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Research Article

The univocal identification and safe dispensation of medicinal products across Europe – challenges and solution proposal

Die eineindeutige Identifizierung und sichere Abgabe von Arzneimitteln in Europa – Herausforderungen und Lösungsansatz

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Abstract

Problem: The Smart Open Services for European Patients (epSOS) piloted the exchange of electronic Patient Summaries and ePrescriptions between selected member states of the European Union (EU). This project basically solved the 'communication' or message transfer problem. However, it encountered a serious 'delivery' problem: the safe dispensation of a medicinal product noted in a prescription from a given country by a retail pharmacist in another country. The reason for this was that the specified medicine could in many instances not univocally be identified – the same name may identify a product with a different active ingredient, or the product with identical composition may carry a different name in the other country. If the prescribed medicine had not been authorised for marketing in the other country, information on its attributes may not be available. This rendered dispensation by the pharmacist impossible, even where substitution would, in principle, be allowed and possible.

Objectives: This paper reports on the goal, activities and achievements of the openMedicine project towards development of a digital solution and its implementation to meet this identification and the resulting delivery challenge. European-wide and cross-Atlantic endeavours to enhance pharmacovigilance by being able to match adverse event reports filed under different drug names which provide, however, for the same active ingredient(s) were developed upon. And the need for and benefits of being able to trace for clinical purposes, e.g. the longer-term treatment with the same active ingredient, even when the name of the prescribed medicine changed several times, were explored.

Methodological approach: The openMedicine project was funded by the European Commission (EC) on behalf of member states to analyse this European-wide problem. Work benefitted from the epSOS project and work by the European Medicines Agency (EMA), the USA Federal Drug Agency (FDA), and standard development organisations (SDOs). Reviews of white and grey literature, reports, regulatory documents, standards and other documents were undertaken. An online survey of 160 experts in all EU member states contributed empirical evidence. Work gained from discussions within an Expert Council representing core players and stakeholders in Europe and North America, and regional workshops across the EU and at the FDA. They also contributed towards validation of results.

Results: The fragmentation of national markets for medicinal products lies at the root of the identification problem. About 600,000 different products are marketed across the Union, but even in a large country like Germany only ca. 50,000 are readily available. The great flexibility of marketing authorisation holders to provide different names for the same or equivalent products in different countries adds to this identification challenge, and naming issues related to legacy products complicate it further. – Options to identify medicinal products in a prescription

are analysed, like noting a package code, the brand name of the product, the specification of an active substance only, or of a subset of similar products, from which the pharmacist has to choose. The EU-wide adoption of the International Standards Organisation's (ISO) Identification of Medicinal Products (IDMP) suite of standards, as already under way by EMA and FDA for pharmacovigilance purposes, is proposed. Through globally agreed coding of packages, medicinal as well as pharmaceutical products, substances, dose forms, and other identifying attributes as needed, the identification as well as partly the 'delivery' problem can be solved. This will require linking to a central data base maintained by EMA, and the synchronisation of national as well as commercial medicinal and pharmaceutical product data bases with it. The full solution of the delivery problem will, however, also depend on the introduction – in countries where this is not yet allowed – and the relaxation respectively harmonisation of national substitution rules. Of course, if no equivalent product is available, delivery will fail – or require import from another country.

Conclusions: Implementing digital infrastructures facilitating the univocal identification of medicinal products in regulatory and clinical contexts will generate long-term benefits for patient safety, pharmacovigilance, and positive socio-economic impacts for all key players. Harmonising the identification of medicines in regulatory processes as well as clinical documents is well on its way, but a European approach towards common processes for validation of contents, error mitigation, of linking from central hubs to national and regional levels, updates and mappings to other systems will require intensified cooperation of all stakeholders in years to come.

Keywords: medicine, medicinal product, univocal identification, ePrescription, cross-border healthcare, ISO IDMP, WHO-UMC, European Medicines Agency – EMA, Federal Drug Agency – FDA

Zusammenfassung

Fragestellung: Das *Smart Open Services for European Patients (epSOS)* Pilot-Projekt testete erfolgreich eine elektronische Infrastruktur, um zwischen ausgewählten Mitgliedsstaaten der Europäischen Union (EU) Dokumente mit Patienten-Notfalldaten sowie eRezepte auszutauschen. Allerdings ergab sich aufgrund der nicht gelösten eineindeutigen Identifizierung von medizinischen Produkten in der ausländischen Apotheke ein erhebliches 'Abgabe'-Problem. So identifiziert u.U. der gleiche Produktname in unterschiedlichen Ländern Arzneimittel mit unterschiedlichen Wirkstoffen, und identische Produkte können unterschiedliche Namen je nach Land haben. Wenn das verschriebene Produkt in dem anderen Land nicht vermarktet wird, fehlen üblicherweise auch die Informationen über seine Zusammensetzung. Dies führt regelmäßig dazu, dass ein ausländisches Rezept nicht eingelöst werden kann, selbst wenn ein äquivalentes Produkt verfügbar und Substitution erlaubt ist.

Zielsetzung: Die folgenden Ausführungen berichten über das übergeordnete Ziel, die Aktivitäten sowie zentrale Ergebnisse des *openMedicine*-Projektes. Es wurde die Entwicklung einer internationalen, digitalen Lösung zur eineindeutigen Identifizierung von Arzneimitteln vorangetrieben. Ausganspunkt waren europaweite und transatlantische Bemühungen zur grundlegenden Verbesserung der Pharmakovigilanz, um z.B. Berichte zu Risiken und Nebenwirkungen von Medikamenten mit unterschiedlichen Namen, die jedoch den gleichen Wirkstoff enthalten, schneller zusammenführen zu können. Im klinischen Bereich wird es eine solche Lösung z.B. erlauben, auf einen Blick zu erkennen, wenn einem Patienten über einen längeren Zeitraum Medikamente mit unter-

schiedlichen Namen verschrieben wurden, die jedoch alle den gleichen Wirkstoff beinhalten.

