Business rules for global PhPID construction

Global IDMP Working Group

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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
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 identify active substance(s) with a Global Substance Identifier (GSID),
2. To identify the global dose form attributes with a Global Dose Form Identifier (DFID),
3. To identify strength expressions with a Global Strength Definition Identifier (SDID).

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 of for example European Union, United States, Canada, Brazil and Japan; and World Health Organization.

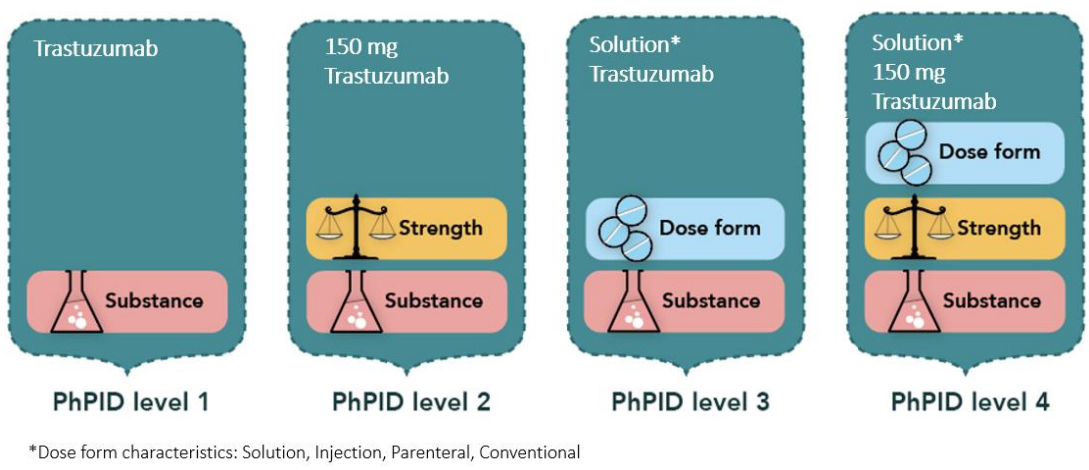

Figure 1. PhPIDs are generated at four levels for a specific pharmaceutical product

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.

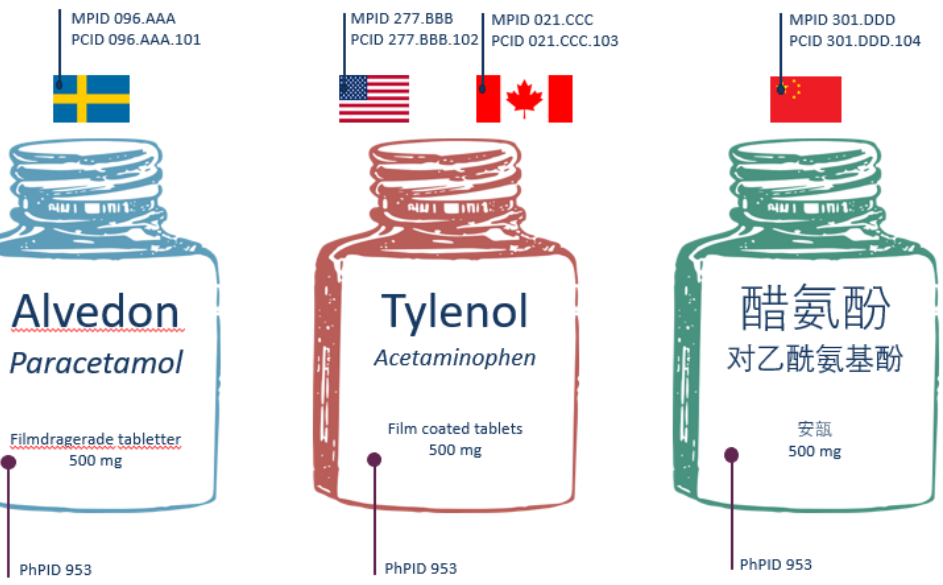

Figure 2. Harmonisation of medicinal products in different jurisdictions to the same PhPID

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. GSIDs can also be assign on substance specified level(s) (SSG) if sufficient information is provided by the requestor.

