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Health informatics — Identification of medicinal products — Implementation guidelines for ISO 11616 data elements and structures for the unique identification and exchange of regulated pharmaceutical product information

Informatique de santé — Identification des médicaments — Lignes directrices pour l'implémentation des éléments de données et structures ISO 11616 pour l'identification unique et l'échange d'informations réglementées sur les produits pharmaceutiques

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 215, *Health informatics*.

Introduction

This document gives guidelines for implementing ISO 11616, one of the five ISO IDMP standards. The five ISO Standards and four ISO Technical Specifications, when used together, provide the basis for exchanging data elements that will support the unique and unambiguous identification of Medicinal Products. The primary purpose of this document is to provide technical guidance to software implementers; short descriptions of business rationale are also included, where relevant, to provide context. Thus, this document focuses on business and technical considerations for implementation that will construct and parse well-formed, transmittable IDMP messages. Following transmission of required data elements, unique identifiers are to be produced in conformance with the standards to support applications where it is necessary to reliably identify and trace regulated biopharmaceutical products. However, this document does not include extensive information on creation or maintenance of identifier repositories. Reference is made to regional guidance/implementation guides to support practical implementation within a given region/jurisdiction. The development of an ISO technical report for identifying core principles for the maintenance of identifiers and terms for ISO IDMP is to be developed and referenced for applicable ISO IDMP standards and corresponding technical specifications.

Health informatics — Identification of medicinal products — Implementation guidelines for ISO 11616 data elements and structures for the unique identification and exchange of regulated pharmaceutical product information

1 Scope

This document defines the concepts required to associate pharmaceutical products with an appropriate set of PhPID(s) in accordance with ISO 11616.

Pharmaceutical identifiers and elements are to represent pharmaceutical products as represented in a Medicinal Product as indicated by a Medicines Regulatory Authority. The suite of ISO IDMP standards can be applied to off-label usage of Medicinal Products, but is currently outside of the scope of this document.

Reference to ISO 11238, ISO 11239, ISO 11240 and ISO 11615 and HL7 messaging standards, HL7 Reference Information Model (RIM), HL7 V3 Common Product Model (CPM) and HL7 V3 Structured Product Labelling (SPL) can be applied for pharmaceutical product information in the context of this document.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 3166-1, *Codes for the representation of names of countries and their subdivisions — Part 1: Country codes*

ISO 11238, *Health informatics — Identification of Medicinal Products — Data elements and structures for the unique identification and exchange of regulated information on substances*

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

ISO 11240, *Health informatics — Identification of Medicinal Products — Data elements and structures for the unique identification and exchange of units of measurement*

ISO 11615, *Health informatics — Identification of Medicinal Products — Data elements and structures for the unique identification and exchange of regulated Medicinal Product information*

ISO/TS 19844, *Health informatics — Identification of Medicinal Products — Implementation guidelines for data elements and structures for the unique identification and exchange of regulated information on substances*

ISO/TS 20440, *Health informatics — Identification of Medicinal Products — Implementation guide for ISO 11239 data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging*

ISO/TS 20443, *Health informatics — Identification of Medicinal Products — Implementation guidelines for ISO 11615 data elements and structures for the unique identification and exchange of regulated Medicinal Product information*

3 Terms and definitions

No terms and definitions are listed in this document.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at http://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

4 Conformance

— *Mandatory*: Defining elements *necessary* for the unique identification of Medicinal Products per the ISO IDMP standards/technical specifications.

— *Conditional*: Conditional applies to the "*within category*" data elements, as applicable, when there are alternative data sources for a given data element(s) to identify a medicinal/pharmaceutical product. Regional implementation of the ISO IDMP standards/technical specifications may elevate the conditional conformance categories to "*mandatory*" per regional requirements.

— *Optional*: When listed at the category level (e.g. specified substance), optional corresponds to ISO categories or data elements that are not absolutely necessary for the *unique* identification of medicinal/pharmaceutical products according to the ISO IDMP standards/technical specifications. Regional implementation of the ISO IDMP standards/technical specifications may elevate the optional conformance categories to "*mandatory*" or "*conditional*" per regional requirements.

