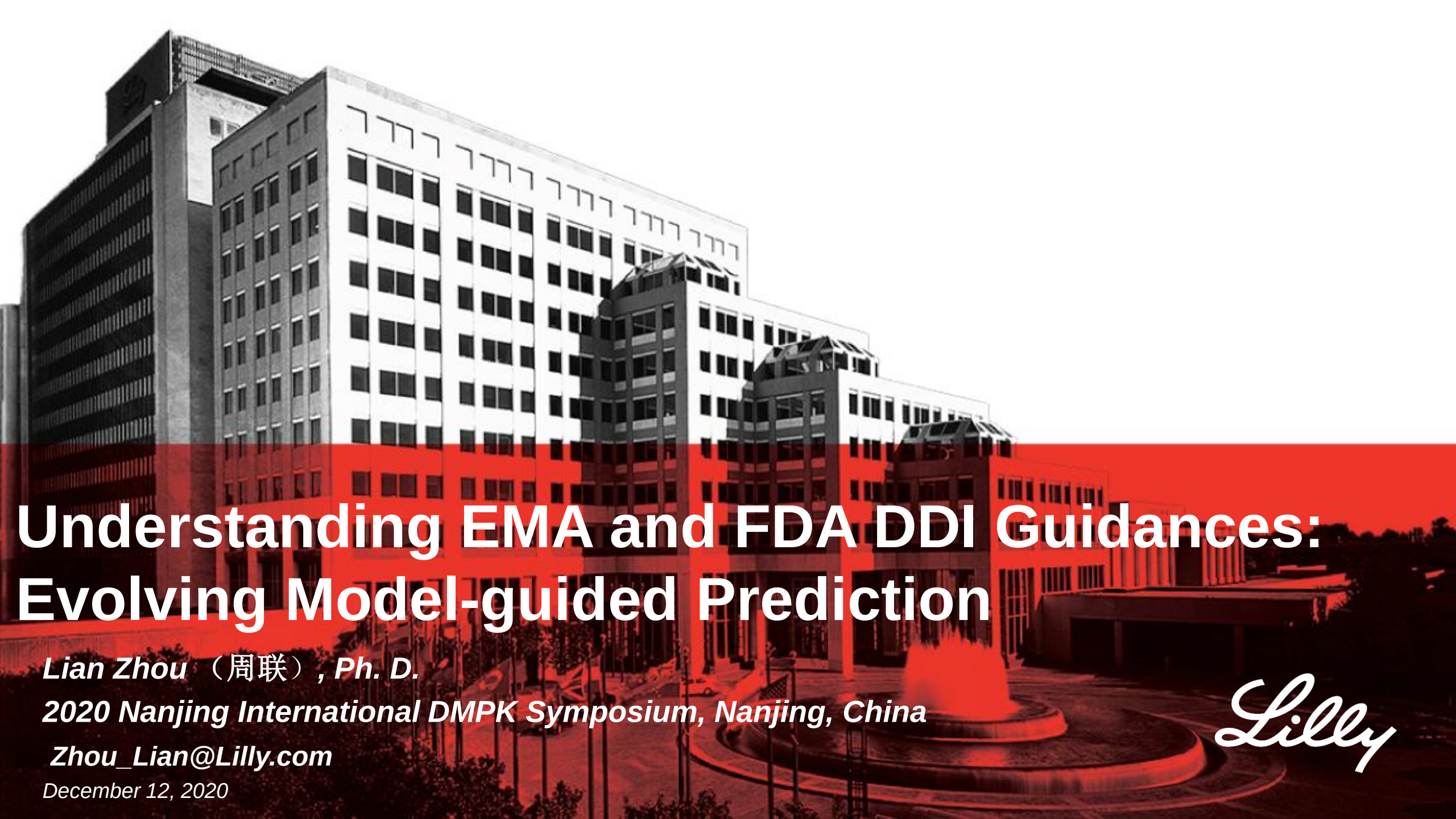

Understanding EMA and FDA DDI Guidances: Evolving Model-guided Prediction

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Presentation Overview

Introduction

- Evolving EMA and FDA Drug-Drug Interaction (DDI) Guidance

Model-guided DDI Prediction（模型指导下的DDI预测）

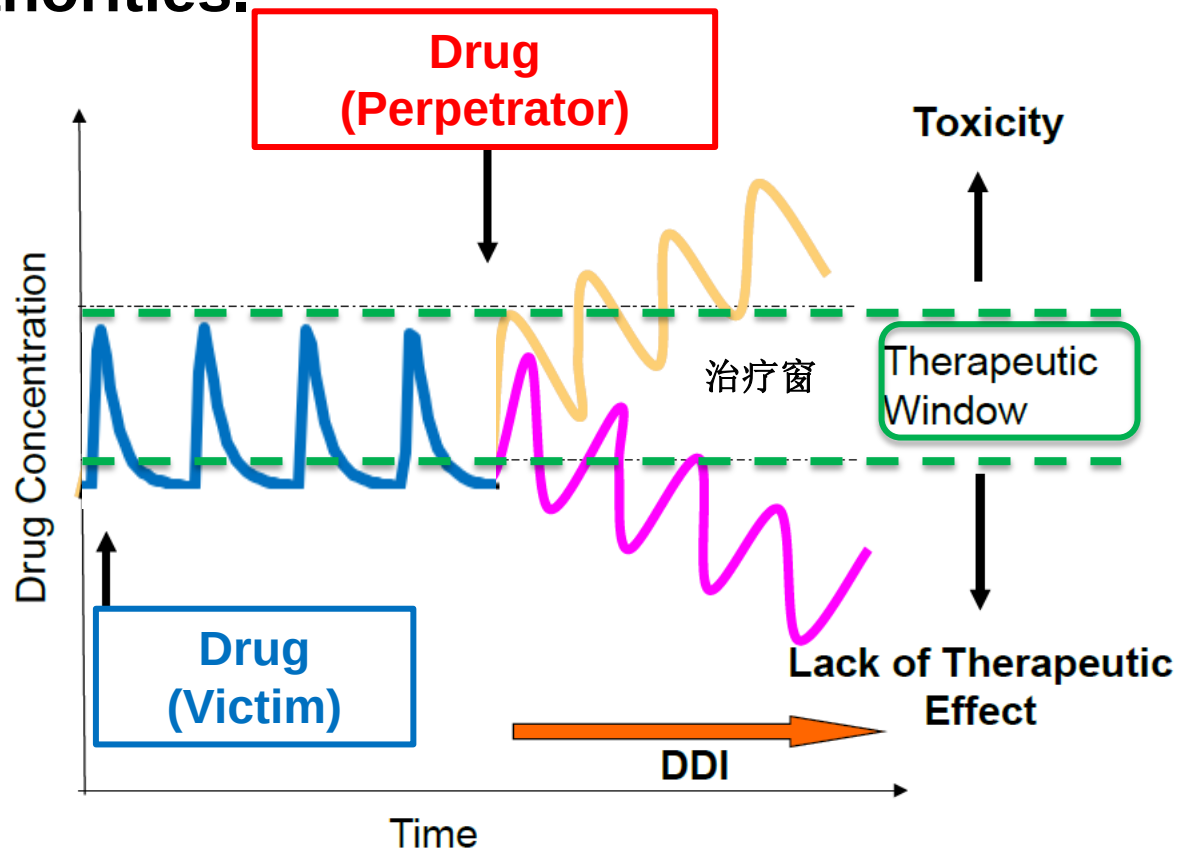
- In vitro data integration
- Case study
  - Reverse translation: PBPK model-guided challenging of early assumptions leading to additional in vitro DDI studies

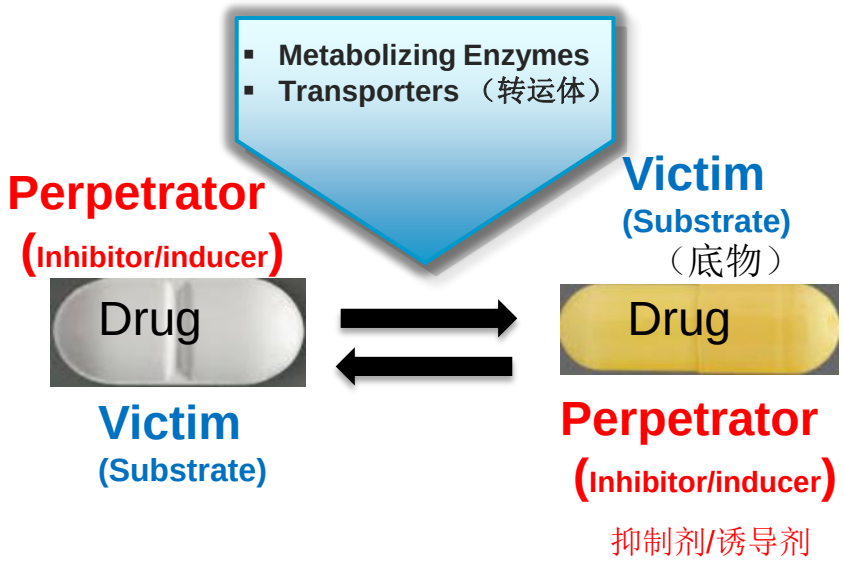
DDI Potential of Metabolites （代谢产物的DDI）

Aldehyde oxidase (AO) and carboxylesterase (CES)

