A Comprehensive and Scientifically Accurate Pharmaceutical Knowledge Ontology based on Multi-source Data

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Abstract: Recently, knowledge graphs have been applied by large pharmaceutical companies to improve the efficiency of drug discovery. Specifically, knowledge graphs based on drug ontology have been used for many purposes. Current drug ontologies have different scopes, but mainly focus on the description of basic drug information. Here, we describe a comprehensive pharmaceutical knowledge ontology, including information of active ingredients, indications, inactive ingredients, drugs, clinical trials, organs and tissues, literature, patents, targets, therapeutics, and biomolecules. Using multiple data sources, we apply a seven-step method for ontology modelling using Protégé software. A comprehensive pharmaceutical knowledge ontology model is established to complete the knowledge representation of drug information. By means of ontology theory, the pharmaceutical knowledge is modelled, standardized and networked, so as to clarify the knowledge structure and quickly acquire related knowledge and logical relationships. In the future, knowledge graphs based on this ontology could be helpful to deal with the dispersion, heterogeneity, redundancy and fragmentation of medical big data, to share and integrate pharmaceutical data, and to provide a set of solutions for the networked development of pharmaceutical knowledge.

1 INTRODUCTION

Drug discovery is a complex process with a development cycle of 10-15 years and an average research and development cost of $2.6 billion (Wouters et al., 2020). In recent years, knowledge graphs have been applied by large pharmaceutical companies to improve the efficiency of drug discovery; for example, AstraZeneca is applying BenevolentAI for drug development for chronic kidney disease (CKD) and idiopathic pulmonary fibrosis (IPF), showing the application and development prospect of knowledge graph technology in such tasks. Knowledge graphs based on drug ontology have been used for many purposes, such as comparative effectiveness research (Hanna et al., 2013), adverse drug reactions (Cai et al., 2015; Hur et al., 2018), and clinical data warehousing (Podchiyska et al., 2010). RxNorm was created to address a lack of standardization of drug names and to make them interoperable by integrating drug terms into a reference system (Nelson et al., 2020). RxNorm currently integrates terminology information from most drug knowledge base vendors (e.g., First DataBank, Multum, Micromedex, Gold Standard), as well as drug ingredients from standard terminology

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(e.g., SNOMED CT, MeSH). RxNorm focuses on drug names and codes; however, clinical information and administrative information are out of scope (Bodenreider et al., 2018). Based on the RxNorm drug terminology and the Chemical Entities of Biological Interest ontology (ChEBI), Hanna et al. (2013) built Drug Ontology (DrOn), a modular, extensible body of drugs, ingredients, and biological activities, originally created to enable comparative effectiveness. OCRx is a Canadian drug ontology system built to provide a normalized and standardized description of drugs authorized to be marketed in Canada. OCRx is focused on clinical drug description (i.e., substance, strength, route of administration, pharmaceutical form) (Nikiema et al., 2021). Sharp (2017) created a drug-indication database (DID), a database of structured drug-indication relations intended to facilitate building practical, comprehensive, and integrated drug ontologies.

Current drug ontologies have different scopes, for example, RxNorm and OCRx describe drugs available in the U.S. and Canada, respectively, and mainly focusing on the description of basic drug information. However, the current lack of comprehensive pharmaceutical knowledge ontology covering drug targets, adverse drug reactions, clinical trials, patents, literature and other classes limits the application of drug ontology.

In this paper, we describe a comprehensive drug knowledge ontology, including active ingredients, indications, inactive ingredients, drugs, clinical trials, organ and tissue targets, literature, patents, therapeutics, and biomolecules. We use ontology theory to model, standardize and network pharmaceutical knowledge, which is convenient for clarifying the knowledge structure, quickly obtaining relevant knowledge and logical relationships, and helping to deal with the dispersion, heterogeneity, redundancy and fragmentation of medical big data. The purpose of this ontology is to aid the sharing and interaction of pharmacy data and provides a set of solutions for the development of pharmacy knowledge network.

2 METHODS

Ontology theory has been widely used for knowledge presentation; common building methods are seven-step method, Skeletal Methodology, IDEF5, and METHONTOLOGY. Based on a comprehensive analysis of the existing approaches to the construction of drug ontology, we applied a seven-step method developed by Stanford University School of Medicine to construct a pharmaceutical knowledge ontology using Protégé software (Musen et al., 2015).