5 Concepts required for the unique identification of pharmaceutical products

5.1 General considerations for elements required for the unique identification of pharmaceutical products

This clause, along with Annex A and Annex B, describes the elements and messaging required to uniquely identify and characterise a pharmaceutical product. It provides the requirements to support pharmaceutical product identification. Examples are given in Annex C.

Pharmaceutical product identification (PhPID) shall be based on the following subset of elements that describe the pharmaceutical product (see Figure 1):

a) active substance(s)/specified substance(s);

NOTE The substance(s) within the ingredient role "active" and "adjuvant" are utilised to define the PhPID.

b) strength(s), strength units (units of measurement and/or unit of presentation);

c) reference strength(s) includes reference substance(s) (i.e. active moiety and its corresponding strength);

d) administrable dose form;

e) medical device, when it is a component of a Medicinal Product.

5.2 Principles required for the unique identification of a pharmaceutical product

The following principles for the unique identification of a pharmaceutical product shall apply:

a) a Medicinal Product may relate to one or more pharmaceutical products as part of a treatment regime [e.g. a kit, which might be a combination pack containing vaginal tablets (500 mg) and an external vaginal cream (10 %)];

b) the characterisation of the pharmaceutical product(s) based on the active substance(s)/specified substance(s), the (reference) strength thereof, the administrable dose form(s), and the medical device (e.g. a scaffolding for cell-based products) being part of the Medicinal Product (e.g. drug/device combination);

c) the description of the pharmaceutical product(s) in the pharmaceutical dose form approved for administration, where applicable, after reconstitution and as authorised in accordance with the regulated product information;

d) the association of the regulated (investigational) Medicinal Product and the pharmaceutical product(s) using the PhPID(s).

6 Identifying characteristics for the identification of pharmaceutical products

6.1 Pharmaceutical product identification strata and levels

PhPID sets shall be represented within two strata (active substance stratum and specified substance stratum), both of which contain four PhPID identification levels, for each pharmaceutical product contained in a Medicinal Product.

PhPID sets shall be generated using the substance standard (see ISO 11238 and ISO/TS 19844), the strength and administrable dose form section (see ISO 11239 and ISO/TS 20440) and the unit(s) of measurement standard (see ISO 11240) as illustrated below.

Reference strength shall be repeated in both PhPID strata. The reference strength shall be derived from the active moiety/moieties of an active substance(s) depending on the specific product characteristics.

All the PhPID strata can be described at four different levels from 1 to 4 as shown in Table 1.

Table 1 — Four levels of PhPID

PhPID active substance stratum	PhPID_SUB_L1 → substance(s) PhPID_SUB_L2 → substance(s) + strength + reference strength PhPID_SUB_L3 → substance(s) + administrable dose form PhPID_SUB_L4 → substance(s) + strength + reference strength + administrable dose form
PhPID specified substance stratum	PhPID_SpSUB_L1 → specified substance(s) PhPID_SpSUB_L2 → specified substance(s) + strength + reference strength PhPID_SpSUB_L3 → specified substance(s) + administrable dose form PhPID_SpSUB_L4 → specified substance(s) + strength + reference strength + administrable dose form

A pharmaceutical product may refer to a drug that is associated with a medical device. In this instance, the device term and term ID (i.e. unique device identifier) shall be displayed with the active substance(s) and specified substance(s) terms for the product at all applicable PhPID levels. This association shall be made by directly associating the assigned PhPIDs to a Medicinal Product and its corresponding MPID/PCID as outlined in ISO 11615 and ISO/TS 20443.

Strength is not applicable to a device.

A region may further refine the requirements in relation to specification of the medical device as part of this document at implementation so that this information is to be specified only if required.

A pharmaceutical product may refer to a drug that is associated with an adjuvant (e.g. vaccine). In this instance, the adjuvant term and term ID shall be displayed with the active substance(s) and specified substance(s) terms for the product at all applicable PhPID levels. This association shall be made by

directly associating the assigned PhPIDs to a Medicinal Product and its corresponding MPID and PCID as outlined in ISO 11615 and ISO/TS 20443.

Strength shall indicate quantity, unit of measurement and/or unit of presentation.

Administrable dose form is derived from the pharmaceutical product.

Placebos shall be captured as active substances when utilised as a comparator. Regional implementation guides will provide more information as some regional regulation defines what is considered a placebo or active substance.

