FDA Critical Path Transporter Workshop
Bethesda, MD, October 3, 2008

Evaluation and Labeling of Drug-Drug Interactions - Focusing on Transporters -

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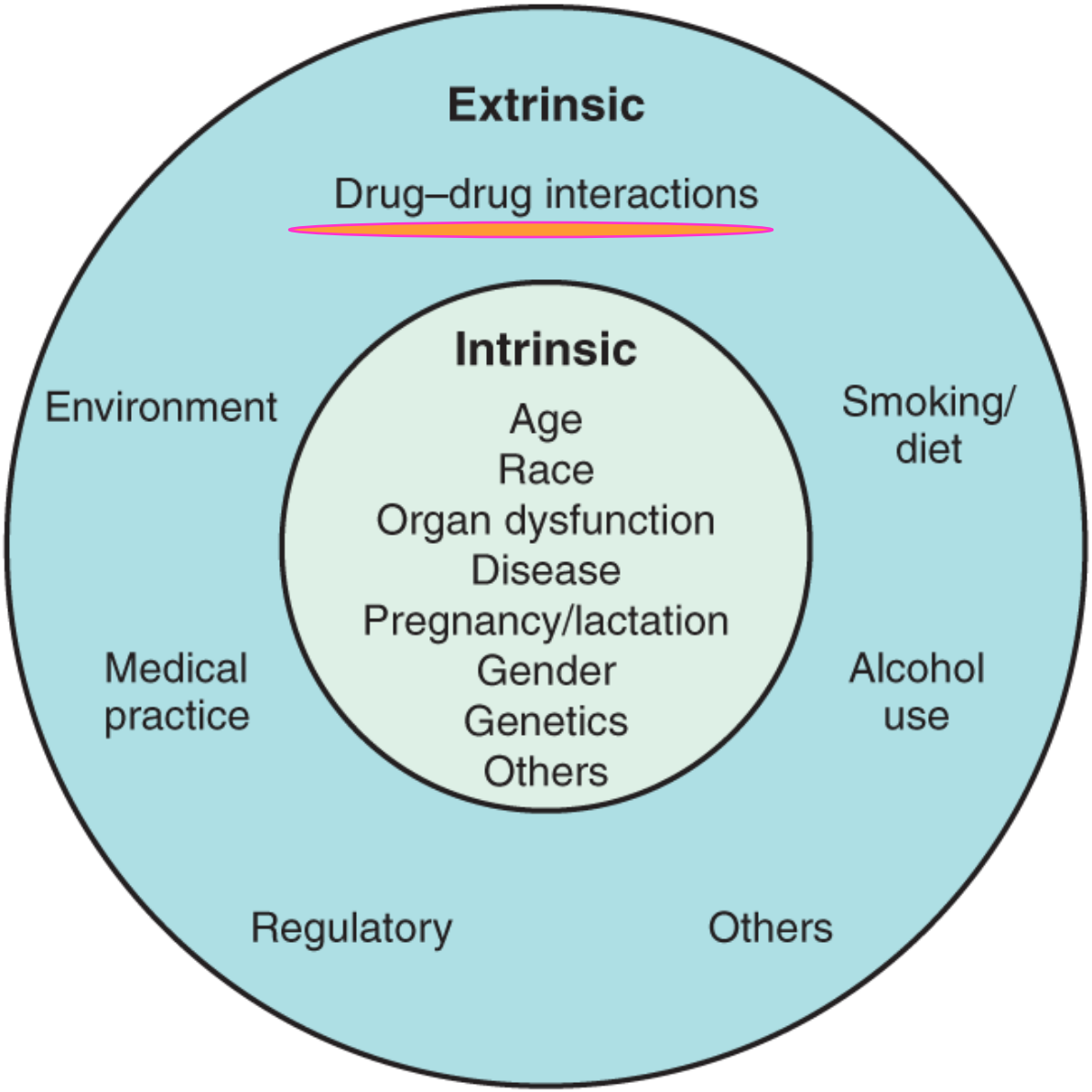
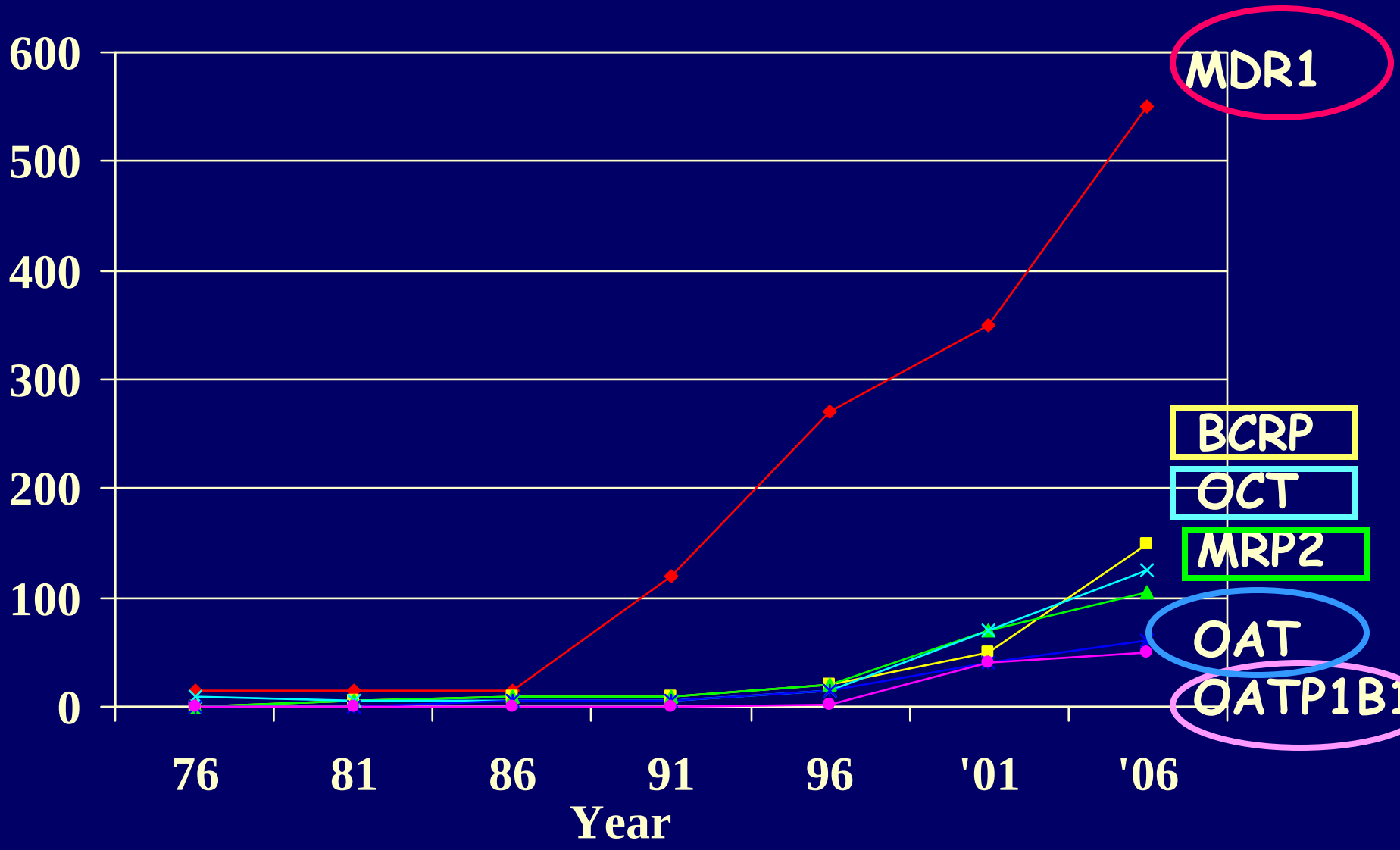


