Identifying Drug-Drug Interactions using PharmaPendium

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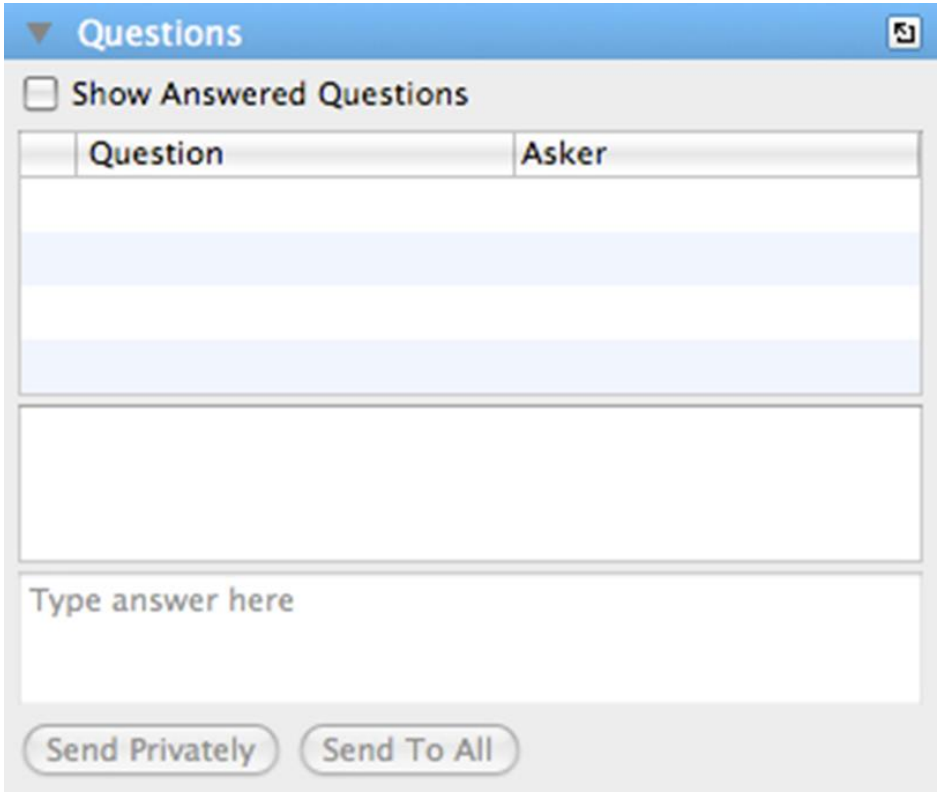
Need to know

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:

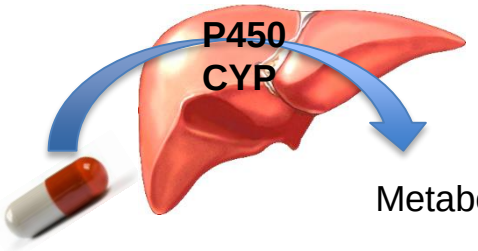
- More drugs — and many more combinations of drugs — are being used to treat patients than ever before.
  - Between 1995 and 2010, the proportion of adults dispensed ≥5 drugs **doubled** to 20.8%, and the proportion dispensed ≥10 **tripled** to 5.8%.[1]
- The rate of ADRs increases exponentially after 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

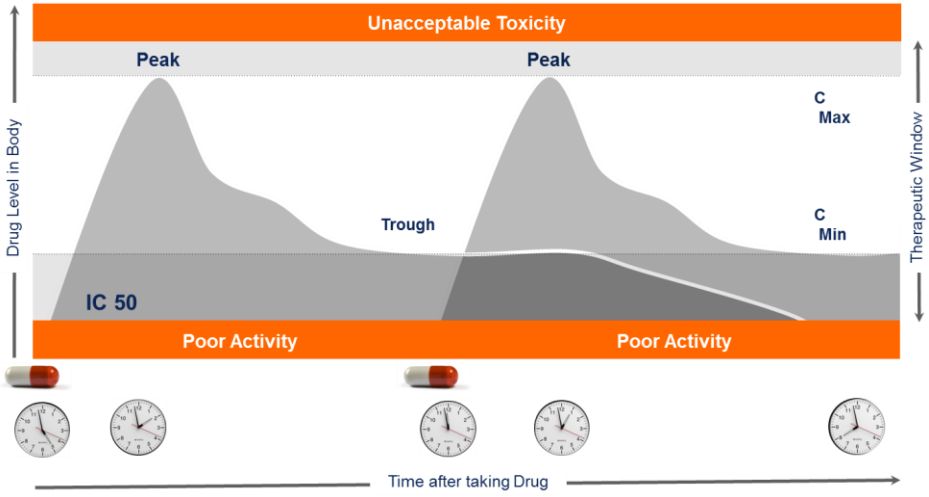
Measured by AUC (area under the curve), which increases/decreases

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

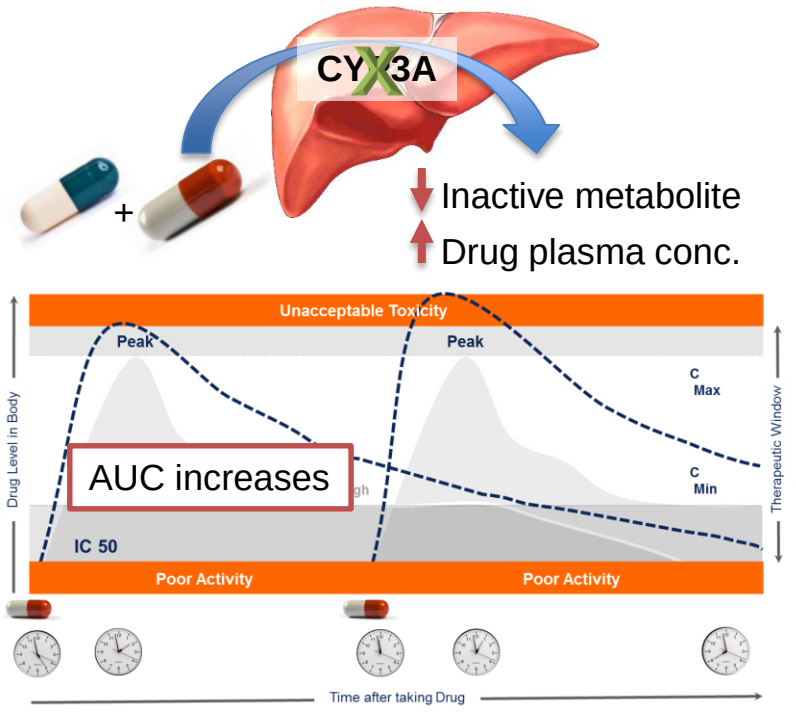
Concomitant drug = two or more drugs are taken at (almost) the same time



