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R&D Solutions

Identifying drug-drug interactions using PharmaPendium

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Empowering Knowledge

Agenda

- Brief overview of drug-drug interactions
- Introduction to DMPK Solution
  - Metabolising enzymes & transporters data
    - Demo
  - Drug-drug interaction risk calculator
    - Demo of proprietary drug as a victim
    - Demo of proprietary drug as a perpetrator
- Questions

Early and ongoing assessment of Drug-Drug Interactions 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**

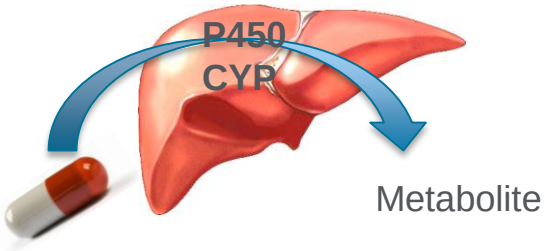
- According to the FDA, DDI-related adverse drug reactions are on the r
  - More drugs — and many more combinations of drugs — are bein used to treat patients than ever before.
    - Between 1995 and 2010, the proportion of adults dispensed drugs doubled to 20.8%, and the proportion dispensed ≥10 tripled to 5.8%.[1]
  - The rate of ADRs increases exponentially after a patient is on 4 o 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

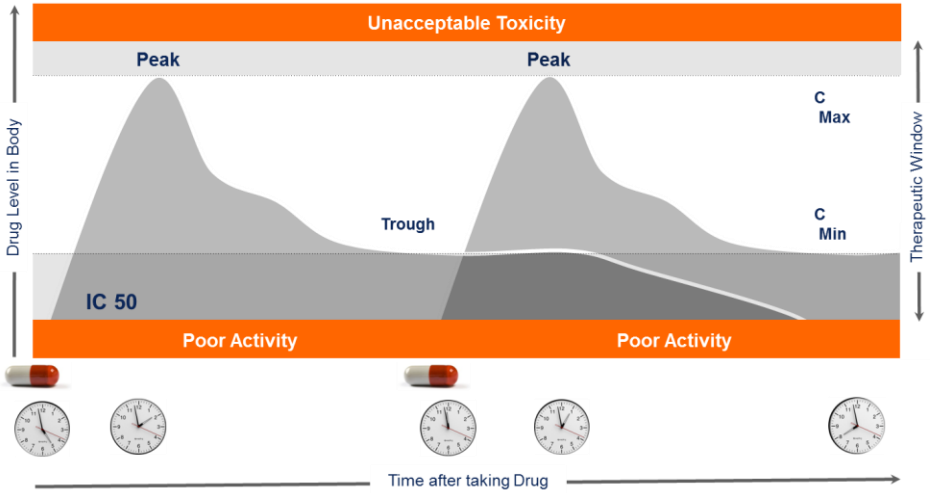
Measured by AUC (area under the curve), which increases/decreases

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

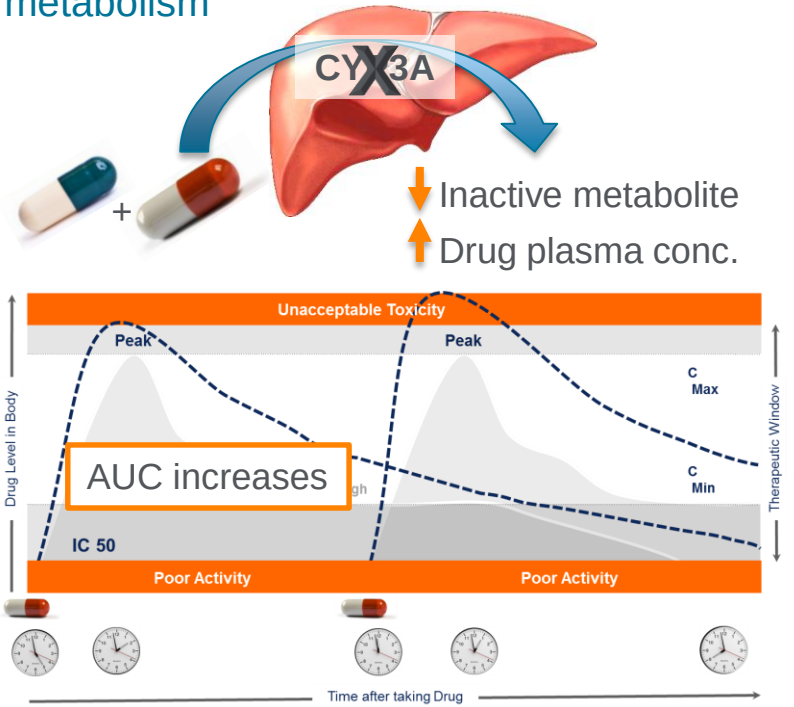
Concomitant drug = two or more drugs are taken at (almost) the same time



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

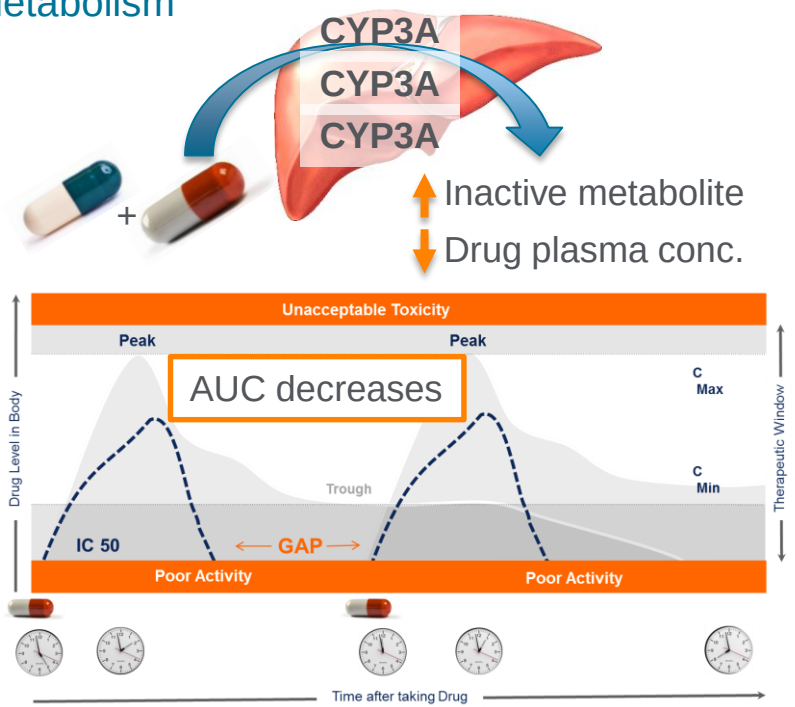
Dosage is timed so that plasma concentration levels remain high enough to maximize efficacy and low enough to avoid toxicity.

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**.

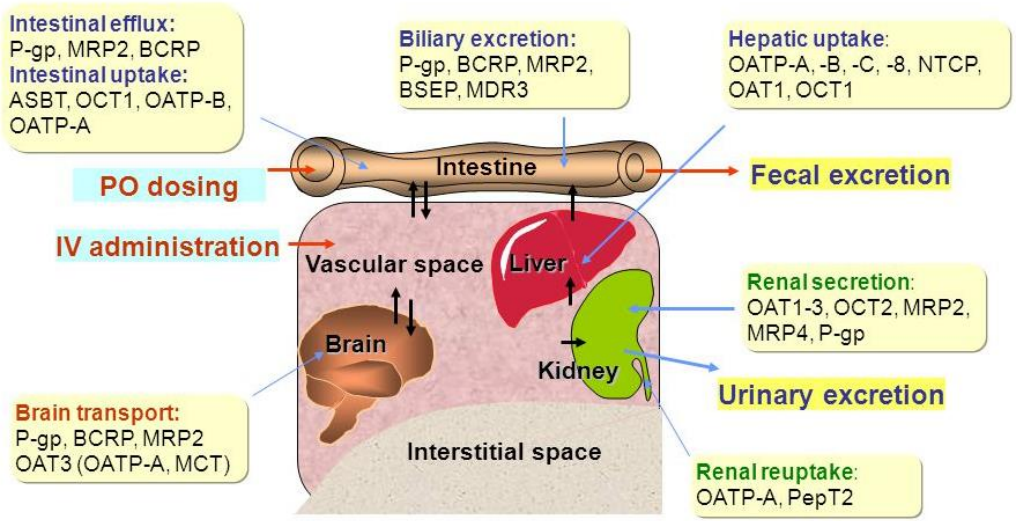
Concomitant drug **induces** CYP-mediated metabolism



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**

DMPK Solution

Supports informed decision-making by providing a more complete picture of potential DDIs for drug candidate risk assessment

- Comprehensive data from FDA and EMA Approval packages and literature provides a greater understanding of pharmacokinetic 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 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.
- Data can be utilized from the PK and MET modules to calculate the risk of DDIs between a candidate and marketed drugs

DMPK Solution content enables prediction and assessment of drug interactions

Source Documents

2.3M+
pages of FDA approval documents

215K+
pages of EMA approval documents

10.4M+
FDA AERS reports

690K+
Pages from FDA Advisory Committee Meetings

Extracted Data

4485
Drugs indexed & fully searchable

1.64M+
PK data lines

315K+
Metabolizing enzyme and transporter data lines

DDIRC

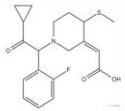
238
unique drugs assessed as a victim

521
drugs assessed as a perpetrator

Search using a wide range of MET and PK parameters

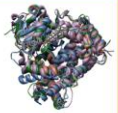
Metabolites

Created, when available

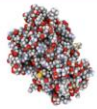


CYPs

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)

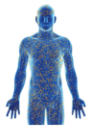
DDI Studies

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

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

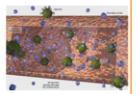
Absorption

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



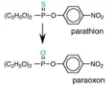
Binding

Includes:
- Cell binding
- Protein binding



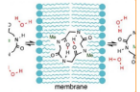
Biotransformation

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



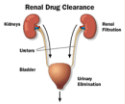
Distribution

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



Elimination

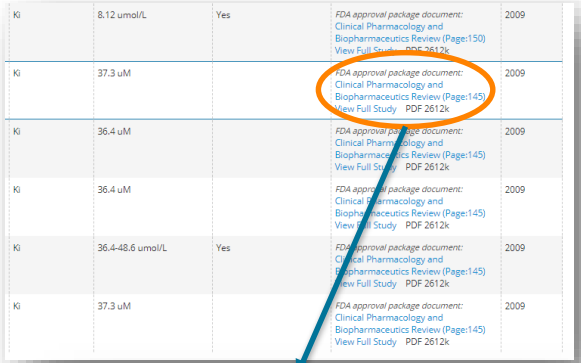
Includes:
- Clearance
- Excretion values
- Half life
- Rate constants
- Time



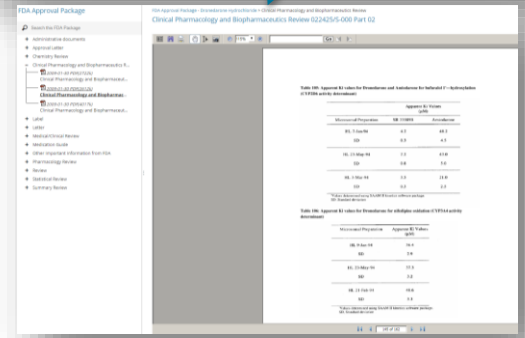
Species

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

Go directly to the page from where the data was extracted rather than just linking to the citation



Ki	8.12 umol/L	Yes	FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:150) View Full Study PDF 2612k	2009
Ki	37.3 uM		FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009
Ki	36.4 uM		FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009
Ki	36.4 uM		FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009
Ki	36.4-48.6 umol/L	Yes	FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009
Ki	37.3 uM		FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k	2009



Discover additional important information by searching the entire approval package, not just labels

Drug-drug interaction risk calculator

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Empowering Knowledge

DDI risk is continually assessed throughout drug development

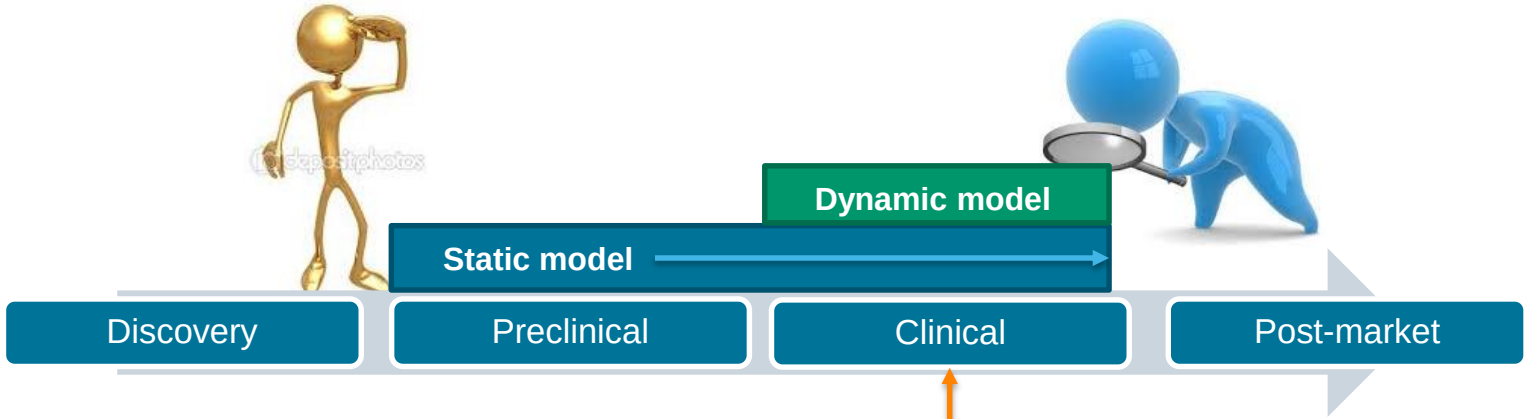
The FDA recommends a stepwise, model-based evaluation of metabolism-based interactions

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 – e.g., SimCyp) 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

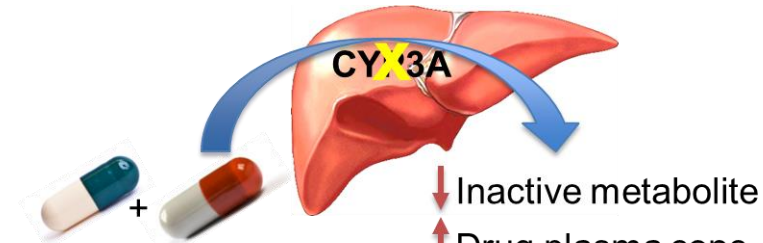
PharmaPendium DDI Risk Calculator (DDIRC)

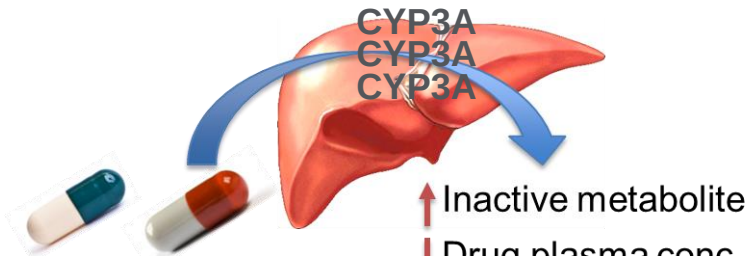
identifying potential *Victims* and *Perpetrators* involved in drug-drug interactions

- The potential for drug-drug interactions needs to be investigated throughout development
  - effects of other drugs on the investigational drug
  - effects of the investigational drug on other medicinal products

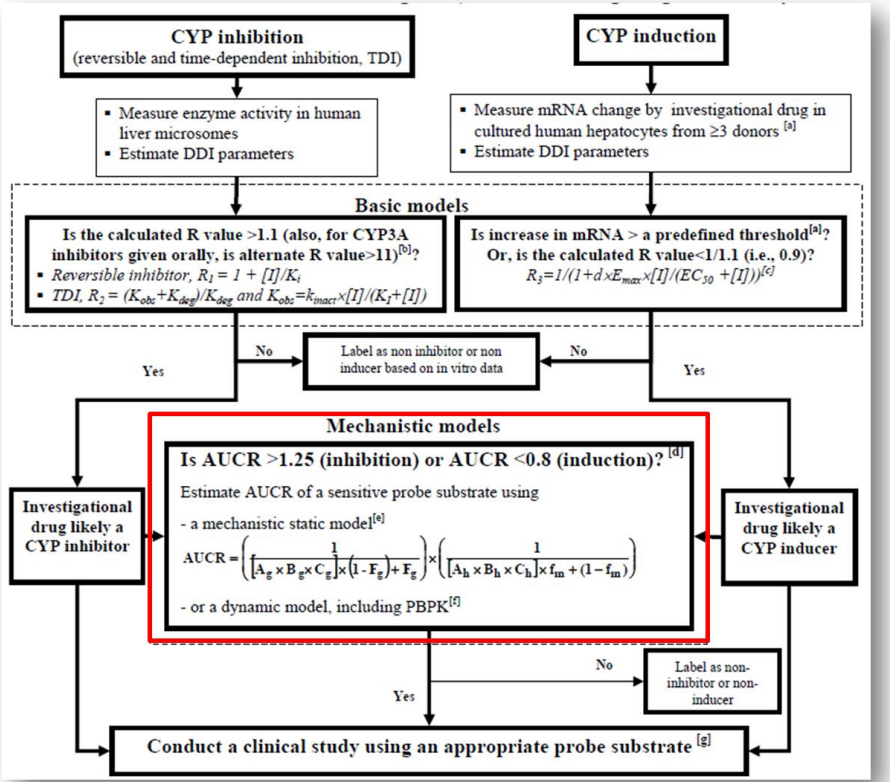
The **perpetrator** drug is the drug that **affects** the pharmacokinetics of another drug
The **victim** drug is the drug **affected** by the drug-drug interaction

Drug A is a perpetrator Drug B is a victim





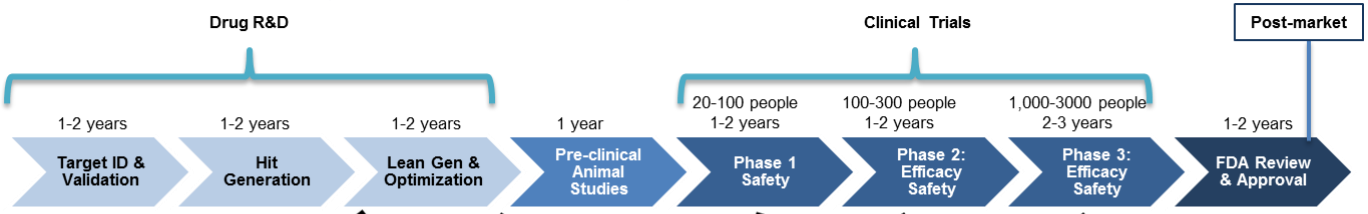
DDIRC is compliant with FDA guidance



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"

