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Abstract (for dissemination)	<p>This document presents clusters as a tool for grouping products with the same preselected attributes. It explores the concepts behind cluster formation and useful attributes which can help in a cross-border setting for such purpose.</p> <p>On the other hand, as part of compound medication explores other descriptive needs required in the identification of medicinal products. It also outlines the reverse identification of medicinal products in different contexts along with some of the resources available for it.</p>
Keywords	Cluster, legal basis, survey, reverse identification, procedure identifier, procedure number, cross-border identification, compound medication, compound medication

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This deliverable contains original unpublished work except where clearly indicated otherwise.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 Deliverable 4.1

Relationship to the overall goal of the project and to other work in this WP/other WPs:

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

Work package 4 focuses on validating the concepts listed in WP2 on applicability to new use cases such as prescribing a medicinal or a pharmaceutical product only by specifying a cluster of products, exploring other descriptive needs and reverse identifying products starting from attributes description.

WP1 revised and identified gaps and problems in describing medication in the epSOS piloting. In this work package, different elements were classified as being in the scope of epSOS and from those which were out of the scope, some expected to be further assessed as part of the openMedicine project and one of the elements was the cluster of products.

WP2 solution was built upon the ISO IDMP standards and in accordance with the EMA implementation activities regarding this particular concept of standardised medicinal products identification. It is therefore important to underline that in the proposed solution of work package 2, it is assumed that the ISO IDMP approach is implemented in order to streamline e-prescribing and e-dispensing processes in the cross-border context.

WP3 work, being a continuation of the WP2 achievements, is based on the same foundation and the same assumption as the above described assumptions. WP3 analyses various references in order to identify any possible medicinal product types that might need additional identifiers not foreseen in WP2 or new attributes not included in the ISO IDMP standards.

In this context, following those assumptions the present deliverable complements the outcomes of task WP2 and WP3. It develops further and extends the results of deliverable 2.2 (D 2.2) where a comprehensive set of openMedicine identifying and descriptive attributes were formulated and also complements the gaps identified in D.3.1. This, in turn, will feed into task D2.3 to complete and finalise the openMedicine identifying and descriptive attributes.

WP5 explores the status of substitution at European level to provide a concise framework and approach for analysing the substitution challenges. Substitution definition still poses a challenge in Europe, as it does when applying it to the cluster context. WP4 and WP5 worked closely together for the elaboration and distribution of a survey in relation to substitution and cluster formation. These concepts are closely related.

Objective:

The main objectives of WP4 are to validate the concepts listed in WP1 in relation to applicability of new use cases: prescribing a medicinal or pharmaceutical product only by specifying a cluster or a class of products, which was out of the scope of this WP.

Investigate applicability of the concepts defined in WP2 and WP3 and finally to investigate what attributes are needed for reverse identification of a product.

Approach/methods applied:

From the beginning, WP4 members have been closely working with other work package leaders. The contents of this WP are of different nature and at the same time are closely related to previous WPs. Alignment of WP2, WP3 and WP4 was mandatory in order to address the gaps identified during the elaboration of these deliverables. The involvement in those WPs helped defining and aligning the contents and scope of the different WPs.

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 and Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency is regulatory framework which openMedicine pivots around. Nonetheless, this regulatory framework was in need of further description and understanding of its contents and procedures particularly in relation to the marketing authorisation applications.

All the information related to a medicinal product (MP) is contained in a marketing authorisation dossier which is presented to the regulatory agencies in a structured and harmonised manner. The particular requirements of a dossier reveal the different attributes of medicinal products. Sometimes these medicinal products are different in nature; sometimes their differences rely on the way the documentation is presented, without necessarily changing the active substance, the strength, dose or pharmaceutical dose form. The WP4 approach investigates the differences of what might be considered as the “same pharmaceutical product” in relation to the differences in the contents of the modules of a dossier and how these attributes can be used for cluster formation.

The other important piece of information which was of high relevance in a cross-border setting was the procedure type used when submitting a marketing authorisation application to a regulatory agency. This concept, although mentioned in previous deliverables, was not deeply analysed. It also revealed differences in how attributes were allocated and how they could help the identification of medicinal products in a cross border setting.

Cluster formation, when used as a tool for grouping up medicinal products with similar attributes, revealed a very complex and specialised area used in different contexts. While the aim was to understand better its use around Europe and know more about how and why clusters are created in different member states, through the elaboration of a Lime Survey we explored what member states did. Nonetheless, further investigation will be required.

When the indication of a medicinal product, the treatment group of patients, the route or method of administration or the posology of a particular medicinal product are different from those authorised, then an MP is being used off-label. The five ISO IDMP standards being implemented at European level leave out of scope the use of off-label medication. This was analysed as another descriptive need as part of the identification of an MP in this WP, and its importance in relation to pharmacovigilance.

Finally, the identification of medicinal products starting from the product description is explored in this work package. Reverse identification of an MP is required in many instances outside those of the ePrescription context. This process is required in the regulatory, clinical and logistics contexts, which are all connected with each other. The resources used for the identification process are different depending on the context and the country. Some databases containing physical attributes of an MP are described in this WP.

Results:

Already existing data models are used in drug databases for cluster creation. The ISO IDMP identifiers will be used to build the EMA data base which at this point allows us to build upon its theory. Attributes matching in a cross border setting. Attributes are differently assigned according to the jurisdiction but as Europe is becoming more and more harmonised in formats and procedures, in relation to marketing authorisation dossiers, then other attributes assigned will contribute to the identification of MP in a cross border setting such as those with same dossier. Procedure numbers, in decentralised and mutual recognition procedures, embrace two or more medicinal products with the same dossier. Centrally authorised MPs have attributes which are valid throughout the EU. Marketing authorisation number, in centralised procedures, is a key attribute for identification in a cross-border setting, not being so

in decentralised (DC), mutual recognition (MR) or national procedures. Nonetheless, the procedure identifier is a key attribute for these first two, MR and DC procedures. Nationally authorised products still remains an identification challenge in a cross border setting.

Understanding the legal basis of a dossier contributes to determine the interchangeability or prescribability of medicinal products under regulatory perspective and it is also used for cluster creation. Whereas for the generic legal basis therapeutic equivalence is defined by regulation, under other legal basis such as hybrid, well-established use and biosimilars further guidelines and consensus are needed.

A different perspective is needed when using clusters in a prescribing context where the terms prescribability or interchangeability and switchability can contribute to a safer use of medicines in a cross border setting.

The European Medicines Agency, in charge of the supervision of medicinal products, implements Pharmacovigilance regulation which aims at reducing the adverse events caused by medication, to protect public health through the monitoring, assessment and evaluation of the use of MP. As part of the openMedicine objectives, we work towards the unique identification of MP and, therefore, contributing to a better and safer use of medication in a cross border setting. Currently the article 57 database, which will become ISO IDMP compliant, is connected to the repository of the Periodic Safety Update Reports (PSURs).

When identifying other descriptive needs such as those of the off-label uses of medication, it also revealed the need to identify the use outside the licence terms of MP in a cross border setting, aligning with the pharmacovigilance requirements.

The reverse identification of medicinal products happening in a context such as a hospital (where a patient accidentally takes more medication than expected, for example) it is also evolving to contribute to better safety in medicines use. The tools for such purposes are becoming more sophisticated and whether they are provided by public or private institutions they are required for many contexts. To better enable the unique identification of MP new requirements at the packaging level have been set in European Union aiming at reducing falsified medicines. On the other hand, some of the physical characteristics of MP such as colour or imprint are not standardised or mandatory; they are industry assigned.

1 Introduction

1.1 Objectives and tasks of WP4

WP4 has as the main objective to validate work from previous work packages. In particular, in WP1, the applicability of prescribing a medicinal or a pharmaceutical product only by specifying a cluster or a class of products was validated, as this was out of the scope of ep-SOS. In addition, WP4 investigates the applicability of the concepts defined in WP2 and WP3.

Another objective in this WP is related to the reverse identification of a product and what attributes are needed to do so.

The special identification needs of pharmaceutical products in particular use cases are addressed in this WP. We have three sub-tasks and finally one deliverable:

- **Subtask 4.1** more precisely when not prescribing an individual medicinal or pharmaceutical product but prescribing a class of products or a “cluster” of medicinal products and leaving to the pharmacist to select the medicinal product to be dispensed.
- **Subtask 4.2** addresses the issues related to products administrated in a different administration form than the original form, being it as a separate medicinal product or as a mixture/cocktail of different products, e.g. cytostatic baxter treatments. Being the resulting cocktail a new instance of a medicinal product.
- **Subtask 4.3** will investigate how the openMedicine options enables identification of a medicine starting from the product unit description (reverse identification).

1.2 Methodology adopted

Close cooperation with other WPs has been carried out throughout the project, which allowed aligning the contents of the different WPs and covering the gaps identified in the walk-through of other deliverables.

WP2 approach started with the analysis of a common set of concepts and the detailed analysis of the data elements and the applicable standards, identifying the processes in which a medicinal product is involved and the many standards related to those processes. The use cases considered revealed certain descriptive aspects relevant but not fully explored, such as procedure number or identifier.

WP3 assessed the WP2 solution starting by analysing the regulatory frameworks relevant to the different MP, using 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 and Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency as the starting point for this analysis. This Directive and this regulation contain the provisions for the requirements of the dossiers presented to regulatory authorities to obtain an authorisation to place a medicinal product on the market, particularly the Directive. The Regulation 726/2004 contains the provisions which drove EMA to create the so-called article 57 database.

Although the legal basis of a medicinal product, the dossier for a marketing authorisation presented to the regulatory authorities as well as the type of procedure used for it, were important aspects in relation to the Regulation and the Directive mentioned in the above para-

graph, the origin of the attributes and how these attributes were assigned, was an area not entirely explored.

Chapter 1 where this section belongs to, it is the introduction.

Chapter 2 contains the references used for the elaboration of this deliverable.

Chapter 3 includes the terms and acronyms contained in this deliverable.

It is in Chapter 4 that the description of data model structures for drug database starts, some of the core concepts for creating those databases and the core concept for the future EMA database: the PhPID.

Chapter 5 discusses other attributes relevant from for cluster formation, which have not been discussed extensively in previous work packages. It includes the marketing authorisation dossier, the legal basis for the marketing authorisation (MA) dossiers and duplicate applications.

Chapter 6 discusses relevant attributes derived from Marketing Authorisation procedure type: centralised, decentralised, mutual recognition and national procedures and their role in a cross-border setting.

Chapter 7 describes some examples and cluster formation and some clusters created using attributes from previous chapters.

Chapter 8 contains a summary of the Lime survey elaborated in conjunction with WP5 regarding clusters and substitution.

Chapter 9 describes the different instances where we find compound medication including compound medication being used under the terms of their licence and Compound medication being used off-label.

Chapter 10 summarises the key concepts in pharmacovigilance, the importance to reduce adverse events and data collection in this context.

Chapter 11 explores the identification of medicinal products starting from product description, meaning the reverse identification of a MP. It explores the physical attributes of a pharmaceutical and medicinal product helping us identify the products and some of the existing databases already available to aid identification in the different contexts where it is needed.

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EN ISO 11616, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated pharmaceutical medicinal product.

EN ISO 11238, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances.

EN ISO 11239, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging.

EN ISO 11240, Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of units of measurement.

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GUIDELINE ON THE PACKAGING INFORMATION OF MEDICINAL PRODUCTS FOR HUMAN USE AUTHORISED BY THE UNION, July 2013
http://ec.europa.eu/health/files/eudralex/vol-2/c/bluebox_06_2013_en.pdf

RAEFAR- Spanish Regulatory Medicines data base

CIMA – Medication information center. (Centro de información de medicamentos de la AEMPS).<https://cima.aemps.es/cima/fichasTecnicas.do?metodo=detalleForm>

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3 Acronyms, terms and definitions

ABE- Average bioequivalence

AMP- Actual Medicinal product

AMPP- Actual Medicinal Product Pack

CHMP- Committee for Medicinal Products for Human Use

CMDh- Coordination group for the mutual recognition and decentralised procedures- Human

CTD-Common technical document

eAF- electronic Application Forms

EC- European Commission

EMA- European Medicines Agency

epSOS- European patients Smart open service

EU- European Union

FDA- Food and drug administration (USA)

GRHC- Gastro resistant hard capsules

HVDP- Highly variable drugs

IBE- Individual Bioequivalence

ICH- International conference of harmonization.

ISO IDMP- International standards for the identification of medicinal products

MA- Marketing authorisation

MAH- Marketing authorisation holder

MAN- Marketing authorisation number

MPID- Medicinal product identifier

MP- Medicinal product

MS- Member states

NA- Not applicable

NTID- Narrow therapeutic index drugs

PBE- Population Bioequivalence

PhPID- Pharmaceutical product identifier

PRAC- Pharmacovigilance Risk Assessment Committee

RMP- Reference medicinal product

RMS- Reference Member State

SmPC- Summary of product characteristics

SNOMED-CT- Systematised Nomenclature of Medicine (clinical terms)

VMP- Virtual Medicinal Product

VMPP- Virtual Medicinal Product Pack



VTM- Virtual therapeutic moiety

WP- Work package

EU- European Union

4 Data model structures for drug databases

4.1 Substance

A substance is defined in ISO 11238 as “any matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical”. Substances will be defined according to the Pharmacopoeial terminology and defining characteristics will be used when available and appropriate. In some instances the defining elements are dependent on the type of substance (i.e. chemical, protein, nucleic acid, polymer, structurally diverse, mixture, which helps defining a molecule according to the complexity of their structure).

On the other hand, a substance can be classified according to its origin: human (e.g. blood and blood products) animal (microorganisms, whole animals, part of organs, animal secretions, toxins, blood products..) vegetal (microorganism, plants, parts of plants, vegetable secretions...) or chemical origin (e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis).

When a substance is intended to be used in a manufacturing of a medicinal product it enters a regulatory cycle and acquires multiples attributes along the process. According to the attributes and defining characteristics associated, we will find substances classified and belonging to different groups in relation to their origin, structure, legal framework, intended use, type of regulatory application used, etc. We may choose what classification can help us in the identification according to our needs, focusing on the classification that is relevant in each moment.

Regulatory agencies need to be able to define substances in an unambiguous manner and ISO IDMP provides a framework to do so in the regulatory context. Deliverable 3.1 discusses the terminologies, codes and dictionaries for MP having substances as the core element. As no global data base exists at the moment for substances based on different classification systems (CAS, InChI, EC Number), starting from substances different abstract concepts can be assigned to help identify MPs.

Below, there is a description of some of the concepts used to as starting point for a model to for MP dictionaries.