E.g., Drug A is administered orally and metabolised by CYP3A

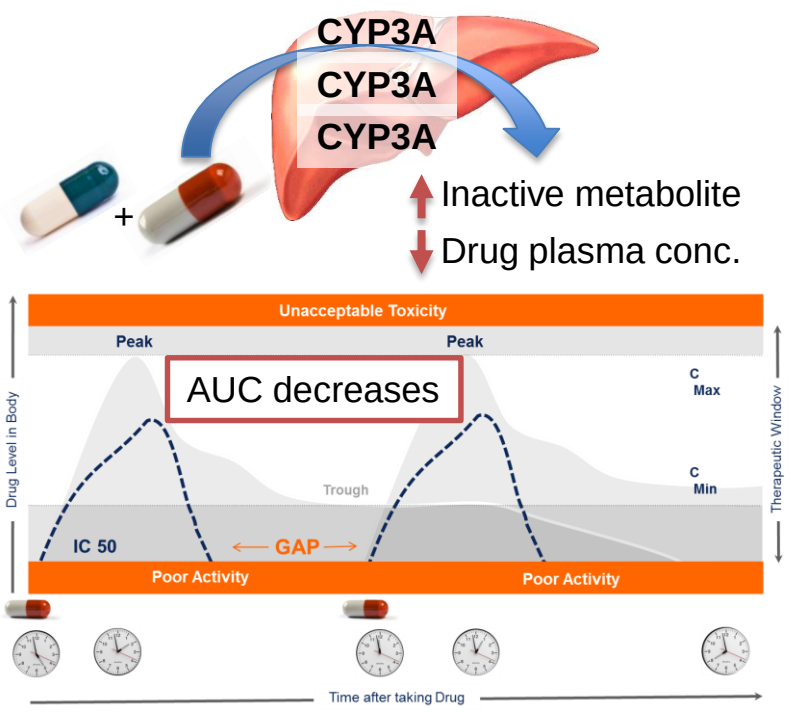
Dosage is timed so that plasma concentration levels remain high enough to maximize efficacy and low enough to avoid toxicity.

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**.

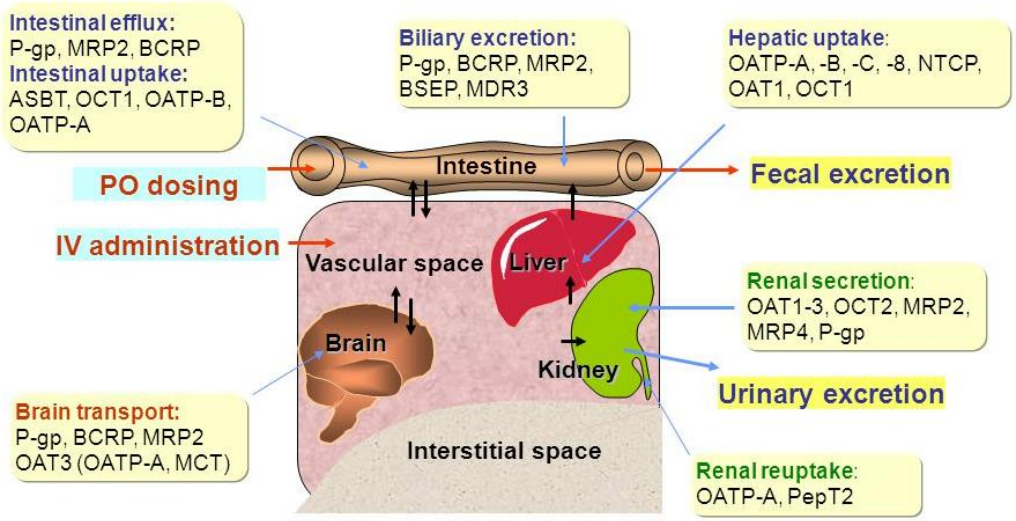
Concomitant drug **induces** CYP-mediated metabolism



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)

