Title

Dynamic enhancement of drug product labels through semantic web technologies: A linked open data store of scientific information that updates and elaborates on medication safety statements present in drug product labels

Objective

Demonstrate a novel approach to updating and expanding upon information present in drug product labels that is useful for determining a drug's safety. The approach will use natural language processing and scientific discourse ontologies to build a linked open data store of scientific information that updates or elaborates on medication safety statements present in drug product labels.

Stakeholders

Several stakeholders are listed below. Please see the section "Value Proposition" for a listing of the potential benefits that each might receive from this use case:

- Academics
- Clinical researchers
- Drug regulators
- Maintainers of drug information resources
- Patients
- Pharmaceutical industry

Summary

FDA-approved drug product labeling (also called packages inserts or *PIs*) is a major source of information intended to help clinicians prescribe drugs in a safe and effective manner. Unfortunately, drug product labeling has been identified as often lagging behind drug knowledge in the scientific literature, especially when it has been several years since a drug has been released to the market. Out-of-date or incomplete PI information can increase the risk of otherwise preventable adverse drug events (ADEs). This can occur directly if the PI fails to provide information that is needed for safe dosing or to properly manage (or avoid) the co-prescribing of drugs known to interact. Clinicians might also be indirectly affected if they depend on third party drug information sources and these sources fail to add information that is available in the scientific literature but not present in the PI. Some current examples of incomplete and/or out-of-date PI information should help to illustrate these points.

Example one: Multiple studies indicate that drug-drug interactions (DDIs) are a significant source of preventable ADEs [1,2]. Factors contributing to the occurrence of preventable DDIs include a lack of knowledge of the patient's concurrent medications and inaccurate or inadequate knowledge of interactions by health care providers [3, 4]. Currently, at least two PIs for drug products containing the antidepressant bupropion fail to mention a known DDI caused by clopidogrel. Specifically, Turpeinen *et al.* found that the area under the concentration time curve (AUC) of bupropion increased 60% when given to 12 adult males who had taken clopidogrel for four days [14]. Unfortunately, a clinician searching the bupropion PI for "clopidogrel" would find no mention at all in Aplenzin ER insert [15], and mention of only a hypothetical interaction in the generic tablet insert [16]. Moreover, only one of three online DDI checking tools (MICROMEDEX ®, Medscape ®, and Epocrates ®; search done in November

2011) was found to list the interaction. Bupropion does not have a narrow therapeutic range, so such an increase might be relatively benign for most patients. However, individual variation in drug metabolism and frailty might increase the risk that some patients, such as frail senior citizens, would experience and ADE (e.g., fall) or a side-effect (e.g., headache).

Example two: Citalopram, the most commonly prescribed antidepressant in long-term care [18], is one of twelve antidepressants that are susceptible to both an age-related decrease in clearance and at least one clearance-reducing PK DDI. The combination of factors affecting drug clearance can increase the chance that patients will experience an adverse drug event [17,18]. For example, the clearance for citalopram occurs by multiple mechanisms but primarily involves two metabolic pathways (CYP2C19 and CYP3A4), with approximately only 20% of the drug cleared renally [19]. While in healthy adults the combination of clearance routes should make it less susceptible to dramatic changes in systemic concentration if affected by a PK DDI, the same might not be true for a frail elderly patient with impaired hepatic function. Unfortunately, the citalopram PI [21] does not provide quantitative information on age-related clearance reduction, despite this information being available in several published scientific papers [22-24]. This information is important because increased blood levels of citalopram can potentially increase the risk of QT interval prolongation and Torsade de Pointes [20].