4.2 Core concepts used in dictionaries

Medical dictionaries use common vocabularies to allow the identification of medicinal products in the clinical and the regulatory world. The requirement of national identifiers has produce as a result different member states delivering a standard electronic vocabulary (terminology) and identifiers which can serve different purposes either in the clinical context, to identify medicines to be prescribed, for example, or in the regulatory context with the aim of facilitating the electronic transfer of data for pharmacovigilance purposes between the different system providers. These data are reused according to the context or the business cases needed.

The European Medicines Agency (EMA) through the so-called article 57 database will be using standardised terminology at international level with a structured model which will allow data reuse at European level.

If we take the examples of dictionaries created based on a subset of SNOMED CT as it is in the case of countries like Belgium, Spain or the UK, we can see how unique identifiers are generated for the identification of MP and devices and then these identifiers used to facilitate

the ePrescription service or electronic patient record, but their use could also be extended to other fields such as auditing.

The main two elements described of these dictionaries are:

- products as concepts (called virtual medicinal products or VMP) e.g. atenolol 50 mg tablets or latex catheter 20 gauge.
- and real products (called actual medicinal products or AMP) e.g. atenolol 50 mg tablets made by AAH pharmaceuticals or Tenormin LS 50 mg tablets from AstraZeneca.

4.2.1 Virtual therapeutic moiety (VTM)

It is the abstract representation of a substance(s) formulated as a medicinal product, intended by an authorising health care professional for use in the treatment of a patient.

Examples: Co-amoxiclav, omeprazol, prednisolone

4.2.2 Virtual Medicinal Product (VMP)

A Virtual Medicinal Product (VMP) is an abstract concept representing the properties of one or more clinically equivalent Actual Medicinal Products, where clinical is defined as relating to the course of a disease.

Examples: Co-amoxiclav 250/125 mg tablets,
omeprazol 20 mg capsules

4.2.3 Actual Medicinal product (AMP)

An Actual Medicinal Product (AMP) is a single dose unit of a finished dose form (unless the product is presented as a continuous dosage form), attributable to an identified supplier that contains a specified amount of an ingredient substance.

Examples: Atenolol 100 mg tablets (Almus Pharmaceuticals Ltd)
Tenormin 100 mg tablets (AstraZeneca UK Ltd)

4.2.4 Virtual Medicinal Product Pack (VMPP)

A Virtual Medicinal Product Pack (VMPP) is an abstract concept representing the properties of one or more quantitatively equivalent AMPPs.

For every Actual Medicinal Product Pack (AMPP) there will be a corresponding VMPP. A VMPP will have at least one AMPP and may have many AMPPs linked to it.

Examples: Atenolol 100 mg tablets x 28 tablet Generic
Estracombi TTS transdermal patches x 8 patches

4.2.5 Actual Medicinal Product Pack (AMPP)

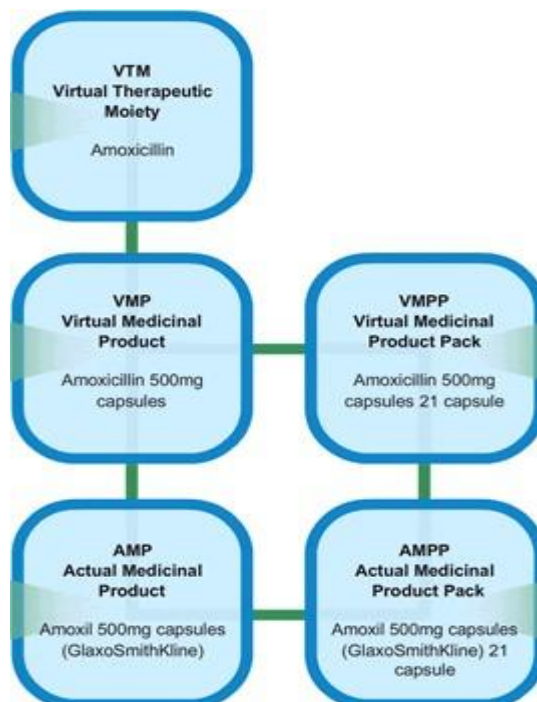
An Actual Medicinal Product Pack (AMPP) is the packaged product that is supplied for direct patient use or from wherein AMPs are supplied for direct patient use. It may contain multiple components each of which may or may not be an AMPP in their own right.

At this actual pack level, the dictionary includes information that is required for prescribing, dispensing and for reimbursement, e.g. legal status, Schedule 1 information, price etc.

Examples. Atenolol 100 mg tablets (Sandoz Ltd) x 28 tablet
Augmentin 375 mg tablets (GlaxoSmithKline UK Ltd) x 21 tablet

This model has five basic components: VTM, VMP, AMP, VMPP and AMPP, each component represented in a box, and describes a product at different levels of granularity to support various use cases (being for prescribing in primary or secondary care, for recording information, pharmacovigilance and so on).

Figure 1 – Example of data model dictionary



Source: [http://www.nhs.uk/PrescriptionServices/Documents/dmd_data_model_\(2\).gif](http://www.nhs.uk/PrescriptionServices/Documents/dmd_data_model_(2).gif)

4.2.6 Pharmaceutical Product identifier (PhPID)

ISO IDMP 11615:2012 defines a *PhPID* as: a unique identifier for a pharmaceutical product. A *pharmaceutical product* as: the qualitative and quantitative composition of a Medicinal Product in the dose form approved for administration in line with the regulated product information.

A subset of elements identifies a pharmaceutical product:

- Active Substance(s)/Specified Substance(s)
- Strength(s) - Strength units (units of measurement and/or unit of presentation)
- Reference Substance (active moiety)
- Reference Strength (basis of strength per active moiety)
- Administrable Dose Form
- Medical device: when it is a component of a medicinal product
- Adjuvants

4.2.7 International Nonproprietary Name (INN)

INN is a nomenclature system. International Nonproprietary Names (INN) identifies pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognised and is public property. A non-proprietary name is also known as a generic name (it is important not to confuse with “generic medicinal product” described in section 5.3.4.1).

International Nonproprietary names are intended for use in pharmacopoeias, labelling, product information, advertising and other promotional material, drug regulation and scientific literature, and as a basis for product names, e.g. for generics. However, the INN programme does not include:

- names for mixtures of substances,
- substances that are not fully characterised (only in exceptional cases)
- herbal substances (vegetable drugs)
- homoeopathic products.
- substances that have a long history of use for medical purposes under well-established names such as those of alkaloids (e.g. morphine, codeine), or trivial chemical names (e.g. acetic acid).

The cumulative list of INN currently contains some 7,000 names designated since the time the system initiated in 1953 and this number is a growing number.

In the regulatory context, according to electronic application form (eAF) used for submitting the information for the request of a marketing authorisation, the name of the active substance for a MP should be stated in the following order of priority¹:

1. INN, accompanied by its salt or hydrate form if relevant,
2. European Pharmacopoeia,
3. National Pharmacopoeia,
4. Common name,
5. Scientific name.

Therefore the same INN might be associated with the same active ingredient contained in different MP.

As an example, INN carbamazepine, is the active ingredient in the following MPs in the UK:

- ✓ Carbamazepine (non-proprietary)
- ✓ Tegretol (Novartis)
- ✓ Carbagen (Generic)

INN prescribing refers to the use of this nomenclature on a prescription instead of using a brand name or a branded generic name. When the INN is used in a prescribing context it will also include the corresponding strength and the method of administration². In this way, we can generate prescribing groups or clusters (see section 7.3.1).

International non-proprietary name (INN)	Brand/fantasy name	Strength	Method of administration
Carbamazepine	None	200mg	Oral (tablets)
Carbamazepine	Tegretol	200mg	Oral (tablets)
Carbamazepine	Tegretol	200mg	Oral (chewable tablets)
Carbamazepine	Tegretol prolonged release	200mg	Oral (tablets MR)
Carbamazepine	Carbagen MR	200mg	Oral (tablets MR)

4.3 PhPID vs VMP

PhPID and VMP can both be used in dictionaries to identify MP. Their “extended versions” of each of these elements can be expressed as packs as well.

¹ http://esubmission.ema.europa.eu/eaf/eAF%201.20.0.1/maa_human_v1.20.0.1.pdf (section 2.1.2)

² Chapter 3: Operational Rules for the implementation of INN prescribing. INN prescribing

e.g. atenolol 50 mg tablets 28 pack (VMPP or similarly PCID in the case of ISO IDMP).

If we add the manufacturer, we can now get Actual Medicinal Product Pack (AMPP), which in case of using MPID it would already be one associated.

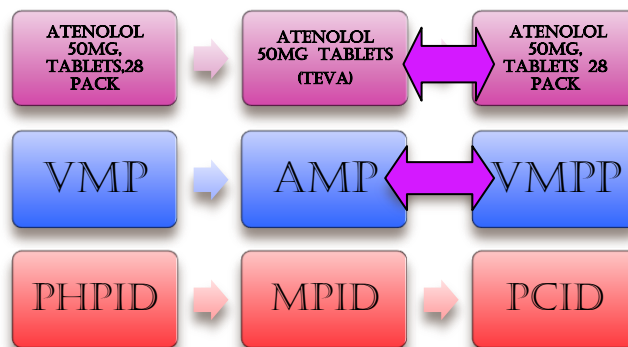
When using the PhPID or the VMP we might have all the information required at the point of prescription, but not necessarily at the point of dispensation.

their

An example would be where a doctor wants to prescribe atenolol to their patient. On his computer they would identify the virtual medicinal product pack (VMPP) or following the same principles but when it is ISO IDMP terminology the product can be identified at a PCID level but with different describing attributes, as a PCID would also have a manufacturer.

- **atenolol 50 mg tablets, 28 pack.**

This would be written on the prescription. (No manufacturer specified).



On receiving the prescription the pharmacist can see the version of the product they have available e.g. atenolol 50 mg tablet, 28 pack made by AAH Pharmaceuticals. This would be the actual medicinal product pack, AMPP (not included in the diagram).

In the case of ISO IDMP attributes the relationship is more linear. An MPID would have a manufacturer associated and a PCID. Both, manufacturers and package size. VMPP and PCID could be recorded as the product dispensed.

We can see that the relationships among the elements are different, whereas with VMP, AMP and VMPP, the relationship is not direct, but in the case of PhPID with the MPID and the PCID there is a certain hierarchy.

Although the mapping of PhPID and VMP is possible, the relationship is not 1 to 1. They are both different ways in which the same thing can be described.

5 Other attributes relevant for cluster formation

WP2 solution was built upon ISO IDMP standards. The attributes from these standards along with some of the other attributes we describe below, such as those derived from the legal basis of an application form for a marketing authorisation and the type of dossier, are relevant for cluster formation.

Using ISO IDPM model, having as main identifiers the PhPID and the MPID which are considered as part of the elements that define this model are the core elements in a theoretical cluster formation in the cases described below. At this point in time, the PhPID has not yet been generated by the EMA and, therefore, all the PhPID or MPID described below are hypothetical and the models are theoretical.

Another important attribute is the marketing authorisation number. This is a known and established attribute and it is also included in ISO IDMP. It is used by all regulatory authorities and in the openMedicine dataset.

5.1 Attributes described and used in previous work packages

5.1.1 PhPID

As described in the previous section a PhPID is a unique identifier for a pharmaceutical product. A pharmaceutical product is defined as the qualitative and quantitative composition of a Medicinal Product in the dose form approved for administration in line with the regulated product information.

5.1.2 Marketing authorisation number

A marketing authorisation number is an identifier assigned by a medicines Regulatory agency to a medicinal product once they grant authorisation to place that product in the market. This marketing authorisation is granted within a specific jurisdiction.

The marketing authorisation number is required for the unique identification of medicinal products but it may refer to the following principles:

- a) To a medicinal product without specific discrimination between the different pack sizes, so under the same marketing authorisation we have several pack sizes of the same product.
- b) To a medicinal product and one or more packages, allowing for discrimination at product and package level. Unlike the case above, we have for each pack size of the same product with authorisation number differentiated at product and package level.
- c) To a medicinal product presentation, which means for each product presentation a different authorisation number is assigned.

A marketing authorisation number might be assigned centrally, in which case the authorisation number is the same for each MS; or nationally, in which case the identifier is assigned nationally and is usually different in each MS.

5.1.3 Medicinal product Identifier (MPID)

According to ISO 11615:2012, the MPID is a unique identifier allocated to a Medicinal Product supplementary to any existing authorisation number as ascribed by a Medicines Regula-

tory Agency in a jurisdiction. This is for indexing purposes and to contribute to improved patient safety by allowing for the unique Identification of Medicinal Products worldwide.

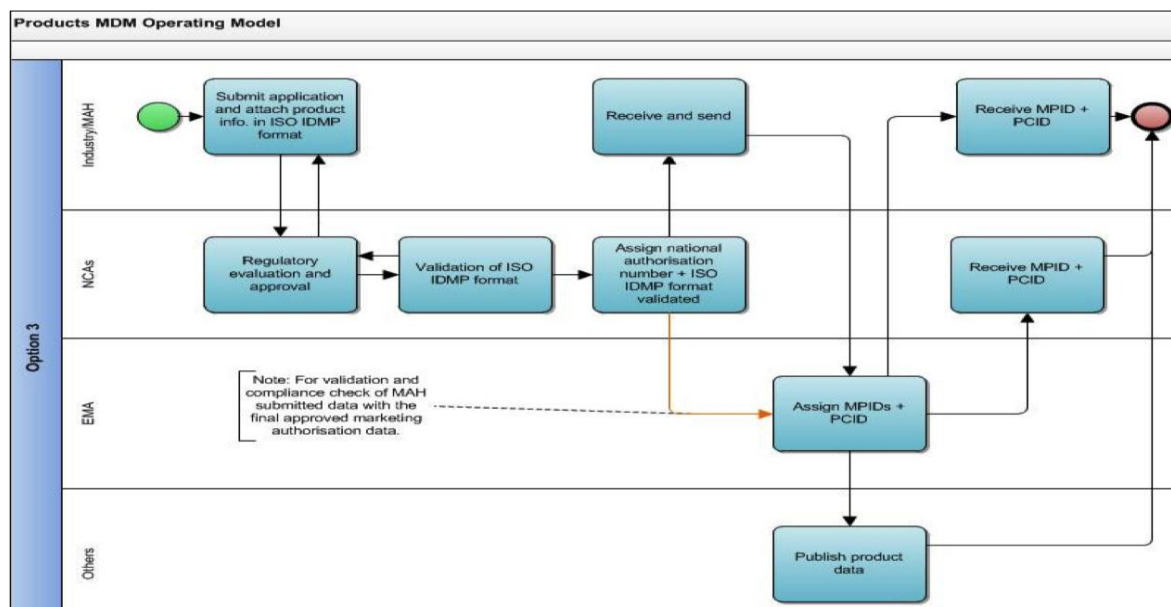
The Common segment pattern is:

1. Country code segment: this segment shall reflect the country code of a jurisdiction, where a MP is authorised.
2. MAH code segment (MAH of the product, Marketing Authorisation Holder): this code segment shall reflect the unique identifier of the MAH (organisation) of the MP. An international coding system for unique MAH (organisations) identifiers can be applied.
3. MP code segment shall reflect a unique MP identifier assigned to the MP. It utilises the following attributes to define a single MP to which a code is assigned:
 - a. MA in relation to jurisdiction
 - b. Legal status of supply (prescription only, over the counter sale)
 - c. MP name
 - d. The ingredient substances and their strength
 - e. Device where the MP is combined with a medical device and where the pharmacological, immunological or metabolic action should be considered as the principal mode of action; the medical device is presented as part of the medicinal product.
 - f. Therapeutic indication (s) as authorised for the medicinal product.

