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Deliverable abstract

UNICOM Task 8.4 aims to improve a core international pharmacovigilance activity: processing and analysis of individual case safety reports (ICSR) that describe one or more suspected adverse drug reactions that occur in a single patient. This deliverable provides coding guidance and principles for the accurate and consistent representation of drug information (including vaccines) in the ICSR message, focusing on Medicinal Product Identifiers (MPIDs) and Pharmaceutical Product Identifiers (PhPIDs) (with or without name parts) that will result from the implementation of ISO IDMP standards.

Analysis of a purposive sample dataset of drug verbatims, retrieved from reports of suspected adverse drug reactions from multiple sources, identified specific areas that require additional guidance. General considerations are provided for selecting MPIDs and PhPIDs, as well as guidance and considerations on more specific topics such as the use of context, historic identifiers, and name parts. All guidance areas are illustrated with practical examples.

This deliverable also provides recommendations for practical IDMP implementation aspects (e.g., PhPID generation) and for handling drug information in general (e.g., grouping concepts, use of name parts), aimed at improving ICSR data management and pharmacovigilance analysis.

Keywords: Pharmacovigilance, ISO IDMP, ICSR, ICH E2B(R3), EU ICSR Implementation Guide, case processing

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List of abbreviations

Abbreviation	Complete form
ADR	Adverse Drug Reaction
AEFI	Adverse Events Following Immunisation
CAS	Chemical Abstracts Service
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EU-SRS	European Substance Registration System
G-SRS	Global Substance Registration System
GVP	Good Pharmacovigilance Practice
HALMED	Agency for Medicinal Products and Medical Devices of Croatia
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
ID	Identifier
IDMP	Identification of Medicinal Products
INN	International Nonproprietary Names
ISO	International Organisation for Standardisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board (The Netherlands)
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA® trademark is registered by ICH).

MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MPID	Medicinal Product Identifier
NCA	National Competent Authority
NHS	National Health Services
PCID	Packaged Medicinal Product Identifier
PhPID	Pharmaceutical Product Identifier
PhV	Pharmacovigilance
PMS	(EMA) Product Management Service
SDG	Standardized Drug Grouping
SID	Substance Identifier
UCUM	Unified Code for Units of Measure
UMC	Uppsala Monitoring Centre
WHO	World Health Organisation
XEVMPD	EudraVigilance eXtended Medicinal Product Dictionary (art 57 database)

1 Executive summary

From 2012 onwards, the International Organization for Standardization (ISO) published a series of standards and technical specifications called together the Identification of Medicinal Products (IDMP). The UNICOM project aims to give an ultimate impulse to the implementation of ISO IDMP among drug databases of European countries to support safe cross-national e-prescription and pharmacovigilance activities. UNICOM Task 8.4 aims to improve a core international pharmacovigilance activity: processing and analysis of individual case safety reports (ICSR) that describe one or more suspected adverse drug reactions that occur in a single patient. This document provides coding guidance and principles for the accurate and consistent representation of drug information (including vaccines) in ICSRs, focusing on Pharmaceutical Product Identifiers (PhPIDs) and Medicinal Product Identifiers (MPIDs) as IDMP identifiers.

A sample set of drug verbatims with all types and granularities of medicinal product descriptions has been analysed, using existing guidance available in the ICH E2B(R3) Implementation Guide and EU ICSR Implementation Guide. It appeared that unambiguous identification of medicinal product in the ICSR is not always possible as the drug information provided by the reporter may be imprecise. Specific areas were identified that need further guidance to improve accurate and consistent coding of MPIDs and PhPIDs. Practical examples illustrate that by taking reliable contextual information (such as reporting country, reporting mechanism, timing, primary receiver) into account, an ‘imputed level of drug information’ is achieved, which leads to a more precise selection of MPID or PhPID. Further examples address the use of historic IDMP identifiers, name part data elements and various scenarios of coding drug verbatims. The processes of data retrieval and analysis are impacted by the level of detail captured via the ISO IDMP identifiers used in the ICSR. Examples illustrate that although routine signal detection activities may generally start at a broad level, more specific information and groupings may be necessary to investigate a potential safety issue.

The last section provides recommendations for practical IDMP implementation aspects (e.g., PhPID generation) and for handling drug information in general (e.g., grouping concepts, use of name parts), aimed at improving ICSR data management and pharmacovigilance analysis. It is acknowledged that ongoing discussions on implementation of IDMP may lead to changes to the ISO standards and/or Technical Specifications, with potential impact on the identifiers resulting from the practical implementation of these standards. Also, it is not yet clear who will generate PhPIDs and if these will become available at global scale. These moving parts emphasize the need to support the pharmacovigilance stakeholder community with up-to-date guidance relevant to their specific IDMP use case. While this guidance has been developed within the European UNICOM project there is a need to establish global consensus in the use of IDMP identifiers in ICSRs. Considering the highly regulated pharmacovigilance environment, it is recommended to explore a possible role of international (global) organisations as an owner for IDMP ICSR coding guidance, to be responsible for its ongoing development and revision as the IDMP implementation progresses.

2 Introduction

2.1 Background

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The European Union (EU) pharmacovigilance system is underpinned by a legal framework (Regulation (EC) No 76/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012) that establishes roles and responsibilities, principles and procedures for the regulatory network (national competent authorities: NCAs, European Medicines Agency: EMA, and European Commission: EC) and pharmaceutical industry (referred to as Marketing Authorisation Holders: MAHs).

Safety monitoring through collection and analysis of suspected adverse drug reaction (ADR) reports is a cornerstone of pharmacovigilance. Reports of suspected ADRs are initially collected by MAHs and NCAs (or their regional/national pharmacovigilance centres) and originate from a variety of sources, including healthcare providers, patients/consumers and medical literature. Onward exchange of suspected ADRs is based on legal requirements and involves a large number of stakeholders worldwide. Gathering suspected ADRs into international databases facilitates the detection of drug safety signals – which might not be apparent from the data of a single country – and increases the probability of detecting rare adverse drug reactions. For the purpose of this document, two international pharmacovigilance databases are highlighted:

- ▶ EudraVigilance: the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or are being studied in clinical trials in the European Economic Area (EEA). The EMA operates the system on behalf of the EU medicines regulatory network. By end 2020 the database holds over 18.6 million Individual Case Safety Reports (ICSRs) referring to over 10.5 million individual cases.
- ▶ VigiBase: World Health Organisation's (WHO) global safety database for medicinal products, with over 27 million reports of suspected adverse drug reactions. VigiBase is developed and maintained by Uppsala Monitoring Centre (UMC) on behalf of the WHO. Reports have been submitted since 1968 by members of the WHO Programme for International Drug Monitoring.

As from 30 June 2022, MAHs and EU regulators are required to use the International Organisation for Standardization (ISO) ICSR 27953-1 (2011) standard for the submission of suspected ADR reports to EudraVigilance (in line with Article 26(2)(a) of the Commission Implementing Regulation (EU) No 520/2012). The modalities on how to implement and apply the ISO ICSR standard are defined in the International Council for Harmonisation (ICH) E2B(R3) documentation. This ISO ICSR message in ICH E2B(R3) format is also used for the exchange of ADR reports between the EMA and WHO UMC. Conceptually, the ICSR can be considered a standard format that is capable of accommodating direct database-to-database transmission to describe one or more suspected adverse reactions to a medicinal product that occurred in a single patient at a specific point in time. A valid ICSR should include at least

one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction, and at least one suspect medicinal product.

This ISO ICSR message in ICH E2B(R3) format has placeholder data-elements for providing information on the medicinal product(s) in line with ISO standards for the Identification of Medicinal Products (IDMP). Until the relevant IDMP terminologies and identifiers become available and are agreed for use in the ICSR message, free text can be used in the ICSR to describe medicines, both for the suspect product and for any concomitant medications. However, pharmacovigilance analysis is hampered by the use of free text and lack of standardisation of medicinal product information between systems and across jurisdictions. In addition, it takes valuable resources to match medicinal products and active substances provided as free text in ICSRs to the different drug dictionaries that are used in pharmacovigilance databases.

Figure 1 illustrates the exchange of EU ICSRs between NCA/pharmacovigilance centres, EMA, pharmaceutical industry and WHO UMC with use of different drug dictionaries in their respective pharmacovigilance systems. The EMA uses the Extended EudraVigilance Medicinal Product Dictionary (known as XEVMPD or "Art57 database") whereas WHO UMC uses the WHO Drug Dictionary (WHO Drug). Pharmaceutical industry may use their own internal database. Furthermore, it is known that NCAs or their pharmacovigilance centres use different drug dictionaries, sometimes even a drug dictionary that is used in the clinical domain. This necessitates the conversion of ICSR data from one drug dictionary terminology to another.

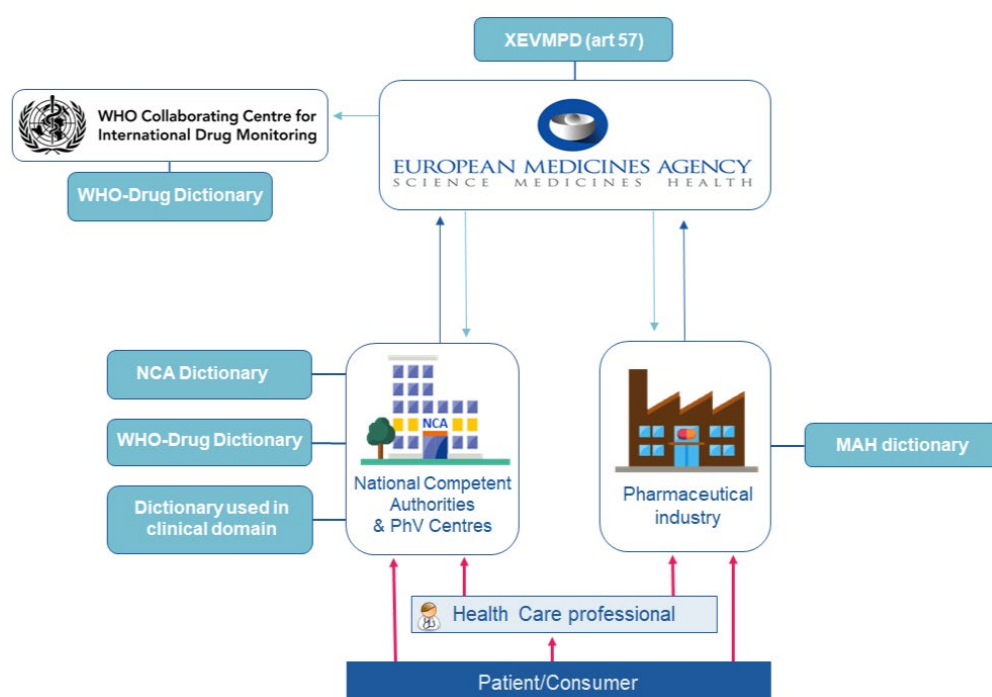


Figure 1. Flow of ICSRs and different Drug Dictionaries used

Light and dark blue arrows indicate exchanges in ICSR format. Patients and Health Care professionals can report suspected ADRs to NCAs/pharmacovigilance centres or pharmaceutical industry via various means, for example webforms, phone, apps, etcetera.

Upon receipt of a suspected ADR, the verbatim (literal term used by the reporter or provided via the reporting mechanism) of a medicinal product can contain different levels of precision, depending on the source and method of collection. Selecting the most precise IDMP identifier is necessary to maximally specify reported medicinal products. Structured data entry, retrieval and analysis at different levels of precision and aggregation are vital in order to enable effective and accurate pharmacovigilance analysis. Taking into account the international dimension of ADR reporting, the use of ISO IDMP identifiers in the ICSR message is expected not only to bring efficiency gains to ICSR processing, but most importantly to strengthen pharmacovigilance processes.

2.2 Objective and scope

The objective of this document is to provide coding guidance and principles for the accurate and consistent representation of drug information (including vaccines) in ICSRs for stakeholders involved in coding activities for ICSRs, including but not limited to pharmaceutical industry, regulatory authorities, regional/national pharmacovigilance centres (depending on the relationship with the authorities and their requirements).

Readers should be familiar with all relevant legislation and available guidelines, such as:

- ▶ Applicable pharmacovigilance legislation, i.e., Regulation (EC) No 76/2004, Directive 2001/83/EC (EC, 2001) and Commission Implementing Regulation (EU) No 520/2012 (EC, 2012)
- ▶ Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2) (EMA, 2017)
- ▶ ICH E2B(R3) Implementation Guide (ICH, 2016)
- ▶ EU ICSR Implementation Guide (Rev 2) (EMA, 2021)
- ▶ ISO IDMP terminology (see also section 2.3).

The EU legal provisions on pharmacovigilance and the extensive EU guidance apply to all medicinal products authorised in the EU, including herbals and vaccines. Monitoring the safety of vaccines has specific challenges that should be borne in mind when designing and implementing pharmacovigilance activities for vaccines. It is acknowledged that in the context of vaccines the term Adverse Event Following Immunisation (AEFI) is used at international level instead of 'ADR'. In this document, no distinction will be made between ADRs and AEFIs as the overall objectives and processes of pharmacovigilance are similar for vaccines and other types of medicinal products.

The scope of this document is limited to post-authorization ICSRs (spontaneous and solicited), and independent of the drug role characterization as suspect/concomitant/interacting. The guidance can also be used for coding concomitant medication in clinical trial reports; however, it should be kept in mind that the guidance has been developed for post-marketing purposes and not for the specific clinical trial reporting use case. This guidance focusses on the practical aspects and challenges of using identifiers resulting from the implementation of ISO IDMP 11615 (Medicinal product Identifiers: MPIDs) and 11616

(Pharmaceutical product identifiers; PhPIDs). This guidance also considers the use of ‘name part data elements’ as per EU ICSR Implementation Guide (Rev 2) (EMA, 2021a). Relevant information regarding the use of the 3 other ISO IDMP standards (ISO 11238, ISO 11239 and ISO 11240) is presented in section 2.3.

The examples provided in this document may not reflect practices and requirements in all regions. Not every potential IDMP selection situation is addressed in this document and common sense should always be applied. This document does not specify regulatory reporting requirements, nor does it address database issues. As experience with IDMP increases and as IDMP implementation activities emerge, the guidance in this document may need to be updated (see also Recommendation 6.3).

2.3 Context IDMP and ICSR

IDMP aims to uniquely identify and exchange information on medicinal products. It consists of several levels of identification, with their own ISO standards and Technical Specifications (implementation guides) (see figure 2).

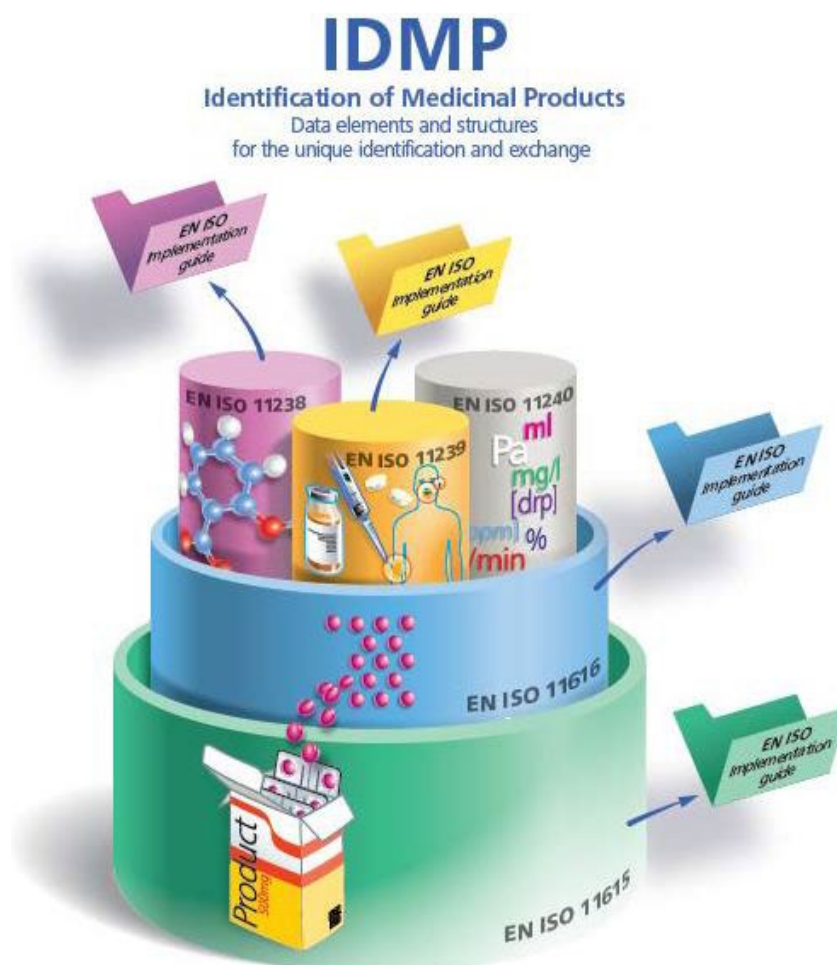


Figure 2. Graphic representation of IDMP data elements and structures

2.3.1 ISO IDMP standards

Below, a concise overview of the relevant ISO IDMP standards is provided:

ISO 11238 - Substances
<p>Medicinal products consist of substances which can be active ingredients, excipients, or constituents (e.g., impurities, degradants, extraction solvents, vehicles, active markers). There are two levels of ingredients: Substance and Specified Substance, which are further defined by several attributes, including whether the substance is a chemical, protein, nucleic acid, polymer, or structurally diverse (e.g., tissue, gene, blood). Specified Substances can have further attributes, such as grade or purity, manufacturing information and specifications. Once a substance has been defined, a unique (global) identifier (ID) can be assigned and maintained in a (global) system. The ICSR contains a data-element (ICH E2B(R3) - G.k.2.3.r.2b) to provide a (specified) substance ID (SID). The SID should be provided in the ICSR when a PhPID does not exist, but a substance name has been assigned an ID, and is known by the sender e.g., for investigational medicinal products or excipients. If a MPID, PhPID or SID is not available, but the Substance name is known, then this can be entered as free text in the data element (ICH E2B(R3) -G.k.2.3.r.1). For this guidance, which is limited to post-authorization ICSRs, it is assumed that all active substances will have a corresponding PhPID as well, and that further guidance on providing (specified) SIDs in the ICSR would not be needed.</p>

ISO 11239 - Pharmaceutical dose forms, units of presentation, routes of administration and packaging
<p>This standard describes the controlled terminologies to use to characterise pharmaceutical dosage form, routes of administration, units of presentation and packaging. Of these, only pharmaceutical dose forms and routes of administration are relevant for the ICSR message. The Routes of Administration and Dosage Form terms in the European Directorate for the Quality of Medicines (EDQM) Standard Terms (ICH, 2020) database comply with the ISO 11239 standard. ICH selected EDQM as the maintenance organization for the Dosage Forms and Routes of Administration terms for human medicinal products to be used in ICSRs.</p> <p>ICH published supplementary information on the use of EDQM terms in the electronic exchange of ICSRs according to the ICH E2B(R3) Implementation Guide (ICH, 2016). Use of EDQM terms for Dosage forms and Routes of administration shall become mandatory as of 30 June 2022 in relation to reporting obligations to EudraVigilance. It is expected that more detailed user guidance will be made available by EMA to support change management activities.</p>

ISO 11240 – Units of Measurement

This standard defines that the Unified Code for Units of Measure (UCUM) standard, an existing standard for units of measurement, is used to define the strength of medicinal products. UCUM is already an integral part of the ISO ICSR standard, and the ICH E2B(R3) Implementation Guide explains how to use UCUM in the ICSR message (ICH, 2016). ICH has also published a list of UCUM units for use in the ICH E2B(R3) drug dosage and cumulative dosage data elements.