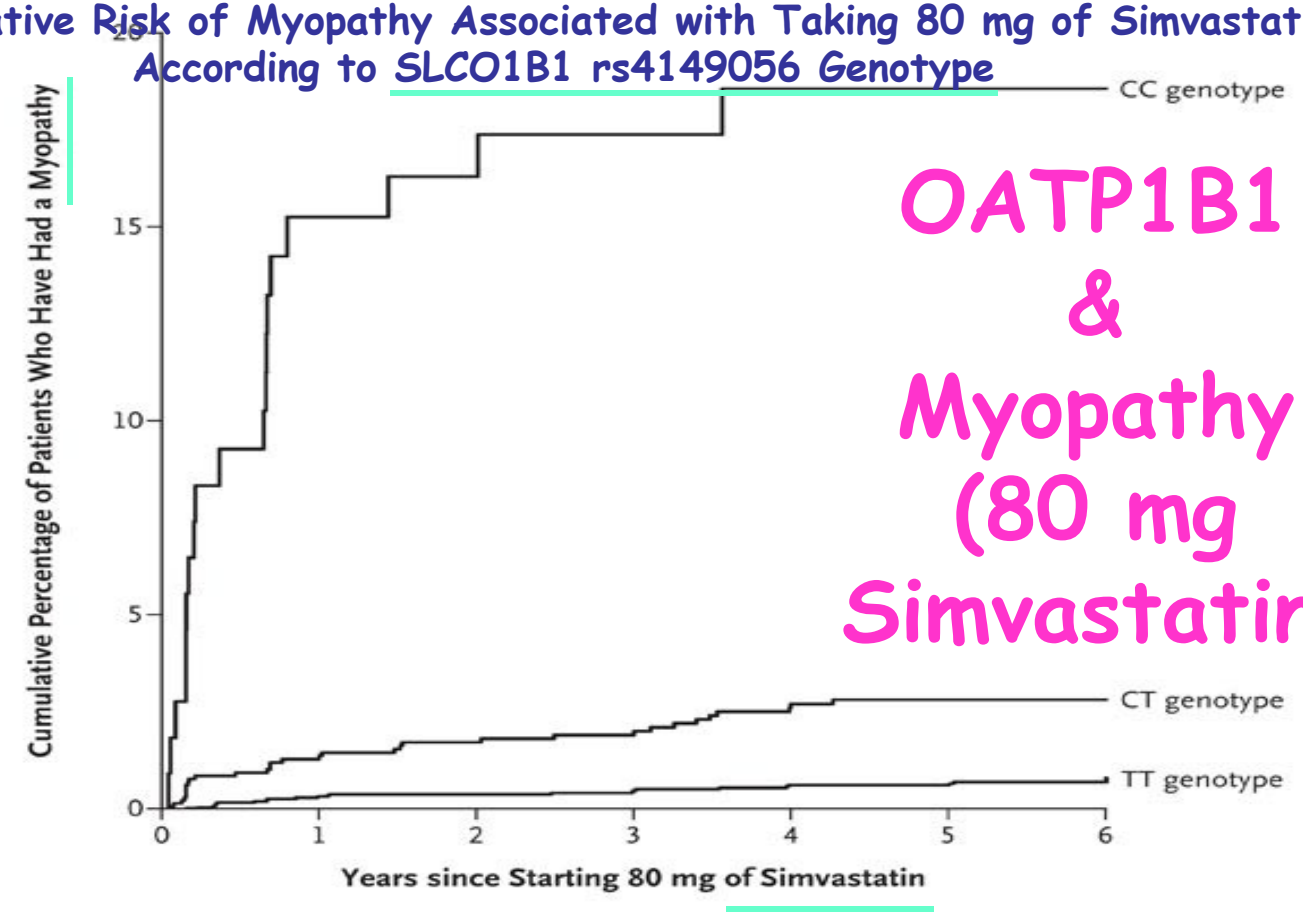
<Huang S-M, Temple R, Clin Pharmacol Ther. 84(3): 287-294, 2008>

Number of published papers/patents



<Survey via Biovista; courtesy: Aris Persidis>
http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4248s1-6-FDAHuang_files/frame.htm

Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype



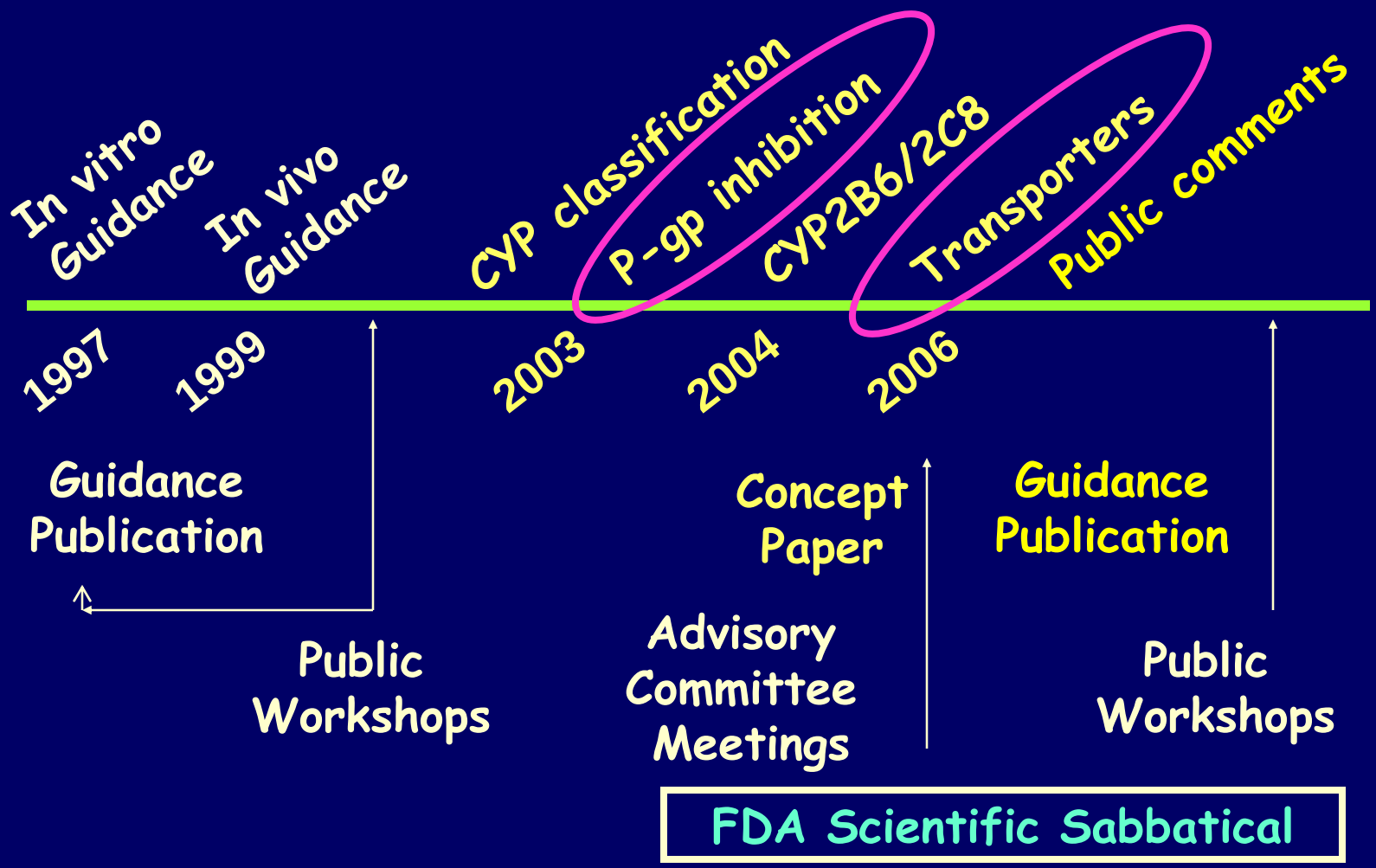
OATP1B1 & Myopathy (80 mg Simvastatin)