GSID identifier

The structure of the GSID identifier follows ISO/IEC 15459 – Part 3 (Ref ISO/IEC 15459) and ISO TS 19844:2017 and is assigned using GSRS software. The identifier is 17 characters long and consists of a Qualifier, Unique text, and Check character. Each GSID will begin with the letters 'GSID' as 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. 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 attributes – release characteristics, intended site, administration method, and basic administrable dose form – to index a term for global IDMP and generation of Global PhPID.

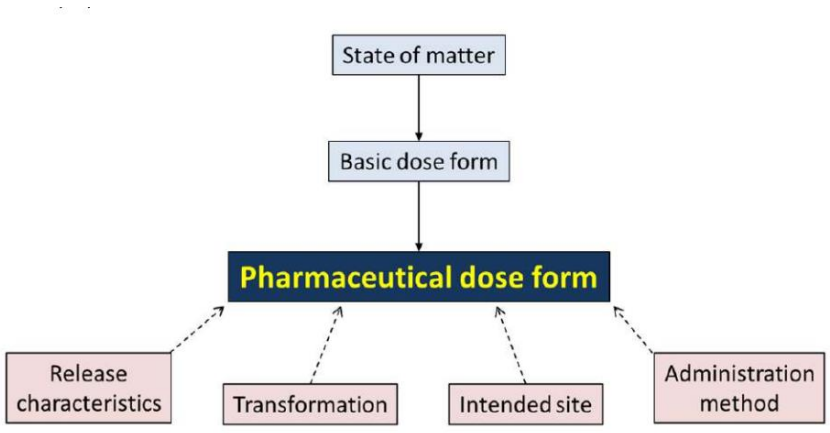

Figure 3. EDQM hierarchy of the pharmaceutical dose form, arranged according to the state of matter and basic dose form, and further characterised by release characteristics, transformation, intended site, and administration method

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.

4. PhPID generation

The processes for generating PhPIDs, as depicted in Figure 4, include validation of marketed pharmaceutical product data. The process is divided into three parts: substance, dose form, and strength. These parts are used to characterise the corresponding product and harmonise it according to ISO IDMP standards, other standards (e.g. EDQM, UCUM), and the business rules described in this document.

Steps in the process:

a. Select GSID(s) for the active ingredient(s) of the medicinal product.
b. Identify the global dose form attributes.
c. Determine how to express the strength (presentation strength, concentration strength, or delivery rate) and specify the numerical value and units.

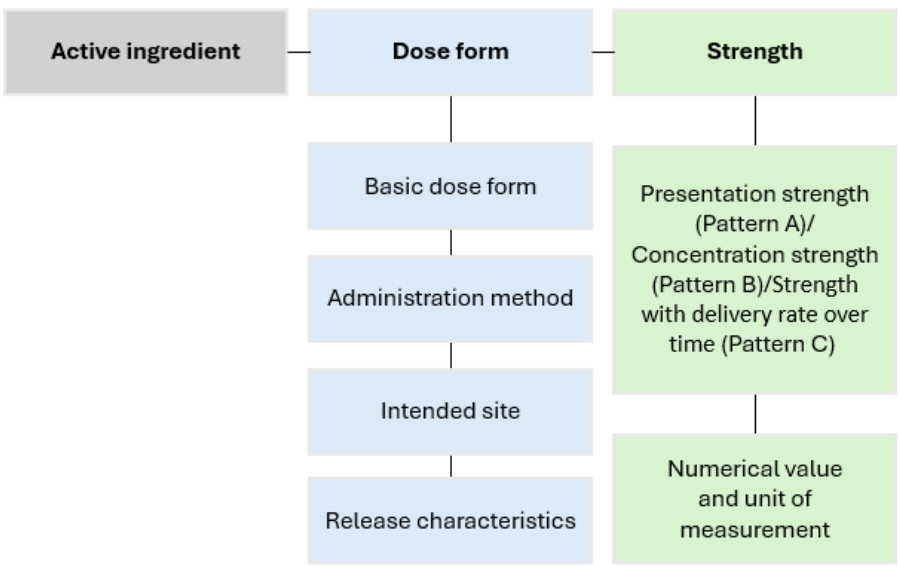

Figure 4. The PhPID is generated using a numerical representation of the substance, dose form, and strength (presentation strength, concentration strength, or delivery rate). The unit of presentation is used to define the strength but is *not* part of the PhPID input string.

