Dynamic Enhancement of Drug Product Labels Through Semantic Web Technologies (A W3C HCLS IG Use Case)

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Overview

- The motivation for the W3C Use Case
- What we are suggesting
- How it can be accomplished
  - Proof of concept
- Issues to be addressed
- Discussion
The problem

• Much of the information in drug package inserts (aka product labels) is incomplete or has not been updated
Missing drug-drug interactions

• Example:
  – “Both clopidogrel and ticlopidine significantly inhibited the CYP2B6-catalyzed bupropion hydroxylation. Patients receiving either clopidogrel or ticlopidine are likely to require dose adjustments when treated with drugs primarily metabolized by CYP2B6.” [1]

• Search bupropion drug package inserts for “clopidogrel”
  – No mention at all in Aplenzin ER insert [2]
  – Mention in the generic tablet insert [3], but refers only to hypothetical interaction

Missing metabolic properties

• Cimetidine inhibition of CYP3A4 and CYP1A2 metabolism

• Fluconazole inhibition of CYP3A4 metabolism
  – Noted in an FDA draft guidance [1] but not directly in the fluconazole solution PI [3]
    • Inferable from the stated interaction with midazolam

• See others like this in [4]

Missing age-related clearance data

• The PI for citalopram [1] notes age-related pharmacokinetic changes
  – “…subjects ≥ 60 years of age were compared to younger subjects in two normal volunteer studies. In a single-dose study, citalopram AUC and half-life were increased in the elderly subjects by 30% and 50%, respectively”

• However, clearance (Cl) would be the preferred measure of age-related change – is there literature on this?
  – Yes! [2-4]

• The package inserts rarely have this information even when published [5]

Is there any requirement that the inserts be kept up to date?

- Yes - 2006 regulations explicitly require that studies of drug-drug interactions, metabolic pathways, and special populations be discussed [1]

"(8)7 Drug interactions.
(i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them."

"(C)12.3 Pharmacokinetics.
...Information regarding bioavailability, the effect of food,..., area under the curve (AUC), pertinent half-lives (t1/2),..., drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (Vd) must be presented if clinically significant ... This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data."


University of Pittsburgh Biomedical Informatics
Why are package inserts important?

• Package inserts are primarily intended to be a reference for prescribing clinicians [1]

Why is the package insert apparently so influential?

- Authoritative
- Simple (for a drug expert) to follow
- Often the only source of information besides FDA approval documentation for new drugs
- No standard for searching the scientific literature
- No standard for judging the quality of published studies
What are we suggesting then?

• “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.”

  - W3C HCLS IG Use Case (http://goo.gl/wP4Mz)
Current use of package inserts
Proposed innovation – take claims present in semantic web resources....
create a linked dataset that merges those claims and identifies where they should be located in the package insert....
...create customized views of the new linked dataset tailored toward various drug experts and decision support tools
The big picture…

Scientific Literature

- embase
- PubMed

Premarket data (i.e., FDA approval documents)

Postmarket data (i.e., pharmacovigilance/pharmacoepi)

Claims present in Semantic Web resources

- Drug Bank
- GeneID
- OMIM
- PubMed
- PubChem
- KEGG
- ChEBI
- Daily Med
- DBpedia
- LinkedCT
- RDP-TGM
- CAS
- SIDER

Linked dataset merging all drug claims into the context of package insert sections

Customized view

Expert Knowledge Base Curator

Tertiary sources of drug information

regulators, pharmacists, pharmacoepidemiologists, pharma, decision support tools, ...

Customized view
How can this be accomplished?
The Structured Product Label (SPL) standard makes this possible

- All package inserts for currently marketed drugs are available in this format [1-3]

FDA law dictates the kinds of claims that should be present in each section

SPL for Drug X containing active ingredient Y

**SPL Header**

**Structured Body**

- **Section code="Clinical Studies"**
  - Completed effectiveness studies with Y

- **Section code="Precautions"**
  - Evidence supported drug interactions with Y

- **Section code="Drug Interactions"**

- **Section code="Clinical Pharmacology"**
  - Evidence Y's metabolic and pharmacologic properties
Many of these claims can be identified in resources on the Semantic Web….

