Assessing modeling and simulation tools and methods for predicting metabolic-based DDI Update from the IQ Work Group

Presented by Scott Obach on behalf of the Induction Working Group

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October 6, 2011

North Jersey Drug Metabolism Discussion Group

Outline

- IQ Consortium DDI Work Groups
- Sub-objectives of the Induction Working Group – General overview
- Models/approaches for the prediction of clinical CYP3A induction
- A look at the new FDA draft decision tree for induction (R3 value)
- Summary/Conclusions

IQ Consortium Drug Interaction Work Groups

General overview

- 2009: Meeting between individuals from PhRMA Drug Metabolism Technical Group and FDA Office of Clinical Pharmacology
  - Agreement that the area of modelling and simulation of DDI from in vitro data is a valuable endeavor
  - Established Industry-FDA-Academia work groups
  - Main Objective: To test various models and approaches for predicting DDI using agreed upon input parameters
  - Two teams formed
    - Inhibition+Inactivation – Discussion for another time
    - Induction – We'll share findings now

To identify method(s) that can reliably use in vitro data to provide quantitative forecasts of clinical DDI across a broad range of drugs and provide a recommendation as to what approach to use to inform the need for clinical DDI studies.

Scope: Development, not early research

Sub-objectives – Induction Working Group

General overview

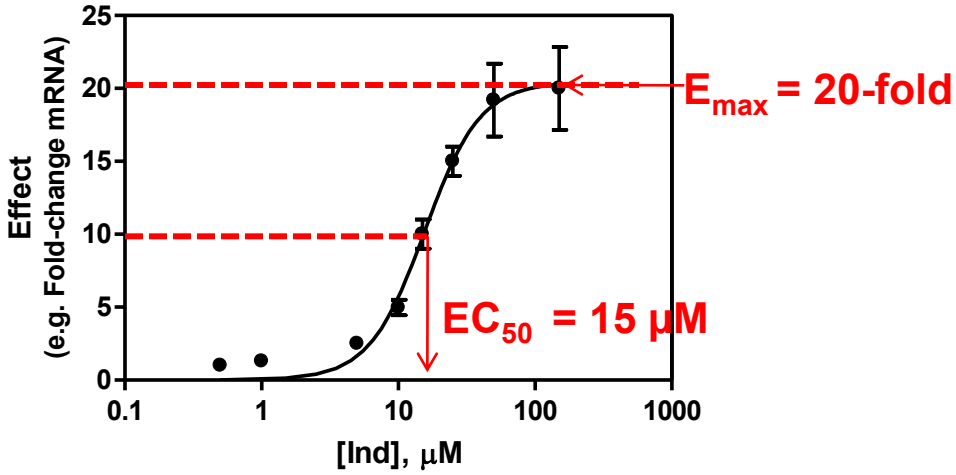
- Define acceptable approaches for the prediction of the clinical induction of CYP3A (models used, input parameters needed, what type of data is needed)
- Standardize input parameters that can be standardized *(e.g. fm_{CYP}, k_{deg})*
- Define criteria for quality of input parameters
- Define the extent to which we need to qualify the models
- Work together to qualify the models identified on the ability to predict clinical DDI

These sub-objectives are in support of the main objective

Predictions of Induction DDI – General Principle

- Most cytochrome P450 (CYP) induction prediction models use a relationship which include the parameters:
  - EC_{50}
  - E_{max}
  - [Inducer]
- These prediction models are generally based upon the same principal, that being the law of mass action for receptor binding (and activation since induction is an agonist property

$$\text{Effect} = \frac{E_{max} \times [\text{Ind}]}{EC_{50} + [\text{Ind}]}$$



Approaches for prediction of clinical CYP3A induction

What models/approaches are being used now?

general methods and examples of approach(es):

- **Empirical Approaches**
  - % of positive control

    FDA Draft Guidance – Drug Interaction Studies 2006; Bjornsson et al *DMD 2003 31:815*
- **Correlation Methods**
  - Relative Induction Score *Ripp et al. 2006 DMD 34:1742; Fahmi et al. 2008 DMD 36:1971*
  - C_{max}/EC_{50}

    Chu et al. 2009 DMD 37:1339; Persson et al. 2006 Pharm Res 23:56
- **Mathematical Equations (Mechanistic Static Models)**
  - Net effect model

    Fahmi et al. 2008 DMD 36:1698
- **Physiologically-Based Pharmacokinetic (Mechanistic Dynamic Models)**
  - Simcyp

    Almond et al 2009 Curr Drug Metab 10:420

Qualification of the different models/approaches

Identification of trials and available in vitro induction data

- Initially identified trials to model from the literature (U. Washington Drug Interaction Database) or from internal sources
  - Literature searches were focused on DDI studies involving common CYP3A substrates (e.g. midazolam, triazolam, alprazolam, simvastatin, buspirone, etc)
  - Compiled a list of perpetrators that caused clinical induction or no induction/inhibition of these CYP3A substrates
- Using the initial search, four victim drugs were chosen to further investigate based upon the number of trials that were available and differences in fm_{CYP} and F_G (midazolam, alprazolam, nifedipine, and simvastatin)
- Identified the *in vitro* (internal) mRNA induction data (and activity) we had with respect to the inducers/non-inducers in the identified trials (EC_{50} and E_{max} data) and consolidated it for use in modeling (median values)

Trials chosen for the model comparison

perpetrator	victim	# of trials
rifampin	midazolam	10
rifampin	alprazolam	1
rifampin	nifedipine	1
carbamazepine	midazolam	1
carbamazepine	alprazolam	1
nafcillin	nifedipine	1
phenobarbital	nifedipine	1
pleconaril	midazolam	1
rosiglitazone	nifedipine	1
Merck MK-1	midazolam	2
Merck MK-2	midazolam	1
pioglitazone	simvastatin	1
pioglitazone	midazolam	1
troglitazone	simvastatin	1
omeprazole	nifedipine	1
phenytoin	midazolam	1
ranitidine	nifedipine	2

- 28 trials (17 victim/perpetrator pairs)

Empirical Approaches

- *e.g.* % of positive control

Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2006
Clinical Pharmacology

3. **Endpoints for Subsequent Prediction of Enzyme Induction**

When analyzing the results of experiments to determine whether a drug induces an enzyme activity, the following issues are relevant.

(a) A drug that produces a change that is equal to or greater than 40% of the positive control can be considered as an enzyme inducer in vitro and in vivo evaluation is warranted.

$$\% \text{ positive control} = \frac{(\text{activity of test drug treated cells} - \text{activity of negative control}) \times 100}{(\text{activity of positive control} - \text{activity of negative control})}$$

0090-9556/03/3107-815–832$7.00
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Perspective

THE CONDUCT OF IN VITRO AND IN VIVO DRUG-DRUG INTERACTION STUDIES: A PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA (PhRMA) PERSPECTIVE

THORIR D. BJORNSSON, JOHN T. CALLAGHAN, HEIDI J. EINOLF, VOLKER FISCHER, LAWRENCE GAN, SCOT
JOHN KAO, S. PETER KING, GERALD MIWA, LAN NI, GONDI KUMAR, JAMES McLEOD, R. SCOTT OBA
STANLEY ROBERTS, AMY ROE, ANITA SHAH, FRED SNIKERIS, JOHN T. SULLIVAN, DONALD TWEEDIE, JOSE
JOHN WALSH, AND STEVEN A. WRIGHTON

Variability in the inducibility of hepatocytes from different donors is commonplace, and the positive control can aid in comparing induction data from different preparations of hepatocytes. As a guide, an induction of at least 40% of the positive control induction level would indicate a positive inductive response. In general, the concentration of test compound used should be based upon the human in vivo C_{max} and the dose.

Intended to indicate an *in vitro* induction response

Empirical Approach- Pros and Cons

e.g. % of positive control

Pros

- Can identify non-inducers

Cons

- Not proven to be predictive of DDI – may lead to false negatives/false positives
- Does not account for EC_{50} value
- What *in vitro* [I] would be relevant to decision making for the clinics?
- What are appropriate positive controls?

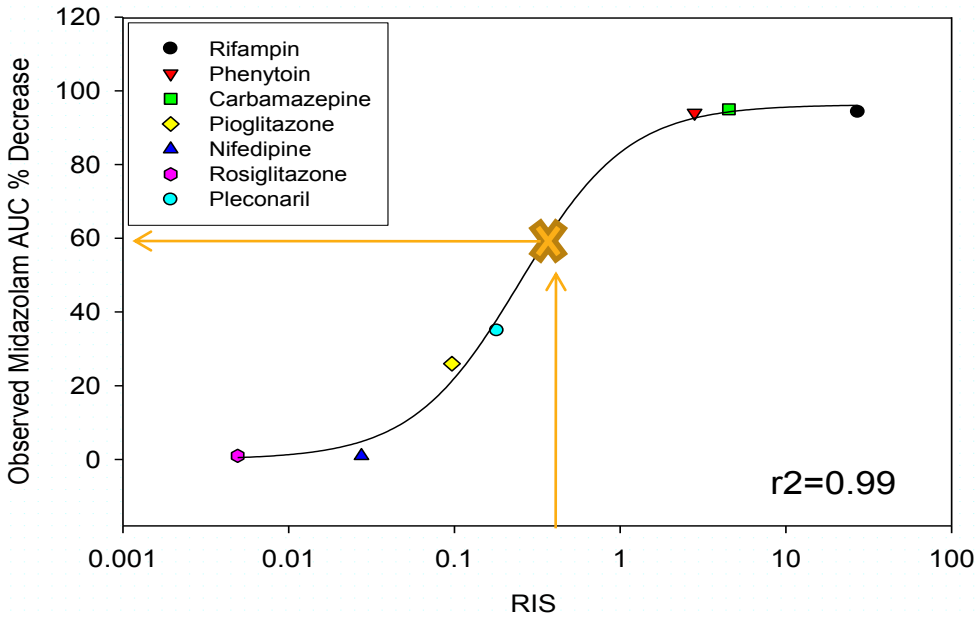
Too simple to be reliably predictive

Correlation Methods

- *e.g.* Relative Induction Score (RIS)

  - Sigmoidal relationships observed between RIS and the percent decrease in the AUC values of a CYP3A substrate (*e.g.* midazolam) after co-administration of enzyme inducers
  - Relationships used to predict *in vivo* induction from RIS for test compounds