The construction process of pharmaceutical knowledge ontology is shown in Figure 1. Ontology modelling is based on hierarchical and structured biomedical thesauri such as MeSH and ICD, combined with authoritative data sources such as Drugbank and PubChem, to develop a standardized glossary and glossary of pharmaceutical ontologies to unify and integrate multi-source data and facilitate inter-term relationships. The next step is to refer to the results of the analysis of the web site data, record the conceptual level, format, and data type of the entity in the data source for the pharmacy terms/entities identified in the data. For relevant text of an entity that cannot be directly identified, entity name recognition is carried out through the biological named entity recognition tool and the standardized terminology. After the entity is identified, the relationship between entities is recognized by the machine learning method, summarizing the properties and inter-entity relations of the new entities, and classifying the entities to determine the hierarchical structure of the data. Finally, experts examine and verify the entities, properties and relationship information, and then incorporate newly identified entities and relationships into existing models. The final realization uses the standard terminology of ontology, annotates the entity, and completes the knowledge representation.

2.1 Data Sources

Data sources are the basis of pharmaceutical knowledge ontology modelling. Data acquired from multiple databases and platforms is listed in Table 1.

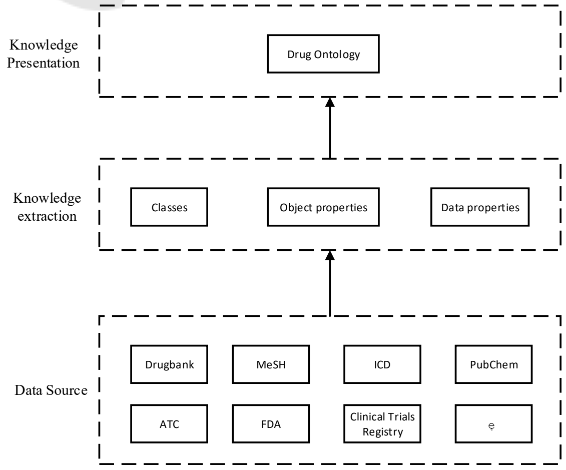


Figure 1: Construction process of pharmaceutical knowledge ontology.

The following section provides an overview of the multiple data sources used here.

Medical Subject Headings (MeSH) is an authoritative thesaurus compiled by The United States National Library of Medicine (NLM). MeSH is a standardized and expandable dynamic thesaurus of medical concepts and is used for indexing, cataloging, and searching of biomedical and health-related information. It includes the subject headings appearing in MEDLINE/PubMed, the NLM Catalog, and other NLM databases.

The International Classification of Diseases and Related Health Problems (ICD) is a tool for recording, reporting, and grouping conditions and factors that influence health. It contains categories for diseases, health-related conditions, and external causes of illness or death. The ICD is used to translate disease diagnoses into an alphanumeric code, which allows data storage, retrieval, and analysis.

DrugBank is a comprehensive, free-to-access online database containing information on drugs and drug targets (Wishart et al., 2006). The latest release (version 5.1.8, released 2021-01-03) contains 14,589 entries. 5,263 non-redundant protein (i.e., enzyme, transporter, carrier) sequences are linked to these entries. Each entry contains more than 200 data fields with half of the information devoted to drug/chemical data and the other half devoted to drug target or protein data (Wishart et al., 2018).

PubChem is an open chemistry database by the National Institutes of Health (NIH). It contains both small and larger molecules such as nucleotides, carbohydrates, lipids, peptides, and chemically modified macromolecules. PubChem collects information on chemical structures, identifiers, chemical and physical properties, biological activities, patents, health, safety, and toxicity (Kim et al., 2019).

The Anatomical Therapeutic Chemical (ATC) system is the official drug classification of the World Health Organization (WHO). In the ATC system, active substances are classified in a five-level hierarchy.

China Medical Information Platform is an expert-certified information platform for all types of medical information, including disease and symptom queries, drug introduction, drug instructions, hospital queries, and expert queries.

Clinical Pathways were released by the National Health Commission of the People's Republic of China and contains clinical pathways for 224 disease species in 19 disciplines.

U.S. Clinical Trials is a web-based resource maintained by the NLM and NIH. Each record presents summary information about a study protocol and includes information such as disease or condition, intervention, title, description, and study design. The European Union Clinical Trials Register, Chinese Clinical Trial Registry, China Drug Trials, and WHO International Clinical Trials Registry Platform are similar platforms for the registration of clinical trials.

Table 1: Data sources for ontology modelling.

