Drug Interaction Studies

Lawrence J. Lesko
Center for Pharmacometrics and Systems Pharmacology
University of Florida at Lake Nona

Southern California Drug Metabolism Discussion Group

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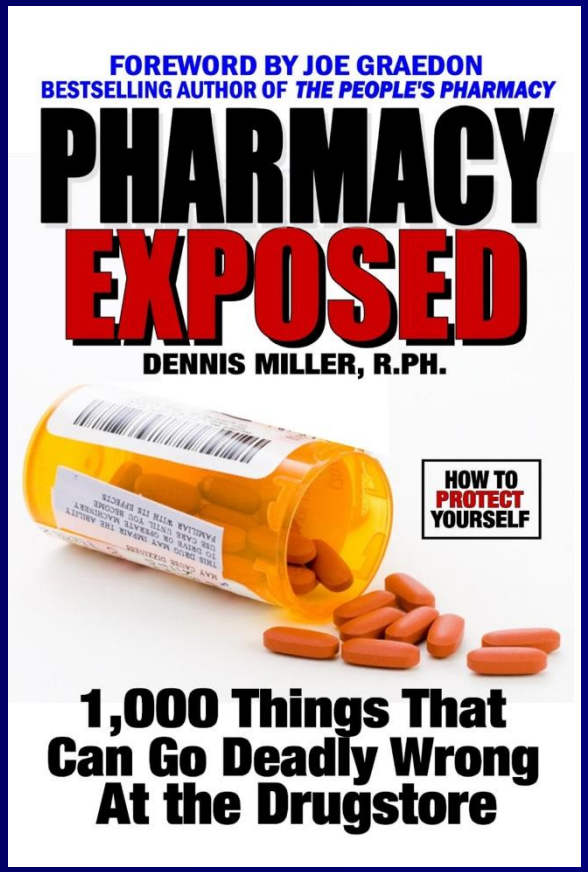
Outline

- PART I: The Big Picture of DDIs – What Are We Trying to Accomplish and Why
- PART II: Regulatory Guidances – How Well Do They Address the Problem
- PART III: Evolving Strategies – Future Shift in the DDIs Study Paradigm

Alternative Outline: Drugs Behaving Badly or Transporters Gone Wild

Part I: Contrarian and Unpopular View of Drug Interactions



Polypharmacy is rampant

- 50% of citizens take 1 Rx
- 25% take 3-5 Rxs
- 10% take > 5 Rxs
- Elderly take > 28 Rxs

DDIs cause 0.05% of ER visits and 0.6% of hospital admissions. Isn't this good news?

Pharmacoepidemiol Drug Safety 2007;16:641-651

As Lee Corso Would Say: "Not So Fast My Friend"

Stomach pain and cramps:	11,000,000 (8.0%)
Chest pains:	7,000,000 (4.4%)
Fever:	5,000,000 (3.2%)
Back pain	4,000,000 (2.5%)
Traffic accidents:	3,500,000 (2.2%)
DDIs:	74,000 (0.05%)

Energy drinks: 21,000
(More when mixed with vodka)

Nat Hosp Ambulatory Medical Case Survey of ER Visits: 2010

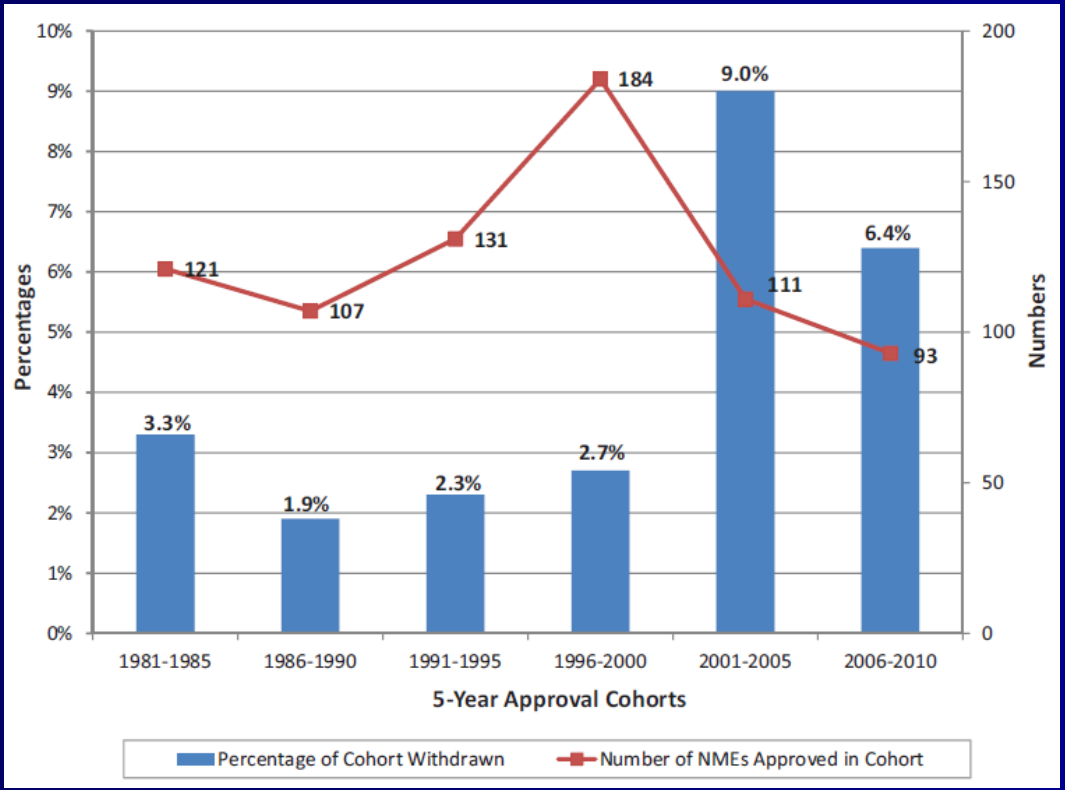
What Do We Know About DDIs in Ambulatory Patients?

