



DELIVERABLE

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D5.2 Meeting the substitution challenge: member state regulations and core cross- border issues

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Authors:

Karl Stroetmann, Jonas Rennoch	empirica

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Abstract (for dissemination)	<p>Dispensing an (e)Prescription for a medicinal product in a cross-border situation regularly poses the challenge that the individual product specified is not or not readily available. This delivery problem may be solved by <i>substitution</i> if permitted by local regulation. In case only an active ingredient (e.g. INN) is specified in the foreign prescription, the pharmacist should be able to <i>select</i> and dispense a medicinal product meeting the specified attributes.</p> <p>This report reviews the initial openMedicine definitions of substitution and selection of a medicinal product at the point of dispensation in a community/retail pharmacy. the revised analytical framework concerning substitution and selection issues. Firstly, the concept of substitution of a medicinal product will be defined, and its operationalisation explored. This allows us to identify core types of substitution useful for further analysis. Around these types of substitution also recommendations on identified challenges in the context of the dispensation of medicinal products specified in cross-border prescription can be developed.</p> <p>Secondly, the concept of selection of a specific medicinal product, when only a subset of medicinal products is identified in a foreign prescription, is also revisited. Chapter 4 presents the survey results. It reports data on the types of prescriptions (paper or ePrescription) prevailing across the Union, on the distribution and regulation of the diverse options to identify medicinal products in a prescription across member states, and on the current state and tendencies of what type of substitution is permitted in member states. Furthermore, information on which type of authority is responsible for the regulation of substitution is presented.</p> <p>Chapter 5 briefly reviews and discusses the European policy context within which this report is set. A core aspect is the need to differentiate whether patients, who present themselves in a foreign member state for (unplanned) health-care, receive</p>
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	<p>a prescription from a 'local' healthcare professional, and have this prescription dispensed by a local pharmacist, or whether patients obtain a prescription in their home country and present this in the context of (planned) healthcare to a pharmacy abroad. Whereas in the first instance the foreign patients are treated like a domestic person when presenting the European Health insurance Card (EHIC), in the second instance – the focus of this report – the patients have to purchase, i.e. to pay themselves for the medicinal product at the point of dispensation. Fully understanding this difference has important ramifications for the recommendations proposed.</p> <p>The final chapter presents core openMedicine conclusions and recommendations on how to improve the handling of substitution and selection challenges at the point of dispensation of a cross-border (e)Prescription.</p>
Keywords	Cross-border ePrescription, substitution, selection, regulation, survey results, recommendations

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

Context and overall goal of the project, relationship to other work packages

To better enable cross-border (and also national level) healthcare delivery, particularly the 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. The aim is to facilitate a global consensus on how to univocally identify and describe unambiguously a medicinal product in various contexts; this concerns primarily dispensation in another country, but also its recording in regulatory or clinical documents across the full life cycle of a medicine.

openMedicine also deals with the challenge that the individual product specified in a foreign prescription is not available and cannot be ordered in a timely fashion from national or European sources. This delivery problem may be solved by *substitution* if permitted by local regulation. In case only an active ingredient (e.g. INN) is specified in the foreign prescription, the pharmacist should be able to *select* and dispense a medicinal product meeting the specified attributes.

Because a patient presenting a foreign prescription must purchase and pay for the medicinal product as stipulated in Directive 2011/24/EU “on the application of patients’ rights in cross-border healthcare”, the ‘local’ regulatory context deriving from third-party payment or reimbursement rules and directing substitution in line with economic and cost saving issues is not applicable. Neither can such rules prevailing in the home country of the patient presenting the prescription impact on the pharmacist abroad.

Work package 5 focuses on substitution challenges and how to cope with them. Work is closely coordinated with all other work packages, particularly with WP 2 work on standards based identification, and WP 4 work on issues and challenges arising whenever an authorised healthcare professional does not prescribe a branded individual originator or generic medicinal product, but a subset (class, cluster) of medicinal products meeting certain attributes (like an active ingredient identified by its INN or an ATC code), or a subset being stipulated by a regulatory authority. In these cases, it is usually up to the pharmacist to *select* the specific medicinal product to be dispensed.

Objective

Whereas the preceding deliverable D 5.1 developed an analytical framework for identifying and classifying core issues arising in the substitution context and validated this framework with experts both from the consortium and external to it, this deliverable reports on and analyses the evidence collected from member states on their handling of substitution issues. It identifies core cross-border challenges to be tackled, and submits initial recommendations for member state authorities to facilitate and improve the ability of pharmacies to dispense medicinal products specified in a prescription issued in another member state, and presents them for discussion and final validation.

Approach/methods applied

Methodologically, work for this deliverable very much gained from both internal discussions and those with external experts. The literature review revealed that substitution is a rather ill-defined and elusive concept, and its definition and understanding seems to depend very

much on the concrete experience and regulation in the respective country where an expert is at home.

Once the survey questions were agreed upon and extensively tested by several experts, the full questionnaire was implemented on an online platform, including a comprehensive introduction and explanation of the objective and intended usage of the results obtained. A brief e-mail text as introduction to the survey was developed. This technical set-up was tested as well to assure easy handling by respondents.

In order to reach as many respondents as possible, the link to the online survey on the platform Lime Survey was distributed to a wide variety of experts in each member state. 166 visits to the online survey page were recorded and results were collected. Of the total number of visits to the site almost 25% (40) did not leave any relevant information and were therefore excluded from the analysis. For 26 member states at least one response was obtained. Of these 26 countries four sent only one (or two) set(s) of identifiable answers, which however were so incomplete/of such low quality that they had to be excluded from further analysis.

After the online distribution of questionnaires, collection of information and initial analysis, further direct inquiries were undertaken with respect to those countries for which information was more or less missing or seemingly of insufficient quality. This second round of distribution provided additional usable information for some of the countries for which already basic information was available, and also for three of the missing countries, raising the number of countries included to 25.

The tables presented in Chapter 4 “Survey results” summarise and report on the triangulated and validated – as far as possible - data for all questions relating to substitution including all data gathered at a later stage. All results should be considered as providing insights into general tendencies and directions across the Union, rather than providing absolute answers. The complexity and idiosyncrasy of substitution issues across individual member states, the difficulty of reflecting a specific issue in a single question, and the problem involved in formulating and understanding such concepts in a foreign language render it most difficult to derive consistent and fully reliable data.

Achievements and results

This report reviews the initial openMedicine definitions of *substitution* and *selection* of a medicinal product at the point of dispensation in a community/retail pharmacy. The concept of ***substitution*** of a medicinal product is defined as:

Substitution is the action of replacing a single medicinal product, univocally specified in a prescription including the quantity to be dispensed, by another medicinal product which differs with regard to one or several of the attributes identifying precisely the one the prescriber noted for dispensation.

In this context, core attributes of medicinal products are:

- Name
 - invented name (originator or innovator product brand name)
 - or

- common name accompanied by a trade mark or the name of the marketing authorisation holder (generic product brand name)¹
- Active ingredient(s)/substance(s)
- Pharmaceutical formulation
- Strength
- Route of administration
- Package size/quantity²

Substitution may take place with respect to one or more of these attributes.

