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Deliverable abstract

The pharmacists use to perform substitution on their daily work, based on each EU MS rules. However this substitution isn't automatic or software based. Our current deliverable proposes the introduction of IDMP attributes and a software support that will enhance smartly this process. We address all the challenges that arise from the cross-border setting. A national process when transferred in the cross-border setting adds tremendous complexity which needs to be addressed by a “smart” methodology on the management of national rules and coding systems.

This deliverable intends to define and create a smart substitution component for integration with eDispensation (eD) systems for cross-border use, employing the "Dispensation Guidelines" described in WP 5 and WP 9. The goal of this component is to implement IDMP business concepts that allow safe dispensing of drugs throughout Europe while complying to national dispensing regulations.

Keywords: ISO IDMP, Substitution, ePrescription, eDispensation

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List of abbreviations

Abbreviation	Complete form
API	Application Programming Interface
ATC	Anatomical Therapeutic Chemical
CDA	Clinical Document Architecture
CEF	Connecting Europe Facility
eD	Electronic Dispensation
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
EU	European Union
EU-SRS	European Substance Registration System
FDA	Food and Drug Administration
FHIR	Fast Healthcare Interoperability Resources
HIV	Human Immunodeficiency Virus
IDMP	Identification of Medicinal Products
IG	Implementation Guide
ISO	International Organisation for Standardisation
MAL	Minimum Attribute List
MS	Member State
OMS	Organisation Management Services
PhPID	Pharmaceutical Product Identifier
RMS	Referentials Management Services
SPOR	Substances, Products, Organisations and Referentials
UCUM	Unified Code for Units of Measure
USA	United States of America
WHO	World Health Organization
WMA	World Medical Association
WP	Work Package

1 Introduction

Despite continued efforts to further develop and successfully apply ISO IDMP in the past, we were not able to securely identify, compare, and dispense, if necessary, through software based assisted substitution, identical pharmaceutical products to patients in national, and especially in cross-border settings.

The pharmacists use to perform substitution on their daily work, based on rules in their MS. However this substitution isn't automatic or software based. Our current deliverable proposes the introduction of IDMP attributes and a software support that will enhance smartly this process. We address all the challenges that arise from the cross-border setting. A national process when transferred in the cross-border setting adds tremendous complexity which needs to be addressed by a “smart” methodology on the management of national rules and coding systems.

A core impact will be in the cross-border context. The aim of safer identification of the medicinal product specified in a prescription at the point of dispensation will enable faster identification of the same product in another country, if available. Furthermore immediate identification of an equivalent (pharmaceutical) product for dispensing where substitution is permitted in accordance with national rules in the country of dispensation.

This deliverable aims to define and design a smart substitute component for integration with eDispensation (eD) systems for cross-border use, utilizing the rules that were defined in WP 5 and WP 9 through the “Dispensation Guidelines”.

This component,by design:

- will be incorporated into the eD interface of the reference portal implementation in Task 6.3
- can be repurposed, if there is an identified need, for alternative eD mechanisms at the Member State (MS) level
- will provide API to be used on other activities in UNICOM, as in Task 8.3 regarding patient facings apps.

This component's purpose is to implement IDMP business principles that permit the safe dispensing of medications throughout Europe, while still adhering to national dispensing regulations.

1.1 Document outline

This deliverable aims to demonstrate the use cases, software logic, and provide resources, by project requirements, in order to give a specific definition and implementation for the Smart Substitution components, to be utilized in cross-border eHealth systems using ISO IDMP.

This deliverable is structured and explained in three primary chapters:

Section 2 focuses on an investigation of substitution types and an early description of substitution.
Section 3 will expand on the preceding section's analysis and outline the required substitute for the UNICOM project.
Section 4 demonstrates how substitution should be, and provides a software architecture diagram to be used.

It is also important to note that this document focuses on the cross-border scenario, taking into consideration the interoperability of required services and the interaction with other UNICOM tasks that require the functionality of the substitution component.

2 Introduction to Task 6.2

These concerns, the univocal identification of the medicine specified in the foreign prescription based on the IDMP attributes, and, if this product is not available and/or if substitution is required by regulation, the safe dispensation of a similar product in line with national law of the Country of dispensation.

2.1 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.

1 The World Medical Association (WMA) 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."
2 Similarly, Duru et al.[3] define 'direct' generic substitution as "replacing a brand-name drug with its less expensive generic equivalent, when available."
3 Johnston et al.[4] 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." The same definition was adopted by the European ePrescription Guidelines.

The last definition of substitution includes substitution between different chemical salts or other chemical forms of the same chemical substance when they have the same biological effect. A number of different dose forms of the same chemical substance can be interchangeable too and can be substituted based on equivalent absorbing time and bioavailability curves through time. We can have groups of dose forms that can be interchangeable, and others, that provide different biological effects, cannot be interchangeable.

Another special case is when an importer company is responsible in an EU country for a medicinal product under a different brand name, with or without differences in the package/dose unit, than the original named medicinal product that it is circulated by the same producer company in other countries. Under EU single market regulations, both medicinal products can co-exist as a result of different imports. Substitution of the same medicinal product that can be available with different brand-names as result of marketing co-promotion from two different companies is another case of substitution. In both cases it is the same medicinal product and probably we could name that a replacement and not a substitution.

A usual case of substitution in our scenario is when a citizen from one country moves to another country, especially for a long stay, where the medicinal product(s) for his chronic medication do(es) not exist. The pharmacist should substitute with a medicinal product as close as possible to the initial medication. Sometimes, a non-substitutable medication (like an antiepileptic drug) does not exist in the new country, or a medicinal product exist in a slightly different strength or different dose form. Such cases are not included for now in this project.

Therapeutic substitution: This is out of scope of this project because therapeutic substitution is when a prescribed substance or drug with a specific chemical substance is changed to another completely

[3] 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.

[4] 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

different chemical substance that has the same therapeutic results. During therapeutic substitution the resulted drug can be for example a substance in the same ATC5 group with a separate ATC code.

Initial prescription and first selection of a medicinal product after substance prescription instead of substitution: When 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. This could include also the first time,a substance is prescribed to patient and has to match only the bio-availability demands defined by dose form.

2.2 Policy arguments for and impact of substitutions

Substitution of medicinal products can be a solution in the cross border unavailability of prescribed medications, although substitution has already other uses. A 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.” Some countries in order to provide a safer way for substitution provide access to bioequivalence information in order for the pharmacist to substitute safely.

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.” When toxic dose for the drug is too close to the effective dose for the drug to be used safely, substitution is not allowed. But there are cases where generic medicinal products may not be bioequivalent to brand-name drugs and should not be freely interchanged for them. This project can improve our awareness about the substitution effect across different countries. --- See there[5] also for a broad discussion of such challenges and associated risks, and references to pertinent medical publications.

2.3 Types of substitution to exclude

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

4 “medicinal product[s] subject to special medical prescription,”

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

5 “subject to restricted medical prescription,”

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

[5]https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5a6d8e953&appId=PPGMS

6 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 authorizations concerning their indication(s) across countries.

7 Substitution of biologics in general through biosimilars

EMA[6] 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 authorized 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. Whereas in the USA several states have regulated the substitution of biologics by biosimilars at the community pharmacy level, this is a hotly debated issue in Europe, 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.

8 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. There, with respect to four therapeutic groups, a prescribed medicinal product must not be substituted by another medicinal product with the same active ingredient.

9 Defining substitution of a medicinal product

In openMedicine substitution[7] 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:

10 Name
10.1 invented name (originator or innovator [brand] product name)
10.2 common name (generic [brand] product name)
11 Package size/quantity
12 Dosage form
13 Strength
14 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 cannot cover all the cases of substitution we presented above. Having substitution for prescriptions and drugs between different countries needs a more relaxed handling of Dosage form and chemical substance. Slight differences between dose forms but with the same pharmacokinetics can be accepted with no clinical difference for the patient to provide substitution for medicinal products across different countries. In order to achieve an automatic support for the clinical pharmacist, bioequivalent dose forms must be grouped. In a parallel process, an ontology of the chemical substances where different salts or other inactive appended portions of the same active moiety with the same bioequivalent effect, can be defined as interchangeable. An active moiety in the same active strength and equivalent dose form for the same route administration with the same clinical results can be the basic foundation that will drive the substitution process.

[6] France's Biosimilar Law May Set Trend Inside The EU - Law360

[7] https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5ae13ddce&appId=PPGMS

3 Definition/Methodology for initial version D6.2 (UNICOM)

It is difficult to have same brand product in all countries. The main goal in the initial phase is to facilitate the substitution of medicines that are equivalent to those prescribed by another EU country. Patient should get a bio-equivalent medication with doses needed for the treatment period.

We follow a rule based approach:

1. a set of rules based on substance,
2. a set of rules based on dose form,
3. rules for cases that should never be substituted according to national law.
4. future rules will include Strength, package etc.

And we make the following assumptions:

1. Rules are local for each member state (Not global)
2. Administrative national rules for substitution are out of scope.
3. Smart Substitution component does not cover therapeutic substitutions. Only generic substitution.

The following cases are encountered:

A) Same brand product under a different name or package size by the same producer or Market Authorization Holder (MAH).

B) Same product with different name, package size, Market Authorization Holder and probably slightly different dose form attributes (e.g., different pill's size or color) (different producer's company for each country)

C) Same chemical substance, same strength and dose form from a different producer

D) Same active moiety substance (but different salt), same active strength and dose form from a different producer

E) Same active moiety substance (with same or different salt), same active strength but a slightly different dose form with the same bioavailability

F) Same active moiety substance (with same or different salt), slightly different active strength and the same or compatible dose form with the same bioavailability

Each medicinal product has one or more active ingredient and a number of inactive ingredients that are different between different manufacturers. Each generic medicinal product has to prove that it is bioequivalent with the non-generic product with bioequivalence studies. If the same medicinal product exists in the country, the substitution should be avoided. In all other cases, substitution should keep the same active chemical substance (or with the same active moiety substance if not possible), the same active strength and the same or (if not possible) a compatible dose form. Further attention should be given in cases where a different dosage is needed after a substitution (5ml dose instead of 10ml dose), as such a substitution can cause misunderstanding to the patient and should not be accepted except the case the prescribed active strength is not available in the country that the dispensation occurs. Also, a number of medicines, based on their ATC5 code or a local country's list, cannot be substituted.

