Metabolism and Drug-Drug Interactions

CAPRA Toxicology Symposium

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15 October, 2012

Bedard ADME-Tox Solutions

Outline

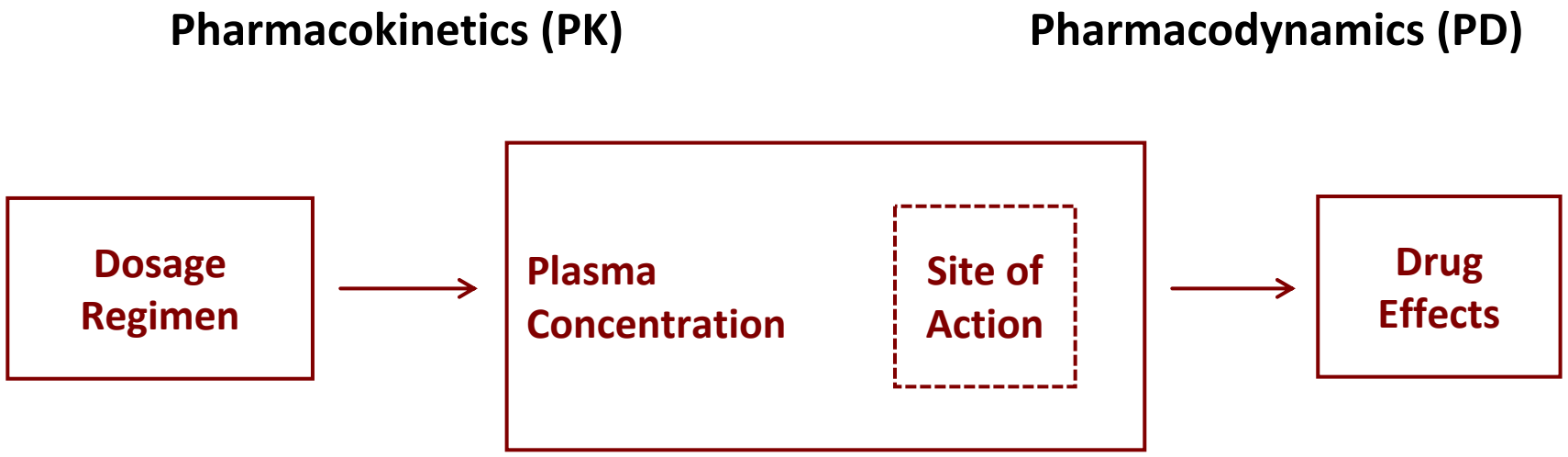
Basic Principles of Drug Metabolism, Pharmacokinetics and ADME

Role of ADME-PK in Drug Discovery and Development

Basis of Drug-Drug Interactions

Draft FDA and EMA Guidance Documents for Drug-Drug Interactions (2012)