A separate unique MPID shall be assigned whenever any of the above items of information for MP are different as applicable to a Medicines Regulatory Agency's process.

This process might result in changes to the MPID for a MP when other existing regulatory identifiers might not change, as it could be the case with a MAN. This implies that the existing regulatory identifiers do not necessarily change in step with the MPID.

Figure 2 – EMA target operating model for assigning MPID.



According to this model, the EMA will assign an MPID after the national agencies have assigned the national authorisation number.

5.2 Marketing Authorisation (MA) Dossier of a Medicinal Product

A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the appropriate Regulatory Agency (national or central). The applicants present the information, regarding the medicinal product (MP), in a structured dossier in order to obtain a Marketing Authorisation. Once the information has been presented and submitted to the Regulatory Agencies, the information will be evaluated. The International Conference of Harmonisation (ICH) framework in November 2000, agreed on a common dossier structure named The Common Technical Document (CTD).

Directive 2001/83/EC of the European Parliament and the Council and Regulation (EC) No. 726/2004 of the European parliament and of the Council lay down the procedures for authorisation, supervision of MP and provide the administrative action to do so. It is in Directive 2001/83 that we find the particulars and documents accompanying an application for marketing authorisation. Those applications pursuant the legal basis to Articles 8 and 10 shall be presented in accordance with the requirements set out in this Directive's Annex I. These legal basis concern the identification of medicinal products, therefore, will be analysed below.

The Commission also provides guidance related to procedural and regulatory requirements³.

The European Community CTD presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied, whether it is a centralised, decentralised, mutual recognition or national, and it is also applicable to all types of products ranging from new chemical entities, radio-pharmaceuticals, plasma derivatives, vaccines to herbal medicinal products etc. It also applies to full and abridged applications.

The CTD is in electronic format and as from 1 January 2016 the use of the electronic Application Forms (eAF) is mandatory for all Marketing Authorisation requests regardless of the procedure. The eAFs must be used for all applications: authorisations, variations and renewals. The information related to this procedure is available on line and accessible to all applicants on the Commission website⁴, to verify the latest updated information.

The Common Technical Document is organised into five modules. The content of Module 1 is defined by the European Commission in consultation with the competent authorities of the Member States, the European Agency for the Evaluation of Medicinal Products and interested parties. The structure of Modules 2, 3, 4 and 5 are common for all ICH regions. These 5 modules contain information which is analytical, pharmacotoxicological and clinical standards and protocols in the respect of the testing medicinal products.

STANDARDISED MARKETING AUTHORISATION DOSSIER

Below, we describe the requirements for “Standardised marketing authorisation dossiers”, as it is referred to in Annex I of Directive 2001/83. This is the dossier used for submitting the information of most medicinal products. Each module contains the following information:

MODULE 1: Administrative information and prescribing information.

This module contains administrative data about the product such as SmPC, labelling, package about the experts who intervened in the process, information regarding environmental

³ web page: http://ec.europa.eu/health/documents/eudralex/index_en.htm

⁴ <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm>

risk assessments. This section also includes the information regarding the Orphan market exclusivity for orphan MPs.

MODULE 2: Common technical document summary

This module contains mainly the summaries of the other modules.

MODULE 3: Quality information

This module is a quality module regarding the drug substance and regarding drug product. It contains their description, composition, manufacturing process, characterisation, stability etc. It also contains quality information regarding excipients.

MODULE 4: Non-clinical study report

This module contains the study reports of the drug tests carried out in animals. These tests will show what the drug does to the body, what the body does to the drug once it is inside it and the toxicity of the drug in terms of the amount used, its effects in the reproductive and developmental cycle of humans and its potential contribution to development of cancer. These are all described as studies of pharmacology, pharmacokinetics and toxicology.

MODULE 5: Clinical study reports

This module contains the information of the clinical studies, meaning the reports of the drug being tested in humans. This module contains the results of how the drug works in the human body, what the human body does when the drug is inside it; reports of the efficacy of the drug and reports of the safety. It would also have the reports of post-marketing authorisation. The studies are the so called bio-pharmaceutical, pharmacokinetics, pharmacodynamics, efficacy and safety. The results of the studies included would be those of the favourable and unfavourable ones.

This Annex I of this Directive also describes the requirements of some medicinal products which present specific requirements. It refers to the following medicinal products:

1. Biological medicinal products
2. Radio pharmaceutical and the precursors
3. Homeopathic medicinal products
4. Herbal medicinal product
5. Orphan medicinal products.

5.3 Legal basis applying

Legal basis is a concept often used as part of the criteria to generate clusters; it is, therefore, important to describe first the administrative contents of a dossier in order to understand the legal basis used when submitting a dossier and how these legal basis apply when creating clusters.

In all the applications submitted, the applicant has to choose the legal basis under which they submit the application. Directive 2001/83/EC of the European parliament and of the council on the Community code relating to medicinal products for human use, sets out the requirements of these bases.

A brief description of what this legal basis mean and what these requirements and procedures mean, including how the contents of their dossier might be modified according to them, are described in this directive and summarised in its Annex I. Further guidance can be found in the European Commission's web page (specified above). The legal basis, which mainly applies when creating clusters, is those of Article 8 and Article 10.

For the purpose of this chapter and those related with clusters we will be assigning fictitious PhPID and MPID. In addition, as there are two concepts (bioequivalence and Reference Me-

dicinal Product) that will be referred to frequently in these legal basis, we include the definition below.

5.3.1 Bioequivalence

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy⁵.

In other words, they are bioequivalent if the amount of product, and rate at which a product reaches plasma and body tissues, is the same as the other product we compare it to.

Bioequivalent products are considered to be therapeutically equivalent, this means that in a clinical context the therapeutic effect expected from one is equivalent to the therapeutic effect of the other and, therefore, they could be interchanged.

The EMA provides guidelines on how to demonstrate bioequivalence of immediate release forms⁶.

The bioequivalence factor will be considered when submitting an application for a generic medicinal product. Nevertheless, other types of applications may also require demonstration of bioequivalence, including variations, fixed combinations products, extensions and hybrid applications.

This concept will help us in the clinical context when different products which contain same PhPID are considered equivalent for a specific patient with specific clinical requirements.

5.3.2 Reference Medicinal Product (RMP)

A reference medicinal product shall mean a medicinal product authorised under Article 6 of Directive 2001/83 in accordance with the provision of Article 8 of the same directive. The reference medicinal product is the product which a generic, a hybrid or a similar biological product will be compared to when proving evidence of bioequivalence.

This reference medicinal product can be authorised in the same country or in another member state. The country where the medicinal product is authorised will be specified on the application or dossier (it includes pre-clinical test and clinical trial data).

5.3.3 Article 8 (3) of directive 2001/83/EC

To comply with this article the application for marketing authorisation must be accompanied by the particulars and documents set out in Article 8(3) of Directive 2001/83/EC and therefore the following documentation must be included in the dossier:

- Information regarding Pharmaceutical (physico-chemical, biological or microbiological) tests.
- Information regarding preclinical (toxicological and pharmacological) tests,
- Information regarding clinical trials data.

Applicants will use this article for submitting:

- **New active substances.** The new substances are those not yet authorised in the European Union territory.

⁵ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

⁶ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

- **Known active substance:** when the substance would have already been authorised in a Member state within the EU.

This active substance might have same or different marketing authorisation holder.

These are known as “full dossiers” because all the information requested in Module 1 to 5 is submitted by the applicant. In some cases the information can cross-referenced other existing info.

- Example: Omeprazole 40 mg hard capsules gastro resistant has been authorised under Article 8.3 legal basis of the above directive, as a known active substance.

PhPID	Substance+ Strength and Unit + Adminis- trable dose Form	Marketing Authorisation Number	Brand name/ Fantasy Name	MPID	Reference MP
PhPID1	OMEPRAZOLE 40 mg GASTRO RESISTANT HARD CAPSULES (GRHC)	65688	ARAPRIDE	MPID1	Not Appli- cable (NA)

5.3.4 Article 10 of Directive 2001/83/EC

These applications will rely in part on the results of pre-clinical tests and clinical trials from a reference medicinal product (section 5.3.2), authorised in the Union/Member State, and in part on new data. This implies that the information presented regarding Module 4 and 5 of the dossier is different in content from the above article.

5.3.4.1. Paragraph 1 of article 10 (generic medicinal product)

A generic medicinal product has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the **reference medicinal product**, and bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

- **Same quantitative and qualitative composition:** it extends only to the active substance and not to the other ingredients, different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance must be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.
- **Same pharmaceutical form:** This criterion relating to the same pharmaceutical form contained in the definition of generic medicinal product is evaluated taking into consideration the standard terms for pharmaceutical dosage forms established by the European Pharmacopoeia. The various immediate-release oral pharmaceutical forms, which would include tablets, capsules, oral solutions and suspensions, are considered to be the same pharmaceutical form for the purposes of Article 10.

When applicants apply for a MA under this legal basis the complete administrative and quality data are provided through Module 1, 2 and 3. The contents of Module 4 and 5 will be “replaced” by bioequivalence data which will be compared to the reference medicinal product.

PhPID	Substance+ Strength and Unit + Administrable dose Form	Marketing Authorisation Number	Brand name/ Fantasy Mane	MPID	Reference MP
PhPID5	OMEPRAZOL 10 mg GASTRO RESISTANT HARD CAPSULES (GRHC)	74013	nil	MPID18	Losec 10 mg caps

The MAH applicant will present the contents of Module 1, 2 and 3, and the contents of Module 4 and 5 will contain the data to demonstrate that this Omeprazol and the Omeprazol in the LOSEC, our reference medicinal product, are bioequivalent.

5.3.4.2. Paragraph 3 of Article 10 (Hybrid medicinal product)

When either the qualitative or quantitative composition in active substances, or the pharmaceutical form of the reference medicinal product is different, or bioequivalence is not demonstrated with the RMP the applicant will use this legal basis.

The contents of module 4 and 5 (pre-clinical tests and clinical trial) will rely on those of the reference product and of some new clinical data.

The additional data will be required under the following circumstances:

- Where the strict definition of a 'generic medicinal product' is not met; where bioavailability studies cannot be used to demonstrate bioequivalence (for example where the new product is supra-bioavailable);
- Where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference product.

PhPID	Marketing Authorisation Number	Substance+ Strength and Unit + Administrable dose Form	Brand name/ Fantasy Name	MPID	Reference MP
PhPID1	68863	Omeprazole 40 mg GASTRO RESISTANT HARD CAPSULES (GRHC)	BELMAZOL	MPID3	Losec 20 mg cap

In this case, omeprazole 40 mg has been authorised as a hybrid MP. The contents of Module 4 and 5 refer to a RMP, Losec 20 mg cap. In these modules, bioequivalence has been demonstrated with LOSEC (Omeprazole) 20 mg GRHC.

This means that Omeprazole 40 mg GRHC has the same qualitative and same pharmaceutical form as Omeprazole 20mg GRHC and they are both bioequivalent (if you take 2 capsules of 20 mg in comparison to 1 capsule of 40 mg they have achieve similar concentration in tissue and blood) but because they are have different quantitative composition (one is 20 mg and the other one is 40 mg) the legal basis applying is that of the Hybrid description.

5.3.4.3. Paragraph 4 of Article 10 (Similar biological medicinal product)

Under this article, an applicant will submit an application to compare a biological product to another reference biological product. There are differences between the similar biological product and the reference biological product owing to the differences in raw materials or differences in manufacturing processes.

In this type of application, the results of appropriate pre-clinical tests or clinical trials (module 4 and 5) relating to these conditions must be provided.

Regarding these results, when compared to the reference medicinal product, the applicant will choose from the following difference(s) indicating if change(s) have happened in

- ✓ the raw material(s)
- ✓ the manufacturing process(es)
- ✓ therapeutic indication(s)
- ✓ pharmaceutical form(s)
- ✓ strength (quantitative change to the active substance(s))
- ✓ route of administration(s)

PhPID	Marketing Authorisation Number	Substance+ Strength and Unit + Administrable dose Form	Brand name/ Fantasy Name	MPID
PhPID1B	113854001	Infliximab concentrated powder for solution for perfusion	INLFECTRA	MPID1B

In this case, the concept interchangeability does not apply in the same way. As the difference will be in all the differences in the above listed, the final decision on interchangeability will rest on the member state.

5.3.4.4. Article 10a (well-established medicinal products)

When an applicant submits an application under Article 10a, detailed scientific bibliography will be submitted to address the non-clinical and clinical characteristics of module 4 and 5 relating to the application.

The applicant will try to demonstrate with detailed references the time over which a substance has been used (at least 10 years), quantitative aspects of the substance, the degree of scientific interest and the coherence in the scientific assessments.

When these legal bases apply the applicant relies on a well-established medicinal use of a specific pharmaceutical product with recognised efficacy and acceptable level of safety and they support it by bibliography.

Modules 1, 2 and 3 shall also be submitted.

PhPID	Marketing Authorisation Number	Substance+ Strength and Unit + Administrable dose Form	Brand name/ Fantasy Name	MPID	Reference MP
PhPID4	65515	Omeprazole 10 mg Hard capsules gastro resistant	BELMAZOL	MPID15	NA
PhPID1	65653	OMEPRAZOL 40 mg Hard capsules gastro resistant		MPID5	

These two products have been authorised under the legal basis of a well-established use of omeprazole 10 mg and omeprazole 20 mg capsules throughout the years.

5.3.4.5. According to Article 10b (fixed combination)

This application type will be used for a new medicinal product which contains at least two active substances not previously authorised as a fixed combination medicinal product.

For applications following this basis, a full dossier will be presented (Modules 1 to 5). Hence, two molecules that already exist and are formulated as one will be considered a new fixed combination medicinal product.

PhPID	Marketing Authorisation Number	Substance+ Strength and Unit + Administrable dose Form	Brand name/Fantasy Name	MPID
PhPID22	113900009	Dapagliflozine/Metformine 5 mg/1,000 mg Film coated tablet	XYGDUO	MPID22

Although Simvastatin and Fenofibrate are products that existed in the market at the time of the submission of the authorisation, this combination of products is considered as a new product and, therefore, all the information related to Modules 4 and 5 will have to refer to the data of a the combined product.