3.1 Chemical Substance, Moiety Substance and other attributes

A medicine has one or more types of active chemical molecules named as active ingredient(s) or active substance(s) responsible for its physiological or pharmacological action. For simplicity a short and easy to learn name (INN: International Nonproprietary Name) is given e.g., amlodipine, instead of (3-ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate). This is the official chemical substance name or active ingredient, but it can exist in a medicinal product with appended inactive portions in the form of different salts, e.g., besylate, adipate, maleate, succinate.

In this case the chemical substance can be e.g., amlodipine besylate but the moiety substance is amlodipine. In order to achieve a stable chemical substance for a dose form, an inactive portion can be added, e.g., Amoxicillin sodium for injection and Amoxicillin trihydrate for a syrup. This chemical molecule complex or salt will be dissolved in the blood or other body fluid, and be released as active form. The declared active strength in medicinal products is usually the strength of the moiety substance for being comparable with other medicinal products with salt or pure chemical substance.

Generally, medicines with the same moiety substance (e.g.pure form, salt or complex) are considered as equal in the same active strength. To support this comparison, we use the “reference substance” or “general substance” or “moiety substance”, that it is a common name for all chemical substances or complexes of a specific substance. For each medicine’s active ingredient, additional information describing the moiety substance that it is equal, can exist as “reference substance” in IDMP. A similar situation exists for medicine’s strength: Due to different molecular masses of different salts from the same moiety, it will present different total chemical strength in order to provide the same active strength of the moiety substance that it is presented as “reference” or “active” strength of the medicinal product. So, in addition to reference substance, we have the “reference strength”.

A third noticeable attribute of a medicinal product is the dose form. The dose form is usually connected with the route of administration or bioavailability needs and therapy expectations to avoid side effects. Multiple dose forms can exist for the same route of administration with different properties. As an example, for the oral route, a prolonged release capsule has different absorption curve compared to a tablet, or a gastro-resistant coated tablet has different absorption site than oral drops. Other dose forms can also exist as solution to taste requirements, e.g., coated tablet, to improve therapy compliance. All those differences do not restrict the co-existence of different dose forms in groups with the same bioequivalent absorption results.

3.2 Minimum attribute list

The Minimum Attribute List (MAL) is including the information needed for exact global identification of medicinal products to arrive to an ordered list of proposed medicinal products for cross border substitution based on prescribed medicine’s attributes and grouping information of dose forms. Further information like package size/description and route of administration are needed to help providing a user assistance to the community pharmacist.

Table 1: Minimum Attribute List for eHealth[8]

#	Attributes from EMA IG V2.1	EMA-SPOR database	Preferred coding system
1.			
1.1	Product Management Service Identifier (PMS ID)		
1.2	Medicinal Product Identifier (MPID)		
1.5	**Authorised Pharmaceutical Form***	RMS	EDQM
1.13			
1.13.3	**ATC code(s)***	RMS	WHO - ATC
1.14			
1.14.1	Full name		
2.			

[8] For more information please refer to deliverable 5.7 “CommonminimumdatasetforimplementationinthenationalNCAandeHealthsolutions”. At the time of submission D5.7 was not yet publicly accessible. All deliverables will be made available on the following website https://unicom-project.eu/public-deliverables/

2.8	Marketing Authorisation Holder	OMS (LOC-ID)	SPOR-OMS
4.			
4.1	Packaged medicinal product Identifier (PCID)		
4.3	Pack size**		EDQM
4.7			
4.7.1	**Package item (container) type***	RMS	EDQM
4.7.5	Package item (container) quantity		
4.10			
4.10.1	Unit of Presentation	RMS	EDQM
4.10.2	**Manufactured Item Quantity***	RMS	UCUM
4.10.3	Manufactured Dose Form	RMS	EDQM
5			
5.1	Ingredient role	RMS	SPOR-RMS
5.5			
5.5.1	Substance	SMS	SPOR-SMS
5.5.2			
5.5.2.2.2	Strength (Presentation single value or low limit)	RMS	UCUM
5.5.2.3.2	Strength (Concentration single value or low limit)	RMS	UCUM
5.5.3.			
5.5.3.1	**Reference Substance***	SMS	SPOR-SMS
5.5.3.3.2	**Reference Strength (Presentation single value or low limit)***	RMS	UCUM
5.5.3.4.2	**Reference Strength (Concentration single value or low limit)***	RMS	UCUM
6.			
-	Pharmaceutical Product identifier (PhPID)[9]		
6.2	Administrable Dose Form	RMS	EDQM
6.3	**Unit of Presentation***	RMS	EDQM
6.6	**Route(s) of Administration***	RMS	EDQM

Both moiety substance and chemical substance can be coded using the EU Substance Registration System (EU-SRS) or any other detailed nomenclature of chemical substances. Additional nomenclatures' codes can co-exist to code a substance in each country. For all chemical substances in each prescribed medicinal product, the chemical substance code can be transformed to moiety or reference substance code and double coded with the chemical substance. For many medicinal products, the chemical substance is also the reference substance. In figure 2, we can see that a moiety substance like Enalapril can have three chemical substances (Enalapril maleate, Enalapril Sodium, Enalaprilat) where the last is the active metabolite and can be used only intravenously.

[9] Note: This version of the guidance does not report information on additional identifiers such as the Pharmaceutical Product Identifier (PhPID). Further details on the related definitions and defining elements will be available at later stage as it requires further discussions prior the implementation.

Grouper of SUBSTANCES

	G-S			S_PAI_ID		S-MID		S-MMID
PLLno		Grouper of Substance	(Modified) substances with the attribute of Precise Active Ingredient		Moiety		Moiety+modifier	
1	TBD	diclofenac	diclofenac sodium	100000092272	diclofenac	100000092272	diclofenac sodium	100000092272
			diclofenac potassium	100000092368	diclofenac	100000092272	diclofenac potassium	100000092368
			diclofenac diethylamine	100000091074	diclofenac	100000092272	diclofenac diethylamine	100000091074
			diclofenac epolamine	100000085789	diclofenac	100000092272	diclofenac epolamine	100000085789
2	TBD	amoxicilline	amoxicillin sodium	100000090113	amoxicillin (anhydrous, explicitly)	100000091596	amoxicillin sodium	100000090113
			amoxicillin trihydrate	100000092629	amoxicillin (anhydrous, explicitly)	100000091596	amoxicillin trihydrate	100000092629
3	TBD	carbamapezine	carbamazepine	100000092127	carbamazepine	100000092127		
4	TBD	amlopdine	amlodipine besilate	100000090079	amlodipine	100000085259	amlodipine besilate	100000090079
			amlodipine mesilate	100000089571	amlodipine	100000085259	amlodipine mesilate	100000089571
			amlodipine maleate	100000089370	amlodipine	100000085259	amlodipine maleate	100000089370
5	TBD	simvastatine	simvastatine	100000091786	simvastatine	100000091786		
6	TBD	enalpril	enalapril maleate	100000091343	enalapril	100000092359	enalapril maleate	100000091343
			enalaprilat	100000153305"	enalapril	100000092359	enalaprilat	100000153305"
			Enalapril sodium	100000153305"	enalapril	100000092359	Enalapril sodium	100000153305"
7	TBD	omeprazole	omeprazole sodium	100000090186	omeprazole	100000092047	omeprazole sodium	100000090186
			omeprazole magnesium	100000085918	omeprazole	100000092047	omeprazole magnesium	100000085918
8	TBD	cefuroxime	cefuroxime sodium	100000091436	cefuroxime	100000092667	cefuroxime sodium	100000091436
			cefuroxime axetil	100000093039	cefuroxime	100000092667	cefuroxime axetil	100000093039
9	TBD	salbutamol	salbutamol sulfate	100000090564	salbutamol	100000091629	salbutamol sulfate	100000090564
10	TBD	potassium clavinalate	Potassium clavinalate	100000093061	clavulanic acid	100000091629	Potassium clavinalate	100000093061
11	TBD	Insulin glargine	insulin glargine	100000085460	insulin glargine	100000085460		
12	TBD	teriparatide	teriparatide acetate	100000084795	teriparatide	Non existing ?	teriparatide acetate	100000084795
13	TBD	drospiridone	drospirenone	100000092375	drospirenone	100000092375		
14	TBD	ethinylestradiol	ethinylestradiol	100000091721	ethinylestradiol	100000091721		
15	TBD	calcium carbonate	calcium carbonate	100000091518	calcium carbonate	100000091518		
16	TBD	ergocalciferol	ergocalciferol	100000090229	ergocalciferol	100000090229		
17	TBD	paracetamol	paracetamol	100000090270	paracetamol	100000090270		
18	TBD	diazepam	diazepam	100000092362	diazepam	100000092362		
19	TBD	morphine	morphine hydrochloride	100000090494	morphine	100000091372	morphine hydrochloride	100000090494
			morphine sulfate	100000076239	morphine	100000091372	morphine sulfate	100000076239
			morphine tartrate	100000076257	morphine	100000091372	morphine tartrate	100000076257
20	TBD	enoxiparin	enoxaparin sodium	100000090152	enoxaparin	100000085598	enoxaparin sodium	100000090152
21	TBD	hydrocortisone	hydrocortisone sodium succinate	100000092550	hydrocortisone	100000092635	hydrocortisone sodium succ	100000092550
			hydrocortisone valerate	100000086711	hydrocortisone	100000092635	hydrocortisone valerate	100000086711
			hydrocortisone acetate	100000092260	hydrocortisone	100000092635	hydrocortisone acetate	100000092260
			hydrocortisone butyrate	100000085172	hydrocortisone	100000092635	hydrocortisone butyrate	100000085172
			hydrocortisone aceponate	100000084215	hydrocortisone	100000092635	hydrocortisone aceponate	100000084215
			hydrocortisone probutate	100000085172	hydrocortisone	100000092635	hydrocortisone probutate	100000085172
			hydrocortisone cypionate	100000086187	hydrocortisone	100000092635	hydrocortisone cypionate	100000086187
			hydrocortisone sodium phosphate	100000086691	hydrocortisone	100000092635	hydrocortisone sodium pho	100000086691
22	TBD	lidocaine	lidocaine hydrochloride	100000139489	lidocaïne	not present	lidocaine hydrochloride	100000139489
23	TBD	trastuzumab	trastuzumab emtansine	100000128434	trastuzumab	100000089314	trastuzumab emtansine	100000128434
			trastuzumab deruxtecan	100000174462	trastuzumab	100000089314	trastuzumab deruxtecan	100000174462
24	TBD	imatinib	imatinib	missing	imatinib	missing		
25	TBD	clomipramine	clomipramine hydrochloride	100000090503	clomipramine	100000084546	clomipramine hydrochlori	100000090503
26	TBD	metformin	metformin hydrochloride	100000091366	metformin	100000085448	metformin hydrochloride	100000091366
			metformin pamoate	100000091840	metformin	100000085448	metformin pamoate	100000091840