Fahmi et al. 2008 DMD 36:1971



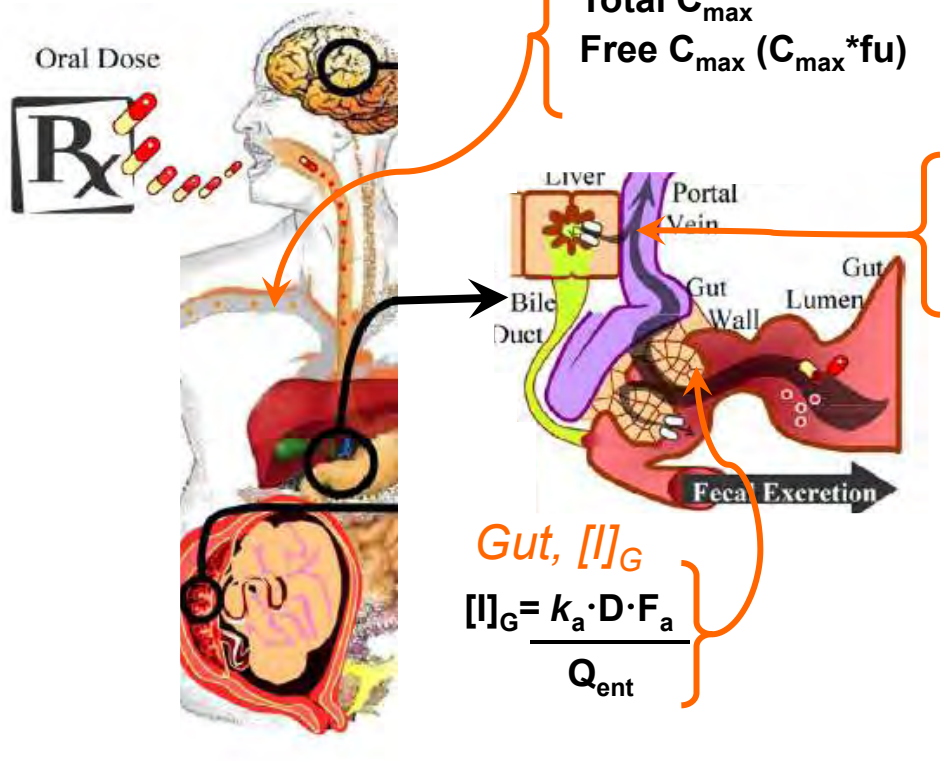
$$\text{Relative Induction Score (RIS)} = \frac{E_{max} \times [Ind_u]}{EC_{50} + [Ind_u]}$$

What value to use for [I]?

The value of [I]

Inducer concentration to use in correlation methods or in static models

All are surrogates... however, some have been preferred *e.g.* free C_{max} for inactivation and induction and free portal C_{max} for reversible inhibition*



Systemic

Total C_{max}

Free C_{max} (C_{max}*fu)

Hepatic

Total Portal C_{max}

Free Portal C_{max} (Portal C_{max}*fu)

Gut, $[I]_G$

$$[I]_G = \frac{k_a \cdot D \cdot F_a}{Q_{ent}}$$

$$\text{Portal } C_{max} = C_{max} + \frac{k_a \cdot D \cdot F_a}{Q_H}$$

k_a = absorption rate constant
D = dose
F_a = fraction of dose absorbed
Q_H = hepatic blood flow
Q_{ent} = enterocytic blood flow

*Fahmi et al (2009) DMD 37:1658, and references therein

Correlation Methods – Pros and Cons

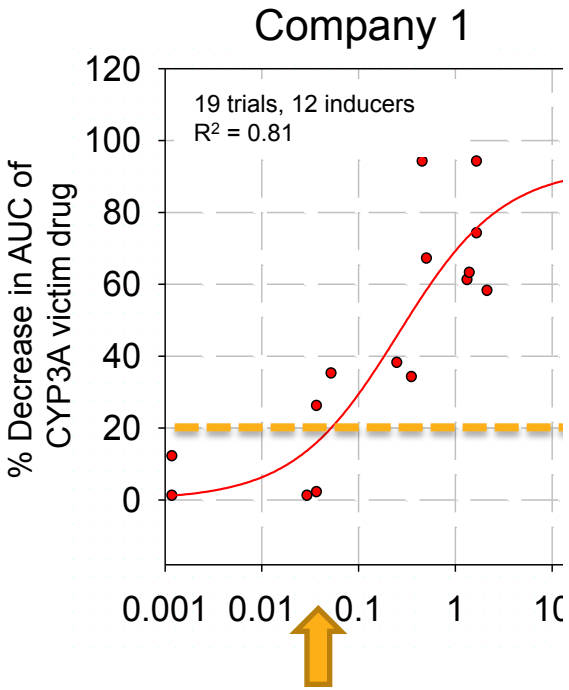
Pros

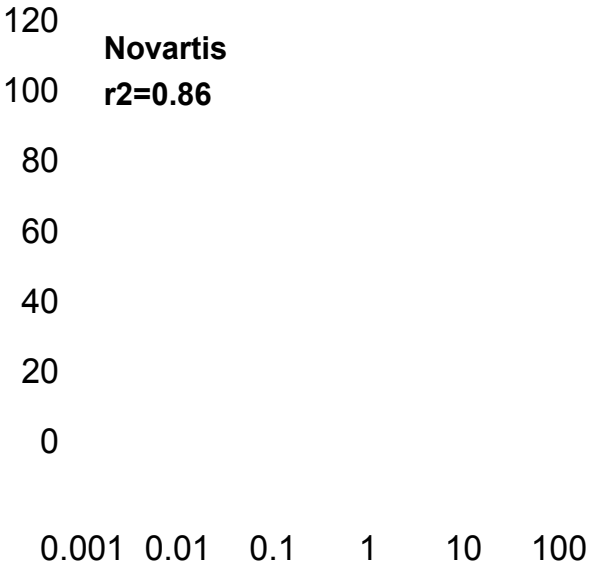
- Published reports of good correlation with clinical outcome for CYP3A inducers
- Can use these models with relatively simple assumptions about human PK (*e.g.* C_{max}). No need to simulate the entire conc.-time profile

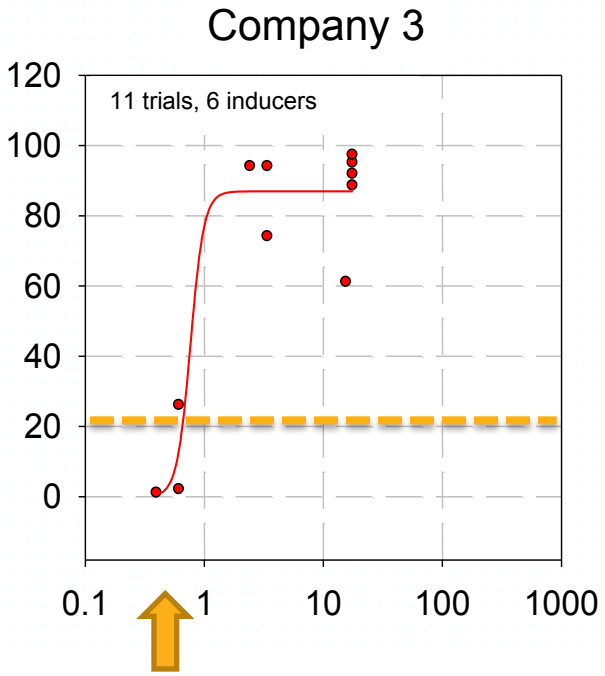
Cons

- A calibration curve is needed for each laboratory/lot of hepatocytes for calibrator compounds (~6-8+)
- Does not account for CYP3A inducers that are also inhibitors/ inactivators
- Limited to CYP enzymes in which there is sufficient clinical data available to set up a calibration curve (*e.g. CYP3A*)
- Unlikely universal cut-off criteria (*e.g.* RIS value) can be established

Correlation M

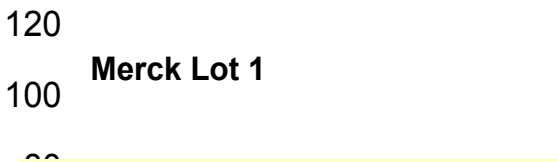


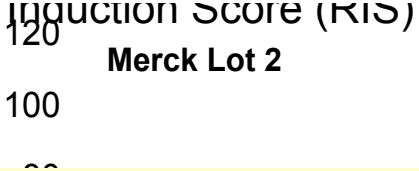




Relative Induction Score (RIS)

$$RIS = \frac{}{EC_{50} + [Ind_u]}$$



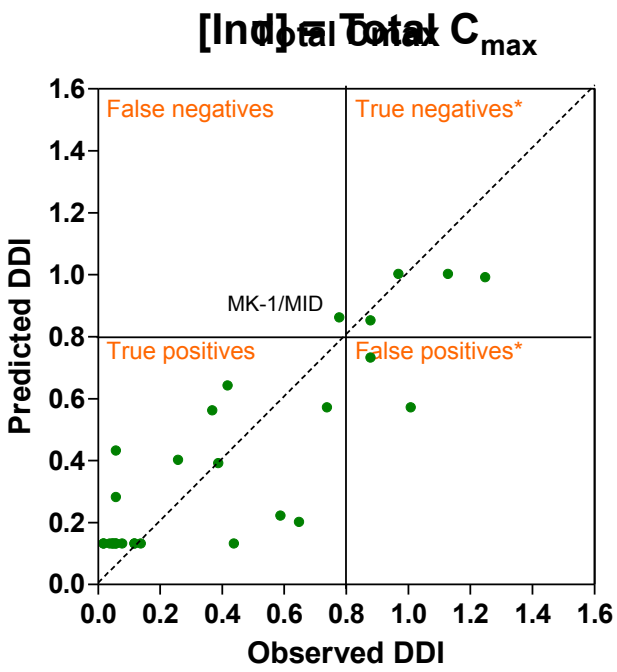


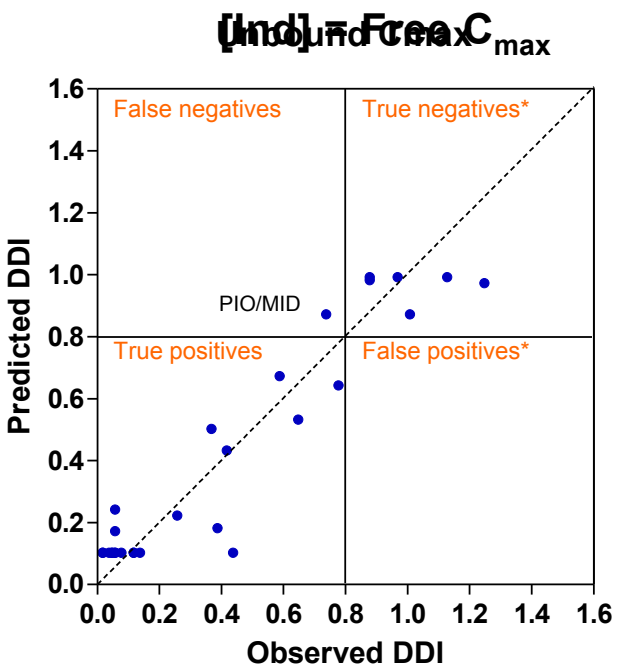
Universal cut-off values of RIS are <u>not</u> recommended as they can be very different between investigators.
Similar conclusions were made for $C_{max,u}/EC_{50}$.

