CERTARA
Implementing Translational Science

simcyp
simulator | consultancy | education

Benefits and Challenges in Using Physiologically-Based IVIVC for Drugs Undergoing First Pass Metabolism

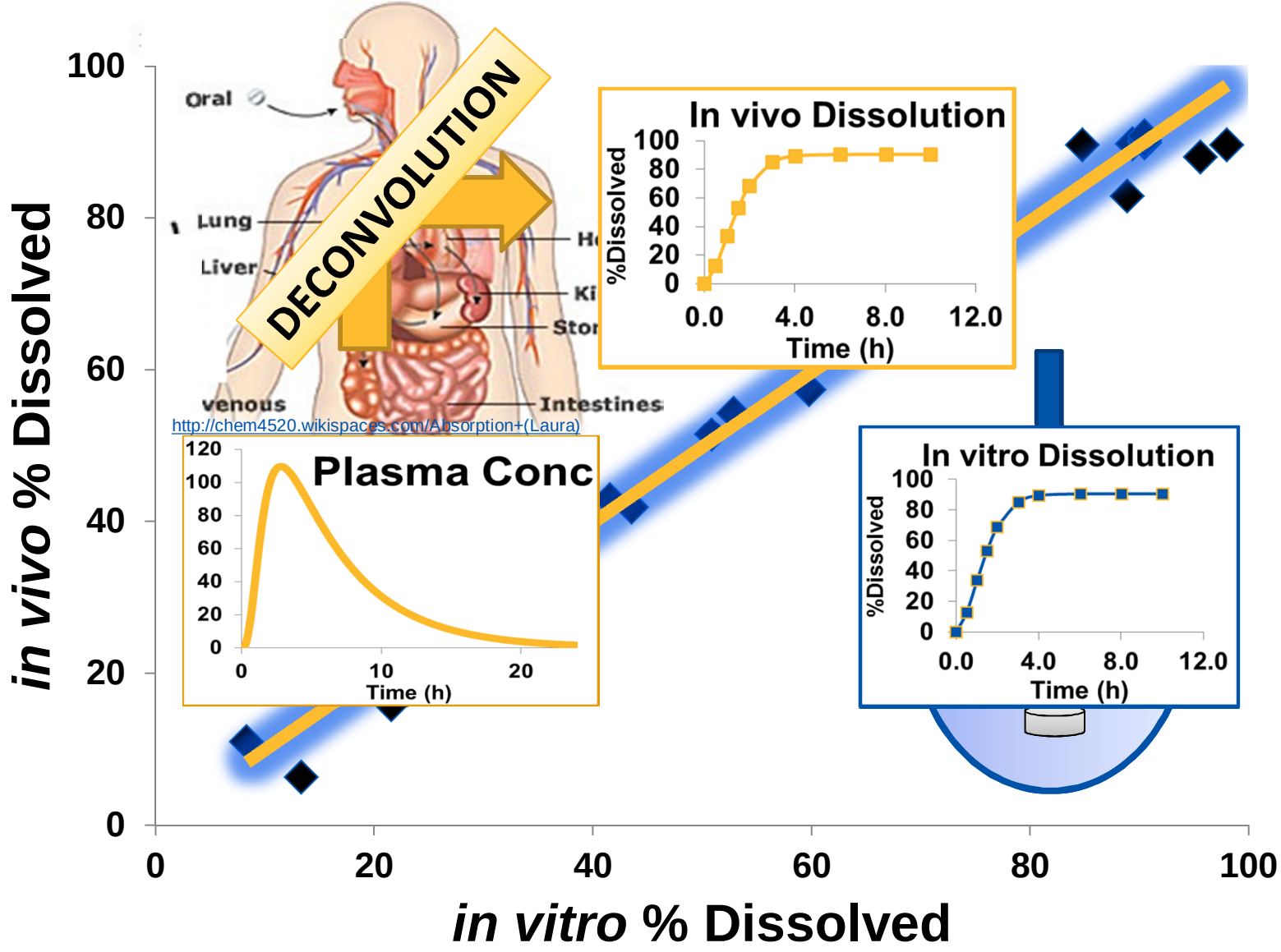
Shriram Pathak, PhD

Simcyp (a Certara Company)

PKUK 2014 Meeting, 6th November 2014

Tripos simcyp Pharsight

How to Develop IVIVC?



What is Deconvolution?

$$Response = Input * System\ behaviour$$

If you know ***R*** and ***S***, you can find ***I***

Input ***is the rate of release/dissolution from administered formulation***

System behaviour ***is how the human body processes the drug (Disposition)***

Response ***is the result (Plasma Concentration-time profile) of what happens (system behaviour) to the drug after a particular input (formulation) is given to the system***

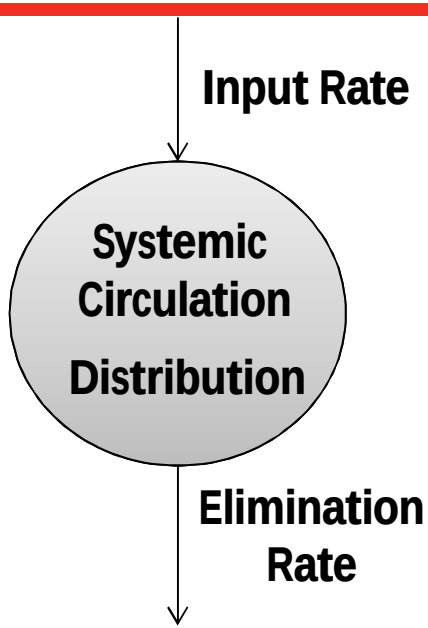
What you deconvolute and its quality depends on how you define the system and parameterise it

CERTARA

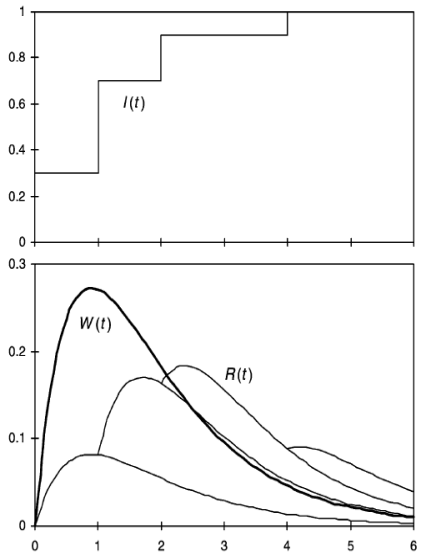
Image courtesy Wikipedia; Ref Date- Oct 2014

