TECHNICAL SPECIFICATION

ISO/TS 16791

Second edition
2020-09

Health informatics — Requirements for international machine-readable coding of medicinal product package identifiers

Informatique de santé — Exigences pour une identification internationale, lisible par capture automatique, des produits médicinaux

Reference number
ISO/TS 16791:2020(E)

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Published in Switzerland

Contents

Page

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).

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For an explanation of 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 www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 215, *Health informatics*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 251, *Health informatics,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO/TS 16791:2014), which has been technically revised.

The main changes to the previous edition are as follows:

— adjustment of definitions to the latest IDMP standard (ISO 11615), adding definition for aggregation;

— improvement of 5.2.1.4;

— improvement of 5.3 with a clear distinction between product authentication and supply chain integrity;

— improvement of Annex D;

— Addition of Annex E.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html

Introduction

Globally, healthcare regulators, medicinal product suppliers, and healthcare providers, among others, are facing increased pressure to ensure a more secure and safer supply chain for medicinal products. The primary objective is to ensure optimal patient safety outcomes. Organizations such as the World Health Organization (WHO), the European Union and the US Congress, along with many other healthcare organizations are also seeking robust systems that will deliver outcomes to enhance overall supply chain integrity, to prevent product falsification and to improve patient safety, especially at the point of care.

Machine-readable coding is a technology capable of achieving these stated outcomes. Therefore, the core purpose of this document is to provide guidelines for machine-readable coding based on globally harmonized and interoperable standards for wide scale international implementation.

This document outlines the requirements to implement international machine-readable coding on medicinal product packages in the healthcare supply chain; this process cannot be isolated from more general identification practice with medical devices or other categories of products. It assists all stakeholders implement, use, and optimize Automatic Identification and Data Capture (AIDC) technologies in their respective enterprises with a particular attention to Health Informatics. In that respect, this document complements ISO 11615.

As AIDC offers a wide spectrum of potential solutions, particularly for data carriers such as barcodes, it has highlighted the importance of properly defining data structures to prevent ambiguity when information is encoded and captured.

Furthermore, the semantics of data carried can be defined by a number of organizations (also called "issuing agencies"), some with commercial activities, some with a national emphasis, and others with a standard development organizations' objective. This particular specification focuses on the GS1®[1)] System of Standards.

The majority of supplies (such as processed food, office supplies, apparels, medical devices and equipment, medicinal products, etc.) in healthcare around the world use the GS1® System of Standards for AIDC as it is multi-sectorial and a globally implemented system of standards. Interoperability along the supply chain is easier to achieve once a single system of standards is used in any market, including healthcare.

This document is intended to guide healthcare packaging designers, regulatory affairs specialists, logistics operators, and others to implement AIDC solutions for healthcare.

NOTE 1 See Reference [39].

NOTE 2 See Reference [40].

1) GS1® is a registered trademark. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO.

Health informatics — Requirements for international machine-readable coding of medicinal product package identifiers

1 Scope

This document provides guidelines on identification and labelling of medicinal products from the point of manufacture of packaged medicinal product to the point of dispensing the product.

This document outlines best practice for AIDC barcoding solutions for applications. Users can, however, consider the coding interoperability requirements for other AIDC technologies, e.g. Radio Frequency Identification (RFID).

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 11615:2017, *Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated medicinal product information*

ISO/TS 19256, *Health informatics — Requirements for medicinal product dictionary systems for health care*

3 Terms, definitions and abbreviated terms

For the purposes of this document, the following terms and definitions apply.

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

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

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

3.1 Terms and definitions

3.1.1
aggregation
aggregated packaging
hierarchical, parent-child relationship between a containing object (i.e. parent) and one or more objects (i.e. children) which are contained

Note 1 to entry: When the content of a delivery is not homogeneous, aggregation shall be provided by using a univocal identification of the delivery, such as with a Serial Shipping Container code (SSCC); see Annex C.

3.1.2
application identifier
AI
GS1® prefix that defines the meaning and purpose of the data element that follows, as defined in ISO/IEC 15418 and GS1® General Specifications

[SOURCE: ISO/IEC 19762:2016, 01.01.82]

3.1.3
automatic identification and data capture
AIDC
methods or technologies for automatically identifying objects, collecting data about them, and entering that data directly into computer systems, eliminating manual entry

Note 1 to entry: The methods or technologies typically considered as part of AIDC include barcodes which can be linear or 2-dimensional symbols and Radio Frequency Identification (RFID) tags/chips.

3.1.4
authentication
comparing the attributes of the object itself to what is known about objects of that origin

Note 1 to entry: Attributes include unique identifier besides overt, covert, and/or forensic solutions.

3.1.5
medicinal product batch identifier 1
BAID1
unique identifier allocated to a specific batch of a medicinal product, which appears on the outer packaging of the medicinal product

Note 1 to entry: It is constructed by using the batch number assigned by the manufacturer and the expiration date. This is for indexing purposes and to contribute to improving patient safety by allowing for the unique identification of a medicinal product at the package level.

[SOURCE: ISO 11615:2017, 3.1.51]

Note 2 to entry: BAID1 is market specific.

3.1.6
medicinal product batch identifier 2
BAID2
unique identifier allocated to a specific batch of a medicinal product, which appears on the immediate packaging, where this is not the outer packaging

Note 1 to entry: It is constructed by using the batch number assigned by the manufacturer and the expiration date. This is for indexing purposes and to contribute to improving patient safety by allowing for the unique identification of a medicinal product based at the level of the immediate container.

[SOURCE: ISO 11615:2017, 3.1.52]

Note 2 to entry: 'immediate packaging' corresponds frequently to 'primary packaging'. See Annex B.

3.1.7
batch
lot
specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture

[SOURCE: ISO 11615:2017, 3.1.8 — modified, "lot" was added as a preferred term.]

3.1.8
batch number
lot number
identifier assigned to a specific batch of a medicinal product or item resulting from a manufacturing process at a specific point of time

[SOURCE: ISO 11615:2017, 3.1.9 — modified, "lot number" was added as a preferred term.]

Note 1 to entry: A batch number permits its manufacturing history to be traced.

Note 2 to entry: A batch number is made of series of ASCII characters.

3.1.9
barcode
optical machine-readable representation of data, showing data about the object to which it attaches

Note 1 to entry: Originally, barcodes represented data by varying the widths and spacings of parallel lines, and can be referred to as linear or one-dimensional (1D). Later they evolved into rectangles, dots, hexagons, and other geometric patterns in two dimensions (2D). Although 2D systems use a variety of symbols, they are generally referred to as barcodes as well.

3.1.10
dispense medication
prepare and give out a medicinal product in accordance with a prescription

Note 1 to entry: This includes assessing the pharmaceutical appropriateness including decision support.

Note 2 to entry: See also ISO/TS 19293:2018.

3.1.11
global trade item number
GTIN®[2)]
number that is used for the unique identification of trade items worldwide

[SOURCE: ISO/IEC 15420:2009, 3.7 — modified, digit length removed.]

EXAMPLE 1 GS1® Identification Key which comprises a GS1® Company Prefix, an Item Reference and Check digit.

EXAMPLE 2 Used to identify trade items such as medicinal products and medical devices.

Note 1 to entry: See Annex A for the relationship between MPID, PCID, and GTIN®.

3.1.12
healthcare system
organization of people, institutions, and resources to deliver healthcare services to meet the health needs of target populations

3.1.13
identification
way information about an object, such as a trade item, can be found in IT systems, such as databases

Note 1 to entry: It refers to a sequence of characters (numerals and/or alpha characters). The identifier is intended to be a unique sequence structured according to a globally agreed architecture or syntax, and can or cannot contain inbuilt significance.

3.1.14
identification schema namespace
container for a set of identifiers that allows the disambiguation of homonym identifiers residing in different identification schema

3.1.15
identifier
ID
description that is sufficient to represent an object in a given environment identification schema

Note 1 to entry: This concept is generic and applies to all identifications mentioned in this document.

2) GTIN® is a registered trademark. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO.

3.1.16
machine-readable code
code, readable by a machine, that contains information used to establish a relationship between a physical object such as a medicinal product package and data sources such as medical, production, logistical and/or reimbursement coding systems

3.1.17
manufacturing
manufacture
process of production from the acquisition of all materials through all processing stages, including final packaging

3.1.18
marketing authorization
authorization issued from a medicines regulatory agency that allows a medicinal product to be placed on the market

[SOURCE: ISO 11615:2017, 3.1.40]

3.1.19
marketing authorization holder
organization that holds the authorization for marketing a medicinal product in a region or country

[SOURCE: ISO 11615:2017, 3.1.41— modified, "or country" added.]

3.1.20
medicinal product
pharmaceutical product or combination of pharmaceutical products that may be administered to human beings for treating or preventing disease, with the aim/purpose of making a medical diagnosis or to restore, correct or modify physiological functions

Note 1 to entry: The same definition applies for animal health.