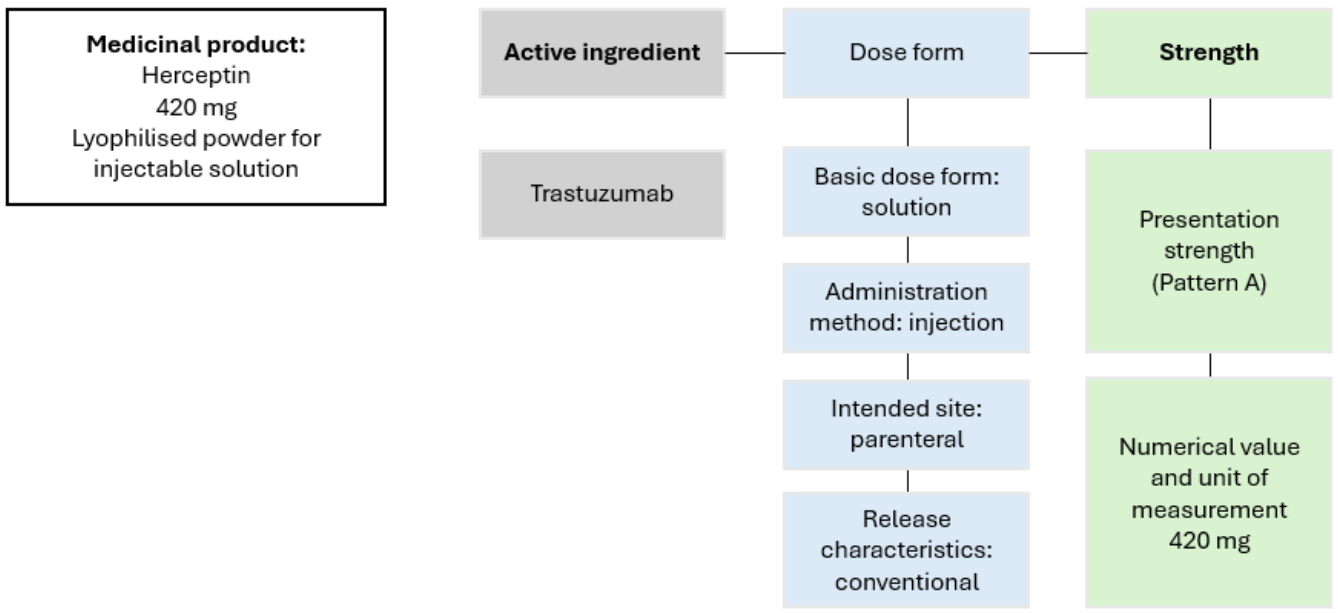

Figure 5. An example of how Herceptin® is processed based on the approved business rules.

The PhPID input string is constructed using three major components: substance, strength, unit and dose form attributes. The order and constitution of the input string for the MD5 hash function are strictly defined by the following requirements:

1. Substance

- The substance is represented by a GSID.
- Substances will be alphabetically ordered by GSID and separated by a pipe (|).

2. Strength

- The amount is represented alphanumerically, with a number between 1-999 and two decimals separated by a point (.). 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.
- A presentation strength or a concentration strength is used according to business rules patterns.
  For presentation strengths (P), **two values should be used**. For example, if the presentation strength is 3.00 mg, it appears as **[3.00;3]** in the PhPID input string.
  For concentration strength (C), **up to eight values should be used to allow expression of a strength range defined by a lower and a higher limit**. For example, **2.00 mg/5 h** would be represented as **[2.00;3;5;72;;;;]** in the PhPID string.
- Units are defined by UCUM (translated into numeric values by UMC in-house mapping tables).

3. Dose form attributes

- The dose form is represented by the global dose form attributes based on BDF, AME, ISI, and RCA in this order from EDQM.
- Multiple AME & ISI are represented within square brackets ([ ]) and ordered by ID (lowest to highest).