UCUM specifies the usage of an algorithm to validate the correct format of a unit. To support stakeholders, a list of valid laboratory test units has been published for use in the EU as the UCUM algorithm does not indicate whether the unit is appropriate for the ICSR data element being used (e.g., lab test result unit being used in a drug dosage data element).

ISO 11616 – Pharmaceutical Product Identifier

This standard describes the use of PhPIDs. It defines the data elements, structures and relationships between data elements that are required for the exchange of regulated information, in order to uniquely identify pharmaceutical products. Each pharmaceutical product has a set of PhPIDs. A PhPID uniquely associates medicinal products with the same or similar pharmaceutical composition. The PhPID, or more correctly a set of PhPIDs, is generated by an algorithm using the SID, the pharmaceutical dose form ID and the (reference) specific strength.

The same PhPIDs will be assigned to all medicinal products that have the same characteristics including substance, dosage form and strength, separate from any other details such as regulatory authorisation, organisation, packaging or naming and regardless of where they were authorized. The PhPID can be specified at various levels of detail for a given pharmaceutical product.

PhPID level	Defining attribute
Active substance stratum	
PhPID L1	Active substance(s)
PhPID L2	Active substance(s) + Strength(s) (+ reference strength if applicable)
PhPID L3	Substance Term(s) + Administrable dose form
PhPID L4	Active substance(s) + strength(s) (+ reference strength if applicable) + administrable dose form
Specified substance stratum	
PhPID_SpSUB_L1	Specified substance(s)_
PhPID_SpSUB_L2	Specified substance(s) + strength + reference strength
PhPID_SpSUB_L3	Specified substance(s) + administrable dose form
PhPID_SpSUB_L4	Specified substance(s) + strength + reference strength + administrable dose form

ISO 11615 – Medicinal Product Identifier

This standard describes the use of MPIDs. The MPID uniquely identifies a medicinal product, reflecting (but not replacing) any other authorization numbers allocated by a regulator. The 11615 ISO standard describes the detailed data elements and their structural relationship required for the unique identification of regulated medicinal products. Data elements that identify and characterize a medicinal product include the product name (authorised by regulatory agency), clinical particulars (e.g., indications, contraindications), pharmaceutical product (substance, dosage form, route of administration), medicinal product packaging, marketing authorisation (e.g., authorisation number, application information), and manufacturer/establishment.

The MPID is the most precise level of identifying the product given to the patient in the ICSR (except for the batch number). According to the EU ICSR Implementation Guide (EMA, 2021a), MPIDs should only be used when the information provided by the primary source includes the MPID or if enough information is provided by the primary sources that the correct MPID can be selected unambiguously. ISO standard 11615 also describes the use of a Packaged Medicinal Product Identifier (PCID), which uniquely identifies a medicinal product based on its packaging. This identifier is not further described as the ICSR message does not have a dedicated data element for the PCID.

2.3.2 Name parts

Medication name parts are a means of specifying the name of a medicinal product as separate components. This allows for input name strings to be automatically matched to possible medical products, rather than through manual classification activities. Use of name parts in the ICSR has not been agreed at the level of ICH E2B(R3), but is a regional extension of the ICSR specification. Extensive information on the name parts is provided in the EU ICSR implementation Guide (EMA, 2021). The following name parts are available in the ICSR (table 1):

Table 1. ICSR name parts

Concept Name	Concept code	Example
Container name	CON	Pre-filled syringe
Device name	DEV	InjectPen
Form name	FRM	Soft capsules
Invented name	INV	TotalFlu
Scientific name	SCI	For TotalFlu: Influenza vaccine (surface antigen, inactivated, prepared in cell culture)
Strength name	STR	50mg
Trademark name	TMK	Syncopharm
Intended use name	USE	For multiCure Heartburn relief: heartburn relief

See section 4.6 for considerations in coding name parts.

Of note:

The EMA SPOR programme will also introduce a Product Management System Identifier (PMS ID). The PMS ID is an identifier that is stable throughout the product lifecycle, including across any change of the MAH. The PMS ID will be associated to the MPID concept but will also be associated (within the PMS system) with all previous inactive MPIDs where MPIDs changed during the lifecycle of the medicinal product. This PMS ID is not meant to be used in the ICH ICSR message. This document will therefore not further describe or use this identifier.

2.3.3 ICSR Drug Section

The ICH E2B(R3) ICSR structure is shown in Figure 3. ISO IDMP identifiers are relevant for ICSR Section D (Patient characteristics, more specifically data elements for 'Relevant Past Drug History' and 'Relevant Past Drug History of Parent') and Section G (Drug(s) information). This guidance focusses mainly on ICH Section G (Drug(s) information), but similar principles can be applied when populating the MPID and PhPID data elements in the ICSR Patient Section D.

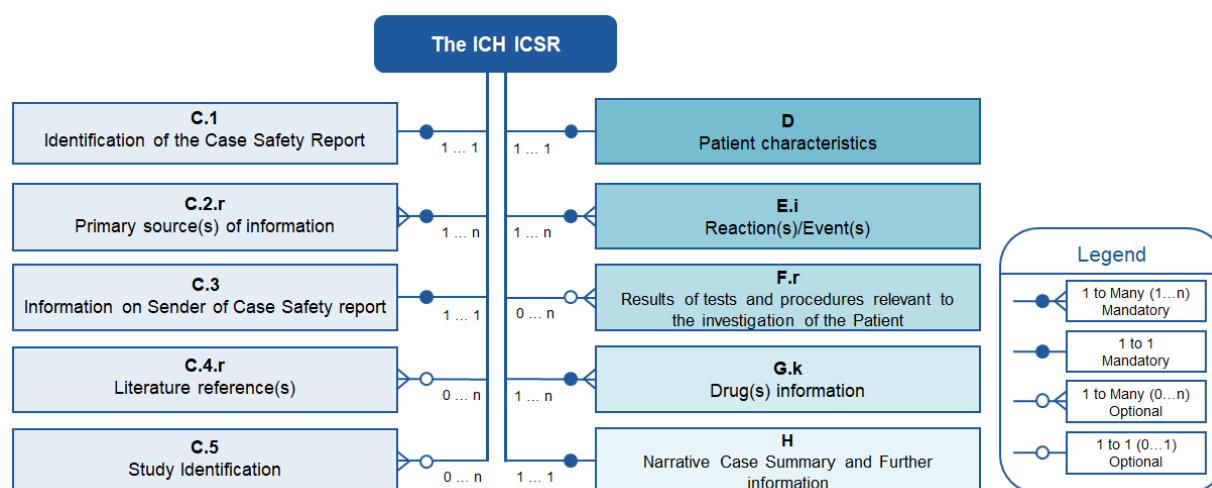


Figure 3. ICH E2B(R3) ICSR structure

The following table (table 2) summarises the ICSR data elements relevant for ISO IDMP identifiers and their corresponding IDMP standards:

Table 2. ICSR data elements relevant for ISO IDMP identifiers

ICH E2B(R3) Section	ICH E2B(R3) Element id	Element Name	ISO standard
D. Patient Relevant Past Drug History	D.8.r.2b	Medicinal Product Identifier (MPID)	11615
D. Patient - Relevant Past Drug History	D.8.r.3b	Pharmaceutical Product Identifier (PhPID)	11616
D. Patient- Relevant Past Drug History of Parent	D.10.8.r.2b	Medicinal Product Identifier (MPID)	11615
D. Patient- Relevant Past Drug History of Parent	D.10.8.r.3b	Pharmaceutical Product Identifier (PhPID)	11616
G. Drug(s) Information	G.k.2.1.1b	Medicinal Product Identifier (MPID)	11615
G. Drug(s) Information	G.k.2.1.2b	Pharmaceutical Product Identifier (PhPID)	11616
G. Drug(s) Information	G.k.2.3.r.2b	Substance/Specified Substance TermID	11238
G. Drug(s) Information	G.k.4.r.9.2b	Pharmaceutical Dose Form TermID	11239
G. Drug(s) Information	G.k.4.r.10.2b	Route of Administration TermID	11239
G. Drug(s) Information	G.k.4.r.11.2b	Parent Route of Administration TermID	11239

ICSR section G.k. Drug(s) Information covers both suspect and concomitant medications, including drugs suspected to have a type of interaction. A minimum of one suspect medication needs to be provided for each valid ICSR. Medications used to treat the reaction/event should not be included here. Although this guidance focusses on the MPID, PhPID and name parts data elements, other data-elements in the drug section need to be populated when applicable. The full ICH E2B(R3) Section G. Drug(s) information (including Name Parts as an EU extension) is shown in figure 4.

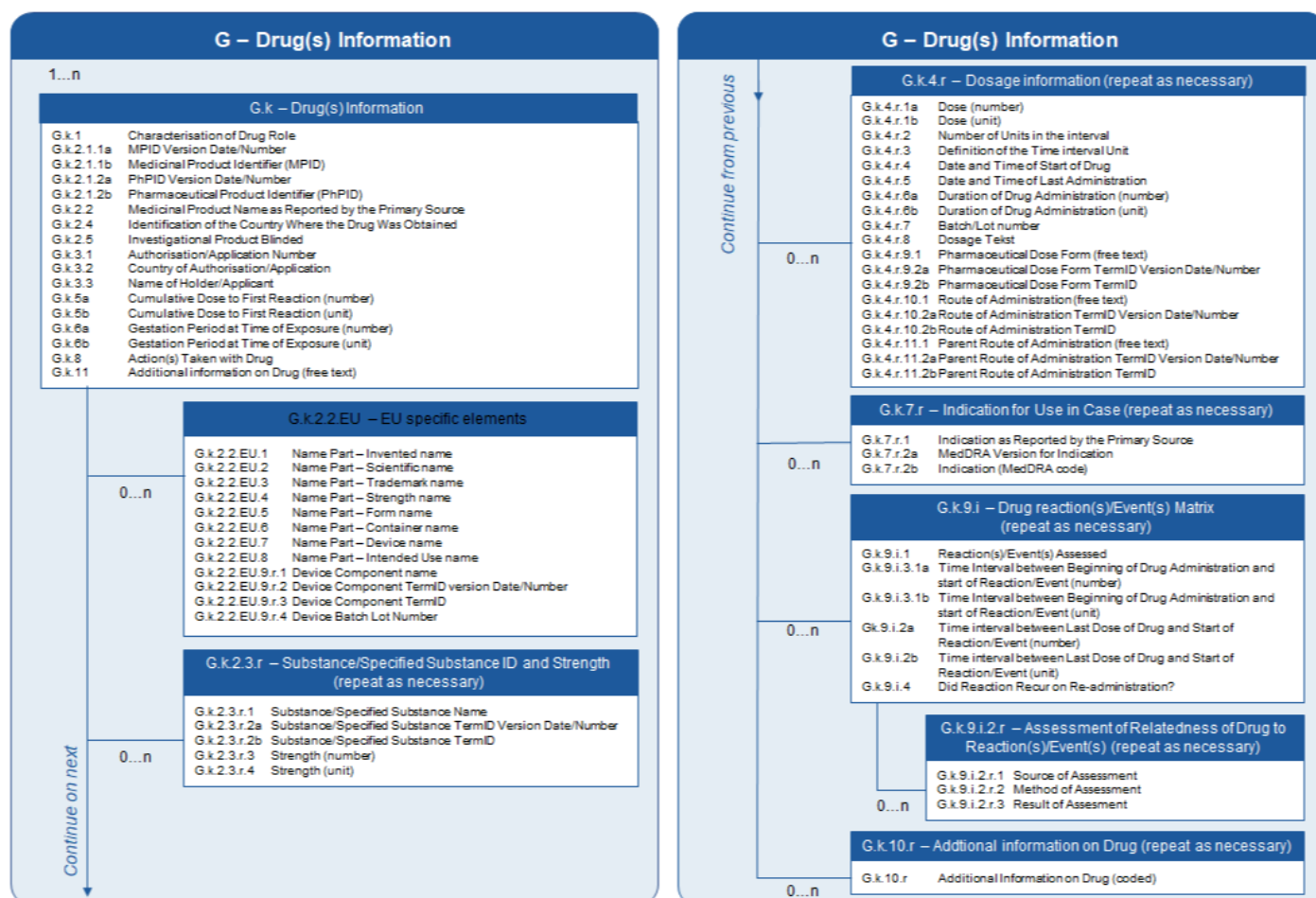


Figure 4. Full ICH E2B(R3) Section G. Drug(s) information

Of note:

Whereas ISO 11615 distinguishes two types of batch identifiers (one for the outer packaging of the medicinal product and one for the immediate packaging), the ICSR drug section has one dedicated data element for the batch number (G.k.4.r.7; free text). Use of this ICSR batch number data element is independent of the implementation of IDMP and will not be further addressed in this document.

For suspected adverse reactions related to biological medicinal products, the definite identification of the concerned products with regard to their manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the names of the biological products and their batch numbers in the ICSR (EU legislation DIR Art 102(e)). A follow-up procedure should be put in place to obtain the batch number where it is not indicated in the initial report of a biological medicinal product (EMA, 2017).

2.3.4 Sources of reports and reporting mechanisms

Spontaneous reports, i.e., unsolicited communications, can be reported by a healthcare professional or consumer to a competent authority, MAH or other organisation (e.g., regional pharmacovigilance centre, poison control centre). The mechanism of reporting can vary (e.g., phone, forms, webforms, literature, apps, internet, lay press, etcetera). Depending on the reporting mechanism, the information provided on a medicinal product may already be subject to some standardisation. For example, webforms or apps may have built in selection options for medications, such as dropdown menus where one should select an option based on (a part of the) verbatim provided or auto-fill features. However, these options may not always capture information that is available 'in the background', e.g., vaccine specific reporting forms may not have an option for selecting the vaccine name, and rather use a description (flu vaccine, HPV vaccine) although there is only one vaccine available or used at time of the report. Furthermore, as pointed out earlier, a variety of drug dictionaries is used.

Although the guidance and coding principles provided in this document may also apply to solicited reports (derived from organised data collection systems, which include among others clinical trials, non-interventional studies, registries, post-approval named patient use programmes, etc), the methodology has focussed on the coding of spontaneous reports. A complete overview on aspects and post-authorisation obligations regarding reporting of individual safety reports is provided in Good Pharmacovigilance Practice (GVP) Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products (EMA, 2017).

3 Methods

To identify areas where guidance is needed for selection of identifiers resulting from ISO IDMP 11615 and 11616 (with or without name part data elements) based on the drug verbatim of an ADR report, a purposive sample dataset was created. Data was provided by HALMED (Croatia), MHRA (United Kingdom), MEB (The Netherlands), WHO UMC, EMA and three MAHs.

Drug verbatim terms were obtained from organisations who can be considered to be primary receivers as they receive ADRs directly from reporters (patients/consumers/carers or healthcare professionals). Drug verbatim terms were also obtained from EMA and WHO UMC, who can be considered secondary receivers as they receive ICSRs from organisations who have already processed ADR information into an ICSR message. The data from the primary receivers originated from different reporting media such as web forms, mobile apps, telephone triage, paper forms or clinical systems (e.g., prescribing or dispensing systems) (see figure 5).

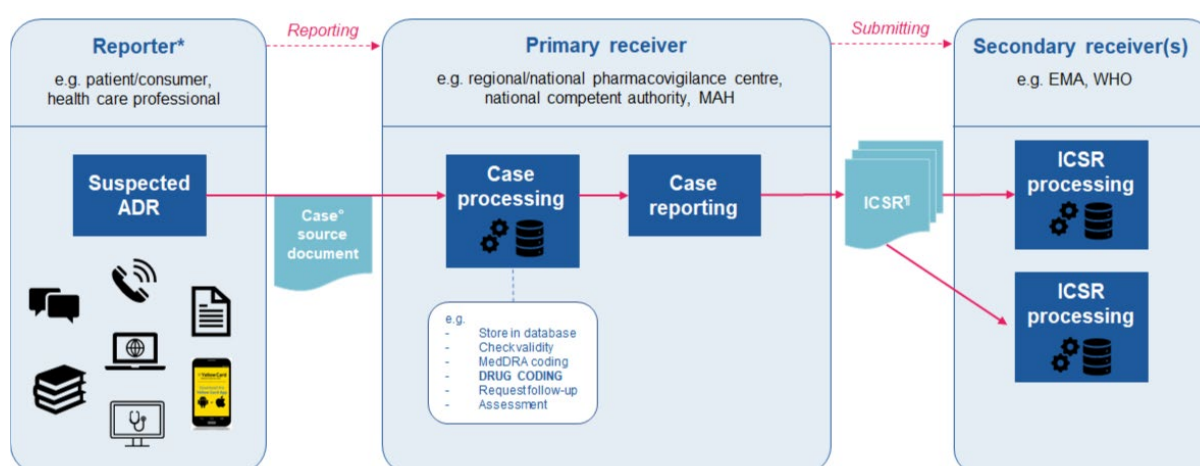


Figure 5. Typical ADR process flow

* The 'Reporter' is usually referred to as 'Primary Source' in ICH E2B (R3) documentation and EU regulatory guidance documents

° Case: the occurrence of one or more suspected adverse drug reactions for one or more suspected medicinal products in a patient at a specific point in time. One case may contain several ICSRs (initial and one or more follow-ups).

† ICSR: refers to the format and content for the submission of an individual report of suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point in time. (GVP VI)

Table 3 illustrates the different levels of precision in drug verbatims and ADR collection methods. The dataset contained free text drug verbatims as well as data obtained using dictionaries (e.g. in a web form or an app) on a wide variety of products.

Table 3. Example of levels of precision in drug verbatims and methods of ADR collection

	Method of ADR collection		
	Yellow card app	Yellow Card Webform	Clinical system
Reporter	Patient/consumer & health care professionals	Patient/consumer & health care professionals	Health care professionals
Drug information	<ul style="list-style-type: none"> ▶ select from a dictionary drop down (supplied by the MHRA; currently limited to (active) substance name only (INN) or main licensed product name) or ▶ use free text in the suspect drug field (in which case it may include strength or dose etc) 		<ul style="list-style-type: none"> ▶ Drug information is provided from the dictionary implemented in their own system (most likely using the NHS Dictionary of Medicines and Devices - Dm+d) and therefore is likely to contain more information relating to dose form and strength.

For the purpose of this guidance, ‘coding’ is used for the process in which both free text drug verbatims and drug verbatims retrieved from drug dictionaries are decomposed into terms that can be machine processed in pharmacovigilance. Generally speaking, ‘coding’ can be defined as the process whereby something stated in human language (either spoken or written) is translated into its meaning by means of identifying the data elements within it (the information model) and the terms that go into those data elements, so that the statement being communicated is (also) machine processable. When drug verbatims are retrieved via drug dictionaries implemented in clinical systems or ADR reporting tools (e.g., webform or reporting app), it may conceptually be more appropriate to refer to ‘mapping’ instead of ‘coding’. Mapping is a process whereby an association (same as, broader than, narrower than) is made between two concepts in two different terminologies covering the same domain of interest. However, in the context of this guidance, ‘coding’ is used for all drug verbatims regardless of the tool/mechanisms from which they originated.

A sample of 150 drug verbatims (as provided by the initial reporter) was selected for coding according to guidance available in the ICH E2B(R3) Implementation Guide (ICH, 2016) and EU ICSR Implementation Guide (EMA, 2021a). Five reviewers each coded a set of 60 drug terms; all terms were consecutively coded by 2 reviewers. The reviewers were blinded for the coding of the paired reviewer. For all terms, it was considered whether an MPID or PhPID level based on the exact verbatim could be assigned, and whether a more specific PhPID level or MPID could be assigned by imputing information based on assumptions. If assumptions were made, these were specified in a comment field. Reviewers also indicated if ICSR name part data elements could be populated (invented name (INV), scientific name (SCI), strength name (STR), trademark name (TMK), and intended use name (USE)) if specific information was available in the drug verbatim but would not be captured within the selected PhPID.