[SOURCE: ISO 11615:2017, 3.1.50, — modified, "(or animals)" removed; notes to entry 1 and 2 removed and a new note 1 to entry added.]

3.1.21
medicinal product identifier
MPID
identifier allocated to a medicinal product supplementary to any existing authorization number as ascribed by a medicines regulatory agency in a region

[SOURCE: ISO 11615:2017, 3.1.53, — modified, "unique" removed; notes to entry removed.]

3.1.22
medicinal product package identifier
PCID
identifier allocated to a packaged medicinal product supplementary to any existing authorization number as ascribed by a medicines regulatory agency in a region

[SOURCE: ISO 11615:2017, 3.1.55, — modified, "unique" removed; note to entry removed.]

Note 1 to entry: See Annex D for relationship between MPID, PCID, and GTIN®.

3.1.23
object identifier
OID
globally unique value associated with an object to unambiguously identify it

3.1.24
outer packaging
external container in which a medicinal product is supplied

[SOURCE: ISO 11615:2017, 3.1.57 — modified, note to entry removed.]

Note 1 to entry: Corresponds frequently to "secondary packaging" (see Annex B).

3.1.25
packaging hierarchy
relationship between a medicinal product package and its grouping in larger/smaller quantities

Note 1 to entry: See Annex B for illustration of "primary packaging", "secondary packaging", etc.

3.1.26
packaged medicinal product
medicinal product in a container being part of a package, representing the entirety that has been packaged for sale or supply

[SOURCE: ISO 11615:2017, 3.1.59]

Note 1 to entry: Corresponds frequently to "primary packaging" (see Annex B).

3.1.27
pharmaceutical product
qualitative and quantitative composition of a medicinal product in the dose form approved for administration in line with the regulated product information

[SOURCE: ISO 11615:2017, 3.1.60]

3.1.28
pharmaceutical product identifier
PhPID
identifier for a pharmaceutical product

[SOURCE: ISO 11615:2017, 3.1.61 — modified, "unique" removed.]

3.1.29
pharmacovigilance
science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem

[SOURCE: WHO, Reporting and learning systems for medication errors: the role of pharmacovigilance centres, 2014, Annex 1]

3.1.30
radio frequency identification
RFID
wireless non-contact system that uses radio-frequency electromagnetic fields to transfer data from a tag attached to an object, for the purposes of automatic identification and tracking

3.1.31
serialization
assigning a unique identifier (e.g. a number) to an item (e.g. pack, case or pallet)

Note 1 to entry: This identifier is stored on a database along with other information about the item (e.g. manufacturer, batch info, etc). Serialization typically includes randomly selected, encrypted, numerical or alpha-numeric serial number.

Note 2 to entry: According to Reference [51], 'unique identifier' is the safety feature which enables the verification of the authenticity and the identification of an individual pack of a medicinal product.

3.1.32
traceability
ability to track forward the movement through specified stage(s) of the extended supply chain and trace backward the history, application, or location of that which is under consideration

[SOURCE: Global Traceability Standard for Healthcare, GS1, 2013, 5.2]

3.1.33
univocal coding
unique identifier
identification that is unique to a specific instance and cannot be confused with another identification

3.1.34
verification
reading unique identifier numbers and checking these in a database

3.2 Abbreviated terms

IHE	Integrating the Healthcare Enterprise
INN	International Non-proprietary Name
NDC	National Drug Code (from US FDA)
OCR	Optical Character Recognition

4 Procedural background

4.1 General

Clause 4 specifies the distinctions between identification and data carriers (machine-readable coding and its international characters). It then focuses on medicinal product and the characteristics of their physical packaging in the marketplace.

Supply chain, traceability, and patient safety require appropriate labelling and the use of packaging identifiers (as described in ISO 11615). Since new processes are in development in many countries to fight against falsification, reimbursement fraud, etc., 4.7 addresses serialization, namely the unit (or instance) identification.

4.2 Identification

In this document, "identification" refers to a sequence of characters (numerals and/or alpha characters). This identifier shall be a unique sequence structured according to a globally agreed architecture or syntax and may or may not contain inbuilt significance.

EXAMPLE 1 The identifier for one pre-filled syringe of XYZ medication is: 7665431234887. The identifier for one telephone-service subscription is: 022 592 74 25.

Uniqueness of the identifier (also referred to as 'univocal coding') is the key to ensuring unambiguous identification. It is important to note that the same sequence of characters can identify different items or objects belonging to different domains (or contexts), but each unique object within a single domain (or context) shall also have an unambiguous identifier. Uniqueness is also governed by the selected identification schema (or namespace) and the domains (contexts) in which the schema applies. The identification schema rules are therefore paramount.

EXAMPLE 2 7665431234887 uniquely identifies the class pre-filled syringe of XYZ medication in the domain "GS1". 022 592 74 25 uniquely identifies a web conference access point in the domain "telephone-service subscription numbers, Switzerland".

There are several types of identifiers in computer systems, varying in structure, purpose, governance, etc. Uniform Resource Identifiers (URIs) are used for electronically available identifiers.

Uniform Resource Identifiers (URIs) can be:

— Uniform Resource Locators (URLs) – which are references to a location and therefore to an identifier in the source location, such as http://somewebesite/products/identifiers...

— Uniform Resource Names (URN) – which identify an object regardless of its location and availability, by means of a value (the identifier of the object) and the namespace (how the identifier is assigned). To ensure uniqueness and availability of the identifiers, there are two approaches – either a hierarchical identifier assignment, or a random identifier creation. Illustrative examples:

  — Object Identifiers (OID), are defined by a naming system with structured (hierarchical), global governance, to ensure that only one entity can assign identifiers in one space.

  — Universally Unique Identifiers (UUID), sometimes called Globally Unique Identifiers (GUID), are practically unique IDs, generated without a global governance. A UUID is randomly generated and the probability of two systems creating the same UUID is extremely low, so the UUID can also be considered unique for practical reasons.

EXAMPLE 3 OID < 2.51.1.1 > delimits the domain "GS1 GTIN" in which product identifier 7665431234887 is unique. OID < 0.0.17.825.0.6.8 > delimits the domain "callingPartyNumber" in which web conference access point 022 592 74 25 is unique.

EXAMPLE 4 In HL7® FHIR®[3] standard, GTINs® can be used to identify a product, OIDs can be used for entities, and URLs can identify other online resources such as prescriptions or documents (e.g. URL for the domain "GS1 GTIN" is https://www.gs1.org/1/gtinrules//en/).

4.3 International machine-readable coding

Machine-readable coding is the process to transcribe and capture identification from a data carrier such as a barcode or two-dimensional symbols.

Univocal coding, as described in 4.2, is required when medicinal products are intended to be used in the international market, if they physically circulate, or if information about them is used across the jurisdictions. That means that the domain (or context) is not national or regional, but global.

International machine-readable coding is not just limited to packaging identifiers; it also encompasses attributes such as batch/lot number, expiry date, and serial numbers. Depending on medicinal product's characteristics, all of these attributes require semantics in such a way as to allow encoding and then capturing, regardless of the origin of the medicinal products. Application identifiers provide the semantics of the data carried in an international machine-readable code, and shall therefore be used uniformly across the global market.

4.4 Medicinal product

Medicinal products are traded in various packaging configurations, between which there is an established relationship. For example, the pharmaceutical product "Painkiller" has a market authorization for 100 mg tablets (medicinal product). These tablets can be packed in 10. Packages of 10 tablets can be bundled by 5; bundles can be grouped into cartons of 12 and cartons can be grouped in shipping cases of 20.

Annex B illustrates these relationships referred to as "packaging hierarchy". There are numerous complex situations which are not illustrated in this document but for which the same principles shall apply.

In the packaging hierarchy, each packaging level shall be uniquely identified.

3) HL7® and FHIR® are registered trademarks. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO.

Medicinal products can be authorized with two or more strengths, each being identified using a different and unique Pharmaceutical Product Identifier (PhPID) and Medicinal Product ID (MPID). “Painkiller” can be marketed in 100 mg and in 200 mg tablets. Each of these strengths corresponds to a different medicinal product. There will be different packaging hierarchies, one for each strength. Again, for medicinal product, all levels of packaging require univocal identification.

4.5 Labelling

The term AIDC is used to describe the process of automatically capturing (without manual key entry) the identifier assigned to a product for a given level of packaging using machine-readable coding. AIDC shall be delivered using a range of technologies including optical symbols, e.g. barcodes, radio frequency identification (RFID) technologies, and biometrics.