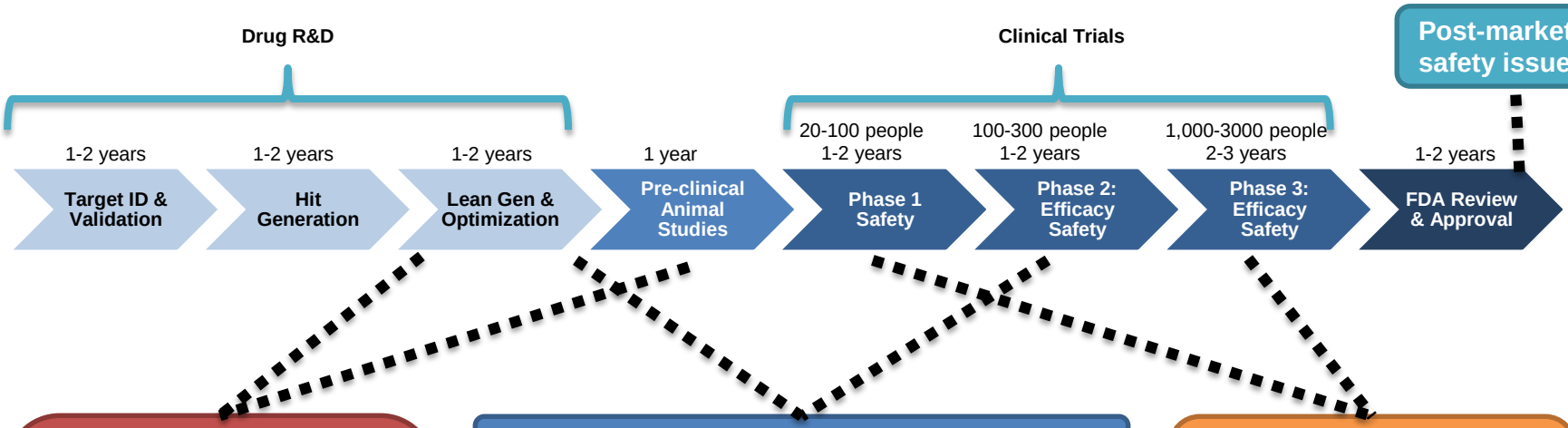


Boehringer Ingelheim
http://slideplayer.com/slide/5810493/

➢ 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

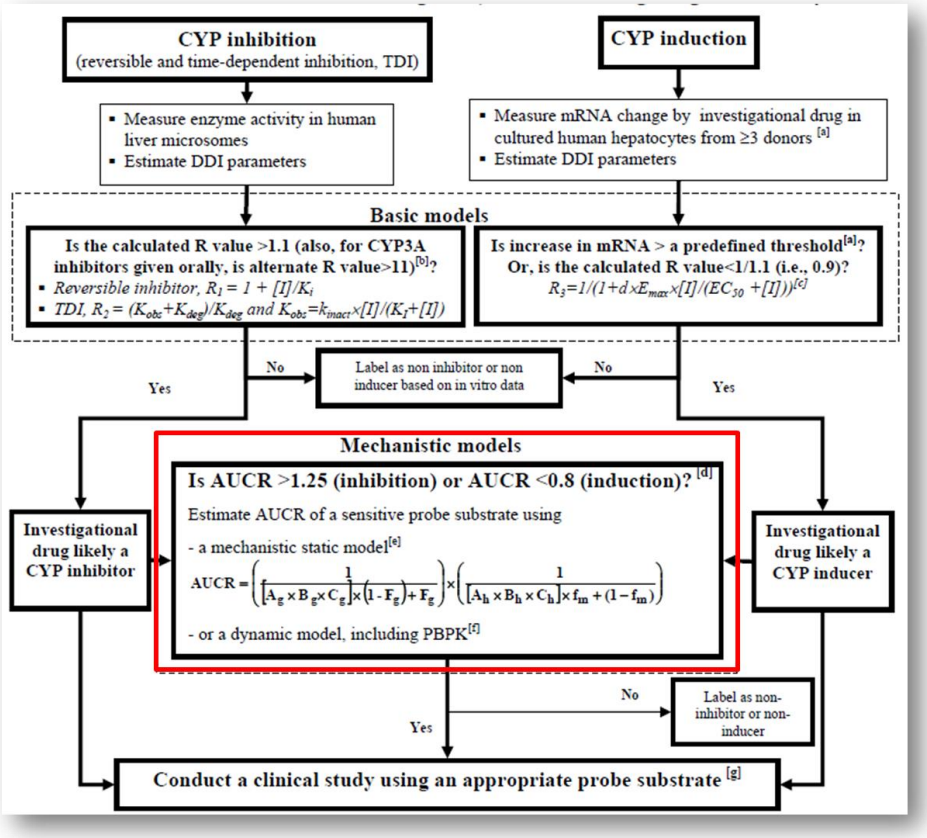
Recommend alternative drugs that may be co-administered to reduce DDI risk*

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).**

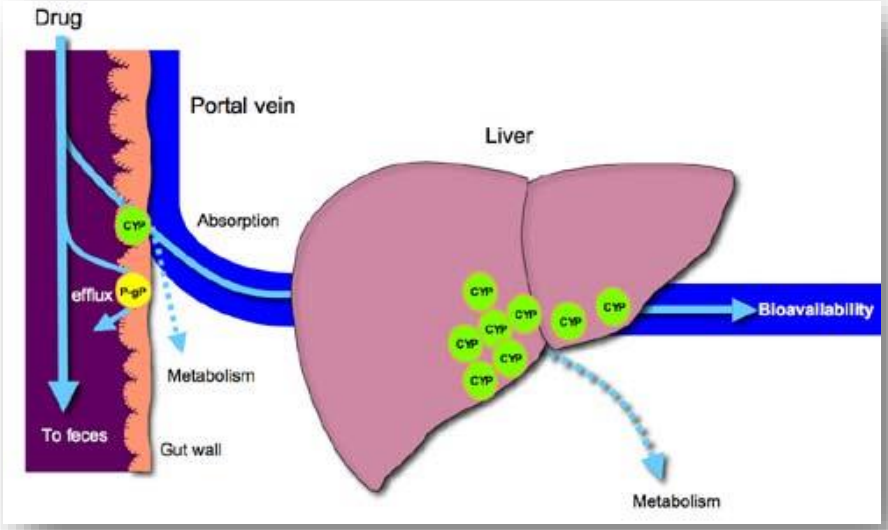
* Also applies to IV administered victim drugs with low clearance (i.e., low hepatic extraction ratio EH<0.3)

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

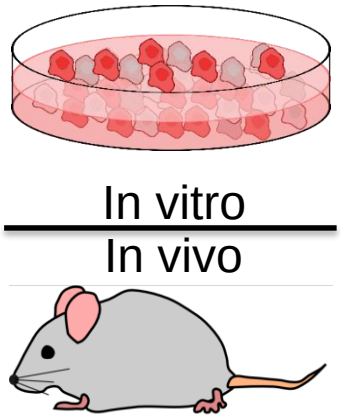


http://usmle1-topscorer.blogspot.co.uk/2011/10/general-pharmacology-2-for-usmle1.html

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.

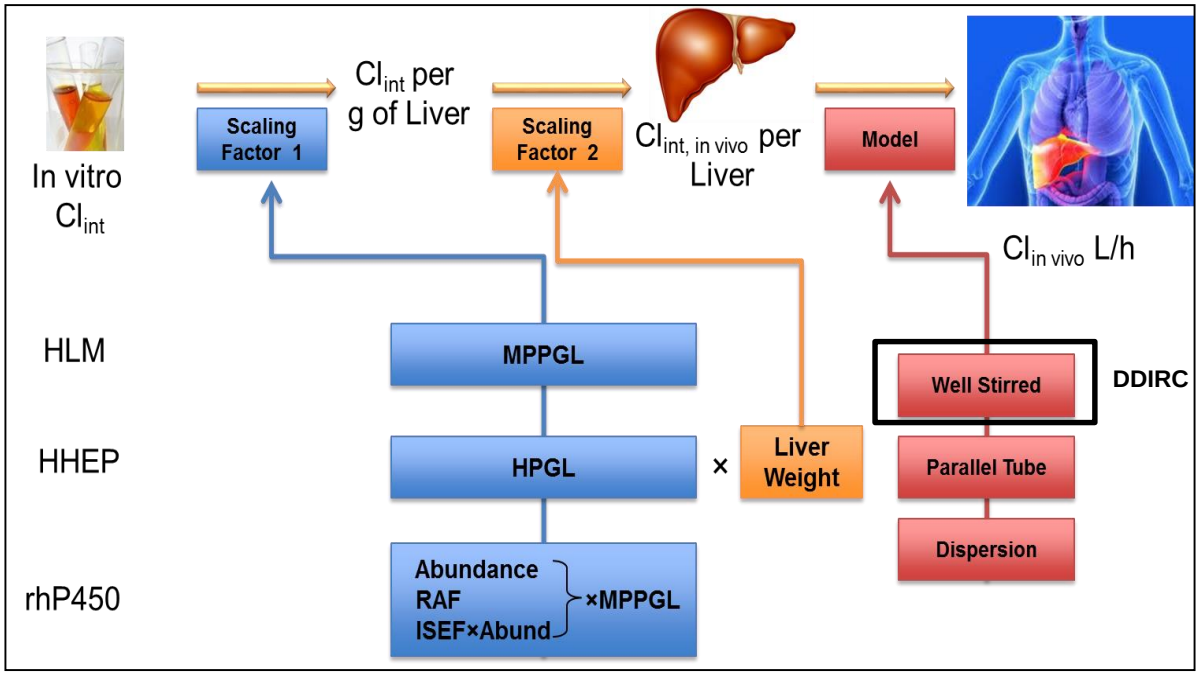
Therefore, data generated with an *in vitro* system can be extrapolated to *in vivo* by scaling up values to correlate with the total amount of enzyme present in the *in vivo* system.

