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D5.1 Meeting the substitution challenge: Member State regulations and core cross-border issues

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Revision history, status, abstract, keywords, statement of originality

Revision History

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| Abstract (for dissemination) | <p>Dispensing an (e)Prescription for a medicinal product for human use by a community pharmacist in a cross-border situation sometimes poses specific challenges. These concern the univocal identification of the medicine specified in the foreign prescription, and, if this product is not available or if substitution is required by regulation, the dispensation of a similar product in line with national law.</p> <p>This deliverable focuses on substitution issues. It defines substitution and its delimitation from selecting a product, and develops an analytical framework to analyse substitution challenges. Next, issues around specifying a medicine in a prescription and the related European directive and guidelines are reviewed, complemented by discussing briefly European and World Medical Association recommendations on substitution.</p> <p>As basis for the online survey of experts in all member states on substitution rules and regulation in their respective country, core challenges to be looked at are identified. Next steps will be the collation and analysis of the survey data as well as the development of recommendations for substitution handling in cross-border dispensation</p> <p>The full text of the questionnaire is appended.</p> |
| Keywords | Cross-border ePrescription, substitution, selection, regulation, survey, questionnaire, guidelines |

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This deliverable contains original unpublished work except where clearly indicated otherwise.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

Relationship to overall goal of the project, to other WPs

To better enable cross-border (and also national level) healthcare delivery, particularly the exchange of ePrescriptions, and safe dispensation of prescribed medicinal products, the openMedicine global initiative advances the unique identification of medicinal products (MPs) and thereby patient safety and the efficiency of our healthcare systems.

In this context, a specific challenge arises when a medicine specified in a foreign prescription is not available or if substitution is required by regulation in the country of dispensation. Work package 5 focuses on substitution challenges and how to cope with them.

Work in this WP is closely coordinated particularly with WP 2 work on standards based identification, and WP 4 work on issues and challenges arising whenever an authorised health-care professional does not prescribe a branded individual medicinal product, but a class of (generic) or a “cluster” of medicinal products and leaves it to the pharmacist to select the medicinal product to be dispensed.

Objective

This deliverable concerns primarily the tasks of developing an analytical framework, drafting a comprehensive survey and to validate it, as well as preparing for collecting the evidence needed for the final task of analysing the empirical results and, based on this evidence, drafting recommendations for substitution handling in cross-border dispensation.

Approach/methods applied

Methodologically, work for this deliverable very much gained from intensive discussions around WPs 1 and 2 and the results obtained there so far. Project team and Expert Board discussions revealed that substitution is a rather ill-defined and elusive concept, and its operational definition and understanding is very much depending on the concrete experience and regulation in the respective country where an expert is at home.

It was decided to also intensively cooperate with WP 4 (work within that WP was to commence only in project month 12 – December of 2015) by including its empirical questions into a single survey, from which a considerable need of coordination emerged. Both WPs came up with quite long lists of information and data requirements, but it was obvious that 2 more surveys – one had already been undertaken by WP 2 - would in all probability overextend the propensity of the relevant European experts to indeed respond in a satisfactory fashion. Drafting a suitable subset of questions to be asked without too much explanatory text and too many questions was a time consuming process. Teleconferences, e-mail exchanges and regular testing of tentative formulations by uninvolved experts were applied.

Desk research was another starting point for the collection of general data on the substitution of prescribed medicines. However, it turned out that beyond high level attempts by international bodies to define the concept of substitution there exist very few publications dealing with the issues at a more detailed level.

Results

This deliverable defines substitution when a single, unique product is specified in a prescription, and its delimitation from selecting a product when only an active ingredient or a group of products is mentioned. It develops an analytical framework to analyse substitution chal-

lenges. Next, issues around specifying a medicine in a prescription and the related European directive and guidelines are reviewed, complemented by discussing briefly European and World Medical Association recommendations on substitution.

As basis for the online survey of experts in all member states on substitution rules and regulation in their respective country, core challenges to be looked at are identified. They provided the basis for the questionnaire which is appended to this paper.

Next steps

The next deliverable will report on curating, collating and tabulating the survey results. Data per country and across member states will be presented. Their further analysis will focus on identifying key substitution challenges in the cross-border context of relevance for at least a significant minority of member states. Taking into consideration the dialectic tension between maximising patient safety and the probability that a cross-border prescription can indeed be adequately filled in another country will become a core aspect. The development of recommendations for substitution handling in cross-border dispensation will follow.

1 Background and project goal

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 electronically exchange patient summaries and ePrescriptions, safely dispensing a prescription from another country is still challenging. This requires that the pharmacist selects the exact match from the range of pharmaceutical products available, or substitutes, in line with national regulations, the prescribed medicine.

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

- One providing (emergency) physician access to basic medical data of an electronic patient summary when treating patients living temporarily abroad or travelling across Europe (eSummary), and
- Another one enabling patients to use a local pharmacy abroad to obtain the medicines 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. This concerns the univocal identification of the medicine, which is noted in a prescription from a given country, by a pharmacist dispensing it in another country. S/He must be able to select from the medicines available in that country the product that matches the prescribed product for safe dispensation to the patient. In cases where this is not possible, or if substitution is required, the pharmacist should be able to dispense a similar product in line with national regulation.

A prescribed medicine can be identified in the prescription by its attributes² in different ways, like by its package identifier, invented or given name, active ingredient name, composition, and others, or also by its grouping (pharmaceutical or therapeutic class)³.

Dispensing the product is also impacted by national or regional regulatory aspects allowing different “grades” of *substitution* by the dispensing pharmacist, or even requiring substitution.

openMedince addresses both the identification and the substitution challenge. The project aims *to reach a global consensus* in order to univocally identify and describe unambiguously a medicine, resulting in the authorised delivery of the appropriate medicinal product. In detail, this concerns developing

- common data models for prescribed medicines
- a common vocabulary for unambiguous definition, description, and identification of medicines
- rules to harmonise practices of substitution
- a roadmap for post-project actions and implementations.

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 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

It should be noted that within openMedicine the substitution discussion is mostly limited to the regulatory context, because a pharmacist can only substitute within the framework of what is permitted or, more likely, required for economic (usually related to reimbursement and cost saving) issues. Clinical aspects of course impact on such regulatory rules, but will not be explored in any detail.

Furthermore, as openMedicine focuses on identification and substitution challenges, we are not concerned directly with reimbursement issues. Nevertheless, indirectly most if not all substitution regulations are driven by economic or cost savings intention to reduce the amount to be reimbursed.

2 Objectives of WP5, context, and methodological approach

This chapter briefly reviews the objectives and tasks of WP 5, describes the overall open-Medicine context and coordination of survey activities across WP 4 and WP 5 tasks, and explores the methodological approach applied when performing the work reported upon.

2.1 Objectives and tasks of WP 5

As described in some detail in the Description of Action (DoA), the objectives of WP5 are to:

- Provide a concise framework and approach for analysing the substitution challenge
- Collect hard evidence on this in the majority of member states
- Analyse the information collected, identify core cross-border issues, particularly in the context of the tension between maximising patient safety and maximising the probability that a cross-border prescription can indeed be adequately filled in another country
- Develop a concrete proposal to overcome the challenges pinpointed
- Validate the proposal and present final recommendations, including a roadmap for MSs to indeed implement them

According to the DoA, these tasks have been planned:

Task 5.1 developed an analytical framework for identifying and classifying core issues arising in the substitution context.

Task 5.2 validated this framework, explored with experts both from the consortium and external to it the issues to be tackled, and will collect evidence from at least 16 member states on their handling of substitution issues.

Task 5.3 plans to analyse the information collected, and - in the context of the tension between maximising patient safety and maximising the probability that a cross-border prescription can indeed be adequately filled in another country – to identify core cross-border challenges to be tackled.

Finally, task 5.4 will, based on all this information and evidence, develop concrete solution proposals and next steps for MSs authorities to facilitate future cross-border healthcare, and submit them for final validation.

2.2 Overall context and coordination of WP 2, WP 4 and WP 5

Whereas WP 1 “epSOS use cases and Conceptual Framework” was to revisit the epSOS experience which led to the overall goal of this Action, and to set the scene for the further work to deal with the challenges identified by epSOS, WPs 2, 3 and 4 concern the wide variety of issues and items surrounding the univocal identification and description of medicinal and pharmaceutical products. Parallel to this work, WP 5 focuses on the challenges surrounding substitution of prescribed medicines in cross border dispensation. When an (e)Prescription for a medicine for human use is to be dispensed in a community pharmacy in another country, the objective is to analyse the substitution possibilities such as to optimise, on the one, patient safety, and on the other the probability that a cross-border prescription can indeed be adequately filled.

This deliverable concerns primarily the initial task of developing an analytical framework, drafting a comprehensive survey and to validate it, as well as preparing for collecting the evidence needed for the final tasks. The task of actually collecting evidence in member states has been delayed due to two major challenges. First the results of the survey undertaken by WP 2, task 2.1, on standards based identification and description enabling dispensing equivalent medicinal products needed to be available, because that survey also touched on the substitution issue. Waiting for its results was to avoid contacting national competent authorities and experts on the same issue in an uncoordinated fashion twice.

Furthermore, it turned out that WP 4, task 4.1, also needed to undertake a member state survey. That task concerns issues and challenges arising whenever an authorised healthcare professional does not prescribe a branded individual medicinal product, be it an original (invented name) or a generic (given name) product, but prescribes a class of products or a “cluster” of medicinal products and leaves it to the pharmacist to select the medicinal product to be dispensed. Very little empirical knowledge is available about this type of prescribing, but it seems that its prevalence is spreading, and therefore, after work on that WP had started, it was decided to collect evidence on its practice and relevance across the Union.

Against this background, it was agreed to postpone the survey of WP 5 on substitution till realistic options to cooperate with WP 4 by including all questions into a single survey were explored, and also the concrete information needs for WP 4 were clearly identified. Both WPs came up with quite long lists of information and data requirements, but it was obvious that 2 more surveys would in all probability overextend the propensity of the relevant European experts to indeed respond in a satisfactory fashion. Furthermore, the more precise questions to be asked were forthcoming, the more it became obvious that there was no prior experience in surveying both fields in such detail. Concepts and approaches, legal and regulatory contexts, experience from national experience and naming of elements to be analysed turned out to be such diverse and difficult to communicate across several countries in a language foreign to most, English, that agreeing on a suitable subset of questions to be asked without too much explanatory text and too many separate questions was a very lengthy, time consuming process.

to such surveys. fully . However, we expect that the survey will be undertaken still in 2015 so that the timely delivery of the final deliverable D5.2 of this WP is not endangered.

