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Health informatics — Clinical particulars — Core principles for the harmonization of therapeutic indications terms and identifiers

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Foreword

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Introduction

The need for improved communication between health agencies, hospitals, pharmacies, pharmaceutical companies and the general public about drug safety and efficacy information requires migration from manual text entry and unstructured data that cannot be coded, to a structured data model that is interoperable across the health care ecosystem.[1] The clinical particulars conceptual class of the ISO 11615 Identification of Medicinal Products (IDMP) data model captures information about a medicinal product's indication(s), contraindication(s), undesirable effect(s) and interactions. Within this conceptual class, the Therapeutic Indication subclass captures information about the therapeutic indication for the target disease or condition for which a medicinal product is authorized, under investigation, or utilized in clinical practice. Therapeutic indications can be described using free text as presented in approved product labelling documents, and as terms and codes from standard terminologies. Consistent and accurate coding of therapeutic indication terms is needed to support a variety of processes and is found in various terminological resources and official documents, which include epidemiological and real-world databases, electronic health records and health authority reporting processes. Therefore, a key principle for terminology mapping is that maps are based on specific use cases, and stakeholders who can provide feedback on the form, content and scope of the mapping should be engaged from the beginning of and throughout the mapping exercise.

A universally accepted terminology for coding therapeutic indications does not yet exist and is not feasible due to differing international medicinal product and healthcare regulations and reporting requirements. There is a difference between the therapeutic indication of a specific medicinal product and the diseases, conditions or problems listed in an electronic health record (EHR). While most EHRs will manage a problem list and/or a list of findings and diagnoses and a medication list, it is less frequent that the indication (or indications) for each specific medication is specified for a particular patient.

In medicinal product labels, a range of authorized indications is listed, often with qualifiers (diagnostic, preventive, curative, disease-modifying) or specified patient target groups. Sometimes, diseases or conditions are explicitly listed as not being indications for a specific drug. For example, "drug x" is not indicated in von Willebrand disease, or "drug y" is contraindicated with Haemophilia A. Use of medicinal products outside the authorized indications is considered off-label.

The indication wording, and thus the related coding, is based on a highly complex process over the years-long development of a pharmaceutical product. The relationship between a medicinal product and an indication is based on evidence from clinical trials, which are often comparative in nature (e.g. placebo versus active substance, or active substance A versus active substance B). Evidence synthesis in systematic reviews is often constrained by a Patient/intervention/comparator/outcome (PICO) statement, which results in a clinical recommendation to prefer or not to prefer the use of a particular medicinal product over another intervention for a particular patient (with a specific disease or condition), aiming at a specific outcome. In a regulatory document, this information is often reduced to a statement that "this medicinal product is indicated for ….".

In regulatory documents, the relationship is specified between a particular medicinal product (with specific substance(s), dose form(s), strength(s) and pack sizes), on the one hand and the indication(s), which are often specified in a detailed form. The formulation of this detailed indication often results from strong and intricate debate between the medical department of a pharmaceutical company, medical experts and regulators. The finesse of such formulation is often difficult to catch by any of the existing terminologies. For example, the therapeutic indications for a preparation that is licensed for over-the-counter (OTC) use can be more restrictive than the indications for the same preparation when prescribed by a clinician. For example, treatment of candidiasis in pregnancy using a clotrimazole must be under the direction of a physician; an OTC preparation is not authorized for this indication.

In handbooks of pharmacology and in drug classifications, indications might be formulated at a higher level of aggregation, and substances can be aggregated to drug classes. Hence, relationships between high level indications and drug classes (rather than individual substances) can be described.

Terminologies describing drug classes (e.g. the Anatomical Therapeutic Chemical (ATC) codes, SNOMED CT®[1)], Standard Drug Groups from WHO Drug, etc.) are built using different principles and dimensions (chemical class, anatomical target, therapeutic intent, mechanism of action, molecular target site), and exhibit variable levels of granularity. The same is true for terminologies describing diseases, conditions and signs and symptoms as proxies for indications. Therefore, using different terminologies (and maps between these terminologies) to establish relationships between medicinal products/drug classes and specific indications/high level indications can be bewilderingly complex. Hence, harmonization of terminologies for therapeutic indications should account for both the specific level of regulatory listing of authorized indications for specific medicinal products, as well as the relationship between high level aggregations of indications and substances.

