

Grenzüberschreitende eRezepte in der EU – ein europäischer Ansatz zur eindeutigen Identifizierung medizinischer Produkte

Cross-border ePrescriptions in the EU – Towards a European approach to univo- cally identify medicinal products

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Zusammenfassung. Um die Sicherheit der grenzüberschreitenden Gesundheitsversorgung zu verbessern, insbesondere den Austausch von eRezepten, befasst sich das von der EU geförderte openMedicine Projekt mit der ein-eindeutigen Identifizierung von Arzneimitteln (AM). Führende Akteure koordinieren und harmonisieren ihre Bemühungen, um

- gemeinsame Datenmodelle für AM
- semantische Bezeichnungssysteme für ihre unzweideutige Beschreibung
- Regeln der Substitution von AM bei der Abgabe in Apotheken
- einen globalen Plan für Implementierungsschritte nach Abschluß des Projektes

zu entwickeln bzw. vorzubereiten.

Ausgehend von den bisherigen Aktivitäten globaler Standardisierungsorganisationen wurden Anwendungsszenarien erarbeitet. Dies betrifft sowohl vom Hersteller verpackte Standard-Arzneimittel als auch spezielle Fälle wie in der Apotheke erstellte Produkte, solche mit mehreren pharmazeutischen Mitteln oder in Kombination mit speziellen Medizinprodukten, biologische Präparate usw. Die globale Standardisierung wird einen erheblichen Nutzen für Gesundheitsversorgung und -systeme haben. Darüberhinaus wird die Vereinfachung und Beschleunigung der Registrierung, Autorisation und Nachverfolgung von Arzneimitteln über ihren gesamten Lebenslauf, einschließlich der Pharmakovigilanz, für alle Beteiligten erhebliche Vorteile generieren. Dies betrifft vor allem Patienten, aber auch die zuständigen nationalen und europäischen Behörden, die Industrie und andere Akteure.

In einem kurzen Addendum wird auf den EU-politischen Kontext und die zu erwartenden Nutzen, aber auch die Kosten einer nationalen und europaweiten Einführung von eRezept-Systemen eingegangen. Trotz gesetzgeberischer Vorgaben zu Beginn dieses Jahrtausends für eine entsprechende interoperable Infrastruktur fehlen bisher Implementationen in Deutschland.

Schlagwörter. Arzneimittel, medizinische Produkte, eindeutige Identifikation, e-Rezept, Interoperabilität, Substitution, grenzüberschreitende Gesundheitsversor-

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Abstract. To better enable safe cross-border healthcare delivery, particularly the exchange of ePrescriptions, the EU funded openMedicine project explores the unique identification of medicinal products (MPs) in such settings. Major stakeholders harmonise their respective efforts to deliver

- common data models for MPs
- a common vocabulary for their unambiguous description
- rules to harmonise practices of substitution at the point of dispensation
- a global roadmap for post-project actions and implementations.

Based on earlier activities of standard development organisations (SDOs), use case scenarios were developed. The univocal identification of MPs is addressed for standard pre-packed ones as well as for special cases like MPs prepared in the pharmacy, with several pharmaceutical products or in combination with a medical device, biologics, etc. Impacts will be considerable for healthcare services and systems globally as well as – through simplifying and speeding up the registration, authorisation and tracing of new products across their full life cycle including pharmacovigilance – for all stakeholders. This concerns in particular patients, but also national and international regulatory agencies, the pharmaceutical industry, and others.

In a concise addendum, the paper briefly reflects on the wider EU policy context and expected benefits and costs of ePrescribing systems from a national as well as a European perspective. In spite of early legal requirements for providing an appropriate interoperable infrastructure for ePrescription systems in Germany, no implementations were realised so far.

Keywords. Medicine, medicinal product, univocal identification, ePrescription, interoperability, substitution, cross-border healthcare, standard development organisations - SDOs, World Health Organisation - WHO, European Medicines Agency – EMA, Federal Drug Agency - FDA

Background and context

The European Union *eHealth Action Plan 2012-2020 - Innovative healthcare for the 21st century* notes that information and communication technologies (ICT) applied to health (eHealth) can increase the efficiency, safety and quality of health services, and unlock innovation in health markets [1]. At the EU member state level, much has already been achieved with respect to unleashing the power and benefits from eHealth applications.

