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Health Informatics — Requirements for a knowledge base for clinical decision support systems to be used in medication-related processes

Informatique de santé — Exigences relatives aux bases de connaissances pour systèmes d'aide à la décision clinique à utiliser dans le cadre des processus liés aux médicaments

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CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

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Foreword

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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).

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Introduction

0.1 Safe and effective usage of medicines is important

When a patient gets his/her medicines prescribed and dispensed, it is not only important that the patient gets the correct medicine and that ordering and reimbursement is supported by using a Medicinal Product Dictionary (MPD), but it is also important that the medicine is safe and effective with respect to the specific situation of the patient.

Because an MPD contains just the identification of the medicines, it is important that an MPD is enriched with clinical decision support (CDS). The aim of CDS is to help prescribe and dispense the medicine that fits the patient's personal situation in respect of effectiveness and toxicity of the medicine. Based on a knowledge base combined with the patient's situation such as comedication, comorbidity, age, laboratory values, diet, allergy, a healthcare professional can be warned for likely side effects or ineffectiveness, and change the therapy.

0.2 Need for a standardized knowledge base

To achieve the aim described in Clause 0.1, there are several success factors, in literature, referred to as the 'five rights'[28]:

— The *right information:* the information should be evidence based and give concrete guidance for action.

— To the *right person:* the alerts should be presented to the person who is the most likely one to take action (e.g. the clinician, the pharmacist, the caretakers).

— In the *right CDS intervention format:* such as an alert, a request to measure certain laboratory parameters, or an answer to a clinical question.

— Through the *right channel:* this can be the clinical information system like the pharmacy information system, or a web-browser that makes available the data of the knowledge base.

— At the *right time in workflow:* for example, during prescription or dispensing, or in batch at night to have certain data available the next morning.

To provide the *right information*, a knowledge base is necessary; and also providing the knowledge to the *right person,* the *right format* and at the *right time in the workflow* is part of a knowledge base, as far as it concerns the 'knowledge' of it.

There are clinical decision support systems (CDSSs) that provide this knowledge, but Helmons stated that there are several barriers for implementing a CDSS, one of them being 'content issues' like: 'Typically installed without any validated decision rules, which have to be developed and/or validated in each individual institution (also called 'having to reinvent the wheel')'[26].

Therefore, a (technically) validated, standardized knowledge base is the recommended basis for CDS.

The needs for a standardized knowledge base are as follows:

— There is an overwhelming amount of data in the summary of product characteristics (SPC), guidelines, literature and handbooks. Prescribers, physicians and pharmacists cannot easily find what to do for a certain drug combination or drug-disease combination. The most relevant data and accompanying recommendations are curated from literature and put in rules in a knowledge base.

— Information about the availability, safety and efficacy of medication to be used for the prescription by physicians is often outdated even when the information is available electronically (e.g. in the drug interaction management system in a doctor's office). Linking the information from the Medicinal Product Dictionary to a CDSS that uses a validated, standardized knowledge base makes sure that during prescribing/dispensing up-to-date information is always used.

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— While the population is still growing, people become older and have more comorbidity and polypharmacy, the need for smart knowledge base rules that provide the basis for generating alerts with a high specificity and sensitivity, is increasing.

— Besides assuring that the most precise and current information is to be used in the knowledge base for the benefits of the patient, this specification will also provide a basis or 'handles' how to map the information to the MPD, the IDMP vocabulary and their own local data in EHR and pharmaceutical domains.

0.3 Focus — A knowledge base for drug-related problems that cohere with the intended drug use

This document is about a standardized knowledge base to be used in medication-related processes. In the context of this document, this means a knowledge base that has its focus to enhance decisions and actions in drug-related problems that cohere with the intended drug use, namely once a drug has been chosen, in any domain of prescribing, dispensing, administering of the drug and monitoring the patient.

Aspects like choosing the right drug according to guidelines and patient coaching for the correct usage are not included in the scope of this document (which does not mean that the requirements that are described in this document are not useful for knowledge bases with such kind of scopes).

0.4 Why this document: general principles versus medication specific aspects for developing a knowledge base

Describing how a structured, standardized knowledge base should be developed, what are the criteria to take into account, is a rather general process. As such it is not specific for medication processes. Assessing literature and developing rules is also applicable for other domains.

In this respect, this document contains two sorts of requirements. First, there is the overarching level, not specific for medication processes. This includes, for example, the requirements for selecting and assessing literature, updating the knowledge base. Secondly, there is a medication-specific level in this document. This includes the area to which the requirements are applied: if the requirement is to determine which kind of people will assess the rules, the document mentions the disciplines in healthcare: such as pharmacists, physicians.

0.5 Use cases

The use cases for a knowledge database for drug-related problems are primarily decision support based on validated, standardised rules to enhance decisions in the process of:

— prescribing

— dispensing

— administering

— monitoring the therapy of the patient.

Besides that, decision support based on a standardised knowledge base can also be useful for (not exhaustive):

— travel medicines

— health counselling.

0.6 Target users of this document

The target users of this document for a knowledge base in medication-related processes include:

— Academic organisations in the field of pharmaceutical healthcare, that develop knowledge bases for medicines;

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— Vendors and other parties developing CDSSs (based on knowledge bases as described in this document), like (not exhaustive):

  — clinical or pharmacy information systems

  — hospital ward information system

  — doctor‘s office information systems

  — decision aids for patients.

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Health Informatics — Requirements for a knowledge base for clinical decision support systems to be used in medication-related processes

1 Scope

This document specifies the requirements for developing a knowledge base for drug-related problems that cohere with the intended drug use, to be used in rule-based clinical decision support systems (CDSS), such as the criteria for selecting a raw data source and the quality criteria for the development and maintenance for the rules or clinical rules for drug safety. It also describes the process of how to develop a knowledge base, the topics to be considered by the developers of a knowledge base, and it gives guidance on how to do this.

This document gives guidelines for the development of a knowledge base:

— with rules to enhance decisions and actions in drug-related problems that cohere with the intended drug use;

— which can be used by all kinds of healthcare professionals, such as those who prescribe, dispense, administer or monitor medicines;

— which can be used in every care setting, including chronic and acute care, primary and specialized care;

— which is a repository of evidence/practice bases rules, assessed by experts;

— which is meant to be used in conjunction with a medicinal product dictionary;

— whose knowledge is structured in rules and therefore to be used in the type of rule-based CDSS.

This document does not:

— describe the exact content of a knowledge base i.e. the outcome of the process of developing rules.

— provide the requirements for a clinical decision support system, the software that uses the knowledge base combined with the patient's data, and presents the outcome of the rules to the healthcare professional. These requirements are described in ISO/DTS 22703[1)].

— give the requirements for non-medication knowledge bases. Some aspects of the requirements in this document are general in nature and applicable to other kinds of knowledge bases, but this document does not address all of the requirements of non-medication knowledge bases.

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, *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 Healthcare*

1) Under preparation. Stage at the time of publication: ISO/DTS 22703.

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3 Terms and definitions

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
clinical decision support
type of service that assists healthcare providers in making medical decisions, which typically require input of patient-specific clinical variables and provide patient-specific recommendations

[SOURCE: ISO/TR 14639-2:2014, 2.8, modified — Note 1 to entry has been deleted.]

