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D6.3 openMedicine Recommendations and Roadmap for Implementation

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Abstract (for dissemination)	<p>This document presents some of the conclusions of the openMedicine project. We formulated two high level and ten action-oriented recommendations.</p> <p>All of them, except one, address issues related to the univocal 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.</p> <p>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.</p> <p>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.</p> <p>A panel of experts/stakeholders engaged across the full lifecycle of a medicine was involved directly in the openMedicine project, and/or through three Expert Council Meetings plus an USA-EU meeting at FDA premises in Washington, DC. The second part of the deliverable builds on the recommendations developed and presents a roadmap for their implementation.</p> <p>The implementation and roll-out of the conclusions will take quite some time. It needs to happen in a very complex legal and regulatory context, considering clinical use and social context. An important number of 'interested' parties does not always have the same interests.</p>
Keywords	Univocal identification of medicinal products, pharmaceutical product, pharmaceutical product identifier, IDMP, EN/ISO 11615, EN/ISO 11616, openMedicine roadmap, recommendations, standardisation, ePrescription, patient summary, cross-border healthcare

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise.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

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Executive Summary

The openMedicine project is a Coordination and Support Action (CSA), launched as part of the Horizon 2020 PHC 2014 call for proposals. It 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. Regularly, not an identical or all of the equivalent medicines available meeting the specifications of the prescription issued in country A could be identified as such in the foreign country B. In other cases correctly identified equivalent medicines could not be dispensed due to local substitution rules.

Furthermore, the epSOS project validated its services solely for packaged and branded originator or generic medicinal products. No substance name (INN) based prescriptions, nor 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] confirm previously defined levels of structuring and/or presentation of "medicinal products" [12610], starting with substances, pharmaceutical products, medicinal products and medicinal product packages, thereby providing for unique identifiers at four different levels.

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 and dosage form (and route of administration). That identifier is called the Pharmaceutical Product ID (PhPID). The implication is that, for example, a tablet of 400 mg carbamazepine for oral usage has the identical PhPID in every country, independently of the name given to that medicinal product by the marketing authorisation holder in a specific country.

Each of the four core 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 longer term perspective of a European reference data base maintained by the European Medicines Agency (EMA) in cooperation with member state regulatory authorities. It should be based on the ISO/CEN 11615 and 11616 and further standards globally agreed upon, plus the respective coding systems and vocabularies. It will cover all regulated medicines and their packages authorised in any of the member states.

Two of the recommendations (3 and 4) are added in order to enable in the short term, more specifically during the Phase I of the CEF programme, 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 of EMA to be the authoritative data source for all the supra-national medicinal product related information. This requires the actual Article 57 (2) (pharmacovigilance) drug database to be complete with respect to all medicinal products authorised for marketing in the European Union, validated, translated and structured in a way fully IDMP compatible.

The urgent need expressed by the Member States to have the validated Article 57 database available would be de facto critical for those countries participating in phase 1 of the CEF.

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

Key results and outcomes of the openMedicine project are summarised in the openMedicine Implementation Roadmap; its intention is to give guidance towards the further implementation of IDMP across Europe. It reflects that the full roll-out of the ePrescription, eDispensation and Patient Summary services 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 reduce the sense of urgency 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 USA FDA (Food and Drug Administration) as essential to any cross-border services. This also has an important impact on the further development and timing of the roll-out scheme of the openMedicine services.

Considering the strong wish expressed by the Member States at the eHealth Network meeting in Brussels, November 21st, 2016, it has been strongly recommended to start with upgraded and validated Article 57 data *for those countries participating in wave 1 of the CEF*. The final decision on this is not 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.

In this overall environment, 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 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. Identification of the prescribed medicinal product goes further than recognising the name of the product. The pharmacist will dispense the prescribed medicinal product if he has the same medicinal product directly available. 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 not feasible, and substitution is permitted, the pharmacist may substitute the specified medicinal product by another one in line with national regulation.

The 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 identifying attributes² in different ways, like by its package (e.g. GTIN³) or national medicinal product identifier, invented (originator) or given (generic) brand name, active ingredient, pharmaceutical dosage form, strength, route of administration and perhaps others. In some countries some prescriptions may only prescribe a set or class of medicinal products meeting certain criteria (like an INN⁴ or ATC prescription specifying only an active ingredient plus other attributes), or products being grouped by their pharmaceutical or therapeutic class⁵ 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

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

how medicines can be communicated in the cross border setting." Whereas the epSOS project basically solved the electronic "communication" or message transfer problem, it encountered 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 Expanding Health Data Interoperability Services (*EXPAND*) Thematic Network project⁶ was an initiative undertaken by 20 national and regional health authorities and competence centres for semantic interoperability, Standards Developing Organizations (SDO), and others. It reported in one of its documents complementary problems and issues encountered during the epSOS project, while investigating whether openMedicine could offer a solution for the challenges encountered. This EXPAND document has been added to this deliverable as Chapter 12.

1.3 Cooperation

Fostering coordination and cooperation across Union member states being one of the kernel expectations of the openMedicine brief, this Action opened its 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 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 trans-Atlantic workshop organised in close cooperation with FDA in Washington, DC, during spring of 2016.

The openMedicine consortium on its own already formed 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 council members were also invited to one US-EU workshop on the unique and global identification of medicinal products. Each of these council meetings and the workshop were attended by approximately 30 representatives from core stakeholder and actor groups as well as 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 regional and national workshops and dissemination meetings. The list of these sessions was published in Deliverable D7.2

⁶ http://cordis.europa.eu/project/rcn/191815_en.html

Through all of these activities and workshops openMedicine succeeded in reaching out towards 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 also 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 levels of compliance 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 and 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 “1st annual report on the activities of the Expert Council”, and D 6.2 presented a “Report on validation activities”, this deliverable reports on and summaries core project work and outcomes, which include core, distinct recommendations addressed to various players and stakeholders in this domain, and a brief roadmap outlining the way to go forward 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 solutions developed are in line with the requirements regarding unambiguous identification and description of medicinal and pharmaceutical products.

2. The openMedicine legal and regulatory context

2.1 The overall health policy 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 domains.

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 of the core challenges of openMedicine..

2.2 EU directives and regulations

2.2.1 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 identified as a priority area of regulatory attention, in spite of member states having retained sole responsibility⁷ for the organisation of national health systems and services. This concerns, inter alia, these directives:

⁷ This is the reason why only directives, but no regulations were issued.

- 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 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 May 1975 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, Directive 2001/83 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

Directive 2011/24 the core directive providing framework conditions for a European-wide healthcare services market, and as a part of this it provides requirements on the electronic exchange of patient health data, including ePrescriptions.

2.2.2 Regulations and directives on 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).⁸ Nevertheless, there exist some regulations as well as directives 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. Amongst them we mention

2.2.2.1 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".

In the light of a Commission report on the experience gained with Regulation (EEC) No 2309/93, it has proved necessary to improve the operation of the authorisation procedures for the placing of medicinal products on the market in the Community and to amend certain administrative aspects of the European Agency for the Evaluation of Medicinal Products. In addition, it was concluded that the name of the Agency should be simplified and changed to the European Medicines Agency.

⁸ 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.

It was reviewed and consolidated by

Regulation 726/2004/EC Regulation of the European Parliament and the Council of 31th March 2004 Laying Down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency

Defines in detail the documentation to be provided and the procedures to be compliant with when submitting a request for marketing authorisation for a (new) medicinal product.

2.2.2.2 Regulation on orphan medicinal products

Regulation 141/2000/EC, in which pharmaceuticals developed to treat rare diseases are referred to as "**orphan medicinal products**", laid down procedures for the designation of orphan medicines, and it defines incentives for the development and placing onto the market of designated orphan medicines ..

2.2.2.3 Directive and Regulation on Falsified medicinal products

For more than two decades, falsified medicinal products have become a serious threat to patient safety. Therefore 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 will soon become mandatory for each package of a medicinal product for which a prescription is required.
- This new unique medicinal product package ID will link to more information about origin and authenticity of the medicinal product contained in the respective package.
- The details were laid down in "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 2.2.2.4 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 [INN] 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"

2.3 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

2.4 ISO/CEN standards

Furthermore, there exist

- ✓ international standards
 - through CEN adoptions, are mandatory to be applied in national contexts of all E.U. Member States, and
- ✓ agreements on guidelines etc. which thereby also 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).

ISO has developed or adopted in recent years (and is expanding/updating) a full suite of standards and accompanying implementation guidelines establishing definitions and concepts, and describing data elements and their structural relationships required for the unique identification of

- ✓ Medicinal products
- ✓ Pharmaceutical products
- ✓ Substances
- ✓ Pharmaceutical dose forms, units of presentation, etc.
- ✓ Units of measurement

– the IDMP (identification of medicinal products) suite of standards. They are applicable to both authorised and developmental medicinal products for human use.

In the following list standards marked with an * are directly related to the domain of application of openMedicine, while the standards marked with ** are part of the wider 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

2.5 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 has to be 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 the 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.

List concepts

[Add new concept](#)
[How to read this table?](#)
[All](#)
[Export to Excel](#)

Click on a term to view the concept.

Showing 1 to 25 of 623 entries

Search:

Show 25 entries

Previous 1 2 3 4 5 ... 25 Next

Term	ID	Main term	Synonymid	Definition	Validated	Project
------	----	-----------	-----------	------------	-----------	---------

Figure 1 User Interface

Term	ID	Main term	Synonymid	Definition	Validated	Project			
administrable dose form	203	No	0	Yes	No	openMedicine			
combined pharmaceutical dose form	220	No	0	Yes	No	openMedicine			
dose	225	No	0	Yes	No	openMedicine			
dose form	226	Yes	0	Yes	No	openMedicine			
dose regimen	584	No	0	Yes	No	openMedicine			

Figure 2 Result of a query

Definitions for the selected concept

- 1 physical manifestation of a Medicinal Product that contains the active ingredient(s) and/or inactive ingredient(s) that are intended to be delivered to the patient 

Reference: [ISO 11615:2012]

Created: 09/05/2015

- 2 physical manifestation of a product that contains the active ingredient(s) and/or inactive ingredient(s) that are intended to be delivered to the patient 

Reference: [ISO 11616:2012]

Created: 15/11/2015

- 3 The physical characteristics in which the prescribed medicinal product shall be administered (e.g. tablet, solution, ointment). 

Reference: ISO 17523:2016(E)

Created: 16/11/2016

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 – Standards Knowledge Management Tool

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. Access to the keywords is less user friendly as you need to identify first a standard and you get the definitions within that standard.

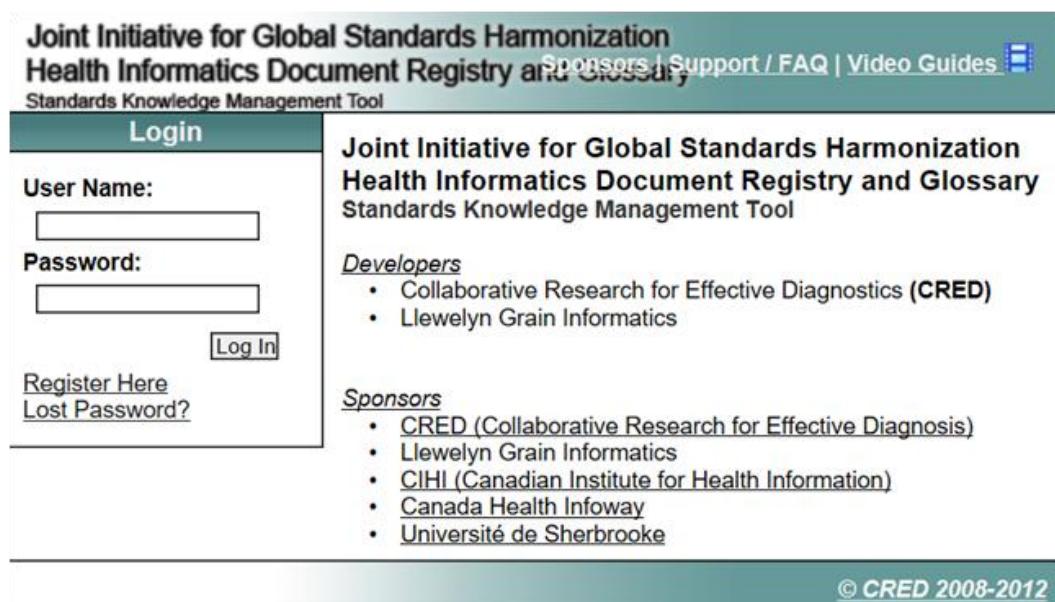
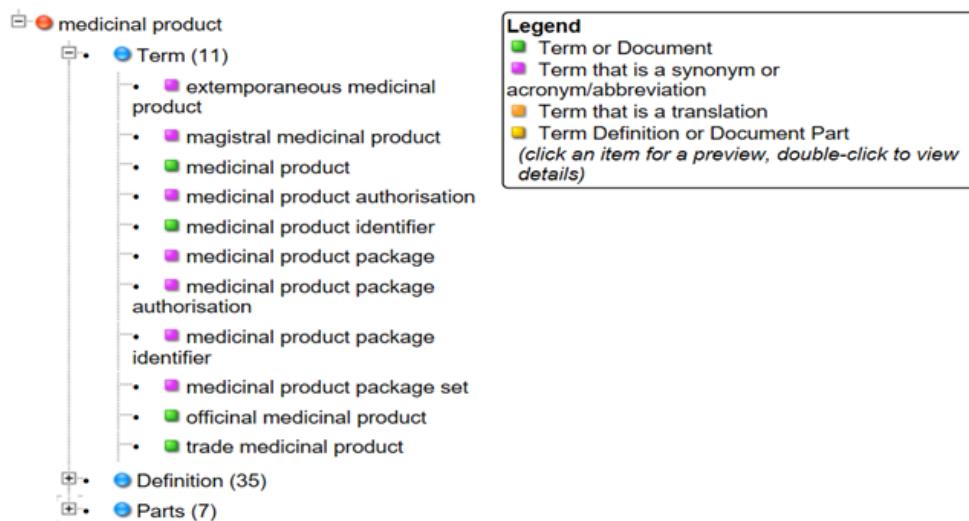


Figure 4 SKMT login screen

The date (2008-2012) might be an indicator for a lack of maintenance. This 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**

Search Details

medicinal product Add Watch Print

Language: English

◆ Definitions (Click on the title to see details.)