2.3 Methodological approach

Methodologically, work for this deliverable very much gained from the intensive discussions around WPs 1 and 2 and the results obtained there so far. Discussions at the F2F meetings in Bonn, Amsterdam, Dublin and Milano revealed that substitution is a rather ill-defined and elusive concept and issue, and its definition and understanding is very much depending on the concrete experience and regulation in the respective country where an expert is at home.

Furthermore, as it was decided to cooperate with WP 4 by including all questions into a single survey, a large need of coordination and discussion emerged. Both WPs came up with quite long lists of information and data requirements, but it was obvious that 2 more surveys would in all probability overextend the propensity of the relevant European experts to indeed respond in a satisfactory fashion. Furthermore, the more precise questions to be asked were forthcoming, the more it became obvious that there was no prior experience in surveying both fields in such detail. Concepts and approaches, legal and regulatory contexts, experi-

ence from national or regional professional work, and naming of elements to be analysed turned out to be such diverse and difficult to communicate across several countries in a language foreign to most, English, that agreeing on a suitable subset of questions to be asked without too much explanatory text and too many questions was a very lengthy, time consuming process. Teleconferences, e-mail exchanges and regular testing of tentative formulations by uninvolved experts were applied.

Desk research was another starting point for the collection of general data on the substitution of prescribed medicines. However, it turned out that beyond high level attempts by various international bodies to define the concept of substitution there exist very few, if any publications dealing with the issues at a more detailed level. Serious scientific surveys covering several countries seem to be totally missing, and substantial papers dealing only with basic conceptual or theoretical issues could not be identified.

External experts from the Expert Council were informally approached and contributed to the work of this deliverable, and also at the F2F Expert Council Meeting in London the substitution issue was briefly touched.

Only the Pharmaceutical Group of the EU (PGEU) association representing European community pharmacists has so far undertaken a brief survey of its membership covering also substitution issues in a large number of member states. Albeit at an in-depth discussion of the evidence obtained it turned out that the material was difficult to interpret once a more detailed analysis was attempted. Methodologically, it helped the project team to further explore the issue of substitution and develop the framework and questionnaire presented below, but the evidence as such turned out to be of little value for our work.⁴

All the information, knowledge and insights gained contributed to the development of the framework and questionnaire presented in the following chapters.

2.4 What follows

Chapter 3 reviews various definitions of substitution as available in the literature and elsewhere, identifies different types of substitution, and explore the difference between substitution and selection at the point of dispensation. Policy arguments for and the potential clinical impact of substitution are briefly discussed. Suggestions for excluding certain types of substitution from further discussions are made. Finally, an openMedicine definition of substitution of a medicinal product is provided.

Chapter 4 identifies the basic types of a prescription – paper, electronic, cross-border – relevant for this paper, explores the four basic options for the specification of a medicine in a prescription, and presents a detailed list of attributes which may be mentioned in a prescription. The EC non-exhaustive list of elements to be included in cross-border medical prescriptions is presented, and the European ePrescriptions dataset for electronic cross border exchange discussed. How substitution has been dealt with in the epSOS pilots and the ePrescription Guidelines is reviewed, and the World Medical Association recommendations on substitution are finally noted.

⁴ See <http://www.pgeu.eu/en/component/attachments/attachments.html?id=128&task=download>. Due to data protection and confidentiality concerns, detailed material could not be made available to openMedicine.

In chapter 5, in order to develop appropriate survey questions, first core issues relating to the Identification of a medicine in a prescription are identified, followed by a brief discussion of potential levels at which substitution may occur. This then leads to a presentation of the core research questions selected to be surveyed.

3 Analytical framework

This chapter will review various definitions of substitution as available in the literature and elsewhere, identify different types of substitution, and explore the difference between substitution and selection at the point of dispensation. Next, policy arguments for and the potential clinical impact of substitution are briefly discussed. Suggestions for excluding certain types of substitution from further discussions are made. Finally, an openMedicine definition of substitution of a medicinal product is provided.

3.1 Definitions of substitution

- Defining substitution

The Oxford Dictionary defines substitution as “the action of replacing someone or something with another person or thing.”⁵ The concept of substitution is a familiar one in economic theory and consumer practice.⁶ Many products may be used as substitutes for others such as margarine for butter, or tea for coffee. If the price of one becomes too high, the other product may be used even though it isn’t a perfect substitute for the preferred one.

This economic concept has been translated into the health sector and market, particularly the market for medicinal products. In its “Statement on Drug Substitution”⁷ the World Medical Association (WMA)⁸ notes that “the prescription of a drug represents the culmination of a careful deliberative process between physician and patient aimed at the prevention, amelioration or cure of a disease or problem. This deliberative process requires that the physician evaluate a variety of scientific and other data including costs and make an individualized choice of therapy for the patient. Sometimes, however, a pharmacist is required to substitute a different drug for the one prescribed by the physician.” And it underlines that this practice must be based, first of all, on national regulatory authorities making sure the bioequivalence and the chemical and therapeutic equivalence of prescription drug products from both multiple and single sources. “Quality assurance procedures should be in place to ensure their lot-to-lot bioequivalence and their chemical and therapeutic equivalence.”⁹

- Generic medicinal products, bioequivalence, and substitution

The concept of bioequivalence is fundamental in the context of generic medicinal products, and such products are a core object of substitution. A generic medicinal product is one “which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability

⁵ <http://www.oxforddictionaries.com/definition/english/substitution>

⁶ Substitute goods are „different goods that, at least partly, satisfy the same needs of the consumers and, therefore, can be used to replace one another. Price of such goods shows positive cross-elasticity of demand. Thus, if the price of one good goes up the sales of the other rise, and vice versa.“ <http://www.businessdictionary.com/definition/substitute-goods.html>

⁷ WMA (World Medical Association). Statement on Drug Substitution. Adopted by the 56th WMA General Assembly, Santiago, Chile, October 2005 and reaffirmed by the 200th WMA Council Session, Oslo, Norway, April 2015. <http://www.wma.net/en/30publications/10policies/d13/>

⁸ The World Medical Association is an independent confederation of free professional medical associations, representing physicians worldwide. It is a partner of the WHO Global Health Workforce Alliance becomes speaking for doctors in international affairs. See http://www.who.int/workforcealliance/members_partners/member_list/wma/en/

⁹ WMA (World Medical Association). Statement on Drug Substitution

studies.”¹⁰ “The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product.”¹¹ ¹² “Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy.”¹³

3.2 Types of substitution

Usually two major types of substitution of a medicine at the point of dispensation are distinguished –generic and therapeutic substitution. These two types are not necessarily mutually exclusive or disjunct, because both are more or less motivated by economic or cost-savings intention.

- Generic substitution

The World Medical Association in its “Statement on Drug Substitution” defines generic substitution as follows: “In a generic substitution, a generic drug is substituted for a brand name drug. Both drugs have the *same active chemical ingredient, same dosage strength and same dosage form.*”¹⁴

Similarly, Duru and others define ‘direct’ generic substitution as “replacing a brand-name drug with its less expensive generic equivalent, when available.”¹⁵

Johnston et al. define it as follows: “Generic substitution occurs when a different formulation of the same drug is substituted. All generic versions of a drug are considered by the licensing authority to be equivalent to each other and to the originator drug.”¹⁶ The same definition was adopted by the European ePrescription Guidelines.¹⁷ However, it remains unclear how “dif-

¹⁰ Directive 2001/83/EC, Article 10(2)(b) – “The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. Furthermore, the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form.” Committee for Medicinal Products for Human Use (Chmp). Guideline on the Investigation of Bioequivalence. London, 20 January 2010, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, p. 4. – http://www.bpac.org.nz/BPJ/2009/generics/docs/bpjse_generics_bio_pages_4-8.pdf: „Bioavailability is a measurement of the extent of a therapeutically active medicine that reaches the systemic circulation and is therefore available at the site of action.“

¹¹ For details, see Committee for Medicinal Products for Human Use (Chmp). Guideline on the Investigation of Bioequivalence. London, 20 January 2010, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

¹² A “reference medicinal product shall mean a medicinal product authorised under Article 6 [“No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93], in accordance with the provisions of Article 8.” Directive 2001/83/EC, Article 10 2. (a)

¹³ For details, see Committee for Medicinal Products for Human Use (Chmp). Guideline on the Investigation of Bioequivalence. London, 20 January 2010, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

¹⁴ Italics by the authors

¹⁵ Duru, O. K., et al. (2014). Potential savings associated with drug substitution in Medicare Part D: the Translating Research into Action for Diabetes (TRIAD) Study. *Journal of general internal medicine*, 29(1), 230-236.

¹⁶ Johnston, A., et al. (2011). Generic and therapeutic substitution: a viewpoint on achieving best practice in Europe. *British journal of clinical pharmacology*, 72(5), 727

¹⁷ Guidelines on ePrescriptions Dataset for Electronic Exchange under Cross-Border Directive 2011/24/EU - Release 1, Nov. 2014, p. 25

ferent formulation” and “same drug” are to be defined. And it is likely that different “licensing authorities” use variant interpretations of what means “equivalent to each other and to the originator drug.”

It seems that in these definitions “brand name” is referring to the originator, innovator or reference medicinal product. This use of “brand name” is not in line with European official definitions. In the EU, Article 6 of Regulation (EC) No 726/2004 “laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency” stipulates that “each application for the authorisation of a medicinal product (...), otherwise than in exceptional cases relating to the application of the law on trade marks, shall include the use of a single name for the medicinal product.”¹⁸ According to Article 1(20) of Directive 2001/83/EC “on the Community code relating to medicinal products for human use”, the name of a medicinal product “may be either an invented name not liable to confusion with the common name, or a common name or scientific name accompanied by a trade mark or the name of the marketing authorisation holder.” In line with the definition introduced in D2.1¹⁹ and global²⁰ use, both types of name will be identified as “brand name”, or known as proprietary or trade name.