5.3.4.6. Article 10c (informed consent MA application)

When an informed consent marketing authorisation application form is submitted for a MP, a medicinal product possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form of an authorised product is presented. In this case, consent has been given by the existing marketing authorisation holder to use their data in support of this application presented. The consent relates to the use of the data content in Module 3-5.

Although some of the criteria of this application are common to generic medicinal products, it does not concern generic medicinal products. The authorised product and the informed consent application can have the same or different MAH.

PhPID	Número de Registro	Substance+ Strength and Unit + Administrable dose Form	Brand name/Fantasy name	MPID
PhPID23	1151051009	Dapagliflozine/Metformine 5 mg/1.000 mg film coated tablet comprimidos recubiertos 56 tablets	EBYMEC	MPID 23

5.3.5 Summary of the contents of a dossier according to legal basis

This Box below shows how different modules vary in content according to the legal basis used.

Figure 3– Comparison of Module´s content according to legal basis.

	Module 1- Adminis- trative information	Module 2- Summaries	Module 3- Quality	Module 4-Non Clinical Reports	Module 5- Clinical study reports
Article 8 (3) - New product (Full applica- tion)	✓	✓	✓	✓	✓
Article 10					
Paragraph 1 Article 10- Generic	✓ , 1	✓	✓	Bioavailability data and bioequivalence with RMP	
Paragraph 3 Article 10- Hybrid	✓ , 1	✓	✓	Rely in part of results of pre-clinical tests and clinical trials of a RMP, in part of new data	
Paragraph 4 Article 10- Similar Biologi- cal	✓ , 1	✓	✓	✓ ⚙	✓ ⚙
Article 10a- Well established use	✓	✓	✓	Provided as bibliography	
Article 10b- Fixed combination	✓	✓	✓	new pre-clinical tests or new clinical trials relating to that combination must be pro- vided	
Article 10c- informed consent	✓	✓	Consent obtained for all 3 modules (for indication or presentation) for a MP authorised and in the market		

RMP- reference medicinal product

1 The application form for an article 10 application should clearly identify the reference product (could be refer to a product that does not exist anymore)

⚙ does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the similar biological medicinal product and the reference biological medicinal product.

5.4 Duplicate and multiple MA applications

The application for multiple marketing authorisations for an identical product under centralised, mutual recognition and decentralised procedure can be done by applicants.

As a duplicate is an independent authorised medicinal product, there is no definition of a “duplicate” in the pharmaceutical legislation. However, for practical purposes, the Co-ordination Group for Mutual recognition and Decentralised procedures (CMDh) has defined “a duplicate application by reference to the first application or marketing authorisation as follows:

- ✓ same dossier (copy of modules 1, 2, 3, 4 and 5);
- ✓ same legal basis according to Directive 2001/83/EC, as amended;
- ✓ different trade name;
- ✓ same or different applicant/marketing authorisation holder.”

The request may come from the same or from a different applicant/MAH of the initial application/authorisation.

The applicant should indicate in the cover letter of module 1 of the dossier:

- ✓ That the application is a duplicate
- ✓ That the dossier is identical to the medicinal product taken as a reference
- ✓ The existence of other duplicate applications pending or submitted simultaneously.

In this case the product taken as reference is for copying the information and not for comparing it, as it happens with generic, hybrid or biosimilar medicinal products as described above.

When using centralised procedures applicants can request a duplicate for a MA under article 82 (1) of regulation No. 726/2004. The commission can grant this application “when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or for co-marketing reasons”.

5.5 New attributes derived in a cross border setting

5.5.1 From a legal basis

The legal basis is taken into account when grouping up medicinal products but is it not the only consideration.

From the analysis of the legal basis we can conclude that:

- Same active ingredients, with the same quantitative and qualitative and pharmaceutical dose form can have different legal basis and, therefore, different attributes. When grouping products it is important to establish the purpose they are serving.

The following questions might help:

- ✓ Are we just grouping up MPs which contain specific data elements like active substance, strength, pharmaceutical dose form and device?
- ✓ Are we also interested in the interchangeability of the products being grouped, in which case bioequivalence is an important concept?
- On the other hand, 2 medicinal products (a RMP and the MP that is being compared to) can have the same qualitative and same pharmaceutical form but different quantitative dose and might be bioequivalent and, therefore, interchangeable if given in the same dose as a multiple dose (example: 40 mg as 2x20 mg).

Therefore, the following attributes are important when applying these concepts:

- ✓ **Reference medicinal product** in relation to a generic, hybrid and biosimilar, as the concept described above. This will help identify the products that are bioequivalent and, therefore, interchangeable.
- ✓ **Generic medicinal product:** by definition a generic medicinal product is interchangeable with its reference medicinal product. A generic product and a reference product may be considered to have the same pharmaceutical form if they have the same form of administration as defined by the Pharmacopeia. These pharmaceutical forms considered the same for the terms of bioequivalence and can generate different PhPID.
- ✓ **Hybrid medicinal product:** hybrid medicinal products can be interchangeable (in a proportionate dose) with the RPM when bioequivalence has been proved.
- ✓ **Informed consent:** in relation to a marketing authorisation

5.5.2 Duplicate applications

Duplicate applications have not got specific attributes to allow identification. The dossier contains such information which will allow us identification of two medicinal products which have the same dossier but are being put in the market under a different trade name.

6 Relevant attributes derived from Marketing Authorisation procedure type

When an applicant submits the dossier in Europe, the regulatory procedure can be different according to which country(ies) they want to authorise the product in. They might want to authorise it only in their member state, several member states (MS) or all member states. Moreover, in some cases when the MP is in the scope of mandatory products to be authorised by the EMA, they will have to follow a centralised procedure.

The type of legal process applied to authorise or maintain a MP marketing authorisation is what is called the procedure type. This will include renewals, variations or revocation of a Marketing authorisation.

During this procedure, a procedure number will be assigned by the Regulatory Agency in relation to the specific procedure followed. Depending on the procedure, the numbering system will be different.

We discuss below the different types of procedures in the EU. According to the procedure the responsibility for the authorisation relies on a different regulatory agency, which may be the national agency or the European Medicines Agency. As stated previously the number of countries participating in each procedure may range from one to several.

These procedures are followed by 28 MS, nonetheless Norway, Iceland and Liechtenstein have adopted through a EEA agreement the complete Community acquis on medicinal products and are consequently parties to the Union procedures. Therefore, where in Article 2 of Regulation (EC) No. 726/2004 and Article 8 of Directive 2001/83/EC, reference is made to the applicant being established in the Community, this can be extended to include Norway, Iceland and Liechtenstein.

The marketing authorisations granted by Norway, Iceland and Liechtenstein are eligible for the mutual recognition and decentralised procedure in the same way as the marketing authorisations granted by Member States.

6.1 Centralised procedure

When a marketing authorisation is granted following the centralised procedure, it is valid for the entire EU market. It is granted in accordance to Regulation (EC) No. 726/2004. The application will be submitted to the EMA, which is the authority responsible for the evaluation, and once it has been granted it confers the same rights and obligations in each of the Member States as a marketing authorisation granted by a Member State. It can, therefore, be commercialised in any of them.

Under this procedure, the EMA will assign the procedure number.

Some medicinal products are included in the mandatory scope of the Centralised procedure. We list such human medicinal products below:

1. Medicinal products developed by means of one of the following biotechnological processes:
 - Recombinant DNA technology,
 - Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
 - Hybridoma and monoclonal antibody methods.

2. **Advanced therapy medicinal products** as defined in Article 2 of Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products.
3. Medicinal products that are designated as **orphan medicinal** products pursuant to Regulation (EC) No. 141/2000
4. Medicinal products for human use containing a **new active substance which**, on the date of entry into force of this Regulation, was not authorised in the Community, for which the therapeutic **indication is** the treatment of any of the following diseases:
 - acquired immune deficiency syndrome,
 - cancer,
 - neurodegenerative disorder,
 - diabetes,
 - auto-immune diseases and other immune dysfunctions,
 - viral diseases.

Most centralised procedures are for innovative medication but they are not the only ones. Some other type of medicinal products could choose this procedure as an optional procedure. It could be the case also for some generic products.

When a product is authorised under the centralised procedure, a procedure number is allocated. Under this procedure number one to several medicinal products can be authorised. Amongst these medicinal products we can find different strengths, pharmaceutical dose forms and different packages of the same active substance. Usually the same marketing authorisation holder (MAH) requests MA for several formats of the same active substance. In this case, different EU Authorisation numbers exist in relation to a same Brand name.

- **Xigduo (Metformin and dapagliflozin)**



This is a new active substance used in diabetes mellitus type II.

The **procedure number** is EMEA/H/C/002672.

Under this same procedure number, with brand name Xigduo, we find 12 different products with:

- Six of these products are Xigduo (*Dapagliflozin/Metformin 5 mg/850 mg tablets*) with 6 different container sizes. Each of them has a different marketing authorisation number.
 - 5 mg/850 mg **001-006** Packages 14, 28, 56,
- The other 6 products with different strength to the previous Xigduo (*Dapagliflozin/Metformin 5 mg/1000 mg tablets*) with 6 different pack sizes again.
 - 5 mg/1000 mg- **007- 012** Packages 14, 28, 56.

EU/1/13/900/001-12 (MA numbers) with different strength and package sizes. See clusters below in section 7.2.4

6.2 Decentralised procedure (DC)

The applicant may request the authorisation of a medicinal product to be authorised in one or several member states. A Reference Member State (RMS) will be chosen to do the assessment and the scientific evaluation but the authorisation should be granted in accordance with the decision made by the RMS and the concerned MS. All MS concerned will receive the relevant information of the applicant. The applicant must give assurance that the dossier submitted, including the proposed summary of product characteristics (SmPC), labelling and package leaflet, is identical in all the member states involved. Differences in proposed prescription status and names of the medicinal product are acceptable, in line with national rules in force.

- **Omeprazole Mylan** was authorised via this procedure

More than 15 countries were involved in Europe for the authorisation of this product being Poland the Reference Member State. They were in charge of the assessment and the scientific evaluation.

The procedure number was assigned by Poland:

- PL/H/0152/001/DC-10mg Gastro Resistant capsules, Hard
- PL/H/0152/002/DC-20mg Gastro Resistant capsules, Hard
- PL/H/0152/003/DC-40mg Gastro Resistant capsules, Hard

Once the MS' involved have come to a positive agreement the medicinal product will be granted a marketing authorisation and a marketing authorisation number will be assigned to each of the instances above in all the countries involved.

6.3 Mutual recognition procedure (MR)

Like the decentralise procedure, this procedure is based on the recognition by national competent authorities of the assessment performed by the competent authorities of one Member State.

In cases where national authorisations are requested for the same medicinal product in more than one Member State and the marketing authorisation holder has already received a marketing authorisation in a Member State, the applicant/marketing authorisation holder must submit an application in the Member States concerned using the procedure of mutual recognition. The Member States concerned should then recognise the marketing authorisation already granted by the reference Member State and authorise the marketing of the product on their national territory.

The marketing authorisations granted by Norway, Iceland and Liechtenstein are eligible for the mutual recognition procedure in the same way as the marketing authorisations granted by Member States.

- **Losec (omeprazole) 20 mg cap** Procedure number/Identifier NL/H/2081/002/E/001.
- **Losec (omeprazole) 40 mg powder for solution for infusion** Procedure number/Identifier NL/H/2081/005/E/001

When the application of Losec capsules was submitted the product was already authorised in the UK since 1989. The Netherlands was the Reference Member State and many other countries were involved. Therefore, the marketing authorisation already granted in the UK would have been harmonised and recognised.

In a decentralised and mutual recognition procedure, the procedure identifier is assigned by the Reference member state and it is a unique combination of 6 numbers.⁷

6.4 National procedures

The competent authorities of the Member States are responsible for granting marketing authorisations for medicinal products which are placed on their markets, except for medicinal products which are authorised under Regulation (EC) No. 726/2004 (“Union Authorisations” - see Section 6.1 of this chapter), the products which are in the list of mandatory products that have to follow a centralised procedure.

6.5 Relevant Attributes for Identification of Medicinal Products in a cross border setting

From the procedures described above, different attributes are generated. Different attributes derived from each procedure will serve different purposes.

In all the procedures describe above, we will find a common attributes like procedure number/ID associated. In the case of centralised, decentralised and mutual recognition, this procedure ID will help us identify products which are the same or equivalent from the regulatory point of view but are described differently according to their jurisdiction. The fact that they are authorised in different countries implies allocation of different values for the same “field”. This in informatics terms translates into a different medicinal product.

It is important to point out what we refer to when we refer to different medicinal products. It is important first to know what we are the attributes which will allow us to call two medicinal products the same as according to the context we might be talking in terms of pharmaceutical product, medicinal products, regulatory context or country.

• Procedure number or identifier in a MR or DC procedure

In mutual recognition and decentralised procedures, under the same procedure number we will find several MP from different countries with:

- ✓ The same contents of the dossier submitted
- ✓ The same assessment report
- ✓ The same summary of product characteristics
- ✓ The same package leaflet
- ✓ The same label.

• Marketing Authorisation EU number

Unlike in national, decentralised and mutual recognition procedures, in centralised procedures the marketing authorisation number (MAN) is going to be the same for the EU, therefore the MP can be uniquely identified with it in all the MS. It is important to bear in mind that not all the presentations of the same MP will be available in all MS.

In this type of procedure several MP are included under the same Procedure number. We can find different strengths of the same preparation, or we can find different presentations of the same medicinal product.

⁷ Volume 2A Procedures for marketing authorisation. Mutual recognition.

7 Cluster formation

Cluster formation is a powerful tool used in different contexts within the regulatory and the health care system. It helps identifying certain medicinal products with a list of attributes chosen that will help serve a specific purpose. We have seen in section 4 how core elements, such as VMP or INN, are being used in the identification of products which serve as core elements for medical dictionaries.

A general definition of a cluster means grouping up items under a predefined criteria. If we follow this definition we can actually create uncountable groups. They can be used as a helpful tool according to the context.

At the same time these might be:

- **Dynamic clusters:** which means that a cluster is created “on the spot” at the point of use and it is not distributed. The dynamic cluster's contents or attributes are defined by the criterion chosen/defined at the moment of usage. The selection criterion applied on a drug database.
- **Static clusters** which are distributed “already made” and there is usually an authority involved in the creation of them. They are allocated a number or a name and the attributes defining them are preselected.

In this section, we want to analyse and find out more about clusters used and created in a regulatory context and clusters used in a prescribing context.

