Modeling Dermal Drug Absorption from Complex Semisolid Formulations: Insights from Multi-Phase, Multi-Layer MechDermA Model

Topical Drug Development - Evolution of Science and Regulatory Policy II

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Disclaimer

The views expressed in this presentation do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

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Outline of the Presentation

1. Introduction of IVIVE and its application for dermal drug delivery

2. Metamorphosis of topically applied formulations – Modeling Challenges

3. Skin PBPK model structure and input parameters required

4. Case Study 1 – Metronidazole commercial formulations (Gel and Cream)

5. Case Study 2 – Acyclovir commercial formulations (Cream)

6. Conclusions

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Understanding *In vitro* to Predict *In vivo – In vitro In vivo Extrapolation* (IVIVE) *with Physiologically Based Pharmacokinetic (PBPK) Modeling*

Mechanistic Models

Scaling factors

in vitro parameter

in vivo parameter
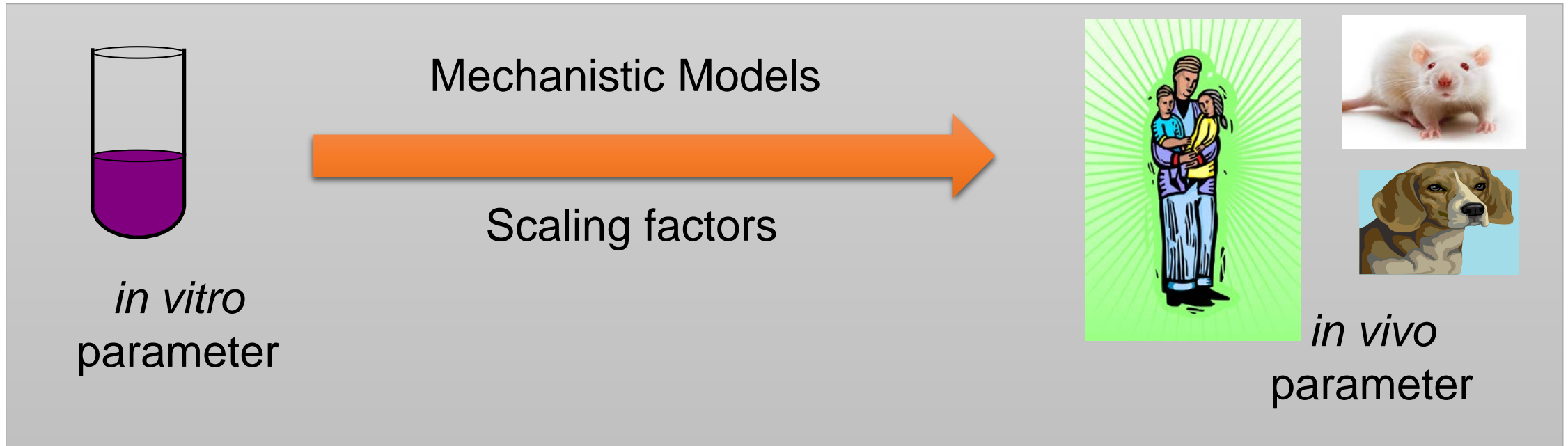
- Information obtained from surrogate *in vitro, ex vivo* or animal studies is used to provide quantitative solutions to predict the *in vivo* behavior of drugs in a target human population prior to undertaking clinical study

- This approach is widely used now in field of metabolic clearance/drug-drug interaction prediction and gastrointestinal absorption.