Cumulative No. and Percentages with Myopathy

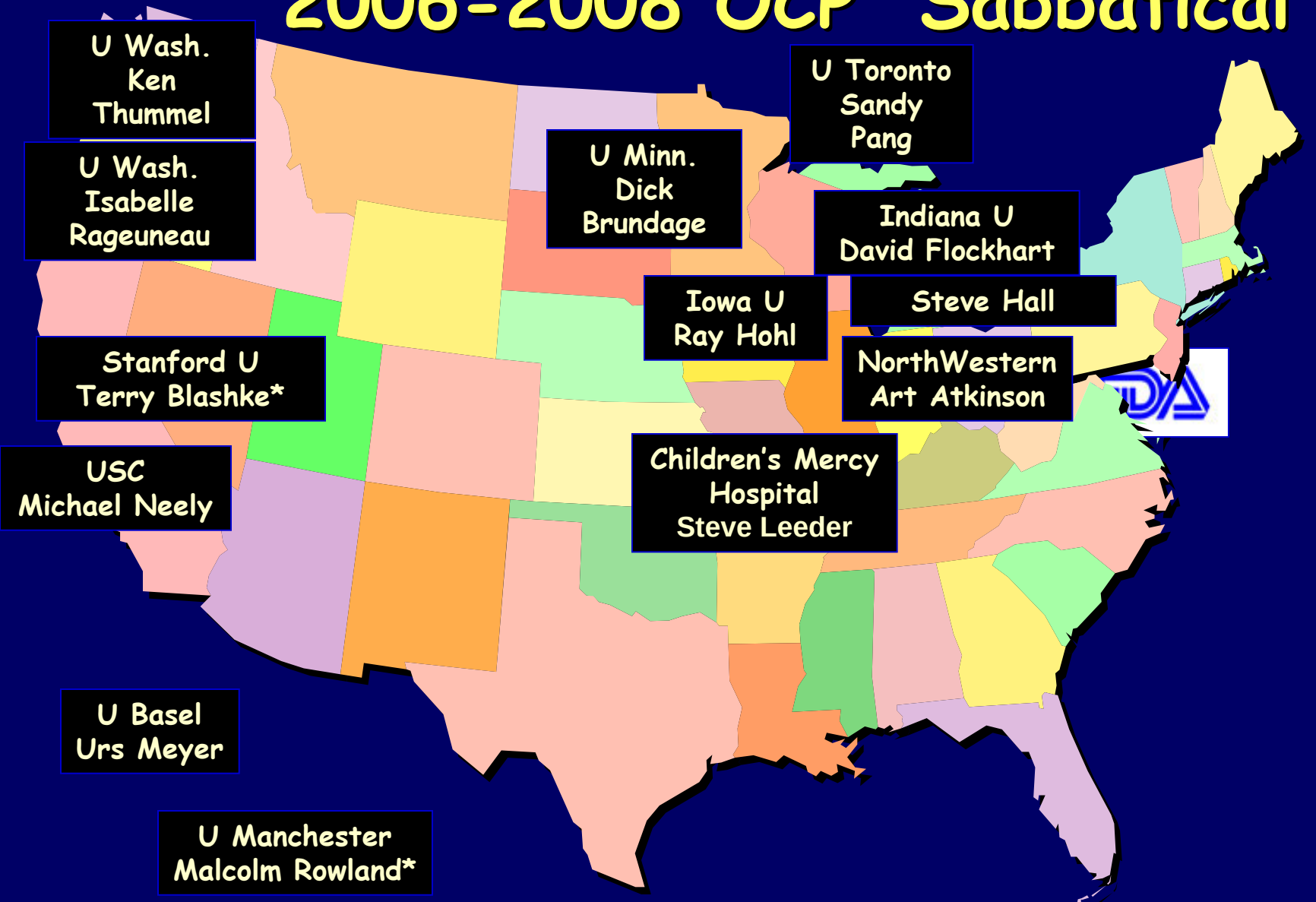
Genotype	Population Frequency	Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	*no.*	*% of total*	*no.*	%	*no.*	*% of total*
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

The SEARCH Collaborative Group. N Engl J Med 2008;10.1056/NEJMoa0801936

Discussions on Drug Interactions



2006-2008 OCP "Sabbatical"



* Prior to 2006

Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 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 (CBER) Toni Stifano, 301-827-6190.

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

September 2006
Clinical Pharmacology

Draft published for public comment September 11, 2006 http://www.fda.gov/cder/guidance/6695dft.pdf

What's New

Metabolism, transport, drug-interaction info key to benefit/risk assessment

October 2006, advisory committee meeting:
http://www.fda.gov/ohrms/dockets/ac/cder06.html#PharmScience
http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4248s1-index.htm
<Huang, Temple, Throckmorton, Lesko, Clin. Pharmacol. Ther. Feb 2007>
<Huang, Strong, Zhang, Reynolds, Nallani, Temple, et al, J Clin Pharmacol, June, 2008>
<Zhang, Zhang, Strong, Reynolds, Huang, Xenobiotica, July 2008>

CYP Enzymes

Decision trees--
When in vivo studies are recommended per in vitro data

- Substrate (25% metab)
- Inhibitor (I/Ki > 0.1)
- Inducer (40% control)

Classification of

- Inhibitors
- Inducers
- Substrates

What's New?

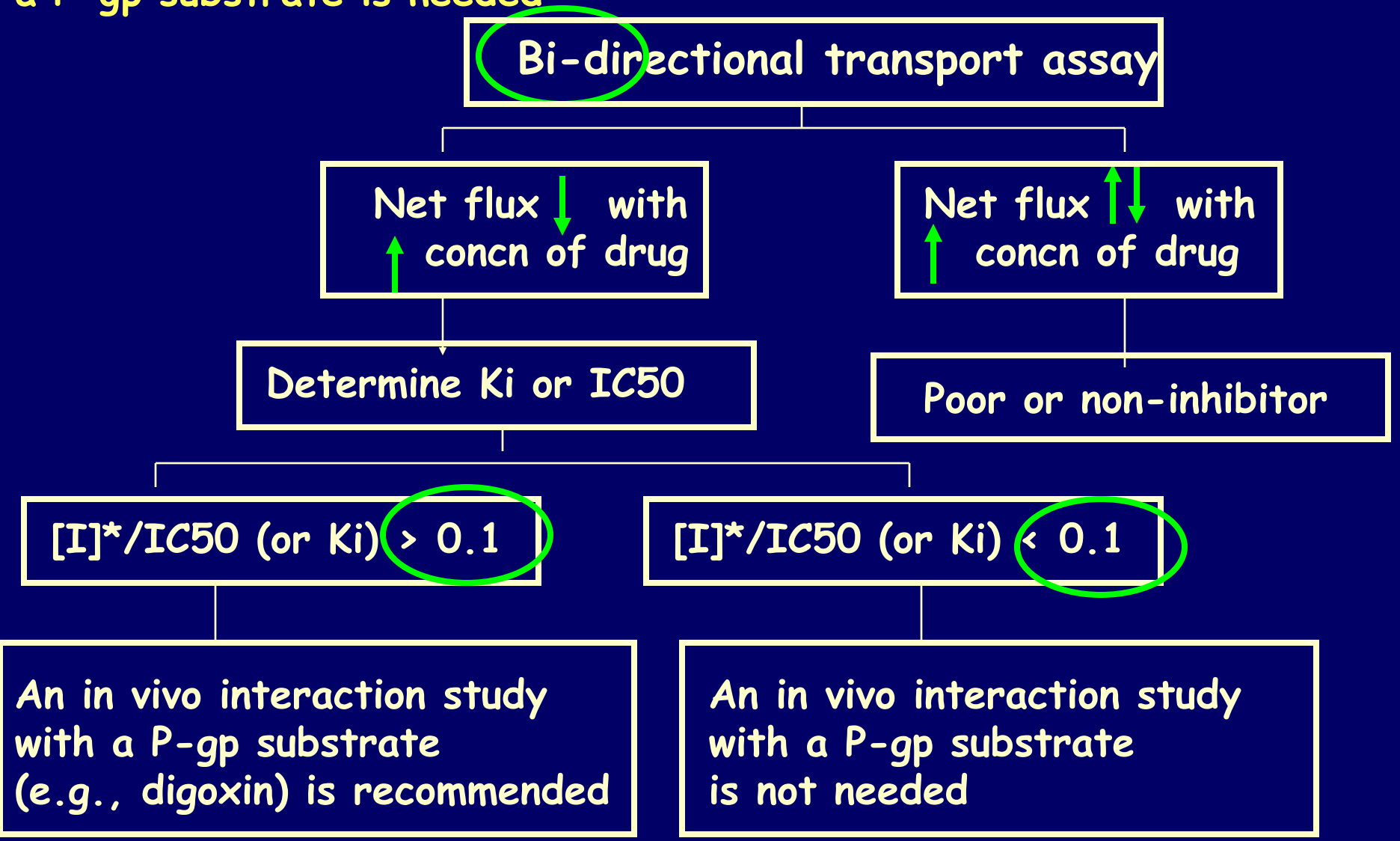
Transporters (P-gp)

Decision tree—
When in vivo studies are recommended per in vitro data

- Substrate (flux ratio)
- Inhibitor (I/Ki)
- (Inducer)