Drug Interaction Knowledge Base
- Pharmacokinetic drug interactions with Y
- Drug metabolic pathways for Y
- Enzyme inhibition
- Age-related clearance (in process)

ClinicalTrials.gov
- Completed effectiveness studies with Y

DrugBank
- Drug interactions with Y

ClinicalTrials.gov: http://thedatahub.org/dataset/linkedct
DrugBank: http://thedatahub.org/dataset/the-drug-interaction-knowledge-base
...and then linked to package insert sections published on the Semantic Web

Linked SPLs: http://thedatahub.org/dataset/linked-structured-product-labels
Proof of concept
Overview of the proof of concept

- http://goo.gl/rs3Fy
  - Package inserts for drug products containing citalopram and venlafaxine
  - Created using three Semantic Web nodes
    - http://thedatahub.org/dataset/linkedct
More about the data nodes

- [http://goo.gl/rs3Fy](http://goo.gl/rs3Fy)

SPL for Drug X containing active ingredient Y

- **SPL Header**
- **Structured Body**
  - Section code="Clinical Studies"
  - Section code="Precautions"
  - Section code="Drug Interactions"
  - Section code="Clinical Pharmacology"

- Completed effectiveness studies with Y
- Evidence-supported drug interactions with Y
- Evidence-supported metabolic properties for Y

2. [http://thedatahub.org/dataset/linkedct](http://thedatahub.org/dataset/linkedct)
Scientific discourse in the “DIKB”

- [http://goo.gl/rs3Fy](http://goo.gl/rs3Fy)

SPL for Drug X containing active ingredient Y

**SPL Header**

**Structured Body**

- **Section code=“Clinical Studies”**
- **Section code=“Precautions”**
- **Section code=“Drug Interactions”**
- **Section code=“Clinical Pharmacology”**

* Expert-curated
* Uses SWANCO
Take the drug interactions section of a drug package insert...

7 DRUG INTERACTIONS

MAOI's: concomitant use contraindicated (4). Avoid MAOI's 14 days before starting venlafaxine and 7 days after stopping venlafaxine (5.2). Cimetidine: Caution in patients with pre-existing hypertension, in elderly patients and patients with hepatic dysfunction. (7.2) Haloperidol: Increase in Haloperidol AUC and Cmax. (7.4) Ketoconazole: Increase in venlafaxine and O-desmethylvenlafaxine AUC and Cmax. Caution when using venlafaxine with substances that inhibit both Metoprolol: Possibly reduced blood-pressure lowering effect despite increased metoprolol plasma levels. Caution should be exercised with co-admini CNS-active drugs: Caution when using venlafaxine with such drugs. (7.10) Serotonergic drugs (e.g., triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's Wort): Potential for serotonin syndrome. Careful pati Tryptophan supplements: Concomitant use not recommended. (7.10)

7.1 Alcohol

A single dose of ethanol (0.5 g/kg) had no effect on the pharmacokinetics of venlafaxine or O-desmethylvenlafaxine (ODV) when venlafaxine was adm venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they we
Make it simple for the package insert reader to see claims that could expand or update the information in this section…

<table>
<thead>
<tr>
<th>Drug Interaction</th>
</tr>
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<tbody>
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<td><strong>(see DIKB claims for this section)</strong></td>
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7 DRUG INTERACTIONS

