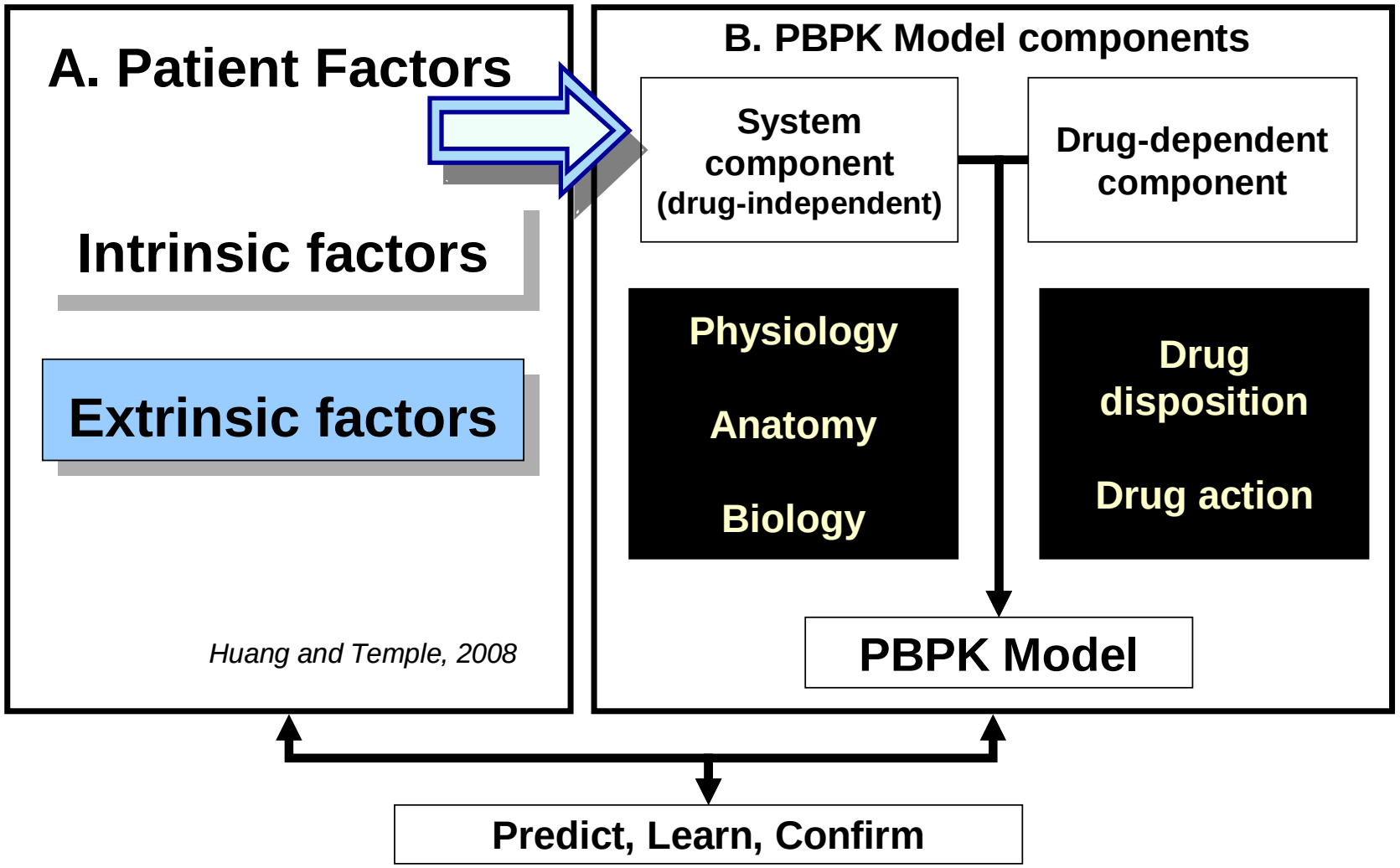
Application of PBPK Modeling and Simulations in Drug Development

Ping Zhao

Division of Pharmacometrics
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration

15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, Washington DC, USA

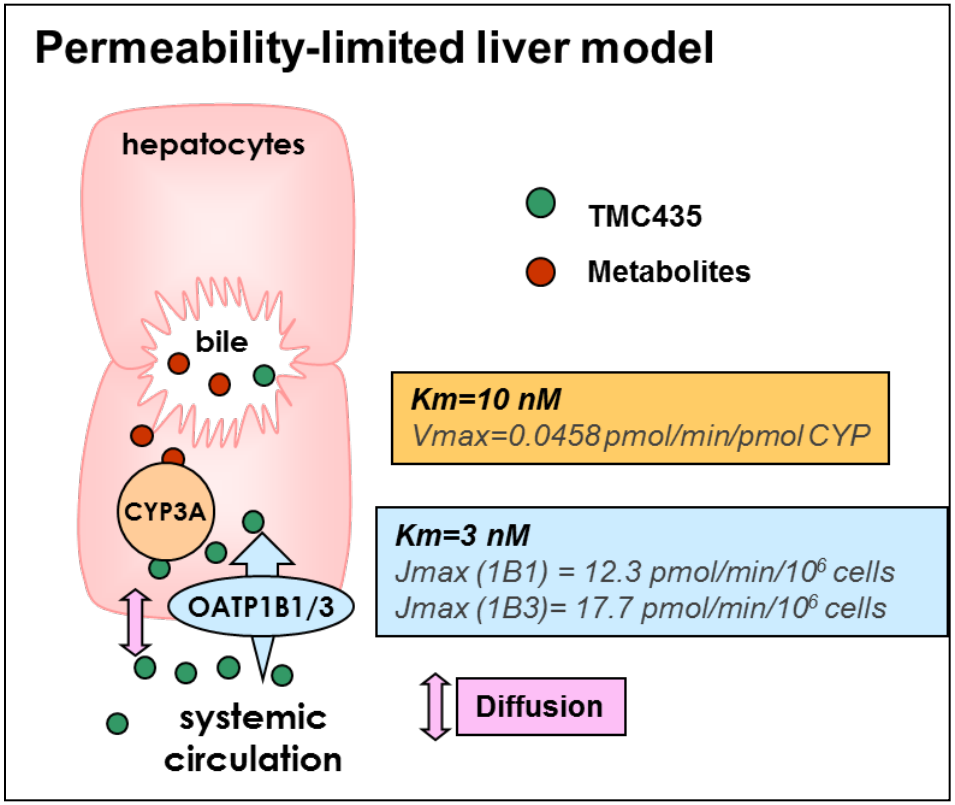
Physiologically-based Pharmacokinetic (PBPK) Models and Evaluation of Patient Factors