When a physician prescribes *only an active ingredient* (or a pre-defined subset of medicinal products), and not a specific, single medicinal product, the dispensing pharmacist has to *select* an appropriate product from the specified subset, meeting also the other attributes specified in the prescription like strength or pharmaceutical formulation. The concept of **selection** of a medicinal product is defined as:

Selection is the action of selecting a unique medicinal product from the subset of medicinal products specified in a prescription.

Chapter 4 presents the triangulated survey data received from experts in 25 member states. It reports on the types of prescriptions (paper or ePrescription) prevailing across the Union, on the distribution and regulation of the diverse options to identify medicinal products in a prescription, and on the current state of what type of substitution is permitted in member states. Furthermore, information on which type of authority is responsible for the regulation of substitution is provided.

In almost all (21) countries substitution of medicinal products is permitted; only four countries prohibit it in principle.

In 13 countries it is permitted to substitute an originator (given) brand name product by a generic brand name product. It seems that in some countries the prescription of an originator product implies that the prescriber prohibits substitution. In 18 countries it is possible to substitute a generic brand name medicinal product by another generic product. 11 countries allow substitution of the quantity/box size within certain limits, usually defined by a “similar” or smaller box size. 8 of these countries only permit a smaller size.

Substitution with respect to strength is virtually absent. Only one country allows the dispensation of pharmaceutical dosage units with lower strength, if their combined strength is as prescribed. Some countries allow in an urgent context the preliminary dispensation of e.g. tablets with half the strength.

Substitution by a medicinal product with a different active ingredient is not permitted in any of the countries. This implies that therapeutic substitution is not an issue at all across member

¹ In the EU, Article 6 of Regulation (EC) No 726/2004 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.” 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 D2.1 and global use (cf. FDA www.drugs.com), both types of name are identified as “brand name”,

² 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.

states. In eight countries, some medicinal products cannot be substituted; they are listed in a special document, or certain criteria have been defined to identify them.

In almost all countries (18), the prescriber can indicate in the prescription that e.g. for clinical reasons substitution is interdicted. Similarly, in 17 countries patients may also intervene in the substitution process and request another – or the originally prescribed - medicinal product to be dispensed. However, this almost regularly involves extra cost for the patient.

Chapter 5 briefly reviews and discusses the European policy context within which this report is set. A core aspect is the need to differentiate whether patients, who present themselves in a foreign member state for (unplanned) health-care, receive a prescription from a ‘local’ healthcare professional, and have this prescription dispensed by a local pharmacist, or whether patients obtain a prescription in their home country and present this in the context of (planned) healthcare to a pharmacy abroad. Whereas in the first instance the foreign patients are treated like a domestic person when presenting the European Health insurance Card (EHIC), in the second instance – the focus of this report – the patients have to purchase, i.e. to pay themselves for the medicinal product at the point of dispensation. Fully understanding this difference has important ramifications for the recommendations proposed.

openMedicine conclusions and recommendations

Core summary conclusions and recommendations are:

Information on the handling of a cross-border prescription in the context of the cross-border healthcare Directive 2011/24/EU pertaining to ‘planned’ healthcare should be made widely available, particularly that the patient has to pay for the dispensed medicinal product. Such a ‘private’ prescription may also allow for the import of the prescribed medicine from another country by the pharmacist, thus avoiding the need to substitute.

Due to different marketing authorisation procedures, and because many ‘old’ products were authorised before EU-wide regulations were established, medicinal products are often not available in all member states, and regularly with different names. This necessitates substitution in many, if not most instances.

Member states which do not allow substitution should consider relaxing this rule with respect to cross-border prescriptions, if the foreign prescription identifies a medicinal product which is exactly the same as a nationally authorised product (same attributes, same marketing authorisation holder), but with a different name.

If substitution is allowed in the foreign country where the patient presents a cross-border prescription, local regulation always prevails. Successful substitution will become both more likely and easier, also for medicinal products containing more than one active ingredient, once for all products available in any member state the central EMA ISO IDMP data bank providing for the respective pharmaceutical product identifier (PhPID) for each medicinal product becomes available.

Member states permitting substitution should consider allowing substitution of both originator and generic brand name medicinal products by locally available products which have exactly the same key attributes (active ingredient(s), strength, pharmaceutical dose form, route of administration). Once a PhPID for each medicinal product becomes available, products with the same PhPID should be allowed to be substituted by another one with the same PhPID unless prohibited by the prescriber.

Member states permitting substitution should consider for cross-border prescriptions allowing substitution of box size by a package of up to 10% - 15% more entities as well as by a

The issue of therapeutic substitution should be deleted from the list of topics to be discussed further. Neither does an operationalised definition exist which could be applied by a community pharmacist, nor is it allowed in any member state.

In line with Implementing Directive 2012/52/EU member states should encourage in the cross-border context prescribing by INN whenever therapeutically justifiable. Once the PhPID is available for all medicinal products, this code should be used for prescribing whenever only an active substance (rather than a specific medicinal product) is to be prescribed.

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 exchange electronic patient summaries and ePrescriptions, safely dispensing a prescription from another country is still challenging. This requires that the community or hospital retail pharmacist is able to read the prescription – three different alphabets are used across the Union – and to identify the medicinal product specified. If directly available, the pharmacist will dispense it; otherwise s/he may order it from national sources or from abroad if in line with national regulation and obtainable in due time. If this is for whatever reason not feasible, and substitution is permitted, the pharmacist may substitute the specified medicinal product by another one in line with national regulation.

The recently finished epSOS project (Smart Open Services for European Patients; 25 countries participated)³ developed two cross-border eServices:

- One providing (emergency) physician access to basic medical data of an ePatient Summary when treating patients living temporarily abroad or travelling across Europe, and
- Another eService enabling patients to visit a pharmacy abroad to purchase the medicinal product prescribed at home and recorded in an ePrescription.

It turned out that dispensing a prescription in a cross-border situation sometimes poses a specific identification challenge – also called the “delivery” problem of ePrescription. This concerns the univocal identification of the medicinal product, which is noted in a prescription from a given country, by a pharmacist dispensing it in another country. S/He must be able to identify from the medicinal products available in that country, or which can be ordered within an appropriate time span, the product that matches the prescribed one. In cases where this is not possible and if substitution is permitted, the pharmacist should be able to dispense an equivalent product in line with national regulation.

A prescribed medicinal product can be specified in a prescription by identifiers and/or its attributes⁴ in different ways, like by its package (e.g. GTIN⁵) or national medicinal product identifier, invented (originator) or given (generic) brand name, active ingredient, pharmaceutical dosage form, strength, route of administration and perhaps others. Another possibility available in some countries is that not a specific medicinal product is identified, but only a subset of medicinal products meeting certain criteria (like an INN⁶ prescription specifying only an active ingredient plus other attributes), or products being grouped by their pharmaceutical or therapeutic class⁷ as defined by a regulatory authority or statutory insurance.

openMedicine addresses both the identification and the substitution challenge. With respect to identification, the project aims *to reach a global consensus* in order to univocally identify and describe unambiguously a medicinal product in various contexts; this concerns primarily

³ www.epsos.eu

⁴ For details see WPs 2 and 3 in particular, and also the list of attributes identified here in Appendix III.