Deconvolution: Limitations of Conventional Methods

- Wagner-Nelson and Loo-Riegelman Methods
  - Assumes human body (system) as one or two compartments
  - Cannot be used for nonlinear elimination
  - Deconvolutes systemic input rate which is a composite function of dissolution + GI Transit + Permeation + First Pass

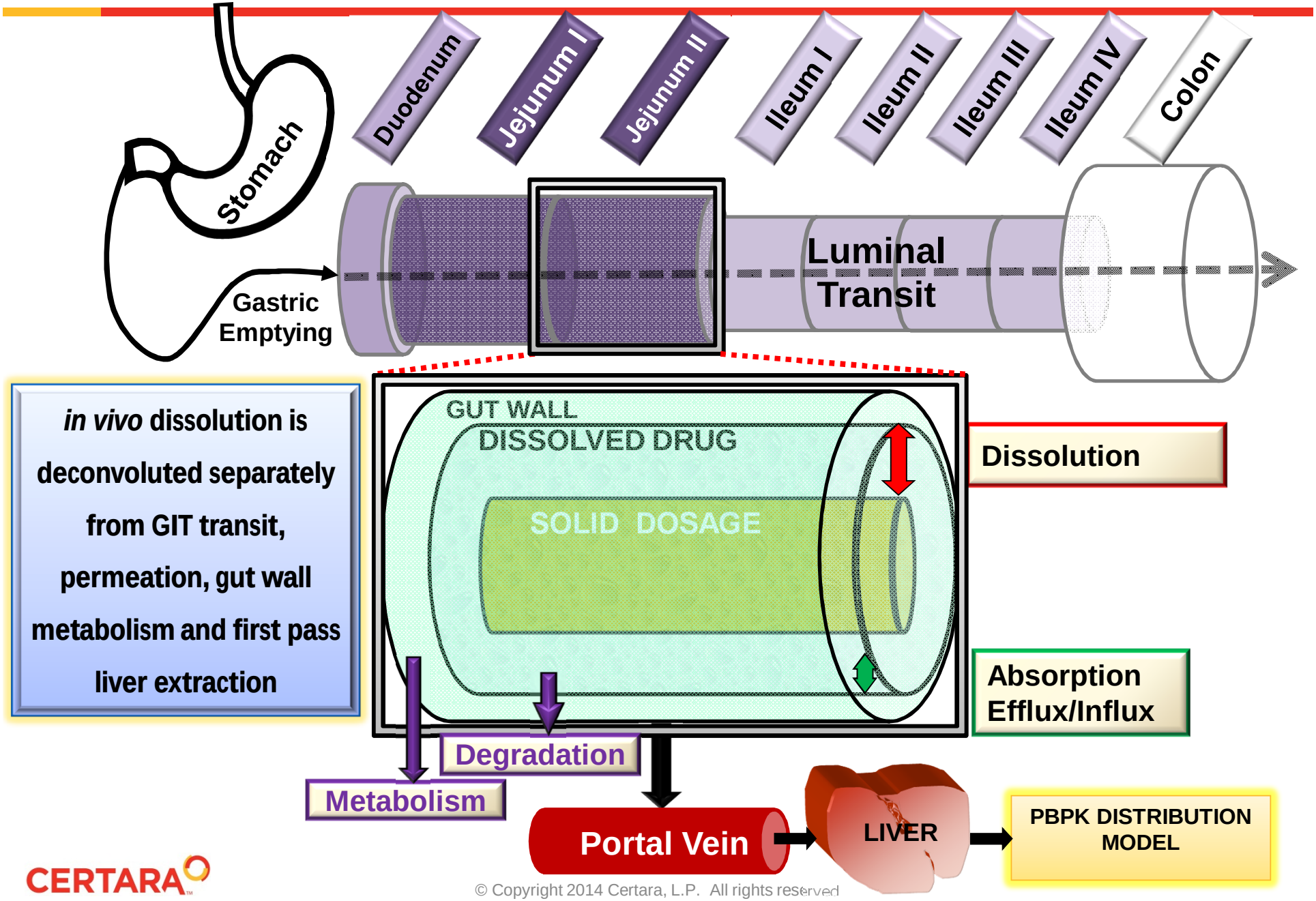


- Numerical Methods
  - No physiological assumptions but mathematical assumptions: input site is the same for all formulations and input rate is constant (infusion) between two time points
  - Depending on the UIR used, it deconvolutes a composite function of dissolution + GI Transit + Permeation + First Pass