Drug claims databases with almost 3 million patients receiving more than 30 million Rxs dispensed over a 12 month period – were analyzed by clinical pharmacists.

- A total of 244,703 cases of potential DDIs were identified. The incidence of serious AEs was relatively low (less than 1%).
- The top 10 drug interaction pairs by incidence were with co-prescribed older drugs such as statins, warfarin, SSRIs, digoxin and diuretics

JMCP 2003; 9: 513-522

But What About Market Withdrawals Because of DDIs?



Most common reasons are serious AEs underreported or not reported at all in labels.

Drug Information Journal 2012;46:694-700

The Regulatory Tipping Point for DDIs Occurred 15 Years Ago

Regulatory agencies shifted emphasis to a more proactive risk management approach to DDIs partly because of withdrawal of high profile drugs such as *mibefradil (1998), terfenadine (1998), asetemizole (1999), cisapride (2000)* and *cerivastatin (2001).*

All but cerivastatin cause long QT Torsade's de Pointes and all involved both CYPs and transporters.

There have been 21 drugs removed from market since 2001 and none cited *dangerous DDIs* as the risk.

So Why the Big Concern? Psychology of Perceived Risks

- Over-react to "intentional" actions (74,000 DDIs) and under-react to natural phenomena (5M for fever)
- People exaggerate serious AEs from DDIs – although rare – and downplay benefit of drug pairs
- People worry about a few spectacular risks (DDIs) but downplay common risks (energy drinks)
- Public scrutiny of risks renders caution (DDIs) while accepted risks (traffic accidents) hardly make news

Part II: New Regulatory Guidances for DDI Studies

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

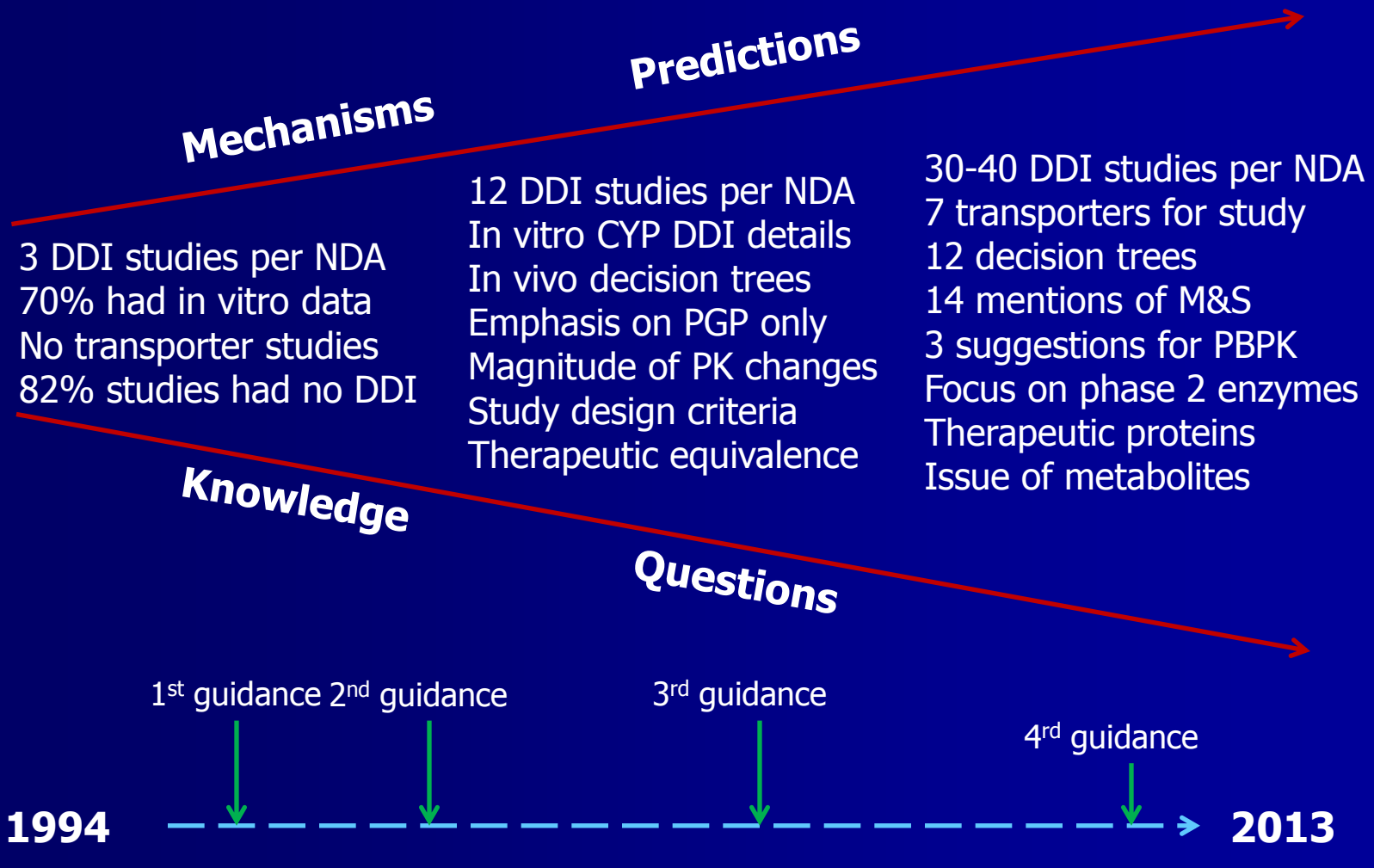
21 June 2012
CPMP/EWP/560/95/Rev. 1
Committee for Human Medicinal Products (CHMP)

Guideline on the Investigation of Drug Interactions

Final

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

Why DDIs Are Getting Harder and Harder to Study



Unintended Consequences for Sponsors

- Larger industry DMPK and CP groups focused on DDI programs which increase costs of development
- Lost opportunities to focus resources on more important decisions such as optimal dosing
- More clinical DDI studies have not provided higher quality information in label for clinicians
- Sorting the "wheat" (clinically significant DDIs) from the "chaff" (all DDIs) is increasingly difficult
- Things will get worse without public discussion of alternative strategies to the recent trends in DDIs