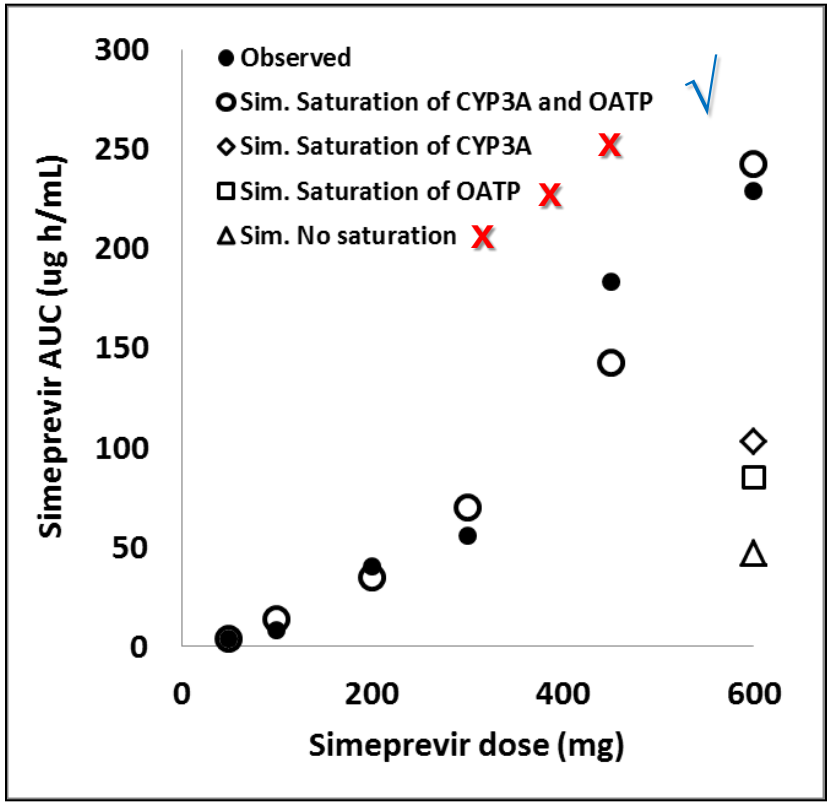


Adapted from Zhao P, et al Clin Pharmacol Ther 2011

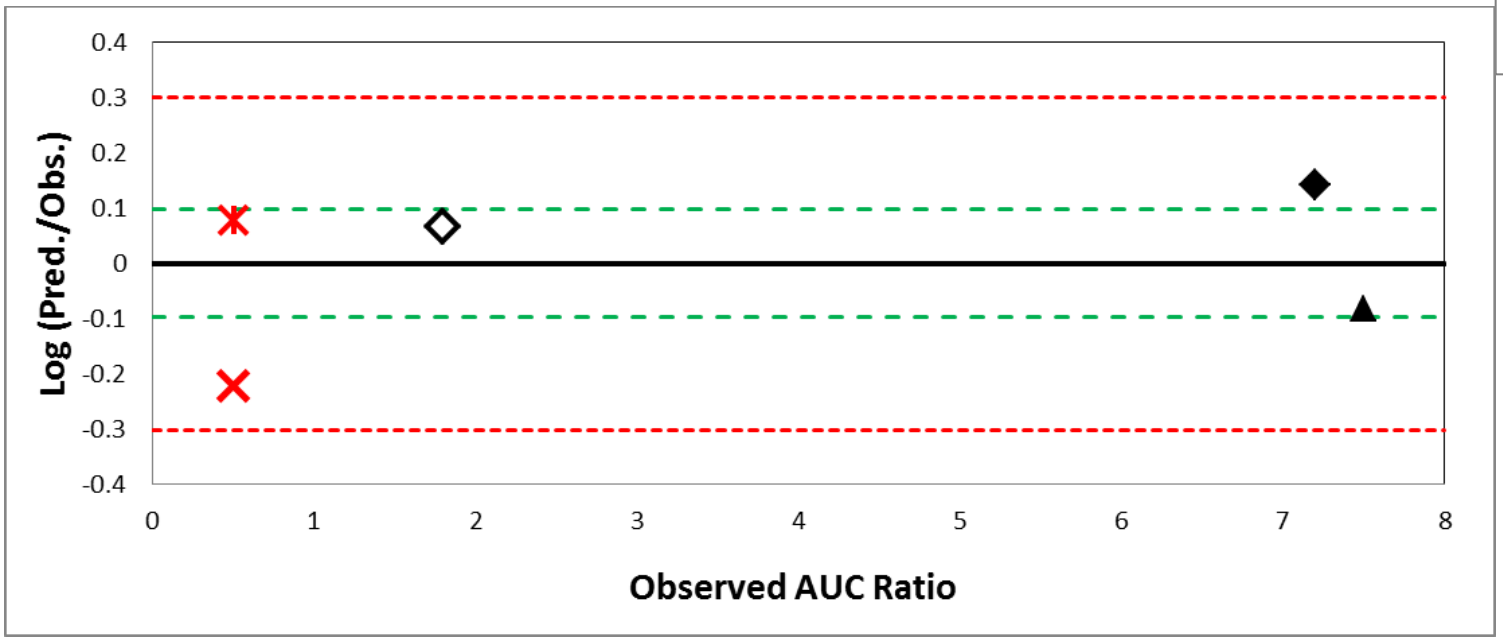
Case Study: FDA Review of Simeprevir

Can saturation mechanisms explain nonlinear pharmacokinetics of simeprevir?





Simeprevir PBPK Model Described the Effects of Various Enzyme/transporter Modulators



Fold over(+) or under (-) prediction

±1.25 fold

±2-fold

Similar effects by CYP3A inducers:

* Rifampin (Strong)
× Efavirenz (Moderate)

