PBPK Modelling of Transdermal Selegiline Disposition Discrepancy in Special Populations

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Session Description and Objectives

This Session describes a case study on how PBPK modelling can be useful in evaluating the disposition differences in special populations to inform if they require a closer clinical monitoring for untoward effects.

Background

- ✓ Selegiline (SEL) transdermal patch was approved for the treatment of major depressive disorder (MDD).
- ✓ Suicidality is the major risk factor of antidepressant therapy and they require a closer therapeutic drug monitoring (TDM) . Systemic concentrations are generally monitored to correlate this therapeutic risk.
- ✓ Pharmacokinetics of Selegiline along with it metabolites is well established in healthy and elderly populations but not in Adolescents, Renal and Hepatic impaired populations.

Objective

- ✓ To evaluate the disposition discrepancies of SEL and its metabolites between healthy and special populations *In Silico* using using a comprehensive parent/metabolite(s) PBPK model.
- ✓ The model outcomes inform whether these special populations require a careful clinical monitoring in the MDD patients to minimize the therapeutics.

Biography and Contact Information

- ✓ Santosh is currently working as Research Associate (Dermal absorption) in the modelling and simulation group at Certara Simcyp from Jan, 2019.
- ✓ At Simcyp he is working on US FDA Dermal grant related projects and consultancy projects.
- ✓ Prior to joining Simcyp, Santosh pursued his Ph.D in Pharmacokinetics and Metabolism at CSIR-Central Drug Research Institute, India.

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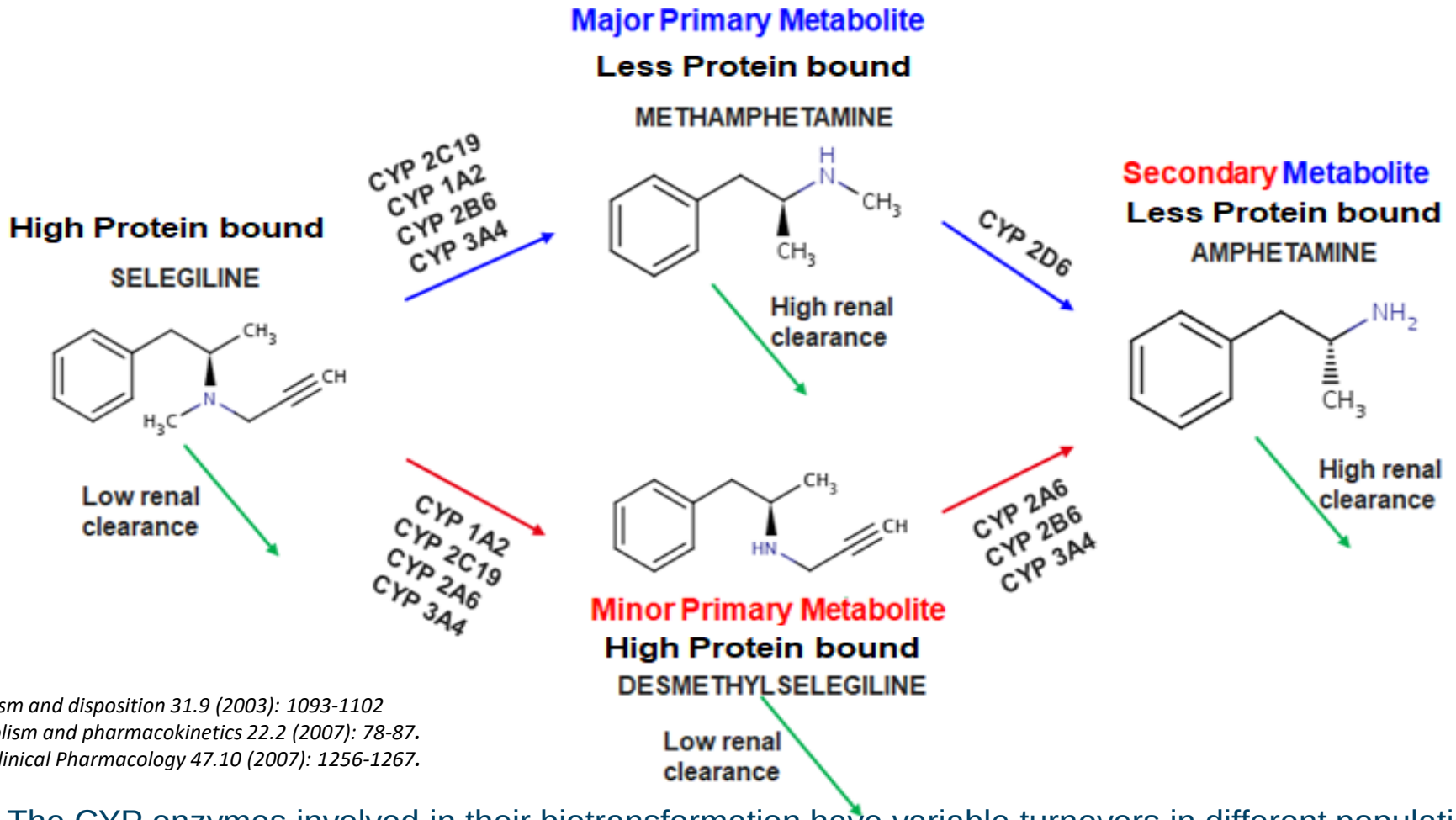
Schematic Representation of Biotransformation of Selegiline and its Metabolites