Example – Boceprevir: Protease Inhibitor Approved for Hepatitis C

- ✓ CYP3A4 substrate and potent CYP3A4 and PGP inhibitor
- ✓ *In vitro* transporter studies on OATB1B1, OATP1B3, BCRP, MRP2 – no in vivo DDIs expected based in IC_{50}/C_{max} . Label silent.
- ✓ 16 *in vivo* DDIs (10 on other drugs) including ritonavir. Label had no dose adjustments.
- ✓ Contraindicated with CYP3A4 substrates and potent CYP3A4 inducers
- ✓ PMRs included 4 additional clinical DDI studies on likely co-administered drugs and digoxin

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258Orig1s000TOC.cfm

Unanticipated Clinical Effects Show Limitations of DDI Studies

FDA Drug Safety Communication: Important drug interactions between Victrelis (boceprevir) and ritonavir-boosted human immunodeficiency virus (HIV) protease inhibitor drugs

Effectiveness of both drugs reduced significantly when used together (8 Feb 2012). Unanticipated decrease in exposure due to mixed inhibitor/inducer effects on CYPs and uncharacterized transporter effects

Drug	Dose	Boceprevir	Cmax	AUC	Cmin
Ritonavir	100 mg daily x 12 days	400 mg TID x 15 days	0.73 (0.57-0.93)	0.81 (0.73-0.91)	1.04 (0.62-175)

http://www.fda.gov/Drugs/DrugSafety/ucm291119.htm

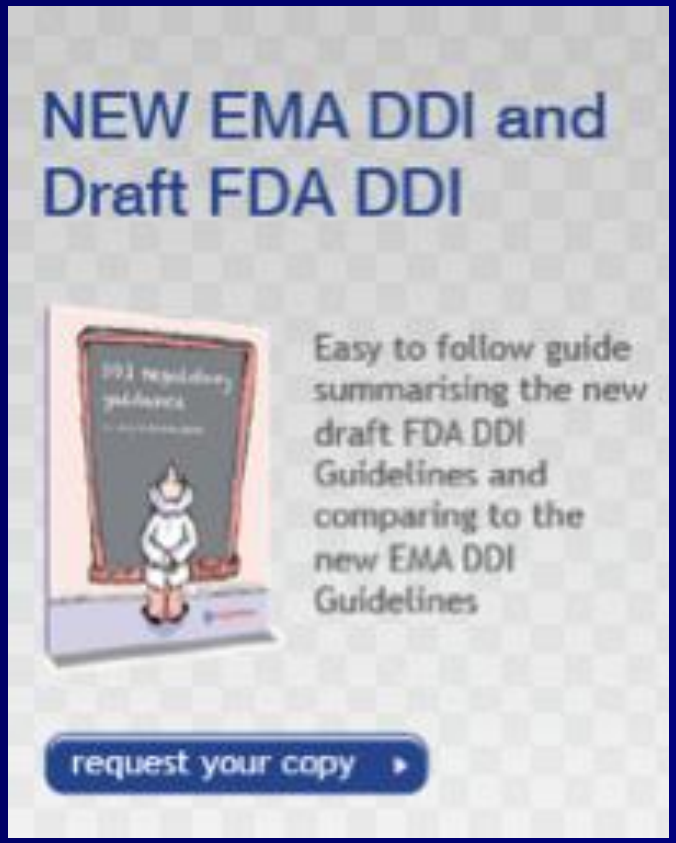
Example–Teleprevir: How Can DDI Studies Be Made More Efficient?

- ✓ 14 *in vitro* studies, CYPs and P-gp
- ✓ 15 clinical studies, effects on teleprevir
- ✓ 23 clinical studies, effects on other drugs
- ✓ 2 ongoing clinical studies at time of review

No dose adjustments recommended in label
One CI from a study actually conducted

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

How Do They Compare?



www.cyprotex.com/ddiguide

Remarkably similar

- Reaction phenotyping
- *In vitro* enzyme systems
- Enzymes of interest
- Transporter substrate ID
- Recommended transporters
- Metabolite % thresholds
- Attention to polymorphisms

