Stanford University SPARK
(Translational Research Program)
September 23, 2015

Regulatory and Scientific Challenges for Drug-Drug Interactions

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Office of Clinical Pharmacology, OTS, CDER, FDA

Drug Interactions
- One Survey -

- National survey of 3005 community-residing older adults (>57 YO) in US
- 80% of individuals takes ≥ 1 medical product (prescription, OTC, supplement)
- 50% takes at least 5 medical products
- 30% takes at least 5 prescription drugs

→ 1/25 at risk of major drug-drug interactions

Qato DM, et al, JAMA 2008; 300:2867-2878.

Drug Interactions

Potential Major Medication Interactions by Age and Gender*

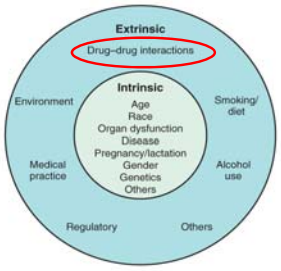
Medication Interaction†	Interactions, Weighted No.						Potential Interaction Effect
	Age 57–64 y (n = 1016)		Age 65–74 y (n = 1082)		Age 75–85 y (n = 878)	Total (N = 2976)	
	Men (n = 525)	Women (n = 491)	Men (n = 543)	Women (n = 539)	Men (n = 377)	Women (n = 501)	
Prescription-prescription							
Albuterol-atenolol	0	1	1	0	1	1	5	Decreased effectiveness
Albuterol-metoprolol	0	1	1	1	2	1	6	Decreased effectiveness
Warfarin-simvastatin	3	2	4	3	7	3	25	Increased risk of bleeding/rhabdomyo
Clopidogrel-warfarin	0	0	0	1	1	1	3	Increased risk of bleeding

Qato DM, et al, JAMA 2008; 300:2867-2878.

- Do we need an updated list such as this one? ("Drug Interaction Checks" enabled as part of the EHR implementation- HealthIT.Gov)
- Which databases? (e.g., the above used micromedex)
- When are we concerned about complex interactions (multiple drugs)?

→ Critical in the mechanistic understanding of these PD- and PK-based interactions and the ability to extrapolate to untested conditions

Many Factors Affect Drug Exposure/Response



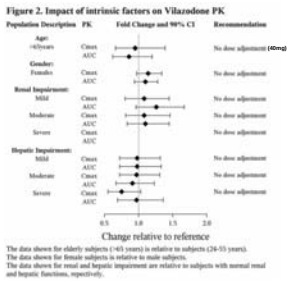
It is critical to evaluate how these factors affect drug exposure/response

Ultimate goal → Optimal dosing for patients with these individual factors

Huang S-M, Temple R, Clin Pharmacol Ther 84: 287-294, 2008

Dose Adjustment (1)
Impact of Intrinsic Factors

- What *intrinsic factors* (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and
- What is the impact of any differences in exposure on efficacy or safety responses?

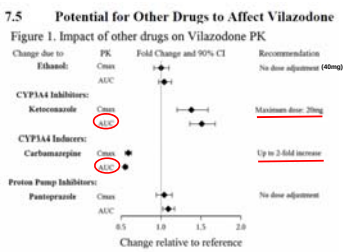


Dose adjusted from the population dose(s) for individual groups of patients with specific intrinsic factors

April 2014 labeling: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022567s011lbl.pdf

Dose Adjustment (2)
Impact of Extrinsic Factors

- What *extrinsic factors* (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or –response?
- What is the impact of any differences in exposure on response?



Dose adjusted from the population dose(s) for individual groups of patients with specific extrinsic factors

April 2014 labeling: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022567s011lbl.pdf

Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or Lei Zhang, 301-796-1633.

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

February 2012
Clinical Pharmacology

What is new?

- Transporters
- Decision trees
- Model-based prediction (mechanistic approaches)
- Phase 2 enzymes
- Therapeutic proteins
- Metabolites

Received public comments

- Reviewed specific comments and revising
- Split into two documents
- Collaborative work ongoing

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm 7 S-M Huang

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm 8 S-M Huang

Classifications

CYP Enzymes	Strong Inhibitors	Moderate inhibitors	Weak inhibitors
	≥ 5-fold increase in AUC	≥ 2 but <5-fold increase in AUC	≥ 1.25 but <2-fold increase in AUC

CYP Enzymes	Strong Inducers	Moderate Inducers	Weak Inducers
	≥ 80% decrease in AUC	50- 80% decrease in AUC	20-50% decrease in AUC

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm;
U Washington drug interaction database
http://www.druginteractioninfo.org/