Methodischer Ansatz: Das *openMedicine*-Projekt wurde von der Europäischen Kommission in Abstimmung mit den Mitgliedsstaaten finanziell gefördert, um eine europaweite Lösung für die eineindeutige Identifizierung von Medikamenten voranzutreiben. Dabei konnte auf vorhergehende Arbeiten von epSOS, der Europäischen Arzneimittel-Agentur (EMA), der USA Federal Drug Agency (FDA) sowie von Standardentwicklungsorganisationen (SDOs) zurückgegriffen werden. Eine Analyse von weißer und grauer Literatur, Berichten, Regulierungsverordnungen, Standards und anderen Dokumenten wurde durchgeführt. Eine Online-Umfrage bei 160 Experten in allen EU-Mitgliedsstaaten lieferte weiterführende empirische Daten. Diskussionen im Experten-Beirat des Projektes, in dem alle wichtigen Akteure sowie Experten aus Europa und Nordamerika vertreten waren, und auf regionalen Workshops in mehreren EU-Ländern lieferten grundlegende Einsichten und dienten der Validierung der Ergebnisse.

Ergebnisse: Grundlegende Ursache des Identifizierungsproblems ist die Fragmentierung der nationalen Märkte für Arzneimittel. EU-weit werden ca. 600.000 verschiedene Produkte vermarktet, aber selbst in einem großen Mitgliedsstaat wie Deutschland sind nur ca. 50.000 kurzfristig verfügbar. Auch die Option, unterschiedliche Produktnamen für gleiche oder äquivalente Medikamente zu vergeben, sowie die nicht-normierten Namen alter Produkte, die seit vielen Jahrzenten vermarktet werden, tragen dazu bei.

Die vielfältigen nationalen Optionen, um eine bestimmte Packung zu verschreiben, oder einen Medikamentennamen, einen Wirkstoff, oder auch nur eine spezifische Gruppe bestimmter Medikamente, aus denen der Apotheker wählen muss, werden analysiert. Das namensunabhängige, wirkstoffbezogene Konzept des pharmazeutischen Produktes wird eingeführt. Es wird vorgeschlagen, zur Lösung der aufgeworfenen Fragestellungen europaweit die „Identifiction of Medicinal Products (IDMP) suite of standards“ der Internationalen Standardisierungs-Organisation (ISO) einzusetzen. Da EMA und FDA für globale Pharmakovigilanz-Zwecke auch ISO IDMP verwenden werden, würde dies es erlauben, u.a. die dort entwickelten Wörterbücher und Kodierungssysteme zu nutzen.

Durch die damit verbundene eineindeutige Kodierung von Packungen, medizinischen sowie pharmazeutischen Produkten, Wirkstoffen, Darreichungsformen sowie weiterer, der Identifizierung dienenden Eigenschaften können das Identifizierungs- und z.T. das ‚Abgabe‘-Problem gelöst werden. Dies setzt die Anbindung nationaler und kommerzieller Pharma-Datenbanken an die zentrale EMA-Datenbank voraus. Um das Abgabe-Problem weitergehend zu lösen, wird es darüber hinaus notwendig sein, die Substitution von Arzneimitteln auch in den Ländern zu erlauben, die dies bisher untersagen, sowie möglichst länderübergreifend die Substitutionsregeln zu harmonisieren. Wenn in dem anderen Land kein gleiches oder äquivalentes Arzneimittel verfügbar ist, wird die Abgabe dennoch nicht möglich sein. Hier bietet sich gegebenenfalls die Option an, das Medikament aus dem Ausland zu importieren.

Diskussion: Die Implementierung von digitalen Infrastrukturen, die die eineindeutige Identifizierung medizinischer Produkte in marktregulierenden wie medizinischen Versorgungs- und Forschungskontexten unterstützen, verspricht einen langfristigen Nutzen für Patientensicherheit sowie Pharmakovigilanz. Dies lässt darüber hinaus substantielle sozioökonomische Vorteile für alle zentralen Akteure erwarten. Die Standardisierung und Harmonisierung der Identifikation von Arzneimitteln in regulatorischen Prozessen sowie medizinischen Dokumenten ist ein mühsamer, langfristiger Prozess. Im strikt regulierten europäischen Pharmakovigilanz-Bereich wurde er bereits vor vielen Jahren angesto-

ßen, aber auch im klinischen Bereich sollte er umfassend eingeführt werden.

Schlüsselwörter: Arzneimittel, medizinische Produkte, eineindeutige Identifikation, eRezept, grenzüberschreitende Gesundheitsversorgung, ISO IDMP, Standard-Entwicklungsorganisationen, WHO-UMC, EMA, FDA

1 The challenge

Enabling the delivery of safe and efficient cross-border healthcare is a policy priority of the European Union (EU) [1]. Towards this end, member states (MSs) of the EU have been taking down borders by implementing and piloting "Smart Open Services for European Patients (epSOS)" to electronically exchange ePatient Summaries and ePrescriptions [2]. To support and enhance the safety and continuity of cross-border (and also national level) healthcare through interoperable patient data exchange, and to deliver concrete solutions for these two priority use cases, selected MSs are implementing such service applications on a continuing base.

The European Commission (EC) is developing a Digital Services Infrastructure (DSI), a platform for offering digital services across the Union, which will be used by MSs for service delivery in domains like eHealth, Cybersecurity, eJustice, eProcurement, Public Open Data, and others. Across domains, building blocks like eDelivery, eID, eInvoicing, eSignature and eTranslation will offer basic capabilities that can be made use of by any European project to facilitate the delivery of digital public services across borders [3]. Financial support is provided through the telecommunications section of the Connecting Europe Facility (CEF) – which supports trans-European networks, infrastructures and services also in transport and energy [4].

