TECHNICAL SPECIFICATION

ISO/TS 20451

First edition
2017-10

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

Reference number
ISO/TS 20451:2017(E)

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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.

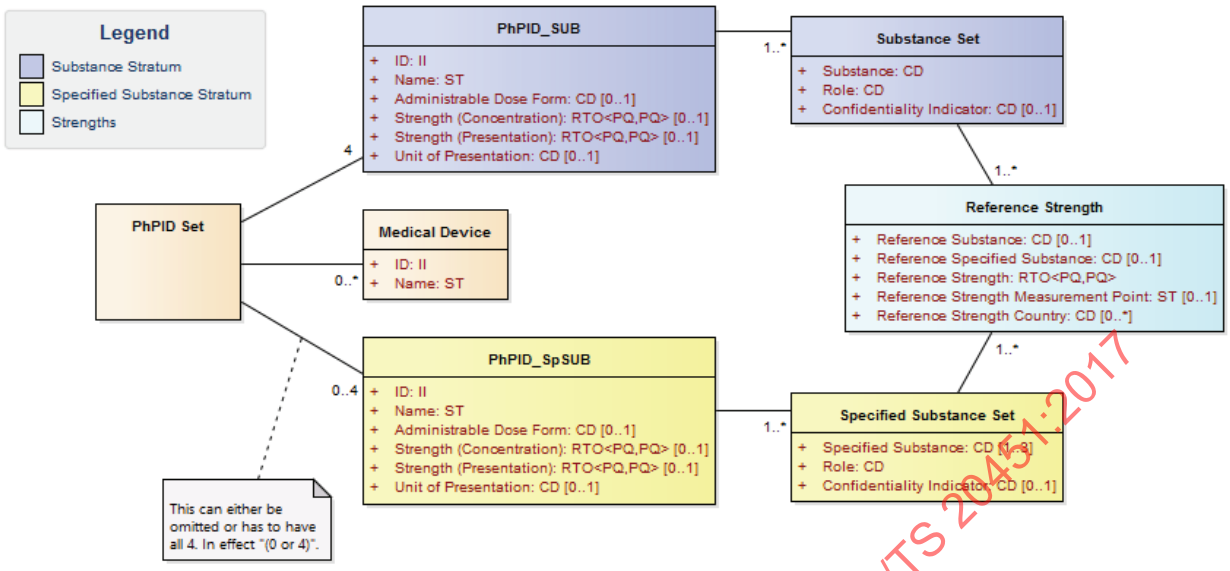

Figure 1 — Detailed model of the pharmaceutical product identification (PhPID)

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.

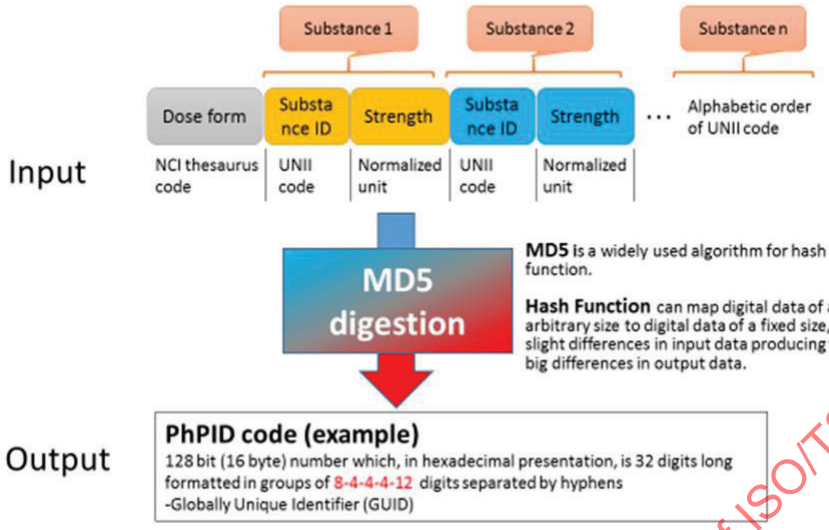

Figure 2 — Conceptual representation of the PhPID construction

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.

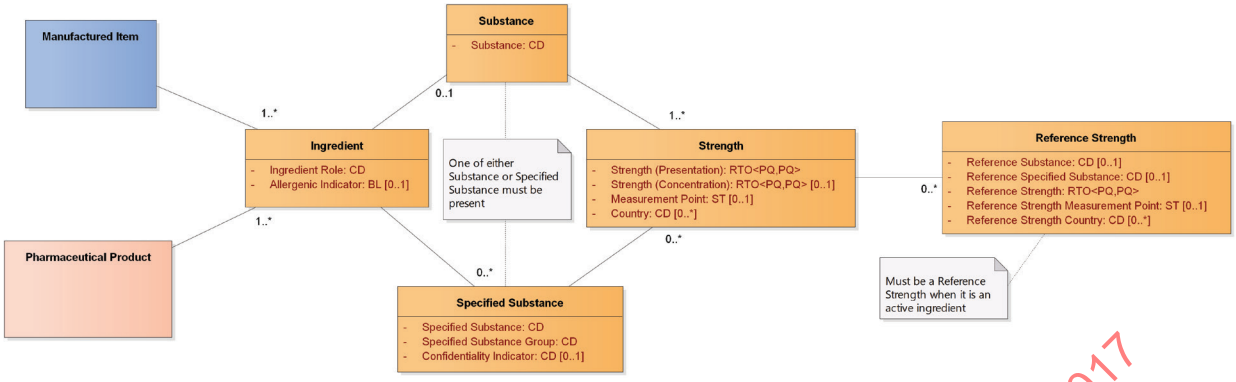

Figure 3 — Ingredients, substance and strength section detailed description diagram

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).

7.2.2 Substance

A substance can be specified for an ingredient in the role described.

User guidance	The substance shall be described in accordance with ISO 11238, ISO/TS 19844 and its resulting terminology. A term and a term identifier shall be used. NOTE For further details, refer to ISO 11238 and ISO/TS 19844.
Example(s)	— Insulin human — Amoxicillin trihydrate
Conformance	Mandatory
OID	Substance/specified substance code concept per regional implementation guidelines for ISO 11238 and ISO/TS 19844.

7.2.3 Specified substance

A specified substance can be specified for an ingredient in the role described.

NOTE The overall specified substance category is **optional**. The conformance criteria below correspond to jurisdictions which chose to implement specified substance category in their respective regions.

User guidance	When a specified substance is described, it shall be presented in accordance with ISO 11238, ISO/TS 19844, and its resulting terminology. A term and a term identifier shall be used. NOTE For further details, refer to ISO 11238 and ISO/TS 19844.
Example(s)	— Specified Substance Group 1: simeticone — Specified Substance Group 2: insulin human crystalline — rDNA manufacturer A — Specified Substance Group 3: water for injection (USP) — Specified Substance Group 4: insulin human crystalline — rDNA manufacturer A — highly purified (USP) — produced by three critical processes
Conformance	Conditional
OID	Substance/specified substance code concept per regional implementation guidelines for ISO 11238 and ISO/TS 19844.

7.2.4 Specified substance group

User guidance	The group to which a specified substance is assigned in accordance with ISO 11238, ISO/TS 19844, and its resulting terminology can be specified. A term and a term identifier shall be used.
Example(s)	— Specified Substance Group 1 — Specified Substance Group 2
Conformance	Conditional
OID	Substance/specified substance code concept per regional implementation guidelines for ISO 11238 and ISO/TS 19844.

7.2.5 Confidentiality indicator

User guidance	The confidentiality level of the substance/specified substance information described for the ingredient can be specified using an appropriate controlled vocabulary. The controlled term and a term identifier shall be specified. It is applicable for the all the strata when the active substance(s) and specified substance(s) is determined to be confidential/trade secret.
Example(s)	— Confidential — Trade secret — No restriction
Conformance	Mandatory
OID	Substance/specified substance code concept per regional implementation guidelines for ISO 11238 and ISO/TS 19844.

7.2.6 Strength

The strength of the substance or specified substance shall be specified as a quantity of the substance/specified substance present in a given pharmaceutical product. A numerator value and numerator unit as well as a denominator value and denominator unit shall be specified.

Strength can be expressed in two ways: strength (presentation) and strength (concentration).

When the strength of a pharmaceutical product that has undergone a transformation (e.g. reconstitution) is to be specified, it shall be specified using the strength resulting from transformation undertaken exactly in accordance with the regulated product information.