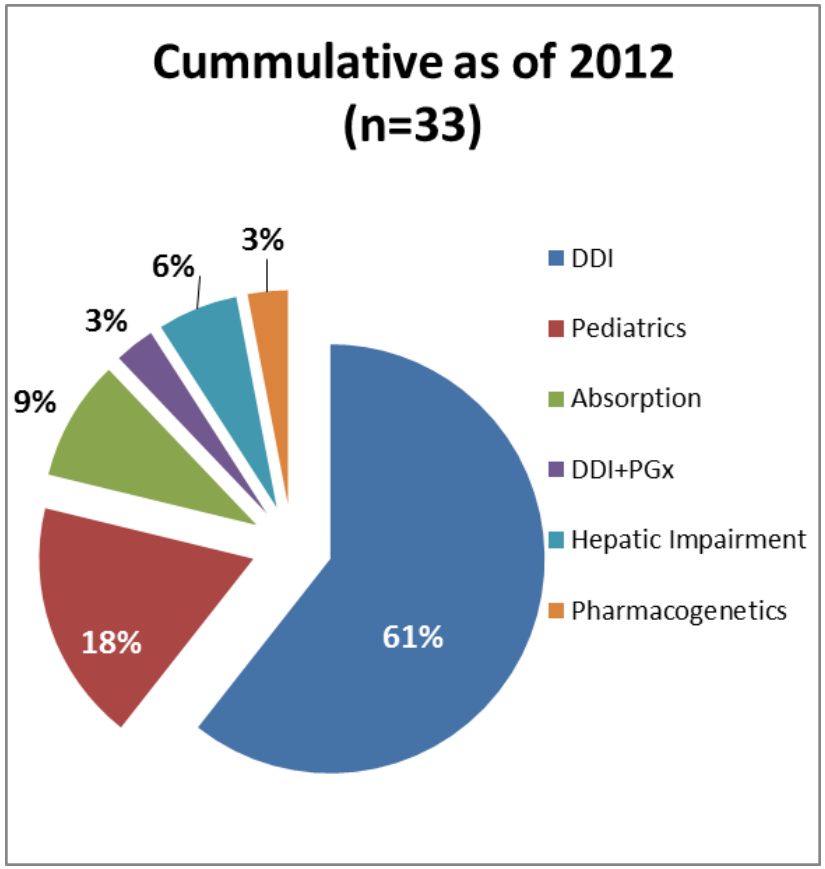
Differential effect of strong CYP3A inhibitor ritonavir:

◊ Single dose simeprevir
♦ Steady state simeprevir

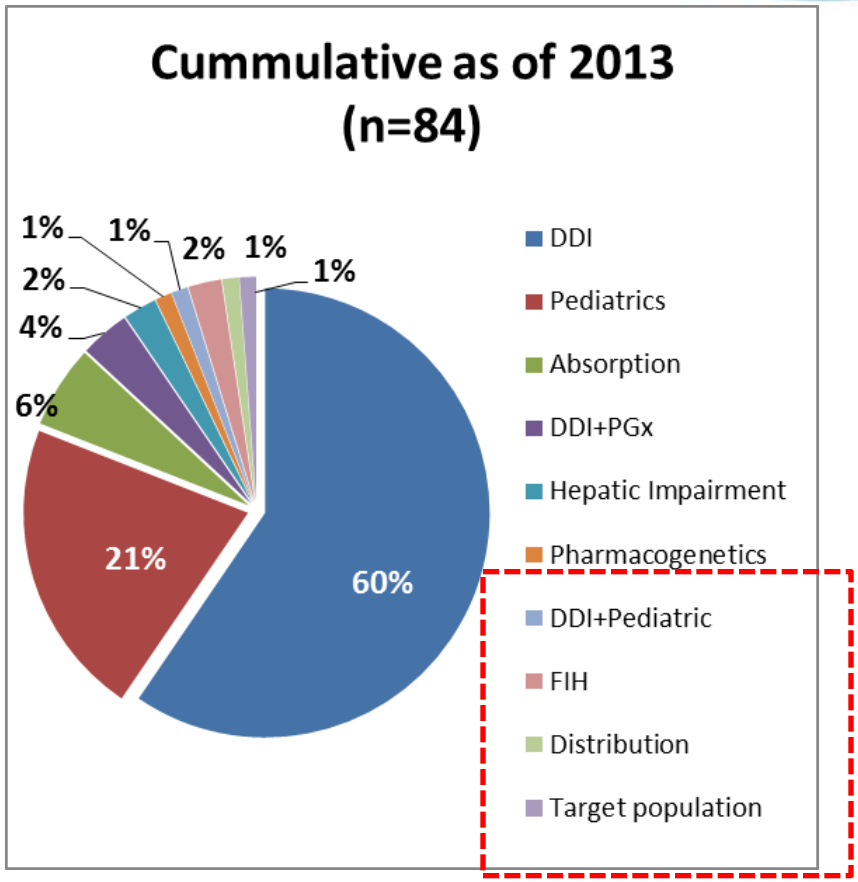
Similar effects by CYP3A inhibitors when simeprevir is dosed to steady state:

♦ Ritonavir (Strong)
▲Erythromycin (Moderate)

By Sponsors, How is PBPK Being Utilized?