Whereas the epSOS pilot services basically solved the electronic 'communication' or message transfer problem, they encountered a serious 'delivery' problem: the safe dispensation of a medicinal product noted in a prescription from a given country by a retail pharmacist dispensing it in another country. S/he must be able to select from the medicinal products available in that country the one that matches the prescribed product for safe dispensation to the patient. However, this turned out to be a difficult task, because, e.g., the same name may identify a product with a different active ingredient, or a product with identical composition may carry a different name in the other country. And if the prescribed medicine had not been authorised for marketing in the other country, information on its attributes may not be available for univocal identification. This then rendered dispensation by the pharmacist impossible, even where substitution would, in principle, be allowed and possible.

Both within the regulatory and the clinical context a variety of further use cases exist where the univocal identification of a medicinal product respectively the underlying pharmaceutical product(s) is of key importance. However, a solution approach towards the identified 'delivery problem' will be the main focus of this paper.

2 Goal and objectives

This paper reports on the activities and achievements of the openMedicine project [5] towards solving the identification and delivery problems. The overarching goal was to address the challenges around the univocal identification and safe dispensation of a medicinal product intended for human use in an ePrescription presented in another country. When a prescription is prepared by using software connected to a medicinal products database, but printed on paper afterwards, similar issues arise. The openMedicine project was funded by the European Commission on behalf of member states to analyse various aspects of these questions and help to advance a comprehensive solution approach.

Whereas identifying the preferred medicinal product and specifying it in a prescription by a healthcare professional in the home country of the patient is usually not an issue, its univocal identification at the dispensing site in a community or hospital retail pharmacy abroad may be a tricky issue, and is often an unsolvable task. The same holds, e.g., for understanding the prescribing history or the list of active medications in an electronic patient summary, or similar clinical document of a foreign person.

A further objective was to learn from and integrate into such discussions European-wide and cross-Atlantic endeavours to enhance pharmacovigilance by being able to match, e.g., adverse event reports filed under different drug names which provide, however, for the same active ingredient(s). And to explore the need for being able to trace, e.g., for clinical purposes the longer-term treatment with the same active ingredient, even when the name of the prescribed medicines changed several times.

3 Methodological approach

The openMedicine project lasted for two years (January 2015 to December 2016). Methodologically, work benefitted from results and experience of the epSOS project [2], from earlier work performed by the European Medicines Agency (EMA), the USA Federal Drug Administration (FDA), and standard development organisations (SDOs), particularly the International Organization for Standardization (ISO) [6].

Reviews of white and grey literature, reports, regulatory documents, standards and other documents all contributed substantially.

An online survey in early 2016, placed at the LimeSurvey platform [7], of about 160 experts in all EU member states

contributed empirical evidence on the prevalence of ePrescribing systems across countries of the Union, on prescribing options and substitution rules, as well as on prescribing by subsets of medicinal products (like international non-proprietary name [INN], or Anatomical Therapeutic Chemical [ATC] classification system based, or nationally defined clusters of medicinal products). Experts and key players were identified via their European and national associations and by a snowball approach, starting from the networks of project consortium partners and members of the project Expert Council. Meaningful, analysable results were obtained from about 100 experts for 25 countries.

After the collection of information and initial analysis, further direct inquiries were undertaken with respect to those countries for which some information was missing or seemingly of low quality. In addition, whenever possible, results were double-checked through internal reviews by consortium partners and other experts to ensure validity of results as much as possible.

Work gained from both internal discussions within the consortium and with external experts. The project team consisted of national regulatory agencies, standard development organisations, regional healthcare providers as well as private research institutes. Core results were developed based on earlier work by team members and others, tested against a great variety of use cases, synthesised in deliverables available on the project website [5], and explored and validated in various internal workshops, three meetings of the Expert Council representing all core players and stakeholders across Europe and North America, and a further workshop at FDA facilities in Washington, DC. EMA, the World Health Organisation Uppsala Monitoring Centre (WHO-UMC), as well as FDA participated both through membership in the Expert Council and informal involvement in core project work.

Furthermore, many critical discussions during workshops and dissemination events attended by national competent authorities and representatives of core player groups contributed towards further improving the quality, validity and relevance of outcomes. These meetings covered almost all regions of the EU and were attended by experts from close to 20 countries.

4 The fragmentation of global markets, and the naming and identification of medicinal products

4.1 EU marketing authorisation procedures for medicinal products

The fragmentation of national markets for medicinal products lies at the root of the identification problem. A key determinant is the differences in marketing authorisation procedures for medicinal products. In the EU, three different procedures for evaluating new medicinal products and granting marketing authorisation prevail [8]

- Centralised procedure: This procedure came into operation only in 1995. Applications are made directly to the European Medicines Agency and lead to the granting of a European Union marketing authorisation by the Commission which is binding in all Member States. It is compulsory only for selected medicinal products, like those manufactured using biotechnological processes, for orphan medicinal products, and for human products containing a new active substance which was not authorised in the Union before May 2004 and which are intended for the treatment of certain diseases.
- Mutual recognition procedure: Applicable to the majority of conventional medicinal products, this procedure is based on the principle of recognition of an already existing national marketing authorisation by one or more other member states.
- Decentralised procedure: It is also applicable to the majority of conventional medicinal products. Through this procedure an application for the marketing authorisation of a medicinal product is submitted simultaneously in several member states, one of them being chosen as the “Reference Member State”. At the end of the procedure national marketing authorisations are granted in the reference and in the concerned Member States.

Furthermore, purely national authorisations are still available for medicinal products to be marketed in one member state only.

A result is that most medicinal products are marketed only in some, but usually not all member states. Experts of EMA estimate that about 600,000 different medicinal products are marketed across the Union. But even in a large country like Germany probably not more than 50,000 are readily available. The German ABDA database holds “information on more than 50.000 German original and generic pharmaceutical products and more than 120.000 international marketed pharmaceutical products” [9].

4.2 Naming of medicinal products and substances

Another serious problem, partially related to the different procedures for granting marketing authorization, is the variability in naming options. Unless products are centrally authorised, the pharmaceutical company holding the marketing right may vary the corporate (brand) name – be it an originator or a generic brand (or trade) name – across countries. Adding to this the legacy of medicinal products which have been marketed in a given country for 50 or even many more years – before European regulations became effective, the challenge is obvious.