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 (Cl_{int}) values are determined (K_m and V_{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 ($Cl_{int,\ in\ vivo}$)
- The '**Well Stirred' model** is applied to determine level of hepatic clearance in the body $Cl_{in\ vivo}$/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

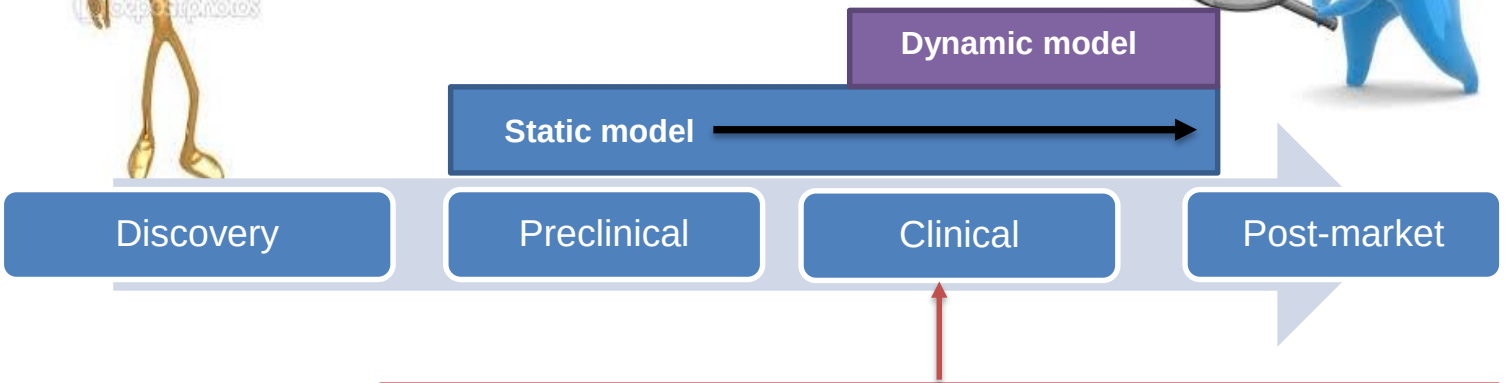
The FDA recommends a stepwise, model-based evaluation of metabolism-based interactions

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 assesses 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 paramaters for Dronederone

1. Use comparative pharmacokinetic information for Dronederone to identify the Cmax value needed for DDIRC*
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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

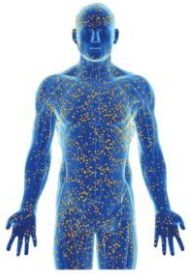
* In cases where you cannot identify comparative Cmax or Ki values, default settings can be used to run an initial analysis in DDIRC.

Pharmacokinetic module

Extracted information lets you limit search to specific parameters including:

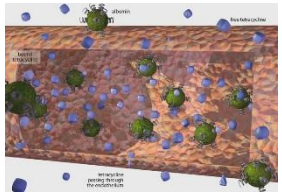
Absorption

Includes:
- % Absorbed
- Bioavailability
- Concentrations
- Fraction absorbed
- Time values



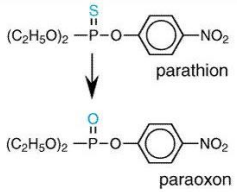
Binding

Includes:
- Cell binding
- Protein binding



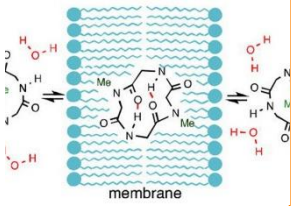
Biotransformation

Includes:
- Enantiomeric ratio
- Metabolic ratio
- Metabolic stability
- Metabolic transformation



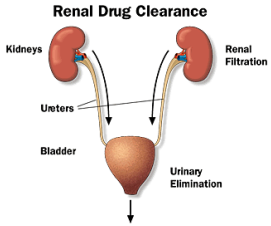
Distribution

Includes:
- Accumulation
- AUC
- Permeation
- Steady state
- Time value
- Tissue distribution
- Volume of distribution



Elimination

Includes:
- Clearance
- Excretion values
- Half life
- Rate constants
- Time



Species

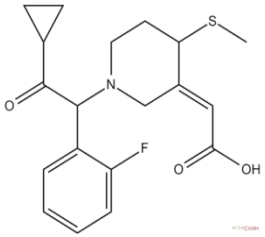
Includes:
- Human
- Vertebrates
  - Birds
  - Fish
  - Mammals