⁵ Global trade item number (GS1): https://en.wikipedia.org/wiki/Global_Trade_Item_Number

⁶ INN stands for international non-proprietary name:

⁷ 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

dispensation in another country, but also its recording in regulatory or clinical documents across the full life cycle of a medicine.

With respect to substitution, the discussion is mostly limited to the situation when a medicinal product can be identified at the point of dispensation in a community pharmacy in another country, but is neither available at the pharmacy nor can be ordered in a timely fashion from national or European sources. Because the patient presenting a foreign prescription must *purchase* the medicinal product,⁸ the “local” regulatory context deriving from third-party payment or reimbursement rules and directing substitution in line with economic and cost saving issues is not applicable. Neither can such rules prevailing in the home country of the patient presenting the prescription impact on the pharmacist abroad.

⁸ Cf. Recitals of Directive

2 Objectives, context, and methodological approach

This chapter briefly reviews the objectives and tasks of WP 5 “Substitution of prescribed medicinal products”, describes the coordination of work across work packages, explores the methodological approach applied, and provides a preview of what follows.

2.1 Objectives and tasks

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

- Provide a concise framework and approach for discussing and analysing the substitution challenge
- Collect empirical 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
- As the need arises, develop recommendations to overcome the challenges pinpointed
- Reflect these recommendations in the roadmap to be developed by WP 6.

Whereas the preceding deliverable D 5.1 developed an analytical framework for identifying and classifying core issues arising in the substitution context and validated this framework with experts both from the consortium and external to it, this deliverable reports on and analyses the evidence collected from member states on their handling of substitution issues. It identifies core cross-border challenges to be tackled, and submits initial recommendations for member state authorities to facilitate and improve the ability of pharmacies to dispense medicinal products specified in a prescription issued in another member state, and presents them for discussion and final validation.

2.2 Overall context and coordination across work packages

As mentioned in the preceding deliverable, the task of collecting evidence in member states was delayed due to two major challenges. First the results of the survey undertaken by WP 2 on standards based identification and description enabling dispensing equivalent medicinal products needed to be available, and it turned out that WP 4 also needed to undertake a member state survey on the challenge of selection facing a pharmacist when a prescription specifies only a subset of similar medicinal products, but not a single one. Consequently it was decided to collect evidence together in a single survey.

Because there was no prior experience in surveying both fields in such detail, the process of defining concepts, agreeing on how to operationalise and measure them was a complex, time consuming process.

Unfortunately, further delay was due to a lengthy follow-up on several countries for which initial survey results did not become available or were insufficient, and for some countries were data needed further exploration.

Because of the complexity of the subject, also internal discussions and agreement on concepts and how to interpret results was not an easy, straightforward task.

2.3 Methodological approach

Methodologically, work for this deliverable very much gained from both internal discussions and those with external experts. The literature review revealed that substitution is a rather ill-defined and elusive concept, and its definition and understanding seems to depend very much on the concrete experience and regulation in the respective country where an expert is at home.

Once the survey questions were agreed upon and extensively tested by several experts, the full questionnaire was implemented on an online platform, including a comprehensive introduction and explanation of the objective and intended usage of the results obtained. A brief e-mail text as introduction to the survey was developed. This technical set-up was tested as well to assure easy handling by respondents.

In order to reach as many respondents as possible, the link to the online survey on the platform Lime Survey was distributed to a variety of experts in each member state. Direct contact was made to medical and pharmacist associations in order for them to either answer the questions of the survey themselves or to forward the link to appropriate respondents. In addition the same regulators that had been asked to provide insight for the survey of WP 2 were contacted again in order to share their view on the current matters. Lastly, direct contact was made with individual experts through the partners involved in the openMedicine project and experts on the expert council of the project.

Responses for the aforementioned survey on the issues of substitution and cluster prescription were collected during the spring of 2016. 166 visits to the online survey page were recorded and results were collected. Of the total number of visits to the site almost 25% (40) did not leave any information, especially regarding the country of origin, and were therefore excluded from the analysis. From the rest, about 10% did not leave any useful and analysable data regarding the questions on substitution and cluster prescriptions.

Of the 28 member states that were contacted, 26 states handed in at least one response for their country. Of these 26 countries four send only one (or two) set(s) of identifiable answers, which however were so incomplete/of too low quality (answering only a couple of questions regarding the context of substitution and cluster prescriptions, if answering at all), that they had to be excluded from further analysis.

In total, the initial number of usable responses was 104 covering 22 countries in total, which became the base for further analysis. For most countries, not all answers on each question were identical, and in some cases there was quite a variety of responses from the same member state. This left the team with the task to triangulate the collected data per individual country, and usually a 'majority vote' was taken when differences occurred. In some cases it was possible to identify a single respondent as the most trustworthy expert, based on the comprehensiveness and quality of answers provided compared to other respondents.

For most countries the number of responses was between 1 and 9 sets of answers, with the exception of Bulgaria, for which 34 responses were counted. The Bulgarian responses were collected mainly from local pharmacists (contact details were made available by most of the respondents), which suggests both a close communication between the pharmacist organi-

sation, which received the survey from empirica, and community pharmacists, as well as a great interest in the topic.

After the online distribution of questionnaires, collection of information and initial analysis, further direct inquiries were undertaken with respect to those countries for which information was more or less missing or seemingly of low quality. Through various channels individual experts in these countries were identified, contacted and asked to support our survey by answering themselves or directing the team to other competent persons. This second round of distribution was not done via Lime Survey; rather, the exact same survey was distributed in word and pdf format via email. This second round of distribution provided additional usable information for some of the countries for which already basic information was available, and also for three of the missing countries, raising the number of countries included to 25.

In addition, whenever possible results were double checked through internal reviews by consortium partners to ensure validity of results as much as possible.

The tables to be presented in Chapter 4 “Survey results” summarise and report on the triangulated and validated – as far as possible - data for all questions relating to substitution including all data gathered at a later stage. However, as response rates varied considerably across countries and the final quality of responses cannot be judged by team members, no guarantee can be given concerning the definite validity of data for individual member states. Therefore it was decided by the consortium not to report data per single country. All results should be considered as providing insights into general tendencies and directions across the Union, rather than providing absolute answers. The complexity and idiosyncrasy of substitution issues across individual member states, the difficulty of reflecting the situation in many countries through a single question, and the problem involved in formulating and understanding such concepts in a foreign language render it most difficult to derive consistent and fully reliable data.

2.4 What follows

Chapter 3 will present and discuss the revised analytical framework concerning substitution and selection issues. Firstly, the concept of substitution of a medicinal product will be defined, and its operationalisation explored. This allows us to identify core types of substitution useful for further analysis. Around these types of substitution also recommendations on identified challenges in the context of the dispensation of medicinal products specified in cross-border prescription can be developed.