Of note:

Construction of an MPID will use a common pattern with 3 segments:

- ▶ Country code segment
- ▶ Marketing Authorization Holder (Organisation Identifier) code segment
- ▶ Medicinal Product code segment (Unique Medicinal Product Identifier)

- ▶ Examples: NL-MAH X-12345, ES-MAH Y-45678, etc

MPIDs will be generated by regional regulators and will be made publicly available. For the EU it is foreseen that MPIDs will be automatically generated by the EMA PMS system following the successful submission of the medicinal product data in PMS.

A PhPID will be a non-semantic identifier generated by an algorithm based on the core elements for identification of a pharmaceutical product ((specified) substance, dose form, strength).

- ▶ Example: 8663a93b-5627-7466-306d-fd794b7d268a

Discussions are ongoing on having a global organization responsible for generating and maintaining PhPIDs. In theory, if the core elements ((specified) substance, dose form, strength) are standardised globally, PhPIDs can be generated by individual stakeholders themselves, using the MD5 hash generator (a free online tool).

At the time of writing, no real MPID or PhPIDs are available. Throughout the document guidance can only refer to coding 'an MPID' or 'coding PhPID L1-L4' as applicable. Alternatively dummy

Full agreement, i.e., both reviewers agreed on both the direct coding of the verbatim and any coding based on imputation, was observed for only 15% of the verbatims reviewed (see examples below). Partial agreement was observed for approximately 46% of all verbatims reviewed; meaning that both reviewers agreed on at least part of the coding. For the remaining 39% of verbatims, no agreement was observed between the two reviewers. Several reasons were observed from the commentary section, indicating for example that one reviewer did not code because they felt the verbatim represented a product that is not strictly “a medicinal product” and therefore should not be dealt with in the medicinal product section of the ICSR. For other verbatims, neither the direct coding nor the indirect coding had a match on levels of PhPID (no two reviewers agreed that any of the verbatims could be reliably coded to an MPID).

The low observed levels of agreement between reviewers in coding verbatims with currently available guidance indicates that the available guidance is not clear enough, leaves too much room for interpretation by reviewers, and does not provide sufficient steering in particular situations.

Examples:*Full agreement:*

Verbatim: "Amlodipine besilate 5mg"

- ▶ Reviewer 1: Direct coding: PhPID = L2; Imputation – none
- ▶ Reviewer 2: Direct coding: PhPID = L2; Imputation – none

Partial agreement:

Verbatim: "Hoggar night"

- ▶ Reviewer 1: Direct coding: INV = Hoggar Night; Imputation PhPIDL1;
- ▶ Comment: all 3 products have same MAH and active substance we would maybe impute active substance here
- ▶ Reviewer 2: Direct coding: INV = Hoggar Night; Imputation PhPIDL2;
- ▶ Comment: only 25mg is available, therefore PhPIDL2. It is not possible to be more specific as there is a normal tablet and a melt tablet available

No agreement:

Verbatim: "Aciclovir AL 800"

- ▶ Reviewer 1: Direct coding: SCI = Aciclovir; STR = 800 (mg); TMK = AL; Imputation: PhPIDL2
- ▶ Reviewer 2: Direct coding: PhPIDL2; Imputation: PhPIDL4

Focussing on challenges raised by the reviewers and differences in coding results, specific areas were identified that need further guidance to improve accurate and consistent coding of PhPID levels and MPIDs based on drug verbatims. These areas, illustrated by practical examples, will be discussed in section 4. For some areas relevant guidance in GVP Module VI or EU/ICH Implementation Guides was already available and has been referenced as applicable.

4 Guidance and coding principles

4.1 Current guidance in ICH and EU ICSR Implementation Guides

Both the ICH E2B(R3) Implementation Guide (ICH, 2016) and the EU ICSR Implementation Guide (EMA, 2021a) provide basic guidance on how to populate the ICSR drug section taking into account different levels of precision. As a general principle, the most precise structured information should be provided when identifying medicinal products and redundant information does not have to be repeated. For example, if a MPID is provided, there is no need to provide a PhPID. Likewise, if a PhPID is provided, there is no need to provide information for substance. The decision tree provided in figure 6 should be used for entering medicinal product information in the relevant E2B(R3) drug data elements. Although the free text 'Medicinal Product Name as Reported by the Primary Source' (E2B(R3) G.k.2.2) is a mandatory data element, the sender of the ICSRs should attempt to code the verbatim text using ISO IDMP identifiers where possible. If appropriate, structured name parts should be provided as well. If the sender can answer 'yes' to a question listed in the diagram below this is the information that should be provided in the ISO ICSR message in addition to the product name as provided by the primary source. If the answer is 'no' then the sender should progress to the next question (figure 6):

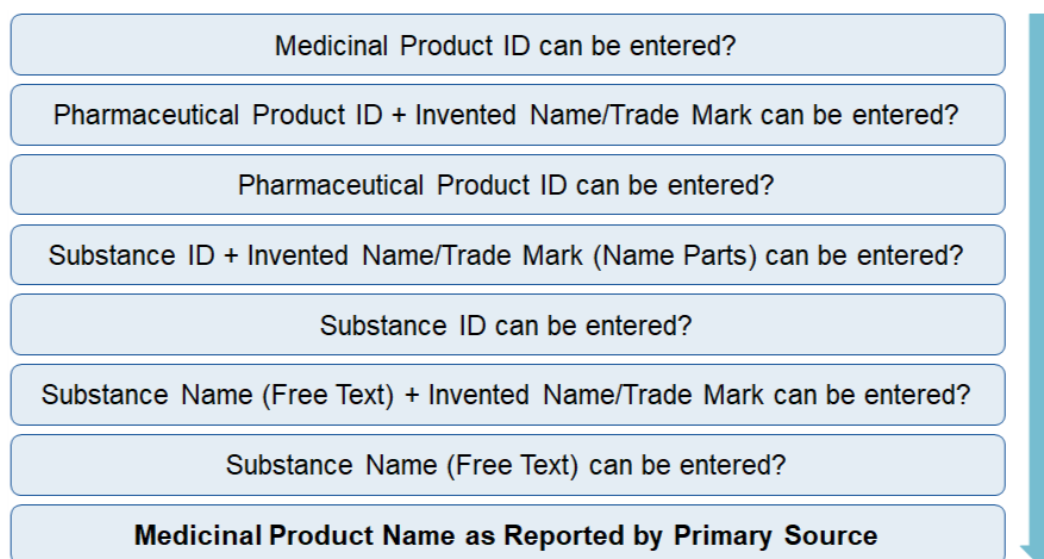


Figure 6. EU ICSR decision tree for entering medicinal product information

4.2 General considerations for selection of MPIDs

The MPID is the most specific level of product identification in the ICSR. However, given the specificity of the MPID, there are limitations in coding the free text drug verbatim to MPID level. According to the ISO IDMP 11615 standard, a new MPID can be assigned to a product following a substantial change in the product (e.g. change in indication) but also for more administrative reasons (e.g., change in

marketing authorization holder). The EU ICSR Implementation Guide states that the MPID should only be used when the information provided by the reporter (a) includes the MPID, or (b) if enough information is provided by the reporter so that the correct MPID can be selected unambiguously (EMA, 2021a). It is expected that the first situation, where an MPID is provided directly by the reporter, will become more relevant over time, with MPIDs being available for example via the patient medication record or via barcode scanning of the product (see Recommendation 6.4). In the second situation, one should be very careful in selecting the MPID, even when the drug verbatim is very specific. The lack of stability of an MPID and the complexity of its constitution means that many drug verbatims cannot have an MPID accurately coded based on the information provided if more than 1 MPID would be available for that product.

Example:

A suspected ADR was reported for 'ellaOne 30 mg tablet'. There is only one such product licensed in the EU. The legal status of supply changed from prescription only to over the counter, which also led to assignment of a new MPID. Based on the drug verbatim it will not be possible to accurately select an MPID for the ICSR.

Example:

The Croatian Drug Agency HALMED received an ADR report with drug verbatim 'Paclitaxel Pliva'. There is only one product called Paclitaxel Pliva on the Croatian market thus it would be imputed that it is 'Paclitaxel Pliva 6 mg/ml koncentrat za otopinu za infuziju'. If this product has only 1 MPID, it is possible to use this in the ICSR.

If there is not sufficient information available from the case or the context to select the correct MPID when multiple MPIDs are available, one should select the most precise PhPID level.

Of note:

As a general rule, the MPID should be selected:

- ▶ As long as a medicinal product has only one MPID; *AND*
- ▶ The drug verbatim provides sufficient details; *AND/OR*
- ▶ Sufficient details can be imputed from the context provided.

Specific consideration should be given to seasonal vaccines, such as Flu vaccines. For a seasonal influenza vaccine, the strains can change with the season. This implies that a new MPID shall be assigned for this vaccine each time the strains are changed. Details of vaccines administered are often not available to the vaccinee, resulting in a non-specific drug verbatim when reporting an ADR. Nevertheless, it may be possible to select MPIDs using contextual information such as the date of administration of the vaccine, the region, and knowledge on the specific vaccines used in a vaccination programme, as illustrated by the Flu vaccine example in section 4.4.1.

Organisations creating ICSR messages should not modify the MPID information based on the territory of the receiving organisation. If a case from the USA has the local MPID (provided by FDA), this should not be replaced with an equivalent EU MPID, just for the purpose of submitting to EudraVigilance.

4.3 General considerations for selection of PhPIDs

The PhPID is the next level precision down from the MPID. Depending on the level of detail provided in the drug verbatim and/or contextual information, the most accurate PhPID level should be coded. The information that is needed to code more precise levels of PhPID may be known from the drug verbatim or may be imputed based on contextual information such as country, as explained in section 4.4.1.

At the time of writing this document, several details of generating PhPIDs are still under discussion, for example on how to express dose form and strength. Different proposals would result in a more or less granular PhPID. The sample set of drug verbatims demonstrated that the information on the drug can also be more or less specific. In view of this uncertainty around PhPID generation, not all potential options for PhPIDs are discussed in detail in this document. For the purpose of this guidance, it is assumed that sets of PhPIDs will be available at all substance levels (base and salt/modifier level) and will be generated using the pharmaceutical dose form (table 4):

Table 4. PhPID sets based on substance level

PhPID level	PhPID set for substance base	PhPID set for substance with salt
PhPID L1	Ibuprofen	Ibuprofen lysine
PhPID L2	Ibuprofen 400mg	Ibuprofen lysine 684mg (equivalent to ibuprofen 400mg)
PhPID L3	Ibuprofen tablet	Ibuprofen lysine tablet
PhPID L4	Ibuprofen 400mg tablet	Ibuprofen lysine 684mg (equivalent to ibuprofen 400mg) tablet

Example:

A drug verbatim 'ibuprofen' would be coded with PhPID L1 for 'ibuprofen' (from the PhPID set for the substance base). A drug verbatim of 'ibuprofen lysine' would be coded with PhPID L1 'ibuprofen lysine' from the PhPID set for the substance/salt, as appropriate.

Example:

MAH Servier has announced that their branded versions of perindopril erbumine (Coversyl® and Coversyl Plus®), also known as perindopril tert-butylamine, have been discontinued and replaced with a different salt called perindopril arginine (Coversyl arginine® and Coversyl arginine Plus®). The two salts are not directly equivalent. Perindopril arginine 2.5mg, 5mg and 10mg per day, correspond to perindopril erbumine 2mg, 4mg and 8mg per day, respectively.

The marketing authorization number of both products remain the same, however, new MPIDs are assigned. The product will also have a new set of PhPIDs assigned for the substance perindopril arginine.

When an ADR is reported for 'Coversyl', there is not enough information to select an MPID. Only a PhPID L1 for 'perindopril' can be selected as it is not known which salt is applicable. Also the TMK name part data element should be populated.

4.4 General principles for coding medicinal products

Consistent coding of medicinal products in ICSRs promotes accurate documentation of ICSRs, facilitates efficient data sharing and supports signal detection and signal analysis activities. In general, when the drug information provided in an ICSR cannot be coded because of confusing information (e.g., a drug class is provided), efforts should be made to follow-up the case in order to collect the missing information regarding the suspected medicinal product. Coding to MPID or PhPID level should be done at the most precise level possible. It should be acknowledged that unambiguous identification of the medicinal product is not always possible: depending on the source and method of ADR data collection, the drug verbatim can have different levels of precision and relevant contextual information to aid identification of the product may not be available.

4.4.1 Use of context

The use of (in particular) free text and/or non-internationally standardised terms for medicinal product information leads to a wide variation of drug terms transmitted in data element G.k.2.2 (Medicinal Product Name as Reported by the Primary Source). Selection of MPIDs or PhPIDs while adhering as close as possible to the drug verbatim may lead to loss of relevant information that may be known/imputed from the context. This is illustrated by the following examples:

Example:

A suspected ADR is reported to LAREB (Dutch pharmacovigilance centre) with the drug verbatim '0.9 NaCl'. In the Netherlands there is only one 0.9 NaCl product marketed, namely 0.9 NaCl Baxter. As the case originates from The Netherlands and at that point in time there was only one product marketed, the receiver may assume that this report concerns 0.9 NaCl Baxter. Imputing this information may contribute to selection of a more precise level of PhPID or a MPID.

Example:

A consumer contacts Janssen Pharmaceuticals about an ADR with 'methylphenidate 18mg'. Methylphenidate is the suspected medication, therefore the MAH can assume that the report concerns their own methylphenidate product (Concerta 18mg tablets with prolonged release) and select the appropriate IDMP identifier (at least PhPID Level 4, or MPID if appropriate). However, if the ADR was reported to the national pharmacovigilance centre, other methylphenidate 18mg products should be taken into account and only the PhPID L2 would be coded.

Example:

Country A has received a report of a suspected ADR associated with a covid-vaccine. The report does not specify the name of the vaccine. At the time of vaccination, the only covid vaccine available in Country A was Comirnaty (Pfizer) mRNA vaccine. By using this background knowledge, a PhPID Level 4 could be imputed. As long as only 1 MPID would be available for the Comirnaty (Pfizer) mRNA vaccine, even the MPID could be imputed. Without using contextual information, based on only 'covid vaccine' as drug verbatim it would not even be possible to code PhPID level 1.

Example:

The electronic health record (EHR) system in country B facilitates ADR reporting to the national competent authority. This reporting mechanism provides reliable drug verbatims, which are retrieved directly from the patient's medication record that is using the National Medicinal Product Dictionary.

Example:

In December 2019 a consumer contacts a national pharmacovigilance centre to report a suspected ADR for the yearly flu vaccine that was administered a week ago. As it is known which flu vaccine is administered in the yearly flu vaccination programme in that region, the MPID for the influenza vaccine with the Medicinal Product Name "Drug-FLU season 2019/2020" can be selected for ICSR Drug sSection G.k.

The consumer also reports that he experienced a similar ADR with the flu vaccine administered in December 2018. Based on the knowledge which flu vaccine is administered in the yearly flu vaccination programme in that region, the MPID for the influenza vaccine with the Medicinal Product Name "Drug-FLU season 2018/2019" can be selected for ICSR Section D.8 'Relevant Past Drug History'.

The primary receiver of the case is of relevance when selecting the PhPID or MPID. If the NCA/regional/national pharmacovigilance centre is the primary receiver, one needs to take into account the products that are available in their territory. If the MAH is the primary receiver one should consider whether the suspected medication concerns their own product, even if this is not stated within the verbatim, or whether the report may concern a product of another MAH. For reported co-suspect and/or comedications, the MAH cannot assume that these involve their own product and the products available in the country should be taken into account.

Also, the country of reporting can be of relevance when selecting the PhPID/MPID. In general, the marketing status of the product in the country of reporting should be taken into consideration. Exceptions should be made in situations where the reporter specifies that the medicine has been obtained abroad or when a medicinal product appears to have no marketing authorisation in the country of reporting. Indication for use (as mentioned by the reporter) may help to specify a product with a non-unique brand name (see also section 4.5.1).

Of note:

The 'imputed drug information' is based on the drug verbatim as provided by the reporter (primary source) and takes into account contextual information to achieve a more precise level of drug identification (figure 7).

Contextual aspects to be taken into consideration, either alone or in combination:

- ▶ Primary receiver
- ▶ Country
- ▶ Reporting mechanism
- ▶ Timing/context of drug administration

The imputed drug information is used as the basis for selecting MPIDs and PhPIDs (with/without name parts).

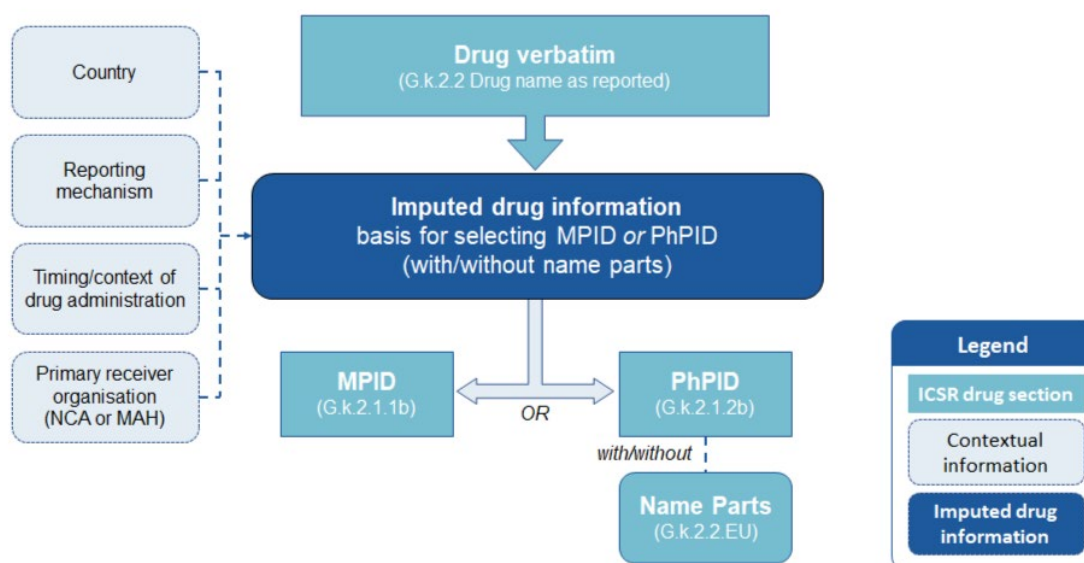


Figure 7. Flow chart of using Imputed Drug Information to select MPID or PhPID

4.4.2 Use of historic identifiers

In some occasions, adverse drug reactions associated with drugs that have been taken a long time ago are retrospectively reported. The use of historic identifiers is not only relevant to select the most specific PhPID or MPID in Section G.k. of the ICSR, but also for Section D.8. Relevant past drug history (as shown in the example for the seasonal flu vaccine).

Example:

In 2013, triggered by a newspaper article about a possible risk of long-term developmental effects in children born to women treated with valproate, a mother is contacting the national pharmacovigilance centre to report ADHD as a suspected ADR for her 20-year-old son. The mother used valproate (specified by strength, dosage form and brand) during her pregnancy for treatment of epilepsy.

In this example of retrospective reporting for valproate (assuming that no historic MPID is available), there is sufficient information to code to PhPID L4 and provide the trade name in the 'TMK' name part data element.

If no appropriate identifiers are available at all (either current or historic), free text should be provided in the ICSR. It is expected that coding 'historic MPIDs' will only become relevant over time. Baseline MPIDs will be generated via PMS once PMS goes live, based on the information that is valid for a product at that point in time, and new MPIDs will be generated moving forward.