Huang et al, J Pharm Sci, 2013



Pan, ASCPT Annual Meeting, 2014, Atlanta, GA

- **Increased use of PBPK by drug developers**
- **Majority of the cases were related to drug-drug interactions (~ 60%); pediatrics ranks the second**

FDA OCP experience suggests that PBPK may be useful in

- Planning PK trial designs
- Predicting PK as a result of intrinsic and/or extrinsic factors and assessing the impact of sources of variability for untested clinical scenarios
- Evaluating or confirming dosing recommendations in specific populations

Sinha et al, Clin Pharmacol Ther, 2014

PBPK analyses have supported addressing the following questions in antiviral drug development

1. Drug interaction study was conducted at high dose of drug A. Does inhibitor have the same effect when drug A is given at therapeutic (lower) doses?

2. What is the predicted exposure difference in the liver between Asian and Caucasian for an HCV drug B that undergoes saturable hepatic uptake and metabolism?

3. When a patient is switched from an HIV PI combo regimen to a single agent drug C, how many days of overlap should be allowed to ensure viral suppression?

4. Dose of drug D needs to be doubled when co-administered with an enzyme inducer. Upon discontinuation of the inducer, when can dose of drug D be reduced?

Application of PBPK to Support Dose Selection: FDA Public workshop, March 10, 2014

- Presentations on PBPK application from FDA, industry and academia
- Panel 1 discussed potential applications of PBPK in drug evaluation, and areas relevant to drug development and review that are currently amenable to the use of PBPK
- Panel 2 discussed assessment of model fidelity and best practices in reporting

PBPK applications: current status

	Applications	Status
Drug-drug Intearctions	*Drug as enzyme substrate*	• *Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling*
	Drug as enzyme perpetrator	• *Use to confirm the lack of enzyme inhibition* • *Additional evidence needed to confirm predictive performance for positive interactions*
	Transporter-based	• *In vitro-in vivo extrapolation not mature due to lack of information,* • *Complicated by transporter-enzyme interplay* • *Predictive performance yet to be demonstrated*
Specific populations	*Organ impairments (hepatic and renal)*	• *Predictive performance yet to be improved* • *System component needs update*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Additional specific populations and situations	Pregnancy, ethnicity, geriatrics, obesity, disease states Food effect, formulation change, PH effect (including DDIs on gastric pH) Tissue concentration	

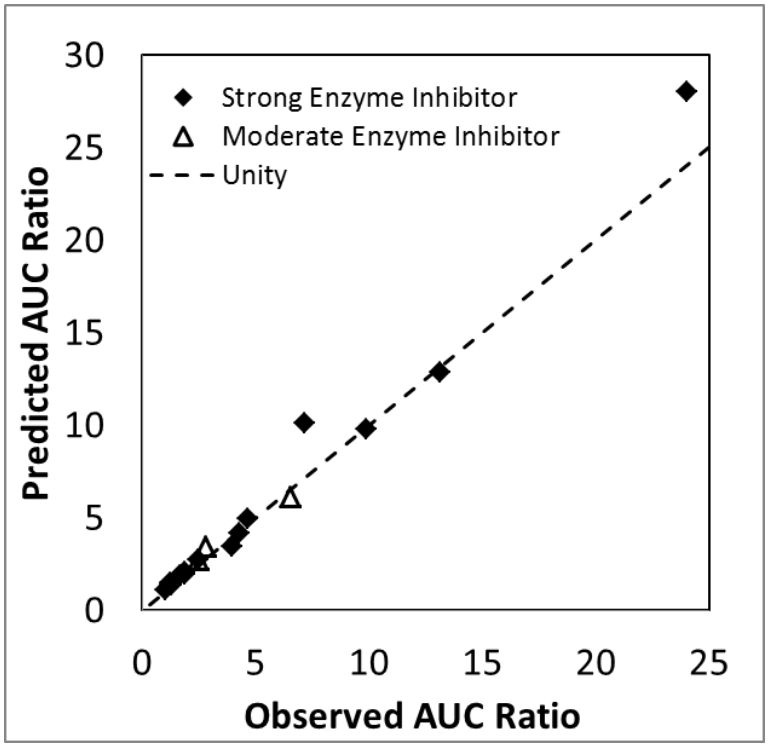
DDI Prediction: Drug as Enzyme Substrate

