American Society of Clinical Pharmacology and Therapeutics Annual Meeting

Roundtable: How Should Simulated DDI Results be Communicated in the Label?

Chairs:

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Panelists:

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Clinical Assessor, Medicines Evaluation Board, Netherlands; Member, Pharmacokinetics Working Party, European Medicines Agency

San Diego, CA, USA. March 10, 2016

Learning objectives

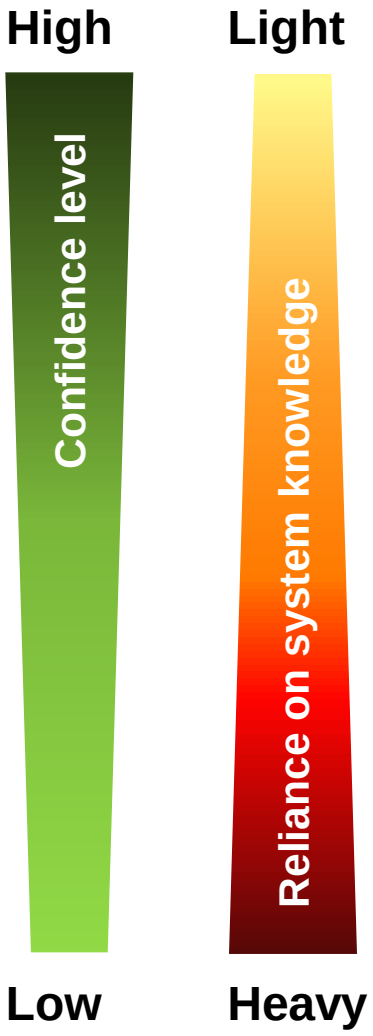
- Be updated on recent regulatory experience in including PBPK simulation results in US labels
- Discuss challenges and heterogeneity of using simulated data for regulatory decision making
- Brainstorm solutions towards clarity and consistency of using PBPK information in product labels

Introduction

The views expressed in this presentation are personal and do not represent official policy of the FDA

PBPK applications: current status

	Applications	Status
Drug-drug Interactions	*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* • *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 an update*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Others with limited experiences	*Pregnancy, ethnicity, geriatrics, obesity, disease states* *Food effect, formulation change, PH effect (including DDIs on gastric PH)* *Tissue concentration*	