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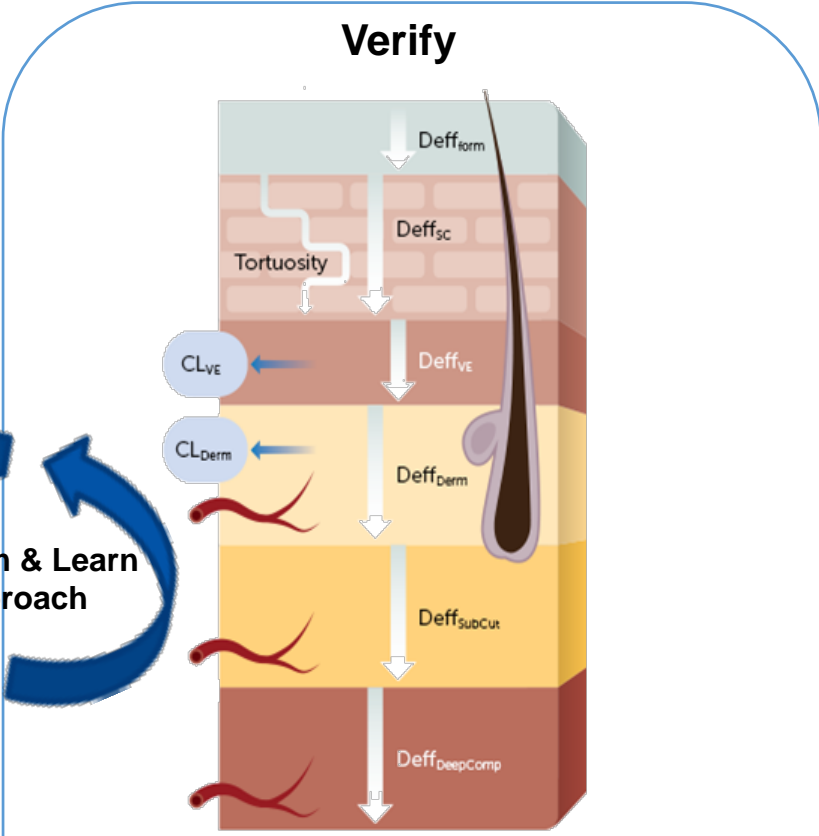# Dermal *in vitro in vivo* extrapolation (IVIVE) – A step towards Virtual Bioequivalence Complex Topical Products

Input
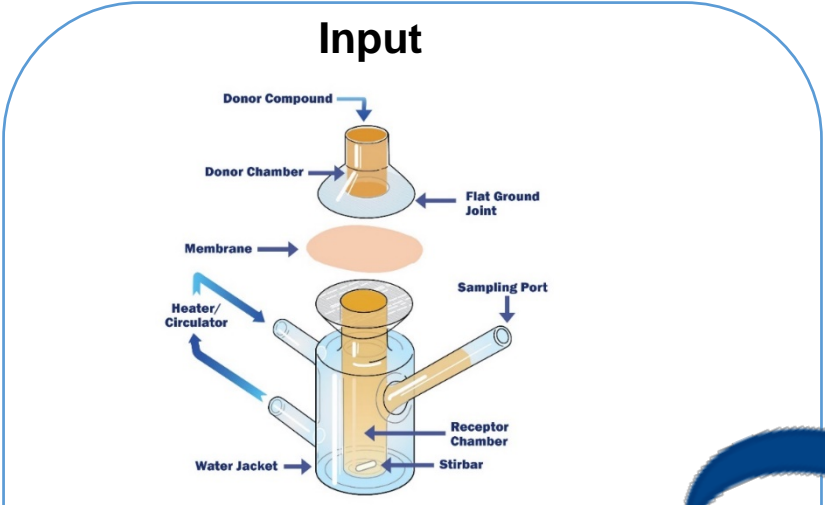
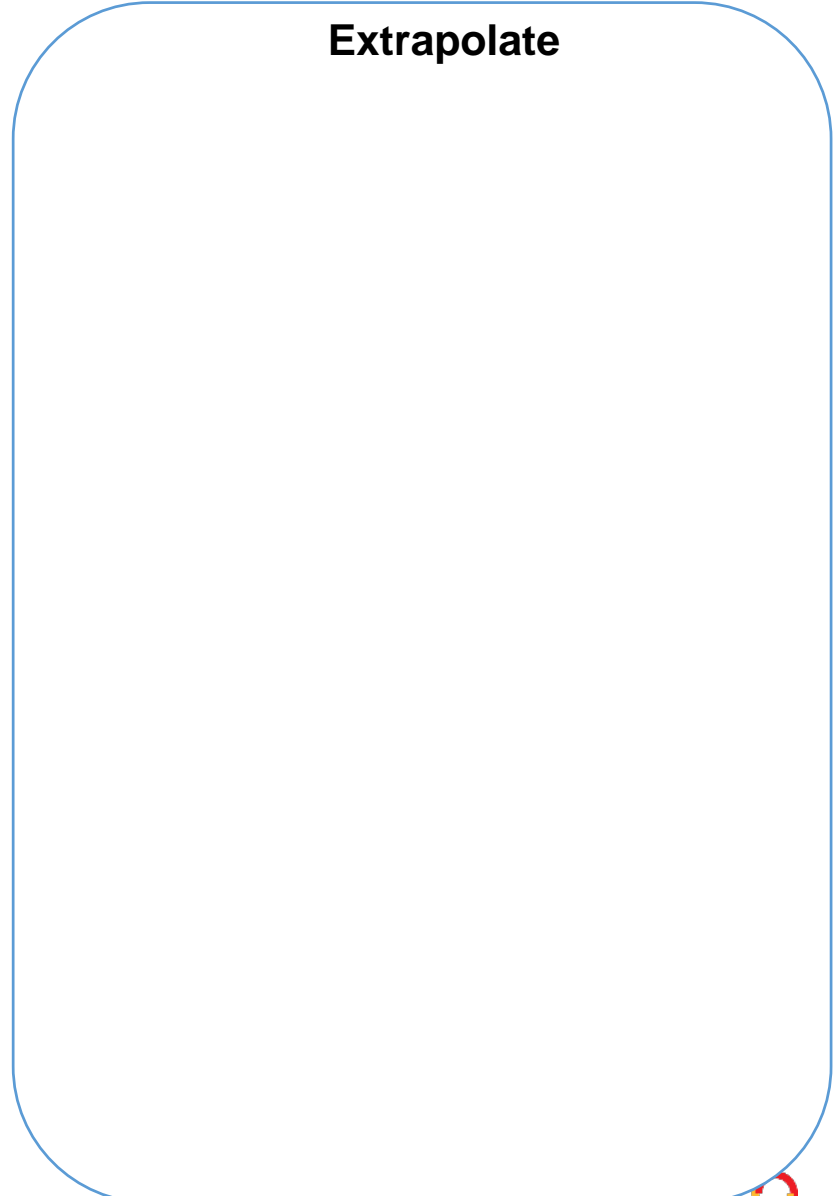*In vitro* **Release/Permeation Studies**

