

R&D Solutions

Identifying drug-drug interactions using PharmaPendium



Sherry Winter, PhD
Sr. Solution Marketing Manager
s.winter.1@Elsevier.com



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 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 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

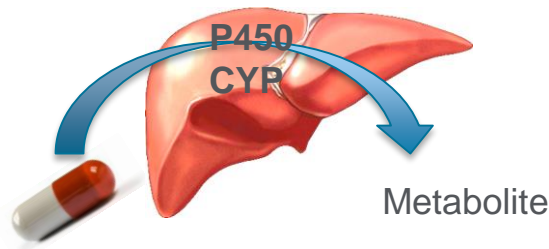


¹ Guthrie et al. BMC Medicine (2015) 13:74

Drug-drug interactions can increase toxicity or reduce clinical efficacy

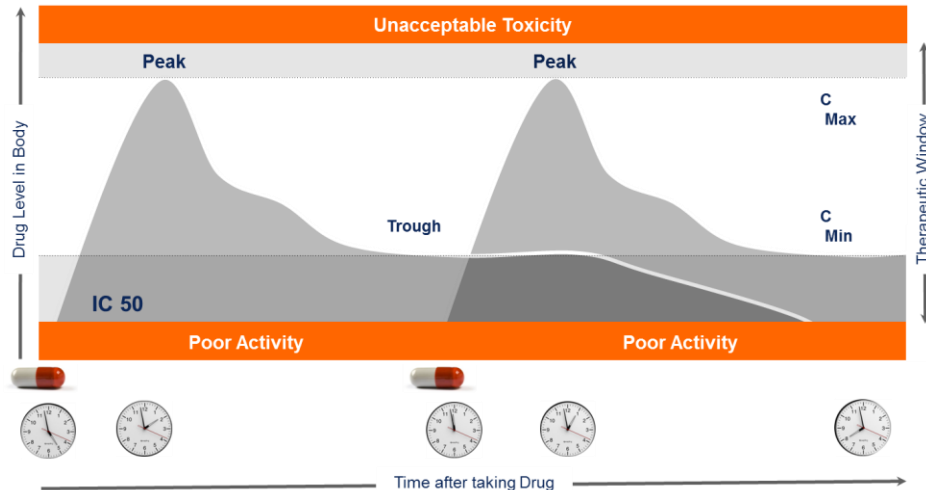
Measured by AUC (area under the curve), which increases/decreases

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

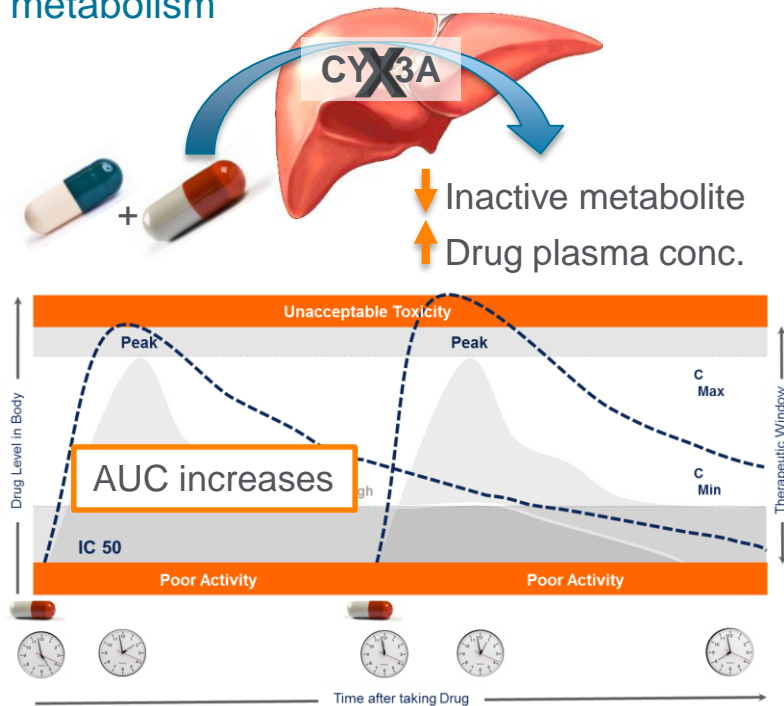
Concomitant drug = two or more drugs are taken at (almost) the same time



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

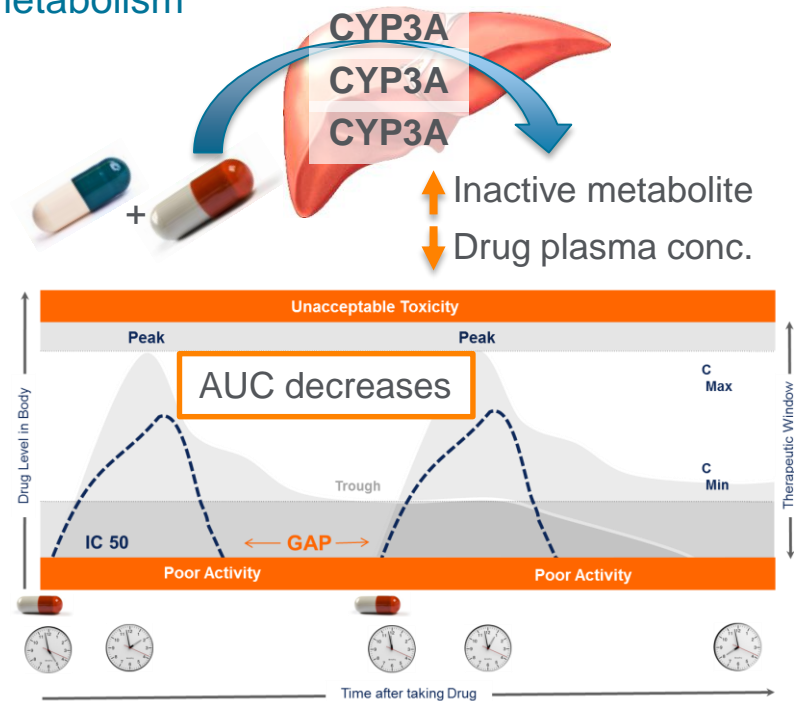
Dosage is timed so that plasma concentration levels remain high enough to maximize efficacy and low enough to avoid toxicity.

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**.

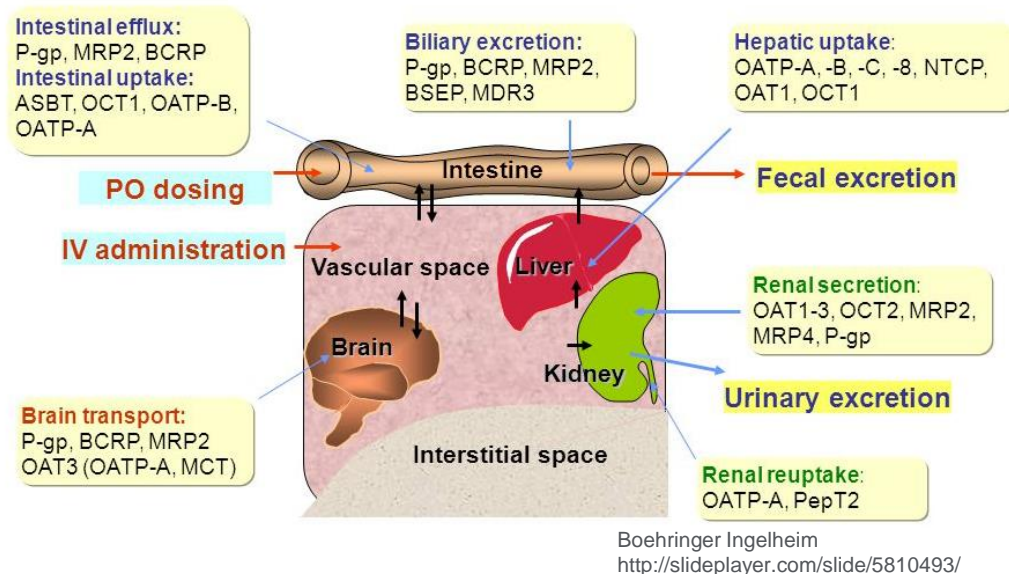
Concomitant drug **induces** CYP-mediated metabolism



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**

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

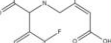





238

unique drugs
assessed as a
victim


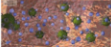




521

drugs assessed
as a perpetrator

Search using a wide range of MET and PK parameters

<p>Metabolites</p> <p>Created, when available</p> 	<p>CYPs</p> <p>Either involved in the metabolism or up/down regulated by the drug, quantitative and qualitative data</p> 	<p>Phase 2 Enzymes</p> 
<p>Transporters</p> <p>And drug effects on transporters</p> 	<p>In Vitro</p> <p>Dynamic parameters such as CLint (Intrinsic Clearance) and Km (Michaelis Constant), Vmax (Maximum rate of reaction)</p> 	<p>DDI Studies</p> <p>Ratio of AUC, Clearance, etc. in presence of another drug.</p> 

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

<p>Absorption</p> <p>Includes:</p> <ul style="list-style-type: none"> % Absorbed Bioavailability Concentrations Fraction absorbed Time values 	<p>Binding</p> <p>Includes:</p> <ul style="list-style-type: none"> Cell binding Protein binding 	<p>Biotransformation</p> <p>Includes:</p> <ul style="list-style-type: none"> Enantiomeric ratio Metabolic ratio Metabolic stability Metabolic transformation 
<p>Distribution</p> <p>Includes:</p> <ul style="list-style-type: none"> Accumulation AUC Permeation Steady state Time value Tissue distribution Volume of distribution 	<p>Elimination</p> <p>Includes:</p> <ul style="list-style-type: none"> Clearance Excretion values Half life Rate constants Time 	<p>Species</p> <p>Includes:</p> <ul style="list-style-type: none"> 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	<p>FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:150) View Full Study PDF 2612k</p>	2009
KI	37.3 uM		<p>FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k</p>	2009
KI	36.4 uM		<p>FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k</p>	2009
KI	36.4 uM		<p>FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k</p>	2009
KI	36.4-48.6 umol/L	Yes	<p>FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k</p>	2009
KI	37.3 uM		<p>FDA approval package document: Clinical Pharmacology and Biopharmaceutics Review (Page:145) View Full Study PDF 2612k</p>	2009