6.2 PhPID specified substance

As described in ISO 11238, specified substance(s) shall capture detailed characteristics of single substances or the composition of material that contains multiple substances or multiple physical forms.

The elements necessary to define specified substances shall be divided into four groups to facilitate implementation.

These groups are described as follows.

a) Specified Substance Group 1. Elements shall be used to describe material that contains multiple substances, solvents used in the preparation of herbal or allergenic extracts, specific marker or signature substances present in plant or animal derived materials, the physical form of a substance, when relevant, and any properties essential to the description of the material.

   The element groups used to define a Specified Substance Group 1 shall include constituents, physical form and property.

   NOTE 1 This grouping of elements allows for the definitions of many materials in commerce that are used in the formulation of Medicinal Products.

b) Specified Substance Group 2. Group 2 elements shall be used to capture the manufacturer of either a substance or Specified Substance Group 1 along with minimal manufacturing information.

   The minimal manufacturing information shall include the overall production method type (i.e. synthetic, extractive, recombinant), production system type (i.e. cell line, plant or animal tissue) and production system (specific cell line).

   NOTE 2 Group 2 elements would allow the tracking of the substance to the manufacturer. It also allows the distinguishing of synthetic peptides from recombinant peptides and the capture of the product cell line.

c) Specified Substance Group 3. Group 3 elements shall capture the grade of the material along with the source that defines the given grade.

   Group 3 elements shall be used to distinguish specific pharmacopoeia grades and technical grades of material.

   The grade for each pharmacopoeia shall be a separate substance if a pharmacopoeia monograph related to a substance is not harmonised.

   NOTE 3 For most active pharmaceutical substances, generally recognised pharmacopoeias are USP, Ph. Eur. or JP. For herbal substances, the grades would be standardised, quantified and unstandardised.

d) Specified Substance Group 4. Group 4 elements shall contain the most detailed information on a substance. This information shall include critical manufacturing processes, specifications (e.g. impurities and related substance limits would be captured using constituents), unitage, reference material and analytical methods used for potency determination.

NOTE 4 The specific information described for Specified Substance Group 4 is often submitted in regulatory submissions in an unstructured manner that is difficult to capture and organise. The fields developed here will attempt to organise and structure the data in a manner that will facilitate its use in both review and compliance activities. It is anticipated that the suite of ISO IDMP standards will extend into more granular regulatory content as adoption increases by stakeholders and the standards extend deeper into additional regulatory and clinical use cases over time.

6.3 Pharmaceutical product specified substance identification (PhPID SpSub)

The PhPIDs for specified substance(s) shall be generated from three of the four groups (Groups 1 to 3) identified within ISO 11238 and ISO/TS 19844.

Groups 1, 2, and 3 contain necessary data elements for more detailed pharmaceutical product identification which supports the scope and purpose of this document.

Groups 1 to 3, as assigned to an active substance(s), shall be utilised within this document for pharmaceutical product identification with corresponding PhPIDs attributed as applicable.

Group 4 is a more comprehensive level of substance identification that is not necessary for the purposes of pharmaceutical product identification and shall not be utilised for PhPID generation.

Specified substance information shall be represented with the active substance(s) elements within a pharmaceutical product and within a Specified Substance Group 1, as applicable.

Groups 2 and 3 shall be associated directly with the active substance(s) of a pharmaceutical product and to a Specified Substance Group 1 as applicable.

ISO/TS 19844 addresses the assignment and association of specified substance groups for defined product classes. See ISO 11238 and ISO/TS 19844 for detailed information related to substance and specified substance elements and identification.

A region may further refine the requirements in relation to specification of specified substances as part of this document at implementation such that this information is to be specified only if required.

6.4 Cardinality

The relationships within the elements of a pharmaceutical product shall respect the following cardinality:

— a PhPID has one administrable dose form (cardinality relationship: 1..1);

— a PhPID may have zero to one unit of presentation (cardinality relationship: 0..1);

NOTE This is often used specifically at the point of delivery to the patient in cases where a quantitative unit of measurement is not applicable.