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

DDIRC informs DDI studies and clinical trials

- 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 interactions 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 impacted 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

	Sensitive substrate	AUC increase
CYP1A2	Caffeine	×1
CYP2B6	Bupropion	×1
CYP2C8	Repaglinide	×1
CYP2C9	Celecoxib	×1
CYP2C19	Omeprazole	×1
CYP2D6	Dextromethorphan	×1
CYP3A4/5	Lovastatin	×5.5
	Nisoldipine	×4.5
	Buspirone	×4.1
	Sildenafil	×2.2
	Saquinavir	×2
	Midazolam	×1.9
	Felodipine	×1.8
	Alfentanil	×1.6
	Triazolam	×1.6
	Maraviroc	×1.3
	Aprepitant	×1
	Darunavir	×1

Understanding how to manage DDI risks impacts CT design and may allow marketing of a drug that would otherwise have an unacceptable level of risk

DDIRC workflow and drug library

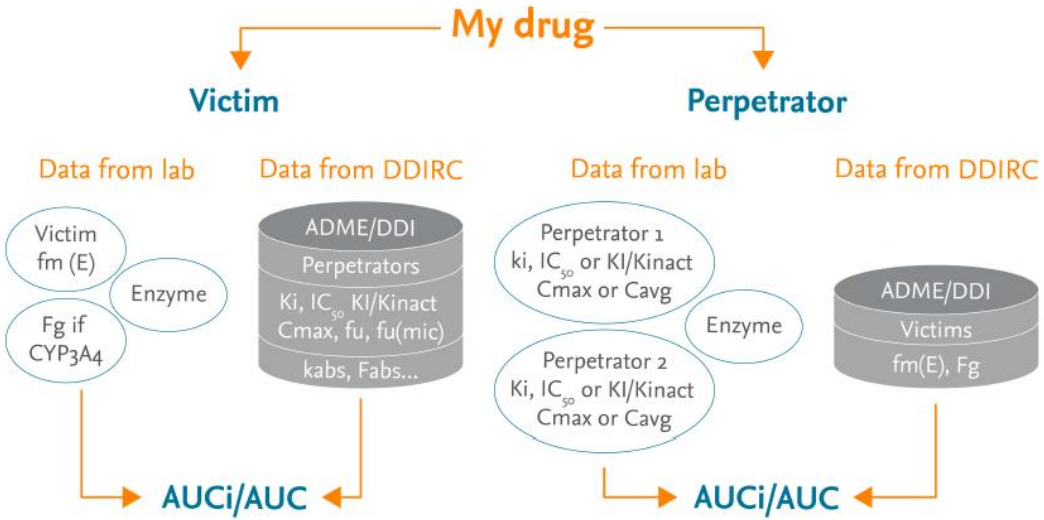


Figure 2. An illustration of the DDIRC workflow for victim and perpetrator drugs

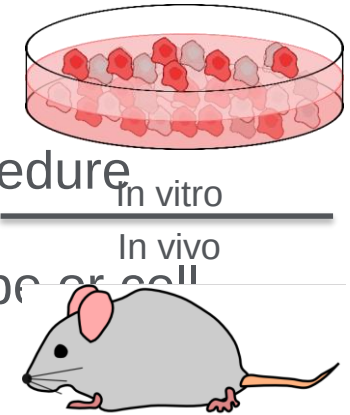
Data from DDIRC comes from the **extensive drug library**

238
unique drugs assessed as a victim

521
drugs assessed as a perpetrator

How does the DDI Risk Calculator work?

It uses a **Mechanistic Approach**, extrapolating *In vitro* data on drug metabolism to humans in order to predict drug-drug interactions (called **In vitro In vivo extrapolation** or **IVIVE)**



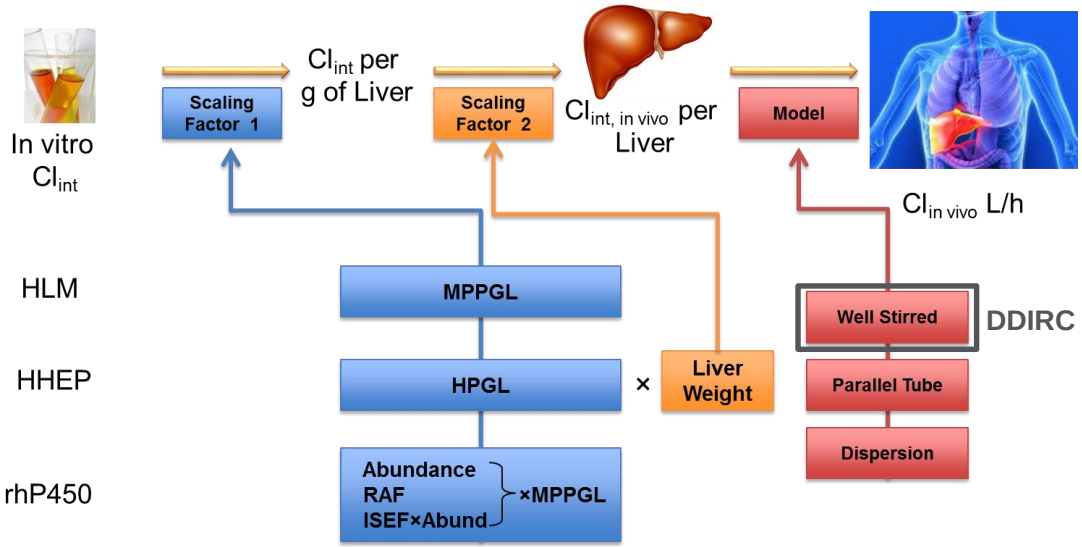
Some background:

In vitro refers to techniques used to perform a given procedure 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

How does it work?

Several scaling factors are applied to extrapolate *In vitro* data to *In vivo*



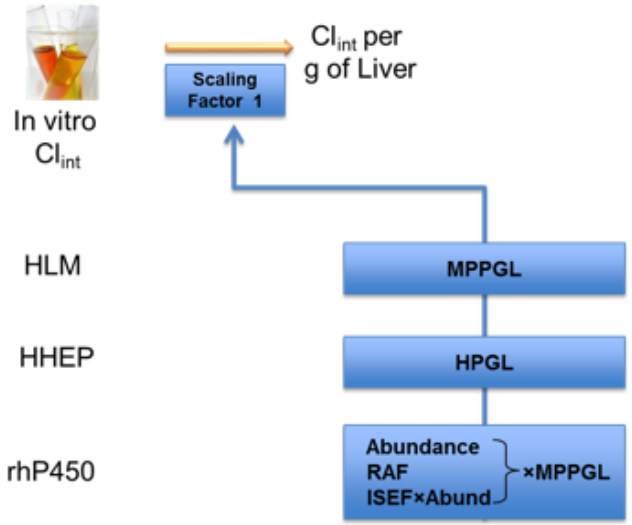
Predicting hepatic clearance

In vitro clearance (Cl_{int}) values are determined (K_m and V_{max})

- **Scaling Factor 1** extrapolates this 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)

Step-by-step

Scaling Factor 1



Different scaling factors are applied depending on the *In vitro* system used

Data from *In vitro* kinetic studies (measuring K_m and V_{max}) of drug metabolism are used to estimate hepatic drug clearance

There are different *In vitro* approaches using different human derived materials:

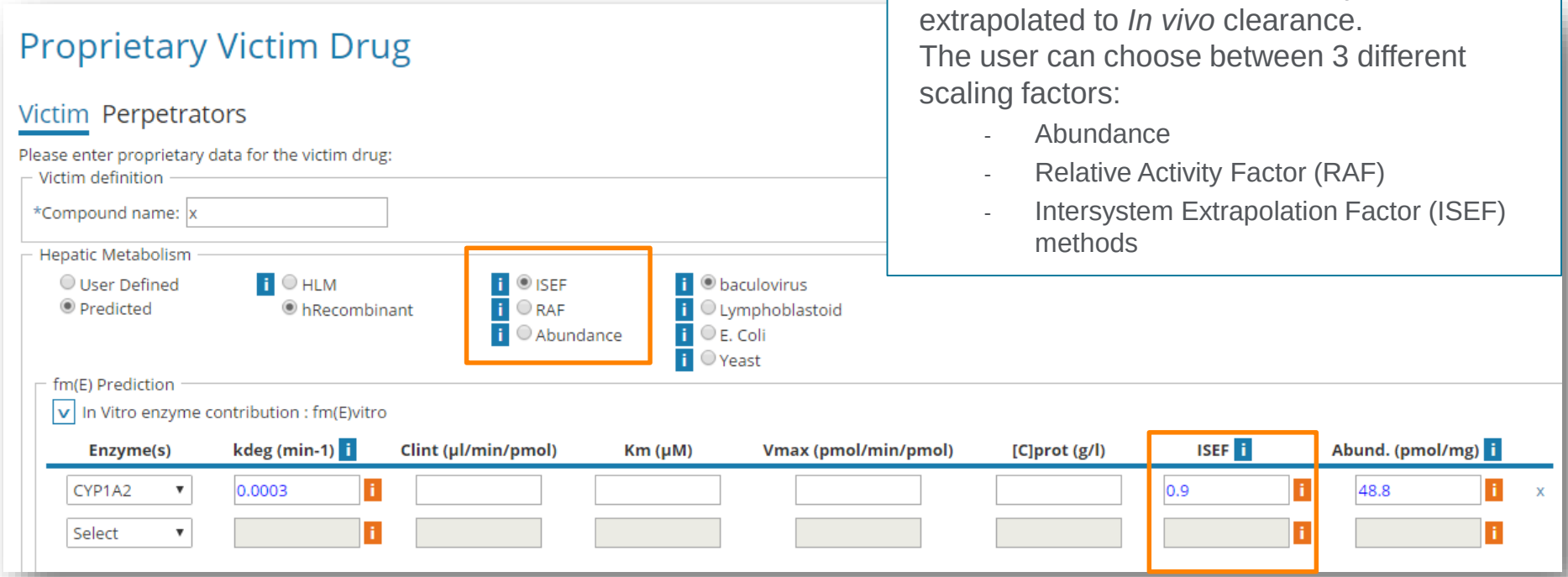
- Human Liver microsomes (HLM)
- Human hepatocytes (HHEP)
- Recombinant enzymes (rhP450) using different cell systems:
  - Baculovirus
  - Lymphoblastoid
  - E. Coli
  - Yeast

Step-by-step

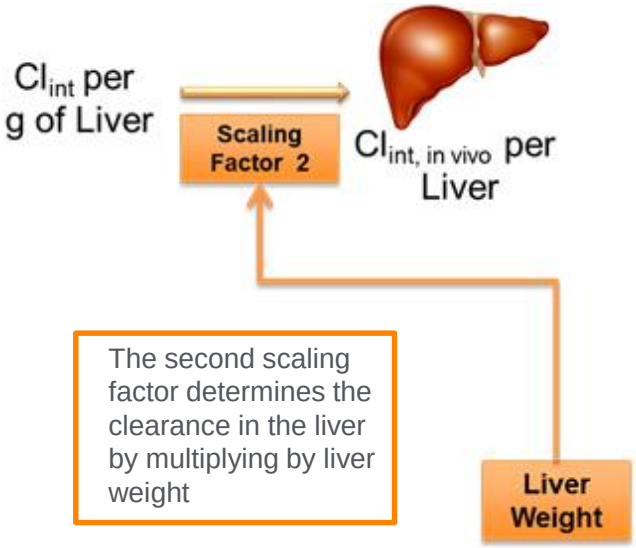
Scaling Factor 1 (continued)

Results from recombinant enzyme experiments are scaled up to human liver microsomes (HLM) **using values from the DDI Risk Calculator** before they are extrapolated to *In vivo* clearance.
The user can choose between 3 different scaling factors:

- Abundance
- Relative Activity Factor (RAF)
- Intersystem Extrapolation Factor (ISEF) methods

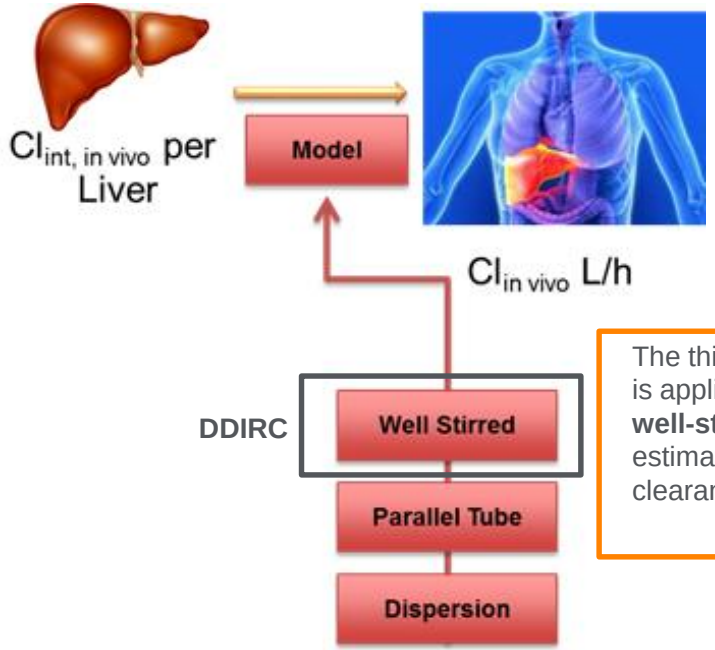


Step-by-step
Scaling Factor 2



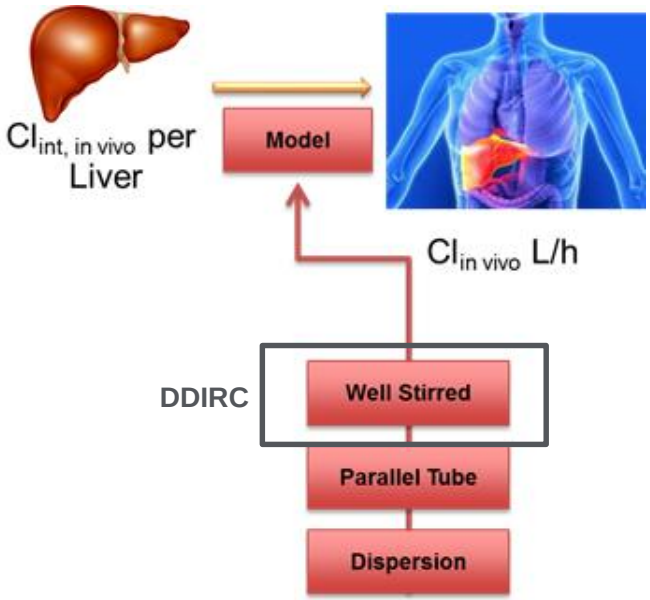
The second scaling factor determines the clearance in the liver by multiplying by liver weight

Step-by-step
Scaling Factor 3



The third scaling factor is application of the **well-stirred model** to estimate hepatic drug clearance

DDIRC uses the Well-Stirred Model of hepatic drug clearance



Well-stirred model: the liver is a single compartment and drug concentration is assumed to be equal throughout

Parallel-tube model: the liver is a group of identical tubes arranged in parallel, producing a concentration gradient of drug in the liver along the blood flow path

Dispersion model: the liver is a meshed organ with internal blood dispersion. Drug concentration is calculated to be in between that of the well-stirred and dispersion models

The well-stirred model is the most commonly used model to estimate hepatic clearance.

- ➢ It will result in a slight over-estimation of DDIs

Handbook of Essential Pharmacokinetics, Pharmacodynamics and Drug Metabolism for Industrial Scientists 2002, Kwon, Younggil

DDIRC Demo: Test compound as a victim

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Empowering Knowledge

Test compound as a victim

- Predict interaction between test compound and perpetrators
- Determine the potential to interact with antiarrhythmic drugs

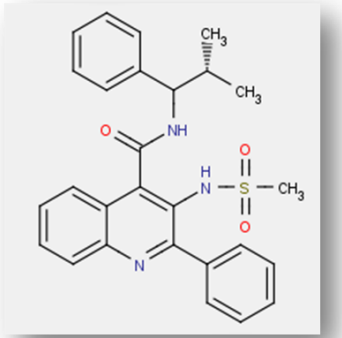
Recombinant Intrinsic Clearance

Cell system: Insect cells Infected with Bacculovirus

- **M1**: 3A4 Km=8.6µM Vmax=0.87 pmol/min/pmol [C] prot=0.5 mg/ml

- **M2**: 3A4 Km=32µM Vmax=3 pmol/min/pmol [C] prot=0.5 mg/ml
  2C9 Km=4 µM Vmax=0.1 pmol/min/pmol [C] prot=0.5 mg/ml

Physiochem. and binding properties of test compound



➢**Binding**:
- fu (plasma): 0.4-0.5
- Rb: 0.55 Default

➢**Physchem**

Molecular weight:	459.2
Total weight:	459.2
PSA:	88.16
pKa (pH 7.4):	7.66
logP:	4.28
logD (pH 7.4):	4.11
HBA (pH 7.4):	4
HBD (pH 7.4):	2
Rotatable bond count:	6
Polarizability (pH 7.4):	53.03
Refractivity:	128.96
Matching Lipinski rules:	4
Matching Veber rules:	2

Values powered by JChem from ChemAxon

Appendix – includes screenshots from demos

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Empowering Knowledge

Demo: What significant changes in metabolising enzymes or transporters activity has been observed for antineoplastic drugs?