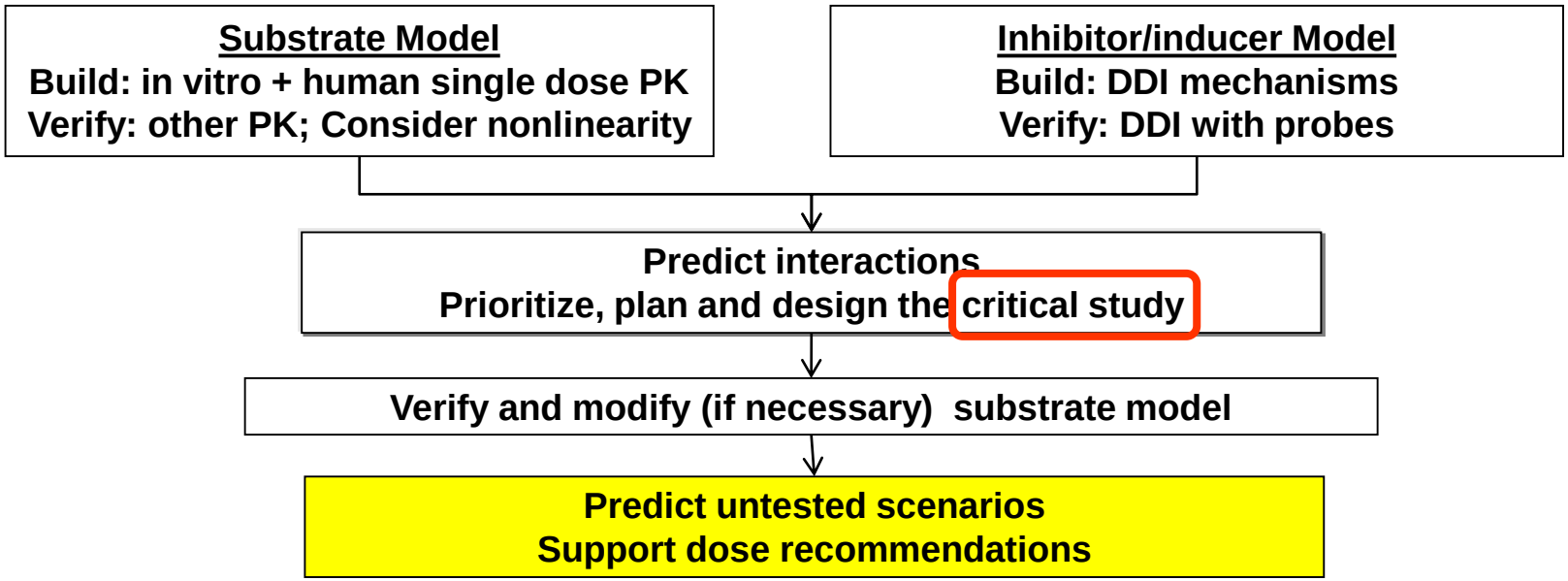
Wagner, CPT-PSP, 2015

PBPK prediction of CYP modulation

- **Predictive performance demonstrated**

Vieira, Clin Pharmacol Ther, 2014; Wagner, Clin Pharmacokinet 2015, 2016

- **Workflow proposed**



Wagner, CPT-PSP, 2015

Drug labels with dosing recommendations informed by PBPK

	2009	2010	2011	2012	2013	2014	2015
Products	**1** *REVATIO*	**3** *CARDIZEM LA* *BILTRICIDE** *XOLEGEL**	**2** *XARELTO* *EDURANT*	**1** *ICLUSIG*	**4** *SKYLA** *OLYSIO* *IMBRUVICA* *OPSUMIT*	**7** *MOVANTIK* *CERDELGA* *JAKAFI* *ZYKADIA* *LYNPARZA* *EDURANT* *BLINCYTO*	**8** *FARYDAK* *ARISTADA* *ODOMZO* *LENVIMA* *COTELLIC* *TIVICAY* *TAGRISSO* *ALECENSA*
PBPK reviews (IND, NDA, BLA)	6	12	14	16	47	38	40

**: Not a DDI application*

Eliglustat (CERDELGA, approved 2014)

- ❑ Rare disease, priority review
- ❑ Metabolized by CYP2D6 (~80%) and CYP3A (~20%)
- ❑ High clearance, nonlinear PK: time-dependent CYP2D6 inhibitor
- ❑ Clinical drug interaction studies
  - *With strong CYP2D6 inhibitor paroxetine: AUC increased by ~8-fold*
  - *With strong CYP3A inhibitor ketoconazole: AUC increased by ~4-fold*
- Pharmacogenetic effects: AUC ratio poor metabolizers/extensive metabolizers (PM/EM) ~ 8-fold

What are exposure changes with various CYP inhibitors in subjects with different CYP2D6 genotypes?

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf

Label – Section 7.1

Table 3: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Drug Interaction Studies or on Predicted Interaction in EMs and IMs

		Recommended CERDLEGA Dosage, by CYP2D6 Metabolizer Status		Simulated conditions
	CYP450 Inhibitors	EM	IM	
√	Strong or Moderate CYP2D6 inhibitors concomitantly with Strong or Moderate CYP3A inhibitors	Contraindicated	Contraindicated	2x2x2=8
	Strong CYP2D6 inhibitors e.g., paroxetine	84 mg once daily	84 mg once daily	Obs
√	Moderate CYP2D6 inhibitors e.g., terbinafine	84 mg once daily	84 mg once daily	1x2=2
	Strong CYP3A inhibitors e.g., ketoconazole	84 mg once daily	Contraindicated	Obs
√	Moderate CYP3A inhibitors e.g., fluconazole	84 mg once daily	Not recommended	1x2=2

Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Predicted Interaction in PMs