References

Salonen, Jarmo S., et al. Drug metabolism and disposition 31.9 (2003): 1093-1102

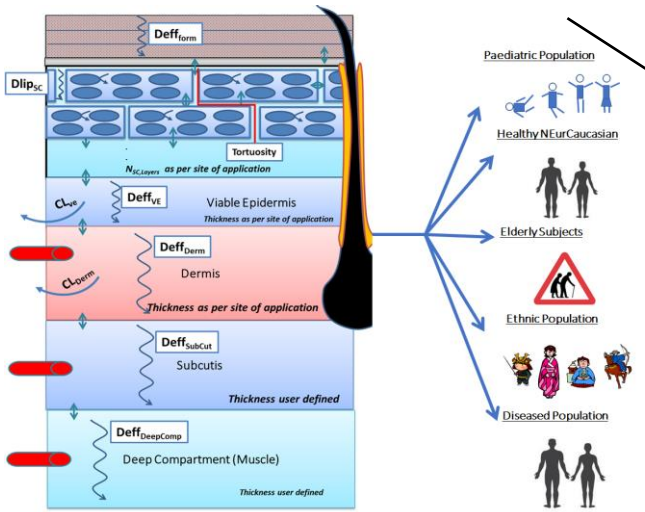
Benetton, Salete A., et al. Drug metabolism and pharmacokinetics 22.2 (2007): 78-87.

Azzaro, Albert J., et al. The Journal of Clinical Pharmacology 47.10 (2007): 1256-1267.

The CYP enzymes involved in their biotransformation have variable turnovers in different populations.

Comprehensive Parent/Metabolite(s) PBPK model

Transdermal Absorption



Multi-Phase Multi Layer Mechanistic Dermal (MPML-Mech Derma) Absorption Model

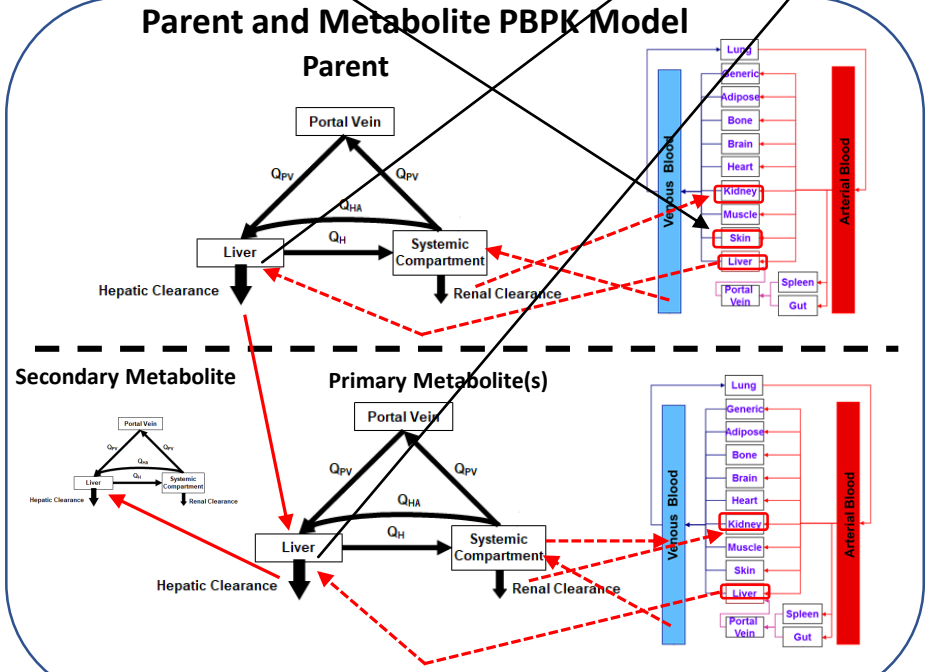
	Parameter	Value
Partition coefficients	Lipid: vehicle	85.03
	Sebum: vehicle	915.9
	VE:SC	24.8
	Skin: blood	2.44
Diffusion coefficients	SC lipid	3.22E-05
	VE	0.002
	Dermis	0.002
	Sebum	0.0008
Keratin Binding	Kon/koff 78.8/0.93	
Patch release rate (1/h)	First order : **0.04**	