No classification system recommended

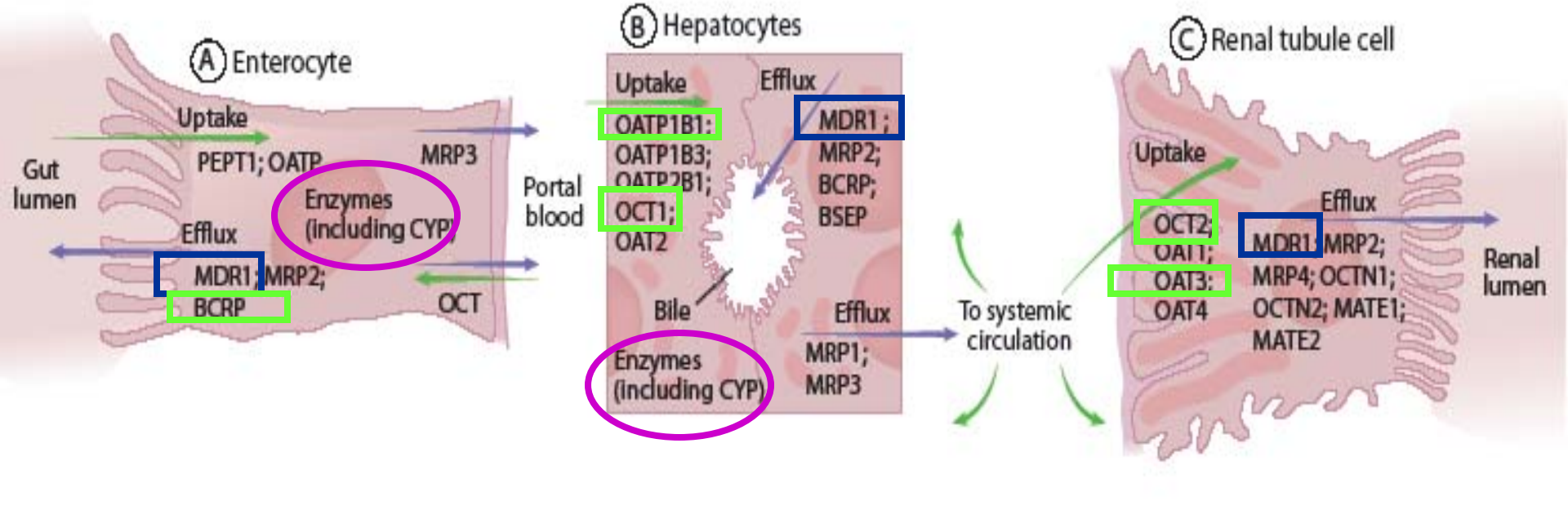
Figure 1. Decision tree to determine whether an investigational drug is an inhibitor for P-gp and whether an in vivo drug interaction study with a P-gp substrate is needed



*Alternate approach: [I]2/Ki > 10

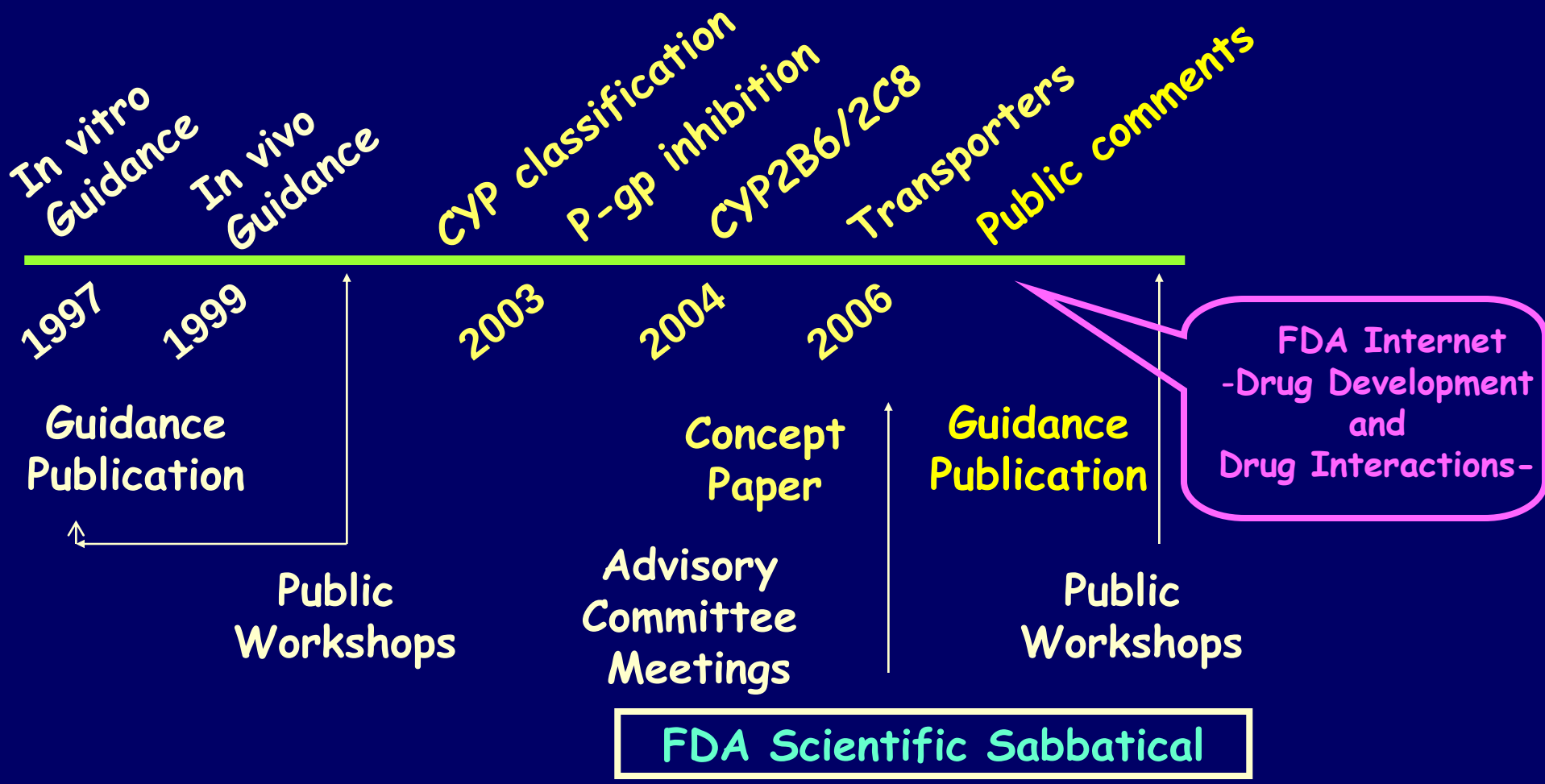
<L Zhang, Y Zhang, JM Strong, K Reynolds, S-M Huang, Xenobiotica, July 2008>

Selected efflux & uptake transporters in the gut wall (a), liver (b), and kidneys (c)



Huang S-M, Lesko LJ, and Temple R, "Adverse Drug Reactions and Pharmacokinetic Drug Interactions", Chapter 21, Adverse Drug Reactions and Drug Interactions in Part 4, FUNDAMENTAL PRINCIPLES: Clinical Pharmacology, "Pharmacology and Therapeutics: Principles to Practice," Ed. Waldman & Terzic, Elsevier (in press)

Discussions on Drug Interactions



----------FDA Publications----------

http://www.fda.gov/cder/drug/drugInteractions/default.htm

Drug Development and Drug Interactions

Questions Asked during Review

Drug interactions evaluated?

Clinical significance of the finding (exposure-response)?

Labeling language?