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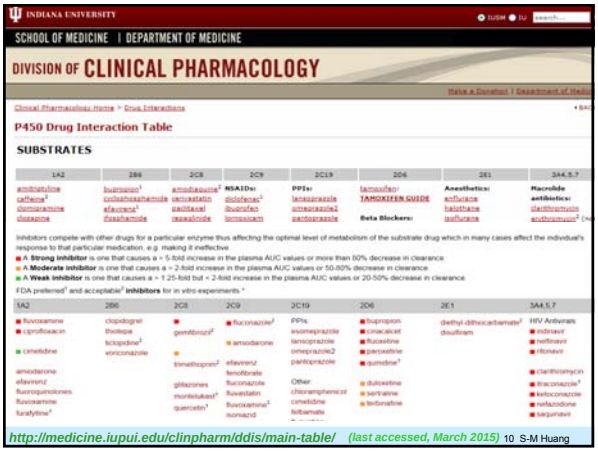

http://medicine.iupui.edu/clinpharm/ddis/main-table/ (last accessed, March 2015) 10 S-M Huang

Dasatinib & CYP3A

2 DOSAGE AND ADMINISTRATION

2.1 Dose Modification

Concomitant Strong CYP3A4 inhibitors: CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) may increase dasatinib plasma concentrations. Grapefruit juice may also increase plasma concentrations of dasatinib and should be avoided.

Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible, is recommended. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease should be considered. Based on pharmacokinetic studies, a dose decrease to 20 mg daily should be considered for patients taking SPRYCEL 100 mg daily. For patients taking SPRYCEL 140 mg daily, a dose decrease to 40 mg daily should be

Drugs at the FDA (Sprycel,"DOSAGE and ADMINSTRATION) 2015 Labeling
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021986s016s017lbledt.pdfhttp://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

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Simeprevir & CYP3A

----------DRUG INTERACTIONS----------

- Co-administration of amiodarone with sofosbuvir in combination with OLYSIO may result in serious symptomatic bradycardia. (5.1)
- Co-administration of OLYSIO with drugs that are moderate or strong inducers or inhibitors of CYP3A may significantly affect the plasma concentrations of simeprevir. The potential for drug-drug interactions must be considered prior to and during treatment. (5.7, 7, 12.3)

→ Therefore co-administration with moderate or strong inducers or inhibitors of CYP3A is not recommended (5.7, 7)

Drugs at the FDA (OLYSIO: HIGHLIGHTS;2015 Labeling
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205123s008lbl.pdf