When taking contextual aspects into account, imputation of elements relevant to the medicinal product is considered appropriate as this leads to the selection of a more precise PhPID or a MPID and relevant information will not be lost when reliable contextual information is used. This approach is different from coding reaction/event verbatims in MedDRA®. The MedDRA Term Selection: Points to Consider document states that the lowest level term (LLT) should be selected that most accurately reflects the reported verbatim information and that no information should be added (e.g., do not infer medication error, lack of efficacy, etc) (MedDRA, 2021). Furthermore, non-current terms should not be used for MedDRA term selection.

In the following sections, guidance is provided on how to deal with uncertainties and imputation of information during the selection of PhPIDs or MPIDs when coding medicinal product information in ICSRs.

4.5 Points to consider when selecting MPID or PhPID based on a drug verbatim

4.5.1 Verbatims with brand name

A drug verbatim may be provided as the brand name, either alone or in combination with other name parts. When only one product (one pharmaceutical form, one strength) is available on the market and only one MPID is available (as explained in section 4.2), one may use this knowledge to impute the MPID or the most specific level PhPID L4, even if other name parts, such as strength and pharmaceutical form, are not mentioned in the verbatim.

Example:

An ADR with drug verbatim 'Opdivo' is reported to a national pharmacovigilance centre. Only one Opdivo (nivolumab) product is licensed, namely 'Opdivo 10mg/ml, concentrate for infusion'. The MPID can be selected as long as the product has been assigned only 1 MPID. When multiple MPIDs have been assigned, in this situation even when the drug verbatim has only stated the brand name, the most specific PhPID level (PhPID L4, corresponding to nivolumab 10mg/ml concentrate for infusion) can be selected by imputing strength and pharmaceutical form.

4.5.1.1. Brand name with different compositions depending on the country

When multiple medicinal products exist with the same brand name but contain different active substances in different countries, and only the brand name is provided, it is important to take various aspects into account when populating the drug section. According to the EU ICSR Implementation Guide (EMA, 2021a), it is important to take into consideration the data element 'Identification of the Country Where the Drug Was Obtained (ICH-E2B(R3) G.k.2.4) if available'. If not available, the country of the reporter (ICH E2B(R3) data element Primary Source for Regulatory C.2.r.5) can be used. If this is not available, coding should be based on the composition of the product in the country where the reaction/event occurred. Also indication for use (as mentioned by the reporter) may help to identify a product with a non-unique brand name.

Example:

A German ADR report for the drug 'Carmen' would be coded with PhPIDs that are relevant to lercanidipine (assuming that the drug was also obtained in Germany). However, an Irish ADR report for the drug 'Carmen' would use PhPIDs for the combination of drospirone and ethinylestradiol (assuming that the drug was also obtained in Ireland).

Example:

A reporter might state "Avastin was taken for the indication of non-small cell lung cancer". Avastin as the brand name is available from different manufacturers with different active substances:

- ▶ Avastin - Bevacizumab (monoclonal antibody)
- ▶ Avastin - Simvastatin (HMG CoA reductase inhibitor)
- ▶ Avastin - Atorvastatin (HMG CoA reductase inhibitor)

In this example, since the indication was for cancer, it can be assumed that the Avastin - bevacizumab is the most appropriate to capture, whereas the other two Avastins are for lowering cholesterol.

If no MPID can be selected, the PhPID for bevacizumab should be selected and the TMK name part data element should be populated with 'Avastin'.

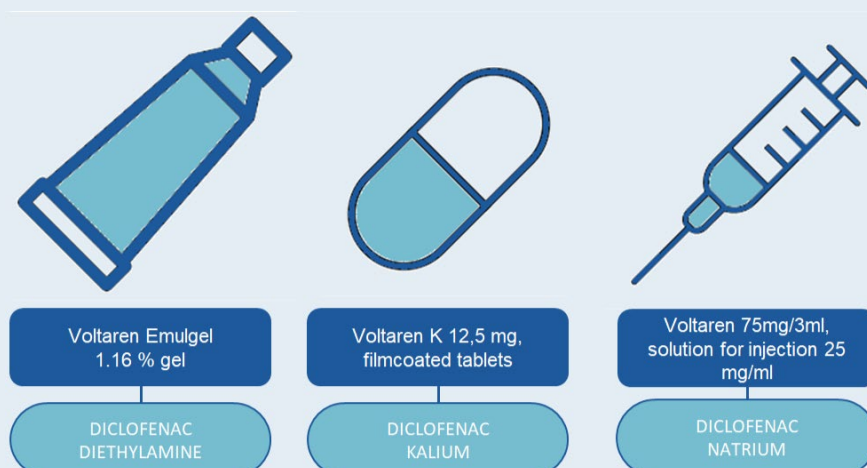
4.5.1.2. Brand name with different compositions in a single country

A brand name may refer to a range of products. When a brand has different compositions in a single country, and a drug verbatim provides only this brand name without information on its active substance(s) or its pharmaceutical form, it is not possible to code unambiguously.

Combining the guidance in GVP VI (EMA, 2017) (stating that all active substances which are in common to all pharmaceutical forms/presentations in the country of authorisation) and the EU ICSR decision flow (figure 6) results in selection of PhPID L1 (if available).

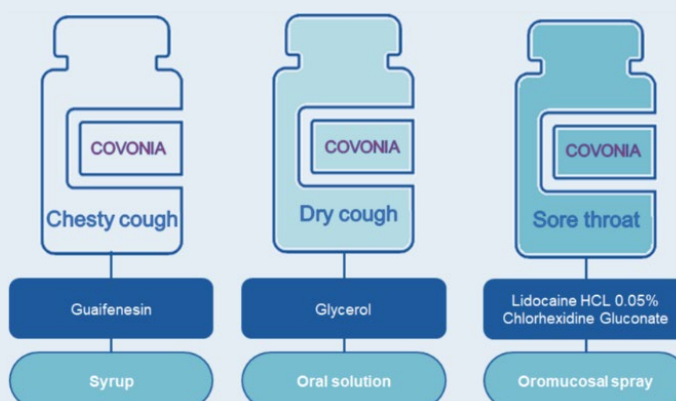
Example:

A report with drug verbatim 'Voltaren' should be coded with PhPID L1 for 'diclofenac' (if available) as this is common to all pharmaceutical forms/presentations.



Example:

A report of a suspected ADR with a drug verbatim 'Covonia' without any further details cannot be coded. In this situation only data element G.k.2.2 'Medicinal Product Name as Reported by the Primary Source' (the drug verbatim) should be populated. The GVP VI recommendation to provide active substances which are common to all presentations does not apply.



4.5.2 Products with multiple active substances

According to ISO standard 11616, products that consist of multiple active substances will have PhPIDs reflecting the combination of active substances. Excipients are not reflected in the PhPID.

Example:

Separate sets of PhPIDs are available for pioglitazone mono products, metformin mono products, and pioglitazone/metformin combination products.

A capsule containing 15mg pioglitazone and 850mg metformin has the following PhPID set:

PhPID L1 → pioglitazone + metformin

PhPID L2 → pioglitazone 15 mg + metformin 850 mg

PhPID L3 → pioglitazone + metformin capsule

PhPID L4 → pioglitazone 15 mg + metformin 850 mg capsule

Example:

Afrin 0.5mg/ml nasal spray contains the active substance oxymetazoline hydrochloride. There are different presentations, such as a chamomile version that contains glycerol and chamomile flavour as excipients. A drug verbatim of 'Afrin chamomile nasal spray' can be coded to PhPID L3 for oxymetazoline hydrochloride nasal spray'; the chamomile flavor excipient is not used for generating PhPID.

Example:

Amlodipine/perindopril fixed dose combinations are available as amlodipine besilate with perindopril arginine, perindopril tert-butylamine or perindopril tosilate and PhPID sets will be available for these precise combinations accordingly. Coding a drug verbatim of 'amlodipine besilate/perindopril' raises the challenge that it is not clear which perindopril is involved. If it will not be possible to select a PhPID (if no PhPID will exist for this partly imprecise combination), SIDs for 'amlodipine besilate' and 'perindopril' will have to be used.

- ▶ SIDs should be used instead of PhPIDs in this particular example, as coding amlodipine besilate and perindopril as separate PhPIDs would lead to creating multiple drug sections in the ICSR (see Figure 4), whereas there is only one drug involved.

Example:

Coding the drug verbatim 'Aspirin + Vitamin C' will have to take into account that Vitamin C is an active substance and should lead to selection of a PhPID L1 for 'aspirin/vitaminC'.

Example:

A drug verbatim 'NovoMix 30' refers to the product name 'NovoMix 30' (30% insulin aspart and 70% insulin aspart protamine). NovoMix 30 belongs to a range of insulin medicines containing the active substance insulin aspart (100 units/ml) combined with protamine to make it longer acting. Based on this verbatim a PhPID L4 can be selected.

4.5.3 Drug verbatims with strength and dose

Drug verbatims may contain numbers that correspond to the product strength, which helps in selecting a more accurate PhPID. It should be considered that numbers may not always correspond to product strengths, but are part of a product name or rather reflect a dosage regimen. Drug verbatims may also contain additional statements to indicate dosing frequency, e.g., 'on mornings'. Additional information in the case information on dosage may help distinguishing between strength and dosage and may subsequently help in selecting appropriate PhPID levels. In some situations a statement on a dose (1st, 2nd dose) may even be relevant for selecting a specific pharmaceutical product.

Example:

A small number of medicines are only taken weekly e.g. oral methotrexate, or are formulated to be taken once weekly instead of once daily e.g. alendronate 10mg daily/alendronate 70mg once a week. When receiving a drug verbatim 'alendronate 70mg once a week' it is not known whether the patient took an oral solution or an oral tablet (two tablets of 35 mg versus one tablet of 70 mg). Based on this verbatim only a PhPID L1 for alendronate can be selected and the dosage should be captured in the ICSR dosage data elements.

Example:

Sputnik V (a COVID-19 vaccine, also known as Gam-COVID-Vac) uses different adenoviruses, called rAd26 and rAd5, for the first and second doses, respectively. A drug verbatim of 'Sputnik V – second dose' should lead to selection of the PhPID that reflects the rAd5 adenovirus.

At time of writing this guidance there is ongoing discussion whether the PhPID generation should use 'presentation strength' or 'concentration strength', or both (see Recommendation 6.1).

4.5.4 Drug verbatims with route of administration and/or dose form 'intended site'

The drug verbatim can mention an 'intended body site' as part of the dose form, for example ear spray, eye drops, nasal spray. This should be handled different from 'route of administration'. EDQM has defined the 'intended site' as 'the general body site at which a pharmaceutical product is intended to be administered, for example auricular, ocular and oral. The intended site is a general term that is used to group related pharmaceutical dose form concepts, and is not intended to describe a precise site or route of administration.' The current understanding is that PhPIDs will become available that can reflect the intended site, as the PhPID generation will be based on the 'pharmaceutical dose form' (and not on 'basic dose form'). Therefore, when a drug verbatim reflects the intended site matching the dose form, this will be captured as part of the PhPID (figure 8).

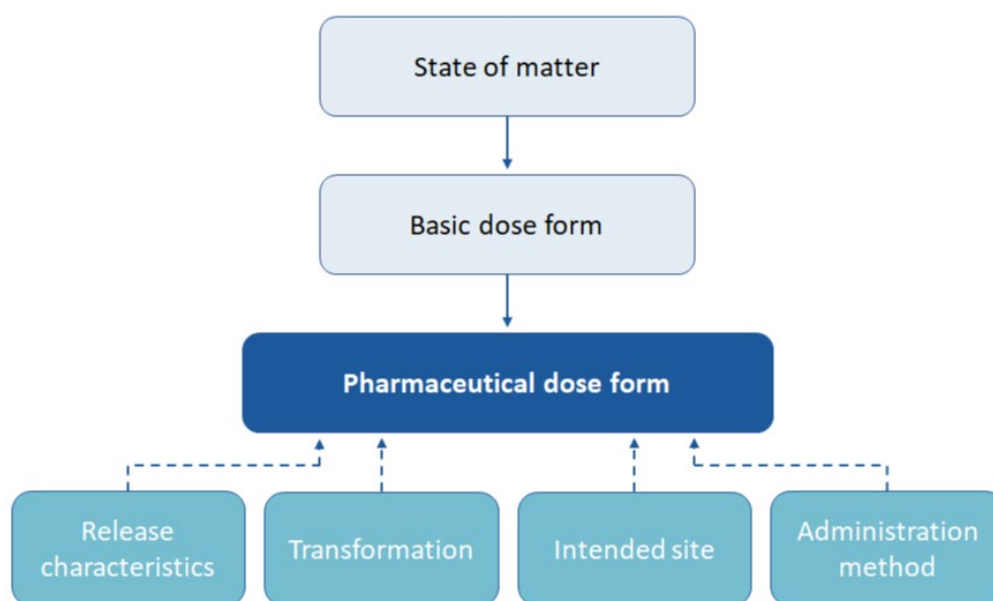


Figure 8. Hierarchy of the pharmaceutical dose form, arranged according to the state of matter and basic dose form, and further characterised by release characteristics, transformation, intended site, and administration method (adapted from EDQM, 2018).

Example:

In the PhPID for 'beclometasone nasal spray' the intended site as part of the pharmaceutical dose form is 'nasal'.

In the PhPID for 'fentanyl transdermal patch' the intended site as part of the pharmaceutical dose form is 'transdermal'.

'Route of administration' has been defined by EDQM as the 'path by which the pharmaceutical product is taken into or makes contact with the body, for example intravenous use, oral use, ocular use, oromucosal use'. A drug verbatim may seem to reflect the route of administration, for example when this is part of the official medicinal product name as licensed and shown on the package. However, the route of administration is not part of the PhPID generation. When receiving a drug verbatim with a route of administration, this can be ignored for selecting the PhPID.

Example:

Dehydrobenzperidol is available as solution for injection, separately for intravenous (IV) and intramuscular (IM) use. The same PhPID will be selected for drug verbatim 'dehydrobenzperidol IM solution for intramuscular injection 2,5mg/ml, solution for injection' and for 'dehydrobenzperidol IV solution for intravenous injection 2,5mg/ml, solution for injection'.

It should be noted that the actual path through which the patient received the medicine may be different from the authorised route of administration. For example, when there is a need for parenteral administration or when a medication error has occurred. A special situation to consider is when a child/foetus has been exposed to a medicine via maternal exposure (transmammary or transplacental routes of administration). Therefore, it is not considered good practice to automatically populate the ICH E2B(R3) specific data element for route of administration (G.k.4.r.10) based on the drug verbatim.

Example:

The ADR 'dry eyes' is reported with the suspected drug verbatim 'ofloxacin 3mg/ml, 0.5ml. Ofloxacin is an antibiotic used for eye and ear infections, available as drops. Both eye drops (Trafloxal and generic product available) and ear drops (Otiflox) have a strength of 3mg/ml and a dosage of 0.5ml for one time usage. Even if route of administration or indication are provided, one should be very careful in selecting PhPIDs or MPIDs, as off-label use and/or medication error cannot be excluded (e.g., eardrops were accidentally administered to the eye).

Example:

A parent-child report involves a breast-feeding infant who experienced slightly elevated TSH (thyroid stimulating hormone) after being exposed to lithium through the mother. It was reported that the mother used '3 tablets of 400mg lithium daily'. Based on this drug verbatim PhPID L4 for lithium 400mg tablets should be selected as suspected medication. The route of administration (G.k.4.r.10.) for the patient who experienced the ADR (the infant) is 'transmammary'. The route of administration for the mother ('oral') should be captured in data element Parent Route of Administration (G.k.4.r.11)

4.5.5 Drug verbatims with acronyms, abbreviations and synonyms

Abbreviations and acronyms are frequently used (for example for drug prescriptions), and may refer to the substance, dosage form and also route of administration. When a prescription is used as a basis for reporting a suspected ADR, such abbreviations and acronyms may be used as drug verbatim. It is possible to code a PhPID (or (Specified) SID if necessary) based on the acronym/abbreviation, although with caution. Where possible, relevant reference information (e.g., from health care professional

organisations) should be used to ascertain the correct interpretation of the acronym/abbreviation. When it is not possible to interpret the acronym, clarification of such terms should be requested, preferably at the time of data collection. When acronyms refer to a treatment regimen (such as chemotherapy regimens, where the acronym 'XELOX' is used to refer to a treatment with oxaliplatin and capecitabine) this should be split into IDMP codes for the individual medicines.

Example:

A rheumatologist reports a suspected ADR for 'MTX 30mg'. In this specialism the acronym MTX is widely used for methotrexate and PhPID L2 for methotrexate 30mg can be selected.

Example:

A suspected ADR is reported for 'azelastine 0.5mg gtt.'. The abbreviation 'gtt' is used on prescriptions for 'guttae', meaning 'drops' in Latin. Azelastine is available in eye drops and nasal spray. The addition of 'gtt' in the drug verbatim is therefore very likely to refer to 'azelastine 0.5mg eye drops'. The use of this information results in selecting a more granular and detailed PhPID 4.

Example:

An ADR is reported for 'perindopril tert-butylamine'. This is a synonym for the substance 'perindopril erbumine'.

Example:

An ADR is reported for 'Nitro drip'. As it is not clear whether this drip contained nitroglycerin or nitroprusside, it is not possible to assign any IDMP identifier.

Abbreviations in the drug verbatim can also be part of the officially licensed product name, for example reflecting the trademark (e.g., AL, EG), combined medication/other ingredients (e.g.: HT, HTZ) or duration of action (e.g., SR). These should be handled as product name parts, see section 4.6.

4.5.6 Excipients

The EU legislation [DIR Art 1(3b)] defines 'excipient' as 'any constituent of a medicinal product other than the active substance and the packaging material', for example colouring matter, preservatives, adjuvant, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances. Adverse reactions can occur with the excipients, for example allergies, lactose intolerance or effects of sugar in diabetic patients. Excipients are not taken into consideration for generating PhPID, but it is expected that

(Specified) SIDs will become available for excipients. GVP Module VI provides guidance for the situation where the reporter (primary source) suspects a possible causal role of one of the excipients of the suspected medicinal product (EMA, 2017).

In this situation, the ICSR Drug Section G.k. 'Drug(s) Information' should be repeated:

- ▶ One entry for the information on the suspected medicinal product
- ▶ A separate entry specifying the suspected excipient. The (Specified) SID for the excipient should be used if available, otherwise free text should be used.

This suspicion of an ADR with the excipient should also be specified in the ICSR case narrative. GVP Module VI further recommends that if available, tests results (positive or negative) in relation to the causal role of the suspected excipient should be included in the ICSR Section F.r 'Results of tests and procedures relevant to the investigation of the patient'.

Example:

When receiving a case of an allergic reaction to tartrazine as an excipient in 'Claritromycine ratiopharm 250 mg, filmomhulde tabletten' the drug section in the ICSR should be repeated and populated as follows:

The first iteration of Drug Section G.k should provide:

- ▶ G.k.2.2 Medicinal Product Name as Reported by the Primary Source: 'Tartrazine excipient of Claritromycine ratiopharm 250 mg, filmomhulde tabletten'
- ▶ PhPID L4 for clarithromycine 250mg filmcoated tablet (if coding MPID is not possible)
- ▶ Name parts: SCI = Claritromycine; TMK = ratiopharm; STR = 250 mg ; FRM = filmomhulde tabletten

The second iteration of Drug Section G.k. should provide:

- ▶ G.k.2.2 Medicinal Product Name as Reported by the Primary Source: 'Tartrazine excipient of Claritromycine ratiopharm 250 mg, filmomhulde tabletten'
- ▶ Data element G.k.2.3.r.b can be used if the (Specified) Substance ID for the excipient is available, otherwise 'tartrazine' can be provided as free text in data element G.k.2.3.r.1 Substance/Specified Substance name.