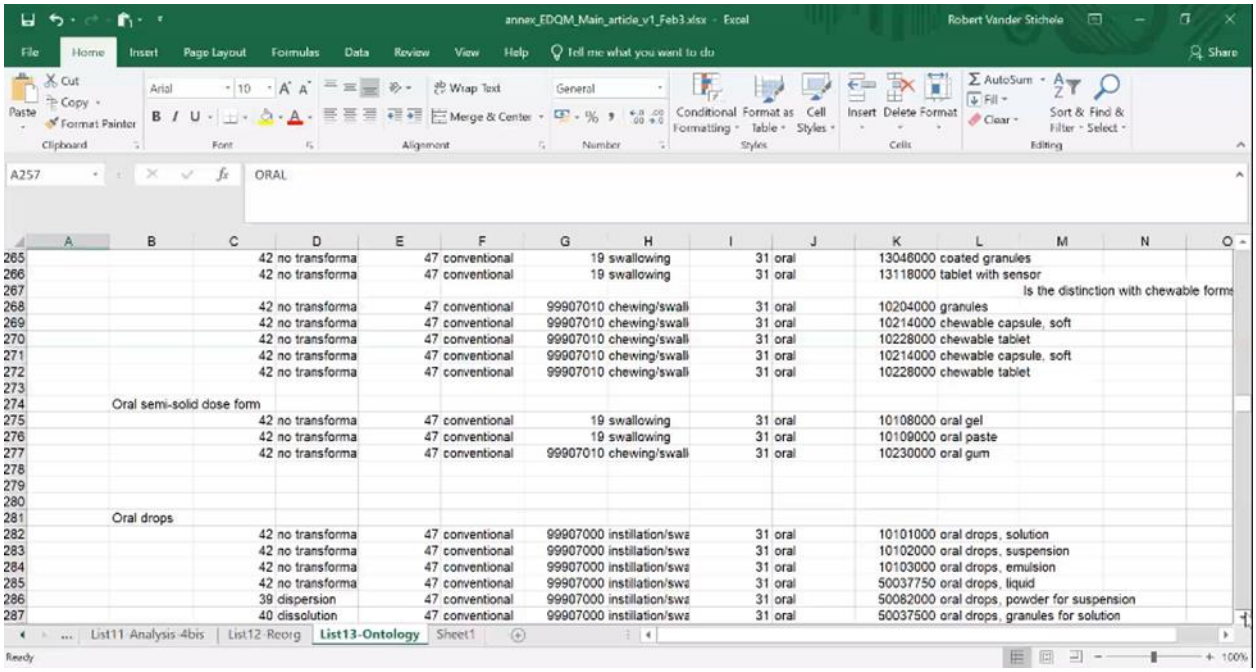
full codes | Value set moiety | Valuevset moiety+modifier | Substance-Hierarchy | +

Figure 1: A snapshot of grouping chemical substances with their reference substance

The dose form is another obstacle in standardizing substitution: Different pharmaceutical dose forms exist for medicinal products based on the favored administration route, the absorbance's curve needed, the avoidance of side effects and the patient's perceptions for better compliance. Pharmacopoeia's technology nowadays provides many different dose forms to achieve patient's and doctors' needs and some of the dose forms have practically the same pharmacokinetic absorption. In order to facilitate the substitution when dispensing a prescription from another country, it is needed to identify dose forms of the same administration route with the same therapeutic bioavailability and group them together as interchangeable for the purpose of substitution. We need a three-level ontology for the dose form and all dose forms in one category of this ontology are equivalent for substituting a medicinal product: The basis for this ontology is the terminology of EDQM Standard Terms. IDMP requires the labeling of the dose form to be standardized to the EDQM Standard Terms. Having a dose form labeled with EDQM, will indicate to which dose form group of equivalent dose forms, this particular dose form belongs. This method can help to identify candidate medicinal products for substitution, if the prescribed dose form is not available. In T8.1 a proposal for such an ontology of dose forms was made, which needs to be further elaborated and validated, before it can be used as a resource in T6.6.

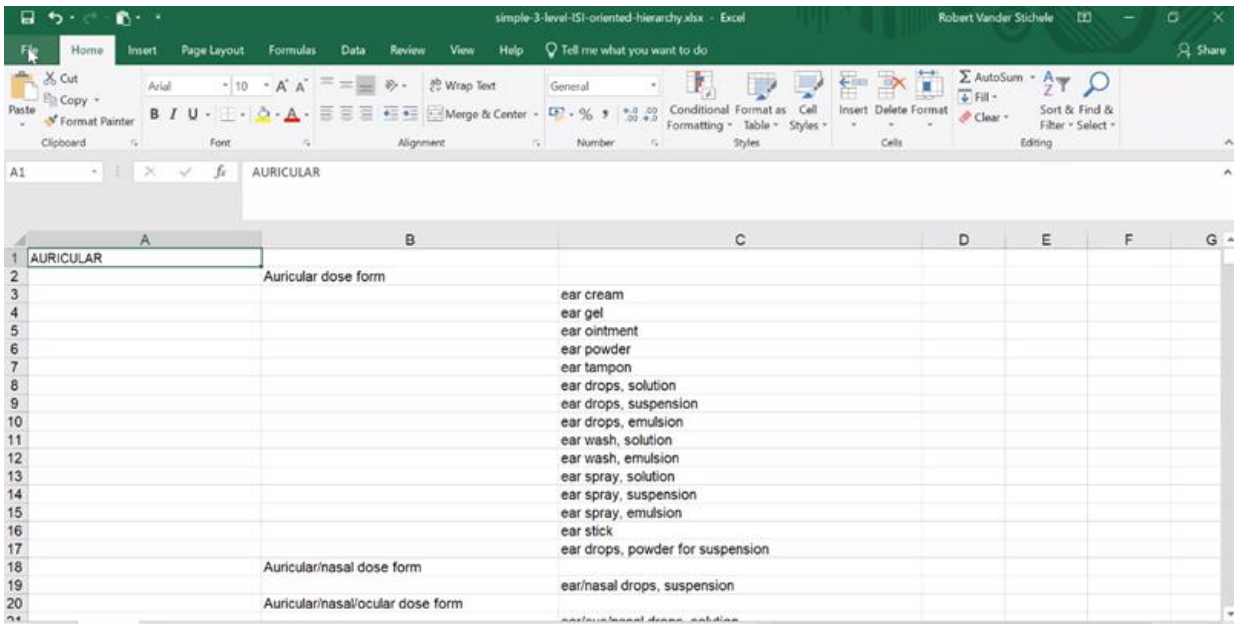
There are cases where a medicinal product can have multiple intended sites. Some eye drops can only be used in the eye, other can also be used in the ear. In figure 3, we can see an EDQM dose form (column L) together with the intended site(column J) and the Dose form group (column B). In figure 4, the EDQM group Auricular dose form includes a number of so different dose forms, having at the same

time gel, cream, drops, spray and stick forms, as their pharmacokinetic absorption and bioavailability are the same.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
265				42 no transforma		47 conventional		19 swallowing		31 oral	13046000 coated granules				
266				42 no transforma		47 conventional		19 swallowing		31 oral	13118000 tablet with sensor				
267												Is the distinction with chewable forms			
268				42 no transforma		47 conventional		99907010 chewing/swall		31 oral	10204000 granules				
269				42 no transforma		47 conventional		99907010 chewing/swall		31 oral	10214000 chewable capsule, soft				
270				42 no transforma		47 conventional		99907010 chewing/swall		31 oral	10228000 chewable tablet				
271				42 no transforma		47 conventional		99907010 chewing/swall		31 oral	10214000 chewable capsule, soft				
272				42 no transforma		47 conventional		99907010 chewing/swall		31 oral	10228000 chewable tablet				
273															
274		Oral semi-solid dose form													
275				42 no transforma		47 conventional		19 swallowing		31 oral	10108000 oral gel				
276				42 no transforma		47 conventional		19 swallowing		31 oral	10109000 oral paste				
277				42 no transforma		47 conventional		99907010 chewing/swall		31 oral	10230000 oral gum				
278															
279															
280															
281		Oral drops													
282				42 no transforma		47 conventional		99907000 instillation/swa		31 oral	10101000 oral drops, solution				
283				42 no transforma		47 conventional		99907000 instillation/swa		31 oral	10102000 oral drops, suspension				
284				42 no transforma		47 conventional		99907000 instillation/swa		31 oral	10103000 oral drops, emulsion				
285				42 no transforma		47 conventional		99907000 instillation/swa		31 oral	50037750 oral drops, liquid				
286				39 dispersion		47 conventional		99907000 instillation/swa		31 oral	50082000 oral drops, powder for suspension				
287				40 dissolution		47 conventional		99907000 instillation/swa		31 oral	50037500 oral drops, granules for solution				

Figure 2: EDQM groups and standard terms for dose forms



	A	B	C
1	AURICULAR		
2		Auricular dose form	
3			ear cream
4			ear gel
5			ear ointment
6			ear powder
7			ear tampon
8			ear drops, solution
9			ear drops, suspension
10			ear drops, emulsion
11			ear wash, solution
12			ear wash, emulsion
13			ear spray, solution
14			ear spray, suspension
15			ear spray, emulsion
16			ear stick
17			ear drops, powder for suspension
18		Auricular/nasal dose form	
19			ear/nasal drops, suspension
20		Auricular/nasal/ocular dose form	

Figure 3: An example of an EDQM group

The real strength of the full chemical salt or ester is not usually used to describe a medicinal product. Usually, the reference strength (the strength of the active moiety) is used to be comparable with other medicinal products with the same moiety but with different modifiers. A small number of medicinal products will continue to use total strength like in medicinal products with Calcium.

