Business rules for PhPID construction

Global IDMP Working Group

Public Version 1.0

1 May 2024

Glossary of terms, definitions, and abbreviations

AdmDF	Administrable dose form
Anvisa	Brazilian Health Regulatory Agency
BoSS	Basis of strength substance
CDF	Combined pharmaceutical dose form
CDISC	Clinical Data Interchange Standards Consortium
CV	Controlled vocabulary
DFID	Dose Form Identifier
EDQM	European Directorate for the Quality of Medicines & HealthCare
EPHMRA	European Pharmaceutical Market Research Association
EUTCT	European Union Telematics Control Terms
FDA	U.S. Food and Drug Administration
GIDWG	Global IDMP Working Group
GSID	Global Substance Identifier
HL7	Health Level Seven
HL7 FHIR	Fast Health Interoperability Resources specification
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual case safety report
IDMP	Identification of Medicinal Products
INN	International Nonproprietary Names
INNM	International Nonproprietary Names Modified
ISO	International Organization for Standardization
ManDF	Manufactured dose form
MHRA	UK's Medicines & Healthcare products Regulatory Agency
MPID	Medicinal Product Identifier
PCID	Packaged Medicinal Product Identifier
PDF	Pharmaceutical dose form
Ph. Eur.	European Pharmacopoeia
PhPID	Pharmaceutical Product Identifier
PV	Pharmacovigilance
SDID	Strength Definitions Identifier
SI	International Systems of Units
SPC	Summary of Product Characteristics
SNOMED-CT	Systematized Nomenclature of Medicine, Clinical Terms
TS	Technical specification
UCUM	Unified Code for Units of Measure
UMC	Uppsala Monitoring Centre
UNICOM	Up-scaling the global univocal identification of medicines
UoM	Unit of measurement
USP	U.S. Pharmacopeia
WG	Working group
WHO	World Health Organization

Active substance	The substance responsible for the activity of a medicine
Actuation	A unit of presentation used to express strength or quantity for a particular dose form or container, such as: • Metered dose spray • Inhalation powder, metered dose • Parenteral prefilled pen, metered dose
Administrable dose form (AdmDF)	Pharmaceutical dose form for administration to the patient, after any necessary transformation of the manufactured items and their corresponding manufactured dose form has been carried out.
Administration method (AME)	General method by which a pharmaceutical product is intended to be administered to the patient.
Basic dose form (BDF)	Generalised version of the pharmaceutical dose form, used to group together related pharmaceutical dose forms.
CAS Registry Number	An identifier that usually identifies a single substance.
Chemical substance	A type of substance that can be described as a stoichiometric or non-stoichiometric single molecular entity and is not a protein, nucleic acid, or polymer substance.
Concentration strength	The strength of a substance expressed as the amount of substance per unit of measurement. For example, '2 mg/mL', '2 mg/L'.
Container	An item of packaging that is part of a medicinal product and is used for storage, identification and/or transport of the components of the medicinal product.
Controlled vocabulary	A finite set of values that represent the only allowed values for a data item.
Dose	A specified quantity of medicine, to be taken at one time or at stated intervals.
Dose form	Physical manifestation of a medicinal product that contains the active ingredient(s) and/or inactive ingredient(s) that are intended to be delivered to the patient. Dose form, dosage form, and pharmaceutical dose form are synonymous.
Globally unique identifier	Identifier that is different from any other such identifier in any domain namespace.
Hash function	Any function that can be used to map data of arbitrary size to fixed-size values.
Ingredient	The ingredient is the material used in the preparation of a medicinal/pharmaceutical product, either alone or in combination with other ingredients.
Intended site (ISI)	General body site at which a pharmaceutical product is intended to be administered.
Internal data validation tool	Internal system that ensures the accuracy, integrity, and reliability of the data used for validation and PhPID generation.
Jurisdiction	Geographical area within a country/region or subject matter to which the medicines regulatory agency applies.
Liquid (as state of matter)	A state of matter consisting of molecules in a non-rigid structure that retains its volume but conforms to the shape of any container applying pressure to it and is subject to flow.
Liquid (as basic dose form)	A type of liquid pharmaceutical dose form consisting of a pure substance in a liquid state.
Manufactured dose form (ManDF)	Pharmaceutical dose form of a manufactured item as manufactured and, where applicable, before transformation into the pharmaceutical product.
Manufacturer	An organisation that holds the authorisation for the manufacturing process.
Mapping	An alternative representation of a single concept in one code system expressed in two or more different concepts from a different code system.
Marketing authorisation	Authorisation issued from a medicines regulatory agency that allows a medicinal product to be placed on the market.
Marketing authorisation holder	Organisation that holds the authorisation for marketing a medicinal product in a region.
MD5 hash function	A hash function producing a 128-bit hash value.
Medical device	Any instrument, apparatus, appliance, software, material, or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for diagnosis, prevention, monitoring, treatment, or alleviation of disease.
Medicinal product	Any pharmaceutical product or combination of pharmaceutical products that may be administered to human beings (or animals) for treating or preventing disease.
Medicinal Product Identifier (MPID)	Unique identifier allocated to a medicinal product supplementary to any existing authorisation number as ascribed by a medicines regulatory agency in a region.
Medicinal regulatory agency	Institutional body that, according to the legal system under which it has been established, is responsible for the granting of marketing authorisations, clinical trial authorisations, and manufacturing authorisations for medicinal products.

Microbiological requirements	Microbiological quality control of medicinal product administration to a patient and pharmaceutical preparations and monitoring of production areas depend on the detection and quantification of microorganisms (e.g. requirements for injection might be higher than for oral medications).
Moiety	An entity within a substance that has a complete and continuous molecular structure.
Molecular weight	Mass of one molecule of a homogeneous substance or the average mass of molecules that comprise a heterogeneous substance, which is derived from the molecular structure or the molecular formula.
Multi-dose	A container that holds a quantity of the preparation suitable for two or more doses. Could be either for a single patient or for different patients. Could be the same dose or a varying amount per dose.
Packaged Medicinal Product Identifier (PCID)	Unique identifier allocated to a packaged medicinal product supplementary to any existing authorisation number as ascribed by a medicines regulatory agency in a region.
Parenteral use	The term parenteral relates to the internal body as the intended site of administration, other than the natural openings and cavities such as the gastrointestinal tract, auditory canal, nasal cavity, lungs, etc.; the pharmaceutical product is usually administered by breaking the skin, such as by injection, infusion, and implantation.
Partial use	A container that holds a quantity of the preparation intended for partial use on one occasion only. Products are normally dosed individually based on, for example, body weight or body surface area.
Pattern framework	The pattern framework determines how the strength should be expressed for certain types of pharmaceutical products (PhP), using presentation strength or concentration strength.
Pharmaceutical dose form	Physical manifestation of a medicinal product that contains the active ingredient(s) and/or inactive ingredient(s) that are intended to be delivered to the patient. Dose form, dosage form and pharmaceutical dose form are synonymous.
Pharmaceutical product	Qualitative and quantitative composition of a medicinal product in the dose form approved for administration.
Pharmaceutical Product Identifier (PhPID)	Unique identifier for a pharmaceutical product.
Pharmacovigilance	The process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines.
Presentation strength	The strength of a substance described as a qualitative term describing the discrete unit in which a pharmaceutical product is presented, such as weight per tablet.
Primary use	The most important or most common method of administration and/or indication, where a medicinal product is authorised for use in more than one way.
Quantitative composition	Amount of substance (3.1.35) and specified substance (3.1.32) constituents of the investigational or authorised medicinal product (3.1.19) expressed in a ratio scale (ISO 11216 2017).
Reference strength	Strength of an active substance(s) and/or specified substance(s) used as a reference from which the strength of an investigational or authorised medicinal product (3.1.19) is described. The strength of the active substance(s) and/or specified substance(s) shall be described as a quantity of the substance present in a given unit of the pharmaceutical product or manufactured item.
Reference substance	The reference substance refers to the substance that the reference strength is based on.
Region	Area, especially part of a country or the world, having definable characteristics but not always fixed boundaries.
Release characteristics (RCA)	A description of the timing by which an active ingredient is made available in the body after administration of the pharmaceutical product, in comparison with a conventional, direct release of the active ingredient.
Route of administration	Path by which the pharmaceutical product is taken into or makes contact with the body.
RTO<PQ,PQ>data type	Data type that supports the strength data to be given as a numerator and a denominator, each with units. It allows both a low and a high value to be specified as well as upper and lower ranges. If both low and high values are the same, the interval is equivalent to a single value. If the low value is zero or not valued, the range is interpreted as not greater than the high value. Similarly, if the high value is zero or not valued, the range is interpreted as not less than the low value.
Salt	Ionic substances formed from the neutralisation reaction of an acid and a base.
Semi-solid	A state of matter consisting of molecules in a non-rigid structure that can retain its shape and volume but that is not resistant to such change.
SHA2	Secure Hash Algorithm 2 is a set of cryptographic hash functions.
SHA3	Secure Hash Algorithm 3 is a set of cryptographic hash functions.
Single dose	Single dose refers to a preparation intended for use on one occasion only, i.e. for a single patient as a single injection/infusion and can be either for total or partial use.
Solid	A state of matter consisting of molecules in a rigid structure that is resistant to change in shape or volume.
Specified substance	Refers to groups of elements which describe multi-substance materials or specifies further information on substances relevant to the description of medicinal products. This could