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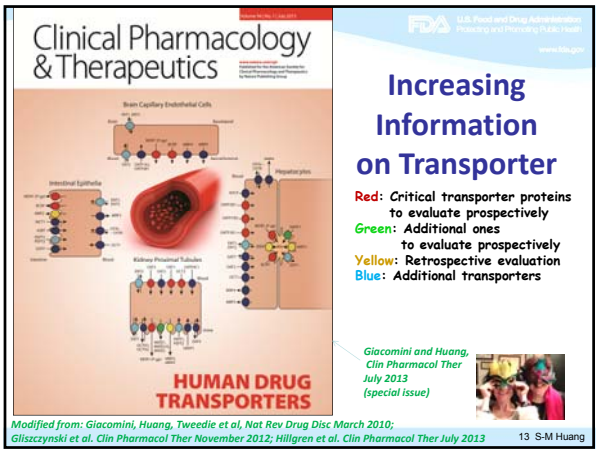
Clinical Pharmacology & Therapeutics
HUMAN DRUG TRANSPORTERS
Increasing Information on Transporter
Red: Critical transporter proteins to evaluate prospectively
Green: Additional ones to evaluate prospectively
Yellow: Retrospective evaluation
Blue: Additional transporters
Giacomini and Huang, Clin Pharmacol Ther July 2013 (special issue)
Modified from: Giacomini, Huang, Tweedie et al, Nat Rev Drug Disc March 2010; Gliszczynski et al. Clin Pharmacol Ther November 2012; Hillgren et al. Clin Pharmacol Ther July 2013
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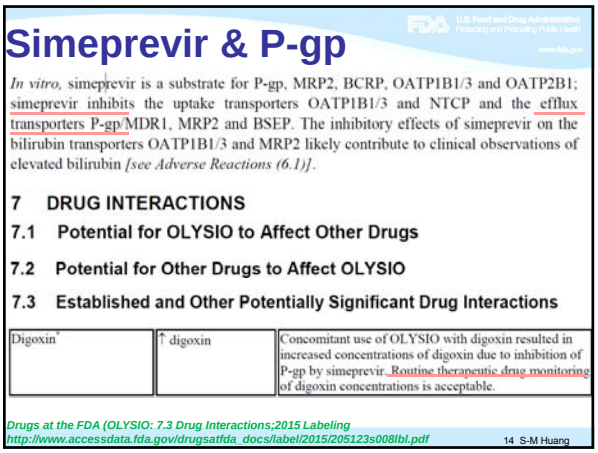
Simeprevir & P-gp
In vitro, simeprevir is a substrate for P-gp, MRP2, BCRP, OATP1B1/3 and OATP2B1; simeprevir inhibits the uptake transporters OATP1B1/3 and NTCP and the efflux transporters P-gp/MDR1, MRP2 and BSEP. The inhibitory effects of simeprevir on the bilirubin transporters OATP1B1/3 and MRP2 likely contribute to clinical observations of elevated bilirubin [see Adverse Reactions (6.1)].
7 DRUG INTERACTIONS
7.1 Potential for OLYSIO to Affect Other Drugs
7.2 Potential for Other Drugs to Affect OLYSIO
7.3 Established and Other Potentially Significant Drug Interactions
Digoxin
↑ digoxin
Concomitant use of OLYSIO with digoxin resulted in increased concentrations of digoxin due to inhibition of P-gp by simeprevir. Routine therapeutic drug monitoring of digoxin concentrations is acceptable.
Drugs at the FDA (OLYSIO: 7.3 Drug Interactions;2015 Labeling
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205123s008lbl.pdf
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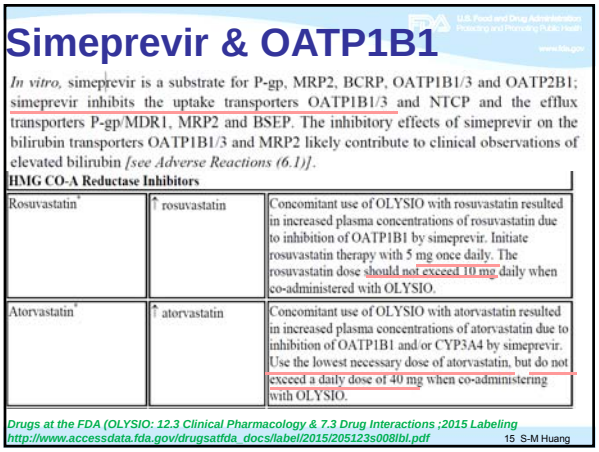
Simeprevir & OATP1B1
In vitro, simeprevir is a substrate for P-gp, MRP2, BCRP, OATP1B1/3 and OATP2B1; simeprevir inhibits the uptake transporters OATP1B1/3 and NTCP and the efflux transporters P-gp/MDR1, MRP2 and BSEP. The inhibitory effects of simeprevir on the bilirubin transporters OATP1B1/3 and MRP2 likely contribute to clinical observations of elevated bilirubin [see Adverse Reactions (6.1)].
HMG CO-A Reductase Inhibitors
Rosuvastatin
↑ rosuvastatin
Concomitant use of OLYSIO with rosuvastatin resulted in increased plasma concentrations of rosuvastatin due to inhibition of OATP1B1 by simeprevir. Initiate rosuvastatin therapy with 5 mg once daily. The rosuvastatin dose should not exceed 10 mg daily when co-administered with OLYSIO.
Atorvastatin
↑ atorvastatin
Concomitant use of OLYSIO with atorvastatin resulted in increased plasma concentrations of atorvastatin due to inhibition of OATP1B1 and/or CYP3A4 by simeprevir. Use the lowest necessary dose of atorvastatin, but do not exceed a daily dose of 40 mg when co-administering with OLYSIO.
Drugs at the FDA (OLYSIO: 12.3 Clinical Pharmacology & 7.3 Drug Interactions ;2015 Labeling
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205123s008lbl.pdf
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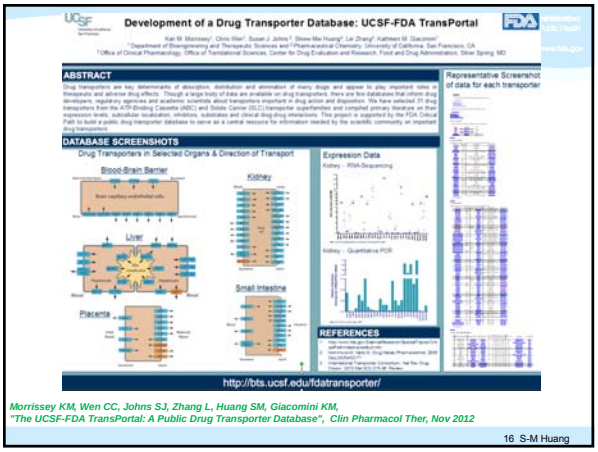
Development of a Drug Transporter Database: UCSF-FDA TransPortal
ABSTRACT
DATABASE SCREENSHOTS
Drug Transporters in Selected Organs & Direction of Transport
Blood-Brain Barrier
Kidney
Liver
Small Intestine
Placenta
Expression Data
REFERENCES
Representative Screenshot of data for each transporter
http://bts.ucsf.edu/fdatransporter/
Morrissey KM, Wen CC, Johns SJ, Zhang L, Huang SM, Giacomini KM,
"The UCSF-FDA TransPortal: A Public Drug Transporter Database", Clin Pharmacol Ther, Nov 2012
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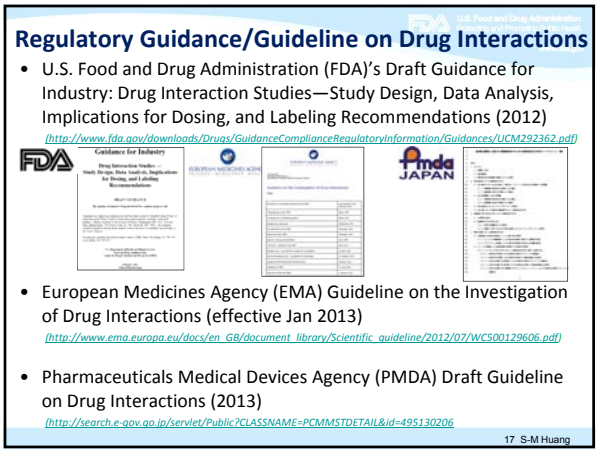
Regulatory Guidance/Guideline on Drug Interactions
U.S. Food and Drug Administration (FDA)'s Draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (2012)
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)
European Medicines Agency (EMA) Guideline on the Investigation of Drug Interactions (effective Jan 2013)
(http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)
Pharmaceuticals Medical Devices Agency (PMDA) Draft Guideline on Drug Interactions (2013)
(http://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495130206
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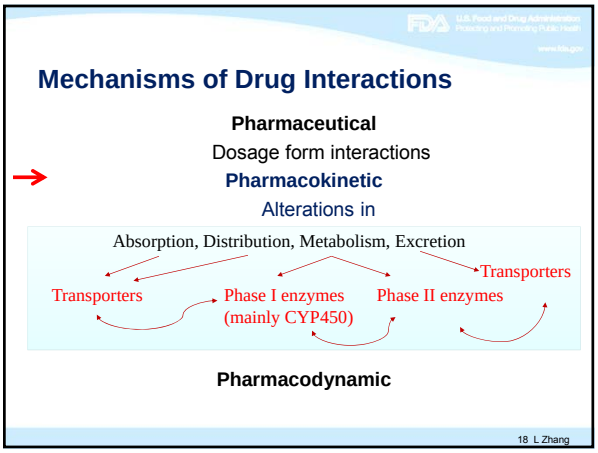
Mechanisms of Drug Interactions
Pharmaceutical
Dosage form interactions
Pharmacokinetic
Alterations in
Absorption, Distribution, Metabolism, Excretion
Transporters
Phase I enzymes (mainly CYP450)
Phase II enzymes
Transporters
Pharmacodynamic
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Major PK Drug Interactions Mechanisms

