to the cross-border dimension of the openMedicine solution. Several Member States and associated countries have yet or will have "national" solutions running meanwhile. This may cause additional problems when implementing the expected cross-border services.

The consortium considered an intense global cooperation between national agencies and between EMA (European Medicines Agency) and the FDA (Food and Drug Administration) as essential to any cross-border services, see chapter 5 of deliverable D6.3A. This has an important impact on the development and roll-out scheme of the openMedicine services. Indeed EMA also intends to be the authorised data source for all the supra-national medicines related information. This requires the actual Article 57 &2 drug database to be complete, validated, translated and structured in a way fully IDMP compatible.

Considering the strong wish expressed by the Member States at the eHeath Network meeting in Brussels, November 21st, 2016 it has been decided to start with upgraded and validated Article 57 data *for those countries participating in wave 1 of the CEF.* The final decision on his isn't our competence.

A large number of stakeholders will be involved in the implementation of the roadmap but finally, at least during the first period, speed of realisation will highly depend on the progress made in building EMA databases, its validation and maintenance.

The documented roadmap is to be considered as a proposal taking into account the actual context and status of parallel developments.

1 The openMedicine mandate

1.1 Policy background

Enabling the delivery of safe and efficient cross-border healthcare is a policy priority Enabling of the European Union. However, while the European Union is taking down borders among member states to exchange electronic patient summaries and ePrescriptions, safely dispensing a prescription from another country is still challenging. This requires that a community or hospital retail pharmacist is able to read the prescription – three different alphabets are used across the Union, and 22 official languages prevail – and to identify the medicinal product specified. If directly available, the pharmacist will dispense it; otherwise s/he may order it from national sources or from abroad if in line with national regulation and obtainable in due time. If this is for not feasible, and substitution is permitted, the pharmacist may substitute the specified medicinal product by another one in line with national regulation.

The recently finished epSOS project (Smart Open Services for European Patients; 25 countries participated)[1] piloted two cross-border eServices:

- One providing (emergency) physician access to basic medical data of an ePatient Summary when treating patients living temporarily abroad or travelling across Europe, and

- Another eService enabling patients to visit a pharmacy abroad to purchase the medicinal product prescribed at home and recorded in an ePrescription.

It turned out that dispensing a prescription in a cross-border situation sometimes poses a specific identification challenge – also called the "delivery" problem of ePrescription.

A prescribed medicinal product can be specified in a prescription by identifiers and/or its attributes[2] in different ways, like by its package (e.g. GTIN[3]) or national medicinal product identifier, invented (originator) or given (generic) brand name, active ingredient, pharmaceutical dosage form, strength, route of administration and perhaps others. Another possibility available in some countries is that not a specific medicinal product is identified, but only a subset of medicinal products meeting certain criteria (like an INN[4] or ATC prescription specifying only an active ingredient plus other attributes), or products being grouped by their pharmaceutical or therapeutic class[5] as defined by a regulatory authority or statutory insurance.

1.2 Mandate and goal

openMedicine addresses both the identification and the substitution challenges. The DoA (Description of Activities) for the openMedicine project describes its mandate as follow:

"The overall *goal* of the proposed Co-ordination and Support Action (CSA) is to contribute towards and enhance the safety and continuity of cross-border (and also national level) treatment through interoperable ePrescriptions, and to develop concrete solutions to the challenges identified in this context. As the Call text notes: "The challenge in ePrescription is how medicines can be communicated in the cross border setting." Whereas the epSOS project basically solved the electronic "communication" or message transfer problem, it encoun-

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[1] www.epsos.eu

[2] For details see WPs 2 and 3 in particular, and also the list of attributes identified here in Appendix III.

[3] Global trade item number (GS1): https://en.wikipedia.org/wiki/Global_Trade_Item_Number

[4] INN stands for international non-proprietary name:

[5] Therapeutic Class is defined as group of similar medications classified together because they are intended to treat the same medical conditions, like pharmacological or therapeutic subgroup, or the active ingredient's chemical group. For details see WP 4

tered a serious "delivery" problem: the univocal identification of the medicinal product, which was noted in a prescription from a given country, by a pharmacist dispensing it in another country (initially across the Union, but eventually globally)…"

The mandate of openMedicine is clearly limited to two concepts : coordination and support action and two domains: the identification of medicines in a cross border setting and substitution.

The EXPAND project reported complementary problems and issues encountered during the epSOS project while investigating whether openMedicine could offer a solution. This EXPAND document has been added to this deliverable as Chapter 8.

1.3   Cooperation

Coordination being one of the kernel expectations of the program we opened our activities to all willing and relevant stakeholders. .

Coordination with the most significant stakeholders has been realised from day one of the project by including the European Medicines Agency (E.M.A.), the FDA (Food and Drug Administration, USA), the World Health Organisation through its Uppsala cooperation centre for pharmacovigilance (Uppsala Monitoring Centre - UMC. A special "thank you" is addressed to E.M.A. for co-chairing all three openMedicine expert council meetings as well as the Transatlantic workshop organised in close cooperation with FDA in Washington, DC, during spring of 2016.

The openMedicine consortium on its own already forms a platform for cooperation between member state regulatory and regional authorities, standards development organisations (SDOs), consultants and experts, including organisations which had been involved already in the epSOS project.

Furthermore, to provide for close cooperation and coordination of activities, members of the openMedicine project team participated in other PHC34 interoperability focused projects (eStandards, ValueHealth and Assess CT) and attended several of their meetings.

The project organised three Expert Council Meetings in Europe (London at EMA in June of 2015, Brussels at CEN – CENELEC Management Centre in January of 2016, and London again at EMA in October of 2016) and was invited to one US_EU workshop on the unique and global identification of medicinal products. Each of these council meetings and workshops were attended by approximately 30 experts from both sides of the Atlantic. For more information about these activities see Deliverables D6.1 and 6.4.

The consortium organised and/or participated in about 12 workshops and dissemination meetings The list of these sessions was published in Deliverable D7.2

Through all of these activities and workshops openMedicine succeeded in reaching out at all relevant stakeholder groups relevant for the planning, implementation and maintenance of the standards and processes which will be necessary for the univocal identification of medicinal products across the Union and beyond this als across the Atlantic (Canada and USA).

1.4   Objectives and tasks

This section briefly reviews the objectives and tasks of WP 6 "Validation, Recommendations and Roadmap", describes the coordination of work across work packages, and explores the methodological approach applied, Standards and even more acceptance of standards is a

question of reaching a consensus between interested parties. Quality and completeness are two other important issues to be addressed, and reaching of

g their status has to be verified. The same applies for extensions to existing standards and for recommendations to European and National Competent Authorities. The consortium has had, through its core and expert partners, a unique opportunity to reach such a consensus, because all important and relevant stakeholders have been present or were represented.

As described in some detail in the Description of Action (DoA), the objectives of WP 6 were to obtain:

- Consensus on the identification issues enabling dispensing of the same or a medicinal product equivalent to the one prescribed, both in a cross border or in a national setting.
- Consensus on the descriptive attributes that facilitate the identification of pharmaceutical and medicinal products.
- Agreement on the infostructure and infrastructure required to realise this identification
- Agreement on a number of recommendations at regulatory basis to improve the present unsatisfactory situation.
- Acceptance by the different stakeholders of the recommendations.
- Develop a realistic roadmap to realise the options proposed.

This WP had 3 tasks assigned:

- Cooperation with expert partners
- Validation
- Recommendations and Roadmap

Whereas the preceding deliverable D 6.1 Expert Council Activities reported on xx , and D 6.2 "Report on validation activities" reviewed xx, this deliverable reports on and summaries core project work in few distinct recommendations and a brief roadmap outlining the way to go to indeed fully implement the ISO IDMP standards and facilitate reaching the benefits to be expected also in the clinical domain.

1.5   Methodological approach

Methodologically, work for this deliverable relied very much on the work and results obtained in the preceding work packages, and it also gained fundamentally from both internal discussions and those with external experts. Core results were taken over from earlier work, synthesised in deliverables and explored in various internal workshops, and the three meetings of the Expert Council were a key approach towards validating and better specifying the results obtained such that they could be easier communicated to a wider audience. Also the many discussions during national and regional dissemination events were recorded and contributed towards further improving the quality, validity and applicability of outcomes.

Part of this approach were also these steps:

- Extensive informal usage of the competence present in the core team as well as present in the Expert Council, e.g. through informal discussions, short teleconferences and exchanges of e-mails.
- Identification and assignment from the Expert Council of at least one "expert reviewer" for each of the tasks and deliverables. Their prime mandate was to support and assure a high quality of all outputs, consistency of project results, and the overall quality of the work process.

- Preparation discussion and validation of recommendations and a roadmap together with all Work Package Leaders and Expert Council members.

A further methodological aspect was that in the earlier work already a set of core cross-border healthcare and clinical use cases was selected and utilised where the univocal identification of pharmaceutical and medicinal products represents a central challenge for patient safety and high quality performance of regulatory and clinical tasks, including continuity of treatment over the life cycle of a medicinal product and long-term care for chronically ill patients. This also included the key aspect of pharmacovigilance improvement. All of this served to test and demonstrate the usefulness, benefits and practicability of the solutions developed within the project

The deliverables provided by WPs 1 to 5 were validated with the supporting expert organisations to assure that the solution developed are in line with the requirements regarding unambiguous identification and description of medicinal and pharmaceutical products.

2 The openMedicine legal and regulatory context

The purpose of medicinal treatment is to restore and improve patient's health and well-being. On the other hand, whatever treatment is given, none of them should harm the patient:

An impressive set of European as well as national regulations and laws has been introduced in order to support effectiveness and safety of any kind of medicinal treatment.

Budget constraints, public as well as private, combined with the need to provide products for less frequently occurring or rare diseases, challenging economic arguments also linked to more focused target populations have in recent decades added a new degree of complexity to the creation, production, marketing, prescribing, dispensing and administering of medicinal products.

As the Union and also the single market for services develop, there is at the same time an increasing need for cross-border availability not only of medicinal products but also of health and care related information (patient summaries including medication data), most - but not exclusively - in border areas within the Union.

For decades investments have been made by health authorities and SDOs (Standard Developing Organisations) to standardise the content and the exchange of the available patient data, in order to increase interoperability between systems, between professionals and between applications and knowledge.

All of this also impacts on the globally univocal identification of medicinal products. As a consequence, openMedicine had to address relevant Union directives, guidelines, regulations and standards applicable in these heavily regulated "economic" activities: health and healthcare, data exchange, privacy protection, as well as production and use of healthcare products and services. Various "authorities" address the issue of identification of medication items in the ePrescription, eDispensation and Patient Summary services as topic in their legal and regulatory documentation.

We do not intend to be exhaustive or to suggest specific additions, tools and/or vehicles to published rules and regulations relevant at any stage of a medicine's lifecycle. We neither address the full content of the respective official document. We limit us to identifying the domain of application, the issue(s) addressed and, the "identification" related or complementary elements where they are of importance for further discussions.

2.1 EU directives and regulations

2.1.1 Directives related to medicinal products

Already in the very early days of the European Economic Community (EEC) issues and challenges in the health services domain related to treatment with medicinal products received considerable attention and were identifyied as a priority area of regulatory attention, in spite of member states having retained sole responsibility[6] for the organisation of national health systems and services. This concerns, inter alia, these directives:

- Directive 65/65/EEC   Council Directive of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal

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[6] This is the reason why only directives, but no regulations were issued.

- products (65/65/EEC). As amended by Directives 83/570/EEC, 87/21/EEC, 89/341/EEC and 93/39/EEC.
- Directive 75/318/EEC   Second Council Directive of 20 May1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (75/319/EEC). As amended by Directives 83/570/EEC and 93/39/EEC.
- Directive 91/356/EEC   Commission Directive of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use (91/356/EEC).
- Directive 92/27/EEC   Council Directive of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets (92/27/EEC).
- Directive 93/42/EEC   Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.
- Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use

From today's perspective, this is the main and most relevant directive dealing with medicinal products. It lays down the rules for manufacturing, importing placing on the market, and wholesale distribution of medicinal products as well as active substances used for their production.

- Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patient's rights in cross-border healthcare

This is the core directive providing framework conditions for a European-wide healthcare services market, and as a part of this requirements on the electronic exchange of health data, including ePrescriptions.

2.1.2 Regulations for specific aspects related to ePrescription and to medicinal products

The stipulation that national and regional healthcare service provision is the sole responsibility of member states was upheld in the Treaty on the Functioning of the European Union (TFEU).[7] Nevertheless, there exist some regulations impacting in our domain, because the Union is

responsible respectively may regulate areas like public health including pharmacovigilance, training and education, data protection and privacy, or manufacturing of products

Regulation on the procedures for the authorisation and supervision of medicinal products

Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products.

This was and still is a core Regulation concerning all issues around medicinal products. Initially EMA was named "European Agency for the Evaluation of Medicinal Products".

It was reviewed and consolidated by

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[7]   The Treaty of Lisbon was signed in Lisbon, Portugal, by the prime ministers and foreign ministers of the 27 EU Member States on December 13, 2007. It came into force on January 01, 2009.

Regulation 726/2004/EC Regulation of the European Parliament and the Council of 31th March 2004

Defines the documentation to be provided and the procedures to be compliant with when submitting a request for authorisation.

Regulation on orphan medicinal products

Regulation 141/2000/EC, in which pharmaceuticals developed to treat rare diseases are referred to as "**orphan medicinal products**".

Directive and Regulation on Falsified medicinal products

Directive 2011/62/EU amending Directive 2001/83/EC as regards the prevention of the entry in the supply chain of falsified medicinal products

- The directive introduced a new identifying attribute for the medicinal product package. The safety feature is mandatory for each package of a medicinal product for which a prescription is required.
- The unique medicinal product package ID links to more information about origin and authenticity of the medicinal product.