Metabolizing enzyme and transport module

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

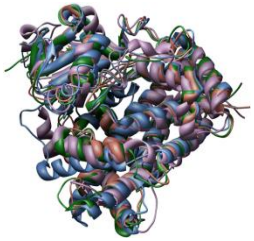
Metabolites

Created, when available

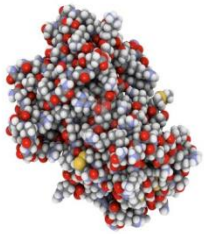


CYPs

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

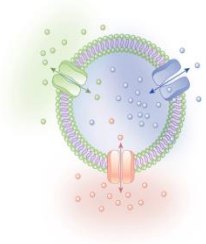


Phase 2 Enzymes



Transporters

And drug effects on transporters



In Vitro

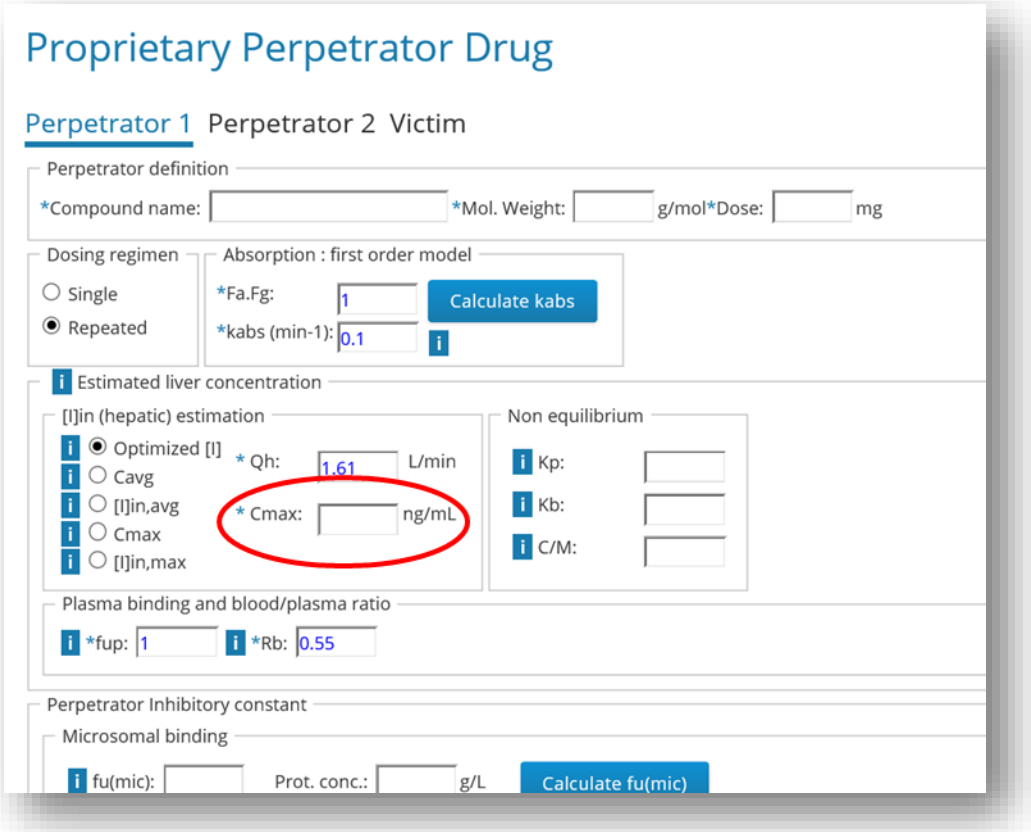
***Dynamic* parameters** such as CLint (Intrinsic Clearance) and Km (Michaelis Constant), Vmax (Maximum rate of reaction)

DDI Studies

Ratio of AUC, Clearance, etc. in presence of another drug.

All with drug as: **Substrate, inducer or inhibitor**

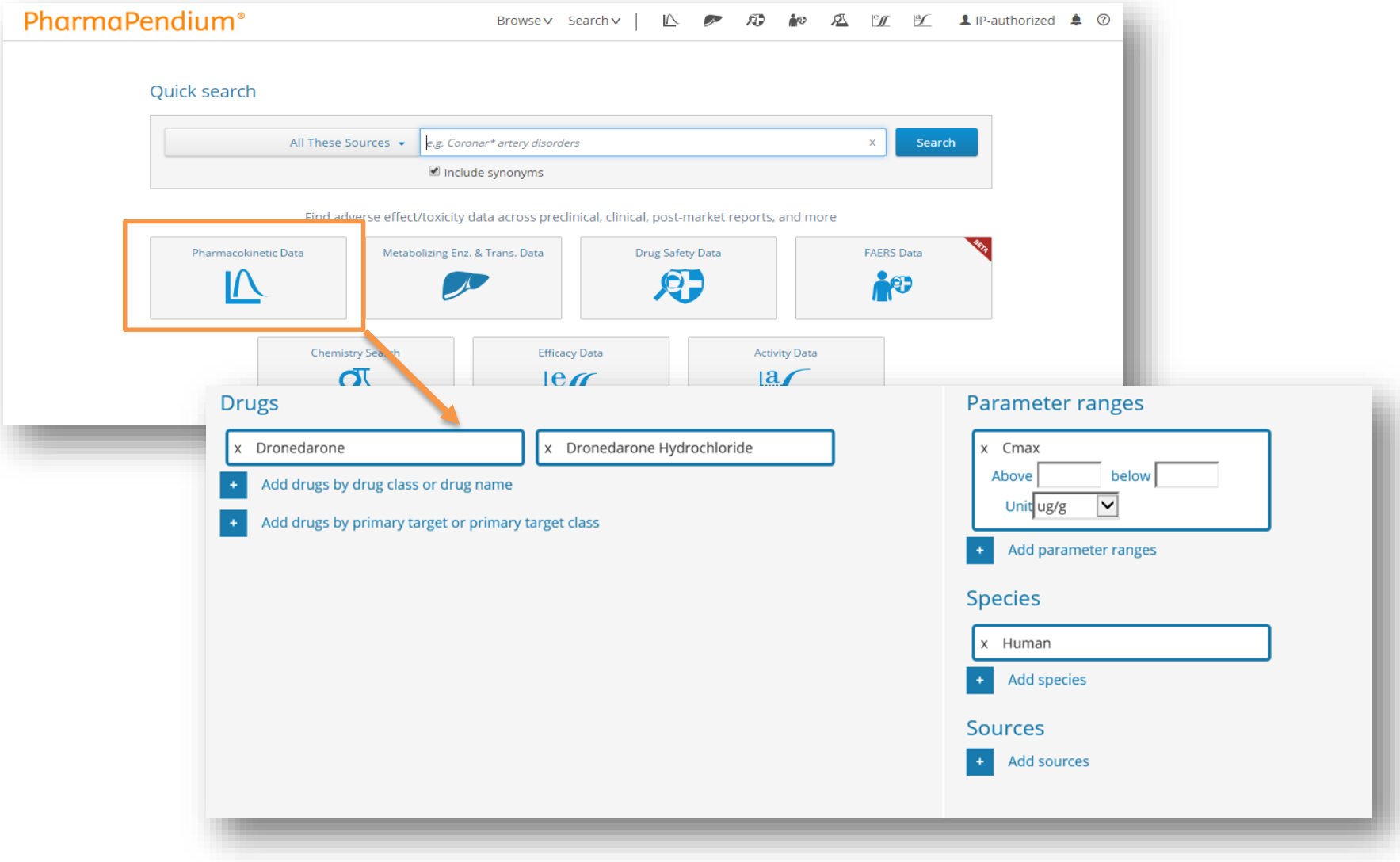
Use comparative PK information for Dronederone to identify the Cmax value to input into the DDI Risk Calculator