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

[illegible]

$$\frac{-B \pm \sqrt{B^2 - 4ac}}{2a} = \frac{-(b/3a) \pm \sqrt{(b/3a)^2 - 4ac}}{2}$$

Drug-drug interaction risk calculator

DDI risk is continually assessed throughout drug development

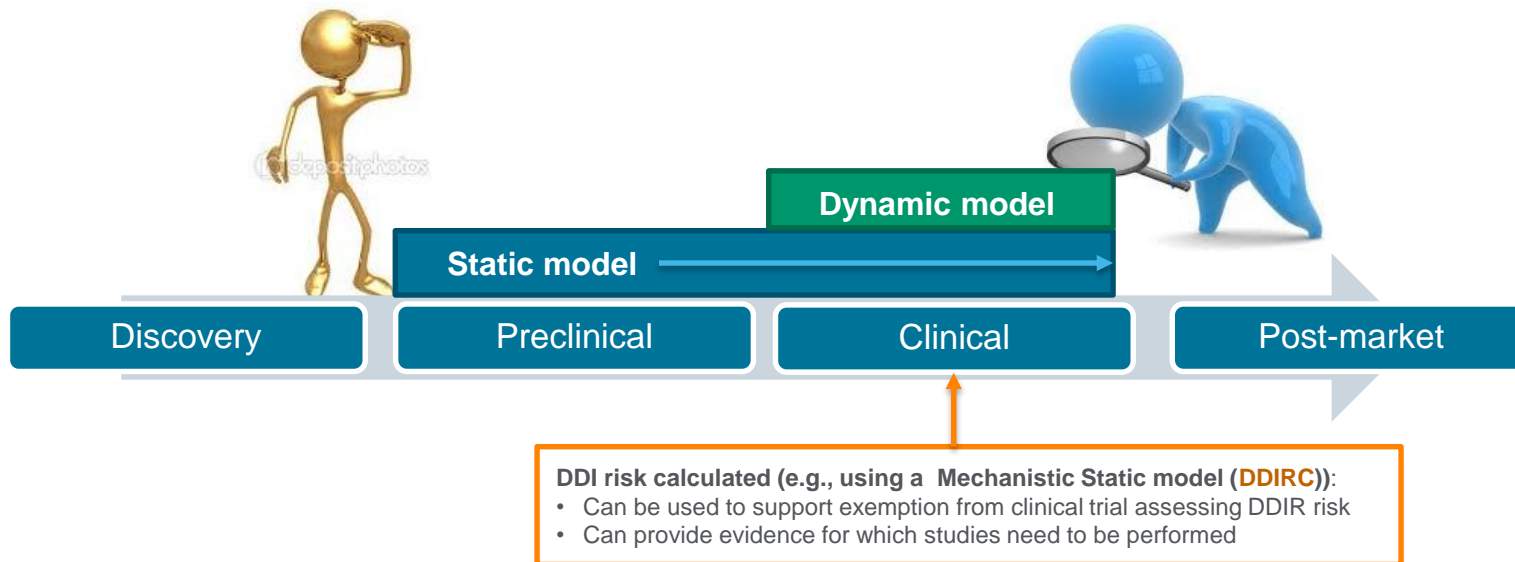
The FDA recommends a stepwise, model-based evaluation of metabolism-based interactions

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 **complementary** 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



PharmaPendium DDI Risk Calculator (DDIRC)

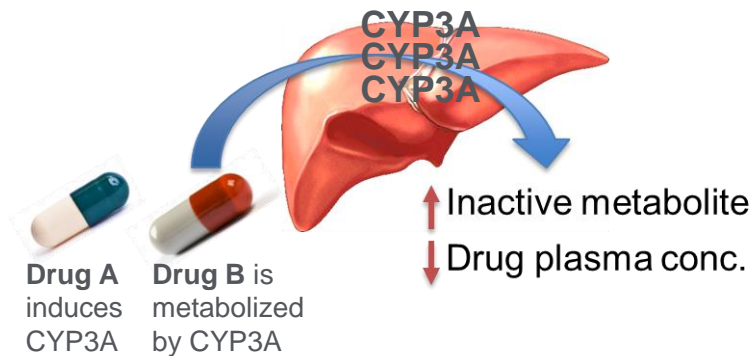
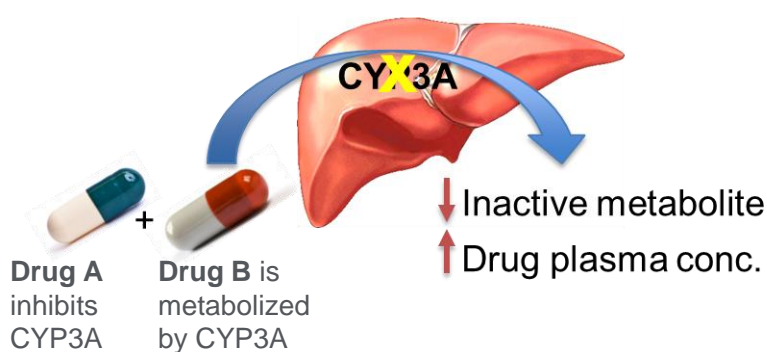
identifying potential *Victims* and *Perpetrators* involved in drug-drug interactions

- 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

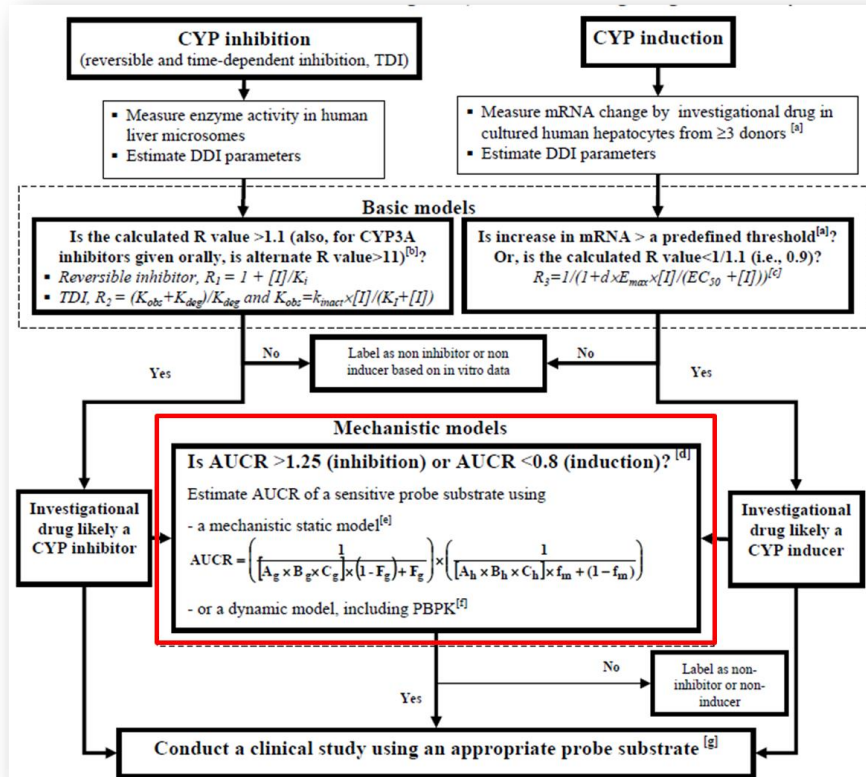
The **perpetrator** drug is the drug that **affects** the pharmacokinetics of another drug

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



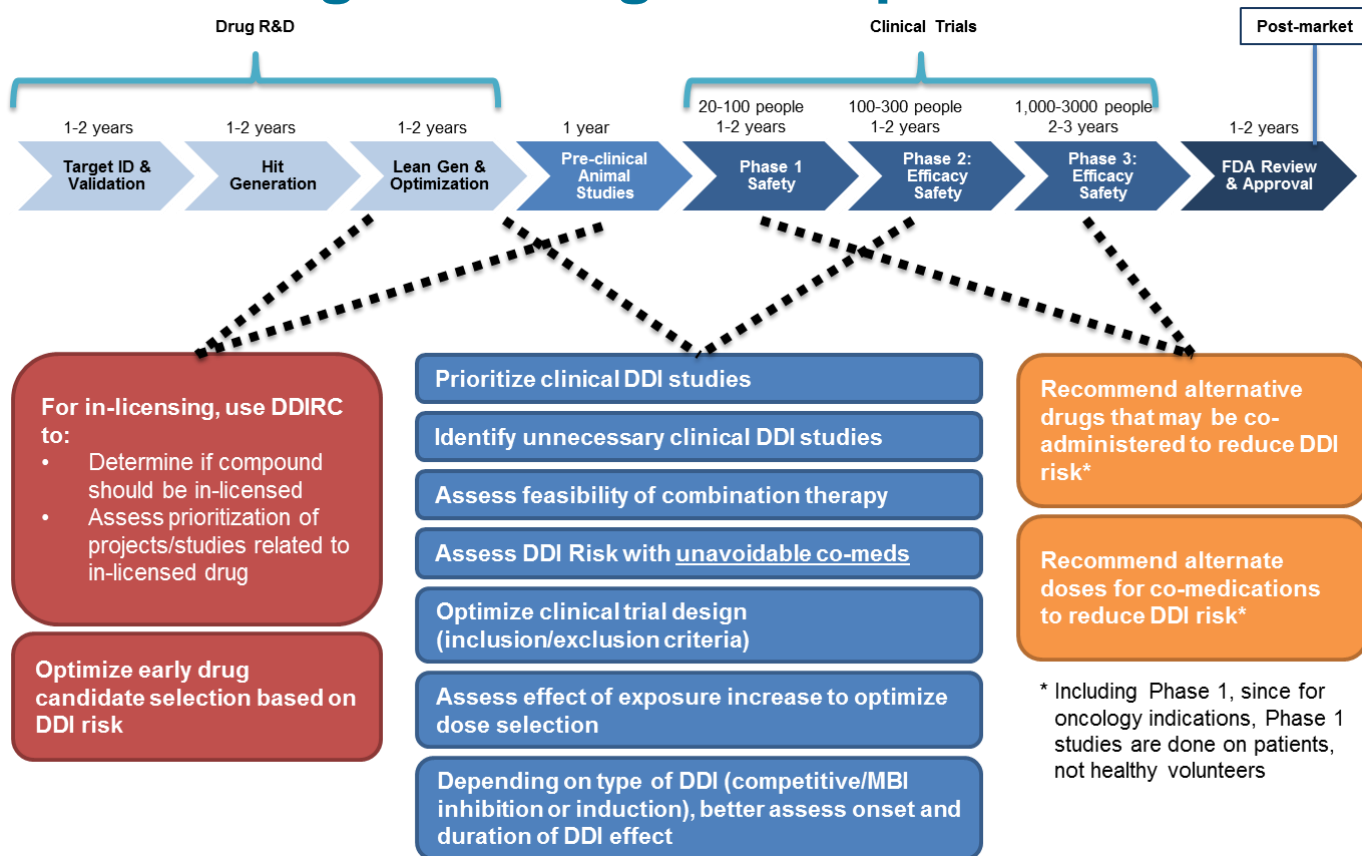
Guidance for Industry Drug Interaction Studies

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



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.