	CYP450 Inhibitors	Recommended CERDELGA Dosage for PMs	Simulated conditions
√	Strong CYP3A inhibitors e.g., ketoconazole	Contraindicated	1
√	Moderate CYP3A inhibitors e.g., fluconazole	Not recommended	1
√	Weak CYP3A inhibitors e.g., ranitidine	Not recommended	1

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205494Orig1s000lbl.pdf

Panel questions

1. If dosing recommendations in the label were derived from PBPK simulation, should the label include simulation results? If so, how much details should be included?
2. Currently, a substrate's PBPK model needs to be verified with clinical DDI data (e.g., with a strong CYP inhibitor) before it can be used to support dosing recommendations in the label. Under what conditions can simulations using "non-verified" model be included in the label?
3. Should findings that are derived from modeling or simulation (e.g., pop-PK, PBPK, etc.) be communicated differently in labeling compared to similar information derived from a clinical study?

Labeling basics

PLR (Physician Labeling Rule) FR 71 1/24/2006

- This labeling contains information necessary for safe and effective use. It is written for the **health care practitioner audience**, because prescription drugs require ‘‘professional supervision of a practitioner licensed by law to administer such drug’’

21 CFR (Code of Federal Regulations) 201.56

- The labeling must contain a summary of the **essential** scientific information needed for the safe and effective use of the drug.
- The labeling must be **informative and accurate** and neither promotional in tone nor false or misleading in any particular.
- The labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.
- The labeling must be based whenever possible on data derived from **human experience**. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness.
- Conclusions based on animal data but necessary for safe and effective use of the drug in humans **must be identified as such** and included with human data in the appropriate section of the labeling.

21 CFR 201.57

- 7 Drug interactions. This section must contain a description of **clinically significant** interactions, either **observed or predicted**, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them.
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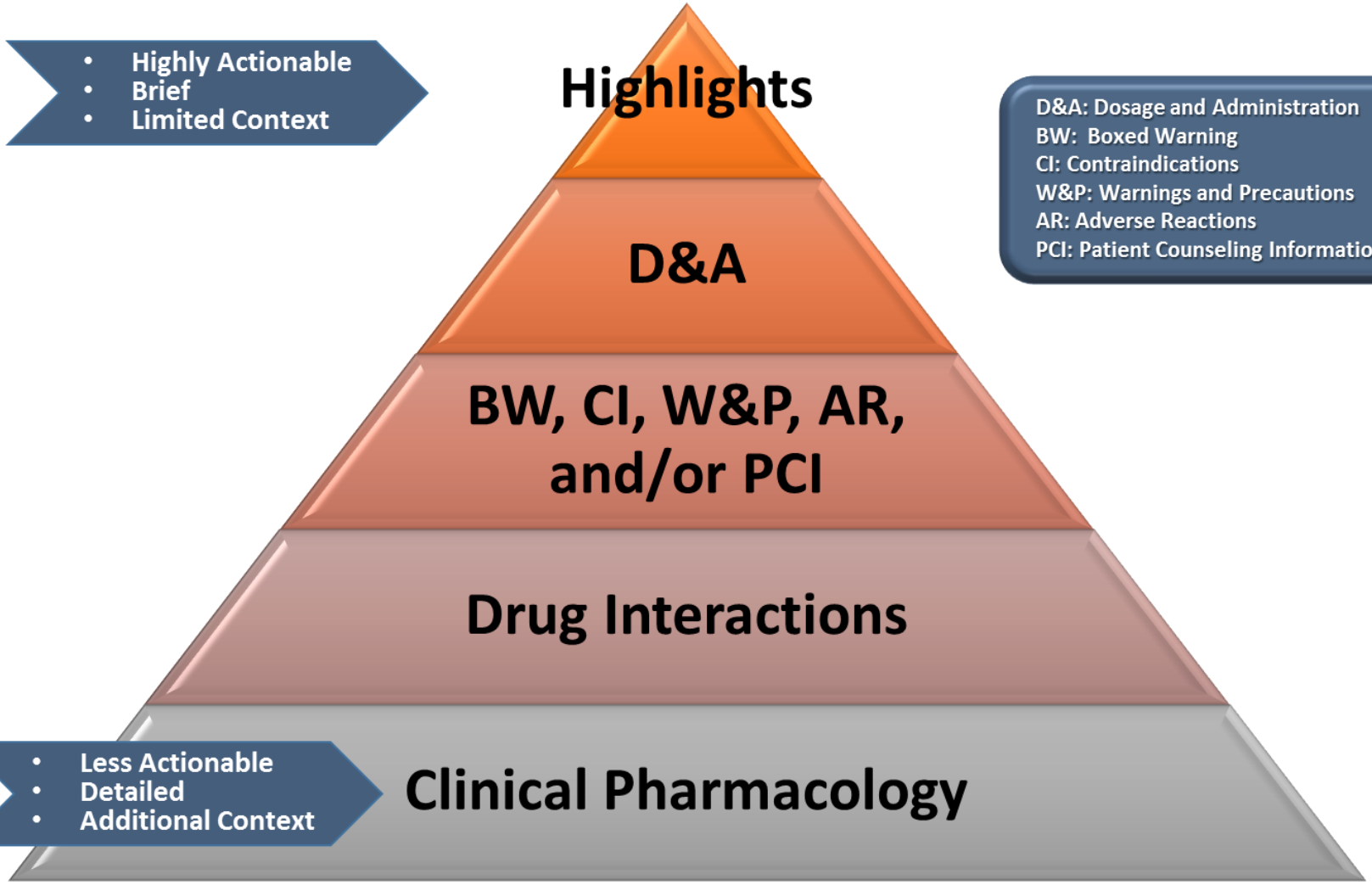
DDI in the label