7.2.7 Pharmaceutical product code concept for representing the normalised strength for liquid preparations

A product code concept PhPID as described for liquid preparations (e.g. volume per container and at the unit level) shall be included.

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.

EXAMPLE PhPID for a 5 mg/5 ml container as approved and labelled with PhPID representing the pharmaceutical product at the 1 mg/ml unit level.

NOTE All pharmaceutical products, regardless of the total volume per container, would share the product code concept PhPID as an addition should the concentrations be identical. The same PhPID conformance criteria are applicable for the creation, implementation, and maintenance of the product code concept to represent normalised strengths for liquid preparations.

7.2.8 Strength (presentation)

User guidance	The strength (presentation) shall be specified. It is defined as the quantity or range of quantities of the substance/specified substance present in the dosage form, unit of presentation, or in the volume (or mass) of the single pharmaceutical product or manufactured item. When required for expression of strength, the unit of presentation shall be specified in accordance with ISO 11240, ISO 11239, ISO/TS 20440 and its resulting terminology. The controlled term and a term identifier for the unit of presentation shall be specified in the associated manufactured item or pharmaceutical product. For strength expressed using standard units, the unit of measure symbol and the symbol identifier as defined in ISO 11240 and its resulting controlled vocabulary shall be specified.
Example(s)	— 20 mg (per "each" tablet — as a unit of presentation) — 10 mg/5 ml — 3,1 g/5 ml to 3,7 g/5 ml
Conformance	Mandatory

Where the strength is defined on the basis of a "unit of presentation", the term and term identifier shall be used with the corresponding controlled vocabulary.

NOTE The "unit of presentation" is the same as the form code of the product containing the ingredient.

7.2.9 Strength (concentration)

User guidance	The strength (concentration) can be specified. It is defined as a quantity or range of quantities of the substance/specified substance present per unitary volume (or mass). For example: — 2 mg/ml; — 1,55 g/ml to 1,85 g/ml. NOTE 1 This attribute is only required when the strength (presentation) attribute is valued with the denominator as a non-unitary amount. Example: — Strength (presentation) = 25 mg/5 ml; strength (concentration) = 5 mg/ml. NOTE 2 For solid dose forms, strength (concentration) is generally the same as strength (presentation) and therefore is not required to be expressed separately; the strength (presentation) only is required. The representation of this information is described in this clause. When required for expression of strength, the unit of presentation shall be specified with its corresponding controlled terminology. The controlled term and a term identifier for the unit of presentation shall be specified in the pharmaceutical product. For strength expressed using standard units, the unit of measure symbol and the symbol identifier as defined in ISO 11240 and its resulting controlled vocabulary shall be specified.
Conformance	Conditional

NOTE The "unit of presentation" is the same as the form code of the product containing the ingredient.

7.2.10 Measurement point

User guidance	There are Medicinal Products in jurisdictions where strength is measured at a particular point (for example, the strength of the ingredient in some inhalers is measured at a particular distance from the point of aerosolisation). In these instances, the measurement point can be described using text, as applicable.
Conformance	Conditional

7.2.11 Country

User guidance	The country or countries for which the strength and measurement point are valid can be specified using values from ISO 3166-1 alpha-2 code elements. If a measurement point is specified, a country or countries should be described.
Conformance	Conditional

7.2.12 Reference strength

Strength can be further described by reference strength.

A reference strength is an expression of the strength in terms of a reference substance and a reference specified substance.

The reference strength is one of two cases. The more frequent case has the reference substance as the active moiety of the ingredient.

EXAMPLE 1 Metoprolol succinate (190 mg) equivalent to 100 mg metoprolol tartrate.

One may quantify the active moiety relationship to express the amount of active moiety.

EXAMPLE 2 Lithium carbonate 300 mg refers to 8,1 mmol lithium ion.

7.2.13 Reference substance

User guidance	If a reference substance needs to be specified based on the regulated product information, it shall be described in accordance with ISO 11238, ISO/TS 19844, and its resulting terminology. A term and a term identifier shall be used.
Conformance	Mandatory (repeated if identical to the strength of the substance)
OID	Substance code concept OID

7.2.14 Reference specified substance

User guidance	If a reference specified substance needs to be described based on the regulated product information, it shall be described in accordance with ISO 11238 and its resulting terminology. A term and a term identifier shall be used.
Conformance	Mandatory
OID data type	Specified substance code concept OID

7.2.15 Reference strength

The reference strength shall be specified. A numerator value and numerator unit as well as a denominator value and denominator unit shall be specified.

7.2.16 Reference strength measurement point

User guidance	The reference strength measurement point, if applicable, can be described.
Conformance	Conditional

7.2.17 Reference strength country

User guidance	The country or countries for which the reference strength and measurement point are valid can be specified using values from ISO 3166-1 alpha-2 code elements. If a measurement point is specified, a country or countries should be described.
Conformance	Conditional

8 Pharmaceutical product: adjuvants and devices

8.1 General considerations

This clause describes the Medicinal Product in terms of its qualitative and quantitative composition and in the pharmaceutical dose form approved for administration in line with the regulated product information. These characteristics of the Medicinal Product are referred to as “pharmaceutical product”.

For certain medicines, an adjuvant or device may be associated with a pharmaceutical product, for example, to support the administration of the medicine. In these instances, the pharmaceutical product will contain the adjuvant and device component information as an additional characteristic when applicable.

Both Medicinal Product and pharmaceutical product are represented in SPL as top-level manufactured product elements. The Medicinal Product (with its MPID) shall be specified first, followed by the pharmaceutical product.

The pharmaceutical product is associated with various pharmaceutical product characteristics, which can describe various aspects of the pharmaceutical product, such as its onset of action.

The pharmaceutical product may be associated with a device class, which represents information about any device to support the administration of the product, and therefore is of type “integrated device”; in this case, the device is in effect an “ingredient” of the pharmaceutical product.

The pharmaceutical product is associated with a set of PhPIDs.

For messaging, see Annex B.

8.1.1 Detailed description of pharmaceutical product and device information

Figures 4 and 5 show detailed descriptions of pharmaceutical product and device information.

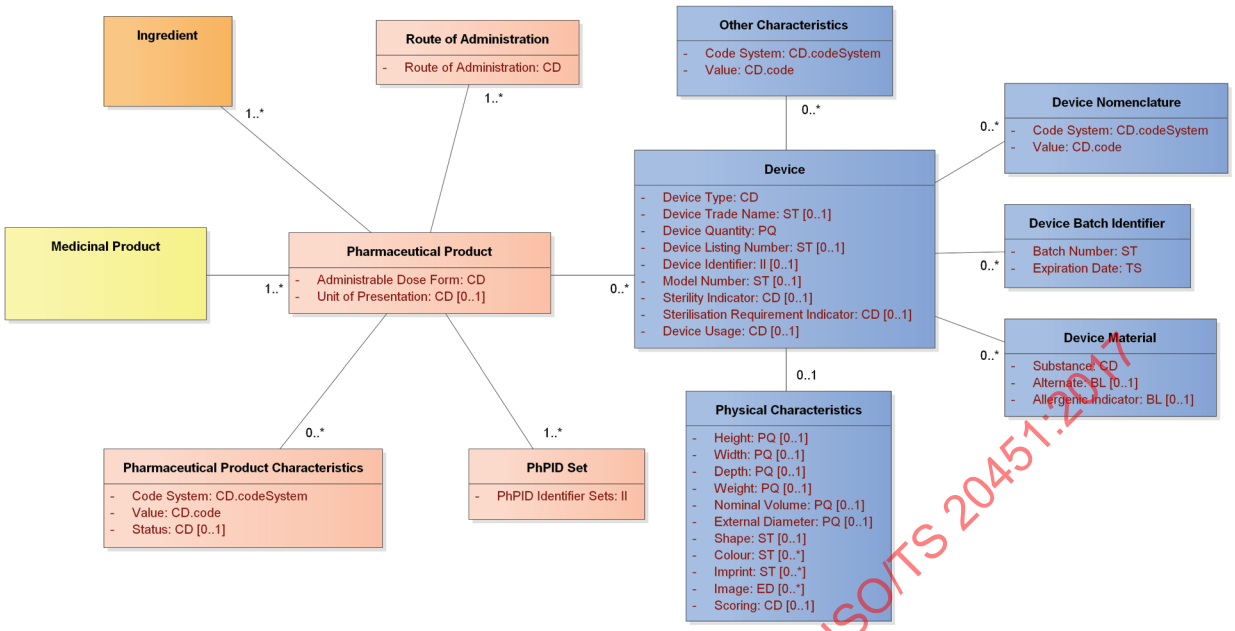

Figure 4 — Pharmaceutical product and device section detailed description diagram

