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PBPK Modelling in Generic Drug Product Assessment

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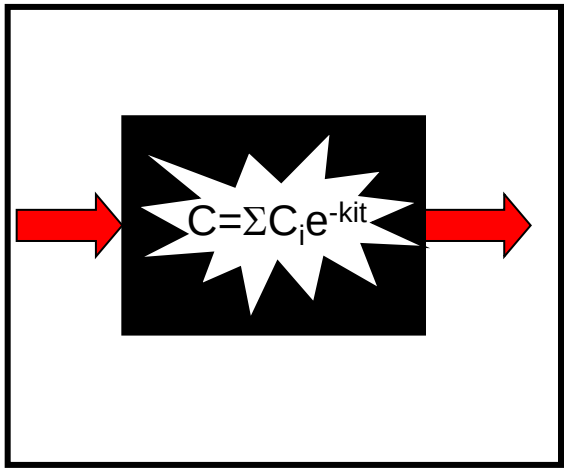
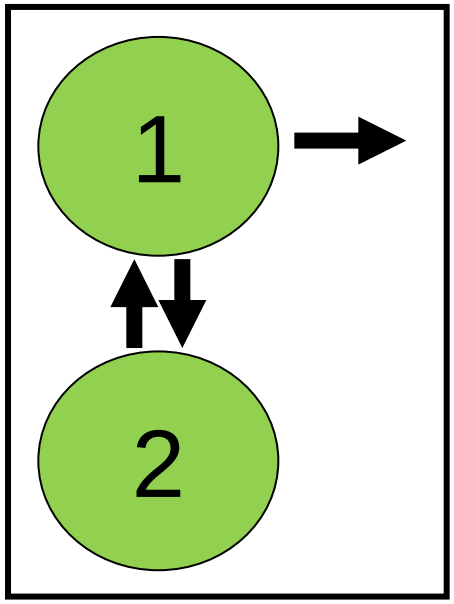
Tripos SIMCYP Pharsight

Typical Models Used to Describe Pharmacokinetics

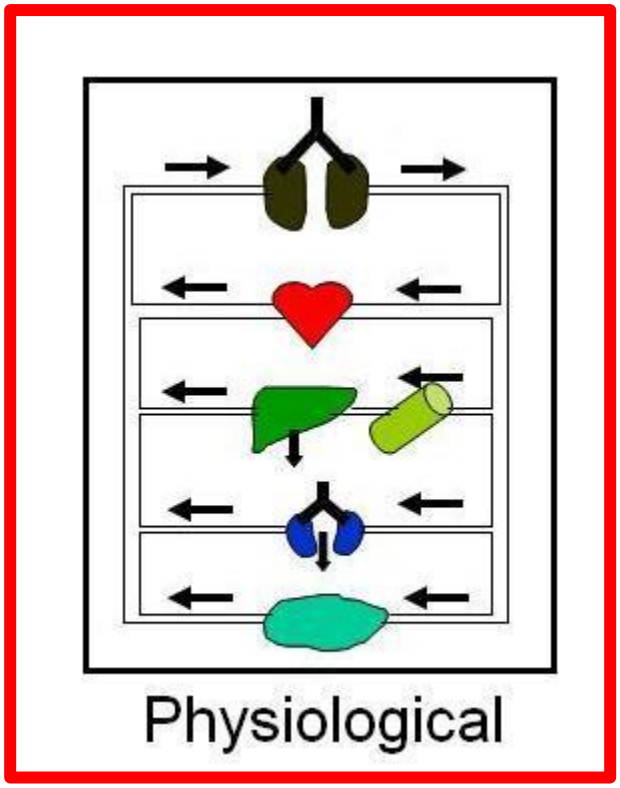
Three type of models can be used to describe concentration time profiles (PK).