+

Understanding Q1, Q2 and Q3 properties of topical products

- **Composition**
- **Drug Solubility in different phases**
- **Drying Rate (weight loss)**
- **Specific gravity**
- **Particle size (solid particles/droplets)**
- **Rheology**
- **Precipitation characterization**
- **Excipient penetration**
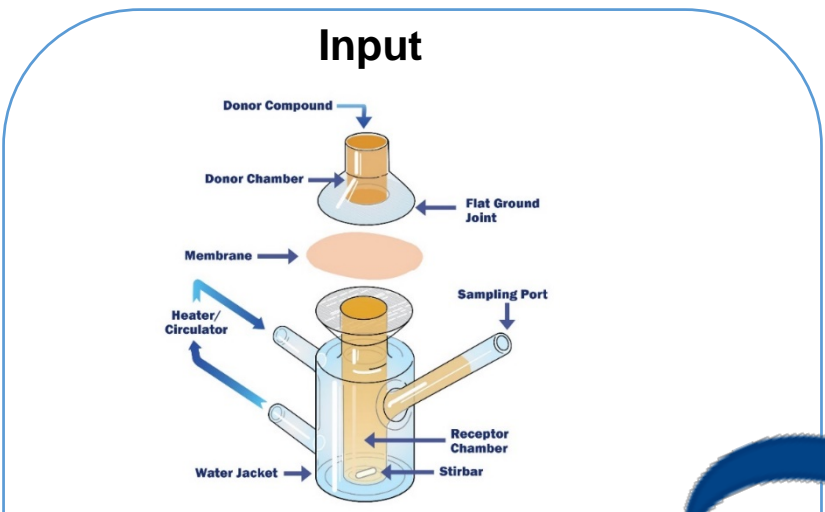
Confirm & Learn Approach

Verify

Mechanistic Dermal Absorption Model

- Confirm key drug/formulation parameters: partition and diffusion coefficients
- Verify model performance with challenge formulations (different strengths, non-Q1, Q2, Q3 formulation)

Extrapolate

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Q1 – Qualitative Q2 – Quantitative Q3 – Microstructure

Dermal *in vitro in vivo* extrapolation (IVIVE) – A step towards Virtual Bioequivalence Complex Topical Products