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

Real example of how DDIRC impacted clinical trial design

Sensitive substrate		AUC increase
CYP1A2	Caffeine	x1
CYP2B6	Bupropion	x1
CYP2C8	Repaglinide	x1
CYP2C9	Celecoxib	x1
CYP2C19	Omeprazole	x1
CYP2D6	Dextromethorphan	x1
CYP3A4/5	Lovastatin	x5.5
	Nisoldipine	x4.5
	Buspirone	x4.1
	Sildenafil	x2.2
	Saquinavir	x2
	Midazolam	x1.9
	Felodipine	x1.8
	Alfentanil	x1.6
	Triazolam	x1.6
	Maraviroc	x1.3
	Aprepitant	x1
	Darunavir	x1

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

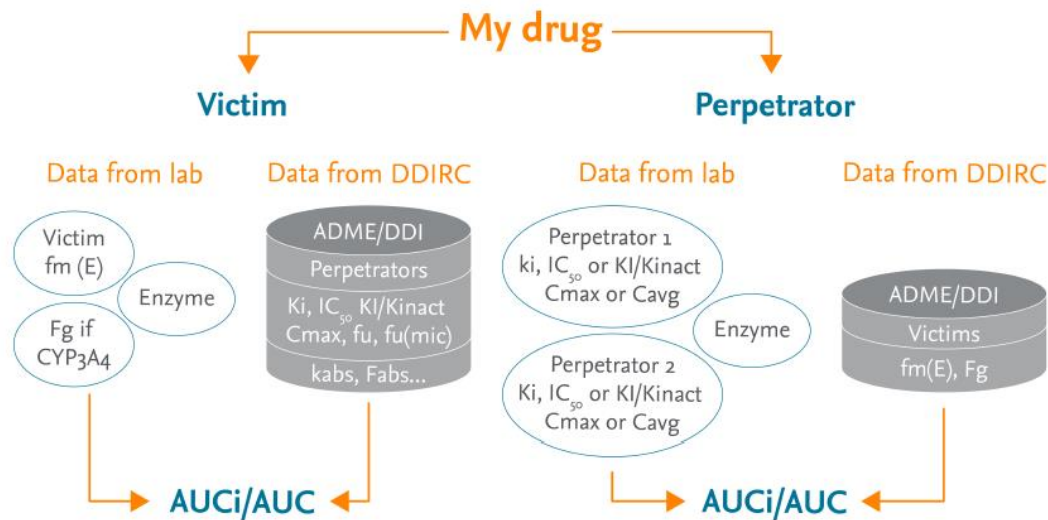


Figure 2. An illustration of the DDIRC workflow for victim and perpetrator drugs

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

238

unique drugs
assessed as a
victim

521

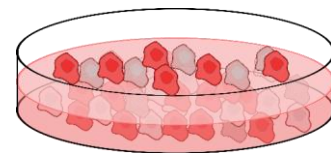
drugs assessed
as a perpetrator

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**)

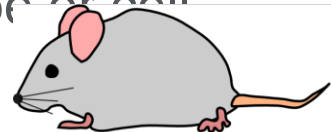
Some background:

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 vitro

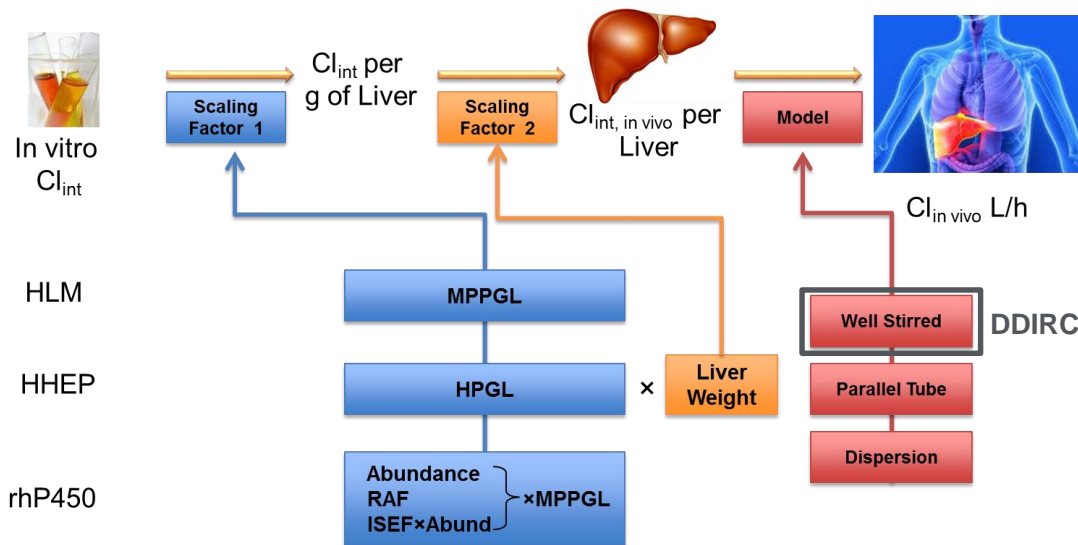
In vivo



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*



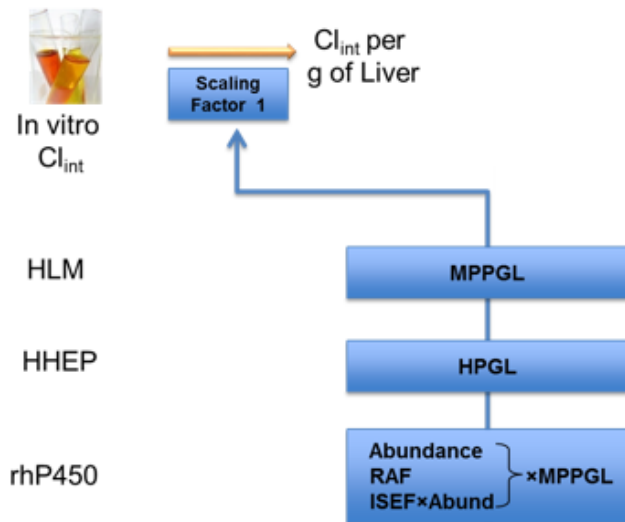
Predicting hepatic clearance

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)

Proprietary Victim Drug

Victim Perpetrators

Please enter proprietary data for the victim drug:

Victim definition

*Compound name:

Hepatic Metabolism

☐ User Defined
☒ Predicted

☒ HLM
☒ hRecombinant

☒ ISEF
☐ RAF
☐ Abundance

☒ baculovirus
☐ Lymphoblastoid
☐ E. Coli
☐ Yeast

fm(E) Prediction

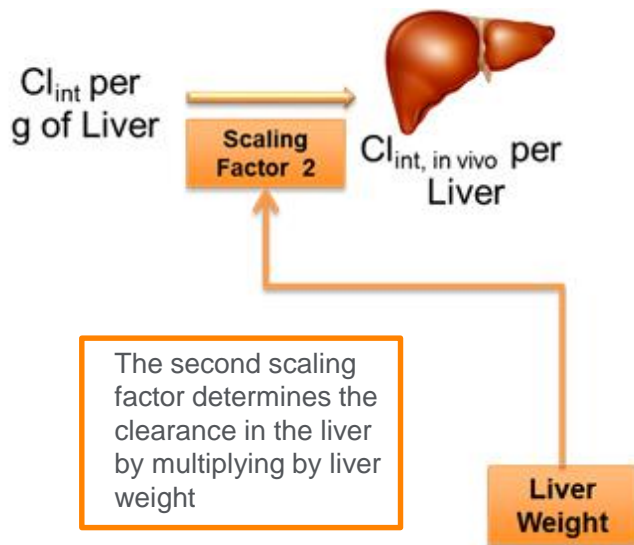
☒ In Vitro enzyme contribution : fm(E)vitro

Enzyme(s)	kdeg (min ⁻¹)	Clint (μl/min/pmol)	Km (μM)	Vmax (pmol/min/pmol)	[C]prot (g/l)	ISEF	Abund. (pmol/mg)
CYP1A2	0.0003					0.9	48.8
Select							

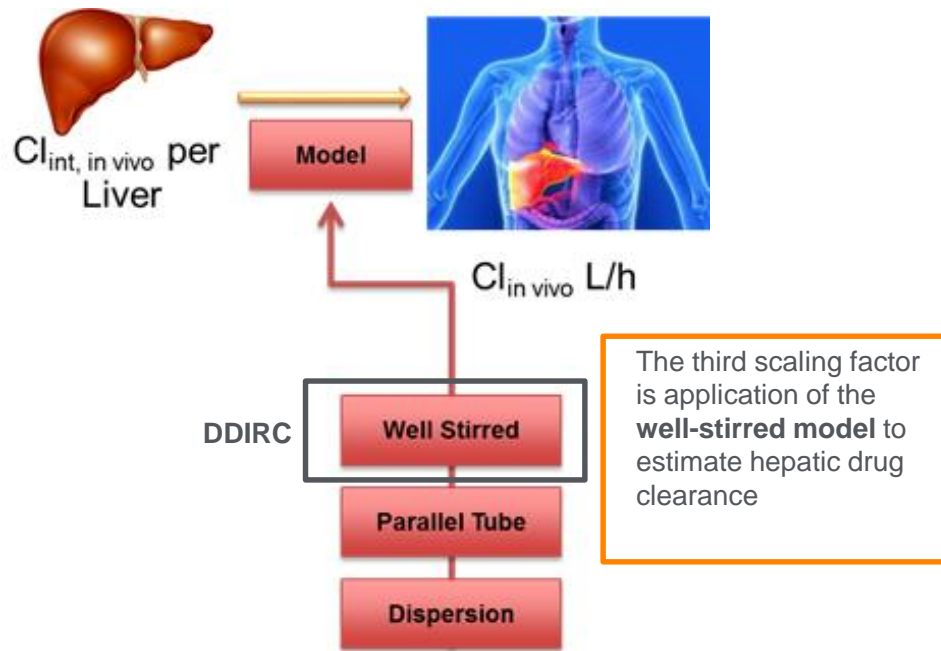
Results from recombinant enzyme experiments are scaled up to human liver microsomes (HLM) **using values from the DDI Risk Calculator** before they are extrapolated to *In vivo* clearance. The user can choose between 3 different scaling factors:

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

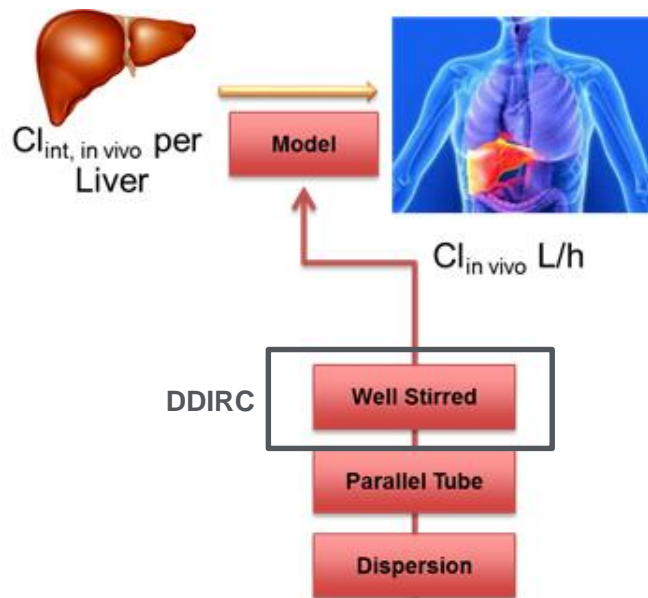
Step-by-step Scaling Factor 2



Step-by-step Scaling Factor 3



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

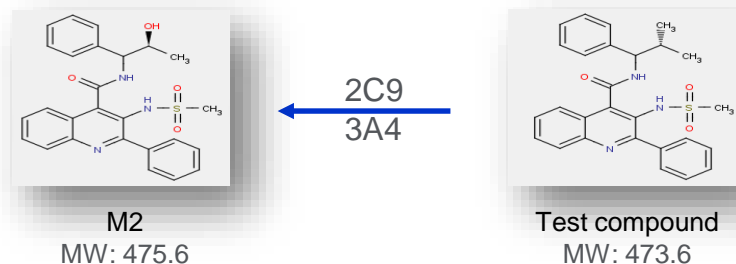
The well-stirred model is the most commonly used model to estimate hepatic clearance.

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

DDIRC Demo: Test compound as a victim

Test compound as a victim

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



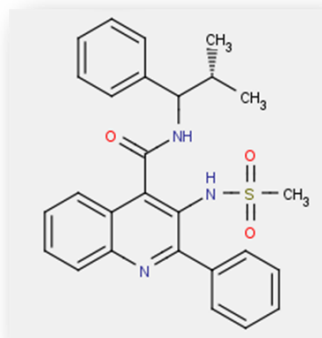
Recombinant Intrinsic Clearance

Cell system: Insect cells Infected with Baculovirus

- **M1:** 3A4 $K_m=8.6\mu\text{M}$ $V_{\text{max}}=0.87$ pmol/min/pmol [C] prot=0.5 mg/ml

- **M2:** 3A4 $K_m=32\mu\text{M}$ $V_{\text{max}}=3$ pmol/min/pmol [C] prot=0.5 mg/ml
2C9 $K_m=4\mu\text{M}$ $V_{\text{max}}=0.1$ 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

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

Search in Metabolising Enzymes & Transporters

Metabolizing Enz. & Transporters data search

Show me preclinical & clinical studies for these:

Search criteria

Drugs

- + Add drugs by drug class or drug name
- + Add drugs by primary target or primary target class

Data type

- + Add data types

Enzyme/transporter name

- + Add enzyme/transporter names

Species

- + Add species

Sources

- + Add sources

Select the drug class antineoplastics

PharmaPendium®

Browse ▾ Search ▾ My tools ^{new}

IP-authorized

Close Done

Metabo

Show me pre

Search crit

Drugs

+ Add drug

+ Add drug

antneoplas|

- Antineoplastics
- Antineoplastics, **other**
- Antineoplastics, **enzymes**
- Antineoplastics, **retinoids**
- Antineoplastics, **antibiotics**
- Antineoplastics, **antimitotics**
- Antineoplastics, **antiandrogens**
- Antineoplastics, **antiestrogens**
- Antineoplastics, **antimetabolites**
- Antineoplastics, **platinum agents**
- Antineoplastics, **alkylating agents**
- Antineoplastics, **epipodophyllotoxins**
- Antineoplastics, **aromatase inhibitors**
- Antineoplastics, **radiopharmaceuticals**
- Antineoplastics, **monoclonal antibodies**
- Antineoplastics, **proteasome inhibitors**
- Antineoplastics, **topoisomerase inhibitors**
- Antineoplastics, **hormones/hormone modifiers**
- Antineoplastics, **biological response modifiers**
- Antineoplastics, **signal transduction inhibitors**
- + ☐ Androgens

Add drugs by drug class or drug name

antneoplastics

- ☒ Antineoplastics
- + ☒ Antineoplastics, alkylating agents
- + ☒ Antineoplastics, antiandrogens
- + ☒ Antineoplastics, antibiotics
- + ☒ Antineoplastics, antiestrogens
- + ☒ Antineoplastics, antimetabolites
- + ☒ Antineoplastics, antimitotics
- + ☒ Antineoplastics, aromatase inhibitors
- + ☒ Antineoplastics, biological response modifiers
- + ☒ Antineoplastics, enzymes
- + ☒ Antineoplastics, epipodophyllotoxins
- + ☒ Antineoplastics, hormones/hormone modifiers
- + ☒ Antineoplastics, monoclonal antibodies
- + ☒ Antineoplastics, other

Search on:

Drugs

x Antineoplastics

Limit MET search

Metabolizing Enz. & Transporters data search

Show me preclinical & clinical studies for these:

Search criteria

Drugs

x Antineoplastics

+ Add drugs by drug class or drug name

+ Add drugs by primary target or primary target class

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

Data type

+ Add data types

Enzyme/transporter name

+ Add enzyme/transporter names

Species

+ Add species

Sources


+ Add sources


Extensive data is extracted and presented in Results

Metabolizing Enz. & Transporters search results 34006 records from ME&T data: [Antineoplastics \(34006\)](#)

Show Filters

Preclinical Data Clinical Data All Data Preclinical and clinical data

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

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

Preclinical Data Clinical Data All Data preclinical and clinical data

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

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

Metabolizing Enz. & Transporters search results

Refine search results:

Apply

Clear All

Drugs

Routes of Administration

Sources

Data type

Enzyme/transporter name

Parent/Metabolite

Test System

Results(qualitative)

Years

2011 - 2020 (16309)

2018 (26)

2017 (972)

2016 (1214)

Preclinical Data

ID

Drug

1

Abarelix

2

Abarelix

3

Abarelix

4

Abarelix

5

Abarelix

34006 records from N

Metabolizing Enz. & Transporters search results

34006

Refine search results:

Apply

Clear All

Parent/Metabolite

Test System

Results(qualitative)

+ ☐ Ambiguous (566)

+ ☐ No (9476)

- ☒ Yes (13454)

☐ Complete (5)

☐ Dominant (2)

☐ Extensive (15)

☐ Great (1)

☐ Greatest (2)

☐ High (4)

☐ Large (1)

☐ Less (58)

☐ Likely (11)

Preclinical Data

Clinical Data

ID

Drug

1

Abarelix

2

Abarelix

3

Abarelix

4

Abarelix

5

Abarelix

In Vitro

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 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	EMA approval document: Assessment Report (Page:14) View Full Study PDF 2752k	2016
3	Everolimus			Cmin ratio	2.371 fold	Yes, Significant	EMA approval document: Assessment Report (Page:14) View Full Study PDF 2752k	2016
4	Everolimus			Cmin ratio	0.455 fold	Yes, Significant	EMA approval document: Assessment Report (Page:14)	2016

Look at the source data to see context

PharmaPendium* Browse Search My tools new IP-authorized

FDA Approval Package

Search this FDA Package

- + Administrative documents
- + Approval Letter
- Approval Package
 - 2017-08-01 PDF(391k) Approval Package 20993...
 - 2017-08-01 PDF(11850k) Approval Package 2099...
 - 2017-08-01 PDF(397k) Approval Package 20993...
 - 2017-08-01 PDF(3538k) Approval Package 20993...
- + Chemistry Review
- + Label
- + Letter
- + Other Important Informatio...
- + Review

FDA Approval Package - Copanlisib > Approval Package

Approval Package 209936/S-000 Part 02

and low expression of genes from stromal and inflammation signatures. As the data are based on a small and heterogeneous subset of patients, the results should be interpreted with caution but are generally consistent with copanlisib mechanism would also be expected to influence pathway activation, submission.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. Copanlisib is primary metabolized by CYP3A. Strong CYP3A modulators have significant effect on copanlisib exposures. Avoid concomitant use of strong CYP3A inducers and consider alternative concomitant medications with less potential for CYP3A induction. Dose reduction to 45 mg is recommended when coadministration of ALIQOPA with a strong CYP3A inhibitor.

There is a DDI potential between copanlisib and substrates of renal transporter MATE2-K. At recommended dosing regimen, copanlisib achieves C_{max} around $1 \mu M$ that is about 10-fold of its IC_{50} ($0.09 \mu M$) for MATE2-K. Metformin is a sensitive MATE2-K substrate used as a concomitant medicine in the pivotal trial to control hyperglycemia. It is also expected that metformin could be used in the management of copanlisib induced hyperglycemia in the clinical setting. Therefore, in order to assess the influence of copanlisib on the PK of MATE2-K substrates such as metformin, a post-marketing requirement will be issued.

