# Drug Ontology for the Public Mexican Health System *

Cecilia Reyes-Peña[1], Mireya Tovar Vidal[1], Maricela Bravo[2], and Regina Motz[3]

[1] Benemérita Universidad Autónoma de Puebla, México
reyesp.cecilia@gmail.com, mtovar@cs.buap.mx
[2] Universidad Autónoma Metropolitana, México mcbc@azc.uam.mx
[3] Universidad de la República, Uruguay rmotz@fing.edu.uy

**Abstract.** With the emergence of the COVID-19 pandemic, a growing need has emerged for well-structured medical knowledge bases that are accessible to physicians, specialists, pharmacists, patients, and the general public. This article describes the process of development and evaluation of an Mexican Drug Ontology[4] with information from the "Basic Table and Catalog of Medicines" published by the Secretary of Public Health. The resulting ontology is composed by 64 classes, 5 object properties, 18 data properties, and has a value ALCQ(D) of "DL Expressivity" measure. The evaluation ontology was carried out in two ways: through the competence of the model and through the review of the quality criteria.

**Keywords:** Drug Ontology, Medical Knowledge Representation, Ontology Design



## 1 Introduction

With the emergence of the COVID-19 pandemic, a growing need has emerged for well-structured medical knowledge bases that are accessible to physicians, specialists, pharmacists, patients, and the general public. The Secretary of Public Health in Mexico, through the General Directorate of Health Information, is responsible for preparing, disseminating and monitoring the regulations for health information management. Among the regulations and standards it establishes, is the Basic Table of Medicines which is an important reference catalog that groups the drugs that can be prescribed. The catalog of medicines contains the keys, description, indication, administration, dose, generalities, adverse effects, contraindications, precautions and risk during pregnancy. Despite the fact that the catalog has clear sections about its content, it lacks a structure that facilitates its management, since queries do not allow filters to be applied to



[4] Mexican Drug Ontology project is available on http://caliope.cs.buap.mx/IngenieriaOntologica/recursos/medicamentos.owl

obtain specific results. In the last decades, the use of ontologies for the representation of drugs and medicines has proliferated [1–3]. According with Gruber [4], an ontology is a formal and explicit specification of a shared conceptualization; that is, a formal abstraction to represent a domain using specific information such as objects, properties and relations by means of a normally hierarchical type structure [5]. Ontologies can be seen as a set of components among which are: instances, properties, concepts and axioms. The main advantages of using ontologies for the medical domain are:

- *Exchange of medical information.* The use of ontologies facilitates the interoperability between different medical information systems.
- *Dynamic search of pharmaceutical information.* The use of ontologies enables the search for information on medications considering different criteria: therapeutic indication, ingredients with a specific mechanism of action, among others.
- *Integration of knowledge.* The use of ontologies facilitates the integration of knowledge and information, making it reusable by various applications and usable for different roles of users, for example: a drug ontology can be used from an application for patients, indicating useful information regarding their treatments; while for a doctor the type of information he needs to consult from a drug ontology focuses on specialized pharmacological and medical aspects; on the other hand, for the pharmaceutical industry the use of a drug ontology has other purposes.

This article describes the design, implementation and evaluation of an ontology for the representation of drugs, with the specific purpose of meeting the regulations and standards established by the Secretary of Public Health in Mexico[5]. For the construction of the ontology, a design methodology was used that reuses methods from some well-known methodologies. The resulting ontology was evaluated using a set of competency questions established in the early design stages. The rest of the paper is organized as follows: Section 2 presents related ontologies that represent information about drugs included in the catalog of medications established by the Secretary of Public Health in Mexico; in Section 3 the methodology used for the construction of the ontology proposed in this work is described; in Section 4 the results obtained are presented and discussed, as well as the evaluation of the resulting ontology; finally Section 5 contains the conclusions of this work and future directions.

## 2 Revision of Related Ontologies and Catalogs

The use of ontologies for the representation and management of information about drugs and medicines is not a recent research topic. Since 2005, there have been initiatives aiming at integrating data and knowledge in the pharmaceutical domain [5, 6]. In this section a comparative analysis of related ontologies and

[5] https://www.gob.mx/salud

catalogs that address the representation and management of drugs and medicines is presented.