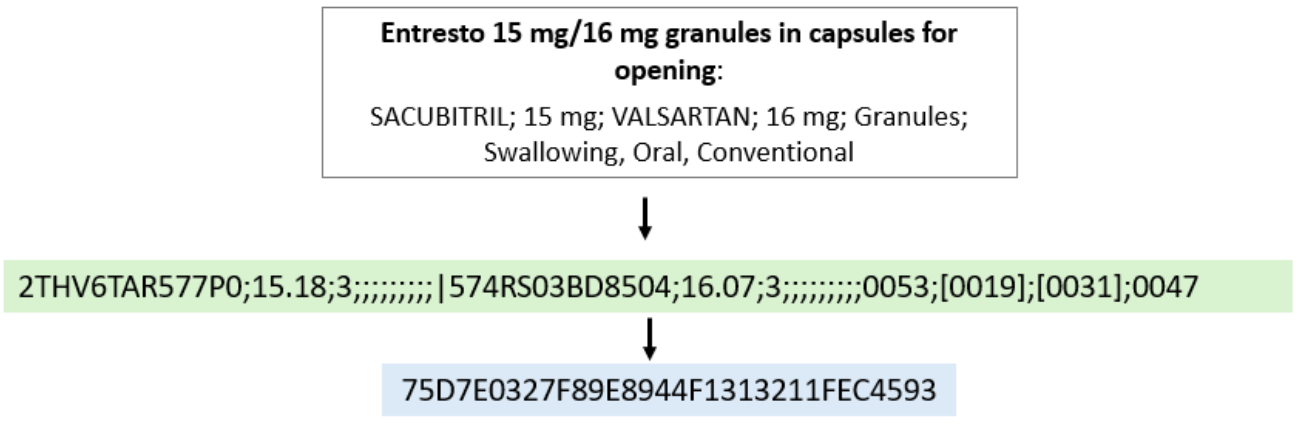

Figure 6. An example of multiple AME and two substances as input in PhPID.

All PhPID input values are separated by semicolons (;).

5. Business rules

Unique and harmonised pharmaceutical product identifiers (PhPIDs) are generated based on medicinal product information by assigning a Global Substance Identifier (GSID) to each substance, mapping and assigning Dose Form Identifier (DFID) and Strength Definition Identifier (SDID), and applying business rules. The purpose of these business rules for Global PhPID is to globally harmonise information for substance, dose form, and strength, ensuring 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.

Medicinal product information is reviewed using the SPC provided by regulators. Where necessary, the information is globally harmonised and standardised for substance, dose form, and strength identification to ensure consistent PhPID construction. To assign one PhPID to products that are similar or identical, even if described differently in SPCs across various jurisdictions, the concept of 'harmonisation' and specific business rules were developed and tested within the Global PhPID Service. This harmonisation is both technology- and process-based, enabling the implementation of global IDMP. In cases where SPC information does not provide enough clarity, the 'Five Region Verification' approach is used.

The Five Region Verification approach, implemented by UMC, aims to mitigate regional variations during previously conducted pilots. It involves analysing substances and products across five key regions: Asia, Europe, Latin America, North America, and Oceania, to understand how specific substances or products are described globally.

5.1 Business rules for assigning GSID to PhPID

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.

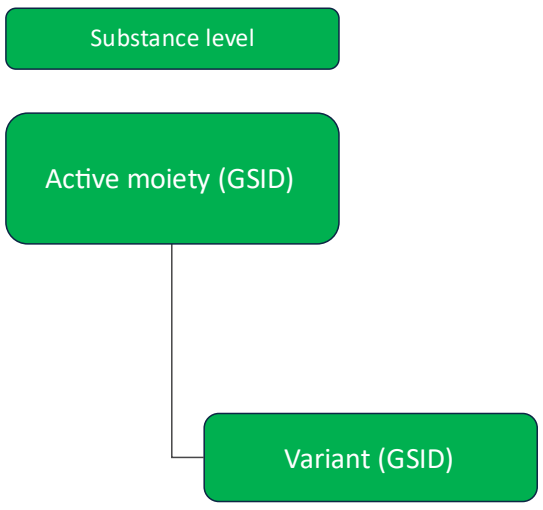

Figure 7. Schematic illustration of the general rule for GSID selection for chemicals used in PhPID generation

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.