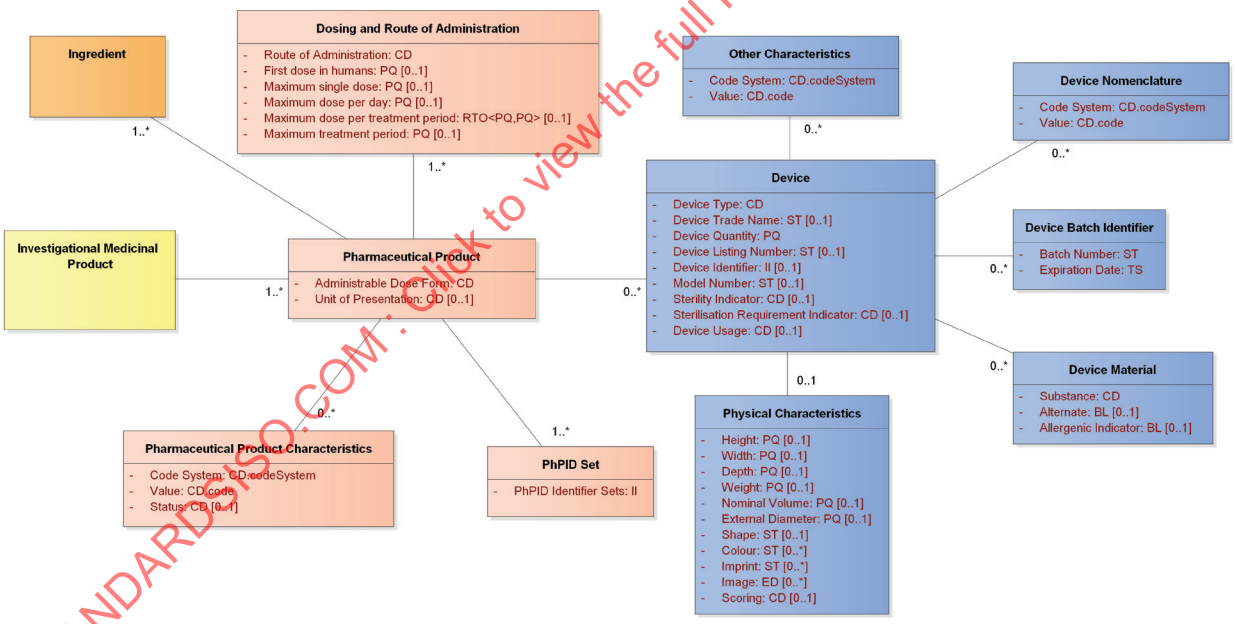

Figure 5 — Pharmaceutical product (investigational Medicinal Product) detailed description diagram

8.1.2 Pharmaceutical product

A pharmaceutical product shall be described in terms of its qualitative and quantitative composition and the pharmaceutical dose form approved for administration (administrable dose form) in line with the regulated product information.

The “qualitative and quantitative composition” in other words is ingredients and parts (when there is a device that is integral to the pharmaceutical product).

This subclause specifies information about the Medicinal Product in the dose form approved for administration to the patient in line with the regulated product information. It also includes the reference to the associated PhPID set(s) and the ingredient(s) for the pharmaceutical product.

8.1.2.1 Administrable dose form

User guidance	This shall describe the administrable dose form in accordance with the regulated product information. This is after it has undergone any necessary reconstitution, where applicable. The administrable dose form shall be specified in accordance with ISO 11239, ISO/TS 20440, and the resulting terminology. The term and the term identifier shall be specified. In certain instances, the administrable dose form differs from the manufactured dose form when a transformation of the manufactured dose form has been carried out. Example: The manufactured dose forms of two manufactured items are described as "powder for solution for injection" and "solvent for solution for injection" which after transformation corresponds to the administrable dose form "solution for injection".
Example(s)	— Tablet — Capsule — Oral solution — Solution for injection
Conformance	Mandatory
OID	Dosage form concept code OID per regional implementation guidelines for ISO 11239 and ISO/TS 20440.

8.1.2.2 Unit of presentation

User guidance	The unit of presentation is a qualitative term describing the discrete unit in which a pharmaceutical product is presented to describe strength or quantity in cases where a quantitative unit of measurement is not appropriate. It is a term and a term identifier as defined in ISO 11239, ISO/TS 20440, and the resulting terminology. For pharmaceutical products whose strength is measured as a quantity of weight or volume, the "unit of presentation" can be specified as the immediate (lowest level) container. For solid dose forms and other items whose strength is described on the basis of the amount in the unit of presentation, and which are counted in integer quantities, the unit for quantity shall be "1 unit" and the unit of presentation shall be the item that is counted, specified as a term and a term identifier as defined in ISO 11239, ISO/TS 20440, and the resulting terminology.
Example(s)	— To describe strength: a spray or puff "contains 100 mcg per actuation" (unit of presentation = actuation) — To describe quantity: a bottle "contains 100 ml per bottle" (unit of presentation = bottle)
Conformance	Conditional
OID	Unit of presentation concept code OID per regional implementation guidelines for ISO 11239 and ISO/TS 20440.

The pharmaceutical product is the final reconstituted form in which the product is intended to be administered. In the case of easy-to-use products, this form is the same as the manufactured form, e.g. an oral tablet is manufactured and intended to be administered in that same form. If a tablet is to be dissolved in 15 ml of water, then the actual administrable dose form is a solution, i.e. the liquid, resulting

from the dissolution of the tablet in water, an activity of reconstitution. Thus, the pharmaceutical product's administrable dose form should be specified as "solution" for oral route, and the ingredients would be specified on the basis of volume of such solution. If the reconstitution instructions are inexact or cannot be fully specified (because of "quantity sufficient …" clauses in the reconstitution specifications), so that the final volume and concentration of the ingredients are not known, then the administrable dose form shall be considered a "portion" of unknown volume, i.e. in the case of the dissolvable tablet, it would be the "portion of solution resulting from dissolving one tablet". Then the ingredients and administration instructions can be specified based on this countable portion.

NOTE Colloquially, even in advanced information systems, one may encounter the dose forms "tablet" or "solution" used without reference to "portion". This may be intuitively understood, but it is ultimately ambiguous. In case of the "dissolvable tablet" (or "tablet for solution"), the administrable dose form is intentionally not the tablet. And in the case of "solution" (without reference to "portion of solution …"), the reference quantity is missing without which ingredients and administration instructions are ambiguous, if not meaningless, e.g. "take one solution in the morning" is undefined and hence defective as administration instruction, but "take the entire (portion of) the solution resulting from dissolving one tablet (in any amount of diluent)", or in short, "take the solution of one tablet in the morning" is clearer. And the more natural phrasing "take one tablet dissolved in water" is still a reflection of the pharmaceutical product as the portion of water with the tablet dissolved in it, which is clearly implied by these words.

8.1.3 Pharmaceutical product characteristics

This class can be used to describe various characteristics of the pharmaceutical product, such as its onset of action.

8.1.3.1 (Pharmaceutical product characteristics) code system

User guidance	This class can be used to describe various characteristics of the pharmaceutical product, such as its onset of action.
Conformance	Optional per regional implementation guidelines for ISO 11615 and ISO 11616
OID	Concept code OID per regional implementation guidelines for ISO 11615 and ISO 11616

8.1.3.2 (Pharmaceutical product characteristics) value

User guidance	The individual value from the code system that describes the actual characteristic shall be specified using a controlled term and a controlled term identifier from the code system specified above.
Example(s)	Characteristic code system: onset of action types Characteristic value: immediate acting Characteristic code system: regulatory classification Characteristic value: advanced therapy Characteristic code system: regulatory classification Characteristic value: biologic
Conformance	Optional per regional implementation guides for ISO 11615
OID	Pharmaceutical characteristic concept code OID per regional implementation guidelines for ISO 11615

8.1.3.3 (Pharmaceutical product characteristic) status

User guidance	This attribute describes the status of a pharmaceutical product characteristic. It shall be specified using a controlled term and a controlled term identifier.
Conformance	Optional
OID	Pharmaceutical characteristic status code OID per regional implementation guidelines for ISO 11615

8.1.4 Device (pharmaceutical product)

A pharmaceutical product may refer to a drug that is associated with a medical device (e.g. drug/device, biologic/device). In this instance, the device term and term ID (unique device identifier) shall be displayed with the 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 defined in ISO 11615 and its corresponding implementation guide. It is a defining element when applicable to a pharmaceutical/Medicinal Product.