- Highly Actionable
- Brief
- Limited Context



D&A: Dosage and Administration
BW: Boxed Warning
CI: Contraindications
W&P: Warnings and Precautions
AR: Adverse Reactions
PCI: Patient Counseling Information

- Less Actionable
- Detailed
- Additional Context

Grillo: http://fda.nakamotogroup.com/ppt/Session3-1of2.pdf

Backup slides

Can PBPK PROSPECTIVELY predict the effect of CYP modulation?

PBPK Model Describes the Effects of Comedication and Genetic Polymorphism on Systemic Exposure of Drugs That Undergo Multiple Clearance Pathways

MdLT Vieira[1], M-J Kim[1], S Apparaju[1], V Sinha[1], I Zineh[1], S-M Huang[1] and P Zhao[1]

Clin Pharmacol Ther, 2014

Predicting the Effect of Cytochrome P450 Inhibitors on Substrate Drugs: Analysis of Physiologically Based Pharmacokinetic Modeling Submissions to the US Food and Drug Administration

Christian Wagner · Yuzhuo Pan · Vicky Hsu · Joseph A. Grillo · Lei Zhang · Kellie S. Reynolds · Vikram Sinha · Ping Zhao

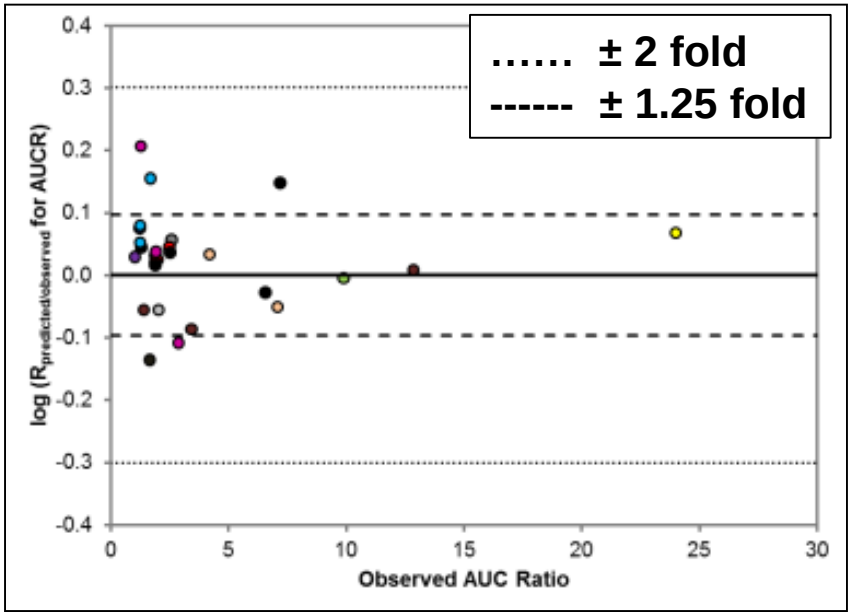
Clin Pharmacokinet 2015

Predicting the Effect of CYP3A Inducers on the Pharmacokinetics of Substrate Drugs Using Physiologically Based Pharmacokinetic (PBPK) Modeling: An Analysis of PBPK Submissions to the US FDA

Christian Wagner[1] · Yuzhuo Pan[2] · Vicky Hsu[1] · Vikram Sinha[1] · Ping Zhao[1]

Clin Pharmacokinet Online 2015

$$R_{pred/obs} = \frac{Pred.\,Exposure\ Ratio}{Obs.\,Exposure\ Ratio}$$



A typical predictability plot

Can PBPK PROSPECTIVELY predict the effect of CYP modulation?

$$R_{pred/obs} = \frac{Pred.\,Exposure\ Ratio}{Obs.\,Exposure\ Ratio}$$

	CYP Inhibition (Vieira, 2014)	CYP Inhibition (Wagner/Pan, 2015)	CYP Induction (Wagner, 2015)
Substrates evaluated	4	15	11
DDI cases to predict	20	26	13
Organization	FDA	9 sponsors	6 sponsors
Substrate model predicts base PK ≤2-fold of obs. CL	100%	87%	91%
$0.80 \leq R_{pred/obs} \leq 1.25$	72% AUC; 70% Cmax	81% AUC; 77% Cmax	77 % AUC; 83% Cmax
$0.50 \leq R_{pred/obs} \leq 2.00$	100%	100%	77% AUC; 92% Cmax
$R_{pred/obs} > 2.00$	0	0	23% AUC; 8% Cmax

Cut-off values are arbitrary

Case 2: Ibrutinib DDI (2013)