7.1 Motivation of a cluster

A regulatory agency can group up medicinal products following regulatory criteria. A Ministry of Health can group MP to serve some prescribing purposes. A reimbursement company can group up those medicinal products that can be reimbursed. The criteria are set by those who create the cluster. Nevertheless, the starting point is usually the regulatory context where clusters are created on the basis of core elements such as active substance, strength, dose and pharmaceutical dose form as a general rule.

Once a drug has been granted a marketing authorisation the MAH can choose to commercialise the medicinal product in a country or not. In the process of managing the entry of medicines in the market, activities surrounding pricing and reimbursement are of major relevance. These activities are set locally.

As part of the national health systems, pharmaceutical prices should be set to promote rational use of medication and access to medicines. While many European countries have not traditionally required active priority-setting for access to medicines many policies are identified across Europe for pricing cost containment and reimbursement⁸.

In the past years, several countries have adopted policies for generic substitution, some countries have made mandatory the substitution between medically equivalent drugs in their national health services. These policies are closely related to reimbursement policies and in many cases are based on the classification of drugs into groups therapeutically interchangeable

⁸ <http://apps.who.int/medicinedocs/documents/s21793en/s21793en.pdf>

7.1.1 Prescribing By INN

As an international nomenclature which identifies active ingredients of medicinal products, INNs are designed to avoid confusion by allocating a rational and distinctive sound and spelling, with the aim of safely prescribing medicines and dispensing them.

The purpose of introducing INN prescribing in Europe was to take advantage and contribute to the rational and safe use of medicines in the prescribing context. Since the global financial crisis INN prescribing was also introduced in Europe as a containment measurement to reduce pharmaceutical expenditure. The way in which the INN prescribing is regulated and was implemented across European countries varied considerably.⁹

A study carried out by the University of Gant looked into INN prescribing across Europe and its legal foundation. This measurement, along with generic substitution, was implemented in 16 countries in the European Union. During the study INN prescribing was defined as prescribing medicinal products using the active ingredient name (INN), also, the corresponding strength and the method of administration (e.g. oral, injection, transdermal...) on the prescription.

7.1.2 Types of cluster following regulatory criteria

Following the examples shown in section 6 we will make use of some of the useful attributes which can help us grouping up medicinal product.

As PhPID have not been generated yet the cluster related to ISO IDMP attributes are only based on theory.

7.1.2.1. PhPID clusters

If we refer to “pharmaceutical equivalence” as: the Medicinal products which contain the same amount of the active substances in the same dosage forms that meet the same comparable standards (this definition does not mean that the products contain the same excipients and/or the same manufacturing process)¹⁰, we find clusters formed based on a nomenclature such as INN, or concepts such as VMP, AMP, etc.

When choosing a PhPID we will group all the medicinal product containing the same attributes defining a PhPID such as substance, strength and Unit, administrable dose form, adjuvant and medical device when appropriate. The PhPID (in blue below) is the core element which groups all pharmaceutical products with the same attributes. Nonetheless it does not take into account any regulatory aspects discussed above, like the legal basis, therefore attributes like generic or an innovative product, quality aspects of the product, the pre-clinical data such as toxicology or the clinical tests will not be “represented” through it. It is when presenting the MA dossier that all this information will be evaluated.

As each MP will have at least one PhPID or equivalent identification code, for the purpose of these examples we also include the MAN of that MP having the same PhPID: PhPID2. This PhPID corresponds to several invented MPIDs.

PhPID	Substance+ Strength and Unit + Administrable dose Form	Marketing Authorisation Number	Brand name/ Fantasy Name	MPID	Marketing Authorisation Holder
PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES (LOSEC)	58377	LOSEC	MPID6	AstraZeneca

⁹ International Nonproprietary Name INN, WHO. <http://www.who.int/medicines/services/inn/innguidance/en/>

¹⁰ Bioequivalence and drug toxicity. Drug safety 11 (1): T6 1994

PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	62763	nil	MPID7	Mylan Pharmaceuticals, S.L.
PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	68788	nil	MPID8	Tarbis Farma, S.L.
PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	68884	nil	MPID9	Teva Pharma S.L.U.
PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	73994	nil	MPID10	Aurobindo
PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	80253	nil	MPID11	Hetero Europe
PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	74958	nil	MPID12	LabRanbaxy (Mundogen)
PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	70290	nil	MPID14	Sandoz Farmaceutica
PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	77388	nil	MPID15	Zentiva

For example, if we choose the attributes “Omeprazole 20 mg gastro resistant hard capsules” a theoretical PhPID2 is generated, and all MPs which contain it are listed. This will include all medicinal products with PhPID2 regardless of the legal basis.

This example just shows some of the products associated to one PhPID2.

If we create a cluster with the PhPID with the following legal basis will be included:

- New products
- Generic
- Hybrid
- Well established use
- Informed consent application forms.

It will also contain duplicates of any of the above.

In the same way, we could choose INN omeprazole and a strength and an administration route to create a cluster. Or a cluster based on the VMP.

This cluster can be formed at a regulatory level. At a further step, these MPs will undergo a further filter, first by determining which ones will enter the health care system and in another step, by choosing those which are suitable for the prescribing context, meaning which ones of them can be grouped together for interchangeability/prescribability or switchability purposes.

These last two concepts will be discussed on section 7.3.

7.1.2.2. PhPID, bioequivalence and reference medicinal product

If we choose a reference medicinal product such as *Losec 20 mg gastro resistant hard capsules (GRHC)* a correlation can be established with the generic products whose reference medicinal product is Losec 20 mg GRHC. This means same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and bioequivalence with the reference medicinal product (Losec) has been demonstrated by appropriate bioavailability studies, therefore the following four medicinal products can be interchanged (1 RMP and 3 generic MP with the same RMP, Losec).

PhPID	Substance+ Strength and Unit + Administrable dose Form	Marketing Authorisation Num- ber	Brand name/ Fantasy Name	MPID	Marketing Authorisation Holder	Legal Basis
PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	58377	LOSEC	MPID6	Laboratorio TAU	Art 8,3 -Known active ingredient
PhPID2	OMEPRAZOL 20 mg GASTRO RESIS- TANT HARD CAPSULES	62763	nil	MPID7	Mylan Pharma- ceuticals, S.L.	art 10,1- generic
PhPID2	OMEPRAZOL 20 mg GASTRO RESIS- TANT HARD CAPSULES	68788	nil	MPID8	Tarbis Farma, S.L.	art 10,1- generic
PhPID2	OMEPRAZOL 20 mg GASTRO RESIS- TANT HARD CAPSULES	68884	nil	MPID9	Teva Pharma S.L.U.	art 10,1- generic

- ✓ All the above *omeprazole 20 mg GRHC* have the same PhPID.
- ✓ Each of them has proved bioequivalence at the regulatory level with Losec as the Reference Medicinal Product.
- ✓ They all have a different marketing authorisation number although they have the same PhPID.
- ✓ The generic medicinal products can be grouped up with their RMP for the purpose of interchangeability. Regardless of the different marketing authorisation numbers.
- ✓ This Cluster will have 1....n MP's.

7.1.2.3. PhPID, bioequivalence and same pharmaceutical dose form

In a regulatory context, certain pharmaceutical forms are considered to be bioequivalent. The various immediate-release oral pharmaceutical forms immediate release oral forms, which would include tablets, capsules, oral solutions and suspensions, are considered to be the same pharmaceutical form for the purposes of Article 10¹¹.

In this instance, and according to ISO IDMP identification attributes, different PhPIDs will be generated containing only one attribute different which will be interchangeable by definition.

This means that a cluster can be form with the same active ingredient, strength and unit and 2 different pharmaceutical dose forms.

- ✓ An example is Omeprazole 20 mg tablet- mups, (dispersible tablets) can be exchanged with omeprazole 20 mg capsules. The PhPID generated as they are 2 different pharmaceutical dose forms.
- ✓ It is also important to notice that difference might exist between the RMP and its generic in terms of excipients

7.1.2.4. PhPID, MPID and Procedure identifier

7.1.2.4.1. PhPID, MPID and Centralised procedure

- Same procedure identifier/number
- Two different PhPID
- Different MPIDs

The following products have been authorised under the same centralised procedure EMEA/H/C/002672

¹¹ http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf

PhPID	MA (EU) Number	Substance+ Strength and Unit + Administrable dose Form	Brand name/Fantasy name	MPID	Pack size
PhPID23	EU/1/13/900/001	Dapagliflozine/Metformine 5 mg/850 mg Film coated tablet	XIGDUO	MPID30	14 tablets
PhPID23	EU/1/13/900/002	Dapagliflozine/Metformine 5 mg/850 mg Film coated tablet	XIGDUO	MPID31	28
PhPID23	EU/1/13/900/003	Dapagliflozine/Metformine 5 mg/850 mg Film coated tablet	XIGDUO	MPID32	56
PhPID23	EU/1/13/900/004	Dapagliflozine/Metformine 5 mg/850 mg Film coated tablet	XIGDUO	MPID33	60
PhPID23	EU/1/13/900/005	Dapagliflozine/Metformine 5 mg/850 mg Film coated tablet	XIGDUO	MPID34	60*1
PhPID23	EU/1/13/900/006	Dapagliflozine/Metformine 5 mg/850 mg Film coated tablet	XIGDUO	MPID35	196 (2*98)
PhPID23	EU/1/13/900/007	Dapagliflozine/Metformine 5 mg/850 mg Film coated tablet	XIGDUO	MPID36	14
PhPID22	EU/1/13/900/008	Dapagliflozine/Metformine 5 mg/1000 mg Film coated tablet	XIGDUO	MPID37	28
PhPID22	EU/1/13/900/009	Dapagliflozine/Metformine 5 mg/1000 mg Film coated tablet	XIGDUO	MPID38	56
PhPID22	EU/1/13/900/010	Dapagliflozine/Metformine 5 mg/1000 mg Film coated tablet	XIGDUO	MPID39	60
PhPID22	EU/1/13/900/011	Dapagliflozine/Metformine 5 mg/1000 mg Film coated tablet	XIGDUO	MPID40	60
PhPID22	EU/1/13/900/012	Dapagliflozine/Metformine 5 mg/1000 mg Film coated tablet	XIGDUO	MPID41	196 (2*98)

7.1.2.4.2. PhPID, MPID and Mutual Recognition

- Same procedure identifier/number
- Same PhPID
- Different MPID

Country of Authorisation	PhPID	Substance+ Strength and Unit + Administrable dose Form	Marketing Authorisation Number	Brand name/Fantasy Name	MPID	Marketing Authorisation Holder	Tipo Procedimiento
Spain	PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	58377	LOSEC	MPID6	Laboratorio TAU	NL/H/2081/001
Austria	PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	1-19207	LOSEC	MPID7	Astrazeneca Österreich GmbH	NL/H/2081/001
France	PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	nl 14652	MOPRAL	MPID8	Astrazeneca	NL/H/2081/001
Italy	PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	28245090	ANTRA	MPID9	Astrazeneca S.p.A	NL/H/2081/001
Greece	PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	39697/09/08-03-2010	LOSEC	MPID10	Astrazeneca S.A	NL/H/2081/001
Hungary	PhPID2	OMEPRAZOL 20 mg GASTRO RESISTANT HARD CAPSULES	OGYI-T-5114/04-06	LOSEC	MPID11	Astrazeneca Kft	NL/H/2081/001

The RMS is the Netherlands In the example we include some of the countries involved in the procedure, not all of them. Each MS will assign a different authorisation number for a product with:

- ✓ The Same contents of the dossier submitted
- ✓ The same assessment report
- ✓ The same Summary of product characteristics
- ✓ The same package leaflet
- ✓ The same label.

7.1.2.4.3. PhPID, MPID and Decentralised procedures.

- Same procedure identifier/number
- Same PhPID
- Different MPID

We take an example where 21 countries were involved in this type of procedure, being Poland the Reference Member State.

In the same way as the decentralised procedure, each country would assign a different marketing authorisation number, and this MA has no correlation to the ones assigned in other MS. However, they all have a common Procedure Number PL/H/0152/001/DC. Under this procedure number we can group up the medicinal product with the same criteria as above, following the example above.

By extension, if the medicinal products are Reference Medicinal products (as the example of 7.2.4.2), those generic medicinal products authorised with that particular RMP (Losec in most countries) can be included in the same cluster. If we take apply it to the examples described we can actually merge the MP from point 7.2.2 with those of 7.2.4.2, as there is only one RMP with the cluster in 7.2.2 are the generics associated.

7.1.3 Clusters and prescriptions

In Europe, clusters are regularly used for different purposes and different contexts.

In WP4 we explore one specific circumstance where a cluster is specified on a prescription and its applicability cross-border.

It is important to differentiate between what it means by:

1. **Prescribing by cluster:** the name or code of the cluster is only indicated on the prescription. This code or name (e.g. “Cluster 99”) is predefined in a specific context, therefore the attributes are known. If the dispensation point recognises that code/name, the attributes defining the cluster can be retrieved. In fact the prescriber is implicitly indicating a number of MP with known attributes.
When the codes/names are allocated nationally, decoding cross – border represents a challenge unless the systems can interoperate and recognise the other country’s code/name.
2. **Prescribing a pharmaceutical or medicinal product which at the dispensing point is identified as belonging to a cluster.** In this case the prescription will contain those attributes required for an electronic prescription (active substance/Brand name, strength, pharmaceutical dose form...). These attributes when retrieved at the dispensing point will lead to a cluster.

The most common use of clusters in a prescribing context is at the point of dispensation.

When we retrieve a pharmaceutical or medicinal product that has been specified on a prescription and we look up the product in our data base. If this MP belongs to a cluster, then at the point of dispensation we will obtain all the MP which form that cluster. A product has been described and identified and this product belongs to a specific cluster in a specific country, and we suppose this cluster has an identifier, either a name or a number.

As we have seen in previous sections clusters can be created with the same PhPID and different MPIDs with generics and their reference medicinal product. In this case, the generic and the reference medicinal product are considered to be therapeutically equivalent, as they are bioequivalent and, therefore, they are considered to have the same efficacy and safety

profile. Nonetheless the debate around generics drug efficacy and safety is ongoing amongst clinicians, pharmacists, patients and other healthcare professionals.

Bioequivalence is a general term. Average bioequivalence, population bioequivalence, and individual bioequivalence are definitions used in the regulatory context which evaluate different parameters of the drugs and of the populations they are being tested on.

- **Average bioequivalence (ABE):** compares average values of bioavailability for the generic drug and the reference drug. It is based only on the comparison of population averages for selected pharmacokinetic measurements.
- **Population bioequivalence (PBE):** takes into account inter subject variability (inter-subject variance) and therefore tackles the issue of interchangeability.
- **Individual bioequivalence (IBE):** takes into account intra-subject and subject-by-formulation variances.¹²

Different regulatory agencies around the globe have different approaches to evaluate and ensure efficacy and safety of in the different categories of drugs. The EMA includes these concepts to evaluate the bioequivalence in the regulatory process in the category of large therapeutic range drugs, narrow therapeutic index drugs (NTID) and highly variable drugs (HVDP). Where therapeutic index can be defined as the relationship between the toxic dose and the minimum effective dose of a drug.