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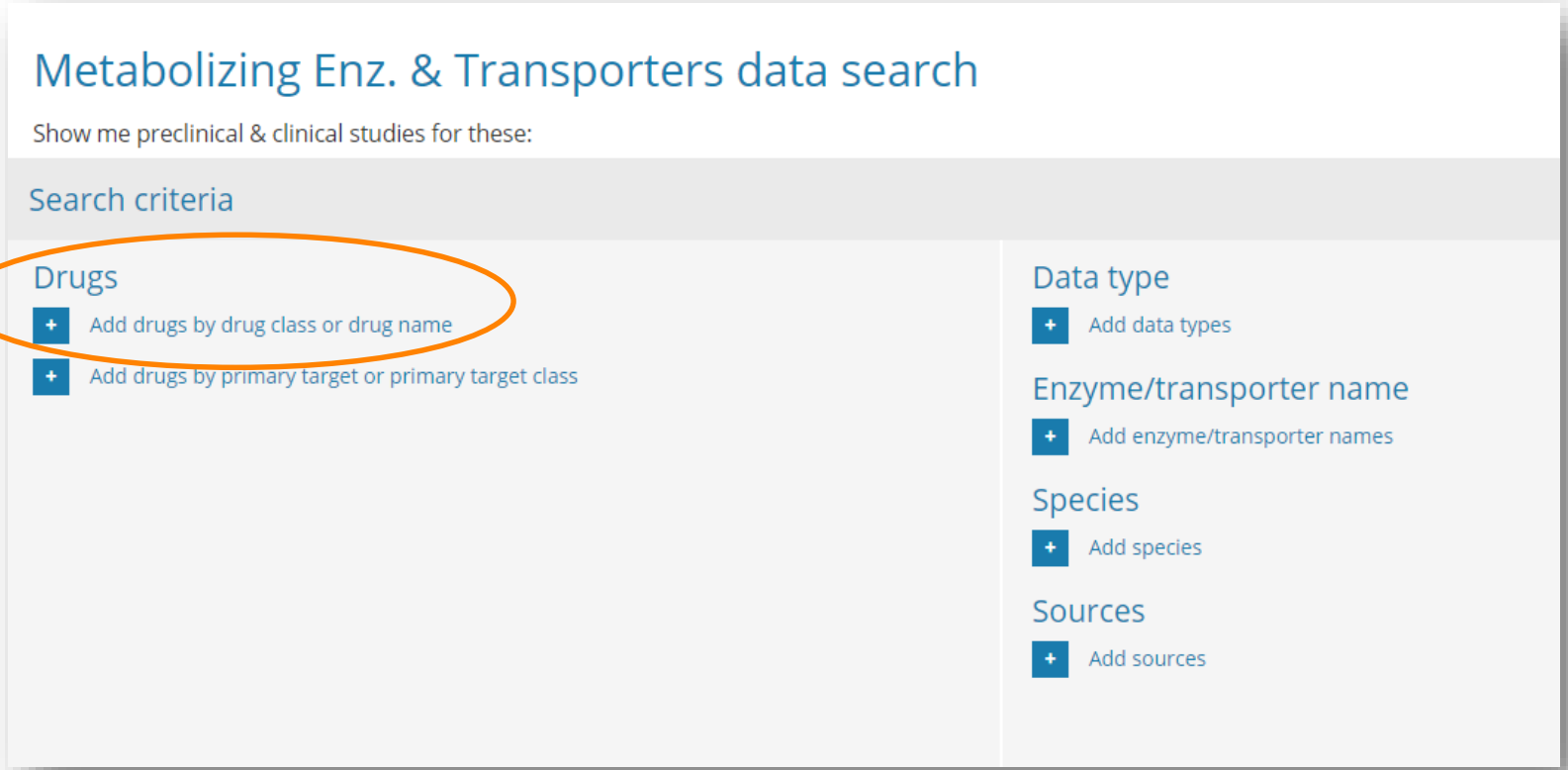
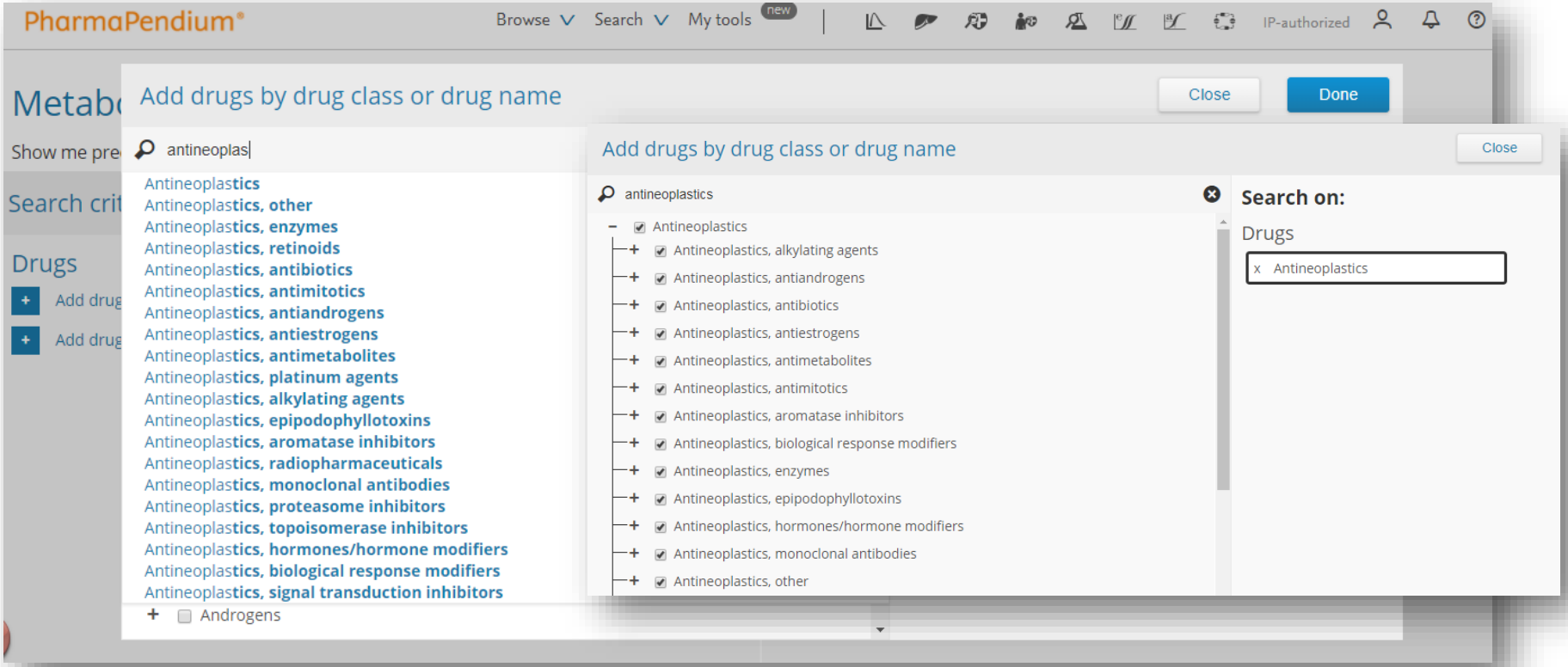
Empowering Knowledge

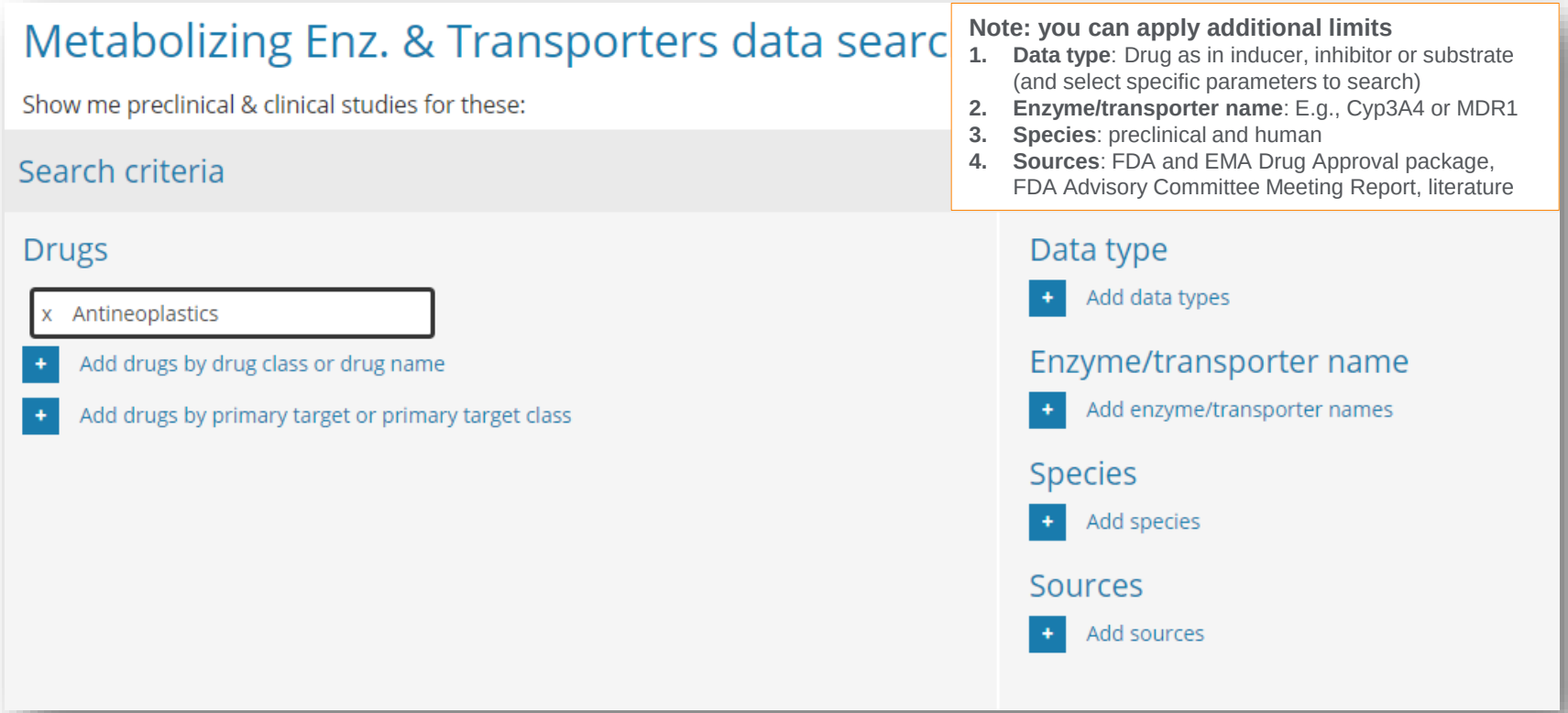
Search in Metabolising Enzymes & Transporters



Select the drug class antineoplastics



Limit MET search



Note: you can apply additional limits

1. **Data type**: Drug as in inducer, inhibitor or substrate (and select specific parameters to search)
2. **Enzyme/transporter name**: E.g., Cyp3A4 or MDR1
3. **Species**: preclinical and human
4. **Sources**: FDA and EMA Drug Approval package, FDA Advisory Committee Meeting Report, literature

Extensive data is extracted and presented in Results

Metabolizing Enz. & Transporters search results **34006 records from ME&T data:** Antineoplastics (34006)

Show Filters

Show/hide columns | Show drugs in... | Save

Preclinical Data | Clinical Data | All Data Preclinical and clinical data

ID	Drug	Parent/Metabolite	Substance Studied	Data Type	Enzyme/Transporter	Test system	Species	Dose	Route
1	Abarelix	Parent	Aberelix	Enzyme Substrate (in vivo)	CYP(unspecified)	Not applicable	Human	Unreported	
2	Abarelix	Parent	Aberelix	Enzyme Substrate (in vitro)	Enzyme unspecified	Hepatocytes	Human	Unreported	In Vitro
3	Abarelix	Parent	Aberelix	Enzyme Substrate (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported	
4	Abarelix	Parent	Aberelix	Enzyme Substrate (in vitro)	Enzyme unspecified	Unreported	Human	Unreported	In Vitro
5	Abarelix	Parent	Aberelix	Enzyme Substrate (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported	
6	Abarelix	Parent	Aberelix	Enzyme Substrate (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported	

Extensive data is extracted and presented in Results

Metabolizing Enz. & Transporters search results **34006 records from ME&T data:** Antineoplastics (34006)

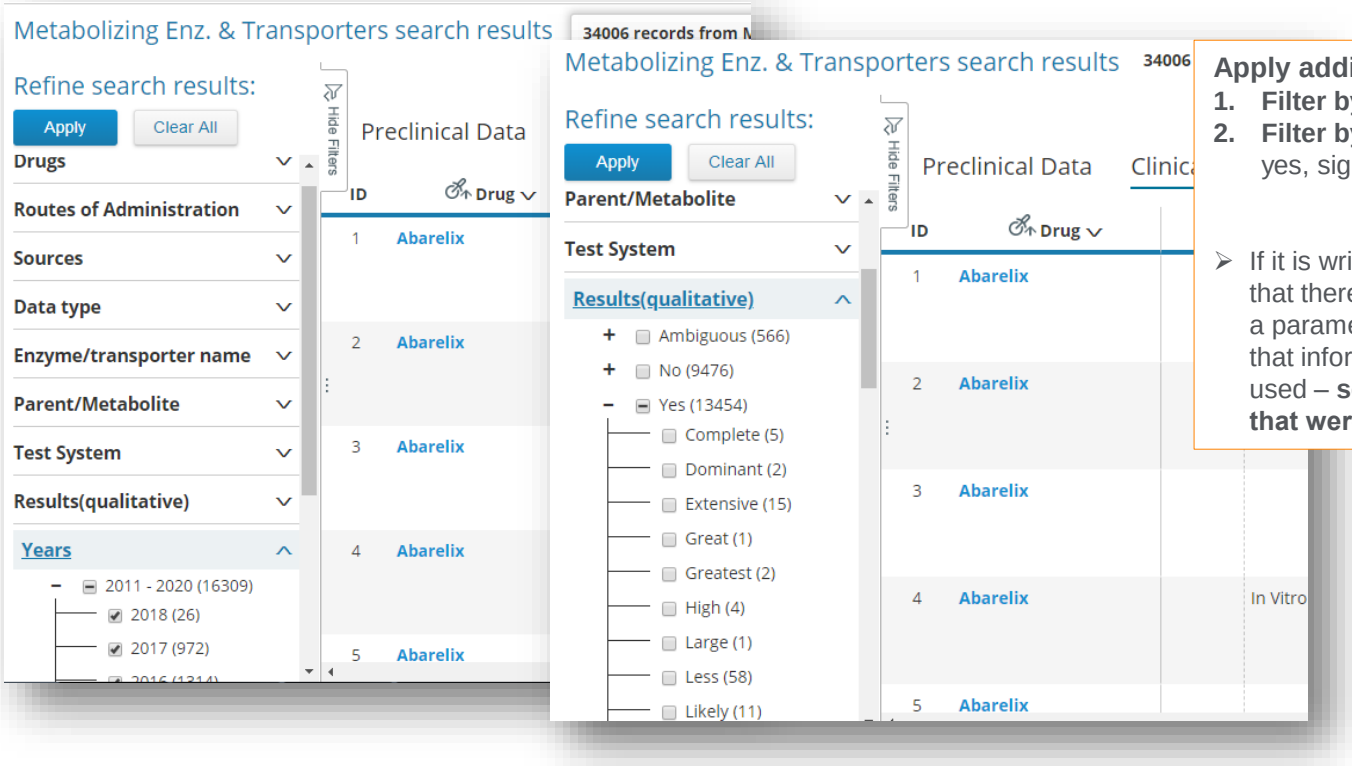
Show Filters

Show/hide columns | Show drugs in... | Save | Expo

Preclinical Data | Clinical Data | All Data Preclinical and clinical data

ID	Drug	Route	Substance measured	Concomitant	Parameter	Value	Result (qualitative)	Source	Year
1	Abarelix		Metabolites		Metabolic transformation		No	*FDA approval package document:* Clinical Pharmacology and Biopharmaceutics Review (Page:35) View Full Study PDF 1349k	2003
2	Abarelix	In Vitro	Metabolites		metabolic transformation (no value)		Yes, Major	*FDA approval package document:* Clinical Pharmacology and Biopharmaceutics Review (Page:12) View Full Study PDF 1349k	2003
3	Abarelix		Oxidative metabolites		Metabolic transformation		Yes, Not significant	*FDA approval package document:* Clinical Pharmacology and Biopharmaceutics Review (Page:12) View Full Study PDF 1349k	2003
4	Abarelix	In Vitro	Conjugated metabolites		metabolic transformation (no value)		Yes, Not significant	*FDA approval package document:* Clinical Pharmacology and Biopharmaceutics Review (Page:12) View Full Study PDF 1349k	2003
5	Abarelix		Conjugated metabolites		Metabolic transformation		Yes, Not significant	*FDA approval package document:* Clinical Pharmacology and Biopharmaceutics Review (Page:12) View Full Study PDF 1349k	2003
6	Abarelix		Metabolites		Metabolic transformation		No	*FDA approval package document:* Clinical Pharmacology and Biopharmaceutics Review (Page:23) View Full Study PDF 1349k	2003

Filter by additional parameters

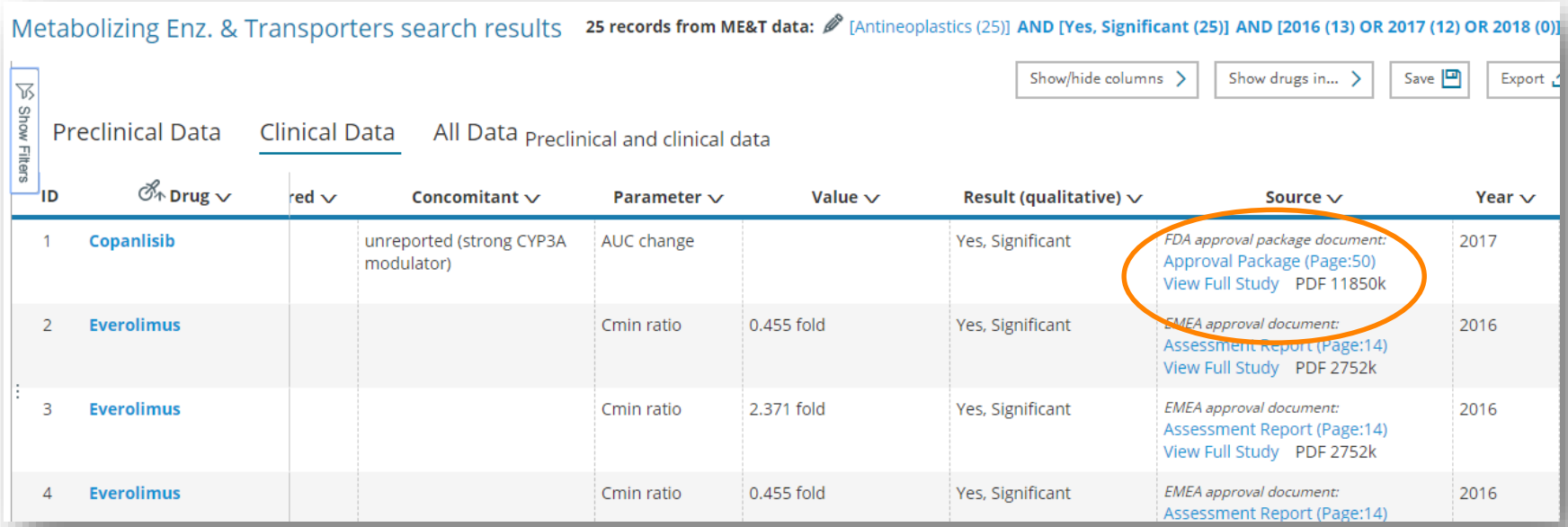


Apply additional filters

1. **Filter by year**: 2016, 2017, 2018
2. **Filter by results (qualitative)**: Select yes, significant

- If it is written in the approval document that there is a significant change (or not) in a parameter (e.g., AUC), then we capture that information, along with the adjective used – **so you can search for results that were described as 'significant'**

Copanlisib showed significant AUC change when CYP3A was tested (the actual enzyme wasn't reported)