	include grade, units of measurement, physical form, constituents, manufacturer, critical manufacturing processes (i.e. extraction, synthetic, recombinant processes), specification and the analytical methods used to determine that a substance is in compliance with a specification. There are four different groups of elements that can be used to define a given specified substance and specific relationships between each group of elements.
State of matter	A physical condition describing the molecular form of a product.
Strength	Synonym of quantitative composition (ISO 11216 2017).
Strength range	An interval defined by a lower and an upper limit of the amounts of substance and specified substance constituents of the investigational or authorised medicinal product.
Substance	Matter of defined composition that has discrete existence, whose origin may be biological, mineral, or chemical.
Synonym	An alternate symbol or name for the same concept within a given language.
Total use	When the entire quantity of a product is intended to be used on one occasion only, e.g. for a single patient as a single injection/infusion excluding overfill that is discarded.
Transformation	Procedure that is carried out to convert a manufactured item that requires such a procedure into a pharmaceutical product, i.e. from its manufactured dose form to its administrable dose form.
Unified Code for Units of Measure	Code system intended to include all units of measures being contemporarily used in international science, engineering, and business. The purpose is to facilitate unambiguous electronic communication of quantities together with their units. A typical application of the Unified Code for Units of Measure are electronic data interchange (EDI) protocols, but there is nothing that prevents it from being used in other types of machine communication
Unit of measurement	Real scalar quantity, defined and adopted by convention, with which any other quantity of the same kind can be compared to express the ratio of the two quantities as a number.
Unit of presentation	Qualitative term describing the discrete countable entity in which a pharmaceutical product or manufactured item is presented, in cases where strength or quantity is expressed referring to one instance of this countable entity. A unit of presentation can have the same name as another controlled vocabulary, such as a basic dose form or a container, but the two concepts are not equivalent, and each has a unique controlled vocabulary term identifier.
Vocabulary	A terminological dictionary that contains designations and definitions from one or more specific subject fields.

2. Scope

This document presents the recommendations of the Global IDMP Working Group (GIDWG) for business rules on assigning Pharmaceutical Product Identifiers (PhPIDs) to marketed medicinal products for human use.

This document provides high-level guidance on the process of assigning globally unique and harmonised identifiers of pharmaceutical products. This process consists of three overarching steps:

1. To uniquely identify a substance with a Global Substance Identifier (GSID);
2. To determine and/or map dose forms;
3. To harmonise strength expressions, units, and patterns.

3. Background

The International Organization for Standardization (ISO) Identification of Medicinal Products (IDMP) standards aim to harmonise specifications for the identification and exchange of medicinal product data between regulatory agencies, pharmaceutical companies, and manufacturers. It provides an international framework for uniquely identifying and describing pharmaceutical products, ensuring consistent documentation and terminologies, and supporting global regulatory activities.

ISO and the European Committee for Standardization have been engaged in the development of a global system for the identification of medicinal products for more than a decade. The original focus was to support worldwide pharmacovigilance and involved the pharmaceutical industry; the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH); and the regulatory agencies of the European Union, United States and Japan; and World Health Organization.

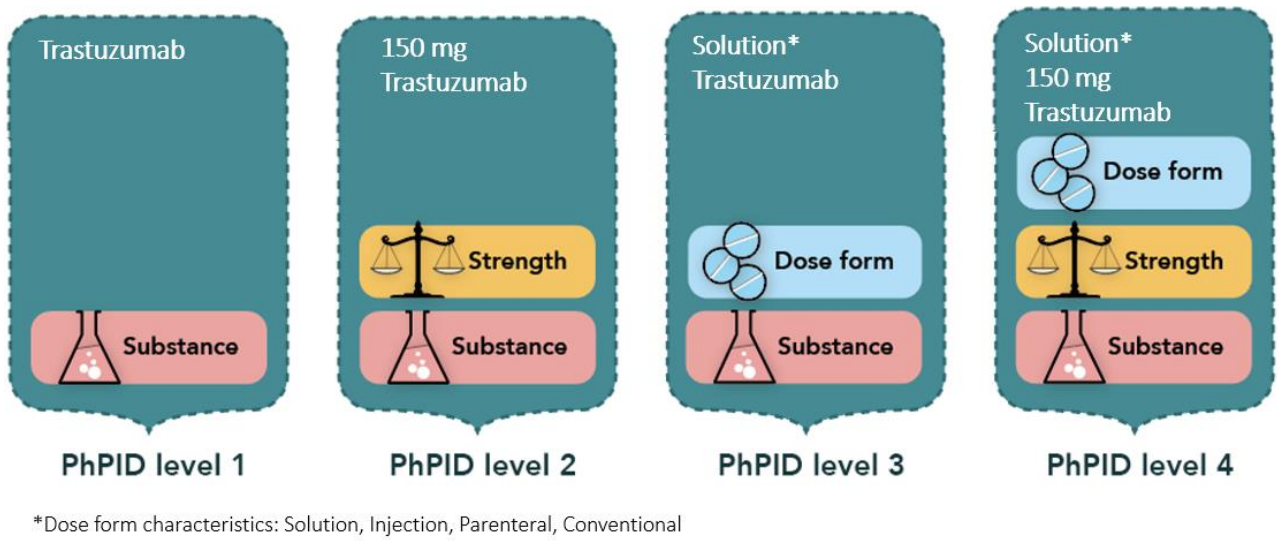

Figure 1. PhPIDs are generated at four levels for a specific pharmaceutical product

A set of ISO/CEN standards was developed under the IDMP umbrella, governing the identification of substances, dose forms, and measurement units.

The goal was to harmonise the identification of medicinal products in different jurisdictions (Figure 2) by implementing a global system of identification at three levels:

- Pharmaceutical Product Identifier (PhPID): a global identifier for the abstract description of a medicinal product, independent of the jurisdiction and the company.
- Medicinal Product Identifier (MPID): an identifier for a medicinal product authorised within a specific jurisdiction and marketed by a specific pharmaceutical company.
- Packaged Medicinal Product Identifier (PCID): an identifier for medicinal product packaging as marketed by a specific pharmaceutical company within a specific jurisdiction, with a defined pack size.