If we go one step further, when creating these clusters for the purpose of generic prescribing it is worth questioning whether generics drugs are as effective and safe as the reference medicinal product. We consider 2 basic situations where we might find these generics being prescribed, (regardless of the terminology used to do so):

- A. At the beginning of a treatment when a patient is being started on new medication, in another words, for the initial therapeutic treatment of a patient.
- B. When treatment has already been started on treatment and therefore a substitution might be required at the point of dispensation.

Situation A comprises the definition of **prescribability** or **interchangeability** for a new patient. This concept takes into account the inter-subject variability. Hence, it does not only take into account ABE but the variances between the generic drug and the reference drug.

In situation B, the definition of **switchability** is considered. A bioequivalence criterion should contemplate parameters covering intra-subject variability and those resulting from interaction between subject and formulation.

These terms and definitions and their appropriateness in use are very technical and complex elements which have been debated and are still under debate. Part of this includes the limitations in terms of feasibility and cost-effectiveness¹³. Describing them in depth and discussing them is not within the scope of this deliverable. Nonetheless, it is worth mentioning that despite the scarce amount of studies in assessing prescribability and switchability, establishing the parameters to relate them to MP could become a useful tool for cluster creation at the national level and consequently international level.

7.1.4 Decision support at dispensing point

In recent decades, pharmacies have been increasingly incorporating the use of automated decision support systems (drug utilisation Review –DUR) generating alerts to help pharmacist identify drug related problems when dispensing prescriptions.

¹² <http://www.jpsr.pharmainfo.in/Documents/Volumes/vol7Issue11/jpsr07111525.pdf>

¹³ Individual bioequivalence: Attractive in principle, difficult in practice.

Drug utilisation review (DUR) is defined by United States Pharmacopeia as “A process to assess the appropriateness of drug therapy by engaging in the evaluation of data on drug use in a given health care environment against predetermined criteria and standards.”

Through the identification of certain groups of medicines on a higher level of abstraction we can identify and group up MPs with the same attributes ranging from the same active ingredient, to the same mechanism of action, to the therapeutic intent or existing interaction for medicinal products, it can help pharmacist at the dispensing point to detect potential problems with drug therapy at any level. A typical example could be the potential interaction due to concomitant use of beta blockers such as salbutamol and beta agonist such as propranolol.

Allowing the pharmacist to assure the appropriateness of the whole prescription (to screen the prescription for correct indication, dose, form, posology...) may be also be helpful in a context when substitution of the MP is also required. This can be added value at a national or international level when appropriate. It can contribute, as a whole, to the improvement of patient safety¹⁴

7.2 Implications of clusters

Generic/INN clusters are clusters created based on the principle of bioequivalence for a given population or a common nomenclature respectively. Using them in a prescribing context for the purpose of cost containment has been a common practice in many European countries.

With the regulatory process, health professionals and consumers can be assured that the generic drugs contain the same active ingredient as the reference medicinal product, the same strength, dosage form and route of administration; have the same use indications and comply with good manufacture practices as well as being bioequivalent. On the other hand, this does not include bioequivalence amongst generics, or bioequivalence amongst MP of article 8 of directive 2001/83 (new active substances, sometimes referred to as innovators).

With regards to the other legal basis (section 5.3) the prescribability and the interchangeability can vary according to the jurisdiction. Hybrid, well established and biosimilars prescribability and interchangeability will depend on the local regulations, as in terms of bioequivalence, hybrids do not always have to prove it; well established do it through the literature presented and in the case of biosimilars the nature of the molecules is such that the complexity is different.

Clusters formation based on the above concepts is not uniform (for further information regarding the interchangeability of biosimilars, refer to deliverable 5.1).

Those clusters created for dispensing purposes include the some drugs for the purpose of selection or substitution. Substitution (which is dealt with in WP5) remains a national decision policy and it is usually influenced by pricing, and regulation the interchangeability concept is, eventually, a case by case decision where not only national regulations are taken into account but also the clinical condition of the patient as well as the availability of the drug.

Other context not yet so much explored is cluster formation in a cross-border setting. Recognising and establishing the products which are the same but identified with different attributes according to the jurisdiction can contribute to a safer use and to facilitate the cross-border health care assistance set up in the European directives. In the same way, establishing a common list of MPs with narrow therapeutic index or common switchability criteria can contribute to the safer use of medication.

¹⁴ http://www.pcne.org/upload/files/35_MedRev_Landerdahl.pdf

8 Cluster survey

The Lime survey was elaborated in conjunction with WP5. Different questions were included in the survey regarding WP 4 and WP5, which concerned clusters and substitution. Although these two themes are separated in the project in two different work packages, they are interconnected in practice. For this reason, we elaborated the survey together as well as for the purpose of simplifying when sending the survey to member states.

The full survey is provided in deliverable 5.1.

As part of the tasks of this work package some use cases were investigated where MP are being prescribed as a cluster of medicinal products.

As differences exist in “prescribing by cluster” and “prescribing a product which at the dispensing point is identified as belonging to a cluster” (for further explanations please go to section 7.3) both perspectives were targeted in the questions.

Question 4 was a separate question from the rest and aimed at finding out if there are any MS which allow “prescribing by cluster” in their prescribing system.

In another section cluster related questions were grouped up. The other questions were aimed at understanding how clusters are formed in the different countries, the attributes included and which institution creates them. The final question was regarding exchanging medicinal products from different clusters.

Q4: Is prescribing by clusters allowed in your country?

There were only 3 positive answers.

This hinted this practice is not a common practice

Q18: are clusters used as a tool in your country?

Those who answered No were not given the option of continuing the survey.

At least 9 countries use clusters as a tool for grouping up medicinal products.

Q19 Organisations stipulating the criteria for cluster formation.

In most cases, where clusters are formed the regulatory agency participates at some point, sometimes the ministry of health was involved too and occasionally a public or statutory health insurance participated too.

Q20 to 23 aimed at understanding better how clusters were formed in a country and the attributes that could define them.

Price was a mayor motivational drive to form them but it was not the only one. Therapeutic and pharmacological classifications were also used as a motivation for cluster creation. ATC code was considered too.

In further questions, participants were asked to define the attributes of the cluster in relation to the content (Q21), meaning what attributes are seen in a cluster: active substance, strength and so on.

In Q22 the aim was to enumerate the identifying attributes of a cluster, more in relation to de MP, such as it being the reference MP, the generic product the original branded etc.

And with Q23 we wanted to investigate the relevance of the legal basis in relation to those clusters formed.

Q24 asked about the possibility of exchanging MP belonging to different clusters

Only 3 countries allowed such possibility

It revealed that cluster formation is indeed a complex area carried out by specialised members in the subject.

After discussions with other team members of the project, it was deemed necessary to further investigate the results to provide with some more consistent and reliable data. Therefore, a further extended analysis will follow.

9 Compound medication

When referring to compound medication we refer to 2 different pharmaceutical products or medicinal products or one or more pharmaceutical products being given as part of the same MP which might suffer or not a transformation (e.g. mixed with a solvent or a diluent) prior to administration hence we need a step prior to administration.

The transformation step required prior administration is normally due to stability, sterility of the medicinal product or due to clinical reasons.

The classification below describes several scenarios according to the way the products are packed prior to being administered. Section 9.1 to 9.3 states those instances of authorised products, with the information of how to mix and/or administer the product, information contained on the product information leaflet. In these sections, we can identify the products using the concepts from WP2 solution but in section 9.4 authorised MP are being used off-label, therefore we will explore the needs related.

9.1 Multiple products packaged as a kit and administered as separate MP

There are some medicinal products which contain two different pharmaceutical products. This instance is that of a product constituted of two units with different substances, strengths or dose form(s) that are intended to be administered independently from each other simultaneously or at different intervals.

e.g. a kit with clotrimazole as a vaginal tablet and clotrimazole as a vaginal cream to be used complementarily but both being pharmaceutical products with different pharmaceutical dose forms and posology).

e.g.: Other MP might contain two different pharmaceutical products with different substances, strengths but the same dose form, like hormone replacement therapy where two different types of substances are taken at different intervals.

WP2 identification concept applicable: PhPID, MPID and PCID datasets

9.2 Multiple products packaged as a kit for reconstitution and administered as one MP

Other type of MP as multiple products packages which also come as a kit (combination pack) are intended to be administered as one medicinal product. These require a transformation step prior to administration (dissolution, mixing, suspension...).

e.g. A powder for solution for injection, and a solvent for solution for injection, which after dissolving the powder in the solvent, will be administered as a solution for injection.

Products without solvents included in the same package (single products) will also have the dose form after reconstitution. These products will be identified in the same way as the described above, as the final administrable dose form.

WP2 identification concept applicable: PhPID, MPID and PCID datasets

9.3 Components of Kit which are not packed together (radiopharmaceuticals)

This instance refers to medicinal product authorised when is marketed as a kit with all components to be reconstituted and intended to be administered as one product (as approved by a regulatory authority).

There may be instances where, due to safety reasons, the radiopharmaceutical components of the kit (a radioactive atom and a molecule or ligand which it joins to be administered), would not be packaged together. Nonetheless, they will be administered as one product.

The description of the manufacturing method of radiopharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product.

- The necessary specifications of the radio-nuclide need to be described in accordance, where relevant, with the general monograph or specific monographs of the applicable pharmacopoeia.
- Compounds essential for the radio-labelling shall be described.
- The structure of the radio-labelled compound shall also be described.
- For radio-nuclides, the nuclear reactions involved shall be described.

WP3 identification concept applicable for radiopharmaceuticals: PhPID, MPID and PCID datasets.

Further description for radionuclides is required.

9.4 Other compounded products

All the compound products described above are included in the ISO IDMP standards, and can be identified in composition and form prior and after administration. However in some cases, usually under a very specialised and supervised context, pharmaceutical or medicinal products are mixed to generate a new medicinal product not contemplated on the SmPC of those MP.

Although these products, as they are authorised products, might be identified in the same way as other products described in previous work packages, D2.2 and D3.1, the way in which they are administered is not authorised, therefore the identification needs varies.

Off-label use of a medicinal product

This relates to situations where the medicinal product is intentionally used for a medicinal purpose differently from the authorised product information.¹⁵

Below we list some of the examples we find in hospitals mainly, of 2 or more medicinal products mixed and administered together as one MP but whose pharmaceutical and/or administration form is not contemplated in the dossier of the MP (including SmPC).

- Several Intravenous antibiotics mixed together and given as one solution
- Palliative care MP being mixed together and given together via syringe drive
- Vitamins and mineral added to a parenteral nutrition bag
- One or more cytotoxics mixed and given in the same syringe
- Patient tailored doses
- Pharmaceutical dose form authorised under a certain route of administration being given as a different one.

¹⁵ Guideline on good pharmacovigilance practices (GVP) Module VI

- Rare disease (without orphan designation of a medication).

The reason for changing the administration requirements of these products could be one or more of the factors listed below,

- Clinical condition of patient:
 - Like organ dysfunction (renal failure, hepatic failure...)
 - Fluid restriction
 - Metabolic unbalance
 - Unable to swallow.
- Off-label product in that particular country but well known efficacy and safety through practice, or through data from the country where is used or other countries.
- Patient convenience or to avoid patient discomfort (example to reduce the number of injections several medicinal products can be mixed together).
- Trials with ethical restrictions (like in neonates/children).

WP2 described a core dataset regarding clinical particulars with some of the following attributes

- ✓ Therapeutic indication
- ✓ Contra-indication
- ✓ Population specifics
- ✓ Interactions.

These could include some of the particulars specified hereinabove.

Overall the pharmaceutical product is identified the same way as others, it can be identified using the openMedicine dataset, in this case what is missing is the regulatory process to support such use, usually because the pharmaceutical companies do not consider profitable or appropriate to request an authorisation for that particular use, or because the usage is experimental and it is on early stages. The collection of the information gathered when the product is being used off-label can be useful for future authorisation requests.

Instructions for use regarding these products follow normally follow the guidance of the bibliography available which is supported during the years of practice.

9.4.1 Identifying the safe use of compound medicinal products

The information contained on a prescription may vary according to countries and country requirements (in some countries a pharmacist will not dispense a drug unless the allergy box has been filled in).

In some instances, prescribers might include information regarding the clinical condition of the patient to make sure the most appropriate medicinal product is dispensed to the patient. This is not only an informative note on the prescription but throughout practice it can lessen adverse events.

Although European prescribing guidelines states the minimum set of attributes for a medicinal product in some cases this might not prove enough.

We will describe some instances when some extra attributes on a prescription will help identifying the correct MP.

This information might be mandatory or not on a prescription and can be conveyed on the prescription itself, obtained from the clinical record if available, or in some circumstances it can be obtained from the patient:

1. Patient's age
It is different authorisation of a MP if given for a child or for an adult.

2. Patient's weight or Body Surface Area
Some MP dosage is based on body weight or BSA (lenograstim).
3. Intolerance/allergies
Peanut allergy
Vegan patients might require capsules with no animal gelatine.
4. Indications according to the unlicensed use or according to a particular indication of the several indications a product might have.
5. Administration instructions when being used off label plus indication that the product is being used off label.
Sucralfate liquid for oral use, being used rectally.
6. Clinical condition of the patient
A patient with a gastrostomy might only be able to use certain soluble medication.

In other instances, MP products can be accompanied of product specific monitoring: booklets for safer use of the medication (certain anticoagulants like warfarin). In any case, when a product is used off-label, a system should be in place for the traceability of the product in case of need of an adverse even report.

When computerised decision support systems are in place the clinical information is collected and transmitted to the patient medical record according to the patient's requirement, this allows the gathering of all the relevant information in order to make the most appropriate decision, and the prescription will be perfectly tailored to the patient.

Unfortunately, a doctor does not always have access to all the information regarding medicinal product in terms of availability or in terms of suitability. Therefore, the situation above cannot always be expected.

It is not only for safety reasons that certain information is needed regarding a patient (via prescription or directly obtained from the patient), it is also because it might compromise the treatment of the patient. The medicinal product use aims at being safe, efficient and rational (which usually takes into account price). When a prescription is not been completed correctly the safety of the patient might be at jeopardy unnecessarily or it could result in the pharmacist not being able to dispense the product, compromising patient's compliance with treatment and consequently patient's condition.

All efforts must be drawn to optimise patient safety.

10 Pharmacovigilance

10.1 Introduction

The World Health Organization (WHO) defines **pharmacovigilance** as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. We could use another words to say that pharmacovigilance is monitoring the safety use of medication.

