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Simcyp

# *PBPK Modeling of Dermally Applied Drug Products to Support Clinical Development and Regulatory Assessment*


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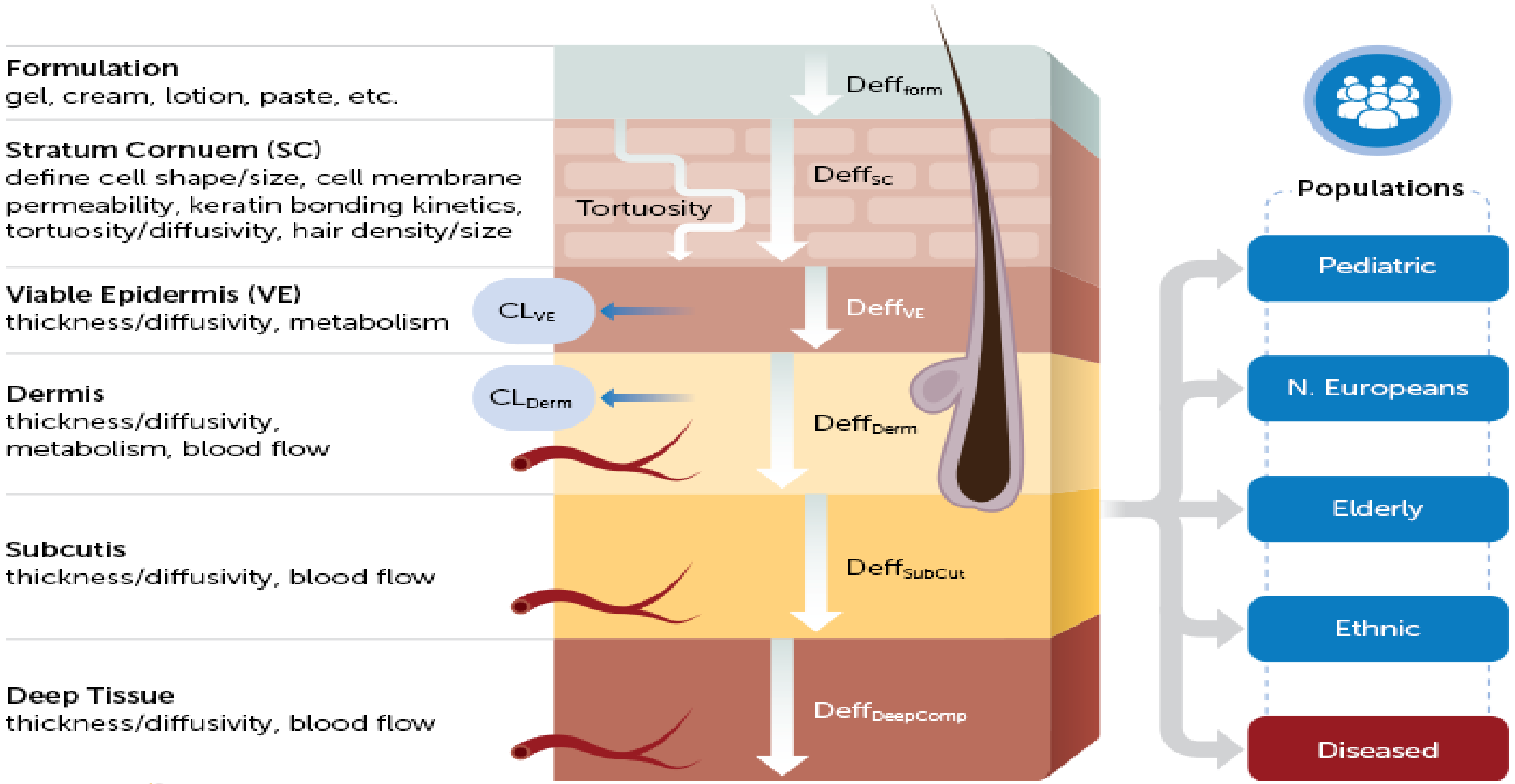
Certara UK Limited


**ASCPT Preconference workshop on PBPK Modelling for the development and approval of locally acting drug products**
**13 March 2019, Washington DC**

# MPML-MechDermA Model

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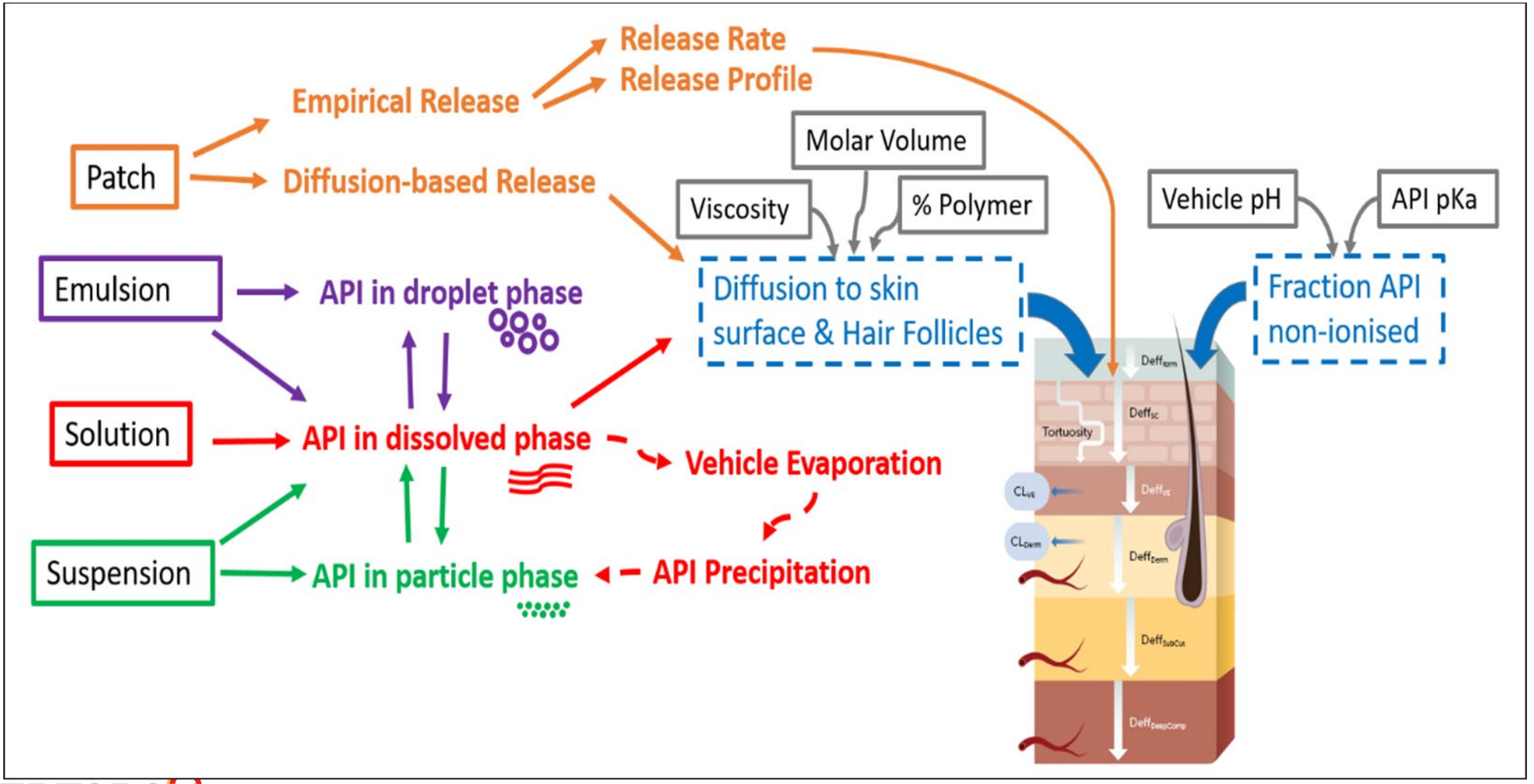
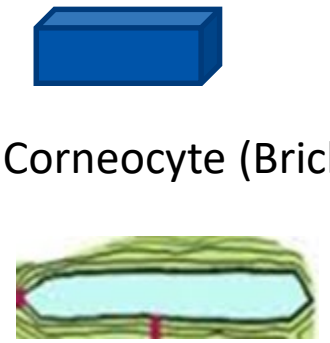
# MPML-MechDermA Formulation Models

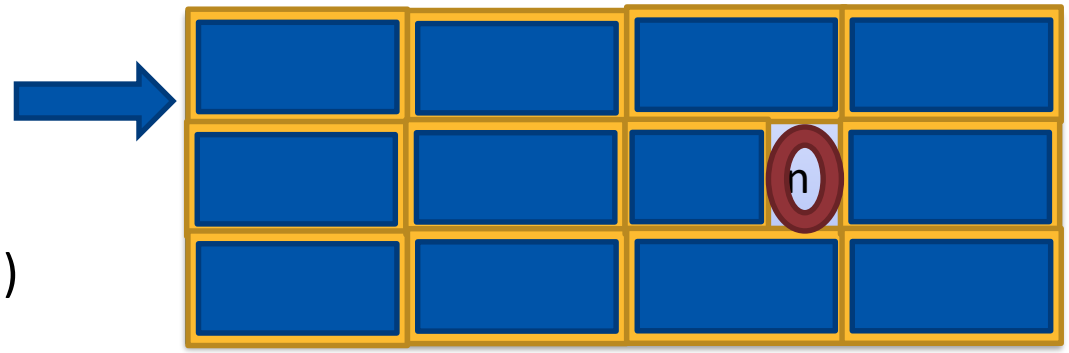


# MPML-MechDermA – Brick and Mortar Model for SC

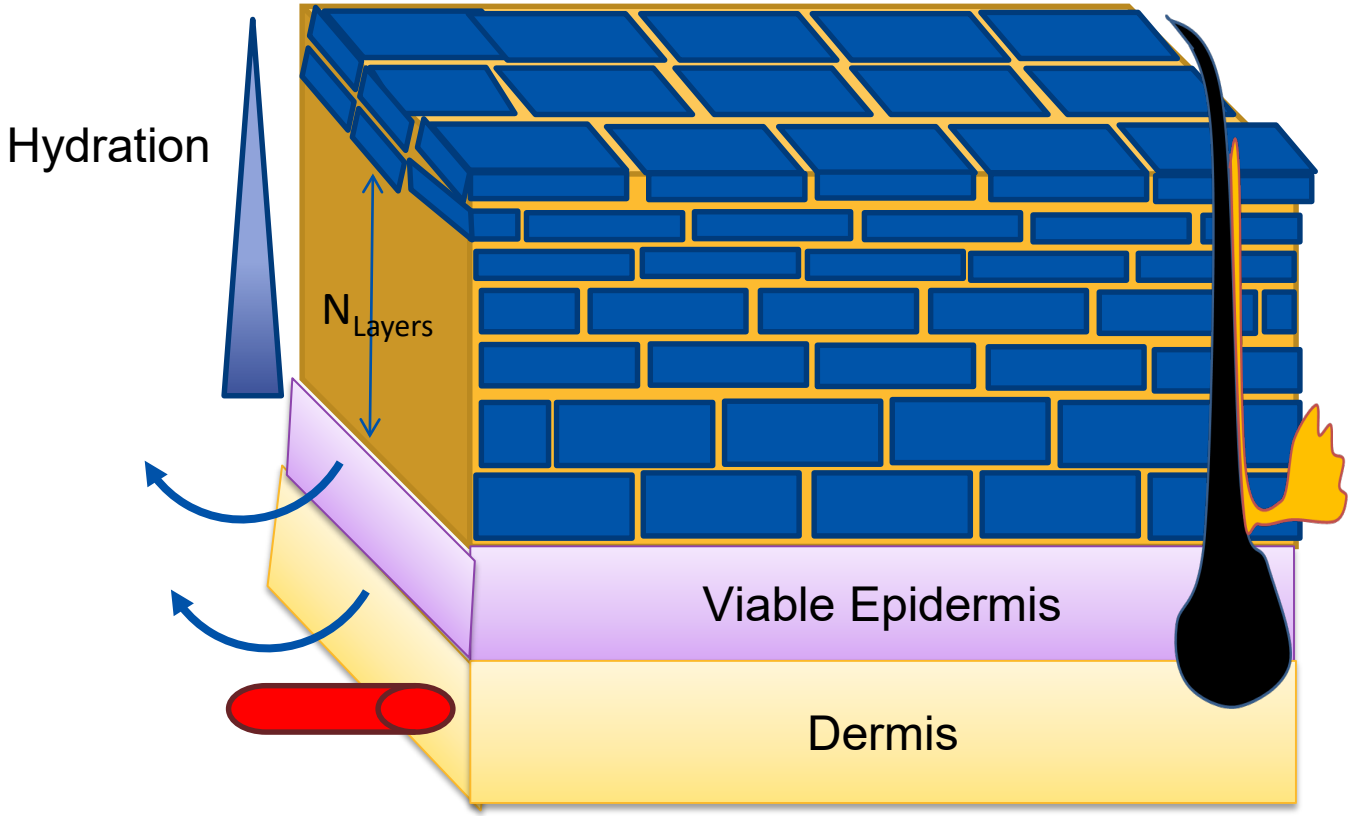


Corneocyte (Brick)