Example three: A number of DDIs can be inferred from information in the PI and/or scientific literature on drug metabolism. For example, Boyce *et al.* predicted 31 novel DDIs (i.e., not studied in clinical trials) affecting a statin drug by using a research-oriented knowledge base of drug mechanisms [25]. The 31 pairs represent potentially interacting drug combinations that a review of the literature indicate had not been studied at the time of the study. Fifteen published case reports claimed the occurrence of a DDI that matched one of thirteen of the 31 novel predictions. Each report was reviewed using a decision support tool for evaluating case reports called the Drug Interaction Probability Scale (DIPS) [26]. The DIPS defines four qualitative levels of certainty that two drugs caused the adverse event(s) mentioned in report; *Doubtful*, *Possible*, *Probable*, and *Highly Probable*. Six novel predictions were matched with case reports that met the DIPS *Probable* level; meaning that the predicted interactions were the likely cause of an adverse event occurring in a patient. Seven novel predictions were matched with reports that met the DIPS *Possible* level; meaning that the predicted interactions could not be excluded from consideration as the cause of an adverse event in a patient. None of these case reports or the DIPS evaluations are available in the PIs for the drugs predicted to be affected by the novel DDIs. Linking this information to the relevant PIs would help clinicians identify potential safety problems that are unlikely to be studied in clinical trials. It can also guide pharmaco-epidemiologists in the selection of questions to address with observational studies.

To address the important limitations discussed above, this use case would explore a novel approach that:

1) Employs natural language processing (NLP) and existing open drug information sources to identify scientific information that updates or expands upon statements present in product labeling in order to discuss age-related changes in clearance, pharmacokinetic drug-drug interactions, and metabolic clearance pathways.

2) Uses Semantic Web technologies, including scientific discourse ontologies and Linked Open Data, to represent the claims (present in both product label and scientific sources) that are

identified using NLP and existing open drug information sources.

One potential application of the resulting linked data set might be to generate an enhanced view of the drug package insert that provides viewers with a more complete and up-to-date view of information on the drug. By design, the linked data set would be dynamic, expanding as new information becomes available in the scientific literature or new sources of literature become available.

Value Proposition

Stakeholder (in alphabetical order)	Potential Value
Academics	The use case would benefit Semantic Web, scientific discourse, and natural language processing researchers by advancing the methods they use and applying them to a challenging real-world problem.
Clinical researchers	Many of the claims in drug package inserts, such as associations between a drug and adverse event identified in pre-market studies, can n be linked to pharmacoepidemiologic studies exploring the clinical relevance of the adverse event in a given population. The new approach to synthesising this knowledge might help clinical researchers more quickly identify gaps of knowledge on a drug's safety that could be addressed by new studies.
Drug regulators	The synthesis of scientific studies linked to package insert claims might help drug regulators (i.e., the US Food and Drug Administration or FDA) to identify package insert claims that are not up-to-date and thus, are not in compliance with their regulations. For example, groups such as the FDA's Center for Drug Evaluation and Research might benefit from the synthesized knowledge representation by more easily noting when an adverse drug event reported using a system such as the Adverse Event Reporting System has been investigated using rigorous scientific methods.
Maintainers of drug information resources	There are a handful of commercial vendors that provide drug information products to a very large proportion of clinicians. These vendors already integrate information from drug package inserts but the synthesis of scientific studies linked to package insert claims might help them more easily identify scientific studies that they should review for inclusion in their drug information products.
Patients	This use case might have benefit for those patients who seek drug information directly from the package insert by pointing them to more up-to-date information. However, it is more likely that patients would receive benefit through intermediaries, such as their clinicians, who

	themselves consult the package insert of drug information products that integrate information from the drug package insert.
Pharmaceutical industry	One of the outcomes of the use case would be a synthesis of scientific studies that might update claims in drug package inserts. This data might make it easier for the pharmaceutical industry to identify package insert claims that are not up-to-date and thus, help them to make changes to the package insert that puts them in compliance with FDA mandates on package insert content such as Code of Federal Regulations 21 Parts 201.56 and 201.57. (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57)

Components

- Use case in detail (listing hypotheses, content sources, etc.)
- Corpus - content sources
- Scientific Discourse Ontology
- Linked Data repository
- “Epistemic markup” - linking knowledge claims to experimental evidence

We propose to make use of a data model to capture and query evidence related to specific assertions about a drug’s pharmacokinetic properties or its pharmacokinetic interactions. Scientific discourse markup would allow the user access to the knowledge claims present in *research articles* and PIs. Once both types of texts are augmented with such markup, unstructured text statements in PIs could be linked to discourse-modeled claims that may update or complete the PI’s information. Scientific discourse annotation could be done manually initially and by training machine learning classifiers we could move to semi-automatic or automatic identification of relevant claims. We would first make use of existing models of scientific discourse to obtain hypotheses, evidence and facts as well as their degree of certainty. These may be modified after a round of annotation and evaluation. ∓

Methods

- Data integration
- Text mining
- Guided machine learning
- Fact extraction
- Scientific Discourse ontologies

NLP technologies involved:

- Entity recognition: Chemical entities, drugs, biological entities
- relation extraction: protein-protein interactions, other types of relations, any relation between two of the above entitites
- supervised machine learning methods for discourse segment recognition.