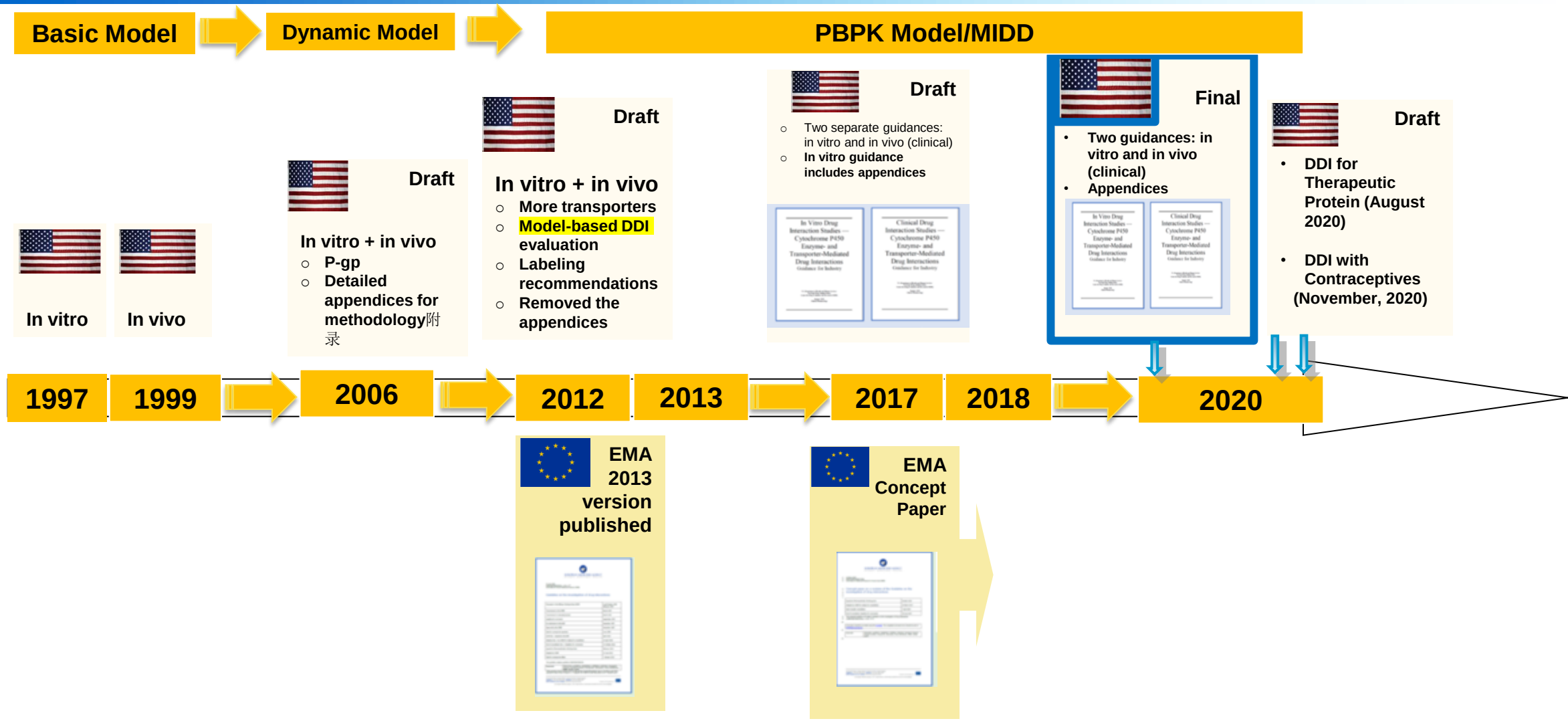
Why DDI?

DDI may increase or decrease plasma/tissue drug exposure which lead to significant toxic consequences or therapeutic incompetence. DDI is major concern for pharmaceutical industry and regulatory authorities.





Evolution of FDA and EMA DDI Guidance/Guideline



2020 DDI Guidances: Scope

- Scope: Evaluation of cytochrome P450 (CYP) or transporter mediated DDIs
- Topics not addressed in the 2020 guidances
  - Therapeutic protein DDIs
  - Gastric pH change-dependent DDIs
  - DDIs involving oral contraceptives
  - Protein displacement-mediated DDIs
  - Phase 2 enzyme-mediated DDIs
  - Pharmacodynamic DDIs
  - Detailed guidance on product labeling language

Source: FDA workshop 2020

EMA 2013 DDI Guideline Scope

In contrast to FDA

- **additional drug interactions**
  - **Drug-food interaction**
  - **DDI on herbal medicinal product**

- **Topics not addressed in the 2013 guidelines**
  - **CYP enzymes other than the top 7 CYPs**
    - **Top 7: CYP1A2, CYP2B6, CYP2C8, CYP2C9,CYP2C19, CYP2D6, CYP3A4/5**

Metabolizing Enzymes

	EMA (2013)	FDA (2020)
Target Cytochrome P450 isozymes	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A	Top 7: CYP1A2, CYP2B6, CYP2C8, CYP2C9,CYP2C19, CYP2D6, CYP3A4/5, Additional 4: CYP2A6, CYP2J2, CYP4F2, CYP2E1
Target metabolic enzymes other than P450s	醛氧化酶 羧酸酯酶	aldehyde oxidase (AO, 2020 new) carboxylesterase (CES, 2020 new) monoamine oxidase (MAO), xanthine oxygenase (XO), flavin monooxygenase (FMO),
	alcohol/aldehyde dehydrogenase (ADH/ALDH), uridine diphosphate-glucuronosyltransferase (UGTs), sulfotransferases (SULTs), glutathione transferases (GSTs)	ADH/ALDH, UGTs, SULTs,

Transporters

- **P-gp and BCRP** (**Efflux Transporters**, in intestine, liver, kidney, blood-brain barrier, etc.)
  When intestinal absorption, biliary excretion, or renal active secretion is likely to be a major cause of the variability in a drug pharmacokinetics and response

- **OATP1B1 and OATP1B3** (**Hepatic uptake transporters**)
  Hepatic/biliary elimination is significant pathway of clearance and
  Physiochemical properties and preclinical findings (e.g., anion at physiological pH, low passive permeability, high hepatic concentrations relative to other tissues)

- **OAT1, OAT3, OCT2, MATE1, MATE2/K** (**Renal uptake or efflux transporters)**
  Significant active renal secretion (≥ 25% of systemic clearance of the drug) or concerns about renal toxicity

Mechanisms and Locations of DDIs

Metabolism-based

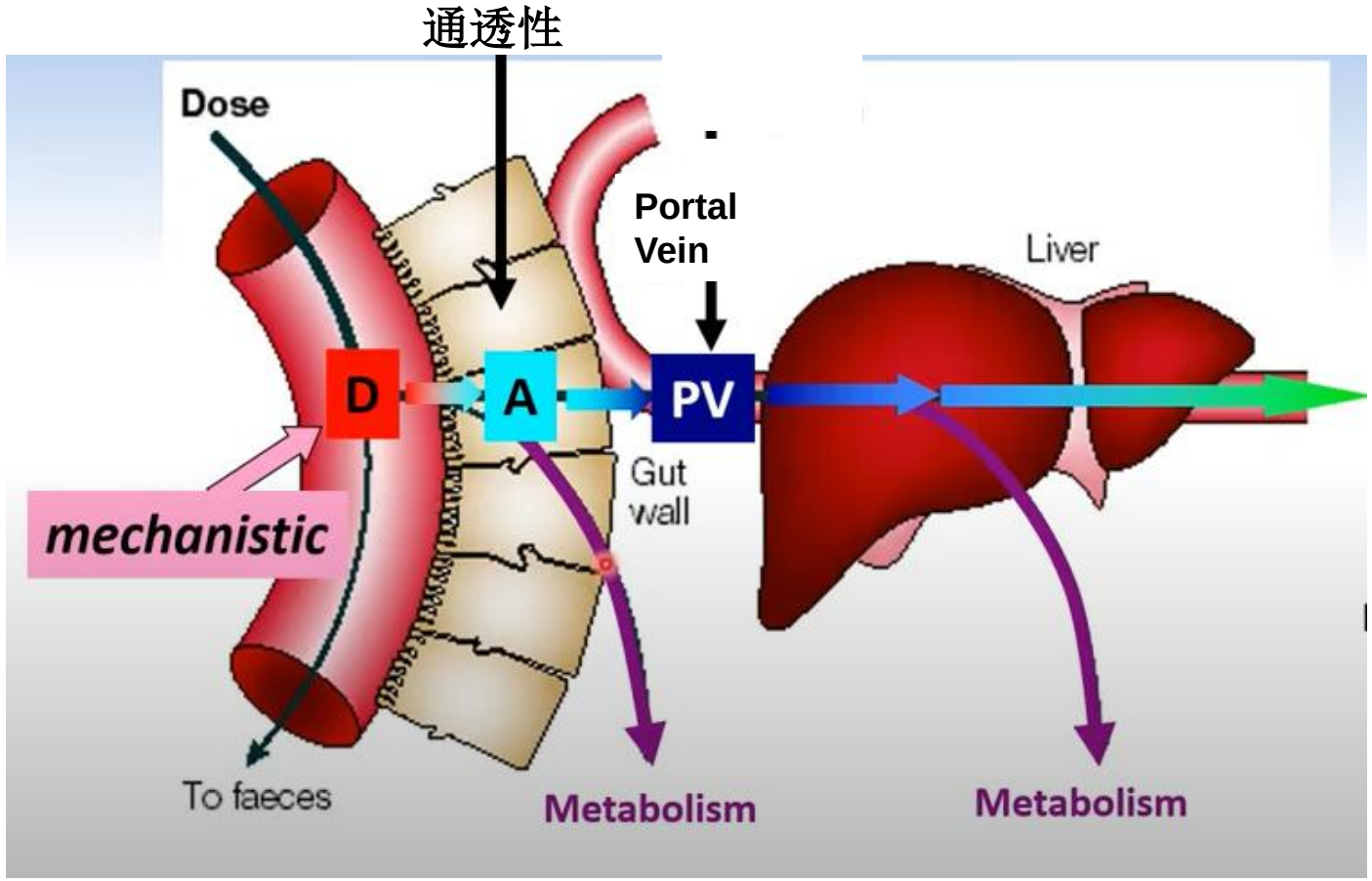
- Inhibition-mediated
  - Reversible inhibition
  - Time-dependent inhibition
- Induction-mediated