Model Unit
(Brick in mortar around)




Top view of the mosaic cellular arrangement in applied area

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# Intra-individual Variability

- Eight different locations
  1. Forehead
  2. Face (cheek)
  3. Volar Forearm
  4. Dorsal Forearm
  5. Upper Arm
  6. Lower Leg
  7. Thigh
  8. Back


- Various structural elements
  1. Skin surface
  2. **Stratum corneum**
  3. Viable epidermis
  4. Dermis
  5. Subcutis
  6. Muscle
  7. Hair

- Various parameters
  1. **Number of layers**
  2. Corneocyte pH
  3. Corneocyte size
  4. Fraction of p/w/l
  5. Tortuosity
  6. Lipids fluidity/th

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# Inputs needed to run the model

## Drug Parameters

MW
LogP
pKa
$f_u$ (QSAR)
Solubility (QSAR)

Skin Model Inputs

Ksc:vehicle (QSAR)
Kdermis:blood (QSAR)
Dsc (QSAR)
Ddermis (QSAR)
fuSC (QSAR)

## Systems Parameters

### *In vitro Simulation*

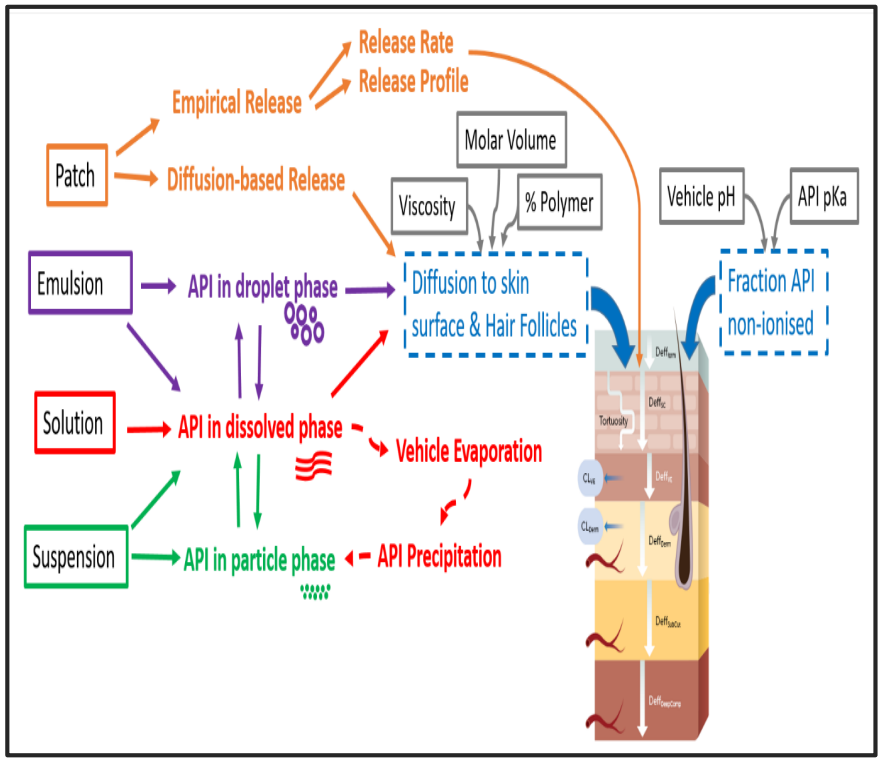
- Type of skin sample
- Thickness of skin sample
- Area of diffusion cell
- Volume and solubility in receptor fluid
- Static or flow through

### *In vivo* Simulation

- Area and Site of Application
- Number of subjects
- Demographics (age, gender)
- Physiology is then populated from database supporting the model or modified by the user

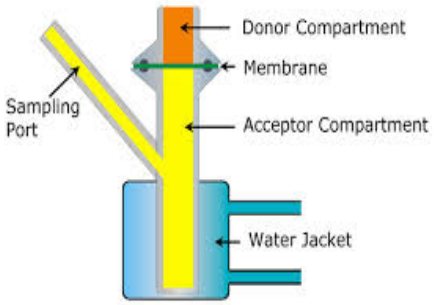
## Formulation Data

- Dose (drug and formulation)
- Type of Formulation
  - ✓ Solution
  - ✓ Emulsion
  - ✓ Particles present?
  - ✓ Patch



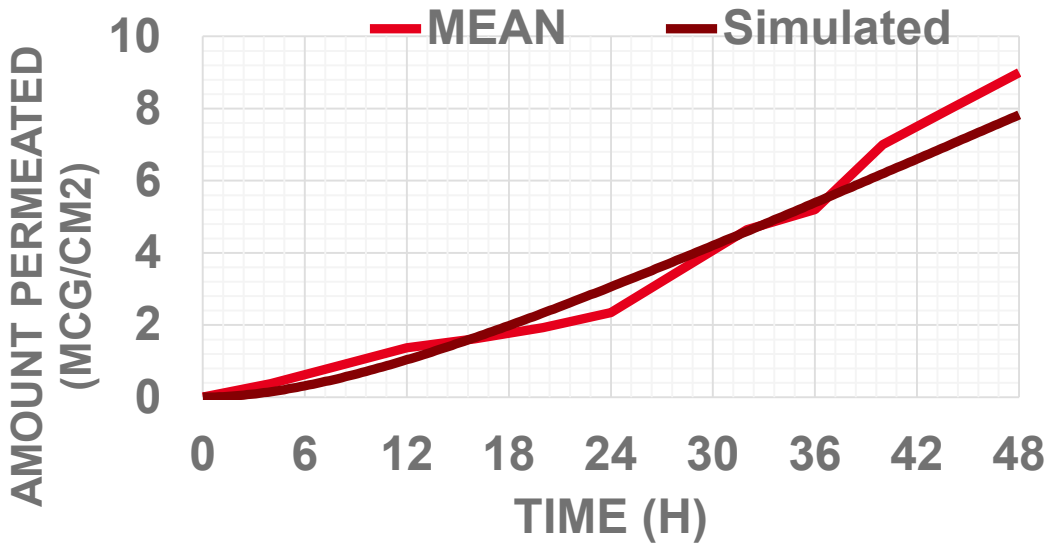
# Simcyp IVIVE: Translating *in vitro* permeability to clinical situations

Define Drug, Formulation and IVPT Set up to simulate




**Simulate IVPT based on prior knowledge**

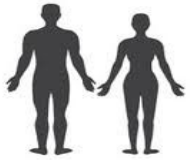
**Compare with Obs, if available**




**If needed, refine model parameters**

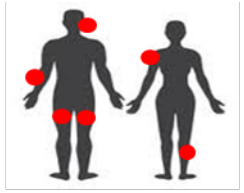
**Run "what if" *in vitro* simulations**

Elderly Subjects



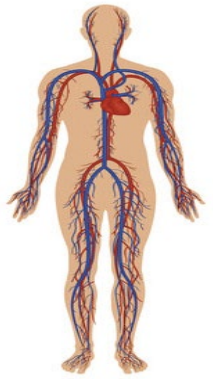
Healthy NEurCaucasian

Paediatric Population



Diseased Population (psoriasis)

Take ***Drug and Formulation*** parameters and combine with in vivo physiology databased



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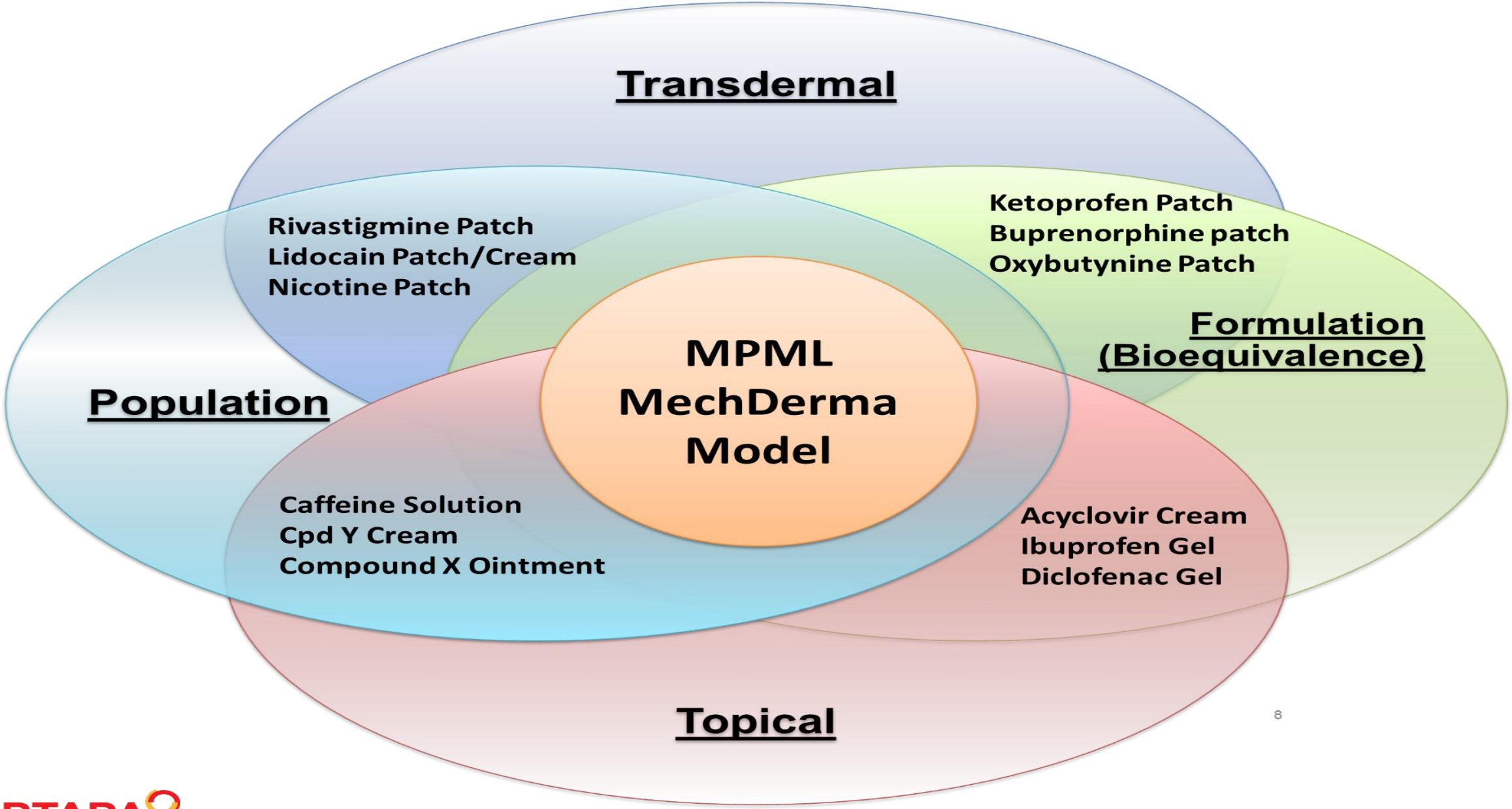
# Model Verification and Application – 11 Different Case Examples