3.2
clinical decision support system
software designed to be a direct aid to clinical decision-making, in which the characteristics of an individual patient are matched to a computerized clinical knowledge base, whereafter patient-specific assessments or recommendations are presented to the clinician or the patient to aid in the process of making evidence based clinical decisions

[SOURCE: Ida Sim e.a., *Clinical decision support systems for the practice of evidence-based medicine*, J Am Med Inform Assoc. 2001 Nov-Dec; 8(6): 527–534, modified]

3.3
dispensing
process by which an individual healthcare provider takes in a prescription, assesses that prescription, selects the prescribed medicinal product and delivers that medicinal product to the subject of care or their representative

Note 1 to entry: In most cases, but not necessarily always, the individual healthcare provider concerned will be a Pharmacist.

[SOURCE: ISO/TS 19256:2016, 3.9]

3.4
dispense record
record of dispensed medicinal product and dispense process

Note 1 to entry: Note 1 to entry: Dispensed medicinal product includes the actual product dispensed identifiers, brand, type, form, quantity etc. Dispense process record includes details of the delivery method, date and recipient (where this is not the subject of care) and the dispenser. The ability to record a comment where assessments of prescriptions are undertaken might also be part of this record.

[SOURCE: ISO/TS 19256:2016, 3.10]

3.5
dose instructions
instructions pertaining to the medication, which describe the amount of medication per dose, method of administration, the frequency or interval of dose, associated instructions for dosing or skipped doses, and other associated parameters necessary for appropriate administration of the medication

[SOURCE: ISO/TS 17251:2016, 2.1]

3.6
drug-related problem
occurrence related to the drug therapy of the patient which (can) lead to a suboptimal outcome of the treatment

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3.7
electronic health record
repository of information regarding the health of a subject of care, in computer processable form

[SOURCE: ISO/TR 20514:2005, 2.11, modified — Note 1 to entry has been deleted.]

3.8
identifier
sequence of characters, capable of uniquely identifying that with which it is associated, within a specified context

[SOURCE: ISO/TS 19256:2016, 3.15]

3.9
knowledge base
facts, information and skills acquired through research, experience, reasoning or education on a specific topic as a set of declarative, hierarchical organization of such statements, and relationships between declarative statements, which serves as the underpinning of decision support systems

[SOURCE: ISO/TS 19256:2016, 3.19 modified]

3.10
medicinal product
substance or combination of substances that may be administered to human beings (or animals) for treating or preventing disease, with the view to making a medical diagnosis or to restore, correct or modify physiological functions

Note 1 to entry: A medicinal product may contain one or more manufactured items and one or more pharmaceutical products.

Note 2 to entry: In certain jurisdictions a medicinal product may also be defined as any substance or combination of substances which may be used to make a medical diagnosis.

Note 3 to entry: Medicinal Product MPID XXXX87456 Slaapdiep tablet / Slaapdiep20 mg tablets National – has a name dedicated to a specific jurisdiction (the code number is just an illustration, not a real identifier).

[SOURCE: ISO/TS 19256:2016, 3.24]

3.11
medicinal product dictionary
consistent representation of medication concepts (set of identifiers) at various levels of detail and with meaningful relationships between the concepts, in order to support use cases in healthcare in which medication plays a role

[SOURCE: ISO/TS 19256:2016, 5.5, modified]

3.12
pharmaceutical product
qualitative and quantitative composition of a medicinal product in the dose form authorized for administration by a regulatory authority, and as represented with any corresponding regulated product information

Note 1 to entry: A medicinal product can contain one or more pharmaceutical products.

Note 2 to entry: In many instances, the pharmaceutical product is equal to the manufactured item. However, there are instances where the manufactured item undergoes a transformation before being administered to the patient (as the pharmaceutical product) and the two are not equal.

[SOURCE: ISO/TS 19256:2016, 3.30, modified — Note 3 to entry has been deleted.]

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3.13
prescribing
process of creating a prescription

[SOURCE: ISO/TS 19256:2016, 3.33]

3.14
prescription
direction created by an authorized healthcare person, to instruct a dispensing agent regarding the preparation and use of a medicinal product or medicinal appliance to be taken or used by a subject of care

Note 1 to entry: The term "prescription" alone is best avoided as it is colloquially used at random for the following terms: new prescription message, prescription set and prescription item. Further, it is also used to describe a prescription form. The use of the terms prescription set, prescription item and new prescription message where appropriate is recommended.

[SOURCE: ISO/TS 19256:2016, 3.34]

3.15
decision rules
logic used to represent the facts to support a logical decision based upon knowledge

[SOURCE: *Handbook. Guide to the principles and desirable features of clinical decision support systems*, Council of Standards Australia, Sydney 2007]

3.16
substance
matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical

Note 1 to entry: Substances can be single substances, mixture substances or one of a group of specified substances. Single substances are defined using a minimally sufficient set of data elements divided into five types: chemical, protein, nucleic acid, polymer and structurally diverse. Substances may be salts, solvates, free acids, free bases or mixtures of related compounds that are either isolated or synthesized together. Pharmacopeial terminology and defining characteristics will be used when available and appropriate. Defining elements are dependent on the type of substance.

Note 2 to entry: Discrete existence refers to the ability of a substance to exist independently of any other substance. Substances can either be well-defined entities containing definite chemical structures, synthetic (i.e. isomeric mixtures) or naturally occurring (i.e. conjugated oestrogens) mixtures of chemicals containing definite molecular structures, or materials derived from plants, animals, microorganisms or inorganic matrices for which the chemical structure may be unknown or difficult to define. Substances may be salts, solvates, free acids, free bases and mixtures of related compounds that are either isolated or synthesized together.

[SOURCE: ISO/TS 19256:2016, 3.41]

4 Abbreviations

For the purposes of this document, the following abbreviations apply.

CDS	clinical decision support
CDSS	clinical decision support systems
EHR	electronic health record
HL7	Health Level Seven
ICD	international classification of diseases

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ICH	international council for harmonization of technical requirements for pharmaceuticals for human use
ICPC	international classification of primary care
ICSR	individual case safety report
IDMP	identification of medicinal products
LOINC	logical observation identifiers names and codes
MPD	medicinal product dictionary
S[m]PC	summary of product characteristics
SNOMED-CT	systematized nomenclature of medicine – clinical terms

5 Positioning of a CDS knowledge base

5.1 Knowledge in healthcare

In healthcare, there are a lot of different processes that can be supported by CDS. 'CDS' is therefore a broad term that includes all kinds of support for enhancing health-related decisions and actions, with pertinent, organized clinical knowledge and patient information to improve health and healthcare delivery.

Examples are CDS for overall efficiency, identifying disease early, aid in accurate diagnosis, for preventive care, for treatment or monitoring and follow-up, or for optimization of drug therapy from different perspectives like quality, cost-efficiency or preventing drug-related problems. CDS for optimising drug therapy often support the check for known drug allergies of patients, comparison of drug and diagnostic test results to ensure that the right drug at right doses are prescribed, alerts in case of drug–drug interactions, suggest medical alternatives, drug doses, routes, and frequencies, duplicate orders.

5.2 Knowledge for drug-related problems that cohere with the intended drug use

As mentioned in 5.1, one of the scopes of a CDS can be to prevent drug-related problems.

In literature, there are different descriptions of what belongs to 'drug-related problems'. Mostly issues like adverse reactions, drug choice problems, dosing problems, drug use problems and interactions are mentioned. Others classify drug-related problems as 'intrinsic' (belonging to the drug) or 'extrinsic' (errors concerning prescribing, transcription, dispensing, administration [including non-compliance]) and 'across settings' (errors occurring on the interface between different healthcare settings), with several subdivisions per class). This shows that these definitions are ambiguous.

For this document, a general definition of 'drug-related problems' is chosen which has its focus on problems once a drug has been chosen, in any domain of prescribing, dispensing, administering of the drug and monitoring the patient.