Secondly, the concept of selection of a specific medicinal product, when only a subset of medicinal products is identified in a foreign prescription, is also revisited.

Chapter 4 presents the survey results. It reports data on the types of prescriptions (paper or ePrescription) prevailing across the Union, on the distribution and regulation of the diverse options to identify medicinal products in a prescription across member states, and on the current state and tendencies of what type of substitution is permitted in member states. Furthermore, information on which type of authority is responsible for the regulation of substitution is presented.

Chapter 5 briefly reviews and discusses the European policy context within which this report is set. A core aspect is the need to differentiate whether patients, who present themselves in a foreign member state for (unplanned) health-care, receive a prescription from a ‘local’

healthcare professional, and have this prescription dispensed by a local pharmacist, or whether patients obtain a prescription in their home country and present this in the context of (planned) healthcare to a pharmacy abroad. Whereas in the first instance the foreign patients are treated like a domestic person when presenting the European Health insurance Card (EHIC), in the second instance – the focus of this report – the patients have to purchase, i.e. to pay themselves for the medicinal product at the point of dispensation. Fully understanding this difference has important ramifications for the recommendations to be proposed.

Based on all this information and evidence, the final chapter presents core openMedicine conclusions and recommendations on how to improve the handling of substitution and selection challenges at the point of dispensation of a cross-border (e)Prescription. They will be submitted to the 3rd Expert Council meeting for final validation.

3 Analytical framework –substitution and selection

In the preceding deliverable, we reported in detail on and analysed the different definitions of substitution reported in the literature and the types of substitution noted. The distinction between substitution and selection was discussed.

Based on a review of European level regulatory constraints, particularly with respect to medicinal products not to be dispensed in cross-border healthcare or not to be substituted, it was suggested to exclude the substitution of certain types of medicines from further considerations. Furthermore, policy arguments for and the potential impact of substitution on clinical treatment were explored.

This chapter will review the initial openMedicine definitions of substitution and types of substitution, and clarify them further. It turned out that there still exists a certain misalignment between an operational definition of this concept and its meaning and understanding in different contexts.

The concept of selection at the point of dispensation will also briefly be revisited.

3.1 Substitution of a medicinal product

In this subsection, definitions of substitution and the main types of substitution are presented.

3.1.1 Defining substitution

In its generic English language meaning, substitution means “the action of replacing someone or something with another person or thing.”⁹

In openMedicine substitution at the point of dispensation in a community or retail hospital pharmacy¹⁰ is understood as replacing a medicinal product, univocally specified in a prescription including the quantity to be dispensed,¹¹ by another medicinal product which differs with regard to one or several of the attributes identifying precisely the one the prescriber noted for dispensation.

Accordingly, the concept of **substitution** of a medicinal product is defined as:

Substitution is the action of replacing a single medicinal product, univocally specified in a prescription including the quantity to be dispensed, by another medicinal product which differs with regard to one or several of the attributes identifying precisely the one the prescriber noted for dispensation.

In this context, core attributes of medicinal products are:

- Name
 - invented name (originator or innovator product brand name)
 - or
 - common name accompanied by a trade mark or the name of the marketing authorisation holder (generic product brand name)¹²

⁹ <http://www.oxforddictionaries.com/definition/english/substitution>

¹⁰ It is assumed that the same will hold for mail-order pharmacies.

¹¹ The quantity may be identified by box size (or by default – the smallest size if no quantity is mentioned), by defined daily dose (DDD) and length of treatment, or by other measures like gram, millilitre etc.

¹² In the EU, Article 6 of Regulation (EC) No 726/2004 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

- Active ingredient(s)/substance(s)
- Pharmaceutical formulation
- Strength
- Route of administration
- Package size/quantity¹³

Substitution may take place with respect to one or more of these attributes. These attributes may be noted individually in a prescription, or implicitly e.g. by a code, like the GS1 global trade item number (GTIN) identifying a specific box, a national code, or a combination of a medicinal product identifier (MPID) and the package size/quantity.

In a more formal, scientific parlance this definition may be formulated with terms used in set theory as follows: At a given level, e.g. in a country, there exists a universe of all medicinal products available. Within this universe, there exists a set of medicinal products (members) which need to be prescribed, in line with national regulation.

From the set of medicinal products to be prescribed, the authorised prescriber specifies in the prescription a single member (also called element). When a patient presents such a prescription in a pharmacy abroad in order to purchase the medicinal product specified, the pharmacist has usually two options, depending on the availability of the specified medicine:

- a) If the specified member is available in the pharmacy or can be made available within an acceptable¹⁴ time span, it can be dispensed to the patient.
- b) If it is not available within an acceptable time span or not at all, it may be substituted by another member if permissible. To perform such substitution, the pharmacist must
 - i. identify, which is the subset of members which meet the criteria for permissible substitution (depending on national regulation)
 - ii. select from these members the one which is readily available, plus apply perhaps additional selection criteria like price.

Logically, substitution requires at this level selection, which is implied by the definition of substitution as a 1 to many relationship. If there exists only a single member which meets the criteria for permissible substitution, the pharmacist has no choice.

If the prescribed medicinal product is not available, and substitution is not permitted or not possible due e.g. to a shortage of medicines, a third option for the pharmacist is to send the patient to a local authorised prescriber.

3.1.2 Types of substitution

From the above it follows that there can be identified several types of substitution depending on the attribute(s) which are changed by the substitution process.

single name for the medicinal product.” 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 D2.1 and global use (cf. FDA www.drugs.com), both types of name are identified as “brand name”,

¹³ 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.

¹⁴ What is acceptable will depend on the respective circumstances, e.g. the urgency of the continuation or start of the treatment.

Exactly the same medicinal product, the same marketing authorisation holder, different brand name (name substitution)

Perhaps the simplest type of substitution is when exactly the same medicinal product is marketed by the marketing authorisation holder under different brand names in different countries, and one is substituted by the other.

This situation, that the same product is marketed under different names in different countries, can in principle happen with the great majority of medicinal products, most of which were already marketed in various member states before the establishment of the European Medicines Agency and the implementation of the centralised marketing authorisation procedure. This procedure came into operation in 1995; it allows pharmaceutical companies to obtain a centralised ('Community') marketing authorisation (MA) valid in all EU and European Economic Area (EEA) countries;¹⁵ the product will bear the same name everywhere. However, it is mandatory only for certain types of products,¹⁶ and today perhaps around 10% of all products contained in the EMA Art. 57 data base have been authorised under this procedure. All others have, in all likelihood, not been authorised in all member states, and may carry different names in some member states.

'Same' medicinal product, different marketing authorisation holder, different brand name (generic substitution)

Once the patent protection and its potential extension by a supplementary protection certificate (SPC)¹⁷ for an innovator medicinal product are expired, other pharmaceutical companies may apply for and market a similarly composed medicinal product under another generic brand name. Commonly it is asserted that medicinal products are the "same" if the

- Active substance(s)
- Strength
- Pharmaceutical dose form

are the same. And in countries, where substitution is permitted, substitution of an originator brand name product by a generic brand name product, or a generic brand name product by another generic brand name product are the dominant type of substitution.