Text mining for DDI

Background

There is no extensive work on drug-drug interaction in the text mining literature, as most research has focused on the interaction between biomedical entitites, such as protein protein interactions, which is the focus of major challenge events like Biocreative and the BioNLP shared task. While molecular biology interactions remain the the main focus of the BioNLP shared task, it has expanded the remit to encompass epigenetics and bacterial interactions [BioNLP 2011].

Other work has looked at the identification of chemicals and small molecules, mainly on the basis of resources such as ChEBI [OSCAR ref].

The extraction of drug-drug interactions has been slowly gaining interest and a SEMEVAL shared task for the extraction of such relations has been scheduled for 2013 [28]. The Drug DDI corpus [27], consisting of 579 documents, 5,806 sentences with a total of 3,160 DDIs will from the training data for the task. These documents (abstracts) were annotated at the sentence level with the assistance of a pharmacist.

As is the case with most systems for relation extraction, identifying drug-drug interactions would involve drug name recognition, resolution of anaphors and aliases, and the identification of relations (interactions).

Related work [Segura-Bedmar et al, 2008] has looked at drug name recognition by processing MEDLINE abstracts using the UMLS MetaMap transfer to recognise pharmacological substances. A rule based system based on nomenclature rules recommended by the WHO INNS helps classify the identified pharmacological substances into groups and also allows the identification of substances not recognised by the MetaMap transfer program. The rule based drug name recogniser was able to detect 74.9% of drug names in the DDI corpus, while the MetaMap transfer alone had 97.5% recall and 100% precision. The addition of the rules improved recall slighly. Preliminary work by the same authors [Segura-Bedmar et al, 2010] has compared two systems for relation extraction, a pattern based one and a machine learning classifier which employs SVMs. The machine learning classifier significantly outperforms the pattern based system.

A different approach to discovering DDIs [Tari et al, 2010] has combined facts extracted from MEDLINE abstracts with biological domain knowledge (drug A induces or inhibits enzyme responsible for metabolism of drug B) to propose DDIs that were not found in DrugBank. Their analysis showed that 81.3% of the interactions were correct. Extracted facts included drug-enzyme interactions and protein-protein interactions. Other possible interactions could be indirect induction through transcription factors, induction or inhibition of transporters.

They have a dual approach in that they combine syntactic parses of sentences with background knowledge on drug metabolism written in logic rules. The parsed sentences are stored in a database and queried to identify drug-relation triples, where the relations are induces, inhibits, regulates, metabolises. The fundamentals of pharmacokinetic behaviour and drug metabolism are encoded in AnsProlog and Prolog rules are also used for cleaning the extracted relations and translating them to logical facts. Theorem proving is then used to identify DDIs for a particular set of drugs. [Very interesting work a variation on which could perhaps make use of Rich's DDI model].

[Lin et al, 2011] have looked at frequency-based methods for predicting the characteristics of pairs of drugs, including adverse events. They use a varient of the tf-idf measure to obtain the

most relevant word tokens as features for

Preliminary work and example

Pharmacokinetic DDIs: A comprehensive list of evidence supporting or refuting pharmacokinetic DDIs identified by pharmacokinetic DDI clinical trials has been compiled by Richard Boyce (in collaboration with a pharmacist and medical doctor, both DDI experts) for the following drugs:

- Antidepressants: desvenlafaxine, duloxetine, escitalopram, citalopram, mirtazapine, selegiline, nefazodone, venlafaxine, paroxetine, sertraline, fluoxetine, bupropion, isocarboxazid, phenelzine, tranylcypromine, trazodone, vilazodone, amoxapine, maprotiline, trimipramine, amitriptyline, desipramine, doxepin, imipramine, nortriptyline
- Antipsychotics: asenapine, iloperidone, paliperidone, aripiprazole, ziprasidone, quetiapine, olanzapine, risperidone, clozapine
- Sedative Hypnotics: eszopiclone, zaleplon, zolpidem, ramelteon

This evidence can be supplemented with evidence from Elsevier's XPharm and citations in DrugBank listed DDIs.