Inhibition
or
Induction

of
Metabolizing Enzymes and/or *Transporters*

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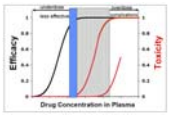
Clinical implications of inhibition and induction of drug metabolizing enzymes or transporters



Perpetrator (Inhibitor or Inducer)

Drug 2

Metabolizing enzyme or transporter

Drug 1

Victim (Substrate)

	Exposure (AUC or C_{max})	
	Induction	Inhibition
Drug 1 (Parent)	↓	↑
Concern	EFFICACY	SAFETY

AUC: Area under the curve plasma concentration-time profile
C_{max}: Maximum plasma concentration

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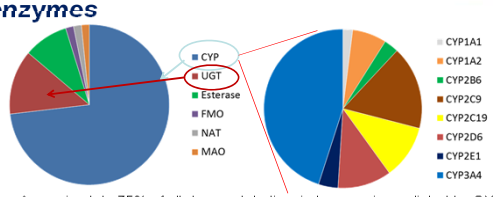
Drugs are metabolized by a variety of *enzymes*



- Approximately 75% of all drug metabolism in humans is mediated by CYP (or P450) enzymes (Phase I enzyme)
- Of the more than 50 CYP enzymes
  - CYP (1A2, 2B6, 2C8, 2C19, 2C9, 2D6, 3A4) account for >95% of xenobiotic metabolism
  - CYP3A is the major CYP, ~50% of drugs were metabolized by CYP3A

Williams et al. Drug Metab Dispos, 2004; Guengerich. Chem Res Toxicol, 2008

UGT: UDP-Glucuronosyltransferase

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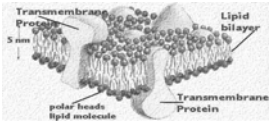
Transporters