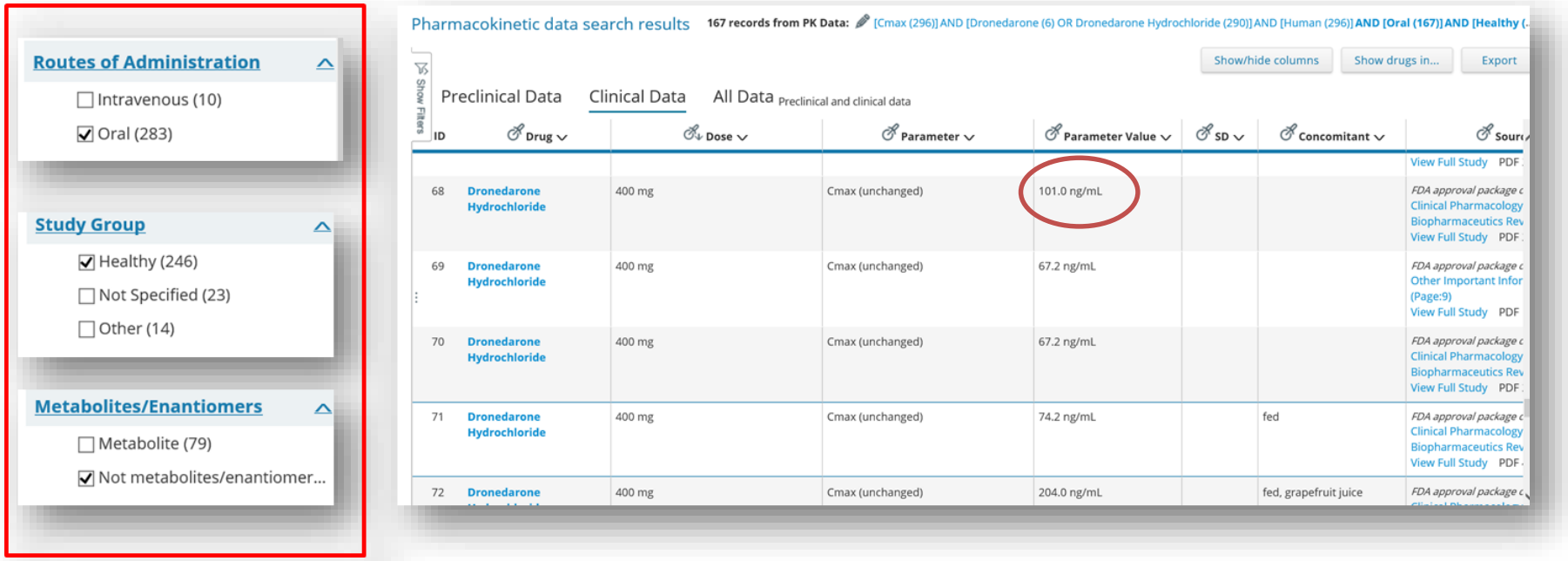
Input the Cmax value into DDIRC

- 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 Dronederone



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 regiment. Enter this Cmax value (101.0 ng/ml) into DDIRC.

Example: Define inclusion/exclusion criteria related to concomitant drugs

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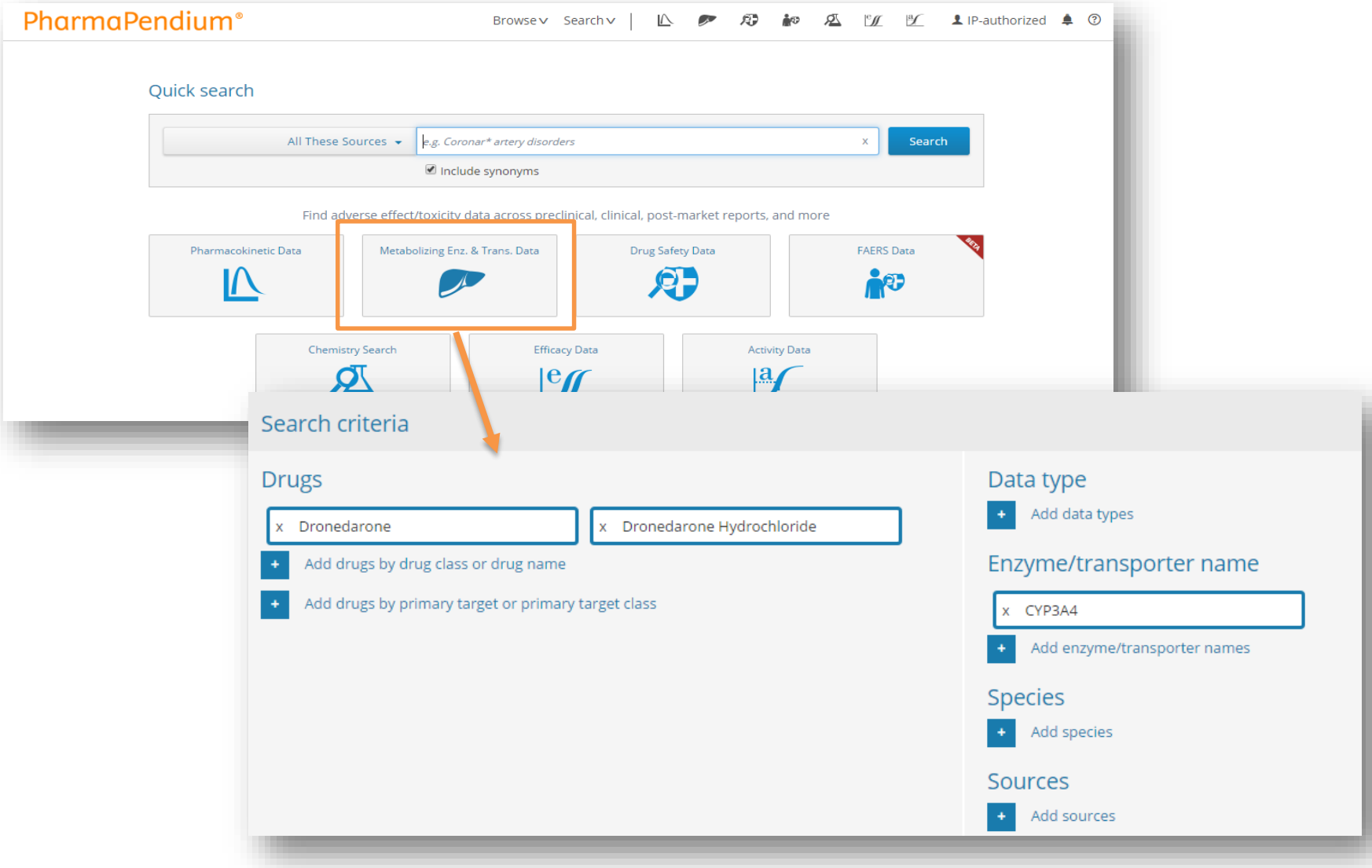
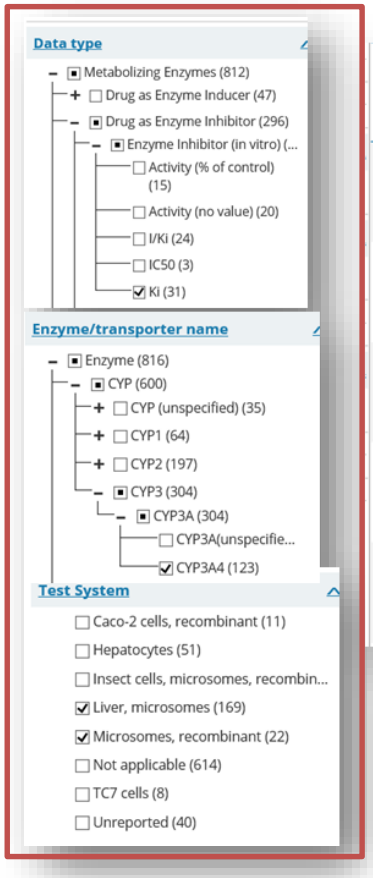
Identify Ki value for Dronederone