4.5.7 Combination packs ('kits')

A medicinal product may contain one or more "pharmaceutical product(s)" (e.g., a kit containing vaginal tablets 500 mg and a vaginal cream 1%, or a kit containing a combination of norethindrone acetate and ethinyl estradiol tablets and ferrous fumarate tablets). When receiving a drug verbatim for these medicinal product 'kits', it is important to be aware how PhPIDs are assigned according to the ISO 11616 standard:

- ▶ Multiple products packaged as a kit and administered as separate medicinal products
 - ▶ A kit containing multiple products that are intended to be administered independent of each other (e.g., at different time intervals in a particular order) will have separate sets of PhPIDs for each product contained within the kit.
- ▶ Multiple products packaged as a kit for reconstitution and administered as one medicinal product
 - ▶ Multiple products packaged as a kit (combination pack) with the intent of being administered as one medicinal product, will have one overarching set of PhPID for the medicinal product at the level of the kit. A combination pack with a powder for solution for injection, and a solvent for solution for injection will have one PhPID assigned using the the administrable dose form of solution for injection.
- ▶ Components of kits not packaged together
 - ▶ A medicinal product authorised to be marketed as a kit with all components to be reconstituted and intended to be administered as one product (as approved by a regulatory authority, for example radiopharmaceutical kits where the radiopharmaceutical components of the kit would not be packaged together due to safety reasons) will have one set PhPIDs using the administered dose.

Example:

A report is received where the suspected ADR occurs immediately after administration of a vaginal tablet, which is part of a clotrimazole kit containing vaginal tablets 500 mg and a vaginal cream 1%. This medicinal product kit will have the following PhPIDs:

	Tablet	Cream
PhPID L1	Clotrimazole	Clotrimazole
PhPID L2	Clotrimazole 500mg	Clotrimazole 1%
PhPID L3	Clotrimazole tablet	Clotrimazole vaginal cream
PhPID L4	Clotrimazole 500mg tablet	Clotrimazol 1% vaginal cream

Based on the drug verbatim, PhPID L4 for 'Clotrimazole 500 mg' tablet should be selected.

4.5.8 Drug classes, other therapies and non-medicinal products

Potentially, drug verbatims can refer to drug classes, other administered therapies (such as radiotherapy), dietary supplements or food products for which no IDMP identifiers will become available. Where an ADR is suspected to be related only to a therapeutic class, the case is considered incomplete and does not qualify for submission as ICSR. Efforts should be made to follow-up the case in order to collect the missing information regarding the suspected medicinal product. When concomitant therapies and products are reported that cannot be structured in ICSR Drug Section G.k., then the data element D.7.3 'Concomitant therapies' should be set to 'true' and details should be provided in the case narrative Section H.1

More detailed guidance on how to include this information in the ICSR is available in GVP Module VI, section C.6.2.2.2. Information on suspect, interacting and concomitant medicinal products (EMA, 2017):

- "Where the medicinal product cannot be described on the basis of the active substances or the invented names, for example when only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should only be reflected in the case narrative. The information should not be included in the structured data elements of the medicinal product name or the active substance name(s). The same applies if a suspected food interaction is reported (e.g., to grapefruit juice)."

For drug/food interactions or interactions with other non-drug compounds GVP Module VI states that only information on the suspected interacting medicine should be included in ICH E2B section G.k.'Drug information'. The information concerning the interacting food or other non-drug compounds should be provided in the case narrative (EMA, 2017).

Example:

A report where 'benzodiazepine' is mentioned as the only suspected drug is not a valid case and should not be submitted as an ICSR. 'Benzodiazepine' as concomitant medication should be mentioned in the case narrative. Data element D.7.3 'Concomitant therapies' should be set to 'true' and details should be provided in the case narrative Section H.1.

4.5.9 Verbatims with herbal drug names

EU legislation on pharmaceutical products for human use also applies to traditional herbal medicines. Herbal medicinal products are defined as any medicinal product, exclusively containing as active ingredients one or more herbal substances, one or more herbal preparations, or a combination of the two. Herbal medicines contain pharmacologically active ingredients, some of which have been

associated with adverse effects, for example aristolochic acid and nephropathy. ADRs may also result from interactions between conventional medicines and herbal medicines.

Although herbal products in some jurisdictions outside EU are not regulated as medicinal products, this major class of products is covered by the IDMP standards. It is expected that MPIDs, PhPIDs and SIDs will become available for herbal drugs over time. Based on the drug verbatim, the most precise IDMP identifier should be selected for the ICSR according to the general principles explained in sections 4.2 - 4.4 of this guidance.

The drug verbatim may reflect product brand names, common names (e.g., St John's wort), or botanical names (e.g., *Hypericum perforatum*). One should be aware of synonyms and that even a common name as 'ginseng' is ambiguous, being associated with drugs derived from at least 12 plants with differing chemistries (Dauncey et al, 2016). It can also be relevant to know which part of the plant is used (e.g., leaf versus root): as the profile of chemical constituents is different in different plant parts, they are considered to be different herbal drugs.

Of note:

Kew's Medicinal Plant Names Services (MPNS, mpns.kew.org) captures all pharmaceutical, common and scientific names (including synonyms) employed for herbal drugs in 150 major medical references, regulatory data sets and pharmacopoeias (Allkin, 2016). This can be a useful resource for pharmacovigilance centres when asking questions to the reporter to increase the clarity and accuracy of an ambiguous herbal drug verbatim.

If herbal medicinal products are not appropriately identified in the ICSR, signals may be generated from reports that mention a particular name e.g., *Aristolochia*, but in fact refer to different plant species or parts with different constituents (Allkin & Patmore, 2018). This is illustrated by the example from WHO below. The reverse may also happen. Signals may be missed if reports referring to the same ingredient are not brought together.

Example:

A company has for years produced a product containing *Senna alexandrina* Miller, which in the labelling is called "Cassia". Another company markets a product that also lists "Cassia" as active ingredient but the product is derived from *Senna armata* Wats, a different botanical species. Then reports of serious ADRs associated with "Cassia" appear and they are so serious that a withdrawal from the market is considered. It may be that only *Senna armata* Wats is causing these problems. In this case the other species, *Senna alexandrina* Miller, risks being wrongly accused because there is no distinction between the labelled names: "Cassia" is the suspected cause (WHO, 2004).

4.6 Use of Name Part elements

Section 2.3.2 of this document describes the product Name Part data elements which are available as EU specific data elements in the Drug Section (G.k.2.2.EU) and in the Relevant Past Drug History (D.8.r.1.EU) of the ICSR. Populating ICSR name part elements is considered useful when no PhPID can be selected, or when a PhPID can be selected but more details of the medicinal product name are known from the drug verbatim. The aim of this section is to provide general guidance and principles for using the ICSR name part data elements. More reflections and recommendations on the name parts (including the suggestion to explore a potential alternative) are provided in Recommendation 6.2.

According to the EU ICSR Implementation Guide ‘product name parts should be used if the MPID cannot be selected and if the medicinal product has been reported as a brand/invented name’ (EMA, 2021a). Here, the ‘invented name’ is understood to be the officially licensed name as per section 1 of the Summary of Product Characteristics (SmPC). It is important to note that drug verbatims are often not reported as the brand/invented name and that a drug verbatim may only partially reflect the officially licensed name. For example, reporters may use the product name as shown on the package, which can be different from the officially licensed name as stated in the SmPC.

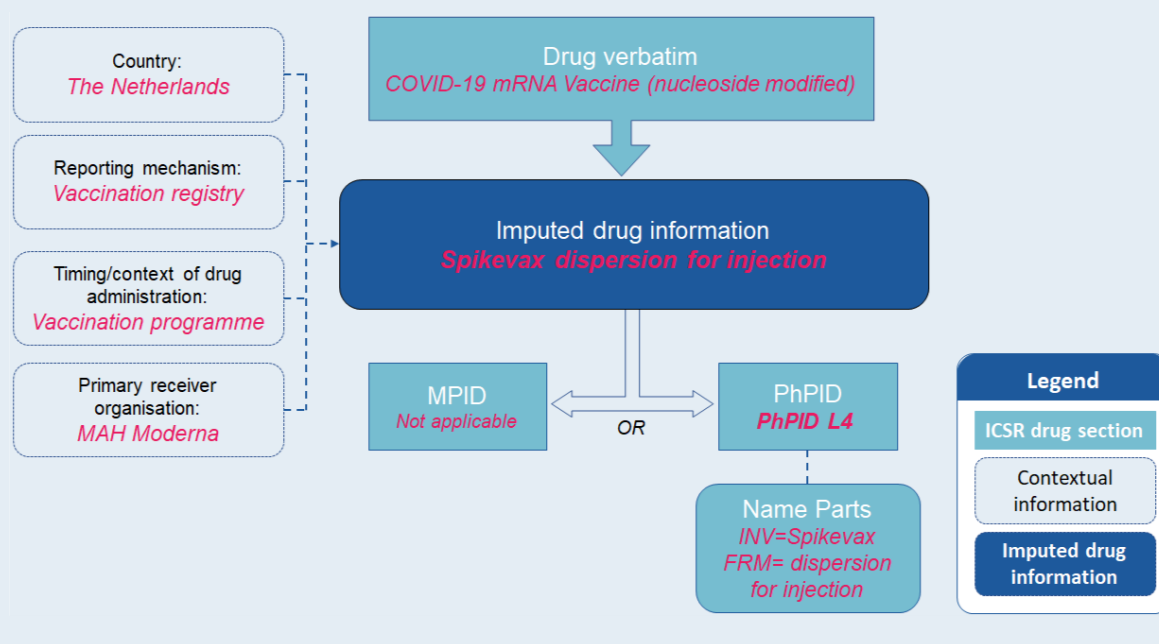
Nevertheless, even if the drug verbatim is not very specific, it may be possible to impute the brand/invented name when contextual information is taken into account as explained in section 4.4. For the primary receiver this ‘imputed level of drug information’ is in practice the basis for selecting the MPID or PhPID as illustrated in figure 7 (section 4.4.1). This figure also illustrates that there is no dedicated data-element for this ‘imputed level of drug information’ in the ICSR message.

Without using name part data elements there is a risk that relevant identifying information on the drug will be known to the primary receiver, but will not be transmitted in the ICSR drug section to any secondary receiver(s). Name Part data elements are particularly informative to secondary receivers when the drug verbatim does not contain a brand/invented name but the primary receiver has more information on the name of the product.

As Name Parts data elements will be used for creating an automatic match between the ICSR and the EMA Product Management System (PMS), it is essential that the free text ICSR Name Part data elements are populated with text strings that exactly match the official product name as stored in PMS. This also implies that there is no need to populate name parts beyond the officially licensed product name.

Example:

'COVID-19 mRNA vaccine (nucleoside-modified)' is used for the Pfizer COVID-19 vaccine (known as Comirnaty) as well as for the Moderna COVID-19 vaccine (known as Spikevax). When receiving a drug verbatim 'COVID-19 mRNA Vaccine (nucleoside modified)' contextual information has to be taken into account for selecting a PhPID. The figure shows that the 'imputed drug information' relates to the Spikevax vaccine, which is used by the primary receiver as the basis for selecting a PhPID. If no name part data elements would be used, the drug section of the ICSR that is transmitted to secondary receiver(s) would not contain any information on the actual brand of the vaccine.



Use of the invented name 'INV' part data element is informative as this captures the brand/invented name which may otherwise not be transmitted (as demonstrated in the Spikevax example above). It is possible that the name parts Scientific Name (SCN), Strength Name (STR) and Form Name (FRM) seem to overlap with information captured in the selected PhPID. It should be noted that the PhPID generation is however based on the actual substance, strength and dose form and not on elements of the product name. The trademark 'TMK' name parts data elements in the ICSR can be very informative to secondary receivers.

Example:

For the drug verbatim 'Tramal Retard' it should be considered that Tramal is available as capsule, solution for injection and tablets. Only tablets are available in a prolonged release formulation (retard) with the following officially licensed product names:

- ▶ Tramal Retard 100mg
- ▶ Tramal Retard 150mg
- ▶ Tramal Retard 200mg

For the purpose of this example, it is assumed that it is not possible to select the MPID. PhPID L3 (tramadol prolonged release tablets) should be selected. Name Part INV (Invented Name) should be populated with 'Tramal'. 'Retard' is considered a dose form and should be captured in the FRM (Form) name part. As the strength is not known the STR (Strength) name part should be left blank. Although it is known that the MAH of the product is Grünenthal, the TMK (trademark) name part data should not be used as this is not part of the officially licensed product name.

Example:

Based on the drug verbatim 'Aciclovir EG 800' at least a PhPID L2 (aciclovir 800mg) can be selected. Knowing that for the 800mg strength only 'tablets' are available in the country where the product was dispensed, a PhPID L4 (aciclovir 800mg tablet) can be imputed.

Based on the officially licensed name of the product involved 'Aciclovir EG 800 mg tabletten' and following the guidance in the EU ICSR Implementation Guide, the ICSR name part data elements should be populated as follows:

- ▶ SCI = Aciclovir
- ▶ TMK = EG
- ▶ STR = 800mg
- ▶ FRM = tabletten

In this example, the 'TMK' (trademark) name part data element with 'EG' is particularly relevant to link the ICSR to the relevant product from MAH Eurogenerics.

For several product name designations such as flavour part (e.g., strawberry), time/period part (e.g., 2020/2021) and combined medication/other ingredients (e.g., DUO)) there is no obvious name part data element available in the ICSR which increases the risk of data entry errors. In order not to lose such information it can be suggested to capture these in the invented name part 'INV'. The drawback of this

approach is that this 'INV' data element will not be an exact match with the information stored in PMS. Further reflections on the Name Part data elements are provided in Recommendation 6.2.

Example:

Sameko Farma is the MAH for three paracetamol 500mg tablet products:

- ▶ Sameko Farma paracetamol 500mg tabletten
- ▶ C1000 paracetamol 500mg tabletten
- ▶ Albert Heijn paracetamol 500mg tabletten

The ICSR submitted by MAH Sameko contains 'paracetamol 500mg tabletten' as the drug verbatim with a corresponding PhPID L4. As Sameko received the report via Albert Heijn supermarket and no other paracetamol brands are sold there, the trademark name part 'TMK' is populated with 'Albert Heijn'. This name part is used to link the ICSR to 'Albert Heijn paracetamol 500mg tabletten'

Example:

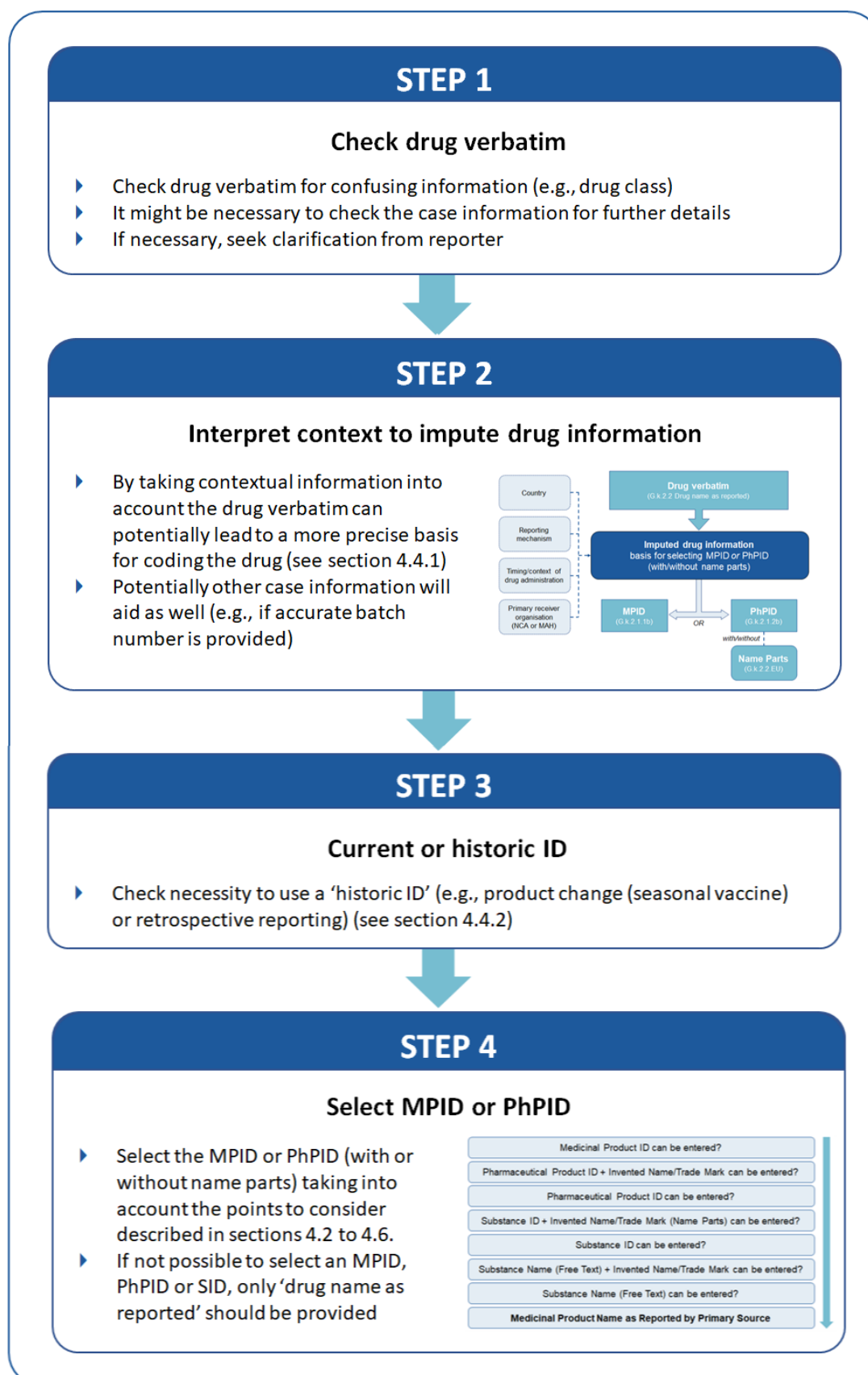
A drug verbatim 'paracetamol 5ml for children' should be coded with the PhPID L1 for paracetamol (note that 5ml is a volume, not a strength, and is not reflected in the PhPID).

In this example, it is assumed that the officially licensed name cannot be imputed (not even partially), as there are many paracetamol products available for the paediatric population, e.g.:

- ▶ Tesco Childrens paracetamol
- ▶ Panadol children
- ▶ Paracetamol paediatric suspension
- ▶ Kids paracetamol
- ▶ Etcetera

Whereas the data entry process may routinely be populating name part data elements, it may not be useful to have the 'intended use' name part element (USE) populated with 'for children' as this will not lead to a reliable match with an officially licensed name.

4.7 Summary of Guidance



5 Considerations for analysis

The processes of data retrieval and analysis are impacted by the level of detail captured via the ISO IDMP identifiers used in the ICSR. The more details are captured at time of data entry, the more options will be available for data analysis. It is important that the pharmacovigilance database employs a hierarchical drug file to support coding of drug verbatims with the best possible detail while also permitting retrieval of information at various levels, allowing different levels of precision and aggregations of data. The drug file should be properly modelled so that it is also possible to identify patterns across the database. Maintaining links and relationships between the medicinal products, (sets of) PhPIDs, and substance hierarchy is essential, as the dictionaries need to make “human” sense of the identifiers and link these different identifiers together.