Other situation we can meet is the different strengths between countries for a small number of medicines: Acetylsalicylic acid can exist in slightly different active strength in different EU countries or

vitamins like Vitamin D are included in different strength in other medicines. These special cases that do not impose a harm for the patient and will probably necessarily be excluded from substitution.

The main obstacle in describing strength is the different types of units that can be used to describe strength. The most common problems that could arise are:

1. Medicinal products where strength can be expressed in terms of mass units, units of biological activity or international units as appropriate. e.g., Insulin Glargine usually is described as IU/ML but can be also described as mg/ml.

2. Many injectable medicinal products are described as strength in mg per vial and other as strength in mg per ml. Approaches may differ for vials for a single dose and for mutli-dose vials.

3. Incompatibility between dose form and units in strength like medicinal products where strength is described as mg/ml and the dose form is drops.

The nomenclature Unified Code for Units of Measure (UCUM)[10] which is quite reliable for machine processing. For a small amount of medicinal products a preferable unit has to be defined and that will be one of the outcomes from the pilot study. For the Coding system, the SPOR system will provide SPOR codes for the relevant UCUM labels. EMA, FDA, and WHO_UMC collaborate in a global working group (GIDWG), to define business rules for the methodology to express strength and the choice of units of measurement, depending on the pattern of dose form.

4 Specifications for technical implementation

In an electronic prescription the machine information as coded by the Clinical Document Architecture (CDA) specifications includes the following elements, also included in the IDMP Minimal Attribute List The substances (one, or in combination products, 2 or more substances).

- The reference strength,
- The administrable dose form,
- The route of administration,
- Optionally the brand name of the medicine

Additional information that can be helpful for presenting to the dispenser during substitution is the dose frequency and the time frame of the therapy.

- Based on the brand name or the substance, the reference substance is acquired. If the reference substance is included in a list that does not allow substitution, then no further steps are followed.
- The strength is acquired and a transformation to reference strength is done, if needed.
- The dose form group will be also acquired from the dose form using EDQM groups. If a special EDQM group exists, the route of administration can lead to include additional EDQM group, e.g., if the EDQM group is “ear-eye drops” and the route of administration is “eye”, then the EDQM group “eye drops” will be included too.

The following steps are required for creating an ordered list of available medicinal products searching the local medicines database using brand name, chemical substance, reference substance, reference strength, dose form, and dose form group:

1. If the brand name exists in the prescription and the reference substance or the medicinal product is not legally allowed to be substituted then this is the only medicine presented in the list.

2. If the brand name exists in the prescription and this brand name exists locally with the same reference strength and dose form, this will be the top in the list.

[10] https://ucum.org/

3. If the brand name exists in the prescription and this brand name exists locally with the same reference strength and dose form group, this will be the top in the list.

4. If no brand name exists in the prescription and the reference substance exists in a list where no substitution is allowed then only medicines with the same chemical substance, reference strength and dose form are returned for the user to select.

5. If a brand name exists in the prescription and the reference substance exists in a list where no substitution is allowed, but this brand name does not exist in the country then only medicines with the same chemical substance, reference strength and dose form are returned for the user to select.

6. If a brand name exists in the prescription but this brand name does not exist in the country, or no brand name exists in the prescription, then medicines with the same reference substance, reference strength and dose form or dose form group are provided in the top of the list, using the following priority. If a medicine is from the same product owner, this is shown on the top.

   I. Same chemical substance, same reference strength, same dose form

   II. Same chemical substance, same reference strength, same dose form group

   III. Same reference substance, same reference strength, same dose form

   IV. Same reference substance, same reference strength, same dose form group

7. If no medicines exist with the above criteria and the same chemical or reference substance with same dose form or dose form group exists but with different reference strength (e.g. tablets of 40 mg are not available but tablets of 20 mg are) then provide a list of found medicines to the user with a warning about this situation.

Following the above process, the user can retrieve easily a compatible list of medicinal products to dispense.

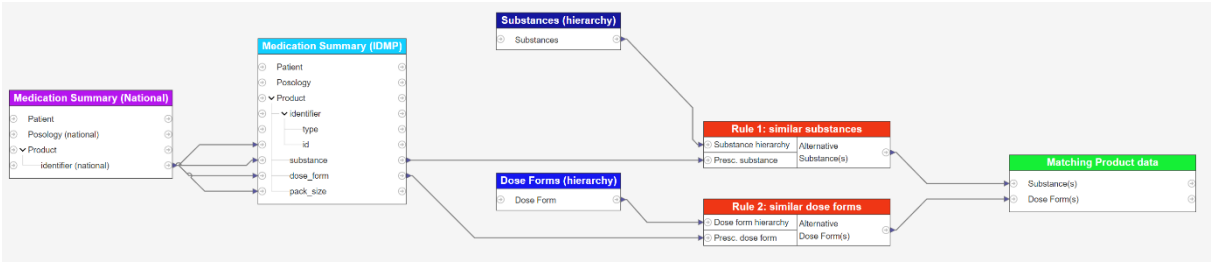


Figure 4: An example of the "mechanics" of how rule-based product identification could work.

In the diagram above:

1. from a national Patient Summary, a system can create an IDMP-compatible Patient Summary by transcoding the key product attributes (MAL) between the national values and the IDMP values – e.g., dose form, substance.

2. then the rules and dependencies have to be very clear - in the above diagram "the function that returns equivalent dose forms uses the IDMP dose form as input and searches the IDMP dose form ontology for dose forms that have the same parent (1) (2)"

3. same for substance (1)

4. Then we have some product attributes, with zero to many values. We then do a lookup for all products that match these values (2)

4.1 Pathway examples for substitution:

1. Medicinal product that substitution is forbidden

A Greek medical prescription for chronic medication with 3 months duration that includes the medicinal product CO.R.F.C.T TEGRETOL 400MG/TAB 30Tab/package and dosage 1 tab once a day is presented to a community pharmacist in Belgium.

Tergretol, a medical product from Novartis, with substance Carbamazepine and with ATC code N03AF01 where N03xxxx medicinal products are in a list that substitution is prohibited by the law. So, we need to find if a medicinal product with the same producer, chemical substance, dose form and strength exists in Belgium. The CO.R.F.C.T dose form means “Controlled-Release Film Coated Tablet” and has the EDQM code “Modified-release tablet”

From the list of the Belgium medicinal products with chemical substance Carbamazepine, and strength 400mg/tablet, we have the following:

PR Tab Tegretol CR 400mg 100 Tablets/Pack (producer: Novartis)

PR Tab Tegrital CR (Carbamazepine 400mg) 200tabs/pack (producer: Novartis)

F.C.Tab Tegretol 400mg 100 Tablets/Pack (producer: Novartis)

F.C.Tab Tegrital (Carbamazepine 400mg) 200tabs/pack (producer: Novartis)

As we can see we have 4 medicinal products with the same strength from the same producer, but none of them is CO.R.F.C.T as dose form. As a generic medicinal product must have different inactive ingredients, and substitution is not allowed for this substance, the Tegrital is excluded. We have the same strength and producer for the remaining products but different dose form, with the medicinal product from the prescription.

The difference between a normal tablet and a prolonged-released tablet is clinically important, and there for medicinal products with prolonged-release formulation cannot be used. One of the medicinal products with the same brand name in the receiving country has a “PR tab” dose form and a “CR” mark inside the brand name meaning “Controlled Release " which is practically the same with the CO.R.F.C.T. from the prescription, but a computer system cannot extract from the brand name this information. In such a case, the EDQM standard terms grouping of dose forms provide the solution for substitution.

2. Medicinal product with moieties.

A Belgium prescription for chronic condition hypertension having a duration of 3 months is presented to a Greek Community Pharmacist that includes F.C.Tab Amlogal Divule 10 mg with dosage 1 tab once a day.

Amlogal is a generic medicinal product with amlodipine maleate as active chemical substance with an active strength of 10mg. The amlodipine maleate is a salt of the moiety amlodipine with ATC code C08CA01. “Film coated tablet” is its EDQM dose unit code, and it is manufactured by SMB Technology.

Amlogal as medicinal product, it does not exist in Greece and its substance ATC code is not in a list that forbids substitution. So, we are searching first for same chemical substance, active strength and dose unit. In the Greek database, from 88 medicinal products with the moiety amlodipine, we cannot find a medicinal product with the same chemical substance, active strength and EDQM dose unit.

After that we are searching for a medicinal product with the same chemical substance, same active strength and the same EDQM dose unit *group*. As result, we have only one medicinal product with Amlodipine Maleate, the same strength but different dose form (Tablet) that it is available. All the others products are out of circulation at the moment.