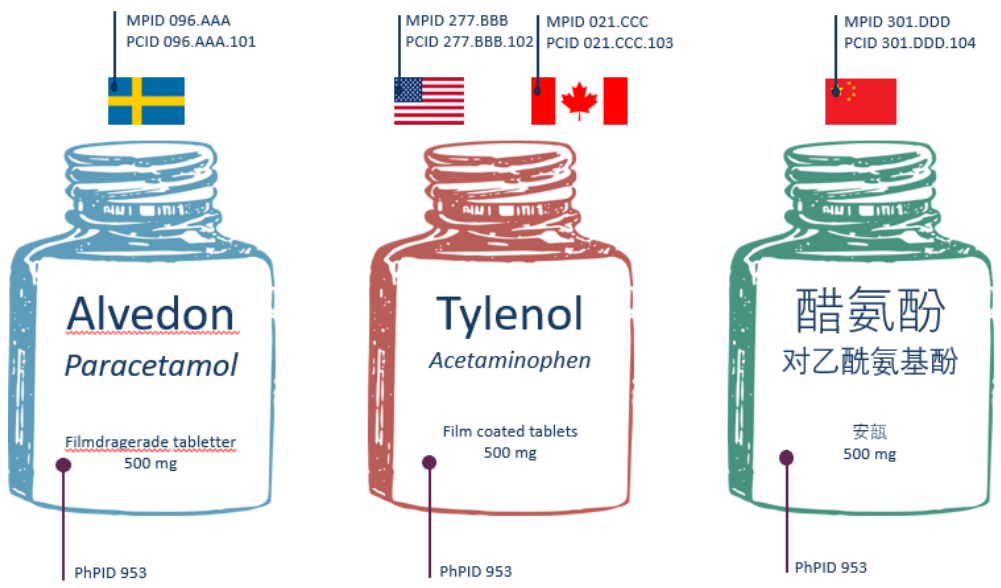

Figure 2. Harmonisation of medicinal products in different jurisdictions to the same PhPID

The MPID and PCID would be governed at supranational and national levels while the PhPID was suggested to be governed at global level, necessitating the appointment of a maintenance organisation. All information is based on marketed products, and confidential information about the substance is not disclosed.

According to the ISO IDMP standards, the PhPID should be based on an MD5 hash function, taking into consideration numerical representations of substance, dose form, strength, and the order of the fields.

3.1 Background on Global Substance Identifier (GSID)

A harmonised, unique, and unambiguous GSID is crucial for generating a Global PhPID. A substance can be assigned a GSID based on the minimal criteria for each substance type defined in the ISO standards for substances, ISO 11238:2018, and its technical specification, ISO/TS19844:2018.

GSID code

The structure of the GSID code follows ISO/IEC 15459 – Part 3 (Ref ISO/IEC 15459) and ISO TS 19844:2017 and is assigned using GSRS software. The code is 17 characters long and consists of a Qualifier, Unique text, and Check character. Each GSID will begin with the letters ‘GSID’ as a prefix, also called a Qualifier. The middle 12 characters are the Unique text – a unique text buildup of random digits and letters. The last character, the Check character, is used as a redundancy check (according to the Luhn mod N algorithm) for error detection on identification numbers. The order for how substance combinations are expressed in PhPID algorithm is: order by GSID (not by substance name) where numbers precede letters, i.e. 9 before A. An example of a GSID is: GSID9ST5UC24F36T3.

3.2 Background on Dose Form Identifier (DFID)

A centrally maintained dose form terminology suitable for global IDMP implementation has not been identified since regional terminologies vary, making mapping between regional terminology and centrally controlled vocabulary complex. To address this issue, a proposal was made to use four of the centralised core European Directorate for the Quality of Medicines & HealthCare (EDQM) dose form characteristics – release characteristics, intended site, administration method, and basic administrable dose form – to index a term for global IDMP and generation of Global PhPID.

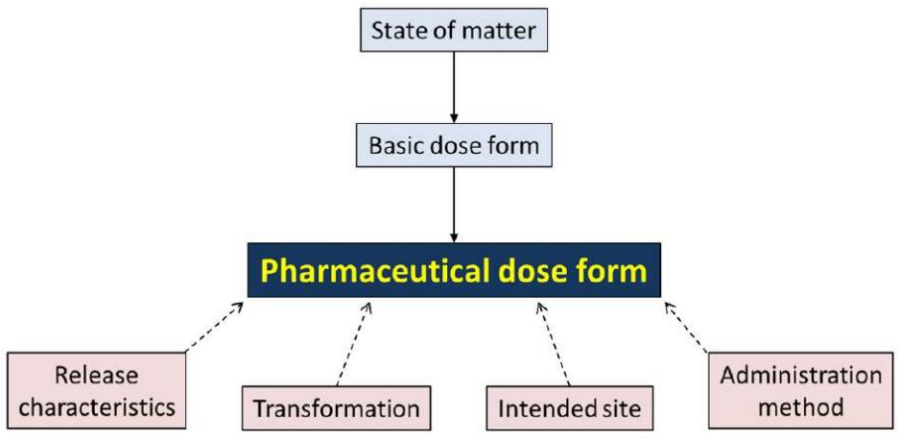

Figure 3. EDQM hierarchy of the pharmaceutical dose form, arranged according to the state of matter and basic dose form, and further characterised by release characteristics, transformation, intended site, and administration method

3.3 Background on Strength Definition Identifier (SDID)

For consistent PhPID, clarification of requirements, structures, and rules for strength expression within the ISO IDMP standard is needed, especially for the use of strength presentation versus strength concentration for different types of medicinal products.

Guidance and rules for strength expression are described in ISO 11240 and ISO 11616. However, guidance for implementing ISO 11238 is also needed, especially for calculating the strength based on molecular weight, which differs between hydrates and anhydrous chemicals.

4. PhPID generation

The processes for generating PhPIDs include the following steps, as depicted in Figure 4.

1. Assigning GSID, including the following sub-steps:
    a. Assigning GSID at substance level or at SSG1 level, when needed
    b. Selecting which GSID to use in PhPID generation.
2. Validation of marketed pharmaceutical product data, including the following sub-steps:
    a. Assigning the active ingredient of the product.
    b. Defining the dose form characteristics
    c. Defining the unit strength and presentation strength or concentration strength. The reference strength may be used to calculate the unit strength; however, the reference strength is not included in the PhPID calculation.

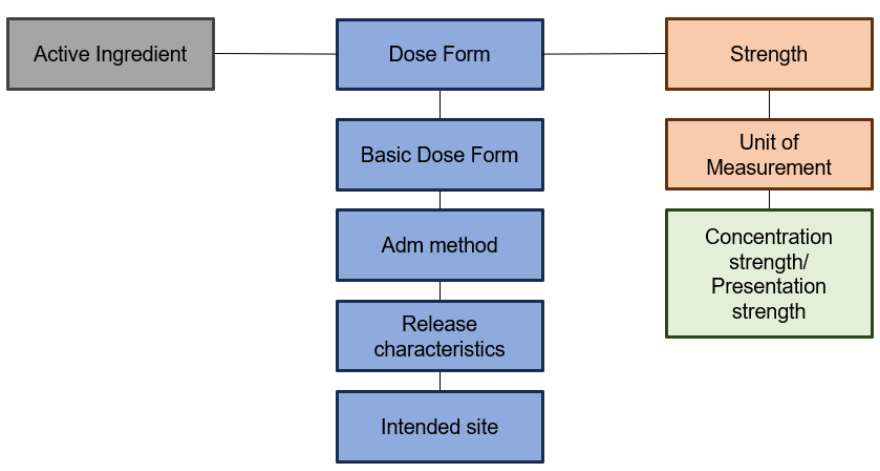

Figure 4. The PhPID is generated using a numerical representation of the substance, dose form, and strength (presentation strength or concentration strength). Unit of presentation is used to define the strength but is *not* a part of the PhPID input string