The “invented” name is assigned by the manufacturer; it may also be called an innovator name. In the EU market, the EMA Committee for Medicinal Products for Human Use (CHMP) has in its “Guideline on the Acceptability of Names for Human Medicinal Products Processed through the Centralised Procedure”²¹ identified certain requirements which such an “invented name” must meet.²² These include, as part of EMA’s role in evaluating the safety of medicinal products in the centralised procedure, aspects like whether the invented name proposed for a medicinal product could create a public-health concern or potential safety risks.

In the EU, a “generic drug” is defined as a “common name” medicine. A common name is, according to Article 1(21) of Directive 2001/83/EC, as amended, “The international non-proprietary name (INN) recommended by the World Health Organisation, or, if one does not exist, the usual common name.” Here also the CHMP “Guideline on the Acceptability of Names for Human Medicinal Products” applies.²³

Note that this implies that several companies may make the same generic medicine, each with their own brand name.

The World Medical Association in its “Statement on Drug Substitution” limits – in principle – generic substitution to the exchange of an invented name by a generic medicinal product with otherwise identical characteristics (“*same active chemical ingredient, same dosage strength and same dosage form*”). We subsume this under economic substitution because it is usually undertaken to lower the costs for the healthcare provider respectively payer.

¹⁸ Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 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. 2004R0726 — EN — 05.06.2013 — 007.001

¹⁹ P. 6

²⁰ Cf. e.g. www.drugs.com or <http://patient.info/health/generic-vs-brand-name-medicines>.

²¹ EMA - Committee for Medicinal Products for Human Use (CHMP). Guideline on the Acceptability of Names for Human Medicinal Products Processed Through the Centralised Procedure.

²² We reference here only the status-quo at the EU level, where „The Centralised Procedure” requires one single name for the medicinal product to be authorised. Where national authorities are involved, this may not be the case.

²³ In the USA, the generic name is assigned by the US Adopted Name Council.

- Substitution by imports

A further form of substitution is when a national medicinal product marketed e.g. in Germany is substituted by the identical product from the same producer which was produced for another (e.g. French) market, where it is sold at a cheaper price, and re-imported into the country of origin, here Germany. Under EU single market regulations, this is an option, as long as the re-imported product meets national regulations with respect to patient leaflet, packaging etc.

- Therapeutic substitution

The World Medical Association defines therapeutic substitution as follows: “Substitution with a *chemically different* drug. The substituted drug belongs to the same pharmacologic class and/or to the same therapeutic class.”²⁴ As medicines may be classified first on their clinical and therapeutic effects and, second, on their mechanisms of action,²⁵ this definition reflects that substitution may be based on the way a medicine is used to treat a particular condition and/or the chemical type of the active ingredient, whereby a particular drug may be classified into one or more drug classes.²⁶

A *therapeutic classification* is based on the usefulness of a specific medicine for a clinical condition, e.g. in treating a particular disease. Such medicines may be antihypertensives, contraceptives, antidepressants.

A *pharmacologic classification* refers to how an agent works at molecular, tissue and body system levels, i.e. it is based on its mechanism of action in the body, e.g. beta receptor blockers, ACE inhibitors (antihypertensives).

Another, similar definition of therapeutic substitution by Duru et al. is “the use of a less expensive substitute that is not biologically equivalent but has a similar clinical/treatment effect as the original medication.”²⁷

Johnston et al. define it as follows: “Therapeutic substitution is the replacement of the originally prescribed drug with an alternative molecule with assumed equivalent therapeutic effect. The alternative drug may be within the same class or from another class with assumed therapeutic equivalence.”²⁸ Exactly the same definition was adopted by the European ePrescription Guidelines.²⁹

However, as to our knowledge no globally or at least Europe-wide agreed classifications exist, such definitions are difficult, if not impossible to operationalise. This is underlined by this note in Duru et al.: “We only included therapeutic substitutions that *all six team members* agreed were clinically appropriate.”³⁰ Effective, therapeutic substitution at the point of dispen-

²⁴ WMA Statement on Drug Substitution, Chile 2005)

²⁵ Cookson, J., Katona, C., & Taylor, D. H. (2002). *The Use of Drugs in Psychiatry: The Evidence from Psychopharmacology*. Gaskell Press.

²⁶ <http://www.drugs.com/drug-classes.html>

²⁷ Duru et al., op. cit, p. 230

²⁸ Johnston, A., et al. (2011). Generic and therapeutic substitution: a viewpoint on achieving best practice in Europe. *British journal of clinical pharmacology*, 72(5), 727

²⁹ ePrescription Guidelines, p. 25

³⁰ Duru et al., op. cit, p. 231. *Italics* by the authors

sation would imply that a community pharmacist can indeed base her/his substitution decision on a reliable regulatory base.

As therapeutic substitution is discussed in the context of constraining rising healthcare costs,³¹ one may classify it not as a separate type, but also as a type of economic substitution.

- Shortage of medicines as a reason for substitution

According to the Pharmaceutical Group of European Union (PGEU) and others like European Association of Hospital Pharmacists (eahp) and EMA, shortages of medicines have been recognised as a public health problem in Europe,³² and elsewhere this phenomenon has also been observed.³³ A recent survey of PGEU members showed that it is an EU-wide challenge. In the UK alone over 1 million branded medicine supply failures occur each year. In the EU all classes of medicines are affected, from complex chemotherapy agents to even basic medication such as aspirin. However, there is yet little understanding of how medicine shortages affect community pharmacists and ultimately the patients they serve.³⁴

In the literature we found theoretical research by Kim and Morton on “A Model of Generic Drug Shortages: Supply Disruptions, Demand Substitution, and Price Control,”³⁵ but no pragmatic discussion of the substitution issue in the context of shortage of medicines at the dispensing end. It is to be assumed that in this case the same rules apply to dispensation at community pharmacies as for the other substitution challenges discussed so far.³⁶

3.3 Substitution versus selection

In instances where a physician prescribes, in compliance with national rules, *only an active or therapeutic ingredient*, but not a specific medicinal product, the dispensing pharmacist has always to *select* an appropriate product from the range of medicinal products meeting the specified criterion and being available. We do not consider this a case of substitution, but rather one of selection.³⁷

Similarly, when only a *predefined group of medicinal products* (by a group name, a code or other identifying elements), e.g. from a pharmaceutical or therapeutic class, is mentioned in a

³¹ Ibidem.

³² Pharmaceutical Group of European Union - PGEU (2012). Statement on Medicine Shortages in European Community Pharmacies. Ref 12.08.28E 003. - European Association of Hospital Pharmacists: Medicines Shortages. EAHP's 2014 survey of the medicines shortage problem: <http://www.eahp.eu/practice-and-policy/medicines-shortages>. EMA: Shortages catalogue at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000376.jsp&mid=WC0b01ac05807477a6. „The shortages catalogue contains information on medicine shortages that affect or are likely to affect more than one European Union (EU) Member State, where the European Medicines Agency has assessed the shortage and provided recommendations to patients and healthcare professionals across the EU.

³³ See e.g. American Society of Health-System Pharmacists (ashap): Drug Shortages: Current Drugs. <http://www.ashp.org/menu/DrugShortages/CurrentShortages>

³⁴ PGEU 2012, op. cit.

³⁵ Sang-Hyun Kim, Fiona Scott Morton (2015). A Model of Generic Drug Shortages: Supply Disruptions, Demand Substitution, and Price Control. Yale School of Management. Jan. 2015

³⁶ Cf. Also Fox, E. R., Birt, A., James, K. B., Kokko, H., Salverson, S., & Soflin, D. L. (2009). ASHP guidelines on managing drug product shortages in hospitals and health systems. American journal of health-system pharmacy, 66(15), 1399-1406.

³⁷ Theoretically, in case only a single medicinal product available meets the selection criterion, the pharmacist cannot select, but has to dispense this medicine. On the other hand, in case no product meeting the criterion exactly is available, but regulation allows dispensation based on a very similar criterion or from another group of very similar products, this constitutes still a selection process, because no unique product was specified in the prescription.

prescription (cluster prescription), the dispensing pharmacist has equally to *select* a specific product from the range of medicinal products being a member of the identified set, or meeting the identifying attributes and being available. We do not consider this a case of substitution either.

In other words, selection takes place when, at the point of dispensation in a community pharmacy, the pharmacist has to *select a specific medicinal product* which meets the selection criteria (e.g. active ingredient; member of a predefined set of medicinal products, ...) specified in a prescription, in line with national law and regulations (Cf. WP 4).

3.4 Policy arguments for and impact of substitution

As the review of the literature and other documents cited in this paper indicates, the main driver for substitution of medicinal products at the point of dispensation is to decrease the cost of medicinal products to the health system. National health ministries, regulatory agencies, statutory health insurances and public health decision makers all are driving such intentions. "The need to manage and minimize costs is increasingly important for healthcare systems across the world. Generic substitution is already used widely throughout Europe and payers are increasingly looking towards therapeutic substitution to make additional savings."³⁸

It seems that this trend has accelerated over the last ten or so years, with some countries already reaching a level of 70% to 80% of all medicines dispensed being either substitutes – e.g. by dispensing the 'product of the month' selected as the presently cheapest one by a regulatory agency, a health insurance or others - or selected by the pharmacist on a prescription specifying only a generic substance or a group of medicines. However, detailed statistics are not available.

And it has been argued that therapeutic drug substitution has the potential to double or even triple annual cost savings compared with savings achieved from generic substitutions.³⁹ Therapeutic drug substitutions are here driven by the intent to promote the use of less expensive substitutes that are not equivalent but have a similar treatment effect as the original medication.

Not surprisingly, big pharmaceutical companies active in the originator medicinal products market or their trade associations attempt to moderate this trend to protect their investment in new drug development and profits. Serious arguments have been advanced within the medical profession as to the potential risks and side effects of substitution. "When switches of medication are driven purely on economic grounds, there may be potential conflicts between the needs of the healthcare provider and those of individual patients, and this may impact on patients' safety and treatment outcomes."⁴⁰ The clinical challenges identified relate to the potentially reduced quality of generic products (e.g., their adjuvant(s) or excipients may differ from the originator product; "only" bioequivalence is assured, not identity; their therapeutic efficiency may be lower; new adverse drug events (ADE) and/or increased severity of

³⁸ Johnson et al., op. cit., p. 727

³⁹ Duru et al., op. cit.