In this context, enabling the delivery of safe cross-border healthcare is a policy priority of the European Union. Delivering efficient cross-border healthcare opens up great opportunities for eHealth applications, but also poses specific challenges, like differences in languages, alphabets, culture, health system structures, regulatory requirements, reimbursement, etc. The recently finished epSOS project (Smart Open Services for European Patients; 25 countries participated) developed cross-border eHealth services providing physicians electronic access to basic patient data (electronic summary, including medication record) when treating patients living temporarily abroad or travelling across Europe, and enabling patients to use a local community pharmacy abroad to obtain their prescription medicines ("ePrescription") [2].

ePrescription refers to prescriptions transferred by electronic communication from the prescribing health professional's IT system to (1) a national/regional repository

where it is accessible by a pharmacy for download at the patient's request, or (2) directly to a pharmacy chosen by the patient. To cope with

- national and EU regulations and laws, liability and data security challenges (interoperability governance domain)
- structural, process and resource issues (interoperability organisational domain), as well as
- technical, document structure and semantic challenges (interoperability data access and exchange domain)

specific organisational structures and processes were set up by epSOS participating countries for the cross-border data exchange via central eHealth national (or regional) contact points, bilateral legal agreements drafted and signed, and a host of documents like technical specifications and guidelines, multi-lingual semantic assets, pieces of tested and certified software etc. developed.

It turned out that dispensing a medicinal prescription poses a specific challenge in this context - the "delivery" problem of ePrescription. This concerns the univocal identification of the medicinal product (MP), which is noted in a prescription from a given country, by a pharmacist dispensing it in another country.

A prescribed medicinal product can be identified in different ways, like depending on its status (authorised, registered, freely available), by its package identifier (e.g. GTIN [3] in Poland), its commercial ("invented" = originator, or "given" = generic [4]) name, by only stating an active ingredient or substance name (e.g. WHO International Nonproprietary Names - INN [5]), or in a few countries also by its grouping (pharmaceutical class, cluster [6]). In addition, except when directly identifying the package, further attributes like overall quantity to be dispensed, strength, dose form/unit of presentation, and the route of administration are usually required.

Specific identification problems may 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" [7].

Although not necessary for identifying the correct product, a posology (quantity per intake, frequency and timing by day, start and duration of treatment) will also often appear in a prescription, perhaps supplemented by information on how often the prescription may be filled again.

Dispensing the 'correct' medicinal product is also impacted by national regulatory aspects allowing different "grades" of substitution by the dispensing pharmacist, or even requiring substitution [8, 9].

Depending on when and by which procedure a medicinal product was authorised for marketing in a single, several or all EU countries [10], the name and/or identification codes may differ across countries; or a product may not be available at all in a given country. It even happens that the same name identifies a different medicinal product in another country. Globally, the same active ingredient (generic, INN substance) may be contained in several hundred branded medicinal products [11].

It is against this background that the European Commission has funded the openMedince project [12] to better enable cross-border healthcare delivery, particularly the exchange of ePrescriptions and safe dispensation of prescribed medicinal products. This global initiative advances the unique identification of medicinal products (MPs) and thereby patient safety in cross-border settings. It aims to reach a global consensus in order to describe unambiguously a medicinal and its pharmaceutical product(s) [13].

This will facilitate information exchange also in a wide variety of other applications, like clinical record keeping, prescribing and computerised provider order entry (CPOE) software, clinical decision support systems, registration and market authorisation of new products, pharmaceutical systems and data bases, pharmacovigilance. openMedicine closely cooperates with the European Medicines Agency (EMA), the US Federal Drug Agency (FDA), and standards development organisations. The work develops upon and extends the presently available ISO IDMP suite of standards (11615/16, 11238-40) for the identification of medicinal products.