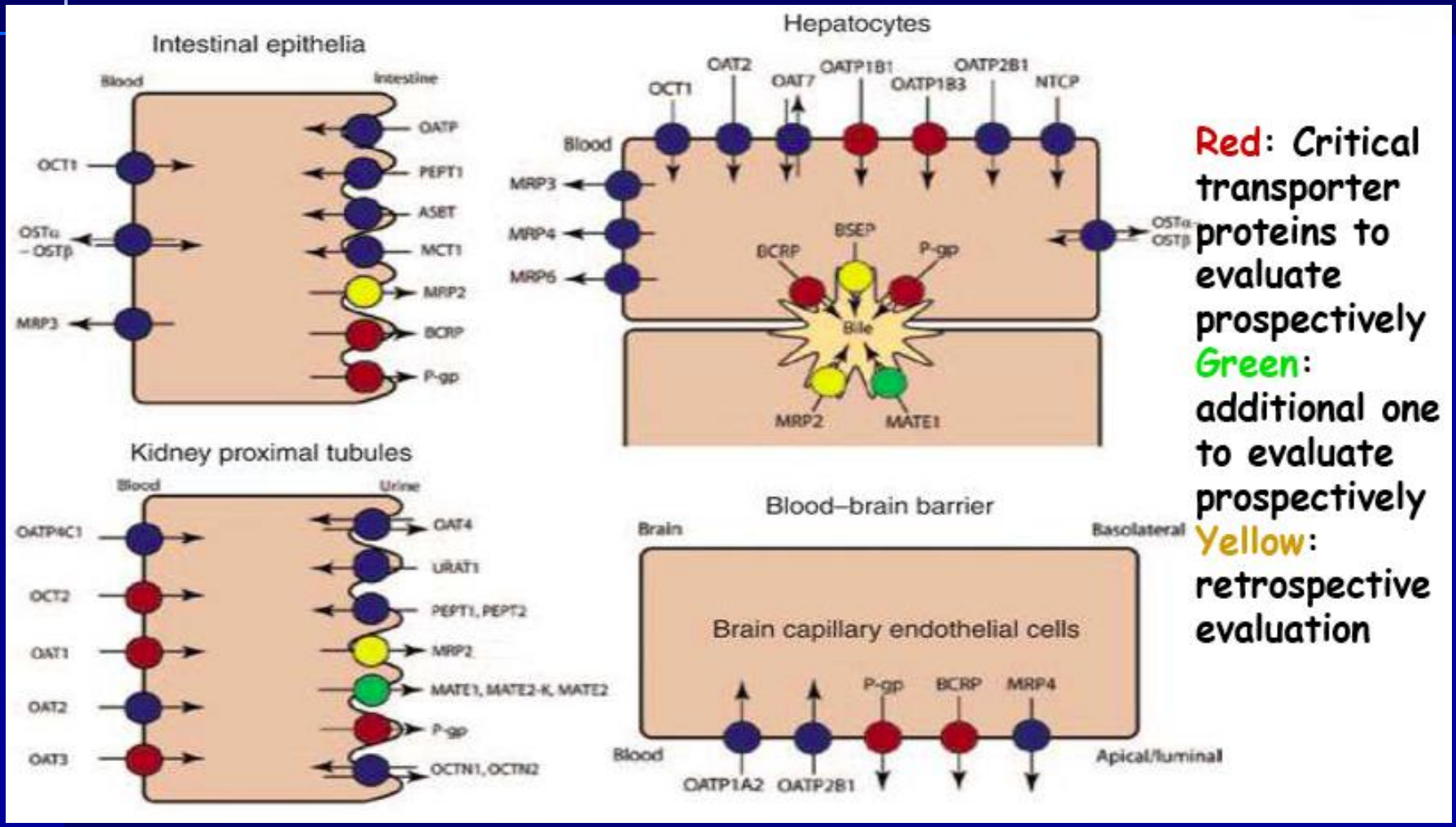
Not Surprising: FDA-EMA Cooperation Around DDI Guidance

Between 2008-2011

- Overall routine and *ad hoc* interactions ~ 50 per mo.
- Staff visits and exchanges on DDIs ~ 6 per yr
- Liaisons – Shiew-Mei Huang and Eva Gil Berglund
- Motivation
  - Share best practices
  - Drug development is global
  - Both agencies review same information
  - Harmonize on recommendations
  - Reduce sponsor burden

Interactions between the European Medicines Agency and U.S. Food and Drug Administration September 2009-September 2010 at www.FDA.gov

Important Transporters In Guidances: Ready for Prime Time?



Red: Critical transporter proteins to evaluate prospectively

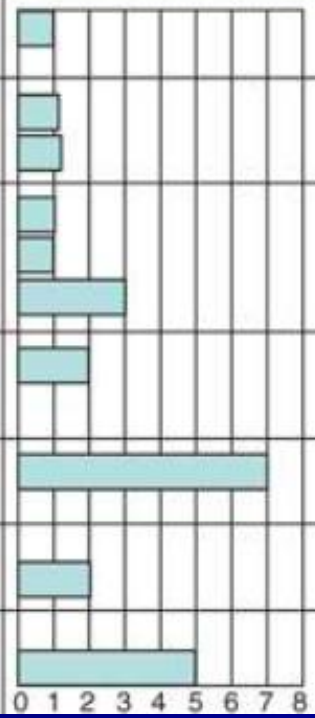
Green: additional one to evaluate prospectively

Yellow: retrospective evaluation

Zamek-Gliszczynski, Clin Pharmacol Ther (November 2012)

Black Swan Events: Surprising DDIs, Unanticipated and Rationalized Afterwards

Rosuvastatin: OATP and BCRP substrate

Group	Ethnic factor	Fold change in exposure (AUC)		Initial dose	Daily dose
1	Control	One-fold		10–20 mg	5–40 mg
2	Hepatic impairment	1.1-fold (mild) 1.2-fold (moderate)		10–20 mg 10–20 mg	5–40 mg 5–40 mg
3	Renal impairment	One-fold (mild) One-fold (moderate) Three-fold (severe)		10–20 mg 10–20 mg 5 mg	5–40 mg 5–40 mg 5–40 mg
4	Race	Two-fold (Asians)		5 mg	5–20 mg
5	Cyclosporine	Seven-fold			5 mg
6	Gemfibrozil	1.9-fold			10 mg
7	Lopinavir/ ritonavir	Five-fold			10 mg

From Drugs@FDA, Rosuvastatin Label (2010)

Current Status of Transporter Studies for 73 NME NDAs – 2012-2020?