Transport-based

- Inhibition-mediated
- Induction-mediated

Absorption-based

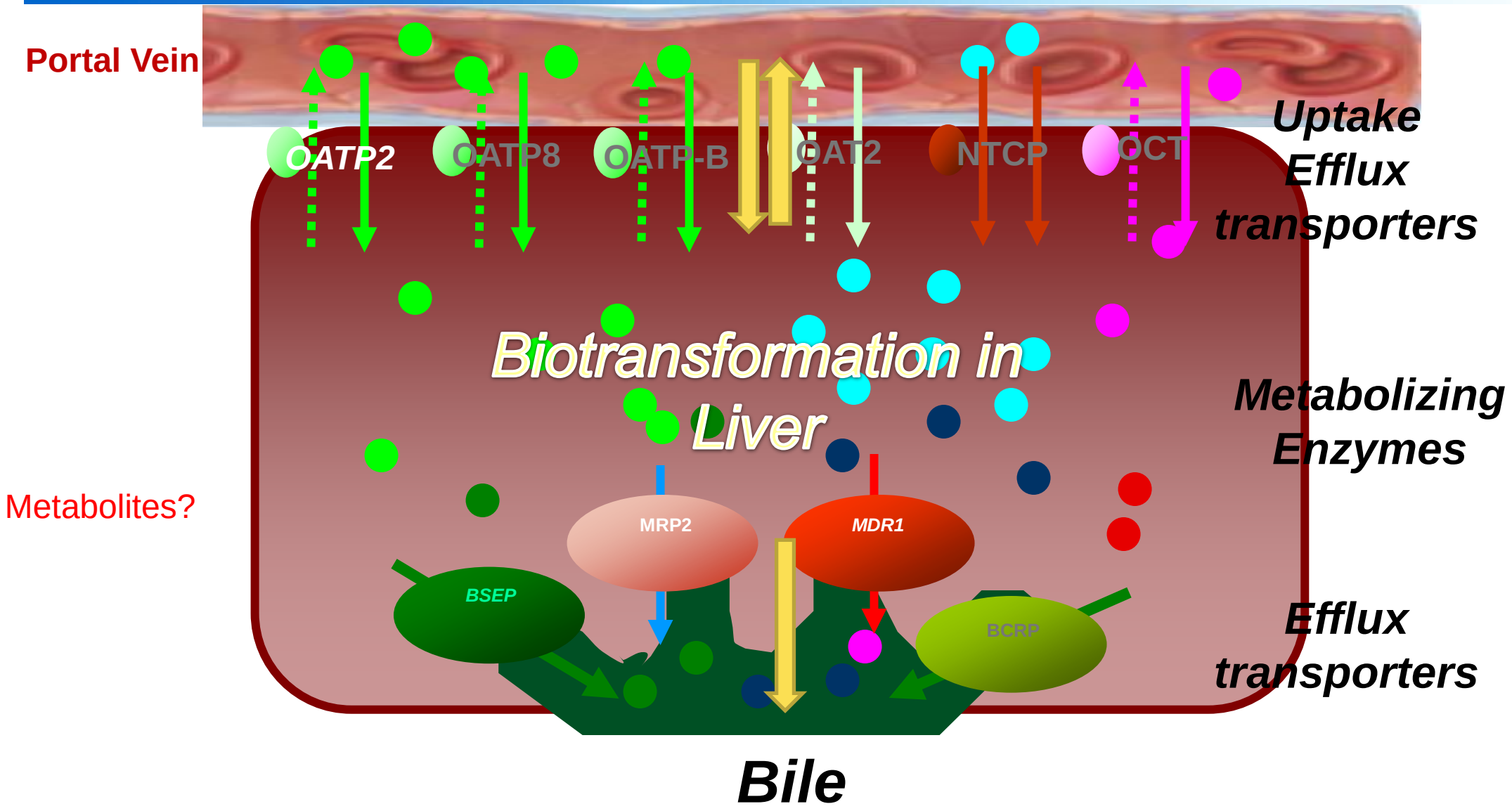
- pH-dependent DDI



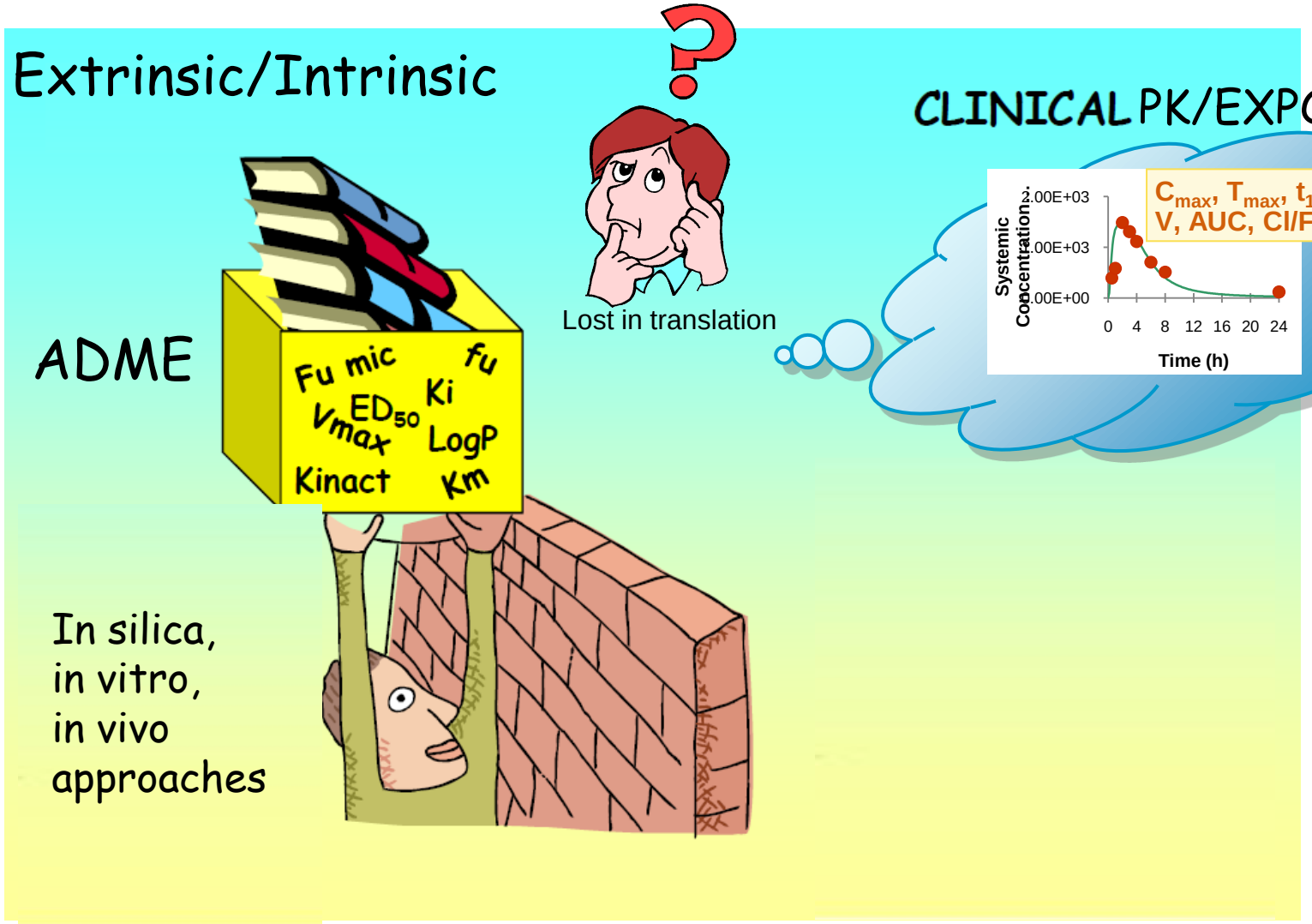
First pass effect
(首过效应）

Dosing → **Systemic circulation**

DDI: Cooperation of Biotransformation and Transport



Prediction of Clinically Relevant DDI



血药浓度的变化

MODEL-GUIDED DDI PREDICTION

模型指导下的DDI预测

- Basic Models
- Static Mechanistic Models
- PBPK Models (Dynamic Mechanistic models)

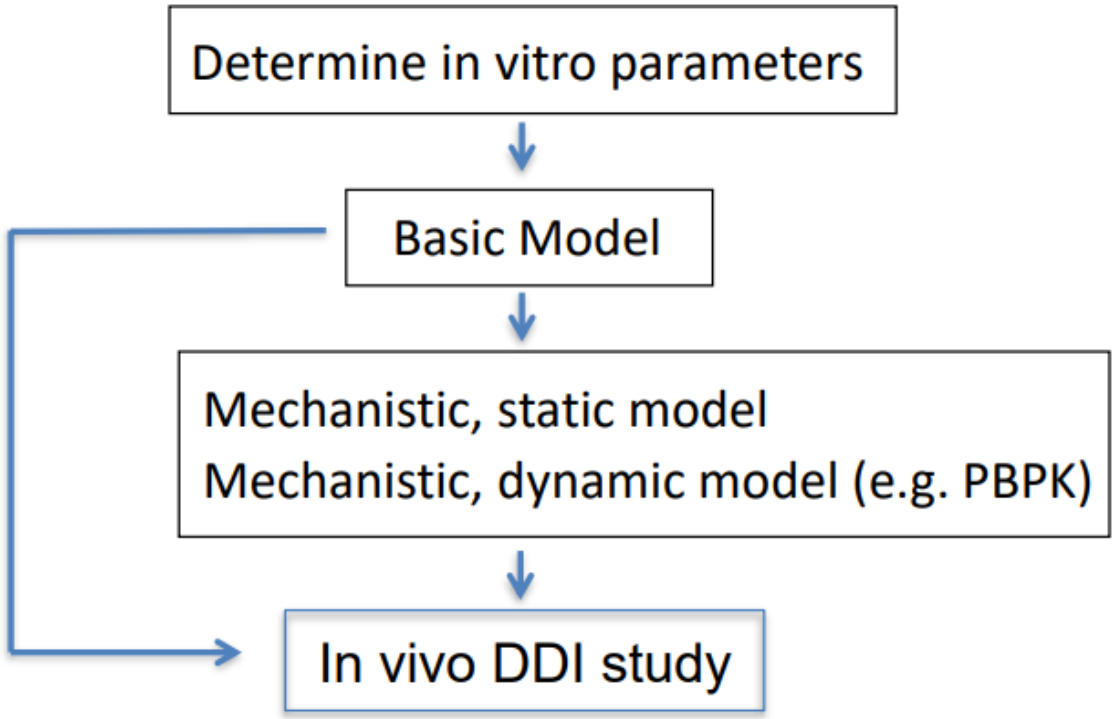
Flow Scheme of Model-Guided DDI Prediction

Example: Determine if NME is an Inhibitor or Inducer of CYPs

（New Molecular Entity/原研药）

CYP inhibitor
(CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A)

CYP inducer
(CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A



Basic Models for CYP Inhibitions

If the R value is above the cut-off, further evaluation of the DDI potential is needed.

- **Reversible inhibition**

$$R_1 = 1 + (I_{max,u} / K_i) \geq \mathbf{1.02}$$

I_{max}: steady-state C_{max} of the inhibitor in plasma;
'u' means unbound (free) drug (Imax,u = Imax x fu,p);
Ki is unbound inhibition constant determined in vitro

$$R_{1,gut} = 1 + (I_{gut} / K_i) \geq \mathbf{11}$$

Only For CYP3A, $R_{1,gut}$ should also be calculated;
I_{gut}: Dose/250mL (a rough estimate of intestinal luminal concentration of inhibitor.

- **Time-dependent inhibition (TDI)**

$$R_2 = (k_{obs} + k_{deg}) / k_{deg} \geq \mathbf{1.25}$$

Where $k_{obs} = (k_{inact} \times 50 \times I_{max,u}) / (K_I + 50 \times I_{max,u})$

暴露浓度变化倍数 R: fold change in exposure = AUC'/AUC

Cut-offs Harmonization Between FDA and EMA

- Conducted analysis based on 119 clinical studies with midazolam as the substrate
- Compared different inhibitor concentrations, i.e., total Cmax or unbound Cmax as the inhibitor concentration and corresponding cut-off values

Model	Model description	Algorithm (R or AUCR) and [I] definition	N^a	Cutoff criteria	FN (n^b)	FP (n^b)	TN (n^b)	TP (n^b)	FNR (%)	FPR (%)	NPE (%)	PPE (%)	RMSE	GMFE
1[c]	Reversible basic (FDA[d])	$R = 1 + [I]/K_i$ and [I]: $[I]_{max}$	117	$R > 1.1$	18	10	21	68	21	32	46.2	12.8	417	3.84
2[c]	Reversible basic (EMA[e])	$R = 1 + 50.[I]/K_i$ and [I]: $[I]_{max,u}$	117	$R \geq 2.0$	20	8	23	66	23	26	46.5	10.8	214	4.15
3	Reversible $[I]_{gut}$ (FDA[d] and EMA[e])	$R = 1 + [I]/K_i$ and [I]: $[I]_{gut}$ (Eq. 1)	116	$R > 11$	0	23	8	85	0	74	0	21.3	$>10^5$	324

- Thus, changed from $C_{max}/Ki \geq 0.1 \rightarrow C_{max,\ unbound}/Ki \geq 0.02$ for reversible inhibitors for harmonization among regulators since prediction performance is similar.
- Also modified the criteria for TDIs from total C_{max} to $C_{max,\ unbound}$ to align with EMA (except that [I]gut is not required).