Metabolizing Enz. & Transporters search results **25 records from ME&T data:** [Antineoplastics (25)] **AND [Yes, Significant (25)] AND [2016 (13) OR 2017 (12) OR 2018 (0)]**

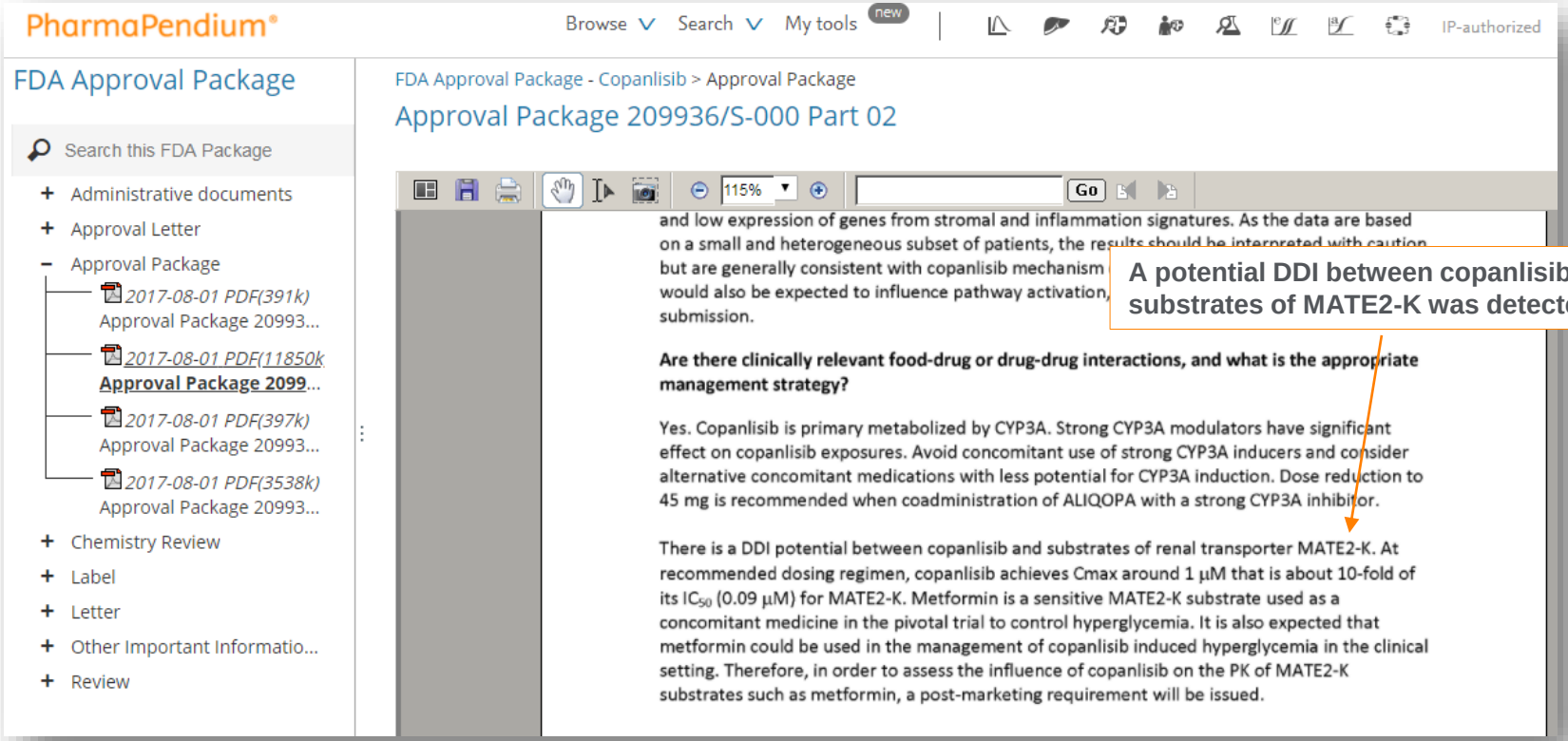
Show/hide columns | Show drugs in... | Save | Export

Show Filters

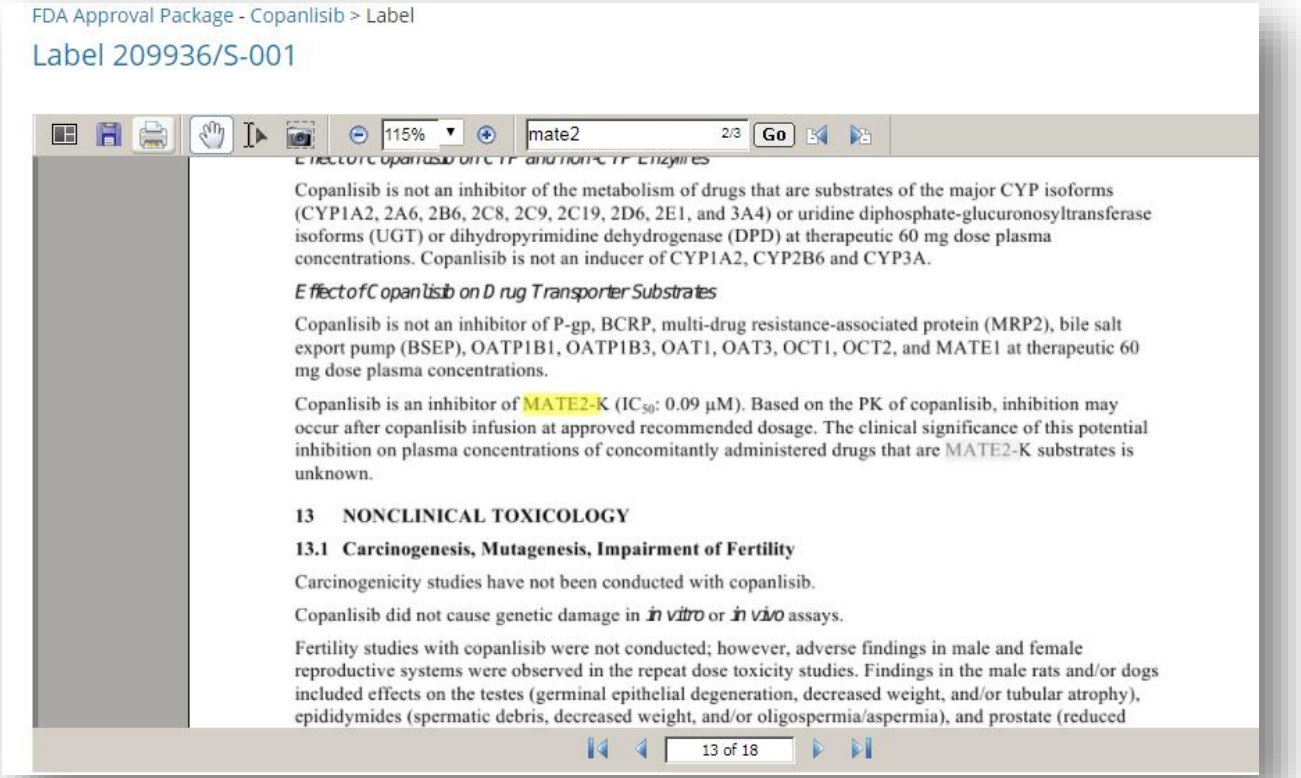
Preclinical Data | Clinical Data | All Data — Preclinical and clinical data

ID	Drug	...red	Concomitant	Parameter	Value	Result (qualitative)	Source	Year
1	Copanlisib		unreported (strong CYP3A modulator)	AUC change		Yes, Significant	*FDA approval package document:* Approval Package (Page:50) View Full Study PDF 11850k	2017
2	Everolimus			Cmin ratio	0.455 fold	Yes, Significant	*EMEA approval document:* Assessment Report (Page:14) View Full Study PDF 2752k	2016
3	Everolimus			Cmin ratio	2.371 fold	Yes, Significant	*EMEA approval document:* Assessment Report (Page:14) View Full Study PDF 2752k	2016
4	Everolimus			Cmin ratio	0.455 fold	Yes, Significant	*EMEA approval document:* Assessment Report (Page:14)	2016

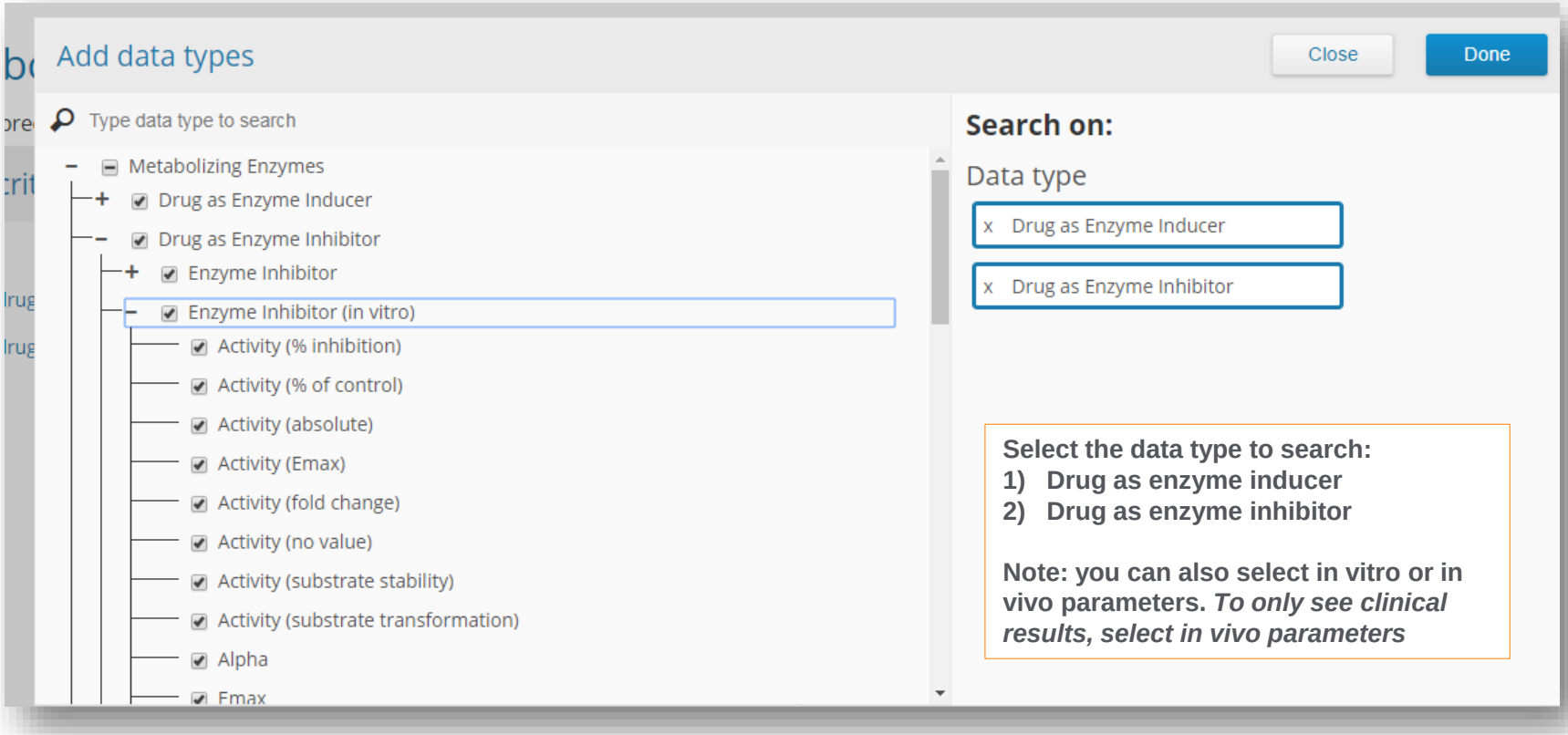
Look at the source data to see context



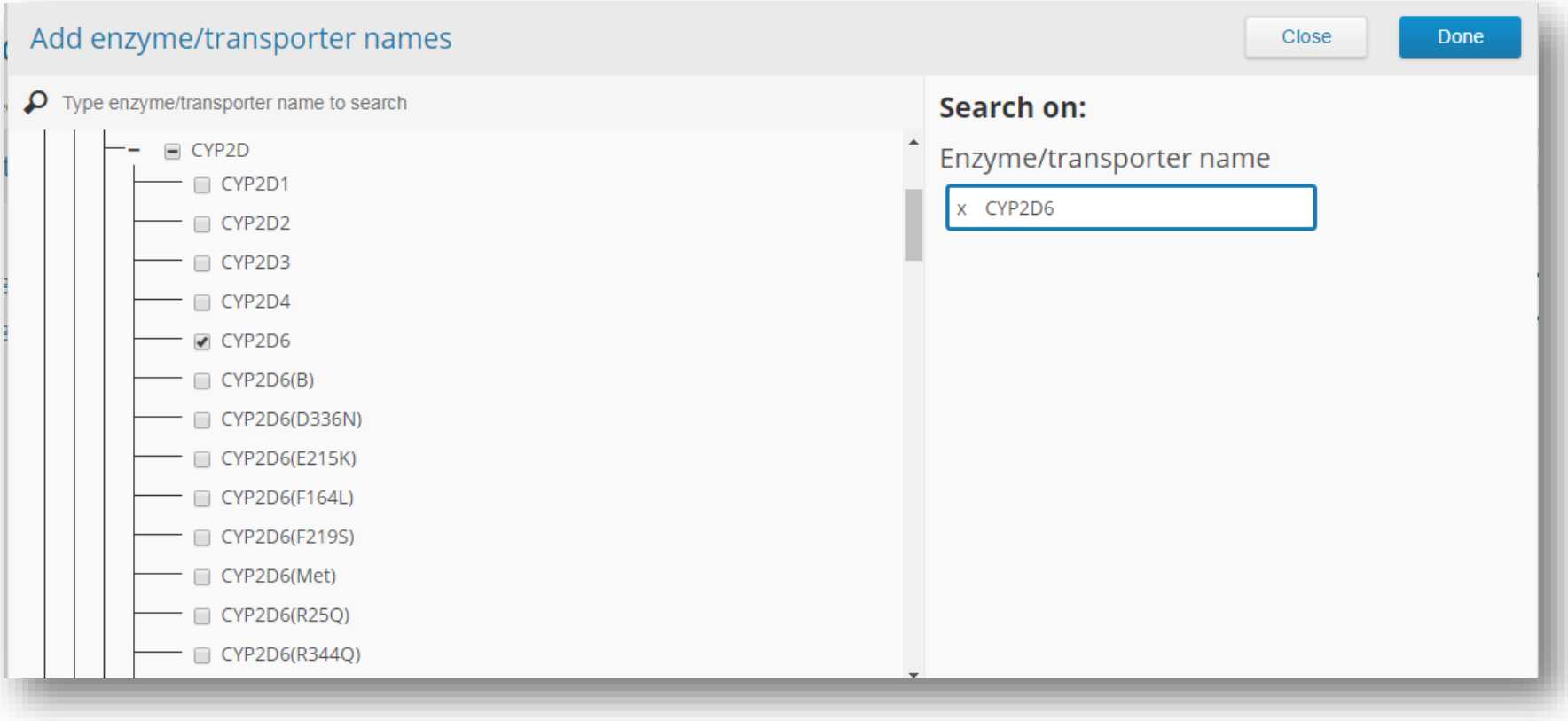
Find more in other sections of the approval document



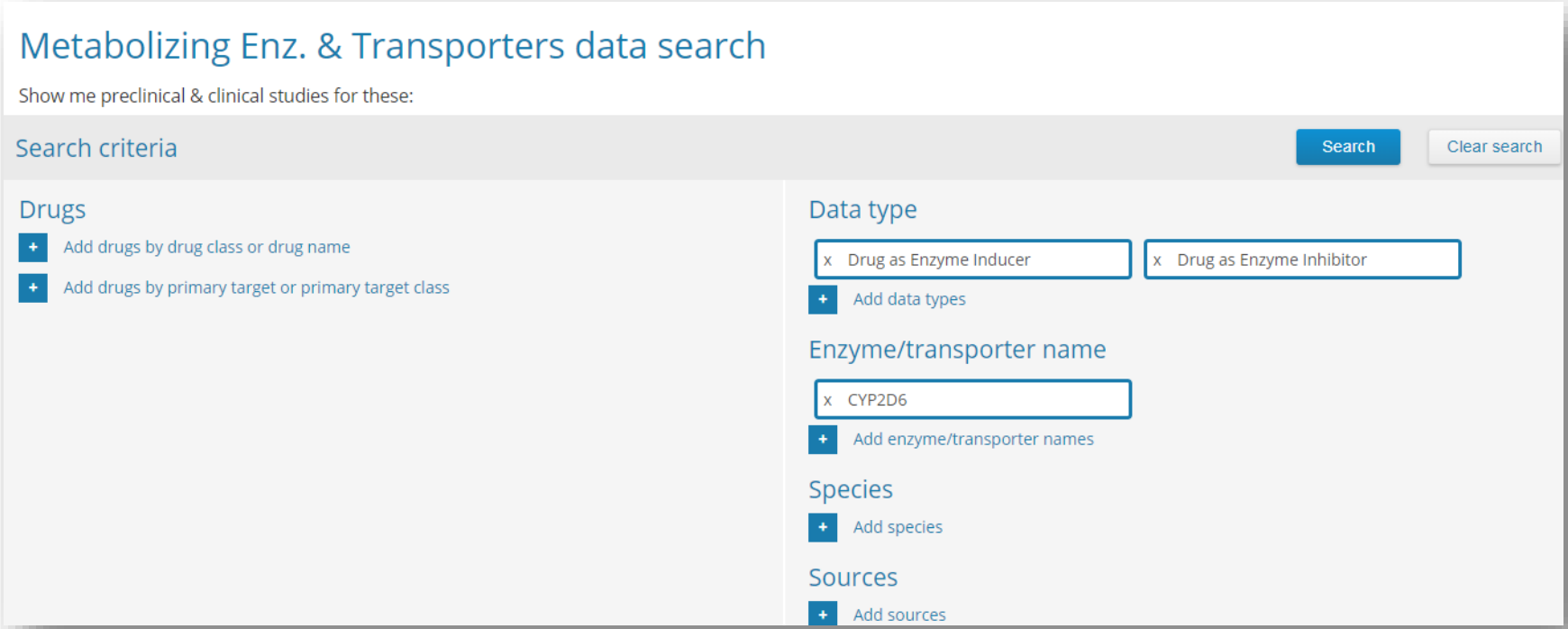
Question: What drugs could interact with my drug, which is metabolised by Cyp2D6