Age-related clearance changes: A comprehensive list of quantitative evidence supporting or refuting age-related clearance changes has been compiled by Richard Boyce (in collaboration with a pharmacist specializing in geriatric pharmacy) for the following drugs:

- Antidepressants: desvenlafaxine, duloxetine, escitalopram, citalopram, mirtazapine, selegiline, nefazodone, venlafaxine, paroxetine, sertraline, fluoxetine, bupropion, isocarboxazid, phenelzine, tranylcypromine, trazodone, vilazodone, amoxapine, maprotiline, trimipramine, amitriptyline, desipramine, doxepin, imipramine, nortriptyline

Drug metabolic pathways: The The Drug Interaction Knowledge Base contains a comprehensive list of evidence supporting or refuting metabolic mechanisms used for pharmacokinetic DDI prediction for al of the drugs listed above and at least a dozen others.

Scientific markup example: We have developed an example of scientific markup for both the literature and the PI based on *Example 1* of this document (see above). The MEDLINE abstract example provided in this hyperlinked document was created by experimenting with SAPIENTA for the scientific abstract and then manually editing the program's automatic markup. The package insert markup was manually created. The example shows in a concrete manner exactly the kinds of markup we would need to created the linked data set that is the focus of this use case.

Specific tasks and milestones

The milestones and tasks are available on http://dbmi-icode-01.dbmi.pitt.edu/trac/roadmap.

Deliverables

1. *Linked Open Data Node:* Triple store and SPARQL endpoint to contain information on:
- age-related clearance changes
- drug-drug interactions
- genetic polymorphisms that affect drug phenotypes.
- dosage, patient characteristics: how to encode these?

2. *Software:* A system that provides pharmacokinetic information on age-related clearance changes, metabolic clearance pathways, and pharmacokinetic drug-drug interactions for psychotropic, antidepressant, and sedative hypnotic drugs that are currently marketed in the United States - both from the existing label and newly extracted facts from the literature.

3. *Written:* A W3C practice note on how to deploy the system for any given drug, and at least one journal article describing significant results from developing the system deliverable and results from user testing.

4. *Oral:* Conference presentation describing the system deliverable and results from user testing.

Partners:
Drug Informatics partners:
- Richard Boyce, University of Pittsburgh

Pharma partner:
- TODO: determine interest from Vijay Bulusu at Pfizer

Possible drug information partners:
- Elsevier data
- Pharmaceutical Press
- EPocrates (Gretchen Jones)

Text mining collaborators:
- Maria Liakata, EBI
-

Scientific Discourse ontology specialists:
- Jodi Schneider, DERI
- Anita de Waard, Elsevier
- Joanne S. Luciano, RPI

Users for testing:
- Pharma partners,
- Pharmapendium developers: able to participate, provide content and provide co-annotators and content evaluators

Content sources:

Source	Provides	API?
FDA-approved Structured Product Labeling from DailyMed (http://dailymed.nlm.nih.gov/dailymed/about.cfm)	Product labels in a structured format for all currently marketed drug products in the United States	XML Download
MEDLINE/PubMed	Indexed abstracts of the scientific literature	XML Download, and web services
PubMedCentral	XML-formatted full text articles	web services
Elsevier	XML-formatted full text articles	?
The DIKB (theda tahub.org/package/the-drug-interaction-knowledge-base)	Quantitative and qualitative claims about drug mechanisms and pharmacokinetic drug-drug interactions for over 60 drugs; primarily psychotropics and HMG-CoA reductase inhibitors (statins). Most claims are linked to the supporting and/or refuting evidence and all evidence items are classified using an evidence taxonomy. The dataset is availllable in relational, linked-data, and Python formats.	Python, linked data, RDB
DrugBank (http://drugbank.ca/)	Detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information. The database contains 6707 drug entries including 1436 FDA-approved small molecule drugs, 134 FDA-approved biotech (protein/peptide) drugs, 83 nutraceuticals and 5086 experimental drugs. Additionally, 4228 non-redundant protein (i.e. drug target/enzyme/transporter/carrier) sequences are linked to these drug entries. Most target information is linked to at least some evidence in the scientific literature or drug package inserts.	Flat file download, linked data (deprecated?)
SIDER	Aggregate, machine readable, dispersed	Database, linked