TAB NOLVAC 10MG/TAB 30tab/package (distributor: Innovis)

COMMERCIAL_NAME_AND_ALL	EDQM	FORM_CC		CONTEN	ose size	PIEC	DOSES_F	ACTIVE_SUBSTANCE_CODE
AMLODIPINE MALEATE/GENERICS TAB 5MG/TAB BTx14	Tablet	TAB	0	5MG/TAB	TAB	14	14	AMLODIPINE MALEATE
AMLODIPINE MALEATE/GENERICS TAB 5MG/TAB BTx28	Tablet	TAB	0	5MG/TAB	TAB	28	28	AMLODIPINE MALEATE
AMLODIPINE MALEATE/GENERICS TAB 10MG/TAB BTx14	Tablet	TAB	0	10MG/TAB	TAB	14	14	AMLODIPINE MALEATE
AMLODIPINE MALEATE/GENERICS TAB 10MG/TAB BTx28	Tablet	TAB	0	10MG/TAB	TAB	28	28	AMLODIPINE MALEATE
NOLVAC TAB 10MG/TAB BTx28 σε BLISTERS	Tablet	TAB	0	10MG/TAB	TAB	28	28	AMLODIPINE MALEATE
NOLVAC TAB 10MG/TAB BTx30 σε BLISTERS	Tablet	TAB	1	10MG/TAB	TAB	30	30	AMLODIPINE MALEATE

The above medicinal product (Nolvadec) can be a safe selection for substituting the Amlogal in the prescription.

To provide more alternative options to the community pharmacist, the next step is to check if more medicinal products exist when looking with the moiety of amlodipine and the same other characteristics: We have no products with amlodipine as reference substance, active strength of 10 mg and dose unit of “Film coated tablet”.

Next step is to look for medicinal products with amlodipine as reference substance, active strength of 10 mg and the same dose unit EDQM *group*. With these criteria, seven more medicinal products are available:

COMMERCIAL_NAME_AND_ALL	EDQM	FORM_CC		CONTEN	ose size	PIEC	DOSES_F	ACTIVE_SUBSTANCE_CODE
NORMODIN TAB 10MG/TAB BTx14	Tablet	TAB	1	10MG/TAB	TAB	14	14	AMLODIPINE BESYLATE
AMLIBON BESYLAB 10MG/TAB BT x 30 σε BLISTERS	Tablet	TAB	1	10MG/TAB	TAB	30	30	AMLODIPINE BESYLATE
NORDEX/MEDICAL PHARMAQUALITY TAB 10MG/TAB BTx14 (1 BL,x 14)	Tablet	TAB	1	10MG/TAB	TAB	14	14	AMLODIPINE BESYLATE
AMLODIPINE BESILATE/TEVA TAB 10MG/TAB BT x 30 (3x10)	Tablet	TAB	1	10MG/TAB	TAB	30	30	AMLODIPINE BESYLATE
AMLOTENS TAB 10MG/TAB BTx30 (BLISTER 3x10)	Tablet	TAB	1	10MG/TAB	TAB	30	30	AMLODIPINE MESILATE MONO
NORVAGEN TAB 10MG/TAB BT x 30 (σε BLIST)	Tablet	TAB	1	10MG/TAB	TAB	30	30	AMLODIPINE BESYLATE
NORMODIN TAB 10MG/TAB BTx28	Tablet	TAB	1	10MG/TAB	TAB	28	28	AMLODIPINE BESYLATE

As we can notice, we have six medicinal products with the moiety of Amlodipine Besylate and one medicinal product with the moiety of Amlodipine Mesilate. So, the community pharmacist has now eight medicinal products to choose from and dispense the Belgian Medical Prescription.

4.2 Technical approach

In order to express the described rules in a software-compatible structure, a higher aggregated level should be used, as demonstrated in section 4B. Having an Amlodipine pharmaceutical product in Belgium, for instance, results in a pharmaceutical product as represented in Figure 5: Schematic substitution example. Consequently, the software has access to all the essential data required to conduct the substitution, if applicable. By returning from the pharmaceutical to the medicinal products, it is possible to identify either a substitute for the requested medicinal product or the same medicinal product in cases where an identical match exists.

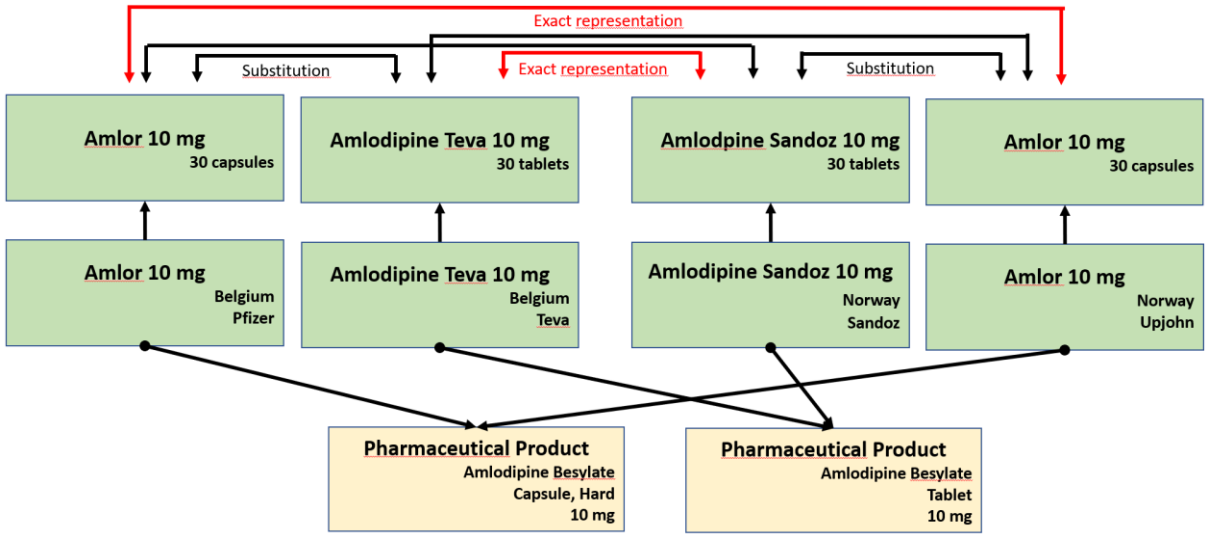


Figure 5: Schematic substitution example

From software implementation perspective, the algorithm has to follow the rules identified above, in order to perform validations based on Substance, Dose form and Strength. Initially, there has to be a validation whether the substance is allowed to be substituted following the MS national rules of the receiving countries. If it is allowed, then the rest rules shall apply. That requires the algorithm to fetch data from a database. To do this, it should use a standard API provided by the database. In the duration of the project, we can use T6.1 as an implementation of that API, using FHIR standards to retrieve the data about the products as determined by the rules. Finally, the results, for example in the methodology provided above, are returned to the user, in case of an API request, to populate the dispensation choices to the pharmacist. A schematic representation of the above is shown in Figure 6: Substitution component schematic representation.

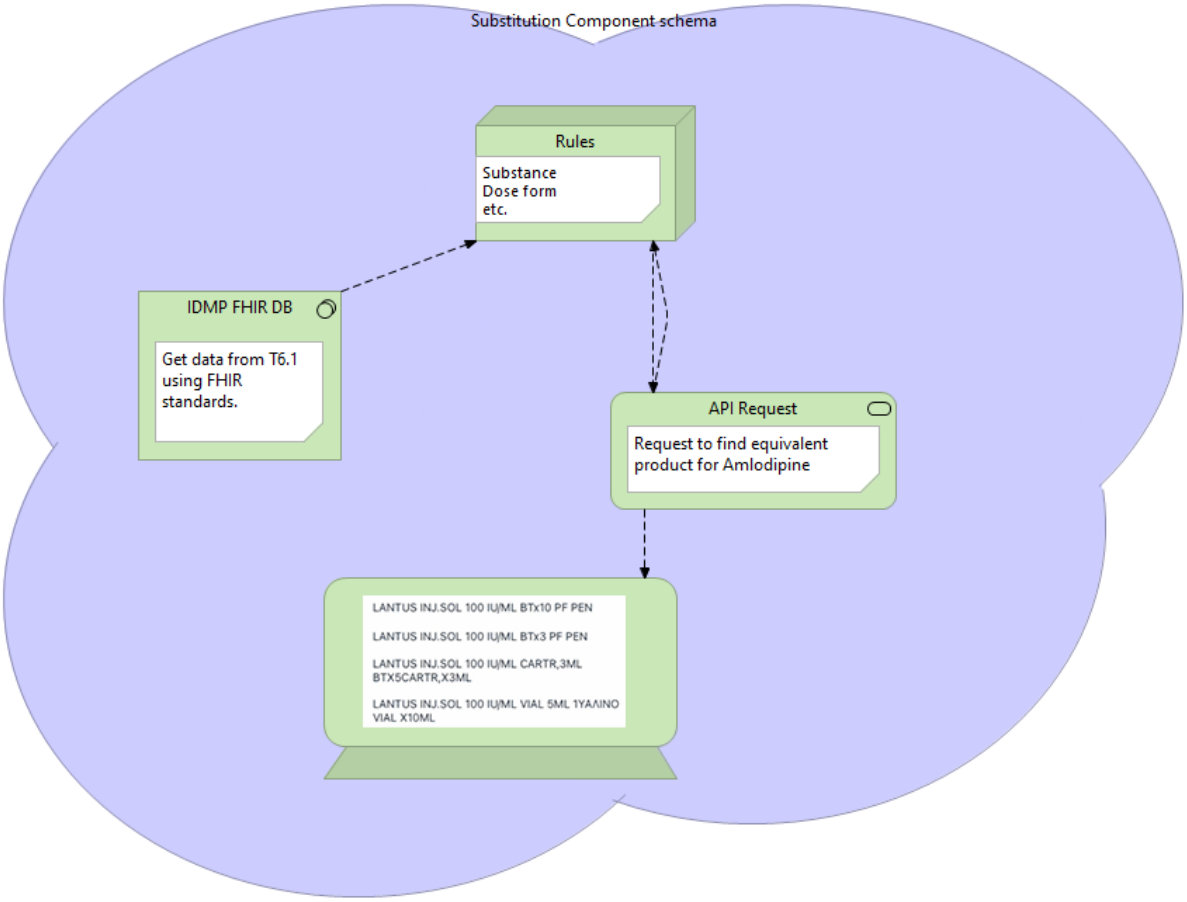


Figure 6: Substitution component schematic representation

5 Appendix 1- Set of rules based on Substances

This appendix contains the first rule based on the substances grouping.