Empirical



Compartmental



Physiological

Empirical and compartmental models are fitted to observed data to explain the data whereas physiological models can be used for a priori prediction and then refine as data becomes available

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Examples of PBPK in Product Design and Assessment

- Application in QbD
- Establishing IVIVC/IVIVE with in vitro dissolution experiments
- Extrapolating from adult to paediatric or disease population
- Assessing impact of food effect
- Assessing gut-level drug-drug interactions e.g. PPI
- Virtual Bio-equivalence Assessment
- Assessing untested scenarios to fill data gaps in generic product assessment

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QbD and Particle Size Specifications/Assessment

- Some examples

Utility of Physiologically Based Absorption Modeling in Implementing Quality by Design in Drug Development

Xinyuan Zhang,[1] Robert A. Lionberger,[1,2] Barbara M. Davit,[1] and Lawrence X. Yu[1]

Application of Absorption Modeling in Rational Design of Drug Product Under Quality-by-Design Paradigm

Filippos Kesisoglou[1,2] and Amitava Mitra[1,2]

- To use it for regulatory purposes, there needs to be "model qualification criteria" especially when some parameters are fitted and/or assumed
- Is the physiology in PBPK platforms needs to be scientifically traceable or arbitrary/assumed values acceptable?
- Is simulation with a PBPK "platform defined average human" good enough or a population simulation is needed?

Extrapolating Formulation Assessment from Adult to Pediatric

- Some examples

Exploratory Investigation of the Limiting Steps of Oral Absorption of Fluconazole and Ketoconazole in Children Using an *In Silico* Pediatric Absorption Model

Rodrigo Cristofoletti [1, 2], Naseem A. Charoo [3, 4], Jennifer B. Dressman [2, *]

Using Physiologically Based Pharmacokinetic (PBPK) Modelling to Gain Insights into the Effect of Physiological Factors on Oral Absorption in Paediatric Populations

Angela Villiger,[1,3] Cordula Stillhart,[1] Neil Parrott,[2] and Martin Kuentz[3,4]

Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents

Trevor N. Johnson[a], Diansong Zhou[b], and Khanh H. Bui[b,*]

- What paediatric physiology to use when there is scarce and contradictory?
- What is “model qualification criteria” especially when some physiology/drug parameters are fitted or assumed?

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Assessing the impact of food with PBPK

- Some examples

Differences in Food Effects for 2 Weak Bases With Similar BCS Drug-Related Properties: What Is Happening in the Intestinal Lumen?

Rodrigo Cristofoletti [1,2], Nikunjkumar Patel [3], Jennifer B. Dressman [2,*]

Quantitative prediction of formulation-specific food effects and their population variability from *in vitro* data with the physiologically-based ADAM model: A case study using the BCS/BDDCS Class II drug nifedipine

Nikunjkumar Patel [a,*], Sebastian Polak [a,b], Masoud Jamei [a], Amin Rostami-Hodjegan [a,c], David B. Turner [a]

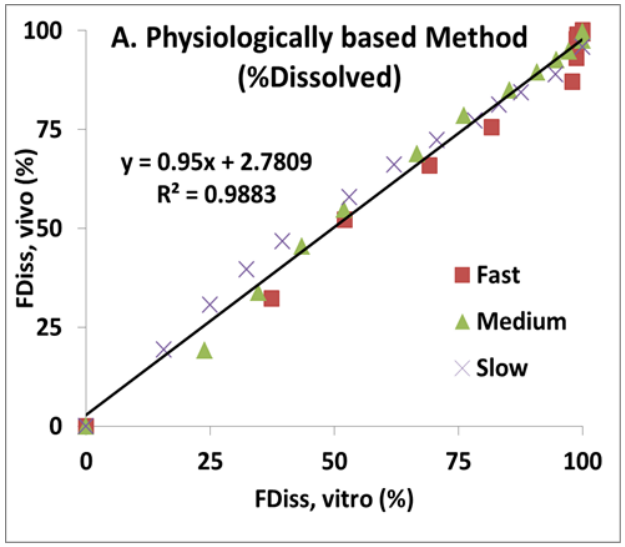
Case Studies for Practical Food Effect Assessments across BCS/BDDCS Class Compounds using *In Silico*, *In Vitro*, and Preclinical *In Vivo* Data