Commission Delegated Regulation 2016/16 of 2 October 2015

- Supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use

Implementing Directive 2012/52/EU

Implementing Directive 2012/52/EU of 20 December 2012 laying down measures to facilitate the validation of medical prescriptions issued in another Member State

> *"Medicinal products should therefore be indicated using the common name in order to facilitate the correct identification of products which are marketed under different brand names across the Union and of products that are not marketed in all Member States. That common name to be used should be either the International Non-proprietary name recommended by the World Health Organisation or, if such name does not exist, the usual common name. In contrast, the brand name of a medicinal product should only be used to ensure clear identification of biological medicinal products as defined in point 3.2.1.1.(b) of Annex I to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Co"*

2.2 Implementation Guidelines in support of cross-border healthcare

A number of Guidelines were issued in application of Article 14 (2) (b) (i) of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011.

The following Guidelines were issued

1. Guideline on the Patient Summary
2. ePrescription Guideline
3. General Guidelines for Electronic Exchange of health data under the cross-border directive 2011/24/EU

2.3   EN/ISO standards

Furthermore, there exist international standards which, through CEN, are mandatory to be applied in national contexts, and agreements on guidelines etc. which thereby become more or less mandatory in national contexts, e.g. for countries participating in projects implementing an electronic (health) infrastructure across member states through the Connecting Europe Facility (CEF).

The standards marked with an * are directly related to the domain of application of openMedicine, while the standards marked with ** are part of the IDMP suite of standards.

- EN ISO 11615**, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated medicinal product information
- EN ISO 11616**, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information
- ENV 12610*, Health Informatics — Medicinal product identification — 1996
- EN ISO 21090, Health informatics — Harmonized data types for information exchange
- EN ISO 17523*, Health Informatics — Requirements for electronic prescriptions — 2016

2.4   Reference tables

The standards marked with an * are directly related to the domain of application of openMedicine, while the standards marked with ** are part of the IDMP suite of standards.

- EN ISO 11238**, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances;
- EN ISO 11239**, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration   and packaging;
- EN ISO 11240**, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of units of measurement

3 openMedicine concepts and definitions

Most of the Directives, Guidelines and Standards contain a section with "third party" definitions" and a set of "internal" definitions, internal to that document.

A very clear and unambiguous definition of the concepts used is essential for a good understanding and for real interoperability across applications, domains, languages and jurisdictions.

Concepts and definitions should be as much as possible consistent with each other, at least within the same standard or directive.

Each difference in definition for the same concept between standards addressing the same domain of application should be heavily justified.

The same term may of course have a different definition when addressing a different domain of application.

3.1 Definitions in Directives, Guidelines and Standards – Reusing them

One of the issues is reinventing within each research project a new definition for the same or very similar concepts.

By considering only the Directives and the standards directly related to the identification of medicinal and/or pharmaceutical products as well as the Directives related to ePrescription we identified up to five different definitions for the medicinal product and three different definitions for the pharmaceutical product.

Term: medicinal product

1. product intended to 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: Directive 65/65 EEC - modified
   Last update: 26/03/2015
2. 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], [ISO 11616:2012]
   Last update: 24/04/2015
3. substance or combination of substances, which can be administered to human beings for treating or preventing disease, making a medical diagnosis or to restore, correct or modify physiological functions
   Reference: ISO 17523:2016(E)
   Last update: 22/09/2016
4. any substance or combination of substances presented as having properties for treating or preventing disease in human beings
   Reference: DIRECTIVE 2001/83/EC
   Last update: 27/09/2016
5. any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis
   Reference: DIRECTIVE 2001/83/EC
   Last update: 27/09/2016

Term: pharmaceutical product

1. 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
Last update: 24/04/2015
2. product consisting of one or more ingredients
Reference: [ENV 12610 : 1997[
Last update: 27/04/2015
3. qualitative and quantitative composition of a medicinal product in the dose form authorized for administration by a regulatory authority and as represented with any corresponding regulated product information
Reference: [ISO 11616:2012]
Last update: 15/11/2015

A concept may have more than one definition, provided that this is due to (completely) different domains of application and that the definitions are not interchangeable.

Some concepts are "overdue", due to changes in science or reality, e.g. the introduction of concept "pharmaceutical product ID" now couldn't be integrated in the Directive 2001/83/E .

The next chapter illustrates how complex and how difficult it is to agree on consistent concepts and definitions, even worse over years over decennia.

This brings us to a (possible) recommendation:

A joint taskforce should be considered to harmonise the concepts and their definitions and to update actual Directives and Standards.

The composition and the mandate of the Taskforce should be agreed on by the SDO's, the Health authorities, EMA and the eHealth community.

3.2   Definition retrieval

Retrieving the most suitable definition applicable in a given context isn't always easy.

3.2.1   openMedicine dictionary

One of the openMedicine partners developed, in order to facilitate the selection of one of the existing definitions for a given concept a display tool for the concepts and their definitions applicable / addressing the domain of mainly the medication and more precisely that of the identification of medication items in the ePrescription, the

eDispensation and in the Patient Summary.

The dictionary has in total 623 concepts listed and defined, covering the domains addressed in the openMedicine project medicines, ePrescription, eDispensation and the Patient Summary.

Are included

- the EN/ISO standards
- the directives
- the guidelines more especially he implementation guidelines for the listed services
- the concepts listed in the different work packages

as well as appropriate terms and concepts related to the services to be provided.

Figure 1 User Interface

Figure 2 Result of a query
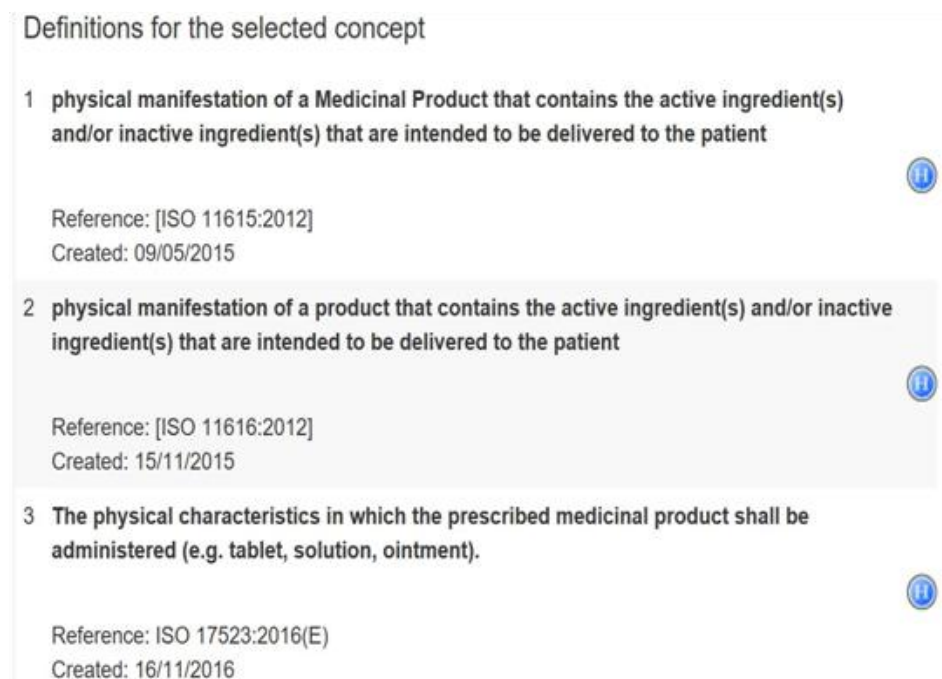
Figure 3 Three definitions for the same concept

The application can be activated through the web: www.open-medicine.eu .

The application is free accessible by using the userid/password combination "ex-pert/expert". After 30.6.2017 a personal password will be requested.

For more information please address your questions and remarks to www.eurorec.org/.

3.2.2 SKMT

ISO TC215 developed also a tool to retrieve definitions of concepts as documented within the different ISO/EN standards, the "standards knowledge management tool".

Registration is free of charge at http://skmtglossary.org/

Difference between the tools:

- Both tools enables retrieval and display of the concepts and there definition(s), limited to our domain of application and per keyword only

- The ISO tool (Joint Initiative for Global Standards Harmonisation) enables retrieval of terms and definitions **per standard** and per keyword. It includes ALL the standards, in-creasing number of definitions not applicable an

Figure 4 SKMT login screen

The date (2008-2012) might be an indicator for a lack of maintenance.Ths might be an issue at global level.

The next screen illustrates a powerful query interface.

Figure 5 SKMT Query interface and initial result

Generic Search

Figure 6 SKMT Kind of Medicinal Product

Figure 7 SKMT Medicinal Product Definitions (main)

Figure 8 SKMT up to 35 different definitions

The definitions provided under de title "medicinal product" are not the 11615 and 11616 definitions of IDMP but the previous 12610 MPID definitions, including definitions as well as a set of descriptive attributes from medicinal products.

3.3 openMedicine concepts and definitions

The concepts identified and/or defined during this project and/or by the openMedicine consortium and listed in the deliverables of the respective workpackages. They will not be repeated here.

4 Identification: the ultimate goal

As its predominant goal, the openMedicine project addressed the identification of a medicine or medicinal product in a retail ePrescription by the prescribing healthcare professional, at the dispensing site in a high-street or hospital retail pharmacy, or in an electronic patient summary, electronic health record or similar document while a patient is consulting a health-care profes-sional for treatment.

We are, regarding prescribing and dispensing medication items, addressing solely the identi-fication aspects within an electronic prescription and the computer supported dispensing of medicinal products.

openMedicine focuses on a cross-border dispensing and administering of a medication item and on the cross-border use of the medication related information within a patient summary.

4.1 Prescribing a medicinal product: the identification issue

Despite the European directives and guidelines, despite a large number of national regula-tions, we still have an impressive variation in how a prescribed medicinal product is identified in an ePrescription.

Further analysing the phenomenon we have to conclude that the completeness of the identi-fication of a medicinal product in a prescription depends on:

- The prescriber's knowledge of medicinal products, his good-will to comply with the rules and the context of production of that medicinal prescription
- The method of data-entry: handwritten on a prescription form or by using an EHR/CPOE/ePrescribing system and subsequently printing on paper or exported as an electronic prescription.
- The context in which the prescription EHR system is linked to a drug database and has no problem to retrieve all the data-elements required to produce a 'complete' prescription.

4.1.1 De facto identification in national (paper) prescrip-tions

A prescribed medicinal product can be identified unambiguously within its jurisdiction of pre-scription in many different ways and by using a set of identifying attributes, from minimal to the complete set identifying attributes.

In some cases, even only the full medicinal product name is enough to identify the package of the medicinal product to be dispensed, e.g. when there exists only a sin-gle box, or the smallest box is the default value.

To illustrate the case consider the following example: A GP in Belgium visits a patient and prescribes a product for his Parkinson disease. He prescribes AZILECT, marketed by Lund-beck. Is only available in packages of 28 tabl of 1 mg rasagiline (mesilate). It has as national package code CNK 229-50. It has as ATC code N04BD02.

Different options to specify the medicinal product in a possible prescription are illustrated. Each of theme clearly identifies what product has been prescribed and will – at least in some countries – be dispensed

1.	R/ Azilect 1 Box of 28 tab of 1mg	package name/description + Qty
2.	R/ Azilect 1mg 28 tab	package name Or MP name + strength + dose form + Qty
3.	R/ Azilect 28 tab 1 box	MP name + dose form + Qty + Qty pack
4.	R/ Azilect 1mg	MP name + strength

All these prescriptions - even when not fully compliant to the national regulation – can be dispensed because each prescription unambiguously identifies the prescribed medicinal product plus the quantity (package).

The use of the first or the second type of prescription depends on the national marketing options and the regulatory context: are we prescribing usually per package or per number of product units.

5.	R/ Rasagiline 1mg 28tab	INN prescription Substance name + strength + dose form + Qty
6.	R/ N04BD02 1mg 28 tab	ATC prescription code of the substance + dose form Qty

The fifth and sixth prescription are the so called "generic" prescriptions. The first one by using the INN name and the latter one by using the ATC code. The product to be dispensed is in both cases univocally identified by the composition, because no other medicinal product with this active ingredient is marketed in the country.

These examples illustrate the great variety a paper prescription may allow to univocally specify the medicinal product to be dispensed. Ideally, this freedom should be translat-ed into the digital health and cross-border services world.

4.1.2 Electronically generated prescriptions

The Context

Prescriptions generated by an EHR application are expected to be of a superior quality in both scenarios printed from the application as well as exported as an ePrescription file.

This added quality is due to the use of an interactive authorised and correctly maintained drug database, translating prescriber's choice into a 'standard compatible prescription file', including the appropriate identifiers.

The quality improvement of prescriptions generated by an EHR application is not limited to the formal aspects of the prescription but includes clinical aspects too as improved selection, dosage control, surveillance, monitoring and last but not least data exchange with other stakeholders.

Purely text based EHR generated prescriptions should be considered as outdated and dis-couraged.

The quality improvement is a reality in both sub-scenarios: outprint of the prescription as well as managing an ePrescription either addressed to a pharmacy or made available on a prescription server.

Implementing ISO-IDMP

Particularly in workpackages 2 and 3, openMedicine in detail reviewed, assessed and suggested further improvements of the ISO IDMP (identification of medicinal products) suite of standards. In summary, these standards define in great detail a set of attributes and their relations to identify different, but interrelated levels at which medicinal and pharmaceutical products as well as their active and non-active substances may be described. Both the European Medicines Agency (EMA) and the US Federal Drug Agency (FDA) have been and still are heavily involved in creating, validating and implementing these standards. CEN has ratified or will adopt them as European standards. In the field of pharmacovigilance and for other purposes, they will become mandatory in the EU. Also European pharmaceutical manufacturers will need to comply with these standards, e.g. when submitting their "summary of product characteristics (SmPC)" for the marketing authorisation of new medicinal products, or pharmacovigilance notices.