Input

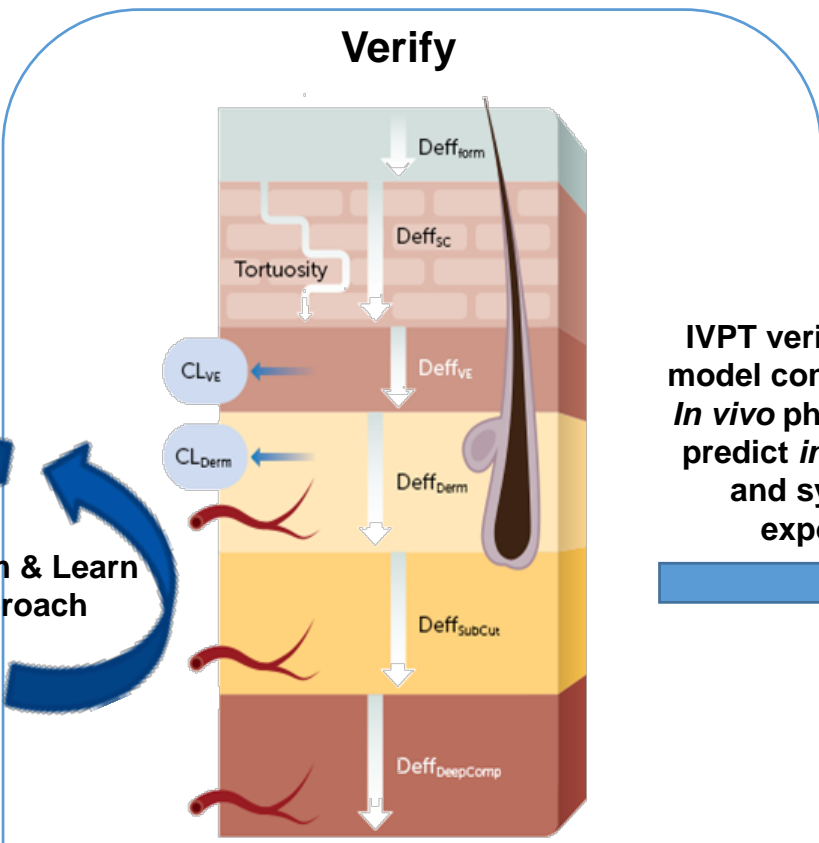*In vitro* **Release/Permeation Studies**

Confirm & Learn Approach

***Understanding Q1, Q2 and Q3 properties of topical products***

- **Composition**
- **Drug Solubility in different phases**
- **Drying Rate (weight loss)**
- **Specific gravity**
- **Particle size (solid particles/droplets)**
- **Rheology**
- **Precipitation characterization**
- **Excipient penetration**

Verify

Mechanistic Dermal Absorption Model

- Confirm key drug/formulation parameters: partition and diffusion coefficients
- Verify model performance with challenge formulations (different strengths, non-Q1, Q2, Q3 formulation)