A drug-related problem is an occurrence related to the drug therapy of the patient which (can) lead to a suboptimal outcome of the treatment. The aim of detecting drug-related problems is firstly to minimize the risk of unintended harm or discomfort associated with the use of a product and secondly to maximize the effectiveness of the drug used by the patient. This includes not only rules about how to optimize the therapy of the drug once it will be used, but also recommendations if the drug itself is non-optimal (either obsolete, or not effective enough given the patients' characteristics).

This definition has its focus on drug-related problems that cohere with the intended use of a drug. Aspects like choosing the right drug according to guidelines (efficacy) and patient coaching for the correct usage are not included in this definition.

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Beside drug-related problems, also the costs of a medicinal product can be a real issue. If there are therapeutically equal choices between medicines, the costs for the patient can influence the choice. If the developer of a knowledge base would like to take this into account, this should be clearly separated from the knowledge that deals with the drug-related problems. In order to distinguish which outcome of a rule supports the optimal therapeutic usage of a drug and which outcome has just to do with the costs.

5.3 The structure of the knowledge

CDS can be expressed in four ways:

— Type one provides categorized information that requires further processing and analysis by users before a decision can be made.

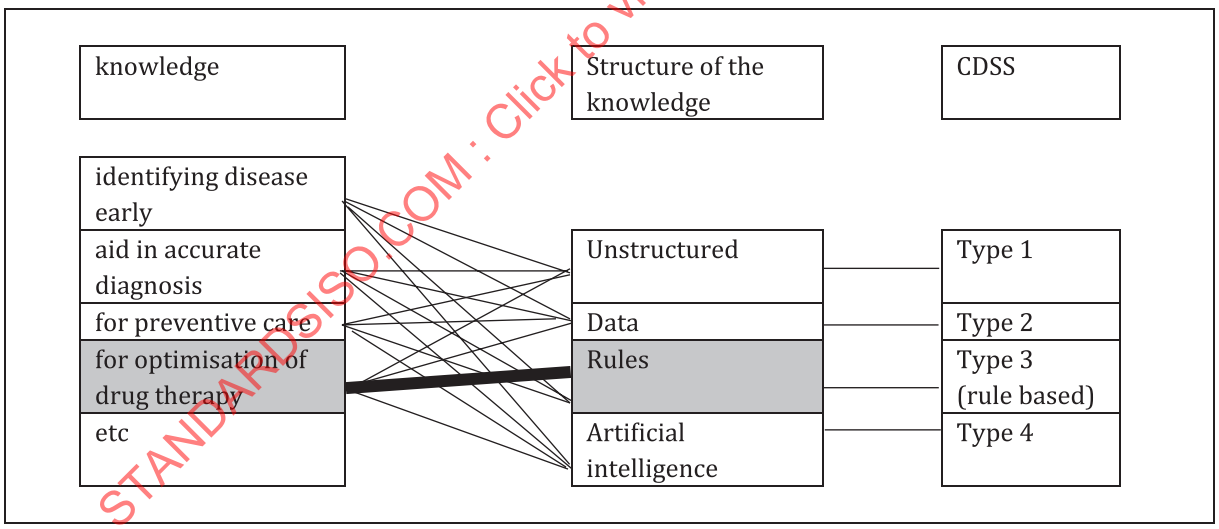
— Type two present the clinician with trends of a patient's changing clinical status and alerts clinicians to out-of-range assessment results and intervention.

— Type three use deductive inference engines to operate on a specific knowledge base and automatically generate recommendations based on changing patient clinical condition, with the knowledge and inference engines stored in the knowledge base. These systems require computer readable rules and an underlying computer electronic health record system that is also computer processable.

— Type four use more complex knowledge management and inference models than the other three decision support types. These systems include case management reasoning, neural networks, or statistical discrimination analysis to perform outcome or prognostic predictions.

The focus of this document is on a knowledge base that contain rules which are assessed by a team of experts, based on criteria to 'digest' the general references, handbooks, guidelines or whatever sources are chosen, into useful rules (type three).

The focus of this document is depicted in Figure 1.



NOTE Depicted in grey is within the scope of this document.

Figure 1 — Knowledge base for drug-related problems to be used in rule-based CDSS

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5.4 Knowledge base in relation to the healthcare information system

5.4.1 Introduction

The knowledge base (see Figure 2) is the basis for a CDSS to be used in healthcare. The CDSS uses drug data (medicinal product dictionary, MPD) and patient information (electronic health record, EHR) and is part of (or at least linked to) the clinical or pharmacy information system.

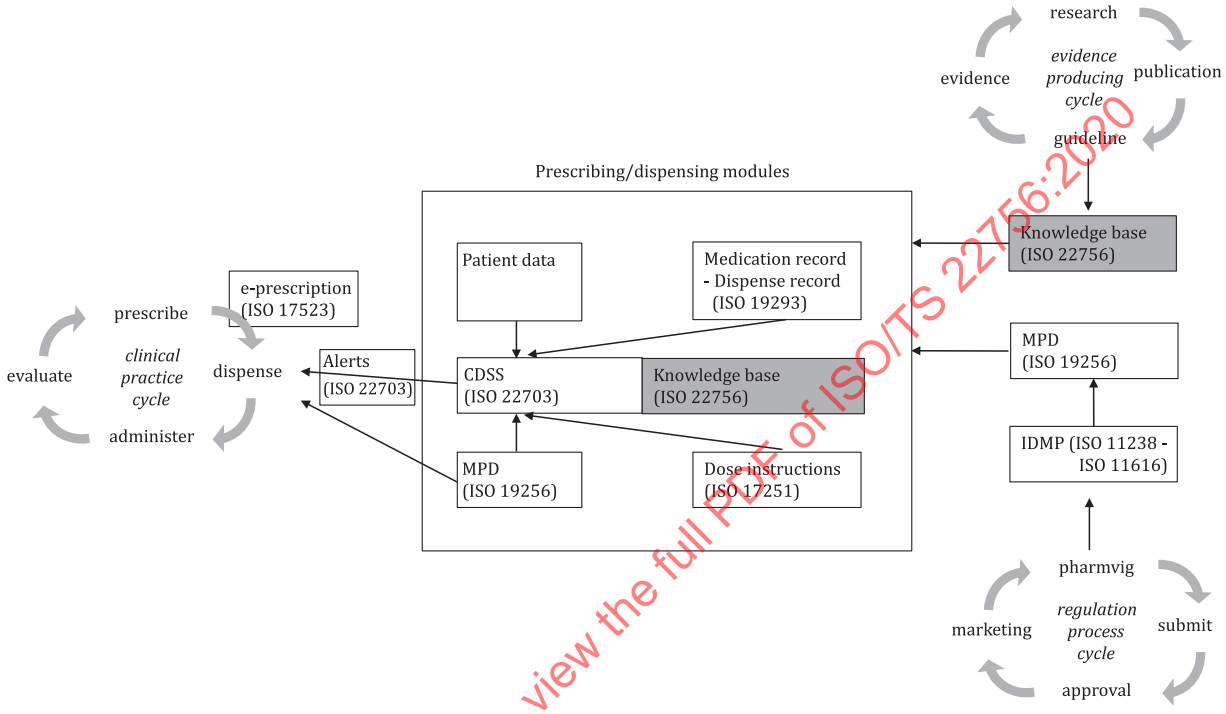

Figure 2 — The knowledge base in relation to the prescribing/dispensing modules (computerized physician order entry system and pharmacy information systems, the clinical practice cycle, and the regulation process cycle)

5.4.2 Relation with EHR

For rules that aim to detect/prevent drug-related problems, it is important to include patient data from the EHR, including the medication record, dispense record and/or medication administration record (eMAR). For example, if there is a drug choice problem because of a wrong drug for a certain disease, it is necessary to know the disease of the patient.