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# Model Verification/Application Dataset Profile

| | Compound | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Formulation type | solution | | x | | x | x | | | | x | x | x |
| | emulsion | | | | | x | | x (with particles) | x (paediatric) | x | | |
| | paste | | | | | | | | | | x | |
| | patch | x | x | | | x | x | | x (adult) | | | x |
| Formulation reported | matrix patch | x | | | | x | x | | | | x | |
| | reservoir and other patches | | | x | | | | | x | | | |
| | gel | | | | x | x | | | | x | | x |
| | cream | | Not clear | | x | | | x | x | x | x | |
| | ointment | | | | | | | | | x | x | |
| Place of application | forehead | | | | | | | | | | | |
| | inner forearm | | | | x | | | | x | x | x | |
| | outer forearm | | | | | | | | x | | | |
| | upper arm | x | | | | | x | | x | | | |
| | face | | | | x | | | x | | x | x | |
| | lower leg | | | | | | | | x | x | | |
| | upper leg | | | | | | x | | x | | x | x |
| | back | x | x | x | | | x | | | | x | x |
| Exposure data | plasma | x | x | x | x | x | x | | x | x | x | x |
| | dermal flux and IVPT | | | | | | x | x | | | | x |
| | SC | | | | | x | | | | x | | |
| | subcutis | | | | | x | | | | | | |
| | muscle | | | | | x | | | | | x | |
| | synovium fluid | | | | x | x | | | | | x | |
| | synovium tissue | | | | | x | | | | | x | |
| | cerebrospinal fluid | | | | | | x | | | | | |
| Chemical character | acid | | | | x | x | | | | x | x | |
| | ampholyte | x | | | | | | x | | | | |
| | base | | x | x | | | x | | x | | | x |
| | zwitterion | | | | | | | | | | | |

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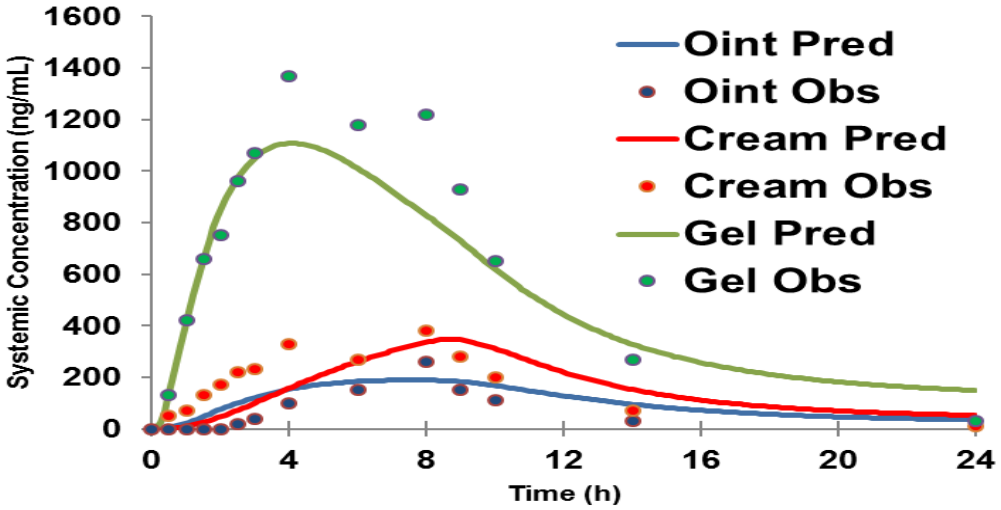
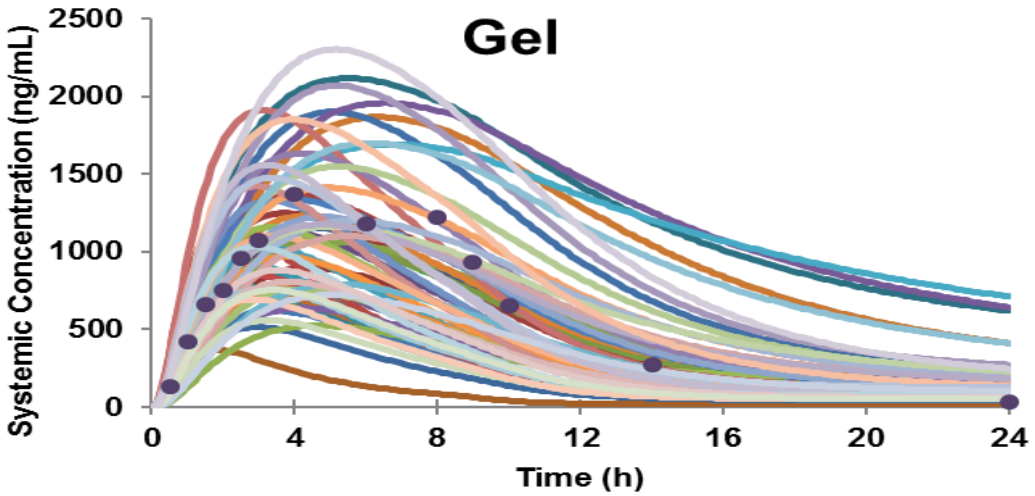
# Studying Formulation Impact - Ibuprofen

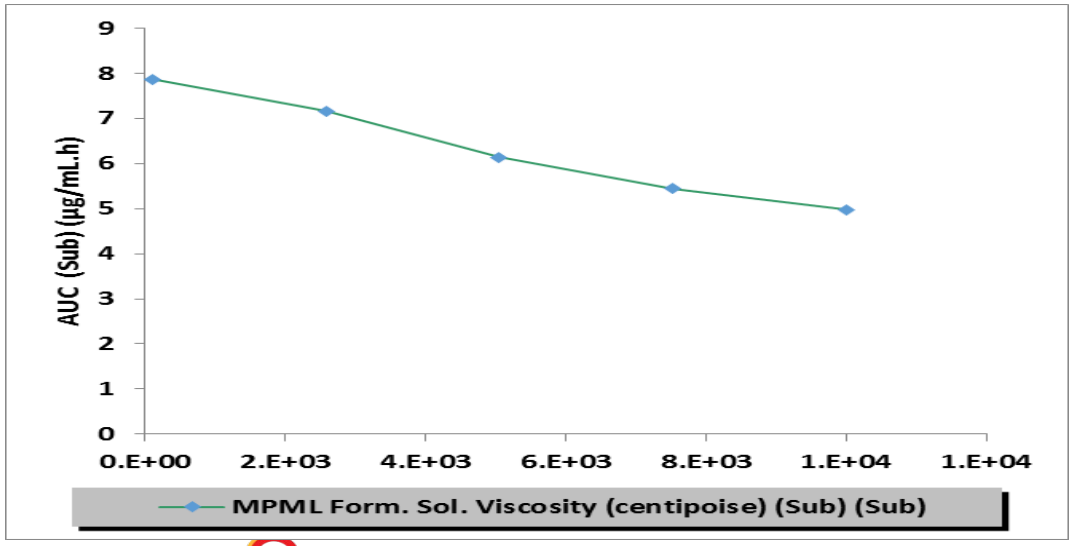
## Compare Formulations

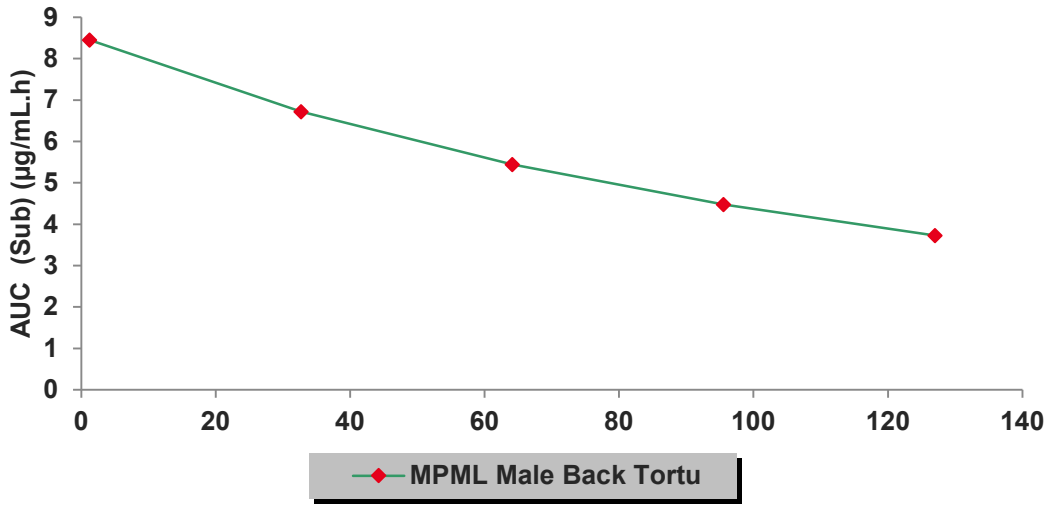



## Simulate Population Variability




## Identify clinically-relevant Critical Product Quality/Physiology Attributes

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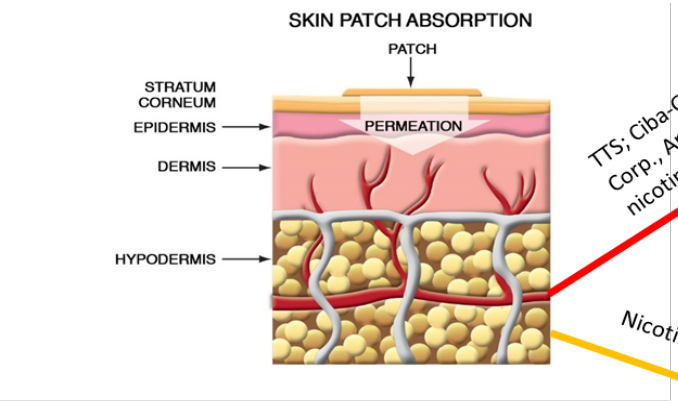
# Predicting local and systemic exposure after nicotine patch




TTS; Ciba-Geigy Corp., Ardsley, N nicotine-$d_0$

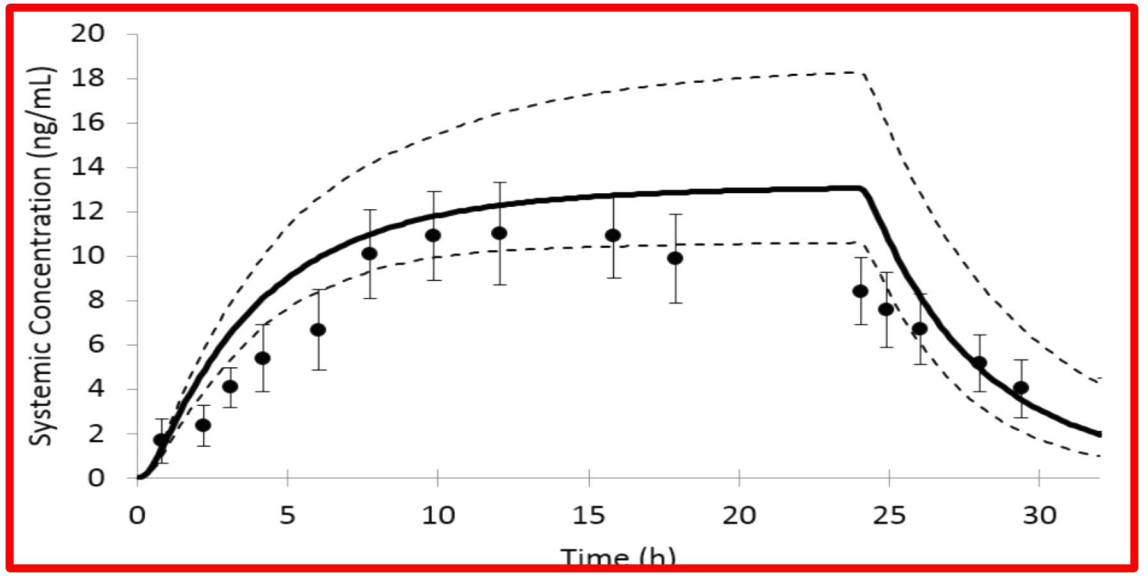
Systematic concentration

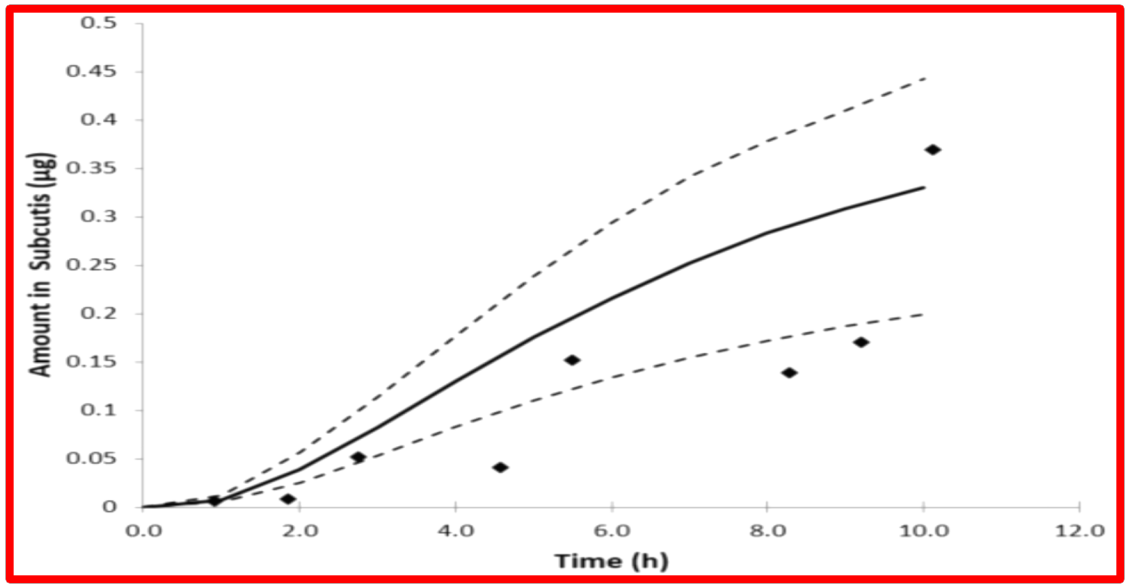
(Benowitz, Keith et al. 1991)