**ChEBI**[6] Ontology [7, 8] is a database and ontology of chemical entities of biological interest. ChEBI is a freely available dictionary of molecular entities focused on "small" chemical compounds.

**DINTO** [1] is a Drug Interaction Ontology that represents the mechanisms that can produce drug-drug interactions, including pharmacodynamic and pharmacokinetic mechanisms. The objective of DINTO is to support applications in the pharmacovigilance domain. The concepts included in DINTO are: drug information imported from ChEBI Ontology, the effects of the drugs, the role or bioactivity of a drug, the pharmacokinetic processes that drugs undergo in the body, the pharmacokinetic parameters, the drug related procedures intended to avoid or reduce the effects of the drug-drug interactions, the drug-drug interactions among other important concepts. **DrugBank**[7] [2] is a database that provides bioinformatics and cheminformatics data about drugs and drug targets. DrugBank is similar to a drug encyclopedia, is widely used by the drug industry, medicinal chemists, pharmacists, physicians, students and the general public.

**RxNorm**[8] is a normalized naming system for generic and branding drugs, it supports semantic interoperation between drug terminologies and pharmacy knowledge base systems. RxNorm is produced by the National Library of Medicine. RxNorm provides a set of REST Web services to allow any application to interact with the vocabulary. RxNorm can be downloaded in RDF format to be used as an ontological resource.

**DRON**[9], the Drug Ontology is an ontology of drug products, their ingredients, and their packaging, it reuses contents from RxNorm.

The Systematized Nomenclature of Medicine Clinical Terms (**SNOMED-CT**)[10][3] is a comprehensive, multilingual clinical healthcare terminology, that enables consistent representation of clinical content in electronic records, supports the exchange of health information, and is mapped to other international standards. SNOMED CT was designed with the cooperation of United Sates, United Kingdom, Canada, New Zealand and Australia, and is used across these countries as the recommended clinical reference terminology for clinical information systems.

**Mexican Catalog of Medicines**[11]. In accordance with the regulations of the Secretary of Public Health in Mexico regarding information systems for health electronic registration, it is the obligation of health service providers that use the Electronic Health Data Registration Information System (SIRES), to maintain updated catalogs and comply with their guidelines. The objective of this standard is to guarantee the exchange and interpretation of information

[6] https://www.ebi.ac.uk/chebi/init.do
[7] https://www.drugbank.ca
[8] https://www.nlm.nih.gov/research/umls/rxnorm/index.html
[9] https://bitbucket.org/uamsdbmi/dron/src/master/
[10] http://www.snomed.org/
[11] http://www.dgis.salud.gob.mx/contenidos/intercambio/medicamentos_gobmx.html

from electronic records that allow the correct coding, recording and subsequent exploitation of health information. Regarding medicines, the Secretary of Public Health publishes annually the "Basic Table and Catalog of Medicines" with the purpose of keeping the registry of medicines in prescriptions and for administrative purposes of the supply of medicines. This catalog of medications allows consulting the drug indications and verify interactions with other medications and allergies, as well as adequate doses and administration.

There are several international sources of standardized and ontology-based medical information for drug representation and drug interactions. However, all these references require that medical personnel in Mexico be able to understand the structure and organization of ontologies, for example SNOMED, despite the existence of a Spanish version, it is difficult to access in countries that are not collaboratorsl and requires a high computational performance. Although the fact that the drug catalogs in Mexico follow international standards, the information exchange system established by the Mexican standard has very strict specifications that must be met by health service providers in Mexico. Therefore, it is necessary to develop a specific drug ontology that meets and complies with Mexican regulations. Likewise, this ontology must follow the principles of design and approval of international references.