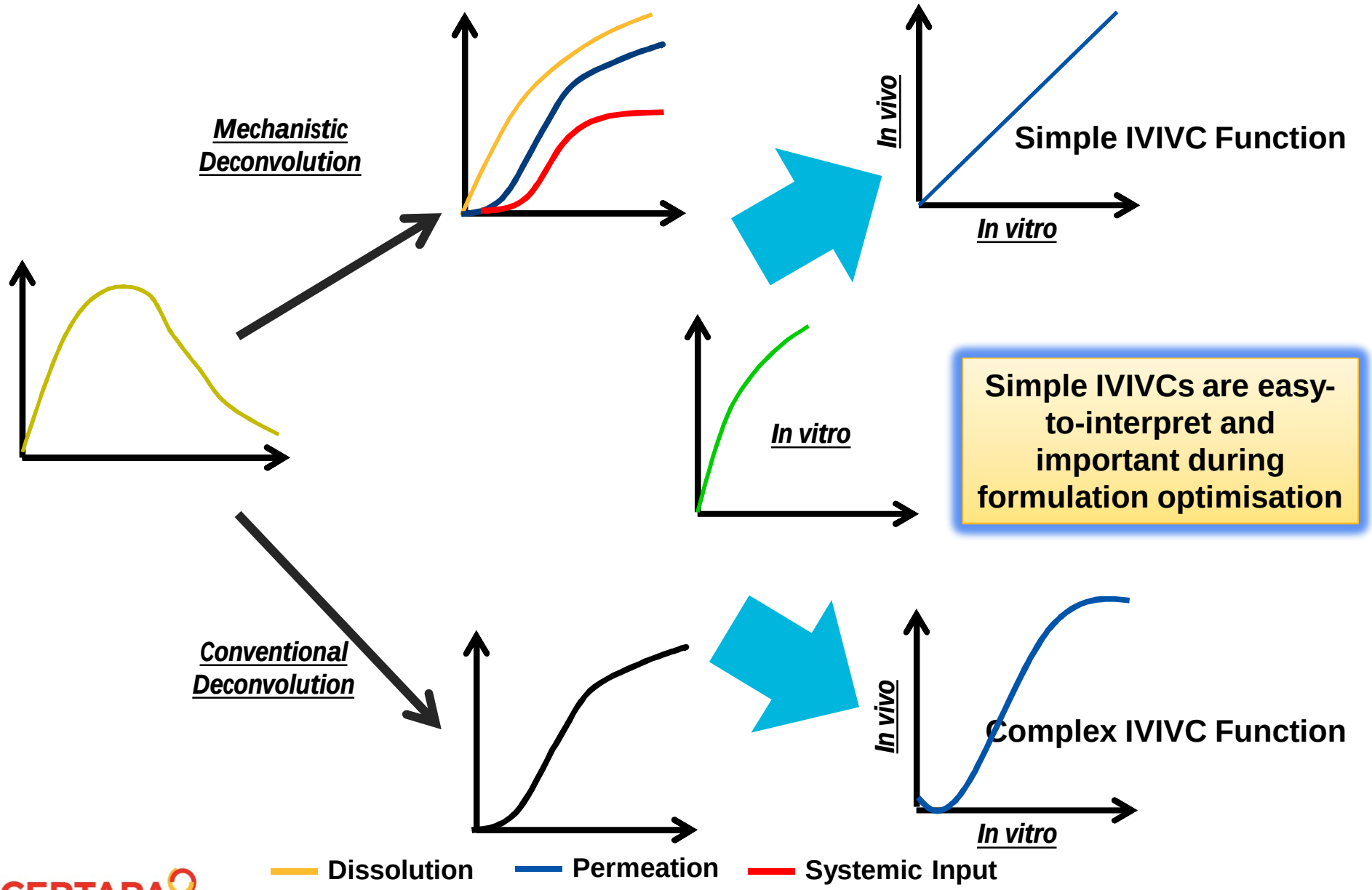
Langenbucher (2003) EJPB 56(3), 429

Mechanistic Deconvolution: e.g. ADAM Model



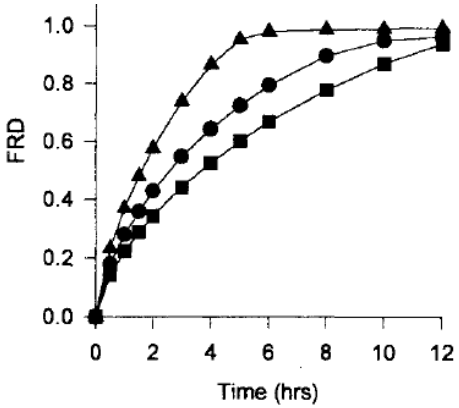
in vivo **dissolution is deconvoluted separately from GIT transit, permeation, gut wall metabolism and first pass liver extraction**

Advantages of Physiologically-based IVIVCs



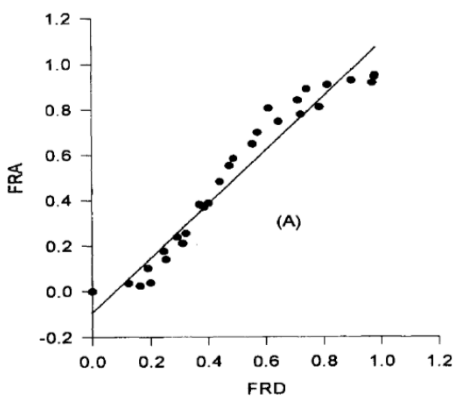
Case study 1: IVIVC for Metoprolol ER formulations

Reported Model 1: Numerical Deconvolution with Oral Solution as UIR

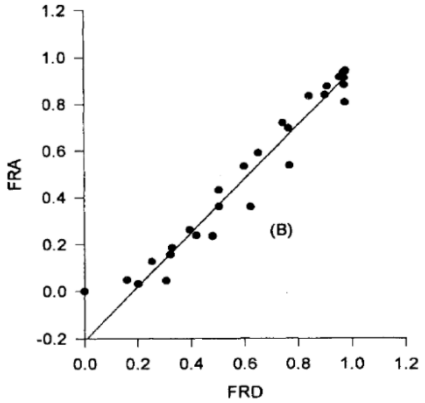


In vitro

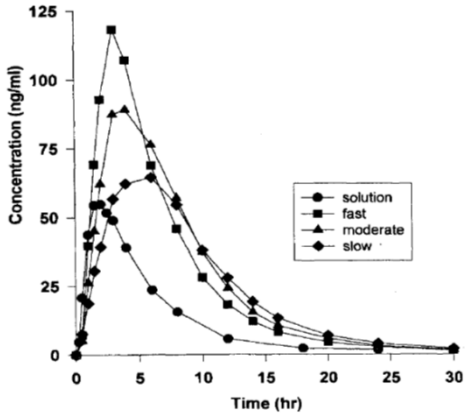
In vitro in vivo correlation



USP II, pH 6.8, 50 RPM



USP I, pH 6.8, 150 RPM

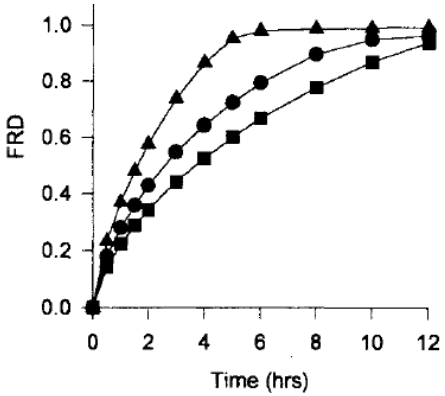


In vivo

Eddington *et al*. (1998) Pharm Res 15(3) 466

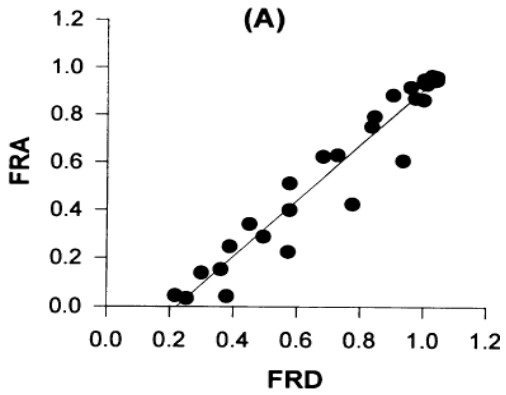
Metoprolol IVIVC Using a Differential Equation-Based FPE Model