Simulations performed on Simcyp Simulator version 18

Physicochemical properties

Parameter	Selegiline	Meth amphetamine	Desmethyl Selegiline	Amphetamine
Molecular weight	187.28	149.23	173.26	135.2
Log P	2.7	2.07	2.46	1.8
pKa (Monoprotic base)	7.44	9.87	9.8	9.9
B/P	1.34	1.49	1.19	1.35
Fu	0.1	0.85	0.47	0.84

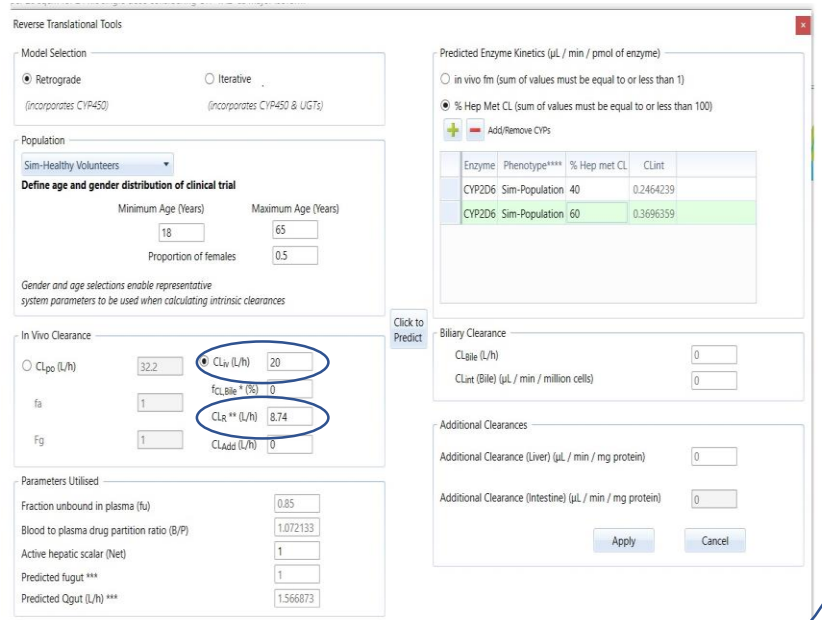
Parent and Metabolite PBPK Model



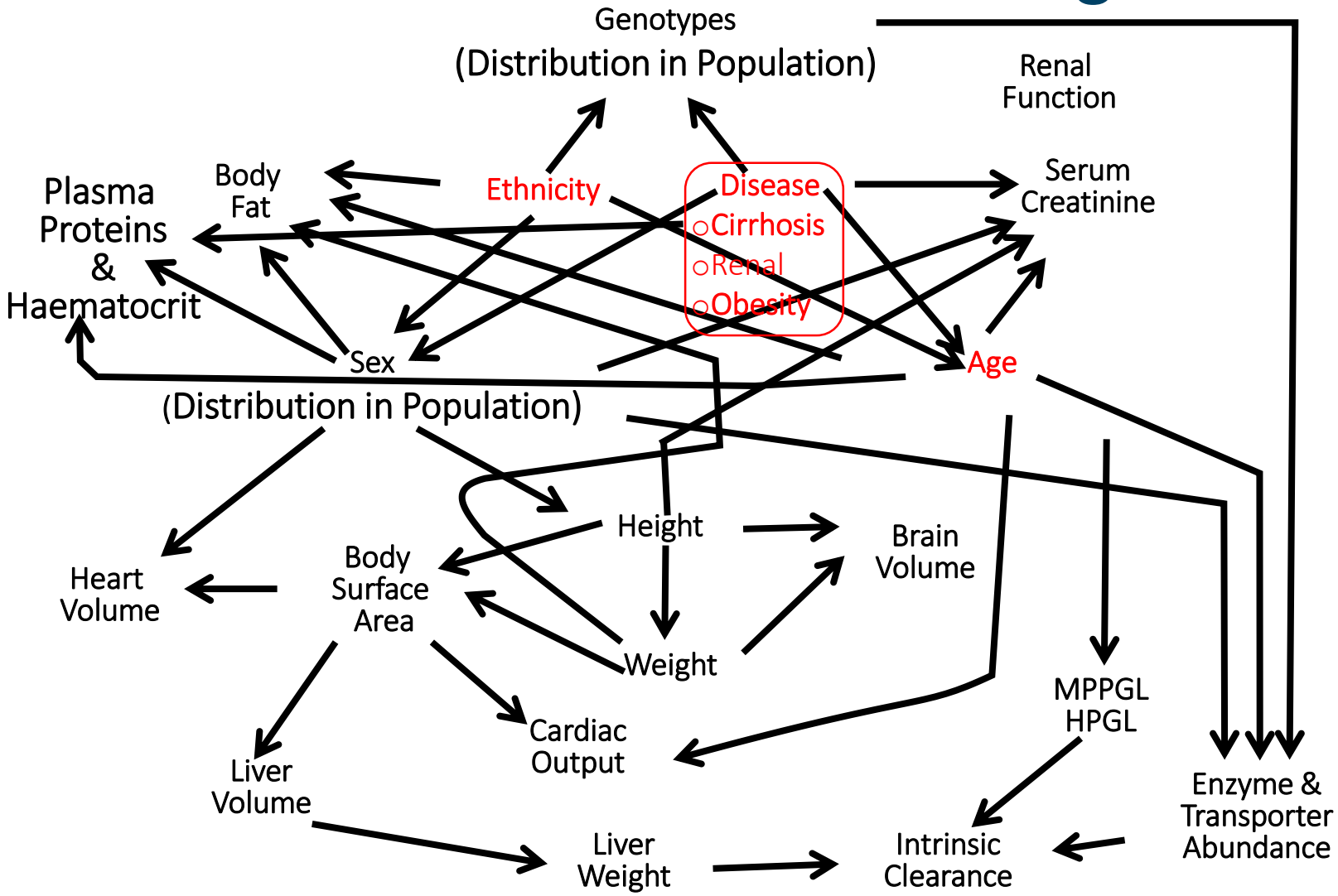
Reverse Translational Tool