Case 1

Rosuvastatin (Crestor®)

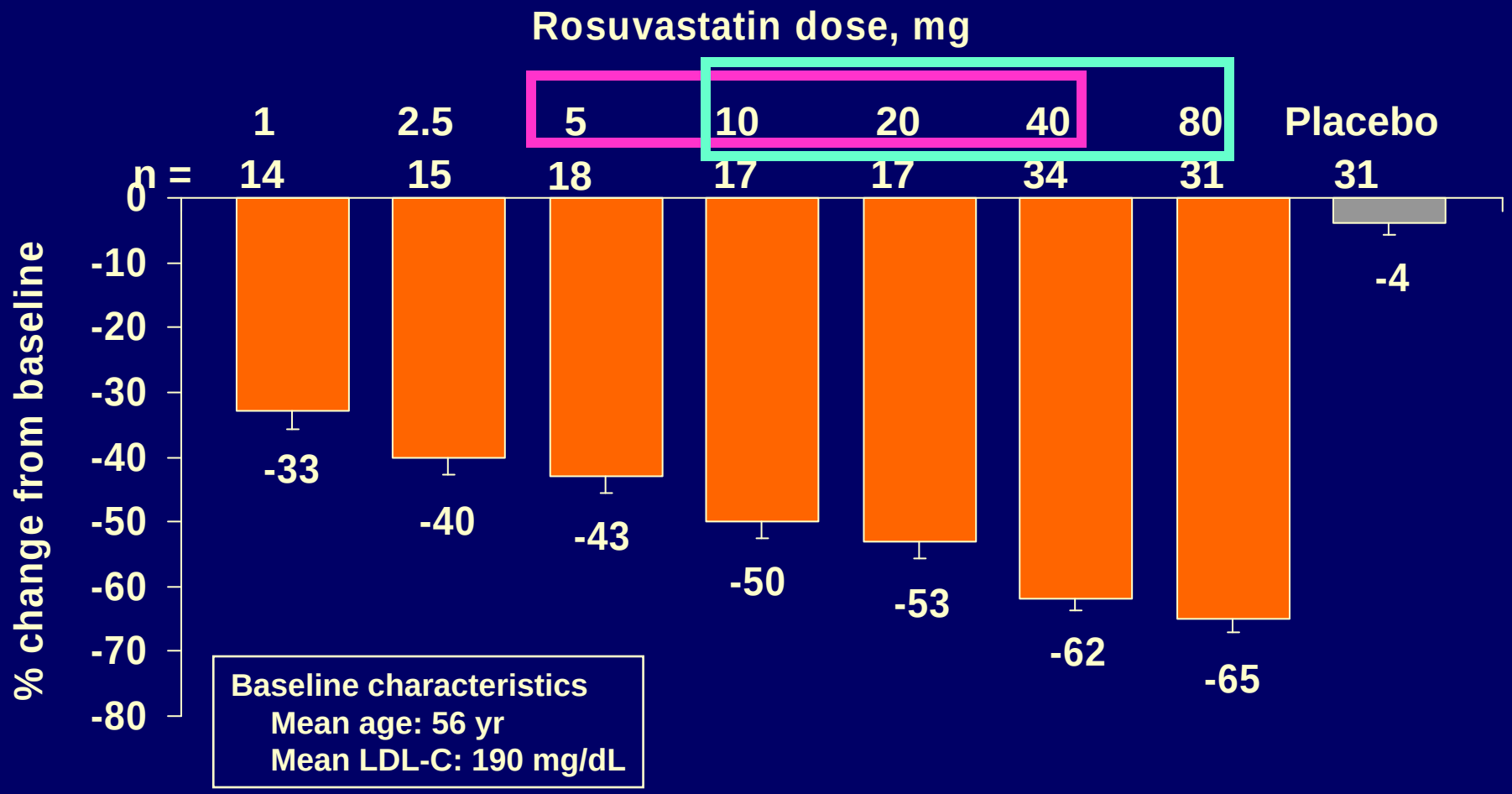
- Not extensively metabolized (10%) CYP2C9
- F=20%, fe= 6%
- Substrate for P-gp and OATP1B1*
- Interaction studies conducted-

Effect *of* other drugs
Cyclosporine; Gemfibrozil
Lopinavir/ritonavir
Fenofibrate; Antacid
Erythromycin, Ketoconazole, Itraconazole, Fluconazole

Effect *on* other drugs
Warfarin
Digoxin
Oral contraceptives

(Data compiled from labeling for Crestor (rosuvastatin; AstraZeneca); Clin pharm review- S Chung; Labeling from http://www.accessdata.fda.gov/scripts/cder/drugsatfda. November 2007 labeling) * literature

LDL-C: % Change From Baseline Rosuvastatin (Crestor®) vs Placebo



< .001 vs placebo; data presented as LS mean ± SE; Trials 8 and 23 Pooled (Wk 6)

<Crestor® Clinical Development Efficacy, Dr. James Blasetto, MD, MPH, AstraZeneca July 9, 2003> http://cdernet.cder.fda.gov/ACS/index.html

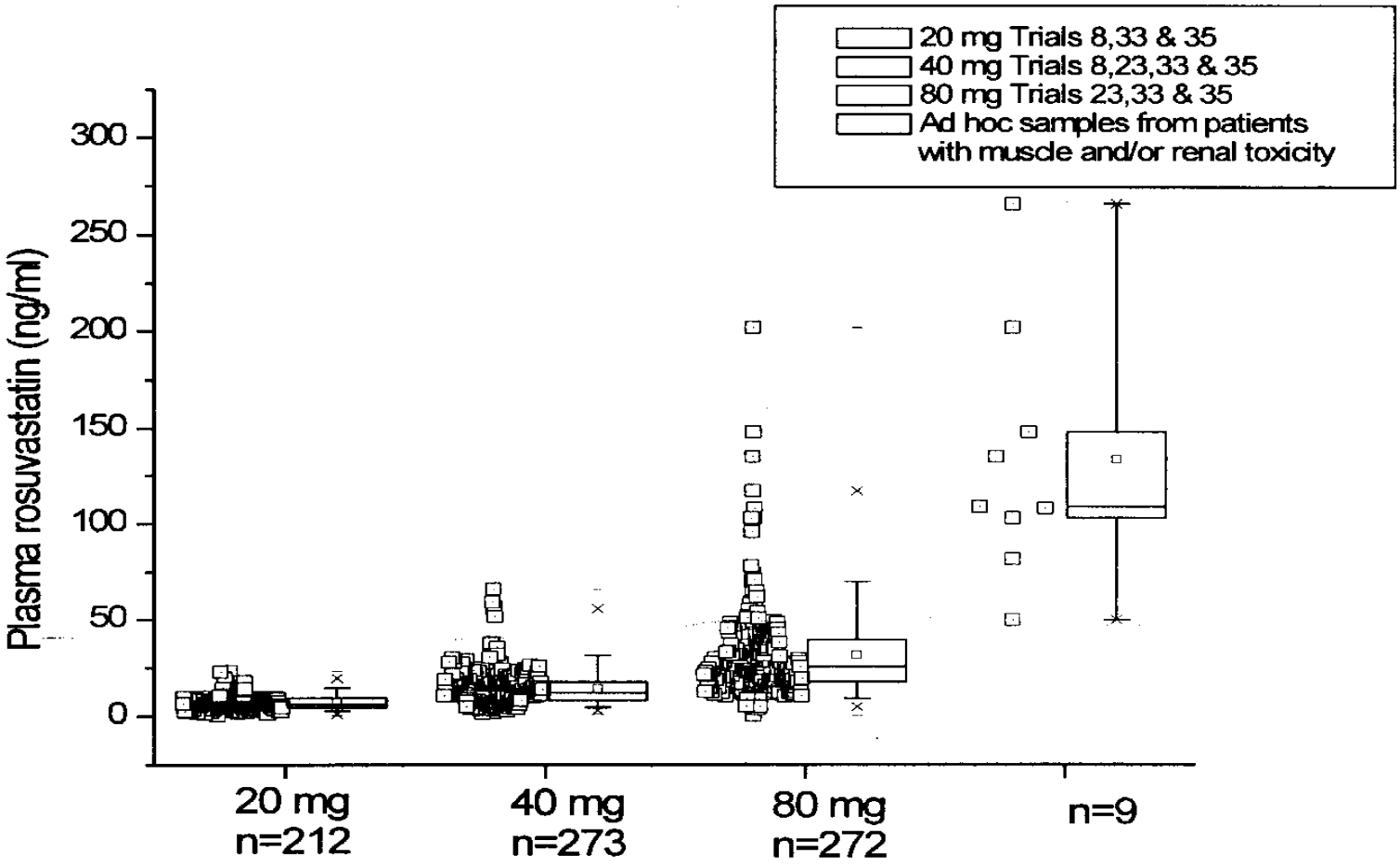
Incidence of CK elevations and myopathy in phase II/III

	(mg)	CK>10xULN	MYOPATHY (all cases)
Baycol	0.4	1.6%	1.0-1.6%
	0.8	2.1%	0.9-1.0%
Rosuva	Pbo	0%	0%
	5	0.4%	0.2%
	10	0.2%	0.1%
	20	0.2%	0.1%
	40	0.4%	0.2%
	80	1.9%	1.0%
All marketed STATINS[a]	5-80	0.03-0.9%	0-0.5%

Data from Tables 10, 11 FDA briefing packet

<Crestor® William Lubas, MD, PhD, CDER, FDA, Advisory Committee meeting, July 9, 2003>
http://cdernet.cder.fda.gov/ACS/index.html