For more than 40 years, standardized optical carriers such as linear barcodes and two-dimensional symbols have been used by trading partners for AIDC. RFID was once considered as a technology that could be used for hands-free mass identification and still remains among the possibilities for the future AIDC widespread adoption. Likewise, trading partners have not adopted other AIDC solutions, such as OCR and biometrics, because of lack of efficiencies, ease of encoding, decoding, and the use of proprietary algorithms. However, the use of AIDC based on standardized optical carriers does offer the possibility for users to attain more efficient and effective logistics and material management. For medicinal products, the possibility of implementing AIDC at the point of care given is enabled.

The number of possible optical symbols available needs to be contained and standardized. Effective AIDC uses globally standardized symbols with standardized globally-agreed data encoded in the symbols. This ensures overall efficiency, i.e. the same type data structures encoded in a set of pre-defined symbols shall be used by any geography or economy, regardless of the type products (e.g. food, medicinal products, office devices, etc.). As a result, manufacturers shall standardize their production processes by using consistent AIDC symbols and eliminating variability. From a user’s perspective, this increases global interoperability since the identification schema namespace is widespread.

There are many devices and software solutions available for encoding and decoding the data in the AIDC symbol. All are capable of delivering a wide variety of solutions because of the use of global standards. Software and devices ensure that they are focused on delivery standard solutions that are interoperable. In 2017, IHE released a new profile (“Uniform Barcode Processing), to help software vendors meet these requirements[42].

Mass production requires high quality label printing. In addition to manufacturers selecting the right optical symbol (data carrier) and correct data for the symbol, suitable software shall ensure that the print quality of the AIDC symbol is satisfactory for reading purposes. Testing symbol readability is an essential process. Some ISO deliverables, e.g. the ISO/IEC 15426 series, have been developed for testing and measuring the readability of barcodes. Manufacturers (labellers) shall further pay particular attention to packaging/label design so that the placement of labels on packaging ensures that the AIDC process is not compromised. Data encoded in the symbol should be printed in human readable format to ensure process continuity where readers may not be available, or by equipment failure.

4.6 Package identifier

There are a number of identification relationships that should be understood for effective AIDC of Medicinal Products. This includes the relationship between Pharmaceutical Product Identifier (PhPID), Medicinal Product Identifier (MPID), Packaging Identifier (PCID), Marketing Authorization number, and Global Trade Item Number (GTIN®). The relationship between Marketing Authorization number and GTIN® varies depending on regulatory framework. There are two main scenarios:

— The Marketing Authorization number and the GTIN® can be the same (i.e. the same sequence of characters). Examples of this situation can be observed in the US or in France (see Annex D).

NOTE In some countries, such as France or Austria, GTINs® are generated by including a national number maintained by another authority than the marketing authorization holder. In this circumstance, one uses the acronym "NTIN" (National Trade Item Number). Usually NTIN correspond to secondary packaging. Primary packaging and higher levels of packaging are identified by following the normal GTIN® allocation rules.

— A single Marketing Authorization number is delivered by a central Regulator for different markets. Different GTINs® shall be used to distinguish the different packages of the same medicinal product as the actual packaging differs from one market to another. An example of this situation is seen in Europe (i.e. there is central marketing authorization, but there is country specific packaging in the European Member States). The Marketing Authorization number issued is related to the GTIN® in a database, not via AIDC.

Annex D illustrates the current scenario in some countries.

The GTIN-14 standard is defined as the unique 14-digit identifier for trade items; it includes, in sequence, the following:

a) Indicator digit: The indicator digit is a one-digit logistical code, which value can be a zero (0);

b) Country code: The country code is the country code corresponding to the GS1® member organization of which the brand/license owner is a member;

c) Brand/license owner code - Company prefix: The brand/license owner code is a code allocated to the brand owner by the GS1® member organization of which the brand/license owner is a member;

d) Product code: Product codes are unique numbers. The value for product code is arbitrary and is at the discretion of the brand/license owner;

e) Check digit: A final digit calculated from the other digits of GS1® GTIN® (and some other Identification Keys). This digit is used to check that the data has been correctly composed.

4.7 Serialization

The serial number is an attribute of the product identifier (Global Trade Item Number, GTIN®). This means that the combination GTIN + Serial Number provides the uniqueness required to develop tracking and/or verification to the 'instance' level of the item for a given level of packaging.

NOTE Some regulations refer to "unique identifier", which corresponds to the combination GTIN + Serial Number.

Serial numbers can be either alpha or numeric characters. Alpha characters, as well changing a character set (see ISO/IEC 8859-1 and ISO/IEC 10646), requires more space in the data carrier, but increases the numbering capacity with fewer characters. The user community has limited the size of the serial number to a maximum of 20 characters.

Serial numbers are allocated to secondary or tertiary level packaging and shall not be found on the primary package (unit of use, i.e. blistered solid forms) packaging. A medicinal product marketed in its primary package [i.e. hospital packaging (bottle) containing hundreds of solid form] shall have a GTIN® and should be serialized.

When medicinal product packaging is assigned a GTIN® and is serialized by the manufacturer at the time of production, the combination GTIN + Serial Number shall be stored in a database so that events about each item shall be recorded by supply chain partners.

5 Usage requirements

5.1 General

Machine-readable coding systems (AIDC systems) are both widespread and international. The initial requirements arose from the need of businesses to implement automated re-ordering from suppliers

(often, wholesalers) and when combined with AIDC at the point of sale, allowed businesses to adopt a non-specific AIDC schema regardless of product type.

Over the years, AIDC or international machine-readable coding has grown in importance. AIDC is now used for stock management, traceability, patient safety, and in the combat against product falsification. Clause 5 provides a review of the business processes and normative requirements for medicinal products; similar processes are in place for other type of products such as medical devices.

5.2 Traceability

5.2.1 Principles

5.2.1.1 General

For the purpose of this document, traceability is considered from the point of manufacture to the finished and packaged medicinal product, ready for supply according to the market authorization. Traceability ends when the medicinal product has been dispensed, applied, or administered.

Traceability requires identification and other related information about the medicinal product being captured or exchanged throughout the supply chain.

Traceability can be required at different levels of granularity. Depending on regulatory requirements, trading partner needs and business requirements, traceability shall be enabled by product identification (level one), by production batch and expiry date (level two), and by serial number, (level three). See 5.3 for more information.

NOTE When identification is required at the level of a unique serial number, the term “unique identifier” is commonly used.

EXAMPLE 1 European Union, Directive 2011/62/EU of the European Parliament and of the Council (…) on the Community Code relating to medicinal products for human use (…), “unique identifier” in Article 54a, § 2 (a).

As medicinal products are assembled in a packaging hierarchy, identification data shall be labelled in a machine-readable form ready for AIDC on each level of the hierarchy.

Each level of packaging requiring traceability needs a distinct identifier (GTIN®). Such distinct identifier shall never be re-used (this applies to all packaging hierarchies). Batch number and expiry date shall be consistent/identical on the different levels of the hierarchy.

In some special cases (for example, kits where two or more different items are grouped in a single secondary packaging), the batch number and expiry date applied to the secondary packaging and higher levels of packaging refers to the grouping as a whole.

EXAMPLE 2 Sweetdream i.V. in a kit (BAID_1) including a vial with powder (BAID_2) and a second vial with water for injection (a second BAID_2 level).

5.2.1.2 Repackaging

If for any reason the medicinal product is repackaged along the supply chain channel, this process is considered a manufacturing step and traceability shall be secured from the original pack to the resulting ‘repackaged’ pack. Subsequently, the re-packager or the local distributor as a contracting party or local product ‘sponsor’ is legally responsible for the repackaged medicinal product. This change should lead to a new GTIN® (e.g. for changes such as a new leaflet in another language being included in the packaging), however the assigned expiry date should remain unchanged.

5.2.1.3 Compounded preparation

Compounded preparations are medicinal products generally consisting of active substances that can be combined with excipients, formulated into a dosage form suitable for the intended use (with a patient),

where necessary after reconstitution, presented in a suitable and appropriately labelled container. New identification shall be issued to these products to secure traceability to the final use.

5.2.1.4 Reconstitution

Reconstitution is the manipulation to enable the use or application of a medicinal product with a marketing authorization (e.g. solving a powder to a solution) in accordance with the instructions given in the summary of product characteristics or the patient information leaflet. The identification of the separate products that are used to make the final product shall be available and linked to the reconstituted product for traceability of the process.

5.2.1.5 BAID — Batch/lot number

In the IDMP model, the BAID1: Medicinal Product Batch Identifier 1 shall use the batch number / lot number and the expiration date together with the PCID. The PCID: medicinal product package identifier identifies the packaged medicinal product, which represent a conceptual authorized packaging, where the batch/lot number identifies the production from a manufacturing operation step. The BAID incorporates in one single identifier both the concept of the authorized packaging and the output of a production step. Incorporating also the expiration date informs on the effective expiration date, calculated according to the authorized shelf life.

EXAMPLE 1 For one batch/lot, sold in one market, only one batch/lot number will correspond to one BAID, linked to one PCID.

EXAMPLE 2 For one batch/lot, distributed in two different markets (authorization through two national procedures), the batch/lot number will be linked to two BAID, linked to two PCID.