Example 1: Analysis using FDA PBPK knowledgebase

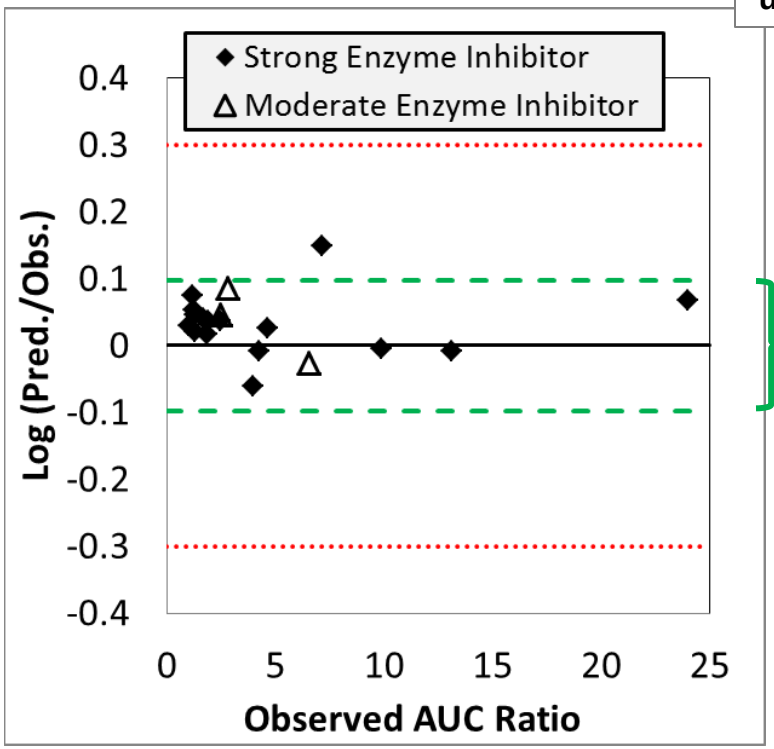
- *Criteria*

(a) model simulated PK and observed PK comparable;
(b) clinical interaction data were not used for model building