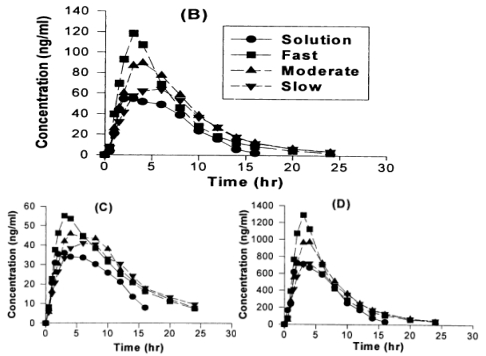
Reported Model 2: FPE Parent / Metabolite Model



USP II, pH 6.8, 150 RPM

In vitro in vivo relationship





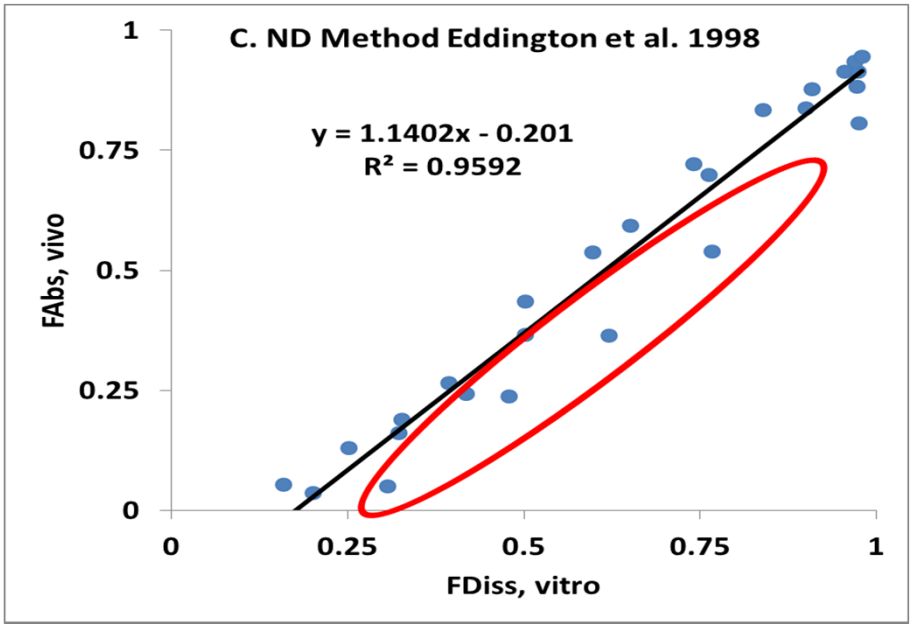
In vivo Parent and Metabolite Data

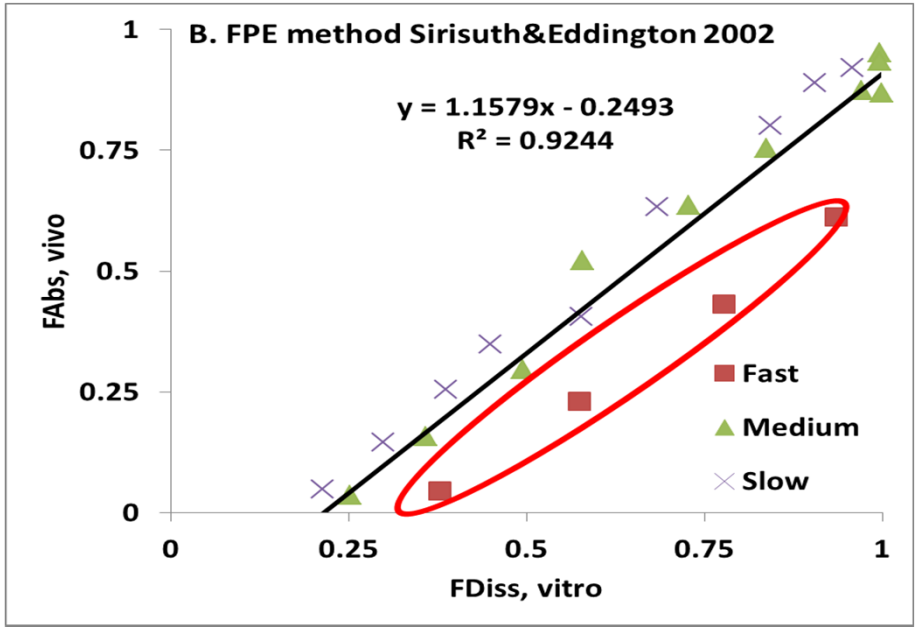
Parameters	Direct approach				Indirect approach			
	Slow	Moderate	Fast	Average	Slow	Moderate	Fast	Average
Metoprolol								
C_{max}	− 83.6	− 65.0	− 67.8	72.2	− 9.26	1.94	3.10	4.77
AUC	− 46.6	− 43.0	− 41.0	43.5	9.27	11.5	11.4	10.77
AHM								
C_{max}	–	–	–	–	− 7.96	0.65	3.20	3.94
AUC	–	–	–	–	12.7	10.3	10.1	11.0
Acid metabolite								
C_{max}	–	–	–	–	− 13.1	− 1.81	3.54	6.14
AUC	–	–	–	–	9.69	11.5	12.7	11.3

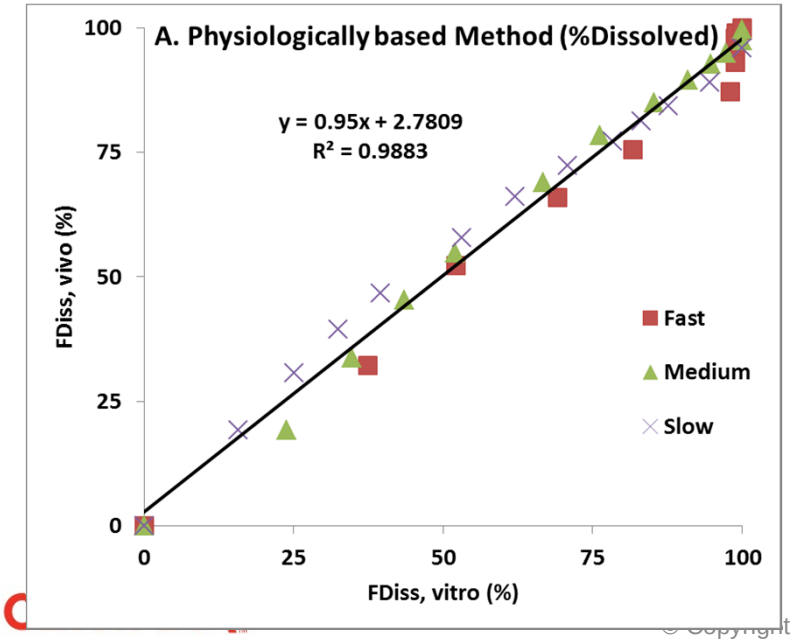
Despite using parent and metabolite data in the IVIVC, prediction errors were equal or higher than ND.