## 3 Design Methodology

In this section, the proposed design methodology for working with information from catalogs is described (see Fig. 1), as well as some generalities of its application to the catalog of medicines. This methodology is composed of nine stages and reuse some resources from other well-know methodologies as Knowledge Adquisition stage from Methontology [9]; Class, hierarchy and Properties definition from DMTO (*Diabetes Mellitus Treatment Ontology*) [10]; and Evaluation from MODC (*Methodology for Ontology Design and Construction*) [11], these stages are describes in next:

1. *Ontology Purpose Identification.* At this stage the answers to the following question must be visualized: *What task do you want the ontology to perform?*. For the information representation about drugs, it is necessary that the ontology serves as a drugs search engine where it indicates the features of the same.
2. *Ontology Scope Delimitation.* In order to measure the scope of the ontology it is necessary to specify the purpose formally and specifically to determine which entities will be involved within the ontology. So the scope of the ontology is indicated to comply with the representation of the drugs, their doses and route of administration, their classification and the active ingredients involved. To reinforce these first two stages of design, it is necessary to ask competency questions that represent real situations about the handling of information within the ontology.
3. *Available Resources Acquisition.* At this stage, the necessary information and knowledge are collected to represent the entities that have been visualized

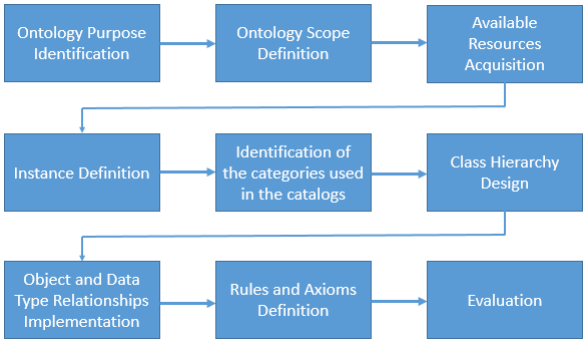
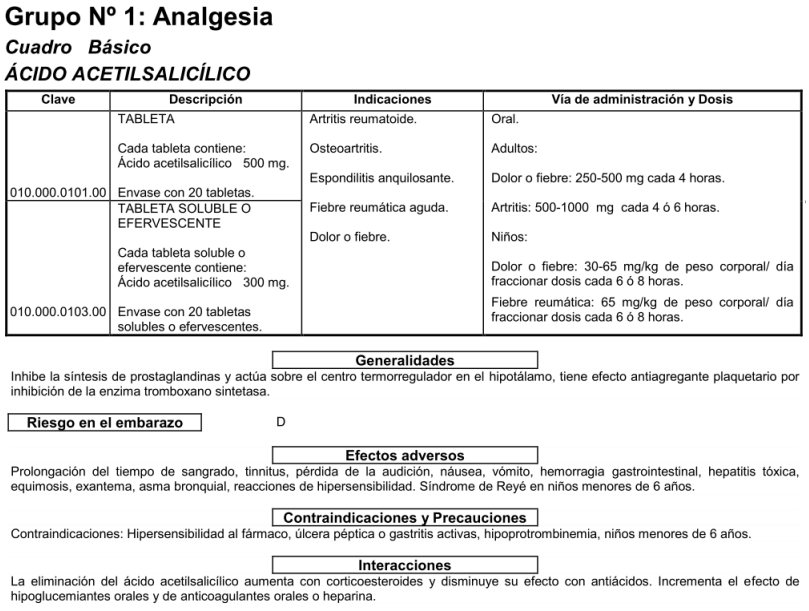



**Fig. 1.** Desing Methodology.

during the scope delimitation, as well as intermediate entities that serve for relating all the elements. To complement the information in the catalog of medicines, information was sought about the classification of pharmaceutical forms and their relationship to routes of administration.

4. *Instance Definition.* The purpose of this stage is defining which elements can be characterized as instances. For this, it is analyzed which elements behave as a minimum unit of information and the relationship they have with others. In Fig. 2 it can be seen that for each presentation of the medicine there is a unique key, so it can be said that the key indicates a minimum unit of information because is associated to well-defined values (others instances) and, has attributes related to data as floats or strings, for example portion of active pharmaceutical ingredients (*Pincipio activo*), portion (*Porción*) and content per container (Contenido por envase). For example 010.000.0101.00 is related to a pharmaceutical form "Tablet" (*Tableta*), a set of doses, one or more routes of administration as "Oral" (*Oral*), and 20 tablets per container (*20 tabletas por envase*) as integer value.
5. *Identification of the categories used in the catalogs:* For working with information from catalogs, it is essential to identify the categories that will be used for the classification and define if they can be used as concepts in the ontology because they group a set of minimum units of information with the same features and formats. In the case of the catalog of medicines, the categories found are:
   - Drug Type (basic table or catalog): indicates the stock availability of drugs in the medical centers.
   - Therapeutic Group: group the drugs according its use in the treatment of the same symptoms or diseases
   - Active Pharmaceutic Ingredient: group the drugs according its active pharmaceutical ingredient. This groups can be associated to different therapeutic groups or drug types.
6. *Class Hierarchy Design.* In this stage, previously identified concepts are considered as well as new ones that help complement the hierarchy. During the