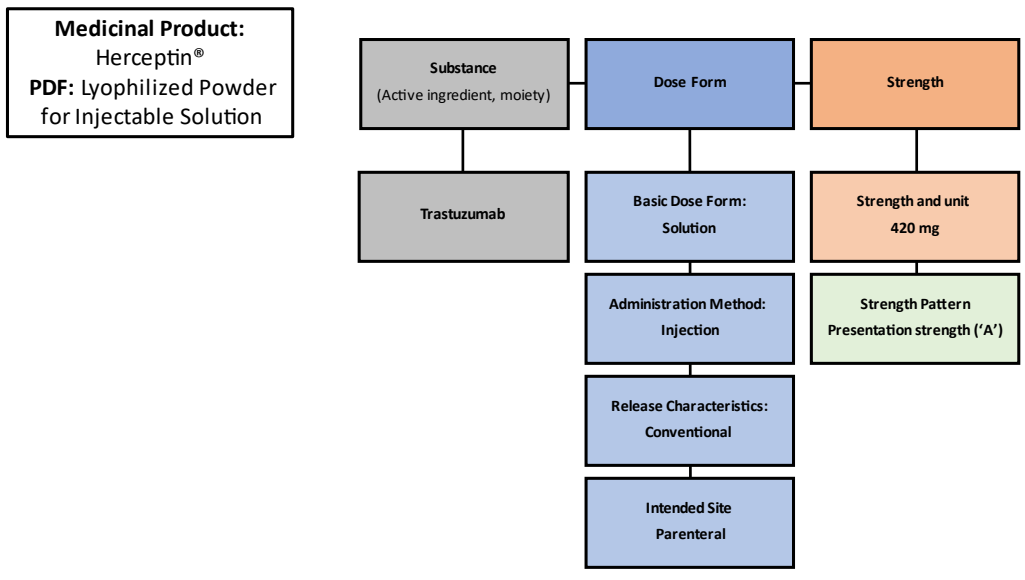

Figure 5. An example of how Herceptin® is validated by the UMC team based on the approved rules. The validation process is split into three parts – substance, dose form, and strength – for characterisation of the corresponding product and harmonisation according to ISO IDMP standards, other standards (e.g. EDQM, UCUM), and the business rules described in this document

The order of input into the MD5 hash function is substance/strength/dose form.

- The identifiers for substance, dose form, and strength will be separated by a semicolon (;)
- Substances will be ordered by GSID and separated by a pipe (|)
- Amount is represented with a point (.) and two decimals
- When multiple dose forms are used, they are represented within square brackets ([ ]) and ordered by ID (lowest to highest)

5. Business rules

The purpose of the business rules for Global PhPID is to globally harmonise and define standardised information for substance, dose form, and strength identification and ensure consistent PhPID construction. Harmonisation supports the global identification of products that are comparable and/or identical, even if the description varies in Summaries of Product Characteristics (SPCs) across different jurisdictions.

5.1 Business rules for assigning GSID to PhPID

Currently, GSIDs for chemicals, nucleic acids, proteins, and polymers have been used to generate Global PhPIDs. GSIDs for structurally diverse substances have not yet been used. The general rule for which GSID to apply to PhPID generation is to use the active ingredient of the product, i.e. the ingredient stated in the SPC. For combination products with two or more active ingredients, the individual GSIDs of all substances will be used to generate the PhPID. A GSID can be assigned at substance level to both active moiety and variants, such as salts (see Figure 6). A GSID can also be assigned at SSG1 level.

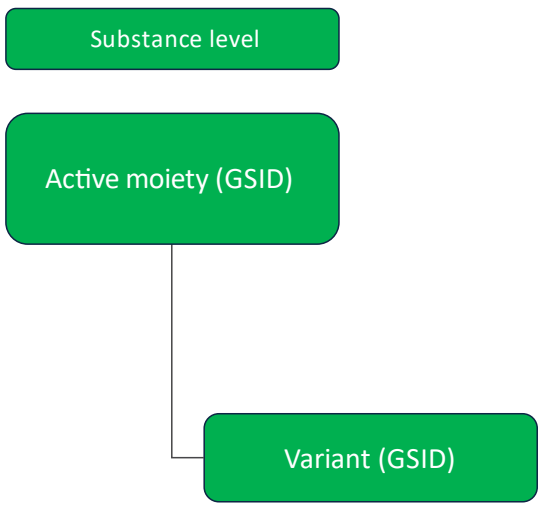

Figure 6. Schematic illustration of the general rule for GSID selection for chemicals used in PhPID generation

Proteins can be assigned a GSID at both substance level and SSG1 level (see Figure 7). The general rule is that the substance level GSID is used for PhPID generation if it enables unique identification.

According to ISO 11238:2018 and ISO/TS 19844, the defining factors at substance level for proteins are amino acid sequence, glycosylation type and –site, and disulfide linkage. All four factors need to be the same if two entities are to be viewed as the same substance. Differences in detailed glycosylation patterns belong to the SSG1 level, which is not used in most PhPID generation.

Four examples of how to choose GSID for PhPID generation:

i. To harmonise the PhPID of medical products containing substances that are hydrated, the PhPID is generated based on the anhydrous form of the substance, see Figure 8. One example is a product containing Lidocaine HCl monohydrate, whose PhPID will be generated using the GSID for Lidocaine HCl. For products containing a protein solvate, the GSID of the active ingredient is used.

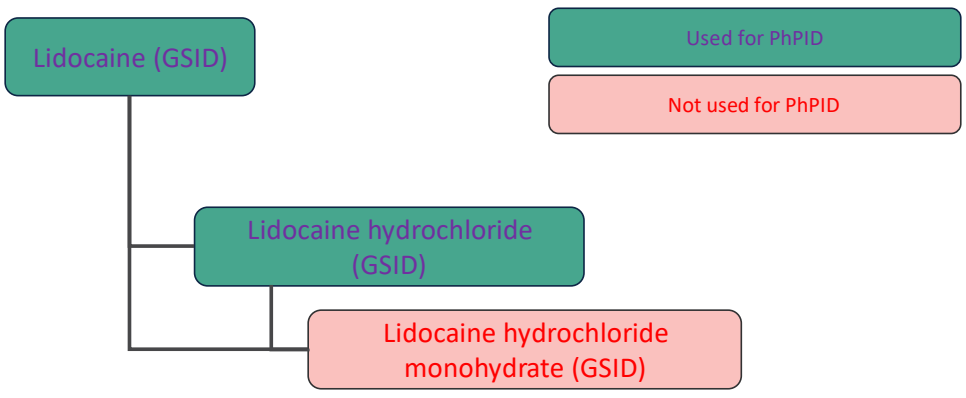

Figure 8. Schematic illustration of the selection of GSID for hydrated and anhydrous substances

ii. For monoclonal antibodies (mAb), the GSID at substance level will be used for PhPID generation, see Figure 2. Consequently, for mAb differing in detailed glycosylation pattern, the GSID corresponding to that information level – SSG1s – will not be used for PhPID generation. For example, Trastuzumab will be assigned one unique GSID at substance level, which will be used for PhPID generation.

iii. An ingredient in a pharmaceutical product can be described either as an active ingredient or as an excipient. This decision is made by each regulatory authority in their own jurisdiction. Some products are described differently in different jurisdictions regarding active ingredients and excipients. To enable harmonisation of comparable products, UMC and the GSID GIDWG group will assess such products to decide which GSIDs should be used for PhPID generation. One example is Herceptin hylecta/SC, which is described with Trastuzumab as active ingredient and Hyaluronidase as excipient in New Zealand and by the EMA. But in the US, it is described with two active ingredients: Trastuzumab and Hyaluronidase. The investigation showed that the most common way to authorise the product is with Trastuzumab as active ingredient and hyaluronidase as excipient. Accordingly, GIDWG decided to harmonise the products by assigning the PhPID based only on Trastuzumab as the active ingredient, see Table 3.

Another example is products with the antibiotic Amoxicillin and the beta-lactamase inhibitor Clavulanate potassium. Most regulators describe both ingredients as active so PhPID generation will be based on two GSIDs.

Table 3. Example of the harmonisation of GSID used in PhPID generation for substances and excipients. All three products will be harmonised to the same PhPID

SPC data				Harmonised data for PhPID	
Product name	**Active ingredient**	**Excipient***	**Strength**	**GSID used for PhPID**	**Strength PhPID**
Herceptin hylecta[1]	Trastuzumab and hyaluronidase-oysk**	NA	600 mg and 10,000 units per 5 mL	Trastuzumab	120 mg/mL
Herceptin SC[2]	Trastuzumab	Vorhyaluronidase alfa**	600 mg/5 mL		
Herceptin (SC)[3]	Trastuzumab	Recombinant human hyaluronidase (rHuPH20)**	600 mg/5 mL		

Roche is the market authorisation holder for all three products

[1] USA, [2] New Zealand, [3] EMA

*Only excipients that are listed as active ingredients in some sources and as excipients in some sources are listed

** The same substance, only New Zealand uses the INN name

iv. For insulins, both the substance level and the SSG1 level GSID can be used in PhPID generation. One example is a fast-acting insulin that contains insulin aspart (substance level), whereas an intermediate-acting insulin contains both insulin aspart (substance level) and insulin aspart protamine (SSG1 level), see Table 4. The PhPID will be based on the GSID of insulin aspart and the GSID corresponding to the insulin aspart protamine (SSG1 level).