A related trans-Atlantic community of EMA, FDA and various other national and supranational organisations collaborates to maintain and further develop these standards and the related code systems.

Particularly for ePrescriptions and, in general, for digital health and cross-border healthcare, these are path-setting developments. Once the relevant European and national IDMP compatible drug data bases have been realised, healthcare professionals may make use of more or less any of the procedures they have used in the past to specify a medicinal product in a paper prescription also when making use of electronic prescribing support. They may identify a package, a medicinal product, or an active substance - plus further identifying attributes as needed – to univocally specify for the pharmacist which particular medicinal product is to be dispensed, or from which subset of specified products the pharmacist may select. Once sufficient characteristics have been specified in the prescription, which may range from a single package ID code to a small set of identifying attributes, the electronic system is able to add various other attributes, codes etc. as may be needed in the respective application context, which will be particularly useful in situations where different health systems, languages and alphabets are involved.

The relationships which exist between the different levels at which a product may be identified and core identifying attributes are illustrated in the following figure:
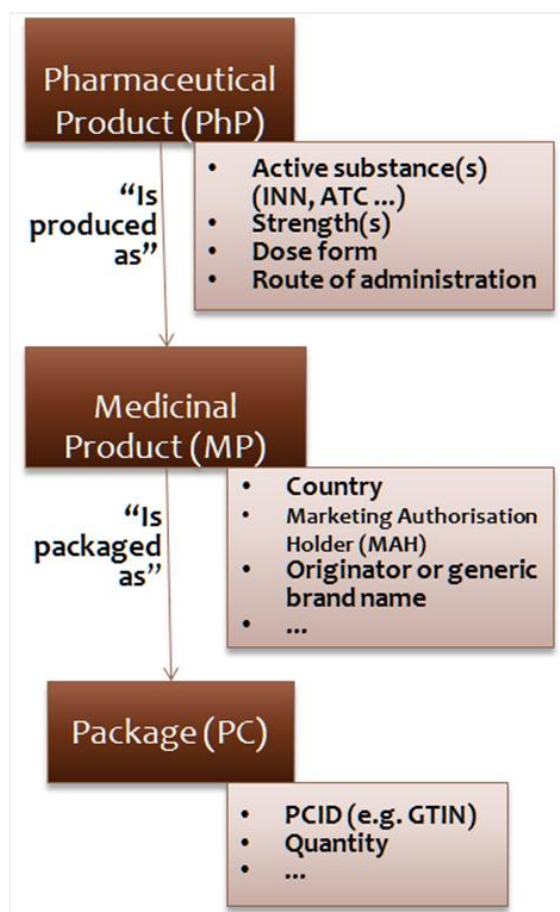
Figure 9 Relationships between identification levels and attributes for medicinal and pharmaceutical products (Source: [c] openMedicine 2017)

The Cross-Border setting

In a cross-border setting, the situation is usually somewhat more complex, as illustrated in the following figure xx. It seems that the most prevalent approach towards specifying a medicinal product in a prescription is still using its innovator or generic (brand) name, plus further attributes as needed, like dose form, strength and units of measurement, route of administration, box size/quantity, and others. If in the country of dispensation exactly the same medicinal product is available, there does not exist an identification challenge.

However, because of the variety of marketing authorisation procedures, legacy medicinal products, marketing strategies of pharmaceutical companies etc., it is regularly the case that the identical medicinal product is not available in the other country. However, in such situations the MPID available from the connected data base allows to identify the linked (globally univocal) PhPID, and through this the full subset of equivalent medicinal products available in the foreign country. Then, whether indeed a medicinal product can be dispensed, is no longer an identification issue, but rather depends on local rules for substitution.

Similarly, when (only) a package or a package ID are specified, this can be immediately linked to the MPID and, if needed, also to the PhPID, and the same considerations apply.

If only an active substance, but not a specific medicinal product, and other attributes are specified in the prescription, again the electronic system allows to retrieve the connected, globally univocal PhPID, and through this the full subset of equivalent medicinal products available in the foreign country. Then again, whether indeed a medicinal product can be dis-

pensed, it is no longer an identification issue, but depends on local rules – whether they allow such types of prescriptions to be dispensed.

The relationships which exist between the different levels at which a product may be identified in the cross-border setting are illustrated in the following figure:
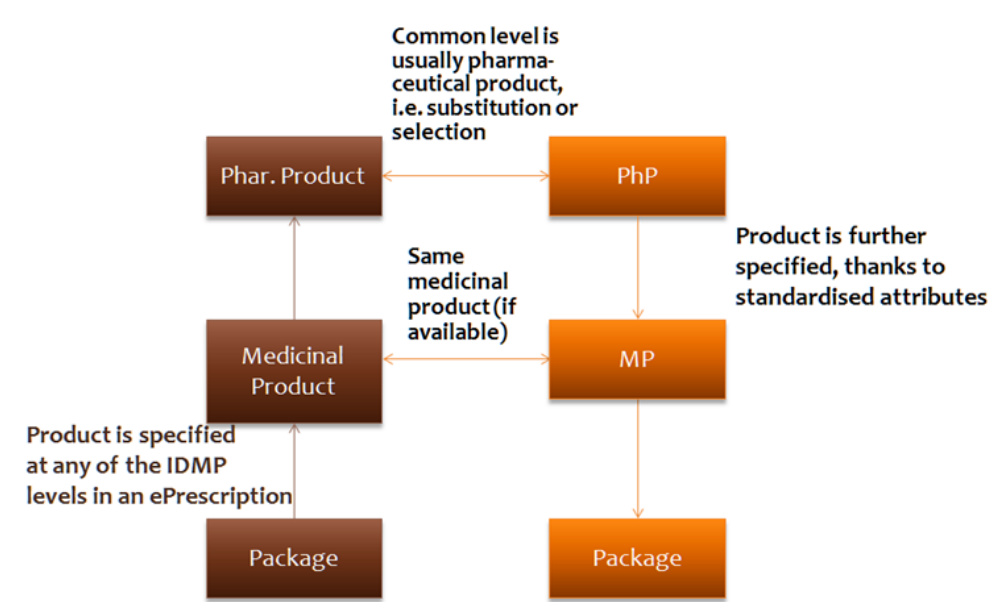

Figure 10 The xBorder ePrescription & dispensation setting (Source: [c] openMedicine 2017)

All of this demonstrates how the electronic prescribing option (be it to generate a paper prescription, be it to exchange an ePrescription) enables, as suggested by openMedicine, to add complementary identifiers, favouring cross-border retrieval of identical or equivalent medicinal products. Including such additional identifiers when producing the ePrescription is essential in order to realise and to ease an automated retrieval of an equivalent medicinal product (package) in cross border settings.

It follows that the electronic systems and data bases must be able to automatically include the MPID and link it to the respective PhPID in cases where a specific medicinal product (or a package of an MP) is noted in a prescription, because it will al-ways allow identifying the box sizes available in the foreign country, if this product is marketed there. If it is not, the PhPID allows for identification of the subset of equivalent, marketed medicinal products carrying this PhPID.

For prescriptions which only specify an active substance and other identifying attributes, the electronic systems must be able to identify the correct PhPID meeting these criteria. Again, because it is globally univocal, it will always be possible to identify in the foreign country a medicinal product linked to this PhPID, if any is marketed there.

Actual Regulatory Identifiers

The e-Prescription option enables, as suggested by openMedicine, to add complementary identifiers, favouring cross-border retrieval of equivalent medicinal products.

Including additional known identifiers when producing the ePrescription is essential in order to realise and to ease an automated retrieval of an equivalent medicinal product (package) in cross border setting.

The IDMP available identifiers that might be included in the ePrescription depends on the kind of presentation of the prescribed product

Prescribed	PCID	MPID	PhPID	SubID	MAN
Package	X	X	X	X	X
Quantity of MP units		X	X	X	X
Quantity of Pharm Product units			X	X	

The MAN – the Market Authorisation Number – can, considering some territorial limitations, be used to uniquely identify a medicinal product package or a medicinal product within a given jurisdiction.

The territorial extend of the Market Authorisation defines the extend of area where the MAN can be considered as a valid and distinct identifier.

Central Marketing Authorisation → European Marketing Authorisation Number
National Marketing Authorisation → Marketing Authorisation in M.S. where request is done
Mutual Recognition Authorisation → Marketing Authorisation in the M.S. of the group based on a number referring to one of the M.S of the group

The number of "centralised procedures" differ between the M.S. and is estimated to be between 5 and 20%.

Including these identifiers into the ePrescription, eDispensing and the Patient Summary does not require any action by the prescriber. The identifiers are indeed available in the distributed or in the connected drug database.

4.1.3 The prescription management

A professional prescription and medication management at clinical level requires identification and linking of individual prescription lines and medication lines.

The following concepts should be supported:

- The prescription (document, collection and the attributes of a document)
- The prescription line
- The medication line

Each line (prescription line / medication line) contains the complete set of identifiers and descriptive attributes linked to each of the prescribed medicines.

These concepts enable traceability of effective dispensing, of substitution, refusal, postponement or cancelling of a prescribed medicine.

An alternative is, at least theoretically, to produce one prescription per prescribed medicinal product.

4.2 Dispensing a prescribed medicinal product: the identification issue

The prescription of a medicine is/can also be defined as an authorisation to dispense an individual medicinal or pharmaceutical product to a patient. The pharmacist is the addressee and the patient is the subject of care.

4.2.1 Routing an ePrescription

The paper based handwritten or the printed prescriptions are obviously handed in person to the pharmacist.

The electronic prescription is *in principle paperless* and send

- to either the pharmacy information system to be processed locally
- to a prescription server to be stored temporally and collected by the proceeding pharmacy after identification of the responsible pharmacist

Direct addressing a medicinal prescription to a pharmacy, even a pharmacy selected by the patient, is not permitted in most of the countries.

The paperless electronic prescription seems equally difficult to realise:

- some countries, regions or even insurance companies still require a full prescription out print despite the electronic prescription being available
- other countries require a "ticket" in order to facilitate retrieval of the prescription or to enable to leave the power to the patient to select which prescription should be processed

These paper requirements are most probably temporally, though some pressure has been experienced from patients and /or patient organisations to have "something".

4.2.2 Identify and dispense the requested medicine

The medicinal prescription is an authorisation to dispense a specified medicinal product, even more precisely a specified package or a specified number of product units of that specified medicinal product.

This is only the case if the when he prescriber specified a package or a quantity of product units / when dispensing is organised per product unit.

The less specific a prescription the larger the pool will be of medicinal products (and their packages) that meet that prescription's details. In this case the pharmacist will **select** within the pool a medicinal product package at its convenience, considering the social security or private insurance rules applicable. Selection is usually only done between **equal** products with the same substance, strength, dosage form and route of administration. They have the same PhPID.

Having the PhPID available will facilitate retrieval and selection of the appropriate medicinal product or package, also in cross-border

The pharmacist may in some circumstances dispense a medicinal product package <u>outside the pool</u> of products or packages that meets the identification details if the prescription. We speak about substitution. Substitution can be based on:

- Stock management in the pharmacy (the specified product is not available and cannot be delivered in due time)
- Limited choice in local formularium

- Private insurance mandatory choice (i.e. the insurance will reimburse only products on its restricted list)

- Social security rule for Third-Party Payment restrict choice

- Emergency situation, as a "break-the-glass" procedure

- Requested by the patient (usually the patient will have to pay the difference to the cheaper product or even the full price)

Furthermore, the prescriber has in most of the Member States the right to forbid substitution for an individual medicinal product by adding "not to be substituted" to the prescription.

In some Member States no substitution is allowed, e.g. Austria.

Note Is cross-border dispensing possible in a country where substitution is not allowed, no way allowed. The product in dispensing country will always be different, will always have a different Market authorisation, even when identical.

4.2.3 eDispensation

Some blockbuster medicinal products are copied numerous time, each copy being an identical or at least equivalent medicinal product. Substitution, if allowed, will result in dispensing each time a different medicinal product. This results if the prescriber isn't informed on what has effectively been dispensed, into an unacceptable situation in which the prescriber is not informed on what product has effectively been dispensed. The EHR does not any longer reflects reality regarding medication.

This opens, at the first glance, two possible options:

- provided patient consent is given or not witholded, each dispensing of a medicinal product prescribed electronically should be reported in a eDispensation note

- substitution should be forbidden as long as the EHR application can't be updated

The eDispensation message refers to each individual line in the prescription. This link enables the receiving application to close the loop and to record the dispensed product or package as an attribute to the medication items.

The added value of dispensation information can be increased by including – with patient consent – information about not prescribed dispensed products (OTC) or about not dispensed prescribed medicinal products.

The exchange of medication related information between prescriber and pharmacist will obviously increase quality and safety of medicinal treatments.

4.3   Medication as part of a Patient Summary

4.3.1   Principles and concepts

A patient summary is defined in the openMedicine dictionary as *"a dataset of essential and understandable health information that is made available at the point of care in order to deliver safe patient care during unscheduled care and planned care with its maximal impact in the unscheduled care"*.

The patient summary is a view on patient data filtered by clinical relevance under responsibility of the maintaining stakeholder, in most Member States a designated physician.

The medication (history) form is an important part of the information about the patient that will be shared through the Patient Summary. The medication history needs to be distinguished from the prescription history. They illustrate two different worlds in their approach to medicines:

- The pharmacist takes in consideration logistic issues that enable him to dispense prescribed medicinal products. His entry point is the package, if dispensing is organised that way. Otherwise processes are expressed in product units.