Sirisuth and Eddington (2002) EJPS 53, 301

Two-Stage Sequential Approach using Linear IVIVC



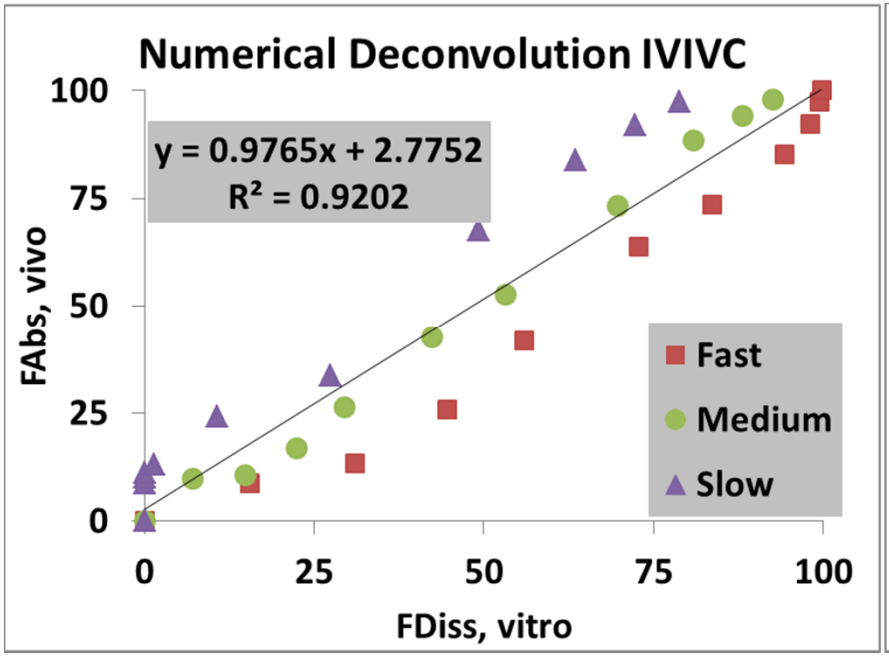


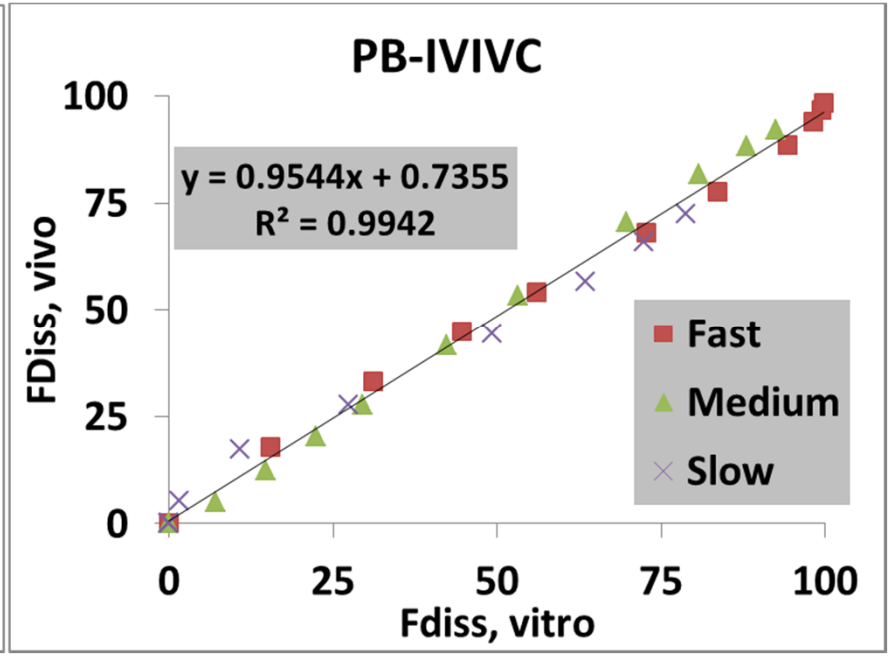


Validation	Formulation	%PE in AUC			%PE in Cmax		
		ND	SM	Simcyp	ND	SM	Simcyp
Internal	Fast	4.52	11.4	-0.34	3.97	3.1	-0.86
	Medium	5.22	11.5	6.07	-0.85	1.94	8.07
	Slow	-0.76	9.27	8.18	-5.67	-9.26	1.84
	AAPE	3.5	10.72	4.86	3.50	4.77	3.59

Patel et al. 2014 9th W PBP meeting, Lisbon

Case Study 2: Diltiazem (BCS I, BDDCS II) CR products





- **Complexities involved**
  - ✓ **Gut-wall metabolism (formulation-dependent non-linearity)**
  - ✓ **Auto-inhibition of CYP3A4 by DTZ and its metabolite**

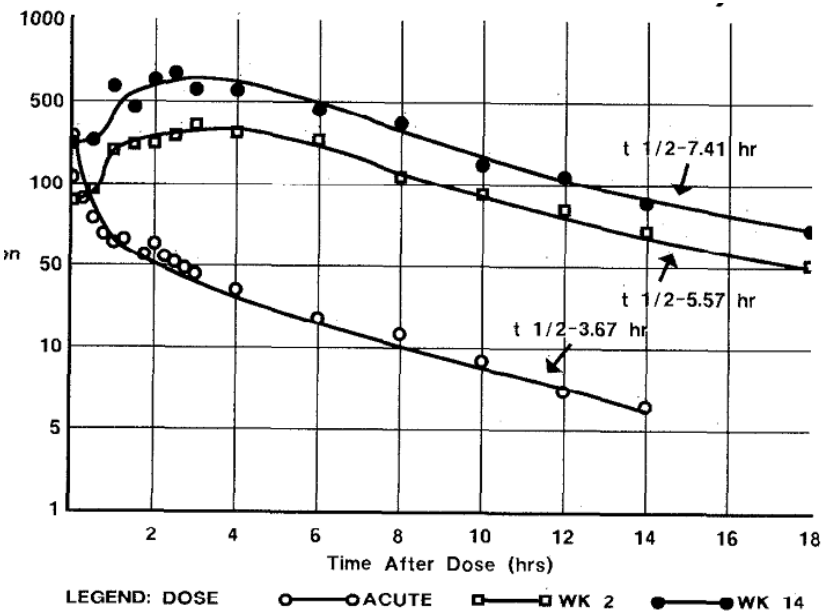
Formulation	%PE in AUC		%PE in Cmax	
	PB	ND*	PB	ND*
Fast	8.33	94	8.63	77.8
Medium	-1.04	57.2	12.31	75.9
Slow	-13.65	47.5	-5.05	65.9
AAPE (%)	7.68	66.3	8.66	73.2
Type of IVIVC	Linear (PB) and Non-linear (ND)			