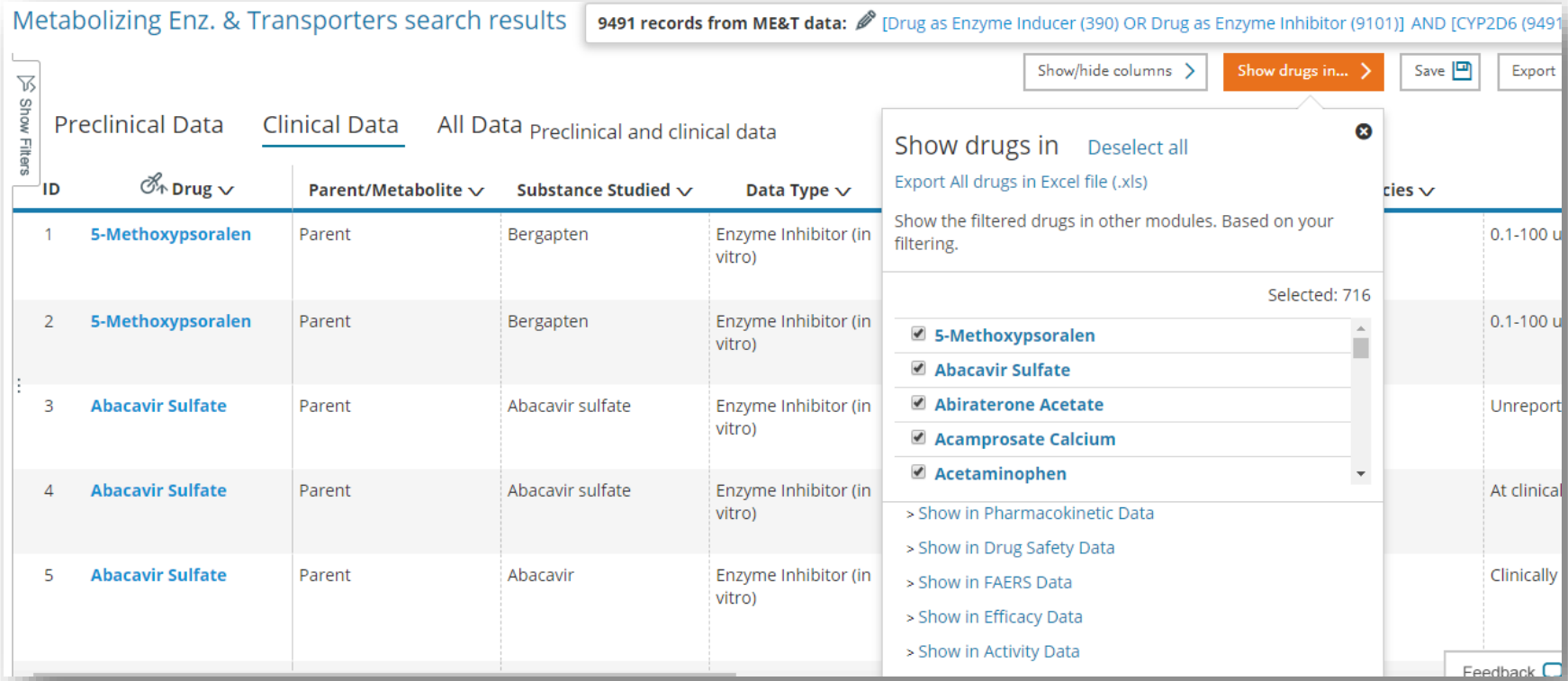
Select the enzyme



Results will be all drugs reported to act as an inducer or inhibitor of Cyp2D6



In 3 steps, see 9491 results for 716 drugs that induce or inhibit Cyp2D6



DDIRC Demo: Test compound as a victim

ELSEVIER

Empowering Knowledge

Test compound as a victim

- Predict interaction between test compound and perpetrators
- Determine the potential to interact with antiarrhythmic drugs

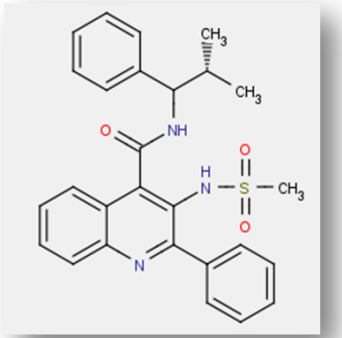
Recombinant Intrinsic Clearance

Cell system: Insect cells Infected with Bacculovirus

- **M1**: 3A4 Km=8.6µM Vmax=0.87 pmol/min/pmol [C] prot=0.5 mg/ml

- **M2**: 3A4 Km=32µM Vmax=3 pmol/min/pmol [C] prot=0.5 mg/ml
  2C9 Km=4 µM Vmax=0.1 pmol/min/pmol [C] prot=0.5 mg/ml

Physiochem. and binding properties of test compound



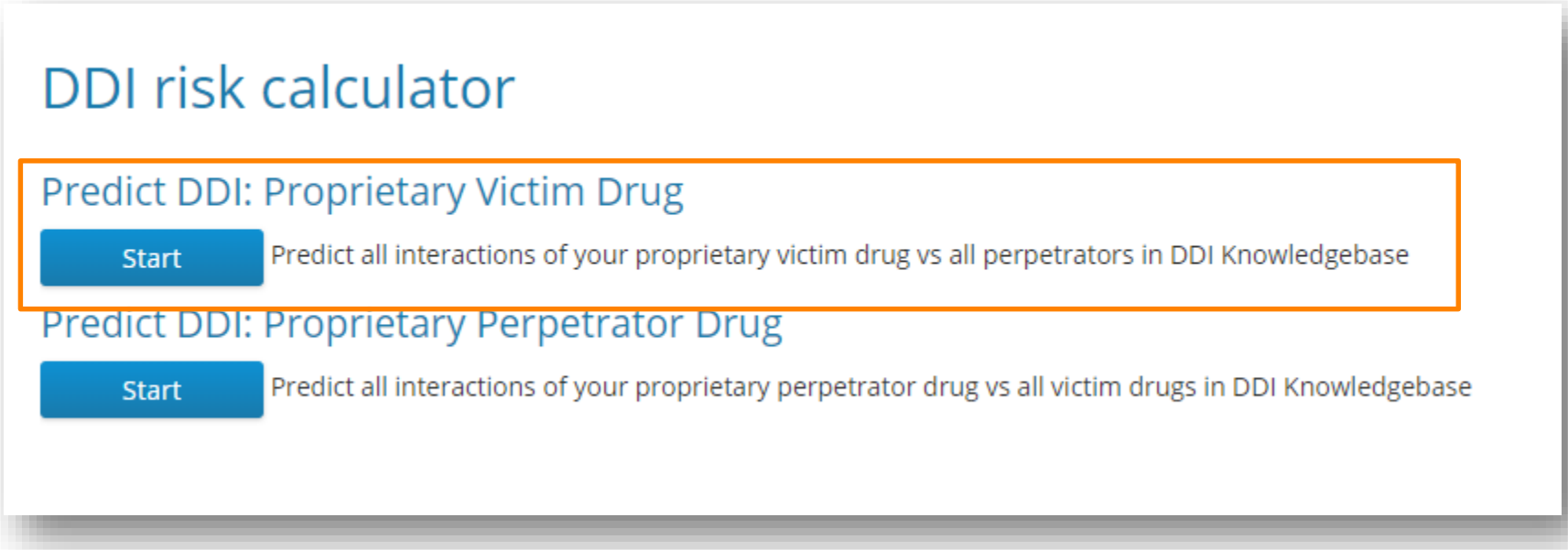
- **Binding**:
  - fu (plasma): 0.4-0.5
  - Rb: 0.55 Default

- **Physchem**

Molecular weight:	459.2
Total weight:	459.2
PSA:	88.16
pKa (pH 7.4):	7.66
logP:	4.28
logD (pH 7.4):	4.11
HBA (pH 7.4):	4
HBD (pH 7.4):	2
Rotatable bond count:	6
Polarizability (pH 7.4):	53.03
Refractivity:	128.96
Matching Lipinski rules:	4
Matching Veber rules:	2

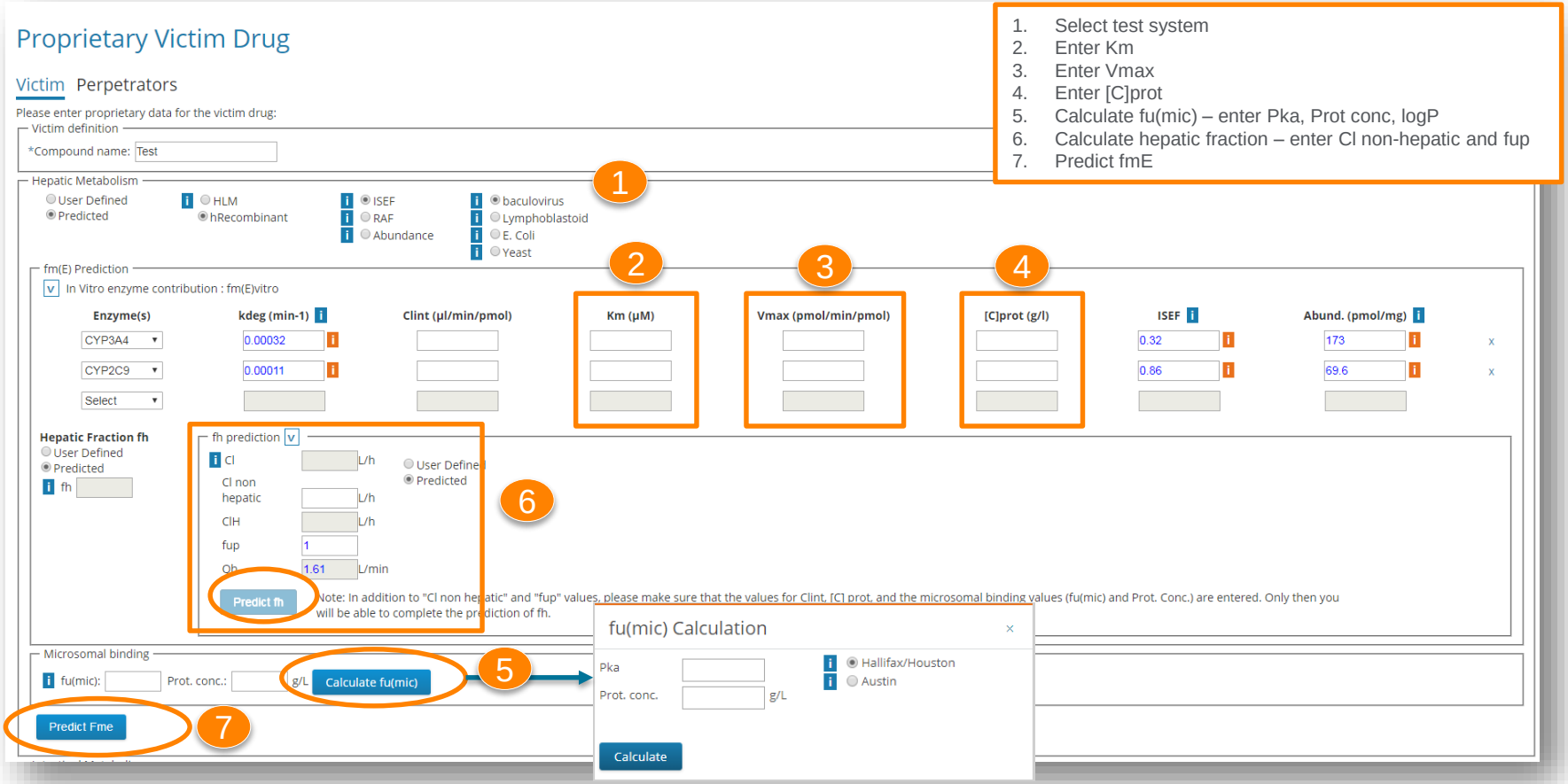
Values powered by JChem from ChemAxon

Predict DDIs with the proprietary drug as a victim

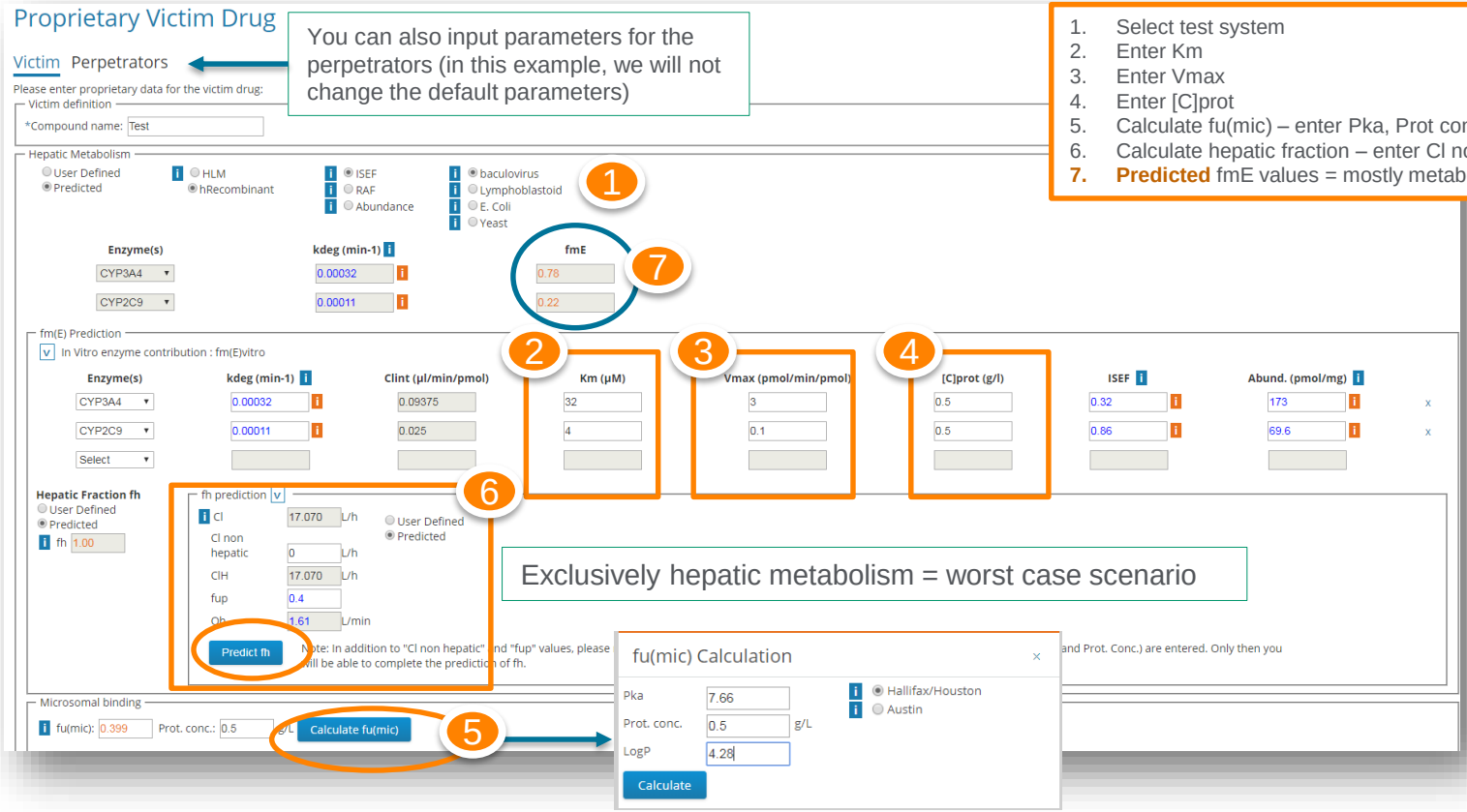


Predict FmE by filling in the indicated information

1. Select test system
2. Enter Km
3. Enter Vmax
4. Enter [C]prot
5. Calculate fu(mic) – enter Pka, Prot conc, logP
6. Calculate hepatic fraction – enter Cl non-hepatic and fup
7. Predict fmE



Predicted FmE

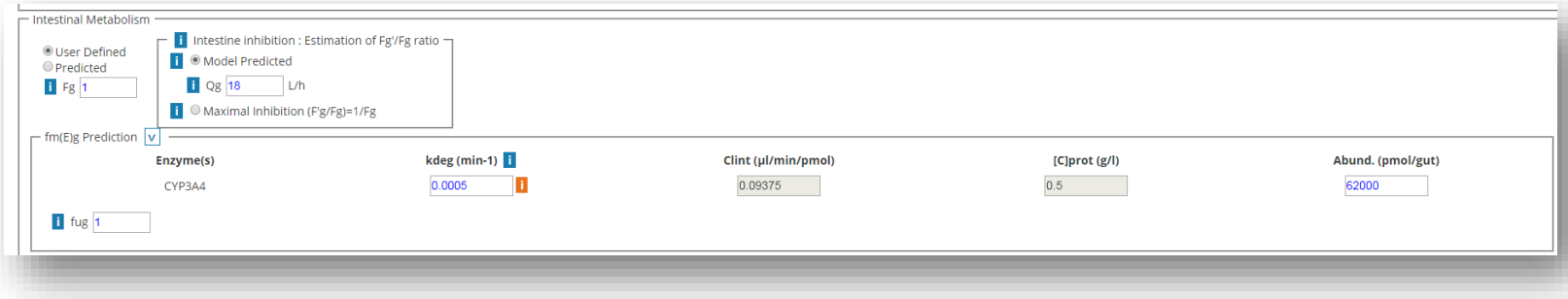


1. Select test system
2. Enter Km
3. Enter Vmax
4. Enter [C]prot
5. Calculate fu(mic) – enter Pka, Prot conc, logP
6. Calculate hepatic fraction – enter Cl non-hepatic and fup
7. **Predicted** fmE values = mostly metabolised by Cyp3A4

Exclusively hepatic metabolism = worst case scenario

Modify intestinal metabolism data (if required)

We have no data on gut metabolism, so leave Fg at 1



Predict interactions

Results for 257 perpetrators – click on blue links for more info

Export data for more info

1. Perpetrator information (Physiochemical properties)
2. Dose (if multiple, click on blue link to see dose effects on AUC)
3. MBI (indicated here if it's mechanism-based inhibition)
4. AUC Ratio – see Bar chart information for legend
5. Count (see next slide)
6. Min, max, mean, SD, median and 5-95th percentile AUC values