Concerning naming of medicinal products for newly authorized medicines, the European Directive 2001/83/EC on “the Community code relating to medicinal products

for human use" stipulates that the name of a medicinal product may be either an

- "invented name not liable to confusion with the common name", or a
- "common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder."

A common name is "the international non-proprietary name (INN) recommended by the World Health Organization (WHO), or, if one does not exist, the usual common name" [10].
WHO has a constitutional mandate to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products" [11]. The INN list registers "pharmaceutical substances or active pharmaceutical ingredients". Each INN is a unique generic name that is globally recognized and public property. Any "authority or manufacturer" may request "to establish a free and unrestricted INN for a decrisbed pharmaceutical substance" after paying a fee of USD 12,000. All INNs are published in a cumulative list which is updated periodically and may include INNs in Latin, English, French, Spanish, Arabic, Chinese and Russian, as well as a reference to other common names. At present, more than 7,000 INNs have been registered [12].
Unfortunately, it follows that, for a given active ingredient, if this substance is recorded in the INN system, its name may nevertheless not be unique because of the language options without providing for a unique code.
And national naming schemes (and coding systems like the German *Pharmazentralnummer* [PZN] and the Pharmacy-Product-Number [PPN]) are usually country specific. They do not cover (all) foreign medicinal products, and cannot be used in a cross-border context. "For example, differences exist between BAN [British Approved Name] and USAN names for the same substance (e.g. acetaminophen is also called paracetamol). In addition to having different names for the same substances, different countries permit the use of different medicinal ingredients" [13].
Furthermore, as the WHO Uppsala Monitoring Centre (UMC) notes, the name of a specific medicinal product may not be sufficient to identify a unique product because

- the same trade name may be used in different countries with different sets of ingredients
- the same name may be used for different pharmaceutical forms which contain different sets of active ingredients
- a product may have changed its composition without changing its name [14].

To add to this confusion, the number of different (brand or trade) names used globally for individual generic medicinal products containing the same active ingredient may be in the hundreds, e.g. for Metoprolol (a beta blocker) more than 400 generic brand names have been identified [15], and more than 300 for Simeticone (an antiflatulent) [16].

4.3 Options to identify medicinal products in a prescription

Given this global chaos in naming of medicinal products and the substances contained in these products, it became necessary to inquire into some detail how in EU member states medicines are indeed identified when a health professional prescribes them for a patient in an ambulatory setting. Therefore in the LimeSurvey mentioned earlier several questions concerned how a country regulates the way in which medicinal products can be specified in a prescription. As can be seen in Table 1, 23 of the 25 countries of the EU for which sufficient information could be gathered allow the name of an innovator ("given") brand name for identification. The use of a generic brand name ("common name plus company name") is permitted in 20 member states. Not specifying an individual medicinal product, but rather prescribing by active ingredient only making use of the international non-proprietary name (INN) or the "anatomical-therapeutic-chemical (ATC) classification" [17], [18] is available in 17 member states. The use of the name or code of a nationally predefined subset of medicinal products (also called cluster prescription) is presently foreseen in four countries only, but may be spreading to others in the near future.

Table 1: Options to identify medicinal products in a prescription (n=25)

Specification of medicinal product (MP)*	Permitted/ an option	Not permitted/ not available
Originator (given) brand name	23	2
Common plus company name (*generic* brand name)	20	5
INN (or ATC – common name = active substance only)	17	8
Country-specific *subset of MPs* (clusters)	4	21

*plus additional attributes like pharmaceutical form, strength, route of administration etc. as needed

Source: openMedicine survey 2016

A prescribed medicinal product may also be identified by its package identifier (e.g. the global trade identification number – GTIN [19] – in Poland). Till now, only very few

countries provide for nationally, by a regulatory authority or an health insurance company defined subsets of equivalent or similar medicinal products, which a physician may or must prescribe rather than a specific product [20]. In such instances, it is up to the pharmacist to select from this subset the concrete medicinal product to be dispensed, e.g. depending on the presently prevailing price. Obviously, this causes new identification challenges in a cross-border context, which are not tackled here.
Specific identification problems may also arise in a cross-border situation when the prescription concerns, e.g., a magistral formula, an officinal formula, a biological product (such "biologics" include a wide range of medicinal products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins), or "advanced therapy medicinal products" [21]. However, the specific identification issues related to such prescriptions will not be discussed here.

4.4 Dispensing options for the pharmacist

From all of this it follows that if indeed the product prescribed in another country can be identified by the local pharmacist and if the prescription is to be dispensed at all in that country, in many, and probably most instances it will be unavoidable to substitute the prescribed medicinal product by an equivalent one if available locally. If no substitution is permitted in that country, no 'delivery' will be possible.
Depending on the urgency of the matter, the pharmacist may, as an alternative, import the prescribed product from abroad, as is, e.g., permitted in Germany. There a pharmacist may order any foreign medicinal product for local dispensation if certain regulatory requirements are met: It can be imported in small amounts if a) ordered by/is for individual patients; b) the medicine has been authorised for marketing in the country of origin; c) a product with the (1) same active ingredient and a (2) 'comparable' strength for the (3) indication area in question is not available in Germany [22].

4.5 Other factors impacting on availability

National and regional differences in medical culture also impact on markets for medicinal products, and thereby on whether a given medicine is marketed in that country or not. Differences in medical training and education, in clinical practice as well as structures and forms of cooperation across healthcare institutions and organisations, in health system policies including reimbursement of drugs, the ethnic composition of populations etc. impact on the location of care, treatment decisions, and both the type and volume of medicinal products prescribed to patients [23], [24], [25].

Furthermore, the identification problem is not unique to the cross-border context. Also in the national context, the univocal identification is highly relevant for purposes like tracing a medicine over its whole lifecycle, the medication management in an electronic patient or health record (EPR, EHR), for pharmacovigilance, indication/contra-indication management, allergy warnings etc.

