Identifying and assessing drug-drug interactions

For more successful analysis and prioritisation of drug candidates

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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
  - Impact of drug-drug interactions (DDIs)
  - How identification of DDIs informs drug development decisions through to post-market

• 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

• Finding information on drug-drug interactions in the literature
  - Leveraging 3-level indexing in Embase to identify DDIs reported in the literature
  - Demo
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 polypharmacy¹

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)
DMPK Solution: Supporting informed decision-making with a more complete picture of DDIs and drug candidate risk assessment

- Comprehensive data from FDA and EMA Approval packages and literature provides a greater understanding of pharmacokinetic (PK) properties of a drug candidate within the context of the complete landscape of approved drugs
- Deepest, most detailed information specific for metabolising enzymes and transporters (MET) enables greater insight into drug-drug interactions for FDA- and EMA-approved drugs

DDI Risk Calculator (DDIRC)

- Fast identification of potential metabolism-based DDIs, informing critical decisions on which drugs to progress, clinical DDI studies to perform and risk mitigation strategies to follow
- Uses PK and MET data to calculate the risk of DDIs between a candidate and marketed drugs
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**)

Previous evidence suggests that 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* data.

**Predicting hepatic clearance**

*In vitro* clearance ($C_{\text{int}}$) 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 ($C_{\text{int, in vivo}}$)
- The ‘Well Stirred’ model is applied to determine level of hepatic clearance in the body ($C_{\text{in vivo}}/L/h$)
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.
Dedicated DDI studies and clinical trials are required during drug development

According to the FDA, the overall objective of interaction studies for a new drug is to determine:

- whether any interactions are sufficiently large to necessitate a dosage adjustment of the drug itself or of the drugs with which it might be used
- whether any interaction calls for additional therapeutic monitoring
- whether there should be a contraindication to concomitant use when lesser measures cannot mitigate risk.

Real example of how DDIRC impacts clinical trial design

No DDI predicted with sensitive substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6

Significant DDI predicted with some sensitive substrates of CYP3A4

CYP3A4 substrates prohibited from clinical trials
DRUG AS A VICTIM

What medications could largely decrease the bioavailability of my drug, thus leading to lack of efficacy?

Which drugs may actually increase the bioavailability of my drug, leading to a risk of potential adverse effects?
Use Case:

The use case is for a drug candidate which is a victim drug. There are only two pieces of information you need to do this use case:

- Compound name
- fmE (fraction metabolized) value(s)

We will demonstrate this use case with a drug candidate being a substrate of CYP2D6. CYP2D6 is largely expressed in the liver and metabolizes approximately 25% of clinically used drugs. Given the importance of this enzyme, we will demonstrate a simple use case that can be used to assess risk of DDIs for drugs which are substrates of CYP2D6.
Summary of Use Case 1

- Demonstrated an example of what kind of DDI Risk can be observed with a drug candidate that is a substrate of CYP2D6
- Enter information on just a few fields to immediately get to the results table. This example focuses more on the output of the data than the input of the data.
- Demonstrated how the visual display of risk enables quick retrieval of insights on DDIs across drug classes
- Directly apply these insights for improving drug candidate selection and clinical trial study design
Finding information on drug-drug interactions in the literature (Embase)
Comprehensive content coverage

Embase is the most comprehensive biomedical database. It contains over 2,900 journals that cannot be found in MEDLINE.

- Over 8,600 Journals
- Indexing of trial- and study types, systematic reviews and meta-analysis
- Content focuses on key areas for drug, disease and device research
- >33m records, including 2.1m+ conference abstracts
- Unique coverage of non-English RCTs
How does Embase deliver value?

- By including literature and information resources in a **timely manner**
- By reading full-text to identify drugs, diseases, adverse affects, clinical trials, drug trade names, etc.
- By enabling advanced search filters to **drill down** a comprehensive search to a relevant and manageable record set.
- By allowing users to **automate searching** and result management.

**Deep indexing using own taxonomy (EMTREE)**

**Very powerful search environment**

**E-mail Alerting**

**API**

**Interoperability**

**We make sure you don’t miss any biomedical literature**

**The only close alternative is reading all the articles**

**Good precision and recall balance**

**Automation and documentation**
Indexing for Embase is a manual process performed by trained indexers with a biomedical background, with the exception of articles designated for automatic indexing.