$$CL_{metH} = CL_{iv} - CL_R$$

$$CLu_{H,int} = \frac{Q_H \times CL_{metH}}{fu_B(Q_H - CL_{metH})}$$

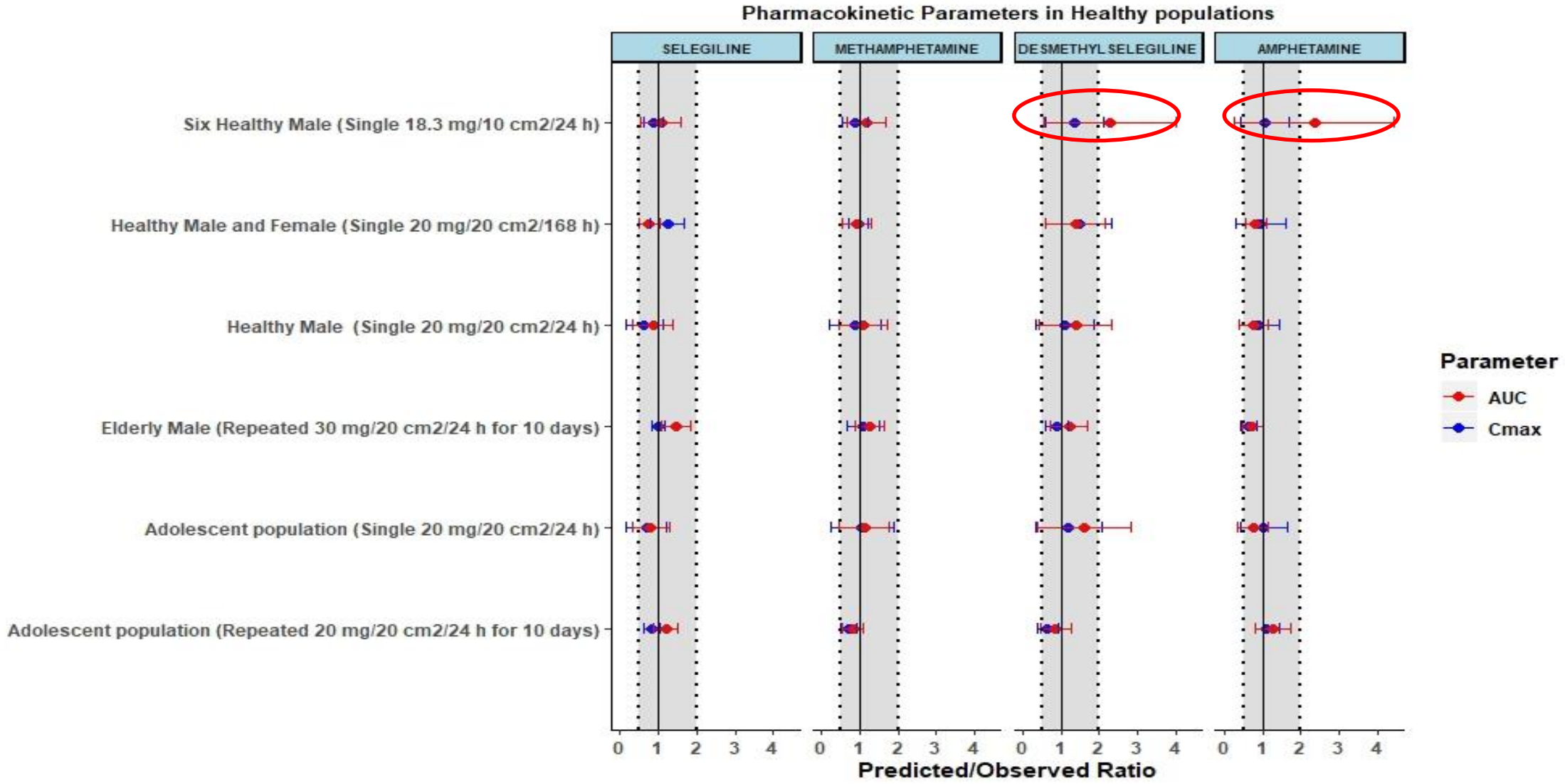


Overview: Covariates Affecting ADME

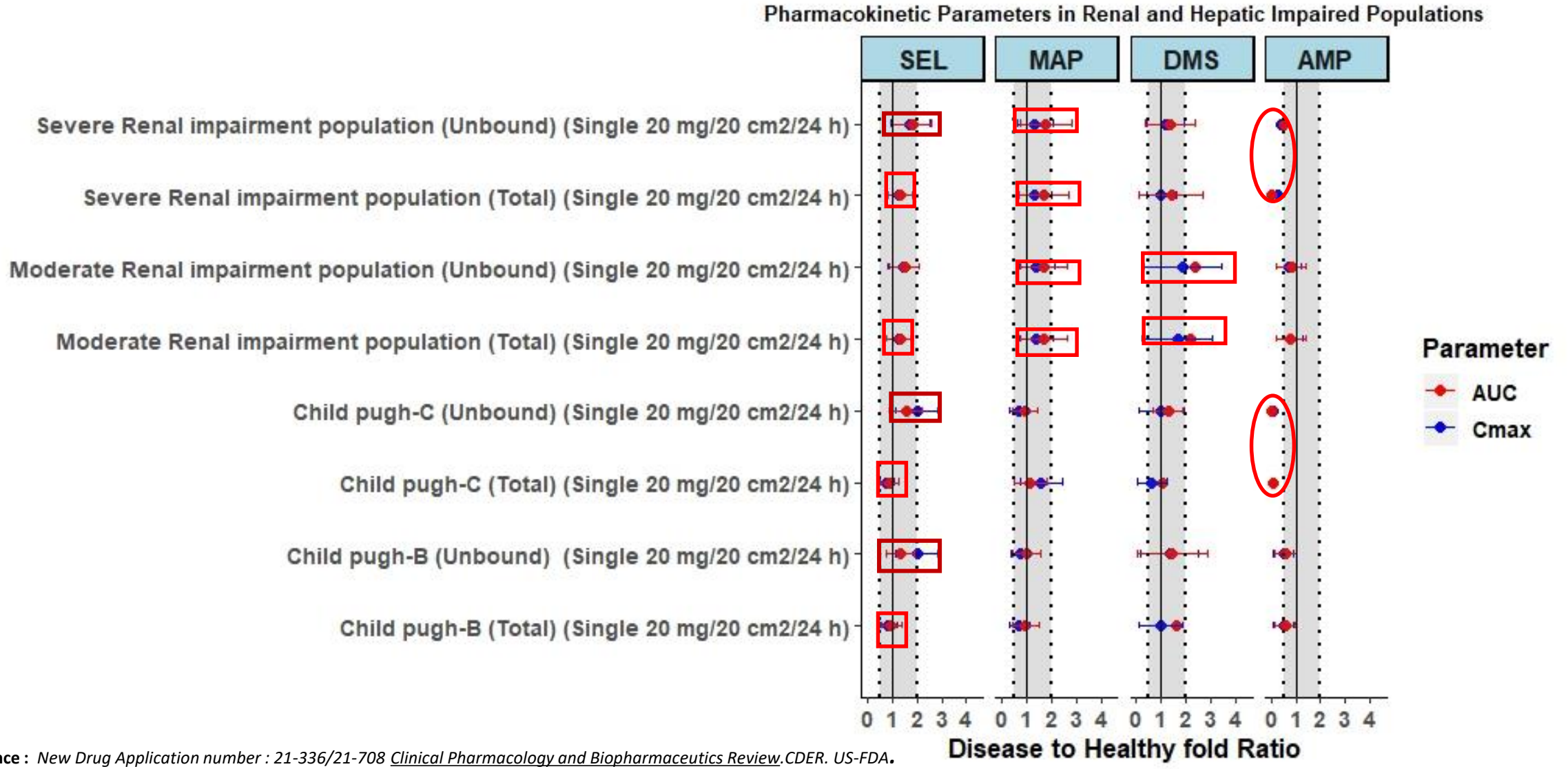