IVPT verified PBPK model combined with *In vivo* physiology to predict *in vivo* local and systemic exposure
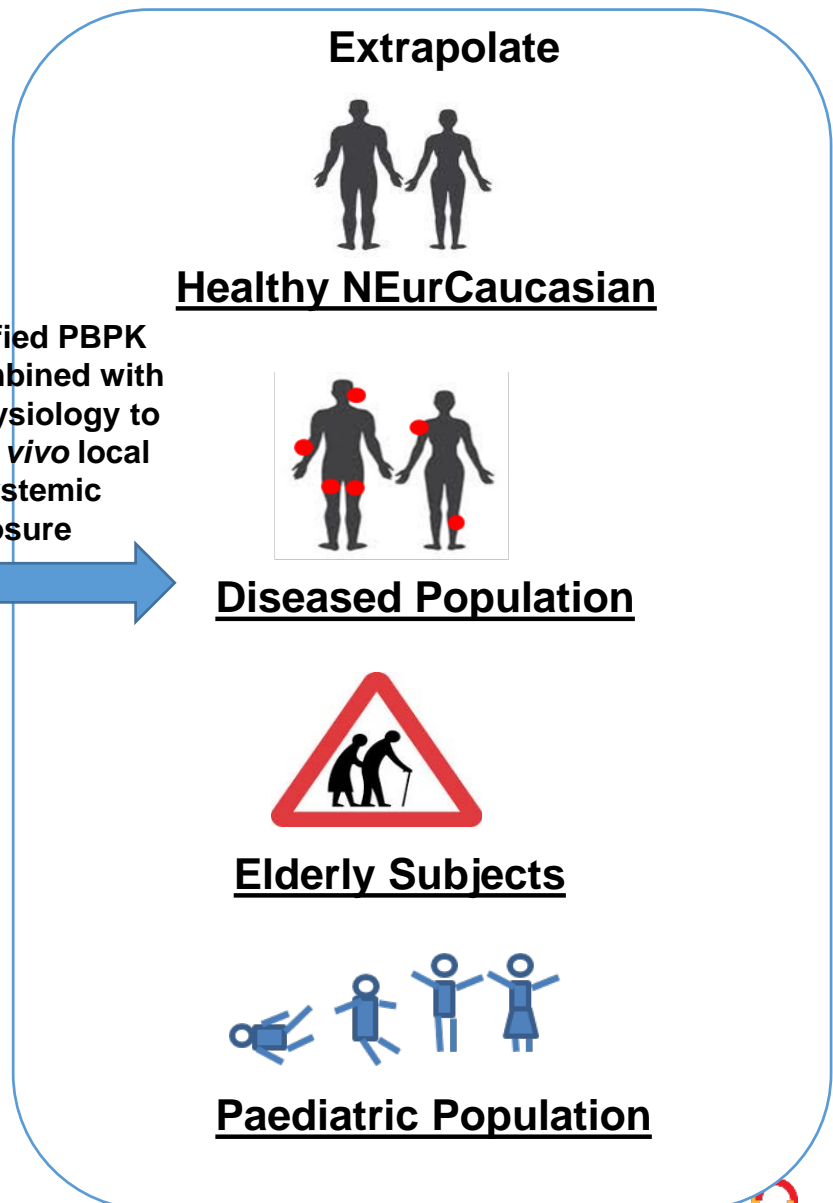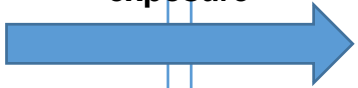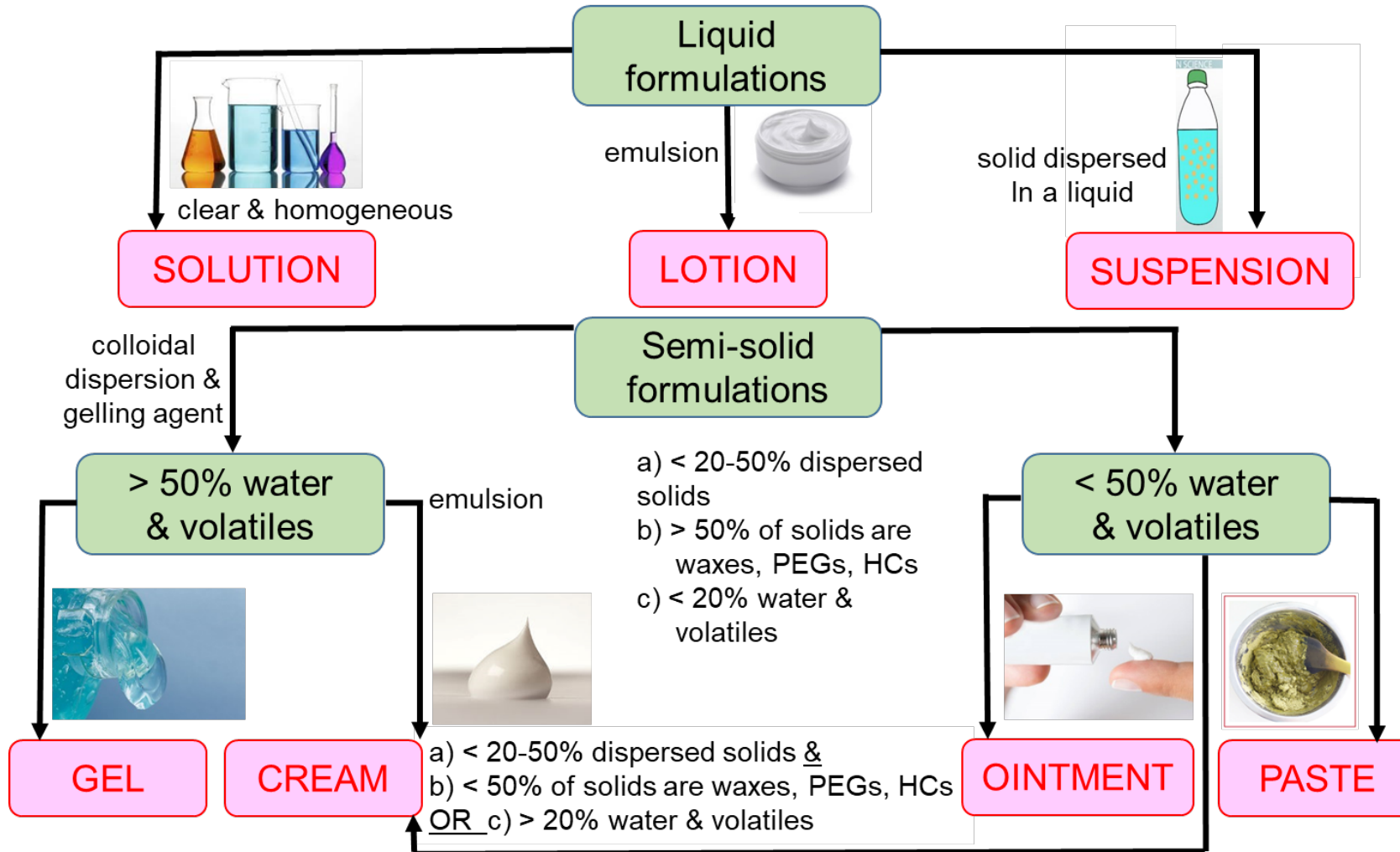
Extrapolate