⁴⁰ Ibid. See there also for a broad discussion of such challenges and associated risks, and references to pertinent medical publications.

known ADE may occur; patient compliance may be reduced because the medicine is not known to them; etc.

These aspects and discussions are of no direct concern to the stated objectives of the openMedicine project. However, as background to the ongoing debate these are relevant challenges to be considered by member states when deciding on how to proceed with cross-border substitution recommendations. On this the next deliverable will develop solution proposals and next steps for MSs authorities to facilitate future cross-border healthcare, and submit them for validation.

3.5 Types of substitution to be excluded or to be discussed further

Besides the reasons mentioned so far for considering substitution, another context within which a substitution could be permitted may be extraordinary circumstances, like

- Unavailability of the prescribed medicinal product, but clinical need for ad-hoc, immediate dispensation (e.g. out-of-hour service, emergency).

It is suggested to exclude such circumstances from further considerations in a cross-border or related context.

It is suggested to also exclude from considerations of substitution in a cross-border context

- “medicinal product[s] subject to *special* medical prescription,”^{41 42}

e.g. those with a substance classified as a narcotic or a psychotropic one, or with a substantial risk of medicinal abuse, and those

- “subject to *restricted* medical prescription,”⁴³

e.g. those reserved for treatments which can only be followed in a hospital environment, or those for outpatients where its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment. Here the risk for the patient in a cross-border context where communication challenges due to differences in language are likely, and the prescribing professional may not be readily available, probably outweighs the potential benefit from a ready substitution.

Furthermore, it is to be noted that

- certain medicinal products cannot be substituted in certain contexts or should usually not be substituted for clinical and patient safety reasons;

these include antibodies, HIV medications, new medicinal products (without a generic product yet available), or products with different authorisations concerning their indication(s) across countries.⁴⁴

⁴¹ EMA - Committee for Medicinal Products for Human Use (CHMP). Guideline on Legal Status for the Supply to the Patient of Centrally Authorised Medicinal Products. London, 26 July 2006, Doc. Ref. EMEA/186279/2006, p. 4

⁴² Article 11 para 6 of Directive 2011/24/EU states that the rule that a medication shall be dispensed on the territory of another member state “shall not apply to medicinal products subject to special medical prescription.”

⁴³ EMA-CHMO, op. cit., p. 5

⁴⁴ Indication means a symptom that suggests certain medical treatment is advisable or necessary: <http://www.oxforddictionaries.com/definition/english/indication>. Across countries, a generic product may refer to the same INN, but nevertheless may have been authorised for different indications, like for a very broad one (pain) or specific types

- Substitution of biologics in general through biosimilars

is still a quite unexplored territory.⁴⁵ EMA defines biosimilars as follows: “A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use.”⁴⁶ As the name already indicates, biosimilars are medicinal products which are 'highly similar' to the reference product, although minor differences are allowed if the differences do not result in clinically meaningful safety, purity and potency differences. Names like “follow-on biologics” or “subsequent entry biologics” are also used.⁴⁷ Whereas in the USA several states have regulated the substitution of biologics by biosimilars at the community pharmacy level,⁴⁸ this is a hotly debated issue in Europe,⁴⁹ and similar regulations in EU countries are virtually absent. The EMA does not have the authority to designate a biosimilar as 'interchangeable' (unlike the FDA in the USA) and therefore does not evaluate biosimilar interchangeability. The decisions on the interchangeability of biosimilars and innovator products rest only with the EU member states. The European Generic Medicines Association (EGA) reports that at least 12 countries across the EU have introduced rules to avert automatic substitution of innovator biologicals with biosimilars.⁵⁰ However, France has recently taken a pioneer step in allowing a restricted form of biosimilar substitution.⁵¹

Other

- medicines may be prohibited from substitution by regulation,

as e.g. stipulated in the German special list of medicinal substances listing products which must not be substituted.⁵² There, with respect to four therapeutic groups, a prescribed medicinal product must not be substituted by another medicinal product with the same active ingredient.

A specific substitution challenge arises in the context of

- “medicinal products on medical prescription for renewable ... delivery.”⁵³

The definition varies across member states where this sub-category exists. The implementation of this sub-category has to be in accordance with national measures and in compliance

of pain (headache, menstrual pains, muscle pain, ...); it may also differ with respect to information on whether it may be administered to children, on how often to be taken...

⁴⁵ Mike Stuart (2012). Is “Biologics Versus Biosimilars” A Different Story Than Brand Names Versus Generics? <http://delfini.org/blog/?p=100>

⁴⁶ http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp

⁴⁷ Mike Stuart, op. cit.

⁴⁸ FDA Drug Daily Bulletin. Massachusetts Enacts Biosimilar Substitution Law. July 2, 2014

⁴⁹ EFPIA LoE Biologics WG (28/09/2015), in its „EFPIA Policy Principles for Off-patent Biologic Medicines in Europe“ states: „Pharmacy level substitution is not an acceptable practice for biologic medicines as long as the biological medicines are not designated as being substitutable by the competent regulatory authority.“

⁵⁰ GaBI Online (2015). Generics and Biosimilars Initiative. Efficacy, extrapolation and interchangeability of biosimilars. Mol, Belgium: Pro Pharma Communications International: www.gabionline.net/Biosimilars/Research/Efficacy-extrapolation-and-interchangeability-of-biosimilars

⁵¹ France's biosimilar law may set trend inside the EU. Law 360. 2014. www.law360.com/articles/507058/france-s-biosimilar-law-may-set-trend-inside-the-eu

⁵² „Substitutionsausschlussliste“ - <http://www.aok-gesundheitspartner.de/bund/arzneimittel/verordnung/substitution/index.html>

⁵³ See Article 70 (2) of Directive 2001/83/EC

with the content of the respective SPC [Supplementary protection certificate].⁵⁴ Regulations controlling access and availability to patients differ across countries, and in case such a prescription is at all to be dispensed in a cross-border situation it seems reasonable to involve a physician as needed. The same applies in cases where before a prescription can be refilled the patient must be seen by a health provider each time. At a more principal level one may discuss whether renewable prescriptions should, except at initial dispensation, be submitted to the substitution option at all. Clinicians and other experts have argued that for patient safety reasons, compliance and familiarity of the patient with the medicine substitution should not be allowed after the first dispensation.

A final issue, which came up in the epSOS context, is whether

- medicinal products with more than one active ingredient
 - also called combination drugs - should be open for substitution in a cross-border context. The challenge is that such medicines are often quite difficult to be identified univocally in a foreign country – “It will be necessary to reach agreement on an international standard to represent multiple active ingredients in medications”⁵⁵ -, and that certain combination drugs are not necessarily available in all markets. This is an issue in need of further discussion once the identification of such products has been explored in WPs 2 and 3 in greater detail.

3.6 Defining substitution of a medicinal product

In openMedicine substitution at the point of dispensation is defined as the exchange of a medicinal product, univocally specified in a prescription, by another one which differs with regard to one or several of these items:

- Name
 - invented name (originator or innovator [brand] product name)
 - common name (generic [brand] product name)
- Package size/quantity
- Dosage form
- Strength
- Route of administration

In other cases, where only (an) active ingredient(s) or a group (“cluster”) of medicinal products are specified in a prescription, i.e. not a single, univocally identifiable medicinal product, plus additional attributes like quantity, dosage and strength, a suitable medicinal product has to be *selected* by the community pharmacist from the set of products meeting the criteria specified in the prescription, in line with the respective legal and regulatory context.

This definition covers all types of substitutions identified above, be it for economic, therapeutic or shortage reasons.

⁵⁴ Ibidem

⁵⁵ Guidelines on ePrescriptions Dataset for Electronic Exchange under Cross-Border Directive 2011/24/EU. Nov. 2014, p. 18

4 Specifying medicines in a prescription, and substitution recommendations

This chapter identifies the basic types of a prescription – paper, electronic, cross-border – relevant for this paper, explores the four basic options for the specification of a medicine in a prescription, and presents the EC non-exhaustive list of elements to be included in cross-border medical prescriptions, as well as the European ePrescriptions dataset for electronic cross border exchange. How substitution has been dealt with in the epSOS pilots and the ePrescription Guidelines is reviewed, and the World Medical Association recommendations on substitution are finally noted.

4.1 Type of prescription – paper, electronic, cross-border

Actual prescriptions issued by a healthcare professional may vary from a formless handwritten prescription to a highly structured electronic prescription, depending on the mode, the type of medicine, and national regulations. There are member states which allow, in principle, a simple formless, handwritten prescription. However, in all further considerations we presume that a template/form providing for (semi-) structured contents exists, which may vary by the type of prescription to be issued, and which may contain mandatory and optional elements. Type refers here to whether it is a

- prescription written on paper – via handwriting or printed through an IT system -, whether it is a paperless
 - ePrescription transferred by electronic communication from the prescriber’s IT system to a national/regional repository or directly to a pharmacy chosen by the patient complying with national regulations and requirements, or whether it is a
 - cross-border prescription (paper or electronic) to be dispensed abroad, (also) complying with the non-exhaustive list of elements to be included in cross-border medical prescriptions according to Implementing Directive 2012/52/EU.

In some countries⁵⁶ there exist several templates, depending, e.g., on whether it is a “standard” medicine, one subject to special medical prescription, or on who will pay for the medicine.⁵⁷ In our survey, we concentrate only on requirements for a “standard” prescription and related substitution and selection challenges. It turned out that otherwise the number of options to be researched would become too large, and the questionnaire too long and too complex to be handled by an online survey distributed to a large number of addresses.

Furthermore, the questions relate only to *items to be noted by the prescriber to identify the medicine* to be dispensed by a community pharmacist, and not to further items which may identify the patient, the prescriber, the reimbursing organisation, co-payment requirements, etc.