* When all 3 formulations were used for IVIVC development.

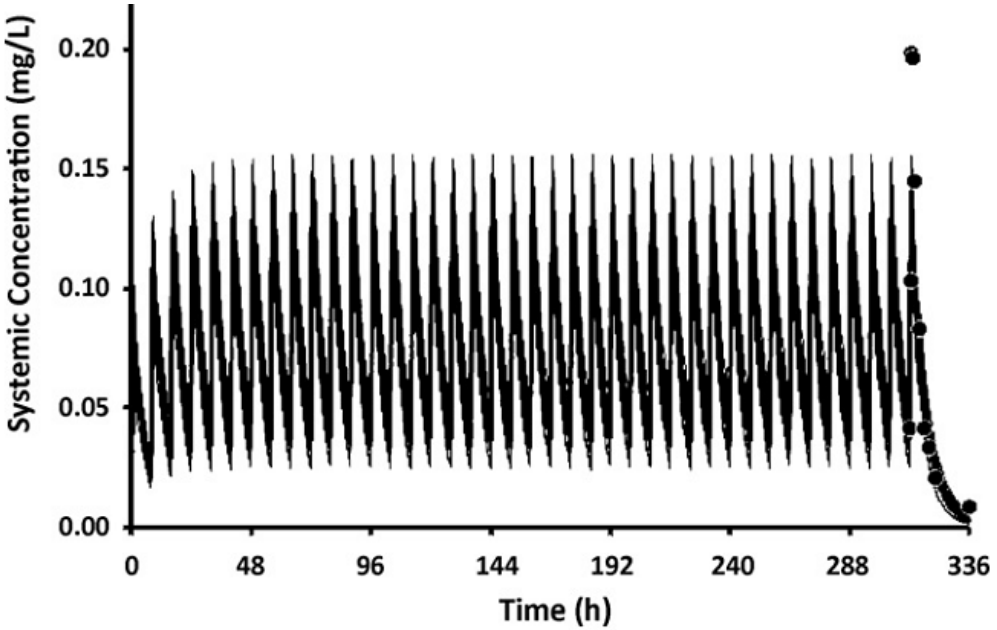
Sirisuth *et al*, 2002 *Biopharm Drug Dispos*

Diltiazem: Considering auto-inhibition

- Is auto-inhibition clinically significant?



Abernethy & Montamat 1987



Rowland Yeo et al 2010

Tsao et al. 1990 "DTZ half-life was 50-100% higher after MD than SD"

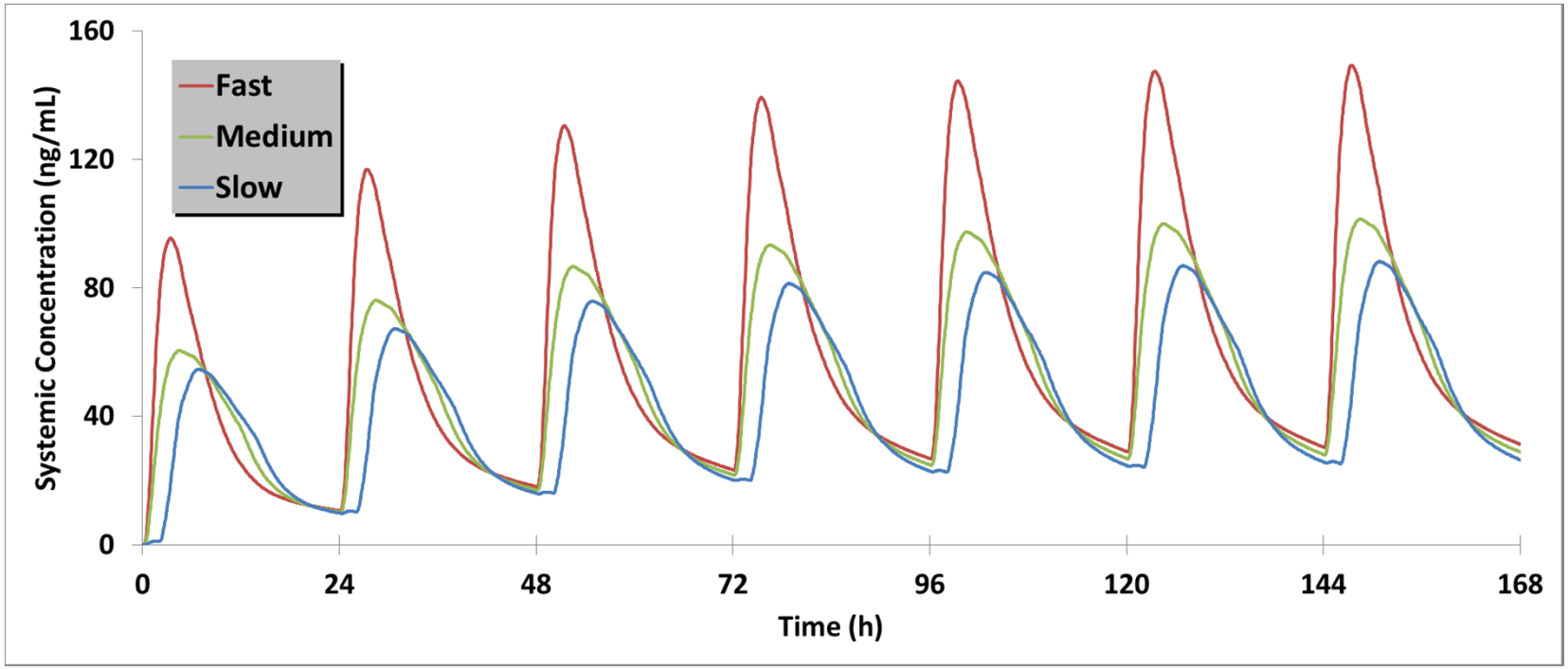
Is an IVIVC or bio-equivalence established based upon a single dose valid at steady state for a drug with formulation-dependent first-pass and mechanism-based enzyme auto-inhibition?