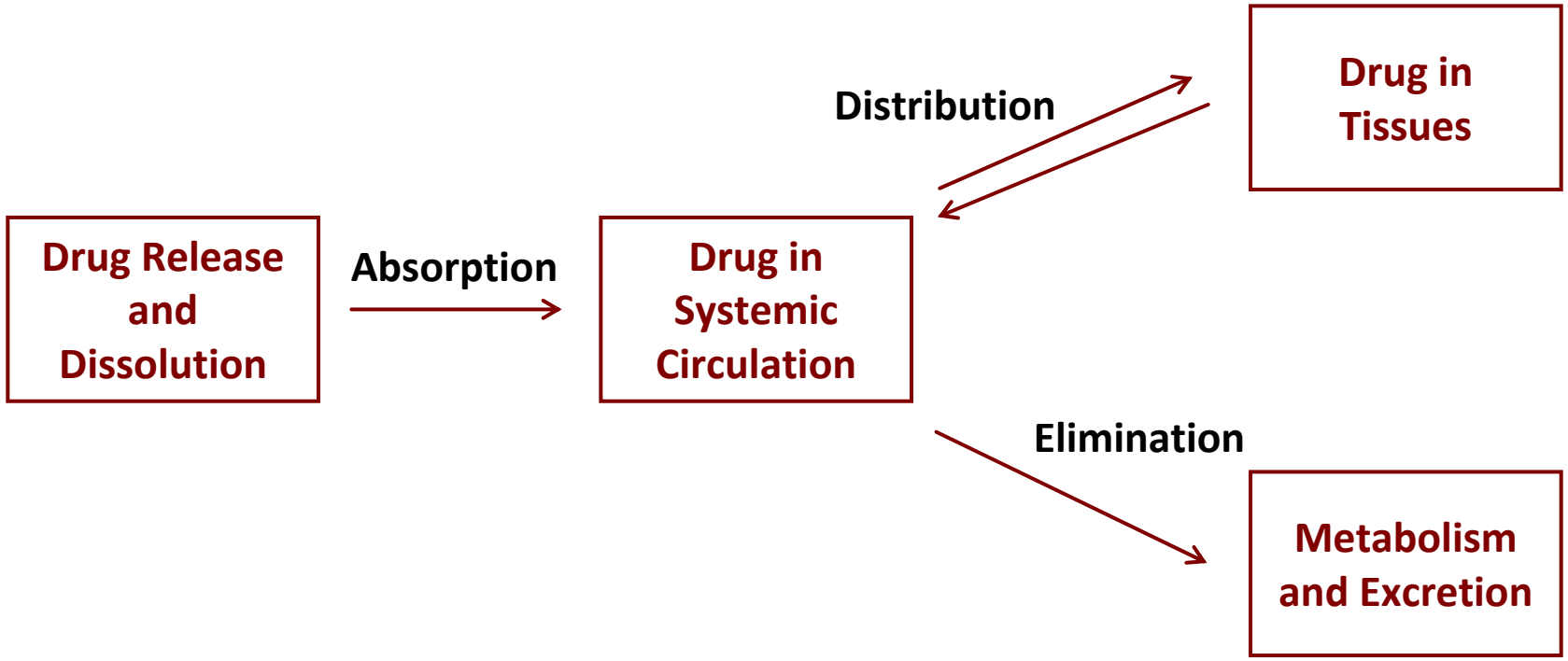
Pharmacokinetics and Pharmacodynamics



Pharmacokinetics: *"What the body does to the drug"*
Pharmacodynamics: *"What the drug does to the body"*

Adapted from: Rowland and Tozer, *Clinical Pharmacokinetics: Concepts and Applications*, 3rd ed., 1995

Pharmacokinetic Processes (ADME)