EXAMPLE 3 For one batch/lot, distributed in two different markets (authorization through EMA centralized procedure), but where authorized shelf lives are different (e.g. legal reasons), the batch/lot number will be linked to two BAID, but linked to only one PCID.

5.2.2 Guidelines

To enable efficient and effective traceability, supply chain partners shall use the same identification schema or data structure, which includes product identification, and if required, batch identification, and expiry date or serial number. Medicinal product package identifiers (as well as BAID) across all packaging hierarchies shall never be re-used. BAID shall enable a unique and immediate identification of both the authorized medicinal product and the batch/lot. Standardized data carriers shall also be used, not only to ensure reading devices can be programmed to capture and process data, but also to provide a robust machine-readable code for AIDC that can be processed automatically regardless of product type, its supplier, or its origin.

Several jurisdictions have adopted international machine-readable coding for AIDC as a regulatory requirement.

EXAMPLE 1 France: Notice to human-use medicinal product marketing authorization holders and head pharmacists of the pharmaceutical establishments cited in article R. 51242 of the French Public Health Code (CSP) 21 February 2007, § 2: “In liaison with the representatives of the pharmaceutical industry, the French Agency for the Safety of Health Products (AFSSAPS) has selected the principle of switching CIP code, from 7 characters to 13 characters, and from barcode 39 to EAN 128 (combined with ECC.200 Data Matrix marking) as per the EAN.UCC system” (see Reference [46]).

In other jurisdictions, stakeholders have added such a clause in their request for tenders.

EXAMPLE 2 Spain: “Technical Commission for Health Services Purchasing and Logistics (CTCL)”, Product identification through shared standards would lead to the unification of the barcode and symbol system so that products could be identified automatically by product suppliers through the use of GS1® codes (…)” (see Reference [47]).

There are also healthcare institutions that recommend the use of international machine-readable coding for AIDC for their healthcare product suppliers (see References [41] or [42]).

5.3 Measures to combat falsification of medicines

5.3.1 Principles

5.3.1.1 General

A falsified medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Falsification equally applies to both branded and generic products.

Preventing falsification can involve various techniques on the secondary packaging. Together with the serialization of each medicinal product pack (i.e. use of a "unique identifier"), these techniques can be - overt, covert, and/or forensic solutions.

In addition, the user community has recognized that serial numbers shall not be issued sequentially (as sequential numbers can be predicted by non-authorized persons) but in a pseudo-randomized manner. Falsifiers face greater difficulty with randomly generated serial numbers. Pseudo-randomized means that each serial number remains unique but over the range of numbers that is not predictable. Serialized numbers shall never be reissued.

As for any traceability process, master data shall be shared between trading partners in a consistent manner.

5.3.1.2 Using serialization

Using the product identifier GTIN® and a serial number to create "unique identifier", there are two main approaches to fight against medication falsification:

— product authentication;

— supply chain integrity [example with DSCSA (ePedigree)].

5.3.1.3 First approach — Product authentication

The product shall be authenticated at the end of the supply chain by validating, in a database, the unique identifier on the medicinal product packaging, besides checking further characteristics (overt, covert, and/or forensic solutions). In this case, the unique identifier shall have been issued by the manufacturer, and shall not have already been verified (dispensed) by another supply chain partner. It is assumed that the first authentication of GTIN® and Serial Number corresponds to the authentic item to be dispensed.

Authentication fails if the same unique identifier is verified repeatedly at dispense points (i.e. more than one instance of the serialized product exists), or if the unique identifier is not referenced in the database (i.e. the given instance of the product was never created by the manufacturer).

In the first situation, when several supply chain partners (dispensers) issue a database query for the same unique identifier, all of the medicinal product packages under review shall be considered suspicious. In the second scenario, when one or more supply chain partners issue a database query for an unknown unique identifier, all of the medicinal product packages under review shall be considered suspicious.

5.3.1.4 Second approach — Supply chain integrity

Supply chain integrity consists of collecting and sharing information ("events") about the medicinal product packaging along the supply chain at each point in the journey, i.e. from the manufacturer to dispensing or administration of the medicinal product to the patient. At each step in the journey, each event shall be recorded and linked to the previous and subsequent event. The integrity of the supply chain shall be verified at each step, in detail. Incoming medicinal products, without the integrity of previously recorded steps, shall be detected and considered as suspicious. This is the model adopted by the US regulation according to DSCSA, and was previously known as "ePedigree".

5.3.2 Guidelines for both approaches

Manufacturer representative associations and regulators recognize that product serialization and the associated data processing provide additional security against falsification. This shall be achieved when product identification (GTIN®) is associated with serial numbers that are generated using pseudo-randomized algorithms (this provides unique product identification). Each manufacturer shall implement secure randomization algorithms that ensure that serial numbers cannot be duplicated or predicted, and at the same time ensure that each serial number remains unique.

Printing pseudo-randomized serial numbers is an in-line process that takes place during packaging. When selecting printing solutions, particular attention should be given to the following:

— printing speed (i.e. line speed and ink drying time);

— verification speed (i.e. in-line reading device to capture the printed symbol and verify data content and then eliminate non-readable or damaged packages, etc.);

— printing quality (readability of symbols, in accordance with ISO/IEC 15415).

Repackaging or re-labelling of products can be accidentally or deliberately used to change the product expiry date and therefore undermine patient safety. A database should be set up by the manufacturer to allow the supply chain partners and, possibly, the patient access to the initial assigned expiry date. A query, with a scanner or mobile device, using the unique identifier on the package should allow the patient to look up and access the information and compare it with the date on the label. If the dates are different, the product can be unsafe to use.

Stakeholders consider a process to pack together secondary packaging as one trade item. When secondary packaging is identified at item level ("unique identifier" or serialization), aggregation in tertiary packaging shall enable retrieving in a database each unique number included in that higher level of packaging. When the content is homogeneous, the higher level of packaging shall be identified with a GTIN® and a serial number. For deliveries, aggregation is provided by grouping homogeneous or heterogeneous secondary packaging and identifying the delivery with a Serial Shipping Container Code (SSCC), linking to an electronic dispatch advice where detailed information is provided.

Implementations operational or in deployment demonstrate the need to dispose of consistent master data. This requires stakeholders to adopt harmonized and synchronized master data:

— For regulatory purposes: master data shall be in accordance with ISO 11615 (IDMP).

— For clinical purposes: master data shall be in accordance with ISO/TS 19256.

— For logistical purposes: master data shall be delivered by providers such as those accredited for Global Data Synchronisation Network (GDSN).

— For independent systems supporting the fight against falsification, master data shall be aligned with ISO 11615 (IDMP).

5.3.3 Product authentication

For the supply chain partner at the end of the supply chain, capturing product identification and serial number on the secondary pack level shall be the basis for implementing an authentication or integrity checking process.

For supply chain partners, such as logistics service providers, it may not be possible to access individual serial numbers on the secondary packaging because they were enclosed in tertiary units, e.g. logistic packaging. In this situation, machine-readable codes on the tertiary level packaging should be used for tracking and tracing (see Annex B). Customers of larger quantities such as hospitals and group purchasing organizations may require manufacturers to aggregate product identification and serial numbers of all items in a tertiary or higher package level and share it with appropriate shipping notice.

Standardized message shall be used between stakeholders for master data as well for transaction data.

5.3.4 Supply chain integrity

Each supply chain partner captures, generates and documents events about the movement of medicinal product packages at instance level. EPCIS (ISO/IEC 19987) is an International Standard for capturing and communicating data about the movement and status of products, logistics units and other assets in the supply chain. It enables trading partners to capture event information about objects as they move through the supply chain, and to share this information with authorized trading partners. EPCIS defines technical standards for a data-sharing interface between applications that capture event information, and applications that need access to such information.

For large packaging, such as cartons, an aggregation process shall be provided at manufacturer level, so that cartons bear their unique number, which links in a data base to the unique numbers of the included packages. Typically, an Aggregation Event represents an event that happened to one or more objects that are physically aggregated together or disaggregated from each other. For example, aggregating secondary packages onto a carton, or removing secondary packages from a carton.

5.4 Improving patient safety at point of care

5.4.1 Principles

Following the release of the 1999 Institute of Medicine's (IOM) report[35], several discussions took place about how medication errors, which are a significant part of the healthcare system dysfunction, could be reduced and eliminated. At that time, the US-FDA proposed a rule for the identification of medicines down to the unit-of-use level (primary package level, i.e. pre-filled syringe, blistered sold forms, etc.). Concurrently, a number of hospitals in The Netherlands and Belgium started to work on "bedside scanning". Since the IOM report, research, reported in academic publications[34], has demonstrated the effectiveness of "bedside scanning", i.e. AIDC at the point of care. This has resulted in implementations in numerous countries. International machine-readable coding enables the infrastructure for AIDC at point-of-care. It allows healthcare providers to implement better patient safety using scanning at the point of care. This shall be independent of the supplier or/and the geographic origins of the product.