A potential DDI between copanlisib and substrates of MATE2-K was detected

Find more in other sections of the approval document

FDA Approval Package - Copanlisib > Label
Label 209936/S-001

115% 2/3 Go

Effect of Copanlisib on CYP and non-CYP Enzymes

Copanlisib is not an inhibitor of the metabolism of drugs that are substrates of the major CYP isoforms (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) or uridine diphosphate-glucuronosyltransferase isoforms (UGT) or dihydropyrimidine dehydrogenase (DPD) at therapeutic 60 mg dose plasma concentrations. Copanlisib is not an inducer of CYP1A2, CYP2B6 and CYP3A.

Effect of Copanlisib on Drug Transporter Substrates

Copanlisib is not an inhibitor of P-gp, BCRP, multi-drug resistance-associated protein (MRP2), bile salt export pump (BSEP), OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE1 at therapeutic 60 mg dose plasma concentrations.

Copanlisib is an inhibitor of **MATE2-K** (IC₅₀: 0.09 µM). Based on the PK of copanlisib, inhibition may occur after copanlisib infusion at approved recommended dosage. The clinical significance of this potential inhibition on plasma concentrations of concomitantly administered drugs that are MATE2-K substrates is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with copanlisib.

Copanlisib did not cause genetic damage in *in vitro* or *in vivo* assays.

Fertility studies with copanlisib were not conducted; however, adverse findings in male and female reproductive systems were observed in the repeat dose toxicity studies. Findings in the male rats and/or dogs included effects on the testes (germinal epithelial degeneration, decreased weight, and/or tubular atrophy), epididymides (spermatic debris, decreased weight, and/or oligospermia/aspermia), and prostate (reduced

13 of 18

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

Add data types

Type data type to search

-

Metabolizing Enzymes

+ ☒ Drug as Enzyme Inducer

- ☒ Drug as Enzyme Inhibitor

+ ☒ Enzyme Inhibitor

- ☒ Enzyme Inhibitor (in vitro)

☒ Activity (% inhibition)

☒ Activity (% of control)

☒ Activity (absolute)

☒ Activity (Emax)

☒ Activity (fold change)

☒ Activity (no value)

☒ Activity (substrate stability)

☒ Activity (substrate transformation)

☒ Alpha

☒ Emax

Search on:

Data type

x Drug as Enzyme Inducer

x Drug as Enzyme Inhibitor

Select the data type to search:

1) Drug as enzyme inducer

2) Drug as enzyme inhibitor

Note: you can also select in vitro or in vivo parameters. To only see clinical results, select in vivo parameters

Add enzyme/transporter names

Done

 Type enzyme/transporter name to search

CYP2D

☐ CYP2D1

☐ CYP2D2

☐ CYP2D3

 CYP2D4

☒ CYP2D6☐ CYP2D6(B)☐ CYP2D6(D336N)☐ CYP2D6(E215K)☐ CYP2D6(F164L)☐ CYP2D6(F219S)☐ CYP2D6(Met)☐ CYP2D6(R25Q)☐ CYP2D6(R344Q)

Search on:

Enzyme/transporter name

x CYP2D6

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

Metabolizing Enz. & Transporters data search

Show me preclinical & clinical studies for these:

Search criteria

Search

Clear search

Drugs



Add drugs by drug class or drug name



Add drugs by primary target or primary target class

Data type

x Drug as Enzyme Inducer

x Drug as Enzyme Inhibitor



Add data types

Enzyme/transporter name

x CYP2D6



Add enzyme/transporter names

Species



Add species

Sources



Add sources

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

Metabolizing Enz. & Transporters search results

9491 records from ME&T data: [Drug as Enzyme Inducer (390) OR Drug as Enzyme Inhibitor (9101)] AND [CYP2D6 (9491)]

Show Filters

Preclinical Data

Clinical Data

All Data

Preclinical and clinical data

ID	Drug	Parent/Metabolite	Substance Studied	Data Type
1	5-Methoxypsoralen	Parent	Bergapten	Enzyme Inhibitor (in vitro)
2	5-Methoxypsoralen	Parent	Bergapten	Enzyme Inhibitor (in vitro)
...				
3	Abacavir Sulfate	Parent	Abacavir sulfate	Enzyme Inhibitor (in vitro)
4	Abacavir Sulfate	Parent	Abacavir sulfate	Enzyme Inhibitor (in vitro)
5	Abacavir Sulfate	Parent	Abacavir	Enzyme Inhibitor (in vitro)

Show/hide columns

Show drugs in...

Save

Export

Show drugs in

Deselect all

Export All drugs in Excel file (.xls)

Show the filtered drugs in other modules. Based on your filtering.

Selected: 716

☒ 5-Methoxypsoralen

☒ Abacavir Sulfate

☒ Abiraterone Acetate

☒ Acamprosate Calcium

☒ Acetaminophen

> Show in Pharmacokinetic Data

> Show in Drug Safety Data

> Show in FAERS Data

> Show in Efficacy Data

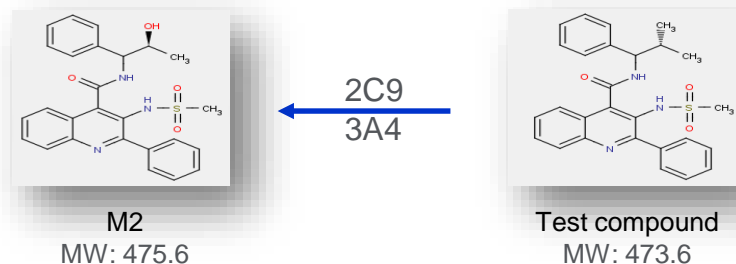
> Show in Activity Data

Feedback

DDIRC Demo: Test compound as a victim

Test compound as a victim

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



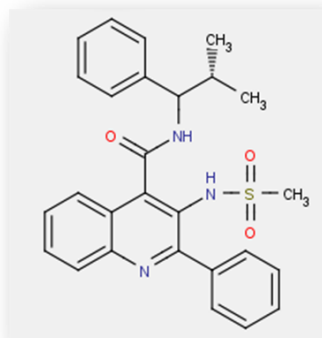
Recombinant Intrinsic Clearance

Cell system: Insect cells Infected with Baculovirus

• **M1:** 3A4 $K_m=8.6\mu\text{M}$ $V_{\text{max}}=0.87$ pmol/min/pmol [C] prot=0.5 mg/ml

• **M2:** 3A4 $K_m=32\mu\text{M}$ $V_{\text{max}}=3$ pmol/min/pmol [C] prot=0.5 mg/ml
2C9 $K_m=4\mu\text{M}$ $V_{\text{max}}=0.1$ 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](https://www.chemaxon.com)

Predict DDIs with the proprietary drug as a victim

DDI risk calculator

Predict DDI: Proprietary Victim Drug

[Start](#)

Predict all interactions of your proprietary victim drug vs all perpetrators in DDI Knowledgebase

Predict DDI: Proprietary Perpetrator Drug

[Start](#)

Predict all interactions of your proprietary perpetrator drug vs all victim drugs in DDI Knowledgebase

Predicted FmE

Proprietary Victim Drug

Victim Perpetrators

Please enter proprietary data for the victim drug:

Victim definition

*Compound name: Test

Hepatic Metabolism

☐ User Defined

☒ Predicted

☒ HLM

☐ hRecombinant

☒ ISEF

☐ RAF

☐ Abundance

☒ baculovirus

☐ Lymphoblastoid

☐ E. Coli

☐ Yeast

Enzyme(s)

CYP3A4

CYP2C9

kdeg (min⁻¹)

0.00032

0.00011

f_mE

0.78

0.22

f_m(E) Prediction

☒ In Vitro enzyme contribution : f_m(E)_{vitro}

Enzyme(s)

CYP3A4

CYP2C9

Select

kdeg (min⁻¹)

0.00032

0.00011

Cl_{int} (μl/min/pmol)

0.09375

0.025

K_m (μM)

32

4

V_{max} (pmol/min/pmol)

3

0.1

[C]_{prot} (g/l)

0.5

0.5

ISEF

0.32

0.86

Abund. (pmol/mg)

173

69.6

Hepatic Fraction f_h

☐ User Defined

☒ Predicted

☒ f_h 1.00

f_h prediction

☒ f_h prediction

☒ User Defined

☒ Predicted

☒ f_h 1.00

Cl non

hepatic

0

L/h

Cl_H

17.070

L/h

f_{up}

0.4

Ob

1.61

L/min

Predict f_h

Note: In addition to "Cl non hepatic" and "f_{up}" values, please will be able to complete the prediction of f_h.

Microsomal binding

☒ f_u(mic): 0.399

Prot. conc.: 0.5

g/L

Calculate f_u(mic)

Exclusively hepatic metabolism = worst case scenario

f_u(mic) Calculation

Pka

7.66

Prot. conc.

0.5

LogP

4.28

Calculate

1. Select test system
2. Enter K_m
3. Enter V_{max}
4. Enter [C]_{prot}
5. Calculate f_u(mic) – enter Pka, Prot conc, logP
6. Calculate hepatic fraction – enter Cl non-hepatic and f_{up}
7. **Predicted** f_mE values = mostly metabolised by Cyp3A4

Modify intestinal metabolism data (if required)

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

Intestinal Metabolism

☒ User Defined
☐ Predicted

Fg

☐ Intestine inhibition : Estimation of Fg/Fg ratio
☒ Model Predicted
 Qg L/h
☐ Maximal Inhibition (Fg/Fg)=1/Fg

fm(EI)g Prediction ☒

Enzyme(s)	kdeg (min ⁻¹)	Clint (μl/min/pmol)	[C]prot (g/l)	Abund. (pmol/gut)
CYP3A4	<input type="text" value="0.0005"/>	<input type="text" value="0.09375"/>	<input type="text" value="0.5"/>	<input type="text" value="62000"/>
<input type="text" value="fug"/>	<input type="text" value="1"/>			