Nicotinell TTS 30

Amount in Subcutis

(Schrolnberger, Brunner et al. 2001)




| | | Predicted | | Observed data | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| Patch order zero release | $T_{max}$ (h) | 23.9 | 0 | 12.06 | 4.8 |
| | $C_{max}$ (ng/mL) | 12.6 | 0.9 | 11.1 | 3.8 |
| | AUC (ng/mL×h) | 300 | 23.1 | 245.7 | 125 |

Martins *et al*. 2018

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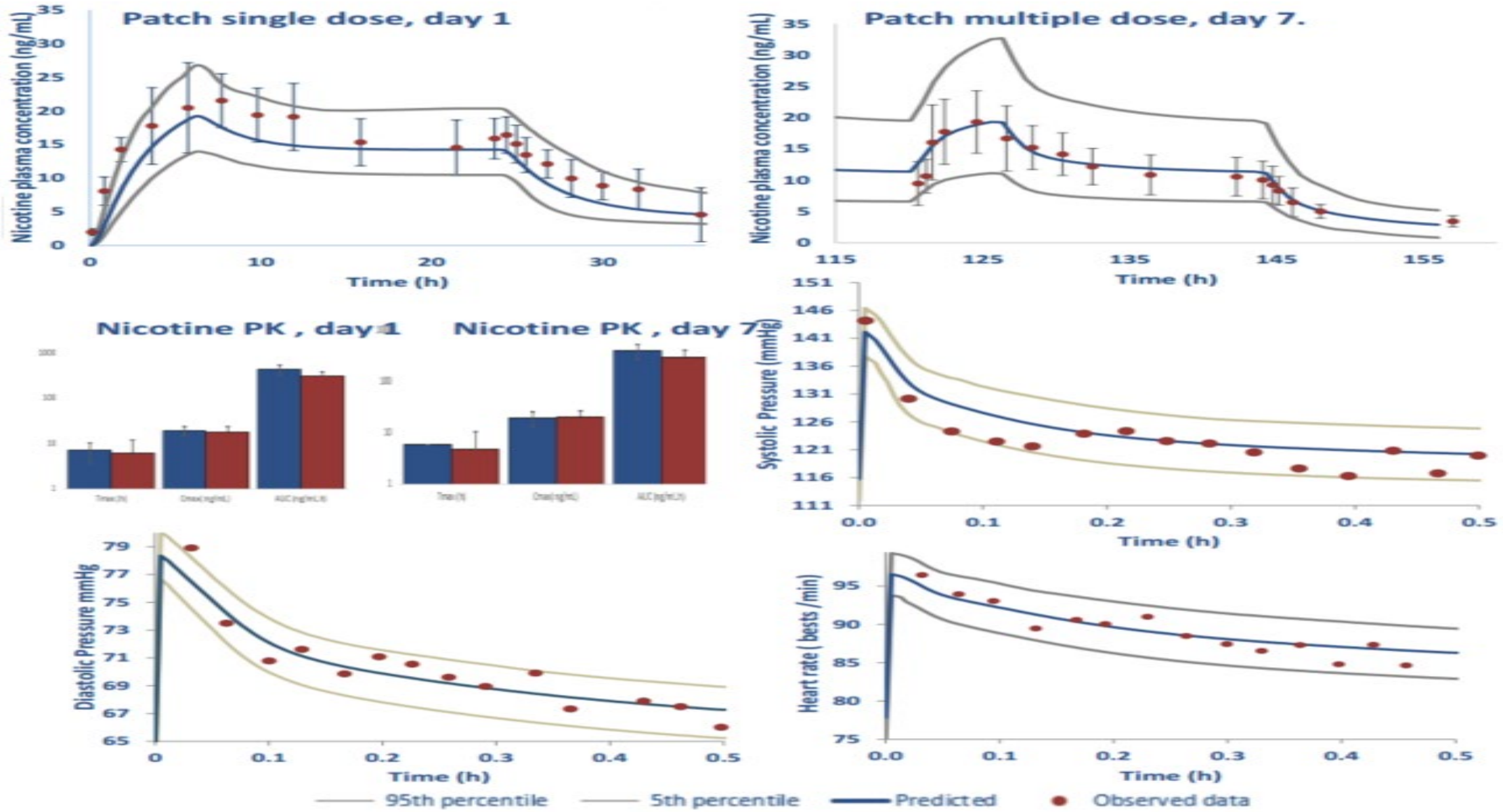
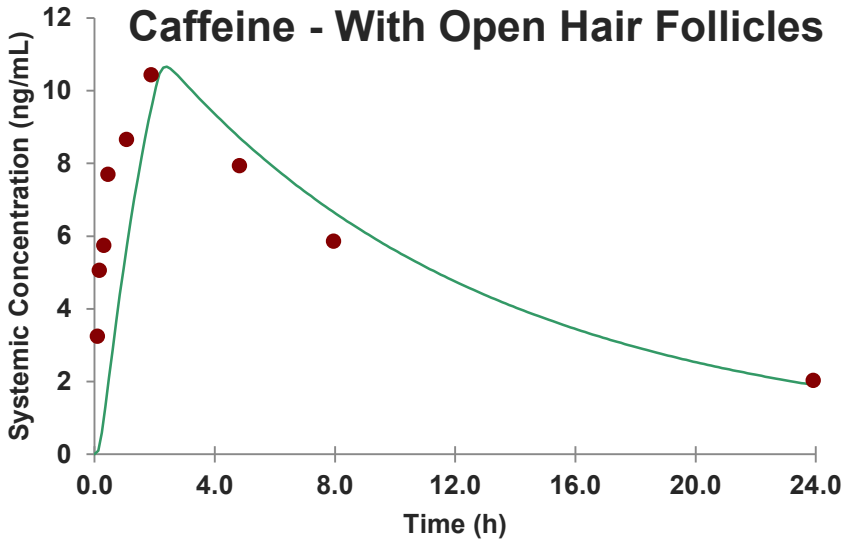
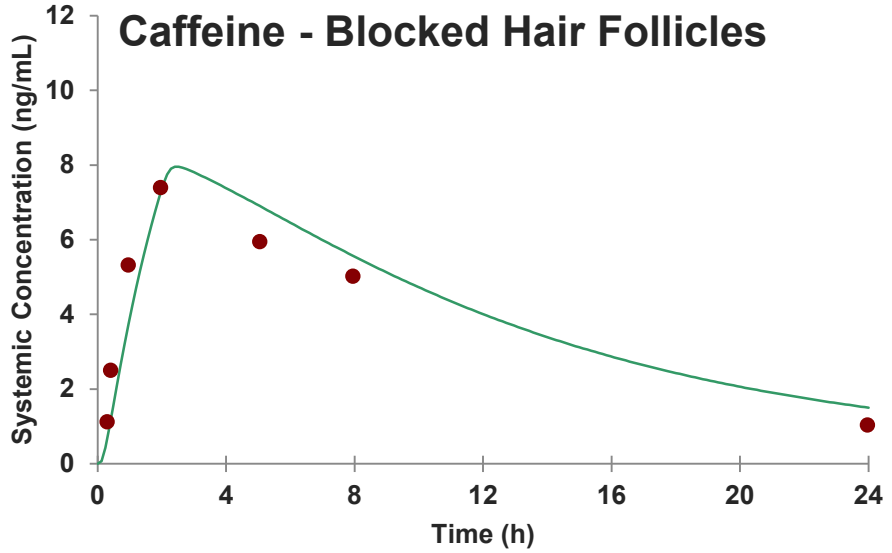
# PBPK-PD Model for Therapeutic Equivalence




Martins *et al*. 2018

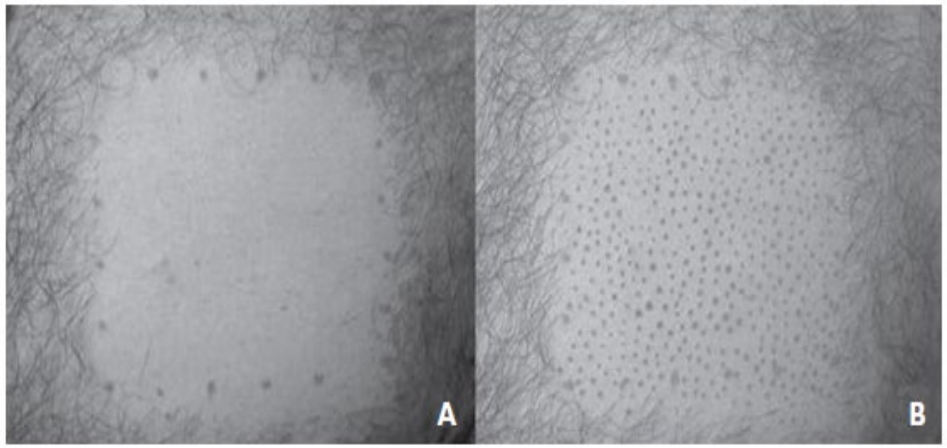
# Caffeine Case Study – Predicting Contribution of Hair Follicle




*Clinical data and trial design from Liu et al. BJCP, 2011, 72, 768*

- When just the hair follicles are closed in model, predictions were higher than clinical measurement
- With reduction in area of block around the hair follicle by wax, the model predicted clinical observation