Filter for information CYP3A4 inhibitor – we will use data obtained using human liver microsomes (HLM)



1	Dronedarone Hydrochloride	CYP3A4	Liver, microsomes	Unreported	Nifedipine, 30 uM	Ki	8.12 umol/L
2	Dronedarone Hydrochloride	CYP3A4	Liver, microsomes	Oxidized Nifedipine	substrate	Ki	37.3 uM
3	Dronedarone Hydrochloride	CYP3A4	Liver, microsomes	Oxidized Nifedipine	substrate	Ki	36.4 uM
4	Dronedarone Hydrochloride	CYP3A4	Liver, microsomes	Oxidized Nifedipine	substrate	Ki	36.4 uM
5	Dronedarone Hydrochloride	CYP3A4	Liver, microsomes	Unreported	Nifedipine, 20 uM	Ki	36.4-48.6 umol/L
6	Dronedarone Hydrochloride	CYP3A4	Liver, microsomes	Oxidized Nifedipine	substrate	Ki	48.6 uM

In this example, we have chosen a Ki value of 36.4 µM (substrate = niffedipine)

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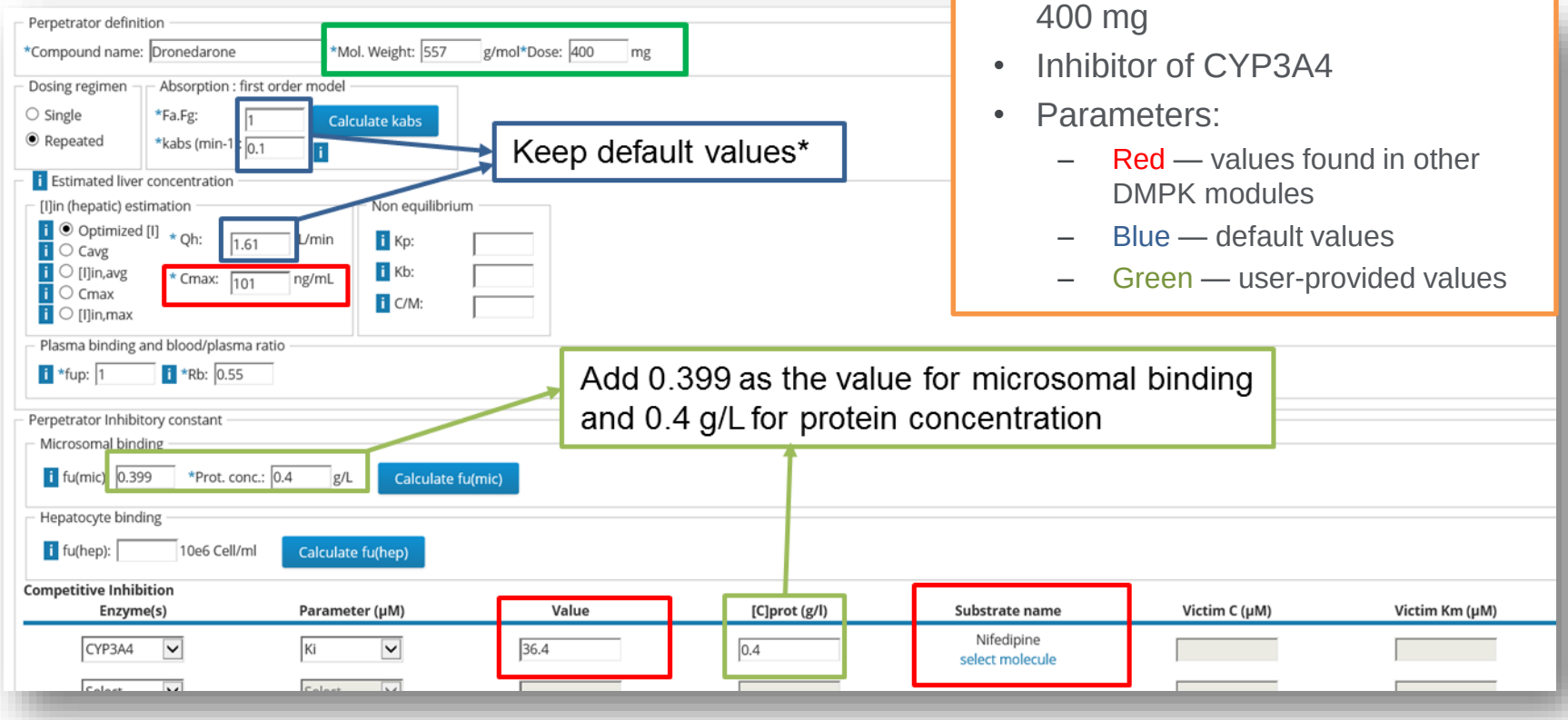
Use DDIRC to identify drugs that are victim for CYP3A4



- 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…)