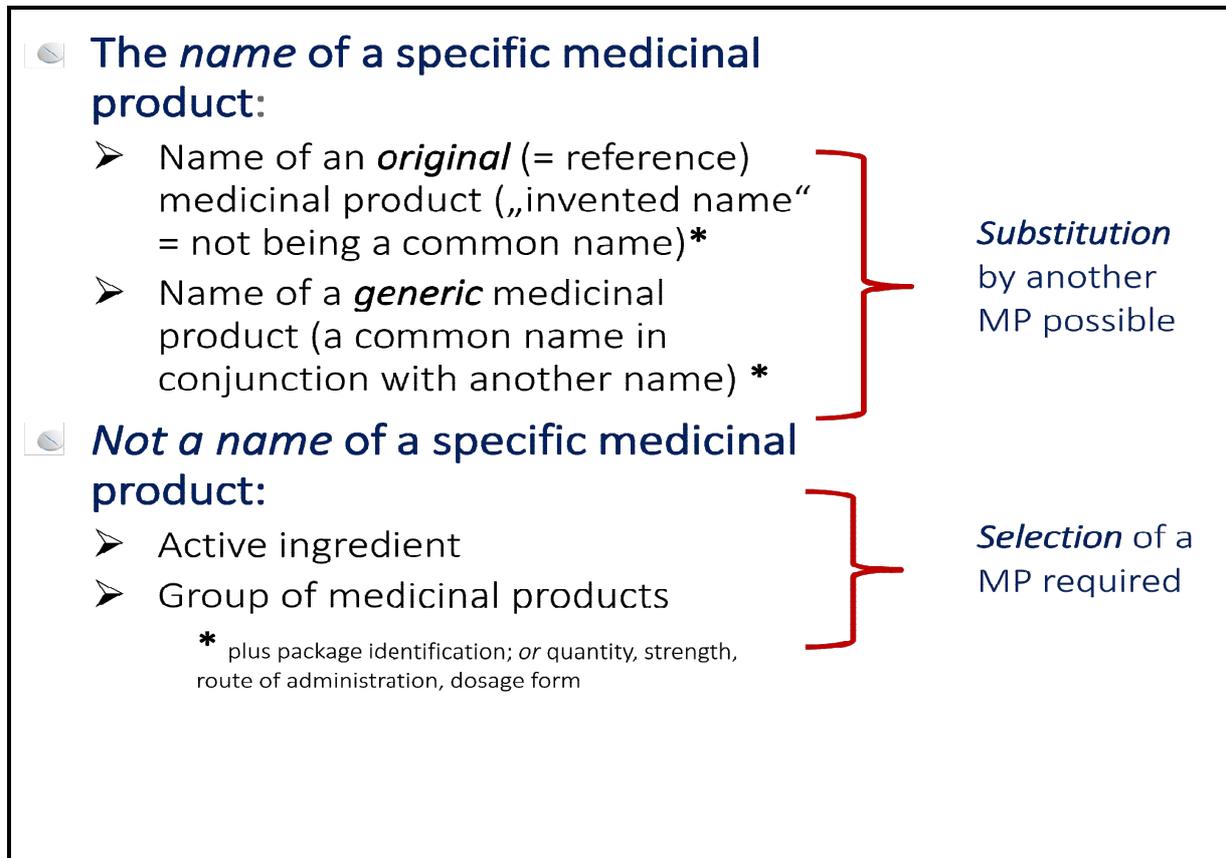
⁵⁶ In Germany, for instance, four different templates are in use (pink = “standard”, reimbursed by statutory insurance, blue = reimbursed by private insurance, green = usually not reimbursed by an insurance, yellow = for products subject to special rules like narcotics).

⁵⁷ This may be paid for as part of national healthcare system services, by a statutory or private health insurance, another agency like social services, or out-of-pocket by the patient.

4.2 Four basic specification options

The content of a prescription with respect to the medicinal product or active ingredient specified varies considerably across the Union. As a first approximation, the following figure depicts the four basic types of identifying a medicine in a prescription to be dispensed by a community pharmacist:

Figure 1: Specification of a medicine in a prescription



This variety opens up a highly complex environment for indeed reliably identifying the prescribed medicine in a cross-border context. As all of this is a prerequisite for applying – or not applying – national substitution rules, in this chapter we first explore general options, regulations and recommendations for elements to be included in cross-border paper and electronic prescriptions. This will then be followed by a succinct review of known international recommendations for implementing substitution.

4.3 Detailed list of attributes

Our research and discussions with experts identified a comprehensive list of mandatory or optional items which may be recorded in a prescription; this list is provided in Appendix III of this paper.

Depending on the specific circumstances of the case (medicine, indication for the prescription, demographics and [cognitive] abilities of the patient, etc.), such detailed information may be highly relevant for the pharmacist in case substitution is to be considered.

4.4 EC non-exhaustive list of elements to be included in cross-border medical prescriptions

The European-wide identification of a medicinal product in a cross-border prescription is an EU priority. In *Directive 2011/24/EU on the application of patients' rights in cross-border healthcare* it was stated in recital 53: "Where medicinal products are authorised within a Member State and have been prescribed in that Member State by a member of a regulated health profession ..., it should, in principle, be possible for such prescriptions to be medically recognised and for the medicinal products to be dispensed in another Member State in which the medicinal products are authorised."

In its Art. 11 2. (c) that Directive states: "In order to facilitate implementation of paragraph 1 [that prescriptions issued for a medicinal product in another member state can be dispensed in any other member state], the Commission shall adopt: "(c) measures to facilitate the correct identification of medicinal products or medical devices prescribed in one Member State and dispensed in another, *including measures to address patient safety concerns in relation to their substitution in cross-border healthcare where the legislation of the dispensing Member State permits such substitution.*"⁵⁸

According to the European "Implementing Directive 2012/52/EU of 20 December 2012 laying down measures to facilitate the recognition of medical prescriptions issued in another Member State,"⁵⁹ a cross-border prescription should contain as part of the "non-exhaustive list of elements to be included in medical prescriptions" for the "Identification of the prescribed product, where applicable," the following elements:

- "'Common name' as defined by Article 1 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
- The brand name if:
 - (a) the prescribed product is a biological medicinal product, as defined in point 3.2.1.1.(b) of Annex I (Part I) to Directive 2001/83; or
 - (b) the prescribing health professional deems it medically necessary; in that case the prescription shall shortly state the reasons justifying the use of the brand name
- Pharmaceutical formulation (tablet, solution, etc.)
- Quantity⁶⁰
- Strength, as defined in Article 1 of Directive 2001/83/EC⁶¹
- Dosage regimen.⁶²
 - Intended site
 - Release characteristics

⁵⁸ Italics are ours.

⁵⁹ Official Journal of the European Union, L 356, pp. 68-70 EN, 22.12.2012.

⁶⁰ Quantity or 'presentation' includes the size of the container (fill-volume/fill-weight) and/or the pack size. The pack size equals number of tablets, number of sachets, number of ampoules, etc. per outer packaging.

⁶¹ Strength is defined as the concentration expressed as the amount of active substance per ml, per puff, per drop, per kg, per m² as appropriate.

⁶² The schedule of doses of a therapeutic agent per unit of time, including: the time between doses (e.g., every 6 hours) or the time when the dose(s) are to be given (e.g., at 8 a.m. and 4 p.m. daily), and the amount of a medicine (e.g., number of capsules) to be given at each specific time.

It is important to note that the Implementing Directive of 2012 does not require any or all national prescriptions to enumerate such elements. In recital 8 it rather notes: “As the overall impact of cross-border healthcare is limited, the non-exhaustive list of elements should apply only to prescriptions intended to be used in another Member State.” “This Directive shall apply to prescriptions, as defined in point (k) of Article 3 of Directive 2011/24/EU, which are issued further to a request of a patient who intends to use them in another Member State.” To assist patients requesting appropriate prescriptions, national contact points referred to in Article 6 of Directive 2011/24/EU should provide patients with adequate information on the content and purpose of this non-exhaustive list.

Furthermore, the Implementing Directive encourages member states to go beyond this limited set of identifying elements by noting in recital 9: “As the principle of mutual recognition of prescriptions derives from Article 56 of the Treaty on the Functioning of the European Union, this Directive does not preclude the Member States from applying the principle of mutual recognition to prescriptions that do not contain the elements set out in the non-exhaustive list. At the same time, nothing in this Directive prevents the Member States from providing that prescriptions drafted on their territory, with a view to be used in another Member State, contain additional elements that are provided for under the rules applicable on their territory, as long as these rules are compatible with Union law.”

4.5 European ePrescriptions dataset for electronic cross border exchange

The “Guidelines on ePrescriptions Dataset for Electronic Exchange under Cross-border Directive 2011/24EU – Release 1”⁶³ respond to Article 11 2. (b) of the Directive 2011/24/EU on the application of patients’ rights in cross-border healthcare, which defines the need for “guidelines supporting the Member States in developing the interoperability of ePrescriptions”. Their primary focus “is to support the objective of cross-border electronic exchange of prescriptions. A secondary focus of the guidelines is to provide material for each Member State to use, if they wish, for reference at national level.”⁶⁴

They are complementary to the Commission Implementing Directive 2012/52/EU laying down measures to facilitate the validation of medical prescriptions issued in another Member State focusing, inter alia, on the “correct identification of medicinal products [or medical devices] including allowance for substitution.”

With respect to the identification of the prescribed medicinal product and further related information, including a note on substitution, the dataset described in detail in “Annex C – ePrescription Dataset covers the items noted in the following table, including a column on comments based on epSOS’ experiences. As can be seen, this data set is much more comprehensive than the one in the Implementation Directive, and already a major step forward in reliable, trustworthy cross-border dispensation of prescribed medicines.

⁶³ Adopted by eHealth Network on 18 Nov 2014.