Otberg *et al*. 2007

Martins et al. 2017 ISSX Meeting

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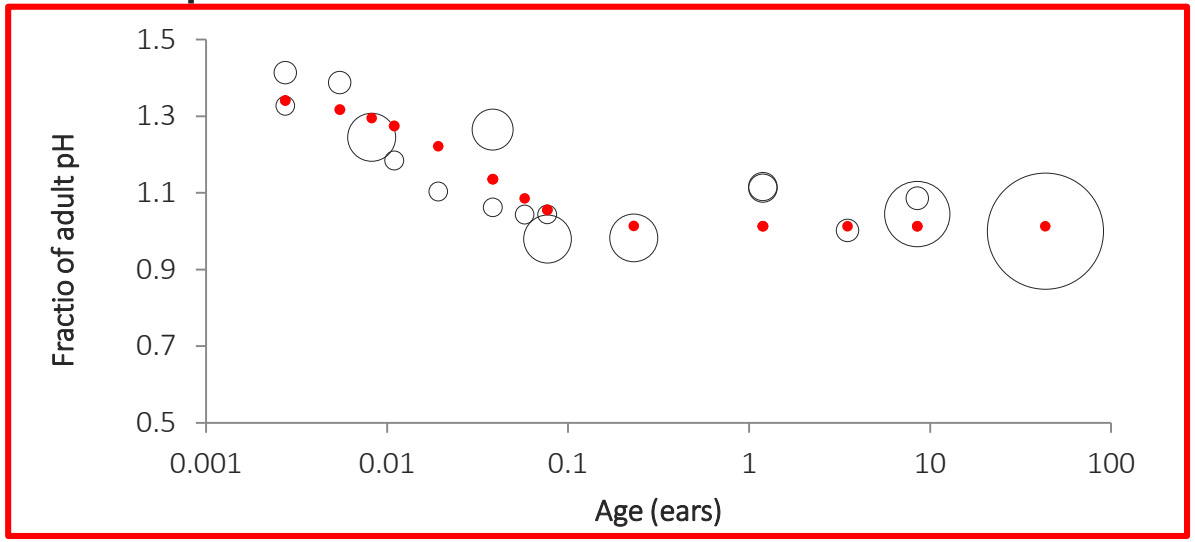
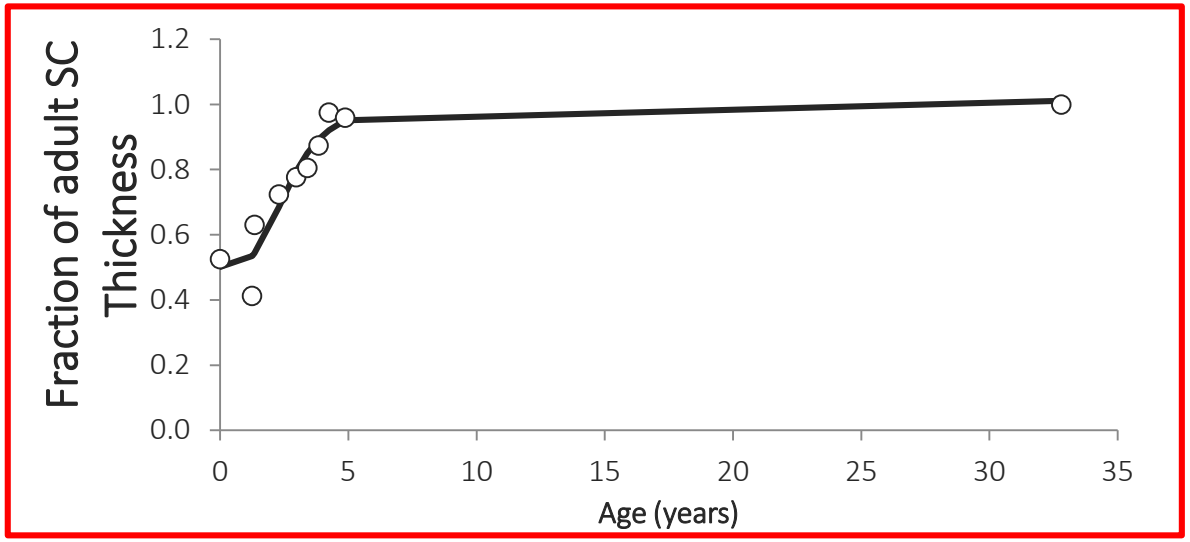
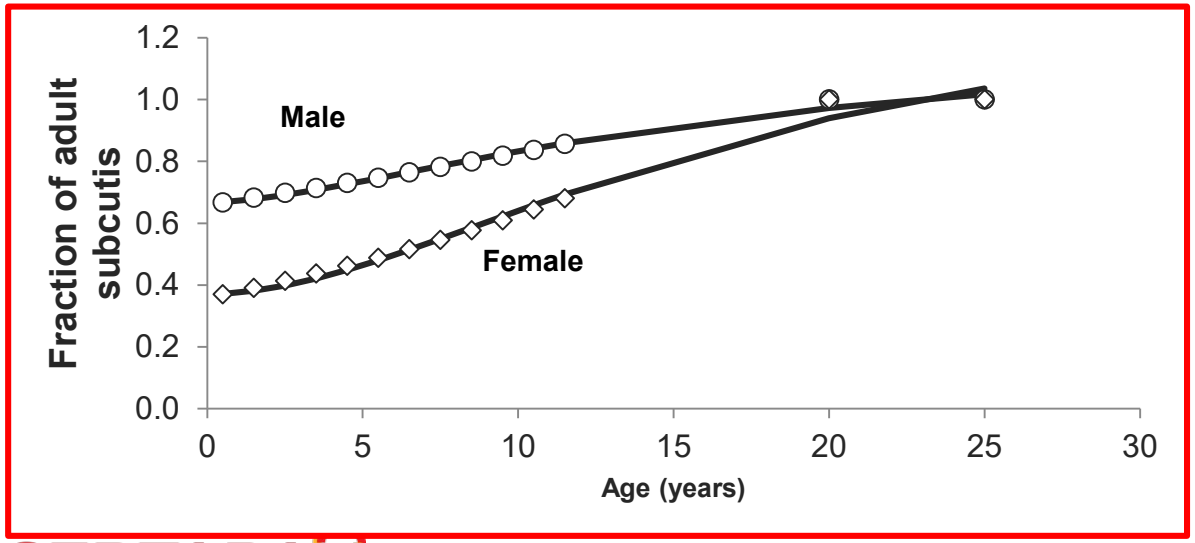
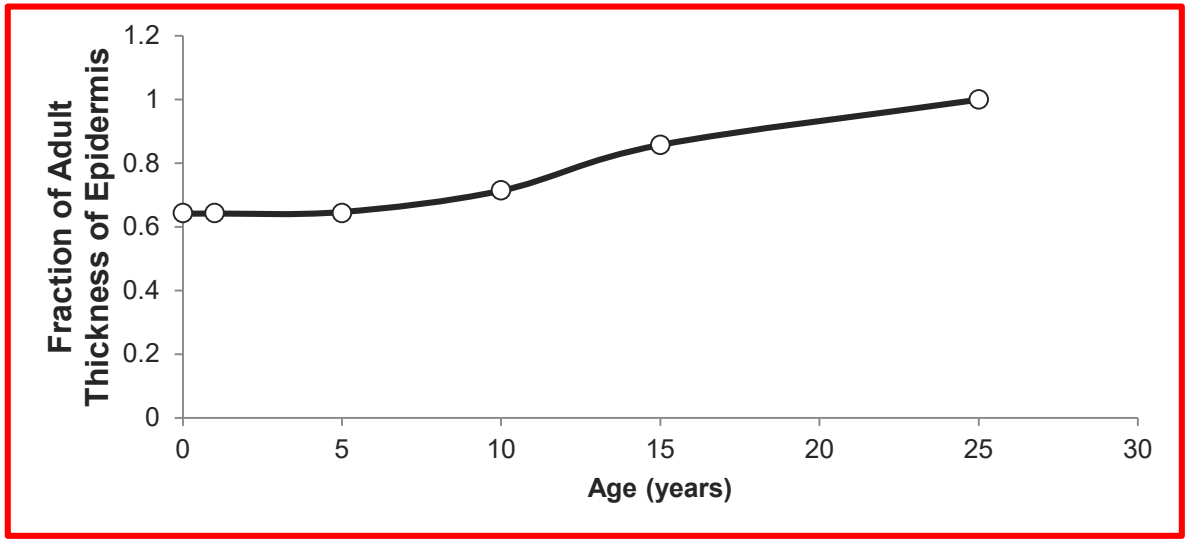
# Age-related Changes in System Parameters

Age-related changes to system parameters (ontogeny) are introduced as a fraction of adult parameters.

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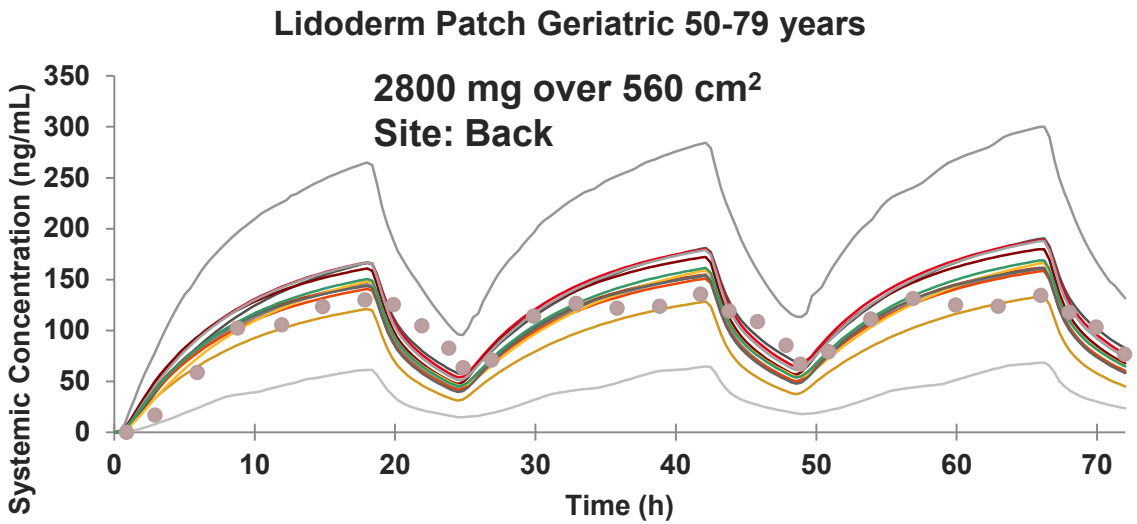
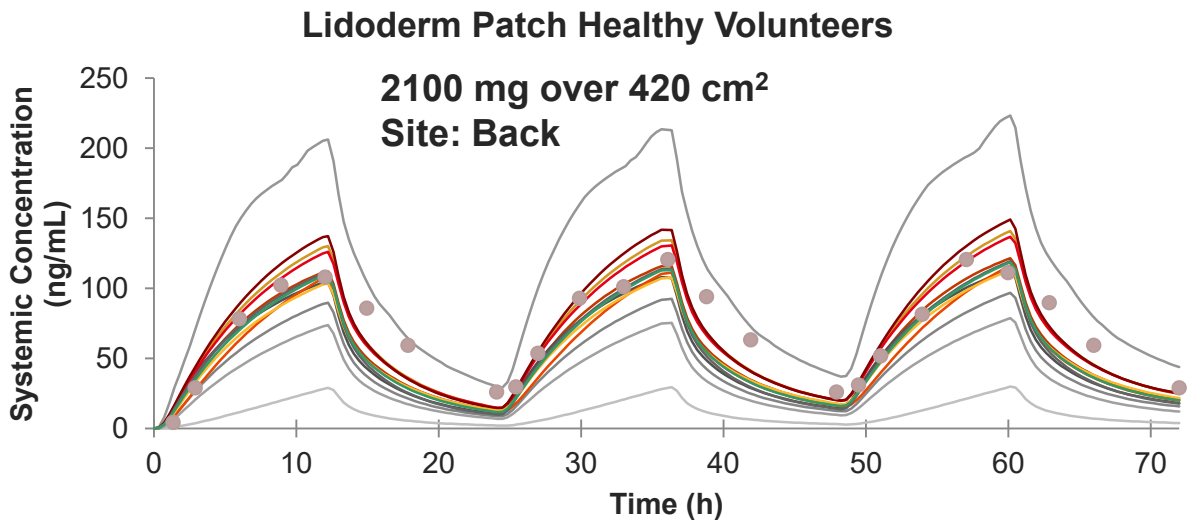
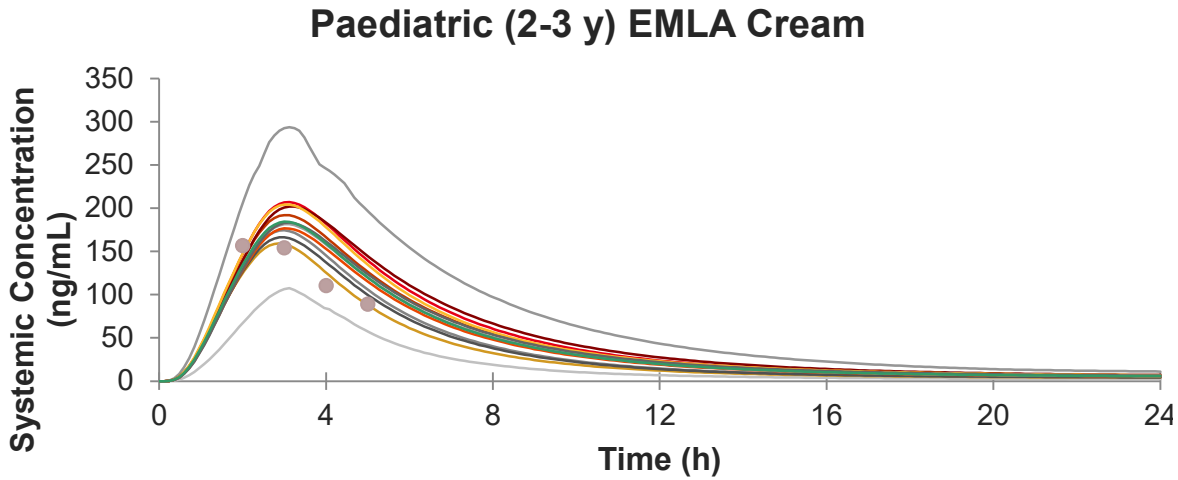
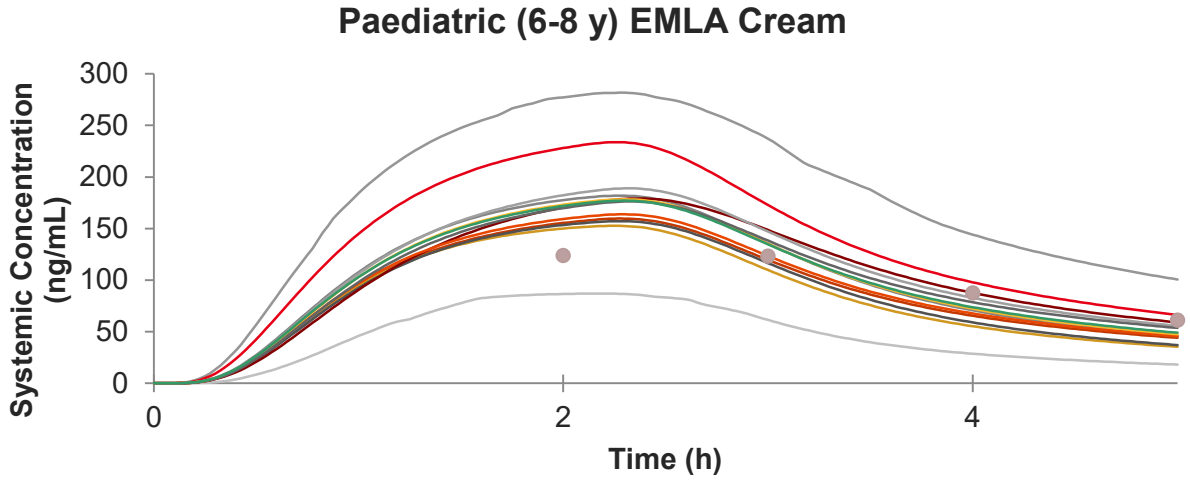
# Special populations (geriatric and paediatric)