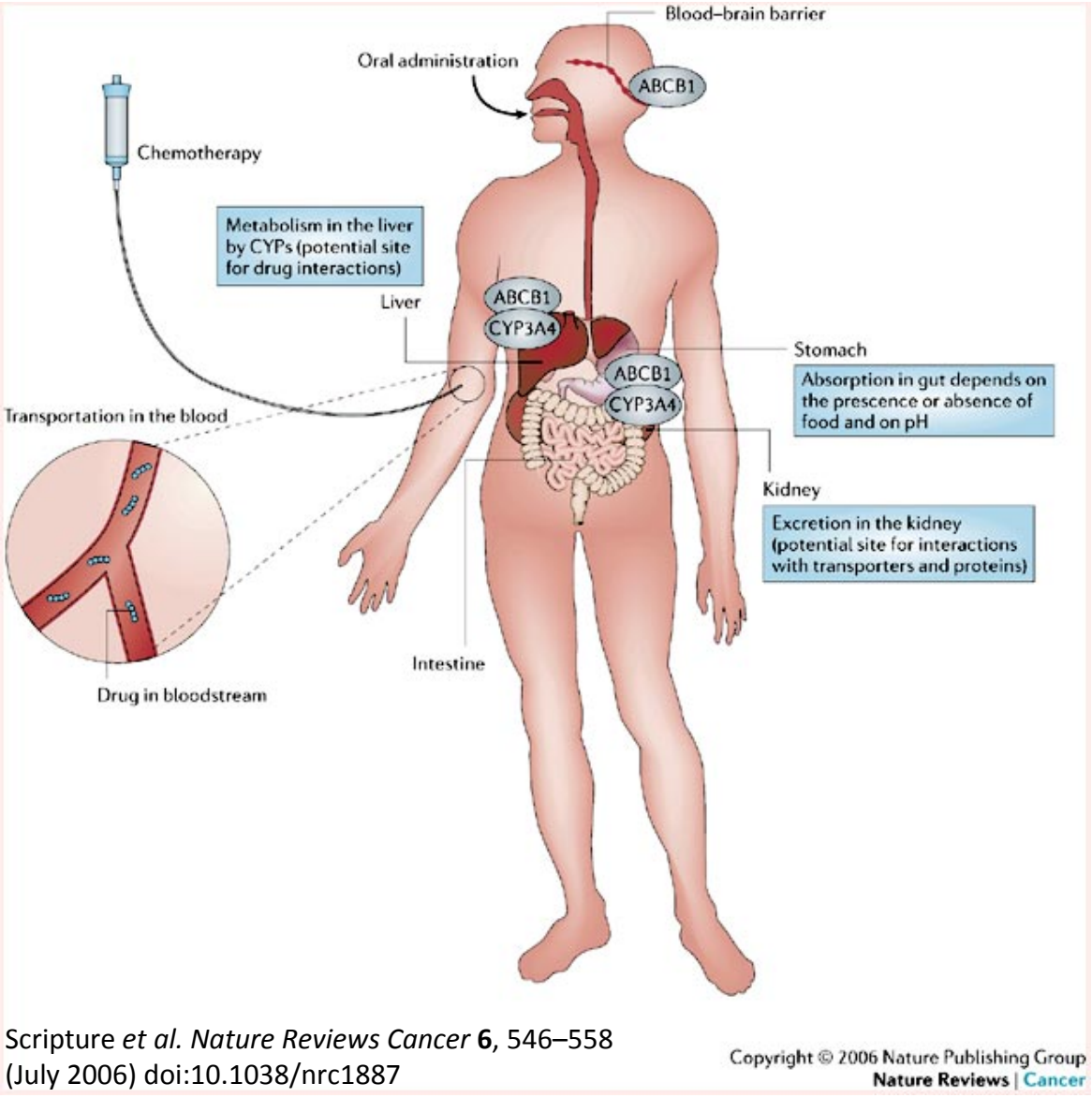


Absorption
Distribution
Metabolism
Excretion

Elimination

Disposition

Sites of Drug Disposition



Scripture *et al. Nature Reviews Cancer* **6**, 546–558 (July 2006) doi:10.1038/nrc1887

Factors which influence drug clearance:

1. **Metabolism:** Cytochrome P450 (CYP) enzymes in liver and gut catalyze drug oxidation reactions and contribute to the metabolism of ~75% of marketed drugs.

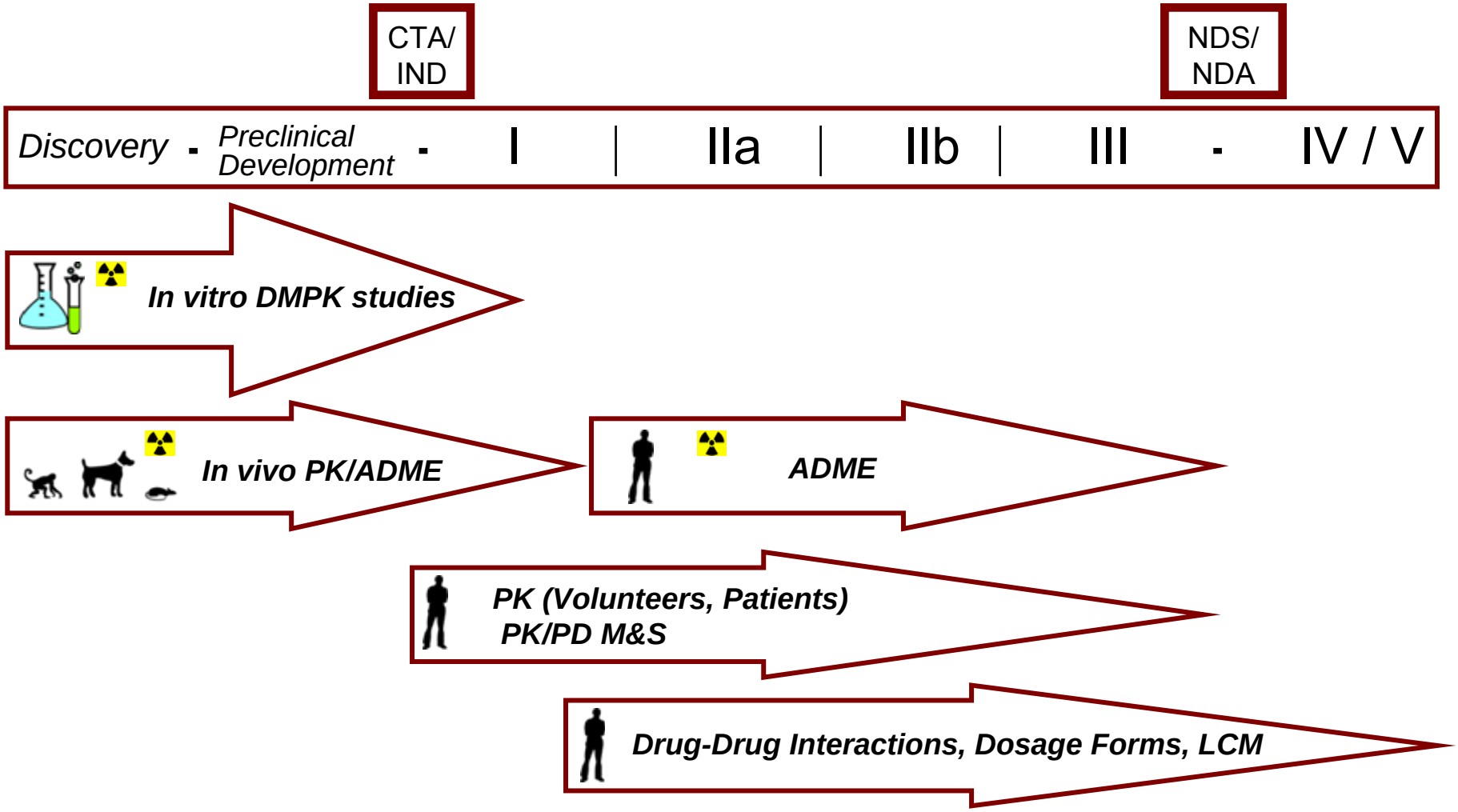
2. **Transport:** Hepatic uptake and biliary efflux transporters Renal uptake and efflux transporters