A rare variant of this type of substitution is when a generic brand product is substituted by its reference innovator brand product due, e.g., to a shortage of equivalent generic product(s).

In fact, however, different generic medicinal products with the same active ingredient may not be 'exactly' the same, e.g. the active ingredient may consist of a different type of substance (e.g. a different salt), or they may differ with respect to adjuvant(s) and/or inactive ingredients (inert ingredients or excipients). Under certain circumstances, e.g. with respect to allergies, such differences can be relevant.

Nevertheless, under most circumstances such products are regarded as equivalent for therapeutic purposes. 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*

¹⁵ http://ec.europa.eu/health/authorisation-procedures-centralised_en.htm

¹⁶ https://en.wikipedia.org/wiki/European_Medicines_Agency

¹⁷ https://en.wikipedia.org/wiki/Supplementary_protection_certificate

*dosage strength and same dosage form.*¹⁸ And the European Commission defines a generic medicinal product as 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 studies.”^{19, 20}

As regards brand names, in the EU an innovator medicinal product may be named by “an invented name not liable to confusion with the common name.” And a generic brand name may be “a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder.”²¹ A “common name” is, according to Article 1(21) of Directive 2001/83/EC, “the international non-proprietary name (INN) recommended by the World Health Organisation, or, if one does not exist, the usual common name.” In other words, the common name identifies the active ingredient.

Note that this implies that several companies may make the ‘same’ generic medicinal product, each with their own brand name, but all containing the same “common name”.

Different active ingredient (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.”²² As medicines may be classified firstly on their clinical and therapeutic effects and, secondly, on their mechanisms of action,²³ 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.²⁴

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).

Here substitution could involve, e.g., substituting the prescribed product by another one

- with a different active ingredient (e.g. ibuprofen instead of paracetamol), but the same therapeutic class), or

¹⁸ Italics by the authors

¹⁹ Directive 2001/83/EC, Article 10(2)(b) – There it is also stated that “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.”

²⁰ On bioequivalence, cf. 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.“

²¹ Article 1(20) of Directive 2001/83/EC on the Community code relating to medicinal products for human use

²² WMA Statement on Drug Substitution, Chile 2005)

²³ Cookson, J., Katona, C., & Taylor, D. H. (2002). *The Use of Drugs in Psychiatry: The Evidence from Psychopharmacology*. Gaskell Press.

²⁴ <http://www.drugs.com/drug-classes.html>

- from a different therapeutic class (e.g. bisoprolol [beta-blocker] instead of a sartan [Angiotensin II receptor blocker])

The problem with therapeutic substitution is that no simple, clear rules exist which would allow for a straightforward operationalisation at the point of dispensation by a pharmacist.

Substitution with respect to other attributes

The types of substitution discussed so far are the major types of substitution observed in practice or discussed in the literature. Further types of substitution may relate to any single one of the following attributes:

- Pharmaceutical formulation
- Strength
- Route of administration
- Package size/quantity²⁵

Substitution by multiple attributes

Particularly in a cross-border situation, substitution with respect to more than one attribute may become relevant. This may be due to certain innovator or generic medicinal products not being available in foreign country B, and that at the same time for the products available the pharmaceutical formulation, the strength, the package size etc. may vary from the specifications in the prescription obtained in country A. In such a situation, in order to be able to dispense a medicinal product, substitution with respect to innovator or generic brand name, quantity, and/or strength may be required. Alternatively, the patient will have to obtain a new, local prescription.

3.2 Selection of a medicinal product

In instances where a physician prescribes, in compliance with national rules, *only an active ingredient*, but not a specific medicinal product, the dispensing pharmacist has to *select* an appropriate product – a member - from the subset of medicinal products containing the specified substance, meeting also the other attributes specified like strength or pharmaceutical form. This is not a case of substitution, but rather one of selection.²⁶

Similarly, when only a *predefined subset of medicinal products* (identified by a group name, a code, or other identifying elements), e.g., from a pharmaceutical or therapeutic class, is mentioned in a prescription (cluster prescription), the dispensing pharmacist equally has to *select* a specific product from the range of medicinal products being a member of the identified subset.

Accordingly, the concept of **selection** of a medicinal product is defined as:

Selection is the action of selecting a unique medicinal product from the subset of medicinal products specified in a prescription.

²⁵ 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.

²⁶ 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.

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

4 Survey results

4.1 Introduction

The following sections report on summary results of the online survey gathering information and data on issues of substitution of medicinal products at the point of dispensation in a pharmacy in member states of the European Union. Of experts contacted in the 28 member states some did not provide an answer to the survey, or provided information which was not usable for detailed analysis. In total data of the following 25 countries are included: Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, England/United Kingdom.

This chapter follows the structure of the survey as outlined in D 5.1 in that firstly the types of prescriptions (paper or electronic) prevailing are identified, and the information that is used in a prescription to identify a specific medicinal product or a subset of specific products. Next the current state of substitution in member states is investigated, including the types of substitution permitted.

As already mentioned, all results should be considered as providing insights into general tendencies and directions across the Union, rather than providing absolute answers. The complexity and idiosyncrasy of substitution issues across individual member states, the difficulty of reflecting a specific issue in a single question, and the problem involved in formulating and understanding such concepts in a foreign language render it most difficult to derive consistent and fully reliable data.

Therefore, no quantitative data by country are reported, only aggregate results. These reflect the general tendency across the Union without necessarily being 'exact'. Furthermore, this analysis can only give a view of the picture at the time when the data were gathered.

4.2 Types of prescriptions – Paper or ePrescription

The first survey question concerned whether ePrescriptions are already in wide use, or traditional paper prescriptions are still prevailing. The results, as can be seen in Table 1 below, indicate the variety of approaches in the European Union member states: about half use mainly ePrescriptions and the other half still use traditional paper prescriptions, while three countries are on their way towards using ePrescriptions more frequently.

Electronic prescriptions were defined as a prescription transferred by electronic means from the prescriber to a national or regional repository/data base, or directly to a pharmacy chosen by the patient. Experimental or pilot implementations of ePrescription services were excluded from consideration. The data are based on subjective estimates, not necessarily official statistics.

Table 1: Types of prescription – paper or ePrescription (n = 25 EU member states)

Electronic prescriptions (transferred electronically to the pharmacy) are not in general use	11 countries
Less than 10% of all prescriptions are electronic prescriptions	3 countries
More than 50 % are ePrescriptions	11 countries

Source: openMedicine survey 2016

4.3 Options to identify medicinal products in a prescription

The next set of questions concerned how a country regulated the way in which medicinal products can be specified in a prescription. As can be seen in Table 2, 23 of the 25 countries allow the name of an innovator (given) brand name for identification. The use of a generic brand name (common name plus company name) is permitted in 20 member states. Not specifying an individual medicinal product, but rather prescribing by active ingredient only making use of the international non-proprietary name (INN) or the anatomic-therapeutic-chemical name (ATC) is available in 17 member states. The use of the name or code of a predefined subset of medicinal products (also called cluster prescription) is foreseen in only four countries.