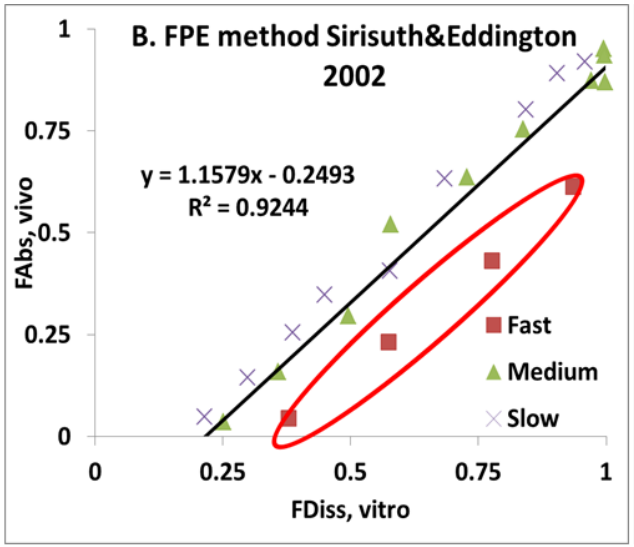
Tycho Heimbach,[1,2] Binfeng Xia,[1] Tsu-han Lin,[1] and Handan He[1]

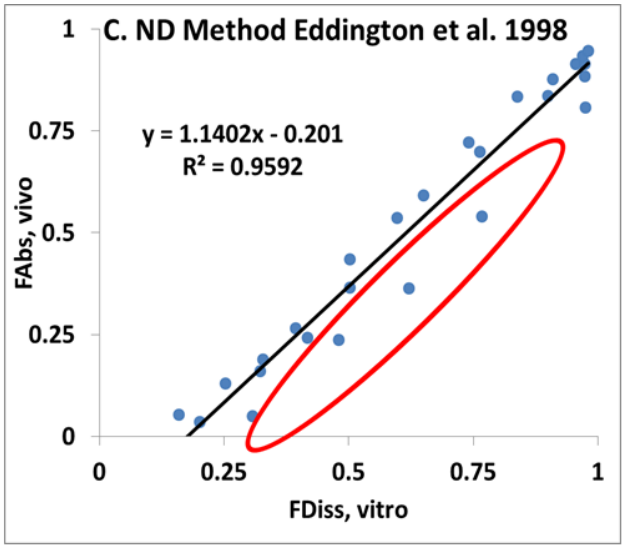
- What to do when QSAR based/assumed inputs are used to parameterise model especially if the model is very sensitive to that parameter?

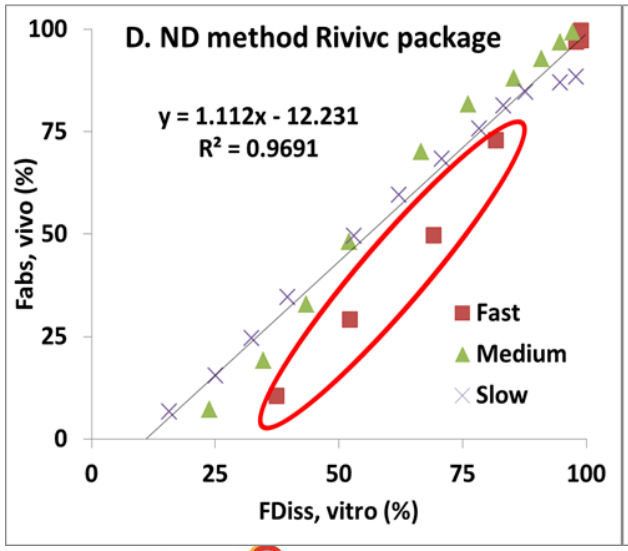
Mechanistic IVIVC

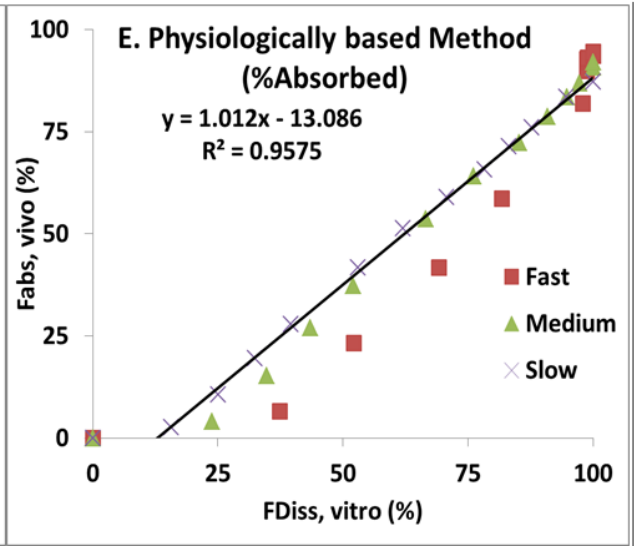
- Advantage with PBPK- deconvolutes dissolution rather than absorption