The most common standard terminological resources used to describe and code medicinal product indication terms are the Medical Dictionary for Regulatory Activities (MedDRA®[2)]), SNOMED CT, the International Statistical Classification of Diseases and Related Health Problems (ICD™[3)]) and Medical Subject Headings (MeSH). Mappings between these terminological resources are necessary for documentation and reporting purposes; however, the different hierarchy levels and variation in the number of terms for each resource introduce significant complexity in the creation and maintenance of terminology maps. Map usage is often restricted by the limited availability of centrally provided and approved map sets and contributes to inefficiencies and redundant manual curation by individual stakeholders for specific use cases. Creation and maintenance of comprehensive maps between clinical terminologies to support coding of indication terms will thus liberate workforce effort and enable more efficient processes, responses and comprehensive reporting.

There are safety and maintenance implications when creating and applying maps that directly impact clinical care and decision-making. Therefore, a key principle is the requirement to identify the use case for any map before creating or using mappings. For example, there is an allowable semantic shift during mapping such as for statistics and billing because of aggregation to a group level, whereas in use cases to support clinical care at the individual (patient) level, no semantic shift can be tolerated because of potential safety issues. Thus, mappings between e.g. SNOMED CT and MedDRA are semantic maps of total meaning focused on adverse events. However, additional maps between these two terminologies with use cases focused on therapeutic indications are possibly needed, so a use case will need to be developed and tested against existing maps before deciding on next steps.

This document describes use cases and principles that are applicable for creation, assessment and selection of maps specific to Therapeutic Indications. This document thus refers to and builds on the following documents regarding terminologies and mapping:

— ISO/TR 14872 on core principles for maintenance of identifiers and terms

— ISO/TR 12300 on principles of mapping between terminological systems

— ISO/TS 21564 on terminology resource map quality measures (MapQual)

1) SNOMED CT® is the registered trademark of a product supplied by the International Health Terminology Standards Organization (IHTSDO). This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named.

2) MedDRA is the registered trademark of a product supplied by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) on behalf of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named.

3) ICD™ (International Classification of Diseases) maintained by the World Health Organization is an example of a suitable product available commercially. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of this product.

Health informatics — Clinical particulars — Core principles for the harmonization of therapeutic indications terms and identifiers

1 Scope

The objective of this document is to establish common principles for the creation, assessment, selection and maintenance of maps between terminological resources used to describe and code IDMP therapeutic indications for investigational and medicinal products, medical devices, combination products, biologics and companion diagnostics. Core maintenance principles, such as reliability, reproducibility and quality assurance of the maps for future indication terminology use, are also discussed. The intended audience for this document includes:

a) Global regulators, pharmaceutical/biopharmaceutical companies, Clinical Research Organizations (CROs) and universities/scientific institutes involved in the development, authorization and marketing of medicinal products

b) Implementers of IDMP seeking more information about coding of Therapeutic Indications

c) Healthcare providers

d) Standards Organizations

e) Implementers and software vendors developing and implementing terminology map sets

f) Patients

2 Normative references

There are no normative references in this document.

3 Terms, definitions and abbreviated terms

3.1 Terms and definitions

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

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

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

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

3.1.1
comorbidity
concurrent condition or co-infection described as part of the indication

3.1.2
electronic health record
EHR
repository of information regarding the health status of a subject of care, in computer processable form

[SOURCE: ISO/TR 20514:2005, 2.11, modified]

3.1.3
electronic health record system
EHR system
system for recording, retrieving and manipulating information in electronic health record

3.1.4
individual map
map
cross map
index from one term to another, sometimes using rules that allow translation from one representation to another indicating degree of equivalence

Note 1 to entry: Entry in a map which indicates how to translate from an individual source concept to a target concept. The term map is often used to indicate a table of individual map entries. It is for this reason that the individual and map tables are being differentiated.