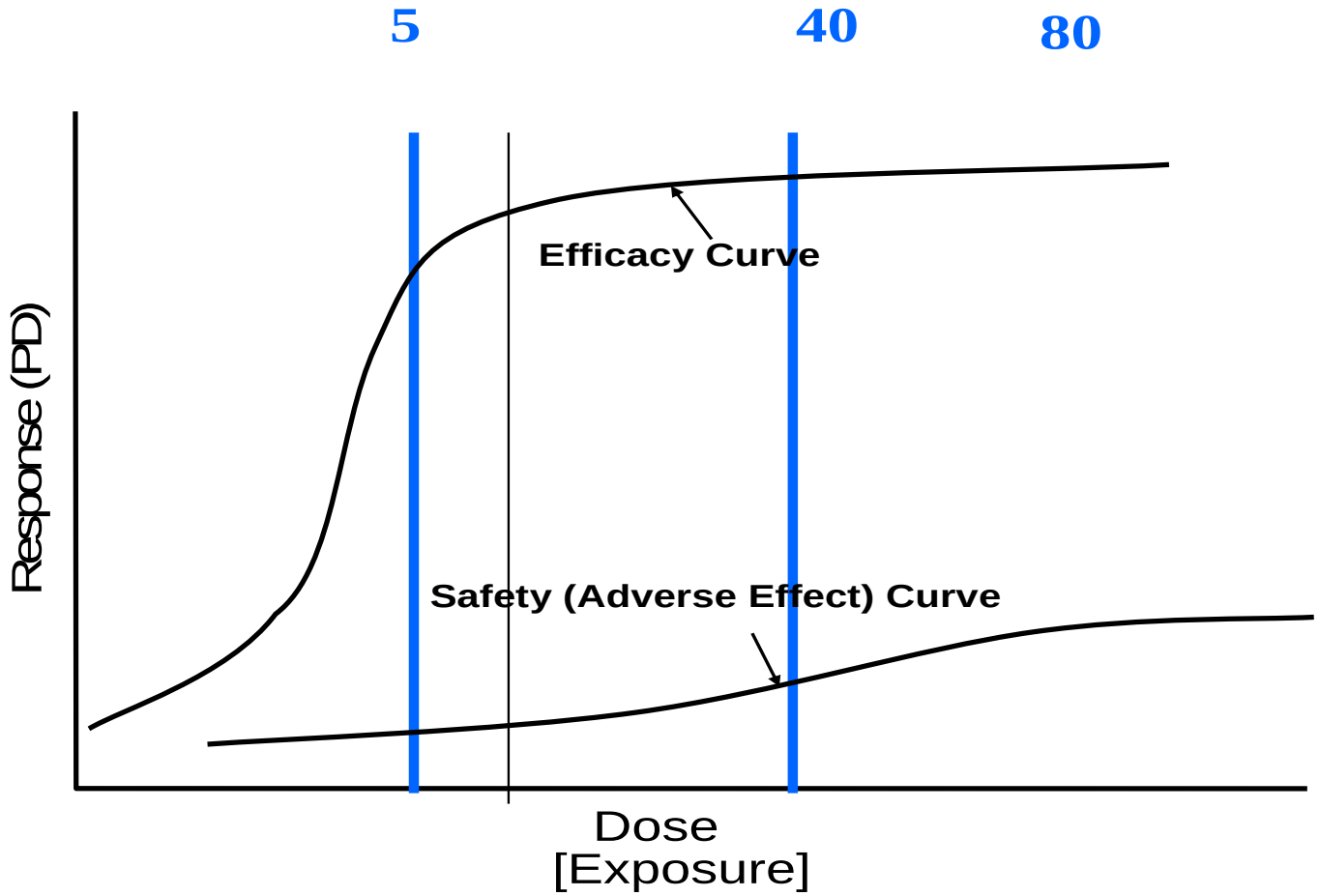
Plasma rosuvastatin concentrations by dose and in patients with rhabdomyolysis or renal toxicity



<Crestor® William Lubas, MD, PhD, CDER, FDA, Advisory Committee meeting, July 9, 2003> http://cdernet.cder.fda.gov/ACS/index.html

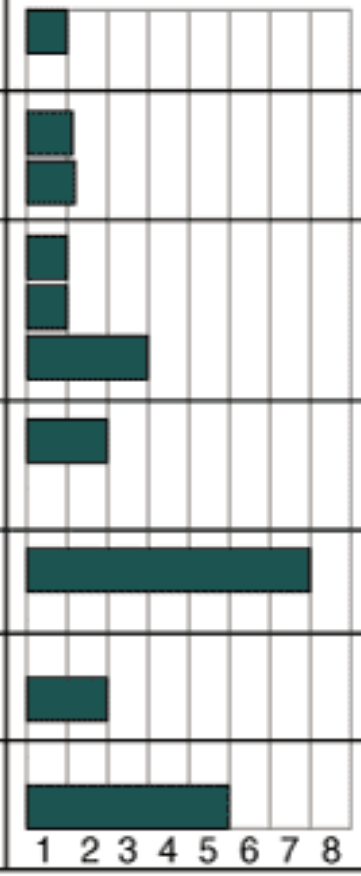
Dosage and Administration

- Approved 5-40 mg



Comparative exposure and dose recommendation in subgroups with various patient factors

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



(Data compiled from labeling for Crestor (rosuvastatin; AstraZeneca); Labeling from http://www.accessdata.fda.gov/scripts/cder/drugsatfda.); **November 2007 labeling**

<Huang S-M, Temple R, Clin Pharmacol Ther. 84(3): 287-294, 2008>

Case 2

Maraviroc (Selzentry®)

- Indicated: in combination with other antiretroviral agents, for treatment experienced adult patients infected with only CCR5 tropic- HIV1- detectable….

- Substrate of CYP3A and P-gp

- %fe: 8%; %F 23-33 %; renal pathway 25%

August 2007 maraviroc (Selzentry) label
<http://www.fda.gov/cder/foi/label/2007/022128lbl.pdf>

Interactions with CYP3A and/or Pgp inhibitors

Co-administered drug and dose	N	Maraviroc Dose	Ratio (90% CI) of maraviroc pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)		
			Cmin	AUC_{tau}	Cmax
CYP3A and/or P-gp Inhibitors					
Ketoconazole 400 mg QD **Keto**	12	100 mg BID	3.75 (3.01-4.69)	5.00 (3.98, 6.29)	3.38 (2.38, 4.78)
Ritonavir 100 mg BID **Rito**	8	100 mg BID	4.55 (3.37-6.13)	2.61 (1.92, 3.56)	1.28 (0.79, 2.09)
Saquinavir (soft gel capsules) /ritonavir 1000 mg/100 mg BID **Saqui/Rito**	11	100 mg BID	11.3 (8.96-14.1)	9.77 (7.87, 12.14)	4.78 (3.41, 6.71)
Lopinavir/ritonavir 400 mg/100 mg BID **Lopi/Rito**	11	300 mg BID	9.24 (7.98-10.7)	3.95 (3.43, 4.56)	1.97 (1.66, 2.34)
Atazanavir 400 mg QD **Ataza**	12	300 mg BID	4.19 (3.65-4.80)	3.57 (3.30, 3.87)	2.09 (1.72, 2.55)
Atazanavir/ritonavir 300 mg/100 mg QD **Ataza/Rito**	12	300 mg BID	6.67 (5.78-7.70)	4.88 (4.40, 5.41)	2.67 (2.32, 3.08)

Cmin:
4-11x inc

AUC:
3-10x inc

Cmax:
1.3-5x inc

Interactions with CYP3A and/or Pgp inducers

Co-administered drug and dose	N	Maraviroc Dose	Ratio (90% CI) of maraviroc pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)		
			Cmin	AUC_{tau}	Cmax
CYP3A and/or P-gp Inducers					
Efavirenz 600 mg QD Efa	12	100 mg BID	0.55 (0.43-0.72)	0.552 (0.492, 0.620)	0.486 (0.377, 0.626)
Rifampicin 600 mg QD Rif	12	100 mg BID	0.22 (0.17-0.28)	0.368 (0.328, 0.413)	0.335 (0.260, 0.431)
Nevirapine* 200 mg BID (+ lamivudine 150 mg BID, tenofovir 300 mg QD) Nevi	8	300 mg SD	-	1.01 (0.65, 1.55)	1.54 (0.94, 2.51)