- MAOIs: concomitant use contraindicated (4). Avoid MAOIs 14 days before starting venlafaxine and 7 days after stopping venlafaxine (5.2).
- Cimetidine: Caution in patients with pre-existing hypertension, in elderly patients and patients with hepatic dysfunction. (7.2)
- Haloperidol: Increase in Haloperidol AUC and Cmax. (7.4)
- Ketoconazole: Increase in venlafaxine and O-desmethylvenlafaxine AUC and Cmax. Caution when using venlafaxine with substances that inhibit both CYP2D6 and CYP3A4. (7.7)
- Metoprolol: Possibly reduced blood-pressure lowering effect despite increased metoprolol plasma levels. Caution should be exercised with co-administration of venlafaxine and metoprolol. (7.8)
- CNS-active drugs: Caution when using venlafaxine with such drugs. (7.10)
- Serotonergic drugs (e.g., triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's Wort): Potential for serotonin syndrome. Careful patient observation advised. (7.10)
- Tryptophan supplements: Concomitant use not recommended. (7.10)
Example: an interaction affecting venlafaxine that may not be in this section…
**Example:** an interaction affecting venlafaxine that may not be in this section...

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**MAOI's:** concomitant use contraindicated (4). Avoid MAOI's 14 days before starting venlafaxine.

**Cimetidine:** Caution in patients with pre-existing hypertension, in elderly patients and patients with GI symptoms.

**Haloperidol:** Increase in Haloperidol AUC and Cmax. (7.4)

**Ketoconazole:** Increase in venlafaxine and O-desmethylvenlafaxine AUC and Cmax. Caution with other CNS-active drugs: Caution when using venlafaxine with such drugs. (7.10)

**Metoprolol:** Possibly reduced blood-pressure lowering effect despite increased metoprolol levels.

**CNS-active drugs:** Concomitant use not recommended. (7.10)

**INFO**

**Claim venlafaxine causes an increase in exposure to haloperidol:**

- **evidence for:**
  - Package Insert venlafaxine-wyeth-122008

- **evidence against:**

**Claim venlafaxine will increase in exposure when given with diphenhydramine (NEW TO SECTION?):**

- **evidence for:**
  - Primary Study 11270914

- **evidence against:**

**NLP determined that evidence for a diphenhydramine/venlafaxine interaction is not mentioned**
Clicking on the link provides a path to evidence for (or against) the drug interaction claim…
One goal is to link directly to statements and sections within scientific documents from which evidence was derived

• For example, assume a drug interaction claim
  – identify core scientific concepts (CoreSC) in the paper containing the evidence for/against the claim (background, methods, results, …)
  – Identify the text containing evidence for/against a claim within the CoreSC
  – Link the specific CoreSC element back to the package insert section (via the interaction claim)

• Currently testing this approach using SAPIENTA (www.sapientaproject.com)
Just a couple of the issues to be addressed

- Ensuring the quality of the claims linked to the package insert sections
  - Provenance is key
  - Would nanopublications help here?
    - The sky could be the limit if a drug information “knowledge market” could be created

- Technical issues with some existing linked open drug data nodes
  - *Now* is the time to improve linked open drug data
    - Correct RDF mappings, accurate encodings
    - Graph and data provenance
Want more information?

- **Use Case description**
  - [http://goo.gl/wP4Mz](http://goo.gl/wP4Mz)

- **Google code project**
  - [code.google.com/p/swat-4-med-safety/](http://code.google.com/p/swat-4-med-safety/)

- **Proof of concept**
  - [http://goo.gl/rs3Fy](http://goo.gl/rs3Fy)

- **Linked data nodes used in the proof of concept**
  - [http://thedatalabs.org/dataset/linkedsct](http://thedatalabs.org/dataset/linkedsct)
Acknowledgements

• The Drug Interaction Knowledge Base team
  – John Horn Pharm.D, Carol Collins MD, Greg Gardner, Rob Guzman

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• Early comments on the Use Case:
  – Michel Dumontier and several others who attend W3C HCLS calls
Discussion/questions
The package insert’s influence is significant

• How frequently do three drug interaction checking tools agree on an interaction by source? (unpublished)
  – 44 interactions from the package insert or scientific literature (25 newer psychotropics)
  – Agreement 3.25 times more likely for package insert only interactions then for literature only

Scientific literature

<table>
<thead>
<tr>
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<tr>
<td>15.4%</td>
<td>38.5%</td>
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<tr>
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