— a PhPID has one or more active substances (cardinality relationship: 1..*);

— a PhPID has one or more active specified substances (cardinality relationship: 1..*);

— a PhPID has one strength (cardinality relationship: 1..1) based on one to many active substances or specified substances (cardinality relationship: 1..*);

For liquid preparations, the strength (presentation) and strength (concentration) shall both be represented.

A separate PhPID shall be generated to represent the strength concentration, i.e. per unit volume as applicable. This shall be known as the product code concept as it represents a calculation of the strength

presentation of a liquid preparation (i.e. total volume per container) as authorised by a medicines regulatory agency.

— a PhPID has one to many reference strengths (i.e. active moieties with a corresponding strength) (cardinality relationship: 1..*) as it relates to the strength of one to many active substances/specified substances (cardinality relationship: 1..*).

6.5 Representation of strength concentration

For liquid preparations, strength shall be represented by both the total volume of the container as authorised by a Medicines Regulatory Authority using strength (presentation) and strength concentration per unit volume (e.g. 1 ml) using strength (concentration). For PhPID generation and assignment, the strength shall be expressed per total volume per container (MPID and PCID) with the corresponding strength concentration per unit volume represented in every instance of PhPID Levels 2 and 4. Both representations shall be considered mandatory elements when illustrating the strength of a pharmaceutical product.

The strength concentration per unit volume shall be calculated from the strength per total volume of the container and presented at all PhPID levels where strength is represented in accordance with the product authorisation by a Medicines Regulatory Agency.

A PhPID shall be generated to represent a strength concentration per unit volume regardless of whether this unit volume is additionally represented as strength per an actual volume within a container presentation. This PhPID will be an abstract PhPID and shall be referred to as a pharmaceutical product concept code (PPCC). The PPCC is necessary to support e-prescribing/e-dispensing activities in cases where what is prescribed is simply a given strength concentration per unit volume with no reference to the strength per total volume per container as authorised by a Medicines Regulatory Agency.

The strength per unit volume shall be included as a data element and mapped to the strength per total volume at all applicable PhPID levels to support the interoperability and exchange of pharmaceutical product data.

The calculation and mapping of strength concentration per unit volume to the strength per total volume at all applicable PhPID levels shall be addressed during regional implementation and maintenance of this document.

See Annex D for examples of representation of strength.

6.6 Pharmaceutical product identifier (PhPID)

The PhPID is a globally unique identifier assigned at the level of the pharmaceutical product and utilises the identifying characteristics as outlined below. For products that need to be reconstituted in accordance with the authorisation by a Medicines Regulatory Authority before they can be administered, the PhPID shall refer to the characteristics of the product after reconstitution.