Reference: Jamei, Dickinson et al. 2009

Pharmacokinetics in Healthy Populations

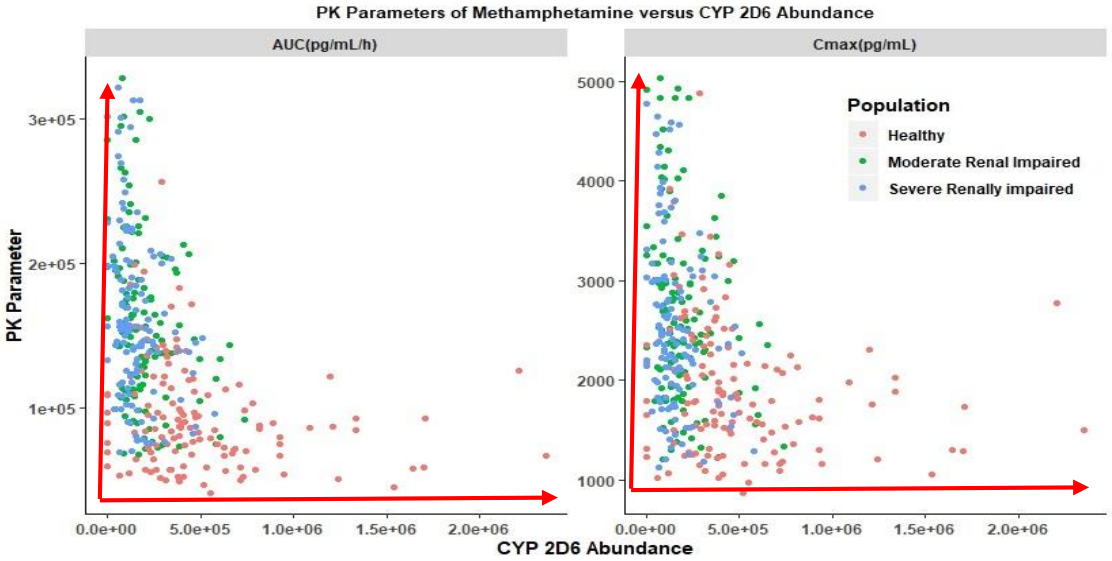


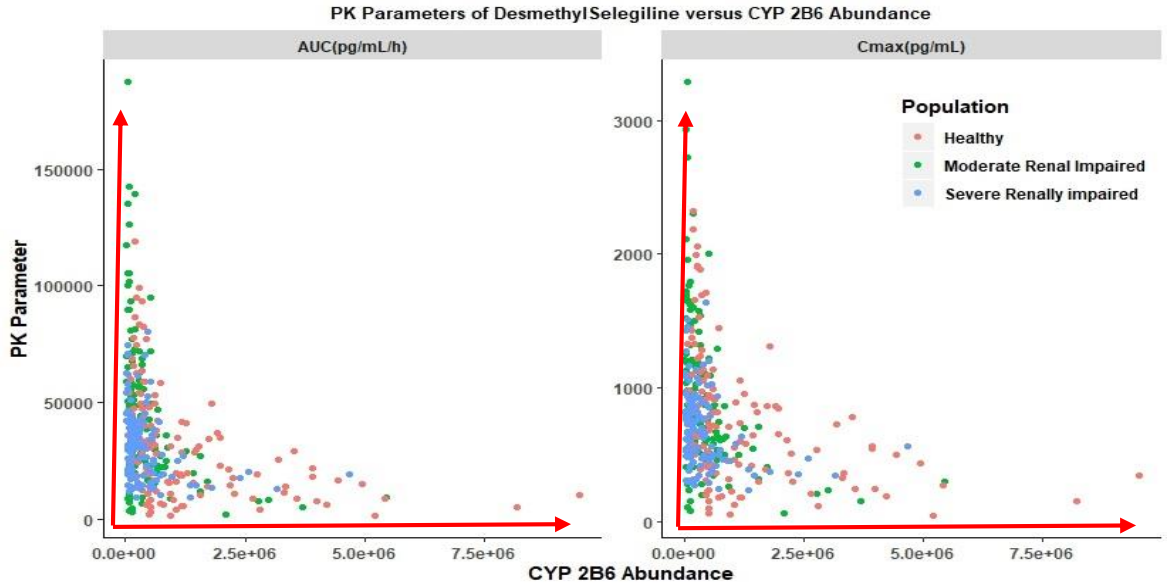
Pharmacokinetics in Healthy and Special Populations