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

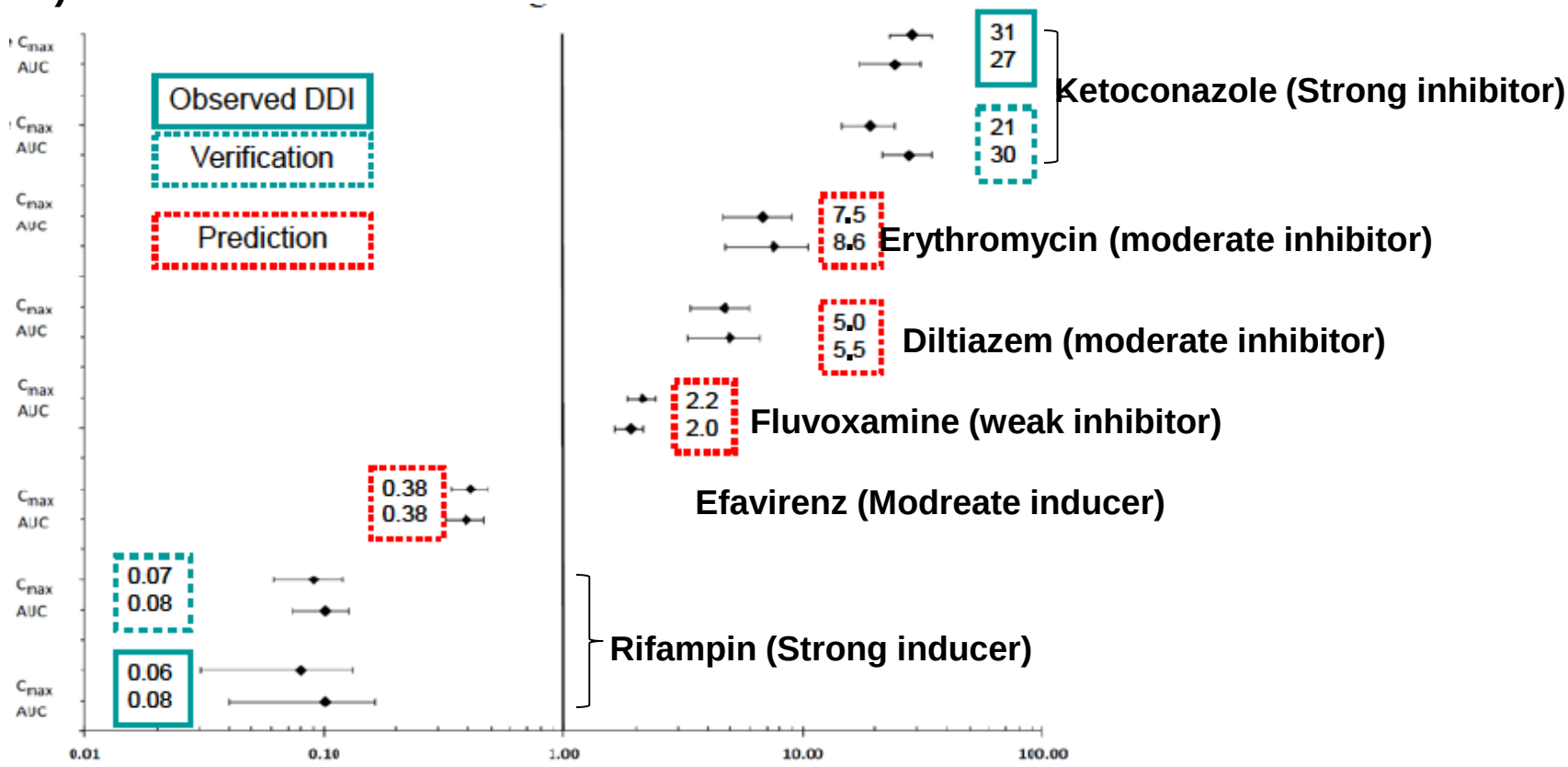
What are expected exposure changes with other CYP3A inhibitors or inducers?

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

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

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

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



http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

PBPK in Ibrutinib Label

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…

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552s000lbl.pdf

Case 3: Ceritinib DDI (2014)

- ❑ Breakthrough review designation
- ❑ Metabolized by CYP3A
- ❑ Nonlinear PK: time-dependent CYP3A inhibitor
- ❑ Clinical drug interaction studies using single dose ceritinib
  - *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 with CYP3A modulators under different ceritinib doses?

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

PBPK in Eliglustat Label

Section 7.1

Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Predicted Interaction in PMs

	CYP450 Inhibitors	Recommended CERDELGA Dosage for PMs	Simulated conditions
√	**Strong CYP3A inhibitors** e.g., ketoconazole	Contraindicated	1
√	**Moderate CYP3A inhibitors** e.g., fluconazole	Not recommended	1
√	**Weak CYP3A inhibitors** e.g., ranitidine	Not recommended	1

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205494Orig1s000lbl.pdf

PBPK in Ceritinib Label

Section 12.3. "…The steady-state AUC of ceritinib at reduced doses after coadministration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC of ceritinib alone"

Section 2.3 "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

Case 5. Ruxolitinib DDI (2014)

- Labeling supplement
- In vitro metabolism: $f_{m,CYP3A}$**:$f_{m,CYP2C9}$**:$f_{m,CYP1A2}$= 0.76**:0.19:**0.05
- Clinical drug-drug interaction studies focused on modulation of CYP3A:

CYP3A modulators	DDI Mechanism	Geo Mean Ruxolitinib Exposure ratio	
		AUC	Cmax
Ketoconazole	Strong inhibitor	1.9	1.3
Erythromycin	Moderate inhibitor	1.3	1.1
Rifampin	Strong inducer	0.3	0.5