Multi-dose studies for MR formulations

- The CHMP NfG on Modified Release Oral and transdermal Dosage Forms requires a multiple dose study for prolonged release products for drugs expected to show accumulation*
- For Diltiazem, accumulation is expected due to reduced first-pass and systemic clearance due to auto-inhibition but the dissolution is not expected to accumulate for Fast and Medium Release formulations
- PBPK models dissolution and absorption as separate processes hence allows simulation of MR formulation at steady state scenario after multi-dosing and estimate accumulation
- Can PB-IVIVC help to simulate such studies?

*EUFEPS BABP Network Open Discussion Forum: Revised European Guideline on Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms. June 2013. Session III: Specific issues for BE assessment, by Alfredo García Arieta AEMPS, Madrid ES.

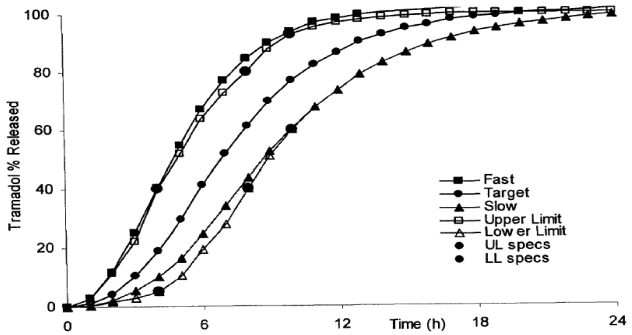
Simulating SS exposure of ER-Diltiazem



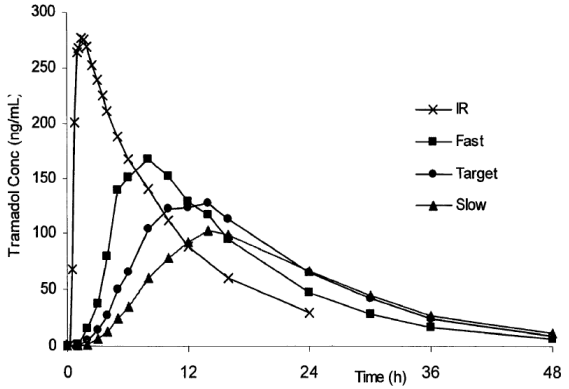
Formulation	AUC Accumulation Index
Fast	1.74
Medium	1.61
Slow	1.46

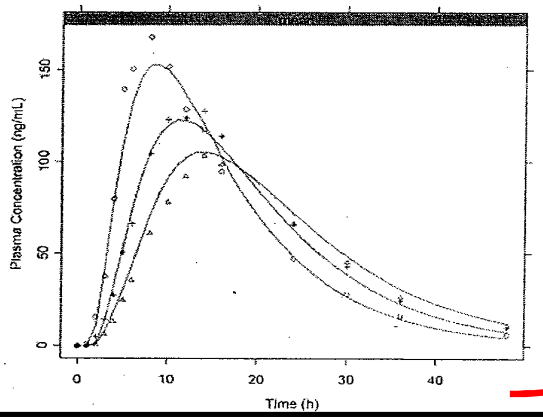
- Such IVIVC linked PBPK simulations could help to evaluate exposure at steady state for ER products based upon single dose clinical studies