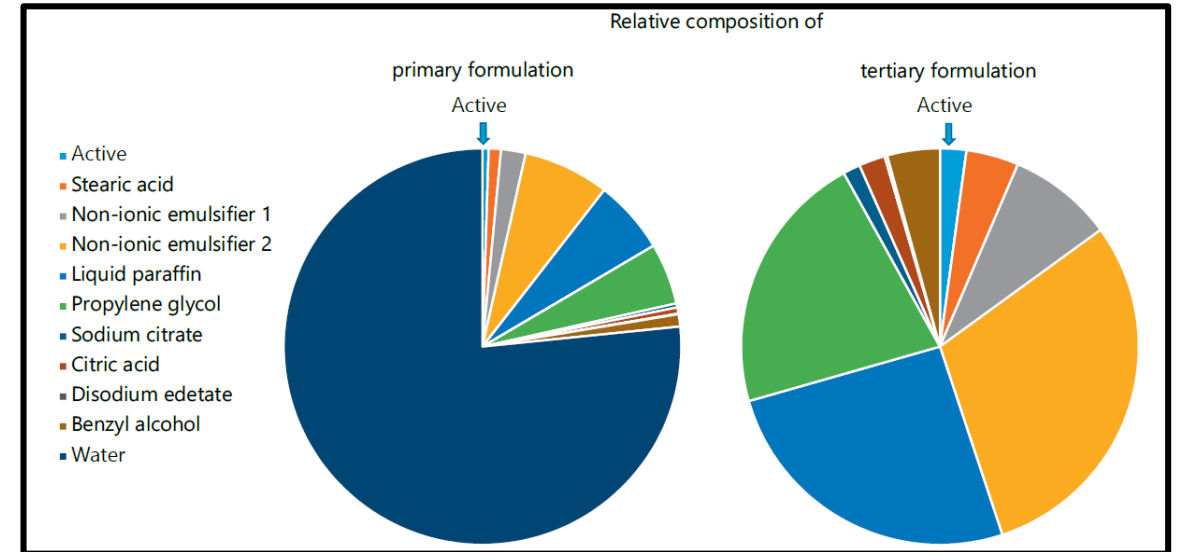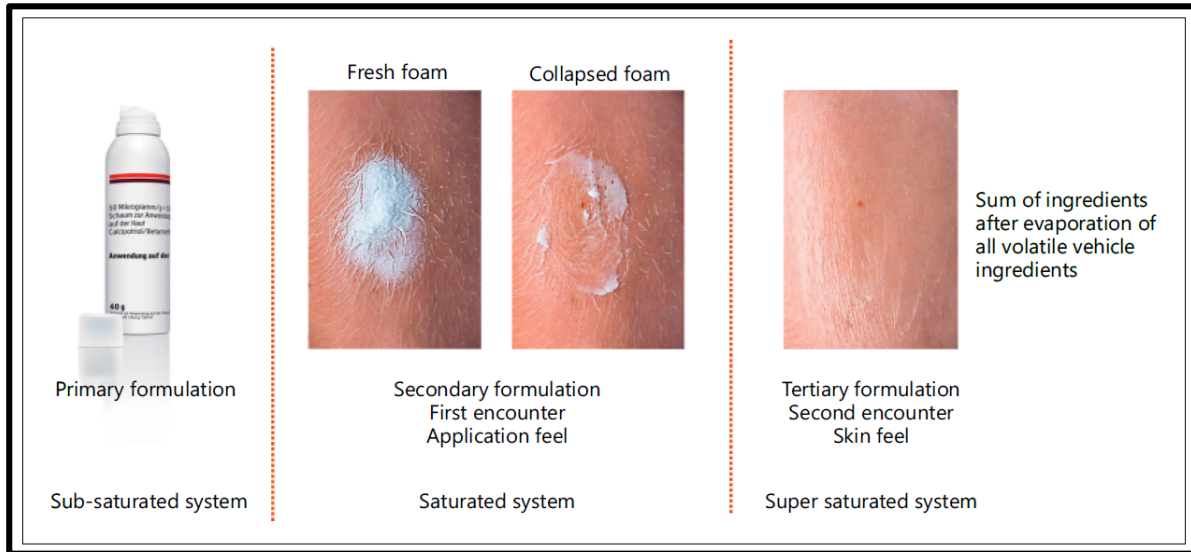**Healthy NEurCaucasian**