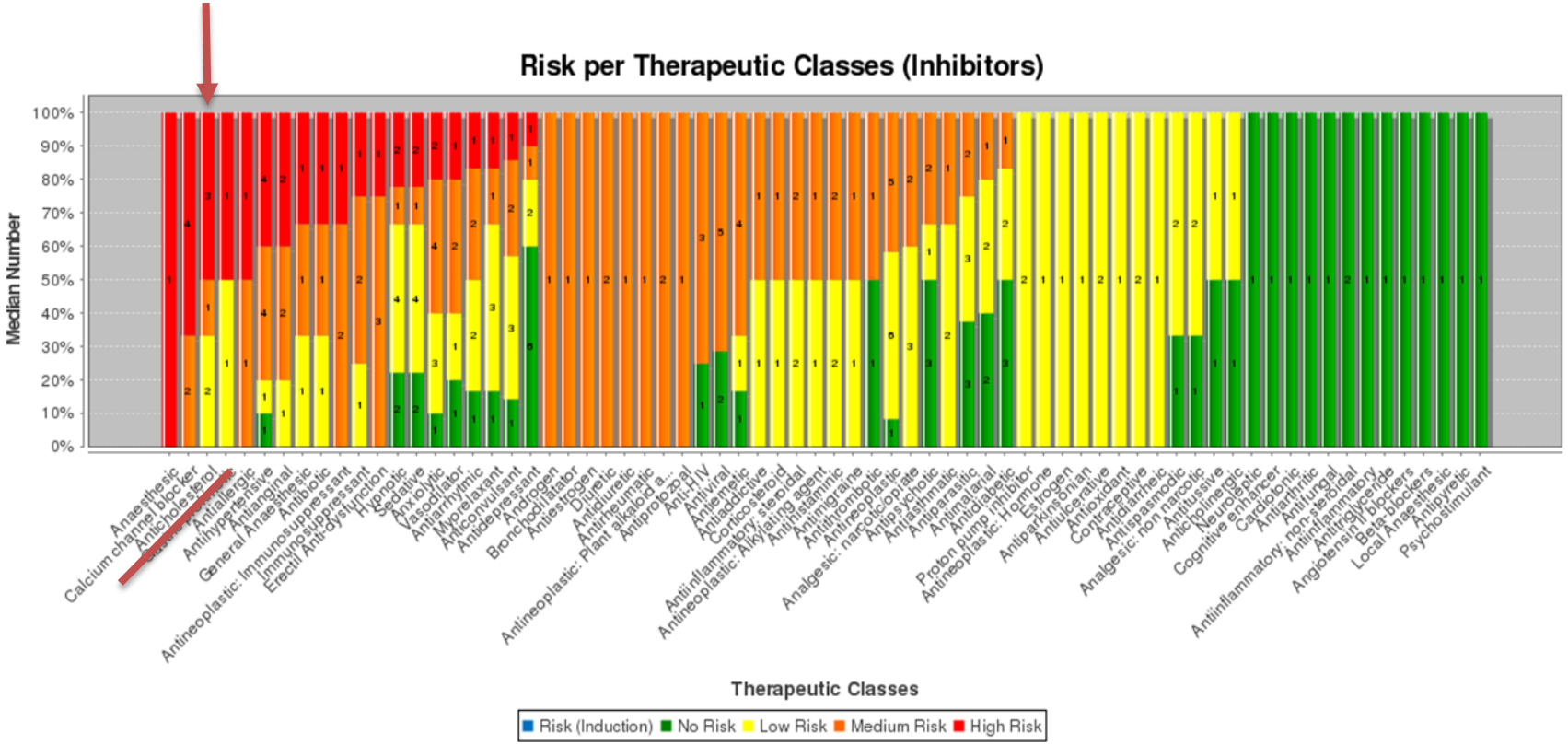
Results show drugs with the highest risk of DDI

ID	Victim	Dose	AUC Ratio	Count	Min.	Max.	Mean	SD	Med.	5-95th P
	Drug Type:Experimental/Investigation									
128	**Saxagliptin** 741054 Antidiabetic Drug Type:Approved	0.4 g		1	2.23	2.23	2.23	0	2.23	2.23-2.23
129	**Sildenafil** 163249 Erectil Anti-dysfunction Drug Type:Approved	0.4 g		2	4.8	5.97	5.38	0.59	5.38	4.86-5.91
130	**Simvastatin acid** 567157 Anticholesterol Drug Type:Unspecified	0.4 g		1	2.52	2.52	2.52	0	2.52	2.52-2.52
131	**Simvastatin** 170569 Anticholesterol Dev.:+ Drug Type:Approved	0.4 g		12	3.95	29.83	12.92	8.86	10	3.95-26.67
132	**Solifenacin** 481020 Antispasmodic Dev.:+ Drug Type:Approved	0.4 g		1	1.61	1.61	1.61	0	1.61	1.61-1.61
133	**Sunitinib**	0.4 g		1	1.51	1.51	1.51	0	1.51	1.51-1.51

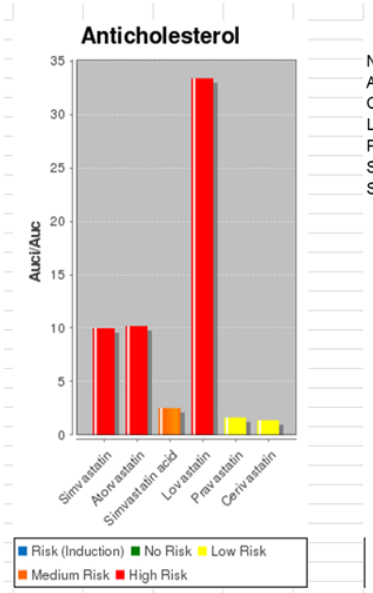
Open up the Drugs tab in the Excel export and view data for 'All therapeutic classes'

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



Victim		Perpetrator1		AUC Ratio						
Name	Therapeutic class	Name	Dose/unit	Min	Max	Mean	SD	Median	5th Perc.	95th Perc.	Count
Atorvastatin	~Anticholesterol~	Dronedarone	0.4 g	6.45	13.96	10.2	3.75	10.2	6.82	13.58	2
Cerivastatin	~Anticholesterol~	Dronedarone	0.4 g	1.39	1.39	1.39	0	1.39	1.39	1.39	2
Lovastatin	~Anticholesterol~	Dronedarone	0.4 g	33.39	33.39	33.39	0	33.39	33.39	33.39	3
Pravastatin	~Anticholesterol~	Dronedarone	0.4 g	1.65	1.65	1.65	0	1.65	1.65	1.65	1
Simvastatin acid	~Anticholesterol~	Dronedarone	0.4 g	2.52	2.52	2.52	0	2.52	2.52	2.52	1
Simvastatin	~Anticholesterol~	Dronedarone	0.4 g	3.95	29.83	12.92	8.86	10	3.95	26.67	12

Color	AUC ratio Range	Category
	>5	High risk
	2-5	Medium risk
	1.25-2	Low risk
	0.8-1.25	No risk
	<0.8	Risk (Induction)

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?

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Thank you!

Any questions?