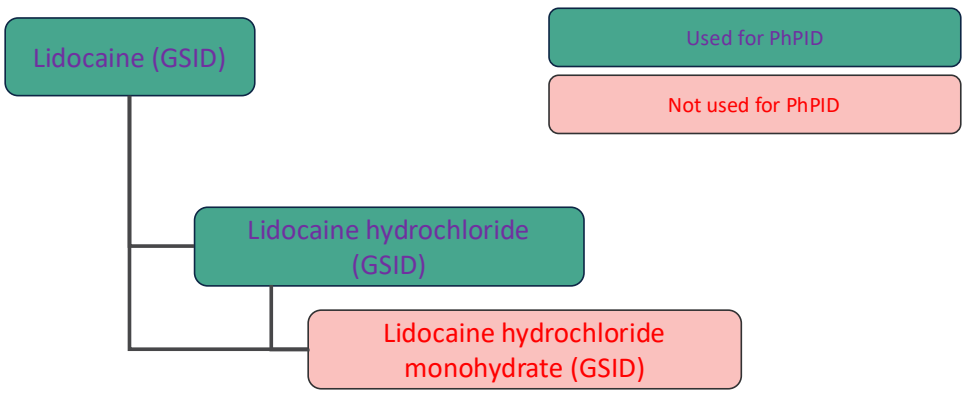

Figure 8. Schematic illustration of the selection of GSID for hydrated and anhydrous substances

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 1. 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 2. 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 attributes to Global PhPID

The purpose of this section is to describe how dose forms are defined for PhPID generation according to the ISO standards (ISO 11616 and ISO 11239) using a set of global dose form attributes based on terminology from EDQM, regardless of regional dose form terminology. These global dose form attributes can be used as a centrally maintained dose form terminology for global IDMP implementation.

The business rules on global dose form attributes are intended to provide a set of guidelines for indexing dose forms of medicinal products using the four global dose form attributes to harmonise information and ensure consistent Global PhPID construction.

The four EDQM dose form attributes, 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 attribute

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 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 3. Examples of business rules for BDFs 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 4. Examples of business rules for BDFs 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 5. Examples of business rules for BDFs 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 attribute

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 6 and 7:

Table 6. 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 7. 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 8 and 9:

Table 8. 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 9. 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 attribute

Intended site (ISI) is described as the general body site at which a pharmaceutical product is intended to be administered (per EDQM's definition).

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 10. 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 11. 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 12. 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 attribute

Release characteristics (RCA) describe the timing by which an active ingredient is made available in the body after administration of the pharmaceutical product, compared to 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.
- RCA selection and assignment is supported by EDQM Standard Terms guidance, both the RCA definitions and the connected RCA(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).
- An important element is the time it takes for the drug to become active in the body, which spans from the moment of injection, ingestion, or application until it starts to take effect. This encompasses not just the release time but also scenarios like delayed, prolonged, or modified absorption
- RCA 'Delayed/Prolonged/Modified' is assigned to medicinal products, irrespective of whether the modified effect is due to a special formulation design, manufacturing method, or variations in the active ingredient. To assign RCA 'Prolonged/Delayed/Modified', it is not required to identify an existing corresponding conventional product. It is sufficient if the product is described as extended, prolonged, depot, etc., in the SPC, or if it is indicated in the SPC/Martindale that the active ingredient variant is a long-acting version of a 'conventional' substance.
- 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 13. 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 14. 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	

*However, insulins will be separated on GSID-level

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

The purpose of this section is to describe how strength is defined and expressed for SDID and PhPID generation according to the ISO standards (ISO 11616 and ISO 11240) in the context of global IDMP implementation.

Strength typically refers to the amount of an active substance in a medicinal product and is expressed as a structured relationship between two elements: numerical value (e.g. 500) and unit of measurement (e.g. mg).

To unambiguously link the strength to the medicinal 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/hydrate*. The reference strength is derived from the active moiety, i.e. the free acid or base of an active substance(s). However, the reference strength is not used for PhPID generation.