5 Solving the global identification challenge

5.1 Defining 'medicinal' and 'pharmaceutical' product

The need for a European-wide, preferably cross-Atlantic or globally univocal identification number or code for a medicinal product and its underlying pharmaceutical product(s) has been acknowledged for many years. A key driver has been the experience by regulatory agencies that information from a variety of sources on adverse drug events collected by their pharmacovigilance systems could not be aligned and traced to the same active substance or pharmaceutical product fast enough than would otherwise have been possible to prevent further harm to patients.
A medicinal product has been defined as "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." Such a product "may contain one or more manufactured items and one or more pharmaceutical products" [26].
Unless it is a recent originator product still protected by an intellectual property right (patent, or supplementary protection certificate – SPC [27]), there usually exists also a variety of different generic medicinal products with a more or less identical composition, which can be subsumed under the same pharmaceutical product name or code. A pharmaceutical product has been defined as "qualitative and quantitative composition of a Medicinal Product in the dose form approved for administration in line with the regulated product information. [...] A Medicinal Product can contain one or more pharmaceutical products" [26].
Whereas a prescription usually specifies a specific package or the quantity of a medicinal product which is to be handed over to the patient, different medicinal products with distinct (brand) names may all contain the same pharmaceutical product. If a single package contains, e.g., two types of tablets with different active ingredients, this single medicinal product contains two different pharmaceutical products.

5.2 The ISO IDMP suite of standards and coding systems

As a first, key step towards solving the identification challenge, the ISO standards family on "Health informatics – Identification of medicinal products (IDMP)" [28] was created with the active engagement of regulatory agencies like EMA, FDA and various national competent authorities, and contributions by standard developing organisations (SDOs) like Health Level Seven (HL7), the European Committee for Standardization (CEN) and other groups that engage in pharma-related standardisation and development of coding systems. These ISO IDMP standards establish definitions and concepts, and describe data elements and their structural relationships that are required for the unique identification of

- Medicinal products and packages (MPID/PCID) – ISO 11615
- Pharmaceutical products (PhPID) – ISO 11616
- Substances (Substance ID) – ISO 11238
- Pharmaceutical dose forms, units of presentation, routes of administration and packaging – ISO 11239
- Units of measurement (UCUM) – ISO 11240

These standards provide for the definition of concepts, data models and their elements, and identify the need for specific coding systems to be applied in concrete applications.
As a further step towards implementations of these standards, EMA and FDA together work on European and trans-Atlantic semantic assets (codes) relating to four domains of master data in pharmaceutical regulatory processes: the so-called SPOR [29] data on

- **S**ubstance data (describing the ingredients of a medicine) and their unique codes
- **P**roduct data (describing the marketing and medicinal information relating to a product)
- **O**rganisation data (providing the contact details of organisations and individuals responsible for various aspects of a medicine over its life cycle)
- **R**eferential data (providing controlled vocabularies, e.g. dosage, pharmaceutical forms, country codes, package codes, weight codes – based inter alia on the Council of Europe, European Directorate for the Quality of Medicines & Healthcare [EDQM] standards and codes [30])

5.3 Creating a unique pharmaceutical product identification

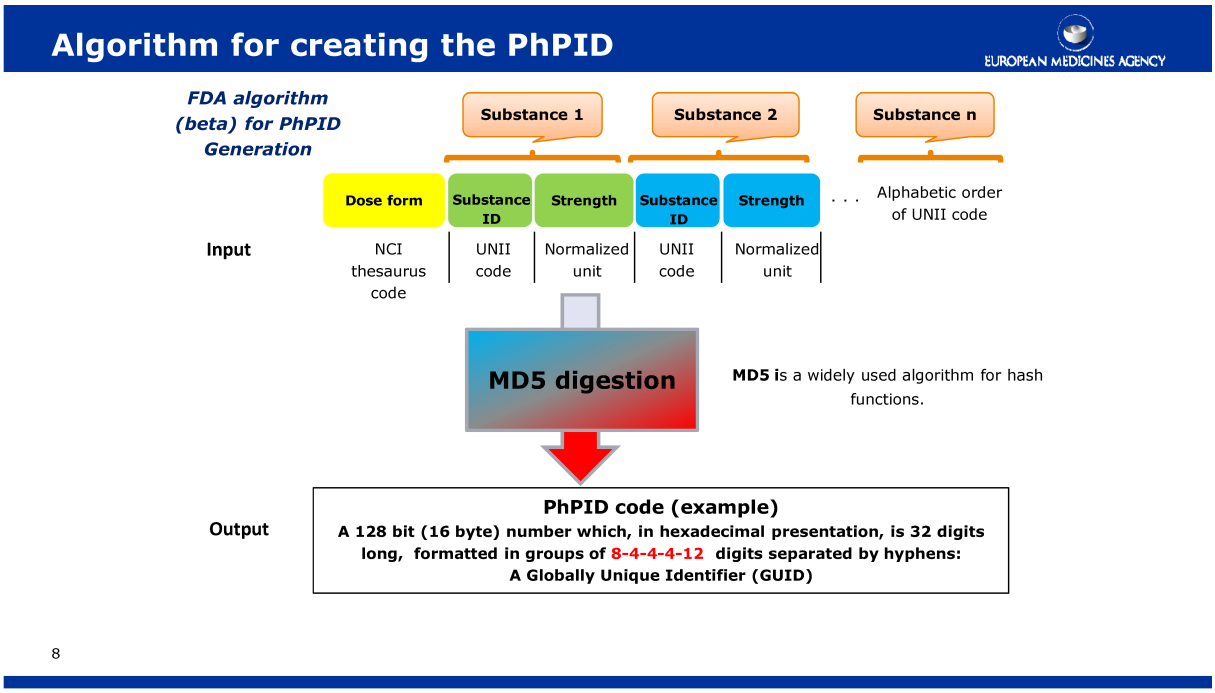
It is foreseen that every single pre-packaged medicinal product (MP) will be assigned a unique identification number – the MPID. And for each package size, a unique package ID (PCID) will become available.
However, in the international context, the more basic concept is the globally unique pharmaceutical product identification number (PhPID). It will probably be registered and controlled by the WHO (UMC). It is foreseen that this PhPID will be derived from the following subset of identifying attributes or data elements and their respective codes:

- Active substance(s)/specified substance(s) ID(s), based on the SPOR substance master data base
- Strength(s) and reference strength – strength units (units of measurement and/or unit of presentation – UCUM code)
- Administrable dose form

This PhPID concept is defined in the ISO IDMP standards. It will be operationalised and implemented after the SPOR databases have become operational.
The FDA has proposed to use the MD5 hash generator, a free online tool, for creating the PhPID code. "An MD5 hash is created by taking a string of any length and encoding it into a 128-bit fingerprint. Encoding the same string using the MD5 algorithm will always result in the same 128-bit hash output" [31].
By applying such a concept, all medicinal products having the same composition and dose form (identifying attributes) will be assigned the same PhPID, respectively two or more PhPIDs in case a medicinal product contains more than one pharmaceutical product. Single pharmaceutical products containing two or more active substances can also be taken care of. This concept is illustrated in Figure 1 on the proposed algorithm for the creation of the PhPID. Taking the numerical codes/units of the attributes identifying the pharmaceutical product, a 128 bit (16 byte) number will be generated which, in hexadecimal presentation, is 32 digits long. It will be formatted in groups of 8-4-4-4-12 digits separated by hyphens. In this manner, a Globally Unique Identifier (GUID) is derived.

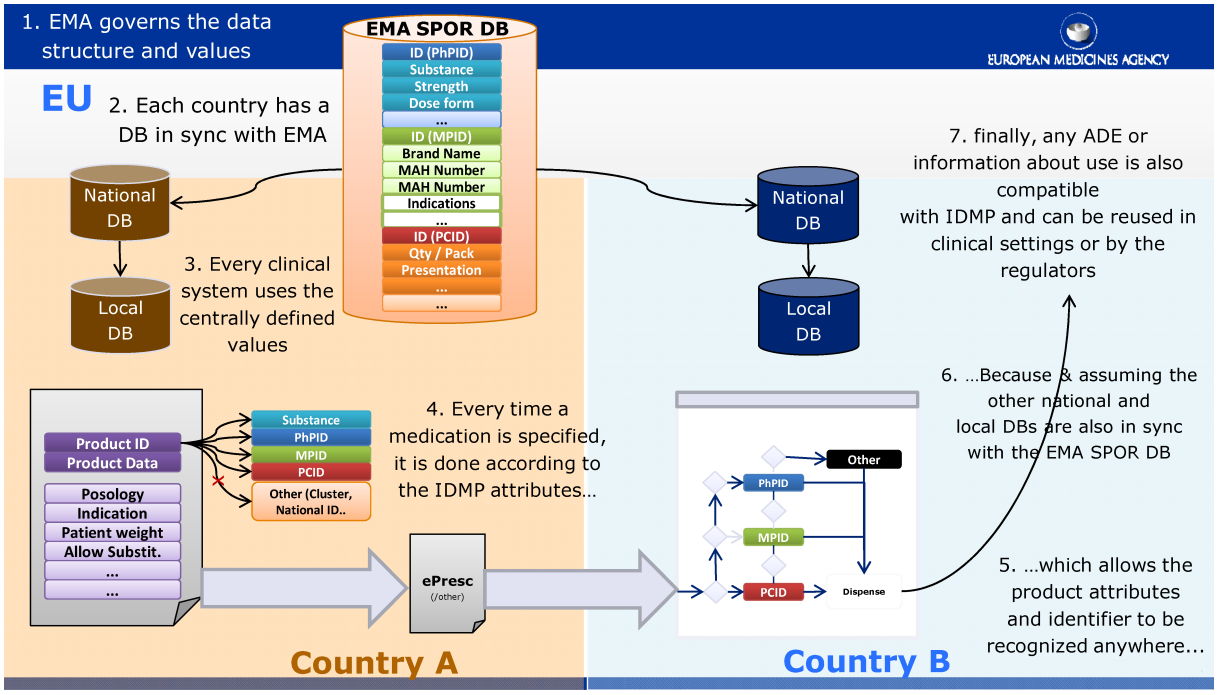
5.4 The mandatory and voluntary use of IDMP standards across the EU

But how will the ISO IDMP suite of standards plus the accompanying data base/code systems become implemented? A logical model of how such globally standardised information on medicinal products, pharmaceutical products and substances including package size may by synchronized and exchanged across member states of the EU, their medicine agencies, and providers of data bases of medicinal products was developed by openMedicine and is illustrated in Figure 2.
Here it is important to note that the European Commission Implementing Regulation (EU) No 520/2012 on "the performance of pharmacovigilance activities" [32] already obliges various players to apply ISO IDMP standards and other terminologies for certain application fields as of July 2016. A European regulation "is a legal act of the European Union that becomes immediately enforceable as law in all member states simultaneously" [33]. It must be distinguished from a directive which first needs to be transposed into national law.
The Implementing Regulation stipulates in its Chapter IV "Use of terminology, formats and standards", article 25



Source: EMA/FDA 2016

Figure 1: Proposed algorithm for creating the PhPID



Source: EMA 2016

Figure 2: Proposed concept for synchronizing data on medicinal products across the European Union

"Use of internationally agreed *terminology*", that "for the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, Member States, marketing authorisation holders and the Agency shall apply the following terminology:"

a) the Medical Dictionary for Regulatory Activities (MedDRA) ...

b) the lists of Standard Terms published by the European Pharmacopoeia Commission as well as

c) to (g) the terminology set out in the ISO IDMP suite of standards.