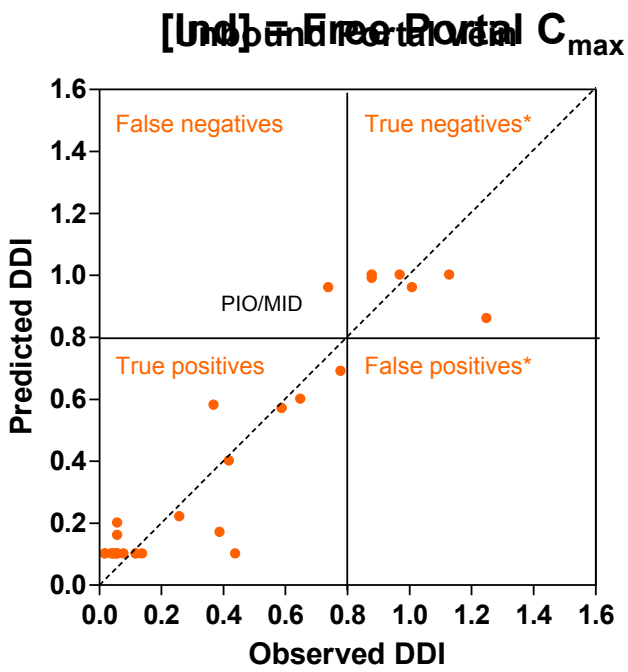
Correlation methods- Results

Relative Induction Score (RIS) Model

Predictions of clinical DDI were made by use of the RIS calibration curve (RIS vs. observed DDI) established for all the trials (n=28, 17 victim/perpetrator pairs)







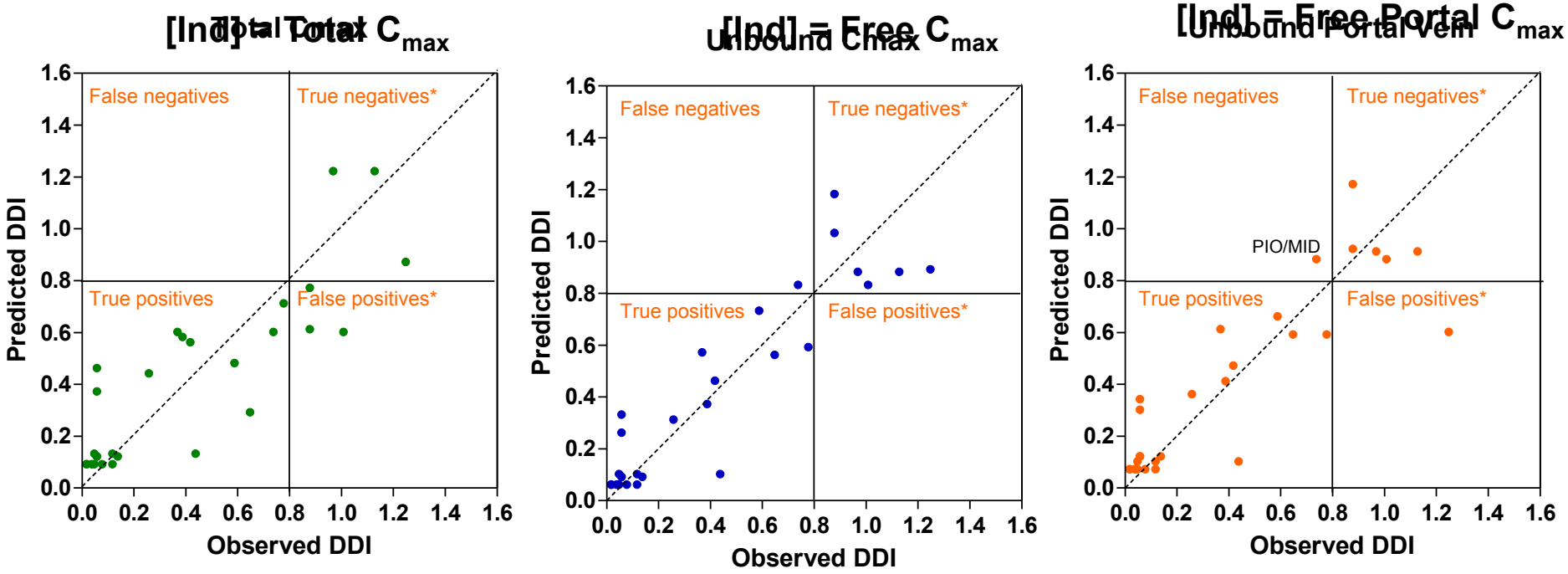
The RIS Model worked very well in the prediction of the induction/non-induction effect within the 0.8-fold (-20%) boundary

* True negatives or false positives with respect to induction

Correlation methods- Results

C_{max}/EC_{50} Model

Predictions of clinical DDI were made by use of the linear regression line of C_{max}/EC_{50} vs. observed DDI established for all the trials (n=28, 17 victim/perpetrator pairs)



The C_{max}/EC_{50} Model also worked very well in the prediction of the induction/non-induction effect within the 0.8-fold (-20%) boundary

* True negatives or false positives with respect to induction

Mathematical Equations (Mechanistic Static Model)

- *e.g.* Net Effect Model

$$\frac{AUC'_{po}}{AUC_{po}} = \left(\frac{1}{[A_H \times B_H \times C_H] \times f_m + (1 - f_m)}\right) \times \left(\frac{1}{[A_G \times B_G \times C_G] \times (1 - F_G) + F_G}\right)$$

$$A = \left(\frac{k_{deg}}{k_{deg} + \frac{[I] \times k_{inact}}{[I] + K_I}}\right)$$ inactivation (TDI)

$$B = 1 + \frac{d \times E_{max} \times [I]}{[I] + EC_{50}}$$ induction

$$C = \frac{1}{1 + \frac{[I]}{K_i}}$$ reversible inhibition

Incorporates:

- f_m (fraction of victim drug metabolized by the affected enzyme)
- F_G for CYP3A (fraction of the victim drug escaping first pass metabolism in the gut)
- Inactivation, induction, and reversible inhibition equations

H= hepatic
G = gut

Mathematical Equations – Pros and Cons

Pros

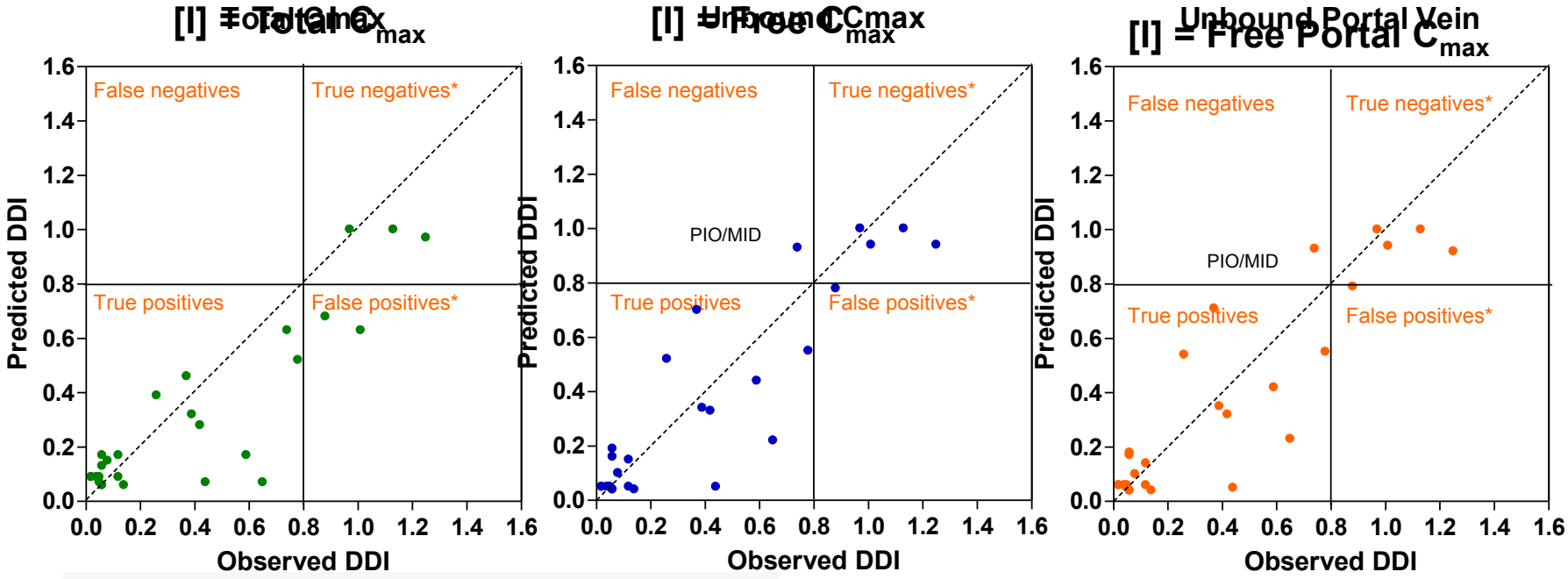
- No calibration curves needed – savings in time, effort, cost
- Can be used to predict DDI for compounds that are both inducers and inhibitors/inactivators of CYPs in gut and liver
- As long as fm_{CYP3A} is estimated properly, can be used for different probe (victim) substrates