No changes: nevirapine

Cmin: 0.22-0.55

AUC: 0.37-0.55

Cmax: 0.34-0.49

Interactions with CYP3A and/or Pgp inhibitors and inducers

Co-administered drug and dose	N	Maraviroc Dose	Ratio (90% CI) of maraviroc pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)		
			Cmin	AUC	Cmax
CYP3A and/or P-gp Inhibitors and Inducers					
Lopinavir/ritonavir + efavirenz 400 mg/100 mg BID + 600 mg QD	11	300 mg BID	6.29 (4.72-8.39)	2.53 (2.24, 2.87)	1.25 (1.01, 1.55)
Saquinavir(soft gel capsules) /ritonavir + efavirenz 1000 mg/100 mg BID + 600 mg QD	11	100 mg BID	8.42 (6.46-10.97)	5.00 (4.26, 5.87)	2.26 (1.64, 3.11)
Tipranavir/ritonavir 500 mg/200 mg BID	12	150 mg BID	1.80 (1.55-2.09)	1.02 (0.850, 1.23)	0.86 (0.61, 1.21)

Lopi/Rito + Efa

Saqui/Rito + Efa

Tipra/Rito

Smaller changes: Tipranavir/ritonavir

Cmin: 6-8x inc

AUC: 3-5x inc

Cmax: 1.3-2.3x inc

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SELZENTRY safely and effectively. See full prescribing information.

SELZENTRY (maraviroc) tablets
Initial U.S. Approval: 2007

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning

- **Hepatotoxicity has been reported. (5.1)**
- **May be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE). (5.1)**
- **Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction. (5.1)**

----------**INDICATIONS AND USAGE**----------

SELZENTRY is a CCR5 co-receptor antagonist indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents (1).

Tropism and treatment history should guide the use of SELZENTRY (1).

----------**DOSAGE AND ADMINISTRATION**----------

When given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ritonavir), delavirdine (2, 7.1)	150 mg twice daily
With NRTIs, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors or CYP3A inducers (2, 7.1)	300 mg twice daily
With CYP3A inducers including efavirenz (without a strong CYP3A inhibitor) (2, 7.1)	600 mg twice daily

----------**DOSAGE FORMS AND STRENGTHS**----------

Tablets: 150 mg and 300 mg (3).

----------**CONTRAINDICATIONS**----------

None (4)

----------**WARNINGS AND PRECAUTI**

- Use caution when administering SELZENTRY to existing liver dysfunction or who are co-infected C (5.1)
- More cardiovascular events including myocardial infarction were observed in patients who received with caution in patients at increased risk of cardio

----------**ADVERSE REACTIONS**----------

The most common adverse reactions (>8% incidence higher frequency compared to placebo are cough, py tract infections, rash, musculoskeletal symptoms, abd dizziness (6).

To report SUSPECTED ADVERSE REACTION 800-438-1985 or FDA at 1-800-FDA-1088 or www

----------**DRUG INTERACTIONS**

- Coadministration with CYP3A inhibitors, includi (except tipranavir/ritonavir) and delavirdine, will concentration of SELZENTRY (7.1)
- Coadministration with CYP3A inducers, includin the concentration of SELZENTRY (7.1)

----------**USE IN SPECIFIC POPULA**

- SELZENTRY should only be used in pregnant w benefit justifies the potential risk to the fetus (8.1
- There are no data available in pediatric patients; t should not be used in patients <16 years of age (8

See 17 for PATIENT COUNSELING INFORMA MEDICATION GUIDE

<http://www.fda.gov/cder/foi/label/2007/022128lbl.pdf>

Use in Specific Populations

- 8.6 Renal Impairment

  Patients with a creatinine clearance of less than 50mL/min who receive maraviroc and a CYP3A inhibitor may be at an increased risk of adverse event… dizziness and postural hypotension

  Pateints …receive mraviroc and a CYP3A inhibitor only if the potential benefit .. outweigh the risk, …monitored for adverse effects

August 2007 maraviroc (Selzentry) label
<http://www.fda.gov/cder/foi/label/2007/022128lbl.pdf>

Postmarketing Study Commitment (PMC)

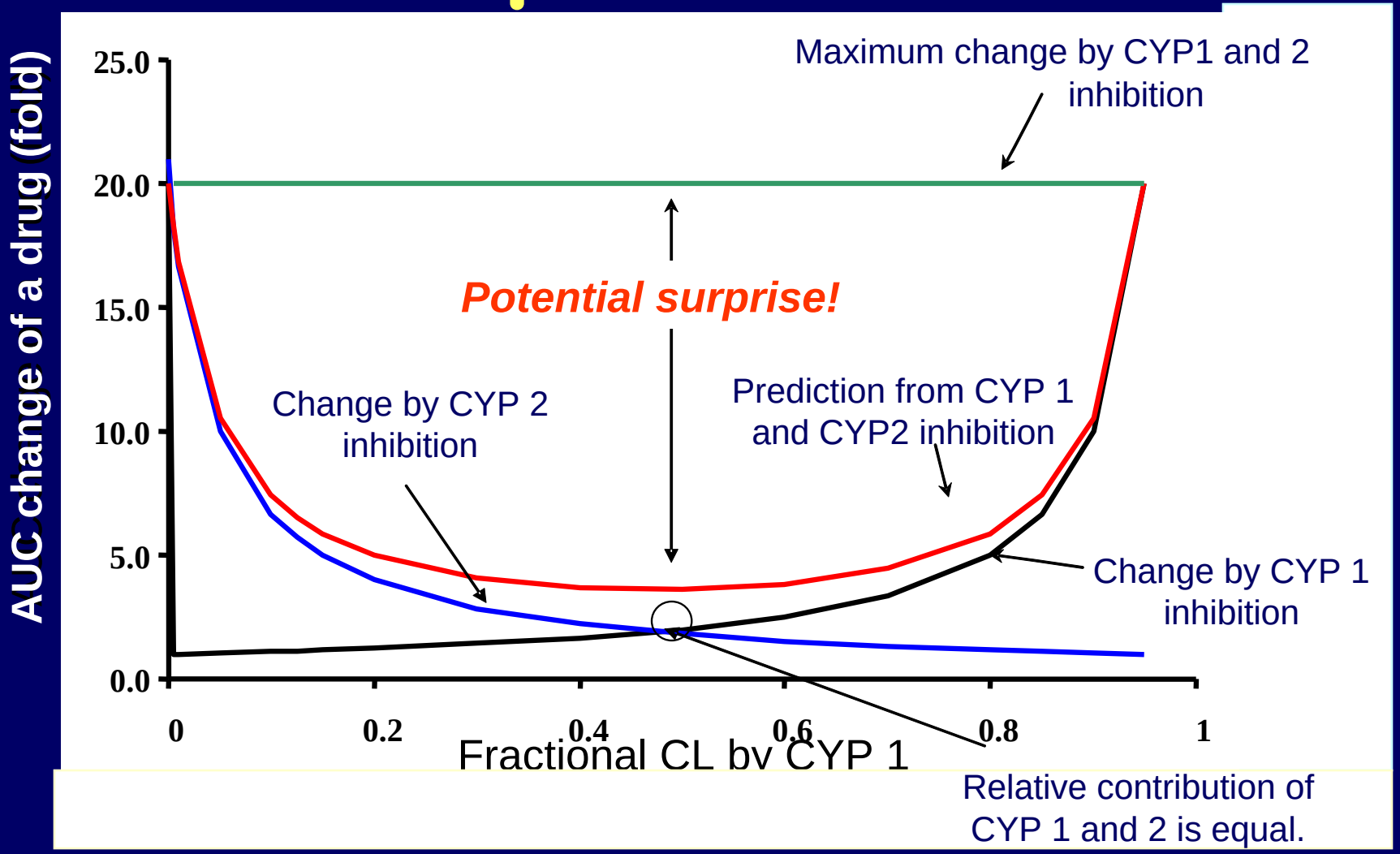
- Renal impairment studies
  - 150 mg with boosted PI
  - 300 mg
- Metabolite inhibition of CYP2D6 (600 mg)
- Maraviroc inhibition of P-gp
- Maraviroc induction of CYP1A2
- PD interactions with PDE5 inhibitors