- Transporters are transmembrane proteins that are inserted in cell membranes to translocate substances across the membrane



- More than 400 transporters are identified
  ~30 Contribute to the efficacy and safety of drugs
- Two super families
  - ABC Transporters (~50 families) (ATP-binding cassette)
    - e.g., P-glycoprotein (P-gp, MDR1)
  - SLC Transporters (~350 families) (Organic Solute Carrier Transporters)
    - e.g., Organic anion transporting polypeptides (OATPs)

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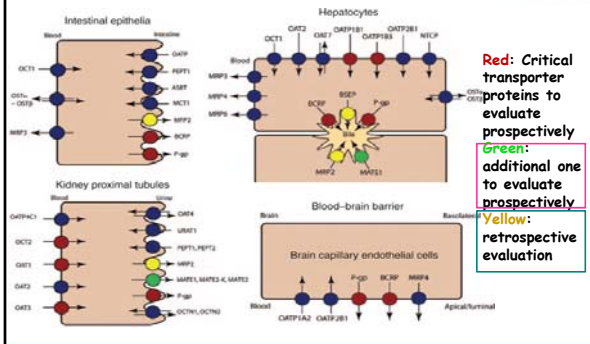
Transporters of Clinical Importance



Red: Critical transporter proteins to evaluate prospectively

Green: additional one to evaluate prospectively

Yellow: retrospective evaluation

Zamek-Gliszczynski et al. Clin Pharmacol Ther November 2012

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Drug Interaction Potential Evaluation

Other drug's effect on NME:

- Whether an NME is a substrate for
  - CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A
  - P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3
  - MATEs

NME's effect on other drug:

- Whether an NME is an inhibitor for
  - CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A and P-gp
  - P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3
  - MATEs
- Whether an NME is an inducer for
  - CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A
  - P-gp (evaluate with CYP3A)

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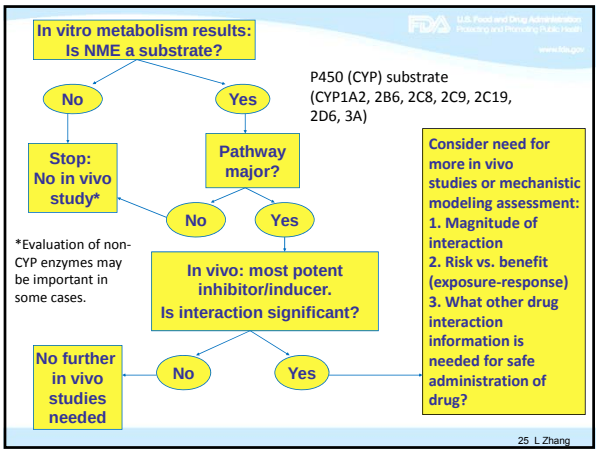