Of note:

ICSRs received during the clinical developmental phase of a product occasionally use a Chemical Abstracts Service (CAS) number to identify the suspected investigational product. The CAS number is a unique numerical identifier assigned to every chemical substance described in the open scientific literature. To support ICSR data analysis covering the complete life cycle of a medicine it is recommended that the hierarchical drug file includes CAS numbers.

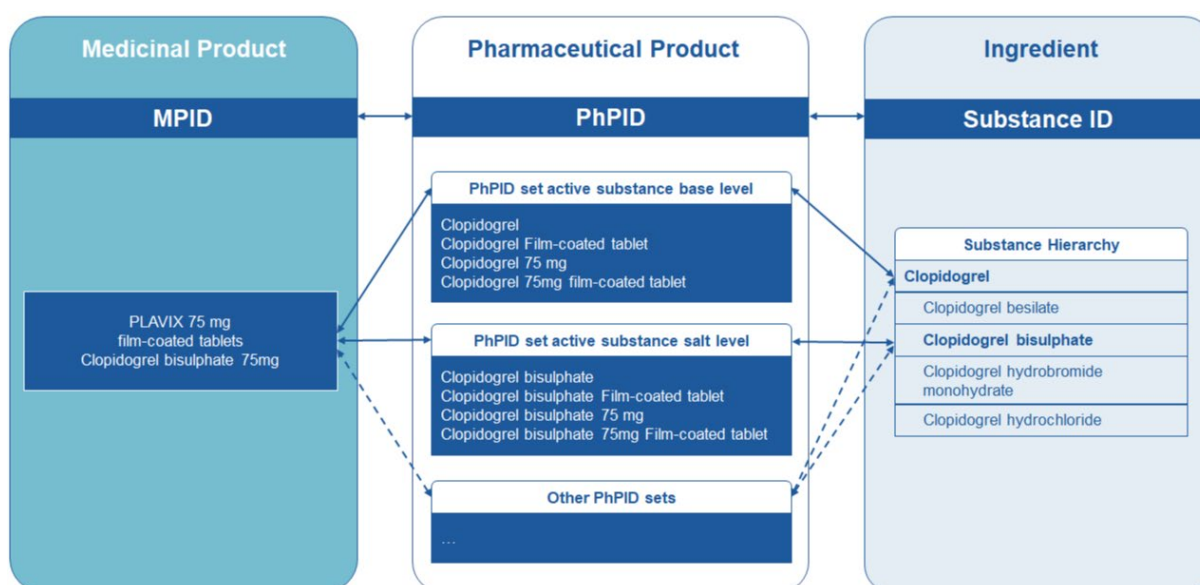


Figure 9. Connections of Different IDMP levels

The hierarchical drug file implemented in the pharmacovigilance database should allow to navigate between the different IDMP levels, while taking into account brands, synonyms as well as historic identifiers (figure 9).

Example:

Free text drug verbatims may refer to the Comirnaty Covid-19 vaccine in many different ways, for example:

- ▶ Bnt162b2
- ▶ Tozinameran
- ▶ Comirnaty
- ▶ Biontech-Pfizer Covid vaccin
- ▶ Pfizer-Biontech Covid-19 Vaccine
- ▶ Pfizer Covid vaccine
- ▶ mRNA Covid-19 vaccine Pfizer
- ▶ mRNA-Pfizer
- ▶ Comirnaty concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified)
- ▶

With only one product licensed as 'Comirnaty' (INN 'tozinameran'), a search in the pharmacovigilance database for suspected adverse drug reactions with Comirnaty or INN tozinameran should retrieve all these ICSRs, regardless of the drug verbatim used and subsequent coding in the ICSR to PhPID level or MPID level.

It is important to realise that the association between PhPIDs and product is not static as substance, strength and dose form may change. Over time, a PhPID may no longer be applicable to a particular product as illustrated by the Coversyl example illustrated in figure 10. Therefore, it is essential that the drug file will keep this history and relationships to support accurate coding and analysis.

Every new ADR report received could potentially contribute to identification of a new safety issue. Signal detection can be based on clinical review of the ICSR, which is often the preferred method when few reports have been received. Due to the large volume of ADR reports received, many organisations use an automated process applying statistical methods to help identify a signal. Quantitative signal detection in large pharmacovigilance databases relies often on disproportionality methods, which are based on comparison of the observed with the expected count of a drug-event association. Often certain additional selection criteria are applied in order to further prioritise the data and to focus on particular areas of interest, such as seriousness of the ADRs, newly marketed drugs, specific drug groups or specific patient populations. The ultimate aim is to detect possible drug safety issues as soon as possible so that prompt action can be taken to protect public health. A search that is too narrowly focused might

exclude cases of potential relevance; a search that is too broad might make it difficult to identify a potential signal. Therefore, routine signal detection methods generally use a top-down approach and start at a broad level.

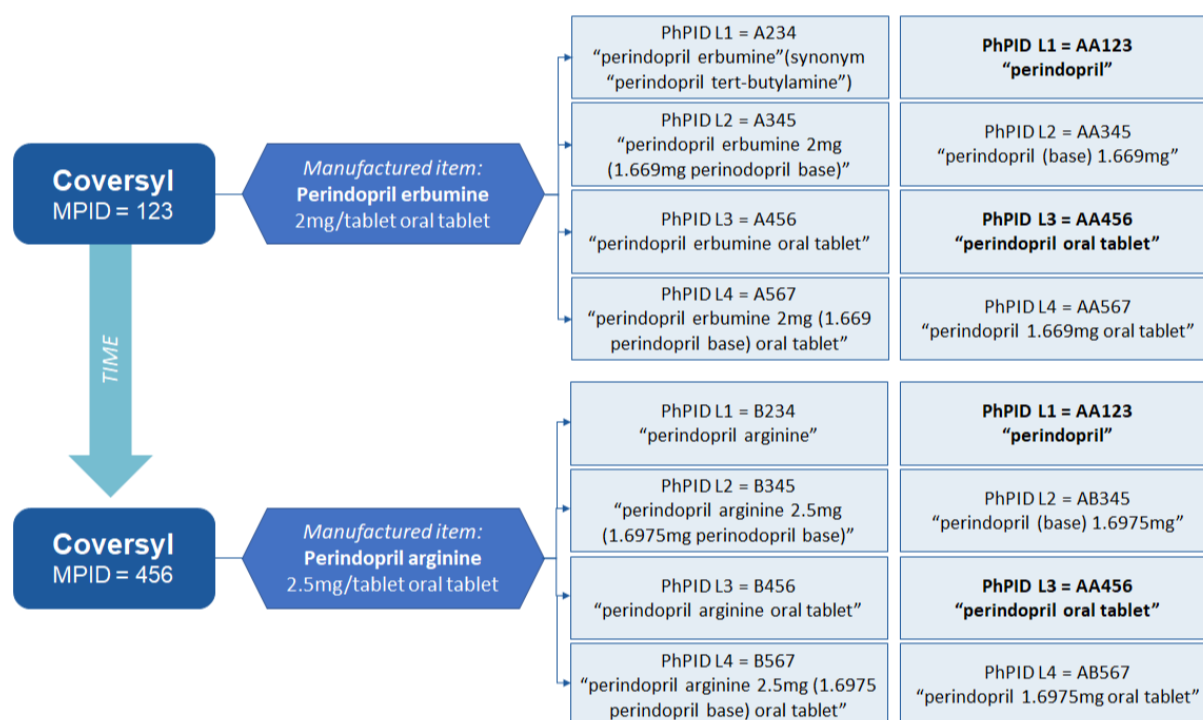


Figure 10. IDMP identifiers over time

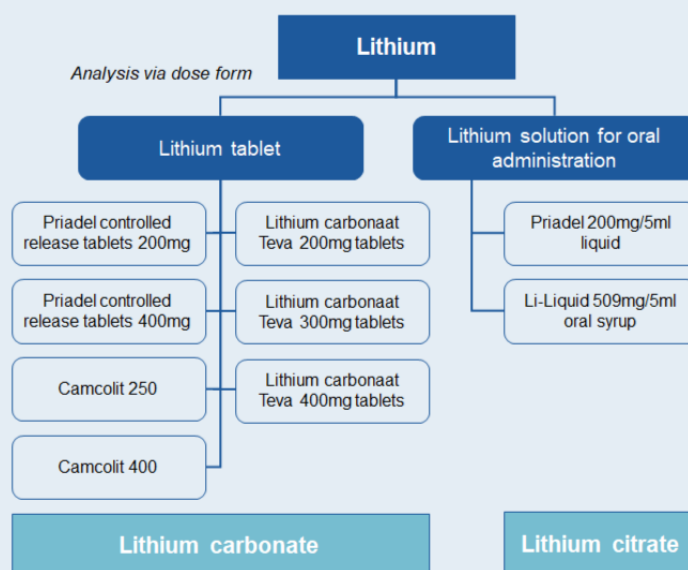
Of note:

For routine signal detection in EudraVigilance the value of the Reporting Odds Ratio (ROR) as a disproportionality method is computed at the active substance (base) level (or the SID of the "base" if no products are licensed with the "base" as active ingredient). This would correspond to PhPID L1 for the substance base level. In EudraVigilance, some grouping of active substances (e.g., by salts), dose form or route of administration is also performed. On occasion, for instance for vaccines, ROR for routine signal detection is calculated in EudraVigilance at the medicinal product level (i.e., brand name). For specific ad hoc analyses other levels or groupings are used.

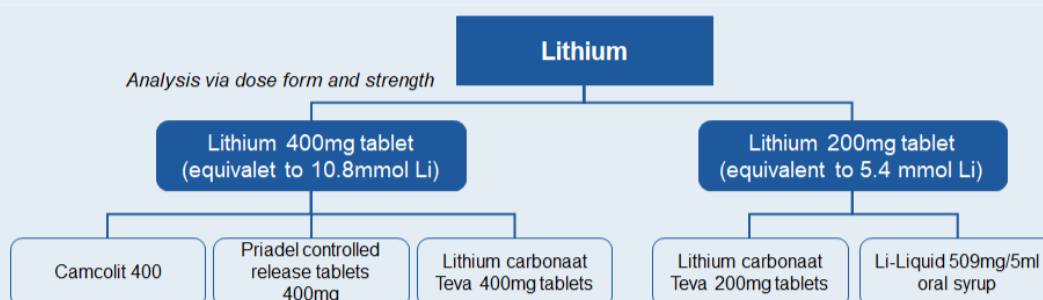
Example:

After first screening of ICSR data at active substance base level, there are several options to use IDMP levels for further analysis as shown in these simplified examples starting with lithium (PhPID L1):

1. Further analysis via dose form (PhPID L3)

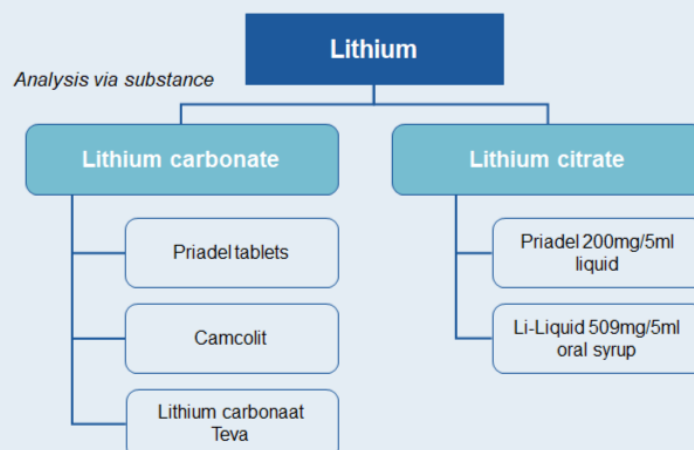


2. Further analysis via dose form and strength (PhPID L4)

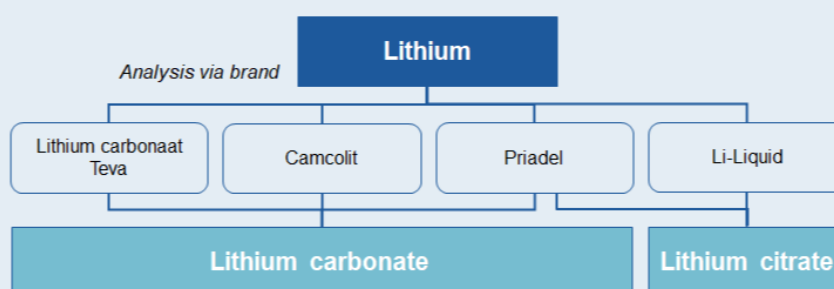


Example (continued):

3. Further analysis via substance hierarchy



4. Further analysis via brand

**Example:**

Routine pharmacovigilance monitoring is usually done at the level of 'diclofenac'. To investigate the potential difference in cardiovascular risk between diclofenac sodium and diclofenac potassium a search in the pharmacovigilance database is performed, retrieving all cardiovascular reports for diclofenac sodium and for diclofenac potassium. This search was triggered by published studies comparing pharmacokinetics and bioavailability parameters between diclofenac sodium and potassium in rabbits (Ahmad, Iqbal & Murtzaza, 2009; Ahmad, 2012).

Although pharmacovigilance analyses generally use a top-down approach and start at a broad level, more specific information on medicinal products can be necessary to analyse a potential safety issue. While routine levels of aggregation (for example active substance with/without salts, dose forms) can be supported by the IDMP identifiers, analysis may require additional groupings or attributes to be taken into account (such as indication, pharmacological effect or metabolic pathway).

Example:

Recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC) illustrate that analysis is performed at different levels of aggregation and using different attributes:

- ▶ Dec 2016: the product information for Proton Pump Inhibitors (i.e., dextansoprazole-, esomeprazole-, lansoprazole-, omeprazole-, pantoprazole-, rabeprazole-containing products) should be amended to include fundic gland polyps (benign) as an undesirable effect.
- ▶ Feb 2016: the product information for carbidopa/levodopa-containing intestinal gels should be updated to reflect the risk associated with the use of small bowel feeding tubes and the development of intussusception.
- ▶ Oct 2018: the product information for tacrolimus systemic formulations should be amended to reflect the increased risk of infections with viral hepatitis.
- ▶ Dec 2015: the product information for post-menopausal hormone replacement therapy products (all medicinal products containing oestrogens, including tibolone, or combined oestrogens-progestagens, which are not pharmaceutical forms for vaginal use) should be updated to amend the warning on ovarian cancer.
- ▶ July 2018: the product information for all antiretroviral medicinal products against HIV should be updated with respect to autoimmune hepatitis.
- ▶ Sep 2016: following cases of medication error associated with accidental overdoses of levetiracetam oral solution formulation, PRAC recommended to amend the package leaflet and enhance the differentiation between presentations by modifying the outer packaging and labels.
- ▶ April 2015: a PRAC review confirmed a small increase in the risk of cardiovascular problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (at or above 2,400 mg per day). Ibuprofen is present in medicines as a mixture of two molecules that are enantiomers (mirror images of each other). Dexibuprofen, the active enantiomer, is sometimes available on its own and was therefore included in this review. A dose of 2,400 mg per day of ibuprofen is equivalent to 1,200 mg per day of dexibuprofen. The review only covered systemic use (intended to act on the whole body, such as use by mouth or by injection); it did not cover formulations such as gels or sprays applied to the skin of the affected area.

As explained before, selecting an MPID for the ICSR is challenging and has limitations. However, even when MPIDs are not provided in the ICSR, using the information that led to MPID changes may be helpful in explaining changes in ADR patterns when doing pharmacovigilance analyses. For example, other types of ADRs may be reported after a new indication has been approved or after the legal status of supply has changed from 'Prescription Only' to OTC.

Of note:

Triggers to assign a new MPID (based on ISO 11615 version 2015) are:

- ▶ Marketing authorization in relation to the jurisdiction;
- ▶ Legal status of supply (e.g., prescription only or “over the counter” sale);
- ▶ Medicinal Product name;
- ▶ The pharmaceutical dose form;
- ▶ The ingredient substance(s) and their strength;
- ▶ Device(s) where a Medicinal Product 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;
- ▶ Therapeutic indication(s) as authorized for the Medicinal Product.

6 Recommendations

This section provides recommendations for practical IDMP implementation aspects and for handling drug information in general, aimed at improving ICSR data management and pharmacovigilance analysis.

6.1 PhPID generation

For pharmacovigilance coding and analysis purposes, it is recommended to have granular PhPIDs available globally. It is also essential that PhPID grouping concepts and relationships will be available and maintained.

The PhPID plays a central role for IDMP implementations, since it provides an abstract level to link medicinal products. Although the PhPID appears to be straightforward, there are several implementation decisions currently under discussion (UNICOM, 2020), which may lead to different levels of specificity of PhPIDs.

First of all, “substance” can refer to different levels of granularity. It is also noted that a global identification system for substances is not yet available for practical usage (input for PhPID calculation).

Secondly, discussions are ongoing if the ‘dose form’ for generating PhPIDs should relate to the administrable dose form (as specified in ISO 11616 standard), manufactured dose form and/or combined pharmaceutical dose form (two or more manufactured items that are combined to create a single administrable pharmaceutical product). Another option under discussion is to use the ‘basic dose form’ (generalised version of the pharmaceutical dose form, used to group together related pharmaceutical dose forms, for example capsule, tablet, powder, solution) for PhPID generation. As there is a need to ensure global PhPIDs it is also discussed to use dose forms characteristics for PhPID generation to facilitate mapping between regional dose form terminologies. Finally, PhPID generation is further impacted by presentation of strength and concentration strength. The issue, here concentrating on therapeutically active ingredients, is that the strength of a medicinal product can be expressed differently depending on which substance the strength is referring to. Since strength has such a close relationship with dose quantity, this issue has a strong impact on both the regulatory domain and patient care. See example below for LOVENOX where the resulting PhPID would be the same or different for a prefilled syringe and an ampoule depending on the way to calculate the PhPID. For more examples on presentation and strength and the impact on PhPID generation, please refer to chapter 8 of the EU International Organization for Standardization Identification of Medicinal Products Implementation Guide (also known as EU ISO IDMP IG) (EMA, 2021b).

Example:

LOVENOX						
Solution for Injection (prefilled syringes)	Strength		EDQM dose form	PhPID by presentation + concentration	PhPID by presentation only	PhPID by concentration only
Strength as SPC	Presentation strength	Concentration strength				
Prefilled syringe 30mg/0.3mL	30mg/syringe	100 mg/1mL	Solution for injection	AAXXY	AAY	XXY
Prefilled syringe 40mg/0.4mL	40mg/syringe	100 mg/1mL	Solution for injection	BBXXY	BBY	XXY
Prefilled syringe 60mg/0.6mL	60mg/syringe	100mg/1mL	Solution for injection	CCXXY	CCY	XXY
Prefilled syringe 120 mg/0.8 mL	120mg/syringe	150mg/1mL	Solution for injection	DDWWY	DDY	WWY
Ampoule 100mg/1ml	100g/ampoule	100mg/1ml	Solution for injection	EEXXY	EEY	XXY
Multiple Dose Vial 300 mg /3 mL	300mg /vial	100mg /1mL	Solution for injection	FFXXY	FFY	XXY

The sample set of drug verbatims demonstrated that the information on the drug can be more or less specific. Therefore, taking into account that ADRs can be reported via different mechanisms, all PhPID levels (PhPID L1-4) and PhPID sets (substance base and with salts, administrable dose form, and manufactured dose form, etc.) that will be used in clinical systems should also be available for use in the ICSR. More specificity at time of data entry leads to more possibilities and accuracy for data analysis (figure 11). To support data analysis, it is important that groupings and relationships between the PhPID levels and PhPID sets are available.