Note 2 to entry: The use of this term is often used in ways which are confusing. It is essential to always make it clear whether you are referring to an individual map or a map table (or set).

Note 3 to entry: In SNOMED CT, each individual map is represented as a row or group of rows in a map Reference Set. It links a single map source concept code (e.g. SNOMED CT Concept ID) to one or more codes in a map target (e.g. ICD Code).

Note 4 to entry: A map is often computable and is the outcome of the mapping process.

[SOURCE: ISO/TR 12300:2014, 2.1.9]

3.1.5
maintenance organization
formal and recognized group or legal business entity involved in the direct or indirect provision of terminology services such as the creation, reconciliation, maintenance and distribution of IDMP controlled vocabularies

[SOURCE: ISO/TR 14872:2019, 3.7]

3.1.6
mapping
process of defining a relationship between concepts in one coding system to concepts in another coding system, in accordance with a documented rationale, for a given purpose

Note 1 to entry: Quality mapping will produce a usable map table, be a reproducible and understandable process.

[SOURCE: ISO/TR 12300:2014, 2.1.12]

3.1.7
map set
map table
map reference set
group of individual maps used to convert a range of entries from source to target code system

[SOURCE: ISO/TR 12300:2014, 2.1.11]

3.1.8
real-world data
RWD
data collected in a non-experimental, non-virtual situation

[SOURCE: ISO/TR 21934-1:2021, 3.9]

3.1.9
structured product labelling
SPL
document markup standard that specifies the structure and semantics of the content of authorized published information that accompanies any medicine licensed by a medicines licensing authority

[SOURCE: Reference [10]]

3.1.10
target population
type of patients or consumers for which the indication of a medicinal product is authorized or is under investigation

[SOURCE: ISO 11615:2017, 3.1.81]

3.1.11
term
linguistic representation of a concept

Note 1 to entry: A term can contain symbols and have variants, e.g. different forms of spelling

[SOURCE: ISO/TR 12300:2014, 2.2.8]

3.1.12
terminology
structured, human readable and machine-readable representation of concepts

Note 1 to entry: This includes the relationship of the terminology to the specifications for organizing, communicating and interpreting such a set of concepts.

[SOURCE: ISO/TS 23541-1:2021, 3.1.5, modified — Note added.]

3.1.13
therapeutic indication
definition of the target disease or condition for which the Medicinal Product is authorized or under investigation

[SOURCE: ISO 11615:2017, 3.1.82]

3.1.14
vocabulary
terminological dictionary which contains designations and definitions from one or more domains or subjects

[SOURCE: ISO 1087:2019, 3.7.5, modified]

3.1.15
off-label
prescribing of a medicinal product for an unapproved/unauthorized indication when a health care provider determines that it is medically appropriate for their patient

3.2 Abbreviated terms

ADR	Adverse Drug Reaction
CT	Clinical Trials
ERP	Enterprise resource planning
ICSR	Individual Case Safety Report
PSUR	Periodic Safety Update Reports
PV	Pharmacovigilance
RIM	Regulatory Information Management

4 Terminologies used for the coding of Therapeutic Indications

4.1 General

The following terminologies are commonly used in various jurisdictions and are required by regulatory agencies for coding medicinal product therapeutic indications.

4.2 SNOMED CT

SNOMED CT is a comprehensive, multilingual clinical healthcare terminology, used in more than eighty countries. It is a resource with comprehensive, scientifically validated clinical content that enables consistent representation of clinical content in electronic health records and is mapped to other international standards. SNOMED CT is owned, administered and developed by SNOMED International, a not-for-profit organization.