This means that a knowledge base has a relationship with the EHR such that the EHR uses some of the knowledge base's information. The data used by the EHR is described in 6.8.

For a proper outcome of a rule, the EHR needs to be accurate. Inaccurate or incomplete patient data can lead to false positive decision support (i.e. irrelevant advice) or false negative decision support (i.e. no advice for patients who are at risk). Frequent inaccurate alerts can lead the clinicians to ignore all of the CDS advice. The problem of knowledge maintenance is important for all types of CDS, not just the alerts and reminders. For this reason, it is important to monitor the accuracy of the patient's record and to address problems encountered.

To ensure the link between the EHR and the knowledge base, both should use the same controlled vocabulary.

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5.4.3 Relation with medicinal product data

A knowledge base to be used in medication processes, should be based on the Medicinal Product Dictionary (MPD) of that country or jurisdiction. The (groups of) medicines mentioned as a trigger for or as a variable in the rule have a direct link to the identification in the MPD.

Through the MPD, the knowledge base has also a link to the international standards (i.e. IDMP). See 6.6 for a more detailed description of the linkage to the MPD or IDMP.

5.4.4 Relation with a CDSS

As mentioned in 5.4.1, CDS consists of a knowledge base and the CDSS, which is the program that combines that knowledge with patient specific information base and a communication mechanism towards the user of the system. Both parts are distinct, but they are tightly connected.

On the one hand, all information in a knowledge base needs to be usable in CDSS. For example, if a rule describes that for a certain drug for creatinine clearance between 30 ml/min/1,73 m^2 and 50 ml/min/1,73 m^2 the dosage should be reduced to 50 %, the rule has to include the codes for creatinine clearance, but the CDSS should be able to search and find the creatinine clearance of the patient (if available) based on this rule.

On the other hand, some of the functions of a CDSS should be fed by the knowledge base, although not all of them. For example, where the 'five rights' as described in Clause 0.2 mention presenting the information in the right format as an alert and at the right time in the workflow, this demands that a CDSS support that there can be a pop-up after the right trigger but it demands from the knowledge base attributes in the rules that tells whether this rule should be a pop-up or not, and the trigger-moment in the workflow.

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6 Requirements for the development of a knowledge base

6.1 Introduction

Optimal decision making by healthcare professionals starts with a knowledge base that is relevant to the information needs of the users. This clause describes key points for such a knowledge base, that helps to develop a knowledge base that meets this need.

6.2 The governance of a knowledge base

Developing a knowledge base that is relevant, evidence based and up to date, is a huge task and requires substantial amounts of resources. It requires an ongoing process with an appropriate governance infrastructure, for which resources are indispensable. In this light, the organization that develops a knowledge base shall have the following characteristics:

— Shall be a centralized organizer, such as an academic unit or a professional organization or association with staff to serve as the driving force to assemble the panel and disseminate information.

— Shall make sure that the decision rules are assessed by a consensus panel of experts to create and maintain a standard set of rules, with oversight by an organization that can ensure that the process is transparent, systematic, evidence-based and that has the resources to do so; this means that the development and maintenance of a knowledge base is preferably hosted by a national or scientific organization. Key elements for developing trustworthy clinical recommendations include that relevant stakeholders are involved. Relevant stakeholders are at least experts with a background in clinical experience in relevant clinical subspecialties and health IT, as well as experts in clinical pharmacology, pharmacokinetics, pharmacoepidemiology and medication safety.

— Governance rules shall be defined for the expert panel which assesses rules: the appointment process, terms of membership, procedural rules (e.g. voting policies and procedures), the framework for executing the steps involved in grading recommendations, policies for managing potential conflict

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of interest, and the policies and procedures of a comprehensive and transparent rule selection process.

The principles and processes that should be considered by developers of knowledge bases in support of proper application of international healthcare terminology standardization are outlined in ISO/TR 12309 and should be respected.

6.3 Structure of the rules

As mentioned in Clause 1, the scope of this document is the requirements for a knowledge base to be used in rule based CDSS. This means that the knowledge base shall be suitable for or shaped as 'rules'. See Annex B for an example. Concerning the structure of the rules, the following is applicable:

— The structure of the rules shall be flexible in order that no limitation in the amount of patient data can be included.

— The rules should be published in a structured/standardized format, so that they can be used by software systems.

6.4 Scoping of the knowledge base content

Define the scope when developing a knowledge base: covering many types of drug-related problems is tempting, but can soon become overwhelming. At least the next categories shall be considered (these categories are overlapping):

— The type of target users: healthcare professionals (e.g. physicians, pharmacists, nurses), patients, patient environment (e.g. inpatient, outpatient, post-acute care) or any combination thereof.

— The type of drug-related problems: drug-drug interactions, contraindications, allergy, dose checking, duplicate therapy, checking of laboratory values, or another kind within the whole field of drug-related problems.

— The type of data the rules will be based: just the characteristics of the medicine or medication data combined with patient data (which is described more in detail in 6.8). The first category (rules based on the characteristics of the medicine) means rules that are just based on properties of the medicine, apart from the situation of the patient. Whether this type of rules can be developed, depends on whether these data are included in the Medicinal Product Dictionary or can be directly derived from the IDMP data. See Annex A for the data concerning approved indication (including paediatric use) and adverse effects that are available in IDMP.

EXAMPLE Rules just based in the characteristics of the medicine are rules that detect off-label use or whether a symptom can be an adverse effect of a medicine.

Scoping decisions shall be made transparent for the target users of the knowledge base.

6.5 Evidence for the rules

An organization that develops a knowledge base, shall decide on which kind of data or evidence the rules will be based. This means the following:

— Decision rules shall be based on the best current evidence available. This can vary from case reports to randomized clinical trials, meta-analyses, and practice guidelines or knowledge that is already assessed internationally that meet standards of quality. Information that has a certain legal status, like the SPC, should be taken into account in that process. Adopting rules from other organisations who meet the requirements of this technical specification is also a possibility. The developers of a knowledge base shall decide which types of evidence and literature will be included and shall make these decisions transparent for the knowledge base users.

— Decision rules may include consensus opinion of the experts who assess the rules. Use of expert advice is particularly important because the quality of evidence can differ between the topics

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for which a decision rule will be developed. Consensus opinion of experts shall not be instead of evidence, but added to the evidence to assess the clinical relevance of it.

See Annex B for an example.

6.6 Medicinal product data used in the rules

6.6.1 Medicinal product dictionary

For the reference to medicines, the knowledge base shall refer to standardised terminology.

In case there is an MPD, the reference for the identification of medicines will be to the MPD. The MPD should be based on ISO/TS 19256, which in its turn is based on IDMP.

Around the world there are many knowledge bases for drug-related decision support in use. Some will be linked already to existing MPDs. Maybe these MPDs do not already completely adhere to IDMP. In case a knowledge base developed according to this document will be linked to an MPD that is not completely IDMP compatible, the requirements for the developing the knowledge base are still valid and relevant. The 'would be' situation is that the knowledge base is linked to an MPD based on IDMP. As described in ISO/TS 19256, there can be a migration period for existing MPDs to comply with IDMP. The next best situation is that a knowledge base is linked to an MPD which is not yet IDMP compatible, but is in the migration phase. In case there is no MPD at all, at least the elements described below shall be considered as the characteristics of medicinal products that are relevant for the link with a knowledge base.