   - Pgp (ABCB1), BCRP, OATPs, OCTs, OATs, MATE

Role of DMPK in Drug Discovery and Development

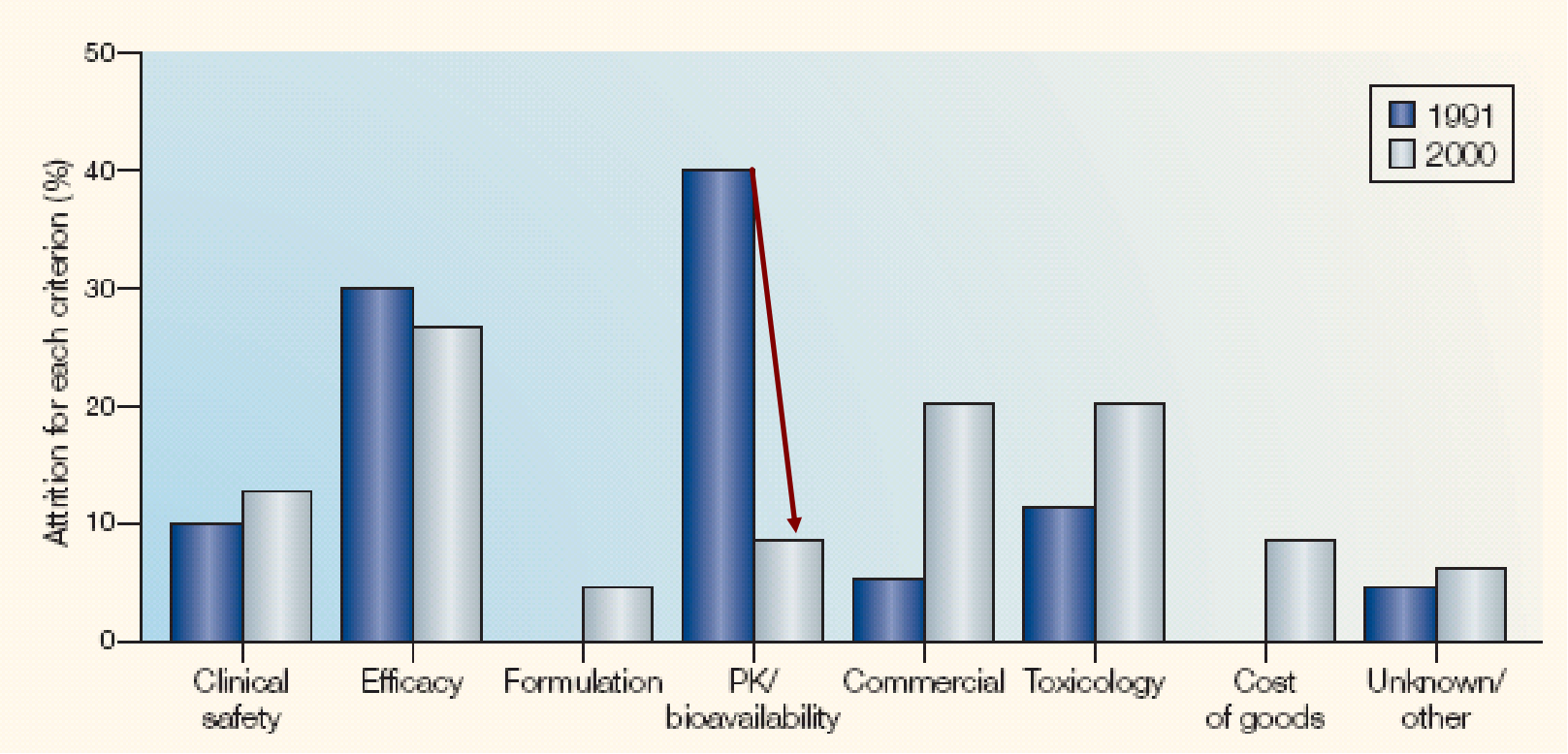
- **Understanding the ADME properties of drug candidates will ensure that:**
  - **The human PK of drug candidates will meet the target product profile**
    - Understand exposure/efficacy relationship (PK/PD)
    - Appropriate PK properties to support desired dosing regimen and combination options
  - **There is adequate exposure in safety studies**
    - Good bioavailability and exposure in safety species (rat, dog, monkey)
    - Adequate coverage of human metabolites in safety species
  - **The drug candidate is clinically safe and commercially competitive**
    - Minimal potential for drug-drug interactions
    - Disposition not solely dependent on a polymorphically-expressed enzyme/transporter (e.g. CYP2D6, 2C19, OATP1B1)
    - Minimal potential to form reactive metabolites, which could lead to drug-induced liver injury

DMPK in Drug Discovery and Development



IND = Investigational New Drug
NDA = New Drug Application
PK/PD M&S = Pharmacokinetics / Pharmacodynamics Modeling & Simulation
LCM = Life-cycle management

Why Potential Drugs Fail...