▼ any substance or combination of substances, which 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 *Candidate*

▼ 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. *Pending*

▼ any substance or combination of substances that may be administered to human beings to treat or prevent disease *Candidate*

Figure 7 SKMT Medicinal Product Definitions (main)

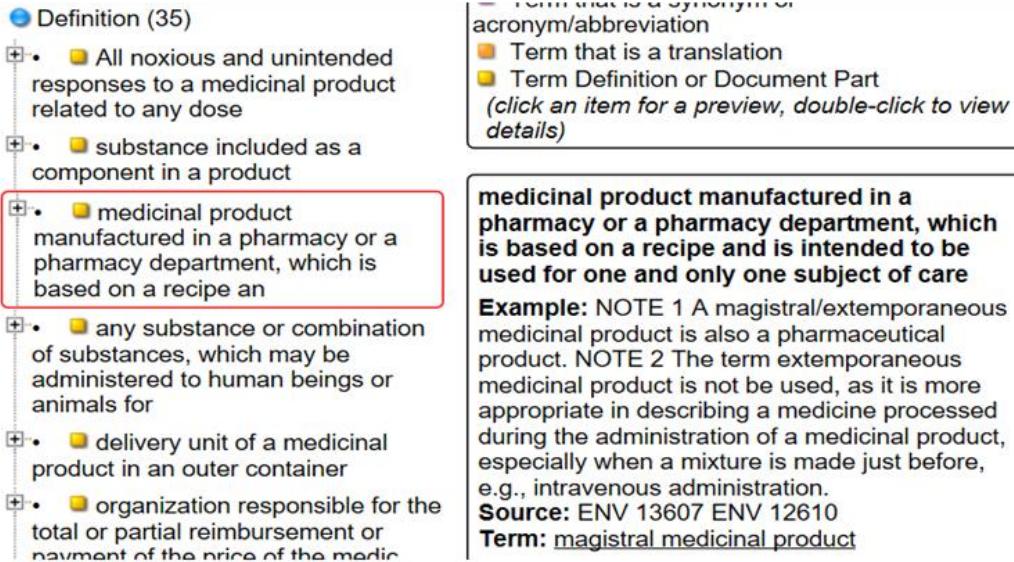


Figure 8 SKMT up to 35 different definitions

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.

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 healthcare professional for treatment.

We are, regarding prescribing and dispensing medication items, addressing solely the identification 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 regulations, we still have an impressive variation in how a prescribed medicinal product is identified in an ePrescription as well as in a paper prescription..

Further analysing the phenomenon we have to conclude that the compliance to the standards for the identification 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) prescriptions

A prescribed medicinal product can be identified unambiguously within its jurisdiction of prescription in many different ways and by using a set of identifying attributes, starting with simply the medicinal product name up to the complete set identifying attributes.

Indeed in some cases the full medicinal product name is enough to identify the package of the medicinal product to be dispensed, e.g. when there exists only one medicinal product package type for that medicinal product.

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 Lundbeck. 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 them 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 translated into the digital health and cross-border services world.

4.1.2 Electronically generated prescriptions

4.1.2.1 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 discouraged.

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.

4.1.2.2 Implementing ISO-IDMP

Particularly in work packages 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 use across the Union the same procedures (decision support) and content. 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. This 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:

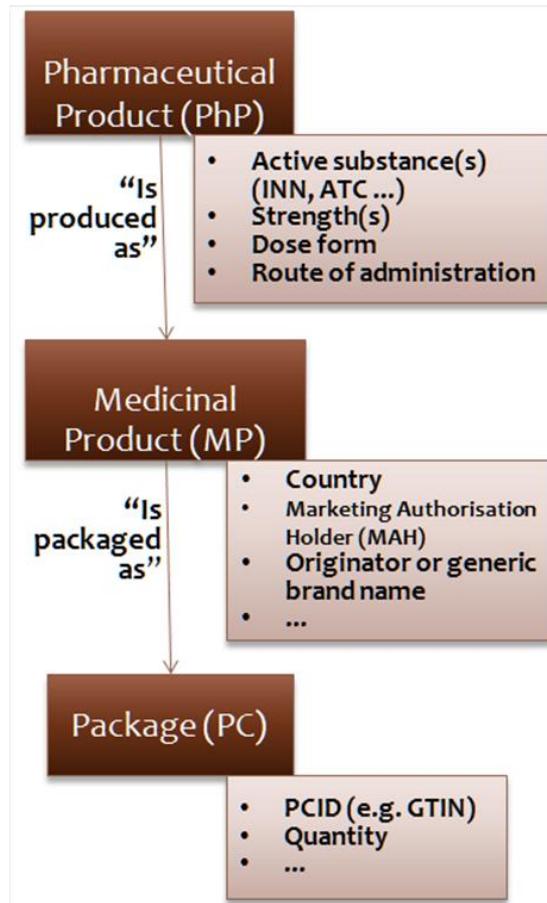


Figure 9 Relationships between identification levels and attributes for medicinal and pharmaceutical products (Source: [c] openMedicine 2017)

4.1.2.3 The Cross-Border setting

In a cross-border setting, the situation is usually somewhat more complex. The same brand name may cover a completely different substance and/or composition.

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 of the prescribed medicinal product retrieved from the connected data base in the country of prescription allows to identify the linked (globally univocal) PhPID and the substance ID, and through this PhPID the full subset of equivalent medicinal products available in the dispensing 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 dispensed, 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:

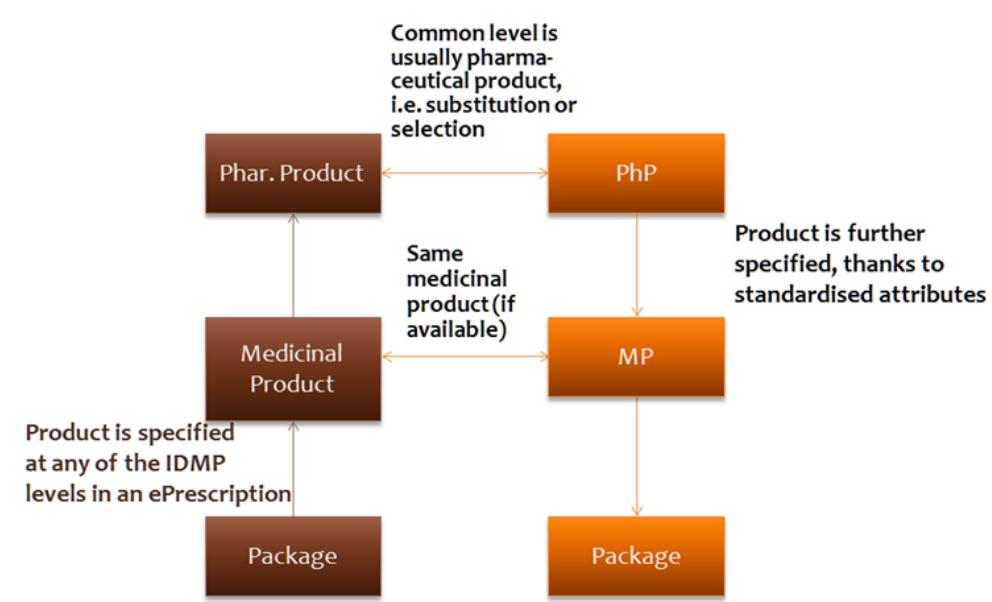


Figure 10 The xBorder ePrescription & dispensation setting (Source: [c] openMedicine 2017)

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 always 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.

4.1.2.4 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	

Table 1 Use of Identifiers per kind of product expression

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 extent 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

Table 2 Territorial extend of a Marketing Authorisation

The number of "centralised procedures" differs 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 of medicines / medication lines with their attributes
")
- The prescription line: one individual medicine (medicinal product or quantity of pharmaceutical product) in a prescription and registered as prescribed entity in a history of prescriptions

- The medication line: one individual medicine (medicinal product or quantity of pharmaceutical product) as medicinal treatment item in an EHR.

A prescription line is linked to a medication line as an attribute; date of last prescription.

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

Directly addressing a medicinal prescription to a pharmacy, even a pharmacy selected by the patient, is not allowed in most countries, regions or even insurance companies.

Regarding the "paperless" electronic prescription

- some countries or regions or 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 medicinal product. This package oriented approach is only the case 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 such a 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, even more in cross-border dispensing.

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

- Stock management issues 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 that are 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 any cross-border dispensing possible in a country where substitution is not at all allowed? The product delivered in the dispensing country will always be different, will always have a different Market authorisation, even when content wise and pharmacologically identical. Is such a ban of substitution acceptable considering the rights of the patient?

4.2.3 eDispensation

Some blockbuster medicinal products are copied numerous times, 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 aware of what product has effectively been dispensed. The EHR does not any longer reflect reality regarding medication.

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

- provided patient consent is given or not withhold, 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 effectively 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 treatment.

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 patient record 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 approaches to medicines and medicinal treatments:

- 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 about the patient's health are important but 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 in the EHR are documenting the effective dispensing. A 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 medication item in an EHR should ideally not be identified solely by its prescribed medicinal product name, considering that the dispensed product may have a different medicinal product name each time. The pharmaceutical product identification seems to be the only stable identification across dispensing sessions. The pharmaceutical product as such does not have something like a medicinal product name. The PhPID is perfect as electronic identifier. The "name" is a composition of at least three elements: substance name, strength and dosage form.

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 (medicinal product name + strength + quantity of product units per package,
 - a medicinal product name (with strength and dosage form)
 - the pharmaceutical product label (substance name + strength + dosage form)
- Either one of these labels 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

4.4.1.1 The context

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

4.4.1.2 Standard epSOS approach

Because different pharmaceutical products may have the same medicinal product name in both the prescribing and the dispensing Member State, no dispensing happens only based on that name.

In the epSOS scenario the dispensing pharmacists requests through the NCP (National Contact Point) services the prescribing Member State to provide the composition (scientific composition) of the product, subsequently translated in the language of dispensing Member State.

4.4.1.3 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

4.4.2.1 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.

4.4.2.2 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. Recommendations

5.1 Context and Genesis

The guiding principle of all openMedicine work was to contribute towards optimising (cross border) health services for patients, including ePrescriptions and their dispensation abroad. Due to different marketing authorisation procedures 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.

Considering that

- both EMA (the European Medicines Agency) and the FDA (Food and Drugs Administration, USA) decided to adopt and implement the EN/ISO suite of standards called IDMP
- all market authorisation forms and dossiers need to be compliant in structure and referentials to the IDMP standard
- the future EMA European Drug Database will be fully structured in an IDMP compatible manner and provide for coded data elements
- the EMA drug database will be available as authoritative European reference data source to national /international drug information providers
- the EMA European Drug Database will be more comprehensive than will be practical for clinical care services, and that therefore it will be required to identify and provide for a subset of ‘active substances’ for clinical use to become available for the healthcare domain
- no major problems were identified while studying the fitness of the Article 57 (2) database as source data for the new IDMP database (see conclusions of WP1 and WP2)

the consortium confirmed the option to implement at the European Union level the IDMP Suite of Standards, as soon as they are available.

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 Union 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 safety for the citizens of Europe.

Furthermore, national, Union-wide and international electronic health data interoperability will indeed become achievable with respect to medication data in ePrescriptions, ePatient Summaries, Electronic Health Records and other documents 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 detail at an internal two-day face-to-face meeting, then 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 reviewed and edited by the editorial board on the 7th October 7th 2016 and on the 10th and 11th November 2016. It turned out that understanding of the issues and challenges, of solutions and options as well as investigating 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 modifications of versions of the recommendations.

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

5.2 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 recommendation? When to start or/and what conditions need to be met by the application (providers) with respect to complying with 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 the IDMP standards [11615 & 11616] as stated in the next recommendations, identification issues are solved for over 99% of prescribed medicines. Magisterial prescriptions require on the other hand still epSOS like translation services.

5.3 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.

As openMedicine is addressing the complete lifecycle of medicines, from innovative substance to pharmacovigilance, we are searching for solutions usable in regulatory as well as in clinical environment.

ATC as well as INN are de facto in use in clinical environments where mainly 'clinical activity' needs to be addressed, where the difference between the "salts" of a substance are less essential than in a regulatory environment. The latter environment requires precisely that distinction, reason why regulatory authorities do not consider ATC and INN as fit for their services.

5.4 openMedicine Recommendations Overview

The next table gives an overview of the 12 recommendations regarding the identification of pharmaceutical and medicinal products.

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 describing and documenting medicines across standards, regulations etc.	Presently, across documents different definitions for the same core concepts are 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 and national medicinal databases.	Considerable initial investment with high benefits for citizens
R12	National rules on substitution in cross-border situations	Improves probability, that a foreign prescription can in-	Comments from professional organisation in annex

	should be considered for harmonisation	deed be dispensed.	
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Table 3 Recommendations Overview

5.5 IDMP based 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) plus the required strength(s) plus dose form defines a 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 and of 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 IDMP identifiers 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: <ul style="list-style-type: none"> - 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 .

5.6 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	<ul style="list-style-type: none"> SPOR project terminated resulting in <ul style="list-style-type: none"> - EMA Substance database - All products on the market (centrally authorised) - Organisations Referentials available EMA drug database "complete" and IMP compatible 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	<p>eHealth Network: decision, supervision, budget</p> <p>eHealth/NCAs: support, assist (translations)</p> <p>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</p> <p>Drug database providers: complemented with national information, update management, distribution towards end users</p> <p>EHR/Clinical Information systems: ability to produce n openMedicine compatible ePrescription, integrate an eDispensation message, produce a Patient Summary that includes openMedicine medication information</p> <p>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</p>
4	Timing	Start at the end of the developments linked to the recommendations 3 and 4, 2019. Start when context available as standards.