8.1.4.1 Device part

User guidance	The device, if reflected in the Medicinal Product name, shall be specified as text, where applicable.
Example(s)	For the Medicinal Product name “Drug XYZ® Precisehaler 200 mg for adults”, the device part is “Precisehaler”.
Conformance	Conditional

Annex A
(normative)

Messaging: Ingredient, substance and strength

A.1 General

The ingredients class and the associated substance, specified substance, strength and reference strength classes are used in the further description of manufactured item and pharmaceutical product class (see Figure A.1).

In addition, the substance class represents the value set that can be used to describe any materials from the device class and the materials and alternative materials attributes of the package item (container) and package (component) classes.

An ingredient shall be specified as a substance and additionally as any of the types of its associated specified substance(s). Any substance or specified substance shall have its strength specified in accordance with the regulated Medicinal Product information as applicable. Additionally, strength can be further specified by description of a reference strength. Again, this shall be specified where applicable in accordance with the regulated Medicinal Product information.

When described, a reference strength shall specify either the substance or the specified substance that it references.

Both manufactured item and pharmaceutical product and their ingredients, as well as the device ingredients of interest, are represented in SPL in the same way:

```
<!-- SPL header -->
<document>
 <component><structuredBody><component><section>...
  <subject>
   <!-- CPM body -->
   <manufacturedProduct>
    <manufacturedProduct><!-- Pharmaceutical Product / Manufactured Item -->
     <ingredient><!-- Ingredient -->
      <quantity><!-- Strength --></quantity>
      <ingredientSubstance><!-- Substance -->
       <activeMoiety>
        <!-- Reference Strength -->
       </activeMoiety>
       <asEquivalentSubstance>
        <!-- Reference Strength -->
```

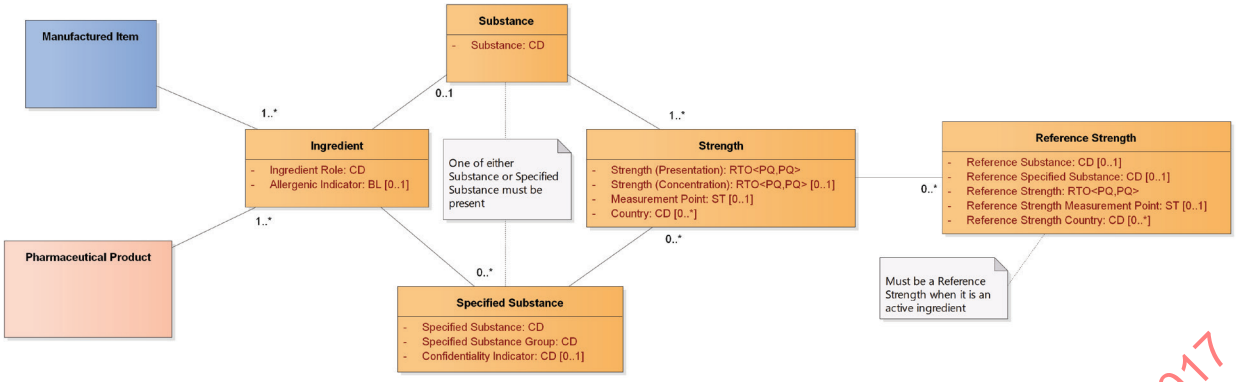

Figure A.1 — Ingredients, substance and strength section detailed description diagram

```
<!-- SPL header -->
<document>
 <component><structuredBody><component><section>...
  <subject>
   <!-- CPM body -->
   <manufacturedProduct>
    <manufacturedProduct><!-- Pharmaceutical Product / Manufactured Item -->
     <ingredient classCode="Ingredient Role"><!-- Ingredient -->
      <quantity><!-- Strength -- >
       <numerator xsi:type="URG_PQ"><!-- Strength -->
        <low value="Strength Low Number" unit="Strength Unit"/>
        <high value="Strength High Number" unit="Strength Unit"/>
       </numerator>
       <denominator value="Strength Denominator Number"
              unit="Strength Denominator Unit"/>
      </quantity>
      <ingredientSubstance><!-- Substance -->
       < code code="Substance Code" codeSystem="Code System (OID)"/>
       <name><!-- Substance Name --></name>
       <activeMoiety><!-- Reference Strength (Active Moiety) -->
        <quantity><!-- Reference Strength Quantity --></quantity>
        <activeMoiety>
         <code code="Substance Code" codeSystem="Code System (OID)"/>
         <name><!-- Substance Name --></name>
        </activeMoiety>
       </activeMoiety><!-- Reference Strength Quantity -->
       <asEquivalentSubstance><!-- Reference Strength (Reference Substance) -->
        <quantity>
         <numerator xsi:type="URG_PQ"><!-- Reference Strength-->
          <low value="Strength Low Number" unit="Strength Unit"/>
          <high value="Strength High Number" unit="Strength Unit"/>
         </numerator>
         <denominator value="Strength Denominator Number"
                unit="Strength Denominator Unit"/>
        </quantity>
        <definingSubstance>
         <code code="Substance Code" codeSystem="Code System (OID)"/>
         <name><!-- Substance Name --></name>
        </definingSubstance>
       </asEquivalentSubstance>
      <ingredientSubstance>
      <subjectOf>
       <substanceSpecification><!-- Specified Substance -->
       <code code="Substance Specification Code" code="Code System (OID)"
           displayName="Substance Specification Name">
```

A.2 Ingredient

User guidance	There shall be one instance of the "ingredient" class for each actual ingredient of either the manufactured item or pharmaceutical product, as appropriate.
Conformance	Mandatory

```
<!-- SPL header -->
<document>
 <component><structuredBody><component><section>...
  <subject>
   <!-- CPM body -->
   <manufacturedProduct>
    <manufacturedProduct><!-- Pharmaceutical Product / Manufactured Item -->
     <ingredient><!-- Ingredient 1 --></ingredient>
     <ingredient><!-- Ingredient 2 --></ingredient>
     <ingredient><!-- Ingredient 3 --></ingredient>
```

or under parts (manufactured item)

```
<!-- SPL header -->
<document>
 <component><structuredBody><component><section>...
  <subject>
   <!-- CPM body -->
    <manufacturedProduct>
     <manufacturedProduct><!-- Package Item (co-package), Kit -->
      <formCode code="C47916" displayName="KIT"
          codeSystem="2.16.840.1.113883.3.26.1.1"/>
      <part>
       <quantity><!-- Part Quantity --></quantity>
       <partProduct><!-- One Part Manufactured Item -->
        <ingredient><!-- Ingredient 1 --></ingredient>
        <ingredient><!-- Ingredient 2 --></ingredient>
        <ingredient><!-- Ingredient 3 --></ingredient>
```

A.2.1 Ingredient role

User guidance	The role of the ingredient as part of the manufactured item/pharmaceutical product should be specified using an appropriate controlled vocabulary. The controlled term and a term identifier should be specified.
Conformance	Mandatory

<ingredient classCode="***Ingredient Role***">

A.3 Substance

User guidance	A substance shall always be specified for each ingredient role described.
Conformance	Mandatory

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
  <ingredientSubstance><!-- Substance -->
```

A.3.1 Substance

User guidance	The substance shall be described in accordance with ISO 11238 and its resulting terminology. A term and a term identifier shall be used. The ingredient refers to the role of the substance in the Medicinal Product, for example: active or excipient. This element (substance) refers to the name of the specific substance.
Conformance	Mandatory

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
  <ingredientSubstance><!-- Substance -->
    <code code="Substance Code" codeSystem="Code System (OID)"/>
    <name><!-- Substance Name --></name>
```

```
 <ingredient classCode="Ingredient Role"><!-- Ingredient -->
   <ingredientSubstance><!-- Substance -->
     <code code="1Y17CTI5SR" codeSystem="2.16.840.1.113883.4.9"/>
     <name>INSULIN HUMAN</name>
```

A.4 Specified substance

User guidance	For each substance, one or more specified substance groups as described in ISO 11238 can be described, as applicable. In case when instead of a substance, a specified substance is applicable, then this element should be provided. Please refer to the definitions of substance and specified substance.
Conformance	Optional Mandatory if a jurisdiction implements the specified substance category in their region.