*Though hydrate information is not included in GSID assignment used in PhPID, the hydrated strength is used, when applicable, to calculate PhPID strength, in case strength is referring to the hydrated substance. Assigning strength for hydrated substances follows general business rules on SDID assignment.

- 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:

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

- 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:

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

- 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 Definition Identifier (SDID) provides guidelines for expressing the strength of medicinal products using three elements: numerical value, unit of measurement, and strength expression. The strength expression can be one of three types: presentation strength, concentration strength, or delivery rate over time. Each of these is paired with a numerical value and a unit of measurement. The SDID is based on the Summary of Product Characteristics (SPC) information to ensure accuracy. When the SPC information is ambiguous, a thorough analysis is conducted. This involves reviewing SPCs from five regions and using the most consistently referenced data, along with insights from UMC's knowledge base.

The SDID assignment process involves selecting the pattern that indicates if strength should be expressed as presentation strength or concentration strength and assigning a numerical value and unit of measurement. The strength of the active ingredient (corresponding to the GSID) specified in the SPC is used for PhPID generation, often requiring thorough review of the SPC. If the SPC only provides a reference strength, this value is used to calculate the active ingredient strength for PhPID generation. A single strength per GSID is mandatory. For example, a medicinal product containing 200 mg immediate-release ibuprofen and 400 mg extended-release ibuprofen will be assigned the PhPID strength of 600 mg ibuprofen. The active ingredient and its variants are critical in defining the appropriate value and unit for SDID and PhPID generation.

5.3.1 Concatenated pattern framework for strength expression

The pattern framework determines how the strength of a pharmaceutical product (PhPID) should be expressed. There are three patterns:

- 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 mg 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 mg/ml. Oral and parenteral liquids are assigned concentration strength with one exception – prefilled syringes which are assigned presentation strength.
- The strength with delivery rate over time 'Pattern C' is when the strength of a substance is expressed as a delivery rate over time such as mg/h.

These patterns are used to decide which unit to use for each medicinal product:

Table 15. Concatenated pattern framework for strength expression

Presentation strength for AdmDF (Pattern A)	Concentration strength for AdmDF (Pattern B)	Delivery rate over time for AdmDF (Pattern C)
Solid countable dose forms Tablets, capsules, suppositories. Effervescent tablet, dispersible tablet, or soluble tablet dissolved/dispersed in a liquid. Implants.	N/A	**Solid countable dose forms** Transdermal patches. Vaginal rings.
Solid continuous dose forms Oral powder and granules, unit dose (e.g. in container sachet, capsule). Metered doses, where UOP actuation is suitable (note, we do not accept range for metered doses). Injections where manufactured dose form is powder.	**Solid continuous dose forms** Oral powder multi-dose dissolved/dispersed in a fixed volume of liquid before being dispensed to the patient (i.e. antibiotics prepared at a pharmacy). Oral powder and granules, multi-dose.	N/A
Semi-solid dose forms Transdermal gel, unit dose and metered dose. Rectal systemic dose forms unit dose.	**Semi-solid dose forms** Semi-solid topical preparations, unit dose and multi-doses (except unit dose preparations for systemic rectal use and transdermal gels). Spray that is not metered dose. Semi-solid systemic rectal preparation with adjustable dose.	N/A
Liquid dose forms Metered doses, where UOP actuation is suitable (note, we do not accept range for metered doses). Parenteral liquids where manufactured dose form is liquid in non-graduated, non-adjustable prefilled syringes/pens. Rectal unit dose.	**Liquid dose forms** Parenteral liquids in containers such as vials, ampoules, and bags. Parenteral liquids in graduated or adjustable prefilled syringes and pens, i.e. prefilled syringes with individual dosing/partial use.	N/A

Unit-dose nebulizer solutions not partial use preparations. Oral and Oromucosal preparations (e.g. prefilled cup, sachet, prefilled needle-free syringe).	Oral liquid preparations, multi-dose. Eye drops, nose drops, ear drops as unit and multi-dose. Nebulizer solutions, multi-dose and partial-use preparations. Spray that is not metered dose. Liquid systemic rectal preparation with adjustable dose.	
Presentation strength for ManDF (Pattern A)	**Concentration strength for ManDF (Pattern B)**	**Delivery rate over time for ManDF (Pattern C)**
N/A	**Solid continuous dose forms** Oral powder multi-dose dissolved/dispersed in a fixed volume of liquid before being dispensed to the patient (i.e. antibiotics prepared at a pharmacy). Oral powder and granules, multi-dose.	N/A

Metered dose: A specific amount of medication is produced following a single operation of a pump, valve, or other equivalent dosing mechanism.
Multi-dose: A container that holds a quantity of the preparation suitable for two or more doses.
Unit dose: A unit dose is the amount of medication administered to a patient in a single dose.