5.7 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	<p>Availability of a structured drug database, validated on its completeness, structured scientific composition, and translation issues.</p> <ul style="list-style-type: none"> • SPOR project terminated resulting in <ul style="list-style-type: none"> - EMA Substance database - All products on the market (centrally authorised) - Organisations • Referentials available • EMA drug database "complete" • Scientific composition structured available <p>Complete standard set of substances</p>
2	Vehicle(s)	The epSOS environment should be used for initial acceptance
3	Stakeholders and their respective roles	<p>eHealth Network: decision level, budget, supervision</p> <p>eHealth/NCAs: role in data gathering, quality of data exchange</p> <p>EMA (and FDA): control of the completeness and the correctness of the information in the Article 57 database</p> <p>Drug database providers: essential role in the distribution of the products, their identifiers and descriptive attributes</p> <p>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</p> <p>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</p>
4	Timing	<p>Drug database IS available, structured and coded: EMA Article 57 database.</p> <p>Limited to centrally authorised products.</p> <p>Possible to pilot with a limited number of Member States, based on a decision by those Member States.</p> <p>Timing should be Q4, 2017</p>

5.8 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 at 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 before the end of 2017

5.9 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 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 Implementation Context		
1	Pre-requisites	<p>Controlled terminologies available, at first for the kernel identifying attributes (strength expressed in UCUM unit, route of administration, dosage form and substances/ingredients).</p> <p>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.</p>
2	Vehicle(s)	<p>Include in the quality criteria for drug databases. Include in quality criteria for clinical information systems, e.g. EHR systems.</p>
3	Stakeholders and their respective roles	<p>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 <i>and as for all the standards for free available to end-users</i></p> <p>eHealth/NCA: standard terminologies ... should be a mandatory requirement for participation in EU funded projects</p> <p>EMA (and FDA): International coordination, also between the domains of use (market authorisation, clinical..)</p> <p>Drug database providers: integrate and distribute for clinical purposes</p> <p>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</p> <p>Health professionals: don't use applications based solely on free text</p>
4	Timing	Can start whenever involved parties decide.

5.10 Adjuvants, 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. Covers only a part of the problem: the medication related allergens. Need to extend to environmental allergens and food allergies?
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 EHR 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

5.11 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.

Standards are not limited to identification and description, but covers also content related matters as indications, contra-indications, effects related to the use of medicinal products.

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.

Remark: Standards are not limited to identification and description, but covers also content related matters as indications, contra-indications, effects related to the use of medicinal products

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 To be added to the quality assessment for clinical record systems
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): <ul style="list-style-type: none">• 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 <ul style="list-style-type: none">• 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

5.12 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	<p>Improved accessibility to standards. Access is actually insufficient for the following reasons:</p> <ul style="list-style-type: none"> • 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	<p>eHealth Network: stimulate cooperation between SDO's consider an initiative to harmonise domain terminologies between domain expertise and European legal documentation</p> <p>eHealth/NCA's</p> <p>EMA (and FDA) follow the standards as much as possible</p> <p>Drug database providers respect the concepts (meta data) and their definitions</p> <p>EHR/Clinical Information systems; respect the concepts and the data model</p> <p>Health professionals</p>
4	Timing	No specific data

5.13 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 or not-to-be prescribed 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	<ul style="list-style-type: none"> eHealth Network: avoid "hijacking" of the database eHealth/NCAs: define a set of quality criteria EMA (and FDA): <ul style="list-style-type: none"> • interface with the database providers for distribution to the end users Drug database providers: <ul style="list-style-type: none"> • 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	Before starting to use openMedicine developments

5.14 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	No reason to postpone

5.15 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	<p>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</p> <p>Availability, preferably coded and properly structured source data, also validated content wise and coded.</p> <p>The actual Article 57 database is composed out of text fragments collected as modules. Structuring the content is very challenging as such, Merging text modules from 27 countries and in 23 languages is not done overnight. They are luckily all based on the same templates.</p>
2	Vehicle(s)	E.M.A is the appropriate organisation, at European level, to build such a database.
3	Stakeholders and their respective roles	<p>eHealth Network: enabler and requiring up-to-date data</p> <p>eHealth/NCAs: is part of their usual task</p> <p>EMA (and FDA): key partners, authentic source, distribution software</p> <p>Drug database providers: maintenance of the internal (national) regulations and reimbursement issues, distribution and maintenance software</p> <p>EHR/Clinical Information systems: adapt the clinical systems once the services provided</p> <p>Health professionals: should only have as 'obligation' to keep his application up-to-date</p>
4	Timing	From 2018 on

5.16 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

6. 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.

6.1 Challenges and context

Harmonising the identification of medicines is much more than an administrative issue, much more than simply assigning an identifier to each occurrence of the medicine related concepts.

The medicines lifecycle aspect is another challenging issue.. agreed on by the openMedicine consortium. Whatever the options might be, first choice should always be the option that fits for the complete lifecycle of "medicines", from substance to administration unit, from innovative and clinical trial environment to pharmacovigilance, clinical care use included.

From the start of the project the ISO IDMP suite of standards was identified as THE solution for cross-border ePrescription services.

This is still the opinion of the consortium. Some issues at operational and at content level should be taken in account before implementing largely the ISO IDMP standard was pushed forward as THE solution for cross-border ePrescription services and for clinical care in general, also considering the impact on the 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.

The impact on clinical care of the ISO IDMP conceptual model is out of discussion. It promises a substantial European added value, impacting on ePrescription, eDispensation reports, ePatient Summaries as well as on clinical decision support, secondary use for research as on the aggregation of information for public care purposes.

The challenges remain nevertheless huge. 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 the 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 most frequently not supporting MPID or PHPID attributes and codes, because at the national level there are few direct benefits from solving cross-border identification, because of semantic issues.

Most of the running services are on package level, the package level being the level mostly addressed in the pharmacy.

Remarkable is the observation that each of the "medicines worlds" are focused on different product levels:

- The regulatory authorities on the substances and the pharmaceutical products
- The pharmacists on the medicinal product packages, level at which national and billing information is added
- The clinical care on the "active principles"

6.2 Further work needed

As explained in the Roadmap (chapter 11) the implementation of ISO IDMP has huge potential health added value mainly through 'future" decision support, pro-active as well as reactive.

The knowledge behind this decision support is universal and is as such a valuable reason to enforce **global** solutions.

We experienced during some of the openMedicine public presentations that some Regulatory Agencies are still reasoning "nationally". There is an urgent need to align all he involved stakeholders on the same strategy.

The global aspect of the decision support will be the main reason to align all the parties involved. Indeed, as documented in chapter 4.1.2, the European Market Authorisation identifies uniquely a medicinal product package across th Union and facilitates dispensing of an identical product.

The products with a "mutual recognition authorisation" are uniquely identified in the participating Member States, mostly neighbouring Member States.

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.

There is nevertheless an important effort to be done in order to validate and – if needed – to adapt the SPOR database to its usage outside the regulatory environment. Some data more especially the data related to the "O" of SPOR (organisations) are useless in clinical care.

The "S" of "substances" need an in-between mapping between the substance identification (chemical)and a reduced list of "active principles" that can be selected for prescriptions.

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.

Looking-up the locally appropriate identifier is standard a 'task' for the dispensing pharmacist. Alternative scenarios are obviously possible for cross-border health services, when a prescriber specifies an innovator or generic brand name, or an active substance and further attributes, and when his/her local ePrescription system has been enabled 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.

6.3 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.
- A working group of European medicinal products data base producers should be installed 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.
- Cooperation 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 fruitful trans-Atlantic cooperation which has already been established in this domain.

7. Preparing for the openMedicine Roadmap

7.1 Context of the openMedicine Roadmap

The grant agreement specifies that an openMedicine Implementation Roadmap should be proposed. The consortium decided to submit an enlarged chapter as part of the Recommendations deliverable.

The full roll-out of the European ePrescription, eDispensation and Patient Summary services, as defined in the openMedicine conclusions and as envisioned by the respective CEF services to start operation in 2018, will take several years from now, and is not expected that they will 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 considers an intense European cooperation between national agencies and EMA (European Medicines Agency), and with the American FDA (Food and Drug Administration) as essential to any routine, sustainable cross-border services, see chapter 5 of this deliverable D 6.3. This has an important impact on the development and roll-out scheme of the openMedicine services. Indeed EMA also intends to be the authoritative data source for all the supra-national medicines related information. This requires the actual Article 57 (2) drug database to be complete, validated, coded and structured in a way fully IDMP compatible.

Considering the strong wish expressed by the Member States at the eHealth Network meeting in Brussels, November 21st, 2016 it has been recommended by openMedicine to start with upgraded and validated Article 57 data for those countries participating in wave 1 of the CEF eHealth service of ePrescription. The final decision on this is, however, not 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 here proposed roadmap is a proposal considering the actual context and status of the different parallel developments.

7.2 The roadmap concept

Wikipedia defines a technology roadmap as "a plan that matches short-term and long-term goals with specific technology solutions to help meet those goals."⁹ This definition fits quite well with what is needed for the implementation of the openMedicine conclusions.

The core set of recommendations of the openMedicine project is – for the univocal cross-border identification and description of medicinal and pharmaceutical products - to build on the ISO-IDMP suite of standards. In particular, to assure the safe identification of equivalent products in another country, it is recommended to assign to each unique active substance (or combination of substances) plus the strength and dosage form a globally unique identifier (PhPID) and to integrate that identifier in the electronic prescription, the eDispensation report, as well as each time a medication item is recorded in a clinical record.

⁹ https://en.wikipedia.org/wiki/Technology_roadmap

*Two concepts are important here: **global** and **identifier**.*

They define the approach and the extent of the project, and obviously also the highway to be reflected in the roadmap.

The cross-border issue, as documented by the epSOS project, is not a "Member States problem" only. The same problem occurs, even without using the epSOS services, e.g. when travelling across the Atlantic or when consulting your patient summary while relaxing in Kenya. The openMedicine compatible "looking-up services" are universally understandable and available as soon as the patient's data are made accessible through the web.

The language issue remains with respect to non-coded data elements, but is less critical for pharmacy/dispensing related services. Correctly coded data (PhPID) are sufficient to retrieve what the users (healthcare professional, pharmacist) are searching for.

A pharmaceutical product has been defined as each unique combination of a substance, a strength and a dosage form (+ linked route of administration)ⁱ. That combination does NOT have a name. It has at most an understandable "description" in the original language.

OpenMedicine suggests strongly to assign a unique universal identifier to each pharmaceutical product, and to agree on the algorithm to produce these identifiers.

The only requirement to be fulfilled in order to dispense the same, an equivalent medicinal product in Greece as prescribed in Belgium is the presence of a global PhPID in the ePrescription and in the Greek Drug Database.

A route documents a possible way to go from "a" to "b". A roadmap illustrates the different routes that may be used when starting from "a". Each of these routes has different roads, one of them being a highway without obstacles. Others may be low speed alternatives with different kinds of obstacles. Drivers are interpreting the indications, trying to get as soon as possible to their final destination.

In preparation for drafting a concrete roadmap, the following sections will address successively

- The actual status of implementation of the openMedicine options
- The motivation to invest in cross border solutions
- The ideal end result
- The involved stakeholders
- The progress to be achieved by each stakeholder
- Risks
- Expected timelines

The next chapter 8 will then describe options and steps to indeed implement core proposals and results of the openMedicine project.

7.3..Actual status of implementation of the openMedicine options

7.3.1 The openMedicine "solution"

The openMedicine consortium identified the missing link that enables – if present in the ePrescription – to select the equivalent medicinal product directly in the national / locally used drug database.

The openMedicine approach works for up to 98% of the prescriptions, the electronic prescriptions. The missing link is the Pharmaceutical Product. Each unique combination of an active substance, a strength and a dosage form is considered as a pharmaceutical product.

The pharmaceutical product has identifying attributes but no name and is therefore difficult to address.

EMA and the FDA (Food and Drug Administration, USA) joint efforts and defined together a univocal global identifier for each pharmaceutical product.

The openMedicine proposal for solving the cross-border issue is based on

1. the availability of an ISO/EN IDMP compatible structured drug database, as source data for ePrescription, medication in a Patient Summary and medication related decision support services
2. the availability of appropriate coded pharmaceutical product identifiers
3. the effective use of the PhPID in ePrescription
4. the effective use of the PhPID in Patient Summaries
5. the effective use of the PhPID in dispensing systems (pharmacy information systems)
6. the effective use of the PhPID in the EHR systems
7. the use of the CEN.ISO standards for the substances, the expression of the strength, and the dosage form and the route of administration

7.4 openMedicine elements already available

7.4.1 What is already available?

1. EMA drug database available.
 - Each person or organisation or company that wants to introduce a medicinal product on-the-market, has to complete a form, to submit a dossier
 - The form consists mainly of text modules (semi-structured text)
 - The "scientific composition" description of a medicinal product is up to now text based
 - The completed form needs to be submitted either directly to EMA in case of a centralised procedure or to a national drug agency the latter being obliged to submit the dossier at EMA
 - Up to some weeks ago (Spring 2017) completeness of the database was estimated at 98%.
- ⇒ *EMA Drug Database is very comprehensive: when restricting the need solely to prescribing, even too much information is available. Much more data are contained in the EMA database than what is needed to univocally identify a medicinal product (package).*

⇒ *EMA Drug Database has its focus on pharmacovigilance and the market authorisation process, and not on clinical care needs. openMedicine documented how importantly the database meets the requirements for clinical use as defined by the epSOS project. To optimise resource use, it should cater to both domains.*

2. Agreements on practicalities between EMA and FDA are already in place for:
 - the algorithm to produce the PhPID
 - on who will assign PhPIDs: both EMA and FDA
 - when?
 - o As part of the process of building the IDMP compatible drug database but there are no major problems identifiable why to wait with this until completion of the IDMP compatible drug database
 - o Migration of data from the Art. 57 data base to the IDMP compatible drug database might be done horizontally, starting with the relevant identifying attributes and the potentially interactive modules
 - Initial validation of the algorithm was done in the USA
 - ➔ EMA and FDA) are considering to make the identifying algorithm publicly available
3. Controlled vocabularies
 - Available for all three identifying attributes:
 - o the pharmaceutical dosage form
 - o the units when used in expressing the strength (EDQM) (EDQM)
 - o the route of administration is handled as a part of the dosage form.
 - 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.
 - These controlled vocabularies are actually distributed and maintained, in compliance with ISO/EN standards.