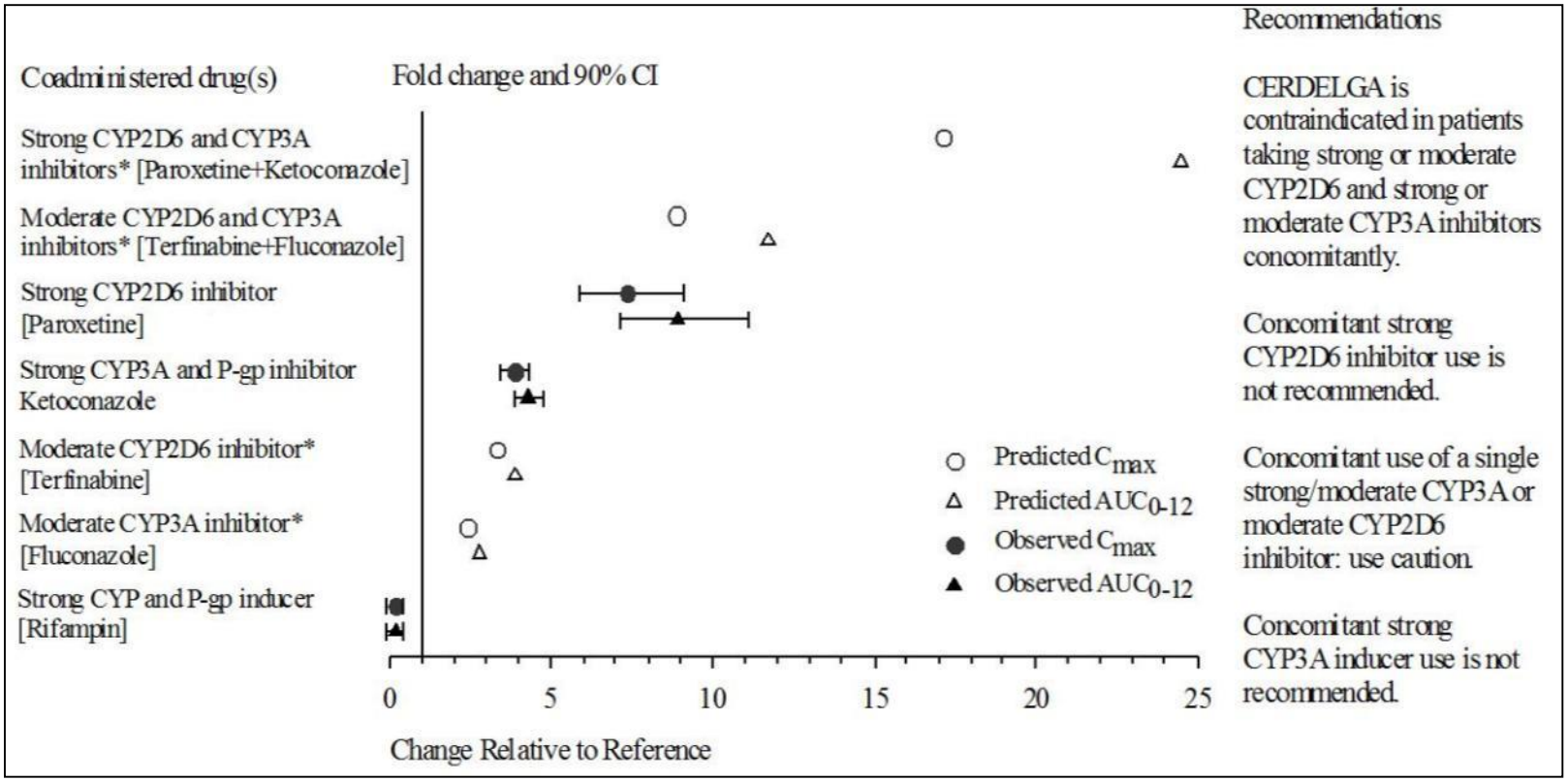
Shi, Clin Pharmacol Ther, 2015

What is ruxolitinib exposure change with moderate CYP3A AND strong CYP2C9 inhibitor fluconazole?