No.	Data Source	URL of Data Source
1	MeSH	https://www.nlm.nih.gov/databases/download/mesh.html
2	ICD-10	https://icd.who.int/browse10/2019/en
3	ICD-11	https://icd.who.int/browse11/l-m/en
4	DrugBank	https://go.drugbank.com/releases/latest
5	PubChem	https://ftp.ncbi.nlm.nih.gov/pubchem/
6	ATC	https://www.whocc.no/atc_ddd_index/
7	China Medical Information Platform	https://www.dayi.org.cn/
8	Clinical Pathways	http://www.nhc.gov.cn/yzygj/
9	US Clinical Trials	https://www.clinicaltrials.gov/ct2/resources/download
10	European Union Clinical Trials Register	https://www.clinicaltrialsregister.eu/ctr-search/search
11	Chinese Clinical Trial Registry	http://www.chictr.org.cn/searchproj.aspx
12	China Drug Trials	http://www.chinadrugtrials.org.cn/
13	International Clinical Trials Registry Platform	https://trialsearch.who.int/
14	FDA Orange Book	https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm
15	Japanese Orange Book	http://www.jp-orangebook.gr.jp/cgi-bin/search_h/search_e.cgi
16	List of Reference Preparations for Generic Drugs (China)	https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/index.html
17	FDA Inactive Ingredients Database	https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download

The publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book) identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act and related patent and exclusivity information. It contains information regarding active ingredient, proprietary name, applicant, application number, dosage form, route of administration or patent number of approved drug products. The Japanese Orange Book is a similar guide published in Japan.

The List of Reference Preparations for Generic Drugs published by the National Medical Products Administration of China is the basis for registration application and consistency evaluation of generic drugs in China. Inquiry contents include generic name, English name or trade name, license holder, specifications, dosage form, remarks, sources and other information.

The Inactive Ingredients Database provides information on inactive ingredients present for FDA-approved drug products. It contains information on route of administration, dosage and dosage form, CAS Number, UNII, potency amount and potency unit on inactive ingredients.

2.2 Modelling of Classes

Based on hierarchical and structured biomedical lexicon such as MeSH and ICD, combined with relevant terms from authoritative data sources such as Drugbank and PubChem, we developed a standardized glossary and term annotations using a pharmaceutical knowledge ontology.

13 concepts were extracted as first-level semantic types (classes), named Drug, Indication, Therapy, ClinicalTrial, Product, Food, InactiveIngredient, Patent, Reference, Organ, Targets, Biomolecule and Organism. Each class was extracted from one or more of the corresponding data sources, shown in Table 2 (data source numbers are from Table 1).

Table 2: Extraction of the classes from data sources.

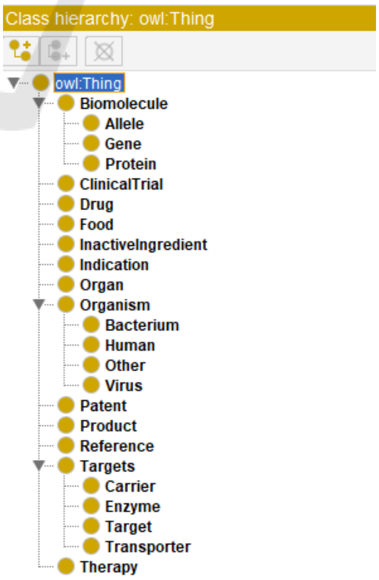
No.	Class	Data Source No.
1	Drug	1, 4, 5, 6
2	Indication	1, 2, 3, 4, 7
3	Therapy	1, 8
4	ClinicalTrial	9, 10, 11, 12, 13
5	Product	4, 14, 15, 16
6	InactiveIngredient	17
7	Food	4
8	Patent	4
9	Reference	4
10	Organ	7
11	Targets	4
12	Biomolecule	4
13	Organism	1, 4

2.3 Modelling of Object Properties and Data Properties

Sentence and word segmentation were executed on data collected from multi-source heterogeneous sources to generate pre-processed data. Name information of a plurality of entities defined in the concept layer was extracted from the pre-processed data by the named entity recognition, and the name information was contained in the entity statement of the data. The relationship extraction method based on the depth neural network identifies the relationships between different entities defined in the concept layer from the entity statements.

Specifically, with words as the basic units, the entity statements were characterized by word and position vectors, and the vector splicing results corresponding to the entity statements are obtained. These results were input into a deep neural network, and the relationship classification were distinguished, which comprises an attention model, a fully connected neural network layer and a convolutional neural network model. Focused on the deep neural network, the entity sentences with relationships are identified. Syntax was analyzed, and related words were extracted according to the dependency relation among entities, thus obtaining the cause-effect tuples, which include a relationship between different entities.