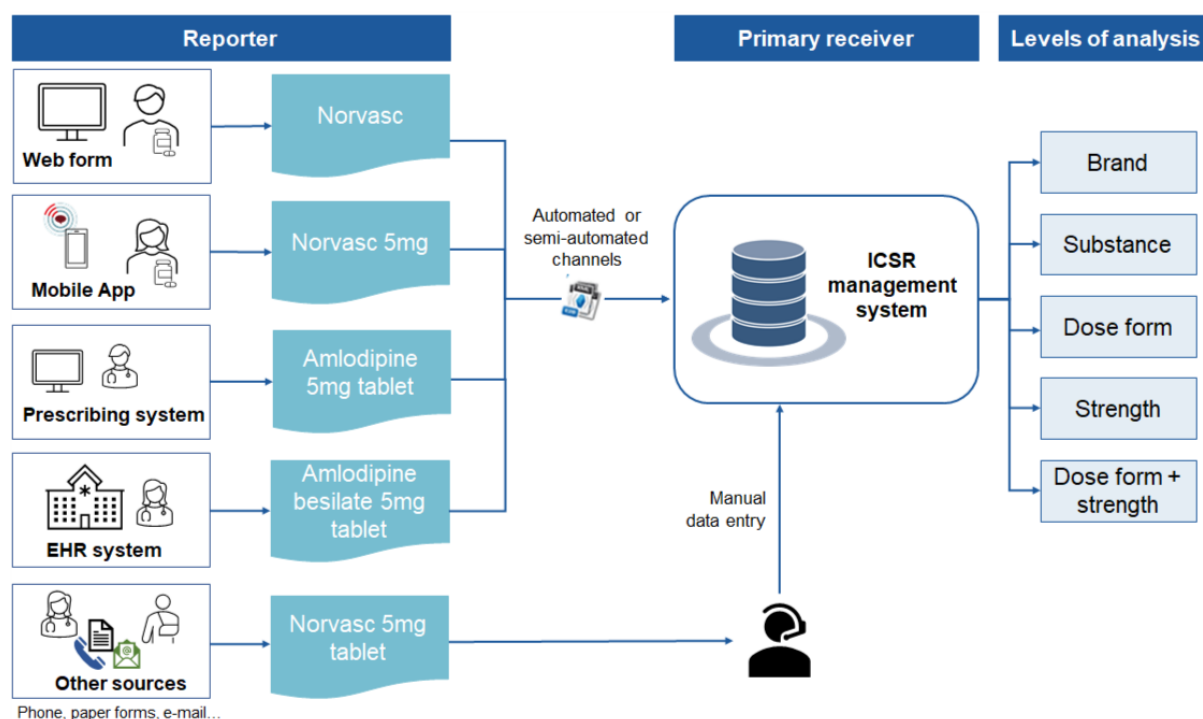


Figure 11. Levels of analysis

A further recommendation on PhPIDs relates to the implementation of a high level PhPID grouping. As PhPID generation is based on (specified) substances as defined in ISO standard 11238, a high level PhPID grouping based on a conceptual level of a substance is currently not foreseen. The need for this PhPID grouping is illustrated by taking the examples of amlodipine and ibuprofen (figure 12):

- ▶ The active molecule amlodipine is never available alone, but always as its salt - besylate, maleate or mesylate - to help in drug delivery. Strictly speaking, 'amlodipine' cannot be defined as a substance according to ISO 11238 and will therefore not have its own identifier that can be used as input for generating the PhPID. Therefore, it is useful to have an additional amlodipine 'group level' to code non-specific drug verbatims such as 'amlodipine 5mg tablet', and to support analysis of all 'amlodipine ICSRs' together.
- ▶ Ibuprofen is available plain as base, as well as with salts. A non-specific drug verbatim of 'ibuprofen 400mg' can refer to 'ibuprofen' as active substance base, but may as well refer to a non-specified ibuprofen. Coding a drug verbatim of 'ibuprofen 400mg' to the PhPID L2 for the active substance base would potentially allocate too many ICSRs to this particular substance.

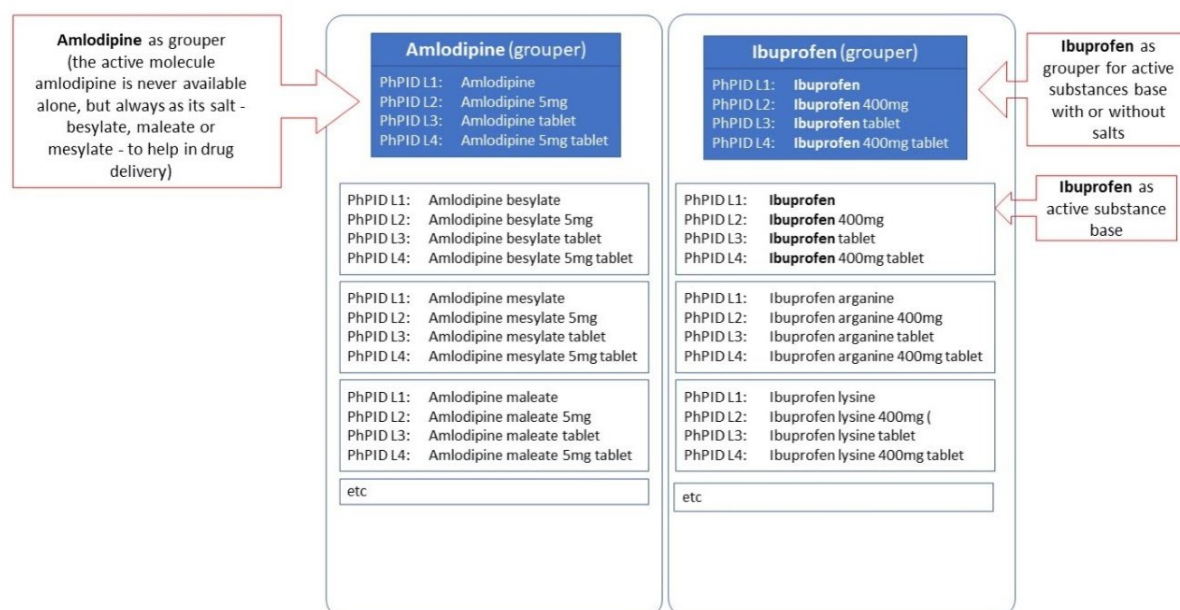


Figure 12. Need for groupers for non-specific drug verbatims

Liposomal products (e.g., amphotericin) is another example that shows the need for a PhPID grouper concept that is “all amphotericin products” that is different from “all amphotericin (plain) products” and “all liposomal amphotericin products”.

It is not currently clear if the Global Substance Registration System (G-SRS) or European Substance Registration System (EU-SRS) will be able to support this recommendation for a PhPID grouper concept, as this would mean that another identifier (code) would need to be generated for the substance grouper concept then for the substance (base/unmodified) concept. Recommendation 6.6 of this guidance will further elaborate on the use of grouping concepts and provide examples on existing concepts used by WHODrug and SNOMED-CT.

6.2 Alternative for Name Parts

It is recommended to investigate and assess the potential benefit of a new ICSR data element 'imputed drug information' as an alternative for using name part data elements in the ICSRs.

Although there is a benefit in populating ICSR name part elements as explained in section 4.6, concerns have been raised about resource implications of having name parts. Name parts do not only require resources when providing information to PMS, but also when populating these in the ICSRs. Furthermore, it has been challenged how useful the Name Part data elements will be in practice. Firstly because the name parts in EMA's PMS system reflect the Name Parts in IDMP and do not accord

with those of the ICSR (see table 5). Although there are similarities, PMS has specified some name parts differently. For example, the intended use name part (USE) of ICSR is specified differently in PMS, which separates the 'Intended Use part' and the 'Target Population part'. In PMS system, also some additional name parts can be specified: Time/period part, Flavour part, and Formulation part.

Table 5. Differences in Name Parts in ICSR and PMS

ICSR		PMS	
Concept name	Example	Concept name	Example
Container name	<i>Pre-filled syringe</i>	Container or pack part	<i>In a vial</i>
Device name	<i>InjectPen</i>	Device part	<i>inhaler</i>
Form name	<i>Soft capsules</i>	Pharmaceutical dose form part	<i>Slow release tablets</i>
Invented name	<i>TotalFlu</i>	Invented name part	<i>BeatCold</i>
Scientific name	<i>paracetamol</i>	Scientific name part	<i>diclofenac</i>
Strength name	<i>50 mg</i>	Strength part	<i>50 mg</i>
Trademark name	<i>Syncopharm</i>	Trademark or company name part	<i>PharmaX</i>
Intended use name	<i>Heartburn relief</i> <i>For children</i>	Intended use part	<i>Migraine relief</i>
		Target population part	<i>For children</i>
		Time/period part	<i>2013/2014 (influenza vaccine)</i> <i>One a Day</i>
		Flavour part	<i>Orange</i>
		Delimiter part	<i>/</i> <i>'and'</i>
		Formulation part	<i>Sugar free</i>

ICSR 'intended use' name part can contain information on target population which is a separate element in PMS

Grey PMS elements are not available in ICSR

Secondly, it will not always be clear in which ICSR name part data element that certain information needs to be captured; this further complicates making an exact match with PMS. A third point to note is that the name parts seem to overlap with the PhPID, with a risk of having contradictory information within a single ICSR.

Technology has progressed since the EU ICSR Implementation Guide and IDMP standards were finalized several years ago. Nowadays full text searches have become more efficient and easier to implement. To investigate if simplification and efficiency gains can be achieved the following is recommended:

- ▶ To investigate if a match to PMS can be achieved via full text search on the ICSR drug section, as an alternative for using name parts.
- ▶ To assess if adding a new free text data element to the ICSR drug section(s) that reflects the 'imputed drug information' could be used for full text searches aiming to find a match with data held in PMS. Several examples in this guidance have demonstrated that the drug verbatim may be less

specific than the ‘imputed drug information’. However, the current ICSR format does not have a data element for the ‘imputed drug information’.

The results would help to assess if this ‘imputed drug information’ (see figure 7, section 4.4.1) could be an easier-to-implement alternative for name parts in the ICSR. If the results show that name parts are considered useful in the ICSR, it is recommended to harmonise the ICSR name part data elements with the ISO IDMP 11615 standard and PMS. This can be achieved via an update of the EU ICSR Implementation Guide. The systematic review of ISO/HL7 27953-2:2011 ICSR standard would be a good opportunity to introduce any necessary changes.

6.3 Future maintenance of IDMP coding guidance for ICSRs

To best support pharmacovigilance stakeholders, it is recommended to explore a possible role of global and/or regulatory organisations as an owner for IDMP ICSR coding guidance, to be responsible for its ongoing development and revision as the IDMP implementation progresses.

The use of IDMP identifiers in the ICSR should improve the quality of data captured on databases, support the effective analysis of data and facilitate electronic exchange of data by providing an internationally accepted standard. Exploiting the benefits of IDMP will require well planned implementation with pharmacovigilance stakeholders to agree on a harmonized approach and timeline. Practical experience with IDMP is still limited and while users are investing time in gaining expertise, there are still many uncertainties. Ongoing discussions on implementation of ISO standards 11238, 11239, 11615 and 11616 may lead to changes to the ISO standards and/or Technical Specifications, with potential impact on the identifiers resulting from the practical implementation of these standards. Also, it is not yet clear who will generate PhPIDs and if these will become available at global scale. These moving parts emphasize the need to support the pharmacovigilance stakeholder community with up-to-date guidance relevant to their specific IDMP use case. This guidance document has been developed within the European UNICOM project and may serve as a starting point to establish global consensus in the use of IDMP identifiers in ICSRs. Considering the highly regulated pharmacovigilance environment, such guidance becomes more effective if it would be supported and maintained by an international organisation such as WHO UMC or SNOMED, or within the regulatory environment, such as EMA or ICH (potentially via the ICH E2B(R3) Implementation Working Group). It is recommended to explore a possible role of these organisations as an owner for the IDMP ICSR coding guidance, to be responsible for its ongoing development and revision as the IDMP implementation progresses.

6.4 Improving data collection

It is recommended to improve pharmacovigilance data collection methods by using drug identification information via the 2D-data matrix or barcode on the medicine package.

As explained in section 4.2, the drug verbatim is often not specific enough to code the MPID, especially when a product has been assigned multiple MPIDs. A long-term solution to improve collection of information on the drugs would be scanning a medicine package with a 2D-Data Matrix code or barcode capturing IDMP product identification. This would retrieve not only the MPID, but also obtain the Product Package Identifier (PCID), batch ID and serial number (figure 13).

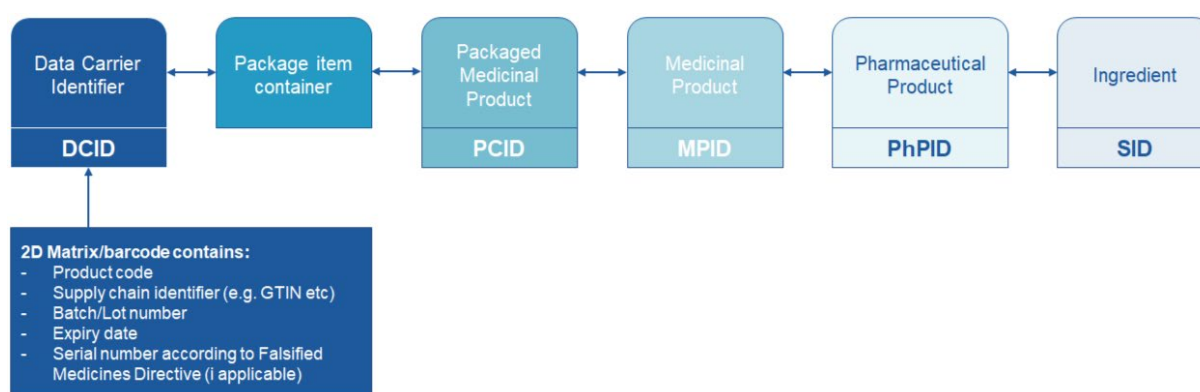


Figure 13. Hierarchy of IDMP product identification

Such scanning can be incorporated in ADR data collection tools (e.g., app) or could be mimicked by adding a photo functionality in an electronic ADR reporting webform. Scanning at the clinical point of care would facilitate accurate record keeping in the EHR and medication records. As long as MPIDs are not directly collected at the time of ADR reporting these will have limited value for ICSR processing.

Example:

Scanning a 2D matrix/barcode can also help to avoid a 'best guess of the PhPID'. When the name on the package is used as drug verbatim, this may result in a 'best guess of the PhPID' which can be different from the most precise PhPID for a product based on the scientific composition (e.g., taking into account salts and reference strength).



For example, if a patient would report a drug verbatim only as 'amlodipine 5mg tablet' (as mentioned on the package) it would not be possible to select the most detailed PhPID for this product which is 'amlodipine besilate 5mg tablet'.

The WEB RADR project also made some recommendations relating to product identification in the context of ADR reporting (Pierce et al., 2019). User based evaluations showed that there are a number of features which were appreciated and facilitate ease of use for ADR reporting; for example, drop downs and 'auto-fill' features which can help with correct spellings and standardised use of terminology. Such searchable lists should include both product and substance names. Furthermore, it was recommended that any searchable lists for drug names do not include duplicates or very similar names. However, from a user perspective free text entry is still needed in addition to the drug dictionary functionalities mentioned.

Example:

Drop downs and auto fill features are implemented in the ADR reporting webform used by the Dutch Pharmacovigilance Centre Lareb.

Step 1:
Drug search starts after typing first 4 characters; both substance and brands are available for selection.
- The search will become more specific when typing is continued
- Free text is captured if reporter continues typing and doesn't make a selection

Step 2:
If a selection has been made for step 1, a list with relevant pharmaceutical form/strengths will appear

Only when both step 1 and 2 result in a selection, the drug verbatim will be coded to most precise product available in the drug dictionary.

The drug terms shown in drop downs can link to applicable IDMP identifiers; the IDMP identifiers don't need to be visible. When drug brand names are provided in the drop down, careful consideration should be taken with linking these to MPIDs, given the complexity of the MPID generation and maintenance lifecycle explained in section 4.2.

6.5 IDMP versioning

As IDMP implementation activities progress, the need for IDMP versioning in the ICSR and potential versioning strategies should be explored further.

Recording the MedDRA version number used to code adverse events and indications etc. is well established in the ICSR, including the requirement to submit an updated ICSR if something significant occurs in the concept area in future versions. At the time of finalizing the ICSR message specification, it was not yet clear how IDMP versioning would work in practice, and ‘placeholder’ data elements were put in place for the version/date-time stamp for each coded element for the medicinal product information. Many terminologies are now available with dynamic updates (using a date/time stamp as the version ID) – although they may have an “anchor version” released once or twice per year (as MedDRA does). The frequency of versioning/release should always be based on the use case(s) that the terminology supports and formal versioning and change management processes and artefacts should be in place, especially for those terminologies where analysis is a primary use case.

The relevance of IDMP versioning in the ICSR depends on the identifier itself (MPID or PhPID) and the IDMP implementation strategy:

- ▶ There is no need to resubmit an ICSR if a new MPID code becomes available. Coding MPID in an ICSR will relate to a very specific product which is relevant to that particular case; this may not necessarily be the most recent MPID available.
- ▶ If for example PhPIDs initially would only be generated at active moiety level, and at some point in the future PhPIDs will also be generated at specified substance level (taking into account the manufacturer of the substance), it could be considered to resubmit the ICSR with the more specific PhPID identifier.

The need for IDMP versioning in the ICSR and potential versioning strategies will need to be explored further as IDMP implementation activities progress. This should also take into consideration if pharmacovigilance systems should be advised to “pull” new information (and if so, what is the minimum time period) or whether there should be some sort of “push” of information to systems.

6.6 Grouper concepts

A potential benefit of implementing different grouping concepts (as available in for example SNOMED CT and WHO Drug) for pharmacovigilance analysis should be further investigated.

Sections 5 and 6.1 illustrated that pharmacovigilance analysis requires different types of groupings. Pharmacovigilance analysis is often started on an information level hereto unaddressed by the IDMP standards. Safety properties of drugs are not always unique to one medical product, resulting in a need to make searches to explore several MPIDs, PhPIDs or drugs sharing the same active ingredient.

Sometimes drug properties are common for groupings of drugs or entire drug classes. To fill this gap, it is recommended to make use of an IDMP compliant drug dictionary that can link IDMP identifiers to the needed grouper concepts to perform the relevant pharmacovigilance analysis, as for example provided by WHO-Drug or SNOMED CT.

6.6.1 Grouper concepts in WHO-DRUG

WHODrug is a comprehensive standardized global drug dictionary used in national and global pharmacovigilance processes within the WHO Programme for International Drug Monitoring, as well as in vigilance activities performed by the pharma industry in clinical trials (Lagerlund et al., 2020). WHODrug is managed by UMC, the WHO Collaborating Centre for International Drug Monitoring, and complies with regulatory standards for new drug approvals and pharmacovigilance globally.

WHODrug has an inbound logic to facilitate analysis of different levels of information. In its most basic format WHODrug links trade names to its corresponding active ingredients and active moieties, but WHODrug also provide information of pharmaceutical form, strength, marketing authorisation holder and country of sales. Medications in WHODrug are classified using the Anatomical Therapeutic Chemical (ATC) system and clustered into Standardised Drug Groupings (SDG), to allow for grouping of medications with one or more properties in common (figure 14).