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
  <ingredientSubstance><!-- Substance --></ingredientSubstance>
  <subjectOf>
    <substanceSpecification><!-- Specified Substance -->
```

A.4.1 Specified substance

User guidance	When a specified substance is described, it shall be presented in accordance with ISO 11238 and its resulting terminology. A term and a term identifier shall be used.
Conformance	Conditional if a jurisdiction implements the specified substance category in their region.
Example	— Specified Substance Group 1: insulin human crystalline — Specified Substance Group 2: insulin human crystalline — rDNA Manufacturer A — Specified Substance Group 3: insulin human crystalline — highly purified (USP) — Specified Substance Group 4: insulin human crystalline — rDNA Manufacturer A — highly purified (USP) — produced by three critical processes NOTE For further details, see ISO 11238 and ISO/TS 19844.

```
< ingredient classCode="Ingredient Role"><!-- Ingredient -->
 <ingredientSubstance><!-- Substance --></ingredientSubstance>
 <subjectOf>
  <substanceSpecification><!-- Specified Substance -->
   <code code="Substance Specification Code"
       codeSystem="Code System (OID)"
       displayName="Substance Specification Name">
```

A.5 Specified substance group

User guidance	The group to which a Specified Substance is assigned in accordance with ISO 11238 and its resulting terminology can be specified. A term and a term identifier shall be used. The “specified substance group” is implicitly associated with the specified substance code. One specified substance code has exactly one specified substance group.
Conformance	Conditional if a jurisdiction implements the specified substance category in their region.

A.5.1 Confidentiality indicator

User guidance	The confidentiality level of the specified substance information described for the ingredient can be specified using an appropriate controlled vocabulary. The controlled term and a term identifier shall be specified.
Conformance	Mandatory for regions implementing specified substance(s)

```
<ingredient classCode="Ingredient Role"><!--Ingredient →
 <confidentialityCode code="B" codeSystem="2.16.840.1.113883.5.25"/>
 <ingredientSubstance><!--Substance →</ingredientSubstance>
```

A.6 Strength

User guidance	The strength of the substance and/or specified substance shall be specified as a quantity of the substance/specified substance present in a given manufactured item or pharmaceutical product. A numerator value and numerator unit as well as a denominator value and denominator unit shall be specified. Strength can be expressed in two ways: strength (presentation) and strength (concentration). NOTE When the strength of a pharmaceutical product that has undergone a transformation (for example, reconstitution) is to be specified, it shall be specified using the strength resulting from transformation undertaken exactly in accordance with the regulated Medicinal Product information.
Conformance	Mandatory at the substance level Mandatory at the specified substance level if a jurisdiction implements the specified substance category in their region.

```
< ingredient classCode="Ingredient Role"><!-- Ingredient -->
 <quantity><!-- Strength -->
  <numerator xsi:type="URG_PQ"><!-- Strength -->
   <low value="Strength Low Number" unit="Strength Unit"/>
   <high value="Strength High Number" unit="Strength Unit"/>
  </numerator>
  <denominator value="Strength Denominator Number"
          unit="Strength Denominator Unit"/>
 </quantity>
 <ingredientSubstance><!-- Substance -->
  <code code="Substance Code" codeSystem="Code System (OID)"/>
  <name><!-- Substance Name --></name>
  <activeMoiety><!-- Reference Strength (Active Moiety) -->
   <quantity><!-- Reference Strength Quantity --></quantity>
   <activeMoiety>
    <code code = "Substance Code" codeSystem="Code System (OID)"/>
    <name><!-- Substance Name --></name>
   </activeMoiety>
  </activeMoiety><!-- Reference Strength Quantity -->
  <asEquivalentSubstance><!-- Reference Strength (Reference Substance) -->
   <quantity>
    <numerator xsi:type="URG_PQ"><!-- Reference Strength-->
     <low value="Strength Low Number" unit="Strength Unit"/>
     <high value="Strength High Number" unit="Strength Unit"/>
    </numerator>
    <denominator value="Strength Denominator Number"
            unit="Strength Denominator Unit"/>
   </quantity>
   <definingSubstance>
    <code code="Substance Code" codeSystem="Code System (OID)"/>
    <name><!- Substance Name --></name>
```

A.6.1 Strength (presentation)

User guidance	Strength (presentation) shall be specified as a quantity of the substance/specified substance present in a given quantity of the pharmaceutical product or manufactured item. The unit of presentation shall be specified in accordance with ISO 11239 and its resulting terminology. The controlled term and a term identifier for the unit of presentation shall be specified in the associated manufactured item or pharmaceutical product. The unit of measure symbol and the symbol identifier as defined in ISO 11240 and its resulting controlled vocabulary shall be specified. Where the strength is defined on the basis of a "unit of presentation", the term and term identifier shall be used as defined in ISO 11239 and its resulting controlled vocabulary.
Conformance	Mandatory

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
 <quantity><!-- Strength -->
  <numerator xsi:type="URG_PQ"><!-- Strength -->
   <low value="Strength Low Number" unit="Strength Unit"/>
   <high value="Strength High Number" unit="Strength Unit"/>
  </numerator>
  <denominator value="Strength Denominator Number" unit="Denominator Unit"/>
```

If the strength is specified as a simple value instead of a range, the format is much simpler:

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
 <quantity><!-- Strength -->
  <numerator value="Strength Low Number" unit="Strength Unit"/>
  <denominator value="Strength Denominator Number" unit="Denominator Unit"/>
```

EXAMPLE 1 "10 mg/5 ml":

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
 <quantity><!-- Strength -->
  <numerator value="10" unit="mg"/>
  <denominator value="5" unit="mL"/>
```

EXAMPLE 2 "2 mg/1 unit of presentation":

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
 <quantity><!-- Strength -->
  <numerator value="2" unit="mg"/>
  <denominator value="1" unit="1"/>
```

NOTE The "unit of presentation" is the same as the form code of the product containing the ingredient.

A.6.2 Strength (concentration)

User guidance	Strength (concentration) can be specified as a quantity of the substance/specified substance present per one unit of the pharmaceutical product or manufactured item, for example, 2 mg/1 tablet. For solid dose forms, this is generally the same as strength (presentation) and therefore is not required to be expressed separately; the strength (presentation) only is required. The representation of this information is described below. The unit of measure symbol and the symbol identifier as defined in ISO 11240 and its resulting controlled vocabulary shall be specified. Where the strength is defined on the basis of a "unit of presentation", the term and term identifier shall be used as defined in ISO 11239 and its resulting controlled vocabulary.
Conformance	Conditional

```
<ingredient>
  <quantity><!-- Strength -->
    <numerator xsi:type="URG_PQ"><!-- Strength -->
      <low value="Strength Low Number" unit="Strength Unit"/>
      <high value="Strength High Number" unit="Strength Unit"/>
    </numerator>
    <denominator value="Strength Denominator Number" unit="Denominator Unit"/>
```

If the strength is specified as a simple value instead of a range, the format is much simpler:

```
<ingredient>
  <quantity><!-- Simple Strength -->
    <numerator value="Strength Number" unit="Strength Unit"/>
    <denominator value="Strength Denominator Number" unit="Denominator Unit"/>
```

EXAMPLE 1 "2 mg/1 ml":

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
  <quantity><!-- Strength -->
    <numerator value="2" unit="mg"/>
    <denominator value="1" unit="mL"/>
```

EXAMPLE 2 "2 mg/1 tablet":

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
  <quantity><!-- Strength -->
    <numerator value="2" unit="mg"/>
    <denominator value="1" unit="1"/>
```

NOTE The "unit of presentation" is the same as the form code of the product containing the ingredient.

A.6.3 Measurement point

User guidance	There are some Medicinal Products in some jurisdictions where strength is measured at a particular point (for example, the strength of the ingredient in some inhalers is measured at a particular distance from the point of aerosolisation). In these instances, the measurement point can be described using text, as applicable.
Conformance	Mandatory

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
  <quantity><!-- Strength --></quantity>
  <ingredientSubstance><!-- Ingredient Substance --></ingredientSubstance>
  <subjectOf>
   <characteristic>
    <code code="Code meaning 'Measurement Point'" codeSystem="Code System OID"/>
    <value xsi:type="CV" code="Measurement Point Code"
        codeSystem="Code System OID" displayName="Point Name">
```

A.6.4 Country

User guidance	The country or countries for which the strength and measurement point are valid can be specified using values from the ISO 3166-1 alpha-2 code elements.
Conformance	Conditional

This country specification is only necessary when the measurement point specification varies in those countries. When two observations are considered different and such difference is not specified by any other attribute, then the observation code should be different. Therefore, the difference of measurement points as applicable in different countries will be primarily indicated by the terminology of the measurement point observation code.

```
<ingredient classCode="Ingredient Role"><!-- Ingredient -->
  <quantity><!-- Strength --></quantity>
  <ingredientSubstance><!-- Ingredient Substance --></ingredientSubstance>
  <subjectOf>
   <characteristic>
    <code code="Code meaning 'Measurement Point', country specific if applicable"
        codeSystem="Code System OID"/>
    <value xsi:type="CV" code="Measurement Point Code"
        codeSystem="Code System OID" displayName="Point Name">
```

The terminology for country specific measurement points is to be defined and maintained by the applicable maintenance organisation.