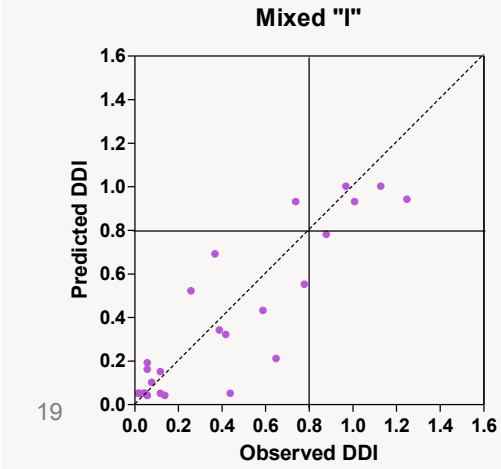
Cons

- Requires more input parameters compared to Correlation Methods (*e.g.* fm_{CYP3A} and F_G for victim)
- It requires an empirical calibrator/scalar factor to bridge *in vitro* data to *in vivo* (*e.g. d)*

Mathematical Equations – Results

Net Effect Model





where:
[I] = free C_{max} for induction and TDI
[I] = free Portal C_{max} for reversible inhibition

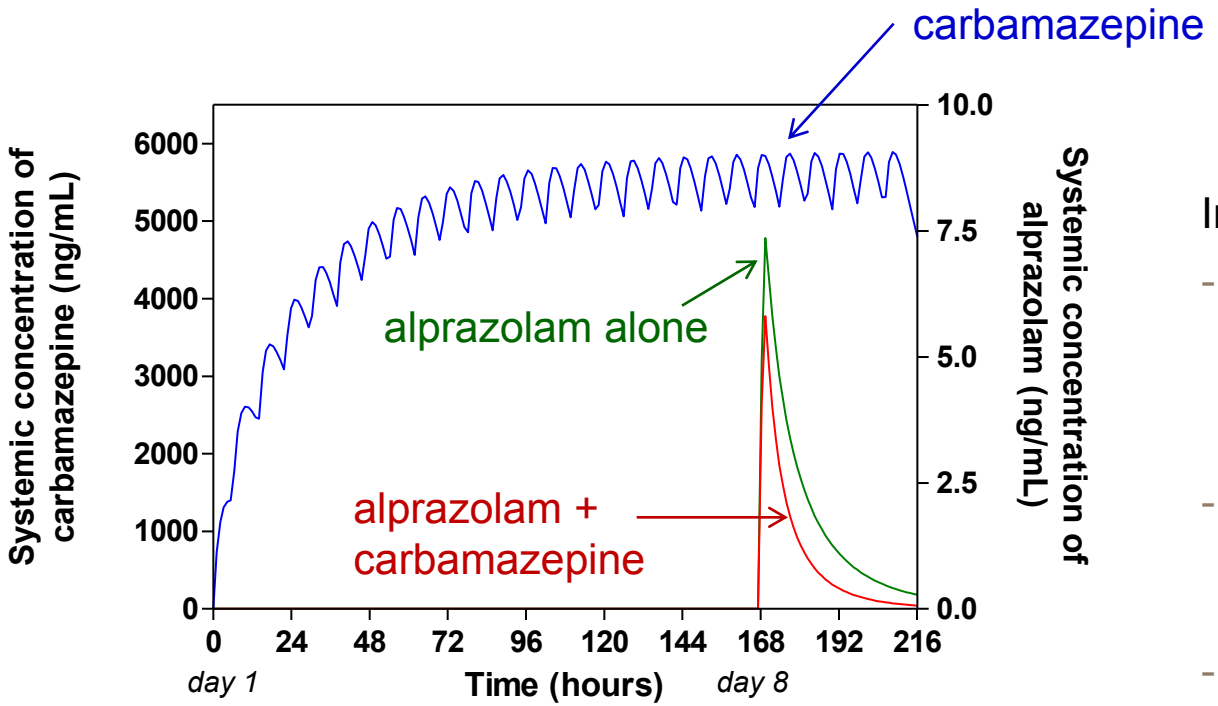
The Net Effect Model also proved to be a good model to predict the induction/non-induction effect within the 0.8-fold (-20%) boundary

One trial (MK-2) is off-scale in the true negative quadrant (predicted DDI of 1.6-3-fold, depending on [I])

* True negatives or false positives with respect to induction

PBPK-based (Mechanistic Dynamic Model)

- *e.g.* Simcyp



100 mg tid carbamazepine 10 days + 0.8 mg alprazolam on day 8

Actual = 58% increase in clearance

Predicted = 52% increase in clearance

Furukori, et al. Neuropsychopharmacology 18:364 (1998)

Incorporates:

- Various algorithms incorporating both physiological and test compound properties
- Simulates time-concentration profiles of both perpetrator and victim
- Inactivation, induction, and reversible inhibition

PBPK-based Model – Pros and Cons

Pros

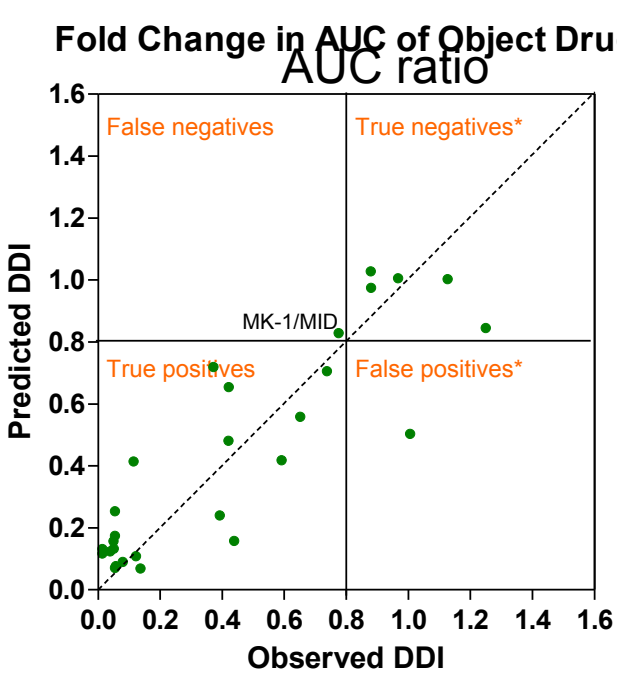
- No calibration curves needed – savings in time, effort, cost
- Can be used to predict DDI for compounds that are both inducers and inhibitors/ inactivators of CYPs in the gut and liver
- Physiologically-based model, incorporates drug and system dynamics and population aspects

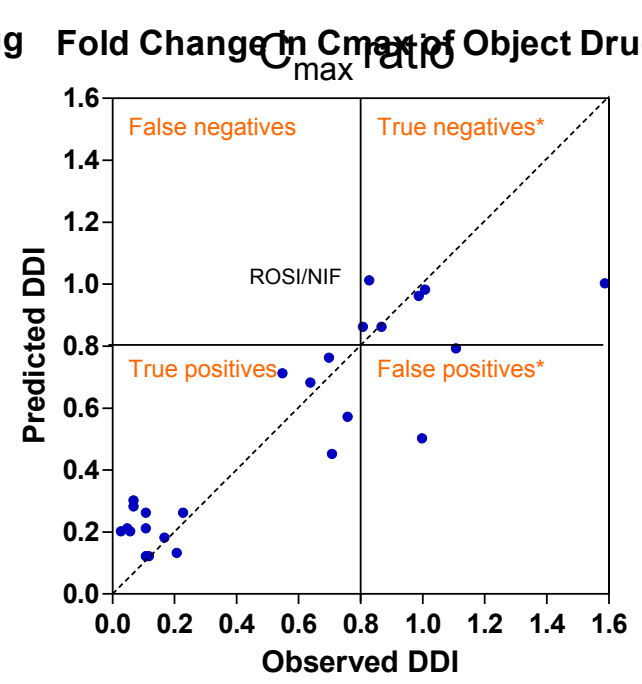
Cons

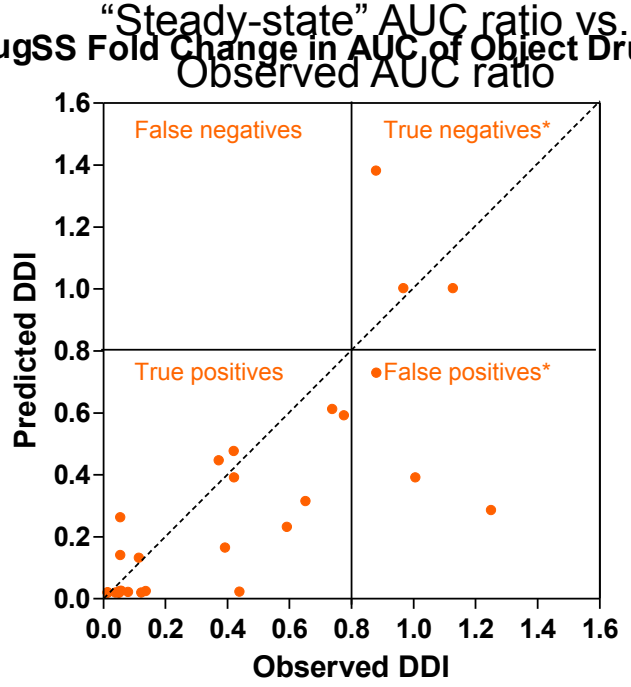
- Accurate predictions require extensive knowledge of drug (victim and perpetrator) parameters
- Requires normalization of *in vitro* induction parameters with rifampin positive control (for IVIVE)
- requires that concentration-time profile of the perpetrator to be accurately predicted

PBPK-based – Results

Simcyp Model







Time-based model more predictive of actual DDI (AUC) than 'Steady-state' model. Also proven to be a good model to predict the induction/non-induction effect within the 0.8-fold (-20%) boundary.