Identification of the product shall be captured by AIDC at the point of dispensing and prior to medication administration to improve patient safety at the point of care. Cross-matching shall be processed with patient's electronic prescription. When using AIDC, other benefits such as last-minute prescription changes can be highlighted, "right" administration time can be verified, and patient records shall be captured without errors and delays that arise when manual recording is used.

5.4.2 Guidelines

Product identification shall be the priority at the point of care. This ensures the correct medication and strength has been selected. The identification can be simply the GTIN® or, depending on the type of product, the GTIN® together with the batch number and the expiry date. Additional attributes may be required for special categories of medicines, e.g. biological products, blood derivatives, oncology products, or parenteral nutrition items.

The GTIN® as an identifier shall remain active, even after the product has been deleted. For medicinal products GTIN® shall never be reallocated.

Regardless of the supplier, the type of product, or its origin, healthcare providers require consistency in the identification data structures and the data carriers (barcodes) in order to implement AIDC at point of care. Likewise, software and hardware vendors require the same consistency of data and machine-readable code to ensure that their products meet the requirements of the healthcare providers' and are affordable to implement.

Annex B illustrates that the same machine-readable coding system shall be used along the product packaging hierarchy. Implementation for manufacturers as well as for business users shall be facilitated with consistency of identifier and symbol. It further reduces the risk of interpretation and de-coding errors.

5.5 Support of healthcare systems

5.5.1 Principles

AIDC, using international machine-readable codes associated with a unique concept description, provides the necessary infrastructure for automatically capturing and recording data in healthcare system. The data capture and recording process usually involves a number of IT systems, such as those for stock management, reimbursement or cost calculation, and patient electronic health records, e.g. public health initiatives such as vaccination programmes, should use international machine-readable coding for data capture in electronic health records, as would code scanning at point of dispensing or administration.

Research organizations that collect market data for commercial or academic analysis, profit from capturing the unique identification of products at various nodes and stages in the supply chain. Some jurisdictions have implemented regulatory processes by leveraging international machine-readable identification: narcotic control, track and trace for radioactive medicinal products, etc.

Examples of other applications where international machine-readable codes provide benefits in healthcare IT systems are as follows:

a) Pharmacovigilance: When patient treatment data are recorded across the community for epidemiology purposes, post-market surveillance, and periodic safety reports, AIDC shall ensure that speedy, accurate, and consistent data are captured for accurate and detailed analysis. GTIN® and attributes such as batch number, expiry date, and serial number are important to be quoted into pharmacovigilance messages.

b) Product recall: If AIDC has been used throughout the supply chain to capture medicinal product identification, this would facilitate efficient realization of where the recalled products are located. In addition, AIDC is used to facilitate accurate retrieval of the recalled products from the storage locations and help prevent dispensing a recalled product.

c) Costing: In healthcare, costs are calculated processes such as Diagnose Related Groups DRGs, “cost based” reimbursement (also called case-based or procedure-based costing), and consumption reporting. Accurate data capture, for each patient, is a prerequisite for accurate costing. AIDC is used to capture product usage (not limited to medicinal products) ensuring the granularity necessary for accurate costing.

d) Statistics: Statistics, respecting privacy of both patients and healthcare providers, are regularly produced by various agencies. Statistics are often generated based on raw data collected using AIDC technologies. Accurate and relevant statistics impact decisions made by companies, healthcare providers, and public health bodies.

e) Regulatory control: Some medications such as narcotics and radiopharmaceuticals have particularly strict reporting requirement by users to Regulatory Bodies. AIDC shall be used throughout the supply chain, dispensing and administration processes to facilitate accurate data capture for reporting purposes.

f) Health programmes: Within healthcare programmes such as homecare treatment of chronic illnesses (e.g. haemophilia, diabetes, peritoneal dialysis), AIDC supports supply chain delivery to the patient and monitoring patient’s compliance.

g) Mobile technology: AIDC enables mobile technology devices and applications to protect the patient from harm, i.e. prevent incorrect product being used, highlight batch numbers that should not be used because of a recall, etc., and populate an electronic patient record by transmitting information to the health record storage location. Several initiatives have been launched, to provide patient access to information related to medicinal products, by scanning a barcode (preferably the medicinal product package identifier). Standardisation work is in progress to support such initiatives. Particular attention has to be given to the source of information to which mobile applications link. Trusted source of information should be certified with reliable solutions, e.g. HON code (see Reference [48]).

h) Shortage: traceability and security of imported foreign products following authorization by the regulatory agency, in their original packaging, due to a lack in the national territory.

5.5.2 Guidelines

Fundamentally, healthcare systems (e.g. patient record systems, medication management systems, pharmacy dispensing systems, procurement systems, finance systems, etc.) shall hold the unique identifier (and associated traceability information such as batch number, expiry date, etc.) for the product at the required level of packaging, and link this to the product master data (e.g. description, pack size, regulatory information, etc.). Given these, different healthcare systems deal in different levels of product packaging (e.g. the pharmacy procurement system can require identification of the tertiary level packaging, but the medications management system will require identification of the primary and secondary packaging), hierarchical linkages between these levels of packaging and their identifiers shall be established and maintained within these systems.

Public health messages (e.g. pharmacovigilance) and files (e.g. vaccination; (international) patient summaries) shall include precise documentation with medicinal product's identification, including unique concept identifier and optionally a unique concept description. This is achieved with a GTIN®, concept description, batch number, expiry date and, when available, serial number.

5.6 Procurement and stock management

5.6.1 Principles

Warehouse and distribution operations are similar in all industry sectors that have a combined product movement-storage-pick operation or facility of any size, whether this facility handles single items, cartons, pallet loads or bulk materials. In recent years, warehouse, distribution operators, and inventory control managers have made significant progress in improving inventory control and stock management in the healthcare sector. The use of international machine-readable codes (barcodes) and scanning devices enabling AIDC has improved procurement and stock management processes, leading to improved supply chain efficiency and performance through more accurate, readily available information[41].

It is clear that organizations benefit through efficiency gains and financially when supply chain, warehouse and logistics operations are based on and use internationally standardized and interoperable coding systems (i.e. identification systems and identifiers). Standardization, as outlined, offers enhanced supply chain visibility that assist all stakeholders both in realizing business efficiencies but also in improving patient safety outcomes.

The benefits of international machine-readable coding can be realized in many areas including the following:

a) Inventory management: Inventory management or stock management are processes that ensure that the right product is in the right place or is transferred to the right place in the correct quantity. The processes move stock to locations that satisfy the production requirements at the lowest handling (storage-pick) cost. The benefits include stock optimization across the packaging hierarchies for procurement and order fulfilment requirements, minimising product spoilage and waste, enhancing warehouse utilization and improving stock visibility, providing more efficient stock audit, and detecting and managing shrinkage. AIDC, based on International Standards, are used throughout the supply chain to capture data accurately for the inventory/stock management systems.

   Several implementations in NHS Trusts in England illustrate increased efficiency by an extensive use of AIDC in warehousing.

b) Product safety alerts - product recall: Product safety alerts signal the need to isolate and remove defective goods from the supply chain. The safety concern can arise due to a manufacturing defect which can harm the user. While the safety alert or product recall procedures can vary between jurisdictions, the use of standardized product identifiers in international machine-readable codes,

and where relevant, additional information such as batch, lot, serial number embedded within code, and AIDC enhances the efficacy of the alert/recall process.

c) Supply chain interoperability: The characteristics and complexity of global commerce has elevated the importance of interoperability to enhance productivity, efficiency, and competitiveness in many industry sectors. Data interoperability based on international identification standards is integral to efficient and agile product life-cycle management systems. A globally standardized product coding system across all packaging hierarchies is viewed as essential for creating seamless integration between applications and supply chain partners. Cooperation and information sharing across organizations helps everyone achieve product quality more cost-effectively while providing benefits that enhanced supply chain visibility provides.

5.6.2 Guidelines

Software vendors shall develop solutions for Warehouse Management, Robotic Dispensing, etc. using international machine-readable coding and AIDC. Using this type of software optimizes/maximizes the benefits and at same time reduces the cost of ownership. The software shall enable the use of product hierarchies, production identification, batch/lot/serial number tracking, expiry date management, as well as managing the space constrained warehouse. In addition, software shall include the use of electronic data interchange, by using International Standards, so that collaborative processes can be operated with supply chain partners. In 2017 IHE has released a new profile ("Uniform Barcode Processing), to help software vendors to meet these requirements[42].

5.7 Overview of guidelines

Table 1 shows an overview of guidelines.