A.7 Reference strength

User guidance	Strength can be further described by a reference strength. A reference strength is an expression of the strength in terms of either a reference substance and/or a reference specified substance. The reference strength is one of two cases. The more frequent case has the reference substance as the active moiety of the ingredient.
Conformance	Mandatory

```
<ingredient classCode="ACTIM">
 <quantity>
  <numerator value="Reference Strength Number" unit="Strength Unit"/>
  <denominator value="Amount of Product Number" unit="Product Unit"/>
 </quantity>
 <ingredientSubstance>
  <code code="Substance Code" codeSystem="Code System (OID)"/>
  <name><!-- Substance Name --></name>
  <activeMoiety>
   <quantity>
    <numerator value="Actual Strength Number" unit="Strength Unit"/>
    <denominator value="Reference Strength Number" unit="Strength Unit"/>
   </quantity>
   <activeMoiety>
    <code code="Reference Substance Code" codeSystem="Code System (OID)"/>
    <name><!-- Substance Name --></name>
```

EXAMPLE 1 Apraclonidine hydrochloride 5,75 mg equivalent to apraclonidine base 5 mg.

```
<ingredient classCode="ACTIM">
 <quantity>
  <numerator value="5" unit="mg"/>
  <denominator value="1" unit="1"/>
 </quantity>
 <ingredientSubstance>
  < code code="D2VW67N38H" codeSystem="2.16.840.1.113883.4.9"/>
  <name> APRACLONIDINE HYDROCHLORIDE</name>
  <activeMoiety><!-- Reference Substance (Active Moiety) -->
   <quantity>
    <numerator value="5.75" unit="mg"/>
    <denominator value="5" unit="mg"/>
   </quantity>
   <activeMoiety>
    <code code="843CEN85DI" codeSystem="2.16.840.1.113883.4.9"/>
    <name> APRACLONIDINE</name>
```

The second, less frequent case has the reference substance as another substance.

```
<ingredient classCode="ACTIR">
 <quantity>
  <numerator value="Reference Strength Number" unit="Strength Unit"/>
  <denominator value="Amount of Product Number" unit="Product Unit"/>
 </quantity>
 <ingredientSubstance>
  <code code="Substance Code" codeSystem="Code System (OID)"/>
  <name><!-- Substance Name --></name>
  <asEquivalentSubstance>
   <quantity>
    <numerator value="Actual Strength Number" unit="Strength Unit"/>
    <denominator value="Reference Strength Number" unit="Strength Unit"/>
   </quantity>
   <definingSubstance>
    <code code="Reference Substance Code" codeSystem="Code System (OID)"/>
    <name><!-- Substance Name -- ></name>
```

EXAMPLE 2 Metoprolol succinate (190 mg) equivalent to 100 mg metoprolol tartrate.

```
<ingredient classCode="ACTIR">
 <quantity>
  <numerator value="100" unit="mg"/>
  <denominator value="1" unit="1"/>
 </quantity>
 <ingredientSubstance>
  <code code="TH25PD4CCB" codeSystem="2.16.840.1.113883.4.9"/>
  <name>METOPROLOL SUCCINATE</name>
  <asEquivalentSubstance><!-- Reference Strength (Reference Substance) -->
   <quantity>
    <numerator value="190" unit="mg"/>
    <denominator value="100" unit="mg"/>
   </quantity>
   <definingSubstance>
    <code code="W5S57Y3A5L" codeSystem="2.16.840.1.113883.4.9"/>
    <name>METOPROLOL TARTRATE</name>
```

Even when a reference strength is not required, one may quantify the active moiety relationship to express the amount of active moiety.

EXAMPLE 3 Lithium carbonate 450 mg refers to 12,2 mmol lithium ion.

```
<ingredient classCode="ACTIB">
 <quantity>
  <numerator value="300" unit="mg"/>
  <denominator value="1" unit="1"/>
 </quantity>
 <ingredientSubstance>
  <code code="2BMD2GNA4V" codeSystem="2.16.840.1.113883.4.9"/>
  <name>LITHIUM CARBONATE</name>
   <activeMoiety><!-- Reference Strength (Active Moiety) -->
    <quantity>
     <numerator value="12.2" unit="mmol"/>
     <denominator value="300" unit="mg"/>
    </quantity>
    <activeMoiety>
     <code code="9FN79X2M3F" codeSystem="2.16.840.1.113883.4.9"/>
     <name>LITHIUM</name>
```

A.7.1 Reference substance

User guidance	If a reference strength substance needs to be specified based on the regulated product information, it shall be described in accordance with ISO 11238 and its resulting terminology. A term and a term identifier shall be used.
Conformance	Mandatory

When reference substance is a moiety of the ingredient substance:

```
<ingredient classCode="ACTIM">
 <ingredientSubstance>
  <activeMoiety>
   <activeMoiety>
    <code code="Reference Substance Code" codeSystem="Code System (OID)"/>
    <name><!-- Substance Name -- ></name>
```

When reference substance is not part of the ingredient substance:

```
<ingredient classCode="ACTIR">
 <ingredientSubstance>
  <asEquivalentSubstance>
   <definingSubstance>
    <code code="Reference Substance Code" codeSystem="Code System (OID)"/>
    <name><!-- Substance Name --></name>
```

A.7.2 Reference specified substance

User guidance	If a reference strength at the level of the specified substance needs to be specified based on the regulated product information, it shall be described in accordance with ISO 11238 and its resulting terminology. A term and a term identifier shall be used.
Conformance	Mandatory if a jurisdiction implements the specified substance category in their region.

When reference substance is a moiety of the ingredient substance:

```
<ingredient classCode="ACTIM">
 <ingredientSubstance>
  <activeMoiety>
   <activeMoiety>...</activeMoiety>
   <subjectOf>
    <substanceSpecification><!-- Specified Substance -->
     <code code="Substance Specification Code"
        codeSystem="Code System (OID)"
        displayName="Substance Specification Name">
```

When reference substance is not part of the ingredient substance:

```
<ingredient classCode="ACTIR">
 <ingredientSubstance>
  <asEquivalentSubstance>
   <definingSubstance>...</definingSubstance>
   <subjectOf>
    <substanceSpecification><!-- Specified Substance -->
     <code code="Substance Specification Code"
        codeSystem="Code System (OID)"
        displayName="Substance Specification Name">
```

A.7.3 Reference strength

User guidance	If a reference strength specified substance needs to be specified based on the regulated product information, it should be described in accordance with ISO 11238 and its resulting terminology. A term and a term identifier should be used.
Conformance	Mandatory if a jurisdiction implements the specified substance category in their region.

```
<ingredient>
 <quantity><!-- Strength -->
  <numerator xsi:type="URG_PQ"><!-- Strength -->
   <low value="Strength Low Number" unit="Strength Unit"/>
   <high value="Strength High Number" unit="Strength Unit"/>
  </numerator>
  <denominator value="Strength Denominator Number" unit="Denominator Unit"/>
```

If the strength is specified as a simple value instead of a range, the format is much simpler:

```
<ingredient>
 <quantity><!-- Simple Strength -->
  <numerator value="Strength Number" unit="Strength Unit"/>
  <denominator value="Strength Denominator Number" unit="Denominator Unit"/>
```

A.7.4 Reference strength measurement point

User guidance	The reference strength measurement point, if applicable, should be described as outlined in A.6.3.
Conformance	Mandatory if a jurisdiction implements the specified substance category in their region.