* True negatives or false positives with respect to induction

Relative accuracy of the various models

$$GMFE = 10^{\frac{\sum \left| \log \frac{\text{Predicted AUC ratio}}{\text{Observed AUC ratio}} \right|}{N}}$$

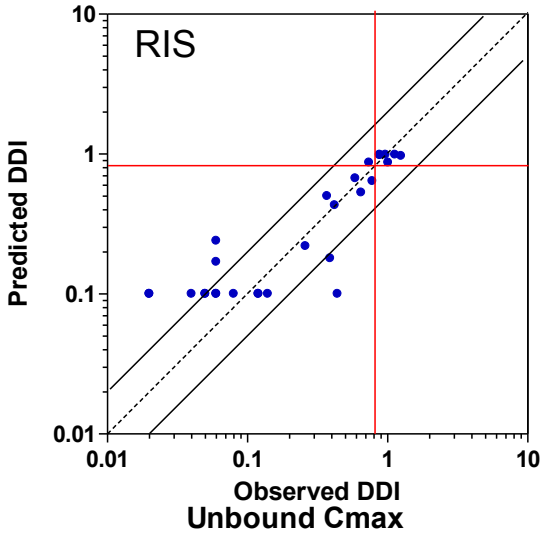
GMFE = geometric mean fold-error
GmedFE = geometric median fold-error

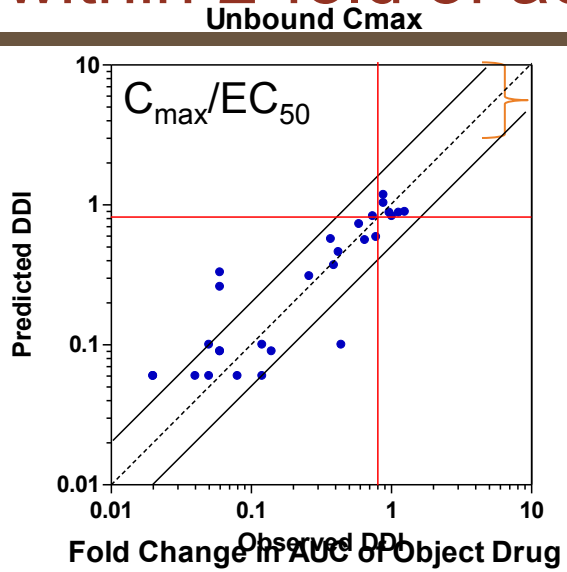
	Correlation Methods						Mathematical Equations				PBPK
	RIS			C_{max}/EC_{50}			Net Effect Model				Simcyp*
[I] =	Total	Free	Free Portal	Total	Free	Free Portal	Total	Free	Free Portal	Mixed	
GMFE	1.99	1.67	1.68	1.88	1.65	1.70	1.96	1.74	1.73	1.75	1.85
GMedFE	1.56	1.29	1.32	1.54	1.33	1.32	1.51	1.38	1.39	1.39	1.51
Scaling Factor (d) **							*0.35*	*0.51*	*0.47*	*0.52*	

In general, all the models predict the actual DDI with similar accuracy, particularly using free or free portal C_{max} for [I] in the non-PBPK models

* Simcyp time-based model, AUC ratio (steady-state model for AUC ratio: GMFE = 2.27; GMedFE = 2.42)
**The scaling parameter for induction (*i.e., d*) in each of the four sets of predictions was estimated through linear regression to a value that minimized the GMFE of the prediction via linear weighted least-squares regression.

Predictions of DDI within 2-fold of actual

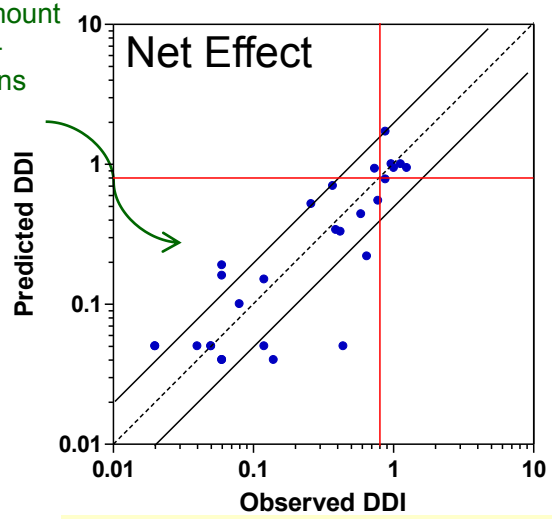


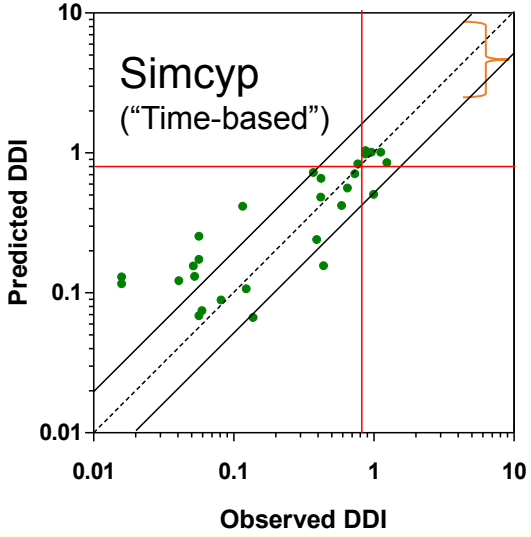


within 2-fold of the actual DDI

← 0.8-fold (-20%)

Least amount of under-predictions





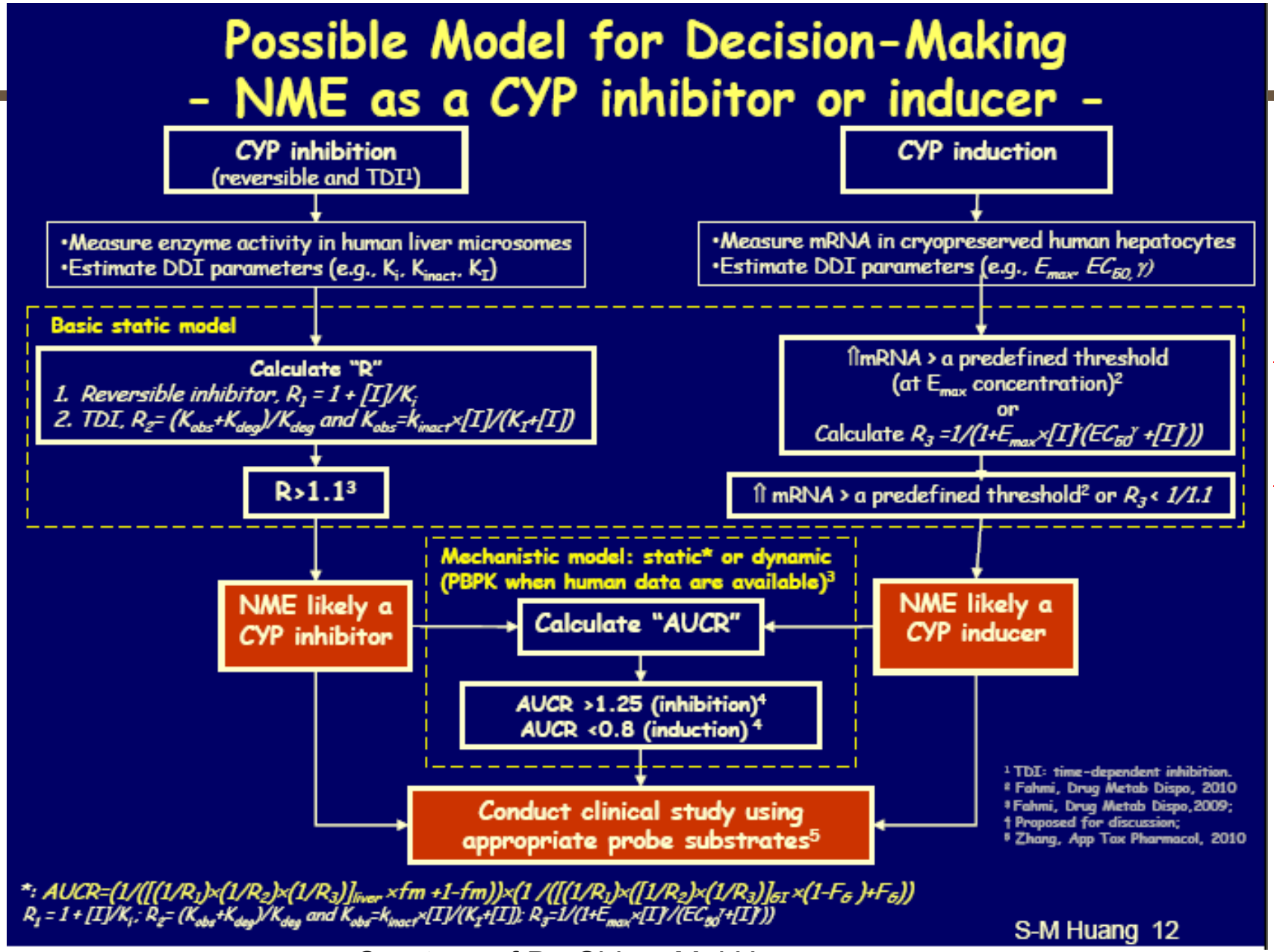
within 2-fold of the actual DDI

← 0.8-fold (-20%)