FDA workshop April 2020

Viera ML, et al. Clin Pharmacol Ther 95(2): 189-198 (2014)

Evaluation Induction Potential of CYPs

- **Correlation method (mRNA)**
  - Predicted positive criteria is defined by known positive and negative controls (e.g., relative induction score (RIS))

- **Basic kinetic model (mRNA)**

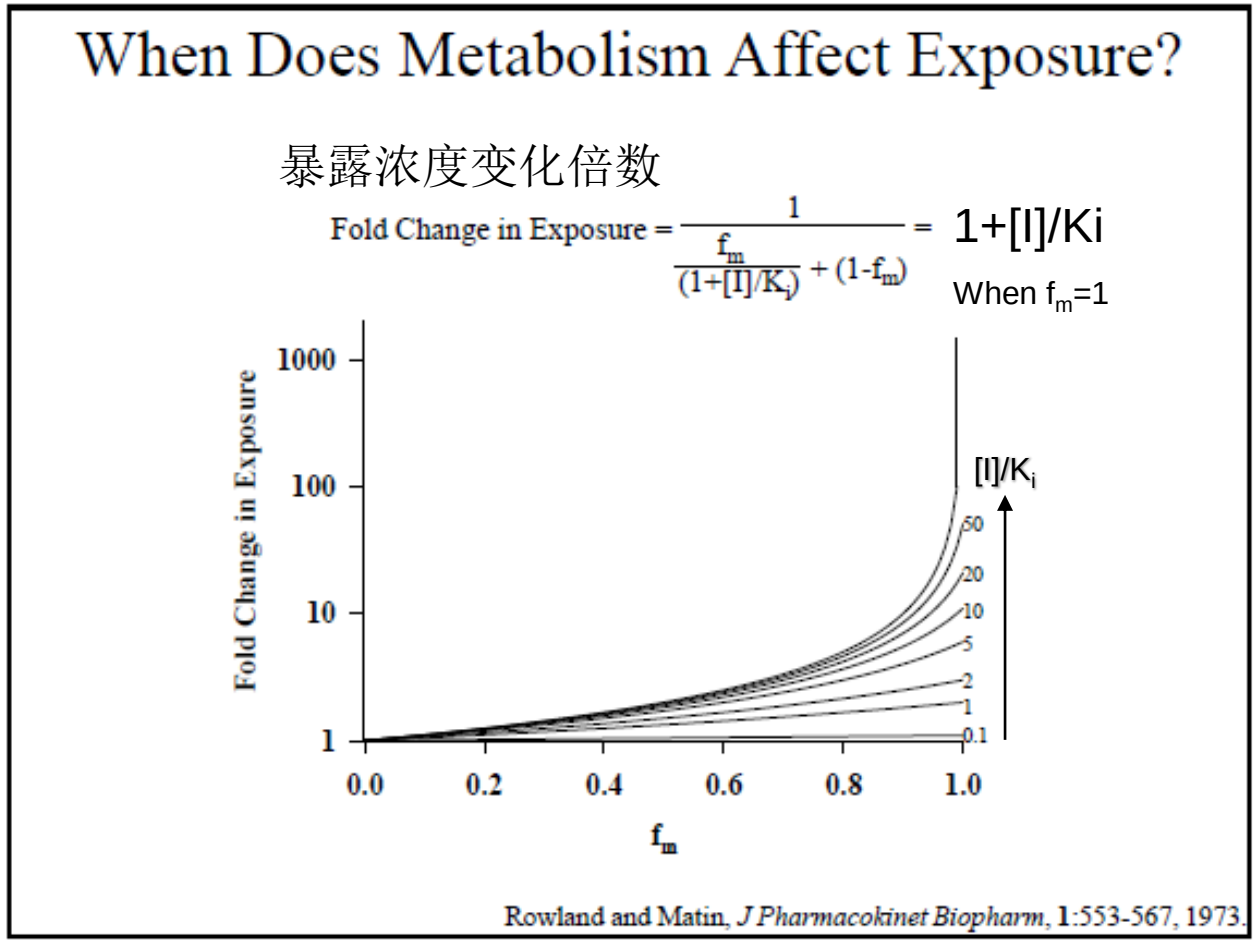
  $\mathbf{R_3} = 1 / [1 + (d \times Emax \times 10 \times Imax,u) / (EC_{50} + 10 \times Imax,u)] \leq 0.8$

- **Enzyme Activity** was added besides mRNA.

  However, no clear recommendation on how to evaluate activity data provided. Need further evaluation.

