Identifying Drug-Drug Interactions using PharmaPendium

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Need to know

Webinar control panel:
- ‘Ask a question’ for questions and comments
- Option for full screen view
- Q&A at the end
Agenda

- Overview
- Using the Drug-Drug Risk Calculator to identify potential DDIs
  - Introduction to DDIRC
  - Example: Using DDIRC to identify potential DDI risk for drugs that are substrates CYP2D6
- Overview of Pharmacokinetic and Metabolising Enzyme and Transporter information in PharmaPendium
  - Example using PK and MET data along with DDIRC
Early and ongoing assessment of DDIs is critical

Drug-drug interactions (DDIs) can lead to severe side effects and have resulted in refusal of approval, severe prescribing restrictions, withdrawal of drugs from the market and, in extreme cases, have caused deaths.

According to the FDA, DDI-related adverse drug reactions are on the rise:
• More drugs — and many more combinations of drugs — are being used to treat patients than ever before.
  – Between 1995 and 2010, the proportion of adults dispensed ≥5 drugs doubled to 20.8%, and the proportion dispensed ≥10 tripled to 5.8%.\(^1\)
• The rate of ADRs increases exponentially after a patient is on 4 or more medications
  – 13% of adults experienced potentially serious drug-drug interactions in 2010, correlating with the increase in polypharmacy\(^1\)

\(^1\) Guthrie et al. BMC Medicine (2015) 13:74
Drug-drug interactions can increase toxicity or reduce clinical efficacy
Measured by AUC (area under the curve), which increases/decreases

A major mechanism of drug metabolism (accounting for ~75%) is via P450 CYP enzymes in the liver.

Drug-drug interactions may result when a concomitant drug* inhibits or induces the CYP-mediated metabolism of a second drug

Concomitant drug = two or more drugs are taken at (almost) the same time

E.g., Drug A is administered orally and metabolised by CYP3A
Dosage is timed so that plasma concentration levels remain high enough to maximize efficacy and low enough to avoid toxicity.
Concomitant drug **inhibits** CYP-mediated metabolism

E.g., Drug A is metabolised by CYP3A. Drug B **inhibits** the activity of CYP3A. Drug A is no longer metabolised at the same rate, resulting in **accumulation of toxic concentrations**.

Concomitant drug **induces** CYP-mediated metabolism

E.g., Drug A is metabolised by CYP3A. Drug B **induces** the activity of CYP3A. Drug A is no longer metabolised at the same rate, resulting in **lower concentrations and decreased efficacy**.
DDIs also occur through inhibition or induction of drug transporters by co-administered drugs

- Transporters often work together with drug metabolizing enzymes in drug absorption and elimination
- They are located in the small intestine, liver and kidney, which are critical for drug absorption and elimination
- Transporters commonly involved in DDIs include P-glycoprotein 1/ Multi-drug resistance 1 (P-gp/MDR1) and BCRP (Breast cancer resistance protein)

- The DMPK solution includes comprehensive information for both metabolising enzymes and transporters
  - The DDI Risk Calculator predicts the risk of metabolism-based drug interactions
The ability to identify potential DDIs informs key decisions throughout drug development.

For in-licensing, use DDIRC to:
- Determine if compound should be in-licensed
- Assess prioritization of projects/studies related to in-licensed drug

Optimize early drug candidate selection based on DDI risk

Prioritize clinical DDI studies
- Identify unnecessary clinical DDI studies
- Assess feasibility of combination therapy
- Assess DDI Risk with unavoidable co-meds
- Optimize clinical trial design (inclusion/exclusion criteria)
- Assess effect of exposure increase to optimize dose selection
- Depending on type of DDI (competitive/MBI inhibition or induction), better assess onset and duration of DDI effect

Recommend alternative drugs that may be co-administered to reduce DDI risk*

Recommend alternate doses for co-medications to reduce DDI risk*

* Including Phase 1, since for oncology indications, Phase 1 studies are done on patients, not healthy volunteers
Drug-Drug Interaction Risk Calculator (DDIRC)
PharmaPendium’s Drug-Drug Interaction Risk Calculator (DDIRC) is compliant with 2012 FDA guidance.

Guidance for Industry Drug Interaction Studies
Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations
February 2012

“This guidance reflects the Agency’s view that the pharmacokinetic interactions between an investigational new drug and other drugs should be defined during drug development, as part of an adequate assessment of the drug’s safety and effectiveness”
How does the DDIRC work?

• DDIRC predicts potential metabolic Drug-Drug Interactions (DDIs) between proprietary drugs and a panel of marketed drugs automatically selected from the DDIRC library.