⁶⁴ Ibidem, p. 3

Table 1: Excerpts from the data set identified in the Guidelines on ePrescriptions Dataset for Electronic Exchange under Cross-border Directive 2011/24EU

| Fields | Field description | Notes from epSOS |
|---|---|---|
| A.1 Core data elements | | |
| A.1.4 Identification of the prescribed product | | |
| A.1.4.1 Name of the item | <p>An identification of the medicinal product [i.e. any substance or combination of substances that may be administered to human beings for treating or preventing disease, with a view to making a medical diagnosis or to restore, correct or modify physiological functions] that is prescribed to the patient. In addition, information may be included regarding the possibility to replace the prescribed product with an alternative equivalent product.</p> <p>Note: the term product includes pharmaceutical products (branded medicinal products, generic/scientific name medicinal products or pharmaceutical preparations [ISO 21549-7:2007]) or non-pharmaceutical products.</p> | <p>Some MS were pushing to exclude this concept because, in their view, it could increase ambiguity and cause patient safety issues. Are names of medicinal products unique in Europe? Would the (additional) usage of a unique ID be better? Magistral medicinal products don't usually have "names" => problem if mandatory.</p> |
| A.1.4.2 Identifier of the item | <p>Medicinal product manufactured in a pharmacy or pharmacy department, which is based on a recipe and is intended to be used for one and only one subject of care [ISO 21549-7:2007].</p> <p>Note 1: a magistral/extemporaneous medicinal product is also a pharmaceutical product.</p> <p>Note 2: the term extemporaneous medicinal product is not to be used, as it is more appropriate for describing a medicine processed during the administration of a medicinal product, especially when a mixture is made just before, for example, intravenous administration. Information about the constituent ingredients if the prescription concerns an extemporaneous preparation or compound medicine.</p> | <p>Outside scope of epSOS</p> |
| A.1.4.3 Strength of the item | <p>The content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form. [Article 1 of Directive 2001/83/EC]</p> <p>Note: strength of the medicinal product may also be derived from the element 'dose regimen'. If for example the prescription contains a statement such as 'take 10mg 3x daily for 9 days' the strength can be derived from this. In such circumstances, strength may not be provided separately.</p> | <p>It cannot be expressed separately from A.1.4.1 because the strength/dilution as a ratio should be provided for each active ingredient in compounds.</p> |

| Fields | Field description | Notes from epSOS |
|--|---|--|
| A.1.5 Prescription information | | |
| A.1.5.1 Pharmaceutical formulation | The formula in which the prescribed medicinal product is/will be administered (e.g. Tablet, solution, ointment) | It should describe compounds and moiety. |
| A.1.5.2 Quantity | Total quantity or volume of the medicinal product that is prescribed Note 1: in some cases quantity might be derived from element 1.5.3 Dose regimen. In this case, the quantity does not need to be stated separately. Note 2: depending on national legislation, this quantity may or may not be dispensed in one dispensation. | This is a complex concept: simple in the case of pills, more complex for liquids. Very various and complex for packs of packages (e.g. 10 syringes of 1 ml). |
| A.1.5.3 Dose regimen | The regimen governing the dose quantity per single administration, the dose frequency, the route of administration and/or speed of administration (in the event of intravenous administration). Note: this information may be used by the dispenser to calculate the quantity to be dispensed. | Few MS have it. Even less as coded element: optional in epSOS |
| A.1.5.4 Duration of treatment | Start and/or stop time of treatment | |
| A.1.5.5 Directions for use | Details about the directions for use of the prescribed medicinal product, such as 'with food' or 'before a meal') and any cautionary advice for correct use of the prescribed drug by the patient | Nearly none has this as a coded concept |
| A.1.5.6 Pharmaceutical preparation description | This also includes extemporaneous preparation, compounded medication and magistral preparation. | |
| A.2 Optional elements of prescription | | |
| A.2.3 Prescription information | | |
| A.2.3.1 Starting date of therapy | The time and date on which it is agreed that therapy will start | End of the therapy is also an optional item of data in epSOS |
| A.2.3.2 Prescription expiry date | The date and optionally time when the prescription is considered to have expired. This might be dependent on local or national policy or legislation, in accordance with the treatment plan or because the therapeutic need for the prescribed medicine has expired. In some countries (e.g. Germany) legislation is so clear that it is not necessary to include it in the prescription. | |

| Fields | Field description | Notes from epSOS |
|-------------------------------------|--|---|
| A.2.3.3 Repeats | Whether an issued prescription allows for several repeating dispensations. In some countries, when medicinal products are dispensed for the first time, the patient may only receive medication for a short period of time. When a patient starts taking medication for a chronic illness, the prescriber can issue a prescription for a longer period that is now separated by repeats. In addition, the maximum quantity (A.1.4.3) of the prescribed product that may be dispensed in one dispensation may be stated here. | |
| A.2.3.4 Minimum dispensing interval | If an issued prescription allows for several repeating dispensations (A.1.4.6), the minimum time interval between dispensations should be stated here [e.g. 5]. This can be important in the case of medicinal products of which patients are prone to take overdoses, e.g. opioids. | |
| A.2.3.5 Reason for prescription | <p>The reason why the medicine is being prescribed, including the option to mention that the medicinal product is being prescribed for 'off label' use. The reason for the prescription gives the dispenser the opportunity to review the prescription for medication safety issues.</p> <p>Note: in some countries it is obligatory to state the reason for prescription on the prescription itself for some or all medicinal products. An example of this in the Netherlands is the prescription of methotrexate, since the indication for which it is used in the Netherlands (chemotherapy or rheumatoid arthritis) greatly impacts both strength and dose interval of the medication.</p> | Conceptually fine, but extremely various and complex, and so de facto not coded hence not transferrable by anyone |
| A2.3.6 Substitution | Substitution handling can be recorded as a code (not a flag!) to indicate whether and to what extent substitution is allowed by the prescriber. | |

4.6 Substitution of a medicinal product in epSOS and the ePrescription Guidelines – status quo⁶⁵

In epSOS pilot applications for transferring cross-border ePrescriptions, only "package size" and "brand name" substitution was permitted. Based on epSOS experience and rules,⁶⁶ and recommendations of the eHealth Network (eHN) experts from the Ministries of Health, the *Guidelines on ePrescriptions Dataset for Electronic Exchange* provide the following preliminary, non-binding recommendations for handling substitution issues in the cross-border context:

"Article 11: Substitution"

- a) The rules of the dispensing Member State shall apply; hence Member States are responsible for application of their rules regarding substitution.
- b) It is acknowledged that the rules for substitution are outwith the remit of the eHealth Network. However, Member States will wish to ensure that agreements regarding substitution are reflected in the information flows to support cross-border ePrescriptions."

Furthermore, the Guidelines contain the following supporting information and explanatory text to aid understanding of the guidelines and the rationale behind the proposals:

"There is no common definition, process or set of rules across Europe regarding the substitution of medication. In order to aid discussion, the following definitions might be used:

- Generic substitution: occurs when a different formulation of the same drug is substituted. Usually, generic versions of a drug are considered by the licensing authority to be equivalent to each other and to the originator drug.
- Therapeutic substitution: is the replacement of the originally prescribed drug with an alternative molecule with assumed equivalent therapeutic effect. The alternative drug may be within the same class or from another class with assumed therapeutic equivalence.

For the purposes of these guidelines, it is recognised that the substitution is not within the scope of the eHN other than in enabling appropriate information exchange to support the agreed policy."

Within a Member State, national dispensing rules shall apply. Most Member States, but not all, allow generic substitution. For cross-border purposes, it is assumed that the rules of the country where the dispensation is made should be accepted by the prescribing country. This issue will be need to be worked out for clarification of the consequences for both sides and proposed in the next version of the guidelines. In formulating these guidelines, some guiding principles have been proposed. Member States may wish to consider these:

⁶⁵ Guidelines on ePrescriptions Dataset for Electronic Exchange under Cross-border Directive 2011/24EU – Release 1; http://ec.europa.eu/health/ehealth/docs/eprescription_guidelines_en.pdf

⁶⁶ For details, see Smart Open Services for European Patients (epSOS). D 3.1.2 Final definition of functional service requirements – ePrescription. Version 1.2, ; 26/03/2010

- Therapeutic substitution is not allowed without formal prior consultation with the prescriber. As a consequence, it is not possible to substitute active ingredients, dose, pharmaceutical form and route of administration.
- For the countries which do not allow generic substitution or for countries which have put specific limitations on generic prescriptions, *it is thus advisable to allow for substitution of package size and/or brand name in these situations:*⁶⁷
 - ✓ in the event of shortages in the pharmacy, where the prescribed product is not available in the country,
 - ✓ urgency: if the product is available in the country but the pharmacist does not have it at that moment and the patient needs it urgently,
 - ✓ if the brand name or size is not authorised or commercially available in country B, or
 - ✓ if the rules of substitution in country B force the change to be made.
- In such cases, [a community pharmacist ? in] Country B will decide the brand name or package size to be dispensed according to their own rules of substitution.”

4.7 World Medical Association recommendations on substitution

In its statement on Drug Substitution, the World Medical Association also offers recommendations for prescribing physicians and dispensing pharmacists:

“1. Physicians should become familiar with specific laws and/or regulations governing drug substitution where they practise.

2. Pharmacists should be required to dispense the exact chemical, dose, and dosage form prescribed by the physician. Once medication has been prescribed and begun, no drug substitution should be made without the prescribing physician's permission.

3. If substitution of a drug product occurs, the physician should carefully monitor and adjust the dose to ensure therapeutic equivalence of the drug products.

4. If drug substitution leads to serious adverse drug reaction or therapeutic failure, the physician should document this finding and report it to appropriate drug regulatory authorities.

5. National Medical Associations should regularly monitor drug substitution issues and keep their members advised on developments that have special relevance for patient care. Collection and evaluation of information reports on significant developments in this area is encouraged.

6. Appropriate drug regulatory bodies should evaluate and ensure the bioequivalence and the chemical and therapeutic equivalence of all similar drug products, whether generic or brand-name, in order to ensure safe and effective treatment.

7. National Medical Associations should oppose any action to restrict the freedom and the responsibility of the physician to prescribe in the best medical and financial interest of the patient.

⁶⁷ Italics by the authors

8. National Medical Associations should urge national regulatory authorities to declare therapeutic substitution illegal, unless such substitution has the immediate prior consent of the prescribing physician.”

Although these recommendations do not focus primarily on cross-border situations, they nevertheless may also prove helpful in developing appropriate recommendations on substitution towards the end of openMedicine.

5 Challenges to be looked at in the context of analysing substitution

In order to develop appropriate survey questions, first core issues relating to the Identification of a medicine in a prescription are identified, followed by a brief discussion of potential levels at which substitution may occur. This then leads to a presentation of the core research questions selected to be surveyed.