**Grupo Nº 1: Analgesia**

***Cuadro Básico***

***ÁCIDO ACETILSALICÍLICO***

| Clave | Descripción | Indicaciones | Vía de administración y Dosis |
|---|---|---|---|
| 010.000.0101.00 | TABLETA<br><br>Cada tableta contiene:<br>Ácido acetilsalicílico 500 mg.<br><br>Envase con 20 tabletas. | Artritis reumatoide.<br><br>Osteoartritis.<br><br>Espondilitis anquilosante.<br><br>Fiebre reumática aguda.<br><br>Dolor o fiebre. | Oral.<br><br>Adultos:<br><br>Dolor o fiebre: 250-500 mg cada 4 horas.<br><br>Artritis: 500-1000 mg cada 4 ó 6 horas.<br><br>Niños:<br><br>Dolor o fiebre: 30-65 mg/kg de peso corporal/ día fraccionar dosis cada 6 ó 8 horas.<br><br>Fiebre reumática: 65 mg/kg de peso corporal/ día fraccionar dosis cada 6 ó 8 horas. |
| 010.000.0103.00 | TABLETA SOLUBLE O EFERVESCENTE<br><br>Cada tableta soluble o efervescente contiene:<br>Ácido acetilsalicílico 300 mg.<br><br>Envase con 20 tabletas solubles o efervescentes. | | |

**Generalidades**

Inhibe la síntesis de prostaglandinas y actúa sobre el centro termorregulador en el hipotálamo, tiene efecto antiagregante plaquetario por inhibición de la enzima tromboxano sintetasa.

**Riesgo en el embarazo** D

**Efectos adversos**

Prolongación del tiempo de sangrado, tinnitus, pérdida de la audición, náusea, vómito, hemorragia gastrointestinal, hepatitis tóxica, equimosis, exantema, asma bronquial, reacciones de hipersensibilidad. Síndrome de Reyé en niños menores de 6 años.

**Contraindicaciones y Precauciones**

Contraindicaciones: Hipersensibilidad al fármaco, úlcera péptica o gastritis activas, hipoprotrombinemia, niños menores de 6 años.

**Interacciones**

La eliminación del ácido acetilsalicílico aumenta con corticoesteroides y disminuye su efecto con antiácidos. Incrementa el efecto de hipoglucemiantes orales y de anticoagulantes orales o heparina.

**Fig. 2.** Instance Definition in the catalog of medicines[12]

class identification stage, classes that do not belong to the same taxonomy were identified, so it is necessary to integrate the relevant concepts obtained in stage number 2. The main taxonomies identified include the concepts: dose, active pharmaceutical ingredient, therapeutic group, drug, pharmaceutical form, route of administration, and risk of pregnancy. The Table 1 indicates part of the class hierarchy.

7. *Object and Data Type Relationships Implementation.* Once the objects have been identified, it is possible to define which elements should be represented as object relationships or data type relationships. The implemented object relationships are about with the drug definition; i.e. for each instance belonging to Catalog or Basic Table Drug classes, it is necessary being associated to some doses, risk of pregnancy, active pharmaceutical ingredient, pharmaceutical form, and route of administration. On the other hand, in data relationships, there are some classes in which their individuals contains information such as names, quantities and descriptions that requires to be represented by data variables (see Table 2).
8. *Rules and Axioms Definition.* This stage aims to identify if there are patterns within the information that are constantly repeated and can be generalized. The found pattern is about rule definition, and indicates the cardinality of the object properties in the Drug class definition.

[12] http://www.dgis.salud.gob.mx/contenidos/intercambio/medicamentos_gobmx.html

9. *Evaluation.* The evaluation is based on applying the consistency criterion by a reasoner agent, as well as, the answer to previously established competence questions by means of the ontology query language.