Table 2: Options to identify medicinal products in a prescription (n = 25)

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

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

Source: openMedicine survey 2016

4.4 Results regarding the current state of substitution

Discovering more about the current state of substitution was the main driver of this survey. The first question on this issue concerned whether substitution was at all permitted in the member state. To this, almost all countries answered that it was permitted or required in some form, while substitution is – in principle - not permitted in four countries (cf. Table 1). Nevertheless, in three of the four countries substitution is permitted under exceptional circumstances, like in an out-of-hours situation when the medicinal product specified in the prescription is temporarily out of stock:

Table 3: Substitution is permitted or not (n = 25)

Substitution of a prescribed medicinal product (MP)	Permitted/an option	Not permitted
Permitted*	21	4
When NOT permitted:		
Substitution is nevertheless permitted under exceptional circumstances, like in an out-of-hours situation when the medicinal product specified in the prescription is temporarily out of stock	3	1

Note:

* In case of long-term treatment, some countries allow substitution only once, e.g. for chronic diseases, at the start of the treatment.

Source: openMedicine survey 2016

Regarding the 21 countries having indicated that substitution is allowed within their borders, further details were asked on the types of substitution and the regulation of substitution (cf. Table 4).

In 13 countries it is permitted to substitute an originator (given) brand name product by a generic brand name product. It seems that in some countries the prescription of an originator product implies that the prescriber intends to prohibit substitution.

This is for instance the case in Estonia, as this comment received indicates: "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."

In almost all countries (18 out of 21) it is possible to substitute a generic brand name medicinal product by another generic product.

11 countries allow substitution of the quantity/box size within certain limits, defined by a "similar" or smaller box size. 8 of these countries only permit a smaller size.

Substitution with respect to strength is virtually absent. Only two countries allow the dispensation of pharmaceutical dosage units with lower strength, if their combined strength is as prescribed. Some countries allow in an urgent context the preliminary dispensation of e.g. tablets with half the strength, and at least one also double the strength if e.g. the tablet has an indentation which allows for easy breaking it into half. This attribute is even noted in the national medicinal products data base. In any case, substitution with respect to strength requires reliable information of the patient how to handle it, which may be difficult if the foreign patient does not understand the local language.

Substitution by a medicinal product with a different active ingredient is not permitted in any of the countries. This implies that therapeutic substitution is not an issue at all across member states at the point of dispensation in a community or hospital retail pharmacy.

In eight countries, some medicinal products cannot be substituted; they are listed in a special document, or certain criteria have been defined to identify them.

In almost all countries (18), the prescriber can indicate in the prescription that e.g. for clinical reasons substitution is interdicted.

Similarly, in 17 countries patients may also intervene in the substitution process and request another – or the originally prescribed - medicinal product to be dispensed. However, this often involves extra costs for the patient, like covering the difference between the cost of the product to be dispensed and the one the patient prefers. In several countries patients will have to cover the full cost of the medicinal product under such circumstances.

Note that in some countries substitution is mostly restricted to those medicinal products which are mentioned in a national list of interchangeable products issued, e.g., by a National Agency of Medicines, and which is updated in regular intervals.

Table 4: Substitution options and constraints (n = 21)

Substitution of a prescribed medicinal product (MP)	Permitted/an option	Not permitted
An originator (given) brand name product may be substituted by a generic brand name product	13	8
A generic brand name medicinal product may be substituted for another generic product	18	3
Different <i>box size</i> (within certain limits – “similar” or smaller box size) ✓ box size may be somewhat larger	11 8	10
Different <i>strength</i> (only lower strength, if combined strength is as prescribed; in certain instances double the strength if, e.g., a tablet can easily be divided into two equal parts)*	2	19
Different active ingredient	0	21
	yes	no
Certain products cannot be substituted (special list, or defined criteria)	8	11
Prescriber may prohibit substitution	18	1
Patient may intervene ✓ When covering the extra cost	17 13	2

Note:

* Some countries allow in an urgent context the preliminary dispensation of e.g. tablets with half the strength.

Source: openMedicine survey 2016

Further information on substitution was obtained through a large number of instructive comments on specifics of the national situation which we were unable to cover in such detail through our questions. For example, in Finland and Sweden a specific list of substitutable products is issued by the National Regulatory Agency of Medicines on a regular basis; medicinal products not mentioned in the list cannot be substituted. Hungary maintains a similar procedure; the list is specified by the National Institute of Pharmacy.

In Slovenia, substitution can only occur among products that are specified in a list defined by the national competent authority, and for which the health insurance fund has established standard prices. Criteria for entry of a medicinal product in the list are defined in the Medicinal Products Act and the pertaining bylaw.

In Croatia, according to the Medicinal Products Act, the national competent authority is responsible for establishing, publishing and maintaining a list of interchangeable medicines on its website once the criteria for establishing interchangeability of medicinal products were set by an ordinance laid down by the health ministry. However, it is not involved in economic aspect of substitution of medicinal products.

In comments received on the question whether the prescribing health professional may prohibit substitution, it was mentioned several times that s/he is required to state the medical need for not permitting substitution, like allergies of the patient, specifics of the disease, known drug safety risks/adverse reactions of the patient, problems in compliance, etc. In such instances, neither the patient is permitted to request nevertheless substitution, nor is the pharmacist allowed to substitute by another product. Continuity of long-term treatment can also be a valid reason for not permitting substitution.

Concerning the possibility of a patient intervening in the substitution action, it was mentioned that, depending on national specifics, several options exist: patients may be requested to first obtain a new prescription, may be required to pay the extra costs, in several countries they are even requested to pay in such a situation the full cost of the different medicinal product. Where the public system does not pay for medicinal products and the patient anyhow has to fully cover the cost like in Poland, pharmacists are required by law to inform the patient about 'cheaper equivalents'; but it is always a patient's decision which product to choose.

4.5 Regulation of substitution

Having clarified core specifics of the different substitution rules, respondents were then asked to identify the national organisations, which have the power to define the specific criteria for substitution of medicinal products, or are involved in such regulatory issues.

As can be seen in Table 5, medicinal products and other competent authorities of the national health system are responsible in 16 countries for establishing such rules. In 13 countries, Ministries of Health set the rules respectively are involved, and public or statutory health insurances in 11 countries. In no country a finance ministry is involved.

Table 5: Authorities involved in regulating substitution (n = 21)

Type of authority	Involved in regulation	Not involved
Ministry of Health	13	8
Medicinal Products Authority (or similar)	16	5
Statutory health insurances	11	10
Ministry of Finance	0	21

Source: openMedicine survey 2016

In comments to these questions, it was noted that in the Netherlands the Dutch Pharmacists Organisation is involved in setting rules for substitution. In Slovenia, the Ministry of Health will become involved in case substitution rules are appealed, and such decisions may even be challenged in the judicial court dealing with issues of public administration.

4.6 Further details on national rules

Based on the large number of comments received, we summarise some of the more important or general ones in the following to further advance our understanding of the sometimes quite complex conditions under which substitution takes place in some countries, and to highlight differences across member states.