7.4.2 What is actually on-going?

1. EMA Article 57 Drug Database Validation
 - National Competent Authorities provided the initial information on the medicinal products in their jurisdiction by using a standard form, also on legacy medicinal products, to feed the Art. 57 DB. Continuously new information is added (within 15 days after national authorization or acceptance of a variation).
 - ⇒ This means that only a semi-automated processing of quality assurance is possible, and that considerable time and resources will be required to obtain a fully validated DB.
 - The Article 57 Database respectively the new IDMP database fits perfectly for regulatory purposes. It contains all 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 majority of the information contained addresses issues related to regulatory aspects. That information is of little to now importance for the roll-out of ePrescription services, eDispensing services and for Patient Summaries.

- EMA estimates that some medicinal products and/or their package information are 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 towards IDMP to validate the actual Art. 57 data first.
 - ⇒ This means that a project building on 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 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 some time, especially if a "one shot" approach is maintained.
 - At some time into the future, EMA will assure the validation and integration of this information into the IDMP compatible database and data source, and assure maintenance of the substances (substanceID);
2. SPOR master data project by EMA:
- The project intend to extract from the EMA Article 57 database, while validating its content, lists of terms, building and maintaining the controlled vocabularies.
 - SPOR stands for Substances, Products (Medicinal Products and Packages), Organisations (regulatory authorities, marketing authorisation holders, research sponsors...) and Referentials.
 - "Substances" include not only active substances, but also inert substances or excipients, colorants, adjuvants.
 - The active substances are the most discriminating identifying attribute of a pharmaceutical product, code excepted. Replacing an excipient with another one will not result in a different PhPID.
 - The active substance or mixture of active substances is the main identifying attribute of a pharmaceutical product.
 - It is expected that the EMA/FDA list will include between 20.000 to 25.000 substances. Presently, EMA is populating a "controlled vocabulary" with substances out of the Article 57 database.
 - It is suggested to not produce one single list of "substances" but clearly distinguish between allergens, excipients, colorants and adjuvants.
 - EMA and FDA will assure maintenance of the substance DB, including the most important substanceID code;

7.4.3 What needs to be done?

1. Substances and clinical use

As the (active) substance name can be used to identify a pharmaceutical product when prescribing "generically", we need for purely clinical purposes

- A manageable list of active substances and their fixed combinations (perhaps around 4000), present in currently authorized medicinal products.
- A process to identifying the "active" substances not only in a consistent way across the regulatory authorities of member states, but also during the complete lifetime of a "medicine"
- 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.

The concept 'moiety' has been added to the data model and should be accepted as a openMedicine concept.

- ⇒ Enable the prescription by "moiety" by expanding the drug database, at least the IDMP compatible drug database

2. Strength and Units: the openMedicine project confirmed the choice for UCUM as standard to identify and label units of measurement.

3. Assign a PhPID

As indicated before, the consortium aligned itself on the strategy agreed on by EMA and the FDA creating a unique global identifier for the pharmaceutical product: the PhPID. This coded identifier is a a globally unique identifier (GUID), based on the following elements

- identification of the (active) substance
- strength or quantity of substance per unit of product
- dosage form

Each time one of these elements changes we have a different composition, thus a different pharmaceutical product

7.5 Standing issues

The focus of openMedicine was on solving the problems encountered when presenting for dispensing an ePrescription to a pharmacist in another Member State. To solve the original problem the consortium needed to invest in understanding the way of thinking of clinical stakeholders or actors involved, and their priorities and expectations.

The way physicians versus pharmacists are looking at a medicine (medicinal product as well as a pharmaceutical product) is different and has different priorities. Adding regulatory requirements increases the complexity and may well be at the origin of some of the remaining issues. This difference is reflected and documented in this chapter, addressing various aspects of processing medicinal product information from a clinical perspective.

We will try to formulate for each issue an advice (to be reflected in the roadmap) on how to solve the problem or to make a round-about.

7.5.1 EMA drug database

Preliminary remark: What follows is based on the actual Article 572 database, but will also apply to the new IDMP DB. The EMA Database contents are the market authorisation dossiers. They are authorisation oriented and not clinical. What is needed are interoperable data that can be applied to interact with patient data, e.g. to provide a health-related added value by means of integrated decision support.

Regarding factual ePrescription or eDispensing related information: mostly a combination of generic scientific information and factual information should be made available.

- ⇒ If EMA wants to be the source of information regarding medicines, it then should consider to either separate¹⁰ the factual and the scientific or authorisation data, or to produce a down-sized version for clinical use.
- ⇒ The conversion into an IDMP compatible drug database might be an opportunity.

7.5.2 Substances

The concept "substance" encompasses active ingredients/substances, inert substances, excipients, colorants as well as adjuvants. Do we need 25.000 terms?

- YES for regulatory purposes. The scientific composition needs to be as precise as possible. Two different salts are; de facto different substances.
- NOT for clinical purpose: not for prescribing, not for reporting, neither for data entry into a patient record.
 - ⇒ List separately – for clinical and for regulatory purposes - the active substances, excipients, colorants...

7.5.3 Moiety

A moiety is a group of clinically equivalent and interchangeable, but chemically different substances.

Such a group has a distinct name. Prescriptions are based either on the moiety name, or by using one of the specific substance names.

Classic example:

- Substance name 1 amlodipine mesilate
- Substance name 2 amlodipine besilate
- Moiety name amlodipine
 - Prescriber He/she prescribes, because it makes no difference clinically, : amlodipine 10mg

Pharmacist dispenses, if within the regulatory context, what is available; or "as usual" to please the patient (who may be used to a specific brand name)

¹⁰¹⁰ Separate means here "accessible/distributable per type of information e.g; the PhPID + values for he attributes for one or a series of countries without the regulatory information

7.5.5 Medicinal product allergies

A medicinal product can initiate an allergic reaction

- Because the product as such is an allergen => apply standard treatment for an allergy
- Because one of the excipients causes such a reaction, e.g. a colorant

No prescription should be given when the patient is known to be allergic to what the prescriber intends to prescribe. The prescribed product might be allergy-free for the patient when dispensed as prescribed in country A, but the "equivalent" product in country B may contain a substance on which the patient reacts. Therefore the dispensing pharmacist should be warned that allergies (in general) are documented for this patient when he dispenses a product for which allergies are documented.

- ⇒ The pharmacist should be informed...that a patient has an allergic condition, either as part of prescription or by consulting the Patient Summary.
- ⇒ It should be defined how to identify a medicinal product or a pharmaceutical product as containing a risk for an allergic reaction.

7.5.6 Gluten / lactose intolerance

A similar scenario applies to Gluten and/or Lactose intolerance.

The dispensing pharmacist should be warned that intolerances are documented for that patient. On the other hand the product should be labelled as containing these substances., the pharmacists being reminded that he needs to check the patient on this.

- ⇒ It should be defined how to identify a product as containing lactose or gluten.

7.5.7 Medicinal product to be recombined

These are the medicinal products composed of pharmaceutical products that need recombination at the point of care. Most frequent is the recombination of a liquid by mixing a powder (pharmaceutical product under dosage form powder) with a solvent (e.g. water).

We have two different dosage forms: the powder to be recombined into a liquid, and the solvent. Each of the forms is linked to a different lifecycle value:

- powder (to be recombined) in the dispensing context
 - solvent in the administration context
- ⇒ Issue to be solved at the level of drug database. Each pharmaceutical and by heritage each medicinal product should have at least two or even three dosage forms:
- the dispensing dosage form
 - the intended administration dosage form
 - the (effective) administration form

7.5.8 Joint packaging of two or more medicinal products

Such a joint packaging is used for specific treatments when more than one medicinal product is to be taken by the patient. Administration needs to be done in a particular sequence, first box A and then box B.

The joint package has a PCID – package ID. Each of the medicinal product has its own MPID.

7.5.9 Magisterial prescriptions

A magisterial preparation is a medicinal product manufactured by or under responsibility of a pharmacist and destined to be dispensed by that pharmacist¹¹¹ to the patient.

We distinguish different classes of magisterial prescriptions:

- 1) Magisterial preparation fully compatible to a formula out of a formularium and prescribed under a name and an identification of that formularium. Example: a formula out of the European pharmacopeia
- 2) Magisterial preparation consisting out a fraction or a quantity of medicinal product and dispensed as a magisterial formula.
- 3) Magisterial preparation manufactured as an individualised set of substances for an individual patient
- 4) Magisterial preparation being individualised towards the patient with a quantity of a specific medicinal product added
- 5) A magisterial formula as mentioned under 1) modified for an individual patient becomes a magisterial formula under 3)

Magisterial formulas are registered:

- a) As a standard medicinal product for case 1)
- b) In a local register at the pharmacy for all other cases (in most countries)

7.5.10 Ad hoc preparations (cocktails)

Pharmaceutical product consisting out of a mixture of defined quantities of several medicinal products, administered parentally under a configurable quantity of that mixture per time unit during a defined time.

7.5.11 Virtual medicinal products

A virtual medicinal product (VMP) is a label identifying the collection of medicinal products from different producers with an identical quantity of substance (substance + strength) plus an identical dosage form (and route of administration). It may also be defined as a collection of medicinal products with the same PhPID. An alternative name is "cluster of medicinal products". Such a VMP code is, e.g., used in the Dm+D drug database in the UK.

7.5.12 Pharmaceutical product clusters

This concept similar to the previous one, though the concept is more oriented to the collection as such, the collection to be used for administrative billing purposes or even for consumption oriented research.

The concept is not frequently used for prescriptions.

A cluster is in principle a collection of medicinal products selected on the basis of any possible criterion. Typical are the formularia in hospitals in some countries, or clusters based on price information.

¹¹¹¹ Or a colleague

7.8 Stakeholders

For the roadmap, it is relevant to identify the major stakeholders or actors to which the roadmap is addressed. We distinguish global / supranational public stakeholders or networks of stakeholders, and national or local partners, be they public or private stakeholders.

The main role for the global stakeholders is to accept or refuse medicinal products access to national health markets, to provide scientific sound information, and to monitor medicinal products' efficiency and safety. Level 1 and Level 2 of the openMedicine data model (Substance and Pharmaceutical product) are per default their domain of expertise and/or competence.

7.8.1 European Medicines Agency- EMA

EMA sits in the driving seat. Delay at EMA has an immediate impact on the implementation of openMedicine. A failure of EMA will endanger the European ePrescription project, or require rescheduling of the project's processes.

EMA has prime responsibility for several topics which impact on the implementation of the openMedicine vision:

1. Defining the rules applying to the authorisation and registration of medicines: substances, pharmaceutical products, medicinal products
2. Coordinating and supervising the National Drug Agencies. Some national drug agencies will need some "stimuli" to align with EMA. See discussion on the "unique identifier"
3. The so called "central or European marketing authorisation ", one authorisation for all the Member States. Approximately 20% of all the medicinal products available applied for a European Marketing Authorisation
4. Centralising authorisation information provided by the pharma industry in a by EMA defined format regarding effects and use of the medicines into the Article 57 DB respectively the new IDMP DB
5. Pharmacovigilance

EMA specific tasks related to openMedicine:

Most of the tasks listed here needs to be done anyway. They are listed here because not performing or delaying such a task will impact directly the result project.

1. Complete and validate the transfer and input into the IDMP drug database
2. Complete and validate through the SPOR project the referentials
3. Provide and maintain the list of substances
 - >> Important is to find a way that renders this list of substances usable for ePrescription or for identification of Pharmaceutical Products in a clinical context.
 - >> Is a solution à la LOINC possible: an extended list of terms used to describe results while another list is used to identify tests and finally a comprehensive list for lab/lab communications
4. Migrate Article 57 DB towards the IDMP compatible drug database, structuring format and most content, including coding where needed
5. Assign the PhPID (in cooperation with FDA)
6. Integrate PhPID in the IDMP compatible drug database
7. Define distribution policy respectively APIs and services to be provided
8. Develop and validate export to external drug database providers
9. Provide direct online, web-based access to the EMA IDMP drug database

7.8.2 European Authorities

The European Union and the European Commission as its executive organ has – with the results of this openMedicine project – the (persuasive) power and the resources to enable and facilitate the realisation of openMedicine recommendations and suggestions.

The Union may issue – if needed – complementary Directives and Guidelines or update/upgrade existing Directives and Guidelines.

As far as involved the Union may mandate and fund her agencies to realise some of the openMedicine recommendations, where they have direct competence.

7.8.3 Global Stakeholders

The involvement of Global Stakeholders and preferably cooperation between them would be important. Considering the global dimension of travelling and the global dimension of decision or monitoring support systems and research, a global approach or at least an intensive cooperation seems required to reduce costs and increase consistency. It would also benefit European industry.

7.8.3.1 F.D.A

The USA Food and Drug Administration is actively involved in the project, as a core partner. The F.D.A. attended all the expert meetings of openMedicine and organised the Washington workshop together with openMedicine.

The F.D.A. closely cooperated with EMA and defined and validated the algorithm to assign an PhPID to the pharmaceutical product, identifying some issues also reported in this deliverable:

- multi-component products
- allergic reaction inducing products
- lactose etc.

The F.D.A. intends to further cooperate with EMA.

7.8.3.2 WHO - Uppsala

The WHO – Uppsala Monitoring Centre [for medicinal products] (UMC) is one of the most important pharmacovigilance centres worldwide with a global scope .

They attended all openMedicine expert councils and are considering a coordination role in the maintenance of the PhPID implementation.

7.8.3.3 WHO - Geneva

The WHO centre in Geneva has a much larger domain of expertise, covering disease, epidemic and/or rare diseases and much more. The WHO centre supported the project without attending the expert council meetings. Efforts should be done to get them really on board.

7.8.3.4 SDOs

SDOs (standard development organisations) are de facto competing against each other, mostly related to the content, the coding tables. Recommendation 5 calls for international coordination and the use of controlled vocabularies.

ISO/CEN developed the IDMP suite of standards and defined, in agreement with EMA and FDO, the 4 level data model, further detailed during the openMedicine project. The 4

levels are the substance (L1), the pharmaceutical product (L2), the medicinal product (L3) and the package level (L4).

Critical regarding interoperability will be the list of substances: several keyword lists are yet available for the substances: the ATC code, the INN term, SNOMED terms.

7.8.4 National Stakeholders

We identified two subsets of national stakeholders: the national public stakeholders and the private stakeholders.