• DDIRC applies to orally administered drugs* undergoing linear “first-pass hepatic metabolism” according to the “well-stirred” model.

• It does so based on a general in vitro in vivo extrapolation (IVIVE) method, using a mechanistic static model (MSM).

* Also applies to IV administered victim drugs with low clearance (i.e., low hepatic extraction ratio EH<0.3)
DDIRC applies to orally-administered drugs undergoing first-pass hepatic metabolism

- Orally administered drugs are absorbed by the digestive system, enter the hepatic portal system and reach the liver before the rest of the body.
- The liver is a major site of drug metabolism – often, only a small amount of active drug reaches the rest of the circulatory system after metabolism in the liver takes place.
- **First-pass metabolism occurs when the concentration of a drug is reduced before reaching systemic circulation**

DDIRC calculates potential interactions occurring during first-pass metabolism (the time when the majority of metabolism, and therefore DDI risk, occurs).

First-pass metabolism is an accepted model to use when calculating DDI risk.

http://usmle1-topscorer.blogspot.co.uk/2011/10/general-pharmacology-2-for-usmle1.html
DDIRC uses *In vitro In vivo* extrapolation (IVIVE)

*In vitro* refers to experimentation performed outside a living organism – e.g., experiments performed in a test tube or cell culture

*In vivo* refers to experimentation using a whole living organism – e.g., experiments performed in an animal model

**What is the basis of extrapolating *In vitro* metabolism data to *In vivo***?

The overall rate of CYP enzyme-catalyzed reaction is directly proportional to the total amount of enzyme present in the system.

Therefore, data generated with an *in vitro* system can be extrapolated to *in vivo* by scaling up values to correlate with the total amount of enzyme present in the *in vivo* system.
DDIRC uses *In vitro* *In vivo* extrapolation (IVIVE)
Several scaling factors are applied to extrapolate *In vitro* data to *In vivo*

**Predicting hepatic clearance**

*In vitro* clearance (\(\text{Cl}_{\text{int}}\)) values are determined (\(K_m\) and \(V_{\text{max}}\))

- **Scaling Factor 1** extrapolates *in vitro* data to clearance per gram of liver
- This number is multiplied by the liver weight (**Scaling Factor 2**) to extrapolate the data to clearance in the liver (\(\text{Cl}_{\text{int, in vivo}}\))
- The ‘**Well Stirred’ model** is applied to determine level of hepatic clearance in the body (\(\text{Cl}_{\text{in vivo}}/\text{L/h}\))
DDIRC is a Mechanistic Static Model

- Mechanistic Static Model (PharmaPendium DDIRC) calculates the system in equilibrium, and thus is time-invariant.
- Uses the average inhibitor concentration (i.e., does not incorporate changes in inhibition over time), giving a static profile of inhibition.
- Early DDI prediction for a drug in development is possible, before elimination routes of the victim compound and the role of gut extraction for the victim and/or inhibitor in humans is defined.
DDI risk is assessed throughout drug development

The FDA recommends a stepwise, model-based evaluation of metabolism-based interactions

**Early development: a wider look**
- **Mechanistic Static models** (e.g., DDI Risk Calculator) provide an overview of all potential DDIs.
- Default parameters in DDIRC allow early predictions. These values are updated with experimental data later on for precise predictions.

**Later in development: a closer look**
- Information in **Dynamic and Static** models is *complimentary* and used to assess DDI Risk between specific drugs and to determine what drugs can be used along with a candidate in clinical studies.
- Mechanistic Dynamic Modelling (PBPK modelling) requires significant input data and the availability of a PBPK model for each interacting drug.

DDI risk calculated (e.g., using a **Mechanistic Static model (DDIRC)**):
- Can be used to support exemption from clinical trial assessing DDIR risk.
- Can provide evidence for which studies need to be performed.
Demo
Example: Define inclusion/exclusion criteria related to concomitant drugs

Your company is in the early stages of developing a new anti-arrhythmic drug that is similar to Dronedarone, a CYP3A4 inhibitor. In other words, your drug is a perpetrator and you need to identify CYP3A4 victims using comparative parameters for Dronederone

1. Use comparative pharmacokinetic information for Dronederone to identify the Cmax value needed for DDIRC*
2. Use comparative metabolising enzyme information for Dronederone to identify the Ki value needed for DDIRC*
3. Use DDIRC to identify drugs that are victim for CYP3A4
   - Quickly get the list of possible drugs that be part of the exclusion criteria in your trial

* In cases where you cannot identify comparative Cmax or Ki values, default settings can be used to run an initial analysis in DDIRC.
Pharmacokinetic module