With respect to the use of internationally agreed formats and standards, article 26 (1) requires that "national competent authorities, marketing authorisation holders and the Agency shall apply the following formats and standards":

a) the Extended EudraVigilance Medicinal Product Report Message (XEVPRM) format
b) ICH [The International Council for Harmonisation] E2B(R2) 'Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of Individual Case Safety Reports'
c) ICH M2 standard 'Electronic Transmission of Individual Case Safety Reports Message Specification'
Note that in the formats and standards domain ISO IDMP is not mandatory. However, in paragraph (2) it is suggested that "for the purpose of paragraph 1 national competent authorities, marketing authorisation holders and the Agency may also apply" the IDMP suite of standards.
Presently, EMA is in the process of implementing IDMP. Following a phased implementation process, pharmaceutical companies will be required to submit data on medicines to EMA in accordance with these formats and terminologies [34].
As a consequence, it seems reasonable – if not ethically mandatory in view of the benefits expected for patient safety, clinical care and many other application fields – to use these terminologies, standards and formats also beyond purely pharmacovigilance-related domains.

5.5 Synchronising medicinal and pharmaceutical product information across Europe – the EMA EudraVigilance data base

When embarking on the road to European-wide and global implementation, it needs to be remembered that EMA already maintains the EudraVigilance system, "a centralised European database of suspected adverse reactions to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA)." It contains information on more than 95% of all medicinal products marketed across the Union, and is expected to become soon complete. Once this so-called Article 57 pharmacovigilance data base [35] is fully transformed and available in the new IDMP format, it will serve as a central authoritative data base for medicinal products across all member states. As proposed in Figure 2, it should then serve as *the* European resource for the cross-border and European-wide univocal identification of medicinal products, and for other clinical and regulatory purposes.
As illustrated, if the local medicinal products data base used by a physician's prescribing system is synchronized with the core identifying and coded attributes available from the EMA data base (or if it can access these data as needed), then any prescription or other clinical document can be filled automatically with all relevant IDMP identifiers without any additional effort. Whether the prescription specifies a GTIN, or a brand name, quantity and other identifying attributes, or an INN/ATC code, it will be possible to univocally identify the active substance, the PhPID, and – if prescribed and available in the foreign country – also the medicinal product ID (MPID) and package ID (PCID).

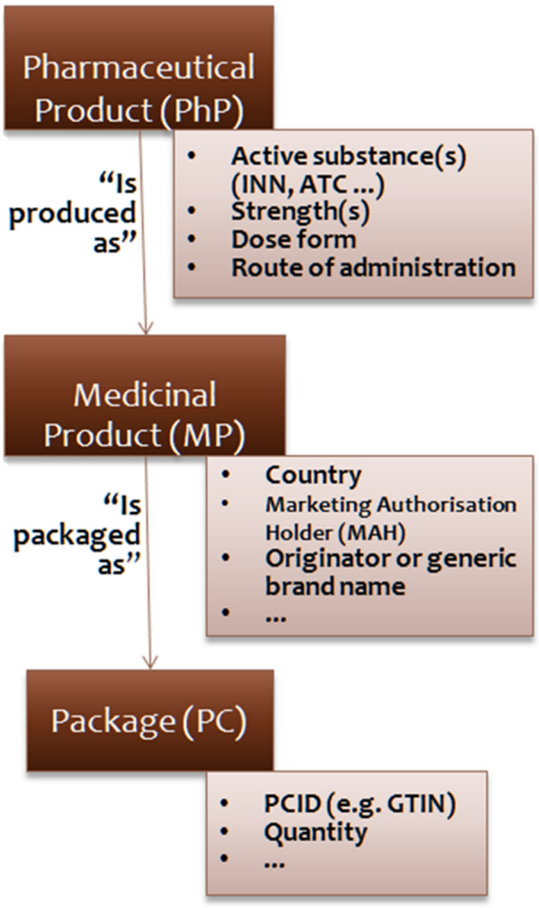
6 The cross-border dispensing process

6.1 Prescribing a medicine

Once such an IDMP compatible data base infrastructure has been implemented in countries where national or regional medicinal products data bases and ePrescribing systems are available to healthcare providers, pharmacies and other players, solving the identification challenge will be much better facilitated than at present.
For healthcare professionals which prescribe medicinal products for their patients, the product selection process can still be performed in the usual manner; no change in clinical or legal practice will be required. 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 set 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 also be useful in situations where different health systems, languages and alphabets are involved.
When the (national) medicinal product data base is aligned with the central European regulator, any of the selected packages and products can be 'mapped' to its set of IDMP attributes. The electronic prescription contains the 'usual' information, but the values used are IDMP-compliant respectively can be automatically retrieved by the software system from a central database. And because the key information is fully coded, semantic interoperability is assured and the prescription is understood in all other countries in which the code system was implemented.
These relationships which exist between the different levels at which a product may be identified in a prescription or elsewhere, and core identifying attributes are illustrated in Figure 3.

6.2 Dispensing a medicine

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 with the identical name is available, there does not exist an identification challenge.
However, because of the variety of marketing authorisation procedures, legacy medicinal products etc. as dis-



Source: openMedicine 2017

Figure 3: Relationships between identification levels and attributes for medicinal and pharmaceutical products