The national stakeholders are the National Drug Agencies and the Ministries in each of the countries. Some countries / most countries have a National Social Security agency too. These national bodies are responsible for

1. Coordination with EMA
2. Relations with pharma industry, getting the dossiers for Marketing Authorisation
3. Relations with Ministries (depending on the countries, sometimes a regional competence, at least in some regions)
4. Ministries of Health (national): either they decide themselves or they delegate to e.g. a National Institute some competence regarding:
 - o Price (market price)
 - o Reimbursement amount
 - o Reimbursement conditions may be contrary to what's suggested by ELA or other agencies
 - o National requirements regarding ePrescriptions

7.8.5 Operational partners

We are listing here categories of involved parties, at national level in principle. Some of them are a division of an international group of vendors/providers.

7.8.5.1 Drug Database Providers

They are crucial to any implementation of the project. The quality of their services will largely be reflected in the acceptance or refusal of the services at least in the countries where there is still a free option not to use ePrescription services.

We distinguish pharmacy oriented and clinical care oriented drug databases:

- Pharmacy databases are
 - comprehensive product DBs adding mainly non-medicinal products available in a pharmacy, but not considered as a medicinal product
 - fully identical to the official information regarding indications, contra-indications, warnings for side effects, dosing etc.
- Clinical databases are
 - more complex; more precisely when a redaction committee validates the information provided,

7.8.5.2 EHR System Providers

EHR system and medication

The Electronic Health (care) Record is the kernel application for the healthcare professional, managing clinical patient data. There is a multitude of EHR systems, each of them managing a subset of the virtual overall patient health and healthcare related data. They offer a number of generic and/or specific functions addressing various domains of interest. They offer beside administrative functions a set of generic functions addressing clinical care, functions of

- data-entry: selection of term or product with appropriate coding and knowledge assistance
- data-retrieval and data-display considering the kind of health(care) related services to be provided
- interoperability services as we have data exchange services (referrals, reports, access services) as well as knowledge support services
- patient data and practice analysis, monitoring and surveillance are increasingly to be addressed by the systems, because simple store and retrieval systems are not meeting anymore the expectations of the patients nor those of the healthcare professionals.

Prescribing a medicine expressed as a number of medicinal product packages, a number of medicinal product units or as a number of pharmaceutical product units is one of the kernel treatment activities of clinicians.

Managing the patient "medication" process (what? from when to when? how much per intake and how many intakes per day or per week etc..) is another aspect of medicinal care, the prescription being the logical consequence of defining a treatment.

EHR system and cross border issues

Here we have to consider what must be done to render the local prescription easily executable in a country different to the one where the prescription has been produced:

ePrescribing

- main change: add the PhPID to the attributes of the prescribed medication
- register the PhPID as an attribute of each medication item
- selecting a drug database that links for each prescribed Medicinal Product (MPID) to the Pharmaceutical Product (PhPID) and that meets the quality requirements for drug databases

eDispensing

- the dispensing message from the pharmacy contains the PhPID of the product dispensed
- the PhPID is recorded as attribute "ID of dispensed product"
- the prescriber has the possibility to question the EMA database on the products with that PhPID

Patient Summary production

- export the PhPID together with other medication related data
- export the PhPID of the medicinal or pharmaceutical product causing an allergic reaction
- add the substanceID if available because
 - o the substance is in reality at the origin of the allergic reaction
 - o the PhPID may not exist in the country of destination \$

Patient Summary reading

- look-up for the PhPID of the Patient Summary
- look-up for equivalent in the local database
- in case no product with the same PhPID in the local database, look-up for the substance ID

7.8.5.3 Pharmacy Information System Providers

Two instances should be differentiated:

ePrescription

- the Pharmacy Information System receives an openMedicine compatible prescription:
 - o the system recognises the PhPID entailed as one of the listed identifiers
 - o the system lists locally the pharmaceutical products and/or the medicinal products and/or the medicinal product **packages** with the same PhPID
 - o the pharmacist dispenses the product chosen by the prescriber or one in agreement with local substitution rules
- the Pharmacy Information System receives an openMedicine compatible prescription
 - o the system recognises the PhPID as one of the listed identifiers
 - o the system does NOT recognise the PhPID in the prescription as one of the PhPIDs in the local drug database
 - o the pharmacist consults the EMA drug database for the substanceID linked to the PhPID in the prescriber's country
 - o the system lists locally the pharmaceutical products and/or the medicinal products and/or the medicinal product packages with the same PhPID
 - o the pharmacist dispenses the product

eDispensing message

- The pharmacy information System produces a dispensing message, including the following data from the prescription:
 - o The medicinal product name and package
 - o The MPID and/or the PCID
 - o The PhPID prescribe
- The pharmacy information system adds the identification data about the dispensed medication
 - o The medicinal product name and package description
 - o The PhPID
 - o The Substance ID

8. The openMedicine Roadmap proposal

8.1 Progress and to-dos – the approach

This section discusses identified work to be done in order to have the openMedicine cross-border services running. The next section then provides details of task description and dates for each of the “tracks” and the steps in each track identified for the roadmap. This proposed roadmap is based on some assumptions:

1. Preliminary work is essential towards the implementation of the openMedicine services, though they are not specific for only cross-border services.
2. Considering that one needs at least two Member States participating in order to validate and really use the openMedicine services, initial efforts are scheduled with a start date for the first Member State and as expected end date the final implementation by a 10th Member State.
3. Though the effort to be invested by the users seems to be rather limited, even then we don't expect a "rush" on the openMedicine solution.
4. The roadmap, as described, is an initial proposal that needs to be further developed to become more concrete while implementing it, in line with the concrete needs of the participating countries.

The openMedicine Roadmap identified

- a large number of "activities" running in parallel and addressing mainly semantic issues to be solved before or while implementing ePrescription services as well as any pharmacy system.
- the efforts required for cross-border services, on top of the standard eServices, are mostly on the semantic issues and more precisely translation services and privacy protection issues.

The roadmap tasks derived from this and the remaining 'to-dos' are first classified in one of the following 5 "tracks":

1. Preliminary mainly semantic issues
2. Build the IDMP compatible drug database
3. Assign and integrate the PhPID
4. Distribution
5. Adapt the clinical and the pharmacy information systems

Then, each task will be described and detailed by these items: each one

- Has a code assigned by us
- Has a task name
- Has a task description
- Has in most cases one or more responsible stakeholders. For some tasks we have a collective responsibility by European, regional or National competent authorities (NCAs)
- Has "involved actors", mostly domain experts
- May have a start date
- Has an expected (initial) realisation date

Note: Start and end date as well as the task descriptions are based on the options taken during the lifetime of the openMedicine project. When indeed implementing this or a modified roadmap, the timing will have to be adjusted accordingly.

8.1.1 Roadmap for preliminary tasks

Table 4 Roadmap proposal for content related preliminary tasks – Semantic issues

A	Track	Task Description	Responsible	Involved	Start	Expected end
A1	Article 57 / available data sources	Completeness: all products and packages for all the countries entered	EMA	Nat, Drug Agencies	ongoing	Q3 – 17
A2	Identifying concepts	Identifying attributes available in DB	EMA		ongoing	Q3 – 17
A3	Scientific Composition	Phase 1: presence and completeness	EMA	Nat. Agencies	Q3 – 17	Q2 - 18
A4	SPOR	Extract/list the values for the different concepts: - Substances - Products (medicinal product, package) - Organisations - Referentials	EMA	Nat. Agencies	ongoing	Q4 -17
A5	G-SRS (ingredients)	Compare/Map substances USA/EMA	EMA / FDA	SDOs	Q3-17	Q1-18
A6	Substance ID	Substances for prescription purposes Substances for scientific composition >>> Listing	EMA	Prescribers	Q3-17	Q4-17
A7	UCUM standards	Mainly maintenance	Regenstrief Institute		ongoing	Q3-17
A8	Dosage Forms	Validation / Completeness dosage forms for – product description - Administration	EDQM	EMA / CEN	ongoing	Q3-17
A9	Route of Administration	Validation / completeness	EDQM	EMA / CEN	ongoing	Q3 17
A10	Allergens	List of non-medicinal allergens List of medicinal allergens	SDOs			02 19
A11	Oher components	Colorants, coatings, filling substances, sweeteners	SDOs	EMA/FDA		Q4 18
A12	Containers	List of outer containers, inner containers, blister, intermediate container	CEN	GS1 (GTIN)		02 18

8.1.2 Roadmap for building the IDMP compatible European drug database

Table 5 Roadmap proposal for building the European IDMP data-base

B.	Task and/or Task group	Task Description	Responsible	Involved	Start Quarter	Expected end Q
B1	Define the universal data model	Define an IDMP data model that covers <u>all</u> possible application needs	CEN	EMA / FDA, Other SDO's	Q3 - 17	Q4 - 17
B2	Define conversion strategy	Conversion = coding and structuring of identifying attributes and composition +> enables ePrescription: - per country, based on readiness etc. - per kind of information: start with identification data, composition... - combination drugs ...	EMA	National Competent Authorities (NCAs)	Q3 - 17	Q1 – 18
B3	Validate conversion process	Select a sample of products out of Article 57 DB to validate set-up of the conversion to IDMP model	EMA	OMC (openMedicine consortium)	Q4 17	Q1 -18
B4	Starting conversion Art. 57 to IDMP	Based on B1 and B2: first conversions of factual datasets.	EMA	Conversion team per country	Q1 – 18	Q2 – 18
B5	Validation set 1	Code driven first set of converted data. The identifying attributes are coded =>no translation needed	EMA	Nat. Agencies involved	Q2 -18	Q3 -18
B6	Complete sample	Add the attributes that can be coded and structured/or	EMA	OMC	Q2 -18	Q3 -18
B7/C 3	<u>Integrate PhPID</u>	Computing PhPIDs is fast, once all conditions are satisfied	EMA			Q3 18
B8	Textual information modules	The textual information is separated/ and/or merged depending on the potential user community (clinicians, pharmacists, regulatory authorities, pharmacovigilance etc.)	EMA	NCAs	Q2- 18	Q4 –18
B9	Integrate textual information	Link the textual background information at the appropriate level: PhPID, Substance, MPID, PCID: centrally	EMA & NCAs		Q3 -18	04 - 18
B10	Full validation of the test set	As soon as possible	EMA &NCAs			Q1 - 19
B11	Export of a validation set	Testing export process	NCAs	Drug DataBase Providers (DDPs)	Q1 - 19	Q2 - 19
B12	Export complete Member State data	Full export of the "scientific data" to be complemented with "national data" of participating countries	NCA/EMA	DDP		Q3 - 19
B13	IDMP drug database - 10 Member States	Some issues might still require a specific solution	NCAs	EMA & SDOs	Q3 - 19	Q2 -20
B14	First export set of data	Complete dataset available for at least 10 Member Sates	NCAs	Pilot teams	Q4 – 19	Q2 – 20

8.1.3 Roadmap for assigning and integrating the PhPID in the database

Table 6 Roadmap proposal for assigning and integrating the PhPID

C	Task and/or Task group	Task Description	Responsible	Involved	Start	Expected end
C1	Formal agreement	Agreement on algorithm , the process, informed consent, who does it?	EMA, FDA	National agencies		Q4 - 17
C2	Solutions for Pharmaceutical product special cases	<ul style="list-style-type: none"> • Moiety: same active substance, different weight • Slightly different strength • Different excipients • Multi-substance products 	OMC	SDOs, EMA	Q02 - 18	Q03 - 18
C3	Validation	Select a subset of pharmaceutical products for validation	EMA	EMC	Q2 - 18	04 - 20
C4	Assign PhPID	Initial validation of solutions	EMA, FDA	SDOs	Q2 - 18	Q1 - 19
C5	PhPID & Allergy	How to indicate that a PhP contains an allergen without translation: simply based on an attribute of the PhPID	OMC	EMA		Q2 - 18
C6	PhPID and intolerances	Tag a pharmaceutical product containing lactose or gluten (if any!)	OMC	EMA, SDOs		Q2 - 18
C7	Integrate PhPID	.. in the IDMP Database validation set	Nat. Agencies	EMA		Q3 - 18
C8	Validation	Validation1 Member State	NCA	EMA		Q3 - 19
C9	Operational	Operational in 10 Member States	NCAs	EMA		Q4 - 20

8.1.4 Distribution of IDMP data base contents

Table 7 Roadmap proposal for the distribution of IDMP data base contents

D	Task and/or Task group	Task Description	Responsible	Involved	Start	Expected end
D1	Distribution Scenarios	Define realistic distribution scenarios	OMC	EMA & + DDPs	Q4 - 17	Q1 - 18
D2	Define access facilities	Content definition and limitations: accessed by - the patient - the healthcare professional user - the medication database providers	EMA + DDPs		Q1 - 18	Q3 - 18
D3	National Data	National complementary information: what?	National Drug Agencies	National Ministries; social security agencies	Q2 - 18	Q3 - 18
D4	Data merging scenario	Integrate National Complementary Information into one set	EMA + DDP	Nat. Drug agencies	Q4 - 18	Q1 - 19
D5	Develop distribution interfaces	Implement D2 to manage accesses	EMA	NCAs/Nat. Drug Agencies, DDPs		Q2 - 19
D6	Validate Patient Interface		EMA	OMC/DDPs	Q3 20	Q4 20
D7	Validate distribution to DDPs		EMA	DDPs	Q2 19	Q4 19
D8	Validate distribution to HC Professionals		EHRsystm Providers	DDPs	Q1 20	Q3 - 20

8.1.5 Customisation of eHealth applications

Table 8 Roadmap proposal for the customisation of eHealth applications

E	Task and/or Task group	Task Description	Responsible	Involved	Start	Expected end
E1	Install distributed drug database / Update	<ul style="list-style-type: none"> - Install appropriate drug database - Update previous installed database 	Drug Database Providers (DDPs).	Clinical system providers, end users	Q3 - 18	Q4 - 18
E2	EMA viewer	Access EMA DB directly from the clinical application	EMA	Clinical system providers	Q3 - 18	Q4 - 18
E3	openMedicine ePrescription	Include PhPID in the prescription Include as many coded data as available in the DDB for core items	Pharmacy syst. &EHR system providers	DDPs	Q4 - 18	Q2 - 19
E4	OpenMedicine medication items	Add the PhPID to the identifying attributes of each medication item in the EHR: <ul style="list-style-type: none"> - <u>Medication scheme</u> - <u>Patient Summary</u> - <u>Medication History</u> Add the PhPID to the identifying attributes of each medication item in the Pharmacy Information System	Clinical Information System providers Pharma Information System providers	End users; Health authorities	03 - 19	03 - 20
E5	Validate standard-scenario openMedicine	<ul style="list-style-type: none"> • PhPID automatically added to ePrescription • Search for same PhPID in local database • List the products with the same PhPID and classified per kind of product: pharmaceutical, medicinal, package. 	Software providers (pharmacy, ePrescribing, EHR systems)	EMA	Q1 - 20	Q4 - 20
E6	Deal with special cases	Provide conceptual and software solutions for dealing with slightly different strength, similarproducts,...	SDOs	OMC, software providers	Q3 - 20	Q1 - 21

8.2 Risks involved in implementing the roadmap

The risks that may affect full implementation and roll-out of the openMedicine cross-border services are multiple and important. We identified three classes of risks: risks due to the political, organisational and ICT environment, risks due to the services as such, and risks due to the users.