Early assessment of ADME properties of lead compounds has greatly lowered drug failure due to poor ADME-PK properties

Kola and Landis. *Nature Reviews Drug Discovery* **2004** *3*: 711-715.

Undesirable DMPK Properties of Marketed Drugs

Drug	Undesirable DMPK Property	Potential Risk for Toxicity	Action
Mibefradil (*Posicor*)	Potent CYP3A4 inhibitor	Perpetrator of drug-drug interactions	Market withdrawal
Terfenadine (*Seldane*)	Extensively and exclusively metabolized by CYP3A4	Victim of drug-drug interactions • Risk of cardiovascular adverse effects upon co-administration with CYP3A4 substrate (↑ $[Terfenadine]_{plasma}$)	Market withdrawal
Celecoxib (*Celebrex*)	Metabolized almost exclusively by CYP2C9 (polymorphic)	Risk of cardiovascular adverse effects due to ↑ $[Celecoxib]_{plasma}$ in CYP2C9 poor metabolizers	Black box warning on drug label
Troglitazone (*Rezulin*)	Metabolism to reactive intermediate	Hepatotoxicity	Market withdrawal

DMPK Criteria for an "Ideal" Drug

- Good aqueous solubility (oral absorption / intravenous formulation) and good permeability (lipophilicity)
- Acceptable PK for intended route / frequency of dosing
  - Low clearance
  - Low "first-pass effect" (liver/gut wall), high (oral) bioavailability
- No pharmacologically active metabolites (unless prodrug)
- No human specific metabolites
- Not bioactivated to reactive metabolites
- "Balanced" clearance
  - Renal excretion of intact drug
  - Biliary elimination of intact drug
  - Metabolism to limited number of products and by multiple enzymes
  - Metabolism should not depend largely on polymorphic enzymes
- Minimal CYP induction
- Low propensity to inhibit drug-metabolizing enzymes/transporters

Drug-Drug Interactions

Drug-Drug Interactions (DDI)

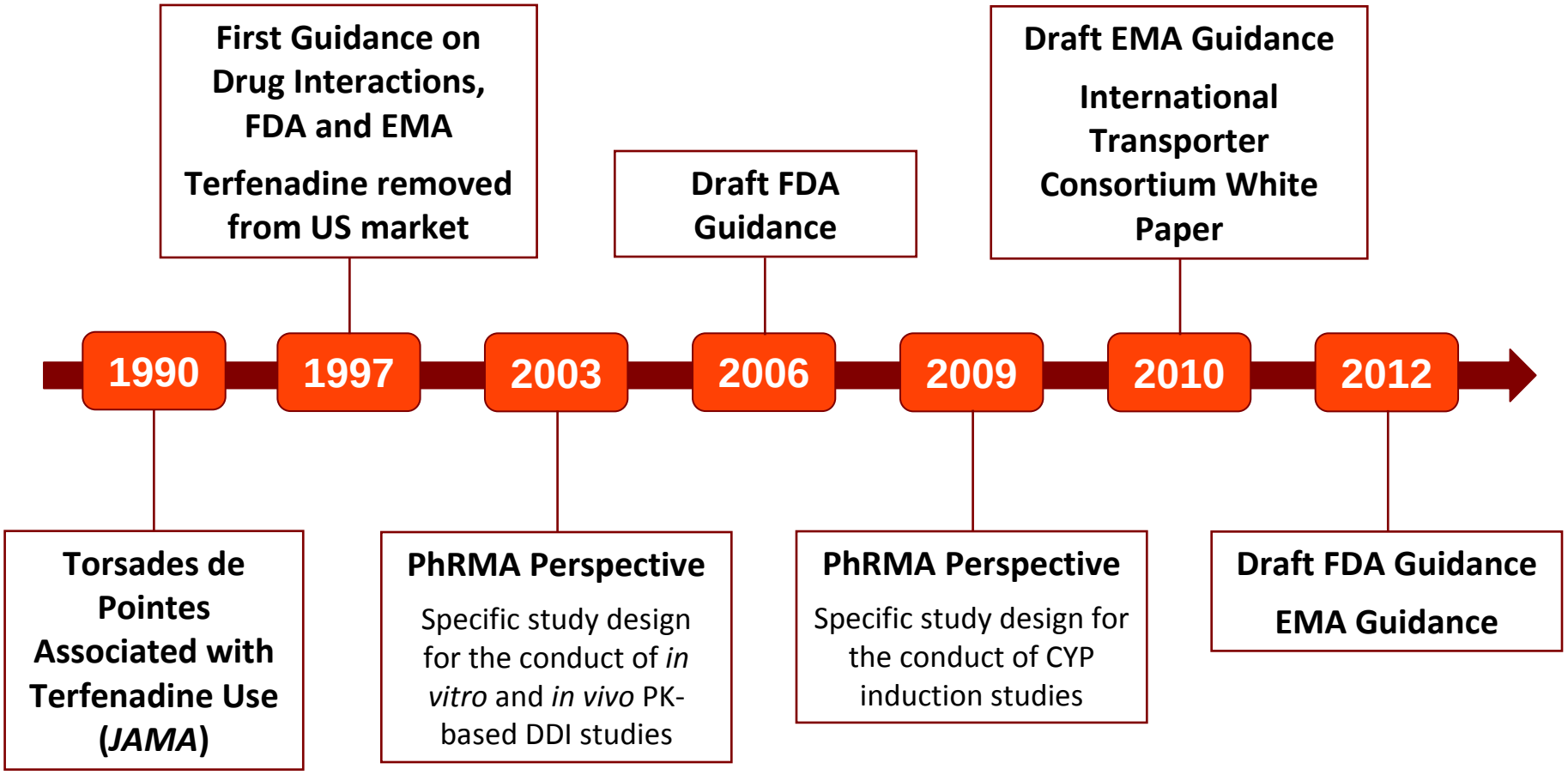
- DDI are one of the primary concerns for co-administered drugs
  - Can lead to decreased efficacy or increase adverse events
- Two categories of DDI: PD-based and **PK-based**
- Types of PK-based DDI:
  - Absorption-driven
  - Excretion-driven: Biliary and renal drug transporters
  - Plasma protein binding (risk is low; may be important for highly bound drugs with narrow therapeutic window)
  - Metabolism-driven:

    Effect of an investigational drug on other drugs – *Perpetrator*

    Effect of other drugs on an investigational drug – *Victim*

    Many mechanisms: CYP inhibition (reversible or irreversible), CYP induction

Evolution of Guidance for Industry on DDI



New DDI Guidance Documents 2012

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, 301-796-1635.

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

February 2012
Clinical Pharmacology

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 June 2012
CPMP/EWP/560/95/Rev. 1
Committee for Human Medicinal Products (CHMP)

Guideline on the Investigation of Drug Interactions

Final

Discussion in the Efficacy Working Party (EWP)	June/October 1996
Transmission to the CPMP	February 1997
Transmission to interested parties	March 1997
Deadline for comments	March 1997
Re-submission to the EWP	September 1997
Approval by the CPMP	December 1997
Date for coming into operation	December 1997
Draft Rev. 1 Agreed by the EWP	June 1998
Adoption Rev. 1 by CHMP for release for consultation	April 2010
End of consultation Rev. 1 (deadline for comments)	22 April 2010
Agreed by Pharmacokinetics Working Party	31 October 2010
Adopted by CHMP	February 2012
ate for coming into effect	21 June 2012
uideline replaces guideline CPMP/EWP/560/95.	1 January 2013

Interaction, guideline, metabolism, inhibition, induction, transport, enzyme, transport protein, transporter, absorption, food, distribution, PBPK, herbal, SmPC

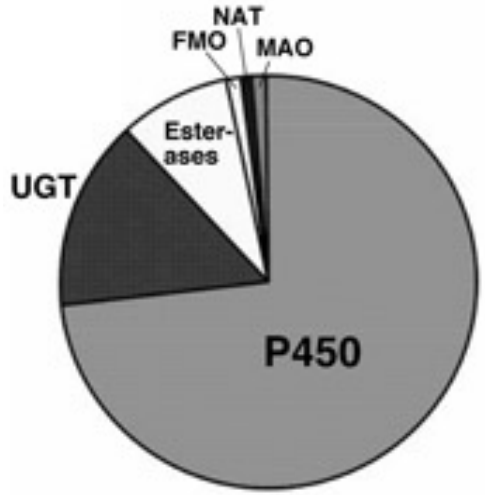
New DDI Guidance Documents 2012

- Significant advances have been made in our understanding of the mechanisms underlying clinically relevant DDIs since the introduction of the first guidance document in 1997:
  - More CYP isoforms for CYP inhibition and induction
  - Inclusion of UGT-mediated DDI
  - Data-driven consideration of less common drug-metabolizing enzymes
  - Transporter-mediated DDI (substrate and inhibition)
  - DDI mediated by metabolites
  - Additional guidance for *in vitro* assay data interpretation (basic and mechanistic models) and decision trees to trigger *in vivo* evaluation
  - Role of dynamic PBPK modeling and simulation

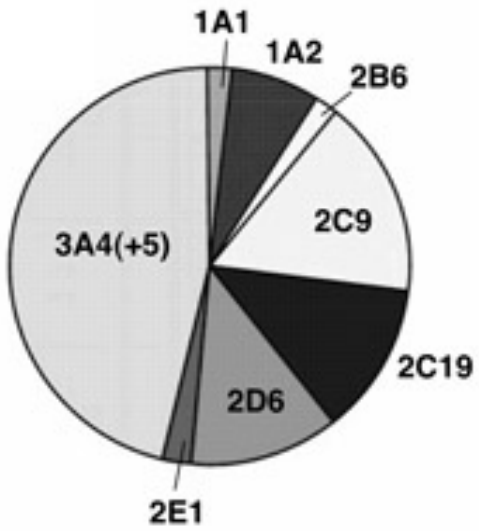
Focus on general strategies and study design for *in vitro* studies