Yoshida K, et al. J Pharm Sci. 2017 Sep;106(9):2209-2213

The Fundamental of DDI: Mathematic Description of Reversible Inhibition

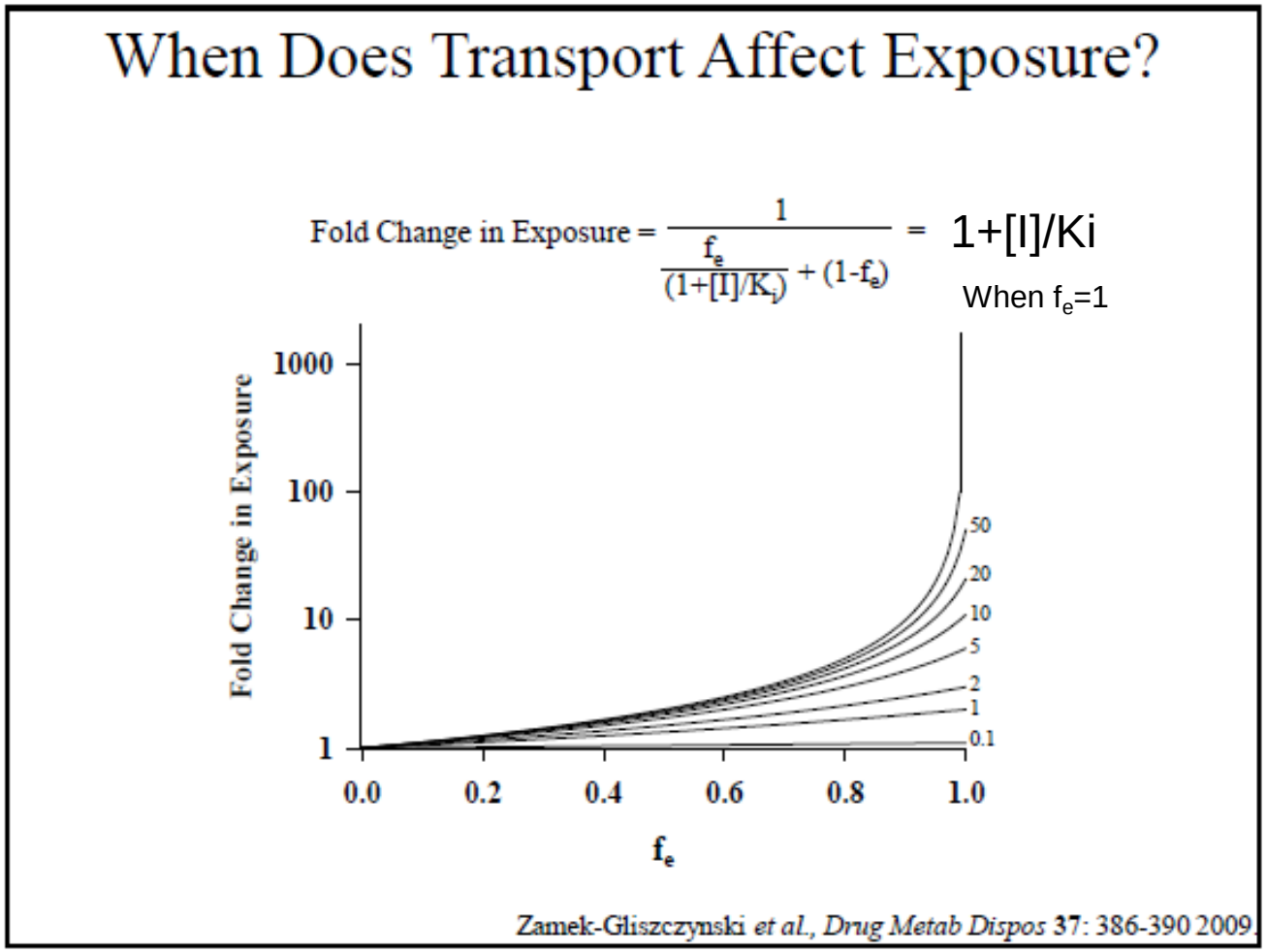


Reversible Inhibition following IV administration

f_m: the fraction of total metabolism mediated by the relevant enzyme

相关酶介导的代谢占总代谢的比例

Transport-mediated DDI



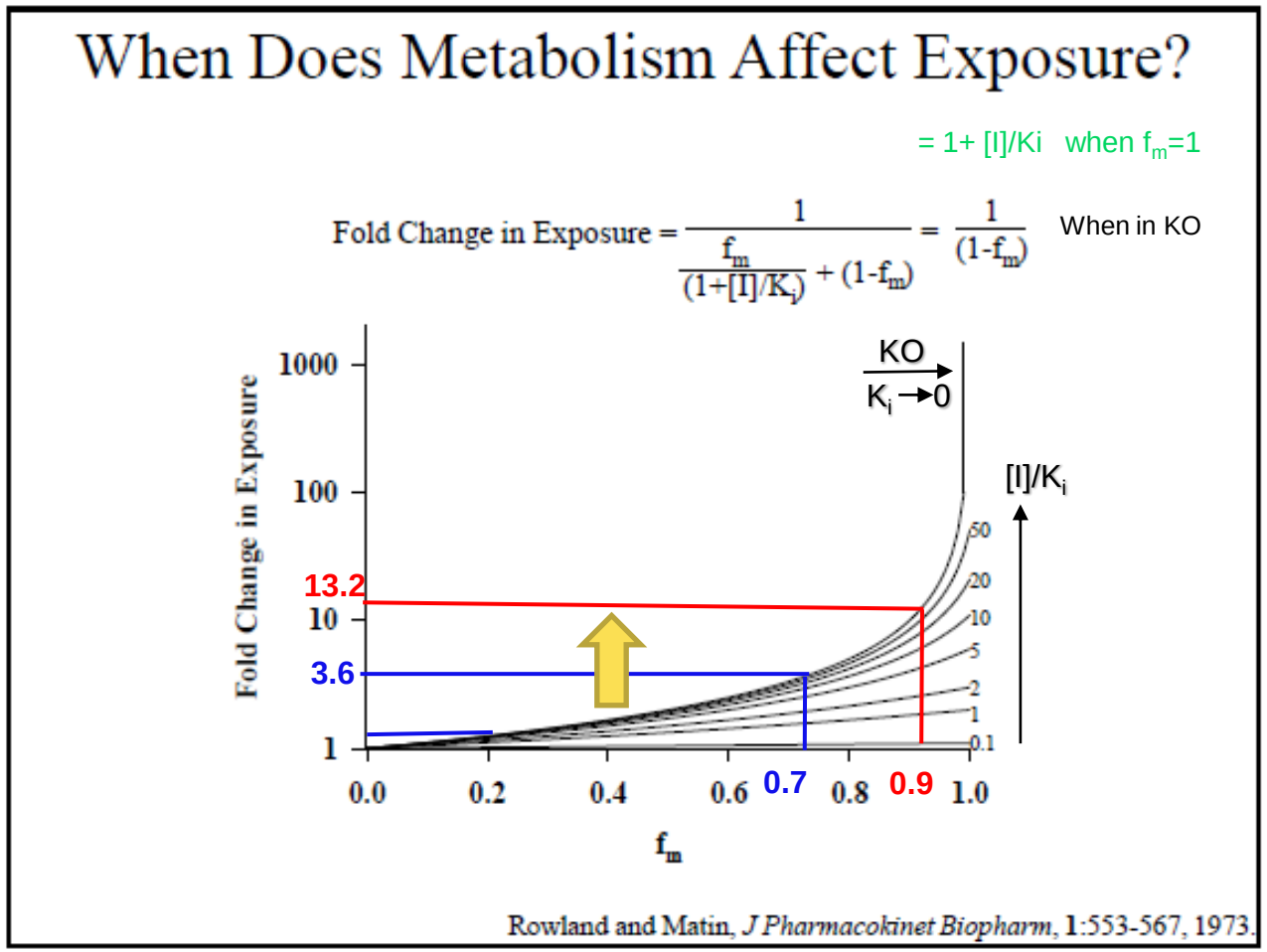
f_e: the fraction of total clearance mediated by a particular excretory transport protein

相关转运体介导的清除率占总清除率的比例

Basic Models for Transporter Inhibition

Transporters	2012 Draft guidance	2017 Draft Guidance	Final Guidance
P-gp/BCRP	$I_1/IC_{50} \geq 0.1$ or $I_2/IC_{50} \geq 10$	$I_2/IC_{50} \geq 10$ (for oral drugs)	Same as 2017
OATP1B1/ OATP1B3	Step 1: $I_{total,\ max}/IC_{50} \geq 0.1$ Step 2: $I_{unbound,\ inlet,\ max}/IC_{50} \geq 0.25$	$I_{unbound,\ inlet,\ max}/IC_{50} \geq 0.1$	Same as 2017
OAT1/OAT3	$I_{unbound,\ max}/IC_{50} \geq 0.1$	Remained the same	Same as 2017
OCT2/MATE1/ MATE2-K	$I_{unbound,\ max}/IC_{50} \geq 0.1$ (only for OCT2)	$I_{unbound,\ max}/IC_{50} \geq$ 0.1 (for OCT2) or 0.02 for (MATEs newly added)	$I_{unbound,\ max}/IC_{50} \geq$ **0.1**

Why Static Mechanistic Models?



f_m: the fraction of total clearance mediated by the relevant enzyme

相关酶介导的代谢占总代谢的比例

Static Mechanistic Models

暴露浓度变化倍数

$$AUCR = \left(\frac{1}{[A_g \times B_g \times C_g] \times (1 - F_g) + F_g}\right) \times \left(\frac{1}{[A_h \times B_h \times C_h] \times f_m + (1 - f_m)}\right)$$

The equation assumes that the drug has negligible extrahepatic clearance.
A is the effect of reversible inhibitions.
B is the effect of TDI.
C is the effect of induction.
F_g is the fraction available after intestinal metabolism.
f_m is the fraction of hepatic clearance of the substrate mediated by the CYP enzyme that is subject to inhibition/induction.
Subscripts 'h' denote liver.
Subscripts 'g' denote gut.

Each value can be estimated with the following equations:

	Gut	Liver
Reversible inhibition	$A_g = \frac{1}{1 + \frac{[I]_g}{K_i}}$	$A_h = \frac{1}{1 + \frac{[I]_h}{K_i}}$
Time-dependent inhibition	$B_g = \frac{k_{deg,g}}{k_{deg,g} + \frac{[I]_g \times k_{inact}}{[I]_g + K_I}}$	$B_h = \frac{k_{deg,h}}{k_{deg,h} + \frac{[I]_h \times k_{inact}}{[I]_h + K_I}}$
Induction	$C_g = 1 + \frac{d \bullet E_{max} \bullet [I]_g}{[I]_g + EC_{50}}$	$C_h = 1 + \frac{d \bullet E_{max} \bullet [I]_h}{[I]_h + EC_{50}}$

Copied from FDA DDI 2020

Static Mechanistic Models

H: Hepatic

G: Gut

Fold Change in Exposure

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

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

Deg： 降解

相关酶介导的代谢占总代谢的比例

逃过首过代谢的比例

$$\text{Fold Change in Exposure} = \frac{1}{\frac{f_m}{(1+[I]/K_i)} + (1-f_m)}$$

Terminology

FDA(2020)

- Based on the effect on a sensitive index CYP substrate
  - strong inhibitor: increases the AUC ≥ 5-fold
  - moderate inhibitor: increases the AUC ≥ 2- to < 5-fold
  - weak inhibitor: increases the AUC ≥ 1.25- to < 2-fold
  - strong inducer: decreases the AUC ≥ 80 percent
  - moderate inducer: decreases the AUC ≥ 50 to < 80 percent
  - weak inducer: decreases the AUC ≥ 20 to < 50 percent
- Based on the effect of a strong index inhibitor
  - sensitive substrate: AUC is increased ≥ 5-fold
  - moderate sensitive substrate: AUC is increased ≥ 2- to < 5-fold

EMA(2013)

same

- **Weak inducer: decreases the AUC < 50%**

same

Sensitive index substrates

- Selected based on systematic review of clinical DDI studies between FDA recommended index perpetrators and sensitive substrates
- Sensitive index substrates:
  - CYP1A2: caffeine, tizanidine
  - CYP2C8: repaglinide
  - CYP2C9: S-warfarin, tolbutamide (both are moderately sensitive substrates)
  - CYP2C19: omeprazole, lansoprazole
  - CYP2D6: desipramine, dextromethorphan, nebivolol
  - CYP3A: midazolam, triazolam

– Note- there are caveats for some of the substrates (explained on the website)

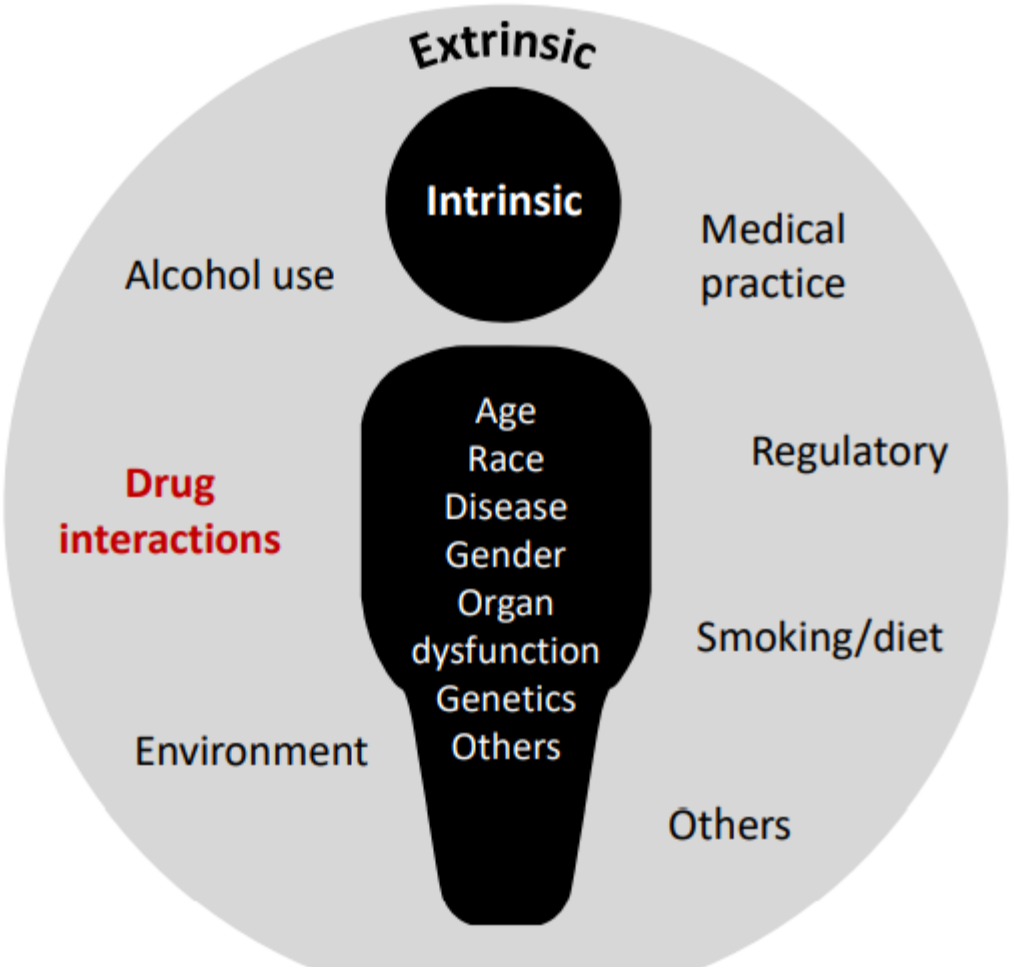
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm
(FDA Drug Development and Drug Interaction page)

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

Factors Affecting Drug Exposure

$$AUCR = \left(\frac{1}{[A_g \times B_g \times C_g] \times (1 - F_g) + F_g}\right) \times \left(\frac{1}{[A_h \times B_h \times C_h] \times f_m + (1 - f_m)}\right)$$