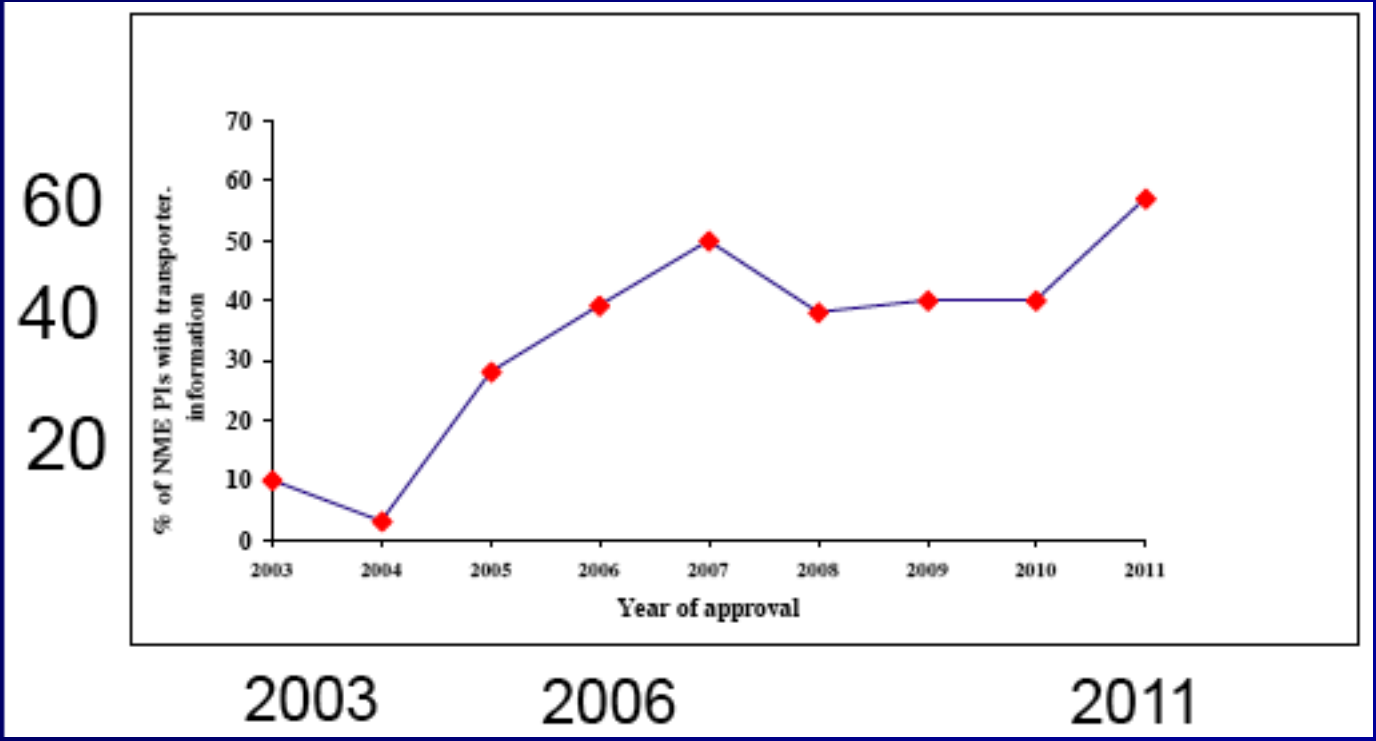
Survey covers NMEs approved between 2003 and 2011

Transporter	NMEs with transporter information in CP review	NMEs tested as substrate *in vitro*	NMEs tested as inhibitor *in vitro*	NMEs tested both as substrate and inhibitor *in vitro*
P-gp	54	53	49	48
BCRP	6	2	6	2
OAT1	1	0	1	0
OAT3	2	1	1	0
OCT	2	2	1	1
OCT2	4	2	3	1
OATP1B1	7	3	7	3
OATP1B3	4	2	4	2

- ✓ For PGP Caco-2 (55%) and MDR-1 transfected cells (36%) used; for all other transporters, transfected cells used
- ✓ *In vitro* methods used in NDAs are in agreement with FDA recommendations and decision trees in guidance

Poster (PIII-10) by Lei Zhang at 2013 ASCPT meeting

More and More Labels With Transporter Information



Transporter information included for descriptive purposes and relatively little is actionable

Challenge With *In Vitro-In Vivo* Correlations and Actionable Labels

- Drug transporters are widely appreciated as determinants of ADME – and drug transfer into CNS
- *In vitro* test systems are qualitative and do not quantitatively predict the *in vivo* situation
- Multitude of transporter DDIs resulting in PK changes are possible but don't trigger dose changes
- Clinically important (AUC > 2X) transporter DDIs are relatively few (< 10)
- Only PGP, OAT, OCT and OATP inhibition are known to have resulted in clinically important DDIs

Important Differences Remain Where Consensus Not Reached

Attribute	FDA	EMA
Enzyme inhibition models that trigger clinical studies	Total conc for [I]; higher threshold	Unbound conc for [I]; lower threshold (liver)
Transporter substrate ID for NMEs	All drugs evaluated for PGP and BCRP; BCS Class I waiver	N/A
Transporter inhibition by NME	All drugs evaluated for 7 transporters	BSEP (PD), MATE1 and MATE 2 (imatinib)
Therapeutic proteins	Cytokine modulators and CYP up- and down-regulation	N/A
pH-dependent solubility	N/A	PPIs, antacids etc.
PD interactions	N/A	Additive or opposing PD

Caution: Similar Guidances, Different Decisions

FDA and EMA guidances are remarkably similar in their general (conservative) approach, non-binding and reasonably detailed.

Facts (experimental data) rendered by DDI studies (some of it complex) cannot make decisions

Reviewers make decisions based on judgment and values; differences between regulators in expectations

Regulators view benefit and risk asymmetrically and tend to focus on "worst case scenarios"