When reference substance is a moiety of the ingredient substance:

```
<ingredient classCode="ACTIM">
 <ingredientSubstance>
  <activeMoiety>
   <activeMoiety>...</activeMoiety>
   <subjectOf>
    <characteristic>
     <code code="Code meaning 'Measurement Point'"
        codeSystem="Code System OID"/>
     <value xsi:type="CV" code="Measurement Point Code"
        codeSystem="Code System OID" displayName="Point Name">
```

When reference substance is not part of the ingredient substance:

```
<ingredient classCode="ACTIR">
 <ingredientSubstance>
  <asEquivalentSubstance>
   <definingSubstance>...</definingSubstance>
   <subjectOf>
    <characteristic>
     <code code="Code meaning 'Measurement Point'"
        codeSystem="Code System OID"/>
     <value xsi:type="CV" code="Measurement Point Code"
        codeSystem="Code System OID" displayName="Point Name">
```

A.7.5 Reference strength country

User guidance	Where a reference strength country is applicable as outlined in A.6.4, it can be specified based on the ISO 3166-1 alpha-2 code elements.
Conformance	Conditional

When reference substance is a moiety of the ingredient substance:

```
<ingredient classCode="ACTIM">
 <ingredientSubstance>
  <activeMoiety>
   <activeMoiety>...</activeMoiety>
   <subjectOf>
    <characteristic>
     <code code="Code meaning 'Measurement Point', country specific"
        codeSystem="Code System OID"/>
     <value xsi:type="CV" code="Measurement Point Code"
        codeSystem="Code System OID" displayName="Point Name">
```

When reference substance is not part of the ingredient substance:

```
<ingredient classCode="ACTIR">
  <ingredientSubstance>
   <asEquivalentSubstance>
    <definingSubstance>...</definingSubstance>
    <subjectOf>
     <characteristic>
      <code code="Code meaning 'Measurement Point', country specific"
          codeSystem="Code System OID"/>
      <value xsi:type="CV" code="Measurement Point Code"
          codeSystem="Code System OID" displayName="Point Name">
```

The terminology for country specific measurement points is to be defined and maintained by the applicable maintenance organisation.

Annex B
(normative)

Messaging: Pharmaceutical product and device

B.1 General

This clause describes the pharmaceutical product in terms of its qualitative and quantitative composition and in the pharmaceutical dose form approved for administration in line with the regulated product information. These characteristics of the Medicinal Product are referred to as pharmaceutical product.

For certain medicines, a device can form an integral part of the pharmaceutical product. In these instances, the pharmaceutical product contains the device component information as an additional characteristic.

A Medicinal Product is associated with the pharmaceutical product class — in terms of its qualitative and quantitative composition and the pharmaceutical dose form approved for administration in line with the regulated product information.

The pharmaceutical product is the result of fully reconstituting the Medicinal Product and all its package items using its various manufactured items [and devices or adjuvant(s) if applicable].

The pharmaceutical product is represented in HL7 SPL as top-level manufactured product elements.

```
<!-- SPL header -->
<document>
 <component><structuredBody><component><section>...
  <subject>
   <!-- CPM body -->
   <manufacturedProduct>
    <manufacturedProduct><!-- Pharmaceutical Product -->
     <!-- Pharmaceutical Product Details -->
    </manufacturedProduct>
    <productOf>
     <reconstitution>
      <consumable>
       <manufacturedProduct>
        <code code="PhPID" codeSystem="PhPID Code System OID"/>
```

The pharmaceutical product is associated with various pharmaceutical product characteristics, which can describe various aspects of the pharmaceutical product.

The pharmaceutical product may be associated with a device class, which represents information about any integral device to support the administration of the product — and therefore is of type “integrated device”. The device can have a set of physical characteristics and other characteristics associated with it.

The pharmaceutical product shall be described in terms of the ingredients it contains (see Figure B.1).

The pharmaceutical product is associated with a set of PhPIDs, as documented in ISO 11616.

```
<!-- SPL header -->
<document>
 <component><structuredBody><component><section>...
  <subject>
   <!-- CPM body -->
   <manufacturedProduct>
    <manufacturedProduct><!-- Pharmaceutical Product -->
     <formCode code="Administrable Dose Form code" codeSystem="Code System (OID)"
          displayName="Form Name"/>
     <asSpecialisedKind>
      <generalisedMaterialKind>
       <code code="PhPID" codeSystem="PhPID Code System OID" .../>
      </generalisedMaterialKind>
     </asSpecialisedKind>
     <ingredient classCode="Ingredient Role"><!-- Ingredient -->
      <quantity><!-- Strength -->
       <numerator xsi:type="URG_PQ"><!-- Strength -->
        <low value="Strength Low Number" unit="Strength Unit"/>
        <high value="Strength High Number" unit="Strength Unit"/>
       </numerator>
       <denominator value="Strength Denominator Number"
              unit="Strength Denominator Unit"/>
      </quantity>
      <ingredientSubstance><!-- Substance -->
       <code code="Substance Code" codeSystem="Code System (OID)"/>
       <name><!-- Substance Name --></name>
       <activeMoiety><!-- Reference Strength (Active Moiety) -->
        <quantity><!-- Reference Strength Quantity --></quantity>
        <activeMoiety>
         <code code="Substance Code" codeSystem="Code System (OID)"/>
         <name><!-- Substance Name --></name>
        </activeMoiety>
       </activeMoiety><!-- Reference Strength Quantity -->
       <asEquivalentSubstance><!-- Reference Strength (Reference Substance) -->
        <quantity>
         <numerator xsi:type="URG_PQ"><!-- Reference Strength-->
          <low value="Strength Low Number" unit="Strength Unit"/>
          <high value="Strength High Number" unit="Strength Unit"/>
         </numerator>
         <denominator value="Strength Denominator Number"
                unit="Strength Denominator Unit"/>
        </quantity>
        <definingSubstance>
         <code code="Substance Code" codeSystem="Code System (OID)"/>
         <name><!-- Substance Name --></name>
        </definingSubstance>
       </asEquivalentSubstance>
      <ingredientSubstance>
      <subjectOf>
       <substanceSpecification><!-- Specified Substance -->
        <code code="Substance Specification Code" code="Code System (OID)"
            displayName="Substance Specification Name">
    </ingredient>
    <part><!-- Device as integral part of the Pharmaceutical Product --></part>
   </manufacturedProduct>
   <subjectOf>
    <characteristic>
     <!-- Pharmaceutical Product Characteristics -->
     <code code="Characteristic Code" codeSystem="Code System (OID)"/>
     <value Characteristic Value (Various Attributes) />
    </characteristic>
   </subjectOf>
   <consumedIn>
    <substanceAdministration>
     <routeCode code="Route Code" codeSystem="Code System (OID)"/>
```

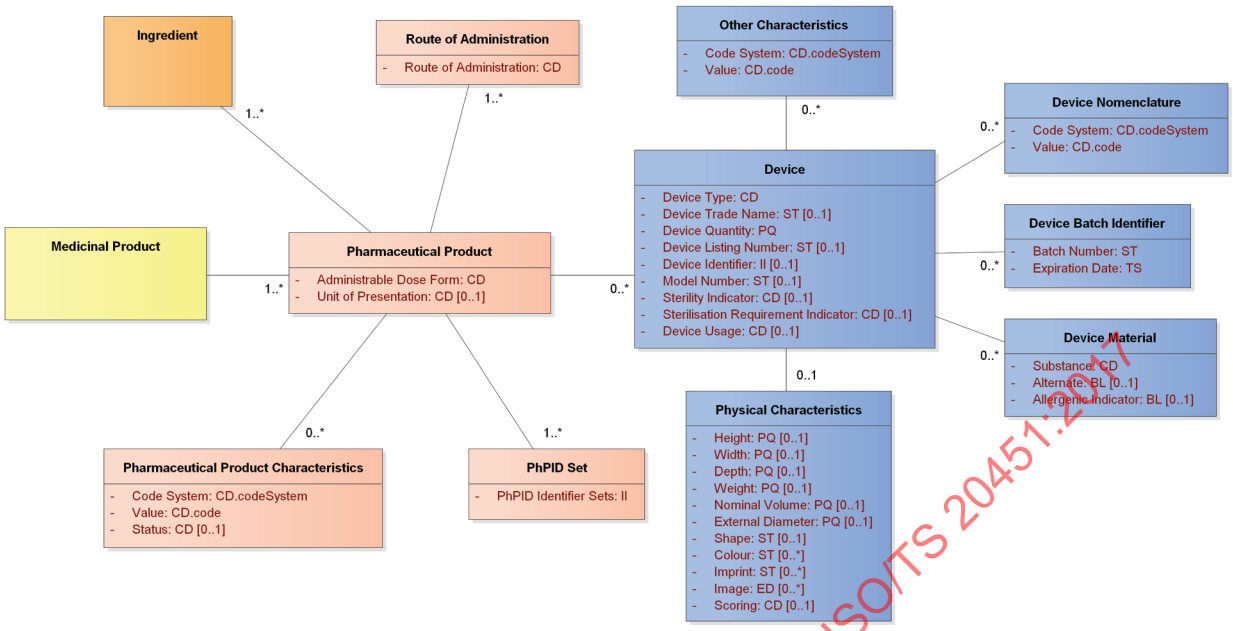

Figure B.1 — Pharmaceutical product and device section detailed description diagram