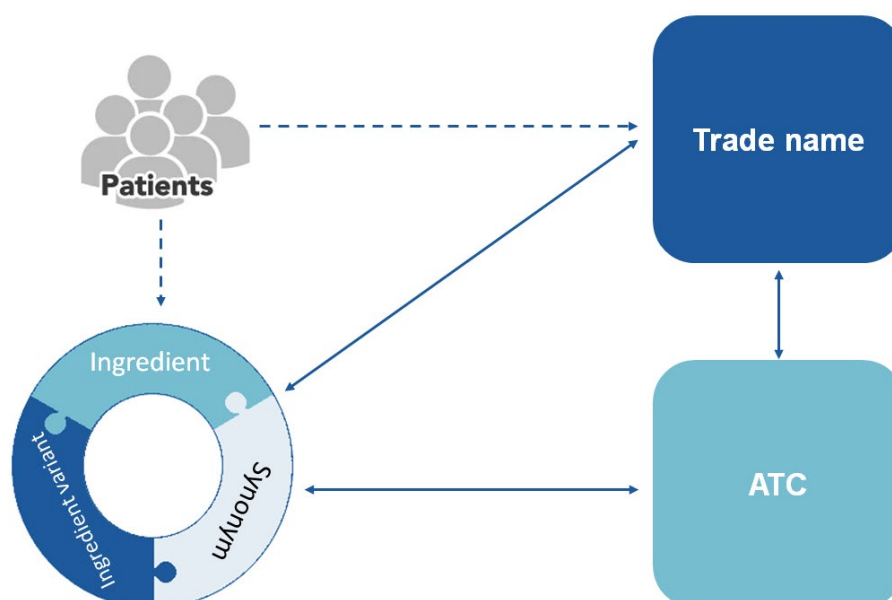


Figure 14. Linking information levels in WHODrug

- ▶ The ATC classification is developed to enable drug utilization studies and has been adopted as a national standard for classification of medicinal products in various countries (WHO, 2021). It is used in pharmacovigilance as the system helps link adverse drug reactions to drug classes. In the ATC classification system, the active substances are divided into groups according to the organ, or system they act and their therapeutic, pharmacological and chemical properties. The ATC system is maintained by the WHO Collaborating Centre for Drug Statistics Methodology, in Oslo, Norway. The WHO International Working Group for Drug Statistics Methodology includes new records in the ATC classification hierarchy on requests from users of the system.
- ▶ The SDGs are groupings of drug ingredients having one or several properties in common. The SDGs can be based on indication, pharmacodynamic or pharmacokinetic properties, chemical structure or any other property of interest and are used as a complement to the ATC classification (WHO-UMC, 2020). The SDGs are used as unbiased search strategies for the most common groupings of medicines in pharmacovigilance and in creating study protocols for clinical trials (e.g., by creating inclusion/exclusion medication lists or identifying protocol violations and deviations). The SDGs are developed by experts in the respective fields and are made available alongside WHODrug to the members of the WHO Programme for International Drug Monitoring, as well as subscribers of WHODrug.

6.6.2 Grouper concepts in SNOMED CT

SNOMED CT is a controlled coded clinical terminology intended for use in electronic health records. SNOMED CT contains concepts with unique meaning and formal logic based definition and is organized into hierarchies. As well as describing medicinal products themselves with concepts at various levels of abstraction based on the pharmaceutical characteristics of the products, SNOMED CT contains “grouper concepts” whereby the medicinal products are grouped based on either structural or behavioural characteristics exhibited by the active substance(s) that the products contain and/or by the general therapeutic role that they could perform (note: not the indication for the product).

- ▶ Disposition - grouping based on mechanism of action or behaviour that the active substance(s) in the product can exhibit (or participate in) given the appropriate context in which to do this;
- ▶ For example: products containing carbachol are included in the “disposition” group with those that are muscarinic receptor agonists.
- ▶ Structure - grouping based on structural composition of the active ingredient substance(s) in the product;
- ▶ For example: products containing chlorpropamide are included in the group of products containing sulfonylurea structure.
- ▶ Structure and Disposition - combination of the above;
- ▶ For example: products containing doxorubicin are included with those having an anthracycline structure and in a group with those having a “disposition” to being antineoplastic.
- ▶ Therapeutic role - grouping based on the therapeutic role that a product is designed to fulfil;
- ▶ For example: products containing granisetron “act as antiemetic agents”.

Disposition (mechanism of action) is distinguishable from therapeutic role, which is context dependent: for example the mechanism of action of timolol is as a beta-adrenoceptor antagonist; this action can be used therapeutically to reduce hypertension when administered in a product given orally or to treat glaucoma when administered in a product intended to be given ophthalmically.

The diagram below shows the grouper concepts and how they are related to two of the main classes of medicinal product concepts (figure 15). Grouper concepts are particularly useful when bringing data together for analysis or for decision support rules. Currently pharmacovigilance analysis primarily uses groups based on active substance, usually (at least initially) without reference to any salt or ester modification of that active substance. Analysis using more abstract grouping may be undertaken using a classification such as the Anatomical, Chemical and Therapeutic classification. SNOMED CT offers a slightly different set of possibilities for grouping, including that the different types of groups can be investigated separately and may therefore offer some additional possibilities for safety data analysis.

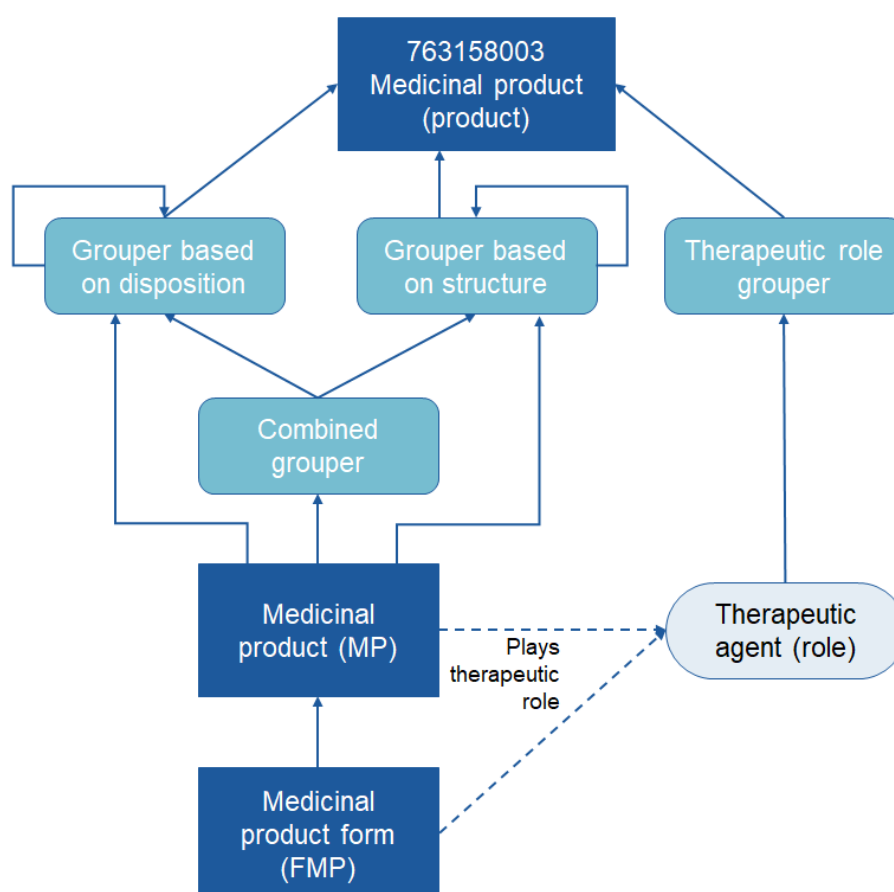


Figure 15. SNOMED grouper concepts

6.7 IDMP coding tools

It is recommended that the design and interface of drug coding tools used in pharmacovigilance systems should support display of contextual information as well as historic identifiers.

When verbatim drug coding for ICSRs is supported by a coding tool, it is important that the design and interface of the tool takes into account the particularities for MPID/PhPID coding. Normally, a verbatim is coded directly on its own. When coding a drug verbatim against MPID/PhPID, it is recommended to take contextual information into account. Therefore, the design of the tool needs to support display of the relevant contextual information. Furthermore, drug coding can be done against a “retired” MPID – which is unusual in coding when normally the current active concept should always be used. It is important that “retired” IDMP identifiers will remain available for coding as well as analysis purposes.

6.8 The option for “open world” medicine concepts

As there can be ambiguity and a lack of clarity to exactly what the reporter was meaning, the option to code using drug concepts with an “open world view” as exists in ontologies such as SNOMED CT might be a consideration for the future.

A small number of clinical terminologies, with SNOMED CT being the main example, operate on the principle of an open world view (the existential restriction) whereby although with each concept has a distinct fully specified name which gives that concept's meaning, it does not “limit” the concept to “only” what is “known to be true”. The implication of the “open world” view for the medicinal product hierarchy in SNOMED CT is that a concept represents the set of (real world) medicinal products that contains “(at least) some substance X as an active ingredient”, but may contain other unspecified active ingredient substances. This “open world” view is useful for analysis and in some types of decision support.

However, the regulation of medicinal products for sale/supply is based on the “closed world” view (the universal restriction), where all active ingredient substances must be explicitly described. This is also the premise for description of medicinal products in the medication process (prescribing, dispensing and administration). Therefore, the medicinal product hierarchy differs from other concept hierarchies within SNOMED CT in that some classes of concepts within it are modelled using this “closed world” view which states that a concept represents a medicinal product that contains “only substance X” as an active ingredient”; no other active ingredient substances are present within it.

The diagrams below (figure 16 and 17) show the overall basic Medicinal product model, excluding grouping concepts representing chemical structure, mechanism of action, or therapeutic role. The first diagram (figure 16) is a class model illustrating the five classes of concepts in the model and the relationships between them, in their three groups (Medicinal product, Medicinal product form, and Clinical drug) plus an additional optional sixth sub-class to be populated in national extensions only

(Medicinal product precise only). Two classes use the existential restriction (Medicinal product, Medicinal product form) and four use the universal restriction (Medicinal product only, Medicinal product form only, Clinical drug precisely and Medicinal product precise Only).

The second diagram shows examples of the five classes that are populated in the SNOMED CT International Release (figure 17).

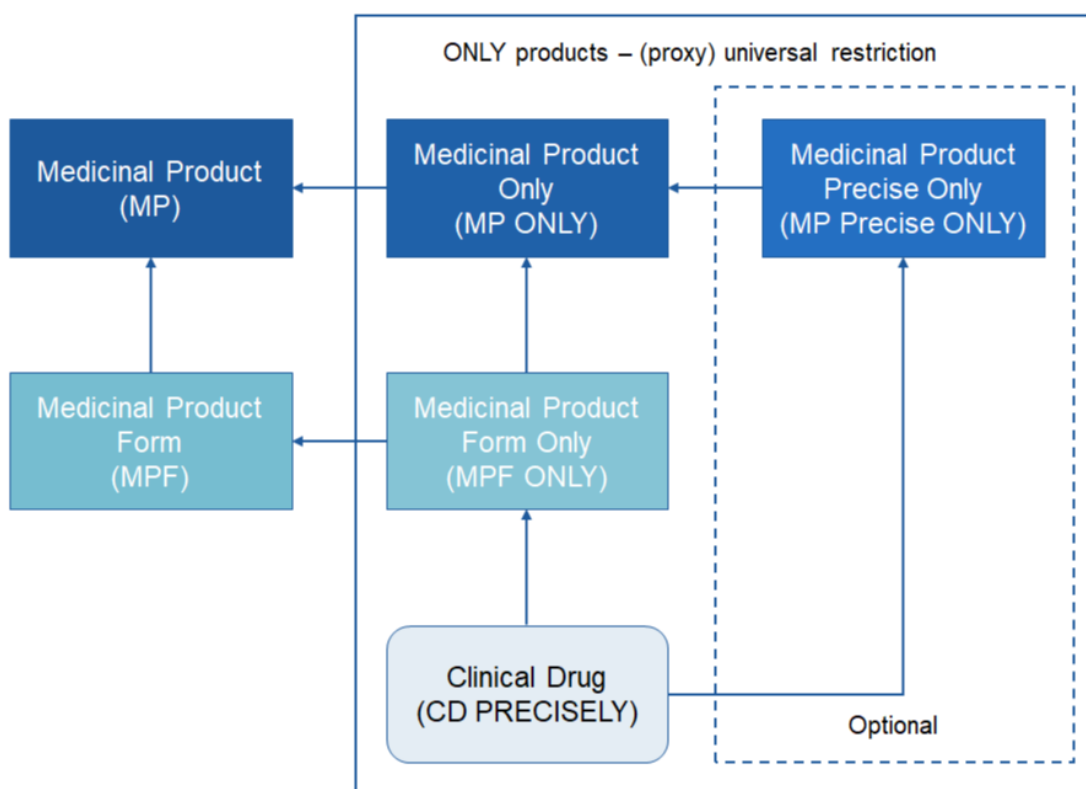


Figure 16. Overall basic Medicinal Product model

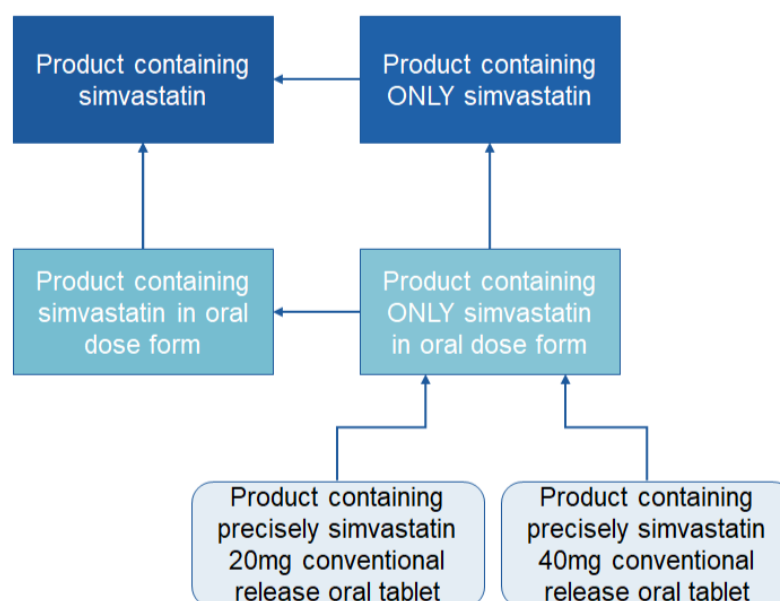


Figure 17. Populated classes in the SNOMED CT International Release

Coming as they do from the regulatory/product authorisation domain, the ISO IDMP identifiers (e.g., PhPIDs) correspond to the “closed world view” concepts in SNOMED CT. However, in pharmacovigilance, particularly when coding drug verbatims, where there can be ambiguity and a lack of clarity to exactly what the reporter was meaning, the option to code using concepts with an “open world view” as exists in ontologies such as SNOMED CT might be a consideration for the future.

6.9 Requirements for medicinal product dictionaries for pharmacovigilance

Requirements for a medicinal product dictionary for pharmacovigilance could be a potential work item for standardization.

ISO/TS 19256 (2016) Health informatics — ‘Requirements for medicinal product dictionary systems for health care’ defines the required characteristics for any Medicinal Product Dictionary-system to support use cases in healthcare. These characteristics include the medication concepts, identifiers and relationships to form a kind of structure that supports the use cases. Drug dictionaries used in pharmacovigilance systems do not need the same information as is needed for clinical care, although there is some overlap, for example the use of synonyms and hierarchies.

Requirements for a medicinal product dictionary for pharmacovigilance specifically could be a potential work item for standardisation, e.g., under the umbrella of ISO TC 215 WG6. A formal set of dictionary requirements taking into account IDMP particularities and grouper concepts needed to perform pharmacovigilance analysis may have significant value in the pharmacovigilance domain to ensure maximum information is available for analysis and providing adequate support for coding drug information.

7 References

- Ahmad, M., Iqbal, M., Murtaza, G. (2009). Comparison of bioavailability and pharmacokinetics of diclofenac sodium and diclofenac potassium in normal and dehydrated rabbits. *Acta Pharmaceutica Sinica*. 2009;44(1):80–4.
- Ahmad, M. (2012). Comparison of bioavailability and pharmacokinetics of diclofenac sodium and diclofenac potassium in normal and alloxan-diabetic rabbits. *Pak J Pharm Sci*. 2012;25(2):301–6.
- Allkin, R. (2016). Kew's Plant Names Services adopted by global health. Retrieved from <https://www.kew.org/read-and-watch/plant-names-services-used-by-global-health>
- Allkin, R. & Patmor, K. (2018). Navigating the plant-names jungle. *Uppsala Reports*, 10 april 2018. Retrieved from <https://www.uppsalareports.org/articles/navigating-the-plant-names-jungle/>
- Dauncey, E.A., Irving, J., Allkin, R., Robinson, N. Common mistakes when using plant names and how to avoid them. *European Journal of Integrative Medicine*, 2016; 8(5):597-601.
- EC (2001). Regulation (EC) No 76/2004, Directive 2001/83/EC. Retrieved from https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf
- EC (2012). Commission Implementing Regulation (EU) No 520/2012. Retrieved from <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF>
- EDQM (2018). Standard Terms: Introduction and Guidance for Use v.2.1.3, 2018. Retrieved from https://www.edqm.eu/sites/default/files/standard_terms_introduction_and_guidance_for_use.pdf
- EMA (2012). List of Signals Discussed at PRAC September 2012. Retrieved from https://www.ema.europa.eu/documents/other/list-signals-discussed-prac-september-2012_en.xlsx
- EMA (2017). Good Pharmacovigilance Practices Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). Retrieved from https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf
- EMA (2021a). EU Individual Case Safety Report (ICSR) Implementation Guide. EMA/51938/2013 Rev 2. Retrieved from https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-union-individual-case-safety-report-icsr-implementation-guide_en.pdf
- EMA (2021b). Products Management Services - Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe Retrieved from: https://www.ema.europa.eu/documents/regulatory-procedural-guideline/products-management-services-implementation-international-organization-standardization-iso-standards_en.pdf
- ICH (2016). Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) E2B(R3) Data Elements and Message Specification v5.02. Retrieved from <http://estri.ich.org/e2br3/index.htm>

ICH (2020). User Guide of EDQM terminologies for Dose Forms and Routes of Administration for Individual Case Safety Reports in E2B(R3) message. Retrieved from <https://ich.org/page/e2br3-individual-case-safety-report-icsr-specification-and-related-files>

Lagerlund, O., Strese, S., Fladvad, M., Lindquist, M. (2020). WHODrug: A Global, Validated and Updated Dictionary for Medicinal Information. Therapeutic Innovation & Regulatory Science 2020:54; 1116–1122.

MedDRA (2021). MedDRA Term Selection: Points to Consider v4.21. Retrieved from https://admin.new.meddra.org/sites/default/files/guidance/file/000571_termselptc_r4_21_mar2021.pdf

Pierce, C.E., de Vries, S.T., Bodin-Parssinen, S. et al.(2019). Recommendations on the Use of Mobile Applications for the Collection and Communication of Pharmaceutical Product Safety Information: Lessons from IMI WEB-RADR. Drug Safety 2019:42; 477–489.

UNICOM (2020). Gap Analysis about Existing and New standards and Profiles. Retrieved from https://unicom-project.eu/wp-content/uploads/2020/09/UNICOM_Gap-Analysis.draft_v12-1.pdf

WHO (2004). WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/43034/9241592214_eng.pdf

WHO-UMC (2020). WHODrug Standardised Drug Groupings. Retrieved from: <https://www.who-umc.org/whodrug/whodrug-portfolio/whodrug-standardised-drug-groupings-sdgs/>

WHO Collaborating Centre for Drug Statistics Methodology (2021). The Anatomical Therapeutic Chemical (ATC) classification system. Retrieved from: <https://www.whocc.no/>