8.2.1 Political and organisational context risks

At the political side, cross-border services are not what most politicians experience as an important problem to be solved with priority. The cross-border ePrescription is not the live saving application. Cross border services are not what voters are urging their governments to invest in.

Luckily investments to set up ePrescription services are happening at the national level anyhow due to the many benefits related to them, and appropriately structured and coded medication data are not only reusable for Patient Summary services, but facilitate language independent decision support too, as described in section 11.6 of this deliverable. But most importantly, all of this contributes substantially towards further improving patient safety as well as the efficiency of healthcare.

An important detail is that the efforts and resources required to upgrade an epSOS compatible ePrescription service into an openMedicine compatible service are minimal. Most of the efforts listed in the roadmap are NOT strictly linked to the openMedicine services but to efforts required to anyhow build an EMA IDMP compatible drug database, e.g. also for pharmacovigilance.

Countries with an ePrescription and/or Patient Summary service already running may be less enthusiast to modify their implementations, even if the efforts are limited or even with sufficient resources available. The more time it will take to have an openMedicine compatible service running, the more efforts it will take to convince them to adapt their solutions.

In summary, the roadmap implementation risks expected at the political and organisational level, including resources required, should be manageable in principle. Nevertheless, with given national priorities and bottlenecks at national competent authorities (as well as at the European level, particularly the impact of BREXIT on EMA), the concrete risks and barriers may be quite considerable in specific contexts, particularly at the national level.

A non-negligible aspect seems to be that due to the time pressure and limitations of CEF supported eHealth services (incl. ePrescription) as well as the priorities and constraints from the piloting participating countries concrete implementation of the roadmap may be impeded and constrained.

8.2.2 Prescribing and dispensing: a multi-dimensional challenge

Prescribing a medicine, initiating a medicinal treatment is more than selecting a medicinal product and producing an (electronic) document, an authorisation to dispense. A prescription must be fit for purpose considering the patient's health needs and clinical conditions. A prescription must comply to European and national limitations (indications, contraindications, dose forms, etc. of available products.). Though European market authorisation regulations and rules prevail in certain instances, national authorities remain in charge of health and healthcare.

Both, regulatory and care related aspects are, for some products, less stable than expected, even at the national level. New indications are added, while sometimes other indications are removed. The latter may be due to a low benefit/risk ratio or to relatively severe adverse events observed or suspected.

Of course non-clinical issues, cost containment issues, can result in limitations on prescribing a given medicinal product. New products, new substances are authorised and subsequently marketed for specified indications. The future marketing authorisation holder decides for what indication authorisation, and also reimbursement, is requested.

Dispensing a medicine is also more than delivering it to a patient. The pharmacist double checks most of the risks that might be related to the prescriptions like overdosing, interactions between medicines, allergies etc. In each instance, a pharmacist verifies, within the limits of the national regulations, if a prescription is fit for purpose. A limitation can be that from the more than 600 000 medicinal products available across the Union only a small percentage is usually available at a given location at a certain time, and the local national regulation for substitution in that Member State apply.

But in summary, no major risks are foreseen from these aspects because national drug systems anyhow will have to cope with them, and the IDMP solutions are expected to rather contribute to more efficient coping with these challenges.

8.2.3 User related risks

We distinguish the patient user and the professional user.

The portal service on the EMA drug database will become an interesting source of information. Acceptance by the patients will depend on the user friendliness and the readability of the information.

An issue that may be difficult to explain is that despite openMedicine services a medicinal product dispensed and reimbursed in his country is not necessarily available and not at all reimbursed at his holiday location.

The prescriber, at least for the default scenario, has to use an adapted EHR system. But because – with appropriate connectivity – this will not interfere with the functionalities he/she is used to, this should not constitute a significant barrier.

The pharmacist's problem to identify the appropriate medicinal product / medicinal product package to be dispensed when processing a cross-border prescription is solved when using an openMedicine compatible pharmacy information system, i.e. for pharmacists there are obvious benefits which should support acceptance and propensity to use the PhPID.

8.2.4 Service Development Risks

The main risks are related to the timeline and technical issues of development, the roll-out and the maintenance, and the timeliness of all these openMedicine developments.

The work to do and subsequently the issues that may have a risk for failure are listed per involved main partner:

- 1) E.M.A. Availability of IDMP compatible drug database
- 2) E.M.A. Database accessibility and export
- 3) SDO's Competing with each other instead of cooperating
- 4) Drug Database Distributing EMA data
 - a. Add National data
- 5) Nat. Drug authority Add national aspects
 - a. Are they all on the same track?
- 6) Ministries of Health Integrate Nat. Priorities
- 7) EHR systems To be adapted in time
- 8) Pharmacy Inf.Syst To be adapted in time
- 9) .

8.3 Timeline

It is always hazardous to predict when a project will "land". This is even more the case when the project has an international dimension and requires common or synergetic decisions by numerous decision makers.

As openMedicine is high on the agenda, some political decisions will surely have their impact, as e.g. Brexit on EMA moving.

This actual timeline is ***based on the options taken by the partners at the end of the openMedicine project***, options translated into a sequential and parallel track of these (sub-) roadmaps:

- A. Preliminary and ongoing semantic and related issues
- B. Building the IDMP compatible drug database
- C. Assign and integrate the PhPID in the database
- D. Distribution of IDMP data
- E. Adapt the e-Health applications to openMedicine services

A start date and "realisation" date is given for each track and "sub-track".

The unit of measuring the duration is "quarters of a year"

Track	Start	Realisation	
A). Preliminary	2017 Q2	2019 Q1	
B) IDMP Drug Database	2017 Q3	2019 Q1	
C) PhPID integration	2017 Q3	2021 Q1	Maintenance from 2019 Q3
D) Distribution	2017 Q3	2021 Q2	
E) Adapt software	2018 Q3	2020 Q4	

Details are provided in the tables to follow:

Table 9 Gantt chart for Track 1: Roadmap proposal for content related preliminary tasks – Semantic issues

		17 Q2	Q3	Q4	18 Q1	Q2	Q3	Q4	19 Q1	Q2	Q3
A1	Availability comprehensive data										
A2	Identifying Attributes										
A3	Scientific Composition										
A4	SPOR										
A5	G-SRS										
A6	Substances for prescriptions and for clinical use...										
A7	UCUM										
A8	Dosage Forms										
A9	Route of Administration										
A10	Allergens										
A11	Colorants...										
A12	Containers										
		17 Q2	Q3	Q4	18 Q1	Q2	Q3	Q4	19 Q1	Q2	Q3

Table 10 Gantt chart for Track 2: Roadmap proposal for building their European IDMP data-base

Table 11 Gantt chart for Track 3: Roadmap proposal for assigning and integrating the PhPID

Table 12 Gantt chart for Track 4: Roadmap proposal for the distribution of IDMP data base contents

Table 13 Gantt chart for Track 5: Roadmap proposal for the customisation of eHealth applications

		18 Q3	Q4	19 Q1	Q2	Q3	Q4	20 Q1	Q2	Q3	Q4	21 Q1	Q2
E1	Install drugdatabase as delivered												
E2	EMA viewer												
E3	ePrescription with PhPID												
E4	Medication items with PhPID in Pat Summary												
E5	Validate standard scenario												
E6	Validate special cases												

This time oriented overview of the tasks enables planning and follow-up of the implementation.

As a further tool to illustrate the roadmap timeline and the role of various organisations, the following

Table 14 Chronological overview underlines the importance and the impact of any delay at EMA.

Some explanations linked to this table:

1. The chronological overview has 5 tracks and 75 task lines.
2. Each task has a responsible party and some supporting partners (generic level. As most tasks are to building, maintaining and interacting with a drug database, most tasks are under responsibility of EMA).
3. Each task has a start and/or end date. Two columns are used for that:
 - * in the left column = started in the indicated quarter
 - * in the right column = ended in the indicated quarter
 - * in both column; task started and ended within the same quarter
4. Involved parties are identified by an abbreviation
 - EMA European Medicines Agency
 - NDA National Drug Agency
 - DDP Drug Database Provider
 - OMC OpenMedicine Consortium
 - FDA Food and Drug Administration (US)
 - SDO Standards Development Organisation

Table 14 Chronological overview

Nr	Year	Q	Code	Task Description	Re-sponsible				
1	2017	2	A1	Availability of comprehensive "raw" source data: investigate	EMA	NDA	*	*	
2	2017	2	A2	Availability of identifying attributes: investigation	EMA		*		
3	2017	2	A4a	SPOR project on "Products"	EMA, SDO	NCA	*		
4	2017	2	A4b	SPOR project on "Referentials"	EMA	SDO	*		
5	2017	2	A4c	SPOR project on "Substances"	EMA		*		
6	2017	2	A7	UCUM updating	Regen-strief		*		
7	2017	2	A8	Dosage Forms updating	EDQM		*		
8	2017	2	A9	Route of administration: updating	EDQM		*		
9	2017	3	A2	Identifying attributes: results	EMA			*	
10	2017	3	A3	Making scientific composition ready for use translation included	EMA			*	
11	2017	3	A7	UCUM updated	Regen-strief			*	
12	2017	3	A8	Dosage Forms updated	EDQM			*	
13	2017	3	A9	Route of administration updated	EDQM			*	
14	2017	3	A5	EMA – GSRS start	EMA	FDA	*		
15	2017	3	B1	Universal Data Model	CEN	OMC EMA	*		
16	2017	3	B2	Agree on migration towards IDMP Drug Database	EMA	NDA	*		
17	2017	3	B3	Sample data migration	EMA	NDA	*		
18	2017	3	C1	Agree rules and maintenance of PhPID	EMA	FDA	*		
19	2017	4	A4	SPOR completed	EMA			*	
20	2017	4	A6	Substances subsets for prescriptions and clinical use	EMA	FDA	*		
21	2017	4	B1	Universal Data Model: report	CEN	OMC EMA		*	
22	2017	4	B2	Migration Strategy	EMA	DDP NDA		*	
23	2017	4	B3	Sample data migrated				*	
24	2017	4	B4	Migration of first data set	EMA	EMA	*		

25	2017	4	C1	Agreement on PhPID assignment and maintenance	EMA NDA	FDA				
26	2017	4	C3	Select representative set of pharmaceutical products	EMA	DDP				
27	2017	4	D1	Distribution scenarios	EMA	DDP	*			
<hr/>										
28	2018	1	B5	Validation first set migrated data	EMA		*			
29	2018	1	B6	Migration structured data completed first set	EMA		*			
30	2018	1	B7	Integrate PhPID	EMA		*			
31	2018	1	B8	Organise and structure text modules	EMA		*			
32	2018	1	C4	Effectively assign the PhPID	EMA	FDA				
33	2018	1	D1	Distribution scenarios completed	EMA		*			
34	2018	1	D2b	Data access by HC Professionals	EMA	OMC	*	*		
35	2018	2	A3	Making scientific composition ready for use translation included	EMA	NDA		*		
36	2018	2	A11	Colorants	EMA	FDA	*	*		
37	2018	2	A12	Containers	EDQM		*	*		
38	2018	2	B4	Migration first dataset	EMA			*		
39	2018	2	B5	Validation of the first dataset	EMA			*		
40	2018	2	B6	First dataset complete	EMA			*		
41	2018	2	B9	Integrate and link text modules	EMA			*		
42	2018	2	C2	Special products				*		
43	2018	2	C4	Assign PhPID to all products	EMA FDA	DDP	*			
44	2018	2	C5	PhPID for allergens containing products	EMA	FDA	*	*		
45	2018	2	C6	PhPID for products with risk for intolerance	EMA	FDA	*	*		
46	2018	2	D3	National information for distribution	NDA	DDP	*			
47	2018	3	B7	Integration PhPID complete for dataset						
48	2018	3	B8	Structuring dataset completed	EMA					
49	2018	3	C2	Special products completed	EMA			*		
50	2018	3	D3	National information for distribution	NDA	DDP			*	
51	2018	3	D7	Interface Dataprovider validation	EMA	DDP	*			
52	2018	3	E1	Install drug database as delivered	EHR			*		
53	2018	3	E2	Viewer on EMA Drug Database	EMA			*		
54	2018	3	B9	Text modules integrated	EMA			*		
55	2018	4	A11	Colorants	EMA	SDO				
56	2018	4	C7	Integrate the PhPID identified pharmaceutical products PLUS the updates	EDP					
57	2018	4	D4	Merge national and generic information	DDP	EMA				

58	2019	1	A10	Allergens (medicinal)	EMA	SDO	*			
59	2019	1	B10	Full validation test set available	EMA		*			
60	2019	1	C4	Assign PhPID identifiers to pharmaceutical products	EMA	NDA				
61	2019	1	D2a	Data access by patients: definition rights and scenarios.	EMA	NDA	*			
62	2019	1	D2c	Data access by data providers	EMA	DDP	*	*		
63	2019	1	D4	Cross border international information to be merged with national information	EMA	DDP		*		
64	2019	2	D7	Interface Database provider and/or distributor	EMA	DDP		*		
65	2019	2	D5	Develop the interfaces for distribution on the central database	EMA		*	*		
66	2019	3	D2a	Define access by patients	EMA	NDA		*		
67	2019	3	D8	Validation Healthcare Professional Interface to the database	EMA	SEV				
68	2019	4	D9	First Member State complete and distributed database			*	*		
69	2019	4	E5	Validate standard scenario	EMA					
<hr/>										
70	2020	1	D6	Validation Patient Interface on drug database	EMA	DDP	*			
71	2020	1	E4	PhPID in Patient Summary	EMA					
72	2020	2	E6	The use of PhPID in special cases	EMA	HER				
73	2020	4	D6	Validation Patient Interface on drug database	EMA	DDP		*		
74	2020	4	E5	Validate standard scenario final	EMA			*		
<hr/>										
75	2021	2	D10	10 Member States operational			*	*		

9. Conclusions

This deliverable enabled us to formulate some recommendations and suggestions to facilitate ePrescription, electronic reporting of dispensing a prescribed medicine and issuing a Patient Summary.