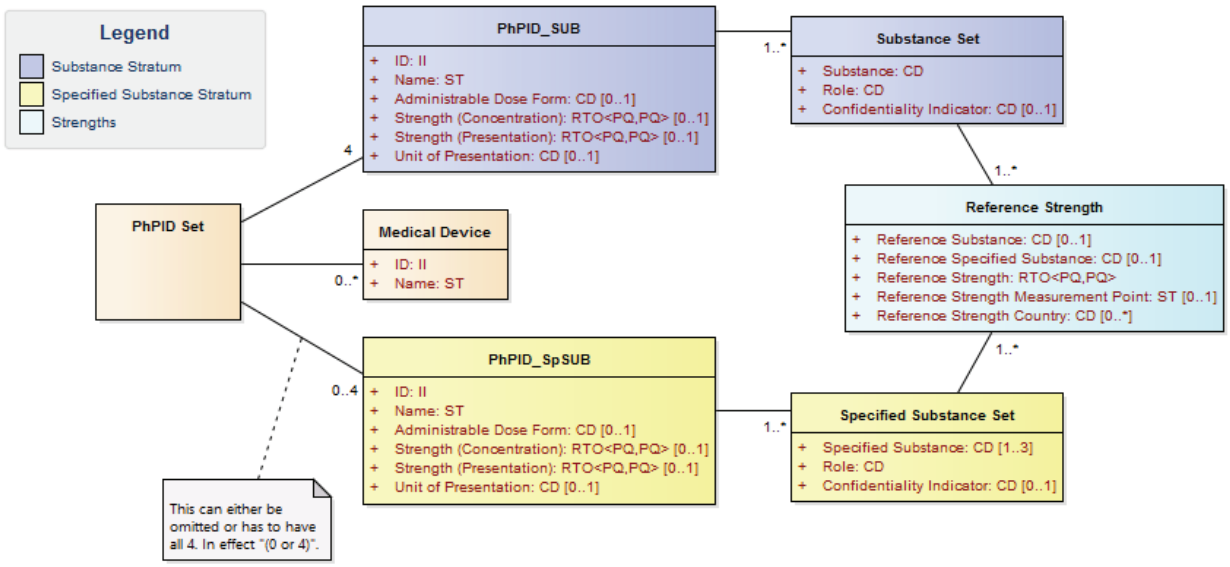

Figure 1 — Detailed model of the pharmaceutical product identification (PhPID)

NOTE For more detailed information regarding the specific data elements classifying a particular substance(s) and specified substance(s), see ISO 11238 and ISO/TS 19844. The details of these elements are defining attributes for pharmaceutical product identification and assignment of PhPIDs.

6.7 PhPID algorithm and product code concept

The PhPID algorithm can be created by computing the MD5 digest over a data structure describing the identifying characteristics for pharmaceutical product identification as described in ISO 11616 and this document. MD5 hash codes are a 128 bit (16 byte) number which, in hexadecimal presentation, is 32 digits long. The hexadecimal digits are formatted in groups of 8-4-4-4-12 digits separated by hyphens.

To generate a single, unique PhPID, it is necessary to define rules for each of the elements to be used as inputs.

Figure 2 shows a conceptual representation of the PhPID algorithm. Please note that this conceptual representation does not represent all inputs (e.g. adjuvants or devices) which are also defining PhPID generation as applicable. The conceptual representation, illustrating an MD5 digest, is a pipe-delimited sequence of form code (dose form), followed by the active ingredients separated by the “pipe delimiter” (“|”) in alphabetic order of their substance code (e.g. UNII). Each active ingredient is represented by the active ingredient code and the strength.

The non-proprietary name shall be included as part of the PhPID substance level nomenclature.

The human readable PhPID nomenclature shall be represented by the non-proprietary name (e.g. INN, USAN) of the pharmaceutical product, active substance(s), pharmaceutical dose form, strength, and reference strength. In addition, the adjuvant and device name can be described as part of the PhPID nomenclature as applicable.

NOTE For examples of PhPID for products containing adjuvant(s) and device(s), please refer to regional implementation guides.

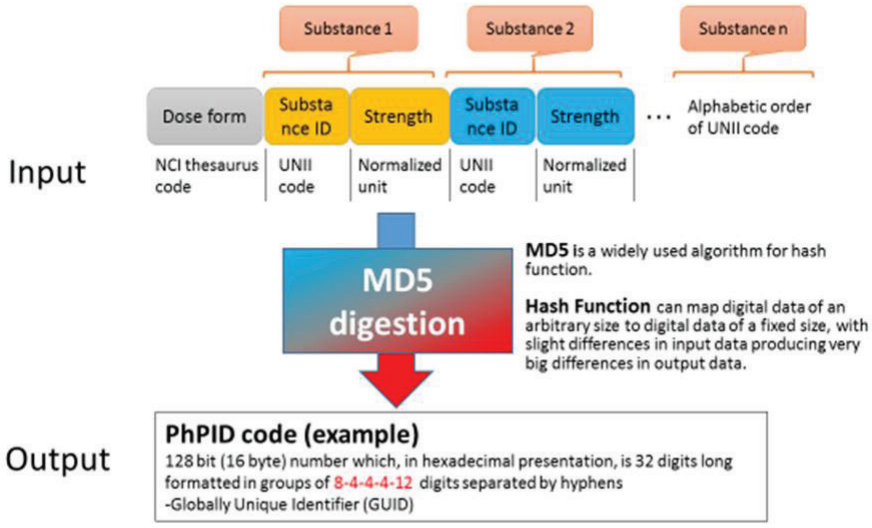

Figure 2 — Conceptual representation of the PhPID construction

7 Ingredient, substance and strength

7.1 General considerations

This clause describes the ingredients of the pharmaceutical product through its representations as the manufactured item(s) as indicated within a jurisdiction (see ISO 11615) and the pharmaceutical product(s).