1. Goal and objectives

The overall goal of the openMedicine initiative is to enhance the safety and continuity of cross-border (and thereby also national level) health services through interoperable ePrescriptions of medicinal products for human use, to develop concrete solutions to the delivery problem identified at the community pharmacy level, and to contribute also to further identification challenges across the full life cycle of medicinal products and a wide variety of use cases. Concrete objectives are to provide for respectively contribute towards

- a common data model based on and extending standards in use for prescribed medications
- an unambiguous vocabulary for the description and identification of medicinal and pharmaceutical products
- robust rules to account for and gradually harmonize concepts and practices of substitution at the point of dispensation in a community pharmacy
- an actionable global roadmap to advance post-project implementation realising interoperable and safe eHealth services across local, state, and international borders
- coordination of practical solutions and policy recommendations of OpenMedicine with the policy recommendations of the EU/US roadmap process for eHealth cooperation.

openMedicine is an ambitious undertaking to support health policy development across European countries and globally in a matter that may affect all people, since it impacts safety and quality of healthcare in general, and cross-border healthcare in particular.

2. Process and activities

The work benefits from earlier activities of regulatory agencies and global SDOs. The ISO 11615/11616/11238/11239/11240:2012 standards family on “Health informatics -- Identification of medicinal products (IDMP)” [14] was created with the active engagement of regulatory agencies FDA and EMA, and intense debates in the ISO, HL7, CEN groups that engage in pharmacy standardisation. Meanwhile WHO, which maintains several coding systems including the Anatomical Therapeutic Chemical (ATC) Classification System [15], collaborates with the International Health Terminology Standards Development Organisation IHTSDO in various harmonisation projects. There is need to bring these activities together, particularly also as EMA requires that medicinal product companies submit data using IDMP starting soon. This is a big change both for

EMA and the pharmaceutical industry [16]. On the other hand, it is going to affect the information offered by the European Union Drug Regulating Authorities Pharmaceutical Database (EudraPharm), the database of medicinal products that EMA maintains. Also the experience of the European project to foster “Smart Open Services for European Patients - Open eHealth initiative for a European large scale pilot of patient summary and electronic prescription” (epSOS) [2] has shown that, particularly on the issue of cross-border ePrescription/eDispensation, further standardisation activities are urgently needed.

The unique contribution of the openMedicine initiative will be to develop upon this earlier work, identify differences, inconsistencies and gaps across already existing standards, and thereby help to harmonise global standardisation. As a first step, the project developed a concise conceptual framework to guide its work, based on the interoperability domain framework as depicted in Figure 1 [17], and use case scenarios where the identification of an MP is an issue, including pharmacological and pharmacokinetic attributes, clinical indications and risks to be considered. Next, the identification and description of pharmaceutical products is addressed, not only for standard pre-packed medicinal products, but also for some special cases like MPs with multi-components, biologics, or special packaging as well as those cases where a prescription for a medicinal product only specifies a cluster or class of products. Furthermore, investigations are undertaken to clarify what attributes are needed for reverse identification of a medicinal product.

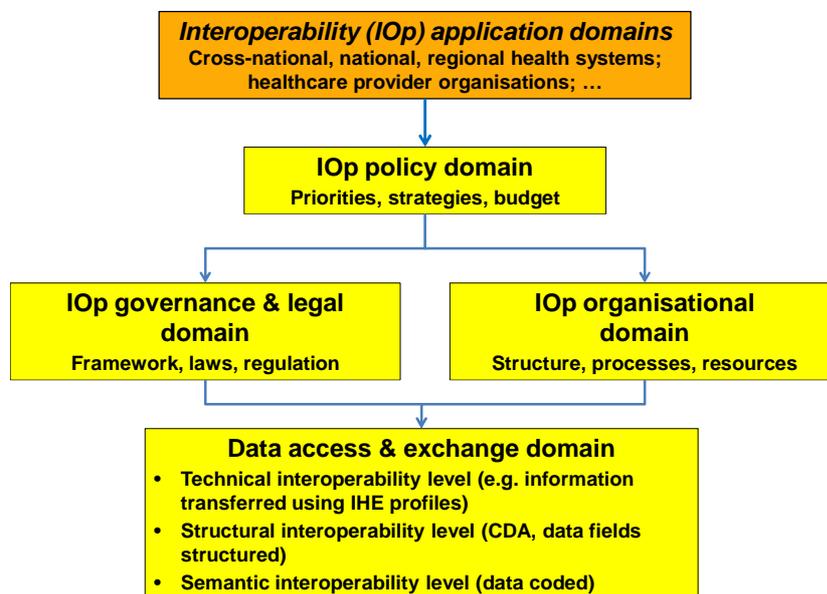


Fig-

ure 1. Interoperability Domains

Substitution of medicinal products at the point of dispensation is a challenge in a cross-border setting due to widely divergent rules. Empirical evidence on the tension between maximising patient safety and maximising the probability that a cross-border prescrip-

tion can indeed be adequately filled in another country is gathered and analysed to develop concrete solution proposals to overcome the challenges pinpointed.