Indexers read and analyze the full text of articles in order to identify relevant concepts (drugs, diseases, devices, clinical trials, drug trade names) and index them with the most specific Emtree terms.

Index terms are controlled by the Emtree thesaurus resulting in consistent coverage of concepts that may be expressed in many different ways in the literature.
Indexing: subheadings

**Subheadings** are Emtree terms that are also used as concept qualifiers for drugs, diseases and devices to refine their meaning, providing a very precise idea of what an article covers (provide additional information about the context, e.g. drug induces an adverse drug reaction).
Indexing: key subheadings

Nine subheadings are denoted *key subheadings*.

<table>
<thead>
<tr>
<th>Term</th>
<th>Key Subheading</th>
</tr>
</thead>
<tbody>
<tr>
<td>drug</td>
<td>adverse drug reaction</td>
</tr>
<tr>
<td>drug</td>
<td>drug combination</td>
</tr>
<tr>
<td>drug</td>
<td>drug comparison</td>
</tr>
<tr>
<td>drug</td>
<td>drug interaction</td>
</tr>
<tr>
<td>drug</td>
<td>drug therapy</td>
</tr>
<tr>
<td>device</td>
<td>adverse device effect</td>
</tr>
<tr>
<td>device</td>
<td>device comparison</td>
</tr>
<tr>
<td>disease</td>
<td>drug therapy</td>
</tr>
<tr>
<td>disease</td>
<td>side effect</td>
</tr>
</tbody>
</table>
Indexing: triple-linking

**Triple-indexing** is three level indexing of the full text of an article. It consists of:
- Concept (drug or device or disease)
- Key subheading (**relationship**)
- Linked concept (e.g. stomatitis, hypertension, stroke, nausea, etc.)

Triple indexing has started in Q1 of 2007 for the **drug triples** (drug therapy from Q2 of 2009). **Devices** began in Q2 of 2014.

![Diagram of Everolimus and Erythromycin interaction](image)
How can drug-drug interactions be searched

Filter options
For each drug manually extracted semantic relationships can be identified and filtered
1. search a drug name
2. use drug filter

Search query language
• 'irbesartan'/'drug interaction'
• 'irbesartan'/'drug interaction'/'aliskiren'
Relationships identified in literature with triple-indexing can identify relationships of the drug Everolimus

Data analytics based on manually extracted semantic relationships between:

- Drug – Disease
  - Adverse Reactions
  - Therapy
- Drug – Drug
  - Interactions
  - Combinations
  - Comparison

Very valuable for:

- Drug repurposing
- Drug development
- Drug safety
Demo

1) a **post-market example** where you want to see if there are mentions of DDI’s in the literature with your drug and others

2) after you use DDIRC to predict potential interactions, you can use Embase to take a look at drugs that belong to the same **drug class** to see for which drugs there are DDI’s reported and what effect the DDI has
Example 1. Marketed drug: losartan

1. Search drug name
2. Use drug filter
3. Export the list of interacting drugs

This can be used to better inform which drugs should most likely not be co-administered.
Example 2. DDIRC and Embase are complimentary

Once you’ve id’d a DDI using the risk calculator, you can take a much more in-depth look in the literature (Embase) to see if anything similar has been reported. The two are complimentary.
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Embase searches:
'diltiazem'/'drug interaction' AND [2010-2017]/py
'losartan'/'drug interaction' AND [2010-2017]/py
'irbesartan'/'drug interaction' AND [2010-2017]/py
Example 3. Drug class: antihypertensives

You can use Embase to take a look at drugs that belong to the same drug class to see for which drugs there are DDI’s reported and what effect the DDI has. This can be used to better inform which of antihypertensive drugs have higher potential for DDI.

Embase search:
'antihypertensive agent'/exp/'drug interaction' AND [2010-2017]/py
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 is on ‘Informing drug development and regulatory approval strategies with comparative pharmacokinetic data in PharmaPendium’ on May 23rd.
- The next Embase webinar is on how to ‘Get the best out of Embase with systematic searching using Emtree’ and will take place May 24th.
- Please fill out the survey that appears on your screen after leaving the webinar.

Any questions?
Thank you!

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