Table 4. GSIDs for insulins used in PhPID generation			
Product active ingredient	**Substance level**	**SSG1 level**	**Which level to use for PhPID generation**
Insulin aspart	GSID	N/A	Use GSID for substance level for PhPID generation.
Insulin aspart protamine	N/A	GSID	Use GSID for SSG1 level for PhPID generation
Insulin aspart and Insulin aspart protamine	GSID N/A	N/A GSID	Use GSID for substance level and SSG1 level, respectively, for PhPID generation.

5.2 Business rules for assigning dose form characteristics to Global PhPID

The purpose of this section is to describe how dose forms are defined using a set of dose form characteristics from EDQM, regardless of regional dose form terminology, and how these dose form characteristics can be used as a centrally maintained dose form terminology for global IDMP implementation.

The business rules on dose form characteristics are intended to provide a set of guidelines for indexing dose forms of medicinal products using the four core EDQM dose form characteristics to globally harmonise and define capture of standardised information for global dose form identification and ensure consistent PhPID construction.

The four EDQM dose form characteristics, namely basic administrable dose form, administration method, release characteristics, and intended site, are to be assigned to medicinal products based on the following business rules:

5.2.1 Business rules for assigning basic dose form characteristics

Since basic dose form (BDF) represents a general type of pharmaceutical formulation (e.g. tablet, capsule, cream, ointment, solution, emulsion) used for medicinal products, it is a valuable tool in defining and harmonising dose form information associated with medicinal products.

BDF is assigned based on the following principles:

- The BDF is regularly identified from the submitted pharmaceutical dose form as verified in the SPC.
- The BDF always refers to administrable dose form (AdmDF) as per ISO standard 11239.
- Only one BDF per AdmDF is assigned.
- BDF selection and assignment is supported by EDQM Standard Terms guidance, both the BDF definitions and the connected BDF(s), when a product's dose form matches an EDQM PDF (process 'AS IS' is semi-automated: first mapping is performed manually and then incorporated into the Global PhPID knowledge base).
- When a medicinal product does not undergo transformation and keeps the same dose form when being administered to the patient. (Manufactured dose form – ManDF – is equal to AdmDF.)
- The BDF is assigned using a dedicated suite of business rules when a medicinal product may undergo transformation and may be administered in a different dose form to the patient, depending on the ManDF and administrable BDF (AdmBDF). (ManDF is not equal to AdmDF but can be mapped to EDQM Standard Terms.)
- The BDF is assigned using a dedicated suite of business rules (AdmDF cannot be mapped to EDQM Standard Terms without applying harmonisation business rules*) when:
    - A medicinal product's dose form can be expressed differently within different jurisdictions (either the naming or the definitions can differ), sometimes in a way that makes it impossible to assign AdmBDF consistently at the most granular level (e.g. be able to separate BDF 'Patch' and 'Plaster');
    - ManDF can be transformed or taken as several possible AdmBDFs;
    - Different dose form terminologies have different granularity (additional investigation of other sections in the SPC is sometimes needed to find information about BDF);
    - No information on BDF is available (in some rare cases a judgment will be made based on similar medicinal products with the same substance and dose form).

*Harmonisation business rules are being formalised and refined as the Global PhPID Service develops, with more data being processed from different jurisdictions.

Business rules examples

1. For several dose forms, the AdmDF and the ManDF are the same and the BDF is not transformed (examples in Table 9).

Table 9. Examples of business rules for PDFs with the same AdmDF and ManDF					
Medicinal product name	ManDF	AdmDF	ManBDF	AdmBDF	Harmonised AdmBDF for PhPID
Allergyl (promethazine)	Film-coated tablet	Film-coated tablet	Tablet	Tablet	Tablet
Daktarin® (miconazole)	Cream	Cream	Cream	Cream	Cream
Xofigo® (Radium Ra 223 dichloride)	Solution for injection	Solution for injection	Solution	Solution	Solution

2. When the ManDF is different from the AdmDF, the BDF is manually changed from the ManBDF to the AdmBDF (examples in Table 10). For a product example of how dose forms can differ between regions as well change from ManBDF to AdmBDF, see Table 11.

Table 10. Examples of business rules for PDFs with different AdmDF and ManDF

Medicinal product name	ManDF	AdmDF	ManBDF	AdmBDF	Harmonised AdmBDF for PhPID
Hyaluronidase	Powder for solution for infusion	Solution for infusion	Powder	Solution	Solution
Deferasirox®	Dispersible tablet	Oral suspension	Tablet	Suspension	Suspension For tablets that are always dispersed before being taken, the BDF will be 'Suspension'
Lamictal® (Lamotrigine)	Chewable/ dispersible tablet	Chewable tablet Oral suspension	Tablet	Tablet Suspension	Tablet For tablets that can be swallowed and taken as a solution/suspension, the BDF will be 'Tablet'
Berocca®	Effervescent (soluble) tablet	Oral solution	Tablet	Solution	Solution

Table 11. Examples of business rules for PDFs with different AdmDF and ManDF, and same product expressed differently in different regions

Medicinal product name	Country	ManDF	AdmDF	ManBDF	AdmBDF	Harmonised AdmBDF for PhPID
Zithromax® (azithromycin)	UK	Powder for oral suspension	Oral suspension	Powder	Suspension	Suspension
	Korea	Dry syrup	Syrup	Powder	Syrup	
	USA	For oral suspension	Oral suspension	Powder	Suspension	

5.2.2 Business rules for assigning administration method characteristics

Administration method (AME) is the general method by which a pharmaceutical product is intended to be administered to the patient (per EDQM's definition).

AME is assigned based on the following principles:

- The AME is generally assigned based on SPC information and the text included within the dosage and administration. Careful investigation of the SPC is often necessary.
- AME is generally assigned based on primary use.
- One AME or several AMEs can be assigned to a medicinal product.
- AME selection and assignment is supported by EDQM Standard Terms guidance, both the AME definitions and the connected AME(s), when a product's dose form matches an EDQM PDF (process ´AS IS´ is semi-automated: first mapping is performed manually and then incorporated into the Global PhPID knowledge base).
- For medicinal products that have more than one administration method:
    - When assigning multiple AMEs to a PhPID, EDQM Standard Terms guidance is used if an appropriate matching PDF exists. For example, oral/rectal solution – AME 'Administration' and 'Swallowing' are assigned;
    - Whenever a PhPID is assigned multiple AMEs, each individual AME code is included in the PhPID (concatenated from lowest to highest number to ensure consistency).
- Where a medicinal product can be used in more than one way, and there is no appropriate matching EDQM PDF, AME is assigned for PhPID based on the primary use or the term with the strictest microbiological requirements. As stated in the EDQM editorial guidelines cited below:
  For example, a product that can be used as an oral, gastric and gastroenteral solution – AME 'Swallowing' is assigned since oral is considered the primary use. For a product that can be used rectally and as an injection – only AME 'Injection' is assigned due to this having the strictest microbiological requirements.
- The AME is assigned using a dedicated suite of business rules (AME cannot be mapped to EDQM Standard Terms without applying dedicated harmonisation business rules*) when:
    - Dose forms can be expressed differently within different jurisdictions (either the naming or the definitions can differ), sometimes in a way that makes it impossible to assign AME consistently at the most granular level (e.g. be able to separate AME 'Injection' and 'Infusion').

  *Harmonisation business rules are being formalised and refined as Global PhPID develops, with more data being processed from different jurisdictions.