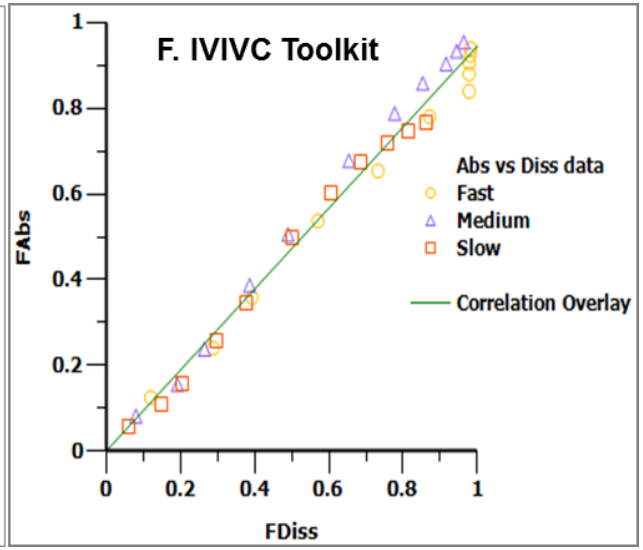












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Population level PB-IVIVC and Extrapolation to Untested Scenarios

Examining the Use of a Mechanistic Model to Generate an In Vivo/In Vitro Correlation: Journey Through a Thought Process *Accepted, AAPS J, 2016*

Bipin Mistry[1], Nikunjkumar Patel[2], 'Masoud Jamei[2], Amin Rostami-Hodjegan[2,3], Marilyn N. Martinez[1*]

- Exploratory analysis showed significant intra- and inter- individual variability
- Mechanistic deconvolution of *in vivo* dissolution for IVIVC
- Model validation criteria
  - Leave-one-formulation out with bootstrap - Leave one individual out

	Adj R^2	Slope
ALL SUBAll FORMS	0.946	0.813
ALL SUBMinus Fast	0.935	0.8
ALL SUBMinus Med	**0.955**	**0.839**
ALL SUBMinus Slow	0.947	0.8
Boot All Forms	0.945	0.812
Boot Minus Fast	0.934	0.798
Boot Minus Med	**0.954**	**0.838**
Boot Slow	0.946	0.799

	Slope	R2 adj	#Obs
ALL	1.045	0.953	210
Minus 1	1.036	0.951	180
Minus 2	1.053	0.954	180
Minus 3	1.063	0.956	180
Minus 5	1.034	0.955	180
Minus 6	1.044	0.952	180
Minus 7	1.050	0.951	180
Minus 9	1.032	0.953	180