## Lidocaine – simulating various formulation and populations




Salem *et al*. 2019 ASCPT Annual Meeting

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# Impact of site of application: Rivastigmine patch

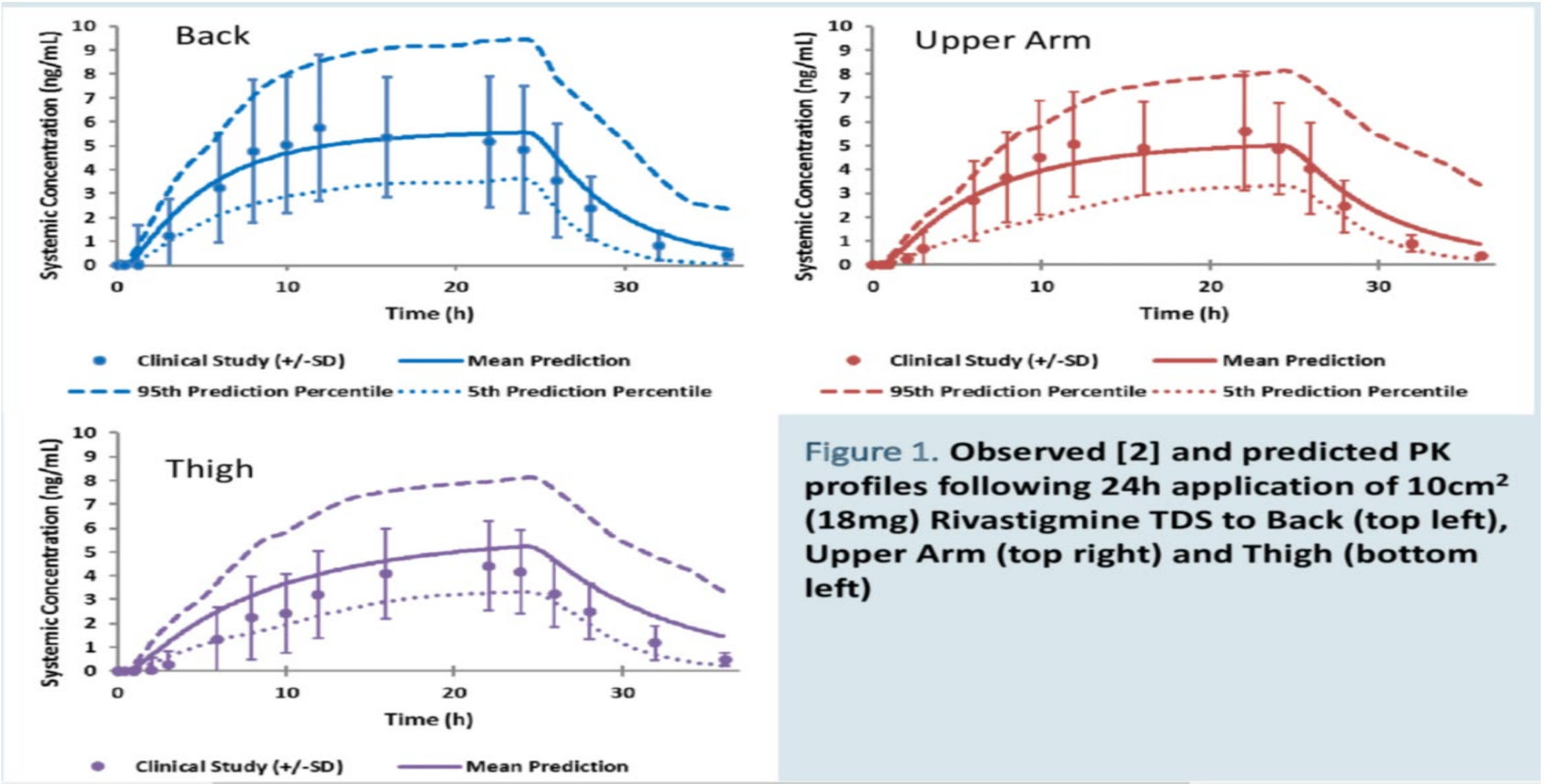


Figure 1. **Observed [2] and predicted PK profiles following 24h application of 10cm² (18mg) Rivastigmine TDS to Back (top left), Upper Arm (top right) and Thigh (bottom left)**

Abdulla et al. 2017 AAPS Annual Meeting

# Pharma Case 1: Support First In Human Exposure Prediction

- Neutral moderately lipophilic small (MW <500) drug formulated as oil in water emulsion with volatile components (~50%) in vehicle
- Animal studies (minipig) performed for topical cream formulation and systemic exposure measured after repeat dose
- PBPK Model developed based on Simcyp in-built QSAR to predict dermal absorption parameters
- PBPK simulated exposure level for high dose simulation was within 2-fold of empirical in-house animal to human extrapolation approach
- Building confidence in FIH dose exposure and formulation impact

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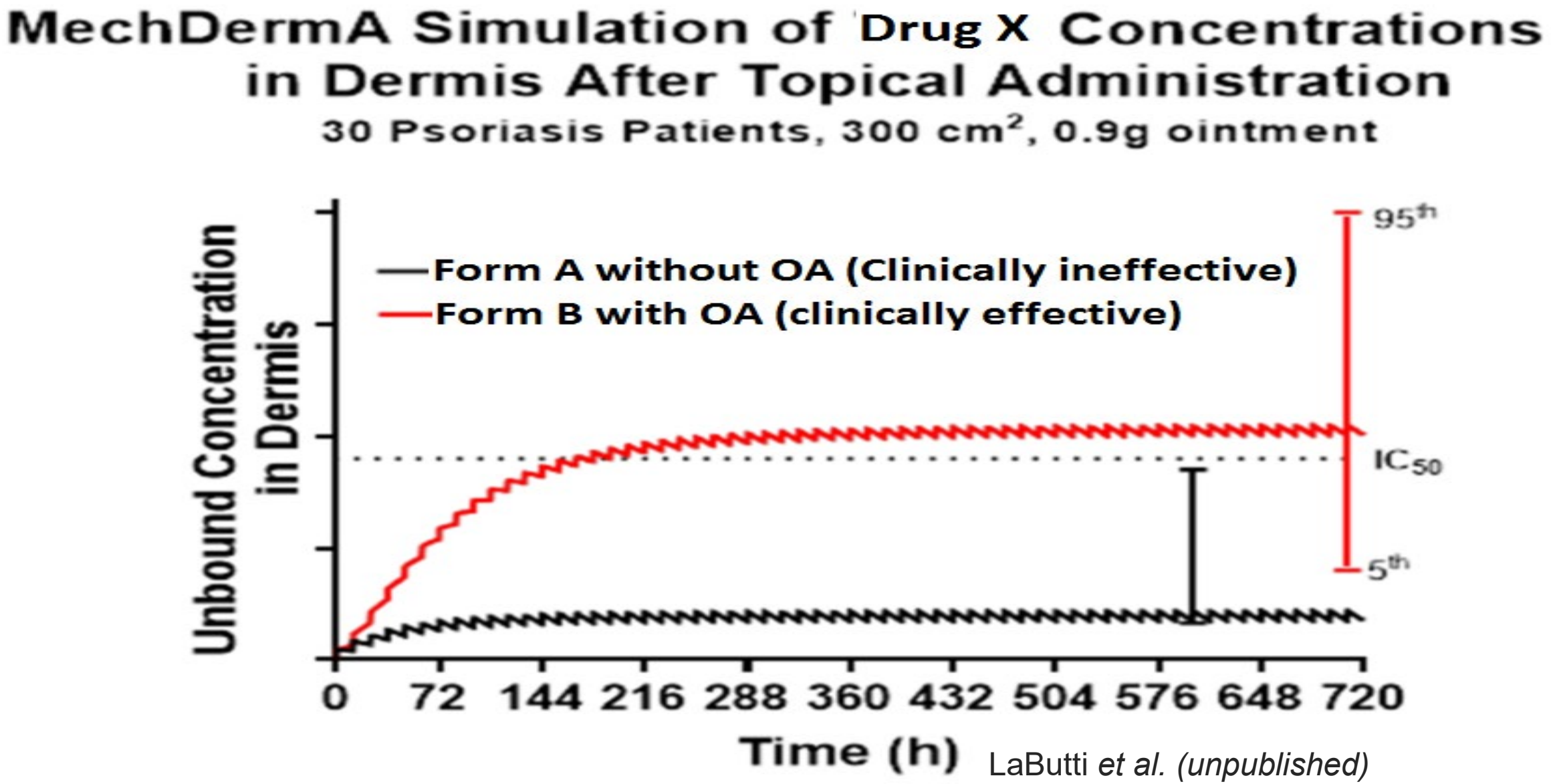
LaButti *et al. (unpublished)*

# Pharma Case 2: Clinically Relevant Product Assessment




LaButti *et al. (unpublished)*

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# Pharma Case 3: DDI risk for safety of topical cream product

- Drug Z is metabolised by CYP2C19, 2C9 and 3A4 with systemic exposure below LOQ (pg/mL) for 80% subjects as drug is locally acting hence by design systemic exposure is minimal
- There was a concern what would be exposure levels in presence of metabolic inhibitors as compared to safety margin of the drug
- PBPK model was developed and verified for two dose levels at single dose and steady state and predictive performance assessed at local tissue exposure level (SC and dermis) and systemic circulation
- The model was used to simulate DDI with metabolic inhibitors as well as worst case scenario where metabolism via CYP2C19 was completely blocked.