 Predict interactions

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

DDI Prediction 257 records from DDI Risk Calculator: Victim: Test

Results

ID	Perpetrator	Dose	MBI	AUC Ratio	Count	Min.	Max.	Mean	SD	Med.	5-95th Perc.
1	(+)-Propoxyphene 91412 Analgesic: narcotic/opiate Dev.: + Drug Type: Approved	Multiple			4	1.061	1.554	1.308			
2	(+)-Warfarin 162426 Antithrombotic Dev.: + Drug Type: Experimental/Investigation	0.007 g			1	1.075	1.075	1.075			
3	(-)-Omeprazole 162827 Antilulcerative Proton pump inhibitor Dev.: - Drug Type: Approved	Multiple			88	1.022	1.078	1.051			
4	(-)-Warfarin 161583 Antithrombotic Dev.: - Drug Type: Experimental/Investigation	0.007 g			5	1.033	1.142	1.094	0.035	1.096	1.045-1.135
5	AMG 487 628746 Dev.: - Drug Type: Unspecified	Multiple			3						
6	Acamprosate 241873 Drug Type: Approved	Multiple			2646						
7	Acetaminophen 99468 Analgesic: non narcotic	Multiple			72	4.048	4.134	4.088	0.025	4.09	4.0

Bar chart information

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

Color codes represent AUC/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...>

Dose effect

Dose	AUC Ratio	Count	Min	Max	Mean	SD	Med.	5-95th Perc.
0.025 g		1	2.82	2.82	2.82	0.0	2.82	2.82-2.82
0.1 g		1	7.778	7.778	7.778	0.0	7.778	7.778-7.778
0.25 g		1	18.223	18.223	18.223	0.0	18.223	18.223-18.223

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

Click on blue text for more information

Export

Data entered into
calculator for test drug

Click on blue numbers or + for protocol information

[illegible]

Exported data (Tab 1) – Results overview

Victim	Name	Perpetrator1	Dose/unit	Min	Max	Mean	SD	AUC Ratio	Median 5th Perc	95th Perc	Count
Test	(+)-Propoxyphene	"Analgesic; narcotic/opiate"	0.065 g	0.065	0.065	0.065	0.003E-4	1.554	1.554	1.554	2
Test	(+)-Propoxyphene	"Analgesic; narcotic/opiate"	0.6 g	1.554	1.554	1.554	0.006E-5	1.554	1.554	1.554	2
Test	(+)-Warfarin	"Antithrombotic"	0.007 g	0.073	1.075	1.075	0.0	0.073	1.075	1.075	1
Test	(-)-Omeprazole	"Antilulcerative-Proton pump inhibitor"	0.02 g	0.023	1.038	1.032	0.004	0.033	1.023	1.037	24
Test	(-)-Omeprazole	"Antilulcerative-Proton pump inhibitor"	0.04 g	0.033	1.078	1.058	0.013	0.062	1.034	1.075	64
Test	(-)-Warfarin	"Antithrombotic"	0.007 g	0.033	1.143	1.094	0.035	0.038	1.055	1.133	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	0.023	1.066	1.066	0.002	0.064	1.047	1.074	441
Test	Acamprosate		0.9 g	0.037	1.141	1.075	0.033	0.088	1.028	1.129	441
Test	Acamprosate		0.666 g	0.023	1.184	1.095	0.043	0.088	1.03	1.167	441
Test	Acamprosate		0.8 g	0.025	1.223	1.117	0.052	0.108	1.038	1.203	441
Test	Acamprosate		1.0 g	0.037	1.271	1.132	0.065	0.123	1.03	1.241	882
Test	Acetaminophen	"Analgesic; non narcotic-Antipyretic"	0.65 g	0.408	4.105	4.076	0.018	0.409	4.048	4.103	24
Test	Acetaminophen	"Analgesic; non narcotic-Antipyretic"	1.0 g	0.403	4.134	4.093	0.026	0.408	4.054	4.133	48
Test	Acetylsalicylic acid	"Analgesic; non narcotic-Antinflammatory; non-steroidal-Antipyretic-Antithrombotic"	0.325 g	1.753	1.825	1.789	0.029	1.789	1.756	1.823	4
Test	Acetylsalicylic acid	"Analgesic; non narcotic-Antinflammatory; non-steroidal-Antipyretic-Antithrombotic"	0.96 g	5.395	5.607	5.5	0.086	5.499	5.401	5.6	4
Test	Adefovir dipivoxil	"Anti-HIV-Antiviral"	0.01 g	0.023	1.106	1.064	0.042	0.068	1.068	1.101	2
Test	Adefovir	"Anti-HIV-Antiviral"	0.01 g	0.023	1.093	1.051	0.0	0.061	1.093	1.101	2
Test	Aliskiren	"Antihypertensive"	0.04 g	0.002	1.006	1.004	0.002	0.004	1.002	1.006	24
Test	Aliskiren	"Antihypertensive"	0.08 g	0.001	1.011	1.007	0.004	0.007	1.009	1.011	24
Test	Aliskiren	"Antihypertensive"	0.16 g	0.008	1.023	1.014	0.008	0.014	1.006	1.023	24
Test	Aliskiren	"Antihypertensive"	0.3 g	0.013	1.056	1.032	0.018	0.031	1.013	1.053	408
Test	Aliskiren	"Antihypertensive"	0.64 g	0.026	1.095	1.06	0.033	0.059	1.026	1.095	24
Test	Aliskiren	"Antihypertensive"	0.85 g	0.036	1.132	1.083	0.046	0.081	1.036	1.132	24
Test	Aliskiren	"Antihypertensive"	1.2 g	0.051	1.166	1.116	0.064	0.134	1.051	1.158	24
Test	Aliskiren	"Antihypertensive"	1.8 g	0.079	1.258	1.164	0.089	0.202	1.079	1.258	24
Test	Alcoseston	"Antiemetic"	0.001 g	0.001	1.001	1.001	0.002	0.001	1.001	1.001	2708
Test	Alcoseston	"Antiemetic"	0.002 g	0.006	1.039	1.014	0.004	0.013	1.009	1.031	2028
Test	Alprazolam	"Anticonvulsant-Anxiolytic-Hypnotic-Myorelaxant-Sedative"	0.001 g	1.001	1.1	1.289E-4	0	1.001	1.001	1.001	245
Test	Alprazolam	"Anticonvulsant-Anxiolytic-Hypnotic-Myorelaxant-Sedative"	0.004 g	1.1	1.1	2.435E-5	0	1.1	1.1	1.1	35
Test	Alprazolam	"Anticonvulsant-Anxiolytic-Hypnotic-Myorelaxant-Sedative"	2.5E-4 g	1.1	1.1	4.758E-5	0	1.1	1.1	1.1	70
Test	Alprazolam	"Anticonvulsant-Anxiolytic-Hypnotic-Myorelaxant-Sedative"	6.3E-4 g	3.1	1.001	1.567E-5	0	1.1	1.1	1.1	35
Test	Alvimopan	"Laxative"	0.006 g	0.001	1.009	1.005	0.002	0.005	1.003	1.009	242
Test	Alvimopan	"Laxative"	0.012 g	0.005	1.019	1.011	0.004	0.01	1.006	1.017	121
Test	Alvimopan	"Laxative"	0.018 g	0.008	1.028	1.016	0.005	0.015	1.01	1.028	121
Test	Alvimopan	"Laxative"	0.024 g	0.011	1.038	1.022	0.007	0.022	1.013	1.038	121
Test	Amilorifoline	"Analgesic; non narcotic-Antidepressant"	0.005 g	1.438	1.955	1.677	0.174	1.645	1.438	1.954	1728
Test	Amilorifoline	"Antianginal-Antihypertensive-Calcium channel blocker"	0.005 g	1.438	1.955	1.677	0.174	1.645	1.438	1.954	245
Test	Amilorifoline	"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	0.988	1.134	1.097	0.039	0.988	1.084	1.134	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	7.020E-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	0.139	0.586	0.37	0.105	0.387	0.181	0.583	4
Test	Aprepitant	"Antiemetic"	0.25 g	0.297	0.661	0.549	0.143	0.498	0.221	0.677	81
Test	Aripiprazole	"Antipsychotic-Neuroleptic"	0.001 g	0.001	1.001	1.001	0	0.001E-6	1.001	1.001	4
Test	Aripiprazole	"Antipsychotic-Neuroleptic"	0.002 g	1.001	1.001	1.001	2.586E-5	1.001	1.001	1.001	162
Test	Aripiprazole	"Antipsychotic-Neuroleptic"	0.003 g	1.001	1.001	1.001	2.76E-4	1.001	1.001	1.001	403

Bar chart information

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

Color codes represent AUC1/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

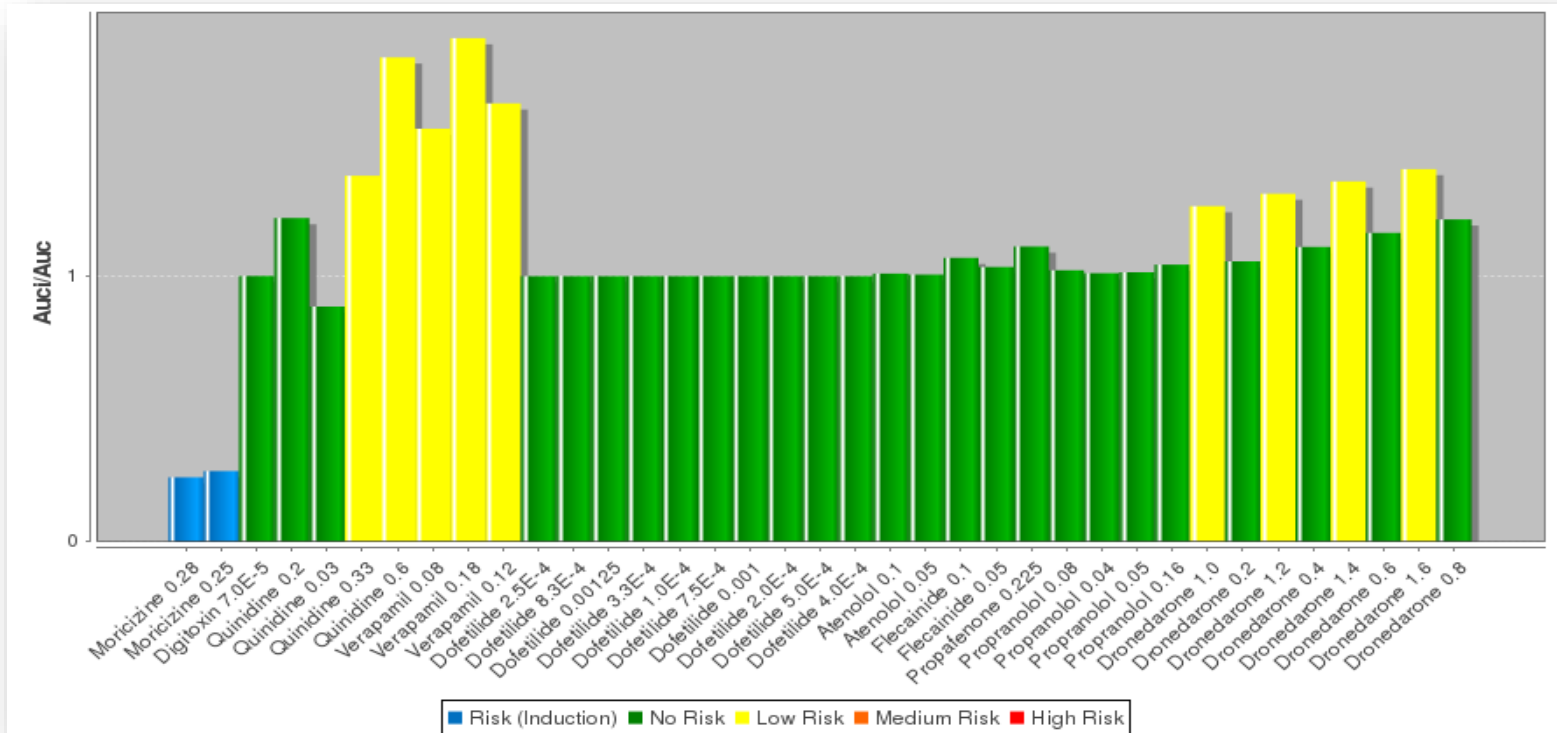
DDI Risk Calculator (DDIRC) Version : 2017.1															
DDIRC database Version: October 2015															
Date: 2018.05.01															
Victim drug Test				Perpetrator drug											
Metabolism				Perpetrator 1											
Enzymes	Name	CYP2C9	CYP3A4	Dosing regimen Repeated											
	kdeg(min-1)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