3. Partner organisations and experts

The following organisations are core partners of this initiative.

- empirica Gesellschaft für Kommunikations- und Technologieforschung mbH, Germany
- Custodix NV, Belgium
- Health Products Regulatory Authority, Ireland
- Health Ministry of Regional Government Lombardia, Italy
- Health Level Seven International (Europe)
- Instytut Logistyki i Magazynowania (for GS1), Poland
- Nederlands Normalisatie Instituut (for ISO and CEN)
- Agencia Española de Medicamentos y Productos Sanitarios Parque Empresarial, Spain

In addition, to enable direct involvement of interested third parties which cannot or may not want to become a direct contractual partner in a project supported by the European Union, the initiative co-opted two international regulatory agencies: the European Medicines Agency (EMA), London, UK, and the World Health Organisation (WHO - Geneva, and the WHO Uppsala Monitoring Centre - UMC). Direct cooperation with the US Food and Drug Administration (FDA) has also been established, and a trans-Atlantic workshop at FDA premises is organised for June, 2016.

Furthermore, to allow for the input and involvement of further (national) regulatory authorities, SDOs like the International Health Terminology Standards Development Organisation - IHTSDO, and major stakeholders (industry, health professionals, patients) the initiative is supported and advised by an Expert Council and selected individual experts.

At the member state level, several national and regional meetings with national competent authorities, healthcare professionals, drug data base producers and others are foreseen. These workshops will examine the implications and potential impacts of implementing global standards for the univocal identification of medicinal products (IDMP) at the national level; review the expected added value for public health, clinical decision support, pharmacoeconomics, and pharmacovigilance; identify challenges and costs of the pending roll-out in EU member states; explore further steps and activities necessary to fully exploit the benefits foreseen.

4. Outcomes

openMedicine will deliver practical solutions ready to be taken over and eventually implemented by countries across the globe to solve two key issues of cross-border prescription services: the univocal identification of medicinal products, and clear rules of how to deal with substitution when presenting a prescription abroad. These solutions concern:

- Data models for prescribed medicinal products developed cooperatively by regulatory authorities and global SDOs, validated by experts and government

representatives. The data models will include ways of clustering medicines according to their active ingredient(s), in view of substitution, and pharmacovigilance needs. This will include agreement on an international standard to represent multiple (active) ingredients in medications and a way to identify changes in that composition, and recommendations on the way to prescribe a class of pharmaceutical products or a cluster of medicinal products instead of a specified product.

- A common vocabulary for unambiguous definition, description, and identification of medicinal/pharmaceutical products which will be developed and validated in a similar fashion with global regulatory agencies and SDOs.
- Clear rules for the cross-border handling of different practices of substitution in Europe
- A roadmap for post-project implementation of the solutions elaborated, including a proposal for the future structures, processes and funding for a (global, virtual) organisation to maintain, further develop and internationally coordinate technical and semantic interoperability assets, issues, and challenges.

5. Impact and benefits

The impact on and benefits for patients, in particular those seeking healthcare services in another country, international travellers and those temporarily working and/or living abroad, will be considerable:

- Any patient can obtain seamlessly at least a medicine equivalent to the one prescribed in another country
- Clinicians reviewing a foreign patient's summary understand fully the medicinal therapy information contained
- Pharmacists can fully identify what is the most appropriate medicinal product in his/her country that fulfils the therapeutic requirements of the product prescribed abroad, in accordance with his/her country laws and substitution rules
- Different actors [regulators (e.g. EMA, AIFA); national/regional/local information systems; pharmaceutical companies; sponsors of clinical trials] are enabled to meaningfully exchange MP data and share the same source of information
- Identifiers can be used by any actor in any country for obtaining the product's "properties"

This work will also contribute towards fostering the innovation capacity of pharmaceutical companies by simplifying and speeding up the registration of new products and afterwards pharmacovigilance activities – innovations which contribute to patient safety and better healthcare.