Drug-Metabolizing Enzymes

Fraction of drug reactions catalyzed by various human enzymes:



Fraction of P450-mediated drug oxidations catalyzed by individual P450s:



FDA Draft Guidance:

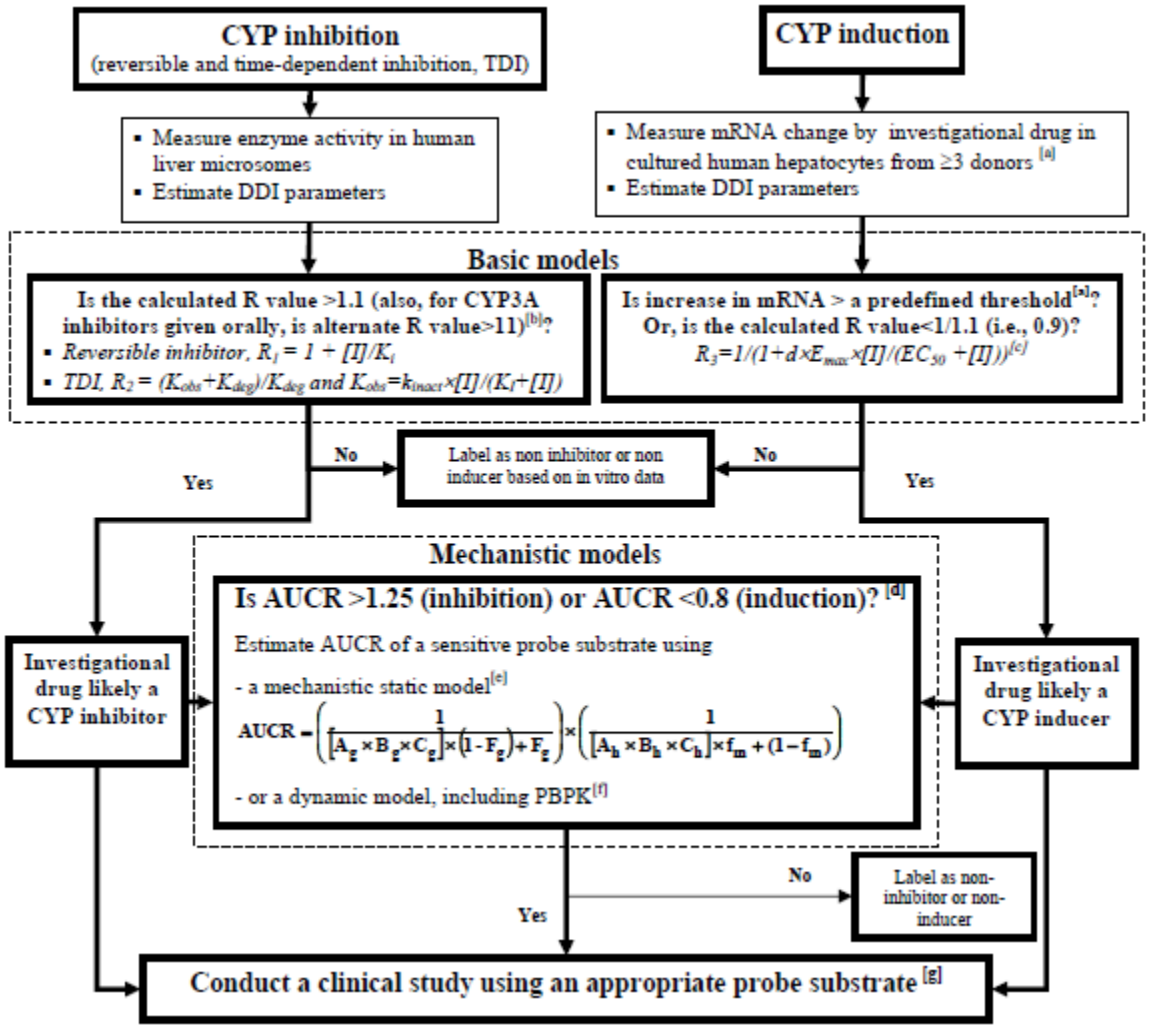
- CYPs for phenotyping and inhibition studies: 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4
- UGTs for phenotyping: 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15 **UGT2B10 missing (high affinity *N*-glucuronidation)**
- Consider less common enzymes for phenotyping (FMO, MAO, AO, ADH, XO, SULT)

EMA Guidance:

- CYP inhibition: 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4
- CYP and non-CYP enzymes for phenotyping
- Consider UGT1A1 and UGT2B7 inhibition for compounds eliminated by glucuronidation

Guengerich, F.P. *Chem. Res. Toxicol.* **2008** *21(1)*: 70-83.