The option to include in the prescription, the patient summary and the dispensing message an additional identifier, the pharmaceutical product identifier (PhPID, solves nearly all the cross-border issues.

This roadmap illustrates the feasibility of the openMedicine option, supported by the European Medicines Agency (EMA) to assign that identifier by using the identifying attributes of a pharmaceutical product as available or to be available in the future comprehensive IDMP compatible drug database.

The IDMP compatible database unfortunately does not exist yet. This means that such a standard compatible drug database needs to be built with at least the full composition of the product, the strength and the dosage form. Track one and two illustrate that this may take in a rather optimistic approach 18 months to get a centrally available IDMP compatible drug database. **18 months from start** to complete the IDMP EMA semantic issues.

Considering that further delay may be expected, e.g. due to the Brexit and resulting relocation of EMA, and considering that, on the other hand, some action points can be implemented in parallel and without interfering with other running developments we suggest a pragmatic plan of implementation: Start and run in parallel simultaneous tracks

This will ideally result in the availability for validation of the services within three to four months after the first release of the PhPID codes. Operational services may then be expected within 6 months after assigning the PhPID codes.

The implementation plan as documented in this deliverable is a chronological step by step approach, creating the context and investing in content first. Once content and context are available, next steps are planned: distribution and finally integration into the dispensing and clinical care applications.

10. APPENDICES

To provide for additional material supporting and explaining the openMedicine approach, recommendations and roadmap, we add here further information and material on these aspects:

- Overview of core EXPAND project conclusions when evaluating remaining epSOS issues (covering both Change Proposals approved by EXPAND and still remaining epSOS challenges).
- Comments received from stakeholders involved in openMedicine
- Strategic Questions received from the eHealthNetwork/JAseHN experts and suggestions provided by openMedicine

10.1 EXPAND evaluates epSOS issues

10.1.1 epSOS Issues

epSOS identified a number of issues to be addressed in order to be able to offer even more reliable, efficient and smooth cross-border ePrescribing and dispensing services than were feasible within the epSOS framework. *Inter alia*, the EXPAND project developed and expanded upon these issues by looking into the “Scope and transferability of key outcomes of epSOS and corresponding actions for transferability and scale up.” For openMedicine challenges, particularly these aspects were of importance:

It is important to know that coded information on the composition (“scientific composition”) of a medicinal product played a crucial role in the epSOS process of identification and retrieval of a medicine in another language or jurisdiction. Even more so, 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 was based on these descriptive attributes, the reliable transfer of the prescribing information to country B nearly fully depended on the respective translation services.

By introducing a coded, jurisdiction-independent identifier openMedicine offers a parallel “high speed” identification option through the Pharmaceutical Product Identifier (PhPID).

The epSOS traditional approach remains useful for some cases where there is no PhPID available, and/or for validation purposes.

10.1.2 Change Proposals approved in EXPAND

During the epSOS pilots the identification of medicinal products in ePrescription/eDispensation documents and Patient Summaries were identified by describing their attributes.

The EXPAND project¹² has taken on most of the open issue previously described, and a change proposal process has been started for some of them after 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 ingredient information (including also the description of multi-active ingredient products)
2. Support for unknown or textual strength information
3. Support for UCUM annotations
4. Dose form information
5. Route of administration information

These proposals can be summarized as follows:

Support for unknown or textual active ingredients [Multi-active ingredient products]	<p>Allow the usage of NullFlavors¹³ for the ingredient/code.</p> <p>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 EMA/Pharmacovigilance ART 57 DB) without losing the capability of conveying the Pharmaceutical Substance ATC code as well.</p> <p>Specified how to convey textual ingredients information.</p>
Support for unknown or textual strengths [Multi-active ingredients products]	<p>Allow the usage of NullFlavors for the ingredient/quantity</p> <p>Specified how to convey structured textual strengths data</p> <p>Identified an optional element for conveying the strength as string (e.g. "600 / 12,5 mg").</p>
Support for UCUM annotations	<p>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.</p> <p>Possible future enhancements:</p> <ul style="list-style-type: none"> • Define specific value set for validating the annotations used (unit of presentation). • Split the unit of measure value set in three separate value sets: <ul style="list-style-type: none"> - a general purpose units value set - a unit value set for strength numerator - a unit value set for strength denominator <p>The first could be the value set currently used.</p> <p>The last ones could be aligned with the value sets used by EMA in its Art 57 DB.</p>
Dose form and route of administration	The EDQM based Value Sets have been aligned in the master value catalogue (MVC) 2.0 to the one used by EMA in Art. 57 database

¹² See <http://www.expandproject.eu>

¹³ The purpose of NullFlavour is to indicate the reason why a given data element has a NULL value.

10.1.3 Remaining epSOS open issues (EXPAND)

The following table provides a synthetic list of the still pending issues encountered during the epSOS pilots, with the indication whether 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.
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 countries of prescription. In the medium term it should be the XEVMPD substance vocabulary, or later the one adopted by ISO IDMP / EMA.
3.4.8	Distinct Value Sets for ingredients		
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 be 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 be considered for prescription	openMedicine	To be analysed
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

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

10.3 Comments received from stakeholders involved in openMedicine

The recommendations presented earlier were submitted for validation to

- The Members of the Expert Council
- The attendees of the Expert Council Meeting in London, Nov. 2016
- The national health authorities of Poland during a Regional Information Session
- The Swedish health authorities with delegates from Norway, Estonia and Finland during a regional workshop

In the following table, we reproduce major written comments received from selected experts after expert council or other meetings. The table identifies the expert, his/her remarks, as well as the openMedicine answer/comment to it.

Expert		Remark	Comment/Reply
1	Jaimie Wilkinson, PGEU	<p>The questionnaire on substitution provided complex and heterogeneous 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 recommendation. The complexity of the results reflect the situation in practice regarding the practice of substitution</p>	Indeed. Chaotic not only between the member states but also within some member states. This challenge is in need of further analysis.
2	Jaimie Wilkinson, PGEU	<p>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.</p> <ul style="list-style-type: none"> • As such, this recommendation violates the principle of subsidiarity, 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 	<p>Nowhere did we state differently</p> <p>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.</p> <p>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.</p> <p>If the EU wants to improve cross-border health services, member states may want to harmonise their rules.</p>
3	Jaimie Wilkinson, PGEU	...that any recommendations should not suggest any form of harmonisation of substitution, for the above reasons, and that if recommendations (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 a European top-down rule should be issued.
4	Harri Nurmi, THE Finland	But I would have also requested recommendation 9 (on substitution) to be removed.	See previous answers

5	Michèle Thonnet France	<p>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.</p>	<p>Agreed, but Guidelines are a duty of the eHealth Network. It is most probably a condition to be successful and accepted by the prescribers.</p>
6	Michèle Thonnet France	<p>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</p>	<p>Indeed. The ideal complete roadmap will take more time than available in the CEF initiative</p>
7	Jeremy Thorp, UK	<p>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.....</p>	Ok
8	Jeremy Thorp, UK	<p>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</p>	<p>It has meanwhile been addressed in the Roadmap</p>
9	Christopher Jarvis EDQM	<p>Pharmaceutical Product ID: 2nd recommendation.</p> <p>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 PhPIIDs, 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.</p>	<p>Indeed, the actual formulation in IDMP seems erroneous and should be reviewed.</p> <p>Considering the lifecycle for which we are defining an identifier we should use manufactured OR pharmaceutical dosage form during the complete lifecycle until the administration (clinical identification) of the medicinal product:</p> <ul style="list-style-type: none"> • Authorisation • Manufacturing • Distribution / Logistic • Prescription <p>Change of dosage form happens at effective administration to the patient. This administrable dosage form includes the form only after preparing the medicine for administration.</p>

10	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/distributors. The openMedicine project information is fully available on the projects web site.
11	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	We reviewed the recommendations. 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 deliverables of the work packages (1 to 5), in the online openMedicine dictionary and through the SKMT application, as documented earlier here.
12	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 is addressed in the roadmap part of this deliverable. It seems more to be a step-after-step approach as none of the concepts should be left out the process.

13	PGEU	<p>1st December, 2016</p> <p><u>Ref: openMedicine Recommendation on the Substitution of Medicinal Products in the EU</u></p> <p>Dear Dr Auer,</p> <p>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.</p> <p>We would like to share our concerns regarding the twelfth recommendation which suggests that <i>“National rules on substitution of medicinal products at the point of dispensing, when specified in a cross-border prescription, should be harmonised”</i>.</p> <p>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.</p> <p>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.</p> <p>We ask for your support to delete this recommendation for the following reasons related to national practices of substitution across Europe:</p> <ul style="list-style-type: none"> • 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; <ul style="list-style-type: none"> ◦ 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. <p> PGEU GPUE Pharmaceutical Group of European Union Groupement Pharmaceutique de l'Union</p> <p>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.</p> <p>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.</p> <p>I remain at your disposal for any further clarifications or questions you may have.</p> <p>Yours sincerely,</p> <p></p> <p>Jurate Švarcaitė, PGEU Secretary General</p>
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13	PGEU	<p>This letter was not addressed to openMedicine, but to the eHealth Network's chairperson.</p> <p>OpenMedicine commented on this as follows:</p> <p>"Dear Dr. Auer, openMedicine recommendation on the substitution of medicinal products in the EU Letter of PGEU to you of Dec. 01, 2016 We received on December 2nd, 2016, a copy of the above letter addressed to you as chair of the eHealth Network. Undertaking an analysis of substitution challenges across member states and suggesting possible actions to harmonise across the EU were stipulations of the H2020 call text for this project as well as a part of the openMedicine contract with the EC. This is aligned with the EU policy aim to strengthen the impact and safety of cross-border eHealth services. Guiding principle is to optimise such services for patients, including ePrescriptions and their dispensation abroad. Due to different marketing authorisation procedures for medicinal products, different marketing strategies of pharmaceutical companies, shortages and other factors, successfully dispensing a foreign ePrescription regularly requires substitution. Open, inclusive debate of the openMedicine results with both member state representatives and a wider audience was undertaken; this included extensive exchanges with PGEU. PGEU was also a member of the Expert Council of the openMedicine project. The brief of this council was to be "advisers to the consortium", but "it will not have any decision power." Recommendations come under the sole responsibility of the openMedicine team. We strongly support and enjoy open, constructive discussions and exchanges on issues of concern to European citizens. At the same time, we emphatically reject any attempt to interfere with the intellectual independence and freedom of research of a support action. We were happy to discuss in detail the concerns of PGEU, but we cannot accept censorship by a lobbying group requesting to "delete" something from a report. If deemed beneficial, we will be readily available for further discussions."</p>
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11. Strategic Questions from the eHealthNetwork / JASeHN experts and suggestions provided by openMedicine

Jeremy Thorpe, as main writer and editor of the revised eHealth Network Guidelines for ePrescription and electronic Patient Summaries, circulated a number of remarks and questions about the openMedicine project, also linked to issues discussed in the context of the openMedicine US-EU expert workshop at FDA premises in Washington, June 20-21, 2016.

This appendix reports on the issues raised, the comments and reactions of the openMedicine project team, and intends to provide some answers to the questions and to identify topics to be addressed in the Roadmap.

As the project is related to the issue of the identification of medicinal products, answers will avoid addressing overall medication use or treatment issues.

11.1 First set of questions and remarks

Question:

"How to create a sustainable environment to enable cross-border exchange of data between 28 (+2) countries each at different stages of maturity, each with their own jurisdictional authority

- *But: not require any change within any MS*
- *"not binding" but ... can be used for MS on a voluntary basis*
- *now they are for cross-border and condition of CEF for each MS*
 - o *21 countries submitted bids*
- *[US] ONC / MU / Standards Advisory"*

Answer:

The remark (sustainable, no change, on voluntary basis) pictures the ideal and final goal of standardisation of data sharing regarding medicinal products and their use across borders.

Sustainability to enable cross-border exchange will depend first of all on whether there is a business case (demand) for such services, and on the complexity of the processes to be performed on the exchanged information related to medication and medicinal products. Efforts need to be done on both sides, issuer and receiver. Choosing globally or at least on transatlantic basis one consistent set of ISO standards reduces, if used maximally, conversion costs and favours sustainability. It's obvious the more structured and coded medication data are, the less costly e.g. translation services will be.

Sustainability does not mean "for free". Including existing older or even orphan products, poorly identified internationally will be an important initial cost. Identification of new products is part of registration and/or market authorisation process and may require fewer resources than expected.

Not requiring any change within any MS is not realistic, more precisely the "not any" statement. Changes are minimal considering that openMedicine and IDMP do not interfere in national or supra-national competences like national marketing authorisation, way of prescribing (per unit of product, per package, on INN or on substance name, or on brand name, or

taking into account billing and social security co-payment rules). The main change is at the level of the drug databases including for each product several identifiers facilitating the identification of a product. These changes are minimal, but mandatory, and transparent to the prescribing end user.

Used on voluntary basis. The medicinal product production, distribution, usage and reporting is yet a very strictly regulated European environment with similar approaches across the Atlantic and indeed some national flavours. Concerning registration/market authorisation and pharmacovigilance, EMA, FDA and national authorities can regulate the mandatory use of standards.

The future PhPID to be introduced by them uniquely identifies regulated medicinal products at European level, including such that the respective identifier can be implemented easily in the prescription, dispensing, EHR data and the patient summaries provided they are included in the public or private medicinal products databases and accessible at the point of care.