In many countries, substitution is mandatory if the dispensed equivalent medicinal product is cheaper than the one specified in the prescription and the public system acts as third-party payer or reimburses the cost later. In other countries, e.g. for INN prescriptions, only one of the three or five cheapest ones has to be dispensed.

In Belgium, for antibiotics and antifungal medicinal products, every brand name prescription is to be interpreted as an INN prescription, and then dispensing of one of the three cheapest products is compulsory.

A quite different situation exists in Malta. A patient may choose whether to buy a medicinal product privately or obtain it from the public system. When buying medicines through a private pharmacy, the pharmacist can switch brands according to his/her discretion and the patient's preference. Substitution is legally permitted in this instance. For medicinal products provided for free through the national health system, the patient is dispensed what is available from the government, i.e. what is procured by the government through a public tender process.

In countries where substitution is, in principle, not allowed, substitution may nevertheless take place if the pharmacist has agreed this with the prescriber and patient beforehand.

An interesting situation prevails in Sweden: “The Medical Products Agency approves all medicinal products, including generics and parallel imported products, with regard to their quality, safety and efficacy. The basic principles for substitution are that the products have the same active substance in the same amount and are otherwise medically equivalent. The Dental and Pharmaceutical Benefits Agency designates the product of the month. It is the product that pharmacies offer their customers when they have to substitute medicines exposed to generic competition. The products of the month are set one month at a time. The company responsible for the product which is cheapest shall provide it to all pharmacies in Sweden.”²⁷

²⁷ See also <http://www.tlv.se/In-English/pharmacy-new/substituting-medicines-at-the-pharmacy/>

5 Policy context

5.1 Dispensation of a prescription abroad – regulatory bases and payment rules

For further discussion, it is important to briefly recall the EU policy context within which this report is placed. One of the core aspects is the need to differentiate whether

- Patients, who present themselves in a foreign member state for (unplanned) healthcare, receive a prescription from a 'local' healthcare professional, and have this prescription dispensed by a local pharmacist, or
- Patients obtain a prescription in their home country and present this in the context of (planned) healthcare to a pharmacy abroad.²⁸

In both cases, a necessary condition is that the patients are covered by their national health system or a statutory health insurance.

In the first case, EU Regulations 883/2004 and 987/2009 on the coordination of social security systems are applicable. If a patient is covered for healthcare expenditures at home (country A) within the public healthcare system, be it of the Beveridge (national health service) or the Bismarck (statutory health insurance) type, and s/he presents the European Health Insurance Card (EHIC) or other acceptable proof of coverage at home, the patient is entitled to receive necessary healthcare treatment with the same rights as people covered in the country they are in (country B).

If patients have been issued a prescription from the country they are in, they need to present it (in some countries together with the EHIC) to a local pharmacy. This means that they will have to pay the same amount at the pharmacy as someone who is covered and living in that country. In some member states this may imply that they do not have to pay anything, while in others they may be required to pay a certain amount towards the cost of their prescription in line with rules in country B.

In the second case, and this is the sole case covered by all discussions in this report, Directive 2011/24/EU on the application of patients' rights in cross-border health-care is applicable. Patients have to pay abroad in country B the full cost of the medicinal product dispensed on the prescription they received at home. This is stipulated in recital 19 where it is stated that cross-border healthcare covers "also the prescription, dispensation and provision of medicinal products and medical devices where these are provided in the context of a health service.

The definition of cross-border healthcare should cover both

- the situation in which a patient purchases such medicinal products and medical devices in a Member State other than the Member State of affiliation and
- the situation in which the patient *purchases* such medicinal products and medical devices in another Member State than that in which the prescription was issued."²⁹

The two cases distinguished at the start of this section are summarised in the following table:

²⁸ A further case not yet explicitly covered by present directives is when a patient makes use of an (online, telemedicine) eHealth service in another member state and presents the prescription obtained abroad to a pharmacy at home.

²⁹ Italics are by the authors.

Table 1: Dispensation of a prescription abroad – regulatory bases and payment rules

Type of cross-border healthcare service	Document involved	Basis of payment	Invoice	Payer
Prescription dispensed in country B received in country B by patient from country A obtaining (unplanned) healthcare in country B – patient covered at home by NHS or statutory health insurance	Local prescription (country B), plus EHIC or equivalent document as needed	Regulations (EC) No 883/2004 and No 987/2009 on the coordination of social security systems	From healthcare provider to National Liaison Body/Contact Point (country B) to National Liaison Body/Contact Point (country A)	NHS or statutory health insurance at home (country A)
Foreign prescription (received in country A) dispensed in country B – patient covered at home by NHS or statutory health insurance	Foreign (xBorder) prescription from country A	Directive 2011/24/EU on the application of patients' rights in cross-border healthcare	To patient	Patient (with the option of reimbursement at home in line with rules in country A)

5.2 Short review of further EU rules

In order to provide further context on EU rules concerning cross-border prescriptions, briefly some other stipulations on this topic are referenced. The purpose is to prepare for final summary statements and recommendations on the subjects of substitution and selection, and how member states may want to deal with certain unresolved challenges in future.

Recital 53 of Directive 2011/24/EU on the application of patients' rights in cross-border health-care states: "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 within the meaning of Directive 2005/36/EC for an individual named patient, 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."

Article 11 of Directive 2011/24/EU deals with the "Recognition of prescriptions issued in another Member State:

1. If a medicinal product is authorised to be marketed on their territory, in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004, Member States shall ensure that prescriptions issued for such a product in another Member State for a named patient can be dispensed on their territory in compliance with their national legislation in force, and that any restrictions on recognition of individual prescriptions are prohibited unless such restrictions are:
 - a) limited to what is necessary and proportionate to safeguard human health, and non-discriminatory; or
 - b) based on legitimate and justified doubts about the authenticity, content or comprehensibility of an individual prescription.

The recognition of such prescriptions shall not affect national rules governing prescribing and dispensing, if those rules are compatible with Union law, including **generic or other substitution**. The recognition of prescriptions shall not affect the rules on reimbursement of medicinal products. Reimbursement of costs of medicinal products is covered by Chapter III of this Directive.

In particular, the recognition of prescriptions shall not affect a pharmacist's right, by virtue of national rules, to refuse, for ethical reasons, to dispense a product that was prescribed in another Member State, where the pharmacist would have the right to refuse to dispense, had the prescription been issued in the Member State of affiliation.

The Member State of affiliation shall take all necessary measures, in addition to the recognition of the prescription, in order to ensure continuity of treatment in cases where a prescription is issued in the Member State of treatment for medicinal products or medical devices available in the Member State of affiliation and where dispensing is sought in the Member State of affiliation.

...

2. In order to facilitate implementation of paragraph 1, the Commission shall adopt:

- a) measures enabling a health professional to verify the authenticity of the prescription and whether the prescription was issued in another Member State by a member of a regulated health profession who is legally entitled to do so through developing a non-exhaustive list of elements to be included in the prescriptions and which must be clearly identifiable in all prescription formats, including elements to facilitate, if needed, contact between the prescribing party and the dispensing party in order to contribute to a complete understanding of the treatment, in due respect of data protection;
- b) guidelines supporting the Member States in developing the interoperability of ePrescriptions;
- c) ...”