CYP Inhibition and Induction: FDA Decision Tree



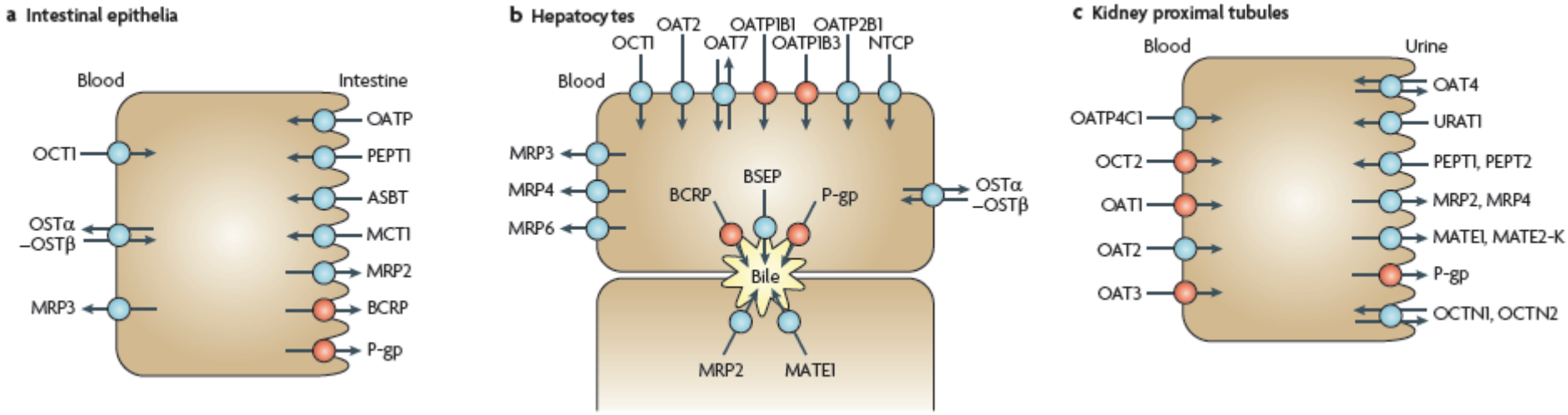
Basic Models
- Simple and practical
- Conservative
- Estimation of R value

Mechanistic Static Models
- Incorporates drug disposition and drug interaction mechanisms

PBPK Models
- System- and drug-dependent parameters
- Dynamic

Draft FDA Guidance for Industry. Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012.

Drug Transporters



Transporter Study	Draft FDA Guidance	EMA Guidance
Substrate ID	Pgp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2	OATPs and any relevant intestinal, biliary, renal transporter
Inhibition	Pgp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2	Pgp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 Also consider OCT1, MATE1, MATE2, BSEP

The International Transporter Consortium (2010) *Nat Rev Drug Disc* **9:** 215-236.

Clinically Relevant Transporter-Mediated DDI

Transporter	Tissue/ Function	Interacting Drug	Affected Drug	Clinical Impact
Pgp	Intestine, kidney, liver/Efflux	Quinidine	Digoxin	CL_r↓34-48%
		Drondarone	Digoxin	AUC↑157%, C_{max}↑75%
BCRP	Intestine, kidney, liver/Efflux	GF120918	Topotecan	AUC↑143%
OATP1B1	Liver/Uptake	Cyclosporine	Pravastatin	AUC↑890%, C_{max}↑678%
OATP1B3	Liver/Uptake	Cyclosporine	Rosuvastatin	AUC↑610%
OAT1	Kidney/Uptake	Probenecid	Acyclovir	AUC↑40%, CL_r↓32%
OAT1/OAT3*	Kidney/Uptake	Probenecid	Furosemide	CL_r↓66%
OCT2/MATE*	Kidney/Uptake/ Efflux	Cimetidine	Metformin	AUC↑50%, CL_r↓27%

*It is not possible to definitively assign specific transporters to these interactions.

The International Transporter Consortium (2010) *Nat Rev Drug Disc* **9:** 215-236.
Draft FDA Guidance for Industry. Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012.

Other Topics Covered in Guidance Documents

Draft FDA Guidance	EMA Guidance
Drug Interactions of Therapeutic Proteins	
Design of *In vivo* DDI Studies	Design of *In vivo* DDI Studies
Strategy for PBPK modeling and simulation and population PK	Strategy for PBPK modeling and simulation and population PK
	Herbal medicinal products and food effects
	Plasma protein binding interactions
	Guidelines for *in vivo* mass balance studies
Labeling Recommendations	Labeling Recommendations

Conclusions

- Significant advances have been since the introduction of the first DDI guidance document in 1997
- Today, clinically-relevant PK-based DDIs can be predicted from a limited number of well designed mechanistic *in vitro* studies using human enzymes and transporters
  - Due to marked species differences, *in vivo* studies in preclinical species cannot be extrapolated to humans
  - CYP-mediated metabolic interactions are relatively well understood
  - *In vitro-in vivo* extrapolation for drug transporter-mediated interactions is expected to continue to evolve
- Evaluation of the potential for DDI should be done early in discovery