- Model then applied to predict formulation performance in CYP2D6 PM subjects

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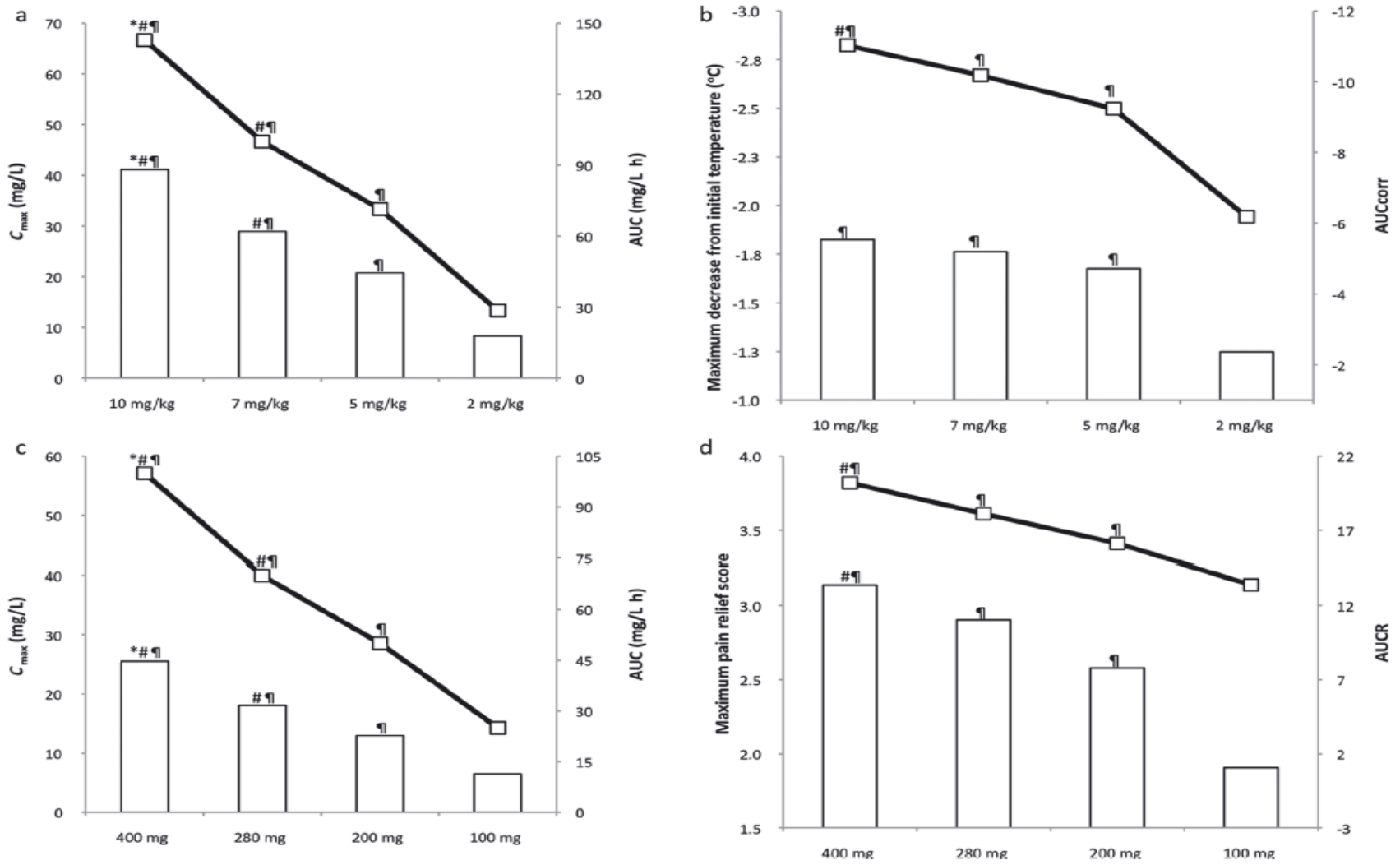
Therapeutic Equivalence Assessment using PBPK Simulations