Details on calculation found in ‘count’ column

Click on blue text for more information

DDI Results details

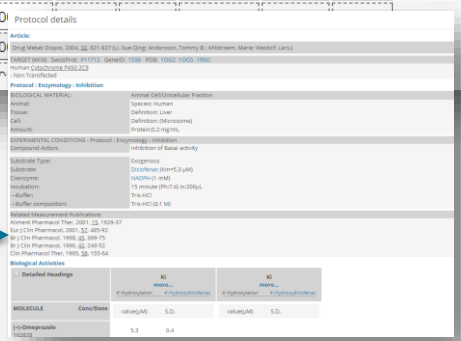
Export

Victim: Test Perpetrator: (-)-Omeprazole

AUCi/AUC	F'g/Fg	Enzyme	fm(E)	Fg	[Iu]g (µM)	I Optimized [I] (µM)	Ki (µM)				Dose	Cmax (µM)	kabs (min-1)	Fa.Fg	Qh	Fu(blood)	Rb	Kb
							Value	[C]prot	Substrate	fu(mic)								
.03	1	CYP2C9	0.22		2.622	+ 1.77	81.5	0.2 g/L	Diclofenac		0.02 g	+ 2.33	+ 0.014	1	1.61	1	0.55	1
.09	1	CYP3A4	0.78		1.226	+ 1.51	46.6	0.2 g/L	Midazolam		0.02 g	+ 2.33	+ 0.006	1	1.61	1	0.55	1
.067	1	CYP2C9	0.22		2.452	+ 3.009	81.5	0.2 g/L	Diclofenac		0.04 g	+ 4.64	+ 0.006	1	1.61	1	0.55	1
.067	1	CYP3A4	0.78		5.244	+ 3.529	46.6	0.2 g/L	Midazolam		0.04 g	+ 4.64	+ 0.014	1	1.61	1	0.55	1
.068	1	CYP2C9	0.22		2.452	+ 3.047	81.5	0.2 g/L	Diclofenac		0.04 g	+ 4.71	+ 0.006	1	1.61	1	0.55	1
.068	1	CYP3A4	0.78		5.244	+ 3.568	46.6	0.2 g/L	Midazolam		0.04 g	+ 4.71	+ 0.014	1	1.61	1	0.55	1
.026	1	CYP2C9	0.22		1.226	+ 1.13	81.5	0.2 g/L	Diclofenac		0.02 g	+ 1.64	+ 0.006	1	1.61	1	0.55	1
.026	1	CYP3A4	0.78		2.622	+ 1.391	46.6	0.2 g/L	Midazolam		0.02 g	+ 1.64	+ 0.014	1	1.61	1	0.55	1
.04	1	CYP2C9	0.22		2.452	+ 2.046	81.5	0.2 g/L	Diclofenac		0.04 g	+ 2.89	+ 0.006	1	1.61	1	0.55	1
.04	1	CYP3A4	0.78		2.452	+ 2.046	46.6	0.2 g/L	Midazolam		0.04 g	+ 2.89	+ 0.0					
.034	1	CYP2C9	0.22		1.226	+ 1.51	81.5	0.2 g/L	Diclofenac		0.02 g	+ 2.33	+ 0.0					

Data entered into calculator for test drug

Click on blue numbers or + for protocol information



Exported data (Tab 1) – Results overview

Victim		Perpetrator1		AUC Ratio							
	Name	Therapeutic class	Dose/unit	Min	Max	Mean	SD	Median	5th Perc.	95th Perc.	Count
Test	(+)-Propoxyphene	~Analgesic: narcotic/opiate~	0.065 g	1.061	1.062	1.061	5.003E-4	1.061	1.061	1.062	2
Test	(+)-Propoxyphene	~Analgesic: narcotic/opiate~	0.6 g	1.554	1.554	1.554	4.065E-5	1.554	1.554	1.554	2
Test	(+)-Warfarin	~Antithrombotic~	0.007 g	1.075	1.075	1.075	0.0	1.075	1.075	1.075	1
Test	(-)-Omeprazole	~Antiulcerative~Proton pump inhibitor~	0.02 g	1.022	1.038	1.032	0.004	1.033	1.023	1.037	24
Test	(-)-Omeprazole	~Antiulcerative~Proton pump inhibitor~	0.04 g	1.03	1.078	1.059	0.013	1.062	1.034	1.075	64
Test	(-)-Warfarin	~Antithrombotic~	0.007 g	1.033	1.142	1.094	0.035	1.096	1.045	1.135	5
Test	AMG 487		0.025 g	2.82	2.82	2.82	0.0	2.82	2.82	2.82	1
Test	AMG 487		0.1 g	7.778	7.778	7.778	0.0	7.778	7.778	7.778	1
Test	AMG 487		0.25 g	18.223	18.223	18.223	0.0	18.223	18.223	18.223	1
Test	Acamprosate		0.3 g	1.012	1.086	1.046	0.02	1.043	1.017	1.079	441
Test	Acamprosate		0.5 g	1.017	1.141	1.075	0.033	1.069	1.026	1.129	441
Test	Acamprosate		0.666 g	1.019	1.184	1.095	0.043	1.088	1.03	1.167	441
Test	Acamprosate		0.8 g	1.025	1.223	1.117	0.052	1.108	1.038	1.203	441
Test	Acamprosate		1.0 g	1.012	1.271	1.132	0.065	1.123	1.03	1.241	882
Test	Acetaminophen	~Analgesic: non narcotic~Antipyretic~	0.65 g	4.048	4.105	4.076	0.018	4.079	4.048	4.103	24
Test	Acetaminophen	~Analgesic: non narcotic~Antipyretic~	1.0 g	4.053	4.134	4.093	0.026	4.098	4.054	4.133	48
Test	Acetylsalicylic acid	~Analgesic: non narcotic~Antiinflammatory: non-steroidal~Antipyretic~Antith	0.325 g	1.753	1.825	1.789	0.029	1.789	1.756	1.823	4
Test	Acetylsalicylic acid	~Analgesic: non narcotic~Antiinflammatory: non-steroidal~Antipyretic~Antith	0.96 g	3.395	3.607	3.5	0.086	3.499	3.401	3.6	4
Test	Adefovir dipivoxil	~Anti-HIV~Antiviral~	0.01 g	1.022	1.106	1.064	0.042	1.064	1.026	1.102	2
Test	Adefovir	~Antiviral~	0.01 g	1.001	1.001	1.001	0.0	1.001	1.001	1.001	2
Test	Aliskiren	~Antihypertensive~	0.04 g	1.002	1.006	1.004	0.002	1.004	1.002	1.006	24
Test	Aliskiren	~Antihypertensive~	0.08 g	1.003	1.011	1.007	0.004	1.007	1.003	1.011	24
Test	Aliskiren	~Antihypertensive~	0.16 g	1.006	1.023	1.014	0.008	1.014	1.006	1.023	24
Test	Aliskiren	~Antihypertensive~	0.3 g	1.013	1.056	1.032	0.018	1.031	1.013	1.053	408
Test	Aliskiren	~Antihypertensive~	0.64 g	1.026	1.095	1.06	0.033	1.059	1.026	1.095	24
Test	Aliskiren	~Antihypertensive~	0.85 g	1.036	1.132	1.083	0.046	1.081	1.036	1.132	24
Test	Aliskiren	~Antihypertensive~	1.2 g	1.051	1.184	1.116	0.064	1.114	1.051	1.184	24
Test	Aliskiren	~Antihypertensive~	1.8 g	1.073	1.258	1.164	0.089	1.162	1.073	1.258	24
Test	Alosetron	~Antiemetic~	0.001 g	1.003	1.014	1.007	0.002	1.006	1.004	1.01	2704
Test	Alosetron	~Antiemetic~	0.002 g	1.006	1.028	1.014	0.004	1.013	1.008	1.021	2028
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	0.001 g	1	1.001	1	1.289E-4	1	1	1.001	245
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	2.5E-4 g	1	1	1	2.245E-5	1	1	1	35
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	5.0E-4 g	1	1	1	4.758E-5	1	1	1	70
Test	Alprazolam	~Anticonvulsant~Anxiolytic~Hypnotic~Myorelaxant~Sedative~	6.3E-4 g	1	1.001	1	5.657E-5	1	1	1	35
Test	Alvimopan	~Laxative~	0.006 g	1.003	1.009	1.005	0.002	1.005	1.003	1.009	242
Test	Alvimopan	~Laxative~	0.012 g	1.005	1.019	1.011	0.004	1.01	1.006	1.017	121
Test	Alvimopan	~Laxative~	0.018 g	1.008	1.028	1.016	0.005	1.015	1.01	1.026	121
Test	Alvimopan	~Laxative~	0.024 g	1.011	1.038	1.022	0.007	1.02	1.013	1.034	121
Test	Amitriptyline	~Analgesic: non narcotic~Antidepressant~	0.025 g	1.015	1.28	1.116	0.042	1.117	1.047	1.193	1728
Test	Amlodipine	~Antianginal~Antihypertensive~Calcium channel blocker~	0.005 g	1.438	1.955	1.657	0.174	1.645	1.438	1.954	245
Test	Amlodipine	~Antianginal~Antihypertensive~Calcium channel blocker~	0.01 g	2.224	2.51	2.337	0.093	2.321	2.226	2.508	245
Test	Amoxicillin	~Antibiotic~	1.0 g	1.046	1.154	1.097	0.039	1.096	1.048	1.154	27
Test	Amprenavir	~Antiviral~	0.45 g	4.545	4.545	4.545	1.505E-5	4.545	4.545	4.545	16
Test	Amprenavir	~Antiviral~	0.6 g	4.545	4.545	4.545	1.19E-5	4.545	4.545	4.545	8
Test	Amprenavir	~Antiviral~	0.9 g	4.545	4.545	4.545	7.026E-6	4.545	4.545	4.545	8
Test	Amprenavir	~Antiviral~	1.2 g	4.545	4.545	4.545	6.297E-6	4.545	4.545	4.545	12
Test	Aprepitant	~Antiemetic~	0.08 g	0.159	0.386	0.27	0.105	0.267	0.161	0.383	4
Test	Aprepitant	~Antiemetic~	0.25 g	0.207	0.491	0.349	0.142	0.349	0.221	0.477	2
Test	Aripiprazole	~Antipsychotic~Neuroleptic~	0.001 g	1	1	1	7.301E-6	1	1	1	81
Test	Aripiprazole	~Antipsychotic~Neuroleptic~	0.002 g	1	1.001	1.001	2.586E-5	1.001	1	1.001	162
Test	Aripiprazole	~Antipsychotic~Neuroleptic~	0.003 g	1	1.001	1.001	2.76E-4	1.001	1.001	1.001	405

Bar chart information

The bar chart displayed in the DDI table is a color coded graphical overview of the risk assessment.

Color codes represent AUCi/AUC ratio ranges corresponding to the FDA classification [1] of CYP inhibitor and inducer potency. The size of each colored segment in the bar represents the percentage of the total number of calculated AUC ratios (for a given victim/perpetrator couple) that falls into one of the following categories:

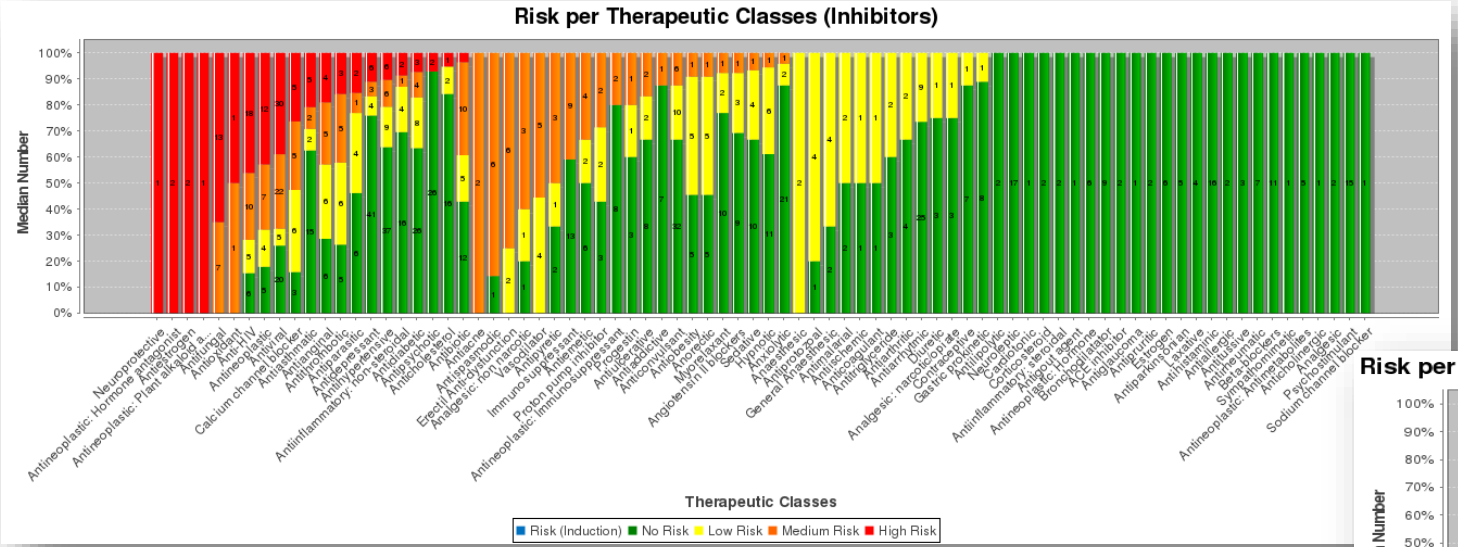
Category	*AUC ratio range*			*Colour*
Risk(Induction)		AUC ratio <	0.8	
No risk	0.8	≤ AUC ratio <	1.25	
Low risk	1.25	≤ AUC ratio <	2	
Medium risk	2	≤ AUC ratio <	5	
High risk	5	≤ AUC ratio		

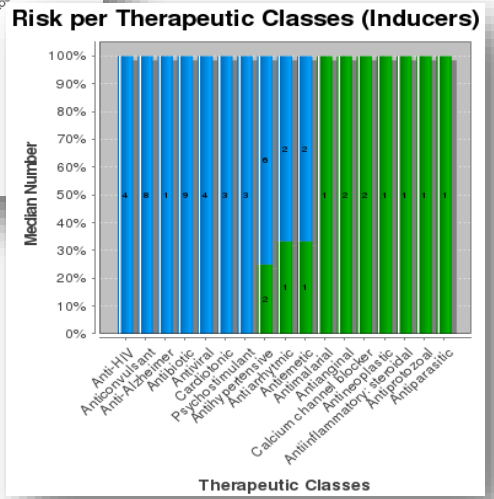
[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula...

Exported data (Tab 2) – Input parameters

DDI Risk Calculator (DDIRC) Version : 2017.1														
DDIRC database Version: October 2015														
Date: 2018.05.01														
Victim drug Test					**Perpetrator drug**									
							Perpetrator 1							
Metabolism						Dosing regimen	Repeated							
Enzymes	Name	CYP2C9	CYP3A4		**Estimated Liver Concentration**									
	kdeg(min-1)	1.1E-4	3.2E-4			[i]in estimation	(Optimized [I])							
fm(E) calculation	fm(E)	0.22	0.78		**Blood or Plasma Binding**									
	Methode used	recombinant (ISEF)	recombinant (ISEF)			fu plasma	No							
	RAF				**Non Specific Binding**									
Scaling factor	ISEF	0.86	0.32			fu(mic)	No							
	Liver Abund. (pmol/m	69.6	173			fu(hep)	No							
Kinetic	Clint (µl/min/pmol)	0.025	0.094											
	Km (µM)	4	32		**inhibitory constant**									
	Vmx (pmol/min/pmol	0.1	3				**Perpetrator**							
	[C] prot. (g/l)	0.5	0.5		Enzyme		Value	Perpetrator Nam	[C]prot (g/L	kinact (min-1	Emax	nH	Induction Type	Victim[C] (µM	Victim Km (µM)
Hepatic fraction														
	fh	1												
	Method used	Predicted												
Clearance														
	Method used	Predicted												
	Cl (L/h)	17.07												
	Cl non hepatic (L/h)	0.0												
	ClH (L/h)	17.07												
	fup	0.4												
	Qh (L/min)	1.61												
Non specific binding														
	fu(mic)	0.399												
	[C]prot (g/L)	0.5												
fu(mic) calculation	Method	Hallifax												
	LogP	4.28												
	pKa	7.66												
Gut Metabolism														
	Fg	1												
	Method used	User defined												
	Qg (L/h)	18												
	fug	1												
F'g/Fg estimation	Method	Model predicted												

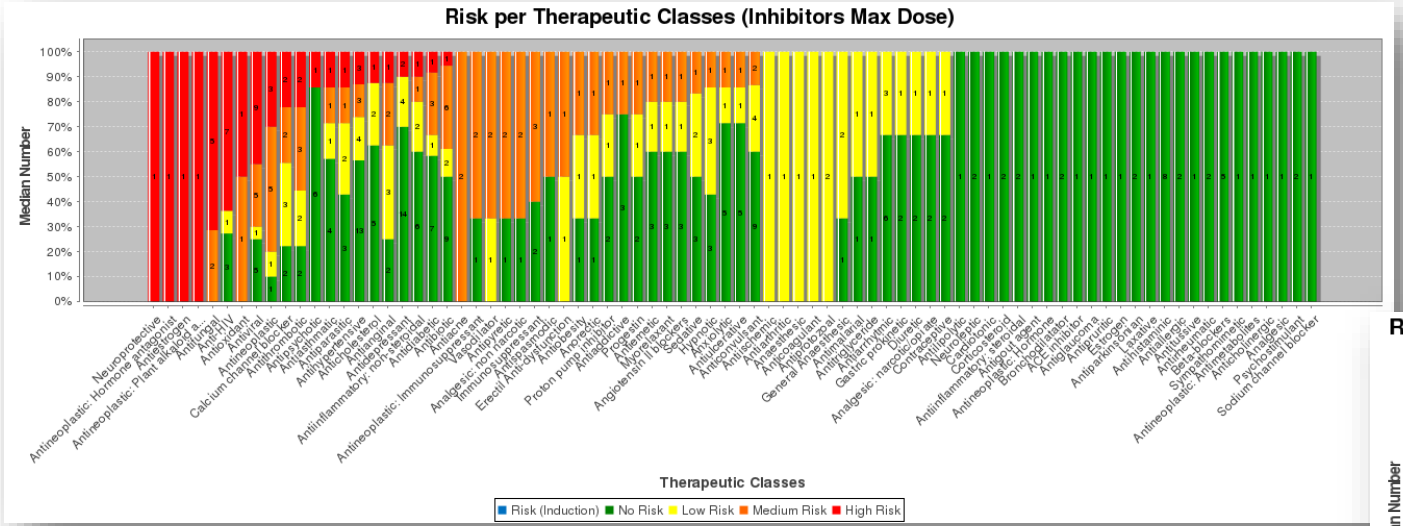
Exported results (Tab 3): Risk per Therapeutic Class