5.1 Identifying the medicinal product

As discussed in WPs 1 and 2, there exist various options to identify a medicinal product univocally. In Section 4.1, four basic types of specification of a medicine in a prescription have been identified. The granularity of the prescription with respect to further attributes like quantity, strength, route of administration, dosage form and perhaps others depending on the specific product in question determines what indeed should or can be dispensed. This may concern, e.g., a certain package with a given size, or a not pre-packaged quantity of product units, any product or a specified group of products that contain a certain active substance, etc.

This granularity of the prescription determines the set of products meeting the prescription, which may be only one, two, or many. If one specific product is identified, the pharmacist will dispense this one if no substitution is permitted, otherwise the one which is in line with national substitution options and requirements. Whether regulation permits the prescriber to prohibit substitution, or the patient to voice its priority – perhaps against a (higher) co-payment – can also impact on this process.

In a cross-border context, the healthcare professional prescribes in line with national regulation in country A, whereas the pharmacist in the other country must dispense in line with its regulation. If substitution is required, it is essential for the pharmacist to retrieve from the prescription all information needed to univocally identify this specific medicinal product, or the pharmaceutical product(s) meeting this specification(s). Based on this information, s/he can only dispense what is allowed to be dispensed in country B, and what is available within a time span reasonable for the patient and its situation. In other words, searching for the most appropriate “substitute” is in such cases initially answering two questions:

- Which medicinal product is marketed in country A under the mentioned name (and perhaps what is the package size if the quantity is not explicitly given, but coded)?
- Is the “same” medicinal product, or one with an identical pharmaceutical product marketed in country B and available at the pharmacy?

If the second question is answered “no”, and substitution rules do not allow for less stringent substitution, then the patient will have to see a prescribing professional.

If the prescription does not identify a single, unique medicinal product, it is a case of selection for the pharmacist. Then, to be able to dispense a product to the patient, this presupposes that such selection is in line with national regulation – or that for the case of cross-border dispensation an exemption clause is stipulated -, and that the pharmacist is able to identify from the national market those products meeting the grouping criteria and the attributes of the products in the prescribed set.

In the following, we will only explore issues with regard to substitution. The survey questionnaire also contains questions with regard to selection, but these and their results will be dealt with in WP 4.

5.2 Levels at which substitution may occur

In the EU, three different procedures for evaluating medicinal products and granting marketing authorisation prevail:⁶⁸

- **Centralised procedure:** Applications for the centralised procedure are made directly to the European Medicines Agency and lead to the granting of a European marketing authorisation by the Commission which is binding in all Member States
- **Mutual recognition procedure:** This is applicable to the majority of conventional medicinal products; it is based on the principle of recognition of an already existing national marketing authorisation by one or more 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.

From this it follows that, if a prescription is to be dispensed at all in another country, in many instances it will be unavoidable to substitute the prescribed medicinal product in some way.

Such substitution may occur with respect to a variety of attributes of the medicine:

- If the "same" medicinal product is marketed under different names, but the package sizes are the same, it would only be a substitution by name
- It may, on the other hand, be the same product with the same name, but different packaging, e.g. 56 tablets instead of 50⁶⁹
- Or it may be a different name plus a (slightly) different package size
- It may be different names, the same active ingredient (generic component), but different adjuvant(s) and/or inactive ingredients (inert ingredients or excipients)
- same active ingredient, but different type of substance (e.g. different salt⁷⁰)⁷¹ ⁷²

⁶⁸ On the following, cf. http://ec.europa.eu/health/authorisation-procedures_en.htm

⁶⁹ It may also happen that the dispensing country B does only allow to dispense the same amount as the prescribed one.

⁷⁰ "Active pharmaceutical ingredients frequently do not exhibit the range of physical properties that makes them directly suitable for development. One of the approaches that is used to modify the characteristics of drug substances is to employ a salt form of the substance, since salts enable one to modify aqueous solubility, dissolution rate, solution pH, crystal form, hygroscopicity, chemical stability, melting point, and even mechanical properties." Harry G. Brittain (2009). Developing an Appropriate Salt Form for an Active Pharmaceutical Ingredient. American Pharmaceutical Review, Dec. 01

⁷¹ In the USA, it has been regulated that "when an active ingredient in a drug product is a salt, the USP Salt Policy provides that the nonproprietary name of the drug product should contain the name of the active moiety (or neutral form), and not the name of the salt." FDA, Office of Pharmaceutical Science (02/20/13). Naming of Drug Products Containing Salt Drug Substances. - https://en.wikipedia.org/wiki/Moiety_%28chemistry%29: A moiety is a distinct "part of a large molecule. Larger moieties are often functional groups. A functional group is a moiety that participates in similar chemical reactions in most molecules that contain it."

Other differences may be with respect to

- dosage form
- strength
- route of administration

Going a step further, in principle substitution may also concern dispensing a medicinal product

- with a different active ingredient (e.g. ibuprofen instead of paracetamol), but the same therapeutic class)
- from a different therapeutic class (e.g. bisoprolol [beta-blocker] instead of a sartan [Angiotensin II receptor blocker])

Very little seems to be known what indeed the national or even regional substitution rules and options are. Obviously all the above (and perhaps other) options and their theoretical interrelationships are impossible to be surveyed in a project like this. In addition, the results achieved may already be obsolete tomorrow due to a change in regulation in any one member state. As a compromise, it was decided to focus as a first approximation to these issues on core substitution options in our survey as described in the next section.

5.3 Core research questions to be surveyed

Given this highly complex domain and the little empirical evidence available, and considering that at this stage it will be impossible to empirically survey *all* potential substitution options arising, it was decided, after long discussions within the project team and at the two Expert Council Meetings, to focus the empirical work with respect to individual MSs on the following issues:

Is substitution permitted or allowed in a member state?

In some countries, a pharmacist may be allowed to substitute the medicinal product identified in a prescription by another, equivalent one. Or s/he may even be required to substitute for an equivalent, but cheaper medicinal product. How is this regulated in your country?

Only if, in principle, substitution is allowed, we inquired,

How is substitution defined in a country?

For this, like for most of the following issues, several pre-worded options were provided, and also the option to state a different definition was given. The aim of this was to make filling in the questionnaire as easy and straightforward as possible.

If applicable, questions on the handling of variant

Box size/quantity, dosage form, dosage strength, route of administration,

followed.

Next, is was inquired

⁷² EMA (Dec. 2015), in its EMA Procedural advice for users of the centralised procedure for generic/hybrid applications notes: "When different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from the one of the reference medicinal product should be submitted"

How is substitution of a medicinal product regulated?

Who defines and regulates these criteria for the substitution of medicinal products?

and, if applicable,

Under which conditions is substitution optional, and under which ones is it required?

It was also asked whether

certain medicinal products are not allowed to be substituted.

Finally, it was inquired whether

The prescriber can prohibit substitution

The patient can oppose substitution.

In countries where substitution *is prohibited*, we asked

Whether nevertheless a pharmacist can substitute a medicinal product specified in a foreign prescription

if the prescribed medicine can be identified, but the product to be dispensed is not readily or not at all available in that country.

On a voluntary base, we also asked for some

demographic data

on the present occupation of the respondent (Community pharmacist, physician [GP or consultant/specialist physician outside of a hospital], nurse, representative of a health or similar ministry, representative of a national/regional regulatory agency)

on the subject field of their professional education (Pharmacy, medicine, nursing, law, business administration or economics).

The intention is to put answers into a wider context in case they differ for the same country.

Furthermore we asked for

contact details

in case any further clarification is needed This would also allow us to send them towards the end of our project a summary of the results of the survey. It was hoped that this may perhaps provide an extra incentive to participate in this survey.

This constitutes already a quite comprehensive and complex set of questions to be asked from experts in member states, but it was hoped that the questionnaire would nevertheless not be too long such as to deter these experts from fully and reliably responding to the questions posted to them in the online "LimeSurvey." Initial returns from more than 80 persons indeed indicate that it will be possible to report in D 5.2 quite reliable data and information for almost all member states.

The full questionnaire is appended to this document respectively available as a separate, easier to read pdf-document.

6 Next steps

This paper has reviewed, analysed and critically evaluated a considerable body of literature and other documents, including internet media. As expected, data and information on the current state of substitution of medicinal products/prescription medicine in member states of the European Union is rather limited, if not absent.

6.1 Online survey

As foreseen already in the Description of Action (DoA), as a next step, which is already well under way, core empirical information on the handling of substitution challenges in member states is gathered. Information as identified above will hopefully allow us to answer many yet open questions, and help us to validate or adapt the current perspective on substitution of medicinal products.

A qualitative and quantitative online questionnaire was drafted on the basis of the performed research. Various internal reviews of the survey questions and further discussions with external experts assisted in refining the survey in order to maximise the quality of information and to improve the quality of the responses hoped for.

The survey was distributed and collects data via the LimeSurvey⁷³ services. With the help of team members, Expert Council members, PGEU and many others it was distributed to a far wider range of recipients than was initially planned in the description of work⁷⁴ in order to exceed the minimum number of responses promised.

6.2 Collation and analysis of survey data

Once the raw data are available, they will be quality reviewed and curated, collated and tabulated. Results per country and across member states will be presented. Where deemed necessary, selected experts will be contacted again.

The further analysis will focus on the dialectic tension between maximising patient safety and maximising the probability that a cross-border prescription can indeed be adequately filled in another country. This will allow us to pinpoint known and identify perhaps new cross-border substitution challenges to be tackled.

6.3 Development of recommendations for substitution handling in cross-border dispensation

Finally, based on all this information and evidence, the team will develop concrete solution proposals and next steps for MS Authorities to facilitate, where prudent and within the regulatory context, substitution of prescribed medicinal products in future cross-border healthcare. They will be submitted to the 3rd Expert Council meeting for final validation.

⁷³ Open source software to create online questionnaires and collect data. <https://www.limesurvey.org/en/>

⁷⁴ Initially, 6 major MSs (DE, ES, FR, IT, PL, UK) and at least 10 further MSs were planned to be included in the online survey.