Patel et al. 2017 AAPS Annual Meeting

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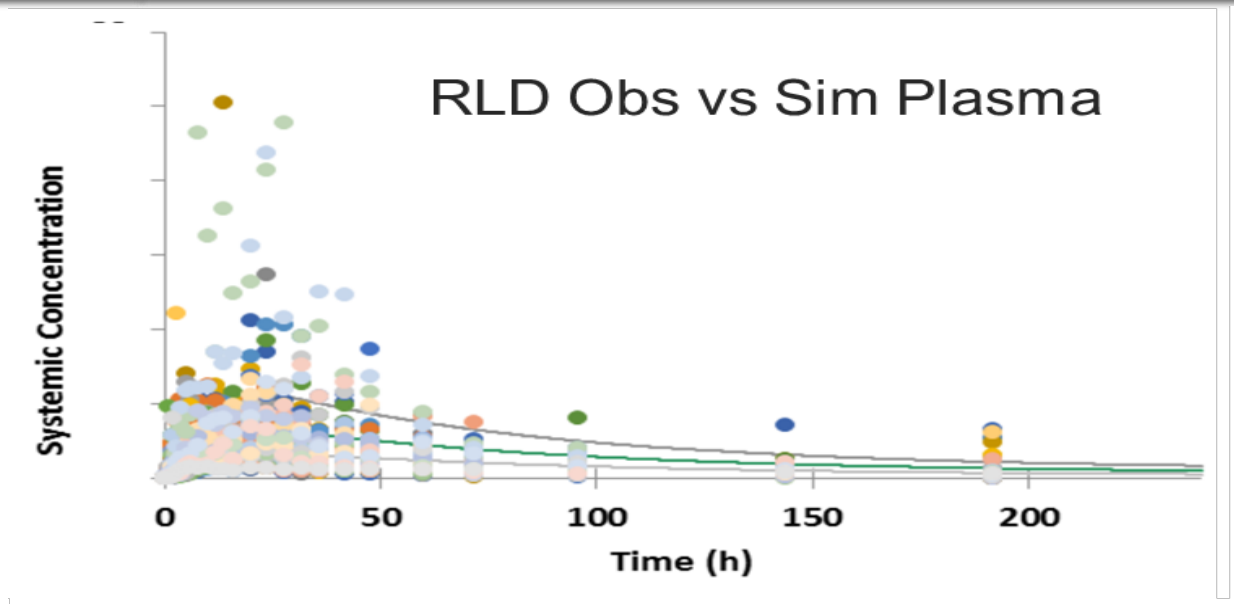
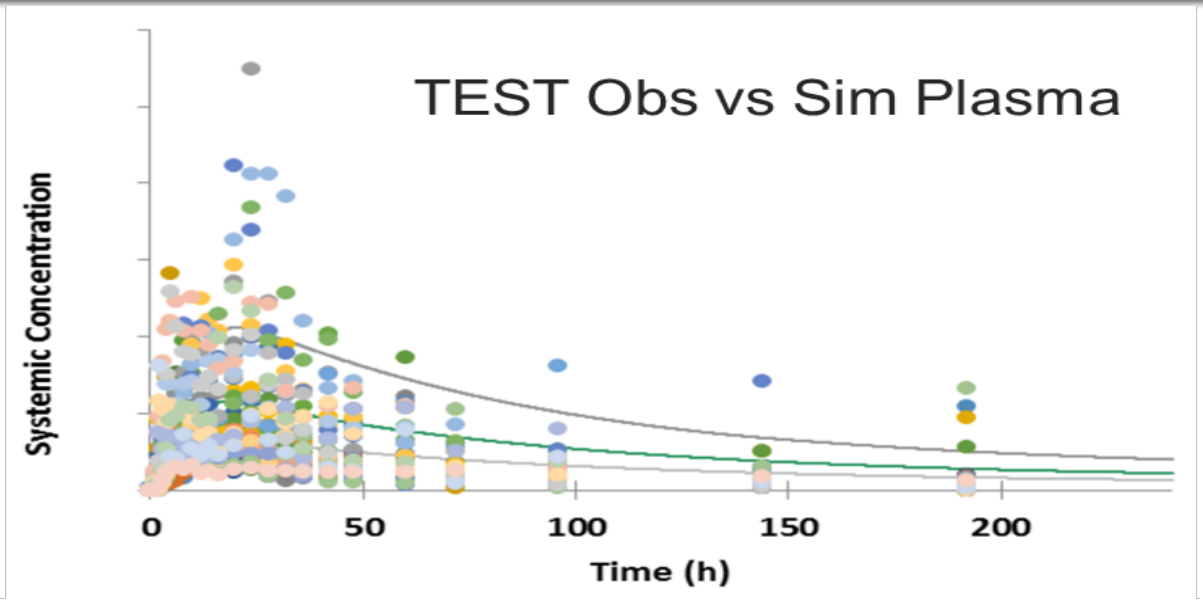
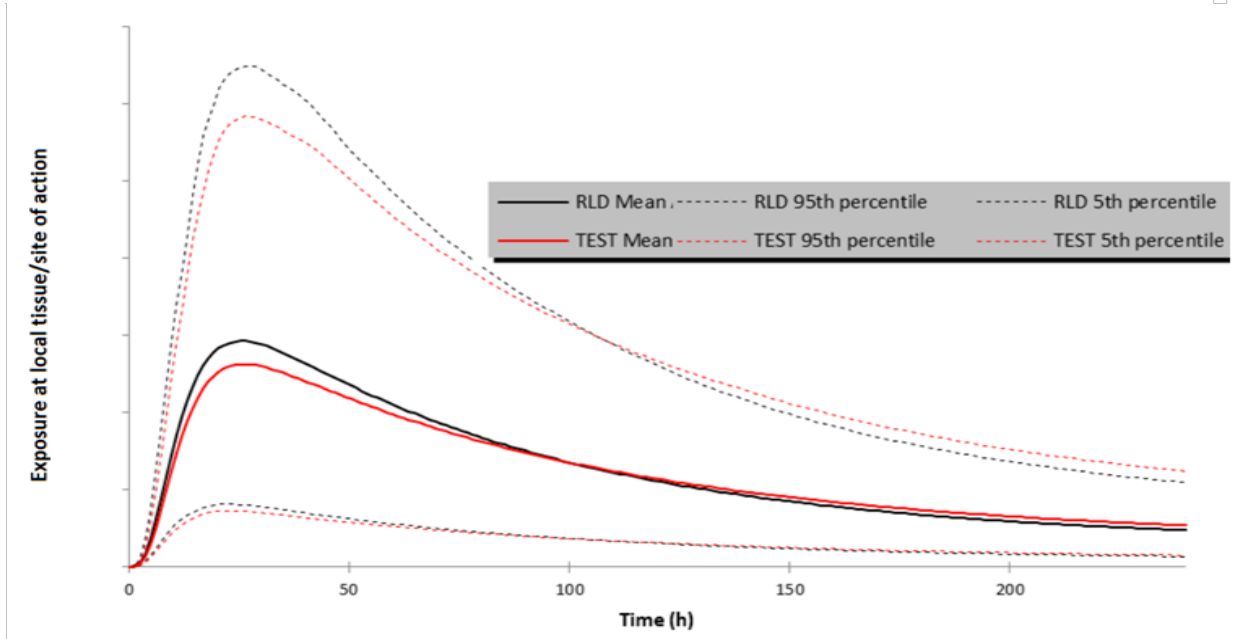
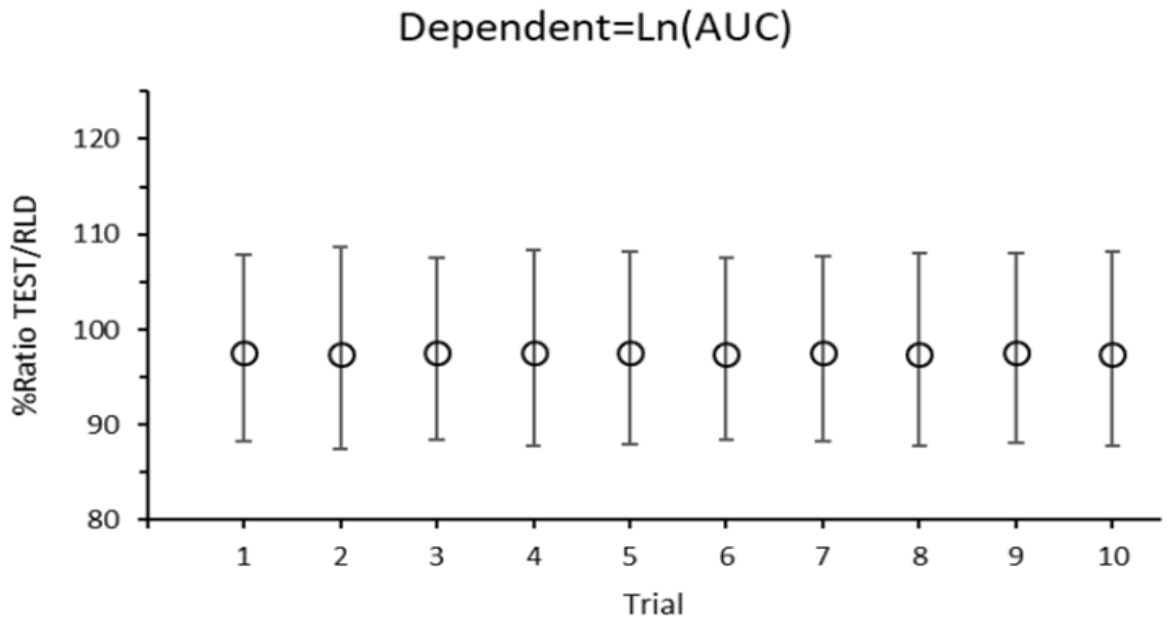
# Pharma Case 4: Virtual BE assessment of locally acting drug product