Nine (9) substrates, 7 sponsors; with 19 interaction studies

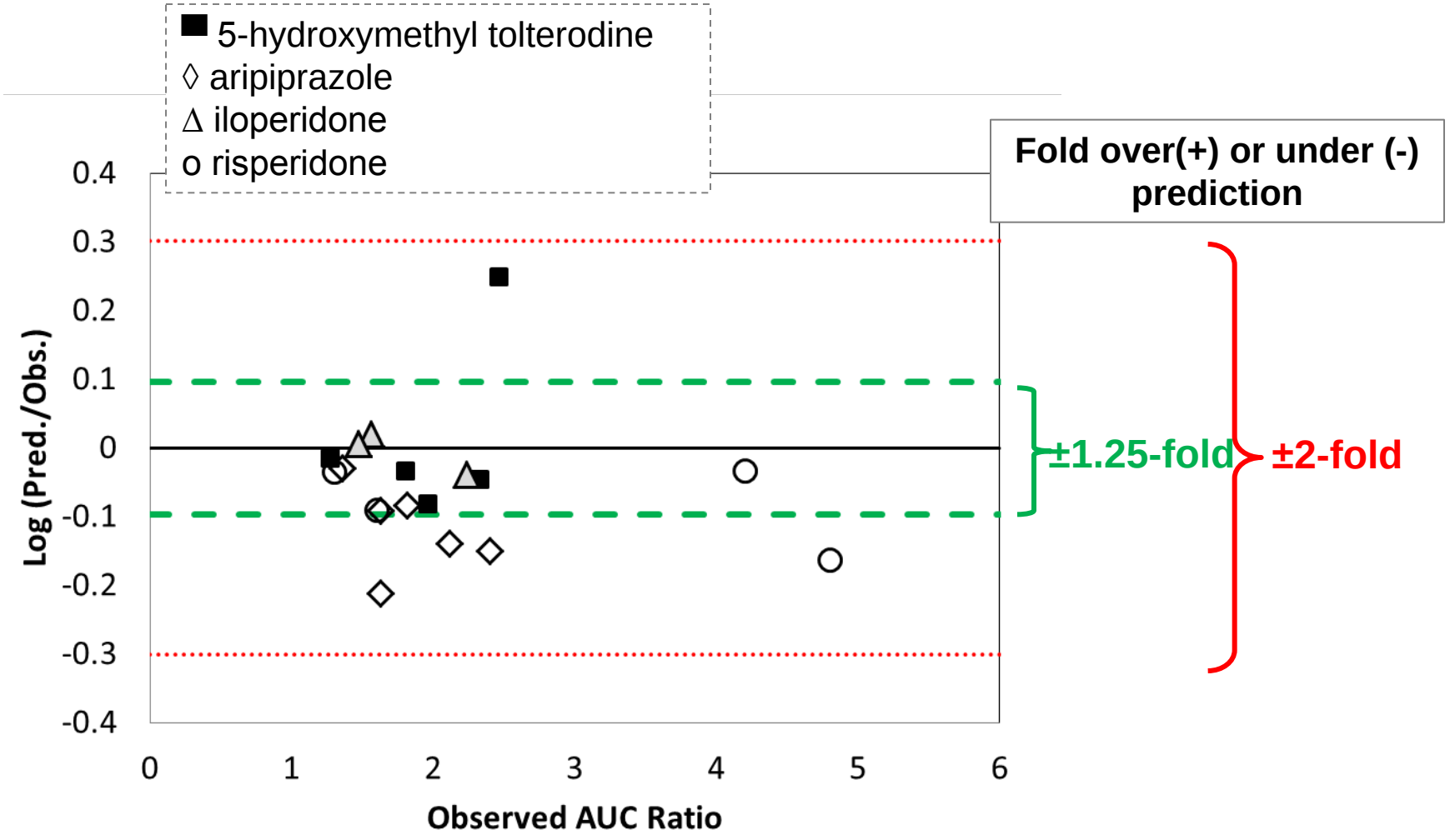


Fold over(+) or under (-) prediction



DDI Prediction: Drug as Enzyme Substrate

Drugs eliminated by CYP3A and CYP2D6



Vieira et al, Clin Pharmacol Ther, 2014

Case study: FDA review of ibrutinib

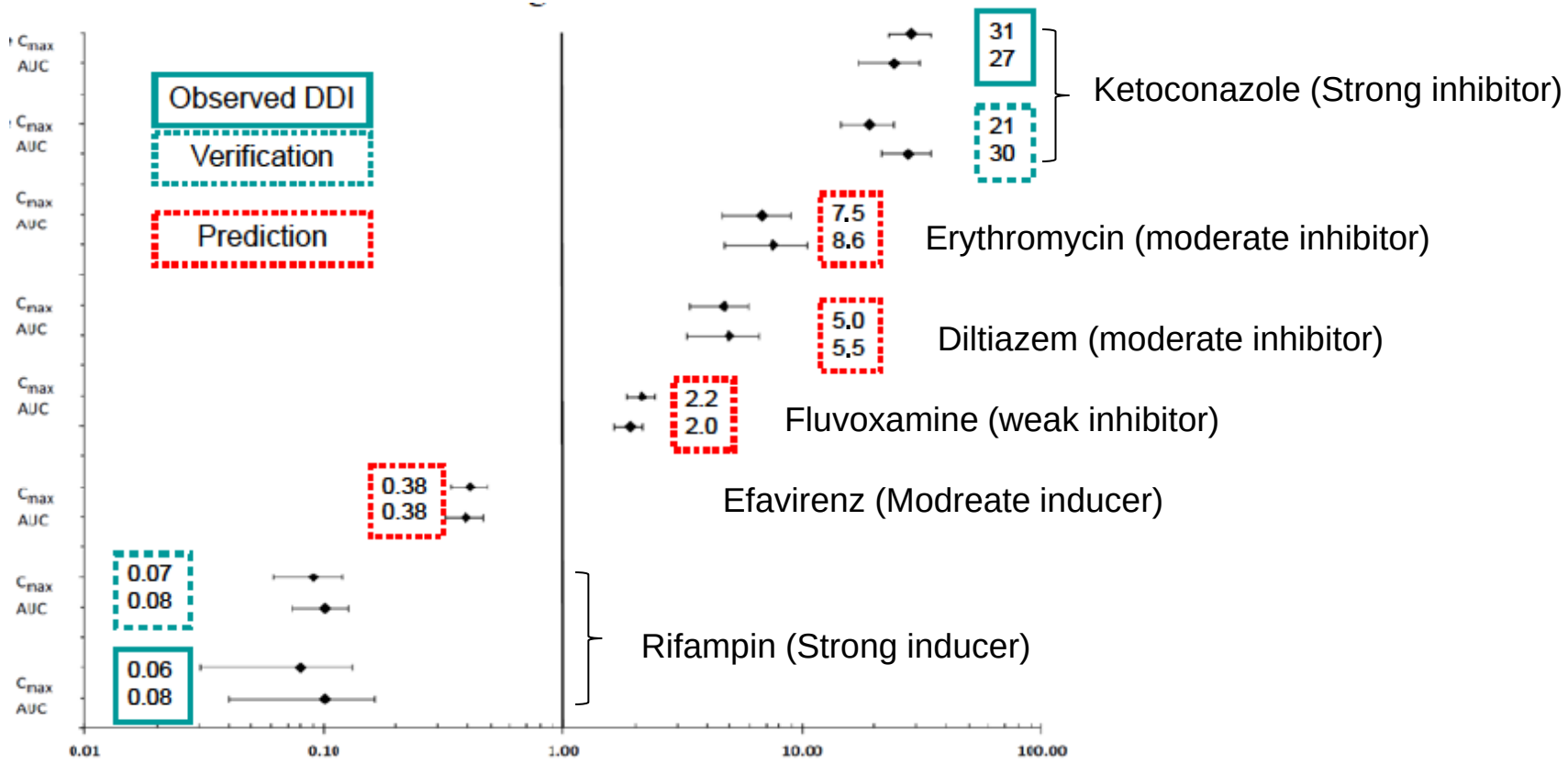
- ❑ Predominantly metabolized by CYP3A
- ❑ Clinical drug interaction studies:
  - *With strong CYP3A inhibitor ketoconazole: AUC increased by ~24-fold*
  - *With strong CYP3A inducer rifampin: AUC decreased by >90%*