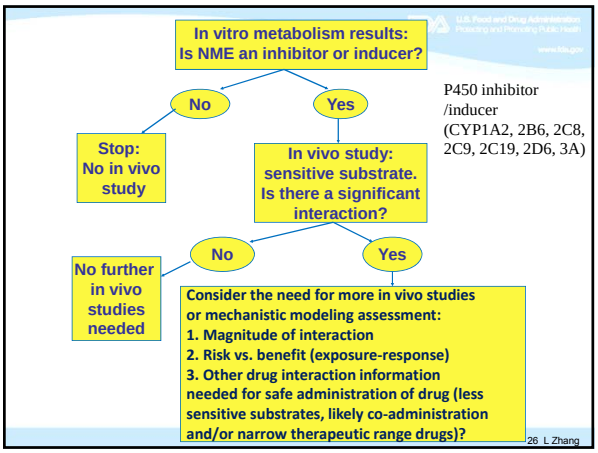

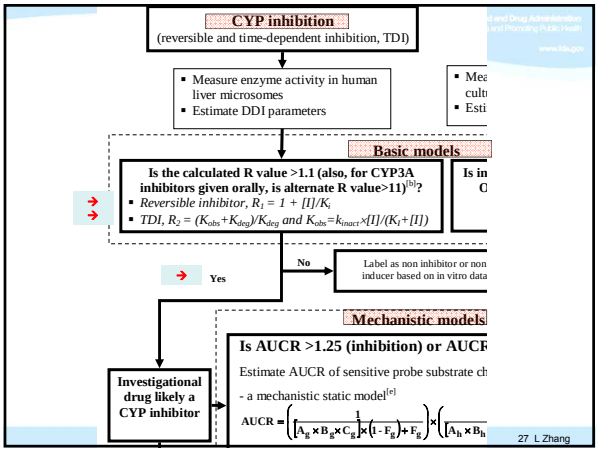

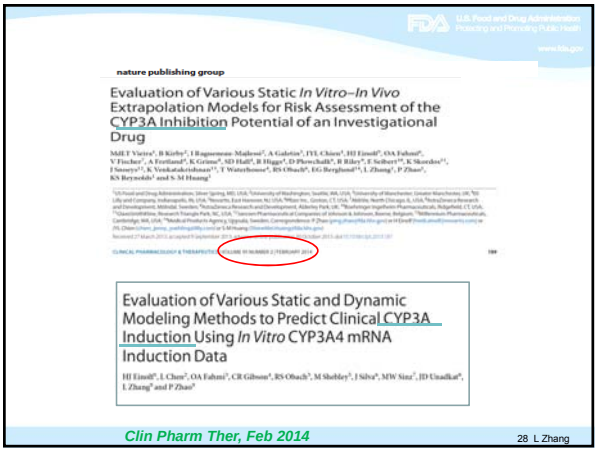

NME as a Substrate

Does the drug level depend on a given transporter?

- Route of elimination
  - Hepatic major
  - Renal major
  - Rate limiting step
- Physicochemical properties of the drug
  - e.g., BCS or BDDCS
- Structure
  - e.g., OATs for anions and OCTs for cations
  - Caveat: some cations transported by OATs (cimetidine, sitagliptin)
  - Similarity to known substrates
- In vitro assays → A mechanistic understanding of the clearance of the drug
  - Sources of variability and potential for DDI
- Other factors to consider for DDI studies:
  - Safety margins, therapeutic range, co-mediations that are known transporter inhibitors in the indicated patient populations, is there known polymorphism of the transport pathway?

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NME as an Inhibitor

Does the drug affect a given transporter?

- Inhibitors can be substrates or non-substrates for a given transporter.
- The need to study DDI depends on whether drugs are likely co-administered with known substrates of major human transporters.
- Other factors to consider: indications, and whether the NME may affect other pathways.

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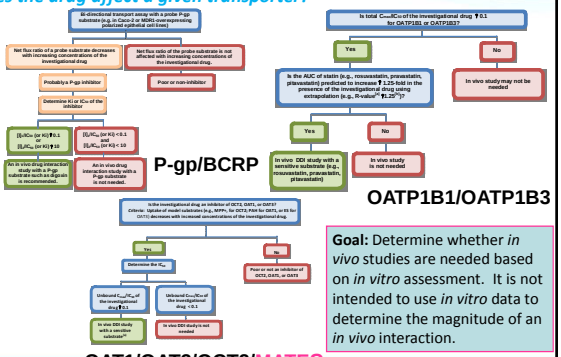
Evaluation of NME as an Inhibitor for Transporters

Does the drug affect a given transporter?



P-gp/BCRP

OATP1B1/OATP1B3

OAT1/OAT3/OCT2/MATES

Goal: Determine whether *in vivo* studies are needed based on *in vitro* assessment. It is not intended to use *in vitro* data to determine the magnitude of an *in vivo* interaction.

FDA 2012 Draft DDI Guidance

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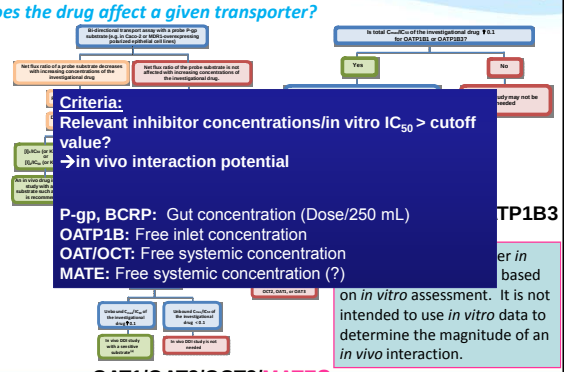
Evaluation of NME as an Inhibitor for Transporters

Does the drug affect a given transporter?



Criteria:
Relevant inhibitor concentrations/in vitro IC_{50} > cutoff value?
→in vivo interaction potential

P-gp, BCRP: Gut concentration (Dose/250 mL)
OATP1B: Free inlet concentration
OAT/OCT: Free systemic concentration
MATE: Free systemic concentration (?)

TP1B3

er *in* based on *in vitro* assessment. It is not intended to use *in vitro* data to determine the magnitude of an *in vivo* interaction.