Standards are the condition sine qua non to realise cross border identification and a range of value added services. The standards should address the identification as such as well as the identifying attributes that may, combined, identify a medicinal product. The IDMP suite of standards fits for purpose. Using other standards will require conversion / mapping services.

Question:

"What are they for?

- Scope: unscheduled care, e-prescription
- Purpose: improve quality and safety of care"

Answer:

We are distinguishing, classifying data exchange/ the different types of datasets exchanged based on

- The addressee : addressed / not addressed
- The role of the message regarding care services :
 - o Order / prescription request / authorisation to provide some services / products
 - Issued by the prescriber
 - Depending on the kind of service and regulation: addressed or not
 - Example: ePrescription (epSOS)
 - o Report
 - report about care services provided
 - Issued by the performer of the care service
 - In principle addressed to the person ordering the service
 - Example: Imaging report, lab report
 - o Request
 - report asked for a person different to the orderer
 - Issued by the performer
 - In principle addressed to the requester
 - o Attestation
 - attestation about the patient
 - Issued by the actual care provider
 - Addressed / not addressed / depending on the context

- File / Datafile composition of patient care related data to be shared
Issued by the usual / involved care provider
Not addressed
Some examples: Patient Summary, SumEHR (Be), Patient Migration File (Be)

Question:

Purpose of the ePrescription services

Answer:

The purposes and advantages of ePrescription services has been documented extensively by the epSOS project. Basically, they all concern patient safety/improved care services and more efficient processes. Hereby a short enumeration of purposes and advantages:

- Improved formal quality the medicinal products prescriptions, e.g. by reducing reading errors of hand written prescriptions
- Improved quality of the content of a medicinal product prescription by assisted selection and improved surveillance on allergies, intolerance and contra-indications as well as dose control
- Improved efficiency and accuracy of dispensing prescribed medicinal products

The epSOS project added a cross-border dimension, **facilitating** the retrieval of the equivalent local medicinal product that fits (best) with a foreign prescription.

openMedicine complements the epSOS project by solving the problem of the secure identification and dispensing of an equivalent product to the originally prescribed medicinal product. It has been proven that the same "medicinal product level identification, e.g. the medicinal product- name" can/is used for completely different medicinal product across the European Union.

Question:

Purpose of the Patient Summary services

Answer:

Patient Summary services intend to facilitate "informed care". Informed care means that an appropriate composition of patient data are made available to/ are shared with the authorised healthcare professional.

The content of the composition depends on its intended use or use scenario:

- The Patient Summary for unexpected care as defined in epSOS: summary at patient level, including a record of active medications.
- The cooperative patient summary used by the care professionals of different collaborating practices: extended patient summary with data on active medications

The Patient Summaries are extracts to "inform" the actual healthcare professional.

A different type of centralised patient data is the "pathology oriented dossiers" to document specific care related to a chronic condition, a rare disease.

11.3 Questions about the relevance and impact of openMedicine results

Question:

What value does openMedicine contribute?

- What will openMedicine recommend?
- Will there be the need for EC documents (e.g. implementing directives)

Answer:

The overall value of openMedicine is to undertake a very thorough analysis of all issues around the univocal identification of medicinal and pharmaceutical products such as to improve patient safety and effectiveness of cross-border healthcare in this domain. This is of added value for patients/citizens, healthcare professionals, and European health systems. Based on these insights, openMedicine provides solution proposals and recommendations for further activities, including a roadmap and timeline for this.

1. *What will openMedicine recommend?*

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 or not at all in a cross border implementation, despite a complex supranational 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 an identified 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 to be dispensed to a patient presenting the ePrescription implies at the same time the need to identify 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 an element or a unit of an universal pharmaceutical product (identified by its PhPID) marketed in a given jurisdiction under a given brand name
- The latter being composed of a specified quantity of active substance(s) (Substance ID), presented in and intended to be administered in a specified dosage form by using a given route of administration to the patient.

As regards recommendations, we suggest as follows:

Considering the medicinal product package at dispensing level as the most frequently used label for a medicinal product, considering that prescriptions may have a different level of identification embedded, considering that we are addressing the electronic prescription and that "adding" complementary identifiers to such a prescription or to a patient summary doesn't require any extra effort by the healthcare professional who uses an openMedicine compatible drug database, openMedicine presents as its **first recommendation:**

A medication item in an electronic prescription, in a dispensing record or in a patient summary should be identified by one or more of the following identifiers as defined by the IDMP standard: the medicinal product package (PCID), the medicinal product (MPID), the pharmaceutical product(PhPID) and or the substance (SubstanceID).

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, we present as **second recommendation**

Identifying and documenting medicines and medicinal treatments should follow a globally standardised structure and refer ad maximum to terminology standards.

Terminology standards listed are for example pharmaceutical forms, substances, inner and outer container, route of administration, etc...

Considering the lifecycle of medicines and medication related information as one continuum from innovation to regulatory phase to production and to marketing, from prescription to dispensing and administering into outcome analysis and monitoring (pharmacovigilance), considering that using different standards for each or several of these stages hampers reuse and sharing of medicinal treatment related data, we present a **third recommendation**

The same standards should be used consistently throughout the complete lifecycle of a medicine.

Considering that the use of the ISO IDMP suite of standards has been made mandatory by EMA and by the FDA in all regulatory documentation and considering that no major problems has been identified during the openMedicine in clinical care, pharma-co-epidemiology, we present a **fourth recommendation**

The use ISO IDMP standards should be mandatory throughout the complete lifecycle of a medicine.

This requires assigning a global unique PhPID to each pharmaceutical product.

Further work should be done to identify in a cross-border context pharmaceutical or medicinal products containing components that may cause allergic reactions or intolerances.

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

Drug databases as well as clinical applications should meet a set of quality criteria addressing structuring coding, compliance of content to EMA or national specifications, completeness and persistence of information regarding meanwhile withdrawn medicines. Completeness encompasses every product that can be prescribed e.g. diagnostic, therapeutic devices, phytotherapy or other not-to-be authorised products.

Considering the importance of the availability of the authorised source data and the huge effort required to realise this fully structured as much as possible language independent database we present a **sixth recommendation**

Sufficient resources should be allocated to make in time available and to maintain the IDMP compatible European Drug Database.

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Considering that cross-border dispensing of prescribed medicinal products may, most frequently results in substituting a prescribed medicinal product with product available at dispensing site, considering that substitution rules are different per Member State and not always implemented consistently we present a **seventh recommendation**

Regulation on substitution should be harmonised or a distinct regulation may be considered for cross-border dispensing of authorised medicinal products

Will there be a need for EC documents?

Some of these recommendations should eventually, once details have been agreed upon and codified, result into new or adapted guidelines

11.4 Questions related to operational aspects

Question:

- Assuming we are recommending IDMP, then what are the timescales – roadmap to full implementation
- Who will generate phpids, when, how quickly
- What will be the maintenance and distribution process; are there slas?
- What criteria will be applied for database to be accepted?
- What must MS do? to what extent must they change ? (e.g. will dm+d co-exist ...?)
- What actions are in the responsibility of national regulatory agencies?
- Are there staging posts – what about short / medium / long term?

NOTE

The questions and the answers are reported as provided "in illo tempore" Some time related issues are outdated. We did keep the original answers.

Answers:**1. Assuming we are recommending IDMP, then what are the timescales – roadmap to full implementation?**

"IDMP" has been adopted by EMA and the FDA as the standard to be implemented and used in future for identification and description of authorised medicinal and/or pharmaceutical products. It has also been imposed for the documentation to be produced as part of the authorisation procedure. The national drug agencies are yet familiar to this aspect.

"IDMP" defined a data model that is used to structure the future IDMP compatible EMA drug (pharmacovigilance) database, structuring, coding and converting from the Article 57 database. The IDMP identification standard has yet been, based on the openMedicine project, WP2.3

"IDMP" consists of a suite of standards for the values of essential identifying attributes.

Timescale [I]llo tempore]

- | | |
|------------|---|
| ○ End 2016 | Article 57 (2) data base completed (ready for validated) |
| ○ Mid 2017 | Start conversion into IDMP compatible |
| ○ Mid 2017 | Converting core textual expressions into structured and coded modules |
| | Agreement on algorithm and assigning the PhPID codes |
| ○ Q4 2017 | Distribution and update management of validation of contents |
| ○ Mid 2018 | Complete IDMP and structured / coded EMA drug database |

2. Who will generate phpids, when, how quickly

The actual option seems to be that only the FDA and EMA will assign PhPID codes to authorised medicinal products.

The algorithm is yet to be defined and is to ensure that it generates for identical products the same codes in Europe as in the US.

Timescale

- | | |
|-----------|---|
| ○ Q4 2016 | final agreement on the algorithm |
| ○ Q4 2017 | IDMP compatible database for validation |
| ○ Q2 2018 | complete IDMP compatible database |

3. What will be the maintenance and distribution process; are there slas ?

We distinguish the maintenance of the content and the maintenance of the related services.

Content maintenance is part of the authorisation procedure, at least regarding assigning a PhPID to a new pharmaceutical product. Products that aren't any more on the market should remain accessible for clinical purposes, even if the product as such can no longer be prescribed.

Service maintenance addresses issues as data entry interface, viewers and more especially web accessing by healthcare professionals and by patients. Special attention should be given to the export to national and to private distributors and integrators of the medicinal product data.

4. What criteria will be applied for database to be accepted ?

The criteria for drug databases to be "accepted" depends, up to certain level, on their intended use and/or users: regulatory authorities, marketing authorisation, clinical care, pharmacovigilance, dispensing etc..

The openMedicine identification approach encompassing the substance identification, the pharmaceutical product identification, the medicinal product identification and the package identification (if used). All should be included in the database and available at the point of prescription, dispensing and administration.

The drug database should be fully structured and coded, where available by using international standards or at least by mapping national, regional or local codes to these international standards

The drug database should be complete for its intended use, i.e. covering all relevant medicinal products. Drug databases intended to support the prescription procedure should contain regulated as well as non-regulated products which nevertheless may be prescribed.

The drug related information (indications, contra-indications, known side-effects and adverse drug reactions, advised dosage and duration...) should be content-wise compatible with the EMA authentic source information. Deviations, approved by the National Regulatory Authority and/or the national health authorities should be reported to the "authentic source". The 'information' can be formatted in a proprietary way for, e.g., eventually offering additional services.

Billing and social reimbursement or co-payment issues are part of the "national" additions essential to guarantee real life use if each drug database.

5. What must MS do? to what extent must they change ? (e.g. will dm+d co-exist ... ?)

Authorising, prescribing and dispensing, marketing and documenting, administering and outcome reporting activities as well billing and co-payment are highly regulated across the Union. Authorisation is in principle at European level (EMA), but still possible (and widely used) at national level. Billing and conditions / ways of co-payment are national competences.

The way prescriptions are formatted, their mandatory content and the way they are processed slightly differ from country, and are frequently related to limitations due sometimes to the paper era.

Including or linking to multiple coded and language independent identifiers or attributes are not at all a problem for the electronic prescription contrary to its paper based sister. Neither should it be a problem to include several identifiers into a medication section of a patient summary.

The Member States should enable these services, primarily for internal purposes,

- by making the paperless electronic prescription at least as valid as the paper version
- by stimulating the eDispense report, thus offering an essential service and added value to the prescriber by updating what has effectively been dispensed
- by supporting Patient Summary services

The Member States should quality asses

- the nationally available drug databases on their completeness and compliance to the information provided by the EMA drug database and their conformity to the IDMP suite of standards, included multiple coding if necessary and available. An IDMP or EMA compatible drug database identifies pharmaceutical products and enables the registration of all four ID's: the substance ID, the PhPID, the MPID and the PCID.
An IDMP or EMA compatible drug database uses the openMedicine values for the identifying attributes of a medicine.
- the Electronic Healthcare Record systems on their capacity to produce a structured and coded prescription, their capacity to integrate eDispensing information and to produce patient summaries. The EHR systems should also be able to produce a prescription intended to be dispensed abroad, including the PhPID.

6. *What actions are the responsibilities of national regulatory agencies?*

The national regulatory authorities are still involved in the authorisation process for those medicinal products for which no European authorisation is required.

The national regulatory agencies are still responsible for the national marketing authorisations and in informing EMA on possible events as e.g. falsified medicinal products.

The national regulatory authorities might be involved in the definition of quality criteria.

7. *Are there staging posts – what about short / medium / long term ?*

Cf. time scale reported earlier

11.5 Final set of questions related cost/benefit issues

Questions:

- *What risks?*
- *What costs?*
- *What benefits?*
- *Communication and engagement – vendors, competence centres, regulators, professional groups*

Answers:

8. *What risks?*

The actual Article 57 (2) EMA Drug Database is based on the mandatory set of information to be provided as part of the authorisation dossier. The database is nearly complete – covering more than 95% of medicinal products offered in any or all member states - and composed by a standard set of mainly text 'modules'. The drug information provided by the industry in their authorisation dossiers needs a quality check, not all the modules being of the same quality.

A process of conversion towards a structured IDMP compatible drug database has been started.

The information needs to be completed by the IDMP/openMedicine identifiers and the coded identifying attributes.

This is a huge enterprise. EMA expects the IDMP compatible and structured drug database to be available per 2018. Delays in assigning PhPID and other identifiers endanger the target date.

9. *What costs?*

We should distinguish the initial cost of setting up the services (data entry, quality assessment, distribution to national level drug databases), feeding the IDMP drug database and setting up the maintenance and dissemination tools on one hand, maintaining content and those tools on the other hand.

The initial cost is estimated at 8 person-years, 2 person-years to develop the tools and to complete the initial Article 57 database, 6 person-years to transform the database into a fully structured and coded database.

The maintenance cost is estimated at 3 FTE for maintenance of content centrally as well as for the services.

10. *What benefits?*

As usual in health informatics, costs are charged to one or more player (like national competent authority), benefits are for others stakeholders. As outlined earlier, huge benefits will come about for patient safety, pharmacovigilance, but also for healthcare professionals and health systems due to higher safety standards, easier handling, and more effective processes.

¹ The route of administration is frequently not mentioned as building block for a pharmaceutical product. The route is then considered as an "annex" to the dosage form. This seems to be a heritage from the pharmacovigilance origin of the art 57 database? Indeed the route of administration is exceptionally determining the adverse effect.