The property information of each entity was modelled as data properties, and the relationship between the entities is modelled as object properties.



Class hierarchy: owl:Thing

- owl:Thing
  - Biomolecule
    - Allele
    - Gene
    - Protein
  - ClinicalTrial
  - Drug
  - Food
  - InactiveIngredient
  - Indication
  - Organ
  - Organism
    - Bacterium
    - Human
    - Other
    - Virus
  - Patent
  - Product
  - Reference
  - Targets
    - Carrier
    - Enzyme
    - Target
    - Transporter
  - Therapy

Figure 2: Classes of pharmaceutical knowledge ontology.

3 RESULTS

3.1 Classes

After data cleansing and parsing, with the help of experts, we extracted 13 classes from multiple data source species. These classes are listed in Table 2. With further analysis of the data sources, a total of 11 second-level semantic types (i.e., subclasses), were identified in three classes: Targets, Biomolecules and Organism. Finally, the classes and subclasses were built in Protégé, shown as Figure 2.

3.2 Object Properties and Data Properties

Using analysis of data sources, and verification by experts, 11 object properties and 5 subproperties, as well as 39 data properties and 43 subproperties were determined. The detailed object properties and data properties are listed in Tables 3 and 4, respectively.

Object properties are used to describe the relationships between pharmaceutical knowledge entities, each of which defines the subject and scope of application, as shown in Table 3. Drugs, for example, includes the following relationships: drug-literature-citation, drug-clinical trial-effective effect, drug-indication-active effect, drug-drug-interaction, drug-drug-active ingredient, drug-target-effective effect, drug-biomolecular-benign/adverse effect. In addition, each entity includes the same basic properties: hasName, hasDescription, hasEntityClass, hasSynonyms, hasSource, and hasID.

3.3 Model of the Pharmaceutical Knowledge Ontology

As with the classes, object properties and data properties were determined. The data level, scope, type and definition of each type of entity were formulated to achieve a structured, standardized and normalized description of pharmaceutical entities. The ontology model of pharmaceutical knowledge based on Protégé is shown in Figure 3. Relationships between classes are represented by lines with arrows.

At this point, the basic architecture of the ontology is complete, and entities can be added into the ontology as individuals in Protégé manually, or by using data association between multi-source data and ontology model by means of technology.

Table 3: Object properties and subproperties defining the relationships between pharmaceutical entities.

No.	Object property	Subproperty	Domains	Ranges
1	isAIRelationOn			
2	isCitationOf		Patent Reference	Biomolecule ClinicalTrial Drug InactiveIngredient Indication Product Targets
3	isClinicalTrialOn		ClinicalTrial	Drug Indication Product Therapy
4	isDrugActionOn		Drug Product	Indication Therapy
5	isIndicationLocationIn		Indication	Organ
6	isInteractionWith		Drug	Biomolecule Drug
7	isProductIngredientOf	isProductActiveIngredientOf	Drug	Product
		isProductInactiveIngredientOf	Inactive Ingredient	Product
8	isProductAdverseReaction On		Product	ClinicalTrial Indication Therapy
9	isProductReferenceOf		Product	Product
10	isTherapyOn		Therapy	Indication
11	isTargetActionsOn	isTargetActionOn	Drug	Targets
		isTargetOrganismOf	Drug	Organ
		isTargetPharmacologicalActionOn	Drug	Targets

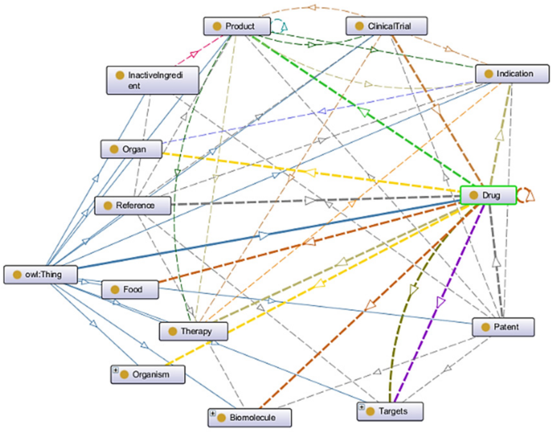


Figure 3: Model of the pharmaceutical knowledge ontology.