What are expected exposure changes with other CYP3A inhibitors or inducers?

What is dosing recommendation in patients who have to take CYP3A inhibitor/inducer?

What are expected exposure changes with other CYP3A inhibitors or inducers?

PBPK-Simulated and observed Cmax and AUC ratios (mean and 95% confidence interval)



Summary of Ibrutinib Case Study

What are expected exposure changes with other CYP3A inhibitors or inducers?

What is dosing recommendation in patients who have to take CYP3A inhibitor/inducer?

Section 12.3: “Simulations…suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 6 to 9-fold in fasted condition;…a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib up to 3-fold”

Section 2.4: “…strong CYP3A inhibitors which would be taken chronically…is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting IMBRUVICA therapy until the CYP3A inhibitor is no longer needed…Reduce IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used…Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of IMBRUVICA toxicity.”

And more in Section 7…

Case study: FDA review of ceritinib

- **Metabolized by CYP3A, time-dependent inhibitor of CYP3A – nonlinear PK**
- **Clinical drug interaction studies using single dose**
  - *With strong CYP3A inhibitor ketoconazole: AUC increased by ~3-fold*

(PBPK simulated 2.4-fold, FDA modified model)

  - *With strong CYP3A inducer rifampin: AUC decreased by ~60%*

(PBPK simulated 69%, FDA modified model)

What are STEADY STATE exposure changes with CYP3A modulators?

Ceritinib PBPK: Exposure Matching for Dose Recommendation

SIMULATED steady state Ceritinib AUC (microgram/mL.h)	Ceritinib once daily dose			
	300 mg	450 mg	600 mg	750 mg
No ketoconazole	4.8	8.1	11.9	16.1
With ketoconazole	9.8	15.0	20.1	25.4

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000ClinPharmR.pdf

AUC ratio 1.6-2.0-fold, dose dependent. Single dose ceritinib: ~3-fold

Labeling 2.3 Dose Modification for Strong CYP3A4 Inhibitors
Avoid concurrent use of strong CYP3A inhibitors…
If unavoidable, reduce the ZYKADIA dose by approximately one-third, rounded to the nearest 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the ZYKADIA dose that was taken prior to initiating the strong CYP3A4 inhibitor.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205755s000lbl.pdf

Submitting PBPK Information to FDA

- Summary of model input parameters and software version
- Logical description of model building and verification processes
- The details of all simulation conditions
- Model files in a executable format

Early communication with the Agency regarding including PBPK into your development plan is strongly encouraged

Summary

- PBPK submissions to the FDA have increased
- Models support decisions on whether, when and how to conduct clinical pharmacology studies, including the support of labeling
- Experience and confidence differ among different applications. Predictive performance for each specific application needs to be demonstrated

Acknowledgement

- **Research:** Manuela dLT Vieira, Yuzhuo Pan, Christian Wagner, Vicky Hsu
- Other fellows

- **Reviews:** Joseph Grillo, Pengfei Song, Qi Liu, Elimika Pfuma, Julie Bullock, Leslie Chinn, Islam Younis, Ruby Leong, Hong Zhao
- ALL Clinical Pharmacology review Divisions

- Joseph Grillo, Lei Zhang, PBPK-Scientific interest group

- **Office Management**: Vikram Sinha, Shiew Mei Huang, Issam Zineh