- A patient record in a pharmacy information system is built around a series of packages prescribed, dispensed and billed. The diagnosis and other information are complementary.

- The prescriber is primarily reasoning in terms of a medicinal treatment by using an active substance, the core part of a pharmaceutical product which may be marketed under one or several product names and commercialised in different medicinal product packages?

- The patient record in a physician's information system is built around patient's condition. Medication items, as defined in next topic, are core elements of the Electronic Health Record. Prescriptions are on the other hand only a way to share and exchange medication data. One chronic treatment will generate a series of prescriptions, subsidiary to the medicinal treatment concept.

All electronic prescribing systems are using a drug database to select the appropriate medicinal product and/or package. These databases are generally comprehensive containing prescription products as well as various non-prescription products, which means all what can be prescribed, independently of the issue if the product can be reimbursed in the given national health insurance system. They are all conceived, with a few exceptions, to be used interactively with patient data to produce prescription data.

A prescriber prescribing Simvastatine, INN prescription excepted, has to select a Simvastatine package with one of the possible medicinal product name and a package description. The treatment will mostly be labelled with the package label. It is frequently because it is even impossible to choose only a medicinal product name because not present in the database.

A possible 13th recommendation could be

> *A medication item in a patient's record should be registered solely or at least also by its pharmaceutical product ID. The pharmaceutical product has a composed name (the substance name, strength and dosage form).*
>
> *The medicinal product package dispensed and the date of the last prescription are then attributes to a medication item.*

4.3.2 What is needed regarding medication information?

The new care provider requested to treat a (foreign) patient essentially wants an answer on three questions regarding medication: *What? How much? Since when?*

The data elements needed in order to be able to display its content are:

- Identification of the medication item, as exported by the Patient Summary of origin.

- The label used to identify a medication item can be :
  - a package label (with strength and dosage form, implicitly defined)
  - a medicinal product name (with strength and dosage form)
  - the pharmaceutical product label

- Either one enables to univocally identify the medication items displayed in the patient summary, at least within the country of origin of the patient summary.
  - Date of end of treatment (date in future; "expected" / date in the past; effective end of treatment in the past)
  - Date of start of the treatment (approx. date)

- Alternative representation of the duration of a treatment:
  - Begin date + duration
  - date + duration

- Posology, more especially the (average) daily dose

4.4 Cross-border interpretation

Before going further in analysing the cross border issues to be addressed when processing a prescription, a patient summary and eventually when addressing a dispensing report, it is important to note that we are only handling IDMP / openMedicine compatible files.

We will briefly explain how an openMedicine compatible ePrescription or Patient Summary file can be processed.

> **An openMedicine compatible ePrescription contains at least a pharmaceutical product ID.**

> **An openMedicine compatible Patient Summary contains for all the medication items at least a pharmaceutical product ID**

We will also briefly document the differences with the earlier epSOS approach. This does not imply that the epSOS approach is no longer valuable. It may still be used in some cases.

4.4.1 Interpret the original prescription

The context:

A pharmacist download at the request of a patient a prescription issued in another language in another country.

Standard epSOS approach:

Because across countries there exist different products with the same name).Though the same medicinal product name is used in his country, the pharmacist does not dispense that product without verifying if it really concern the same (pharmaceutical) product in both the prescribing and the dispensing Member State, (because across countries there exist different products with the same name.

Therefore he asks The NCP services of the prescribing Member State to provides the composition (scientific composition) of the product, subsequently translated in the language of dispension.

openMedicine approach

The pharmacist/ the pharmacy information system undertakes an internal query based on the PhPID of the prescribed medicine to identify equivalent medicinal products. Remember that a collection of all the medicinal products with the same substance + strength + dosage form (+ route) is a "virtual entity" of all the medicinal products identified by the same PhPID..

4.4.2 Search a local equivalent

Standard epSOS approach:

The pharmacist looks up for a product with the same scientific composition in his national drug database. He dispenses in case of a perfect match. Otherwise he substitutes and dispense a 'similar' product if available and if substitution is allowed

openMedicine approach

The pharmacist looks for a product with the same PhPID in his local database. If that's the case then we have an identical product and can we dispense it, if substitution is allowed.

The "costly" translation and comparison of the scientific composition is no longer mandatory to identify the equivalent medicinal product(s).

5 openMedicine's choice

Considering that

- both EMA (the European Medicines Agency) and the FDA (Food and Drugs Administration, USA) decided to adopt and to implement the EN/ISO suite of standards called IDMP

- all market authorisation forms and dossiers needs to be compliant in structure and referentials to the IDMP standard

- the future EMA European Drug Database will be structured and IDMP compatible European

- the EMA drug database will be available as source data to national /international drug information providers

- the EMA European Drug Database will even be too comprehensive for clinical care services and will require a subset of "active substances" to be identified

- no major problems where identified while studying the fitness of the Article 57&2 database as source data for the IDMP database (see conclusions of WP1 and WP2)

the consortium confirmed its original option to implement the so called IDMP Suite of Standards, as soon as they are available.

6 Recommendations

6.1 Genesis

Guiding principle of all openMedicine work was to optimise health services for patients, in-clud-ing ePrescriptions and their dispensation abroad. Due to different marketing authorisation pro-cedures for medicinal products, different marketing strategies of pharmaceutical companies, shortages and other factors, successfully dispensing a foreign ePrescription regularly involves identification issues, which sometimes may become complex, and requires substitution where permitted – or as an alternative a new visit to a local prescriber.

Based on all earlier work, particularly the results of work-packages 2, 3, and 5, and the summary discussion above, this chapter presents and elaborates the various recommendations identified by the consortium. These recommendations are intended to complement ongoing work at the level of national, European and international competent authorities and organisations. The recommendations provide suggestions particularly in domains where European Un-ion issues, challenges and interests are at stake. The further development and implementation of ISO IDMP by relevant players and stakeholders across the Union is mandatory for solving the core challenges around the univocal identification of medicinal products in cross-border healthcare as identified by the epSOS pilot services. The ongoing and planned eHealth service applications in the context of the "Connecting Europe Facility (CEF)" initiative will benefit from the realisation of these recommendations. IDMP implementation will impact both the regulatory and clinical realms, and contribute fundamentally to improved patient safet for the citizens of Europe.

Furthermore, national, Union-wide and international electronic health data interoperability will indeed become achieveable with respect to medica-tion data in ePrescriptions, ePatient Summaries, Electronic Health Records and other docu-ments and messages. Regulatory processes of registration, authorisation and marketing of new medicinal products will be streamlined across their whole life cycle, pharmacovigilance improved, and better patient information facilitated.

The recommendations to follow were developed by the openMedicine team, discussed in de-tail at a two-day face-to-face meeting, presented and extensively explored with the plenum of the expert council attached to this project at its final meeting in London in November of 2016 as well as afterwards with individual persons. They were and edited by the an editorial board on the 7th October 7th 2016 and on the 10th and 11th November 2016. It turned out that under-standing of the issues and challenges, of solution optons andl future possibilities were much more complex and diffuse than initially assumed. Furthermore, interests of specific stakeholder groups also became intervening variables. All of this required further exchanges and modifica-tions.

But in the end, these recommendations come under the sole responsibility of the openMedicine team.

6.2 Rationale

Each one of the following recommendations consists of a rationale describing the why and the context of the recommendation as well as the statement as such.

This statement is then completed with implementation aspects like: who takes the lead? Who are the other involved stakeholders and what is their role in the implementation of that rec-ommendation. When to start or/and what conditions need to be met by the application (pro-viders) with respect to complying with by the regulatory demands.

We need to be aware that they are **recommendations only**. Authorities willing to make some of them mandatory should, depending their competence, put some or most of them into (updated) guidelines and/or regulations.

They are actually listed without classifying them. For each recommendation additional information is provided.

The issue to be addressed by the openMedicine project is the problem encountered in the epSOS project where some medicinal products could not be identified efficiently in a cross border

implementation, despite a complex supra-national set of services and infrastructure.

We identified three scenarios, actually subject to funded research activities, related to sharing medication related information wherein identification problems may occur:

- The electronic prescription presented for dispensing in a pharmacy in another jurisdiction
- The electronic prescription produced in a country with the intention to be delivered/dispensed in a different country
- Medication items as part of a patient summary uploaded for unexpected care

Additionally, we documented that the same medicinal product name in different countries of the Union does not guarantee that we are addressing the same product.

Identifying a medicinal product package is at the same time identifying its composing elements:

- An outer container, eventually additionally a number of inner containers,
- Containing a quantity of product units of a given medicinal product with a medicinal product name (MPID)
- The medicinal product being a universal pharmaceutical product marketed in a given jurisdiction under a given name (PhPID)
- The latter being composed out of a specified quantity of active substance (Substance ID), presented in and intended to be administered in a specified dosage form by using a given route of administration

By using in such a way the IDMP standards [11615 & 11616) enables, as stated in the next recommendations, identification issues are solved for over 99% of prescribed medicines. Magisterial prescriptions requires on the other hand still epSOS like translation services.

6.3 openMedicine Recommendations

The following twelve "recommendations" related to the univocal identification of medicinal products in cross border ePrescriptions, eDispensing reports and ePatient Summaries were validated by the members of the openMedicine consortium and the openMedicine experts.

These recommendations, in a pragmatic approach, take account both of the present situation and shorter term development options, and the longer term goal of implementing a unified and harmonised procedure across the Union and even cross-Atlantic. These possibilities are as follows:

- In the medium and longer term, a globally unique Pharmaceutical Product ID - built by using the IDMP substance standards and the respective data base – is available, and ISO/IDMP compatible European Drug Databases have been implemented. The openMedicine Recommendations 1, 2 , 5-12 reflect this vision.

- In the short-term, support and implementations for cross-border CEF-based services should be based on the actual EMA drug database and the results of the SPORE project implementation as undertaken by EMA and FDA, enabling the CEF projects to start in 2018 with actual service provision. The Pharmaceutical Product ID which can be created on this base is **unique within the Union** and build by using the Article 57 (2) substance standard data base. openMedicine Recommendations 3 and 4 reflect this transitory state.

The **Status Quo,** based on using the INN nomenclature or the ATC classification is not regarded as fit for these purposes.

The main reasons why ATC and INN terms and codes are not fit for identification of the pharmaceutical product or the medicinal product or even the substances of the scientific composition of a medicinal product are:

- ATC is not a terminology nor a value set of uniquely identified concepts: one term /product may have several codes depending on the indication for which it has been prescribed

- INN identifies active principles, not substances; combination products may have one code for the combination not coding the individual substances.

	Addressed issue or functionality	Domain of application	Comments
R1	Univocal identification of the medicine	ePrescription, eDispensation, Patient Summary	Univocal identification of a medicinal product encompasses that a pharmaceutical product and a substance is identified.
R2	Pharmaceutical product ID (global)	Integrate PhPID into the databases used for ePrescription etc.	Essential for crossborder services. Globally unique identifier
R3	Pharmaceutical product ID based on the EMA substance database	Creating a PhPID from presently available EMA Article 57 database	Short term implementation, based on European database
R4	Exchange of ePrescriptions cross border based on Article 57 databases	Asses and validate the suitability, efforts and risks when mapping data elements needed for ePrescription and patient Summary	Short term implementation, based on European database
R5	Attributes of medicines related concepts consistently defined and populated with globally recognised controlled terminologies and codes	The EMA SPOR master data are intended to be such reference data sets. Need to define a subset for prescription and for clinical purposes	Example: EDQM
R6	Identify medicinal products with potential allergens, important adjuvants and excipients, in a cross-border setting	Complementary identification needs	Part of medication monitoring
R7	Assure that the same identifier will be used during the lifetime of a pharmaceutical product	Use the same globally unique pharmaceutical product identifier throughout the complete medicine's lifecycle	For both regulatory and clinical purposes temporal consistency is important.
R8	Harmonisation of terms and concepts	Update and assure consistency of terms and definitions with respect to identifying	Presently, across documents different definitions for the same core concepts are

		describing and documenting medicines across standards, regulations etc.	sometimes used
R9	Quality criteria to be met by Medicinal Product Dictionaries and by clinical applications for recording and processing medicinal information.	Assure correctly coded data, compliance of structure and content with EMA and national specifics, and completeness and persistence of information.	Important role in developing trust in high quality data needed at the point of care as well as for pharmacovigilance etc.
R10	Unique medicinal product name in the Union	Newly marketed medicinal products should have a distinct name from any other medicinal product name, and the same across the Union.	Improves patient safety through consistent naming
R11	Maintenance and Sustainability of IDMP compatible core databases	Assured availability of IDMP compatible European as well as national medicinal databases.	Considerable initial investment with high benefits for citizens
R12	National rules on substitution in cross-border situations should be considered for harmonisation	Improves probability, that a foreign prescription can indeed be dispensed.	Comments from professional organisation in annex

6.4 IDMP identification (R1)

A medicine should be identified by its attributes, or specified by at least one of the identifiers as defined in the IDMP standards (i.e. Pharmaceutical product (s) – PhPID(s), medicinal product – MPID, package – PCID)

All IDMP identifiers for a product and the respective identifying attributes should be electronically accessible to all parties.

The active substance (or set of active substances) with the required strength(s) and dose form that the Health Professional (HP) prescribes define the Pharmaceutical Product(s). The Pharmaceutical Product(s) selected by the HP will be automatically and univocally translated into the PhPID code(s)

When the health professional wants to specify a specific Medicinal Product, or a specific packaged Medicinal Product, the respective originator or generic brand name plus identifying attributes including quantity, or the MPID or PCID(s) will need to be used. For every MPID or PCID there is a unequivocal correspondence to globally unique PhPID(s).