drugs in tested in each class is indicated

drugs in tested in each class is indicated



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)

PharmaPendium®

Browse ▾ Search ▾ My tools new

DDI Prediction 3 records from DDI Risk Calculator: Victim: test

Refine search results:

Apply Clear All

Therapeutic Classes

- ☒ Analgesic: non narcotic (3)
- ☐ Antidepressant (1)
- ☐ Antiinflammatory: non-steroidal (1)
- ☐ Antipyretic (2)
- ☐ Antithrombotic (1)

Molecules ▾

Drug Type ▾

Results

ID	Perpetrator ▾	Dose ▾	MBI ▾	AUC Ratio ▾	C
1	Acetaminophen 99468 Analgesic: non narcotic Antipyretic Drug Type: Approved	Multiple			72
2	Acetylsalicylic acid 34524 Antithrombotic Analgesic: non narcotic Antiinflammatory: non-steroidal Antipyretic Drug Type: Approved	Multiple			8
3	Amitriptyline 4815 Analgesic: non narcotic Antidepressant Drug Type: Approved	0.025 g			17

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

DDI Results details

Export

Victim: test Perpetrator: Acetaminophen

AUCi/AUC	Fg/Fg	Enzyme	fm(E)	Fg	[I]ug (μM)	Kdeg (min-1)	I Optimized [I] (μM)	Ki (μM)				I Optimized [I] (μM)	KI (μM)				kinact (min-1)	Dose	Cmax (μM)	kabs (min-1)	Fa.Fg	Fa	Qh	Fu(blood)	Rb	Kb
								Value	[C]prot	Substrate	fu(mic)		Value	[C]prot	Substrate	fu(mic)										
4.124	1	CYP3A4	0.78		1.887E3	3.2E-4	+ 410.455	1.85E3		Fentanyl		+ 58.924	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 107.1	0.098	+ 0.87	0.87	1.61	1	0.55	1
4.058	1	CYP3A4	0.78		73.258	3.2E-4	+ 72.574	1.85E3		Fentanyl		+ 58.924	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 107.1	0.004	+ 0.8	0.8	1.61	1	0.55	1
4.105	1	CYP3A4	0.78		2.124E3	3.2E-4	+ 454.753	2.8E3		Fentanyl		+ 58.924	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 107.1	0.096	+ 1	1	1.61	1	0.55	1
4.126	1	CYP3A4	0.78		1.887E3	3.2E-4	+ 414.882	1.85E3		Fentanyl		+ 63.351	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 115.2	0.098	+ 0.87	0.87	1.61	1	0.55	1
4.121	1	CYP3A4	0.78		1.735E3	3.2E-4	+ 386.598	1.85E3		Fentanyl		+ 63.351	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 115.2	0.098	+ 0.8	0.8	1.61	1	0.55	1
4.1	1	CYP3A4	0.78		1.848E3	3.2E-4	+ 407.723	2.8E3		Fentanyl		+ 63.351	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 115.2	0.096	+ 0.87	0.87	1.61	1	0.55	1
4.059	1	CYP3A4	0.78		79.669	3.2E-4	+ 73.769	1.85E3		Fentanyl		+ 58.924	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 107.1	0.004	+ 0.87	0.87	1.61	1	0.55	1
4.098	1	CYP3A4	0.78		1.201E3	3.2E-4	+ 272.593	1.85E3		Fentanyl		+ 48.751	1.5	0.5 g/L	Midazolam		0.009	0.65 g	+ 8.64	0.096	+ 0.87	0.87	1.61	1	0.55	1
4.106	1	CYP3A4	0.78		1.271E3	3.2E-4	+ 300.19	1.85E3		Fentanyl		+ 63.351	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 115.2	0.058	+ 1	1	1.61	1	0.55	1
4.095	1	CYP3A4	0.78		1.017E3	3.2E-4	+ 248.395	1.85E3		Fentanyl		+ 58.924	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 107.1	0.058	+ 0.8	0.8	1.61	1	0.55	1
4.123	1	CYP3A4	0.78		1.848E3	3.2E-4	+ 403.295	1.85E3		Fentanyl		+ 58.924	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 107.1	0.058	+ 0.8	0.8	1.61	1	0.55	1
4.048	1	CYP3A4	0.78		47.618	3.2E-4	+ 57.624	2.8E3		Fentanyl		+ 48.751	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 107.1	0.058	+ 0.8	0.8	1.61	1	0.55	1
4.098	1	CYP3A4	0.78		1.106E3	3.2E-4	+ 264.973	1.85E3		Fentanyl		+ 58.924	1.5	0.5 g/L	Midazolam		0.009	1.0 g	+ 107.1	0.058	+ 0.8	0.8	1.61	1	0.55	1

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

Protocol details

Review or Labels:

NDA021449 2002-09-20 (GILEAD)

Protocol : In Vivo

BIOLOGICAL MATERIAL:

Animal

Animal:

Species: Human Caucasian (70%), Black person (10%), Hispanic (10%), Asian (10%) (Either, 71.9+/-13 kg, 31+/-10 year old)

Clinical state:

Healthy

EXPERIMENTAL CONDITIONS - Protocol : In Vivo

Study Design:

Crossover

Tested Compound:

Dosing Regimen: 1000.0 mg oral administration Repeated: (every6 hour) during 3 day

General State:

Conscious

Other Information:

9 doses Except D3: 1*/day

Experimental Synopsis

1st day

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

61

62

63

64

65

66

67

68

69

70

71

72

73

74

75

76

77

78

79

80

81

82

83

84

85

86

87

88

89

90

91

92

93

94

95

96

97

98

99

100

101

102

103

104

105

106

107

108

109

110

111

112

113

114

115

116

117

118

119

120

121

122

123

124

125

126

127

128

129

130

131

132

133

134

135

136

137

138

139

140

141

142

143

144

145

146

147

148

149

150

151

152

153

154

155

156

157

158

159

160

161

162

163

164

165

166

167

168

169

170

171

172

173

174

175

176

177

178

179

180

181

182

183

184

185

186

187

188

189

190

191

192

193

194

195

196

197

198

199

200

201

202

203

204

205

206

207

208

209

210

211

212

213

214

215

216

217

218

219

220

221

222

223

224

225

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

Perpetrator: Acetaminophen	fm(E)	Fg	[I] ₀ (μM)	deg (min)	Optimized [I] (μM)	2		KI (μM)	Substrate	fu(mic)	3		KI (μM)	Substrate	fu(mic)	Inact (min)	Dose	1		Cmax (μM)	kabs (min ⁻¹)
						Value	[C] _{prot}				Value	[C] _{prot}									
5																					
6	0.78	1.887E3	3.2E-4	Optimize	410.455	1.85E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.098	(Column AB)
7	0.78	73.258	3.2E-4	Optimize	72.574	1.85E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.096	(Showing All)
8	0.78	2.124E3	3.2E-4	Optimize	454.753	2.8E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.096	(Showing All)
9	0.78	1.887E3	3.2E-4	Optimize	414.882	1.85E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.098	(Showing All)
10	0.78	1.735E3	3.2E-4	Optimize	386.598	1.85E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.098	(Showing All)
11	0.78	1.848E3	3.2E-4	Optimize	407.723	2.8E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.096	(Showing All)
12	0.78	79.669	3.2E-4	Optimize	73.769	1.85E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.004	(Showing All)
13	0.78	1.201E3	3.2E-4	Optimize	272.593	1.85E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.096	(Showing All)
14	0.78	1.271E3	3.2E-4	Optimize	300.19	1.85E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.058	(Showing All)
15	0.78	1.017E3	3.2E-4	Optimize	248.395	1.85E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.058	(Showing All)
16	0.78	1.848E3	3.2E-4	Optimize	403.295	1.85E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.096	(Showing All)
17	0.78	47.618	3.2E-4	Optimize	57.624	2.8E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.004	(Showing All)
18	0.78	1.106E3	3.2E-4	Optimize	264.973	1.85E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.058	(Showing All)
19	0.78	1.271E3	3.2E-4	Optimize	295.762	2.8E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.058	(Showing All)
20	0.78	1.105E3	3.2E-4	Optimize	254.582	1.85E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.096	(Showing All)
21	0.78	1.409E3	3.2E-4	Optimize	311.389	1.85E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.098	(Showing All)
22	0.78	91.573	3.2E-4	Optimize	90.414	2.8E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.004	(Showing All)
23	0.78	79.669	3.2E-4	Optimize	78.196	2.8E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.004	(Showing All)
24	0.78	2.124E3	3.2E-4	Optimize	454.753	1.85E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.096	(Showing All)
25	0.78	2.168E3	3.2E-4	Optimize	462.983	2.8E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.098	(Showing All)
26	0.78	2.124E3	3.2E-4	Optimize	459.18	2.8E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.096	(Showing All)
27	0.78	73.258	3.2E-4	Optimize	72.574	2.8E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.004	(Showing All)
28	0.78	718.77	3.2E-4	Optimize	182.683	1.85E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.058	(Showing All)
29	0.78	1.106E3	3.2E-4	Optimize	269.401	1.85E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.058	(Showing All)
30	0.78	1.887E3	3.2E-4	Optimize	410.455	2.8E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.098	(Showing All)
31	0.78	1.106E3	3.2E-4	Optimize	269.401	2.8E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.058	(Showing All)
32	0.78	2.124E3	3.2E-4	Optimize	459.18	1.85E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.096	(Showing All)
33	0.78	59.522	3.2E-4	Optimize	59.842	1.85E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.004	(Showing All)
34	0.78	79.669	3.2E-4	Optimize	73.769	2.8E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.004	(Showing All)
35	0.78	1.017E3	3.2E-4	Optimize	252.822	1.85E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.058	(Showing All)
36	0.78	1.226E3	3.2E-4	Optimize	277.246	2.8E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.098	(Showing All)
37	0.78	1.735E3	3.2E-4	Optimize	382.171	1.85E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.098	(Showing All)
38	0.78	660.938	3.2E-4	Optimize	171.907	1.85E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.058	(Showing All)
39	0.78	718.77	3.2E-4	Optimize	182.683	2.8E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.058	(Showing All)
40	0.78	1.271E3	3.2E-4	Optimize	300.19	2.8E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.058	(Showing All)
41	0.78	1.699E3	3.2E-4	Optimize	380.014	2.8E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.096	(Showing All)
42	0.78	1.699E3	3.2E-4	Optimize	380.014	1.85E3		Fentanyl			Optimize	63.351	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.017 g/L	115.2	0.096	(Showing All)
43	0.78	1.226E3	3.2E-4	Optimize	277.246	1.85E3		Fentanyl			Optimize	48.751	1.5	0.5 g/L	Midazolam	0.009	0.65 g	converted from Cmax0.013 g/L	88.64	0.098	(Showing All)
44	0.78	1.735E3	3.2E-4	Optimize	382.171	2.8E3		Fentanyl			Optimize	58.924	1.5	0.5 g/L	Midazolam	0.009	1.0 g	converted from Cmax0.016 g/L	107.1	0.098	(Showing All)

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

$$\frac{-B \pm \sqrt{B^2 - 4ac}}{2a} = \frac{-(b/3a) \pm \sqrt{(b/3a)^2 - 4ac}}{2}$$

DDIRC Demo: Test compound as a perpetrator

Predict DDIs with the proprietary drug as a perpetrator

DDI risk calculator

Predict DDI: Proprietary Victim Drug

Start

Predict all interactions of your proprietary victim drug vs all perpetrators in DDI Knowledgebase

Predict DDI: Proprietary Perpetrator Drug

Start

Predict all interactions of your proprietary perpetrator drug vs all victim drugs in DDI Knowledgebase

Predict DDIs with the perpetrator drug as a perpetrator

PharmaPendium®

Browse Search My tools IP-authorized

Proprietary Perpetrator Drug

Perpetrator 1 Perpetrator 2 Victim

Perpetrator definition

*Compound name: *Mol. Weight: g/mol *Dose: mg

Dosing regimen

☐ Single
☒ Repeated

Absorption: first order model

*Fa.Fg:

1

Calculate kabs

*kabs (min-1):

0.1

Estimated liver concentration

[I]in (hepatic) estimation

☒ Optimized [I] * Qh: 1.61 L/min
☐ Cavg ng/mL☐ [I]in,avg☐ Cmax☐ [I]in,max

Non equilibrium

☐ Kp:

or

☐ Kb:

or

☐ C/M:

Plasma binding and blood/plasma ratio

☐ * fup: 1☐ * Rb: 0.55

Perpetrator Inhibitory constant

Microsomal binding

☐ fu(mic):

Prot. conc.: g/L

Calculate fu(mic)

Hepatocyte binding

☐ fu(hep): 10e6 Cell/ml

Calculate fu(hep)

Competitive Inhibition

Enzyme(s)

Select

Parameter (μM)

Select

Value

[C]prot (g/l)

Substrate name

Victim C (μM)

Victim Km (μM)

Mechanism Based (MBI)

Enzyme(s)

Select

kdeg (min-1)

1

Parameter (μM)

Select

Value

[C]prot (g/l)

kinact Value (min-1)

Substrate name

Induction

Enzyme(s)

Select

Parameter (μM)

Select

Value

Emax

nh

Induction type

Substrate name

Predict interactions

Feedback

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

Perpetrator 1 Perpetrator 2 Victim

Perpetrator definition

*Compound name: test *Mol. Weight: 4738 g/mol *Dose: 40 mg

Dosing regimen

☐ Single ☒ Repeated

Absorption: first order model

*Fa.Fg: 1

*kabs (min-1): 0.1

Estimated liver concentration

[I]in (hepatic) estimation

☒ Optimized [I] * Qh: 1.81 L/min
☒ Cavg * Cmax: 331.5 ng/mL
☒ [I]in,avg
☒ Cmax
☒ [I]in,max

Non equilibrium

☐ Kp:
or
☐ Kb:
or
☐ C/M:

Plasma binding and blood/plasma ratio

☒ * fup: 0.4 ☒ * Rb: 0.55

Perpetrator Inhibitory constant

Microsomal binding

☒ fu(mic): 0.824 * Prot. conc.: 0.2 g/L

Hepatocyte binding

☒ fu(hep): 10e6 Cell/ml

Competitive Inhibition

Enzyme(s)

☒ CYP3A4

Parameter (μM)

Ki

Value

3.8

[C]prot (g/l)

0.2

Substrate name

Midazolam

Victim C (μM)

Victim Km (μM)

Mechanism Based (MBI)

Enzyme(s)

Induction

Enzyme(s)

Parameter (μM)

Value

Emax

nh

fu(mic) Calculation

Pka: 7.66
Prot. conc.: 0.2 g/L
LogP: 4.28

☒ Hallifax/Houston
☐ Austin

Molecule Search

Select molecules containing: midazolam

Name A

Synonyms

1'-4-Dihydroymidazolam
1'-Hydroymidazolam
1'-Hydroymidazolam glucuronide
1'-Hydroymidazolam N-glucuronide
4-Hydroymidazolam
Midazolam
Midazolam N-glucuronide

Ro 21-6347; alpha-hydroxy-midazolam; 1-Hydroymidazolam
Dormicum; Midosed; Rohipnol

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

Proprietary Perpetrator Drug

Perpetrator 1 Perpetrator 2 Victim

Please select the database retrieval rules for the victim drugs:

First Pass Metabolism (gut wall)

☒ Use Fg

☐ Intestine inhibition : Estimation of F_g'/F_g ratio

☐ Maximal Inhibition (F_g'/F_g)=1/ F_g

☒ Model Predicted

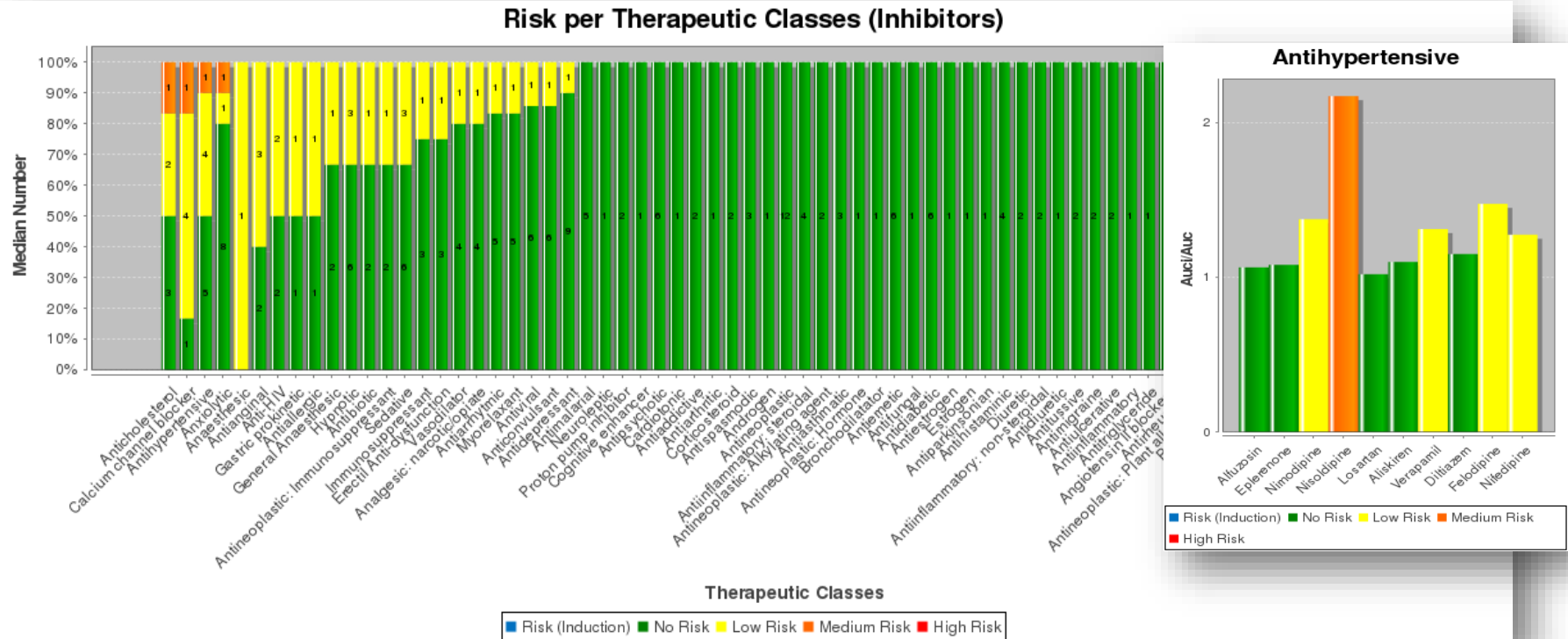
Qg 18 L/h

Predict interactions

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

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

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



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