## 4 Mexican Drug Ontology

Applying the design methodology described in the section 3, we obtain the Mexican Drug Ontology depicted in Fig. 3, it is composed by 64 classes (part of hierarchy classes are described in the Table 1), 5 object properties (see Table 2), 18 data properties, and a value ALCQ(D) of "DL Expressivity" measure. The Medicamento (Drug) class and Grupo_Terapeutico (Therapeutic Group) class are only classes that share individuals; while the rest of classes are disjointed.

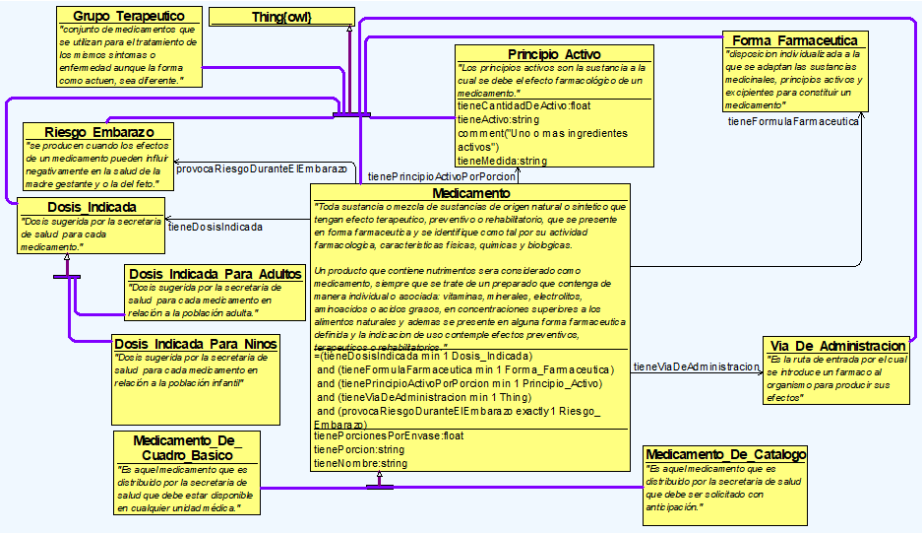



**Fig. 3.** Drug Ontology Diagram.

## 5 Evaluation of Competency

The evaluation of the ontology was carried out in two ways: through the competence of the model and through the review of the quality criteria (consistency and coverage). This section first introduces the translation of competency questions to SPARQL queries and presents the results of those questions. The questions are presented in English (see Table 3), but the ontology model is actually implemented in Spanish to facilitate its use by health experts in Mexico; also are translated to two query language, SPARQL to verify the fulfillment of the purpose and DL-Query because is supported by the use of reasoner agent (HermiT

**Table 1.** Drug Ontology Main Classes Description.

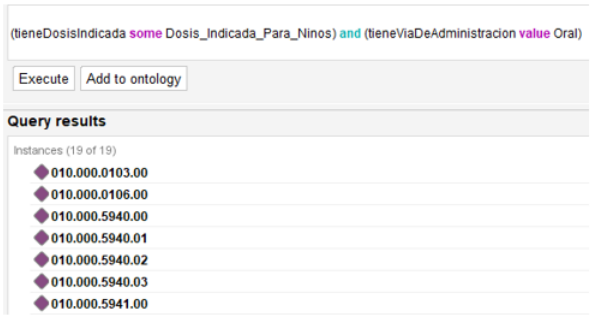
| *Class* | *Superclass Of* |
|---|---|
| Dosis_Indicada (Indicated Dose) | Dosis_Indicada_Para_Niños (Children Dose)<br>Dosis_Indicada_Para_Adultos (Adult Dose) |
| Medicamento (Drug) | Medicamento_De_Catalogo (Catalog Drug)<br>Medicamento_De_Cuadro_Basico (Basic Table Drug) |
| Principio_Activo (Active Pharmaceutical Ingredient) | |
| Grupo_Terapeutico (Therapeutic Group) | Analgesia (Analgesia)<br>Anestesia (Anesthesia)<br>Cardiologia (Cardiology) |
| Vía_De_Adminsitración (Route of Administration) | Cutanea (Cutaneous)<br>Via_Enteral (Enteral Route)<br>Via_Parental (Parental Route) |
| Forma_Farmaceutica (Pharmaceutical Form) | Forma_Solida (Solid Form)<br>Forma_Liquida (Liquid Form) |