Case study 3: IVIVC for Tramadol ER Formulation

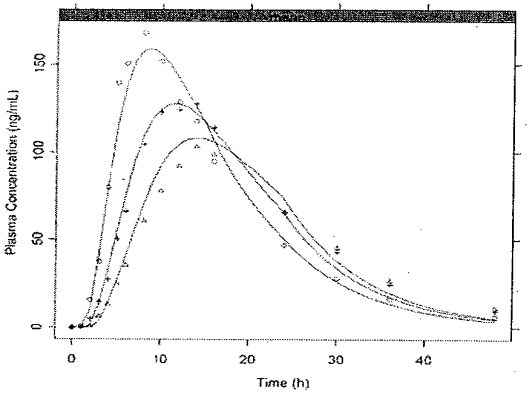


In Vitro In Vivo Correlation





Failed to predict lower bioavailability of slow formulation



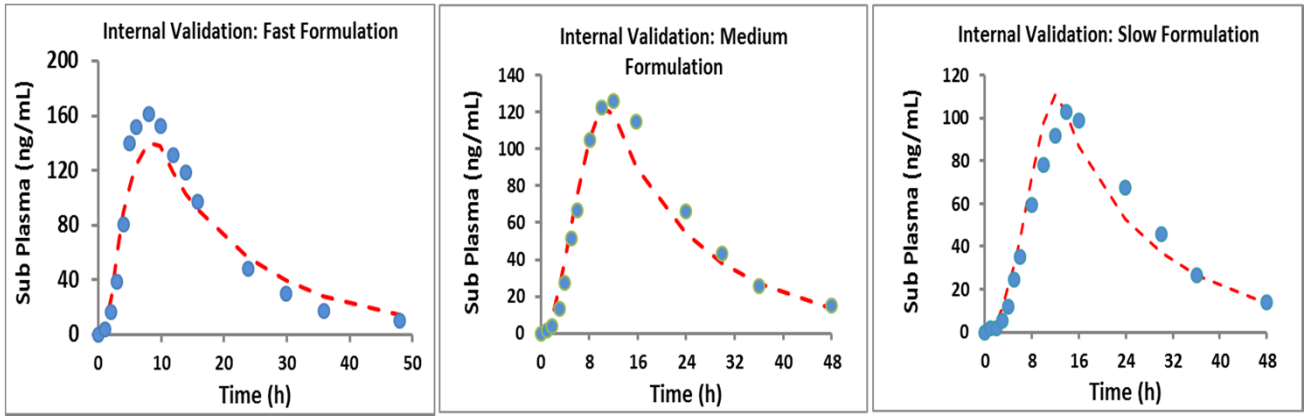
Linear Model

Time scaled Extended Model

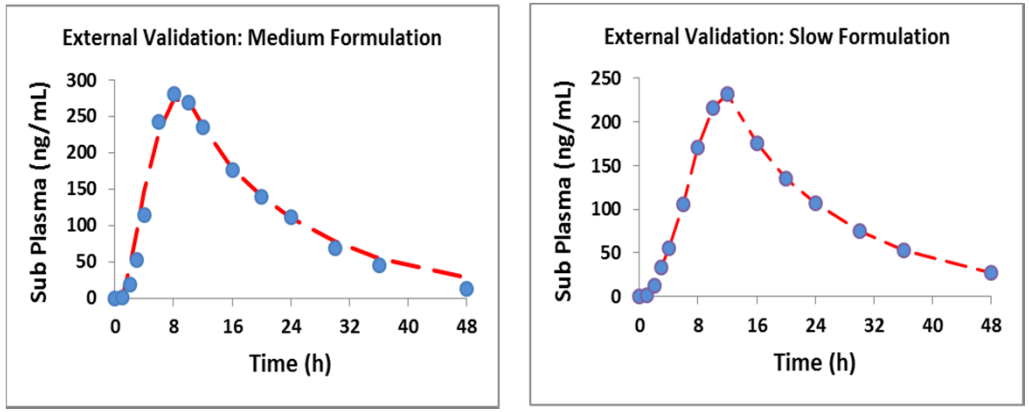
Extended IVIVC model which incorporates time dependent extent of absorption was developed and submitted

PB-IVIVC: Two-Stage Sequential Approach using Linear IVIVC

Internal Validation



External Validation

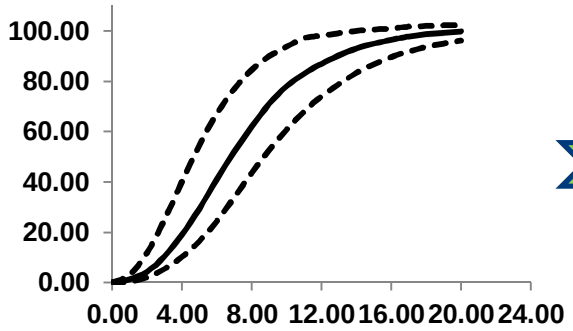


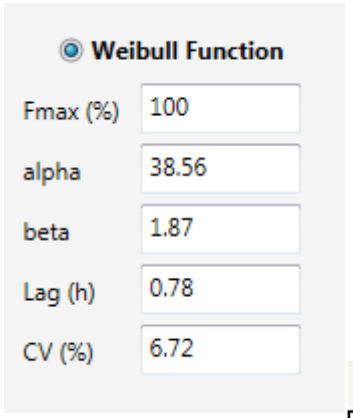
UL & LL Dissolution Specifications

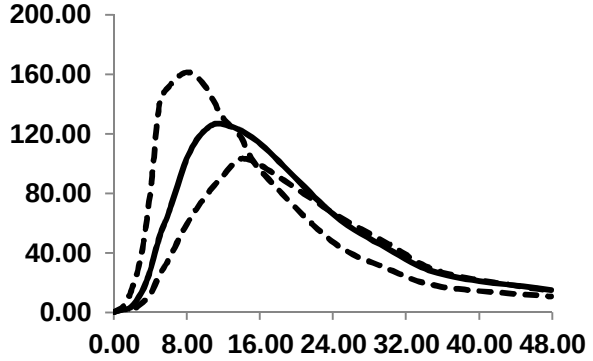
Prediction	Formulation	AUC_{0-t} (ng/mL.h)			Cmax (ng/mL)		
		Obs- Med	Pred	%PE	Obs- Med	Pred	%PE
Dissolution	LL Disso Specs	2746.3562	2283.3879	16.86	126.2574	117.1461	7.22
	UL Disso Specs	2746.3562	2843.2808	-3.53	126.2574	137.0588	-8.56

Pathak et al, AAPS,2014

Application of Absorption Modelling to Predict Virtual Bioequivalence

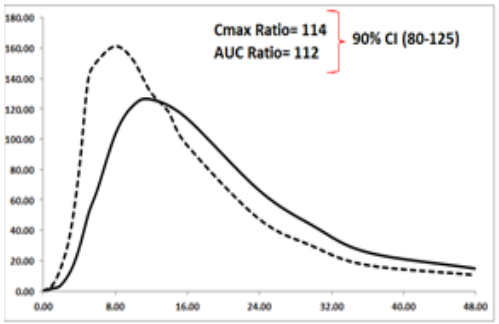


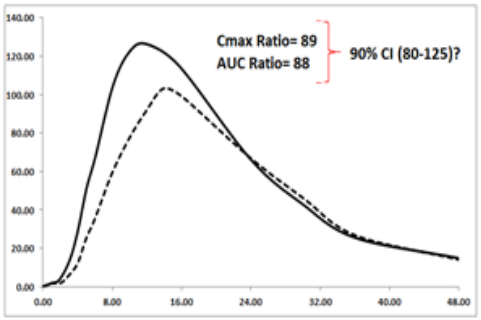


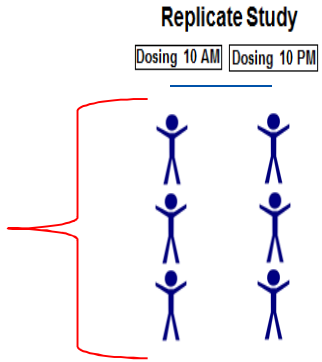


Fast, Target and Slow dissolution profiles of Tramadol ER Formulation

Predicted Plasma profiles in virtual population using SimCYP PBPK Modelling







Virtual Bioequivalence was determined using Phoenix BE module

Inter-occasional variability incorporated into the PK parameters before subjecting it to BE

Objections to More Mechanistic Models

1 –Data hungry!

System vs drug/formulation data?

2- Makes many assumptions!

Assumptions are declared; unlike other models

3- It is not transparent!

Contradiction with previous item!

4- Does not add too much value!

Most of the value is in “internal facilitation” and “informed decision making”

5- Other modelling types can be done too!

Other models by their nature cannot go beyond the data which is used to drive them (no extrapolation)

Slide Courtesy - Amin Rostami Hodjegan (Uni Manchester)

Acknowledgements

- **Simcyp**
  - Nikunjkumar Patel
  - David Turner
  - Sebastian Polak
  - Masoud Jamei
- **University of Manchester**
  - Amin Rostami-Hodjegan (Seconded at Simcyp)
- **Simcyp Consortium Members**

Thank you for your attention