R1	First Recommendation Implementation Context	
1	Pre-requisites	Availability of medicinal product dictionaries at the point of prescription, dispensation including IDMP global identifiers. Availability at the point of care of an appropriate drug database)
2	Vehicle(s)	Adoption of IDMP standards. Validation and promotion projects of IDMP compatible ePrescriptions, eDispensation & Patient Summary services. (cross border)
3	Stakeholders and their respective roles	eHealth Network: adapt and maintain guidelines by including IDMPidenti-fiers
		eHealth/NCAs: translate European rules into national database
		EMA (and FDA): implement IDMP at regulatory level, assign PhPID, provide open access to authentic source data
		Drug database providers: integrate IDMP data (identifiers), add local/regional/administrative and financial information, distribution to end user applications
		EHR/Clinical Information systems: adapt software to the IDMP needs
		Health professionals: no impact on user interface for ePrescription,, eDispensation and Patient Summaries, except that medication management becomes more "generic". The user prescribes eventually a pharmaceutical product instead of a brand name package combination: example: carbamazepine 400mg tablet/oral, 24 tablets instead of Tegretol CR 50 tablets
4	Timing	Final stage of the implementation of the IDMP standard: all the PhPID codes assigned and distributed,and integrated in prescription as well as pharmacy software. PhPID , codes integrated in the prescription file and used in cross-border retrieval of the prescribed equivalent product. To be fully operational in at least 13 Member States: realistically end **2021.**

6.5 Assigning Global PhPID (R2)

Each ePrescription, eDispensation, or medication record in a Patient Summary contains in (an automatically added) pharmaceutical product identifier, preferably the global PhPID assigned by EMA, once available. An authorised mapping to the PhPID should be available in case of using proprietary identifiers.

Each ePrescription, eDispensation or medication record in an Patient Summary may contain additional IDMP compatible identifiers

The PhPID is globally unique, independent of national regulation, language, originator or generic product brand name; it reflects the core attributes of the medicine. Therefore it ideally facilitates expected as well as unexpected cross border searches for medicinal products equivalent to the prescribed one, or identifying, e.g., active medications in an electronic Patient Summary

We distinguish two sets of tasks in the preliminary phase: tasks to be done at European Union level and tasks of transatlantic coordination resulting in a global pharmaceutical product identifier enabling cross border medication services. Similar activities will be required in other regions too if we want a real global identifier.

R2	Second Recommendation Implementation Context	
1	Pre-requisites	• SPOR project terminated resulting in - EMA Substance database - All products on the market (centrally authorised) - Organisations • Referentials available • EMA drug database "complete" • Scientific composition structured available • EU/US joint global substance database • Global referentials
2	Vehicle(s)	Mapping and validation of the completeness of the authoritative central database
3	Stakeholders and their respective roles	eHealth Network: decision, supervision, budget
		eHealth/NCAs: support, assist (translations)
		EMA (and FDA): assigning the PhPID codes; IDMP compatible complete drug database export facilities to service providers, patient access of the interactive drug database distributed
		Drug database providers: complemented with national information, update management, distribution towards end users
		EHR/Clinical Information systems: ability to produce n openMedicine compatible ePrescription, integrate an eDispensation message, produce a Patient Summary that includes openMedicine medication information
		health professionals: no impact on user interface for ePrescription,, eDispensation and Patient Summaries, except that medication management becomes more "generic". The user prescribes eventually a pharmaceutical product instead of a brand name package combination: example: carbamazepine 400mg tablet/oral, 24 tablets instead of Tegretol CR 50 tablets
4	Timing	Start at the end of the developments linked to the recommendations 3 and 4, 2019. Start when context available as standards.

6.6 Pilot PhPID (R3)

> *In the short term, to improve the likelihood that a medicine specified in a cross-border ePrescription can indeed be fully identified and dispensed (or substituted), it should be considered to use for the time being the presently implemented and publicly available EMA substances data base and code system as an additional value set of the Master ValueSet Catalogue*

Considering that the global PhPID will become available only in the longer term, we present Recommendation 3. In order to bridge towards the future full implementation of ISO IDMP, Member States, through the task already assigned to eHMSEG-Semantic to revise MVC 2.0, may want to consider adopting the EMA substances data base and codes as an additional value set (VS) of the Master Valueset Catalogue (MVC), to be used both for ePrescriptions and electronic Patient Summaries. This may require MSs, based on their national medicinal products data base, to transcode national values into this VS, or to use, after validation, the contents of Art.57 data base. On the European road towards full implementation of IDMP, this process would allow to adopt a compatible short term solution already for CEF Wave 1.

R3	Third Recommendation Implementation Context	

1	Pre-requisites	Availability of a structured drug database, validated on its completeness, structured scientific composition, and translation issues.
		• SPOR project terminated resulting in
		  - EMA Substance database
		  - All products on the market (centrally authorised)
		  - Organisations
		• Referentials available
		• EMA drug database "complete"
		• Scientific composition structured available
		Complete standard set of substances

2	Vehicle(s)	The epSOS environment should be used for initial acceptance
3	Stakeholders and their respective roles	eHealth Network: decision level, budget, supervision
		eHealth/NCAs: role in data gathering, quality of data exchange
		EMA (and FDA): control of the completeness and the correctness of the information in the Article 57 database
		Drug database providers: essential role in the distribution of the products, their identifiers and descriptive attributes
		EHR/Clinical Information systems: adapt their software to integrate several identifiers into the prescription, or integrate a dispensing message or to produce a patient summary
		Health professional: no change behaviour required. It might be considered not to modify the medication management as long as the Global PhPID isn't available
4	Timing	Drug database IS available, structured and coded: EMA Article 57 database. Limited to centrally authorised products. Possible to pilot with a limited number of Member States, based on a decision by those Member States.

6.7 Piloting PhPID (R4)

> *As a further step towards IDMP implementation, MSs involved in CEF may want to assess and validate the suitability, efforts and risks involved in mapping the data elements needed for ePrescription and electronic Patient Summary, and for creating a PhPID from the presently available EMA Art. 57 database.*
>
> *As long as the terms for the related concepts aren't globally endorsed (at least across the Atlantic) the PhPID will not be global.*

Considering that the global PhPID will become available only in the longer term, we present Recommendation 4 as a potential further step which may be considered by those member states which are involved in relevant CEF applications. Here it should be reflected that the Art. 57 data base was initially developed for pharmacovigilance purposes.

R4	Piloting Implementation Context	
1	Pre-requisites	See recommendation 3
		Consensus on the purpose and expected results of the (pilot) initial development
2	Vehicle(s)	N/A
3	Stakeholders and their respective roles	eHealth Network: political decision to build a database of pharmaceutical products identified by a PhPID-like identifier based on the Article 57 EMA database
		eHealth/NCAs: See recommendation 3
		EMA: main contractor and owner of the databases. Responsible (jointly with FDA) in assigning PhPID
		Drug database providers: see recommendation 1, but limited to European centrally authorised products
		EHR/Clinical Information systems: adapt the prescribers applications, the pharmacy information systems, the patient summary display systems
		Health professionals: select to-be-prescribed product from a compatible database
4	Timing	As the number of products to be encoded and translated is rather limited
		And as there is no rule imposing all the Member States to start a the same time
		And as most of the work done (clinical composition, dosage form, strength in UCUM remains valid when implementing a fully compatible IDMP compatible application)
		Effective piloting seems feasible mid 2017 on

6.8 Standard controlled vocabularies (R5)

When recording medicines (identified as in the first recommendation) in care process documents (prescribing, dispensing, administration/billing, reports...) both in electronic systems and when sharing that information, the structures used for supporting information (e.g. for dosage instructions) should have standardised definitions/codes and be populated with globally recognised controlled terminologies like EDQM codes (European Directorate for the Quality of Medicines & HealthCare).

Considering the different needs regarding the granularity of identifying attributes between the care process and the regulatory descriptive context appropriate subsets of identifying terms, e.g. substances, should be agreed on

Agreement on terminology standards is required, e.g., for pharmaceutical forms, inner and outer container, route of administration, etc… EMA SPOR master data, through the Referentials Management Services, (RMS) will provide for such a repository.

Considering that the terminology requirements for regulatory purposes includes the terms needed to document comprehensively the scientific composition comprehensively, including excipients, adjuvants on top of the active substances,

Considering that medication use related information should be documented in a comparable, consistent and reliably reusable way across the Union and globally, considering that important stakeholders and services are operating globally, considering that globally different needs in identifying terminology we formulated the fifth recommendation.

R5	mplementation Context	
1	Pre-requisites	Controlled terminologies available, at first for the kernel identifying attributes (strength expressed in UCUM unit, route of administration, dosage form and substances/ingredients).
		Decision by the competent authorities (EMA, National…) which standard will be used, as well as defining the subset of terms required in different use contexts, more especially ePrescription.
2	Vehicle(s)	Include in the quality criteria for drug databases. Include in quality criteria for clinical information systems, e.g. EHR systems.
3	Stakeholders and their respective roles	eHealth Network: align the Member States, as much as possible: same terminologies for the same concepts between and within the Member States, for the same concepts between the professions or at least require "bridges" between them *and as for all the standards for free available to end-users*
		eHealth/NCAs: standard terminologies … should be a mandatory requirement for participation in EU funded projects
		EMA (and FDA): International coordination, also between the domains of use (market authorisation, clinical..)
		Drug database providers: integrate and distribute for clinical purposes
		EHR/Clinical Information systems: use the appropriate terms in the EHR. Terms offered from different coding schemes with similar/identical meaning should store and exchange the codes and the linked coding schemes
		Health professionals: don't use applications based solely on free text
4	Timing	Can start whenever involved parties decide.

6.9 Ajduvants, excipients, allergens (R6)

Further work should be done to identify in a cross-border context adjuvants and excipients of pharmaceutical or medicinal products which may cause allergic reactions or intolerances.

Considering that pharmaceutical and medicinal products may contain adjuvants (substances that may increase the efficacy or potency of the active substance) as well as excipients (inert or inactive substances) that can cause allergic reactions or to which a patient may be intolerant , we present a **sixth recommendation.**

R6	Implementation Context	
1	Pre-requisites	There will be a need to define how to identify a substance as an allergen and to flag a pharmaceutical product as containing such an allergen. Similarly there is need to define how the presence or the change of an adjuvant or an excipient will affect the PhPID
2	Vehicle(s)	The SPOR project analysing the Article 47§2 database
3	Stakeholders and their respective roles	eHealth Network: stimulate the acceptance of a standard list of allergen and standardisation on allergy interaction?
		eHealth/NCAs: provide the raw data as source for analysis
		EMA (and FDA): sharing the SPOR project
		Drug database providers: distribute the standard as interactive data with medication data into the HER
		EHR/Clinical Information systems: integrated allergy recording and surveillance
		Health professionals: using clinical systems that offers medication management, surveillance etc
4	Timing	No reason not to have this item "active" yet. Available 1.1.2018 /30.6.2018 at the introduction of the IDMP drug database

6.10 Medicine's lifecycle (R7)

> *The ISO IDMP suite of standards should be usable and used throughout the complete lifecycle of a medicine. This requires assigning a globally unique PhPID to each pharmaceutical product already at the development stage.*

It has been mandated by the "Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities" to use the ISO IDMP suite of standards and terminologies for pharmacovigilance purposes; the NCAs and EMA decided to adopt the ISO IDMP suite of standards and terminologies also in any other process of the medicinal product lifecycle. Considering the entire lifecycle of the data related to medicines as one continuum across the regulatory and clinical domains, considering that using different (terminology) standards for each or several of these domains hampers reuse and sharing of medication-related data, considering that no major problems have been identified during the openMedicine project in applying this also to clinical care, for pharmaco-epidemiology etc., we present a **seventh recommendation.**

First, the implementation context is presented: Different standards are used during the lifetime of a medicine for identification as well as for describing medicinal product and its effect. IDMP distinguishes 4 levels of "aggregation" 1) substance 2) pharmaceutical product 3) medicinal product 4) medicinal product package and for each level an identifier being the Substance ID, the PhPID, the MPID and the PCID. The first two identifiers are so called "generic" or "member state independent" identifiers. The two last identifiers are Member State marketing specific identifiers.

Considering the link between the identifiers, identifying a medicinal product package is at the same time identifying a value for each of the four identifiers.

Integrating those four identifiers in an electronic prescription will enable the dispensing pharmacist abroad to retrieve the equivalent product in his country.

R7	Implementation Context	
1	Pre-requisites	PhPID assigned to the pharmaceutical products available in the prescribing as well as in the dispensing Member State.
		Integration of these identifiers into the drug databases
2	Vehicle(s)	ePrescription guideline, initially as an option
		Patient Summary Guidelines
		To be foreseen in the eDispensation messaging
3	Stakeholders and their respective roles	eHealth Network: a level of coercion might be needed to realise a large implementation
		eHealth/NCAs: Including these aspects into the quality assessment of the drug databases, the EHR systems as well as in the Pharmacy Information Systems
		EMA (and FDA): • Assign the Global PhID • Assign the temporally European PhPID
		Drug database providers: systematically add the PhPID to the "national" identifiers of a medicine, add/use as much standards as possible (e.g. EDQM
		EHR/Clinical Information systems: Add at least the PhPID to the identification data when • producing an ePrescription, • recording medication item

		• integrating dispensing information
		add supplementary identifiers to clinical concepts overarching different standards
		Add at least the PhPID to medication data in a Patient Summary
		Health professionals: no change in behaviour
4	Timing	Considering the advantages in several area's, e.g. secondary use of these multicoded data, the sooner the better

6.11 Terms and definitions (R8)

Standard Development organisations (SDOs) and other stakeholders should update the terms and their definitions (concepts) used with respect to identifying, describing and recording medicines in order to harmonise them.