Table 2: Set of rules based on Substances

Grouper of Substance	**(Modified) substances with the attribute of Precise Active Ingredient**	S_PAI_ID	**Moiety**	S-MID
diclofenac	dlclofenac sodium	100000092272	diclofenac	100000092272
	dlclofenac potassium	100000092368	diclofenac	100000092272
	diclofenac diethylamine	100000091074	diclofenac	100000092272
	diclofenac epolamine	100000085789	diclofenac	100000092272
amoxicilline	amoxicillin sodium	100000090113	amoxicillin (anhydrous, explicitly)	100000091596
	amoxicillin trihydrate	100000092629	amoxicillin (anhydrous, explicitly)	100000091596
carbamapezine	carbamazepine	100000092127	carbamazepine	100000092127
amlopdine	amlodipine besilate	100000090079	amlodipine	100000085259
	amlodipine mesilate	100000089571	amlodipine	100000085259
	amlodipine maleate	100000089370	amlodipine	100000085259
simvastatine	simvastatine	100000091786	simvastatine	100000091786
enalpril	enalapril maleate	100000091343	enalapril	100000092359
	enalaprilat	100000153305	enalapril	100000092359
	Enalapril sodium	100000153305	enalapril	100000092359
omeprazole	omeprazole sodium	100000090186	omeprazole	100000092047
	omeprazole magnesium	100000085918	omeprazole	100000092047
cefuroxime	cefuroxime sodium	100000091436	cefuroxime	100000092667
	cefuroxime axetil	100000093039	cefuroxime	100000092667
salbutamol	salbutamol sulfate	100000090564	salbutamol	100000091629
potassium clavinalate	Potassium clavinalate	100000093061	clavulanic acid	100000091629

Insulin glargine	insulin glargine	100000085460	insulin glargine	100000085460
teriparatide	teriparatide acetate	100000084795	teriparatide	N/A
drospiridone	drospirenone	100000092375	drospirenone	100000092375
ethinylestradiol	ethinylestradiol	100000091721	ethinylestradiol	100000091721
calcium carbonate	calcium carbonate	100000091518	calcium carbonate	100000091518
ergocalciferol	ergocalciferol	100000090229	ergocalciferol	100000090229
paracetamol	paracetamol	100000090270	paracetamol	100000090270
diazepam	diazepam	100000092362	diazepam	100000092362
morphine	morphine hydrochloride	100000090494	morphine	100000091372
	morphine sulfate	100000076239	morphine	100000091372
	morphine tartrate	100000076257	morphine	100000091372
enoxiparin	enoxaparin sodium	100000090152	enoxaparin	100000085598
hydrocortisone	hydrocortisone sodium succinate	100000092550	hydrocortisone	100000092635
	hydrocortisone valerate	100000086711	hydrocortisone	100000092635
	hydrocortisone acetate	100000092260	hydrocortisone	100000092635
	hydrocortisone butyrate	100000085172	hydrocortisone	100000092635
	hydrocortisone aceponate	100000084215	hydrocortisone	100000092635
	hydrocortisone probutate	100000085172	hydrocortisone	100000092635
	hydrocortisone cypionate	100000086187	hydrocortisone	100000092635
	hydrocortisone sodium phosphate	100000086691	hydrocortisone	100000092635
lidocaine	lidocaine hydrochloride	100000139489	lidocaïne	N/A
trastuzumab	trastuzumab emtansine	100000128434	trastuzumab	100000089314
	trastuzumab deruxtecan	100000174462	trastuzumab	100000089314
imatinib	imatinib	N/A	imatinib	N/A
clomipramine	clomipramine hydrochloride	100000090503	clomipramine	100000084546
metformin	metformin hydrochloride	100000091366	metformin	100000085448

	metformin pamoate	100000091840	metformin	100000085448
perindopril	perindopril arginine	100000088816	perindopril	100000091461
	perindopril erbumine	100000091602	perindopril	100000091461
	perindopril erbumine monohydrate	100000130680	perindopril	100000091461
	perindopril tosilate	100000141420	perindopril	100000091461
tramadol	tramadol hydrochloride	100000093275	tramadol	100000077198
ciclosporine	ciclosporine	100000092121	ciclosporine	100000092121
itraconazole	itraconazole	100000091697	itraconazole	100000091697
goserelin	goserelin acetate	100000086673	goserelin	100000084238
	glyceryl trinitrate	N/A	glyceryl trinitrate	N/A
chloroquine	chloroquine phosphate	100000092628	chloroquine	100000088282
	chloroquine sulfate	100000090551	chloroquine	100000088282
	chloroquine hydrochloride	100000084735	chloroquine	100000088282
	chloroquine diphosphate	100000129152	chloroquine	100000088282
cotrimazole	clotrimazole	100000092074	clotrimazole	100000092074
varencicline	varencicline tartrate	00109205001	varenicline	100000089154
	varenicline dihydrochloride	00109202063	varenicline	100000089154
ibuprofen	ibuprofen sodium	100000085009	ibuprofen	100000090365
	ibuprofen lysine	100000090111	ibuprofen	100000090365
taluprost	tafluprost	100000115886	tafluprost	100000115886

6 Appendix 2 - Set of rules based on Dose forms

This appendix contains the second rule based on the dose forms grouping.

Table 3: Set of rules based on doseforms

AURICULAR			
	Auricular local dose form		
		10701000	ear cream
		10702000	ear gel
		10703000	ear ointment
		10708000	ear powder
		10714000	ear tampon
		10704000	ear drops, solution
		10705000	ear drops, suspension
		10706000	ear drops, emulsion
		10712000	ear wash, solution
		10713000	ear wash, emulsion
		10709000	ear spray, solution
		10710000	ear spray, suspension
		10711000	ear spray, emulsion
		10715000	ear stick
		13006000	ear drops, powder for suspension
	Auricular/nasal		
		50020200	ear/nasal drops, suspension
	Auricular/nasal/ocular		
		50019500	ear/eye/nasal drops, solution
	Auricular/ocular		
		50019000	ear/eye ointment

		50018000	ear/eye drops, solution
		50018500	ear/eye drops, suspension
CUTANEOUS			
	Cutaneous dose form		
		10503000	gel
		10504000	ointment
		10505000	cutaneous paste
		10506000	medicated plaster
		10507000	cutaneous foam
		10508000	shampoo
		10512000	cutaneous liquid
		10513000	cutaneous solution
		10515000	cutaneous suspension
		10516000	cutaneous emulsion
		10517000	cutaneous powder
		10517500	cutaneous patch
		10520000	collodion
		10521000	medicated nail lacquer
		10522000	poultice
		10523000	cutaneous stick
		10525000	impregnated dressing
		10509000	cutaneous spray, solution
		10510000	cutaneous spray, suspension
		10511000	cutaneous spray, powder
		10514000	concentrate for cutaneous solution

		10514500	powder for cutaneous solution
		10501000	bath additive
	Cutaneous /transdermal dose form		
		10502000	cream
		50015500	cutaneous spray, emulsion
		50016000	cutaneous spray, ointment
		50009000	concentrate for cutaneous spray, emulsion
		13066000	tablet for cutaneous solution
		13014000	gel for gel
		13021000	powder for gel
		13115000	medicinal leech
		13124000	medicinal larvae
		13032000	powder for solution for skin-prick test
	Cutaneous/transdermal/nasal		
		50015200	cutaneous/nasal ointment
	Cuteneous/oromucosal		

		13140000	cutaneous/oromucosal solution
		50015450	cutaneous solution/concentrate for oromucosal solution
	Cutaneous/transdermal/parenteral		
		13052000	powder for solution for injection/skin-prick test
		13051000	solution for injection/skin-prick test
DENTAL			
	Dental dose form		
		10401000	periodontal powder
		10405000	dental powder
		10401500	dental cement
		10402000	dental gel
		10403000	dental stick
		10406000	dental solution
		10407000	dental suspension
		10408000	dental emulsion
		10409000	toothpaste
		10410000	periodontal gel
		50017000	dental paste
		50049270	powder for dental solution
		10413000	powder for dental cement
		10414000	solution for dental cement
		13022000	powder for dental gel

ENDOCERVICAL			
	Endocervical dose form		
		13024000	powder for endocervical gel
		11701000	endocervical gel
EXTRACORPERAL			
	Extracorporal dose form		
		12102000	anticoagulant and preservative solution for blood
		12103000	solution for blood fraction modification
		12112000	solution for organ preservation
EXTRACORPORAL/PARENTERAL			
	dose form for dialysis		
		11402000	solution for haemofiltration
		11403000	solution for haemodiafiltration
		50057000	solution for haemodialysis/haemofiltration
		11404000	solution for haemodialysis
		11405000	concentrate for solution for haemodialysis
		50049200	powder for concentrate for solution for haemodialysis
		13107000	solution for cardioplegia/organ preservation
GASTRIC			

	Gastric dose form		
		12114000	stomach irrigation
GASTROENTERAL			
	Gastroenteral dose form		
		12108000	gastroenteral solution
		12110000	gastroenteral suspension
		12111000	gastroenteral emulsion
ENTERAL			
	Enteral dose form		
		12120000	intestinal gel
INTRAPERITONEAL			
	Intraperitoneal dose form		
		50013250	concentrate for solution for peritoneal dialysis
		11401000	solution for peritoneal dialysis
		12111500	intraperitoneal solution
INTRAUTERINE			
	Intrauterine dose form		
		13113000	intrauterine gel
			probably only local : non-systemic
	Intra-uterine device		
		11901000	intrauterine delivery system
			definitely systemic (even if anticonceptive by local action)