[I] = $C_{max,u}$ for static models

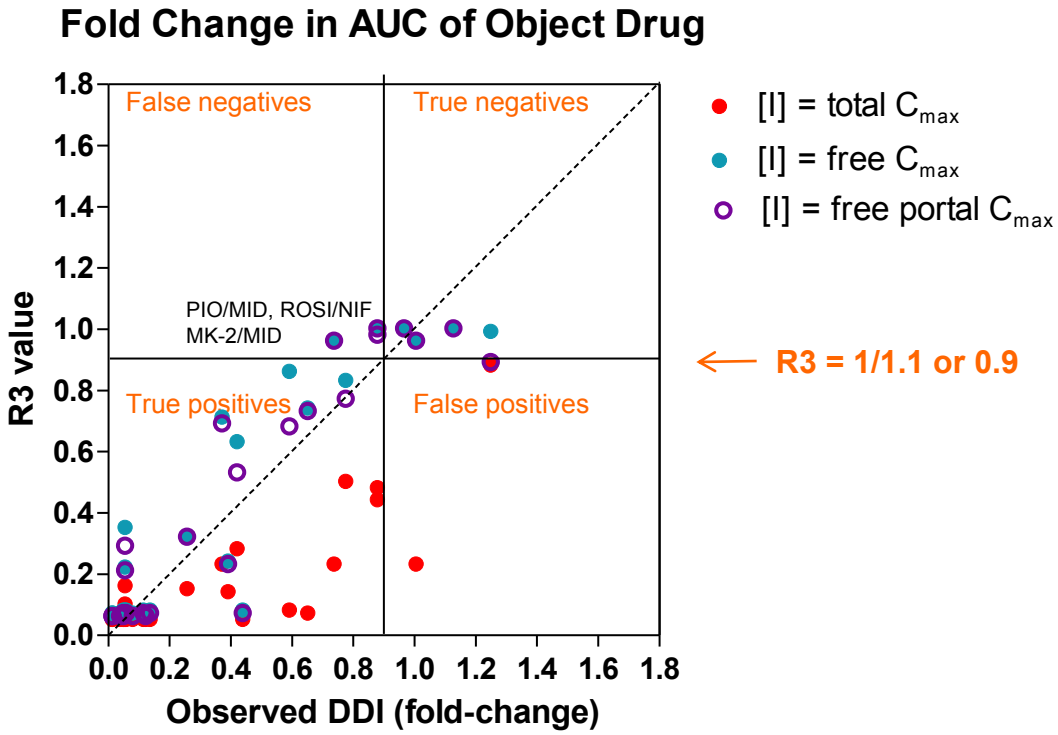
Although all models can properly predict DDI within the 0.8-fold (-20%) boundary, importantly, the least amount of under-predictions were observed with the Net Effect model

New FDA draft guidance decision tree



Courtesy of Dr. Shiew-Mei Huang

Evaluation of the "R3" value to assess risk



$$R3 = 1/[1+(E_{max} \times [I]^{\gamma})/(EC_{50}{}^{\gamma} + [I]^{\gamma})],$$ *where γ = 1 in this case*

R3 value, using [I] as free C_{max} or free portal C_{max}, appears to work well to categorize DDI risk within the R3 = 0.9 boundary. Using total C_{max} would result in many over-predictions and some false positives.

Summary/Conclusions

Highlights of the Working Group outcomes thus far...

- Defined and worked towards the qualification of approaches to predict clinical induction of CYP3A
  - **Results of the predictions**
    - **All the models evaluated appeared to predict the DDI effect within the range of the 0.8-fold (-20%) boundary**
    - **Some differences in the models to predict within 2-fold of actual, with the Net Effect Model having the least amount of under-predictions in this dataset.**
  - **Interpretation across-Co.**
    - **It is not recommended to establish universal cut-off values (RIS, C_{max}/EC_{50}, and even fold-change), as these are likely only valid for a particular lot of hepatocytes and the laboratory**
  - **Ease of use**
    - **The lack of the need to set-up of calibration curves, such as for the Net Effect Model or PBPK models, is a major advantage to these models.**
    - **mRNA is the preferred data to use in these models (better dynamic range and differentiation of induction vs. inhibition/inactivation)**
- Proposed some good starting estimates for those input parameters that we believe can be standardized (with the inhibition team) and defined quality of some important input parameters (*e.g.* EC_{50} and E_{max})

Induction Working Group

A global collaboration across Academia, Pharma, and the FDA

- Heidi Einolf (Novartis)
- Scott Obach (Pfizer)
- Lei Zhang (FDA)
- Ping Zhao (FDA) – *ad hoc*
- Odette Fahmi (Pfizer)
- Mohamad Shebley (Abbott)
- Chris Gibson (Merck)
- Liangfu Chen (GSK)
- Jash Unadkat (University of Washington)
- Mike Sinz (BMS)
- Jose Silva (J&J)

Back-up slides

Input parameters needed in the different models

A review

- Correlation Methods
  - Of test perpetrator (and calibrator compounds): EC_{50}, E_{max}, [I]
  - Known clinical DDI effect of calibrator compounds
- Mathematical Equations (Mechanistic Static Models)
  - Of test perpetrator: EC_{50}, E_{max}, [I]
  - Scaling factor "*d*"
  - If also a reversible and/or TDI: K_i and/or K_I and k_{inact} (also k_{deg} CYP3A4), fu_{mic}
  - Depending on value used for [I]: k_a, f_a, dose may be needed (*e.g.* hep_{intlet} C_{max}), f_u
  - Of victim: fm_{CYP}, F_G
- Physiologically-Based Pharmacokinetic (Mechanistic Dynamic Models)
  - Of test perpetrator (and rifampin control as a calibrator): EC_{50}, E_{max}
  - If also a reversible and/or TDI: K_i and/or K_I and k_{inact}, fu_{mic}
  - Of both victim and perpetrator: physical chemical properties, protein binding and blood cell distribution, absorption parameters, V_{ss}, renal and hepatic clearances (correct fm_{CYP} being calculated for victim), etc.

Input parameters that can be standardized

- fm_{CYP} and F_G for common CYP3A victim drugs (input values we chose to use for this evaluation)
  - Midazolam
    - fm_{CYP} range 0.86-0.94 (used 0.90)
    - F_G point estimate 0.5
  - Alprazolam
    - fm_{CYP} 0.8
    - F_G 0.94
  - Nifedipine
    - fm_{CYP} 0.71
    - F_G 0.78
  - Simvastatin
    - fm_{CYP} 0.92
    - F_G 0.58
- k_{deg} CYP3A
  - Hepatic
    - k_{deg} 0.02/h (t½ 36h)
  - Intestinal
    - k_{deg} 0.03/h

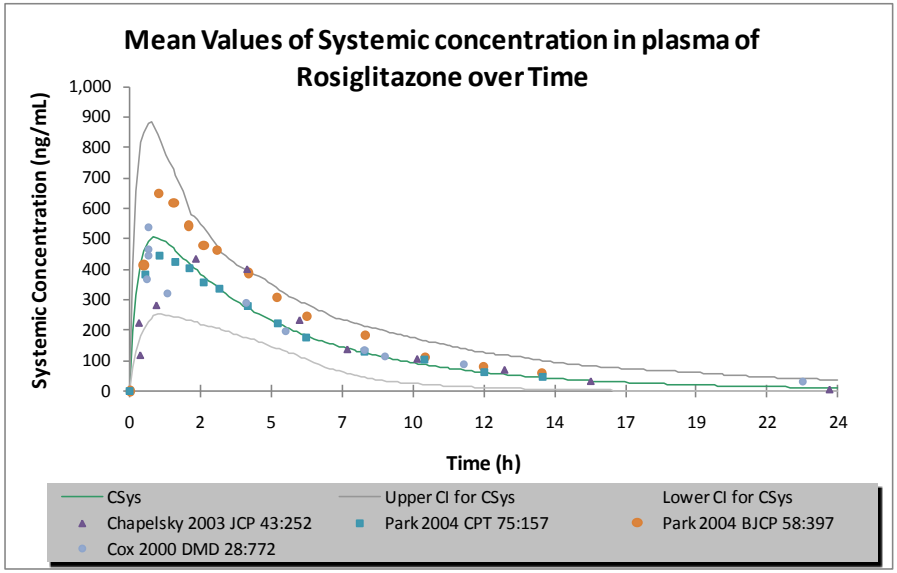
Details of the modeling using Simcyp

- Design of the trials were as described in the publication
  - Demographics (number of subjects, gender, age range)
  - Dose(s), dosing regimen, route of administration
- Victim drug input parameters were used as already provided in Simcyp (Version 10.10 SP1)
- Perpetrator drug input parameters were qualified (in most cases, the compound file had to be built)
  - Ensured *in vitro* induction parameters (EC_{50} and E_{max}) were identical as those used in the other models/approaches (calibration/normalization with rifampin was included)
  - Other DDI parameters were included when available from the literature (K_i, k_{inact} and K_I)
  - Qualified the perpetrator input parameters by comparing simulated time-concentration curves and PK parameters with actual clinical trials

Perpetrator compound model building

Qualification of perpetrator inputs for PBPK modeling

- Example: Rosiglitazone 8 mg single dose (SD)



	AUC (ng/mL.h)	% change compared to actual	TMax (h)	% change compared to actual	CMax (ng/mL)	% change compared to actual	Dose (mg)	CL (Dose/AUC) (L/h)	% change compared to actual	
Mean	2984.80		0.91		515.61		8.00	2.85		
Mean	2930.00	1.87	0.75	21.82	603.00	-14.49	8.00	2.73	4.42	Cox et al 2000 DMD 28:772
Mean	4010.00	-25.57	1.00	-8.63	700.00	-26.34	8.00	2.00	42.90	Park et al 2004 BJCP 58:4 397
Mean	2838.00	5.17	2.00	-54.32	461.00	11.84	8.00	2.82	1.14	Chapelsky et al 2003 JCP 43:252
Mean	2947.90	1.25	0.80	14.21	537.70	-4.11	8.00	2.71	5.05	Park et al 2004 CPT 75:157