Neither SDOs, national authorities, pharmaceutical companies or other stakeholders can solve the challenges identified on their own – we need global cooperation. It is anticipated that the cooperation initiated by this project will serve as the game changer to the situation of global MP identification.

6. Addendum: Benefits and costs from ePrescribing - a European perspective

6.1. European policy context

The motivation for the European Commission (EC) and various member states to involve themselves in cross-border ePrescription services stems from both the perceived need for such services and the directive on patients rights in cross-border healthcare [17]. It is complemented by the European Commission implementing directive on measures to facilitate the recognition of medical prescriptions issued in another member state [18]. It defines a minimum obligatory set of elements any European cross-border prescription should contain, regardless of the medium used (paper or electronic prescription).

An Implementing Committee on cross-border healthcare was created by the patients' rights directive (Article 16, 1.): "it is consisting of representatives of the member states and chaired by the Commission representative." With respect to eHealth aspects, it is complemented by a voluntary "eHealth Network": According to Article 14 1. "the Union shall support and facilitate cooperation and the exchange of information among Member States working within a voluntary network connecting national authorities responsible for eHealth designated by the Member States." The ePrescription interoperability guidelines proposed by the EC were thoroughly reviewed and in 2014 endorsed by this eHealth Network, and they are up for review in 2016/17, based *inter alia* on the outputs of openMedicine.

It is foreseen that the results of the epSOS services for the exchange of ePrescriptions across member states and also of electronic patient summaries will, as of 2017, be adapted and taken forward by interested member states. They will be financially supported for several years by the European Commission Connecting Europe Facility (CEF) [19]. It sets out to establish and maintain digital service infrastructures across the Union, also in the health services domain. The policy goal is to facilitate the deployment of cross-border interoperable ICT services of general interest by overcoming the barriers of the high initial investment costs and risks associated with their deployment. The funding will serve to ensure interoperability and meet the costs of running such eHealth infrastructure services at European level, linking up member states' infrastructures.

The experience of epSOS has shown that bringing member states together to build and deploy interoperable infra- and info-structures also contributes to complementary deployments at national, regional, and local levels. The semantic and technical assets developed in the scope of epSOS, but also the outcomes of other current large scale eGovernment pilot projects, are expected to be transferred into organisational structures facilitated and supported by the CEF.

6.2. Benefits and costs from ePrescribing

The implementation of ePrescribing systems is driven by the benefits expected for the respective healthcare system as well as for cross-border services, for the citizens, healthcare providers, payers, and society at large. To arrive at rational decision making, these benefits should be confronted with the likely costs to be expected by the health system/the states implementing them.

Changing from a paper based prescribing process to an electronic procedure will yield a number of important benefits to stakeholders, key of which is

- patient safety.

Increased medication safety is achieved through the seamless availability of all medications prescribed for a given patient in a standardised digital format, and not in sometimes difficult to read handwriting. This can lead to significant reductions in prescription errors resulting both from drugs dispensed and suggested dosage information the patient obtains. Often, these features are enhanced by IT supported alert or clinical decision support systems which facilitate the prescribing and/or dispensing professional in identifying drug-drug interactions and other safety related problems [20]. However, it has to be acknowledged that the introduction of any new eHealth system may also involve new hazards [21].

Other benefit drivers can be

- More efficient, time saving prescribing process
- Accurate, up-to-date and complete medication records
- Information on medicinal products actually dispensed
- Improved medication stock management
- Easier archiving of prescription records
- Improved public health surveillance and analysis
- Integration with reimbursement and control systems
- Reduced risk of fraud and prescription falsification
- Avoidance of duplicate prescriptions to replace lost or misplaced ones
- Avoidance of early or double refills.