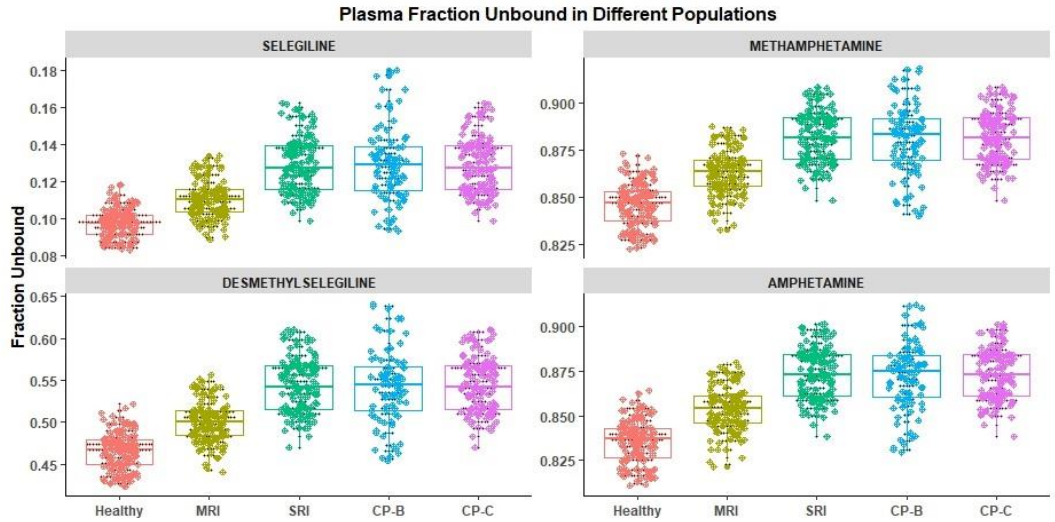


Reference : *New Drug Application number : 21-336/21-708 Clinical Pharmacology and Biopharmaceutics Review.CDER. US-FDA*.