Simulated multiple dose (MD) PK is not substantially different than SD

Evaluations with and without rifampin cal

PBPK-Simcyp model

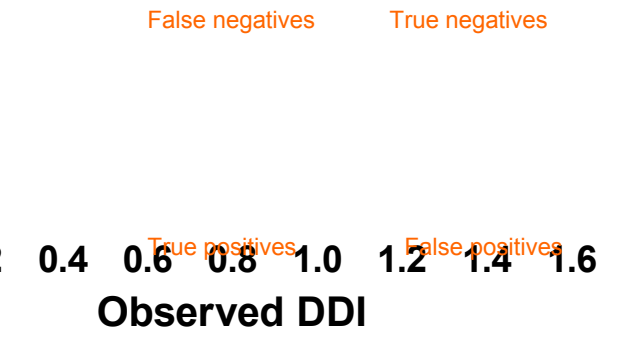
Needs to be updated

- ○ without RIF calibration
- ● with RIF calibration

AUC ratio

C_{max} ratio

"Steady-state" AUC ratio vs. Observed AUC ratio



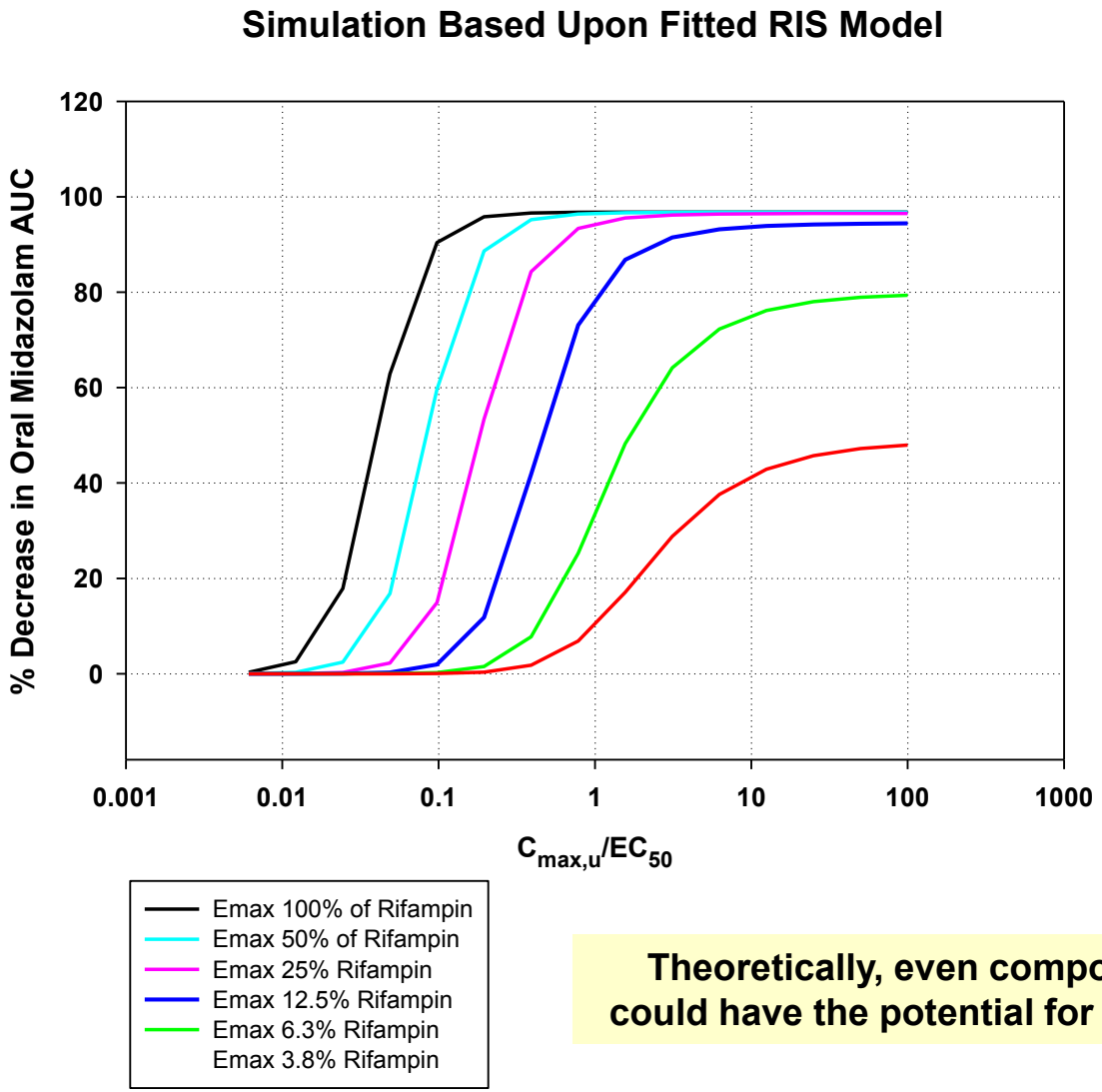
	With RIF Calibration	Without RIF Calibration
GMFE	2.40	2.45
GMedFE	1.35	1.54

	With RIF Calibration	Without RIF Calibration
GMFE	3.48	3.70
GMedFE	1.79	2.21

	With RIF Calibration	Without RIF Calibration
GMFE	2.44	2.64
GMedFE	1.50	2.09

Without RIF calibration, a consistently greater DDI (induction effect) is predicted
In general, the calibration with RIF resulted in lower GMFE or GMedFE values

Why the “40%” rule may result in false neg/pos



- Each curve represents a prediction of DDI from a RIS calibration curve for a test compound
- Each compound (curve) has an EC_{50} of 1 and a different E_{max}, represented as a certain % of RIF
- As the C_{max}/EC_{50} ratio is varied, the projected DDI varies.

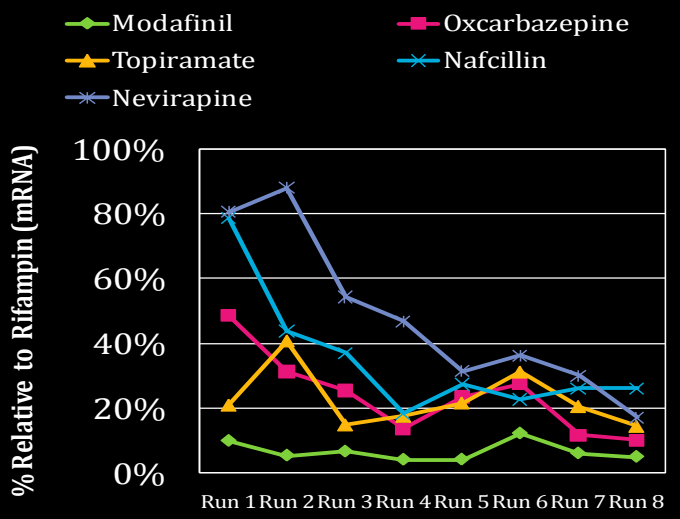
Theoretically, even compounds with a low % of RIF (e.g. ≤25%), could have the potential for a DDI, if “[I]/EC_{50}” is high enough (>0.1)

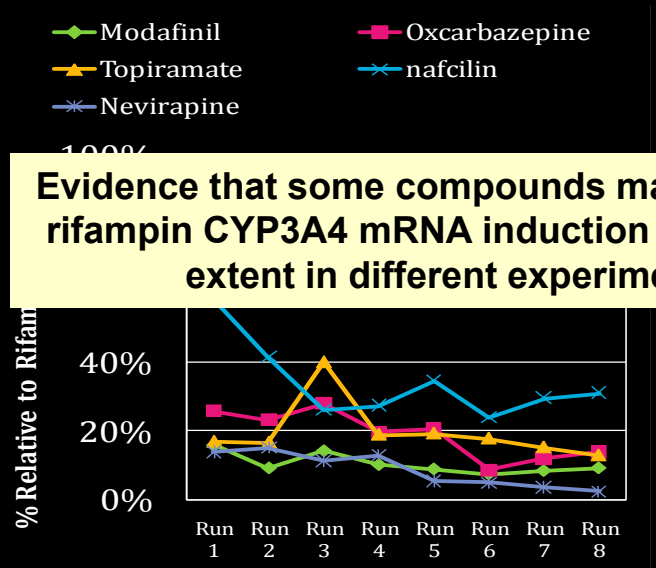
Relative induction of CYP3A4 mRNA by several compounds in replicate experiments

Human Cryopreserved hepatocytes Lot Hu4165

CYP3A4-mRNA — **% Relative to Rifampin (based on mRNA)**

Compound Name	Conc (uM)	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8
Modafinil		10%	5%	7%	4%	4%	12%	6%	5%
Oxcarbazepine	100	48%	31%	25%	14%	23%	27%	12%	10%
Topiramate	100	21%	41%	15%	18%	22%	31%	20%	14%
Nafcillin	100	79%	44%	37%	18%	27%	23%	26%	26%
Nevirapine	100	81%	88%	54%	47%	31%	36%	30%	17%
	10	14	15	31	24	28	25	19	23





Evidence that some compounds may not follow rifampin CYP3A4 mRNA induction to the same extent in different experiments

EC_{50} and E_{max} values determined for Rifampin

Within Co. run-to-run variability using the same lot of hepatocytes

Company 1

	E_{max}
Emax based on mRNA	
Run Name	Lot Hu4165 SD
C100614	43 3
C100607	12 1
C090810	19 1
C100628	24 2
C100628M	24 3
mean	**24**
CV%	**48%**

	EC_{50}
EC50 based on mRNA	
Run Name	Lot Hu4165 SD
C100614	0.43 0.13
C100607	0.35 0.11
C090810	0.70 0.20
C100628	3.6 1.0
C100628M	0.76 0.26
mean	**1.2**
CV%	**117%**

Company 2

Emax based on mRNA	
Run Name	Celsis Lot NPV SD
1	1 11 1.6
2	2 14 0.93
3	3 28 1.0
mean	**18**
CV%	**51%**

EC50 based on mRNA	
Run Name	Celsis Lot NPV SD
1	4.30 2.00
2	0.72 0.07
3	0.60 0.13
mean	**1.9**
CV%	**112%**

Company 3

Emax based on mRNA	
Run Name	SD
1	39
2	27
3	22
4	13
mean	**25**
CV%	**43%**

EC50 based on mRNA	
Run Name	SD
1	1.02
2	1.91
3	1.64
4	1.61
mean	**1.5**
CV%	**24%**

Company 4

Emax based on mRNA	
Run Name	SD
1	52 7.3
2	30 2.02
3	51 3.06
4	40 1.59
mean	**43**
CV%	**24%**

EC50 based on mRNA	
Run Name	SD
1	1.88 0.52
2	0.52 0.14
3	0.82 0.12
4	0.94 0.10
mean	**1.0**
CV%	**56%**

Common fitting algorithms for *in vitro* induction data

Calculation of E_{max} and EC_{50} values

- Simple E_{max} model:

$$\text{Effect} = \frac{E_{max} \times [I]}{EC_{50} + [I]}$$

- Sigmoidal E_{max} model:

$$\text{Effect} = \frac{E_{max} \times [I]^{\gamma}}{EC_{50}{}^{\gamma} + [I]^{\gamma}}$$

- Sigmoid 3-parameter:

$$\text{Effect} = E_{max} / \left(1 + exp\left(-\left([I] - EC_{50}\right)/\gamma\right)\right)$$

EC_{50} and E_{max} values

Collection of data across Co.