Classification of DDI Enzyme Interactions

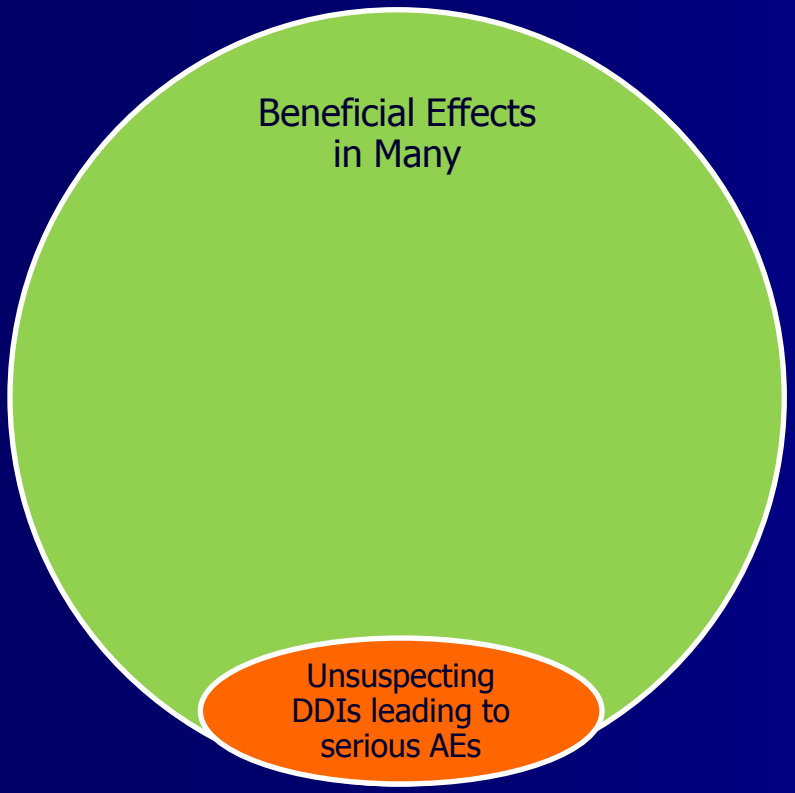
CYP Enzymes	Strong Inhibitors	Moderate inhibitors	Weak inhibitors
Inhibitors	**≥ 5-fold increase in AUC**	**≥ 2 but <5-fold increase in AUC**	**≥ 1.25 but <2-fold increase in AUC**
CYP Enzymes	**Strong Inducers**	**Moderate Inducers**	**Weak Inducers**
Inducers	**≥ 80% decrease in AUC**	**50- 80% decrease in AUC**	**20-50% decrease in AUC**

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm;

Part III: Evolving Strategies and Future Paradigm Shift

- Both FDA and EMA guidances mention "cocktail studies" more than 10 times
- Very little if any literature references on transporter cocktail studies
- Theoretically transporter and CYP enzyme cocktail studies have the same requirements
  - Analytical methods for probe drugs (metabolites)
  - Probe drugs approved for clinical use (safety)
  - Doses within approved range
  - Lack of mutual interaction between probes
  - Probes relevant to therapeutic area

Why Are Clinically Important DDIs So Difficult to Pick Out?



1 in 25 patients are at risk for PK DDIs but only 1 in 500 of these at-risk patient require ER visits or hospitalizations

Problem With Current Strategy: Reductionism—Study of Single Drug-Pairs

Scientific position which holds that a complex system is nothing more than the sum of its parts, and that an account of it can be reduced to accounts of individual constituents.

However, drug development programs do not, and cannot carry out enough clinical DDIs studies to explore the entire interaction space between drugs, enzymes and transporters

Why Are DDIs So Difficult to Study and Predict?

- ✓ Most known ADEs involve common drugs approved over the past 50 years – warfarin
- ✓ Preapproval DDI studies are single drug pairs: results may not be generalizable
  - ✓ Healthy volunteers selected to reduce variability
  - ✓ Limit dose range and other concomitant drugs
  - ✓ Duration of treatment is comparatively short
  - ✓ Relatively small number of subjects exposed
  - ✓ PD not likely to be studies or event rates low

Natural Human Heterogeneity Limits Translation of DDI Studies

1. Subgroups with particular genetic features are more sensitive to DDIs and AEs

2. Demographics – age, weight, sex, race – explains much of the variability in DDIs

3. Disease progression and co-morbidities – and multiple medications – increase risk of DDIs

Regulatory Agencies Know This: Post-Marketing Surveillance

Most serious DDIs and ADEs are still discovered after approval or during phase IV clinical trials and within 2 years in the market

1. FDA adverse event reporting system (AERS)
2. FDA sentinel initiative
3. Physician reports to the manufacturer
4. Safety surveillance of institutional EMRs
5. Third party payer claims database

PBPK Models: Applications Have Increased 4-Fold Since 2004

PBPK mentioned at least 3 times in FDA guidance, in decision trees and recommended in EMA guideline

Ping Zhao, Manuela de L. T. Vieira, Joseph A. Grillo, Pengfei Song, Ta-Chen Wu, Jenny H. Zheng, Vikram Arya, Eva Gil Berglund, Arthur J. Atkinson, Jr, Yuichi Sugiyama, K. Sandy Pang, Kellie S. Reynolds, Darrell R. Abernethy, Lei Zhang, Lawrence J. Lesko, and Shiew-Mei Huang

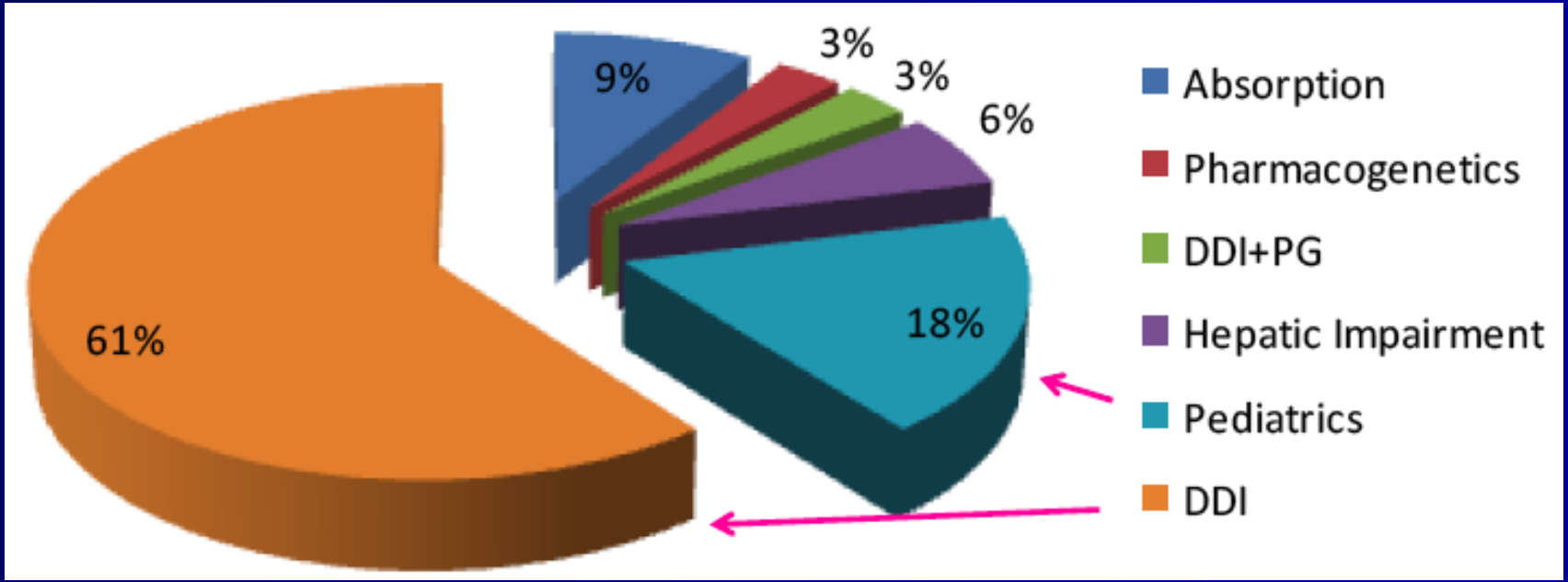
Evaluation of Exposure Change of Nonrenally Eliminated Drugs in Patients With Chronic Kidney Disease Using Physiologically Based Pharmacokinetic Modeling and Simulation