Potential Physiological Covariates



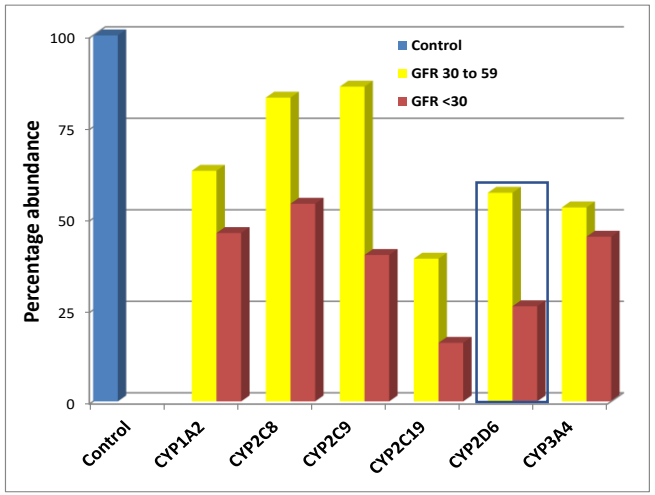


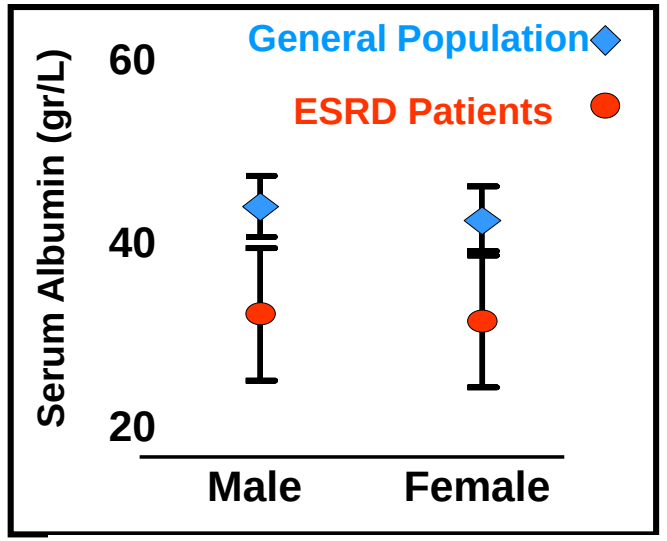


Albumin and CYP Enzyme Expression in Healthy vs Special Populations

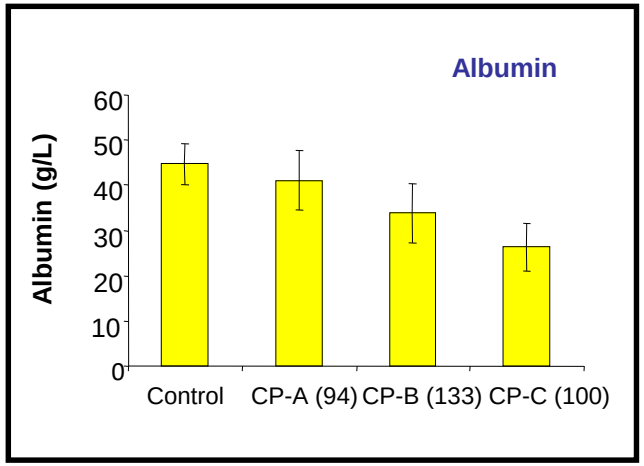
Table 1. Representative Drugs that are Moderately or Extensively Metabolized by Cytochrome P450 (CYP) that Show Reduced Nonrenal Clearance and/or Oral Bioavailability in CKD

Drug[reference]	1° hepatic CYP metabolism pathway	PK changes after oral dosing in CKD
Aliskiren*,[44]	CYP3A4	↑ AUC and C_{max} that did not correlate with CLC_R
Alfuzosin*,[45]	CYP3A4	⇑ AUC and C_{max} ⇑ $t_{1/2}$ (with severe CKD)
Bupropion[46]	CYP2B6 (active metabolites)	⇑ AUC, C_{max}, and $t_{1/2}$ ⇓ CL/F
Carvedilol[47]	CYP2C9, 2D6, 3A4, 2C19, 1A1, and 2E1	⇑ AUC, C_{max}, and ⇔ $t_{1/2}$
Ciprofloxacin*,[48]	CYP1A (40%-50%)	⇑ AUC, 75% ⇓ in CL_R and 50% ⇓ in CL_{NR}
Cyclophosphamide*,[49]	CYP2B6, 2C9, and 3A4 (inactive and active metabolites)	⇑ AUC, ⇓ CL_{total} (intravenous dosing)
Duloxetine*,[50]	CYP1A and CYP2D6	⇑ AUC and C_{max}, ⇑oral F suggested
Erythromycin†,[51]	CYP3A4	⇑ CL_H and ⇓ oral F no correlation with uremic toxins CMPF and indoxyl sulfate
Solifenacin*,[52]	CYP3A4 (active/inactive metabolites)	⇑ AUC and $t_{1/2}$, ⇓ CL/F (trend) CL/F correlates with CLC_R
Tadalafil*,[53]	CYP3A4	⇑ AUC and $t_{1/2}$ and ⇓ CL/F
Telithromycin*,[54]	CYP3A4 (50%)	⇑ AUC and $C_{max\ ss}$
Warfarin*,[55]	CYP2C9	Reduced dosing requirements in moderate and severe CKD





ESRD: End Stage Renal Disease



- ✓ Impaired kidney function not only leads to changes in renal clearance but also decrease in CYP 2B6 and CYP 2D6 expression.
- ✓ Decreased albumin concentration in renal and hepatic impaired subjects affects the PK of high albumin bound drugs.

References:

Rowland Yeo, K. et al Expert Review of Clinical Pharmacology 4 (2) 2011 261-274.
Ladda et al . Advances in chronic kidney disease 23.2 (2016): 67-75.
Oettl, Stadlbauer et alBiochimica et Biophysica Acta, 2008. 1782(7-8): 469-473.
Logan, B. K. et al, Forensic science review 14(1): 133-151.

Summary and Conclusion

- ✓ PK of selegiline and its metabolites was verified at different transdermal doses using an integrated mechanistic dermal absorption and a comprehensive PBPK model.
- ✓ Potential physiological discrepancies that affected the disposition of SEL and its metabolites in Renal and Hepatic impaired populations to that healthy were identified *In Silico.*
- ✓ Free concentrations of SEL were increased by two fold in renal and hepatic impaired subjects. Decreased CYP 2D6 and CYP 2B6 expression in RI patients increased the systemic exposure of Methamphetamine and Desmethyl Selegiline. Increased exposure of primary metabolites, decreased the Amphetamine exposure.
- ✓ The dosage regimen of SEL is a once daily repeated dose for several months. The renal and hepatic impaired subjects would be at a potential risk of untoward effects during selegiline antidepressant therapy.
- ✓ These subjects require a closer clinical monitoring for suicidal tendencies.

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The Simcyp Simulator is freely available, following completion of the relevant workshop, to approved members of academic institutions and other not for -profit organizations for research and teaching purposes.

Questions

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