Table 1 — Overview of guidelines

Usage requirements	Medicinal product package identifiers	Lot/batch number	Expiry date	Serial number
Traceability (see 5.2)	X	X	X	(X)
Measures to combat falsification of medicines (see 5.3)	X	(X)		X Except for primary packaging
Improving patient safety at point of care (see 5.4)	X	X	X	
Support of Healthcare Systems (see 5.5)	X	X	X	X
Procurement and Stock Management (see 5.6)	X	X	X	

6 Economic aspects

6.1 General

Based on Clause 5, implementing machine-readable coding for medicinal products represents a reasonable investment. The level of investment required is impacted by the local, proprietary, or international aspects of the chosen solution and by the market and/or the regulatory influences.

This document is focused on international machine-readable coding and reflects the experiences reported by a considerable number of users, both manufacturers and healthcare providers. In some industries, on a voluntary basis, international machine-readable coding has been adopted and is part of the daily business activities. As healthcare is strongly regulated, this industry has not always been

able to adopt machine-readable coding on a voluntary basis. However, where there are opportunities, adoption of the most widely used international machine-readable coding architecture, namely GS1®, has come to reality.

Recent developments in the healthcare industry are strengthening the need to adopt globally harmonized machine-readable coding. As regulation requires more granular traceability, adoption of proprietary solutions will increase manufacturing costs and user implementation costs.

6.2 Manufacturer perspective

Manufacturers, in both addressing their home markets and other target markets, recognize the need to implement harmonized machine-readable coding system. International manufacturers are likewise seeking common approaches so that they can equip their production lines at different production sites and in different countries with the same methodologies and tools.

Producing medicinal products for specific target markets implies that the packaging must be localized for language purposes and for other specific requirements imposed by the regulator. When these requirements include machine-readable coding, the manufacturer shall establish a country specific solution which is, not only potentially costly, but also requires additional technical controls (particularly for product serialization).

Manufacturers reengineer production lines to address new regulatory requirements, i.e. serialization, a trend that gains more global momentum.

6.3 Healthcare provider perspective

Healthcare providers are at the cross-road for receiving supplies from a wide variety of sources, such as office supplies, food, capital equipment, medical devices, and medicinal products. In many ways, hospitals and retail pharmacies are hubs.

Implementing stock management and internal logistics disciplines and procedures by using common global coding standards and IT network architecture, regardless of vendor, has recognized positive impacts on operational efficiency and consequently, constrained operating budgets. When considering quality and safety of patient care, this is when the product and supply chain identification keys and attributes enter the clinical IT infrastructure. Implicitly, primary packaging level identification availability, managed and maintained by the manufacturers, becomes essential[42]. Disposing at the point of care of international machine-readable coding facilitates implementation of verification tasks by the individual providers. To avoid any workaround, the data capture process shall be quick and transparent, which harmonized coding and architecture make possible.

Annex A
(informative)

Relationship between PhPID and MPID

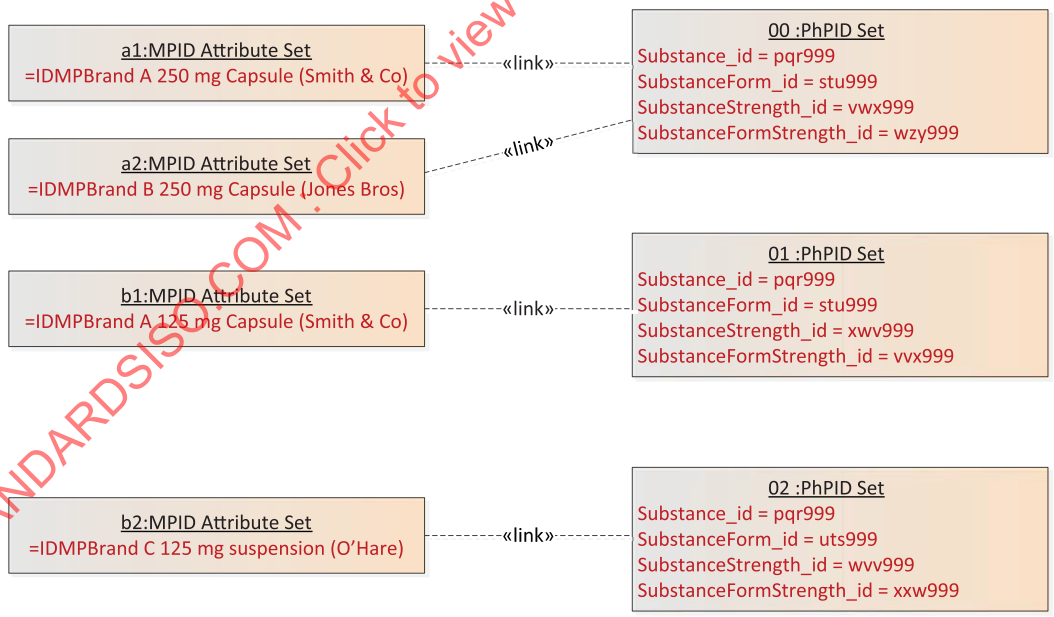
A.1 Introduction

The relationship between PhPID and MPID is explained in ISO 11616:2017, Clause 8. This annex illustrates this relationship; Figure A.1. is reproduced in this document from ISO 11616:2012, 6.1[4] for readability purposes; ISO 11616:2017, Figure 7 includes a similar table.

The relationship between two MPID (for example) has been investigated and illustrated in the context of the EU funded project "openMedicine".

A.2 Example from ISO 11616

If a medicinal product contains the same elements as defined for a particular PhPID level, they will share an identical PhPID. For example, a medicinal product A with a drug substance X, will share a common PhPID1 level with medicinal product B containing the same drug substance X. Furthermore, if medicinal product A and B both contain substance X with an administrable dose form Y, but a different strength, PhPID1 and PhPID3 would be identical, but PhPID2 and PhPID4 levels would have a different PhPID assigned due to the differences in strength.



NOTE Reproduced from ISO 11616:2017, Figure 7.

Figure A.1 — Illustration of the relationship between MPID and PhPID

4) Cancelled and replaced by ISO 11616:2017.

A.3 Example from openMedicine

Figure A.2 represents a use case where a medical prescription is issued in one country and the dispensing occurs in another country.

The prescriber defines the medicinal product at one of the usual levels, depending on the local rules and other factors. When the prescription states a PCID (medicinal product package), the computer system, by using the IDMP structured database, will point to the relevant PhPID (pharmaceutical product identifier). The dispenser system will search the equivalent PhPID in her/his country, and find the corresponding package to be dispensed.

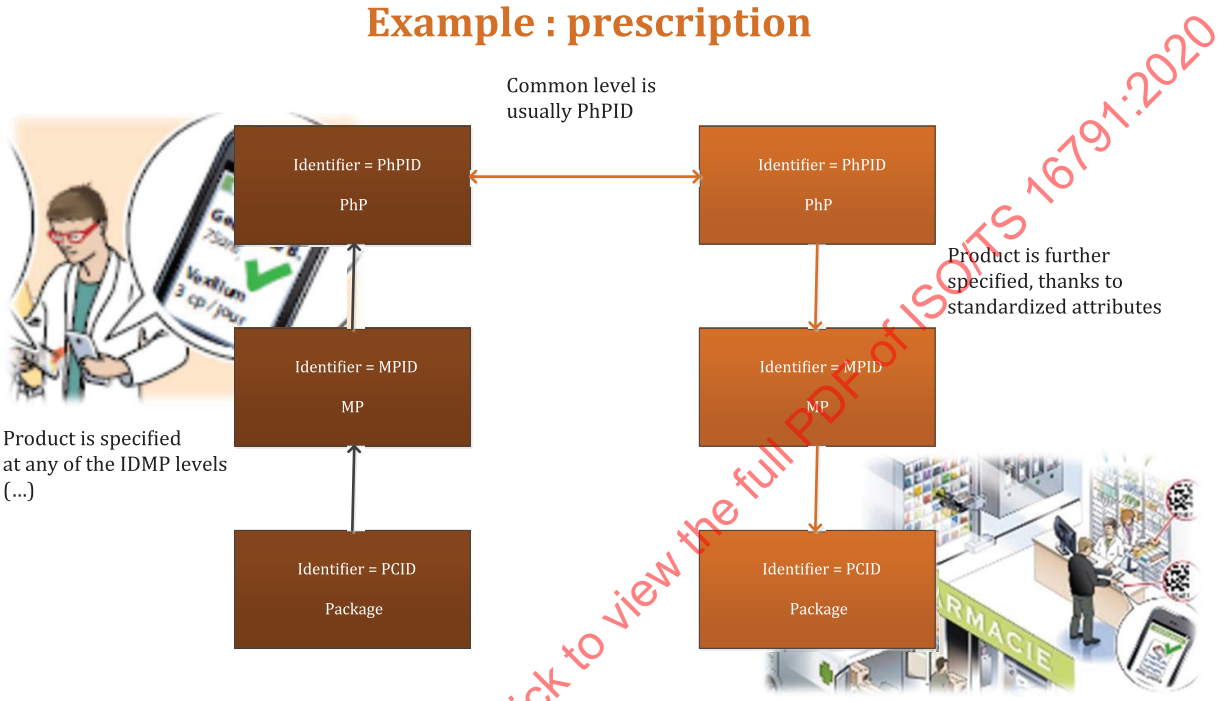


Figure A.2 — ePrescription in a cross border situation

Annex B
(informative)

Packaging hierarchy, relationship between MPID, PCID and GTIN®

B.1 Packaging hierarchy and different GTINs® and attributes

Figure B.1 outlines the use of unique product identifiers for each level of packaging (i.e. 'The Packaging Hierarchy'); the relationship between the packaging hierarchies and the use of additional product attribute information, including batch/lot and expiry information. Depending on the product's characteristics, labelling (identification) requirements can vary.