J Clin Pharmacol January 2012 52: 91S-108S, doi:10.1177/0091270011415528

Rowland, Peck and Tucker. Annu Rev Pharmcol Toxicol (2011)

Regulatory Submissions of PBPK to FDA From 2008-2012 (N=33)

Equal Number of IND and NDA Submissions



FDA reviewers also built 15 PBPK models as part of review work

Zhao, Clin Pharmacol Ther (2012) and Huang, ASCPT Annual Meeting (2013)

Other Uses of PBPK Advocated By Regulators

1. Inform study design – not sure what this means for regulators but industry relies heavily on PBPK for internal decision-making

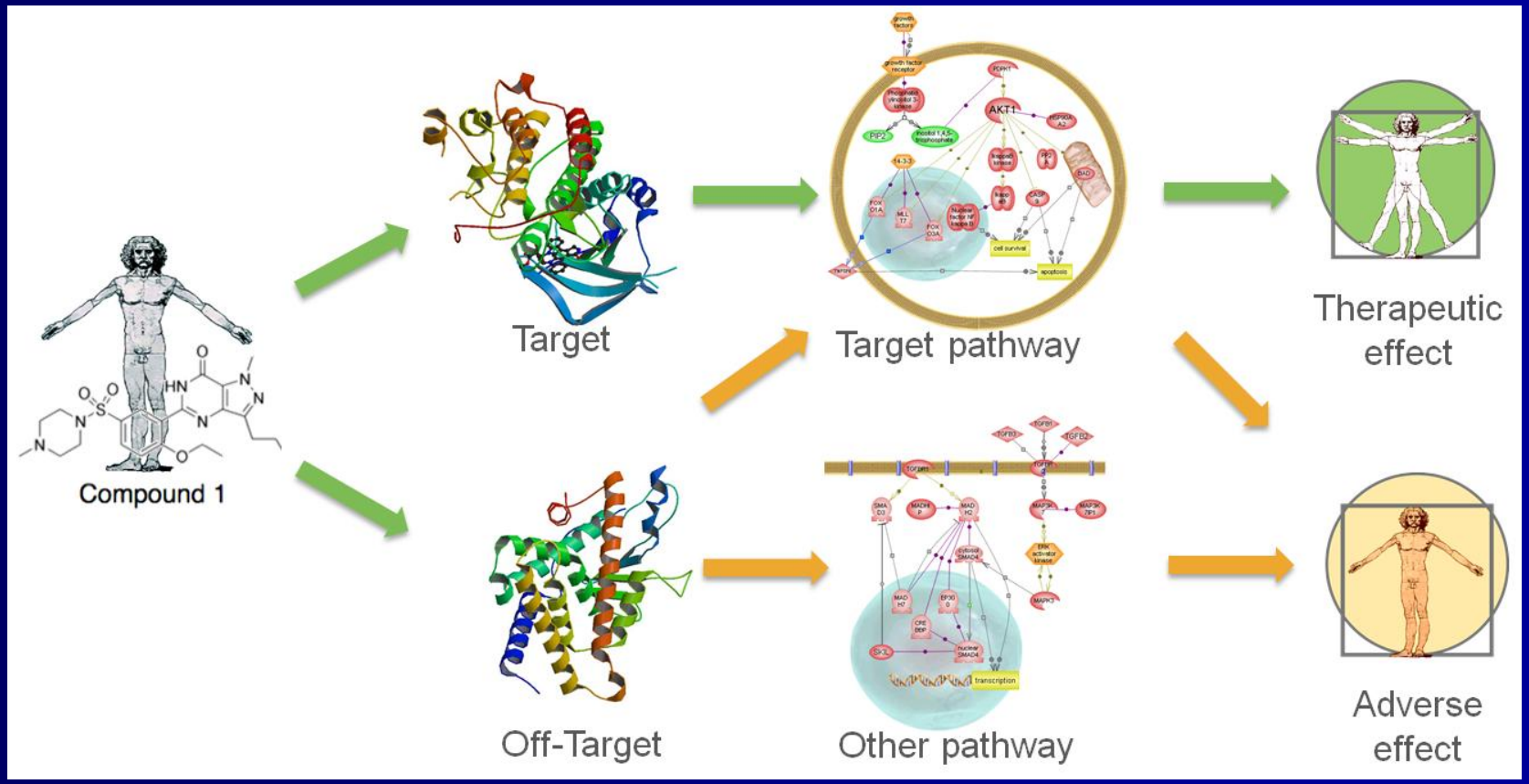
2. Estimate PK changes of more complex scenarios – potential DDI and renal impairment