The regulatory agencies monitor the evidence of safety and efficacy of medication prior to the authorisation through the information submitted regarding clinical trials, but this information is limited so the continuous monitoring is necessary while the medication is in the market.

10.2 Legal framework

The **legal framework** for pharmacovigilance of medicinal products for human use in the EU is given in Regulation (EC) No. 726/2004 and Directive 2001/83/EC on the Community code relating to medicinal products for human use, as amended in 2010 by Regulation (EU) No 1235/2010 and Directives 2010/84/EU and 2012/26/EU respectively, as well as by the Commission Implementing Regulation (EU) No. 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No. 726/2004 and Directive 2001/83/EC.⁽¹⁾

The development of the pharmacovigilance legislation was based on the observation that adverse drug reactions (ADRs), 'noxious and unintended' responses to a medicine, caused around 197,000 deaths per year in the EU.

The new pharmacovigilance legislation, which came into effect in July 2012, was the biggest change to the regulation of human medicines in the European Union (EU) since 1995. It had significant implications for applicants and holders of EU marketing authorisations, as well as for patients, healthcare professionals and regulators. One of the most relevant changes occurring from this implementation, which is also relevant to openMedicine project, is the creation of the article 57 database resulting in making mandatory to all MAH of medicines the submission of the information regarding their medicinal products for the purpose of pharmacovigilance.

The pharmacovigilance system in the European Union (EU) operates between the:

- 1) Regulatory authorities in Member States,
- 2) the European Commission and
- 3) The European Medicines Agency (in some Member States, regional centres are in place under the coordination of the national competent authority).

In order to make this system effective, good cooperation should be fostered between:

- ✓ Marketing authorisation holders,
- ✓ Competent authorities,
- ✓ Public health organisations,
- ✓ Patients,
- ✓ Healthcare professionals,
- ✓ Learned societies and other relevant bodies.

The **objectives** of this EU legislation are:

- To **prevent harm** from adverse reactions arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure.

- **Promoting the safe and effective use** of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

10.3 EudraVigilance

Marketing Authorisation Holders submit and retrieve medicinal product data using the extended EudraVigilance medicinal product dictionary (XEVMPD), also known as Article 57 database. Article 57 database is connected to the repository used for the management and report of adverse drug reactions.

The EMA, on behalf of the EU medicines regulatory network, operates the mentioned system called EudraVigilance for managing and analysing information on suspected adverse reactions to medicines which have been authorised in the European Economic Area (EEA). Its various components through their specific tasks facilitate electronic reporting of suspected adverse reactions related to medicines and the effective analysis of data.¹⁶

This electronic reporting of individual case safety reports (ICSR), evaluation of safety signals and update of product information is mandatory for marketing authorisation holders and sponsors for clinical trials. As part of the post authorisation process the MAH submits the information at defined time during the post-authorisation phase in a pharmacovigilance document which is intended to provide an evaluation of the risk-benefit balance. This document is known as the Periodic safety update reports (PSURs).

The EMA produces a “list of Union and reference dates and frequency of submission of periodic safety update reports” or “EU reference sates (EURD) list”¹⁷ list of active substances and combinations of active substances sorted in alphabetical order, for which Periodic Safety Update Reports (PSURs) shall be submitted according to the dates and frequencies determined by the expert committees (CHMP, CMDh and PRAC)

The EURD list has been compiled in order to facilitate the harmonisation of Data Lock Points (DLPs) and frequency of submission of PSURs for medicinal products containing the same active substance or the same combination of active substances, subject to different marketing authorisations, authorised in more than one Member State. The coordinated submission will allow, where appropriate, the EU single assessment of the related PSURs.

Companies must use the PSUR repository as a single point for all submissions, to submit all centrally and nationally authorised products. All PSURs are submitted to EMA's PSUR repository using the eSubmission Gateway/Web Client:
<http://esubmission.ema.europa.eu/esubmission.html>

¹⁶ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/06/WC500208972.pdf

¹⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133157.pdf

10.4 Adverse event (AE) and adverse reaction

10.4.1 Definitions

Adverse event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment¹⁸.

An adverse event can therefore be any:

- ✓ unfavourable and unintended sign (e.g. an abnormal laboratory finding),
- ✓ symptom, or
- ✓ disease temporally associated with the use of a medicinal product

This adverse event can be, therefore, considered or not to be related to the medicinal product.

Synonyms: Adverse experience.

Adverse reaction:

A response to a medicinal product which is noxious and unintended¹⁹.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.²⁰

Synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure.²¹

Conditions of use outside the marketing authorisation include:

- ✓ off-label use,
- ✓ overdose,
- ✓ misuse,
- ✓ abuse and
- ✓ medication errors.

The main difference between an adverse event and an adverse reaction lies on the causal relationship with the treatment. The first one does not necessarily have one but the second one has at least a reasonable possibility. This relationship is not always easy to establish according to the context.

¹ Definition from Dir 2001/20/EC Art 2(m)

² Definition from DIR 2001/83/EC Art 1(11).

²⁰ Annex IV, ICH-E2A Guideline

²¹ DIR 2001/83/EC Art 101(1).

10.5 Data collection

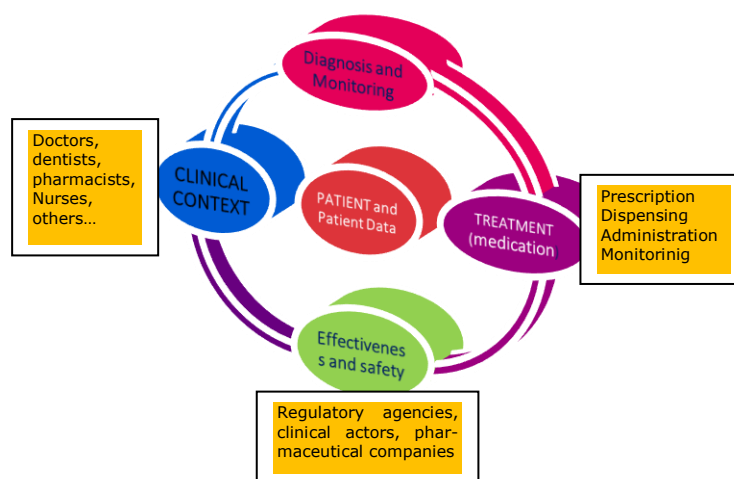
As described in the previous section an adverse reaction can happen when a product is used within or outside the terms of the marketing authorisation.

As the essential aim of the rules governing the production, distribution and use of MP must be for safeguarding public health, data collection aims at reducing the risk of adverse events for the patient.

Although the responsibility of pharmacovigilance conduct relies mainly on the regulatory network (competent authorities in MS, European Commission and the European Medicines Agency) and the MAH, the data are collected through the different actors involved in the clinical process of a MP (prescribing, dispensing, preparing and administration) and coordination amongst actors will be paramount.

In deliverable D.2.2 it contains a description of different cycles in which a medicinal product enters and how they are closely interconnected.

Figure 4- Clinical cycle in relation to a patient and to patient data



As we see in the figure above, the patient is the centre of the clinical cycle and at the same time they are involved in many different processes. All the data collected will be managed for the reporting, evaluation and prevention of undesirable effects.

In openMedicine we aim to better enable cross-border healthcare delivery in the exchange of ePrescriptions and safe dispensation of prescribed medicinal products; therefore we aim to contribute to facilitate pharmacovigilance of MP.

During the cross-border context we expect to see medication being used under terms of a marketing authorisation and outside them. Although overdose, misuse, abuse and medication errors are outside the scope of openMedicine reference to them will be done in chapter 11 in relation to reverse identification of a MP.

10.5.1 Medication use under the authorised terms

The EMA has published a set of guidelines for good pharmacovigilance practice. They contain a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU):

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

The modules fall into two big categories covering the major pharmacovigilance processes and the product -or population- specific considerations.

In the first category we find things like pharmacovigilance systems and their quality, risk management systems, the management and reporting of adverse reactions to medicinal products, post authorisation safety studies and so on.

The second category has been developed for vaccines and biological medicinal products, and two more considerations chapters referring to pregnancy and breast feeding and geriatric population are planned.

10.5.2 Off-label use of medication

Off label use is outside the scope of the international standards ISO IDMP, nonetheless a MP that has been authorised can be identified as an authorised MP. In this case we can highlight the difference on how that particular MP is being used and the fact the information regarding its used might be found obtained from a different source of information.

When the following instances are different from those authorised for the MP:

- ✓ The indication is Different
- ✓ Treatment of a Different group of patient or a patient
- ✓ The route or method of administration
- ✓ The posology prescribed.

Then, the MP will be used off-label.

The obligations of MAHs in relation to the collection and reporting of information related to the off-label use of medicinal products are set out in article 23 (2) of Directive 2001/83.

We can distinguish two different scenarios:

1. When a MP is being used **off-label** and results in **harm** (i.e. associated with the occurrence of suspected adverse reactions), the obligations of an MAH fall in relation to the following points:
 - a. Reporting of individual cases of off-label use associated with suspected adverse reactions
 - b. Periodic reporting of the clinical importance of risks related to the off-label use of a medicinal product
 - c. Risk management planning based on the quantification of off-label use in the context of particular risks and concerns.
2. A MP being used **off-label** causing **no harm**.
 - a. When the use of the MP leads to no harm, the MAH will only have to collect and report information of the off label use.

A patient should be informed by the health care professionals of the off-label use of the medication that has been prescribed for him/her.

10.6 Other descriptive needs

The eHealth network has produced Guidelines on minimum/non-exhaustive patient summary dataset for electronic exchange in accordance with cross-border directive 2011/24/EU. The patient summary dataset contains information regarding a patient's administrative data and clinical data. In the clinical data, we find fields like alerts (which include pharmaceutical and/or medicinal product allergies or sensitivities and medical alerts), medical history (which includes vaccinations, current and previous medical episodes) and medication history.

Taking into account the following points we can find differences in the granularity for the identification of a MP when they are accompanied by Computerised Decision support systems including:

- Drug dictionaries/Medicinal Product Dictionaries
- In the prescribing context: specification of choice and use
- For pharmacy selection and dispensing process -identification of what the patient has previously taken.

All or part of the information provided might be very relevant according to the patient's condition and necessities in a certain clinical context. For example, knowing that a patient had suffered a life threatening reaction to penicillin could be extremely relevant when the patient is prescribed amoxicillin. On the other hand knowing that a patient was treated with paracetamol for a knee pain last year when the patient visits the doctor to be treated for vertigo, might not be so relevant. The difficulty lies on establishing the relevance of the information when the context is known.

For this reasons, throughout practice and throughout the pharmacovigilance processes, the information included on a prescription might not only contain information related to the pharmaceutical product itself but in many instances they will also convey information relevant to the clinical condition of the patient in relation to that particular pharmaceutical product or in relation to a particular condition they are being treated for.

In the process of the correct identification of a medicinal product, all the information can be relevant and may contribute to a safer use of medication. The clinical information of the patient might coincide with that of the SmPC of the MP or it may not.

At the same time the information provided on an ePrescription might constrain the dispensation options.

We give some examples of information included on a prescription which might condition the dispensation process. Information:

- about the indication the MP is being used for;
- about any intolerance/alerts to certain excipients/pharmaceutical product. This is usually to avoid pharmaceutical products which contain them;
- which might state swallowing difficulties so the pharmacist can dispense the most appropriate pharmaceutical dose form;
- regarding flavour, especially In children as having likes and dislikes could be related to the compliance with the medication;
- off-label use;
- narcotics, psychotropic.

The more patient suited that a prescription is, the easier it is to identify and, therefore, choose an MP and eventually prevent adverse events or contribute to compliance with medication.

11 Identification of medicinal products starting from the product description

In D1.2, a number of use cases where unambiguous identification of a medicinal or/and pharmaceutical product is needed, are listed. It defines those outside the application and use of ePrescription.

The use cases are classified under the following broad categories:

- ❖ Clinical
- ❖ Logistics
- ❖ Regulatory
- ❖ Safety issues

In some of these use cases, we explore the need for the identification of MP starting from products description.

11.1 Ways of identifying

11.1.1 Physical attributes of the pharmaceutical product

The visual characteristics of a pharmaceutical product can contribute to its identification. Some of the physical characteristics which can help us in the identification process are described below:

- a. **Pharmaceutical form:** tablet, capsule, a patch, a liquid...
- b. **Shape:** round, oblong, triangular...
- c. **Colour:** red, white, brown...some tablets are colour coded according to their strength (example warfarin)
- d. **Dimensions:** length, diameter, weight
- e. **Flavour:** usually it refers to liquid forms or tablets that can be chewed or sucked.
- f. **Logo or other marking on the surface:** many pharmaceutical manufactures include their logos or add codes to the surfaces of the pharmaceutical form like on tablets, capsules, or even patches, which is unique for the product and can help us in the identification process.
- g. **Image of a medicinal product:** some of the attributes above can be captured in an image.

Usually only one of the attributes above will not be sufficient for the identification of a pharmaceutical product and at least two or more attributes can improve the chances of a better identification.

11.1.2 Physical attributes of the Medicinal Products

As the context in which the identification will be required might be either that of a hospital, a community pharmacy, the industry or at a regulatory level, the services provided to contribute to the reverse identification of a product might be different according to those requirements. Nonetheless, in the majority of cases a drug database is required for such identification.

Some countries have drug identification services either private or public as the source of drug information.

The physical characteristics of a medicinal product might be obtained from:

- A. The immediate packaging/container (in direct contact with the pharmaceutical product),
- B. The intermediate packaging container (between the outer packaging and the immediate container) or in the
- C. The outer packaging (external container in which the medicinal product is supplied).

Title V 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, contains the provisions on the text of the label and package leaflet of medicinal products placed on the EU market, 'Labelling and Package Leaflet'.

More specifically, Article 54 and 55 relate to the information requirements for the mock-up of the outer packaging which will be presented to the regulatory agencies. These particulars shall appear on the outer packaging or, where there is no outer packaging, on the immediate packaging. Article 59 contains the particulars of the package leaflet.

On the other hand, Article 57 provides that MS can include some of their national requirements represented on their “Blue box” content as part of the packaging.²²

- Information on reimbursement
- Price
- Legal status in accordance with the classification of medicinal products contained in Title VI of the same directive
- Different symbols and pictograms
- Identification codes (which include bar codes)

This information is contained in relation to each country according the type of procedure:

- For products authorised following the **centralised procedures** the information required on the blue box can be found in: GUIDELINE ON THE PACKAGING INFORMATION OF MEDICINAL PRODUCTS FOR HUMAN USE AUTHORISED BY THE UNION, July 2015.
- When the products are authorised via a **national, mutual recognition or decentralised procedure** only the requirements from the CMDh apply²³.

The language will be that of the MS and they will be allocated marketing authorisation numbers independently.