OAT1/OAT3/OCT2/MATES

FDA 2012 Draft DDI Guidance

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Recommendations related to transporters

- Recommended sponsors to evaluate major transporters as described in the ITC paper
- Continuing dialog with industry, academia, other regulatory agencies
- Consulting and collaborating with experts in the field (ITC; IQC and academia, CYP inhibition and induction workgroups as an example; sabbatical scientists)
- FDA OCP Transporter Scientific Interest Group continuing research to define/refine in vitro criteria in determining the need to conduct in vivo studies

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In Vitro Methodologies

- *In vitro* assessments are critical to help determine the clearance mechanism and DDI potential.
- "Best Practice" of *in vitro* assay methodology is needed to ensure quality of *in vitro* assessments (e.g., reliable, reproducible and validated).
- The sources of the variability need to be understood, e.g.,
  - Different laboratories
  - Different in vitro cell systems
  - Different substrate/inhibitor
- The processes need to be standardized in each laboratory.
  - Each laboratory may develop criteria internally with known positive and negative controls ("calibration")

Need best practices and standardized approaches

Brouwer KL, et al. Clin Pharm Ther. July 2013.

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Challenges and Gaps between In Vitro and In Vivo --Basic Models for Transporters

P-gp (using $[I]_1$ or $[I]_2$ /IC_{50})
Etravirine or Maraviroc / Digoxin: False positive
→Concomitant induction?
Talinolol / Digoxin: False negative prediction

OATP1B (using Free $[I]_{inlet}$ /IC_{50} , R)
Gemfibrozil / Pitavastatin: False negative
-> Gemfibrozil glucuronide also inhibits OATP1B

Teriflunomide / Rosuvastatin: False negative if only consider OATP1B.
-> BCRP inhibition also involved.

OCT2 (using Free C_{max} /IC_{50})
Dolutegravir / Metformin: False negative using one IC_{50} reported (~20 fold difference from two sources) → non-specific binding?

Considerations:
- Substrate dependent inhibition
- Uncertainty about intracellular concentrations
- Non-specific binding
- Multiple processes (absorption/distribution/excretion)
- Multiple transporters involved
- Transporters-Enzymes Interplay
- Metabolite as inhibitor
- Mechanistic discrepancy

.....

Courtesy: X. Yang

Zhang L, et al. Xenobiotica (2008); Agarwal S, et al. J Clin Pharmacol (2013)
Lepist EI, et al. Kidney Int. (2014; Zong J, et al. J Int AIDS Soc.(2014); TIVICAY Prescribing Information

FDA Model-Based Framework -Mechanistic consideration of individual pathways

Investigational Drug as a Perpetrator (Inhibitor or Inducer)

- Basic
- Mechanistic, static
- Mechanistic, dynamic (including PBPK)

→ Need to consider all mechanisms (enzyme and transporter) to understand the clearance pathway and to be able to describe PK (and PD) variability

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Complexity of Transporter DDI

- **Associated with both drug ADME and DDI potential**
  - *PK of substrate and interacting drug*
  - *DDI mechanism(s) of interacting drug*
- **At all levels of physiology**
  - *Organ/tissue level (≥ 1 transporter, in ≥ 1 organ)*
  - *Cell level (differential expression, uptake and efflux, ≥ 1 cell type)*
  - *Subcellular system*
- **Enzyme-transporter-(permeability) interplay**

Need knowledge integration and mechanistic modeling of local as well as whole body kinetic events

Zhao P, AAPS 2012

37 L Zhang

Physiologically-based Pharmacokinetics Modeling (PBPK)

38 S-M Huang

Janet Woodcock, MD, CDER Director
FDA PBPK Workshop, March 2014

Drug Development..

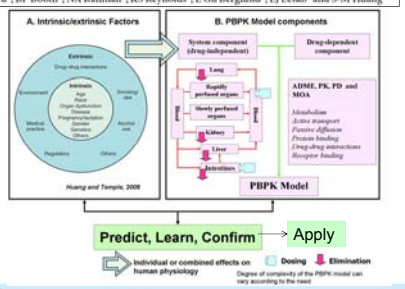
Progressive Reduction of Uncertainty

http://www.fda.gov/drugs/newsevents/ucm387698.htm

39 S-M Huang

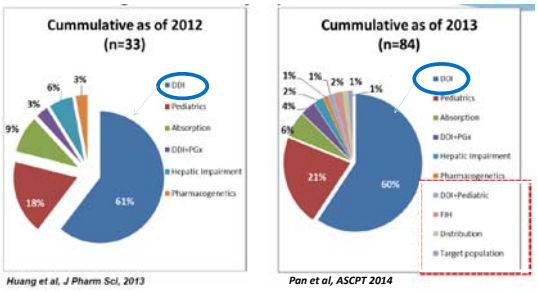
Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review

P Zhao[1], L Zhang[1], JA Grillo[1], Q Liu[1], JM Bullock[1], YJ Moon[1], P Song[1], SS Brar[1], R Madabushi[1], TC Wu[1], BP Booth[1], NA Rahman[1], KS Reynolds[1], E Gil Berglund[2], LJ Lesko[1] and S-M Huang[1]