(http://sideeffects.embl.de/drugs/444/all)	public information on side effects and frequencies. The database lists side effects and frequencies from multiple PIs for a given drug.	data
PharmGKB (http://www.pharmgkb.org/)	Curated knowledge about the impact of genetic variation on drug response with focuses on: • Clinical interpretation of variants associated with drug response • Drug dosing guidelines and genetic tests • Drug-centered pathways • Important PGx gene summaries • Relationships among genes, drugs and diseases	Web services
KEGG DRUG	Comprehensive drug information resource for approved drugs in Japan, USA, and Europe unified based on the chemical structures and/or the chemical components, and associated with target, metabolizing enzyme, and other molecular interaction network information	Web services
Reaxys	Chemical database containing reactions that create a particular compound	?
Pharmapendium	Adverse effect database	?
EMBASE	Triples (including disease, drug name, side effect as entities) with which scientific papers are annotated	

Taxonomies/Ontologies:

Ontology/ Terminology	Purpose	Link
Substance Registration System - Unique Ingredient Identifier (UNII)	Active ingredients tagged “active moiety” in Structured Product Labeling. These active moieties are mapped in the UMLS to numerous other vocabularies including RxNorm.	http://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm

RxNorm	RxNorm connects prescription drug products (using normalized names), active and inactive ingredients, and NDC through a concept unique identifier (RXCUI). It also provides a REST API for executing numerous queries that will be potentially useful for mapping such as “get the UNII for active ingredient X” or “get the SPL set id for drug product Y.” RxNorm can help with mapping dose, form, and other product specific information since these are explicitly modeled. Also, an analysis by Richard Boyce found that the NCBO Annotator had a F-measure of 0.85 (Recall: 0.85, Precision: 0.88) for identifying drug entities in drug package inserts. The analysis produced detailed results than can guide improvements to the use of RxNorm in entity recognition algorithms	http://www.nlm.nih.gov/research/umls/rxnorm/ http://rxnav.nlm.nih.gov/RxNormAPI.html
The Drug Interaction Knowledge Base Evidence Taxonomy	A set of 36 evidence types arranged under seven groupings representing evidence from retrospective studies, clinical trials, metabolic inhibition identification, metabolic catalysis identification, statements, reviews, and observational reports. The DIKB ontology has terms for modeling drug interactions and pharmacokinetic properties.	Table for quick view: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2783801/table/T3/ BioPortal: http://bioportal.bioontology.org/ontologies/1672 OWL: http://dbmi-icode-01.dbmi.pitt.edu/dikb-evidence/DIKB_evidence_ontology_v1.3.owl
MeSH / EMTREE EMMETT (Elsevier health / life science taxonomies / ontologies)	Publication types and scientific literature indexing terms.	
CoreSC [11], SWAN [12] or Discourse	Scientific discourse meta-data	

Segment types [13]		
MedDRA	Adverse event classification - useful if we decide to link adverse events to package inserts.	

Algorithms and Tools

Algorithm/Tool	Description of potential relevance to the project	Available or needs development?
U of Pitt NLP algorithm to identify DDI claims in package inserts	Claims must be identified in the drug package insert in order for them to be linked to scientific discourse. This algorithm can do this for pharmacokinetic DDIs and can classify if a claim is supportive or refutive of a DDI.	Available via Rich Boyce - current performance F1=0.87 for DDI statement identification

Success Criteria

1. Ability to generate mashups for a significant number of PIs that provide complete and up-to-date content on drug metabolic pathways and DDIs.
2. Ease of replication for other drug PIs.
3. Possible test integration into the Structured Product Labeling.

Other desirable outcomes

1. Improved state-of-the-art in claim identification (NLP).
2. Improved state-of-the-art in scientific discourse modeling.

See also

A. Boyce R, Harkema H, Conway M. Leveraging the semantic web and natural language processing to enhance drug-mechanism knowledge in drug product labels. In: ACM Press; 2010:492. Available at: http://dl.acm.org/citation.cfm?id=1883070. Accessed October 6, 2011.

B. http://thedatahub.org/dataset/the-drug-interaction-knowledge-base

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