6.6.2 IDMP

In case there is no MPD, the characteristics as mentioned in Annex A shall be the basis for the identification of the medicines with respect to the knowledge base.

The IDMP has the characteristics of the identification of the medicines as well as the reference to the clinical particulars of a medicine.

The IDMP data model includes a wealth of medicinal product information that can be used for the therapeutic assessment in the course of the prescription process for a given patient.

When IDMP-compliant medicinal product data are available in the country, then the following IDMP data shall be considered in your knowledge base:

— locally available drugs with indications that match the disease status, age group and sex of the patient;

— drug availability information, in terms of the products that share the same pharmaceutical product(s) and indications (including the original and generics drugs), with their local names and pack sizes;

— hints and alerts to reject drugs can result from comparing the patient's demographics, concomitant diseases and medication with the contraindications and interactions as described in the corresponding IDMP submodels, including eventual use restrictions in terms of age, sex or other demographic aspects;

— further useful information can be obtained by exploitation of additional IDMP medicinal product information in the areas of maximum dosing limits, availability for the use with children, patient allergies versus the substances of the product's composition and key data elements that are relevant for the processes of prescription and dosing, see Annex A.

For the identifying fields, see Annex A.

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6.6.3 Interface with an MPD or with IDMP

Decision support for drug-related problems can apply to several levels of hierarchy of a drug. Some rules apply to the medicinal product as such, for example because it's about the excipients. Other rules apply to the active substance, because the dose form does not matter but the rule applies to all medicines with that certain active substance.

For efficiency and quality reasons, the linkage between the knowledge base and the MPD shall be on the appropriate hierarchical level of the drug to which the rule applies. An MPD built according to ISO/TS 19256:2016, 7.3.3 supports this need. This includes the fixed levels with identifiers like the Substance, the pharmaceutical product or the medicinal product, but also flexible groupings based on the separate characteristics. The next hierarchical drug levels shall be available for linkage to the rules in a knowledge base:

— active moiety (whether in a single component or as a combination product)

— combination of active moieties (can be just one active moiety, but that excludes the combination products

— substance plus route of administration

— substance plus route of administration plus dose form

— pharmaceutical product

— medicinal product

— groups of drugs, at any level of abstraction and grouped based on a certain set of characteristics

— groups of any characteristic that is relevant for decision support (e.g. just the dose form, in case of allergy for patches).

The knowledge base can contain, for example, a rule that warns for:

— the influence of a drug on driving. This is for example the case for diazepam. Because all the medicines that contain diazepam have a systemic pharmacological effect, this knowledge rule shall be linked to: diazepam active moiety;

— missing gastric protection if an NSAID (e.g. naproxen) is used by an elderly person. Naproxen is approved as a single substance medicine and as combination product with esomeprazole. The combination product shall be excluded from the warning, because the gastric protection is included. Therefore, this rule shall be linked to: naproxen, on the level of just the 'combination' of this single active moiety (for combinations with other active moieties not being gastric protection, if approved), excluding the level of 'naproxen and esomeprazole';

— dexamethasone in a high dose in the third trimester of pregnancy. This warning is relevant for the systemic products, but not for the local ones like eyedrops. Therefore, this rule shall be linked to the level of: dexamethasone and systemic routes of administration, excluding in this way dexamethasone ocular, dexamethasone auricular and other routes of administration that do not have a systemic effect.

6.7 Dosage data used in the rules

For the safe usage of medicines, the dose instructions plays an important part; therefore, the dose instruction of the drug will be part of the decision support and therefore of a knowledge base. This applies in case a medicine triggers a rule as well as when a medicine is taken into account as comedication.

The data of the dose instruction (see ISO/TS 17251) that at least shall be considered are:

— administration amount (dosage)

— timing of the dose

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— route of administration.

6.8 Patient data variables used in the rules

6.8.1 Introduction

An organization (in the persons of the expert panel members) that develops a knowledge base, shall consider and decide which kind of patient data will be included in the rules, in case rules are developed that include patient data. The choice for including more or less variables, lead to different kind of rules: sophisticated ones with sophisticated patient data or less detailed rules with less patient data.

Based on the international patient summary as described in EN 17269, the following patient data shall be considered to include in the knowledge base, taking into account whether these data are available in the healthcare information systems in the realm where the knowledge base will be used:

— age

— gender

— comedication

— allergy/intolerance-agents

— diagnoses (morbidities)

— pregnancy

— laboratory values.

Beside the data mentioned above (6.8.1), also other data can be relevant to include in the knowledge rules, like body weight, the severity of the disease, pharmacogenetic data, racial data, or anamnestic data. The organization that develops a knowledge base shall decide which of these kinds of data will be included in the knowledge base.

See Annex B for an example.

This also does not mean that these data will be available in the EHR. For how to deal with that, see 6.11.

6.8.2 Interface with the EHR

The rules in a knowledge base can include the different kinds of patient data, as described in 6.8.1. Therefore, the rules shall include a map set to the terminologies for patient data that are used in respective country where the rules will be used, in order that the CDSS is able to interpret patient data.

A prerequisite for doing so is the use of terminologies (such as SNOMED-CT, LOINC, ICPC2, or ICD-10) that assign meaning to the content of data fields. The use of appropriate data standards and terminologies enable semantic interoperability and allow information to be shared across health information systems. They also allow the same conclusions to be derived from the same data sets if the same inference methods are applied in different contexts.

The organization that develops the knowledge base shall ensure that the map set from the knowledge rules to the terminologies are appropriate. This means that there shall be a procedure to make sure that the map set is correct and up to date, and that per map set both organisations that maintain the two terminologies are involved.

Be aware that knowledge base interface with the EHR is key on treatment suitability because suitable prescription is on individual patient basis.

For recording the patient data, the structure of detailed clinical models as described in ISO/TS 13972 can be used. If this is the case in the setting where the knowledge base will be used, it is useful to provide a description which elements of the detailed clinical model relates to which elements in the rules.

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6.9 Right information at the right time

For users of clinical decision support it is important to receive actionable alerts. It is known that a statement about a possible harm without recommending a corresponding action is generally not an effective way to change clinician behaviour. Therefore, guidance on ways to mitigate or avoid the potential for harm is strongly recommended.

In addition, insight in the evidence and other background information also helps to provide the healthcare professional the information which is necessary to appraise the recommendation.

Therefore, requirements and recommendations for information to be available for the user of the knowledge base are:

— The alert shall contain a specific and concise advice (actions required and alternative options) for the healthcare professional that recommends actions, that is guidance on ways to mitigate or avoid the potential for harm.

— Beside the recommended actions, additional information should be available as far as it is described in the evidence used for the rule, such as classification of seriousness, clinical consequences, frequency of harm and exposure, modifying factors, mechanism of action.

— The (certainty of the) evidence and the expert consensus on which the knowledge is based, shall be made transparent for healthcare professionals. For the evidence, it is recommended to summarize the evidence briefly and provide access to the references when possible, beside the evidence ratings.

— Grading of the alerts. It is recommended to limit the total amount of gradings to 2 to 3 at maximum in order to simplify and increase the consistency of these classification systems. Grading of the alerts should be expressed in the advice, using consistent terms and definitions. The aim of these gradings is to make clear for the user of the system the seriousness of the alert.