Considering that different definitions of the same terms in domain specific standards, guidelines, and European directives are used, and considering normal evolution over time, we present our **eighth recommendation**

R8	Implementation Context	
1	Pre-requisites	Improved accessibility to standards. Access is actually insufficient for the following reasons: • standards should be available for free • interface does not allow search on keyword over different standards. Search is standard per standard. • definitions from Directives or Guidelines or Research Projects are not included
2	Vehicle(s)	openMedicine developed a tool enabling to list all the definitions for concepts listed in identified standard
3	Stakeholders and their respective roles	eHealth Network: stimulate cooperation between SDO's consider an initiative to harmonise domain terminologies between domain expertise and European legal documentation
		eHealth/NCAs
		EMA (and FDA) follow the standards as much as possible
		Drug database providers respect the conceptu's (meta data) and heir definitions
		EHR/Clinical Information systems; respect the concepts and the data model
		Health professionals
4	Timing	No specific data

6.12 Quality MPD's & Clinical Applications (R9)

> *Medicinal Product Dictionaries (MPD) as well as clinical applications for recording and processing medicinal information should meet a set of quality criteria e.g. correctly coded, compliance of structure and content with EMA and national specifics, and completeness and persistence of information regarding meanwhile withdrawn medicines. Completeness encompasses every product that can be prescribed, e.g. other not-to-be authorised products.*

Considering the important role of drug databases providing at the point of prescription and at dispensing factual national as well as universal qualitative data and services, we formulate a **ninth recommendation**

R9	Implementation Context	
1	Pre-requisites	ePrescription, eDispensation and Patient Summary services each of them depend on the availability of a drug database containing the appropriate data to enable specific applications to produce the expected documents and medicinal services.
2	Vehicle(s)	The data collected from the IDMP Drug Database directly or by means of distribution sets
3	Stakeholders and their respective roles	eHealth Network: avoid "hijacking" of the database
		eHealth/NCAs: define a set of quality criteria
		EMA (and FDA): • interface with the database providers for distribution to the end users
		Drug database providers: • crucial role in the distribution of the identifiers and the medicines related information from the IDMP European Drug Database to the end-users • comply with quality criteria for drug databases • comply with ISO/DTS 19256
		EHR/Clinical Information systems
		Health professionals
4	Timing	

6.13 Newly marketed medicinal products (R10)

Newly marketed medicinal products should have a distinct name that differs from any other medicinal product name in the Union.

Considering that different medicinal products should have *different* names to avoid confusion which may potentially harm a patient, considering that in fact the *same* medicinal product name has been used for different medicinal products in different member states, we present this **tenth recommendation**

R10	Implementation Context	
1	Pre-requisites	No pre-requisite as being immediately applicable
2	Vehicle(s)	Decision by EMA
3	Stakeholders and their respective roles	eHealth Network: supervision:
		eHealth/NCAs: directly responsible in an individual Member State
		EMA: directly responsible at European Level
		Drug database providers:Nmm/A
		EHR/Clinical Information systems
		Health professionals
4	Timing	

6.14 Maintenance (R11)

> *Sufficient resources should be allocated to make available in a timely fashion the IDMP compatible central European Medicines Database for cross-border health services. Its long-term maintenance needs to be assured.*

The availability of a single, authoritative source of data about medicines across the Union is crucial for patient safety in cross border services and for many other applications. It requires a significant amount of human and financial resources considering that the database must to be fully structured and as much as possible coded, with translation of terms into all EU languages and alphabets.

R11	Implementation Context	
1	Pre-requisites	Completeness and accuracy of the central database depends on the commitment and accuracy of the Member States regulatory authorities and the quality of the data provided by third parties
		Availability, preferably coded and properly structured source data, also validated content wise and coded
2	Vehicle(s)	E.M.A is the appropriate organisation, at European level, to build such a database.
3	Stakeholders and their respective roles	eHealth Network: enabler and requiring up-to-date data
		eHealth/NCAs: is part of their usual task
		EMA (and FDA): key partners, authentic source
		Drug database providers: maintenance of the internal (national) regulations and reimbursement issues
		EHR/Clinical Information systems: adapt the clinical systems once the services provided
		Health professionals: should only have as 'obligation' to keep his application up-to-date
4	Timing	From 2018 on

6.15 Substitution (R12)

National rules on substitution of medicinal products prevail at the point of dispensation. The way substitution is applied within the limits of a prescription and documented in a cross-border dispensation should be harmonised.

Because patients presenting a foreign prescription have to pay for the medicinal product at the point of dispensation, local substitution rules based on cost containment considerations do not necessarily apply. Nevertheless, dispensing of a specific medicinal product prescribed in a foreign prescription will regularly necessitate substituting it by a product locally available (even if it is exactly the same product, but carries a different name). Considering that substitution rules are defined by the Member States, in order to maximise the likelihood that a medicinal product can indeed be dispensed abroad, we present the **twelfth recommendation.**

R12	Implementation Context	
1	Pre-requisites	The right of the patient to get the most appropriate care includes medicinal care. Part of that right is the right to be informed, e.g. linked to travel information
2	Vehicle(s)	Good practice guidelines for ePrescription (more especially about dispensing) should put the rules applicable in each jurisdiction
3	Stakeholders and their respective roles	eHealth Network: bring the issue to the agenda
		eHealth/NCAs: Provide the basic data, the source data to be centralised and quality assessed
		EMA (and FDA): provide the cross border drug database enabling – based on the scientific composition – to identify identical pharmaceutical products (e.g.)
		Drug database providers: distribute the appropriate data to manage substitution at the point of dispensing in the countries they service.
		EHR/Clinical Information systems: systems should document what has been dispensed to the patient compared to what has been prescribed = documenting substitution
		Health professionals: prescribers are mostly not aware of substitution rules
		Patients: should be informed
4	Timing	There is no timing issue

7   Outlook and further work

This chapter summarises core results and identifies further work needed to continue the openMedicine success in alerting European and trans-Atlantic players and stakeholders to the needs and opportunities in the univocal identification of medicinal products, and the big benefits to be expected from the actions recommended.

7.1   Challenges and context

Harmonising the identification of medicines in regulatory processes, in ePrescriptions, eDispensation reports as well as in clinical messages, records and decision support systems (like ePatient Summaries, electronic health records, CPOE and ePrescribing systems) is a European challenge, particularly also when considering the high quality and safe provision of cross-border health services. It impacts on pharmacovigilance, tracing of data across the life cycle of a medicinal product, the aggregation of information for public health purposes and many other health domains. And it promises a substantial European added value.

Across the Union, differences in names of medicinal products and active substances, variations in strength and box size prevail, and the availability of a specific medicinal product varies considerably across member states. This situation necessitates substitution of the prescribed product at thre point of dispensation in many instances if a patient is to be timely served in a pharmacy. The EU-wide implementation of ISO IDMP standards as under way by EMA for pharmacovigilance is a route to mitigate many of these problems. However, presently, national ePrescription and medicines data bases are not supporting MPID or PHPID attributes and codes, because at the national level there are few direct benefits from solving cross-border identification and semantic issues.

7.2   Further work needed

To fundamentally increase the probability, e.g., that a cross-border ePrescription can indeed be dispensed in another member state, it is mandatory to have PhPID information available respectively automatically included from national sources or a central EMA data base, in order to identify medicinal products locally available which are equivalent to the one identified in the prescription. This also applies *mutatis mutandis* to other clinical or regulatory records and contexts.

In the medium term, it will be mandatory to link the EMA IDMP (SPOR) DB with national drug DBs (or use NCPeH procedures) to have identifiers and identifying attributes automatically included into software systems which have to make use of such input for prescribing and other clinical systems. This will also improve and harmonise reporting of adverse drug events and pharmacovigilance.

This requires creating a EU approach to further improve, implement and maintain the EMA SPOR data bases and the supporting coding efforts, thereby also facilitating regulatory processes, and even Big Data applications. A common approach and operating model needs to be developed, including common processes for validation of contents, error mitigation, of linking from central hubs to national and regional levels, updates and mappings to other systems. Harmonisation of prescribing and dispensation practices could be a further focus. A sustainable migration process from the present situation to the ISO IDMP / SPOR adoption should be also addressed.

For cross-border health services, when a prescriber specifies an innovator or generic brand name, or an active substance and further attributes, it must be assured that any local ePre-

scription system will be able to automatically lookup equivalent products available in the dispenser's country by filtering making use of any coded identifier or the identifying attributes reported in the prescription.

Further work and support is also needed for cooperation across SDOs to integrate and agree on standards for medicinal products, pharmacovigilance, usage of these data in the clinical context, for messaging like ePrescription, eDispensation, in ePatient Summaries, clinical electronic records like EHR systems. This may also include the setting up of cross-border pilots to assess and validate the proposed approach in virtual environments with test data.

Work should also concern an assessment of impacts based on benefits and costs to be anticipated. This should include not only regulatory impact, impact on setting global standards and best practice, and impact on clinical data quality and interoperability, but also spill-over effects to pharmaceutical companies, data base producers and competitive advantage of European companies.

7.3 Expected impact & benefits

Considering the present situation and the anticipated future, a wide variety of positive impacts and substantial benefits can be identified:

- Further research and work should lead to the reliable validation of the EMA/FDA/International IDMP data bases and code systems for usage by national competent authorities/national medicines agencies. API/open interfaces are needed; quality and usability of data for national agencies would be improved, and adaptations needed at national/regional level supported.

- The validation of application(s) in the context of NCPeHs and their data needs to support semantic coding and trans-border flow of patient and clinical information (ePrescriptions, ePatient Summaries, eDispensation reports) will be facilitated. Similar considerations hold for other clinical documents.

- Support for sustainability and diffusion of CEF-supported cross-border eHealth services would be another outcome.

- Guidance material should be forthcoming for managing sustainable migration processes from present CEF eHDSI toward the adoption of ISO IDMP standards and connections to the EMA SPOR facility.

- Improvement of pharmacovigilance, inclusion of pharmacovigilance modules into clinical software systems, validation and diffusion will generate great benefits for patient safety and a higher quality of care of health services.

- Ât the industry side, a working group of European medicinal products data base producers should be implemented to complement regulatory and clinical process. Furthermore, awareness rising and the coordination of pre-competitive activities of various players would help to faster advance progress.

- Cooperations of stakeholders like patient representatives, clinicians, pharmacists and others with EMA, national competent authorities, producers of ePrescribing and clinical record systems will generate further benefits and allow for a more effective, efficient consensual and harmonised introduction of IDMP.

- Diffusion to clinical actors, particularly to prescribers, physicians, nurses to understand ISO IDMP data base contents, usage, and value would further support beneficial outcomes for patients.

- It would also further benefit the fruitfull trans-Atlantic cooperation which has already been established in this domain.

8   EXPAND evaluates epSOS issues

epSOS identified a number of issues to be addressed in order to be able to offer reliable, efficient and smooth cross-border dispensing services.

EXPAND made some change proposals and identified some issues to be addressed by openMedicine, at to their opinion.

It is important to know that the composition ("scientific composition") has a crucial role in the epSOS process of retrieval of a medicine in another language or jurisdiction. Even more the translation of the scientific composition from the language of the prescriber into the dispensing language is critical.

Since the identification of a medicinal product in epSOS is based on the descriptive attributes reliable migration nearly fully depend on those translation services.

By introducing a coded jurisdiction independent identifier openMedicine offers a parallel "high speed" identification through the Pharmaceutical Product Identifier.

The epSOS traditional approach remains useful for some cases where there is a PhPID available and/or for validation purposes.

Let us now integrate the EXPAND documents "as such".

8.1   Change Proposals approved in EXPAND

Since epSOS the medications in eP/eD and PS were identified by describing their attibutes.

The EXPAND project[8] has taken in charge most of the issue previously described and a change proposal process has been started for some of them after a selection and prioritization of issues, that took in account also the potential impacts of those changes.