Ibuprofen IR products PK and PD differences with dose



Cristofoletti & Dressman 2014, J Pharm Sci, 103 (10), 3263-75

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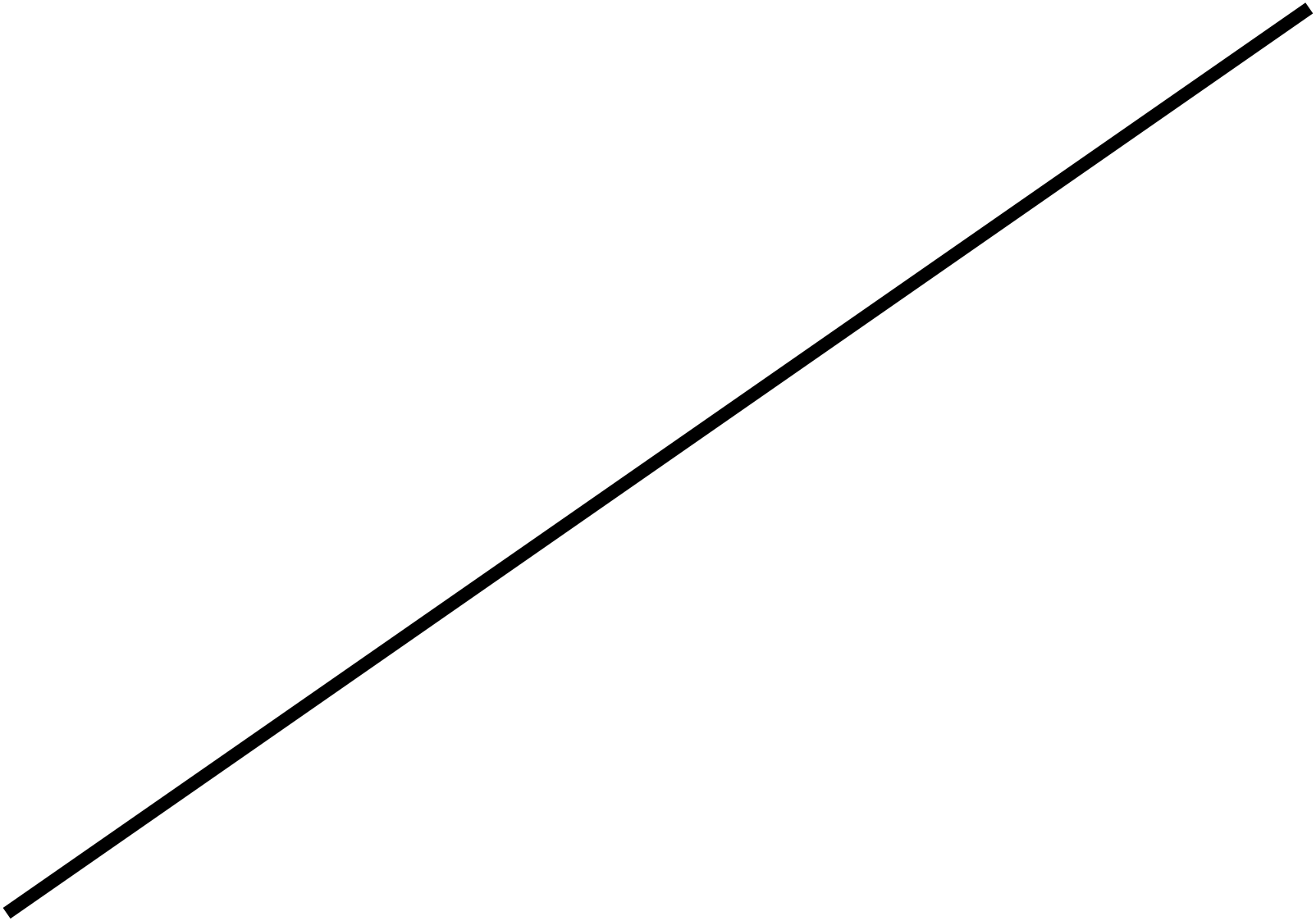
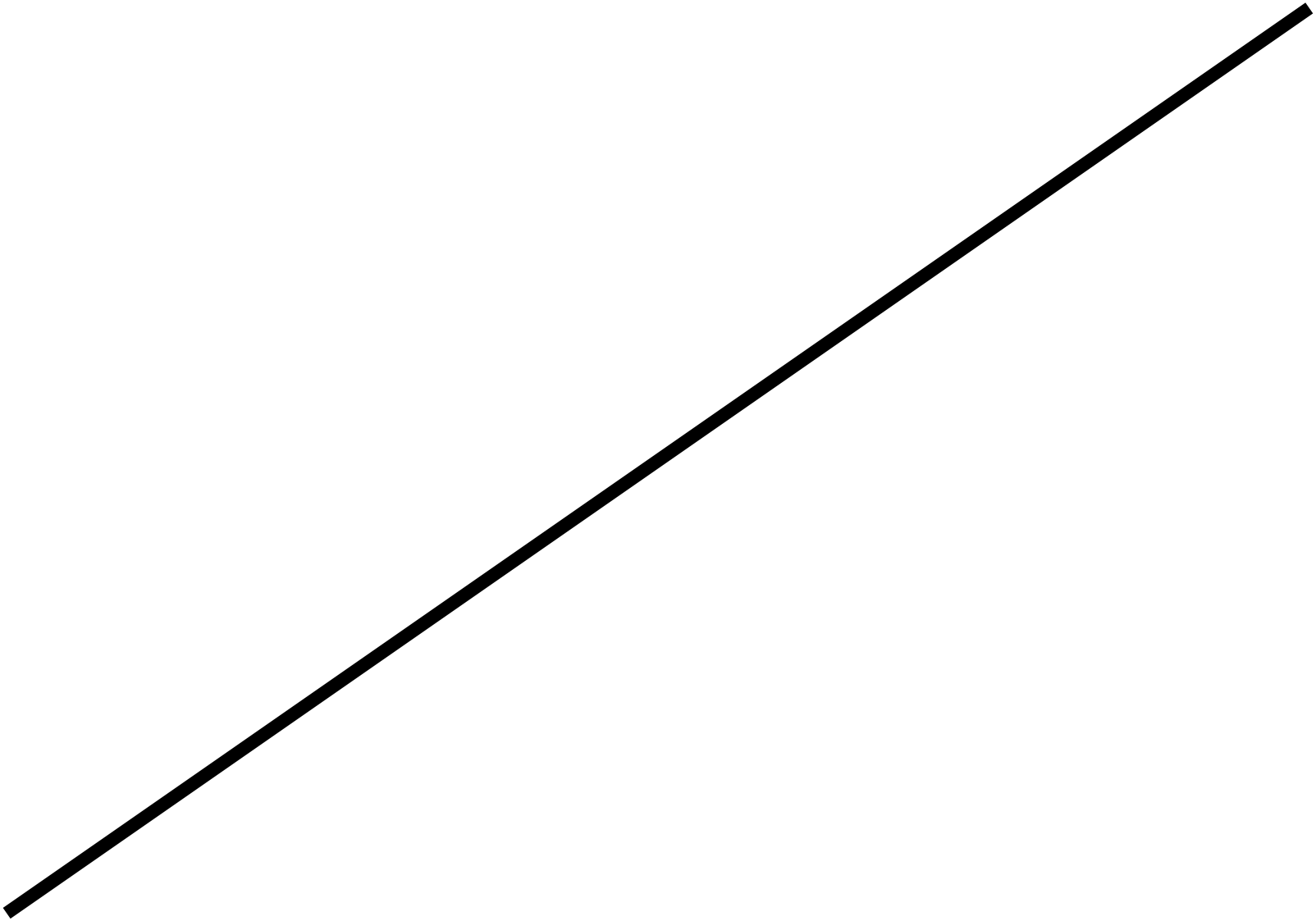
Translating BE from healthy to patient population