6 openMedicine - conclusions and recommendations

6.1 General observations

The dispensation of a cross-border prescription constitutes a cross-border healthcare service as defined in Directive 2011/24/EU on the application of patients' rights in cross-border healthcare. As noted in that directive,³⁰ the patient presenting an (e)Prescription abroad has to purchase it: "If you ... have a prescription from your home country, you will normally have to pay for your pharmaceutical product/s."³¹

It follows that the 'local' regulatory context deriving from third-party payment or reimbursement rules for citizens of that country, which often direct substitution rules in line with economic and cost saving issues, do not apply. Neither can such rules prevailing in the home country of the patient presenting the prescription impact on the pharmacist abroad. In essence then, a cross-border prescription is to be handled like a 'private' prescription, where the seller is the pharmacist and the buyer is the patient who pays in cash or by other means.

If the medicinal product specified in the foreign prescription cannot be identified by the pharmacist, the process stops, and the patient must see a local healthcare professional authorised to issue a new prescription for a medicinal product meeting her/his therapeutic needs and being available in due time.

If the pharmacist can identify the medicinal product, and if it is readily available, the patient can purchase it.

If it is not readily available, but can be ordered for delivery in due time from regional or national sources, or from another member state within the 'local' regulatory context,³² it may be ordered by the pharmacist and dispensed when becoming available.

Recommendation:

Information on the handling of a cross-border prescription in the context of the cross-border healthcare Directive 2011/24/EU pertaining to 'planned' healthcare should be made widely available, particularly that the patient has to pay for the dispensed medicinal product. Such a 'private' prescription may also allow for the import of the prescribed medicine from another country by the pharmacist.

Handling of such a cross-border prescription has to be strictly distinguished from dispensation of a local prescription presented by a foreign patient in the context of receiving unplanned healthcare abroad in the context of EU Regulations 883/2004 and 987/2009 on the coordination of social security systems.

³⁰ See recitals 16 and 50.

³¹ Your Europe: FAQs - Presenting a prescription abroad: http://europa.eu/youreurope/citizens/health/help-from-the-pharmacy/prescription/faq/index_en.htm

³² E.g. in Germany, a pharmacist may order any foreign medicinal product for local dispensation if certain regulatory requirements are met: It can be imported in small amounts if a) ordered by/is for individual patients; b) the medicine has been authorised for marketing in the country of origin; c) a product with the (1) same active ingredient and a (2) "comparable" strength for the (3) indication area in question is not available in Germany.

6.2 Substitution

Most medicinal products available in member states have not been authorised for marketing through the so-called centralised procedure.³³ Only the centralised procedure assures that the same originator or generic brand name is used in all member states.

Due to different market authorisation procedures and many 'old' products authorised before EU-wide regulations were established, medicinal products are often not available in all member states, and regularly with different names. Unless import is an option, this will necessitate substitution in many, if not most instances.

In some member states, substitution by name is prohibited.

Recommendation:

Member states which do not allow substitution should consider relaxing this rule with respect to cross-border prescriptions, if the foreign prescription identifies a medicinal product which is exactly the same as a nationally authorised product (same attributes, same marketing authorisation holder), but with a different name.

In its future ISO IDMP compliant medicinal products data base, EMA should provide for easy matching of identical medicinal products which carry different names in countries.

If substitution is allowed in the foreign country where the patient presents a cross-border prescription, local regulation always prevails in line with the pertaining stipulation in the cross-border directive. In almost all countries, a generic brand name medicinal product may be substituted for another generic product, and in the majority of countries also an originator (given) brand name product may be substituted by a generic brand name product.

Successful substitution, if needed when a cross-border prescription is presented, will become both more likely and easier, also for medicinal products containing more than one active ingredient, once for all products available in any member state the central EMA ISO IDMP data bank providing for the respective pharmaceutical product identifier (PhPID) for each medicinal product becomes available.

Recommendation:

Member states permitting substitution should consider – either for cross-border prescriptions only or for all prescriptions - allowing substitution of both originator and generic brand name medicinal products by locally available products which have exactly the same key attributes (active ingredient(s), strength, pharmaceutical dose form, route of administration).

Once a PhPID for each medicinal product becomes available, products with the same PhPID should be allowed to be substituted by another one with the same PhPID unless prohibited by the prescriber.

In about half of all countries substitution with respect to the size of the box of the medicinal product prescribed is allowed within certain limits. Typical package sizes seem to differ somewhat across countries.

³³ Cf. http://ec.europa.eu/health/authorisation-procedures_en.htm. The other procedures are the mutual recognition, the decentralised, and the solely national procedure for medicinal products to be marketed in one Member State only.

Recommendation:

Member states permitting substitution should consider for cross-border prescriptions allowing substitution of box size by a package of up to 10% - 15% more entities as well as by a somewhat smaller package.

In virtually all countries, substitution with respect to strength of the active ingredient is not permitted. In an urgent situation, a pharmacist may in some countries dispense, e.g., the same pharmaceutical dose form, but with half the strength, and instruct the patient accordingly. Here national rules should prevail.

Similarly, in no country substituting by active ingredient is permitted, at least not without formal prior consultation with the prescriber. No operationalised definition seems to exist which would allow a community pharmacist to perform therapeutic substitution.

Recommendation:

The issue of therapeutic substitution should be deleted from the list of topics to be discussed further. Neither does an operationalised definition exist which could be applied by a community pharmacist, nor is it allowed in any member state.

6.3 Selection

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,”³⁴ 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.”

A common name is, according to Article 1(21) of Directive 2001/83/EC, “the international non-proprietary name (INN) recommended by the World Health Organisation, or, if one does not exist, the usual common name.”

Our survey indicated that about 2/3 of all countries provide at least for the option of prescribing by common name, i.e. an active substance, rather than a specific medicinal product. Usually, the common name is the international non-proprietary name (INN), but it may also be the anatomic-therapeutic-chemical name or code (ATC) – an option which was also adopted within the epSOS pilot project for cross-border ePrescription services.

A known problem with INN or ATC prescribing is that for certain therapeutic situations the identification of the active substance may not be precise enough. Once the global substance data base of EMA and FDA becomes available, this challenge will be solved. And the PhPID will univocally identify for each medicinal product the active substance contained.

³⁴ Official Journal of the European Union, L 356, pp. 68-70 EN, 22.12.2012.

Prescribing by active substance does not result in a substitution challenge; rather, it implies that the pharmacist will have to *select* from the range of available medicinal products one which meets the stipulated specifications.

Recommendation:

In line with Implementing Directive 2012/52/EU Member states should encourage in the cross-border context prescribing by INN whenever therapeutically justifiable. Once the PhPID is available for all medicinal products, this code should be used for prescribing whenever only an active substance (rather than a specific medicinal product) is to be prescribed.