Clin Pharmacol Ther, 2011

Regulatory Submissions with PBPK Data



Huang et al, J Pharm Sci, 2013 *Pan et al, ASCPT 2014*

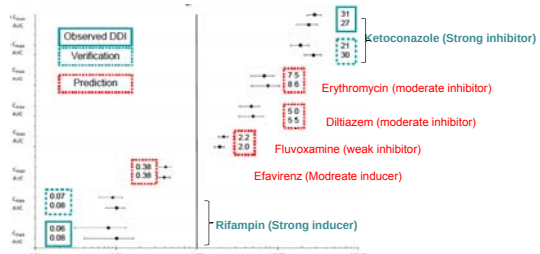
- **Increased use of PBPK by drug developers**
- **Majority of the cases were related to DDI (~60%)**

P Zhao, FDA PBPK Workshop March 2014; http://www.fda.gov/drugs/newsevents/ucm387698.htm

41 S-M Huang

PBPK & Drug Interactions Example: Ibrutinib

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



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

P Zhao, FDA PBPK Workshop March 2014

42 S-M Huang

Ibrutinib Labeling

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

P Zhao, FDA PBPK Workshop March 2014

Eliglustat and CYP2D6

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

CERDELGA is a glucosylceramide synthase inhibitor indicated for the long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test. (1)

Limitations of Use:

- CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect (1)
- A specific dosage cannot be recommended for CYP2D6 indeterminate metabolizers (1)

DOSAGE AND ADMINISTRATION

- Select patients using an FDA-cleared test for determining CYP2D6 genotype (2.1)
- CYP2D6 EMs or IMs: 84 mg orally twice daily (2.2)
- CYP2D6 PMs: 84 mg orally once daily (2.2)

DRUG INTERACTIONS

- CYP2D6 IMs and PMs taking moderate CYP3A inhibitors: not recommended (7.1)
- CYP2D6 PMs taking weak CYP3A inhibitors: not recommended (7.1)
- CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors and CYP2D6 EMs taking strong or moderate CYP3A inhibitors: reduce the dosage to 84 mg once daily (2.2, 7.1)

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

Confidence, Limitation and Challenges of PBPK in DDI Prediction

Application		Level of confidence	Limitations and challenges
DDI prediction	Involving reversible CYP inhibition alone or CYP induction alone	Moderate to high	Accurate in vitro estimation of fraction metabolized by P450, especially when non-P450 enzyme involved. The i.v. clearance and mass balance data for victim (substrate) not readily available at early stages of drug development. Uncertainty in CYP phenotyping and measured in vitro inhibitor constant (K_i).
	Involving time-dependent CYP inhibition	Low to moderate	In addition to caveats above, there is a general over-prediction of in vivo DDI from in vitro data.
	Involving combined reversible, time-dependent inhibition, and induction of CYPs	Low	Difficult to evaluate mechanisms when multiple processes are involved because of limited clinical data.
	Involving modulation of non-CYP pathways	Low to moderate	Lack of prospective evaluation.
	Involving apical active transport	Moderate	Not all in vitro assays provide appropriate inhibition constants.
	Involving basolateral active transport	Low	As above. Predicting intracellular inhibitor concentrations from uptake and efflux transport activity is challenging.

HM Jones et al, Clin Pharmacol Ther March 2015

EDITORIAL

Physiologically Based Pharmacokinetics Is Impacting Drug Development and Regulatory Decision Making

M Rowland[1,2], LJ Lesko[3] and A Rostami-Hodjegan[4,5]*

PERSPECTIVE

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

C Wagner[1], P Zhao[1]*, Y Pan[2], V Hsu[1], J Grillo[1], SM Huang[1] and V Sinha[1]*

ORIGINAL ARTICLE

Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation

T Shepard[1]*, G Scott[2], S Cole[1], A Nordmark[3] and F Bouzom[4]

Clin Pharmacol Ther-Pharmacometrics Sys Pharmacol 2015

Summary

- Drug interactions is one critical factor in determining the best drug or dose for individual patients
- Recent development of molecular biology has improved understanding of the mechanisms behind drug-drug, drug-juice, drug- supplement interactions
- Careful evaluation of drug interaction potential during drug development provides key labeling information for patients
- FDA and other regulatory agencies have provided guidance on the evaluation of drug interactions
- Continual collaborations among stake holders are key to useful information for patients

References

FDA Drug Development and Drug Interactions Website;
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Genomics at the FDA:
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm

Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Clinical Pharmacology Guidance for industry:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

For Consumers:
http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm212747.htm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OTS, CDER, FDA
FDA White Oak
Bldg 51& bldg 64 —Where OCP resides
49 S-M Huang


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