5.3.2 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 information given in SPC. Substance strength, i.e. the 'amount' is expressed in the value range of 1-999.99 with two decimals.

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

Table 16. Business rules on numerical values for strength expression

Value range	Substance strength, i.e. the 'amount' is expressed in the value range of 1-999.99 with two decimals: • 0.1 g or 100 mg, 100 mg is assigned • 1000 mg or 1 g, 1 g is assigned • When given 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 1-999.99 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). 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.
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 for medicinal products, where the strength is indicated on the same GSID, are harmonised. For example, Selincro, a tablet containing Nalmefene with strength listed as 18 mg in the name section and 18.06 mg in the strength section, will have its strength harmonised to 18 mg for SDID.
Combined insulins	The strength for combined insulins (e.g. fast-acting and long-acting) is calculated based on the ratio of ingredients.

5.3.3 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. When no UCUM unit is available, 'Non-standard units and regional units' and units from the 'ICSR implementation guide' are used if possible. If a non-UCUM, non-ICSR implementation guide unit needs to be used, curlicue brackets are added.

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

Table 17. 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, refer to non-UCUM units.	
Processing non-UCUM units	When possible, the non-UCUM unit is converted into a UCUM unit. If no UCUM unit is available, units from the 'ICSR implementation guide' are used if possible. If a non-UCUM, non-ICSR implementation guide unit needs to be used, curlicue brackets are added.	
Unit variation, process for converting between different units	It is important to harmonise units as appropriate. When several units are used for medicinal products with the same substance, products in several regions are investigated to determine which unit is most used. In applicable cases, dedicated 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/ug, 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/ug	
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.	
Strength for patches (and plasters)	Patches (and plasters) are expressed in different ways (e.g. /h, /8 h, /24 h, /72 h). The strength is expressed as the delivery rate given in SPC. Nicotinell® (nicotine) 21 mg/24 h Nicorette® (nicotine) 25 mg/16 h	
Strength for liquid and semi-solid * preparations	Harmonisation of unit for medicinal products that share the same dosage form, active ingredient, and strength:	
	Type of dose form	Process for assigning mg/g or mg/mL
	Liquid and semi-solid * preparations (regardless of whether they are topical/cutaneous or systemic)	1. If the product SPC uses the unit mg/g for semi-solids (e.g. cream, gel, foam, ointment, paste) or mg/ml for liquids (e.g. solution, emulsion), follow this without further investigation of units. 2. If the SPC does not align with the above units regarding mg/g vs mg/ml, investigate if all products, in a Five Region Verification, with same dose form, ingredient, and strength are described with the same unit.

* *For definition of liquid vs semi-solid, follow EDQM:* https://standardterms.edqm.eu/browse/get_concepts_by/SOM/SOM.

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

Table 18. 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 19. 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 20. 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 21. 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 22. 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 23).

Table 23. 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 24).

Table 24. Examples on strength expression for inhalators			
Medicinal product name	**Strength 1 (metered dose delivered by a valve)**	**Strength 2 (delivered dose by actuator or mouthpiece)**	**Harmonised reference strength for PhPID**
Spiriva®	18µg tiotropium (as tiotropium bromide monohydrate)	10µg tiotropium (as tiotropium bromide monohydrate)	18.00 µg tiotropium (as tiotropium bromide)
Symbicort®	200µg budesonide 6µg formoterol (as formoterol fumarate hydratate)	160µg budesonide 4.5µg formoterol (as formoterol fumarate hydratate)	200.00 µg budesonide 6.00 µg formoterol (as formoterol fumarate hydratate)

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