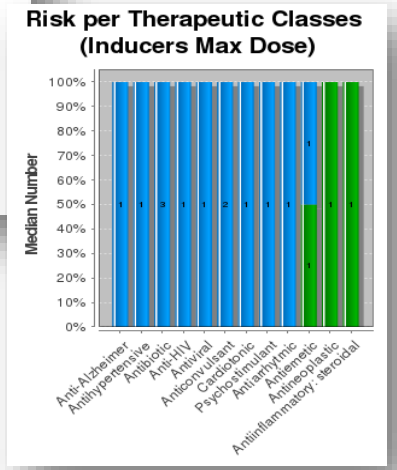




drugs in tested in each class is indicated

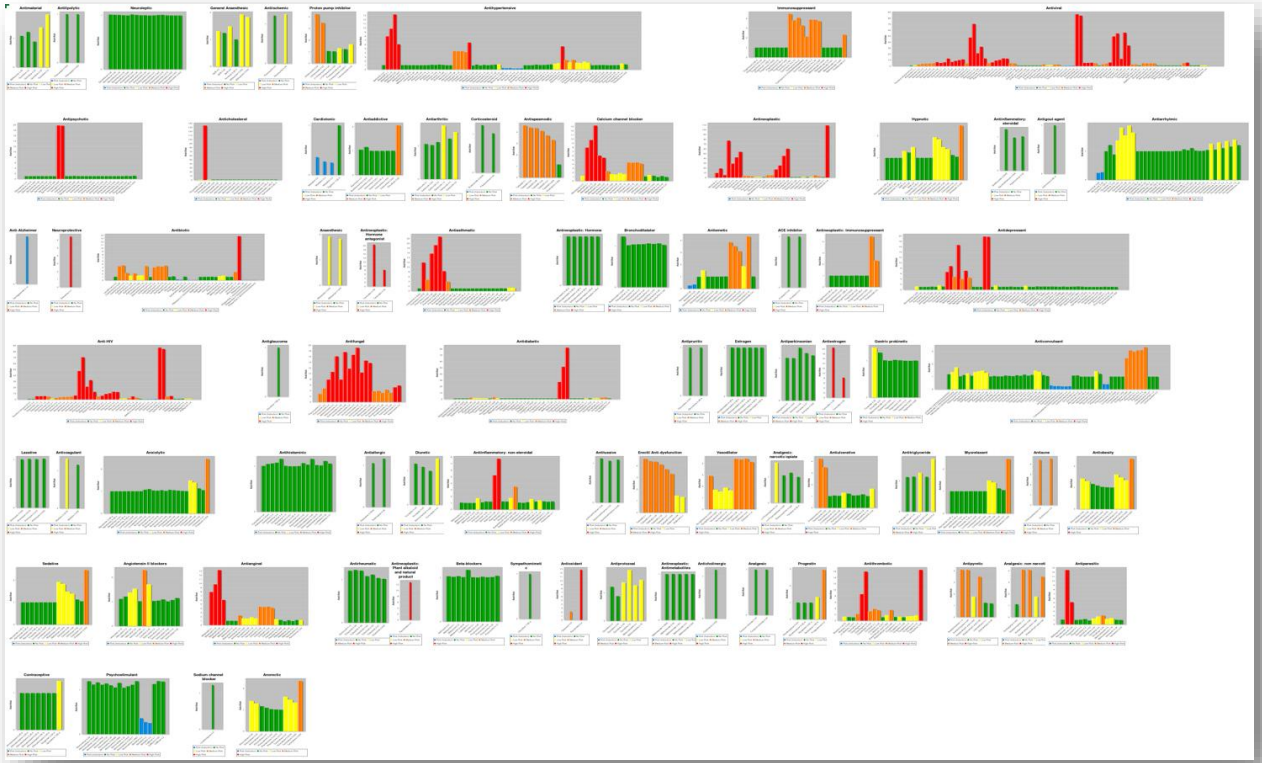
Exported results (Tab 4): Risk per Therapeutic Class – Maximum dose



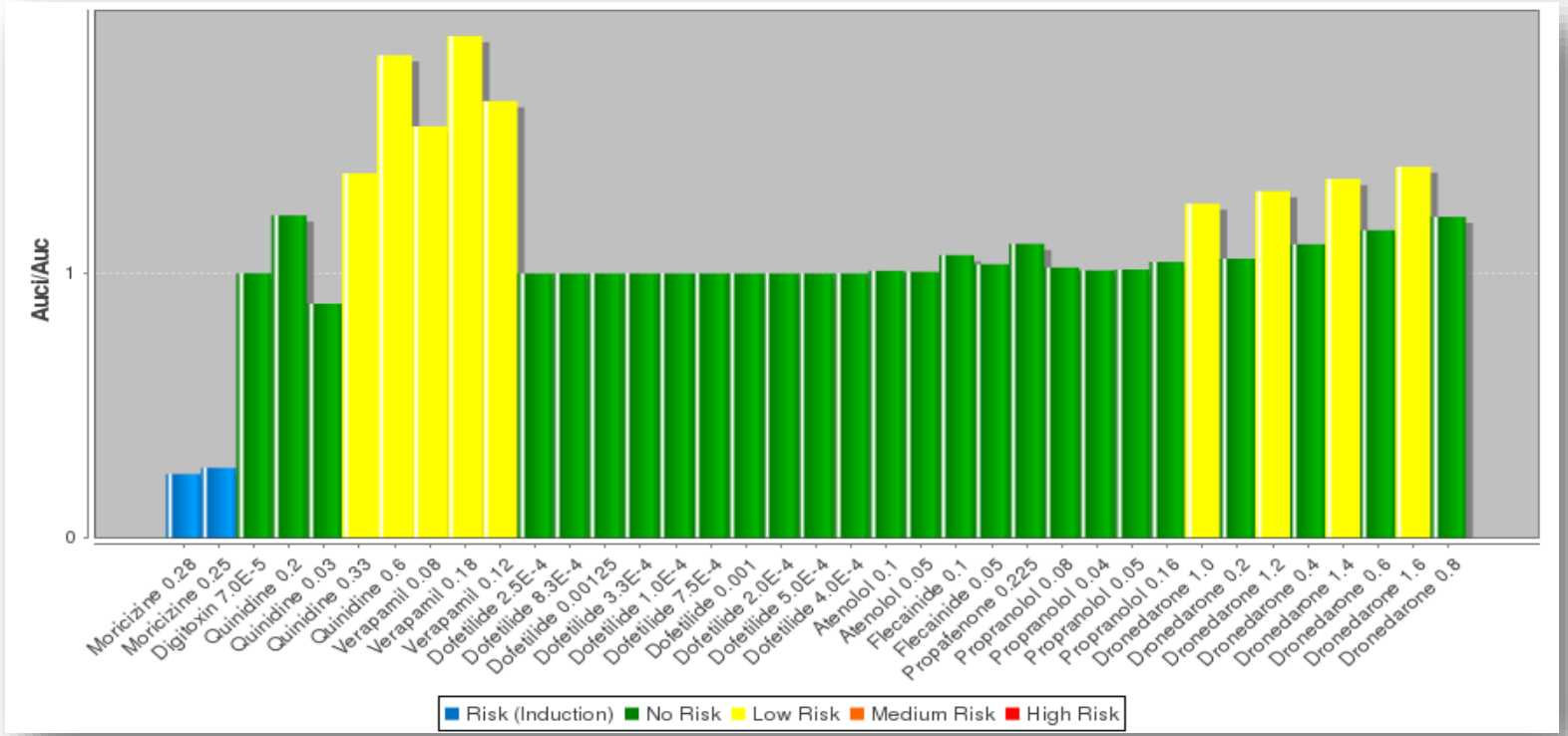


drugs in tested in each class is indicated

Exported results (Tab 5): Risk per Individual drug/dose

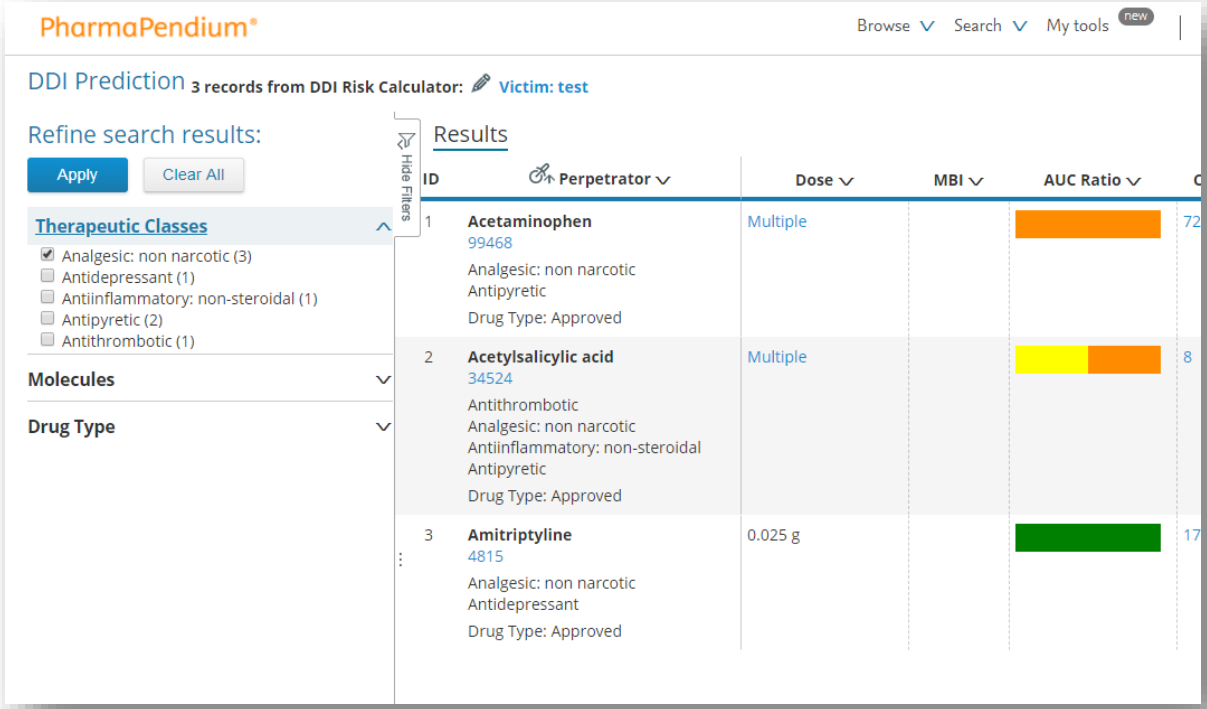


Question – what's the potential to interact with antiarrhythmic drugs

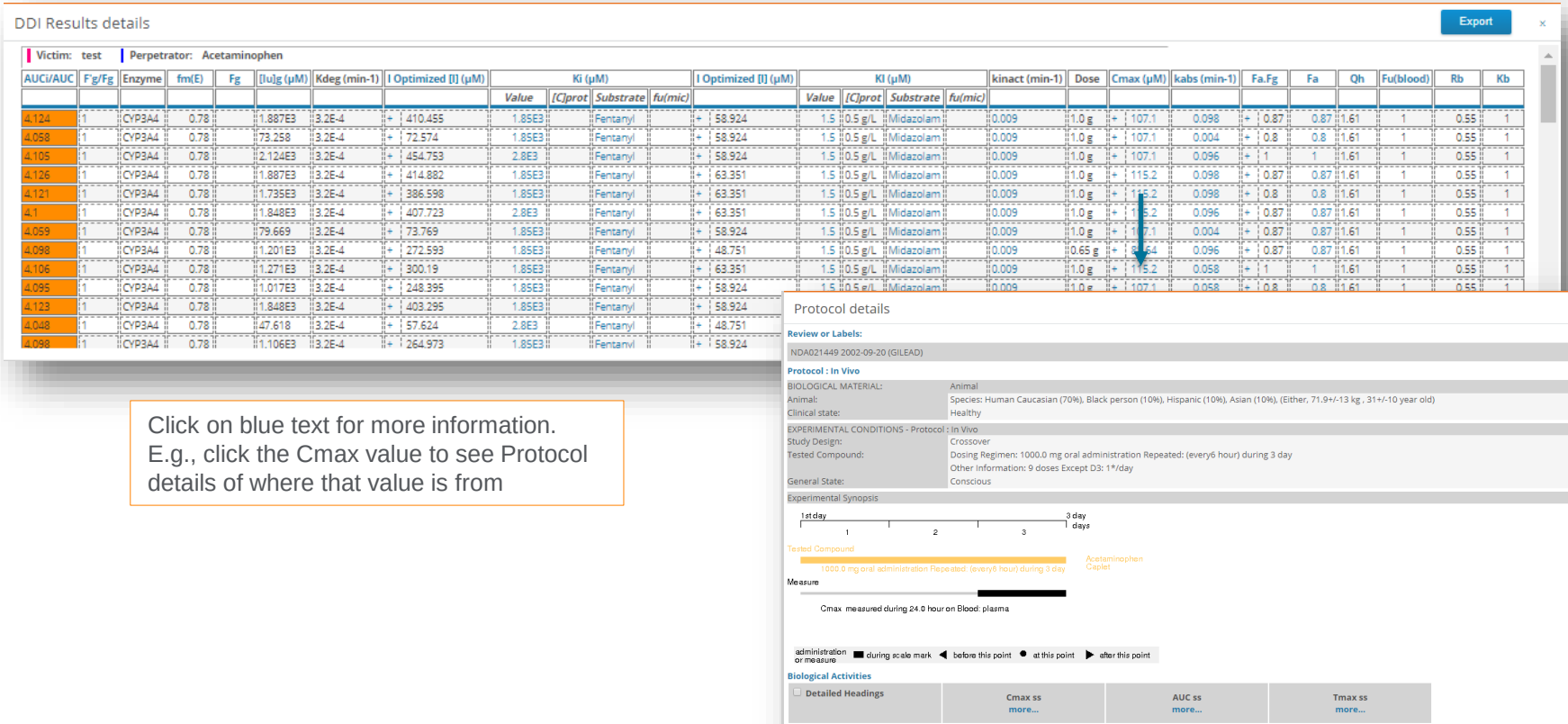


Question: is there a risk of interaction between the test compound and acetaminophen?

- Search for the therapeutic class analgesic, non-narcotic
  - Note: the therapeutic classes are not the same in DDIRC as in PharmaPendium
- See medium risk of interaction
  (Average AUC ratio of ~4)

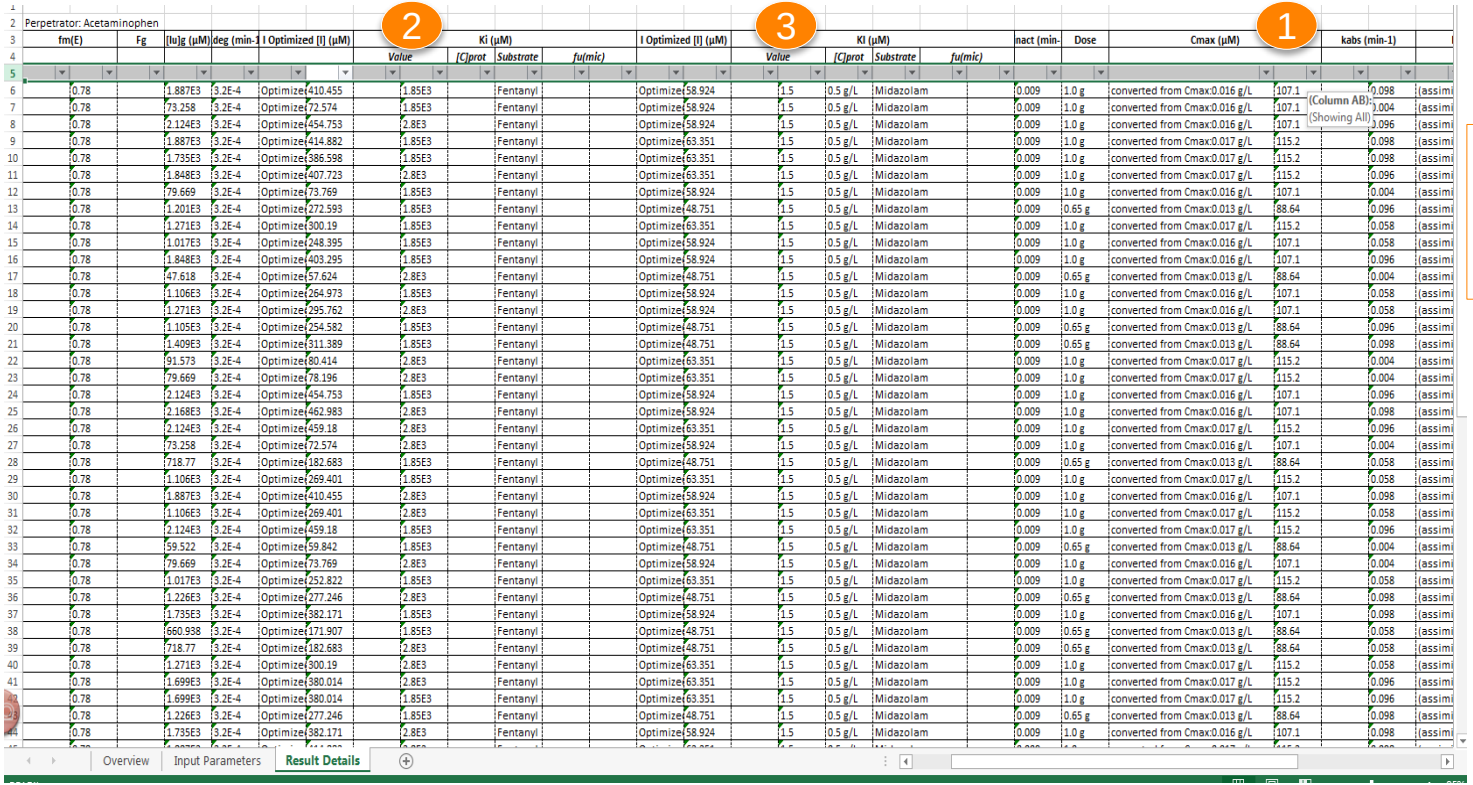


How many Cmax, Ki and KI values were used for the prediction?



Click on blue text for more information.
E.g., click the Cmax value to see Protocol details of where that value is from

How many Cmax, Ki and KI values were used for the prediction?



