



How Should Simulated DDI Results be Communicated in the Label?

Jack Cook, PhD, Pfizer Inc.



What did we Hear at the Advisory Committee Meeting?

- Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting September 25, 2013.
- The committee discussed optimal strategies for the evaluation, interpretation, and communication of drug-drug interaction (DDI) information. FDA sought input on best practices in DDI communication through prescription drug product labels ...



What did we Hear at the Advisory Committee Meeting?

3. DISCUSSION: Some DDIs can be predicted based on *in vitro* studies, other *in vivo* studies, and *in silico* analyses. In those situations, what information about predicted DDIs should be included in prescription drug labeling? Should the labeling list all potential interactions or a subset (based on drug class, likelihood of co-administration, or severity of interaction)?

Committee Discussion: Some committee members stated the following regarding what information ... DDIs should be included in the prescription drug labeling (not ... consensus points):

- Clearly state if DDI information is extrapolated from non-human studies and separate this information from actual empirical studies
- The source should be included in the prescription drug labeling to indicate which model was used (i.e., *in vitro*, *in vivo*, or *in silico*)
- Consider that some stakeholders want details while others want simplified information
- Using historical DDI data to formulate modeling is a reasonable approach in making dosing recommendations
- The information should not be static and labeling should be updated as more information becomes available



What did we Hear at the Advisory Committee Meeting?

Perception – *Some don't believe in silico results*

Transcript Extracts* regarding *in silico* recommendations:

- I would just make the quick comment that **if it's an extrapolation based upon either a simulation or nonhuman studies, that those be clearly stated and kept separate from actual experiences, empirical data in humans, just because there is some examples where the extrapolations don't hold out. ...**
- And if the question is, if we know we have a potent 3A4 inhibitor, can we extrapolate that we'll interact with every other 3A4 substrate in the world? ... I absolutely agree with that. ... I have much more of a **problem with in vitro inhibitor/inducer data**, but not for substrate stuff.
- I have much more **difficulty with extrapolation for dosing recommendations unless you've got real data**, ... But for trying to decide whether two drugs may have an interaction, I think that's absolutely rock solid.
- **This question of believability of data, is essentially what it boils down to, is a big problem for drug interactions to begin with.**

*To best place in context, please read entire transcript



What did we Hear at the Advisory Committee Meeting?

How Clinicians Perceive DDIs

Some are intuitive / universally appreciated ... A few are ingrained

Clinicians otherwise overwhelmed

- Sheer number of DDIs
- Complexity of mechanisms, terminologies

“Our language” is not intuitive

- pharmacokinetic, pharmacodynamic; AUC, Cmax etc.
- Most have only heard of CYP450; Know nothing about transporters

Limited inclination to catch up / keep up

- No appreciation for the quality of evidence

David Juurlink, Divisions of General Internal Medicine, Clinical Pharmacology & Toxicology, University of Toronto, Ontario Poison Centre, Institute for Clinical Evaluative Sciences (ICES)



What did we Hear at the Advisory Committee Meeting?

Labels have diverse readership:

- ¹Links to more detailed info
 - Case reports
 - Reviews
 - PK / PD studies
- If possible, would help to include in label **both simple messages and more detail**

¹David Juurlink, Divisions of General Internal Medicine, Clinical Pharmacology & Toxicology, University of Toronto, Ontario Poison Centre, Institute for Clinical Evaluative Sciences (ICES)

²David W. Bates, MD, MSc; Medical Director of Clinical and Quality Analysis, Partners Healthcare Chief Quality Officer, and Chief, Division of General Medicine, Brigham and Women's Hospital



What IF ...

- One could drill down into a label to get more information (e.g. start with conclusions and drill down to methods and more detailed results)



What IF

The patient's data and the label could “interact”

- Mrs. Smith's recommend dose is 40 mg QD
 - The generally recommended dose is 120 mg QD
 - Mrs. Smith's dose was adjusted by considering:
 - 50% decrease due to her **renal impairment**.
 - 33% decrease due to a drug interaction with **diltiazem**.
 - ...

(one could drill down on each adjustment for more information)

Maybe paper labels should be a thing of the past