DDI Prediction for patients with these individual factors

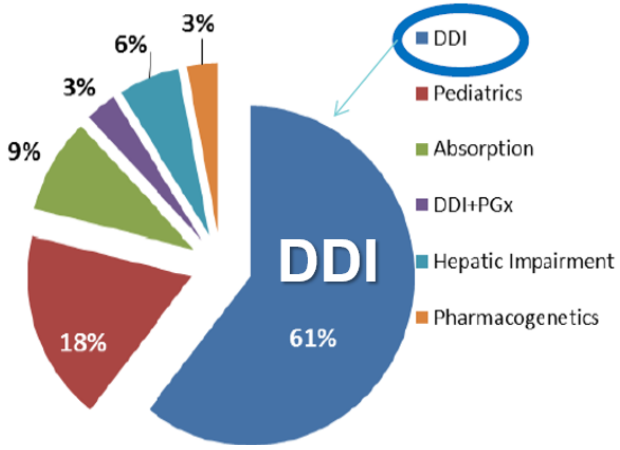
Adapted from: Huang S-M, Temple R, Clin Pharmacol Ther 84: 287-294, 2008
FDA Clinical Pharmacology guidance documents:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

PBPK Regulatory Application

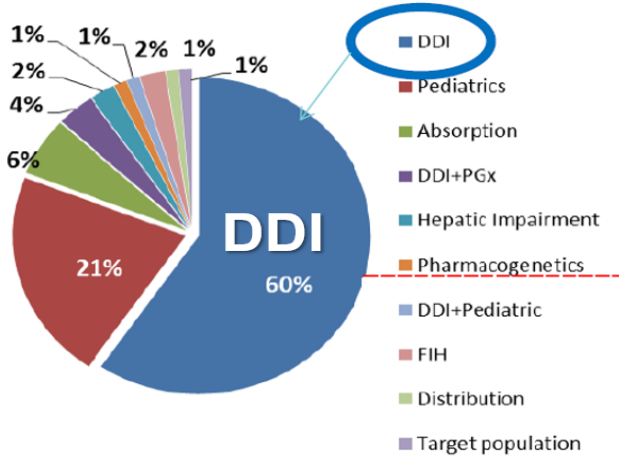
- Physiologically based pharmacokinetic (PBPK) models can replace some clinical studies
- Examples:
  - Impact of weak and moderate CYP2D6 and 3A4 inhibitors
  - Impact of weak and moderate CYP3A4 inducers
- Verify model by comparing clinical and PBPK evaluation: effect of strong perpetrator
- An evolving science
  - New uses are being considered

By Sponsors, How is PBPK Being Utilized?

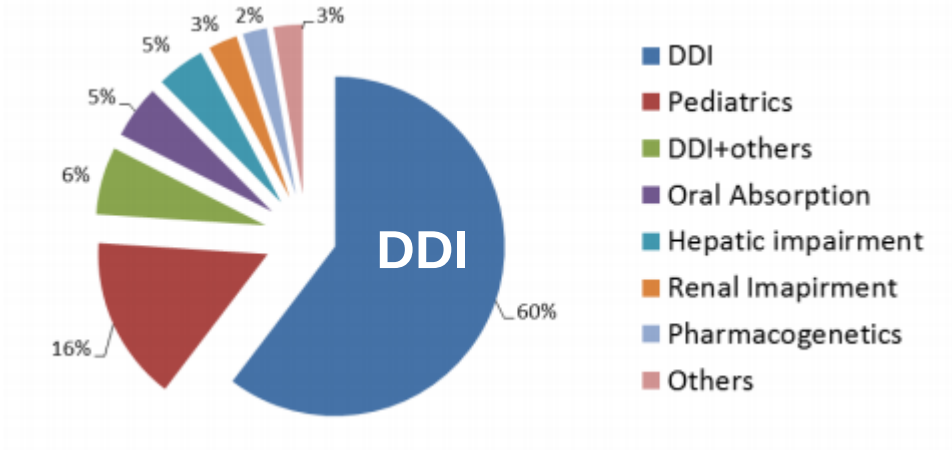
Cumulative as of 2012
(n=33)



Cumulative as of 2013
(n=84)



Cumulative as of Aug 1, 2016
(n=217)



- **Majority related to DDIs (~60%)**
- **Increased use of PBPK by Sponsor**

Source: FDA

Case Study I: Odemzo PBPK Study

- Sonidegib capsules (Odomzo)- treatment of locally advanced basal cell carcinoma
- CYP3A substrate
- Clinical DDI studies were conducted with strong CYP3A inhibitor (ketoconazole) and strong CYP3A inducer (rifampin)
  - with ketoconazole- AUC increased 2.2x; Cmax increased 1.5x
  - with rifampin- AUC decreased 72%; Cmax decreased 54%

Source: Odomzo label

Case Study I: Odemzo PBPK Study

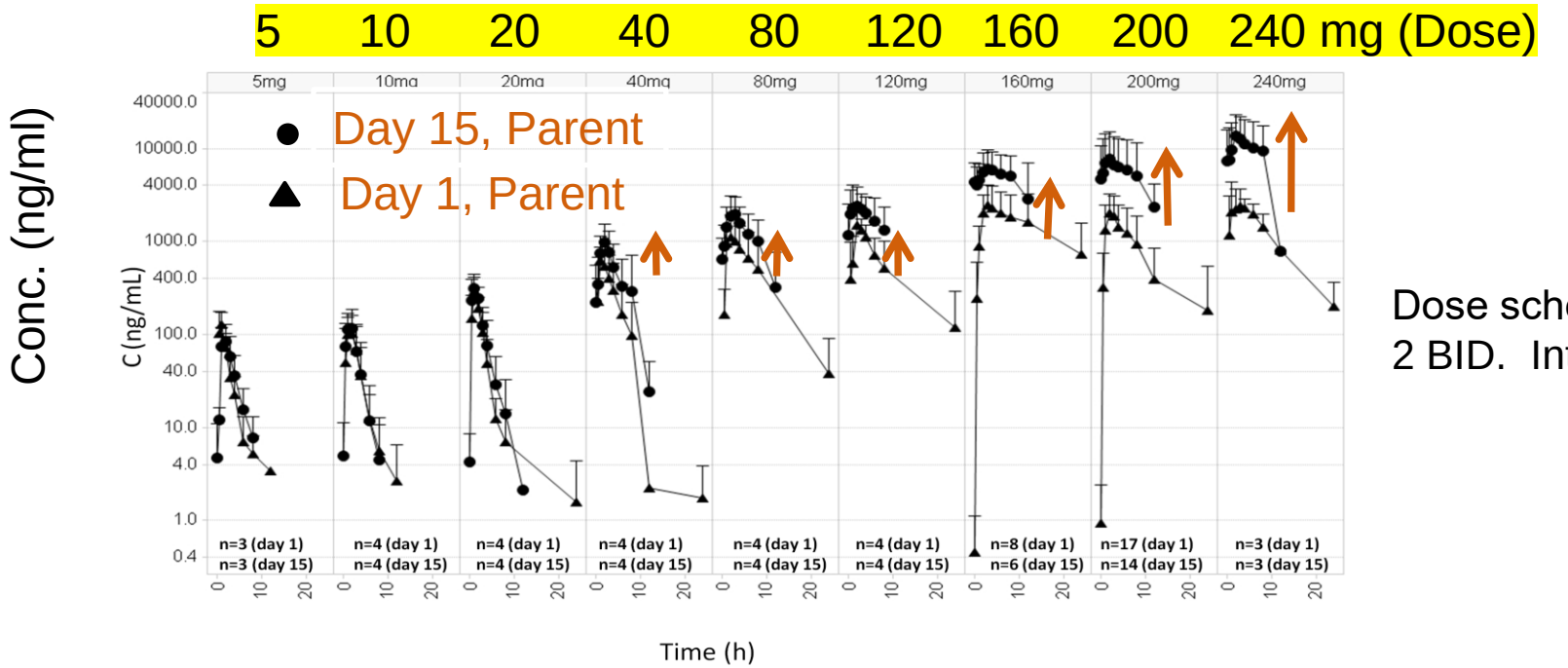
- Sonidegib, continued
- Clinical DDI studies were conducted with strong CYP3A inhibitor (ketoconazole) and strong CYP3A inducer (rifampin)
  - With keto- AUC increased 2.2x; Cmax increased 1.5x
  - With rif- AUC decreased 72%; Cmax decreased 54%

- PBPK
  - With moderate inhibitor (erythromycin)- AUC would increase 1.8x (14d) and 2.8x (4 months)
  - With moderate inducer (efavirenz)- AUC would decrease 56% (14d) and 69% (4 months)

Source: Odomzo label

Case Study II: BMS-911543 Concentration Time Profiles

Issue: dose- and time-dependent non-linear pharmacokinetics

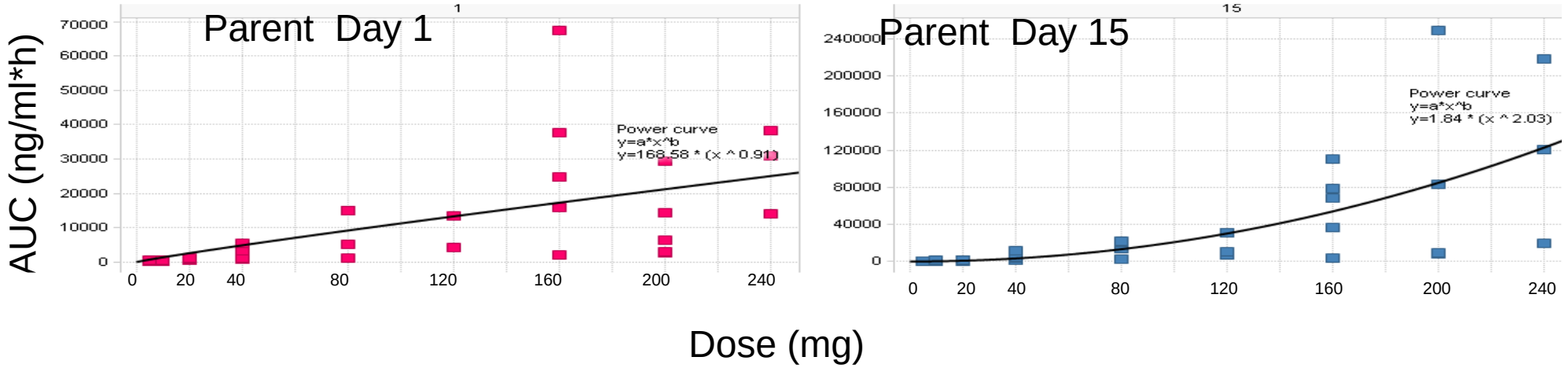


Dose schedule: day 1 QD; ≥day 2 BID. Intensive PK at D1&D15

	5-20 mg	40-120 mg	160-200 mg
$t_{1/2}$ Day 1	2-3 h	~3 h	5-6 h
$t_{1/2}$ Day 15	2-3 h	8.3-9.3 h	11-17 h
Accumulation Index on Day 15	1	2	3-6

L. Zhou et al., *Clinical Pharmacology and Therapeutics: Pharmacometrics & Systems Pharmacology* 4: 286 (2015) **http://onlinelibrary.wiley.com/doi/10.1002/psp4.35/full**

BMS-911543 Exposure vs. Dose



Dose- and Time- dependency

- **AUC approximately dose-proportional on day 1**
- **AUC greater than dose-proportional on day 15**

Auto time-dependent inhibition?