6.10 Quality of the rules

An organization (in the persons of the expert panel members) that develops a knowledge base, shall ensure the quality of the rules. At least the following points shall be addressed:

— There shall be criteria for the assessment of the data, in order to ensure a valid and reproducible outcome. The following elements shall be considered: causality assessment, clinical consequences, frequency, modifying factors, rating of the quality of evidence.

— Validation of the rules:

  — The rules should be validated with test cases, to check whether the outcome of the rule is correct based on the intention of the content of the rule.

  — the rules should be tested in the real world of the healthcare professional before publication, or there should be a valid mechanism to receive feedback from the users once the rules are published (or, if practicable, already before publication in a co-design process with end users). This can be supported by the CDSS, if this contains a possibility that the user of the system can send his experience with the rule back to the maintenance organization of the knowledge base. This can be for example structured information about how the alert is dealt with and unstructured information if a healthcare professional would like to give more detailed feedback about how and why a rule can be improved. The assessment of this feedback is part of the maintenance process.

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6.11 Relation with a CDSS

As mentioned in the Introduction, there is a strong connection between a knowledge base and a CDSS. From the viewpoint of the relation with a CDSS, developers of a knowledge base shall consider the following points:

— The rules shall contain 'handles' to support the right CDS intervention format. The kinds of intervention formats that at least shall be indicated, are whether the rule have to end in an interruptive alert (push), or whether a rule is meant just to answer questions of the clinician on demand (pull). This is necessary, because a key component of improving the relevance of decision support is identifying the decision support with clinical consequences warranting interruption in the ordering process, beside decision support that has less clinical relevance and should be non-interruptive.

— An implementation guide shall be made available for the developers of the CDSS. This implementation guide includes instructions like:

  — what are in general the triggers for the rules (such as automatically by prescribing, manual, automatically by new patient info)

  — description for the intended CDS intervention format at the right time in the workflow

    EXAMPLE if the trigger of a rule is prescribing or dispensing, the intervention format (push or pull information) depends on the 'handles' in the rule; but if the trigger is new patient data like new laboratory values, the intervention format is non-interruptive posted to work lists for resolution at a time convenient to the clinician.

  — can the alerts be 'snoozed' (e.g. delay the response for a predetermined amount of time after its first alerting) and if so, what are the conditions for that

— In case there can be a gap between the data elements in a rule and that availability of that data in the EHR, a mechanism shall be developed that this should be made clear to the target user. This can be done in several ways:

  — It is included in the rules: if certain data are not available, the rule includes a pathway with specific advice for that situation.

  — It is included in the functionality of the CDSS: if the CDSS detects that the rule uses certain data but it is not available, the CDSS alerts this to the target user.

— A mechanism shall be developed to support the traceability between the alert and the rule on which this is based, also with respect to the history. If a certain action is undertaken in the past based on a certain rule, and in between the content of the rule has changed, the content of the rule that was fired in the past shall be traceable. This means that versioning of the knowledge rules shall be available, whether in the knowledge base itself, or in the CDSS or patient record.

6.12 Maintenance

The scope and content of regular maintenance includes the continued updating of the knowledge base. Detailed maintenance processes can be unique to the maintenance organization, infrastructure, jurisdiction and data to be supported, and these can already exist for some established knowledge

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bases, but the following core principles should be considered when upgrading or developing new medicinal product dictionaries.

— Maintenance of the content of the knowledge base:

  — There shall be a process a periodic and timely update of the knowledge rules. The methods to develop and update the knowledge base rules shall be explicitly described and users can find this information easily.

    This means that updates of the literature (including IDMP data) that is used in existing rules and new evidence, shall be checked and assessed within a reasonable time. Preferably before the next release of the knowledge base. If that is not achievable e.g. because of the meeting schedule of the experts who do the assessment, the assessment is preferably done in the next meeting of the experts and included in the rules in the first following update of the knowledge base thereafter.

  — There shall be a process for gathering, storing and analysing the relevant evidence, and criteria for how this is assessed and reflected in the rules.

— Maintenance with respect to the available medicinal products:

  — products that have been included in the MPD, that have entered the market in the region in which the knowledge base is used, or in case the knowledge base is directly linked to IDMP the medicines that are added to the IDMP databases, shall be assessed within a reasonable timeframe. If it is evident that the new product is covered by the existing knowledge rules, the product shall be linked to the knowledge rules before the next update of knowledge base. In case new assessment is necessary (e.g. in case of a new chemical entity in a new drug class), the process as described in the bullet point above is applicable.

  — Removing references to medicines that are withdrawn from the market.

  — There shall be a process for the retrieval, evaluation and approval of change requests.

— Maintenance of the map sets:

  — There shall be a process for maintaining the map sets that are used in the rules. This process includes at least involvement of the owner of the concerning terminology.

— The knowledge base should deploy a strict and transparent versioning approach as far as needed. This is for example necessary if the rules include data that have to be implemented by the CDSS developer before it can be used in the software.

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Annex A
(normative)

Identifying IDMP fields in relation to a knowledge base

Table A.1 lists the identified data fields with explanations from ISO 11615, additional comments and an indication, whether this data field is also referred to by ISO/TS 19256.

Table A.1 — Identifying IDMP data fields in relation to a knowledge base

Medicinal Product Data (IDMP Data Model)				
Domain	**Item**	**Clause/ sub-clause ISO 11615**	**Comments**	**Referred to ISO/ TS 19256**
Medicinal Product Data	MPID	8.2.1	CDSS-internally needed for the unique identification of the product(s)	y
Medicinal Product Data	Combined Pharmaceutical Dose form	9.2.2.2.3	Contains the Pharmaceutical Dose form in the case of Combination Products. EXAMPLE Powder and solvent for solution for injection. The Medicinal Product contains two manufactured items: a powder for solution for injection and a solvent for solution for injection. The pharmaceutical product that is prepared from the two manufactured items is a solution for injection; the authorized pharmaceutical dose form for the Medicinal Product is "powder and solvent for solution for injection".	n
Medicinal Product Data	Paediatric Use Indicator	9.2.2.2.6	Necessary to decide whether a medication is indicated for children See also 6.4	n
Medicinal Product Name	Full Name	9.2.2.8.2	Match existing or new prescriptions by name	y
Medicinal Product Name	Invented Name Part	9.2.2.8.3	Match existing or new prescriptions by name EXAMPLE For the Medicinal Product Name "Drug XYZ® Precisehaler 200 mg for adults" the invented (trade) name part is "Drug XYZ".	y
Medicinal Product Data	Scientific Name Part	9.2.2.8.4	Match existing or new prescriptions by name EXAMPLE For the Medicinal Product Name "Irbesartan/Hydrochlorothiazide Pharma KK" the common (generic) name part is "Irbesartan/Hydrochlorothiazide".	y
Country/Language	Country	9.2.2.9.2	This may be the country of residence or, when the patient is seeking advice from a physician/hospital. It is the country where the Medicinal product needs to be available. Needed for all use cases.	y
Country/Language	Jurisdiction	9.2.2.9.3	This may be the political region of residence or, when the patient is seeking advice from a physician/ hospital. It is the region where the Medicinal product needs to be available. EXAMPLE For the country of Canada, the jurisdiction of Quebec province may be specified.	y