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

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

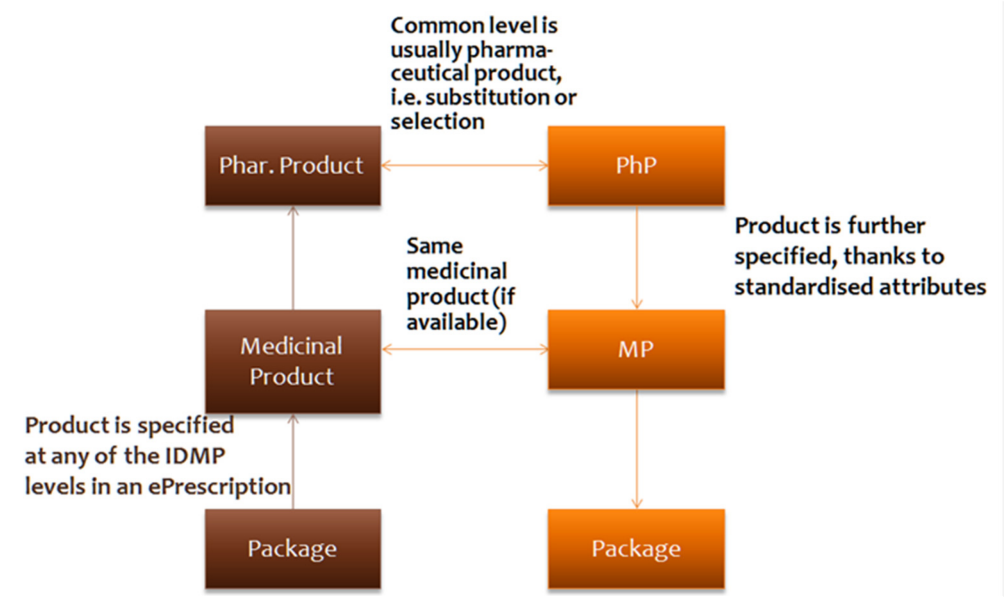
If only an active substance, but not a specific medicinal product, and other attributes are specified in the prescription, again the electronic system allows to retrieve the connected, globally univocal PhPID, and through this the full subset of equivalent medicinal products available in the foreign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

These relationships between the different levels at which a product may be identified in the cross-border setting and then dispensed, are illustrated in Figure 4.

This demonstrates how the electronic prescribing option (be it to exchange an ePrescription, or be it to still generate a paper prescription) enables to add complementary identifiers, favouring cross-border retrieval of identical or equivalent medicinal products.

It follows that the electronic systems and data bases must be able to include the MPID and link it to the respective PhPID in cases where a specific medicinal product (or a package of a medicinal product) 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.



Source: openMedicine 2017

Figure 4: The cross-border dispensation setting

7 Outlook

7.1 Benefits expected

Implementing such electronic infrastructures and systems facilitating and promoting the univocal identification of medicinal products in a wide variety of regulatory and clinical contexts will generate long-term benefits for a diversity of stakeholders, like

- Patients: they will experience safer (cross-border) healthcare, have better access to prescribed medicines abroad, benefit from easier identification of prescribed and dispensed medicines in ePatient Summaries, electronic health records, computerised provider order entry (CPOE) systems and many other clinical contexts.
- Clinicians: they will gain from improved reliability, and easier understanding and comprehension of medication records, and a better understanding of health data of foreign patients.
- Pharmacists: it will allow them the more reliable identification of medicines specified in a (cross-border) prescription, and provide for improved substitution guidance.
- Pharmacovigilance: through the improved identification of medicinal products in question, a faster alignment of reports on adverse drug events (ADEs) related to medicinal products with the same active ingredient(s), but different (generic) brand names will become feasible.
- Pharmaceutical industry: it will benefit from a more efficient, one-time electronic submission of information necessary for marketing authorisation of new medicinal products and other related regulatory processes, and of follow-up information on already marketed products.

7.2 Summary and conclusions

Harmonising the identification of medicines in regulatory processes, in ePrescriptions, eDispensation reports as well as in clinical messages, records and decision support systems is a European challenge, particularly when considering the quality and safety of cross-border health services. It impacts on pharmacovigilance, the tracing of data across the life cycle of a medicinal product, the aggregation of information for public health purposes and many other health domains.

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 not supporting MPID or PHPID attributes and codes, because at the national level there are few direct benefits from solving cross-border identification and semantic issues.

To fundamentally increase the probability that, e.g., a cross-border prescription can indeed be dispensed in another member state, it is mandatory to have the pharmaceutical product identification number (PhPID) available respectively automatically included from national sources or the 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 (and SPOR) data bases with national drug DBs (or to link commercial product data bases directly with EMA) to have identifiers and identifying attributes automatically included into software systems which use such input for prescribing and other clinical systems. This will also improve and harmonise reporting of adverse drug events and pharmacovigilance.
A common European approach and operating model need 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.
Cooperation is needed across SDOs to further harmonise, integrate and maintain these 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.
Work should also concern an assessment of impacts based on benefits and costs to be anticipated for core player groups and stakeholders. Such an assessment should not only concern regulatory impacts and impact on clinical data quality and interoperability, but also spillover effects to pharmaceutical companies, data base producers and the competitive advantage of European companies.

7.3 Limitations

The concrete timeline for the full realisation of the outlined solution is uncertain at this point in time, and may still take several years. However, implementing ISO IDMP by EMA, by pharmaceutical companies and others for pharmacovigilance purposes is already on its way, and the USA and Canada have also embarked on this journey. Commercial medicinal products data base providers have announced informally, that they too will implement these standards and the respective coding systems once EMA respectively FDA IDMP-compatible data bases are fully operational and available to the public.
National regulatory agencies and competent authorities for medicinal products may – or may not – immediately follow suit. There are indications that particularly those in smaller countries may convert as soon as feasible to adopting IDMP and extracting from the EMA data base information on those products which are authorized for marketing in their national health system as the single reference source. In the longer term, this is probably the most cost-efficient procedure. For others, it may be more efficient in the shorter term to adopt a step-wise approach, starting not with overhauling their complete data base, but rather providing links to the EMA data base or mapping only key IDMP data elements into their national system. At this point in time, they are not yet in a position to fully analyse these alternatives and attach cost estimates to such processes.
Whether and when commercial (national) software providers of e.g. hospital information systems, or of patient and medical record systems for physicians in private office, computerised provider order entry and decision support systems etc. will offer IDMP-compatible data bases will largely depend on the reliable availability of the central EMA respectively national data bases.
The proposed solution approach will not be directly applicable to remaining identification issues around country-specific *subsets of medicinal products* specified in a prescription (cluster prescribing), or with respect to magistral or officinal formulae, so-called “biologics”, “advanced therapy medicinal products” and similar medicines.

Notes

Competing interests

The author declares that he has no competing interests.

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