3. Estimate dose for pediatric exclusivity studies using adult data as alternative to allometric scaling

Use of PBPK in Regulatory Decisions

- Few (n=2) examples of PBPK inclusion in labels; suspect findings were absence of DDIs
- Positive PBPK simulations of DDIs would trigger *in vivo* study as was done for PopPK studies
- Negative PBPK results have been used to not ask for DDIs post-approval
- Reviews of PBPK studies by EMA and FDA are quite different
- Accepting negative PBPK DDI results for label purposes and not asking for confirmatory *in vivo* studies has not been achieved

Informatics: Molecular Causation of DDIs and Adverse Events



Source: Dr. David Jackson, Molecular Health (2013)

Data Mining Using Search Engines: Example – Paroxetine-Pravastatin

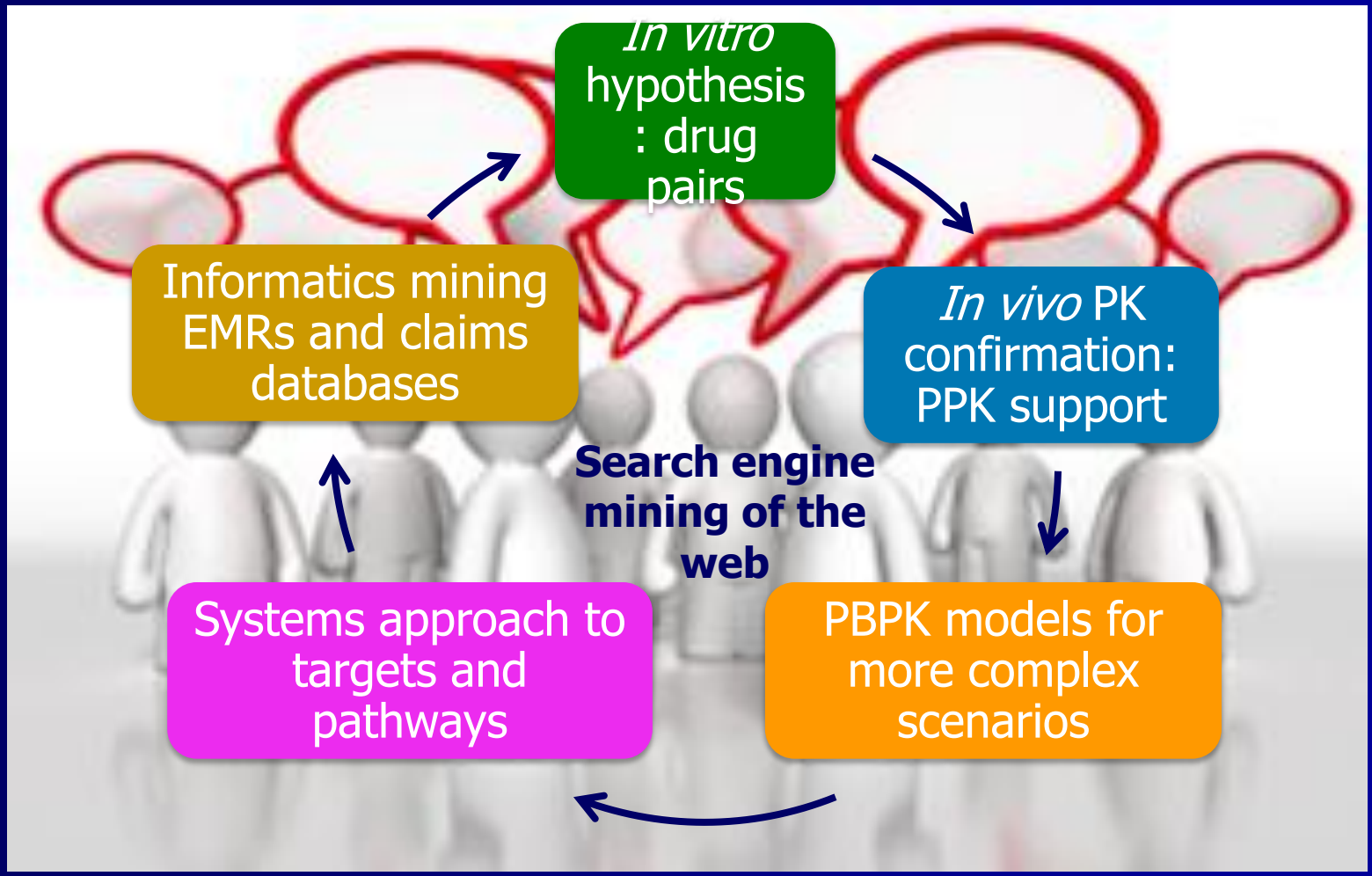
- Hyperglycemia mentioned in paroxetine label as infrequent AE but not in pravastatin label
- Pravastatin label reports results of 30 DDI studies but no study with paroxetine; no PD DDI studies
- Paroxetine is a 2D6 inhibitor; pravastatin has little CYP metabolism and no 2D6 pathways
- Pravastatin ADME influenced by SLC01B and 2B family, SLC22A family, ABC family of transporters in intestine, liver and kidney (11 different transporters)
- GSK has a clinical study underway comparing drugs alone and combined; incidence of T2DM

Crowd-Sourcing: Web-Scale Pharmacovigilance

- Complements and improves upon physician reports in the FDA AERS
- Mined large-scale web search log data for 80 million individual searches for possible DDIs
- Anonymized signals on DDIs can be used for hypothesis about known or undiscovered DDIs
- Companies like Treato[R] collect billions of patient-written health experiences from blogs and forums
- This can be good news (safer drugs) or bad news (false signals)

J Am Med Inform Assoc 2013;20:404-408

Future DDI "Learn-Confirm-Apply" Paradigm: Rapid Learning



Thank You

Questions – Comments

llesko@cop.ufl.edu
407-313-7008