INTRAVESICAL			
	Intravesical/intraurethral dose form		
		11505000	urethral stick
		11502000	bladder irrigation
		11502500	intravesical solution
		11504000	urethral gel
		13045000	intravesical suspension
		13077000	urethral emulsion
		13123000	urethral ointment
		50033400	intravesical solution/solution for injection
		50009750	concentrate for intravesical solution
		50051000	powder for intravesical suspension
		50050000	powder for intravesical solution
		11503000	powder for bladder irrigation
		50049100	powder for concentrate for intravesical suspension
	Intravesical/intraurethral/parenteral dose form		
		50050500	powder for intravesical solution/solution for injection
OCULAR			
	Ocular dose form		

		10601000	eye cream
		10602000	eye gel
		10603000	eye ointment
		10604000	eye drops, solution
		10604500	eye drops, emulsion
		10605000	eye drops, suspension
		10610000	eye lotion
		10613000	ophthalmic strip
		13044000	intraocular instillation solution
		50073500	solution for intraocular irrigation
		10600500	concentrate for solution for intraocular irrigation
		10608000	eye drops, solvent for reconstitution
		10611000	eye lotion, solvent for reconstitution
		13010000	eye drops, powder for solution
		13011000	eye drops, powder for suspension
		13029000	powder for intraocular instillation solution
		50073000	powder for solution for intraocular irrigation
		50074000	solvent for solution for intraocular irrigation
	Ocular dose form, prolonged		
		10609000	eye drops, prolonged-release
		10612000	ophthalmic insert
NASAL			
	Nasal dose form spray		
		10808000	nasal spray, solution
		10809000	nasal spray, suspension
		10810000	nasal spray, emulsion

		50037100	nasal spray, powder for solution
	Nasal dose form solid or semi-solid		
		10807000	nasal powder
			Nasal powder is illicit drug, medicanal product, pleasure habit
			check for systemic forms ?
		10801000	nasal cream
		10802000	nasal gel
		10803000	nasal ointment
	Nasal drops		
		10804000	nasal drops, solution
		10805000	nasal drops, suspension
		10806000	nasal drops, emulsion
		13020000	nasal drops, powder for solution
	Endosinusial dose form		
		50022000	endosinusial wash, suspension
		13041000	endosinusial solution
		13025000	powder for endosinusial solution
	Nasal/oromucosal dose form		
		50036700	nasal/oromucosal spray, solution
		50036500	nasal/oromucosal solution
	Nasal wash/stick		
		10811000	nasal wash
		10812000	nasal stick
	Nasal/oromucosal dose form (2)		

		50037400	nasal spray, solution/oromucosal solution
	Nasal/ocular/pulmonary		
		12131000	solution for provocation test
ORAL			
	Oral solid dose form		
		10209000	cachet
		10210000	capsule, hard
		10211000	capsule, soft
		10219000	tablet
		10220000	coated tablet
		10221000	film-coated tablet
		13046000	coated granules
		13118000	tablet with sensor
		10204000	granules
		10214000	chewable capsule, soft
		10228000	chewable tablet
		10214000	chewable capsule, soft
		10228000	chewable tablet
	Oral semi-solid dose form		
		10108000	oral gel
		10109000	oral paste
		10230000	oral gum

	Oral drops		
		10101000	oral drops, solution
		10102000	oral drops, suspension
		10103000	oral drops, emulsion
		50037750	oral drops, liquid
		50082000	oral drops, powder for suspension
		50037500	oral drops, granules for solution
	Oral form Liquid		
		10104000	oral liquid
		10105000	oral solution
		10106000	oral suspension
		10107000	oral emulsion
		10117000	syrup
		10100500	concentrate for oral suspension
		50010000	concentrate for oral solution
		10111000	powder for oral suspension
		10113000	granules for oral suspension
		10110000	powder for oral solution
		10112000	granules for oral solution
		10118000	powder for syrup
		10119000	granules for syrup
		10120000	soluble tablet

	Oral forms effevescent of dispersible		
		10121000	dispersible tablet
		10121500	dispersible tablets for dose dispenser
		13007000	effervescent granules for oral suspension
		10203000	effervescent powder
		10205000	effervescent granules
		10222000	effervescent tablet
		50001000	chewable/dispersible tablet
		10224000	oral lyophilisate
		10201000	oral powder
		10223000	orodispersible tablet
		10236100	orodispersible film
		10202000	instant herbal tea
		13106000	oral herbal material
	Gastroresistant oral forms		
		10206000	gastro-resistant granules
		10212000	gastro-resistant capsule, hard
		10213000	gastro-resistant capsule, soft
		10225000	gastro-resistant tablet
		13133000	gastro-resistant oral suspension
		13136000	gastro-resistant powder for oral suspension

		50026000	gastro-resistant granules for oral suspension
	Prolonged release oral forms		
		10207000	prolonged-release granules
		10215000	prolonged-release capsule, hard
		10216000	prolonged-release capsule, soft
		10226000	prolonged-release tablet
		13134000	prolonged-release oral suspension
		50056000	prolonged-release granules for oral suspension
	Modified release oral forms		
		10208000	modified-release granules
		10217000	modified-release capsule, hard
		10218000	modified-release capsule, soft
		10227000	modified-release tablet
		13135000	modified-release oral suspension
		50036000	modified-release granules for oral suspension
	Oral/oralmucosal dose form		
		10229000	medicated chewing-gum
		10231000	pillules

	Oral/pulmunary dose form		
		50038500	oral solution/concentrate for nebuliser solution
	Oral/rectal dose form		
		50011000	concentrate for oral/rectal solution
		50029150	granules for oral/rectal suspension
		50052000	powder for oral/rectal suspension
		50037900	oral/rectal solution
		50038000	oral/rectal suspension
OROMUCOSAL			
	Oromucosal spray dose form		
		10308100	oromucosal spray, emulsion
		10308200	oromucosal spray, solution
		10308300	oromucosal spray, suspension
		13017000	laryngopharyngeal spray, solution
	Oromucosal solid dose form		
		10320000	buccal tablet
		13016000	laryngopharyngeal solution
		10321000	lozenge
		10322000	compressed lozenge
		10323000	pastille
		10317000	oromucosal capsule

	Oromucosal prolonged dose form		
		10319000	muco-adhesive buccal tablet
		50039000	oromucosal patch
	Oromucosal liquid dose form		
		13016000	laryngopharyngeal solution
		13016000	laryngopharyngeal solution
		10305000	oromucosal solution
		10306000	oromucosal suspension
		10312000	gingival solution
		10313000	oromucosal gel
		10314000	oromucosal paste
		10314005	oromucosal ointment
		10314010	oromucosal cream
		10314011	buccal film
		10315000	gingival gel
		10316000	gingival paste
		10307000	oromucosal drops
		13003000	concentrate for oromucosal solution
		13026000	powder for gingival gel
	Oromuscular gargling and mouthwash dose form		
		10301000	gargle
		50024000	gargle/mouthwash
		10302000	concentrate for gargle

		10303000	gargle, powder for solution
		10304000	gargle, tablet for solution
		10311000	mouthwash, tablet for solution
		50036050	mouthwash, powder for solution
	Oromucosal/laryngopharyngeal dose form		
		50039500	oromucosal/laryngopharyngeal solution
		50040500	oromucosal/laryngopharyngeal solution/spray, solution
	Sublingual dose form		
		10309100	sublingual spray, emulsion
		10309200	sublingual spray, solution
		10309300	sublingual spray, suspension
		10317500	sublingual film
		10318000	sublingual tablet
		13105000	sublingual powder
		13127000	sublingual lyophilisate
PARENTERAL			
	Prolonged implantation dose form		
		11301000	implant
		11302000	implantation tablet
		11303000	implantation chain
		11303300	implantation matrix
		11303500	implantation suspension
		13043000	implantation paste
		13028000	powder for implantation paste

		50049500	powder for implantation suspension
		13027000	powder for implantation matrix
		13018000	matrix for implantation matrix
	Prolonged injection dose form		
		11208500	prolonged-release suspension for injection
		13076000	prolonged-release solution for injection
		13126000	prolonged-release dispersion for injection
		11208400	powder for prolonged-release suspension for injection
	Injection dose form		
		11201000	solution for injection
		11202000	suspension for injection
		11203000	emulsion for injection
		11204000	gel for injection
		50077000	dispersion for injection
		11209000	concentrate for solution for injection
		13004000	concentrate for suspension for injection
		13139000	concentrate for dispersion for injection
		11209000	concentrate for solution for injection
		13004000	concentrate for suspension for injection
		13139000	concentrate for dispersion for injection
		11206000	powder for suspension for injection
		13013000	gas for dispersion for injection
		13023000	powder for dispersion for injection
		13048000	granules for suspension for injection
		13008000	emulsion for emulsion for injection
		13033000	solution for solution for injection

		13036000	suspension for emulsion for injection
		13039000	suspension for suspension for injection
		13040000	powder for emulsion for injection
		13047000	solution for suspension for injection
		13091000	emulsion for suspension for injection
		11205000	powder for solution for injection
	Infusion dose form		
		11210000	solution for infusion
		11211000	emulsion for infusion
		50017500	dispersion for infusion
		11213000	concentrate for solution for infusion
		13001000	concentrate for concentrate for solution for infusion
		50009300	concentrate for dispersion for infusion
		50009500	concentrate for emulsion for infusion
		11211500	powder for dispersion for infusion
		13012000	gas for dispersion for infusion
		11212000	powder for solution for infusion
		13061000	solution for solution for infusion
		50076000	solvent for solution for infusion
		50048750	powder for concentrate for dispersion for infusion
		50043000	powder for concentrate for solution for infusion
		50048750	powder for concentrate for dispersion for infusion
		50043000	powder for concentrate for solution for infusion
	Infusion/injection dose form		
		13049000	dispersion for injection/infusion
		50021000	emulsion for injection/infusion