**Table 2.** Drug Ontology Object Properties.

| *Object Property* | *Domain* | *Range* | *Cardinality* |
|---|---|---|---|
| provocaRiesgoDuranteElEmbarazo (causesRiskInPregnancy) | Medicamento (Drug) | Riesgo_Embarazo (Pregnancy Risk) | 1:1 |
| tieneDosisIndicada (hasIndicatedDose) | Medicamento (Drug) | Dosis_Indicada (Indicated Dose) | 1:$N$ |
| tieneFormaFarmaceutica (hasPharmaceuticalForm) | Medicamento (Drug) | Forma_Farmaceutica (Pharmaceutical Form) | 1:$N$ |
| tienePrincipioActivo (hasActivePharmaceuticalIngredient) | Medicamento (Drug) | Principio_Activo (Active Pharmaceutical Ingredient) | 1:$N$ |
| tieneViaDeAdministracion (hasRouteOfAdministration) | Medicamento (Drug) | Via_De_Administracion (Route of Administration) | 1:$N$ |

[12] version 1.4.3.456). The answers of some competency questions are shown in the Fig. 4, 5, and 6. About the quality criteria, the ontology was evaluated by consistency and coverage. Consistency, it indicates that there are not contradictions on the ontology [13], and it is checked by an agent reasoner; while coverage, is about how well the ontology represents the domain [14], the ontology, by satisfactorily answering all the questions, indicates that the coverage is complete, since the competency questions contain the relevant terms of the domain established in the early stages of the design methodology.

a)




b)

***Acetylsalicylic Acid***

| ID | Description | Route of administration and Doses |
|---|---|---|
| 010.000.0101.00 | Tablet<br><br>Each tablet contains:<br>Acetylsalicylic Acid 500 mg<br><br>20 tablets per container | Oral<br><br>Adults:<br>Pain or fever: 250-500 mg every 4 hours<br>Arthritis: 500-1000 mg every 4 or 6 hours<br><br>Children:<br>Pain or fever: 30-60 mg/kg body weight per day dividing dose every 6 or 8 hours |
| 010.000.0103.00 | Soluble tablet or effervescent tablet<br><br>Each soluble tablet or effervescent tablet contains:<br>Acetylsalicylic Acid 300 mg<br><br>20 soluble tablets or effervescent tablets per container | |

**Fig. 4.** a) Answer and b) Verification of Results of the Competency Question Number 1.

## 6 Conclusions and Future Work

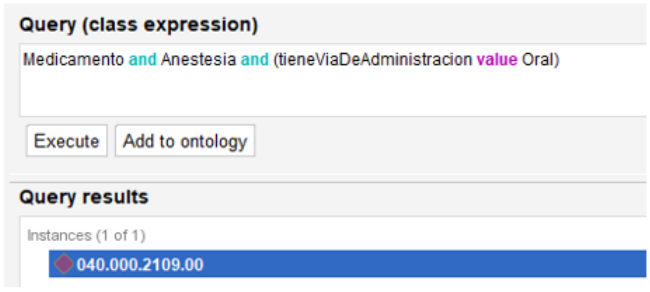
This work describes the process of development and evaluation of Mexican Drug Ontology with information from "Basic Table and Catalog of Medicines" used by the Secretary of Health in Mexico, through a design methodology that starts from the information from catalogs. The ontology obtained was evaluated by answering the competence questions posed in the initial stages of the methodology in order to guarantee the fulfillment of the task for which it was designed through the answers.