In two case studies it was shown that already in a regional context such as Stockholm County or Andalucía estimated net socio-economic benefits may come close to € 100 million and more p.a. [22] They do, however, not necessarily derive from direct financial or cash savings, but rather from intangible benefits such as time saved or delivery of better care which otherwise would have been very expensive to achieve by conventional means. The Andalusian ePrescribing system Receta XXI is a module of Diraya, the region's EHR and general health information system. Specific benefits result because with Receta XXI, general practitioners (GPs) can prescribe for periods of up to one year, thus avoiding repeat visits of patients to their office, and pharmacists' can cancel prescriptions and send them back to the relevant GP for revision in case they discover a patient safety issue.

The major types of cost relate to the annual depreciation of one-time investment/re-investment expenditures, and to implementation/change management, and maintenance/operation costs. Beyond the often intangible costs of change management, considerable direct financial costs in terms of cash outlays have usually to be borne by both the government respectively the healthcare system for the ePrescribing platform and by healthcare provider organisations including pharmacies, which depending on the healthcare system may include physicians operating as independent entrepreneurs. They usually have to carry the one-time investment as well as their respective implementation and maintenance/operation costs over the full life-time of the system.

Partially or totally these costs may be taken over by Third Party Payers or the health system/the government, e.g. through specific reimbursement rules, investment subsidies or other financial models.

From the case studies, it was estimated that over a ten-year period historical overall costs of between € 13 and € 75 per inhabitant may arise, and extra financial outlays of between €7 and €35 per inhabitant, or roughly € 0.70 to 3.50 per year. Mutatis mu-

tandis, these estimates can be extrapolated –with increasing economies of scale - onto other regions and larger countries.

However, these figures will be considerably lower these days for countries where the diffusion of eHealth systems to healthcare providers – including medication record and ePrescription modules – has progressed to a certain degree. Depending on the eHealth infrastructure of the region/country and the diffusion of relevant eHealth applications among healthcare provider organisations, one may expect over a ten-year period annual costs of around € 0.30 to € 1.50 per inhabitant only, depending on the already existing infrastructure, size of the region/country, type of health system, and other factors.

In a cross-border context, this would not yet account for the extra benefits and costs of assuring cross-border ePrescription services. These are difficult to estimate, but considering the marginal relevance of cross-border healthcare service provision, these extra benefits are probably negligible. Substantial benefits will, however, be reaped at the national or regional level. As the epSOS and follow-up experience has shown, such European and trans-Atlantic activities will lead to higher levels of awareness among stakeholders in participating member states. Because participation in such digital cross-border exchange of patient data presupposes the availability of compliant interoperable eHealth services at home, the most substantial beneficial impact will be reaped at the national level, first of all.

Member State collaboration and sharing of information models, semantic assets, value sets, open source components and tools should be strongly encouraged and supported by the EC. Such collaboration avoids redundant work, minimises costs for all and sets positive examples for other regions and countries to follow. epSOS has shown that the initial planning and ICT implementation costs are manageable and – for a larger regional or national system which already avails itself of ePrescription facilities – should not be more than anywhere between € 200,000 and € 2m for a national system to become compliant with cross-border requirements.

6.3. *Lessons to be learned for Germany*

Some 20 years ago the eHealth working Group of the German Federal Government's *Forum Info 2000* initiative [23] identified the implementation of a Germany-wide ePrescription (elektronisches Rezept) system as *THE* core implementation (“Leuchtturm Projekt”) enabling, due to the huge number of more than 900 million paper prescriptions p.a., to harvest a low hanging fruit with great benefits for all. However, due to power games among German health system actors, an integrated national or several regional ePrescribing systems were never implemented, in spite of it being mentioned for implementation already in the 2003 Statutory Health Insurance Modernisation Law [24]: “Der Spitzenverband Bund der Krankenkassen, die Kassenärztliche Bundesvereinigung, ... schaffen die für die Einführung und Anwendung der elektronischen Gesundheitskarte, insbesondere *des elektronischen Rezeptes* und der elektronischen Patientenakte, erforderliche interoperable und kompatible Informations-, Kommunikations- und Sicherheitsinfrastruktur (Telematikinfrastruktur)“ [25].

It seems timely to reflect on the above observations and arguments to re-start such discussions in Germany, and to base related activities on the already freely available evidence, experience and lessons learned in other EU countries and globally.

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