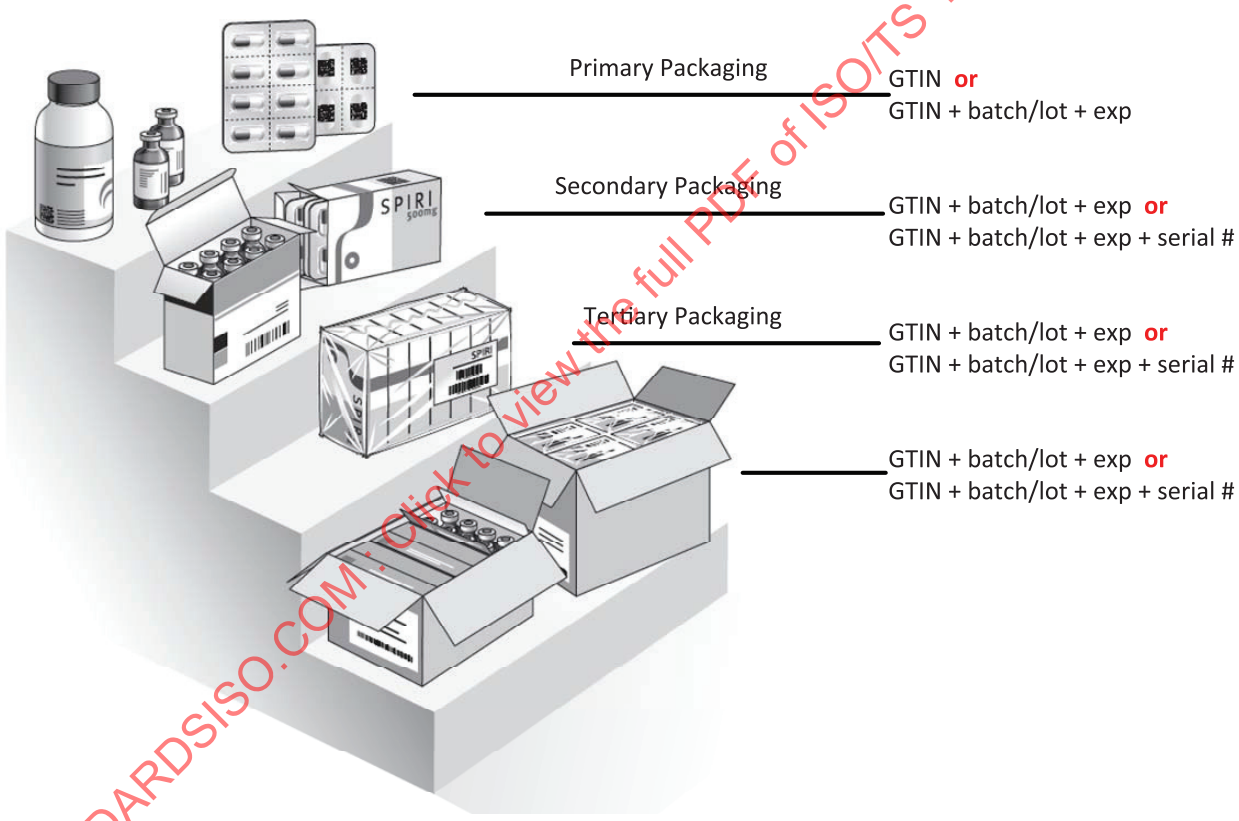


Figure B.1 — Packaging Hierarchy

Products packaged in primary packages can be used in different secondary packages. For example, Doureve 20 mg caplets in blisters of 12 (primary packaging), can be packed in "24" or "96" secondary packs. The same blisters can be packaged for geographical markets (e.g. Switzerland, Belgium). The manufacturer uses the same GTIN® to identify Doureve 20 mg caplets in the primary package; however, the secondary packs will have different GTINs®. When medicines are labelled with an international machine-readable code at primary packaging level, as illustrated, the product identification at the primary packaging level shall be different to that of the secondary packaging.

NOTE Identifying medicinal products in their primary packaging is an emerging requirement. Some countries, such as the USA, Denmark, South Korea and India, have had such requirements for a number of years.

When applying international machine-readable codes to primary packaging, manufacturers shall print the data carrier on a small surface at high speed. It has been demonstrated that DataMatrix (ISO/IEC 16022) is the best symbol for this type of implementation.

B.2 Relationship between MPID, PCID and GTIN®

Figure B.2 shows the relationship between MPID, PCID and GTIN®, when the same primary package is marketed in different pack sizes (secondary packs with two, respectively, one blister).

The PCID is the concatenation of MPID and a Package Description Code segment, which refers to an identifier for each package (see ISO 11615:2017, 8.3.1).

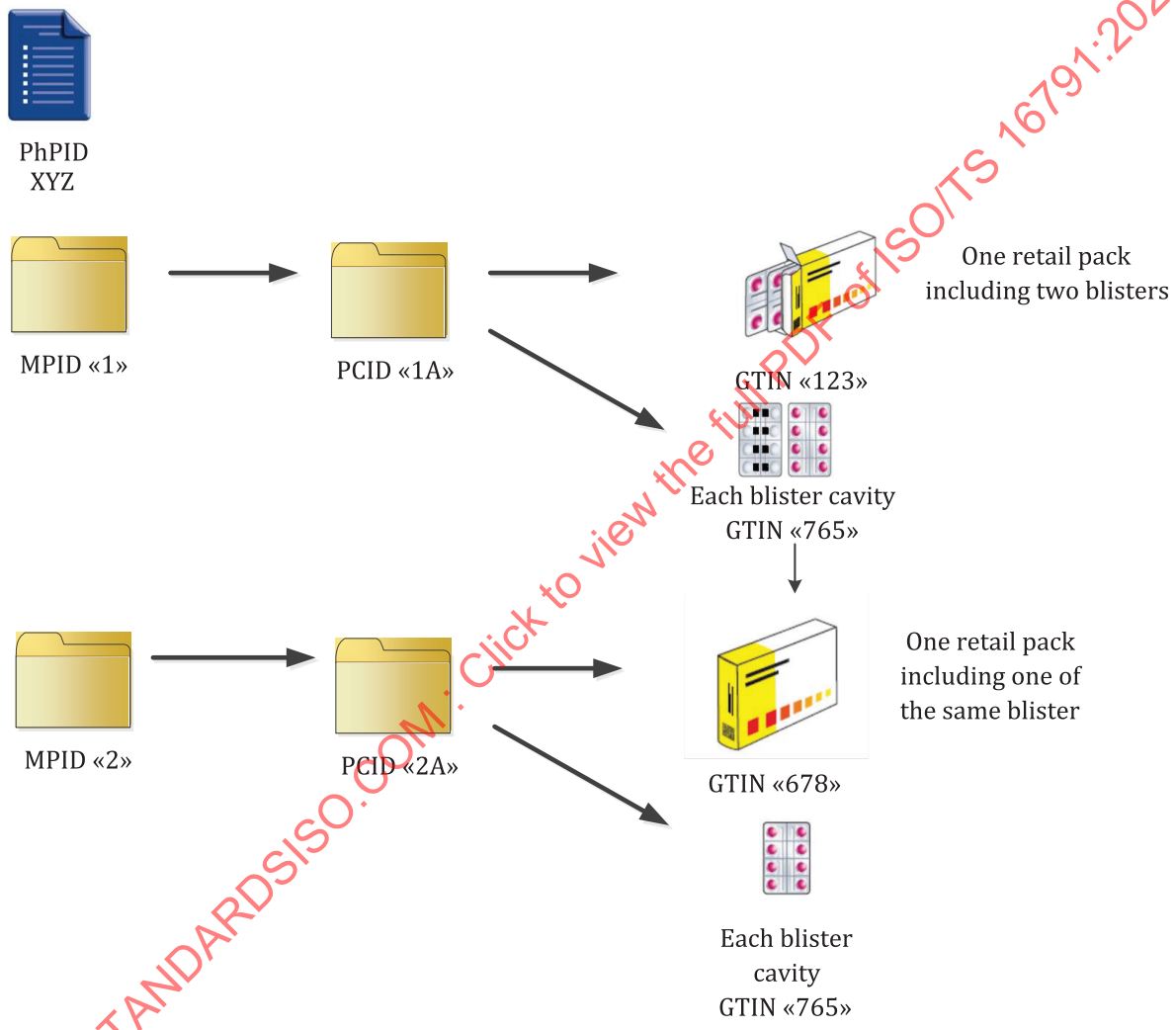


Figure B.2 — Relationship between MPID, PCID and GTIN®

Annex C
(informative)

Identification of trade items and logistic units

Per definition a trade item is any item upon which there is a need to retrieve predefined information and that may be priced, or ordered, or invoiced at any point in any supply chain. Information about a trade item can usually be found in a catalogue or a database[44].