		50060000	solution for injection/infusion
		50079000	concentrate for solution for injection/infusion
		13050000	gas for dispersion for injection/infusion
		50053500	powder for solution for injection/infusion
		11216000	solvent for parenteral use
		50049250	powder for concentrate for solution for injection/infusion
	Injuction for local effect dose form		
		11209500	solution for cardioplegia
PULMONARY			
	Vapour dose form		
		50033000	inhalation vapour, impregnated pad
		50033100	inhalation vapour, impregnated plug
		11115000	inhalation vapour, tablet
		50031000	inhalation vapour, effervescent tablet
		11112000	inhalation vapour, powder
		11113000	inhalation vapour, capsule
		11114000	inhalation vapour, solution
		11116000	inhalation vapour, ointment
		11117000	inhalation vapour, liquid
		50032000	inhalation vapour, emulsion
	Nebulizer dose form		
		11101000	nebuliser solution
		11102000	nebuliser suspension
		11105000	nebuliser emulsion
		13129000	nebuliser dispersion

		13002000	concentrate for nebuliser solution
		11103000	powder for nebuliser suspension
		11104000	powder for nebuliser solution
	Pressurized inhalation dose form		
		11106000	pressurised inhalation, solution
		11107000	pressurised inhalation, suspension
		11108000	pressurised inhalation, emulsion
	Inhalation dose form		
		11109000	inhalation powder
		11110000	inhalation powder, hard capsule
		11111000	inhalation powder, pre-dispensed
		50030000	inhalation powder, tablet
	Medicinal gas dose form		
		12301000	medicinal gas, compressed
		12302000	medicinal gas, cryogenic
		12303000	medicinal gas, liquefied
	Endotracheopulmonary instillation		
		11601000	endotracheopulmonary instillation, solution
		11603000	endotracheopulmonary instillation, suspension
		13009000	endotracheopulmonary instillation, powder for suspension
		11602000	endotracheopulmonary instillation, powder for solution
RECTAL			

	Rectal systemic dose form		
		11013000	suppository
		11014000	rectal capsule
		11015000	rectal tampon
	Rectal local dose form		
		11004000	rectal foam
		11005000	rectal solution
		11006000	rectal suspension
		11007000	rectal emulsion
		11001000	rectal cream
		11002000	rectal gel
		11003000	rectal ointment
		11008000	concentrate for rectal solution
		11010000	powder for rectal suspension
		11012000	tablet for rectal suspension
		13015000	granules for rectal suspension
		11009000	powder for rectal solution
		11011000	tablet for rectal solution
TRANSDERMAL			
	Transdermal dose form prolonged		
		10519000	transdermal patch
	Transdermal dose form		
		10518000	solution for iontophoresis
		10546250	transdermal gel
		10546400	transdermal solution

		10547000	transdermal system
		10548000	solution for skin-prick test
		10549000	solution for skin-scratch test
		10550000	plaster for provocation test
		13102000	transdermal ointment
		10546500	transdermal spray, solution
		10518500	powder for solution for iontophoresis
VAGINAL			
	Vaginal dose form prolonged		
		10915000	vaginal delivery system
			not necessarily systemic !
	Vaginal dose form		
		10910000	vaginal capsule, hard
		10911000	vaginal capsule, soft
		10912000	vaginal tablet
		10913000	effervescent vaginal tablet
		10914000	medicated vaginal tampon
		10904000	vaginal foam
		10905000	vaginal solution
		10906000	vaginal suspension
		10907000	vaginal emulsion
		10901000	vaginal cream
		10902000	vaginal gel
		10903000	vaginal ointment
		10908000	tablet for vaginal solution
		13111000	powder for vaginal solution

		50029500	vaginal solution
	Vaginal device		
		10909000	pessary
MISCALLEANOUS			
	Radiopharmaceuticals		
		50056500	radiopharmaceutical precursor, solution
		12105000	radiopharmaceutical precursor
		12106000	radionuclide generator
		12107000	kit for radiopharmaceutical preparation
	Wound dressings prolonged dose form		
		13128000	prolonged-release wound solution
		30047500	pouch
	Various dose form		
		13042000	epilesional solution
		12101000	denture lacquer
		12115000	sealant
		12115100	sealant matrix
		12115200	sealant powder
		12113000	irrigation solution
		12104000	wound stick
		12119000	medicated sponge
		12117000	impregnated pad
		12117500	impregnated plug
		12130000	medicated thread
		50049300	powder for epilesional solution
		13031000	powder for sealant

		50061500	solution for sealant
		13034000	solution for spray
		13038000	suspension for spray
		13035000	solvent for

7 Appendix 3 - Set of rules for those things that cannot be substituted

This appendix contains the third set of rules, for those things that cannot be substituted. Table 4: Overview of most common groups of products exempted from INN prescribing and Table 5: Overview of the applied regulation of medicines prescribing and generic substitution, summarize the content required to perform the third rule. There are several open issues that need to be addressed in regards to prescribing and substitution of medicines in MS. Specifically, it is important to determine if the current statements on INN prescribing and substitution are accurate and always be up-to-date. In addition, it is necessary to verify if the list of exemptions from substitution or INN prescribing is accurate and relevant. Furthermore, it is essential to determine if the MS has a formal definition of "medicines with a narrow therapeutic window" and, if so, whether this definition is being consistently applied. These issues are critical to address in order to ensure the safe and effective use of medicines within the MS.

Table 4: Overview of most common groups of products exempted from INN prescribing[11]

Country	Anti-arrhythmia agents	Antiepileptic agents	Biologicals & biosimilars	Cardiac glycosides	Coumarin anticoagulants	Immunosuppressive agents	Thyroid hormones	Products used with specific aids
Belgium	Exempted from switching	All exempted from switching	Exempted from INN prescribing	Exempted from switching	Exempted from switching	Exempted from switching	Exempted from switching	Exempted from switching
Croatia	-	-	-	Digoxin exempted from generic substitution	Warfarin exempted from generic substitution	Cyclosporin and tacrolimus exempted from generic substitution	-	Exempted from generic substitution
Estonia	No explicit exemptions for INN prescribing; brand name prescribing only allowed for medical reasons							
Finland	Exempted from generic substitution	Exempted from generic substitution	Exempted from generic substitution	Exempted from generic substitution	Warfarin exempted from generic substitution	-	-	Exempted from generic substitution
France	-	Levetiracetam, lamotrigine, topiramate and valproic acid exempted from	-	-	-	Mycophenolate mofetil exempted from generic substitution	L-thyroxin exempted from generic substitution	-

[11] https://biblio.ugent.be/publication/6928842/file/6928843.pdf

		generic substitution						
Germany	Substitution should be carefully considered	Substitution should be carefully considered	Substitution should be carefully considered	Substitution should be carefully considered	Substitution should be carefully considered	Substitution should be carefully considered	Substitution should be carefully considered	Substitution should be carefully considered
Hungary	No explicit exemptions for INN prescribing or generic substitution. A list of substitutable medicinal products is available.							
Italy	No explicit exemptions for INN prescribing or generic substitution. A list of substitutable medicinal products is available.							
Lithuania	-	Exempted from INN prescribing	Exempted from INN prescribing	-	-	Exempted from INN prescribing	-	-
the Netherlands		Exempted from generic substitution when indicated for epilepsy	Substitution should be carefully considered	Exempted from substitution	Exempted from substitution	Exempted from substitution when indicated for prophylaxis of graft-versus-host disease	Exempted from substitution	

Norway	-	All exempted from generic substitution but only when indicated for epilepsy	-	-	-	-	L-thyroxin exempted from generic substitution	-
Portugal	-	-	-	-	-	Cyclosporin and tacrolimus exempted from generic substitution	L-thyroxin exempted from generic substitution	-
Slovenia	No explicit exemptions for INN prescribing or generic substitution. A list of substitutable medicinal products is available.							
Spain	Flecainide exempted from generic substitution	Carbamazepine, phenytoin and vigabatrin exempted from generic substitution	Exempted from generic substitution	Digoxin and metildigoxin exempted from generic substitution	Exempted from generic substitution	Cyclosporin and tacrolimus exempted from generic substitution	L-thyroxin exempted from generic substitution	Exempted from generic substitution
Sweden	-	Exempted from generic substitution	-	-	-	Exempted from generic substitution	-	Exempted from generic substitution

United Kingdom	-	Advised to prescribe by brand name	Advised to prescribe by brand name	-	-	Advised to prescribe by brand name	Advised to prescribe by brand name	Advised to prescribe by brand name

Table 5: Overview of the applied regulation of medicines prescribing and generic substitution

Country	Brand name prescribing = prescribing of branded generics	INN prescribing	Generic substitution
Belgium	Allowed for all products	Allowed, but with exemptions	Not allowed
Croatia	Mandatory for all products	Allowed for all products	Allowed, but with exemptions
Estonia	Not allowed, only in specific situations	Mandatory for all products	Allowed
Finland	Allowed for all products	Allowed for all products, but rarely used	Mandatory, but with exemptions
France	Allowed for all products	Allowed for all products	Mandatory, but with exemptions
Germany	Allowed for all products	Allowed for all products	Mandatory, but with exemptions
Hungary	Allowed for all products, except lipid-modifying agents	Allowed, mandatory for lipid-modifying agents	Allowed

Italy	Allowed, except for off-patent products prescribed for acute treatment or for the 1^{st} time in chronic treatment	Mandatory for off-patent products prescribed for acute treatment or for the 1^{st} time in chronic treatment	Allowed, but with exemptions
Lithuania	Not allowed, only in specific situations	Mandatory for all products, except biologicals and narrow therapeutic index drugs (antiepileptic agents and immunosuppressive agents)	Not allowed
the Netherlands	Allowed for all products	Allowed for all products	Allowed, but with exemptions
Norway	Allowed for all products	Allowed for all products, but rarely used	Mandatory, but with exemptions
Portugal	Not allowed, only in specific situations	Mandatory for all products, except for tacrolimus, ciclosporin and L-thyroxin	Not allowed
Slovenia	Allowed for all products	Allowed for all products	Allowed for all products