The outer package, or when it is absent, the immediate package, contains information related to the medicinal product which is relevant in the reverse identification process in different contexts:

- A. Composition of active substances
- B. Pharmaceutical form
- C. Warnings
- D. List of excipients
- E. Method of administration
- F. Storage precautions
- G. Manufactures Batch number
- H. Safety features for authenticity and identification of individual packs.

When the immediate package and the outer package of a MP exist, and a MP is presented in the immediate package i.e. the blister pack, the batch number and the expiry date should be on it, along with at least the name of the medicinal product.

²² http://ec.europa.eu/health/files/eudralex/vol-2/c/bluebox_06_2013_en.pdf

²³ http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Application_for_MA/CMDh_258_2012_Rev09_2016_03_clean.pdf

11.2 Contexts where reverse identification might be required

In D1.2, we find a number of use cases where unambiguous identification of a medicinal or/and pharmaceutical product is needed. The following list adopts some of the use cases from D2.1 where reverse identification is needed apart from application and use of ePrescription.

It is important to note that the context of these use cases is very closely interconnected.

11.2.1 Reconciling medication

Medicines are most effective and safe if the patient gets the right medicine(s) in the right combination for his/her situation. Otherwise, the medicine may be not effective or it may even be harmful.

There are several steps taken from the dispensing point to the administration point. In order to ensure the correct medication is administered to a patient, the person administering the drug could do a final check along the different steps, meaning checking certain characteristics of the medication which has been prescribed, dispensed, stored, prepared or is to be administered, against the characteristics provided/available of the medicinal product.

All along this processes mistakes can occur at different levels. They might happen when:

- prescribing,
- dispensing,
- storing,
- preparing,
- and administering a medicine.

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. These are the most common preventable cause of undesired adverse events in medication practice and present a major public health burden. European Union (EU) legislation requires information on medication errors to be collected and reported through national pharmacovigilance system.

The identification attributes, which will contribute to the identification when reconciling information, are:

- substance(s)/specified substance(s)
- administrable dose form
- Medical device, when it is a component of a medicinal product
- Medicinal Product Identifier
- Medicinal Product Package Identifier
- Medicinal Product Batch Identifier
- Physical attributes.

By using some physical attributes of the medication, we can contribute to the correct identification of a pharmaceutical product.

A physical description of a pharmaceutical product (type of pharmaceutical dose form and logo and imprint) along with the name, can contribute to the identification. This is a typical example in nursing homes, where medication is often packed in a container which is not the original container. It is common in nursing homes where patients are normally administered a considerable amount of drugs.

In this case, the medication might be included in the administration box or pack provided, and is presented next to the pharmaceutical product provided:

- Pregabalin 300 mg is prescribed in a multi-dispensing pack

The following information is provided:

Pregabalin 300 mg capsule:



White and light orange, marked “Pfizer” on the cap and “PGN 300” on the body in black ink.

Along with the image the description of the pharmaceutical product is provided.

This information is obtained from reliable sources. It will help verify the product to be administered starting from the product description. This serves a double purpose: reducing dispensing errors and increasing patient safety within the regulatory context.

11.2.2 Abuse and misuse use of MP

In a clinical context, with more or less urgency, it is fairly common the need to determine what product has been taken by a patient in order to find an adequate remedy if appropriate, or to better deal with a clinical condition when a patient presents signs of intoxication.

A patient can bring to the hospital as little as a blister pack of medication or only the pharmaceutical product with no packaging. The patient might be unable to provide the healthcare professional with any information about the product.

The identification of a medicinal product in such circumstances might derive from the following attributes:

- Substance(s)/specified substances(s)
- Administrable dose form
- Medical device, when it is a component of a medicinal product
- Medical product identifier
- Medicinal product package identifier
- Physical description.

The information which will help in the identification process might be obtained from patient, relatives or any person looking after the patient.

The identification of a medicinal product will be in the clinical domain and reporting misuse or abuse of a MP will contribute to its pharmacovigilance.

11.2.3 Adverse events and pharmacovigilance

In the same way as the abuse and misuse of an MP provides data relevant in pharmacovigilance, the reporting of medicinal product related adverse effects facilitates continuous assessment of the risk-benefit ratio of the use of medicinal products, thereby directly contributing to safety.

This is important in the short and long-term use of medication as some side effects of a medicinal product may become apparent only after the medicine is used for a longer period of time and on a larger number of patients.

The following attributes will contribute to the identification of an MP:

- Medicinal Product Name

- Substance(s)/specified substance(s)
- Medicinal Product Identifier
- Medicinal Product Package Identifier
- Batch number, if available.

11.2.4 Product traceability

In the healthcare industry, unique identification of an item plays a crucial role in the traceability process of medicinal products.

Traceability is the ability to verify the history, location, or application of an item by means of documented recorded identification. In other words, traceability means the capability and implementation of keeping track of a given set or type of information to a given degree, or the ability to chronologically interrelate uniquely identifiable entities in a way that is verifiable.

In logistics, traceability refers to the capability for tracing goods along the distribution chain on a batch number or series of number basis.

For example the following products/ingredients may be within the scope of a traceability system:

- Any input to a pharmaceutical product, e.g. an Active Pharmaceutical Ingredient (API) bulk supply
- Any item of packaging used in contact with a product, e.g. a blister pack
- Any finished manufactured product, e.g. a batch/lot of surgical gowns
- Any trade item and logistic unit, e.g. an infusion pump, as a part of a pharmaceutical product.

Supply chains have different business requirements and different expectations in terms of enabling technologies.

The identifiers recommended for traceability are:

- Medicinal Product Name
- Medicinal Product Package Identifier
- Medicinal Product Batch Identifier in the instance of the so-called “lot-based traceability” approach
- Serial number, e.g. individual number of the single package if applicable
- Pharmaceutical product identifier
- Pharmaceutical product batch number
- Ingredient identifier
- Ingredient batch number.

The minimum set required depends on the starting point.

11.2.4.1. Product recall

The process of reverse identifying might be required when a withdrawal of a medicinal product needs to be done from the market.

A recall of a medicinal or a pharmaceutical product means that one or more batches of pharmaceutical products from specific pharmaceutical companies or manufacturer must be withdrawn from the market. A recall will be necessary when, for example, a product could cause damage, injury or inconvenience to the consumer and may affect one or several batches or the whole product. Another instance might be when quality requirements are not met.

Everyone manufacturing or trading pharmaceutical products has to have systems for handling recalls as the recall can happen at any level of the supply chain.

This is the minimum identification data set of attributes for required for identification.

- Medicinal Product Name
- Medicinal Product Package Identifier
- Medicinal Product Batch Identifier
- Serial number, e.g. individual number of the single package if applicable
- Pharmaceutical product batch number.

11.3 Resources for the identification of drugs

Reverse identifying medicinal products is built on reliable sources of information. Different institutions provide different services to aid in the identification process.

Drug identification can be done at physical level by providing certain characteristics to a searcher or by calling an institution which holds such information. The information provided will be analysed and checked against the available sources. An answer with the result will be provided.

There are institutions exist at the hospital level, community level or national level contributing to such identification by using and maintaining those sources of information. These institutions can be public or private.

11.3.1 Regulatory agencies

The EU has a strong **legal framework** for the licensing, manufacturing and distribution of medicines. The collection of information at regulatory level allows the collection of information for further use. At the end of the distribution chain, only licensed pharmacies and approved retailers are allowed to offer medicines for sale, including the legitimate sale via the Internet.

As a regulatory agency the EMA provides with a database containing all medicinal products authorised by a centralised procedure.²⁴

Although there is no specific database for public use containing only physical characteristics, if the name is known, the physical attributes can be checked against either the SmPC or the PIL. The same will be applicable for national agencies managing medicinal product databases provided for stakeholders at a national level.

On the other hand, the FDA provides an emergency service for the identification of drugs based on physical appearance and markings.²⁵

11.3.2 Data bases for drug identification

11.3.2.1. TICTAC

TICTAC communications Ltd. is a private institution and provides drug identification and drug information to the criminal justice and health care sectors in the UK.²⁶

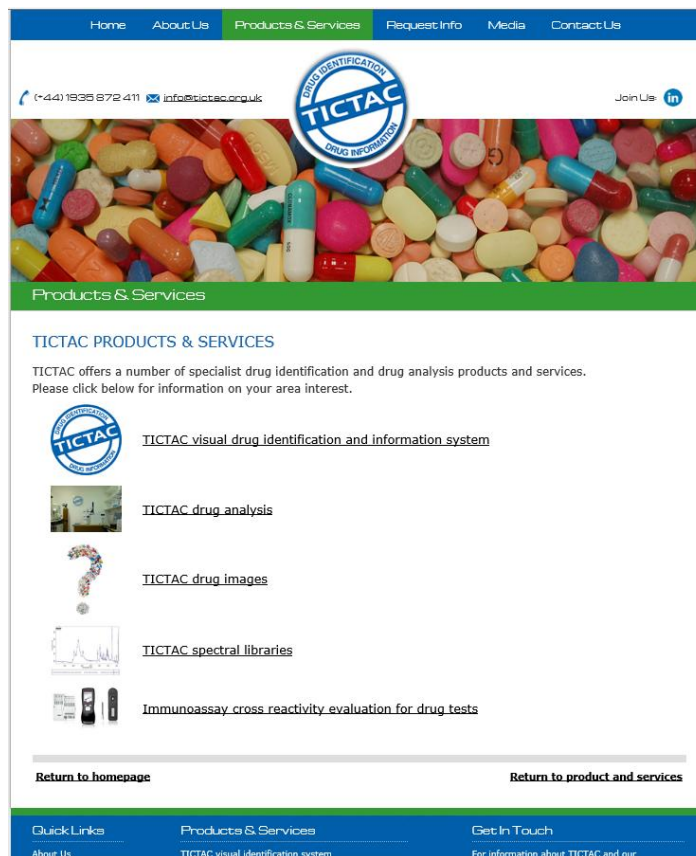
This institution provides the following services related to drug identification.

²⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=WC0b01ac058001ce7e

²⁵ <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082695.htm>


²⁶ <http://www.tictac.org.uk/>

1. **Visual drug Identification and information system:** It contains over 32,000 medicines and drugs for identification of solid forms
2. **Drug analysis:** the drug can be identified with a spectral analysis if contained in their spectral library.
3. **Drug images:** It has over 75,000 images of medicines and drugs.
4. **Spectral libraries:** Are mainly for psychoactive drugs spectral library of Fourier Transform infrared spectroscopy (ATR/FTIR) for new psychoactive substances/legal highs. They also have gas chromatography mass spectrometry (GC-MS) spectra.
5. **Immunoassay Cross reactivity:** is the only place in Europe where immunoassay drug tests can be evaluated for cross reactivity against virtually every medicine and illicit drug your drug tests are likely to come across.



11.3.2.2. Pillbox from the National library of Medicine (NLM)

The National Library of medicine of the United States of America provides with *The Pillbox* website. It was developed to aid in the identification of unknown pills (oral solid dosage form medications). It combines images of pills with appearance and other information to enable users to visually search for and identify oral solid dosage form medications. Once a pill has been identified, additional information is provided, including brand/generic name, ingredients, and the National Drug File identification number.



rapid identification, reliable information

United States
National Library of Medicine
National Institutes of Health



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Identify or Search for a Pill

Imprint: ☐ Pill does not have an imprint.

Shape:

Color:

Size:

Score: ☒ Unknown ☐ 1 ☐ 2 ☐ 3 ☐ 4

Drug Name or Ingredient(s):

Inactive Ingredient(s): ☐ Find pills WITHOUT this ingredient.

Label Author:

DEA Schedule:

Product Code: -

☒ Do not search repackaged and relabeled medications.

11.3.2.3. Medscape

Medscape's Pill Identifier²⁷ helps to identify generic and brand name prescription drugs, Over the Counter medication and supplements. It allows a search from over 10,000 tablets and capsules by imprint, colour, shape, form and scoring.


Once a medication is selected, you will be able to:

- Verify drug name, strength and detailed pill characteristics
- Access drug dosing, interactions, adverse effects and warnings.

Edition: **ENGLISH** DEUTSCH ESPAÑOL FRANÇAIS PORTUGUÊS

Medscape

News & Perspective **Drugs & Diseases** CME & Education



Pill Identifier

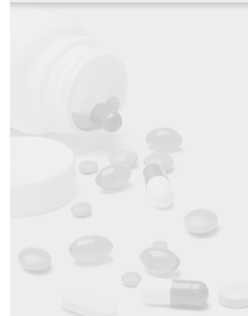
36 | 01

SHAPE

COLOR

FORM

SCORING



Pill Identifier

Medscape's Pill Identifier helps you to ID generic and brand name prescription drugs, OTCs, and supplements. Search from over 10,000 tablets and capsules by imprint, color, shape, form, and scoring.

Once a medication is selected, you will be able to:

- Verify drug name, strength, and detailed pill characteristics
- Access drug dosing, interactions, adverse effects, and warnings

To get started, click on any criteria above.

11.3.3 Medicines information centres

Medicines information centre can exist:

- National or local level (pharmacy or hospitals)
- Industry
- Regulatory level.

²⁷ <http://reference.medscape.com/pill-identifier>

Their aim is to provide information regarding medication at different levels according to the setting.

As an example, the UK has a network (UKMI) which encompasses:

- 220 local medicines information centres based in the pharmacy departments of most hospital trusts
- 14 regional centres
- 1 national centres which is in Wales.

The NLM also has a section with drug information, this Linked to the Pillbox described above.

<http://druginfo.nlm.nih.gov/drugportal/drugportal.jsp>

11.3.4 Toxicology centres

These are centres which provide information regarding the misuse of medication. They usually provide services to health care professional regarding signs and symptoms and treatment options when drugs are being taken accidentally or at higher amounts than the therapeutic dose, which is the usual dose. They can also provide with information regarding the toxicity of a drug during pregnancy and breast-feeding.

Some of the information provided can complement the reverse identification of a MP when it is being used outside the terms of the licence or accidentally.

11.3.5 Falsified medicines

Falsified medicines are fake medicines that are designed to mimic real medicines.

The EU strengthened the protection of patients and consumers by adopting a new Directive on falsified medicines for human use. The Agency is working closely with the European Commission and the EU Member States to implement this Directive and Member States had to start applying its measures in January 2013.

This Directive aims to prevent falsified medicines entering the legal supply chain and reaching patients. It introduces harmonised safety and strengthened control measures across Europe to guarantee medicine authenticity.

This directive will be enforced through applying new measures, grouped into four main pillars:

1. Safety features regarding a unique identifier on the packaging and an anti-tampering device for medicines.
2. New responsibilities for wholesalers at the supply chain level and good distribution practice.
3. Manufacturing of active substances and excipients outside of the EU.
4. An obligatory logo for websites for authorised retailers.

This process involves distinguishing genuine products from falsified ones.