A logistic unit is an item of any composition established for transport and/or storage that needs to be managed through the supply chain.

Each, trade item and logistic unit, is identified in a pre-defined manner.

Trade item and logistic unit might be the same object -if the logistic unit consists exactly on a trade item. In such a case, the same object might carry two identifiers at the same time.

Annex D
(informative)

Examples for Package Identifier

D.1 General

All examples are based on the following calculation algorithm for IDs. When hypothesis may apply, they are depicted in notes.

D.2 PhPID set

PhPID Set consists of 8 different IDs based on the following information:

- 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

D.3 MPID

MPID consists of the following:

- Country code segment
- Marketing Authorization Holder (Organisation Identifier) code segment
- Medicinal Product code segment (Unique MP Identifier)
  - Marketing authorization indicated in a region
  - Legal status of supply as a value/attribute
  - Medicinal Product name;
  - Pharmaceutical dose form;
  - Active ingredient(s)/active moieties and their corresponding strength;

- Device(s) where a Medicinal Product is combined with a medical device and where the pharmacological, immunological or metabolic action should be considered as the principal mode of action; the medical device is presented as part of the Medicinal Product;
- Therapeutic indication(s) as authorized for the Medicinal Product.

NOTE MPIDs are going to be linked with the national codes for business continuity purpose (e.g. Z-index in the Netherlands, CIP in France, PZN in Germany).

D.4 PCID

PCID consists of:

- MPID
- Package description code segment
  - Packaged item (container)(s) — the type, quantity (items per package), material(s) and alternate material(s);
  - Package component(s) — type, material(s) and alternate material(s);
  - Manufactured item(s) — manufactured dose form, unit of presentation, quantity (items per package).

In this case, needles are considered as device, then not entering in the package description code segment.

D.5 EMA Centralized

Procedure	EMA Centralized		
Example of product and presentation:	ISOVac, suspension for injection, 1 pre-filled syringe (glass) + 1 needle, 0,5 ml.		
SKU description [a]*:*	Pack sold in only one market, with one language (Example DE)	Pack sold in only one market, but with multiple languages (Example BE)	Pack shared between multiple markets, with multiple languages (Example DK + FI + SE)
PhPID Set	Unique PhPID set [b]		
Marketing Authorization (MA)	Unique MA (e.g.: EU/1/18/999/003)		
Medicinal Product ID (MPID)	Unique MPID in EU, IS, NO and LI [c]		
Package ID (PCID)	Unique PCID [d] (ref to /003 in MA number)		
GTIN Pack	GTIN for the pack DE	GTIN for the pack BE	GTIN for the shared pack
Primary packaging identifier	GTIN for primary packaging (language specific)	GTIN for primary packaging (language specific)	GTIN for primary packaging (language specific)
EV Code [e] (Medicinal Product)	4 EV codes (EU, IS, NO, LI)		

[a] Goods considered as different according to internal supply chain description rules, produced through different manufacturing routes but leading to the same product (same or different SKU number, according to company internal rules) may share the same GTIN.

[b] Assuming the PhPID Set is calculated based on information shared with the Common Technical Documentation (See Reference [52]).

Another hypothesis can be using information from the SmPC/SPC, however the variability of SmPC is more important. E.g. for strength (Concentration), one may have as local regulatory requirement either a range (between 20 and 30 µg) or an approximate value (~25 µg), which will lead to two different PhPID Sets.

[c] To be confirmed. This will depend on which "Name" field is used in MPID algorithm, and the rules for MPID algorithm. If one uses the trade name, as it is in the vast majority of case unique for centralized, one will have a unique MPID. (EMA SPOR Implementation guidelines shall clarify how to manage specific variations in the trade name such as in in Spain, variations to accommodate local understanding.) If one uses the full name, due to language translation of (e.g.) pharmaceutical dose form part, several MPIDs will be generated.

[d] Uniqueness of PCID is correlated with the uniqueness of MPID. If in some case, one has multiples MPID, one may have multiple PCID.

[e] EV Code (EudraVigilance code) is a unique code assigned to any entity (e.g. substance, product, etc.) entered in the xEVMPD. An EV Code is generated after the record has been inserted successfully in the xEVMPD. xEVMPD (eXtended EudraVigilance Medicinal Product Dictionary) is the European Medicines Agency dictionnary (EVMPD) and exchanging format (xEVPRM) to assist the pharmacovigilance activities in the European Economic Area (EEA).

D.6 (European) National, Mutual Recognition, Decentralized

D.6.1 For product registered in market where each pack is authorized individually:

Procedure	(European) National, Mutual Recognition, Decentralized		
Description of the pack:	IdeaDrug, syrup		
SKU description:	Pack sold in only one market, with one language (Example FR)	Pack sold in only one market, but with multiple languages (Example BE)	Pack shared between multiple markets, with one or multiple languages (Example 1: GB + IE + MT, Example 2: DK + FI + SE)
PhPID Set	Unique PhPID set [ab]		
Marketing Authorization (MA)	Market specific MA	Market specific MA	Market specific MA
MPID	Market specific MPID	Market specific MPID	Market specific MPID
PCID	Market specific PCID	Market specific PCID	Market specific PCID
GTIN Pack	GTIN for the pack	GTIN for the pack	GTIN for the shared pack
Primary packaging identifier	GTIN for primary packaging (language specific)	GTIN for primary packaging (language specific)	GTIN for primary packaging (language specific)
EV Code [c]	1 EV code per marketing authorization (= per pack and per country) and per language: 1 EV code for FR	3 EV codes for BE (3 languages)	Example 1: 3 EV codes : 1 GB, 1 IE, 1 MT Example 2: 4 EV codes : 1 DK, 1 SE, 2 FI (2 languages)

[a] Assuming the PhPID Set is calculated based on information shared with the CTD.

Another hypothesis can be using information from the SmPC/SPC, however the variability of SmPC is more important. E.g. for strength (Concentration), one may have as local regulatory requirement either a range (between 20 and 30 µg) or an approximate value (~25 µg), which will lead to two different PhPID Sets.

[b] What is depicted is the **To-Be situation**. As of summer 2018, when this document has been written, the **As-Is situation** was that PhPID set may be unique or multiple:

If same regulatory requirement, i.e. same CTD between countries, there will be a unique PhPID set

If different regulatory requirement, i.e. resulting in different CTD between countries, there will be different PhPID set.

[c] EV Code (EudraVigilance code) is a unique code assigned to any entity (e.g. substance, product, etc.) entered in the xEVMPD. An EV Code is generated after the record has been inserted successfully in the xEVMPD. xEVMPD (eXtended EudraVigilance Medicinal Product Dictionary) is the European Medicines Agency dictionnary (EVMPD) and exchanging format (xEVPRM) to assist the pharmacovigilance activities in the European Economic Area (EEA).

D.6.2 For product registered in a market where all packs are sharing the same authorization:

Hypothesis 1:

— Products with unique MPID (i.e. the strength of the active ingredient is not expressed in the name of the product), with only 1 authorization.

— Needles are considered as device (i.e. not included in the calculation of the PCID).

Procedure	(European) National, Mutual Recognition, Decentralized			
Description of the packs:	ImmunoVax - Sweden ImmunoVax, 0.5 ml of suspension in pre-filled syringe (Type I glass) with stopper (butyl rubber) with or without needles in pack sizes of 1 or 10. Not all pack sizes may be marketed.			
SKU description:	Pack, composed of 1 syringe, 0 needle	Pack, composed of 1 syringe, 1 needle	Pack, composed of 10 syringes, 0 needle	Pack, composed of 10 syringes, 10 needles
PhPID Set	Unique PhPID set			
Marketing Authorization (MA)	Unique MA (e.g.: 12345)			
MPID	Unique MPID			
PCID	PCID for 1 syringe pack		PCID for 10 syringes pack	
GTIN Pack	GTIN for the pack	GTIN for the pack	GTIN for the pack	GTIN for the pack
Primary packaging identifier	GTIN for primary packaging			
EV Code	Unique EV code (e.g.: PRD654321)			