The change proposals approved by the Member States have been related to these elements:

1. Support for unknown or textual active ingredients (includes also the description of Multi active ingredients products)
2. Support for unknown or textual strengths
3. Support for UCUM annotations
4. Dose form and route of administration

That can be summarized as follows:

Support for unknown or textual active ingredients [Multi-active ingredients products]	Allow the usage of Nullflavors for the ingredient/code. Allow the distinction between the ATC code when used for the Pharmaceutical Substance (represented as drug classification) and the ATC code when used for active ingredient identification. The solution approved will allow future adoption of alternative ingredients code systems (e.g. that used in the ART 57 DB) without losing the capability of conveying the Pharmaceutical Substance ATC code as well. Specified how to convey textual ingredients information.
Support for unknown or textual strengths [Multi-active ingredients products]	Allow the usage of Nullflavors for the ingredient/quantity Specified how to convey structured textual strengths data Identified an optional element for conveying the strength as string

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[8] See http://www.expandproject.eu

	(e.g. "600 / 12,5 mg").
Support for UCUM annotations	Explicitly allow the usage of UCUM annotations when the unit value is '1', without any constrain - in this version -about the conveyed content. Suggest using the English terms. Possible future enhancements: • Define specific value set for validating the annotations used (unit of presentation). • Split the unit of measure value set in three separate value sets: - a general purpose units value set - a unit value set for strength numerator - a unit value set for strength denominator The first could be the value set currently used. The last ones could be aligned with the value sets used by EMA in its Art 57 DB.
Dose form and route of administration	The EDQM based Value Sets have been aligned in the MVC 2.0 to the one used by EMA in Art. 57 database

Those changes impact (partially or completely) on the following issues encountered in epSOS:

• **Fehler! Verweisquelle konnte nicht gefunden werden.**

• **Fehler! Verweisquelle konnte nicht gefunden werden.**

• **Fehler! Verweisquelle konnte nicht gefunden werden.**

• **Fehler! Verweisquelle konnte nicht gefunden werden.**

• **Fehler! Verweisquelle konnte nicht gefunden werden.**

• **Fehler! Verweisquelle konnte nicht gefunden werden.**

8.2   Remaining epSOS open issues (EXPAND)

The following table provides a synthetic list of the still pending issues encountered during epSOS pilot, with the indication if they are in scope or out of openMedicine scope, and a summary of possible solutions. Reference refers the section of openMedicine D1.1 document

Ref.	Open issues	Open Medicine / Others	Identified solutions
3.4.1	Identification of Active ingredients (substances)	openMedicine	Short term solution: allow the usage of unstructured and/or uncoded (textual) information for describing ingredients and strengths.
3.4.3	Multi active ingredients products		Select an appropriate common code system for describing ingredients that could be actually available with the drugs information in all the country of prescription. In the medium term it could be the XEVMPD substance vocabulary or the one adopted by ISO IDMP /
3.4.8	Distinct Value Sets for ingredients		

			EMA.
3.4.2	Strength(s)	openMedicine	Short term solution: the constrains about strength(s) allowing the usage of unstructured textual information for describing strengths [approved in EXPAND] Medium term solution: derive strengths information (structured and unstructured) from the EMA Art 57(2) Database. (to be further analysed) Long term solution should the one adopted by ISO IDMP / EMA..
3.4.5	Units (UCUM) [Units of presentation]	openMedicine	Short term solution: allow the usage of the UCUM annotations as free text (e.g. {tablet}). Medium term solution: bind those terms to a unit of presentation value set
3.4.6	Specialty	Others	To be analysed
3.4.7	CapacityQuantity vs Quantity	Others	To be analysed in light of the solution adopted by ISO IDMP / EMA.
3.4.9	Representation of package composition	openMedicine	To be analysed in light of the solution adopted by ISO IDMP / EMA.
3.4.10	Supply / substance administration quantity attribute	Others	To be analysed
3.4.11	Distinction between coding of medicine on a brand-level and on package-level	openMedicine	To be analysed
3.4.12	Observation code (substitution)	Others	To be analysed
3.2.1	eP/eD Workflow management	Others	To be analysed
3.2.2	Substitution Rules	openMedicine	To be analysed
3.2.3	Substitution indications	openMedicine	To be analysed
3.2.4	Reason for prescribing	Others	To be analysed
3.2.5	Number of packages	Others	Conveying in the prescription the number of packages prescribed and the number of packages already dispensed. Change proposal to be discussed.
3.2.6	Differences in Medicines Classification (e.g. Central nervous system drugs)	openMedicine	To be analysed
3.2.7	Extension of the products to	openMedicine	To be analysed

	be considered for prescription		
3.2.8	Iterated prescriptions	Others	epSOS overcame this issue requiring each country to provide a prescription that describes what can be actually dispensed in that moment. To be analysed
3.2.9	Time-based prescriptions / prescription validity	Others	epSOS overcame this issue requiring each country to provide a prescription that describes what can be actually dispensed in that moment. To be analysed
3.3.1	List of prescription/ medication prescribed	Others	Some piloting country used as workaround that of conveying information about the prescribed medicines using a textual description field in the metadata exchanged. To be analysed

9 Comments from stakeholders

The recommendations were presented for validation to

- The Members of the Expert Council
- The attendees of the Expert Council Meeting in London
- The national health authorities of Poland during a Regional Information Session
- The Swedish health authorities with delegates from Norway, Estonia and Finland

	Expert	Remark	Reply
1	Jaimie Wilkinson, PGEU	The questionnaire on substituion provided complex and heterogenous results, and some elements of the analysis (interpreting different answers on the same topic from the same country etc) were arbitrary and perhaps should not be used as a basis for an EU-wide reccomendation. The complexity of the results reflects the situation in practice regarding the practice of substitution	Indeed. Chaotic not only between the member states but also within some member states
2	Jaimie Wilkinson, PGEU	Substitution is essentially part of the cost-containment practices of MSs, driven mainly by National Competent Authorities / health services / payers etc. As such, this practice falls well within the frame of the organisation of a MS's health service/system. • As such, this reccomendation violates the principle of susidiarity, in that MSs retain the competency for the organisation of their health services and systems • The eRx Guideline asserts that substitution remains the competence of MSs, i.e. country B • As such, there are conflicts with both Article 168 of the TFEU and with parts of openMedicine's own draft documents	Nowhere did we state differently It is not because it's the competence of the MS that we can't try to get all possible options well documented (for the patients) and better streamlined. The patient has the right to know what the rules are in the MS he intends to visit. This means that the information should be accessible.
3	Jaimie Wilkinson, PGEU	that any reccomendations should not suggest any form of harmonisation of substitution, for the above reasons, and that if reccomendations (or "principles" would be an even better word) of substitution are to be made/suggested, they should acknowledge that substitution is a MS competence, they should be of a pragmatic and supportive nature for MS	Agree with the last part of the statement. We never affirmed that there is an European rule to be issued.
4	Jaimie Wilkinson PGEU	that any reccomendations should not suggest any form of harmonisation of substitution, for the above reasons, and that if reccomendations (or "principles" would be an even better word) of substitution are to be made/suggested, they should acknowledge that substitution is a MS competence, they should be of a pragmatic and supportive nature for MS	Harmonisation is a "process", not a fixed status. Recommendation will be adapted
5	Harri Nurmi, THE Finland	but I would have also rewuested recommendation 9 to be removed.	See previous answers

6	Michèle Thon-net France	There is a need to focus the ePrescription Annex on the requirements for CEF implementation. In particular, the scope should be prescribing and dispensing. eDispensation is important; it has been specified and tested, and therefore needs to be included even if few MS are ready to implement.	Agreed? It is most probably a condition to be successful and accepted by the prescribers
7	Michèle Thon-net France	The context of the suite of IDMP standards (Identification of Medicinal Products) will be highly important for the future, but not in the timescales for CEF implementation. IDMP will result in requirements on national drugs databases and – possibly – on local prescribing systems. It would be helpful to include a roadmap that indicates steps and timescales (where known). Release of the guidelines already indicated IDMP as the direction of travel, with the EC recommending EMA as lead organisation. MS were broadly supportive, but concerned Joint Action to support the eHealth Network	Indeed. The ideal complete roadmap will take more time than available in the CEF initiative
8	Jeremy Thorp, UK	The data elements are taken from Implementing Directive 2012/52/EU and Draft International Standard DIS 175233 published June 2016. Reference is also made to other relevant standards, including the ISO Identification of Medicinal Products (IDMP) standards as referred to in the Implementing Directive……	Ok
9	Jeremy Thorp, UK	The point Michèle wanted to make is that in the eP GL reference is made to some future - IDMP standards. The "hypothetical" aspect should be included somehow	Will be addressed in the roadmap
10	Christopher Jarvis EDQM	Slide 4 – Pharmacetical Product ID: 2nd recommendation. The PhPID includes the administrable dose form, which means that the manufactured dose form is not part of it (although it would be included in the MPID/PCID). I wonder if it is worth mentioning that the manufactured dose form(s) might be one of the additional identifiers that are sometimes needed. For example, a 'Powder and solvent for solution for injection', a 'Powder for solution for injection' and a 'Solution for injection' would both share the same PhPIDs, since they all have the administrable dose form 'Solution for injection'. Perhaps this has been discussed previously by the experts, and perhaps there is no case for it, so if you don't think it is necessary to mention it, that's fine by me.	Chris Sorry for the very late answer to your comment. You are right, the actual formulation seems ne erroneous. Considering the lifecycle for which we are defining an identifier we should use manufactured or pharmaceutical dosage form the complete lifecycle until the administration (clinical identification): • Authorisation • Manufacturing • Distribution / Logistic • Prescription Change of dosage form happens at effective administration to the patient. This administrable dosage form includes the form after preparing the medicine for admini-

			stration.
11	Christopher Jarvis EDQM	Just for accuracy, the title of the EDQM is 'European Directorate for the Quality of Medicines & HealthCare'.	Thanks
12	Judith K Jones, Degge, USA	Will there be an international website where this information can readily be found ? This may be discussed later but seems central to the overall objective.	Both FDA and EMA have the intention to make appropriate parts of their database available to individual users as well as to drug database providers/distributers. The openMedicine project information is available on the projects web site.
13	Judith K Jones, Degge, USA	The third through the eighth recommendations, in particular, may or may not be entirely appreciated by those who did not sit through the Open Medicine discussions. They make good sense to me, but may be somewhat confounding to some. They might be enhanced by brief companion documents/comments that provide some term definitions and more importantly, specific examples (generally understandable to those from most countries) to provide a clearer picture of the process	Good suggestion. The issue of the definitions is addressed in chapter 3 of this deliverable. The list of concepts and values and definitions are available in the different work packages (1 to 5), in the openMedicine dictionary and through the SKMT application, as documented.
14	Judith K Jones, Degge, USA	Further, the process of consensus across databases and countries is obviously not simple or straightforward, so there may need to be prioritization of consensus elements as the process evolves.	We agree on the statement that consensus is never simple. This issue will be addressed in the roadmap part of this deliverable. It seems more to be a step-after-step approach as none of the concepts may be left out the process.

15	PGEU	1st December, 2016

Ref: openMedicine Recommendation on the Substitution of Medicinal Products in the EU

Dear Dr Auer,

I am writing to you on behalf of the Pharmaceutical Group of the European Union (PGEU), the association representing more than 400.000 community pharmacists working in 160.000 community pharmacies in 33 European countries. This letter relates to the proposed recommendations arising from the H2020 funded "openMedicine" project, of which PGEU is a member of the Expert Council.

We would like to share our concerns regarding the twelfth recommendation which suggests that "*National rules on substitution of medicinal products at the point of dispensation, when specified in a cross-border prescription, should be harmonised*".

In addition to not clearly addressing a significant or tangible problem, this recommendation also has practical and legal implications for healthcare professionals, patients and service providers. Therefore we have requested that this recommendation be deleted to the openMedicine consortium on several occasions, but to no avail.

Across the EU there are diverse and heterogeneous practices of substitution of medicines at the point of dispensing, which are suited to the regional / national organisation of the respective health systems and are linked to reimbursement. Member States organise their healthcare systems on the basis of local need and national strategies aimed at ensuring the highest level of safety and quality in health services. This, in our point of view, includes national rules on substitution.

We ask for your support to delete this recommendation for the following reasons related to national practices of substitution across Europe:

- Substitution is often directly linked to reimbursement policy and therefore to the Member States' specific health system financing model;

- In some Member States, the prescriber has the option to 'lock' the prescription to prevent any substitution at the point of dispensing;

- There would be a negative effect on pharmacy practice;
  - It would create a two-tier system for substitution practices for pharmacists, who will have to identify and distinguish between the two types of prescription (i.e., cross border prescription *vs* domestic prescription), increasing administration and thereby reducing patient-facing time.

PGEU GPUE
Pharmaceutical Group of European Union
Groupement Pharmaceutique de l'Union

In addition, Directive 2011/24/EU on the application of patients' rights in cross-border healthcare clearly confirms that decisions on substitution is a matter falling under Member States' competence by stating "the recognition of prescriptions issued in another Member State shall not affect national rules governing prescribing and dispensing, (…) including generic or other substitution" (Article 11. 1 (b) which should be read together with Article 11.2(c) of Directive 2011/24/EU)[1].

In conclusion, the PGEU believes that the organisation and practice of substitution remains the competence of Member States for both practical and legal reasons. In this case, and according to the provisions of Directive 2011/24/EU that we have highlighted above, the rules of dispensing and substitution of "Country B" (the dispensing Member State) clearly apply to a prescription from "Country A" (the affiliation Member State). The PGEU calls for this recommendation to be deleted.

I remain at your disposal for any further clarifications or questions you may have.

Yours sincerely,

Jūratė Švarcaitė, PGEU Secretary General

10   openMedicine Roadmap

10.1 Introduction to the roadmap

Numerous definitions of what's a roadmap can be1 listed here. We selected three notorious definitions from the web. From the Cambridge Dictionary: ""a plan for how to achieve something". From the Oxford Dictionary "schedule as part of a lengthy or complex program" and by Wikipedia: "A technology roadmap is a plan that matches short-term and long-term goals with specific technology solutions to help meet those goals."

The Wikipedia definition fits quite well with what is needed for the implementation of the openMedicine conclusions.

This (sub)deliverable starts with a description of the actual identification of medicines nationally and in a cross-border context.

By describing (possibly) ideal identification for ePrescription, eDispensing and Patient Summary services we have defined starting point and destination of the openMedicine roadmap.

The implementation road map consists of several subsequent and/or parallel steps or developments.

Beside the description of the developments we listed for each activity the involved stakeholders and their role, the risks and the expected time line.

Due to a urgent need for the CEF program an alternative proposal is made.

The consortium, being bound by the contractual agreement, focused on a solution for the epSOS problems, offering finally a solution for nearly all epSOS use cases?

The consortium highlighted some not directly related issues, as documented in this Deliverable and that requires further investigation and solution before going operational.

10.2 The IDMP based identification

The main conclusion of the openMedicine project addressed in this roadmap is:

"global identification of medicines in prescription and in medication data requires

- compatibility with the ISO/EN IDMP suite of standards
- the use of a globally unique pharmaceutical product identifier

The IDMP based identification of medicines is based on a four level data model: the substance, the pharmaceutical product, the medicinal product and the package.

A fifth level seems to be more and more in use, the so called "clusters", but out of scope within this project..

The IDMP suite contains beside the identifying standards 11615 and 11616 a number of content related databases, more precisely regarding the substances, the units and the dosage forms.