7 Annex

7.1 Online questionnaire for WPs 4 and 5

7.2 Results from WP 2 survey on substitution issues

As reported in D 2.1, WP 2 undertook a focused survey on:

- A simple survey was sent to regulatory agencies across the EU who are responsible for authorising medicinal products.
- Survey was sent to one or more contact person within each agency
- A number of agencies responded more than once
- Survey was sent to 34 agencies, with 24 unique agency responses.
- All comments received have been anonymised with the exception of question 17 and 18

Here we reproduce only results and comments on identification codes and substitution at national level from WP 2 survey.

Q15 Are the identification codes for products authorised by your agency used in e-prescriptions to identify products or clusters of products or active substances?

Answered: 18 Skipped: 20

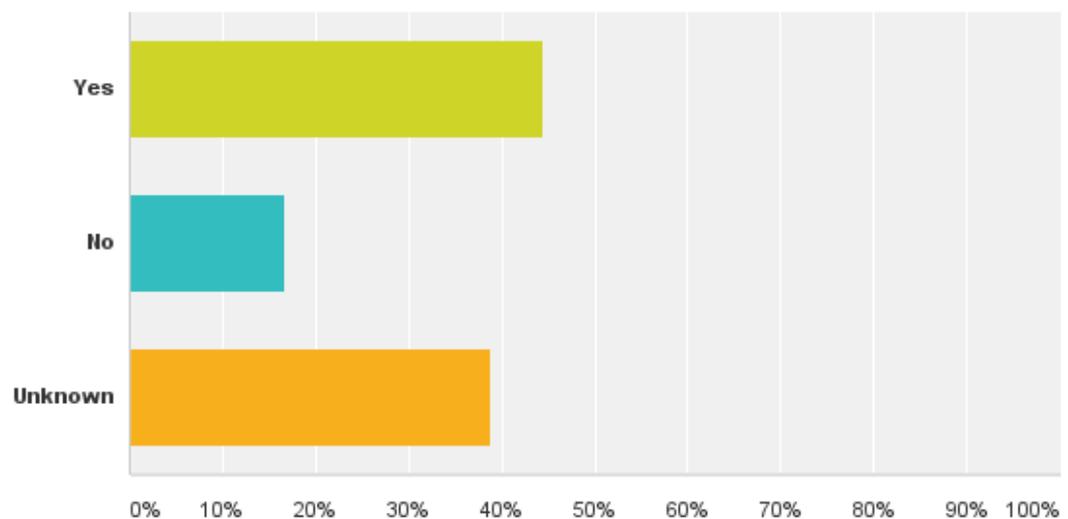


Figure 2: Identification codes for medicines at the national level

Six comments received:

- National number is used for unambiguous product identification and information transfer for e-prescriptions.

- National Marketing Authorisation Number is composed of a 9 digit number, whereby 8 digits are determined by a random selection of numbers, whereas the 9th digit represents the control number calculated according to ISO 7064 (MOD 11, 10). The Marketing Authorisation Number is not changed during the whole medicinal product life-cycle, regardless on changes in the medicinal product data. The main Marketing Authorisation Number characteristic is its uniqueness; there is no medicinal product with the same number as the other one and there is no medicinal product with more numbers. In addition, every single medicinal product packaging of the same product will be a numerical follow up digit code (from 01 to 99) facilitating to differentiate various packaging of the same product, so called packaging sign.
- Unclear as to what the question is asking
- See 13. I suppose this will be the case.
- National Agency gives the special product identification codes to all products (at the package size level). These codes are not printed to the package but they are used in the databases for data exchange. It is mandatory to use these codes at wholesale and pharmacy level (import/export licenses, recording of medicines etc) and for e-prescription.
- The proposal is to use Art57 data and codes in the first implementation of the ePrescription cross border and afterward to start using ISO IDMP codes

Q17 Does your member state / agency allow or manage the substitution of medicinal products ?

Answered: 17 Skipped: 21

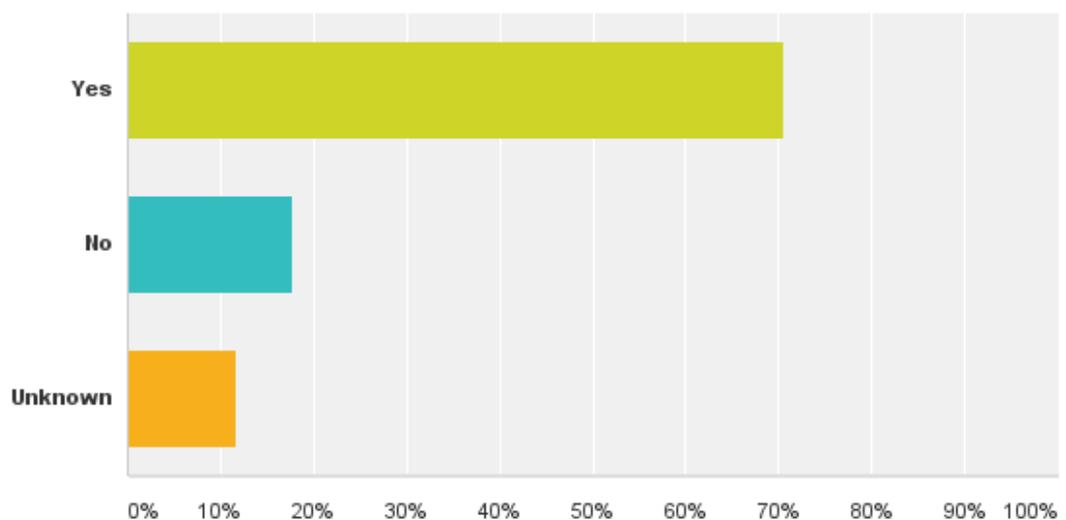


Figure 3: Substitution handling in member states

Ten comments were received:

- NoMA issues a list of products that are approved for pharmacy substitution (generic products). This list is incorporated into the open product data that is published biweekly and used by both pharmacy and doctors systems. For listed products, pharmacies are obligated to offer the cheapest available generic product to the patient. If the patient prefers the prescribed product, the cost-difference between the cheapest product and the prescribed product is covered in full by the patient. The cost of the cheapest product is reimbursed. Doctors may on the basis of individual health grounds deny pharmacy substitution. In these cases the prescribed products is fully reimbursed.
- Generic repository
- We determine which products (name, strength form) may be substituted. The Dental and Pharmaceutical Benefits Agency then uses that to determine which packages may be substituted. This information is then distributed to the health care system by the National Product Register.
- Under the Croatian Medicinal Products Acts, HALMED will be responsible for establishing, publishing and maintain a list of interchangeable medicines on HALMED's website once the criteria for establishing interchangeability of medicinal products is set by the Ordinance laid down by the Minister. HALMED is however not involved in economic aspect of substitution of medicinal products.
- You would need to ask a separate government agency this that deals with prescriptions or perhaps NICE would handle this. from personal experience it would look like this is allowed, unless the brand is specially stated then they can fill the prescription with a generic product. As indicated this would need to be checked.
- Since 1st April 2012, within the new measures taken by the government, in the case of an INN prescription the pharmacist must deliver a medicine belonging to the "group of the cheapest medicines ". In addition, from 1st May 2012 the prescription of antibiotics and antimycotics for acute treatment should be considered as an INN prescription. You can find more information on our website on the following [page](http://www.faggafmps.be/fr/news/news_prescription_dci_substitution.jsp) http://www.faggafmps.be/fr/news/news_prescription_dci_substitution.jsp.
- Substitution (replacement) means that the pharmacy dispenses another and cheaper medicine than the one your doctor prescribed. These medicines: contain the same active substance, in the same quantity, and are used in the same way (for example tablets and capsules for oral intake). The medicines have the same effect, even though they look different and are sold under different names. They are called generic medicines or only generics. At medicinpriser.dk you can see which medicines can be replaced by the medicine that your doctor wrote on the prescription. All the medicines have been scientifically evaluated by the Danish Health and Medicines Authority. The pharmacy must nearly always dispense the cheapest [medicine](https://sundhedsstyrelsen.dk/en/medicines/sale/pharmacies/substitution).
<https://sundhedsstyrelsen.dk/en/medicines/sale/pharmacies/substitution>
<https://sundhedsstyrelsen.dk/en/medicines/prices/medicinal-product-groups-substitution-groups>

- http://www.jazmp.si/en/human_medicines/mutually_interchangeable_medicinal_products/
- interchange of medicines based on active substance, pharmaceutical form and strength of the product is provide for under legislation for a defined set of products
- According to the law a medicinal product should be prescribed by using the name of the active substance in the medicinal product. The person who prescribes the medicinal product may use the name of a proprietary medicinal product if he or she deems the substitution of the medicinal product with another proprietary medicinal product containing the same amount of the same active substance and having the same or equivalent pharmaceutical form to be medically unsuitable for the patient, including where a biological medicinal product is prescribed (link to the regulation <https://www.riigiteataja.ee/en/eli/505022015009/consolide>).

7.3 Detailed list of attributes of medicinal products

Our research and discussions with experts identified the following mandatory or optional items which may, depending on national rules, appear in a given prescription:

Table 2: Comprehensive list of mandatory or optional items which may be recorded in a prescription

| |
|---|
| (a) GTIN code of product box (GS1 Global Trade Item Number) or national equivalent |
| (b) (Other) National identifier |
| (c) Size of box (e.g. box of 20 tablets) |
| (d) (National) Code for box size, e.g. N1, N2 or similar |
| (e) Number of boxes |
| (f) Amount to be dispensed, i.e. no box size (e.g. 16 tablets) |
| (g) Substitution with another product prohibited |
| (h) Strength of the active ingredient(s) |
| (i) Unit of measurement for strength of active ingredient(s) |
| (j) Pharmaceutical dose form (pill, tablet, ointment, ...) |
| (k) Route of administration (oral, intravenous, ...) |
| (l) Dose regimen/how often (3 times a day, only once, ...) |
| (m) When to take the medication (morning, evening, ...) |
| (n) Directions of use (with meal, after meal, in water, with milk, ...) |
| (o) Duration of treatment |
| (p) Starting date |
| (q) Expiry date |
| (r) Number of prescription repeats |
| (s) Minimum dispensing interval |
| (t) Indication / reason for prescribing |
| (u) Pharmaceutical preparation description (materials used in the preparation and/or formulation of the finished dosage form) |