Business rules examples

Examples of medicinal products where the product's dose form can be mapped to EDQM AME(s), Table 19-20:

Table 19. Examples of business rules to harmonise AME for PhPID, chewable tablets			
Medicinal product name	SPC dose form	Administration method according to SPC	EDQM AME used in PhPID
Tylenol® (acetaminophen)	Tablet, chewable	Chew or let the tablet dissolve in the mouth	´Chewing and Swallowing´
Lipitor® (atorvastatin)	Chewable tablet	The tablets can be chewed or swallowed (whole)	
Lamictal® (lamotrigine)	Chewable tablet	Tablet can be chewed or dispersed before swallowing	

Table 20. Examples of business rules to harmonise AME for PhPID, oral drops			
Medicinal product name	Country	SPC	EDQM AME used in PhPID
Flamatrat® (Diclofenaco Resinato)	Brazil	Oral drops, suspension 'The number of drops needed must be counted on a spoon and the contents of the spoon must be ingested'	'Instillation' and 'Swallowing'

1. Examples of products with AMEs that follow specific harmonisation rules for PhPID, Tables 21 and 22:

Table 21. Examples of business rules to harmonise AME for PhPID, cutaneous solutions and cutaneous solution drops			
Medicinal product name	Country	SPC	EDQM AME used in PhPID
Clotrimazol® (clotrimazole)	Brazil	Cutaneous solution drops	Application
Canesten® (clotrimazole)	UK	Cutaneous solution	

Table 22. Examples of business rules to harmonise AME for PhPID, injection and/or infusion			
Medicinal product name	Country	SPC	EDQM AME used in PhPID
Nexium® (esomeprazole sodium)	UK	Powder for solution for injection/infusion	Injection
Nexium iv for injection	US	Powder for injection	

5.2.3 Business rules for assigning intended site characteristics

Intended site (ISI) is described as the general body site at which a pharmaceutical product is intended to be administered (per EDQM's definition). The following ISIs were available for consideration when developing the business rules during end-to-end testing, per Table 25.

ISI is assigned based on the following principles:

- The ISI is generally assigned based on SPC information and the text included within the dosage and administration. Careful investigation of the SPC is often necessary.
- ISI selection and assignment is supported by EDQM Standard Terms guidance, both the ISI definitions and the connected ISI(s), when a product's dose form matches an EDQM PDF (process ´AS IS´ is semi-automated: first mapping is performed manually and then incorporated into the Global PhPID knowledge base).
- ISI is generally assigned based on primary use.
- One ISI or several ISIs can be assigned to a medicinal product.
- For medicinal products that have more than one intended site and it is difficult to select one primary use and/or term with the strictest microbiological requirements. Where it is not possible to identify a primary use or the strictest microbiological requirements, a new business rule may be created to use several ISI to indicate two or more uses.
- The ISI is assigned using a dedicated suite of business rules (ISI cannot be mapped to EDQM Standard Terms without applying dedicated harmonisation business rules*) when:

- Dose forms can be expressed differently within different jurisdictions (either the naming or the definitions can differ), sometimes in a way that makes it difficult to assign ISI consistently at the most granular level.

*Harmonisation business rules are being formalised and refined as Global PhPID develops, with more data being processed from different jurisdictions.

Business rules examples

1. Examples of medicinal products where the product's dose form can be mapped to EDQM ISI(s)

Table 28. Examples of business rules to harmonise ISI for PhPID

Medicinal product name	Country	SPC	EDQM ISI used in PhPID
Compaz® (diazepam)	Brazil	Solution for injection can also be administered by a nasogastric tube	Parenteral (The ISI 'Gastric' should not be assigned. 'Parenteral' will be considered the primary use due to the strictest microbiological requirements)
Gentamicin® (Gentamicin sulphate)	UK	Eye/ear drops solution	'Ocular' and 'Auricular'

2. Examples of products with ISIs that follow specific harmonisation rules for PhPID:

Table 29. Examples of business rules to harmonise ISI for PhPID, multiple topical ISIs including cutaneous use

Medicinal product name	Country	SPC	EDQM ISI used in PhPID
Xylocaine gel	Norway	´Superficial, painful skin damage; anal lesions; urethral anaesthesia; cystoscopy and mucosal anaesthesia, during bronchoscopy and intubation'	Cutaneous/Transdermal (Gel, sprays, ointments, and creams for cutaneous use that can also be for rectal use, oromucosal use, and other sites are assigned the ISI 'Cutaneous´. As long as cutaneous use is included, it will be considered the primary use)

Table 30. Examples of business rules to harmonise ISI for PhPID

Medicinal product	Country	ISI in SPC	Possible EDQM ISI	EDQM ISI used in PhPID
Xylocain Cutaneous spray 100 mg/mL (lidokain)	Sweden	• Odontology • Oto-rhino-Laryngology • Obstetrics • Closure of instruments, tubes and catheters in the respiratory tract and gastrointestinal tract	• Nasal • Oromucosal • Dental • Pulmonary • Vaginal and/or Cutaneous	Cutaneous/Transdermal (Gel, ointment, cream, solution or spray used for the obstetrics indication 'episiotomy and perineal suturing'. The site of this indication is regarded as cutaneous)
Lidocaína solução spray 10% (Lidocaine)	Brazil	• Odontology • Oto-rhino-Laryngology • Obstetrics	• Nasal • Oromucosal • Dental • Vaginal and/or Cutaneous	

5.2.4 Business rules for assigning release characteristics

Release characteristics (RCA) describes the timing by which an active ingredient is made available in the body after administration of the pharmaceutical product, in comparison with a conventional, direct release of the active ingredient (per EDQM's definition).

RCA is assigned based on the following principles:

- RCA is based on SPC information and is sometimes included in the product name or dose form. In some cases, the information can be found in different sections of the SPC, e.g. pharmacokinetics.
- When no information about prolonged/modified/delayed release is found in the label, the 'Conventional' term is assigned.
- The RCA 'Modified' should be used for pulsatile-release products but is sometimes used in SPCs for products that should have RCA as 'Prolonged' or 'Delayed'.
- Only one RCA is assigned per PhPID.
- RCA selection and assignment is supported by EDQM Standard Terms guidance, both the ISI definitions and the connected ISI(s), when a product's dose form matches an EDQM PDF (process ´AS IS´ is semi-automated: first mapping is performed manually and then incorporated into the Global PhPID knowledge base).
- The RCA is assigned using a dedicated suite of business rules (RCA cannot be mapped to EDQM Standard Terms without applying dedicated harmonisation business rules*) when:
    - Dose forms can be expressed differently within different jurisdictions (either the naming or the definitions can differ), sometimes in a way that makes it difficult to assign RCA with consistency.

*Harmonisation business rules are being formalised and refined as Global PhPID develops, with more data being processed from different jurisdictions.

Business rules examples

Table 35. Examples of business rules for RCA for PhPID, microspheres compared to conventional formulation

Medicinal product name	AdmDF	Dosage	EDQM RCA used in PhPID
Sandostatin® (Octreotide acetate)	Suspension for injection	Every 8-12 hours	Conventional
Sandostatin LAR® (Octreotide acetate, in microspheres)	Suspension for injection	Every 4 weeks	Prolonged

Table 36. Examples of business rules to harmonise RCA for PhPID, insulin for injection

Trade name	Ingredient(s)	Type of insulin	EDQM RCA used in PhPID
NovoRapid®	Insulin aspart	Fast-acting	Conventional
Humulin®	Insulin human protamine	Intermediate-acting	
NovoMix®	Insulin aspart/Protamine-crystallised insulin aspart	Intermediate-acting	
Abasaglar®	Insulin glargine	Long-acting	
Fiasp®	Insulin aspart and Nicotinamide (excipient) acting as a modifier by promoting faster absorption	Fast-acting	

5.3 Business rules for generating global Strength Definition Identifiers (SDID) for PhPID

To unambiguously link the strength to the product both the substance strength and the reference substance strength need to be specified in the PhPID Global Service system when the active ingredient is a salt/ester/pro-drug. The identification of substance or reference substance and their corresponding strength is verified in the SPC. The reference strength is derived from active moieties of an active substance(s). However, the reference strength is not used for PhPID generation.