10.2.1 The pharmaceutical product - PhPID

Each original combination of the identifying attributes (active substance, strength, dosage form + route of administration) equals a distinct pharmaceutical product

Level 1 (substance) and Level 2 (pharmaceutical product) are per definition jurisdiction independent or global concepts. The levels 3 to 5 are based on national specificity on top of the IDMP Level 2 specification.

The Level 2 is the so called "pharmaceutical product" with a pharmaceutical product ID or the **PhPID.**

The algorithm to produce a PhPID has been validated by the FDA and shared between FDA and EMA.

The PhPID will finally be assigned by the European Medicines Agency (EMA), at least for Europe.

⇨ The FDA as well as EMA are considering to make the identifying algorithm publically available. This enables early identification of a medicine. We consider nevertheless worthwhile to start with a central database first; followed by a validation period.

10.2.2 Controlled vocabularies - referentials

Controlled vocabularies are available for two of the three identifying attributes: the pharmaceutical dosage form and the units when used in expressing the strength. The route of administration is handled as a part of the dosage form. The issue of the substances is discussed further in this section.

The quality and the maintenance of these controlled vocabularies are crucial, as the value of "identifying attributes" will define whether or not if a we have an new pharmaceutical product or one that exists already. .

This coding system must be preferentially maintained at the European or global level, so that its use is correct and consistent within the regulatory authorities of nations for these products.

The same values for the identifying attributes should result in the same GUID, the same PhPID.

Substances

The (active) substances identification is obviously the main identifying attribute of a medicine, even more for a pharmaceutical product. A pharmaceutical product does not have an identifying (label) name, contrary to a medicinal product.

The concept "substance" encompasses active ingredients/substances as inert substances or excipients, colorants, as adjuvants.

EMA is actually, as part of the SPOR master data project listing all the substances while validating the Article 57 Database.

SPOR stands for Substances, Products (Medicinal Products and Packages), Organisations (regulatory authorities, marketing authorisation holders, research sponsors…) and Referentials. The substances are the most important ones in clinical context.

It is expected that the EMA list will include between 20.000 to 25.000 substances.

Do we need 25.000 substances?

The regulatory authorities needs them to document the full composition of any existing pharmaceutical or medicinal product.

For the identification of the Pharmaceutical Product, only the "active" substances will be used. Replacing an excipient by another one will not result in a different PhPID.

And the problem of excipients being an allergen: this addresses the issue of the attributes of the excipients. Additionally: it doesn't seems to be the rule that for the same pharmaceutical

product one have always the same excipients, e.g. if manufactured in a different manufacturing entity.

Regarding "active" substances what's needed for ePrescription etc.

- A manageable list of active substances and their fixed combinations (less then 4000s), present in currently authorized medicinal products.

- A process to identifying the "active" substances in a consistent way across the regulatory authorities of member states

- A process to identify the therapeutic moiety of clinical relevance within an active substance (e.g. the base of a salt or ester). Example: the therapeutic moiety "amlodipine" used in prescriptions when no distinction is made between amlodipine mesilate and amlodipine besilate

Strength and units

Strength is one of the identifying attributes of a medicinal product or of a pharmaceutical product.

Is defined as a quantity of active substance per unit of product?

The openMedicine 00project confirmed the choice for UCUM as standard to identify and label units of measurement.

Dosage form and Route of Administration

EDQM has been chosen as standard for identification of the dosage form of a pharmaceutical product.

EDQM has embedded the route of administration.

The route of administration is a distinct concept. Merging two separate concept is at least questionable. Most clinical system has a distinct entry for the route of administration. This is even more the case for nursing applications.

10.2.3 European Drug Database

The European Union decided to develop and to maintain, from regulatory point of view, a central and comprehensive drug database. This database will finally be IDMP compatible.

Article 57 §2 Database

National Competent Authorities provide the information on the medicinal products in their jurisdiction by using a standard form. This information is added to the Art 57 Database, on a continuous basis (within 15 days after national authorization or acceptance of a variation).

The Article 57 Database fits perfectly for regulatory purposes. It contains <u>all</u> the information collected about authorised medicinal products. This includes identification information as well as scientific information (pharmacokinetics, pharmacodynamics, chemical formula, indications, side-effects etc..).

⇨ This means that a large majority of the information addresses issues related to regulatory aspects. This information is less important for roll-out of ePrescription services, eDispensing services and for Patient Summaries.

EMA expects that some medicines and/or their package information is still missing in the actual version of the database, estimated at less than 2%.

The scientific composition (active substances, adjuvants, excipients, colorants…) is an important part of the information stored in the Article 57 Database. This information is stored as text. EMA can't guarantee that this information, originated from approx. 30 Member States and participating countries, is error free. EMA wishes before or as part of the transition process to validate the actual Art. 57 first.

⇨ This means that a project as openMedicine, user of a small part of the information, can't really use that useful information until the complete process of validation has been finalised.

The Article 57 §2 database is structured mainly as a set of textual modules, one text per module /per attribute. The scientific composition is one of them.

⇨ This means that the migration towards a structured database needs important resources and will take long time, especially if "one shot" approach is maintained.

EMA will assure the validation and integration of this information into the database, and assure maintenance of the substances (substanceID);

EMA IDMP Drug Database

The IDMP Drug Database will be an evolution from the Art. 57 database containing all the regulatory information, with the identifying attributes codified with the global IDMP identifiers.

10.2.4 Distribution and availability of authorized drug information and identifiers

One of the important issues to be addressed is the availability of the appropriate Medicine related information needed at the point of care of the data-elements

- to prescribe a medicinal product or a pharmaceutical products at the point of care, functionally integrated in the clinical care application

- to dispense a medicinal product package or a number of medicinal product units at the community or hospital pharmacies.

- to report dispensing of a pharmaceutical or a medicinal product (package)

This requires a distribution strategy as well as appropriate tools to manage this distribution.

Possibilities with regard to timing are:

1. Integrated in a periodic update of the factual data
   a) by a public distributor
   b) Idem but by a 'distributor' who adds complementary data and/or services
2. Integrated in a real-time update service

Possibilities with regard to governance are :

1. A central European database, also used for distribution to the Cross Border Competence Centres and national prescribing systems
2. A Central European database, used to validate national authentic sources of medicine (operated within the national e-health systems and governed by the national marketing authorization authorities).

10.2.5 Standing problems to be resolved

The consortium identified some issues to be at least validated in a pilot project.

Description of complex medicinal products

The pharmaceutical product is defined as each original combination of a substance, a strength and a dosage form (+ route of administration).

Prescribing a pharmaceutical product is feasible as long as there are no more than two components to be mentioned in the prescription.

These products want and will most probably have a brand name that can be used.

An alternative approach is prescribing a magisterial formula with the same composition.

List of the issues to be addressed:

- Medicinal products with multiple active ingredients (More then 3)
- Medicinal products composed of pharmaceutical products that need recomposition at the point of care
- Medicinal packages containing multiple medicinal products (e.g. triple Helicobactor Pylori therapy)
- Radiopharmaceuticals
- Complex intravenous solutions for hospital use

Grouping of medicinal products in clusters, classes or groups

In the IDMP identification system, each Medicinal Product, authorized in a specific country and marketed by a specific company, is linked to a global Pharmaceutical Product Identifier (the PhPID).

Based on communalities, medicinal products can be grouped in :

- medicinal products with identical PhPIDs
  - This is the basis for defining the concept of "virtual medicinal product" in the UK Dm+D database of drugs and devices.
- medicinal products with nearly idendical PhPIDs
  - Classes for substitution
  - Classes for INN prescribing
- Grouping of medicinal products into drug groups for specific purposes
  - drug Utilisation purposes
  - drug information to patients
  - pharmacovigilance (see EURD List for Periodic Safety Reports)
  - reimbursement regulation
  - decision support
  - medical education
  - pharmaceutical ontological purposes (chemical class, target, mechanism, therapeutic area, anatomical area).

Excipients, colorants, coatings, filling substances and containers

Central management of the exact composition of all medicinal products in the different member states can be a daunting task. Efficient database synchronisation between a European Drug Database and National Authentic Sources of Medicines can alleviate and distribute the efforts to maintain and validate correct information at all times.

These issues are not directly related to cross border usage of medicinal products.

Pharmaceutical products being sometimes produced in different plants may have some ex-cipients replaced. Modifying an excipient does not result in a new PhPID.

10.2.6 Alignment of general drug information

General Drug Information should be aligned in identical or similar medicinal products or be-tween countries and companies.

Companies are responsible for providing a Summary of Product Characteristics, that is sub-sequently validated by the National Authorisation Authority or by EMA (depending on the authorisation procedure. Once an originator medicine is off-patent, the product can be mar-keted by a number of companies. There can be subtle differences in the Summaries of Prod-ucts' Characteristics of these similar products, due to legal differences in indications, national differences in pharmacovigilance, or differences in the communication style of companies.

In a centralized drug database, a methodology for validating and aligning the objective drug information will be needed.

10.3 openMedicine proposal for a roadmap

10.3.1 The context

The **openMedicine** consortium is neither a SDO (Standards Development Organisation) nor a regulatory authority. This means that it content wise depends on options taken by third par-ties.

Our mandate is to identify a solution to the main problem encountered during the epSOS project, more precisely to identify in a cross border context a medicine that can be dispensed according to a prescription issued in a different Member Sate.

The openMedicine consortium does neither have a mandate or the resources to decide how and when to start to implement the Global Identification of pharmaceutical products.

The parties involved in the process are (not comprehensively listed):

- European and National Health Authorities to take the political and principial
- National Competent Authorities as National Marketing Authorisation Authority also col-lecting the medicine related information and as pharmacovigilance coordinators
- European Medicines Agency as European Marketing Authorisation Authority, as collector and editor of the Art. 57 database, as editor of the future IDMP compatible European Drug Database (for authorized medicines),to assign and maintain the PhPID's
- SDO's to provide the required standards
- Pharmacy Information System providers
- Clinical Information System providers
- National Public and Private Drug Database distributors

10.3.2 The starting point

The European Union decided that the Article 57 database will form the basis of the European Database. It will be the "source" for all authenticated information related to medicines for hu-man use.

They also decided that this database should be structured and standardized using a suite of identifiers based on ISO guidelines. This suite is called the IDMP suite (Identification of me-

dicinal product) and contains 4 basic identifiers : medicinal product (MPID/PCID), Pharmaceutical Product (the above mentioned PhPID), active substance (SubstanceID), and further characteristics (strength, unit of measurement, dosage form, route of administration) . The items to describe these characteristics should originate from controlled vocabularies (governed by EDQM and UCUM). The different IDs and controlled terms will be made available by the European Medicines Agency (EMA) through web sites and services, in multilingual versions.

National competent authorities provide yet their information on their medicinal products in standardized form to the Art 57 Database, on a continuous basis (within 15 days after national authorization or acceptance of a variation). EMA will assure the validation and integration of this information into the database, and assure maintenance of the substances (substanceID); products(MPID/PhPID/PCID); organisations (regulatory authorities, marketing authorization holders, manufacturers, research sponsors); referentials (see characteristics above). These elements are called the SPOR master data.

These options are not discussed, surely when considering the needs of the regulatory and public authorities.

Considering nevertheless the enormity of the task, we may challenge some of the options.

10.3.3 Phases in the roadmap

Three phases are proposed :

1. a preparatory phase
2. a roll-out phase for Europe
3. a globalization phase

The preparatory phase (2017)

A number of parallel activities should be organized:

1. It is imperative that the work on controlled vocabularies for substances and referentials receives the highest priority. The SPOR master data should be completed.
2. Quality asses the Article 57 database, in such a way that it's conversion into a IDMP compatible database
3. Resolve the standing problems more especially regarding the complex medicinal products
4. Address the issue of the medicinal allergens in a cross border environment

Address the issue of the substance identification in ePrescription.

It is recommended to separate controlled vocabularies for

- the naming of physico-chemical entities (coded by e.g. the CAS-number or PubCHEM systems)
- the naming of active substances in marketed medicinal products (the substanceID for the PhPID),
- the naming of therapeutic moieties (parts of active substances that determine the therapeutic activity of a pharmaceutical product) that share (nearly) identical properties e.g. Amlodipine for amlodipine mesilate as well as amlodipine besilaat

Other activities:

- Coordination should be assured with the EURD-list, used to manage the Periodic Safety Reports in pharmacovigilance).

- It is recommended to build a light ontology that binds these related but distinct concepts.

- The governance of this should be with EMA.

- Coordination with EDQM, UCUM, on the one hand and with regulatory authorities of other continents, in particular with the FDA are recommended, to provide an early global alignement between European and RxNorm vocabularies for substances and referentials.

Roll-out phase (2018-2019)

IDMP Drug Database

- Fully structured and validated conversion of the Article 57 database

- National Competent authorities should integrate the above mentioned substance vocabularies and referentials into their national databases on a product by product basis.

- Products yet included in the Article 57 database may be centrally, if needed for use in CEF, country by country

Assign PhPID codes

- This can be done centrally, once all scientific compositions available in IDMP format.

- Intercontinental cooperation should be maintained.

Accessibility

- Access should be given to public and private database provider in order to integrate the PhPID into their distribution set.

- EMA should assure database synchronization between the Art 57 database, on the one hand, and the e-Health Authentic Sources of Medicines and/or databases of the national competent authorities, in the first phase with regard to the European unique identifier, the substanceID, and the referentials.

Consolidation and globalisation phase (2020-)

Address problems possibly emerging from the real implementation.

Intercontinental agencies (EMA, FDA, Japan, Health Canada) should adopt the ISO IDMP Suite, including the vocabularies for referentials.

A global governance system should be established that ensures consistent maintenance of the IDMP suite and the referentials.