The ingredients class and associated active substance, specified substance, strength and reference strength classes are used in the further description of manufactured item as indicated within a jurisdiction (see ISO 11615) and pharmaceutical product class.

Any active substance(s) or specified substance(s) shall have its strength specified in accordance with the pharmaceutical product information as applicable. Additionally, strength can be further specified by description of reference strength. This shall be specified where applicable in accordance with the pharmaceutical product information.

EXAMPLE Paracetamol 600 mg can be represented as 0,6 g in one jurisdiction and 600 mg in another jurisdiction, but will be assigned identical PhPID sets as the strengths are identical but with different representations.

When described, reference strength shall specify the active substance and specified substance that it references.

Pharmaceutical product and their ingredients as well as the device and adjuvant ingredients of interest are represented within the UML model in the manner shown in Figure 3.

Messaging relating to ingredient, substance and strength shall be in accordance with Annex A.

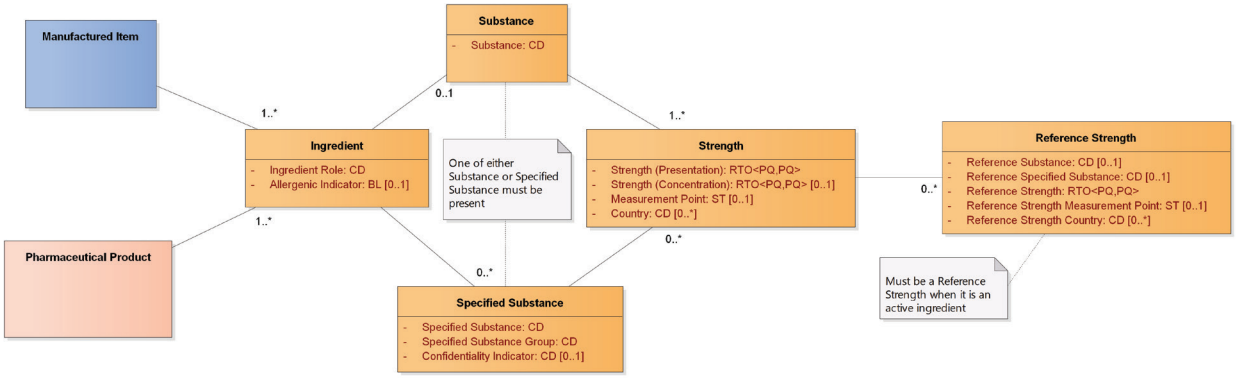

Figure 3 — Ingredients, substance and strength section detailed description diagram

7.2 Ingredient

There shall be one instance of the ingredient class for each actual ingredient of either the manufactured item or pharmaceutical product.

7.2.1 Ingredient role

User guidance	The role of the ingredient as part of the manufactured item/pharmaceutical product shall be specified using an appropriate controlled vocabulary. The controlled term and a term identifier shall be specified. There is a constraint that each ingredient shall be further described as either an active substance(s) or a specified substance(s).
Example(s)	— Active substance — Adjuvant
Conformance	Mandatory
OID	Substance/specified substance code concept per regional implementation of ISO 11238 and ISO/TS 19844.

Table 2 lists the ingredient codes applicable to PhPID; the codes are included in the full upper case letters exactly as specified in Table 2.

Table 2 — Ingredient roles (classCodes)

Code	Description
ACTI	Active ingredient — ingredient that has the pharmacological action. Use only if basis of strength *cannot* be specified; otherwise, use ACTIB, ACTIM, or ACTIR.
ACTIB	Active ingredient, where the entire substance is the basis of strength, e.g. propranolol hydrochloride quantified as the propranolol hydrochloride salt.
ACTIM	Active ingredient, where the active moiety is the basis of strength, e.g. amoxicillin trihydrate equivalent to 250 mg anhydrous amoxicillin.
ACTIR	Active ingredient, where another reference substance is the basis of strength, e.g. metoprolol succinate quantified by amount of metoprolol tartrate with the equal amount of metoprolol active moiety.
ADJV	Adjuvant — ingredient which augments or promotes the pharmacological effect of the active ingredient(s) without itself being considered active (typically used with vaccines).