For future work, the Mexican Drug Ontology will be enriched with non-ontological resources about generalities, interactions, contraindications and cau-

**Table 3.** Competency Questions.

| **Competency Question** | **DL-Query** | **SPARQL** |
|---|---|---|
| What are the medications for children that are administered orally? | (tieneDosisIndicada some Dosis_Indicada_Para_Ninos) and (tieneViaDeAdministracion value Oral) | PREFIX medicamentos:<http://www.owlontologies.com/Medicamentos#> SELECT ?med ?nombre ?dosis ?cant ?ind WHERE {?med medicamentos:tieneNombre ?nombre. ?med medicamentos:tieneDosisIndicada ?dosis. ?dosis a medicamentos:Dosis_Indicada_Para_Ninos. ?dosis medicamentos:tieneCantidadMaxima ?cant. ?dosis medicamentos:tieneIndicacionAdicional ?ind.} |
| Which drugs are given orally and belong to the anesthesia therapy group? | Medicamento and Anestesia and (tieneViaDeAdministracion value Oral) | PREFIX medicamentos:<http://www.owlontologies.com/Medicamentos#> SELECT ?med ?nombre WHERE { ?med medicamentos:tieneNombre ?nombre. ?med a medicamentos:Anestesia. ?med medicamentos:tieneViaDeAdministracion medicamentos:Oral.} |
| What are the drugs that have an amount of active ingrediente per serving greater than 50 mg? | (Medicamento_De_Catalogo or Medicamento_De_Cuadro_Basico) and (tienePrincipioActivoPorPorcion some ((tieneMedida value "MG") and (tieneCantidadDeActivo some xsd:float[>=50f]))) | PREFIX medicamentos:<http://www.owlontologies.com/Medicamentos#> SELECT DISTINCT ?med ?nombre ?principio ?medida ?cant WHERE {?med medicamentos:tieneNombre ?nombre. ?med medicamentos:tienePrincipioActivoPorPorcion ?principio. ?principio medicamentos:tieneMedida ?medida. ?principio medicamentos:tieneCantidadDeActivo ?cant. FILTER (str(?medida) = "MG"). FILTER (?cant >= 50).} |
| What drugs that are administered orally are associated with of risk of pregnancy D? | (tieneViaDeAdministracion value Oral) and (provocaRiesgoDuranteElEmbarazo value Riesgo_Embarazo_D) | PREFIX medicamentos:<http://www.owlontologies.com/Medicamentos#> SELECT DISTINCT ?med ?nombre ?riesgo ?desc WHERE {?med medicamentos:tieneNombre ?nombre. ?med medicamentos:provocaRiesgoDuranteElEmbarazo ?riesgo. ?riesgo medicamentos:tieneDescripcion ?desc.} |
| What are the recommended doses for children of medicines that have ibuprofen as an active ingredient? | (inverse tieneDosisIndicada some (tienePrincipioActivoPorPorcion some (tieneActivo value "IBUPROFENO"))) and Dosis_Indicada_Para_Ninos | PREFIX medicamentos:<http://www.owlontologies.com/Medicamentos#> SELECT DISTINCT ?med ?nombre ?dosis ?principio ?activo WHERE {?med medicamentos:tieneNombre ?nombre . ?med medicamentos:tieneDosisIndicada ?dosis. ?dosis a medicamentos:Dosis_Indicada_Para_Ninos. ?med medicamentos:tienePrincipioActivoPorPorcion ?principio. ?principio medicamentos:tieneActivo ?activo. FILTER (str(?activo)= "IBUPROFENO").} |

a)

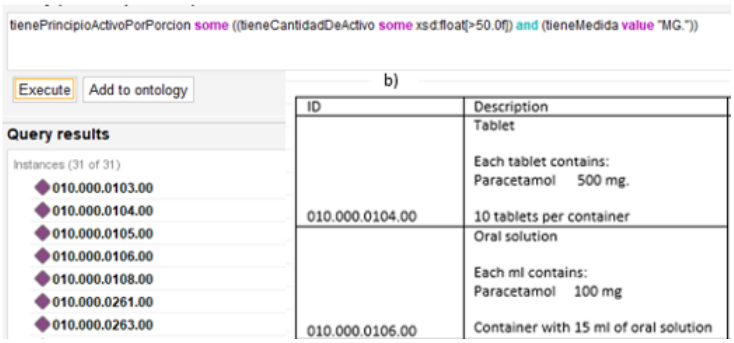



b)

| ID | Description | Route of administration and Doses |
|---|---|---|
| 040.000.2109.00 | Tablet<br><br>Each tablet contains:<br>Midazolam maleate equivalent to 7.5 mg of midazolam<br><br>30 tablets per container | Oral<br><br>Adults:<br><br>7.5 to 15 mg, before sleep |