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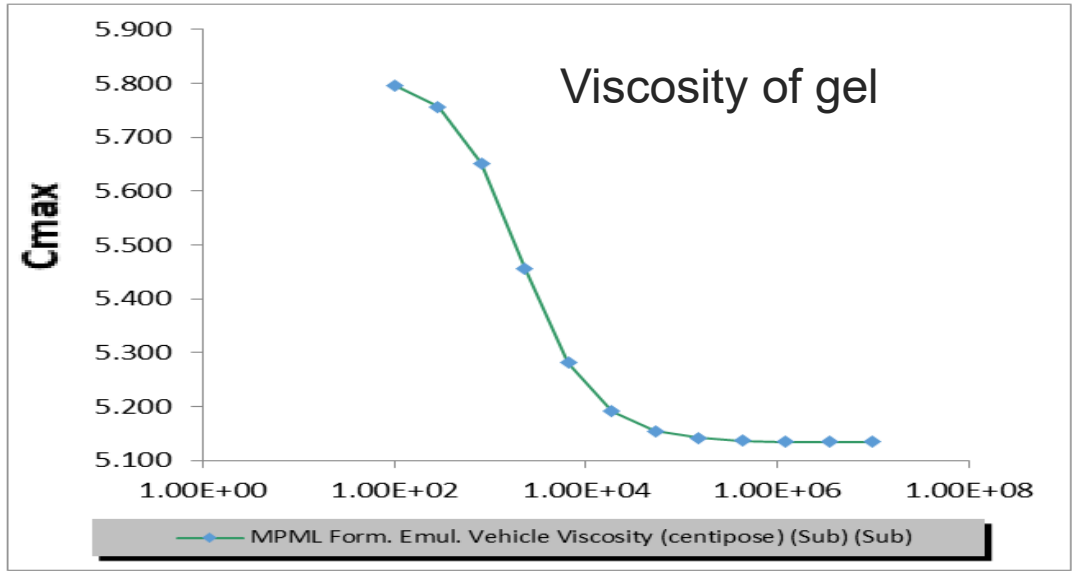
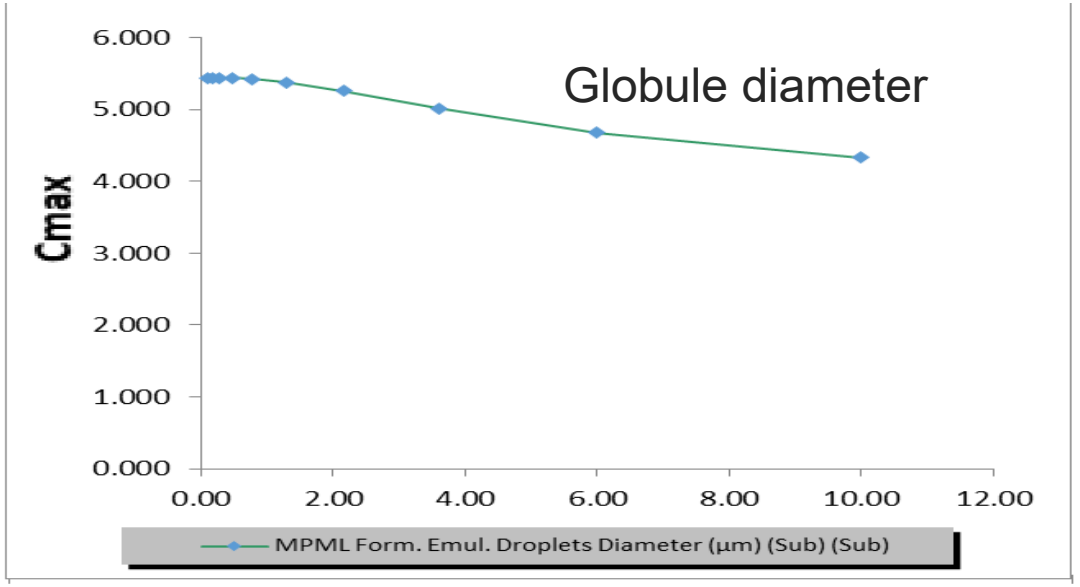
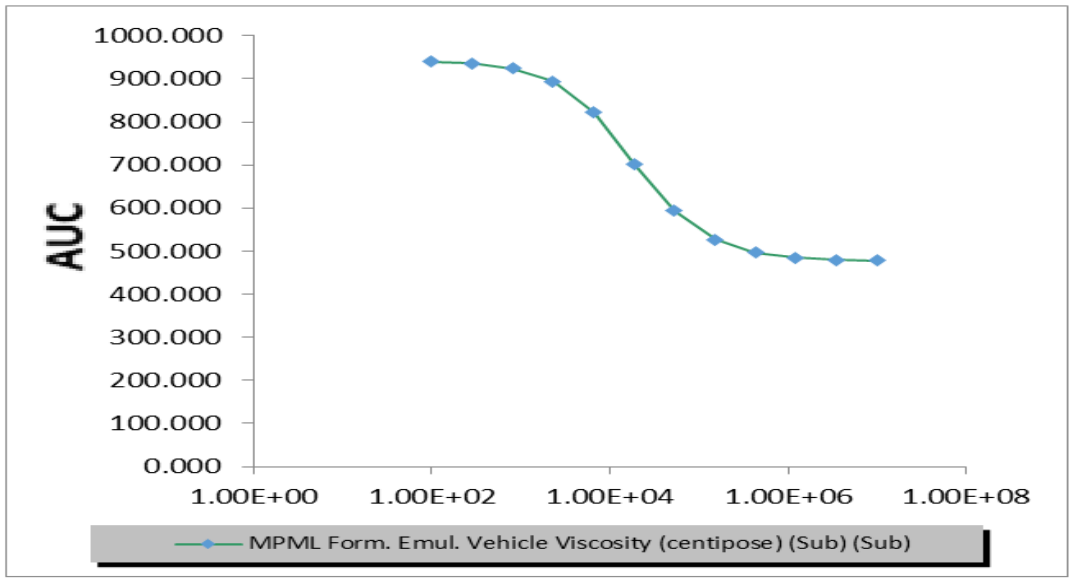
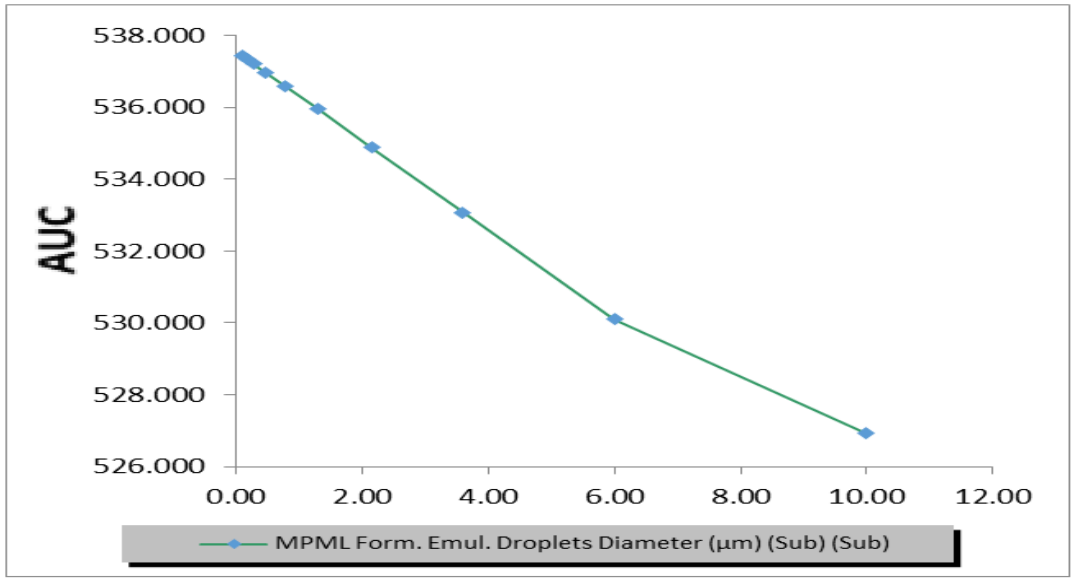
# Identify clinically relevant critical product attributes – Sensitivity Analysis

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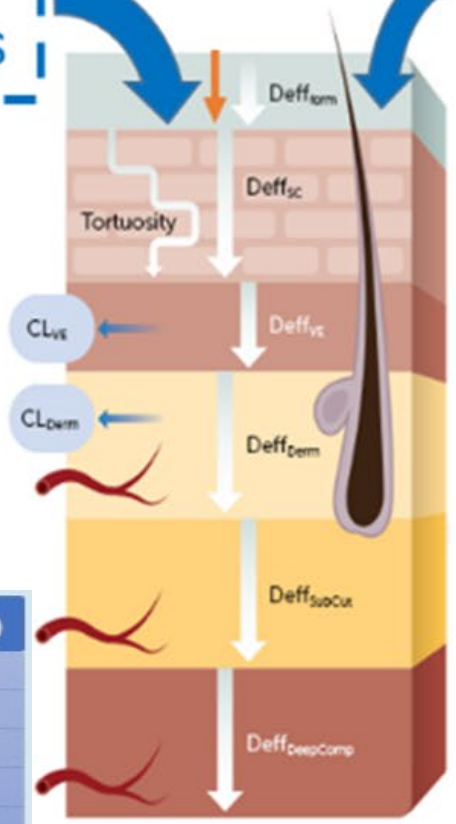
# Acyclovir Products – Simulating Q3 Product Attributes

(Murthy 2015)
Molar Volume
Viscosity
% Polymer
(Murthy 2015)
Vehicle pH
API pKa
(Murthy 2015)
API in droplet phase
Diffusion to skin surface & Hair Follicles
Fraction API non-ionised
(Murthy 2015)
API in dissolved phase
(Murthy 2015)
Vehicle Evaporation
API Precipitation
API in particle phase
(Murthy 2015)




| Formulation Parameters | ZOVIRAX US | ACICLOSTAD |
|---|---|---|
| pH | 7.74 | 4.58 |
| Drug Solubility (mg/mL)* | 0.492 | 0.365 |
| Particle Size (d50) um | 5.06 | 6.75 |
| Viscosity (Pa.S @ 0.0025 $s^{-1}$ shear) | 8360 | 29300 |
| Drying Rate ($h^{-1}$) | 0.02 | 0.07 |
| Oil phase/Continuous Phase Ratio | 1.76 | 2.67 |
| Solid fraction^ | 0.973 | 0.987 |

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# Acyclovir VBE Results and Future Direction

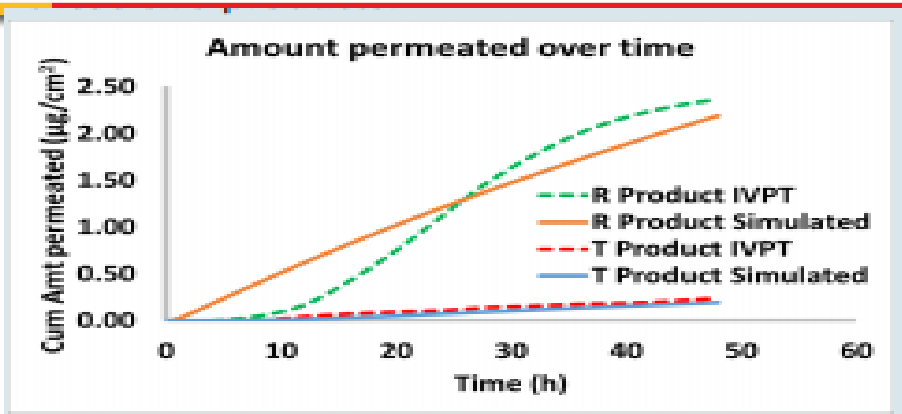


Figure 2. Cumulative amount permeated over time plots

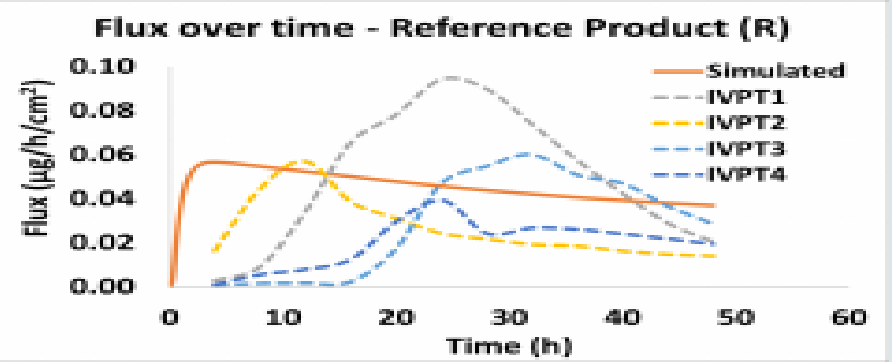


Figure 3. Permeation flux over time for the R Cream

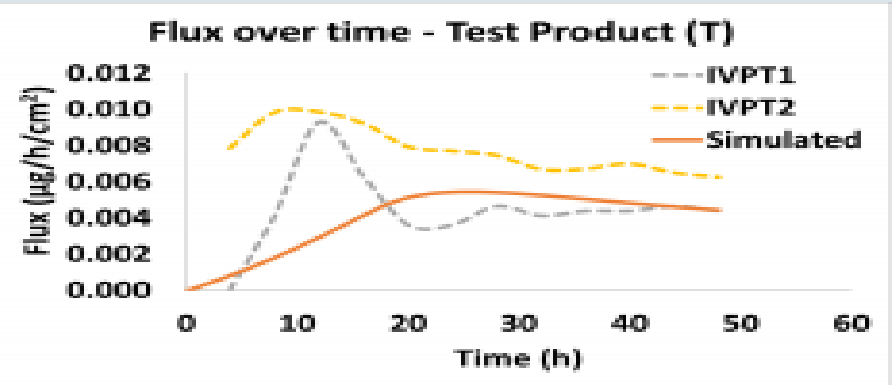


Figure 4. Permeation flux over time for the T Cream

## Key Findings

1. PBPK modeling allows to translate the *in vitro* product characterization to *in vivo* situations in terms of local and/or systemic PK and identify impact of formulation differences on exposure
2. We assumed static maximal and minimal effect of PG on R and T formulations throughout the simulation period which lead to good prediction of steady state flux (establishes importance of excipient) but over- and under- estimates initial transient permeation flux for R and T products, respectively [Figs 2 -4].
3. More mechanistic dynamic modelling of excipient is needed in future as to mimic realistic time-varying impact of excipient rather than static effect from time zero onwards.
4. Kinetic modelling of super-saturation and precipitation is desirable to accurately model the formulations with significant vehicle evaporation leading to structural changes to the formulation.

Patel *et al*. 2017 AAPS

**Collaboration with Uni of Queensland AUS**

***Formulation Meta-morphosis and Dermal Products CQA assessment***

# Conclusions

- PBPK Modelling can be/has been used to support dermal drug product development from early discovery to late clinical stages
- Integrated *in vitro* (Q2/Q3 characterization, IVPT) - *in silico* PBPK modelling paradigm can bridge the gap between *in vitro* and *in vivo* BE assessment of dermal drug products
- More case examples are needed to establish utility of PBPK and identify the gaps in current models
- Mechanistic and dynamic modelling of excipient-skin interactions and formulation metamorphosis are needed to better differentiate and simulate dermal drug products

**Note: 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.**

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