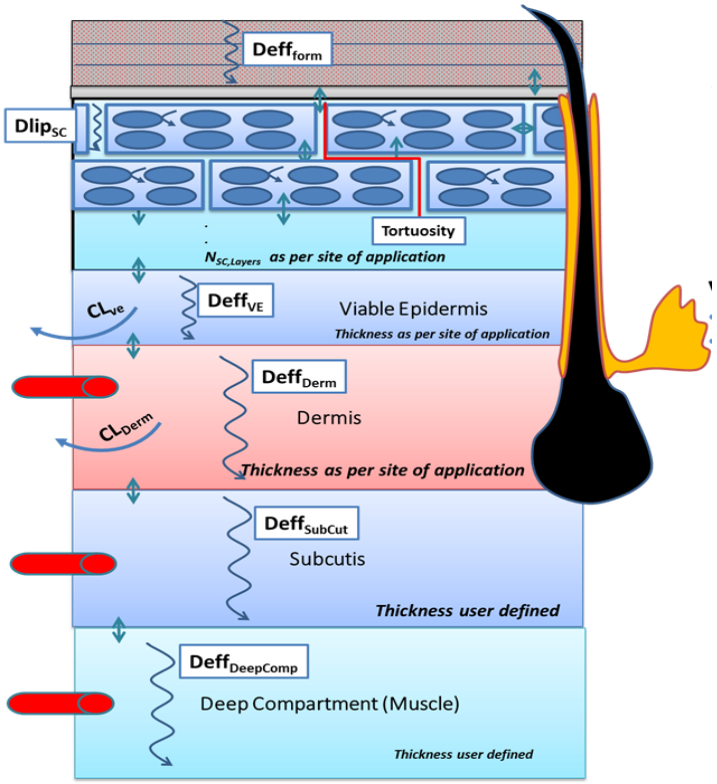


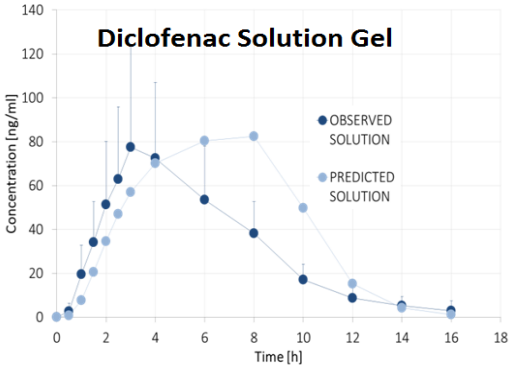
Assessing (virtual) BE in various conditions/populations

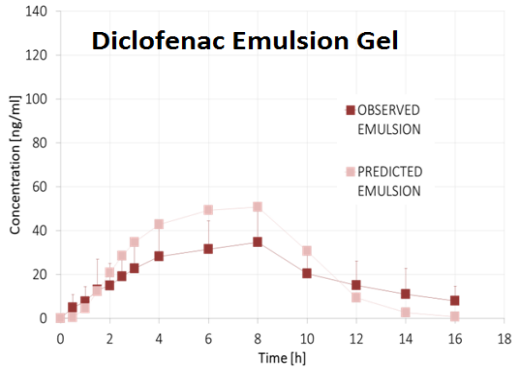


PBPK in Dermal Product Assessment

- As part of GDUFA grant 1U01FD005225-01, we are developing mechanistic PBPK model of skin permeation







Erythromycin applied on skin

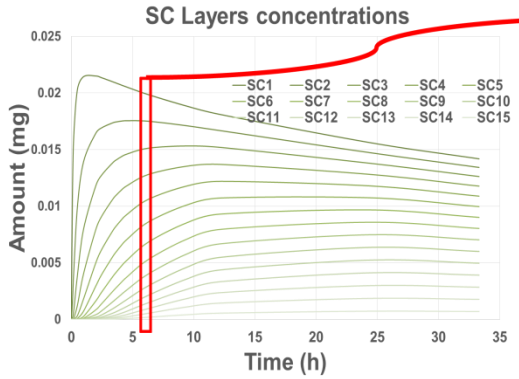


Figure 2. Erythromycin SC individual layers PK profiles.

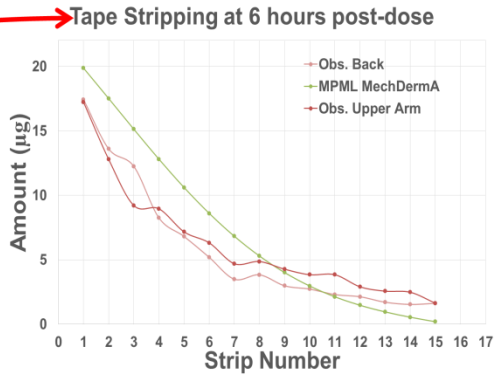


Figure 4. MPML MechDermA skin stripping experiments Predictions vs. Observations

- The PBPK model can be as mechanistic as our knowledge of physiology
- Need more understanding on dermal physiology and kinetics as there are many contradictory data and gaps in currently available public literature

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Ways to increase PBPK utilisation in generic product assessment

- More case examples means more confidence and more learning where it works and where it does not
- Guidelines on “model qualification criteria”
- Establishing “Good Practices” in PBPK modelling
- More research on inter-occasion and intra-subject variability in physiology that impact formulation performance
- Most of the times physiology parameters are collected from different sources or derived which requires understanding on covariations
- More research towards PBPK modelling of enabling and modified release formulations and other routes of administration
- Mechanistic models for assessing excipient impact to have better differentiation of products
- Interdisciplinary collaborations between modellers, biopharm, formulation and clinical scientists e.g. OrBiTo project

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Thank You

Questions?