**Fig. 5.** Answer and Verification of Results of the Competency Question Number 2.

a)




b)

| ID | Description |
|---|---|
| 010.000.0104.00 | Tablet<br><br>Each tablet contains:<br>Paracetamol 500 mg.<br><br>10 tablets per container |
| 010.000.0106.00 | Oral solution<br><br>Each ml contains:<br>Paracetamol 100 mg<br><br>Container with 15 ml of oral solution |

**Fig. 6.** Answer and Verification of Results of the Competency Question Number 3.

tions, and secondary effects of the drugs in order to expand the model coverage; Also, the ontology will integrate into another ontology that represents an active pharmaceutical ingredient classification standard so that it can be used by international users. Finally, the ontology will be validated by experts in order to determine a set of requirements related to application ontology, which is a web drug searcher by SPARQL queries.

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## References


1. M. Herrero-Zazo, J. Hastings, I. Segura-Bedmar, S. Croset, P. Martinez, and C. Steinbeck, "An ontology for drug-drug interactions," *CEUR Workshop Proceedings*, vol. 1114, 01 2014.
2. D. S. Wishart, Y. D. Feunang, A. C. Guo, E. J. Lo, A. Marcu, J. R. Grant, T. Sajed, D. Johnson, C. Li, Z. Sayeeda, *et al.*, "Drugbank 5.0: a major update to the drugbank database for 2018," *Nucleic acids research*, vol. 46, no. D1, pp. D1074–D1082, 2018.
3. K. Donnelly, "Snomed-ct: The advanced terminology and coding system for ehealth," *Studies in health technology and informatics*, vol. 121, p. 279, 2006.
4. T. R. Gruber *et al.*, "A translation approach to portable ontology specifications," *Knowledge acquisition*, vol. 5, no. 2, pp. 199–220, 1993.
5. S. P. Gardner, "Ontologies in drug discovery," *Drug Discovery Today: Technologies*, vol. 2, no. 3, pp. 235–240, 2005.
6. S. P. Gardner, "Ontologies and semantic data integration," *Drug discovery today*, vol. 10, no. 14, pp. 1001–1007, 2005.
7. J. Hastings, P. de Matos, A. Dekker, M. Ennis, B. Harsha, N. Kale, V. Muthukrishnan, G. Owen, S. Turner, M. Williams, *et al.*, "The chebi reference database and ontology for biologically relevant chemistry: enhancements for 2013," *Nucleic acids research*, vol. 41, no. D1, pp. D456–D463, 2012.
8. J. Hastings, G. Owen, A. Dekker, M. Ennis, N. Kale, V. Muthukrishnan, S. Turner, N. Swainston, P. Mendes, and C. Steinbeck, "Chebi in 2016: Improved services and an expanding collection of metabolites," *Nucleic acids research*, vol. 44, no. D1, pp. D1214–D1219, 2016.
9. M. Fernández-López, A. Gómez-Pérez, and N. Juristo, "Methontology: from ontological art towards ontological engineering," *Engineering Workshop on Ontological Engineering (AAAI97)*, 1997.
10. S. El-Sappagh, D. Kwak, F. Ali, and K.-S. Kwak, "Dmto: a realistic ontology for standard diabetes mellitus treatment," *Journal of biomedical semantics*, vol. 9, no. 1, p. 8, 2018.
11. M. Bravo, L. F. Hoyos Reyes, and J. A. Reyes-Ortiz, "Methodology for ontology design and construction," *Contaduría y Administración*, vol. 64, no. 4, 2019.
12. R. Shearer, B. Motik, and I. Horrocks, "Hermit: A highly-efficient owl reasoner.," in *Owled*, vol. 432, p. 91, 2008.
13. J. Morbach, A. Wiesner, and W. Marquardt, "Ontocape—a (re) usable ontology for computer-aided process engineering," *Computers & Chemical Engineering*, vol. 33, no. 10, pp. 1546–1556, 2009.
14. H. Hlomani and D. Stacey, "Approaches, methods, metrics, measures, and subjectivity in ontology evaluation: A survey," *Semantic Web Journal*, vol. 1, no. 5, pp. 1–11, 2014.