The primary purpose of SNOMED CT is to encode the meanings that are used in health information and to support the effective clinical recording of data with the aim of improving patient care. SNOMED CT provides the core general terminology for electronic health records. SNOMED CT provides for consistent information interchange and is fundamental to an interoperable electronic health record. It allows a consistent way to index, store, retrieve and aggregate clinical data across specialties and sites of care. SNOMED CT is used to represent Medical Condition in Structured Product Labelling to facilitate informed decision-making and support long-term patient care. Thus, it is the required terminology for the coding of indications reported to, e.g. the U.S. FDA[14].

4.3 MedDRA

The Medical Dictionary for Regulatory Activities (MedDRA), which is owned by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and maintained and distributed by the MedDRA Maintenance and Support Services Organization (MSSO) and the Japanese Maintenance Organization (JMO), is an international standardized terminology used to exchange regulatory information on medical products in both pre- and post-authorization phases. In developing and continuously maintaining MedDRA, the ICH endeavours to provide a single standardized international, multi-lingual medical terminology which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (i.e. from clinical trials to post-marketing surveillance). Furthermore, MedDRA supports ICH electronic communication within the ICH's Electronic Common Technical Document (eCTD) and the E2B Individual Case Safety Report.[15] MedDRA is the required terminology for the coding of indications for EMA[16].

4.4 ICD

The International Statistical Classification of Diseases and Related Health Problems (ICD) is a global standard classification for reporting diseases and health conditions that is developed and maintained by the World Health Organization (WHO). It is used worldwide in systems such as patient registries, insurance claims systems, mortality and morbidity statistics, and patient health records. ICD is the foundation for the identification of health trends and statistics globally, and the international standard for reporting diseases and health conditions. It is the diagnostic classification standard for all clinical and research purposes. ICD defines the universe of diseases, disorders, injuries and other related health conditions, listed in a comprehensive, hierarchical fashion[17].

In addition, the International Classification of Primary Care (ICPC) is accepted within the WHO Family of International Classifications (FIC) as a classification for primary care or general practice. ICPC, 2nd edition (ICPC-2) classifies patient data and clinical activity in the domains of General/Family Practice and primary care; it allows classification of the patient's reason for encounter (RFE), the problems/diagnosis managed, interventions, and the ordering of these data in an episode of care structure[18].

Since the diagnosis and interventions assigned by the healthcare provider and coded with ICD and ICPC are related to the indications of a pharmaceutical product, mappings between disease terms within these classifications to those used for coding the therapeutic indications are useful in the healthcare domain.

4.5 MeSH

The Medical Subject Headings (MeSH) thesaurus is a controlled and hierarchically organized vocabulary produced by the National Library of Medicine (NLM). It is used for indexing, cataloguing, and searching of biomedical and health-related information. The usage of appropriate descriptors from NLM's Medical Subject Headings (MeSH)-controlled vocabulary thesaurus or terms from another vocabulary, such as SNOMED CT, that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus, is required when posting the primary disease or condition being studied in a clinical trial at clinicaltrials.gov[19][20].

5 Use Cases for Coding of Therapeutic Indications

5.1 General

Medicinal product therapeutic indications are initially proposed for clinical trials and can be further detailed and refined for regulatory submissions, and, if successful, will be included in product labels as part of the marketing authorization process. Details of the indications are recorded and exchanged as text and codes, via regulator and pharmaceutical company systems. Once authorized for distribution, the medicinal products enter the supply chain along with the authorized indication information. This information can then be used within the healthcare domain, including during the prescribing, dispensing, administering cycle, with data stored and processed in clinical support systems, medicinal product dictionaries and electronic health records. If adverse reactions to a medication are encountered, indication information can be sent back to regulators and pharmaceutical companies in reports as part of the pharmacovigilance process. Indication data are also be used as part of the reimbursement process and for pharmaco-epidemiological or other statistical analyses. A high-level view of the flow of indication data is shown in Figure 1. This section describes some of the use cases for indications and the need for harmonization of indication-related data.