B.2 Pharmaceutical product

User guidance	A pharmaceutical product shall be described in terms of its qualitative and quantitative composition and the pharmaceutical dose form approved for administration (administrable dose form) in line with the regulated product information. The "qualitative and quantitative composition" in other words is ingredients and parts (when there is a device that is integral to the pharmaceutical product).
Conformance	Mandatory

```
<!-- SPL header -->
<document>
 <component><structuredBody><component><section>...
  <subject>
   <!-- CPM body -->
   <manufacturedProduct>
    <manufacturedProduct><!-- Pharmaceutical Product -->
     <formCode code="Administrable Dose Form code" codeSystem="Code System (OID)"
          displayName="Form Name"/>
     <ingredient><!-- Ingredient --></ingredient>
      <part><!-- Device (as integral part) --></part>
```

B.2.1 Administrable dose form

User guidance	This shall describe the administrable dose form in accordance with the regulated product information. This is after it has undergone any necessary reconstitution, where applicable. The administrable dose form shall be specified in accordance with ISO 11239 and the resulting terminology. The term and the identifier shall be specified. In certain instances, the administrable dose form differs from the manufactured dose form when a transformation of the manufactured dose form has been carried out. Example: The manufactured dose forms of two manufactured items are described as “powder for solution for injection” and “solvent for solution for injection” which after transformation corresponds to the administrable dose form “solution for injection”.
Conformance	Mandatory

NOTE In certain instances, the administrable dose form differs from the manufactured dose form, i.e. a transformation of the manufactured dose form has been carried out.

EXAMPLE The manufactured dose forms of two manufactured items refer to a powder and a solvent, which after transformation correspond to the administrable dose form solution for injection.

```
<!-- SPL header -->
<document>
 <component><structuredBody><component><section>...
  <subject>
   <!-- CPM body -->
   <manufacturedProduct>
    <manufacturedProduct><!-- Pharmaceutical Product -->
     <formCode code="Administrable Dose Form code" codeSystem="Code System (OID)"
          displayName="Form Name"/>
```

B.2.2 Unit of presentation

User guidance	The unit of presentation is a qualitative term describing the discrete unit in which a pharmaceutical product is presented to describe strength or quantity in cases where a quantitative unit of measurement is not appropriate. It is a term and a term identifier as defined in the ISO 11239 and the resulting terminology. For pharmaceutical products whose strength is measured as a quantity of weight or volume, the “unit of presentation” can be specified as the immediate (lowest level) container. For solid dose forms and other items whose strength is described on the basis of the amount in the unit of presentation, and which are counted in integer quantities, the unit for quantity should be “1 unit” and the unit of presentation should be the item that is counted, specified as a term and a term identifier as defined in the ISO 11239 and the resulting terminology.
Conformance	Conditional

Practical experience

EXAMPLE 1 To describe strength: spray/puff; “contains 100 mcg per actuation” (unit of presentation = actuation).

If the manufactured product is an aerosol for inhalation, and it is delivered from a metered dose inhaler (“dispenser”), then the administrable dose form concept, fully specified, should be “the portion of aerosol dispensed by one actuation of the dispenser”. That is the actual administrable dose form and the thing for which ingredients per actuation can be specified as well as the thing that is referenced in the unambiguous administration instructions (e.g. “take one puff three times a day before meal”). Having any incongruence between administrable dose form and “unit of presentation” would likely be semantically incorrect and practically confusing. In particular, it is incorrect to assume for any

practical purpose that the pharmaceutical product, i.e. the item actually administered is the “inhaler” (the patient does not administer the inhaler as a whole) nor is just the “solution (or powder) for inhalation” (the patient does not measure out an arbitrary amount of the solution (or powder). It is only correctly specified as the “puff” (in common parlance) or, precisely, the “portion of aerosol delivered by one actuation of the dispenser”. Note further that common parlance terms “spray” or “aerosol” or “actuation” are inferior of the initially less scientific-sounding “puff”; the “spray” does not necessarily imply a metered portion (e.g. a common spray bottle with continuous actuation), and an “aerosol” does not imply any defined portion, and, finally, “actuation” strictly denotes an action and not the material dispensed by the said action.

Though it is absolutely necessary that the form code terminology specify how the product is quantified so as to unambiguously specify the amount of ingredient, if it is still desired that a conventional count noun be included, it can be done using the translation element of quantity as follows. But this shall never be a substitute for an unambiguously specified pharmaceutical product form code.

```
<manufacturedProduct>
 <formCode code="Code for 'Portion Delivered by Pump Spray Actuation'"
       codeSystem="Code System (OID)" displayName="SPRAY">
 <ingredient classCode="ACTI">
  <quantity>
   <numerator value="100" unit="ug"/>
   <denominator value="1" unit="1">
    <translation value="1" code="Code for 'Actuation'"
          codeSystem="Code System (OID)" displayName="ACTUATION [UoP]"/>
```

EXAMPLE 2 To describe quantity: bottle; “contains 100 ml per bottle” (unit of presentation = bottle).

This is a perfect anti-example showing why “unit of presentation” where not fully redundant only leads to mistakes when specified. After having distinguished manufactured item from pharmaceutical product, it is highly unlikely that “bottle” is the correct description of the appearance of the true pharmaceutical product. The only reason for specifying “bottle” was if the administrable dose form was in fact “bottle”.

As a package, if the need for specifying “bottle” as a count noun is determined, this can be done on the package specification of the manufactured product as follows:

```
<manufacturedProduct>
 <acContent>
  <quantity>
   <numerator value="100" unit="ug"/>
   <denominator value="1" unit="1">
    <translation value="1" code="Code for 'Bottle' as 'Unit of Presentation'"
          codeSystem="Code System (OID)" displayName="BOTTLE [UoP]"/>
   </denominator>
  </quantity>
  <containerPackagedProduct>
   <formCode code="Code for 'Bottle' as package type"
       codeSystem="Code System (OID)" displayName="BOTTLE">
```

B.3 Pharmaceutical product characteristics

B.3.1 (Pharmaceutical product characteristics) code system

User guidance	This element should be used to describe various characteristics of the pharmaceutical product, such as its onset of action. The code describing the type of characteristic shall be specified using an appropriate identification system.
Conformance	Optional

B.3.2 (Pharmaceutical product characteristics) value

User guidance	This element should be used to describe various characteristics of the pharmaceutical product, such as its onset of action. The individual value from the code system that describes the actual characteristic should be specified using a controlled term and a controlled term identifier from the code system.
Conformance	Optional

```
<!-- SPL header -->
<document>
 <component><structuredBody><component><section>...
  <subject>
   <!-- CPM body -->
   <manufacturedProduct>
    <manufacturedProduct><!-- Pharmaceutical Product --></manufacturedProduct>
     <characteristic>
      <!-- Pharmaceutical Product Characteristics -->
      <code code="Pharmaceutical Product Characteristic Code"
       codeSystem="Pharmaceutical Product Characteristic Code System (OID)"/>
      <value Characteristic Value (Various Attributes) />
```

B.3.3 (Pharmaceutical product characteristics) status

User guidance	This attribute describes the status of a pharmaceutical product characteristic. It shall be specified using a controlled term and a controlled term identifier.
Conformance	Optional

B.4 Device

For pharmaceutical products, only in those situations where the associated Medicinal Product is combined with a medical device and where the pharmacological, immunological or metabolic action should be considered as the principal mode of action should the medical device presented as part of the Medicinal Product be described, using the **device**, **physical characteristics** and **other characteristics** classes. The details of these three classes are as described in ISO 11615 and ISO/TS 20443. For products where this occurs (e.g. the skin scaffold situation), the device is in effect being considered as an "ingredient" of the pharmaceutical product, and is therefore described here, because it will be referenced in the PhPID identification of the pharmaceutical product.