Export Count data and look at Results Details Tab.To see the # of values used:

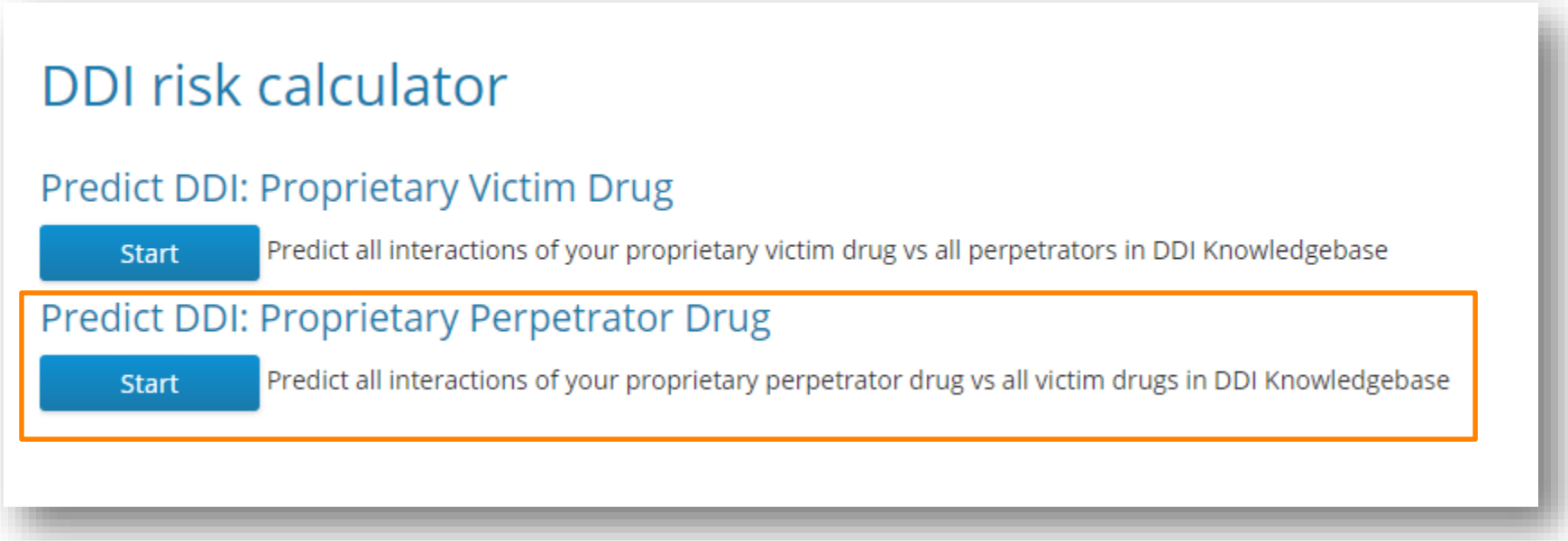
1. Filter by Cmax
2. Filter by Ki
3. Filter by KI

DDIRC Demo: Test compound as a perpetrator

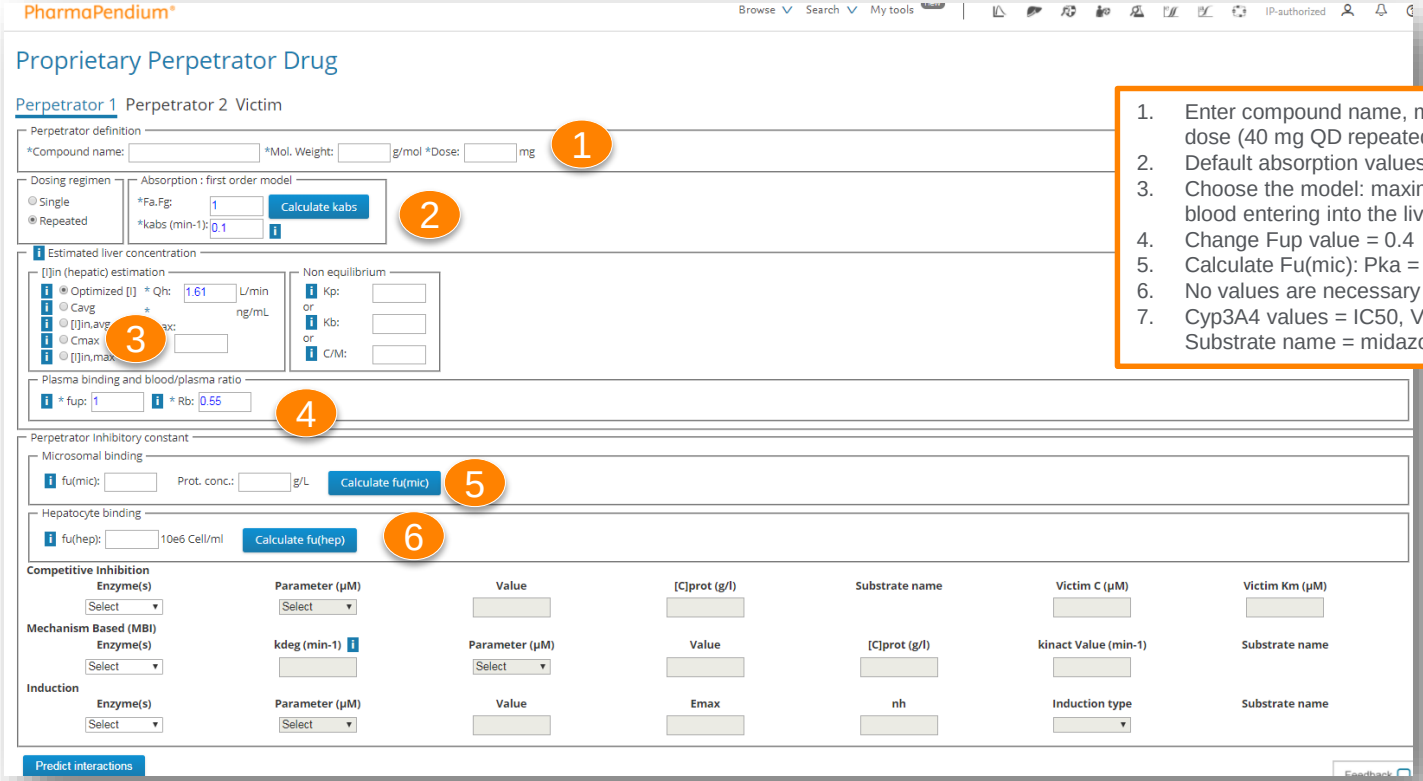
ELSEVIER

Empowering Knowledge

Predict DDIs with the proprietary drug as a perpetrator

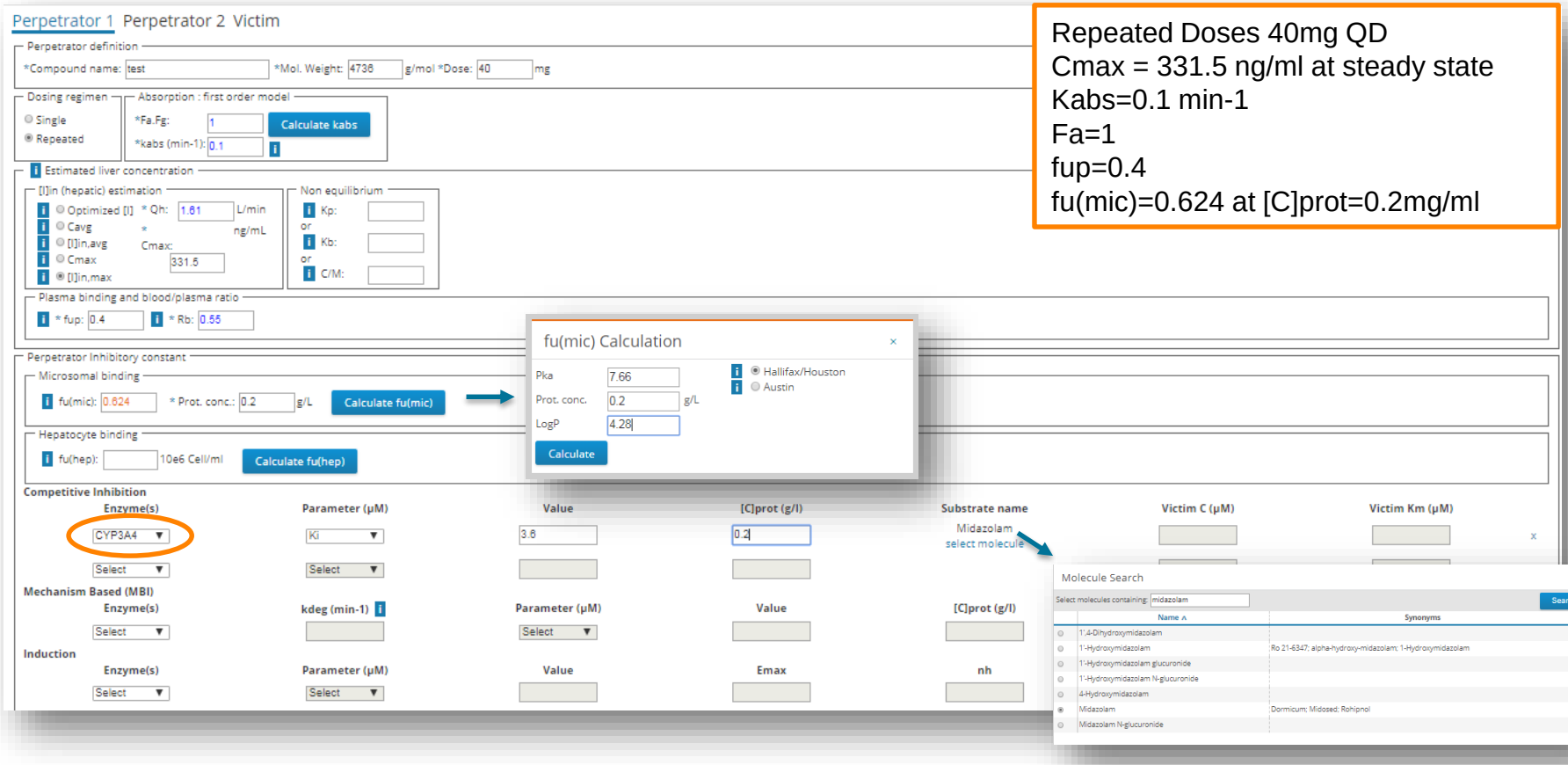


Predict DDIs with the proprietary drug as a perpetrator



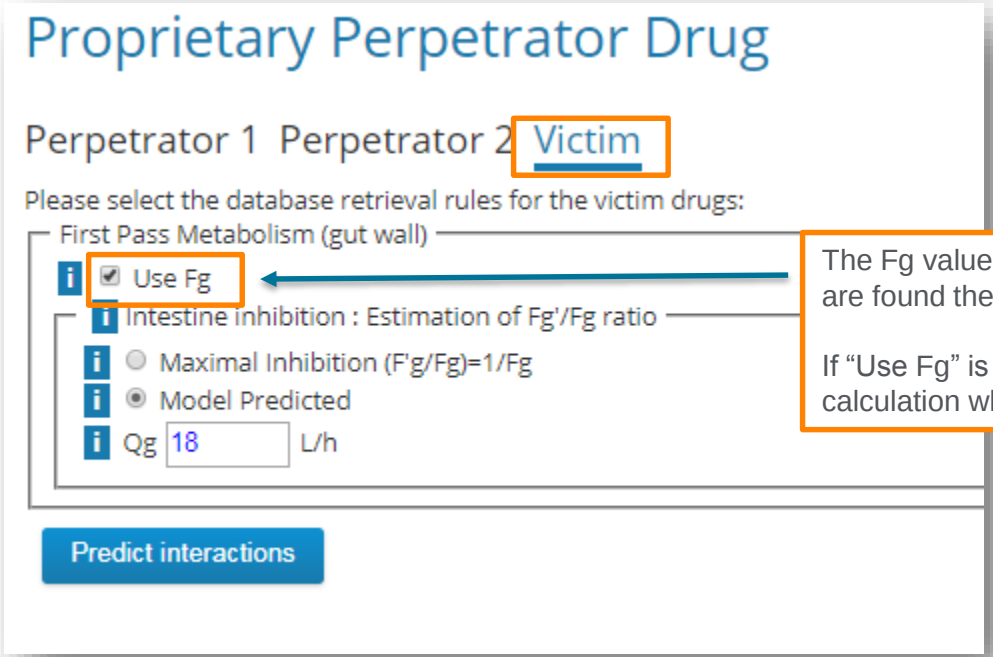
1. Enter compound name, molecular weight (473.5) and dose (40 mg QD repeated dose)
2. Default absorption values are worst-case scenario (Fa=1)
3. Choose the model: maximal systemic concentration in blood entering into the liver and add Cmax (331.5 ng/ml)
4. Change Fup value = 0.4
5. Calculate Fu(mic): Pka = 7.66, [C]prot=0.2, LogP = 4.28
6. No values are necessary for hepatocyte binding
7. Cyp3A4 values = IC50, Value = 3.6, [C]prot = 0.2, Substrate name = midazolam

Predict DDIs with the proprietary drug as a perpetrator



Repeated Doses 40mg QD
Cmax = 331.5 ng/ml at steady state
Kabs=0.1 min-1
Fa=1
fup=0.4
fu(mic)=0.624 at [C]prot=0.2mg/ml

Enter intestinal metabolism values for the Victim

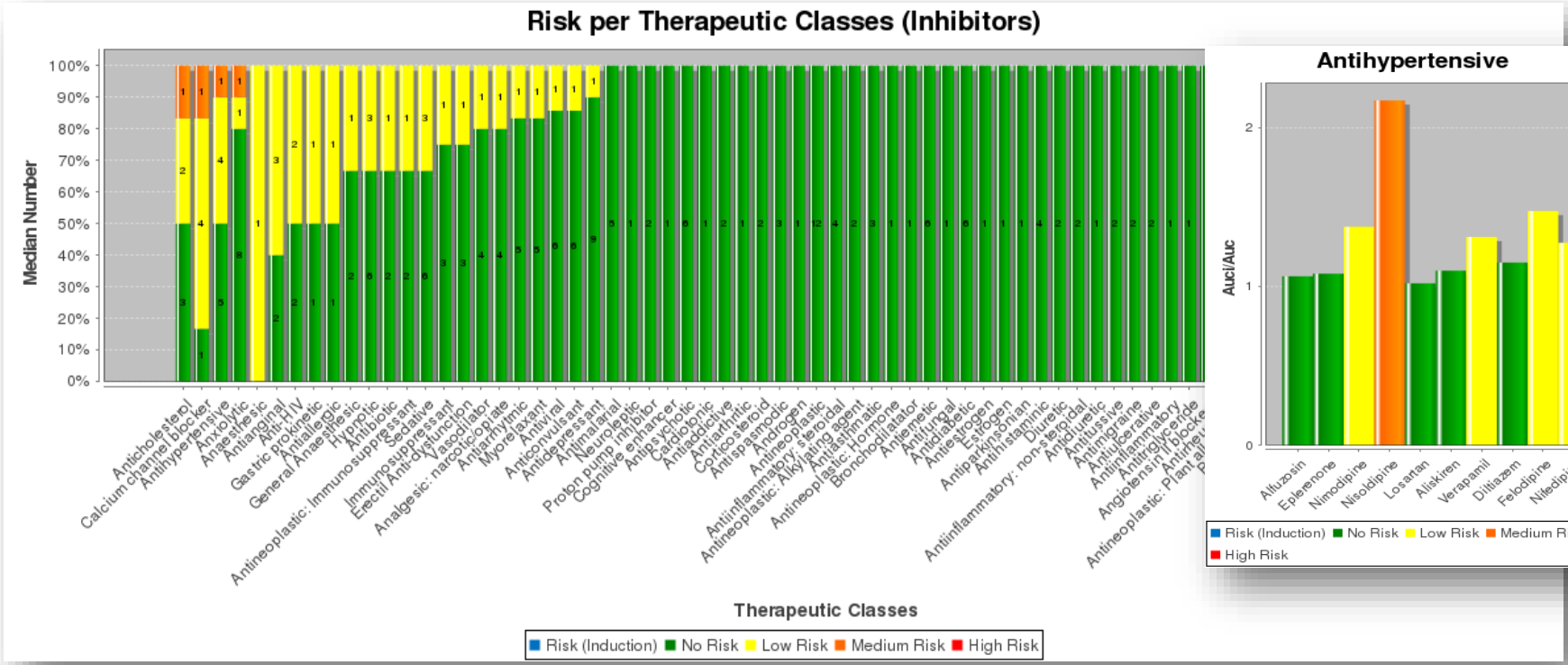


When CYP3A4 or CYP3A5 is selected, there is the option to define if & how intestinal metabolism should be taken into account.

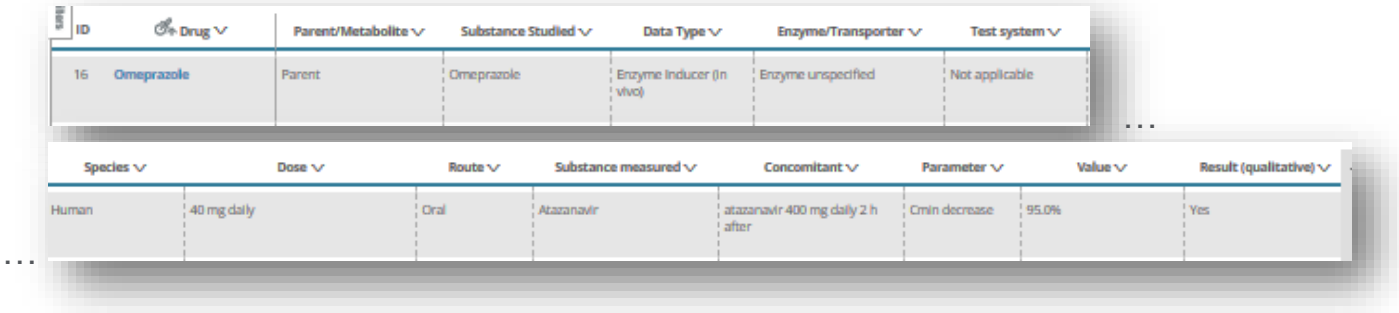
The Fg values will be retrieved from the DDIRC library. If no values are found then a default value of 1 will be used.

If “Use Fg” is unselected, then a default value of 1 is used for calculation which assumes no metabolism in the gut for the victim.

There may be a risk with anticholesterol and antihypertensive drugs



How to understand MET results



ID	Drug	Parent/Metabolite	Substance Studied	Data Type	Enzyme/Transporter	Test system
16	Omeprazole	Parent	Omeprazole	Enzyme Inducer (In vivo)	Enzyme unspecified	Not applicable

Species	Dose	Route	Substance measured	Concomitant	Parameter	Value	Result (qualitative)
Human	40 mg daily	Oral	Atazanavir	atazanavir 400 mg daily 2 h after	Cmin decrease	95.0%	Yes

1. Omeprazole is the “Substance Studied” to see if it is an enzyme inducer. Atazanavir (“Substance Measured”) is used to measure this effect by observing if it’s metabolism is affected in the presence of Omeprazole.
2. In this scenario, Atazanavir is metabolized by enzymes (CYPs) that are induced by Omeprazole. Atazanavir is a substrate of this CYP.
3. Looking at the data, following multiple doses of Omeprazole (40mg daily) and Atazanavir (400mg daily 2 h after), the Cmin of Atazanavir decreased by 95% (in relation to Atazanavir *alone*)
4. Based on the source document, due to the decrease in Cmin of Atazanavir in the presence of Omeprazole, there is a drug-drug interaction with Omeprazole
5. In this study, the metabolizing enzyme is not specified, hence our interpretation is limited to the fact that Omeprazole and Atazanavir have a drug-drug interaction due to a common metabolizing enzyme (probably involving a Cytochrome P450 Enzyme).
6. Additional notes about the fields are:
    1. “Study Type” is an enzyme inducer study
    2. “Result (qualitative)” indicates that it is a positive result