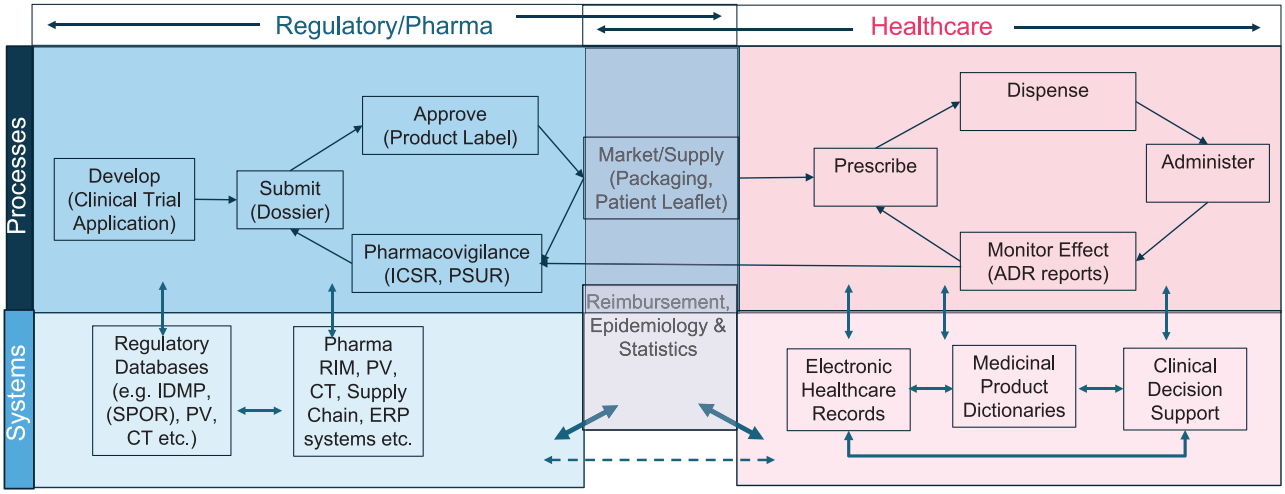

Figure 1 — Processes & Systems Involving Product Indication Data Across Regulatory & Healthcare4

5.2 IDMP data exchange between global regulators and bio/pharmaceutical companies during regulatory processes

5.2.1 Clinical Trials (Medicinal Product Development Lifecycle)

During the development lifecycle of a medicinal product, clinical trials must be conducted to prove the safety and efficacy of the medicine, and indications must be submitted by the pharmaceutical company to the regulator as part of the clinical trial application process (e.g. clinical trial application (CTA) in Europe, Investigational new drug (IND) application for the US). Clinical trials for the same medicinal product are often conducted in multiple countries. Requirements for the description of the indication text and how it is coded vary between regions, so the indication data for the same medicinal product can be recorded differently between regions. The availability of maps between terminologies would facilitate exchange of this data between regions.

5.2.2 Regulatory Submission and Coded Labelling Information

After the successful completion of clinical trials, a regulatory submission for authorization of the medicinal product can be submitted to the regulator. The data submitted will include details of the therapeutic indication(s) to be approved/authorized and to be included in the product label as well as coding of the indication terms.

According to health authority guidance for labelling documents used as the basis for information to health care professionals and patients, therapeutic indications should be clearly stated to reflect in which disease/condition and target population the benefit-risk balance was established to be positive.

Nevertheless, defining the therapeutic indication is quite complex and requires a multidimensional analysis of aspects that influence the benefit/risk assessment with respect to the interpretation of wording in different therapeutic areas. The therapeutic indication is the primary information on the use of a medicine, and it should clearly state the disease/condition and population that a medicine is intended to treat. Examples of such areas of common interest refer to the description of the target population, the severity of the disease, the aim of the treatment (diagnostic indication, prevention, or treatment), the place of the medicinal product in the therapy, the use in combination therapy, as well as the consistency of wording within and across therapeutic areas.

Study data standards describe principles for the exchange of clinical and nonclinical research data between computer systems and provide a framework for the organization of study data. For example, the Clinical Data Interchange Standards Consortium-Study Data Tabulation Model (CDISC-SDTM) provides a standard for organizing and formatting data to streamline processes in collection,