4 DISCUSSION

Pharmaceutical knowledge ontology helps describe and organize pharmaceutical information, and forms a network of pharmaceutical knowledge about pharmaceutical terms and the relationships between them. Combined with computer technology, pharmaceutical-related data can be shared and exchanged in the network. Through the standardization of terms in pharmaceutical knowledge ontology, metadata from different data sets can be unified to eliminate heterogeneity and realize the integration of pharmaceutical data. At the same time, through the relationship between the standardized terms in the ontology, metadata in the data set can also construct the semantic association and realize the index of the metadata content, in order to achieve deeper level conformity, annotation, analysis and mining of the original data.

Knowledge base is a structured, operable and organized cluster in knowledge engineering. With the common demand of solving problems in a particular domain, it is a set of interrelated knowledge slices that are stored, organized, managed, and used in computer memory in a certain knowledge representation manner.

Ontology provides a basic architecture for the establishment of knowledge base. It describes the domain with a set of concepts and terms, and obtains the essential conceptual structure of the domain. Ontology constitutes the core of the domain knowledge representation system. The knowledge base uses these terms to represent information. Ontology-based knowledge base can help users to acquire knowledge most suitable to their needs through these relationships and properties, thus avoiding irrelevant information during knowledge acquisition. Pharmaceutical knowledge ontology can help realize the standardized description and structured organization of pharmaceutical knowledge and information, promote efficient use of pharmaceutical data, and lay a foundation for knowledge graph.

In building this ontology model, we have reached a milestone. However, there are still much more to do in the future. To reach the goal of knowledge graph, further than the ontology model, we need to optimize the data model and realize the data mapping from ontology to relational data and graph database.

5 CONCLUSIONS

Based on the basic concepts and knowledge system of pharmacy, using the idea of ontology modelling, and referring to existing pharmaceutical, biological and medical knowledge ontology models and resource databases, we sort out the concept, scope, classification, hierarchy and structure of pharmaceutical knowledge ontology. We have built a basic ontology model, which can be gradually integrated and updated by analysing and sorting the data content of authoritative global data sources. Finally, a relatively complete pharmaceutical knowledge ontology model was established to complete the knowledge representation of drug information. With this tool, we can not only show pharmaceutical entities and their relationships, and systematically describe pharmaceutical knowledge, but also can integrate and supplement existing biomedical ontologies, in order to further realize the standardization, normalization and structurization of pharmaceutical data in the form of knowledge graph.

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Table 4: Data properties and subproperties defining the basic attributes of pharmaceutical entities.

No.	Data property	Subproperty
1	hasApproved	
2	hasCategory	
3	hasClinicalTrial	hasClinicalTrialDrug hasClinicalTrialIndication hasClinicalTrialStatus hasClinicalTrialTherapy
4	hasCountryName	
5	hasDates	
6	hasDeleted	
7	hasDescription	
8	hasDescription	hasDetailDescription hasSummary
9	hasDrugChemicalIdentifier	hasDrugCas hasDrugInChI hasDrugInChIKey hasDrugIupacName hasDrugUnii
10	hasDrugPharmacology	
11	hasDrugDissolution	
12	hasDrugProperty	
13	hasDrugSpectra	
14	hasEntityClass	
15	hasFunctions	
16	hasGene	
17	hasNames	hasGenericName hasName hasNonProprietaryName hasPreferredName hasSynonyms
18	hasID	
19	hasIndicationDiagnosis	hasIndicationCause hasIndicationCheck hasIndicationChiefComplaint hasIndicationDiagnosis hasIndicationDiagnosisBasis hasIndicationSymptom
20	hasIndicationHospitalDepartment	
21	hasIndicationPathway	
22	hasIndicationSite	
23	hasLink	
24	hasFunctions	hasMainFunction hasSpecificFunction
25	hasMedicalInsuranced	
26	hasOrganisationName	
27	hasOriginalID	
28	hasProductAdverseReaction	
29	hasProductCompany	hasProductApplicantHolder hasProductDistributor hasProductLabeller hasProductManufacturer hasProductPackager
30	hasProductBrand	
31	hasProductCompany	
32	hasProductInfo	hasProductDosage hasProductRoute hasProductStrength
33	hasProductInstruction	hasProductSpecification

Table 4: Data properties and subproperties defining the basic attributes of pharmaceutical entities (cont.).

No.	Data property	Subproperty
34	hasTitle	hasPublicTitle hasScientificTitle
35	hasReferenceInfo	hasReferenceDoi hasReferenceExternalDatabaseID hasReferenceFile hasReferenceLink hasReferencePatentID hasReferencePmid
36	hasRegistered	
37	hasSource	
38	hasDates	hasStartDate hasUpdateTime
39	hasType	

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