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Table A.1 *(continued)*

Medicinal Product Data (IDMP Data Model)				
Domain	**Item**	**Clause/ sub-clause ISO 11615**	**Comments**	**Referred to ISO/ TS 19256**
Country/Language	Language	9.2.2.9.4	The language, in which the local product name is to be expressed.	y
Marketing Status	Country	9.3.2.8.2	Country where product is marketed. This should coincide with the country where the patient seeks advice. Needed to determine the availability of drugs for all use cases. (Not all registered products are also marketed!)	y
Marketing Status	Jurisdiction	9.3.2.8.3	Political region where product is registered. This should coincide with the region where the patient seeks advice. But registration may also be available in the country. Needed to determine the availability of drugs for all use cases.	y
Marketing Status	Marketing Status	9.3.2.8	Describes whether the product is marketed. Needed to determine the availability of drugs for all use cases.	y
Marketing Status	Marketing Date Start/ stop	9.3.2.8.5 9.3.2.8.6	Describes since/until when the product is marketed. NOTE "Placed on the market" refers to the release of the Medicinal Product into the distribution chain. "No longer available on the market" can refer to the fact that the Marketing Authorization Holder has taken a decision to no longer market the Medicinal Product or that the marketing authorization is no longer valid.	y
Marketing Authorization	Marketing Authorization Number	9.3.2.2.2	Needed for unique identification purposes.	y
Marketing Authorization	Country	9.3.2.2.3	Country where product is registered. This should coincide with the country where the patient seeks advice. But registration may also be available in the political region to which the country belongs (e.g. EU). Needed to determine whether the product is registered, relevant for all use cases.	y
Marketing Authorization	Legal Status of Supply	9.3.2.2.4	Prescription only, pharmacy, or over the counter. Needed to determine where the drug can be obtained. EXAMPLE 1 Medicinal product subject to medical prescription. EXAMPLE 2 Medicinal product not subject to medical prescription.	y
Marketing Authorization	Authorization Status	9.3.2.2.5	Needed to assess the authorization status of the drug in the country. EXAMPLES Active/ valid, expired, renewed, not renewed, withdrawn.	y
Marketing Authorization	Authorization Status Date	9.3.2.2.6	Needed to assess the authorization status of the drug in the country. EXAMPLE The marketing authorization expired on 2011–01–01.	y
Marketing Authorization	Validity Period (Start/ End)	9.3.2.2.7 9.3.2.2.8	Needed to assess the authorization status of the drug in the country. EXAMPLE The marketing authorization is valid from 2011-01-01 to 2015-01-01.	y

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Table A.1 *(continued)*

Medicinal Product Data (IDMP Data Model)				
Domain	**Item**	**Clause/ sub-clause ISO 11615**	**Comments**	**Referred to ISO/ TS 19256**
Jurisdictional Marketing Authorization	Jurisdiction	9.3.2.10.3	Needed to assess the authorization status of the drug in the region/ jurisdiction. EXAMPLE The legal status of supply of a Medicinal Product can differ in the various provinces in Canada. While the country of marketing authorization is Canada, the names of the provinces can be specified (as jurisdictions) and the legal status of supply applicable in each province also specified.	y
Jurisdictional Marketing Authorization	Marketing Authorization Number	9.3.2.10.4	Needed to assess the authorization status of the drug in the region/ jurisdiction.	y
Jurisdictional Marketing Authorization	Legal Status of Supply	9.3.2.10.5	Needed to assess the authorization status of the drug in the region/ jurisdiction. EXAMPLE 1 POM – Prescription only medicine, EXAMPLE 2 P – Pharmacy only medicine, EXAMPLE 3 GSL – General sales list medicine.	y
Contra-indication	Contra-indications Text	9.9.2.3.2	The section "Contraindications" shall be used to describe the authorized contra-indication(s) for the Medicinal Product as described in the regulated product information. The information from this section is useful to rule out certain medicinal products. EXAMPLE Contra-indicated in the presence of severe/significant renal impairment.	n
Contra-indication	Contra-indications as "Disease/ Symptom/ Procedure"	9.9.2.3.3	EXAMPLE 1 Contra-indicated in ulcerative disorders of the GI tract. EXAMPLE 2 Contra-indicated in recent or active hepatitis.	n
Contra-indication	Disease Status	9.9.2.3.4	See also 6.5 EXAMPLE 1 Contra-indicated in recent or active hepatitis. EXAMPLE 2 Contra-indicated in refractory heart failure.	n
Contra-indication	Comorbidity	9.9.2.3.5	See also 6.4 EXAMPLE 1 Contra-indicated in myocardial insufficiency due to cor pulmonale. EXAMPLE 2 Contra-indicated in pulmonary oedema due to mitral stenosis.	n

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Table A.1 *(continued)*

Medicinal Product Data (IDMP Data Model)				
Domain	**Item**	**Clause/ sub-clause ISO 11615**	**Comments**	**Referred to ISO/ TS 19256**
Therapeutic Indication	Indication Text	9.9.2.2.2	See also 6.4 The section "Indications" shall be used to describe the authorized indication(s) for the Medicinal Product in accordance with the regulated product information. The information from this section is useful to take certain medicinal products into further consideration for candidate therapies. EXAMPLE Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.	y
Therapeutic Indication	Indications as "Disease/ Symptom/ Procedure"	9.9.2.2.3	See also 6.4 EXAMPLE 1 Treatment of primary hypertension. EXAMPLE 2 Relief of motion sickness. EXAMPLE 3 Prior to emergency surgery.	y
Therapeutic Indication	Disease Status	9.9.2.2.4	See also 6.4 EXAMPLE 1 Treatment of chronic active liver disease. EXAMPLE 2 Management of refractory hypercalcaemia. EXAMPLE 3 Treatment of metastatic breast cancer.	y
Therapeutic Indication	Comorbidity	9.9.2.2.5	See also 6.4 EXAMPLE 1 Treatment of exocrine pancreatic insufficiency due to cystic fibrosis. EXAMPLE 2 Treatment of pneumocystitis pneumonia in AIDS.	y
Therapeutic Indication	Intended Effect	9.9.2.2.6	See also 6.4 EXAMPLE 1 Prophylaxis of acid aspiration. EXAMPLE 2 Diagnosis of hypopituitarism. EXAMPLE 3 Palliative therapy for trigeminal neuralgia. EXAMPLE 4 Reduction of symptoms in hayfever. EXAMPLE 5 Maintenance treatment in end-stage renal failure. EXAMPLE 6 Passive immunization against rabies infection.	y
Therapeutic Indication	Timing/ Duration	9.9.2.2.7	See also 6.4 If there is timing or duration information described as part of the indication as it is referenced in the regulated product information, it can be specified here. EXAMPLE Prevention of atherothrombotic events in patients with ischaemic stroke (from 7 days until less than 6 months).	y

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Table A.1 *(continued)*

Medicinal Product Data (IDMP Data Model)				
Domain	**Item**	**Clause/ sub-clause ISO 11615**	**Comments**	**Referred to ISO/ TS 19256**
Population Specifics	Age	9.9.2.5.2	See also 6.5 The section "Population Specifics" can be used to describe the population for which a particular indication or contra-indication applies as authorized for the Medicinal Product in accordance with the regulated product information. EXAMPLE 1 Contra-indicated in elderly patients with diabetes mellitus. EXAMPLE 2 Contra-indicated in adolescents.	y
Population Specifics	Age Range Low/High	9.9.2.4.3 9.9.2.5.4	See also 6.5 EXAMPLE 1 For treatment of coughs in children older than 12 months and younger than 4 years. EXAMPLE 2 Adults over 35 years with primary hyperlipidaemia.	y
Population Specifics	Gender	9.9.2.5.5	See also 6.5 EXAMPLE For the treatment of men with prostate cancer.	y
Population Specifics	Race	9.9.2.5.6	See also 6.5 EXAMPLE Contra-indicated in Afro-Caribbean patients.	y
Population Specifics	Physiological Condition/ Health Status	9.9.2.5.7	See also 6.5 EXAMPLE 1 Nutritional status: malnourishment, vitamin deficiency, over-weight, under-weight. EXAMPLE 2 Clinical chemistry/haematology: low CD4 count, hyperkalaemia. EXAMPLE 3 General status: debilitation, immunodeficiency.	y
Other Therapy Specifics	Therapy Relationship Type	9.9.2.6.2	If there is information about the use of the Medicinal Product in relation to other therapies described as part of the indication or contra-indication in accordance with the regulated product information, this can be specified using this section "Therapy Relationship Type". EXAMPLE 1 To be used as co-therapy with beta-blockers in the treatment of... EXAMPLE 2 Contra-indicated when past therapy with... EXAMPLE 3 Indicated for second line treatment with steroids for... EXAMPLE 4 Indicated prior to treatment with DMARDs.	y