- If the active substances are given as salts/esters or pro-drugs in the SPC, and the strength corresponds to the salts/esters or pro-drugs, the reference substance strength is calculated as follows:

$$\frac{\text{Substance (mg)}}{\text{substance molecular weight(mg/mol)} \cdot \text{reference substance molecular weight(mg/mol)}}$$

- If the active substances are given as salts/esters or pro-drugs in the SPC, and the strength corresponds to the active moiety, the salts/esters or pro-drug substance strength is calculated as follows:

$$\frac{Reference\ subs\tan c\ e\ (mg)}{reference\ subs\tan c\ e\ molecular\ weight(mg/mol)\ \cdot\ subs\tan c\ e\ molecular\ weight(mg/mol)}$$

- For the substance type Polymers, it is worth noting that they are described using the average molecular weight as they are inherently polydisperse (ISO/TS 19844:2018).

- If the active substance is the active moiety in the SPC, no calculation is required.

The strength used for generating a PhPID is typically the strength of the active ingredient. The product strength indicated in the SPC (given strength) should be used for PhPID generation. This strength is either entered directly on the active ingredient (when the strength indicated in the SPC is on the active ingredient) or calculated from the base strength (as in cases where the base strength is the strength indicated in the SPC and the active ingredient is a salt).

Due to variation in strength expression across regions, verification of strength is performed to determine if the given strength of the product corresponds to a salt form or to the base/active moiety. Harmonisation is performed for differences between SPCs according to business rules, as described in the sections below.

Careful investigation of the SPC is necessary. If limited information on strength is available, a judgment will be made based on similar products on the market with the same substance, strength, and dose form. If no exact strength is related to the substance, the strength interval will be expressed as RTO<PQ, PQ>data type, according to ISO 11616.

5.3.1 Business rules on numerical values for strength expression

Business rules and various data elements should be made explicit to express the above concepts for strength and the extent of their integration in the PhPID, see Table 38.

The strength numerical value is assigned based on the following principles, associated with the substance or specified substance:

Table 38. Business rules on numerical values for strength expression	
Value range	Substance strength, i.e. the 'amount' is expressed in the value range of 1-999 with two decimals: • 0.1 g or 100 mg, 100 mg is assigned • 1000 mg or 1 g, 1 g is assigned • Per day, a number of hours is assigned (e.g. 24 h).
Unit specific rules when strength outside value range	For substantial numbers (e.g. 30 MIU or 30000000 IU for filgrastim) the rule to express substance strength in a value range of 1-999 does not apply. These strengths are instead expressed with an SI prefix, the power of, or writing out zeroes, depending on which unit is used: • SI prefix for Bq (becquerel) • The 'power of' for virus-like particles and cells • Writing out zeroes for IU The SI prefix is added to a Unified Code for Units of Measure (UCUM) unit in applicable cases, resulting in a modified UCUM unit, for example MBq (Mega becquerel).
Value number for denominator	The value number for PhPID denominator should always be 1 (e.g. mg/mL), except for patches and vaginal rings where the PhPID value number can be other than 1 (e.g. 5 mg/16 hours; in this case the value number = 16).
UOP (unit of presentation)	Use UOP for defining and calculating the strength and use the value and denominator (omit the UOP) when entered into the PhPID input string.
Rounding	Slight rounding differences are harmonised. For example, a tablet with Amlodipine besilate with strength expressed as 13.88 mg will be harmonised with a tablet with strength expressed as 13.87 mg.
Recalculating	Strength is recalculated for PhPID to match the rules for denominator and unit. For example, 100 mg/5 mL is recalculated to 20 mg/mL.
Combined insulins	The strength for combined insulins (e.g. fast-acting and long-acting) is calculated based on the ratio of ingredients.

5.3.2 Business rules on standardised units for strength expression

According to ISO 11240, the reference vocabulary for strength should be the Unified Code for Units of Measure (UCUM) standard.

The WHODrug units of measure value list is used as input to generate the PhPID, representing a corresponding unit value (e.g. a UCUM unit value). When a UCUM unit is available this is used. The principle for selecting a unit when no UCUM unit is available is described below in Table 39, 'Non-standard units and regional units'.

The strength unit is assigned based on the following principles, associated with the substance or specified substance:

Table 39. Business rules on unit assignment for strength expression	
Unit standard	UCUM is used, where possible (https://ucum.nlm.nih.gov/ucum-lhc/demo.html) For units that are not covered by UCUM (see non-UCUM units)
Processing non-UCUM units	When possible, the non-UCUM unit is converted into a UCUM unit.
Unit variation, process for converting between different units	It is important to harmonise units as appropriate. When several units are used for a medicinal product(s) with a certain substance, products in several regions are investigated to determine which unit is most used. The PhPID should be generated based on mass rather than biological effect where possible and/or the most used unit. In applicable cases conversion tables are used, such as from the Martindale Drug Reference, SPCs, or other reliable references. These are documented and the same conversion table is used for any future PhPIDs with the same substance.
Unit variation, IU vs g/mg/µg	Unit variations for heparins (e.g. g/mg/µg, IU, or both) are expressed in IU. Hormones should be expressed as either g/mg/µg or IU, for example: o Oxytocin: IU o Vasopressin: IU o Somatropin: g/mg/µg o Insulins: IU

Unit variation, %	% is not used, weight/weight (w/w; mg/g) or weight/volume (w/v; mg/mL) is used instead.
Harmonisation, specific units	Genomes/vector genomes For products with the unit described as 'genomes' or 'vector genomes', the unit used in PhPID is {vector genomes}. CD4+ cells or CD8+ cells For products with the unit described as 'CD4+ cells' or 'CD8+ cells', the unit used in PhPID is {cells/mL} or {cells} depending on the product. Units When the strength is given in 'units' (also expressed as 'u' or 'U'), the unit is changed to 'IU'.
Strength for patches (and plasters)	Patches (and plasters) are expressed in different ways (e.g. /h, /8h, /24h, /72h). The strength is expressed as the delivery rate given in SPC. Nicotinell® (nicotine) 21 mg/24 h Nicorette® (nicotine) 25 mg/16 h
Unit for liquid preparations (e.g. cutaneous solution)*	The unit should always be w/v if concentration strength (even if SPC uses w/w). If SPCs use w/w, the unit is changed to w/v without converting the value. Also, when the strength is given in percent and not specified as w/v or w/v, then w/v is used.
Units for-solid preparations (cream, gel, foam, ointment, paste)*	The unit should always be w/w if concentration strength (even if SPC uses w/v). If SPCs use w/v, the unit is changed to w/w without converting the value. Also, when the strength is given in percent and not specified as w/v or w/v, then w/w is used.

5.3.3 Concatenated pattern framework for strength expression

The pattern framework determines how the strength of a pharmaceutical product (PhP) should be expressed for a certain type of product, using presentation strength or concentration strength. The data validation process revealed dissimilar practices in the expression of strength in different regions and led to the need for further pattern simplification. As a result, the concatenated pattern framework was developed.

The way the strength should be entered (concentration or presentation) is decided by three different patterns that are based on the dose form and use of the product, see Table 40:

- The presentation strength 'Pattern A' is the strength of a substance expressed as a quantitative term describing the discrete unit in which a pharmaceutical product is presented, such as weight per tablet.
- The concentration strength 'Pattern B' is the strength of a substance expressed as the amount of substance per unit of measurement, such as millilitre or gram.
- The concentration strength 'Pattern C´ is when the strength of a substance is expressed as a delivery rate over time.