Prior knowledge on TDI:

CYP3A4 (K_I = 11.2 µM, k_{inact} = 4.5 h^{-1}); CYP1A2 minimal

$F_{m,CYP}$:

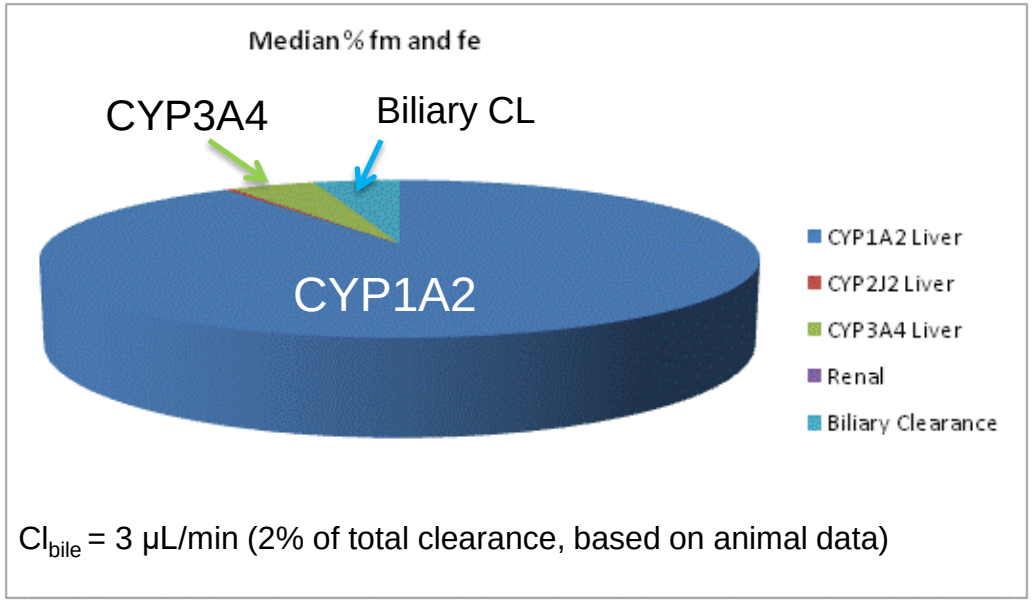
CYP3A4 = 0.7%;

CYP1A2 = 96%

"What if" question:

What if compound produced TDI on CYP1A2?

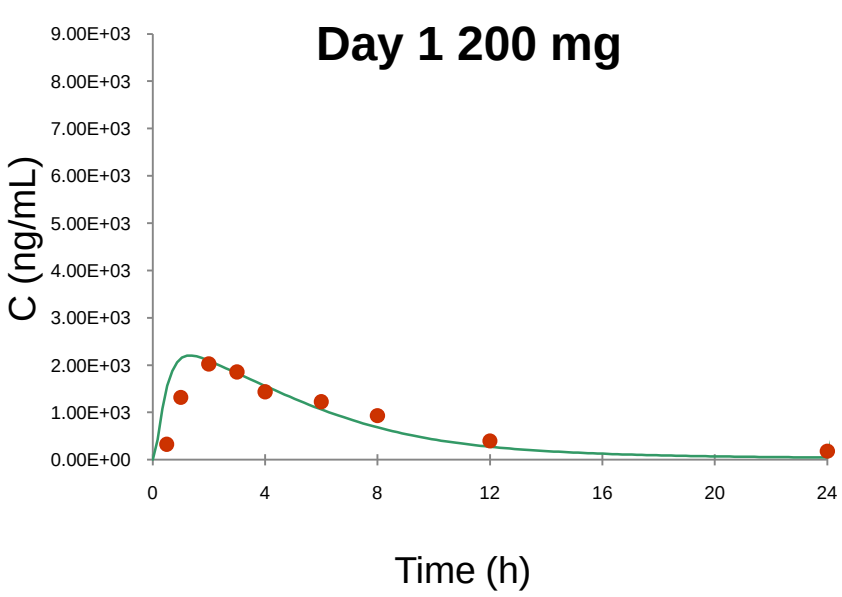
(Reverse translation)

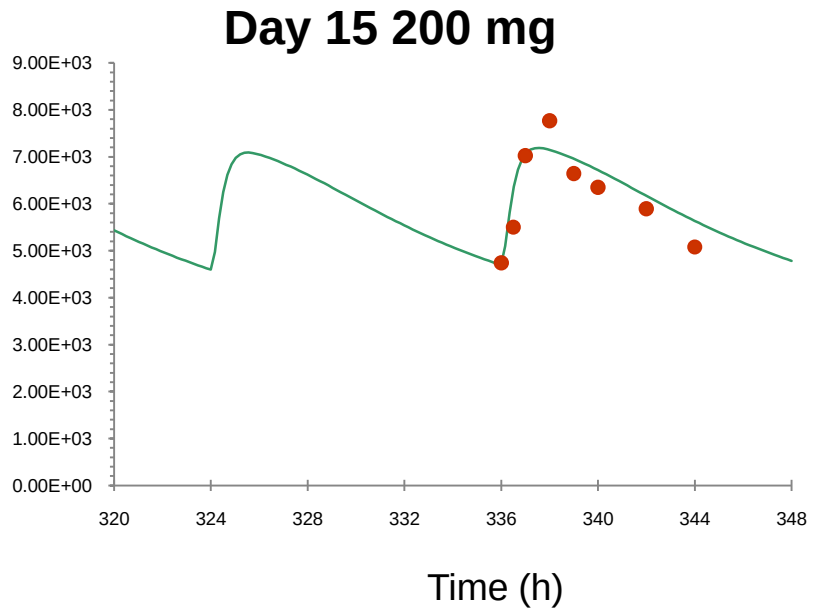


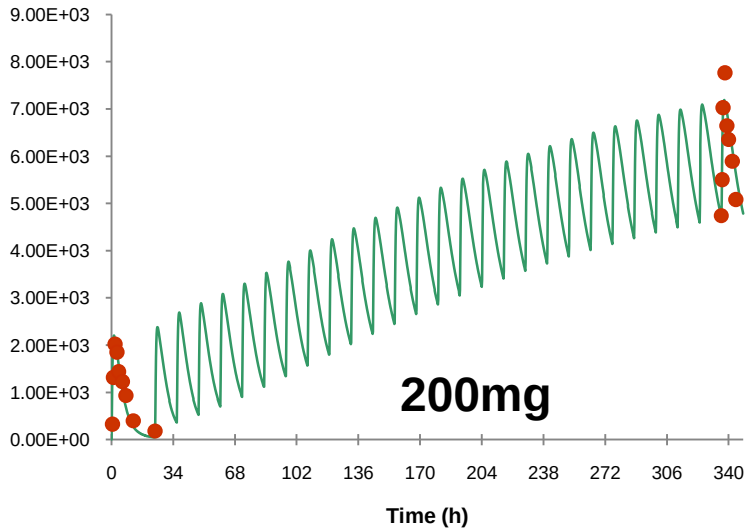
Cl_{bile} = 3 µL/min (2% of total clearance, based on animal data)

L. Zhou et al., *Clinical Pharmacology and Therapeutics: Pharmacometrics & Systems Pharmacology* 4: 286 (2015) **http://onlinelibrary.wiley.com/doi/10.1002/psp4.35/full**

Observed vs. Simulated Mean Plasma Profiles after Incorporation of TDI on CYP1A2







- Green lines: Mean of all trials
- Observed clinical mean concentrations

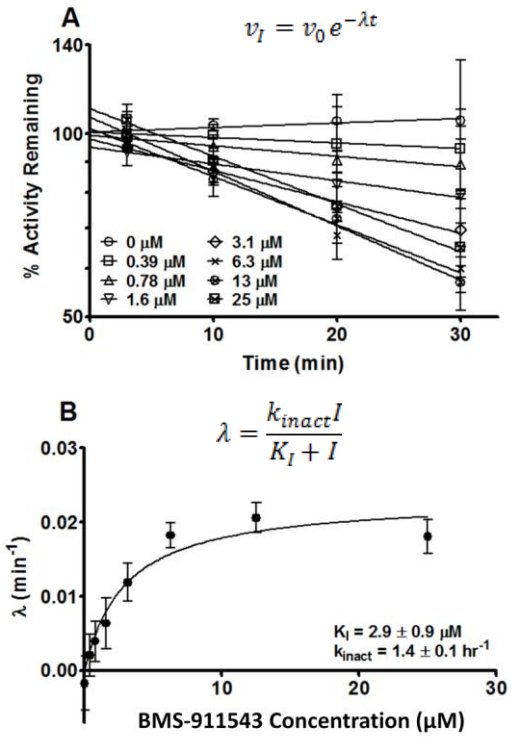
Updating the Model: Time-dependent Inhibitory Effects of BMS-911543

Experiment condition:

- In vitro model: human liver microsomes
- CYP1A2 probe substrate: phenacetin
- BMS-911543 concentrations: 0-25 μM
- Incubation time: 3, 10, 20, 30 min without phenacetin followed by 13.5 min incubation with phenacetin
- Monitor: formation of acetaminophen

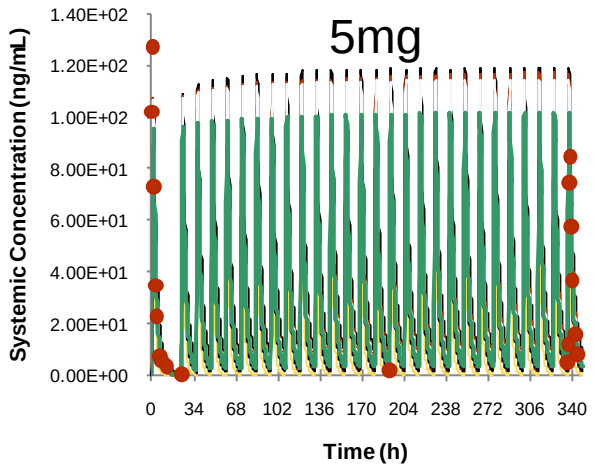
Results:

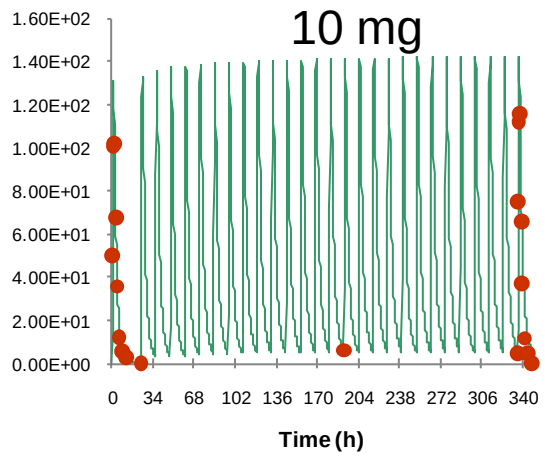
- The concentration associated with half maximum rate of inactivation K_I =2.9 ± 0.9 μM
- The maximum rate of enzyme inactivation K_{inact} = 1.4 ± 0.1 h^{-1}

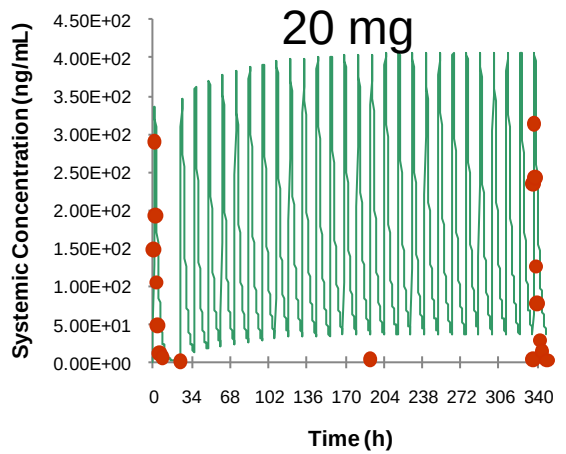


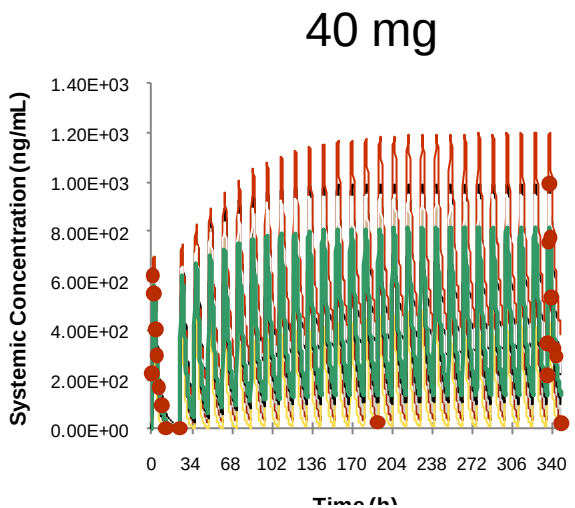
L. Zhou et al., *Clinical Pharmacology and Therapeutics: Pharmacometrics & Systems Pharmacology* 4: 286 (2015) **http://onlinelibrary.wiley.com/doi/10.1002/psp4.35/full**

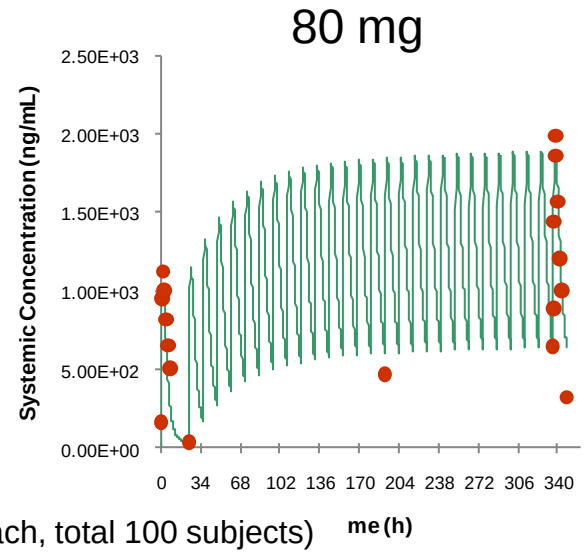
Observed vs. Simulated Mean Plasma Profiles

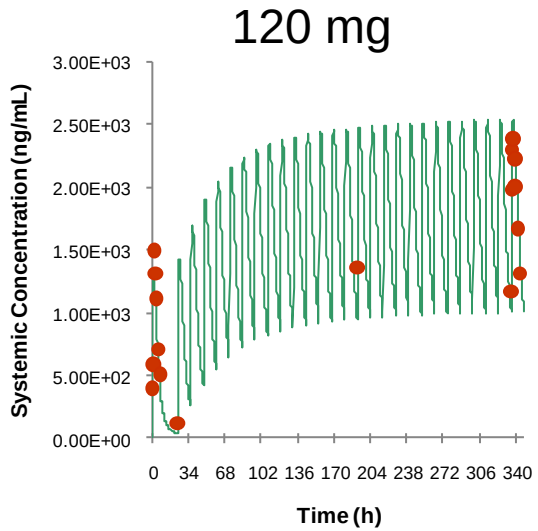












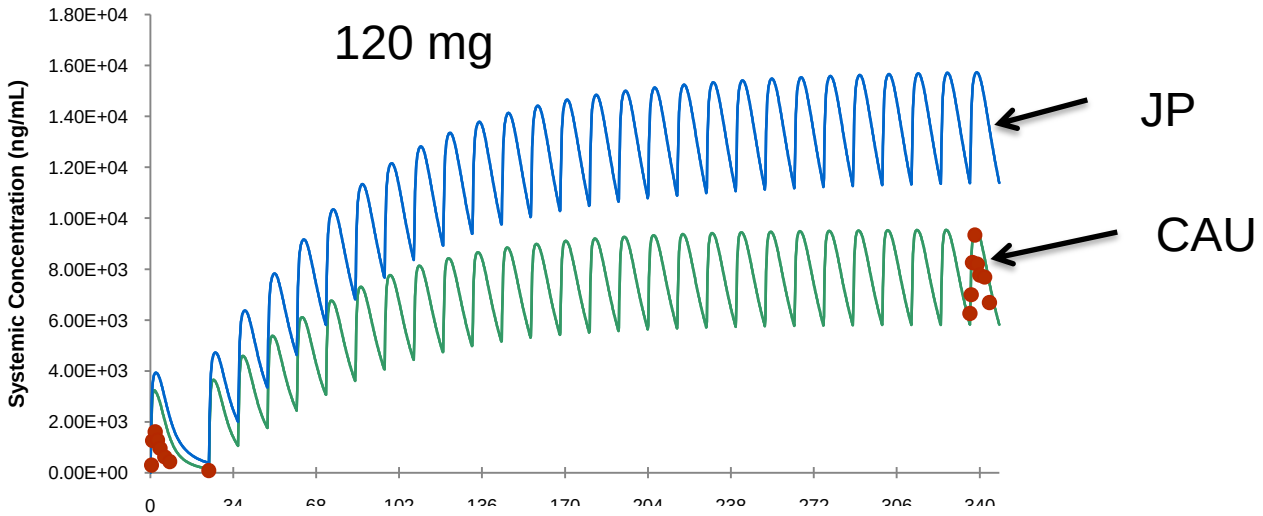
Red lines: Mean of individual trials (10 trials with 10 subjects each, total 100 subjects)
Green lines: Mean of all trials
●: Observed clinical mean concentrations

L. Zhou et al., *Clinical Pharmacology and Therapeutics: Pharmacometrics & Systems Pharmacology* 4: 286 (2015)
http://onlinelibrary.wiley.com/doi/10.1002/psp4.35/full

Predicted Plasma Profiles in Japanese

Caucasian
CYP1A2=52
pmol/mg-protein

Japanese
CYP1A2=44
pmol/mg-protein



	AUC (TAU, Mean), ng*h/ml Simulated (Observed) at 120 mg D15
Caucasian	19900 (19538)
Japanese	39600

Indicates the need for dosage adjustments due to safety concerns

Evaluating the DDI potential of Metabolites

代谢物 DDI

DDI Potential of Metabolites

FDA (2020)

For CYPs

- **As a substrate:** for metabolites with safety concern or significantly contributing to overall efficacy (estimated based on potency, protein binding, tissue distribution of metabolites relative to parent): **Metabolite ≥ 50% of the overall activity**

- **As an inhibitor:**
  for metabolites more polar than parent: $AUC_{metabolite} \geq AUC_{parent}$
  for metabolites less polar than parent: $AUC_{metabolite} \geq 25\% \times AUC_{parent}$
  for metabolite that acts as time-dependent inhibitor (TDI), consider a lower exposure than parent（**removed the cut-off compared to version 2017)**
  Exposure comparison based on **Molar units**!

No need to do in vitro study for metabolites

- If clinical DDI study to be done for parent

For transporters, may be considered

EMA (2013)
For CYPs

- **Phase I metabolites with an AUC greater than 25% of parent and 10% of the total AUC of drug-related substances**

Callegari, Kalgutkar, et al. 2013; Yu and Tweedie 2013; Yu, Balani, et al. 2015

Low Risk of CYP Inhibition Caused by a Metabolite Alone

IQ Group (137 most frequently prescribed drugs, from 18 Pharma)

- **R_{met} strategy (Pfizer)**
  - **$C_{max,\ metabolite} / K_{i,\ metabolite}$, where $K_{i,\ metabolite} = 0.25\ K_{i,\ parent}$**
- **Structure alerts**
  - **Alkene (烯烃)**
  - **Alkyne (炔烃)**
  - **Hydrozine (ABT) (羟嗪)**
  - **Cycopropylamine (环丙胺)**
  - **Dihaloalkane (二卤代烷)**
  - **Furan (呋喃)**
  - **Thiophene (噻吩)**
  - **Phenol and aminophenol (苯酚和氨基苯酚)**

Callegari, Kalgutkar, et al. 2013; Yu and Tweedie 2013; Yu, Balani, et al. 2015

ALDEHYDE OXIDASE (AO, 2020 NEW)
CARBOXYLESTERASE (CES, 2020 NEW)

醛氧化酶
羧酸酯酶

Carboxylesterases (CES)

0090-9556/08/3607-1227–1232$20.00
DRUG METABOLISM AND DISPOSITION
Vol. 36, No. 7
20248/3346402
Printed in U.S.A.

DMD 36:1227–1232, 2008

The Biotransformation of Prasugrel, a New Thienopyridine Prodrug, by the Human Carboxylesterases 1 and 2

Eric T. Williams, Karen O. Jones, G. Douglas Ponsler, Shane M. Lowery, Everett J. Perkins, Steven A. Wrighton, Kenneth J. Ruterbories, Miho Kazui, and Nagy A. Farid

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Questions?