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Table A.1 *(continued)*

Medicinal Product Data (IDMP Data Model)				
Domain	**Item**	**Clause/ sub-clause ISO 11615**	**Comments**	**Referred to ISO/ TS 19256**
Other Therapy Specifics	Medication	9.9.2.6.3	EXAMPLE 1 Prevention of atherothrombotic events in combination with acetyl salicylic acid. EXAMPLE 2 Treatment of type 2 diabetes mellitus combination with sulfonylureas. EXAMPLE 3 Prior to treatment with DMARDs. EXAMPLE 4 Contra-indicated if previous exposure to alkylating agents.	y
Undesirable Effects	Undesirable Effect Text	9.9.2.4.2	See also 6.4 The section "Undesirable Effects" shall be used to describe the undesirable effects of the Medicinal Product as described in the regulated product information. The information from this section is useful to carry out risk/benefit analysis for candidate therapies. EXAMPLE Hepatic toxicity including rare cases of fatalities.	y
Undesirable Effects	Undesirable Effect as "Symptom/ Condition/ Effect"	9.9.2.4.3	See also 6.4 EXAMPLE 1 Hepatic toxicity. EXAMPLE 2 Erythema multiforme. EXAMPLE 3 Headache. EXAMPLE 4 Hypercalcaemia.	n
Undesirable Effects	Symptom/ Condition/ Effect Classification	9.9.2.4.4	See also 6.4 EXAMPLE 1 Gastrointestinal disorders (for undesirable effect = gastric ulceration). EXAMPLE 2 Skin and subcutaneous tissue disorder (for undesirable effect = urticaria). EXAMPLE 3 Nervous system disorders (for undesirable effect = migraine headache).	n
Undesirable Effects	Frequency of Occurrence	9.9.2.4.5	See also 6.4 EXAMPLES Rarely, very rarely, less than 1 %.	n

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Table A.1 *(continued)*

Medicinal Product Data (IDMP Data Model)				
Domain	**Item**	**Clause/ sub-clause ISO 11615**	**Comments**	**Referred to ISO/ TS 19256**
Pharmaceutical Product	Administrable Dose Form	9.8.2.2.2	The section "Pharmaceutical Product" 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. For certain medicines, a device can form an integral part of the Medicinal Product, for example to support the administration of the medicine. 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, describing the product in terms of its qualitative and quantitative composition and the pharmaceutical dose form approved for administration in line with the regulated product information. It is the pharmaceutical product therefore that has route of administration information for the administration process. EXAMPLES Tablet, capsule, oral solution, solution for injection. Needed for prescription purposes.	n
Pharmaceutical Product	Unit of Presentation	9.8.2.2.3	EXAMPLE 1 To describe strength: a tablet, spray or puff "contains 100 mcg per actuation" (unit of presentation = actuation). EXAMPLE 2 To describe quantity: a bottle or vial "contains 100 ml per bottle" (unit of presentation = bottle). Needed for prescription purposes.	y
PhPID Set	PhPID Identifier Sets	9.8.2.6	Needed for unique identification and medicinal product clustering (through their pharmaceutical properties) purposes.	y
Route of Administration	Route of Administration	9.8.2.3	EXAMPLES Oral, subcutaneous, ophthalmic. Needed for prescription purposes.	y
Ingredient	Ingredient Role	9.7.2.2.2	The section "Ingredients" describes the ingredients of the Medicinal Product through its representations as the manufactured item(s) and the pharmaceutical product(s), based on ISO 11238 and ISO/TS 19844, ISO 11239/ISO/TS 20440, ISO 11240 and their resulting terminology. EXAMPLES Active substance, adjuvant, excipient.	y
Ingredient	Allergenic Indicator	9.7.2.2.3	Needed to identify potential use risks, allergies, administration problems, etc.	n
Substance	Substance	9.7.2.3.2	EXAMPLES Insulin human, amoxicillin trihydrate.	y
Specified Substance	Specified Substance	9.7.2.4.2		y

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Table A.1 *(continued)*

Medicinal Product Data (IDMP Data Model)				
Domain	**Item**	**Clause/ sub-clause ISO 11615**	**Comments**	**Referred to ISO/ TS 19256**
Specified Substance	Specified Substance Group	9.7.2.4.3		y
Packaged Medicinal Product	PCID	8.3.1	The section "Packaged Medicinal Product" describes the Medicinal Product in terms of it being a Packaged Medicinal Product as presented for sale or supply. Prerequisite for prescription and dosing.	y
Packaged Medicinal Product	Package Description	9.6.2.2.2	EXAMPLE 1 A Medicinal Product presented as a packaged Medicinal Product with a single package [a bottle containing an oral solution (no outer box)] will have a single package item (related directly to a single manufactured item). EXAMPLE 2 A Medicinal Product presented as a packaged Medicinal Product with an outer package with immediate packaging (a box containing two blister sleeves containing 20 capsules or a carton containing 4 vials of solution for injection) will have two recursed package items: the parent package item to describe the box or carton and the child package item to describe the blister sleeve or the vial (the latter then related to the manufactured item). EXAMPLE 3 A Medicinal Product "kit" presented as a packaged Medicinal Product with an outer package containing more than one type of content, for example, a box containing a tube (of cream) and a blister sleeve containing a tablet, will have a recursed parent package item to describe the box and two child package items to describe the tube and the blister (each then related to an manufactured item). Prerequisite for prescription and dosing.	y
Package Item (Container)	Package Item (Container) Type	9.6.2.3.2	Needed to identify potential use risks, allergies, administration problems, etc.	y
Package Item (Container)	Package Item (Container) Quantity	9.6.2.3.3	Needed to identify potential use risks, allergies, administration problems, etc.	y
Package Item (Container)	Material	9.6.2.3.4	Needed to identify potential use risks, allergies, administration problems, etc.	y
Package Item (Container)	Alternate Material	9.6.2.3.5	Needed to identify potential use risks, allergies, administration problems, etc.	y
Device	Device Type	9.6.2.12.2	Medicinal products may be authorized with a device(s), which may be described using the Device class. Devices may be of several types such as separate administration devices, an integral administration device or a part of a Medicinal Product. 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 Pharmaceutical Product.	y

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Table A.1 *(continued)*

Medicinal Product Data (IDMP Data Model)				
Domain	**Item**	**Clause/ sub-clause ISO 11615**	**Comments**	**Referred to ISO/ TS 19256**
Device Material	Substance	9.6.2.13.2	Needed to identify potential use risks, allergies, administration problems, etc.	y
Device Material	Alternate	9.6.2.13.3	Needed to identify potential use risks, allergies, administration problems, etc.	y
Device Material	Allergenic Indicator	9.6.2.13.4	Needed to identify potential use risks, allergies, administration problems, etc.	n

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