C Lee's presentation

http://www.fda.gov/cder/foi/appletter/2007/022128s000ltr.pdf

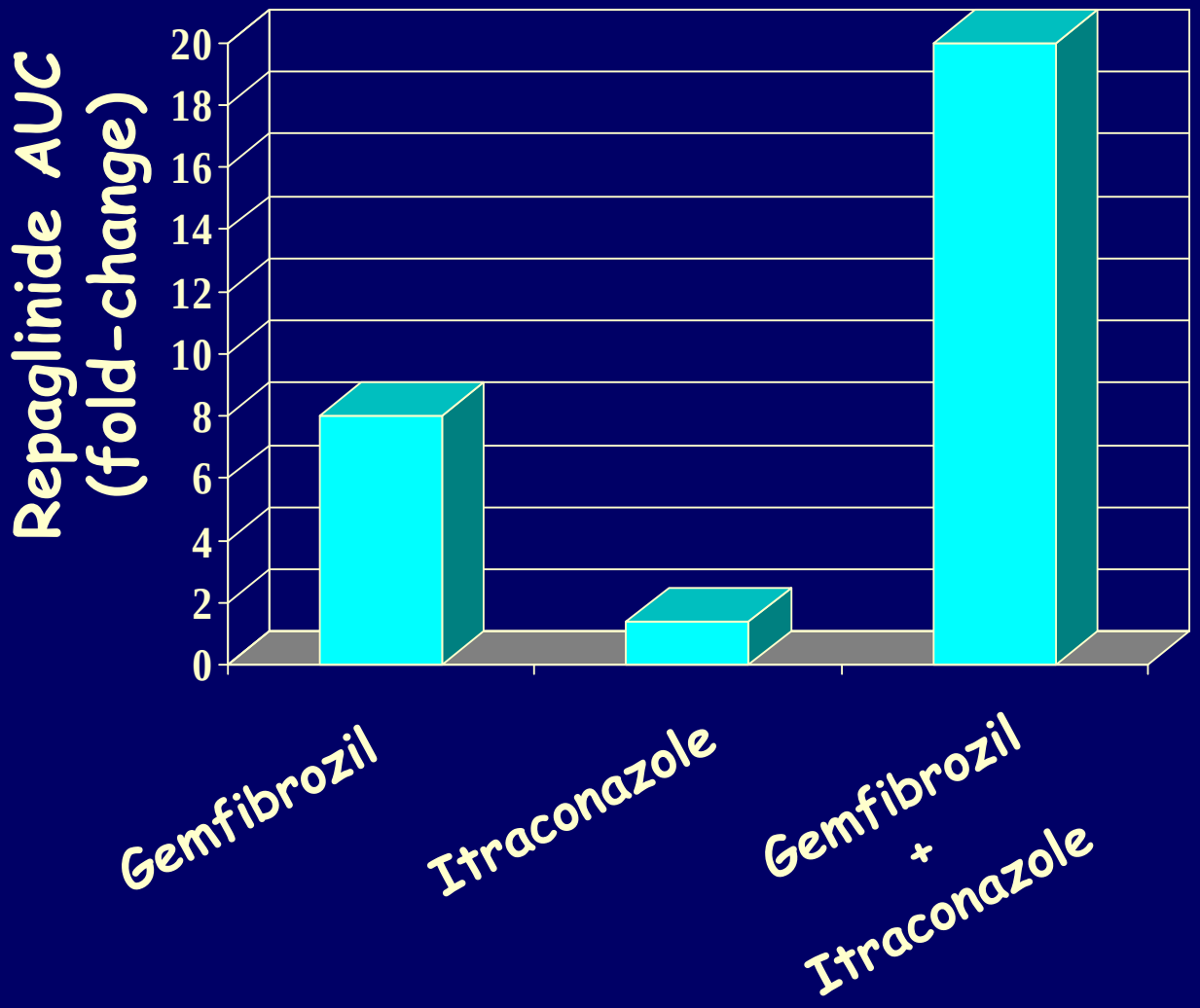
There is a need to understand interactions among multiple (>2) drugs

Multiple inhibition



Thummel K, Chung S, et al, ASCPT, poster II-77, March 23, 2007;
Chung S, Thummel K, et al, AAPS, November, 2007

Combination of CYP and transporter interactions



Mechanism of Interactions:

Gemfibrozil and its glucuronide metabolite inhibit
- CYP2C8
- OAPT1B1

< Data from Neuvonen: Niemi M et al, Diabetologia. 2003 Mar;46(3):347-51 >

Case 3

Ranolazine (Ranexa®)

- After oral dose, 75% in urine and 25% in feces; only 5% excreted unchanged in the urine
- Extensively metabolized by CYP3A and less by CYP2D6; a P-gp substrate
- inhibits CYP3A, CYP2D6, P-gp

Effect *of* other drugs
Ketoconazole, Diltiazem, Verapamil, Cimetidine, Rifampin, Digoxin Paroxetine

Effect *on* other drugs
Simvastatin
Diltiazem
Dextromethorphan (PM)
Digoxin
Warfarin

December 2007 ranolazine (Ranexa) CV Therapeutics label
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory;
http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6563; >

PRECAUTIONS

Effect *of* other drugs	Effect *on* other drugs
-Ranolazine is primarily metabolized by CYP3A and a substrate of P-gp…rifampin, refabutin, rphenobarbital, phenytoin,carbamazepine, St John's Wort *should be avoided*; - *Caution should be exercised* when co-administering P-gp inhibitors, ritonavir or cyclosporine	-Digoxin *dose may have to be reduced*; other P-gp substrates; -inhibits CYP2D6; Dose of TCA, some antipsychotic have to be reduced

-->Labeling includes some, but not all, actionable recommendations

December 2007 ranolazine (Ranexa) CV Therapeutics label <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory; http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6563; >

Transporter Info in the Current Labeling

Current Labeling*

Transporter	Drug Names
P-gp	Ambrisentan, (aprepitant), clarithromycin, fexofenadine, (fosaprepitant), (ixabepilone), lapatinib, posaconazole, ((propafenone)), ranolazine, sirolimus, tipranavir,
OATP1B1	Atorvastatin, [cyclospoprine], lapatinib
OATP	Ambrisentan
Organic anion	Sitagliptin
Organic cation	Metformin, pramipexole, varenicline
BCRP	Lapatinib
MRP	(Ixabepilone)

*This is not an extensive list. Data based on a preliminary survey of electronic PDR, October 1, 2008. Those in "( )" indicated mentioned in the labeling as not a substrate or not an inhibitor ( ), or not studied (( )) or as an inhibitor [ ] for other drugs

IND/NDA Discussions*

Transporter	Recommendations
No data on P-gp (oncology)	Post-marketing commitment as P-gp substrate or inhibitor
OATP1B1 substrate (HIV)	Recommended study with lopinavir/ritonavir
OATP1B1 inhibitor	Sponsor studied rosuvastatin
CYP3A/OATP1B1 inhibitor	Sponsor studied simvastatin

* Not an extensive list; case examples from recent IND/NDA discussions- courtesy of Abraham S, Booth B, Zhang L, Zhang YD

Summary

- CYP-based interactions well defined in general

- Labeling recommendations (language and section) based on clinical significance: exposure-response relationship & benefit/risk ratio

Summary (2)

- Transporter-based interactions have been increasingly evaluated; P-gp-based interactions are among the most evaluated; others include OATP, OCT, OAT, BCRP; results have been included in the drug label

  * Study design issues need to be addressed (e.g., probe substrates, inhibitors)

Summary (3)

- Efforts in development/evaluation of models predicting the extent of drug interactions ongoing at the FDA

  * in vitro to in vivo
  * single pair to multiple interactions
    - multiple CYP inhibitors
    - multiple modulators (CYP/transporter inhibition/induction)
    - effect of other metabolizing enzymes
    - effect of genetics

Drug Interactions working group

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Janet Norden

Kenneth Thummel*
Isabelle Ragueneau *
*(on sabbatical at FDA)

Gilbert Burckart

Many who have provided comments on the guidance

References

- Guidance for industry: Drug Interaction Studies: Study design, Data analysis and Implications for Dosing and Labeling (Issued for public comment, September 11, 2006, http://www.fda.gov/cder/guidance/6695dft.pdf).

- FDA Drug Development and Drug Interactions Website; http://www.fda.gov/Cder/drug/drugInteractions/default.htm, established May 2006

- Huang S-M, Temple R, Throckmorton D, Lesko L, Clin Pharmacol Ther 2007; Feb

- Huang S-M, Strong J, Zhang L, et al, J Clin Pharmacol 2008; June

- Zhang L, Zhang Y, Strong J, Reynolds K, Huang S-M, Xenobiotica 2008; July