- *In vitro* induction data compiled across several Pharma Co. (Pfizer, Novartis, Abbott, Merck, BMS, J&J)
  - rifampin (n=20), carbamazepine (n=7), nifedipine (n=7), phenobarbital (n=8), phenytoin (n=8), pioglitazone (n=7), rosiglitazone (n=5), troglitazone (n=4)
  - Additional data provided by Pfizer (nafcillin, pleconaril, omeprazole, ranitidine) and Merck (MK-1, MK-2)
- Several Co. evaluated each of the 3 fitting algorithms to determine if one algorithm should be favored over the others
  - Akaike Information Criterion (AIC)

AIC = *N**ln (sum of squared residuals)+2P, where *N* = # of observations and P = # of parameters fit in the model

A minimum AIC would be regarded as the best representation of the data. Used for rank ordering models by goodness of fit (with penalty for increasing number of estimated parameters).

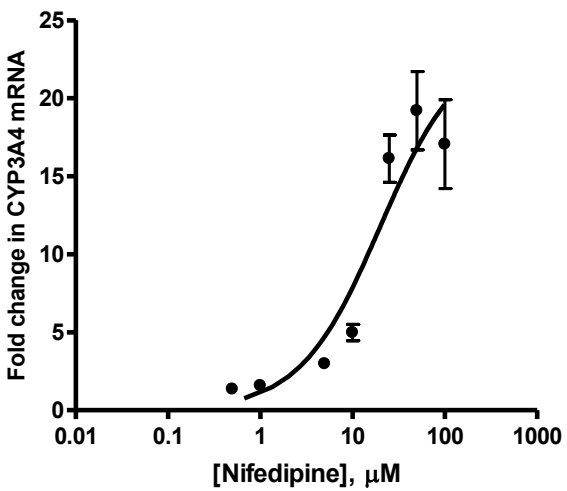
Calculation of EC_{50} and E_{max} values

Use of different fitting algorithms - Example: Nifedipine

mRNA data

$$Effect = \frac{E_{max} \times [I]}{EC_{50} + [I]}$$

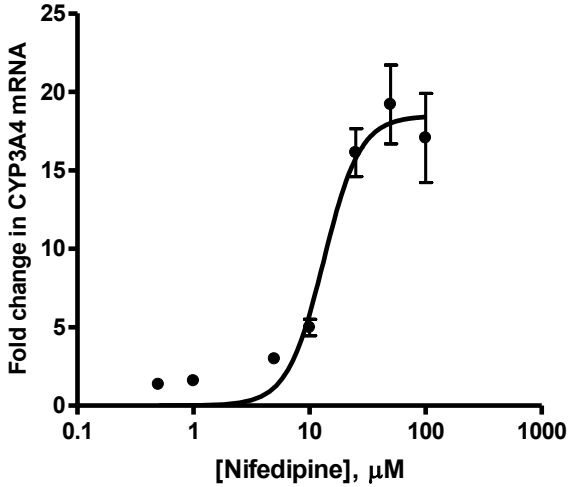
Simple E_{max} model



E_{max} (SE) = 23.5 (4.2)
EC_{50} (SE) = 19.9 (10)
R^2 = 0.9130
AIC = 29

$$Effect = \frac{E_{max} \times [I]^{\gamma}}{EC_{50}{}^{\gamma} + [I]^{\gamma}}$$

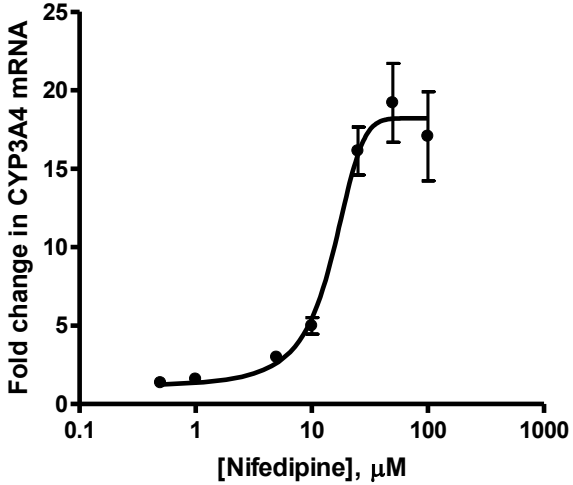
Sigmoidal E_{max} model



E_{max} (SE) = 18.5 (1.4)
EC_{50} (SE) = 13.3 (2.2)
R^2 = 0.9699
AIC = 23

$$Effect = E_{max} / \left(1 + exp\left(-\left(\left[I\right] - EC_{50}\right)/\gamma\right)\right)$$

Sigmoid 3-parameter

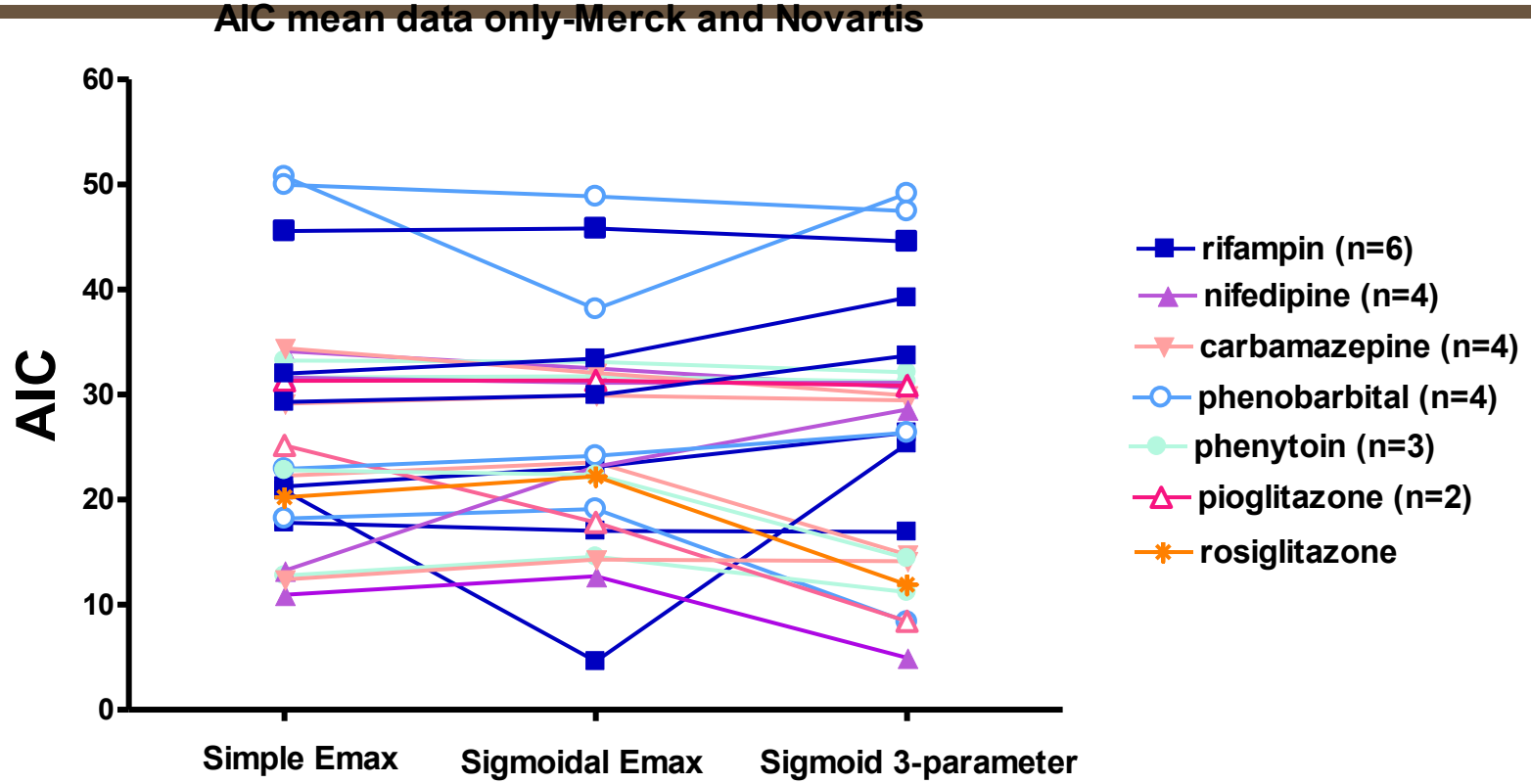


E_{max} (SE) = 18.2 (0.59)
EC_{50} (SE) = 14.6 (1.2)
R^2 = 0.9927
AIC = 13

Standard error (SE) lowest

Calculation of EC_{50} and E_{max} values

Comparisons of different algorithms



- Overall, the team felt that there was no consistent trend and substantial difference to give universal preference of one fitting algorithm over another.
- The recommendation would be to monitor the standard error given and if comparing data, use the same model

Compiled Co. EC_{50} and E_{max} data

Consistently used the Sigmoid 3-parameter model

		RIF	CBM	NIF	PB	PHT	PIO	RSG	TRO
E_{max}									
	Mean ± SD (CV%)	36.8 ± 42 (115%)	18.3 ± 11 (59%)	37.5 ± 34 (91%)	36.6 ± 23 (62%)	19.4 ± 11 (59%)	26.6 ± 17 (64%)	26.1 ± 9.2 (35%)	52.6 ± 40 (76%)
	Median	**21.6**	**14.9**	**28.9**	**33.6**	**17.6**	**21.1**	**23.9**	**37.6**
	N	*20*	*7*	*7*	*8*	*8*	*7*	*5*	*4*
EC_{50}									
	Mean ± SD (CV%)	1.46 ± 1.5 (101%)	47.0 ± 31 (65%)	15.0 ± 12 (80%)	331 ± 229 (69%)	42.0 ± 38 (90%)	20.6 ± 18 (85%)	34.3 ± 18 (52%)	8.35 ± 4.8 (58%)
	Median	**0.849**	**39.1**	**14.5**	**264**	**28.0**	**24.0**	**34.9**	**9.07**
	N	*20*	*7*	*7*	*8*	*8*	*7*	*5*	*4*

The combined data set showed variability in the *in vitro* induction parameters in the range of 35-127%. Based on the results of the predictions, these median values appeared to work relatively well in the models.

RIF = rifampin; CBM = carbamazepine; NIF = nifedipine; PB = phenobarbital; PHT = phenytoin; PIO = pioglitazone; RSG = rosiglitazone; TRO = troglitazone