Extracted information lets you limit search to specific parameters including:

**Absorption**
- % Absorbed
- Bioavailability
- Concentrations
- Fraction absorbed
- Time values

**Binding**
- Cell binding
- Protein binding

**Biotransformation**
- Enantiomeric ratio
- Metabolic ratio
- Metabolic stability
- Metabolic transformation

**Distribution**
- Accumulation
- AUC
- Permeation
- Steady state
- Time value
- Tissue distribution
- Volume of distribution

**Elimination**
- Clearance
- Excretion values
- Half life
- Rate constants
- Time

**Species**
- Human
- Vertebrates
- Birds
- Fish
- Mammals
Metabolizing enzyme and transport module

MET information includes extracted content from FDA and EMA approval documents, FDA advisory committee meetings and journals

**Metabolites**
Created, when available

**CYPs**
Either involved in the metabolism or up/down regulated by the drug, quantitative and qualitative data

**Phase 2 Enzymes**

**Transporters**
And drug effects on transporters

**In Vitro**
*Dynamic parameters* such as CLint (Intrinsic Clearance) and Km (Michaelis Constant), Vmax (Maximum rate of reaction)

**DDI Studies**
Ratio of AUC, Clearance, etc. in presence of another drug.

All with drug as: **Substrate, inducer or inhibitor**
Use comparative PK information for Dronederone to identify the Cmax value to input into the DDI Risk Calculator

Input the Cmax value into DDIRC

➢ Search Pharmaco-kinetic information in DMPK to identify the Cmax measured *in vivo* using 400 mg of Dronedarone in repeated doses
Identify Cmax value for Dronederon
Filter for results on orally administered drugs and healthy subjects. Exclude results for metabolites.

Choose a Cmax value from a trial with no influence of concomitants and related to a multiple dosing regimen. Enter this Cmax value (101.0 ng/ml) into DDIRC.
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Identify Ki value for Dronederone
Filter for information CYP3A4 inhibitor – we will use data obtained using human liver microsomes (HLM)

<table>
<thead>
<tr>
<th></th>
<th>Drug Name</th>
<th>Enzyme</th>
<th>Test System</th>
<th>Activity</th>
<th>Ki</th>
<th>IC50</th>
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<tbody>
<tr>
<td>1</td>
<td>Dronedarone Hydrochloride</td>
<td>CYP3A4</td>
<td>Liver, microsomes</td>
<td>Unreported</td>
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<td></td>
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<td></td>
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<td>8.12</td>
<td>umol/L</td>
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<td>2</td>
<td>Dronedarone Hydrochloride</td>
<td>CYP3A4</td>
<td>Liver, microsomes</td>
<td>Oxidized Nifedipine</td>
<td></td>
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<tr>
<td>3</td>
<td>Dronedarone Hydrochloride</td>
<td>CYP3A4</td>
<td>Liver, microsomes</td>
<td>Oxidized Nifedipine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36.4 uM</td>
</tr>
<tr>
<td>4</td>
<td>Dronedarone Hydrochloride</td>
<td>CYP3A4</td>
<td>Liver, microsomes</td>
<td>Oxidized Nifedipine</td>
<td></td>
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<tr>
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<td>36.4 uM</td>
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<tr>
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<td>CYP3A4</td>
<td>Liver, microsomes</td>
<td>Oxidized Nifedipine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In this example, we have chosen a Ki value of 36.4 µM (substrate = nifedipine)
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Use DDIRC to identify drugs that are victim for CYP3A4

- Perpetrator: Dronedarone, dose 400 mg
- Inhibitor of CYP3A4
- Parameters:
  - Red — values found in other DMPK modules
  - Blue — default values
  - Green — user-provided values

* Using default values results in worst-case scenario (explain…)

Add 0.399 as the value for microsomal binding and 0.4 g/L for protein concentration

Keep default values*
Results show drugs with the highest risk of DDI

Open up the Drugs tab in the Excel export and view data for ‘All therapeutic classes’
Anticholesterol drugs are showing high risk

**Challenge:** Many patients that we would like to enrol in the CT are using anticholesterol therapy
Take a closer look at ‘Anticholesterol’ drugs to evaluate drugs with the highest/lowest risk
Thank You!

• Q&A will be sent to you by email. For more information and questions please contact your regional office
• Our next PharmaPendium webinar will introduce new FAERS search summary tables and visualisations, as well as our new Saved Search functionality on October 31st
• Please fill out the survey that appears on your screen after leaving the webinar

Any questions?
Thank you!

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