PBPK in Ruxolitinib Label

	Original	Revised (July 2014)
Highlight	Strong CYP3A4 Inhibitors: Reduce Jakafi starting dose to 10 mg twice daily for patients with a platelet count greater than or equal to 100 X 10^9/L and concurrent use of strong CYP3A4 inhibitors.	• Strong CYP3A4 Inhibitors **or Fluconazole: Reduce, interrupt, or discontinue Jakafi doses as recommended. (2.7) (7.1). Avoid use of Jakafi with fluconazole doses greater than 200 mg.**
Section 7.1	Ruxolitinib is predominantly metabolized by CYP3A4.	Ruxolitinib is metabolized by CYP3A4 **and to a lesser extent by CYP2C9.**
	Mild or moderate CYP3A4 inhibitors: There was an 8% and 27% increase in the Cmax and AUC of ruxolitinib, respectively, with Jakafi administration (10 mg single dose) following erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for 4 days, compared to receiving Jakafi alone in healthy subjects. The change in the pharmacodynamic marker, pSTAT3 inhibition was consistent with the corresponding exposure information. No dose adjustment is recommended when Jakafi is coadministered with mild or moderate CYP3A4 inhibitors (eg, erythromycin).	**Fluconazole**: The AUC of ruxolitinib **is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and CYP2C9 inhibitor fluconazole** at doses of 100 mg to 400 mg once daily, respectively [see Pharmacokinetics (12.3)]. **Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [see Dosage and Administration (2.7)].**
Link	*http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202192lbl.pdf*	*http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202192**s006**lbl.pdf*

What are exposure changes with various CYP inhibitors in subjects with different CYP2D6 genotypes?



Applicant's draft proposal in managing DDI in non-PMs

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf

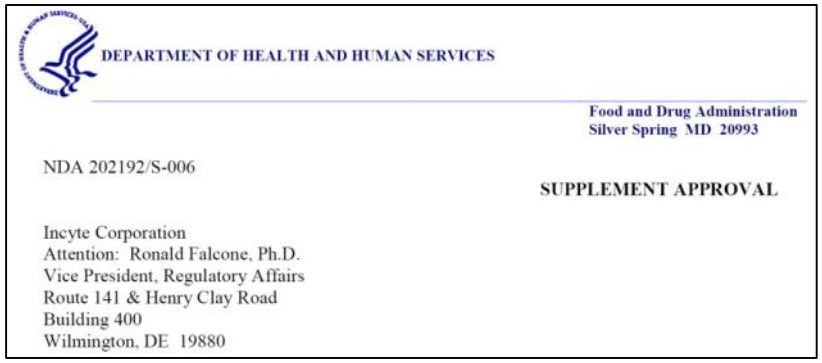
What is ruxolitinib exposure change with moderate CYP3A AND strong CYP2C9 inhibitor fluconazole?

Predicting Drug–Drug Interactions Involving Multiple Mechanisms Using Physiologically Based Pharmacokinetic Modeling: A Case Study With Ruxolitinib

JG Shi[1], G Fraczkiewicz[2], WV Williams[1] and S Yeleswaram[1]

Clin Pharmacol Ther, 2015

"…6 ruxolitinib phase II/III clinical trials, there were 18 courses of ***ruxolitinib/fluconazole*** *concomitant medication found, of which 6 courses (33%) had either ruxolitinib dose reduction or temporary dose-hold due to worsening cytopenias (mainly thrombocytopenia)"*



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192/S-006

SUPPLEMENT APPROVAL

Incyte Corporation
Attention: Ronald Falcone, Ph.D.
Vice President, Regulatory Affairs
Route 141 & Henry Clay Road
Building 400
Wilmington, DE 19880

"… the Dosage and Administration section has been updated to include dose modifications for patients who are on a stable dose of Jakafi® and then start treatment with a strong CYP3A4 inhibitor ***or fluconazole****."*

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/202192Orig1s006ltr.pdf

What are STEADY STATE exposure with CYP3A modulators under different ceritinib doses?

PBPK Predicted steady state Ceritinib AUC (μg/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**

- **Prediction shows similar ceritinib exposure in the presence of ketoconazole when dose is reduced by ~30 %**
- **After single dose ceritinib, observed AUC ratio with ketoconazole was 3-fold**

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