Table 40 provides the necessary guidance to select between the three patterns:

Pattern	Type of product	Examples	Unit of presentation	Strength by presentation	Strength by concentration
A	Solid, countable Solid dose forms in 'container' Metered dose delivered by a metered actuation	Tablets, capsules, suppositories Powder or granules in sachet Inhalers, spray	Tablet, capsule Container (sachet, etc) Actuation (inhaler, etc)	x	-
B	Unit dose or continuous presentation (dosing is individual/not accurate and the total volume in the container is of less importance for dosing purposes)	Vials, unit dose solutions, parenteral liquid, unit dose nebuliser solutions Bulk powders/granules, semi-solid 'bulk' liquids (i.e. eye drops), spray that is not metered dose	N/A since it is the concentration that is relevant	-	x
C	Products enclosed in a 'presentation', where the dose has a delivery rate	Transdermal patches	Patch	-	x As a delivery rate over time

X – applicable

The flow chart in Figure 10 illustrates strength pattern assignment for different parenteral preparations:

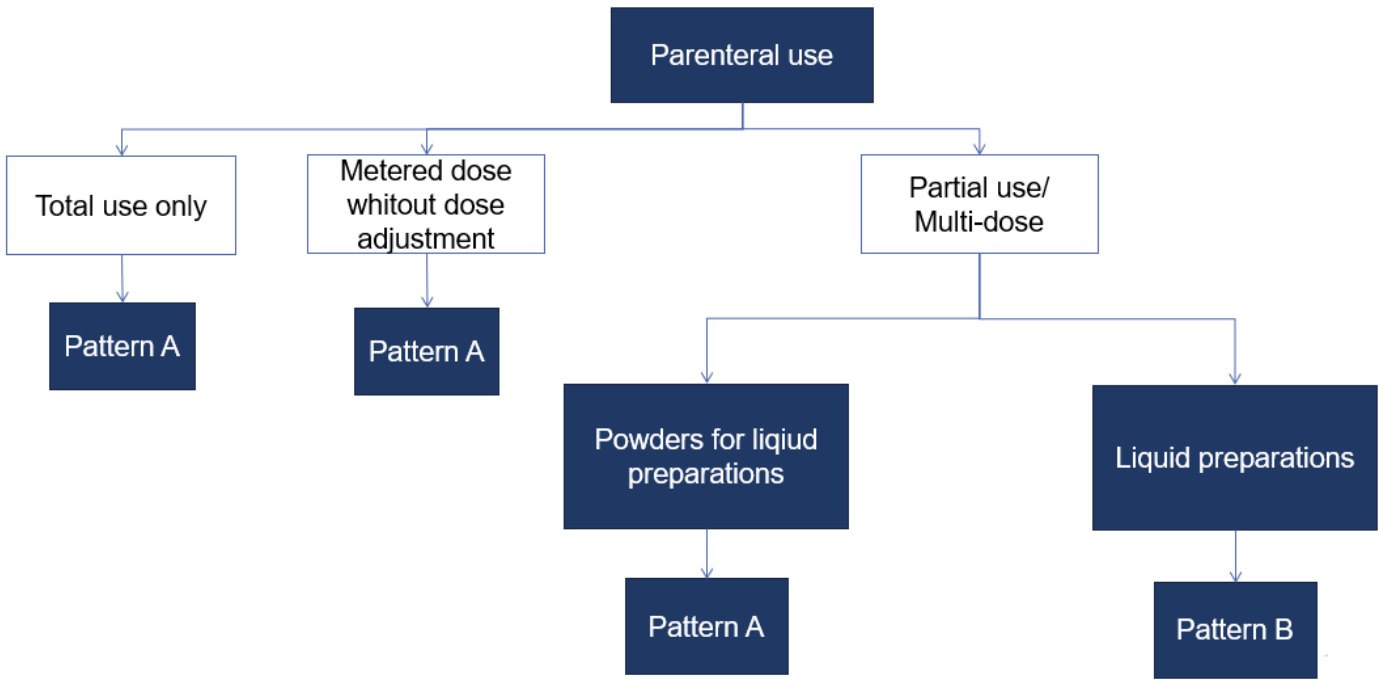

Figure 10. Illustrates strength pattern assignment

Total use: When the amount of preparation in the individual container is given in total as a single administration, i.e. for a single patient as a single injection/infusion (excluding overfill that is discarded). Even though children or people with reduced kidney function might receive a lower dosage. 'Single dose' is not the same as total use. Single dose refers to a preparation intended for use on one occasion only, i.e. for a single patient as a single injection/infusion and can be either for total or partial use.

Partial use: When the dose to be administered is calculated on an individual basis (normally body weight/surface) and any unused quantity of the preparation is to be discarded. Intended for use on one occasion only, i.e. for a single patient as a single injection/infusion.

Multi-dose: A container that holds a quantity of the preparation suitable for two or more doses. Could be either for a single patient or for different patients. Could be same dose or varying amount per dose.

Metered dose: A specific amount of medication produced following a single administration of a pump, valve, or other equivalent dosing mechanism.

Examples of strength expression applying concatenated pattern framework differentiated by pattern:

Table 41. Pattern A for solid, countable				
Medicinal product	SPC dose form	Harmonised BDF	SPC strength	Strength used in PhPID
Phenegran (promethazine HCl)	Suppository	Suppository	25 mg	25 mg

Table. 42. Pattern A for total use,liquid and concentrate				
Medicinal product	SPC dose form	Harmonised BDF	SPC strength	Strength used in PhPID
Lovenox (enoxaparin sodium)	Prefilled syringe	Solution	40 mg/0.4 mL	40 mg

Table. 43. Pattern B for partial use, dosing is individual				
Medicinal product	SPC dose form	Harmonised BDF	SPC strength	Strength used in PhPID
Lovenox (enoxaparin sodium)	Gradually prefilled syringe	Solution	60 mg/0.6 mL	10 mg/mL

Table. 44. Pattern B for multi-dose of continuous presentation				
Medicinal product	SPC dose form	Harmonised BDF	SPC strength	Strength used in PhPID
Locoid (hydrocortisone butyrate)	Cream	Cream	0.1%	1 mg/g

Table 45. Pattern C for transdermal patches				
Medicinal product	SPC dose form	Harmonised BDF	SPC strength	Strength used in PhPID
Durogesic (Fentanyl)	Transdermal system	Patch	25 mcg/hour 3.1 mg per 11 cm^2 system. Each transdermal system is intended to be worn for 72 hours	25 mcg/hour

5.3.4 Specific business rules on strength expression

Where a medicinal product is a coated tablet, releasing different strengths for the same active ingredient, the strength is expressed as the total strength of the entire tablet (Table 46).

Table 46. Example of strengths being released in a different manner	
Medicinal product name	Harmonisation
Advil® 600 mg (Ibuprofen 200 mg immediate-release and 400 mg extended-release)	The strength will be expressed as 600 mg (entire tablet)

Where a medicinal product is given as an inhalator, and the strength of the metered dose and the delivered dose from the mouthpiece differs, the strength to be expressed will be the metered dose instead of the delivered dose (Table 47).

Table 47. Examples of strength expression for inhalators			
Medicinal product name	Strength 1 (metered dose delivered by a valve)	Strength 2 (delivered dose by actuator or mouthpiece)	Harmonised strength for PhPID
Combisal®	25µg salmeterol 125µg fluticasone propionate	21µg salmeterol 110µg fluticasone propionate	25.00 µg salmeterol
Spiriva®	18µg tiotropium	10µg tiotropium	125.00 µg fluticasone propionate
Symbicort®	200µg budesonide 6µg formoterol fumarate hydratate	160µg budesonide 4.5µg formoterol fumarate hydratate	18.00 µg tiotropium

6. References

https://www.frontiersin.org/articles/10.3389/fmed.2017.00114/full

https://www.edqm.eu/sites/default/files/standard_terms_introduction_and_guidance_for_use.pdf

https://standardterms.edqm.eu/

https://standardterms.edqm.eu/browse/get_concepts_by/SOM/SOM

https://ucum.nlm.nih.gov/ucum-lhc/demo.html

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/quality-review-documents-recommendations-expression-strength-name-centrally-authorised-human-medicinal-products_en.pdf

http://antigo.anvisa.gov.br/en/english

https://www.ephmra.org

https://fhir.org

https://www.hl7.org/fhir/overview.html

https://www.snomed.org/about-us

https://www.who.int/teams/health-product-and-policy-standards/inn#

https://www.edqm.eu/documents/52006/389906/standard_terms_introduction_and_guidance_for_use.pdf/c31aaa23-59cc-8d3d-e394-ffe425bf9b7e?t=1649082718997

https://www.ema.europa.eu/en/documents/other/guidance-electronic-submission-information-investigational-medicinal-products-human-use-extended-eudravigilance-medicinal-product-dictionary-xevmpd_en.pdf