Diseased Population

Elderly Subjects

Paediatric Population

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Q1 – Qualitative Sameness Q2 – Quantitative Sameness Q3 – Microstructure sameness

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Liquid formulations

emulsion

solid dispersed in a liquid

clear & homogeneous

SOLUTION

LOTION

SUSPENSION

All these products can broadly be classified as –

1. Solutions
2. Emulsions
3. Suspensions

Semi-solid formulations

colloidal dispersion & gelling agent

> 50% water & volatiles

emulsion

a) < 20-50% dispersed solids
b) > 50% of solids are waxes, PEGs, HCs
c) < 20% water & volatiles

< 50% water & volatiles

GEL

CREAM

a) < 20-50% dispersed solids &
b) < 50% of solids are waxes, PEGs, HCs
OR c) > 20% water & volatiles

OINTMENT

PASTE

Adapted from SR Chaudhuri, AAPS Workshop Nov. 2017 San Diego (co-organisers: S. Raney & SR Chaudhuri)

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Metamorphosis of Topical Formulations

Fresh foam | Collapsed foam

Sum of ingredients after evaporation of all volatile vehicle ingredients

Primary formulation — Sub-saturated system

Secondary formulation
First encounter
Application feel — Saturated system

Tertiary formulation
Second encounter
Skin feel — Super saturated system

Relative composition of

primary formulation — Active

tertiary formulation — Active

- Active
- Stearic acid
- Non-ionic emulsifier 1
- Non-ionic emulsifier 2
- Liquid paraffin
- Propylene glycol
- Sodium citrate
- Citric acid
- Disodium edetate
- Benzyl alcohol
- Water

Pressurized formulation | Evaporation of propellants | Foam on the skin — A supersaturated solution of Cal and BD

Concentration of dissolved Cal/BD

Amount of propellant in the formulation

Pre application | Application and spreading on the skin | Post application — Time

Change in concentration of active ingredients dissolved in the aerosol form formulation over application time. BD Betamethasone dipropionate, Cal calcipotriene

Image adapted from Lind et al, Dermatol Ther (Heidelb) 2016; 6: 413–425.;Suber et al, Curr Probl Dermatol. Basel, Karger, 2018, vol 54, pp 152–165

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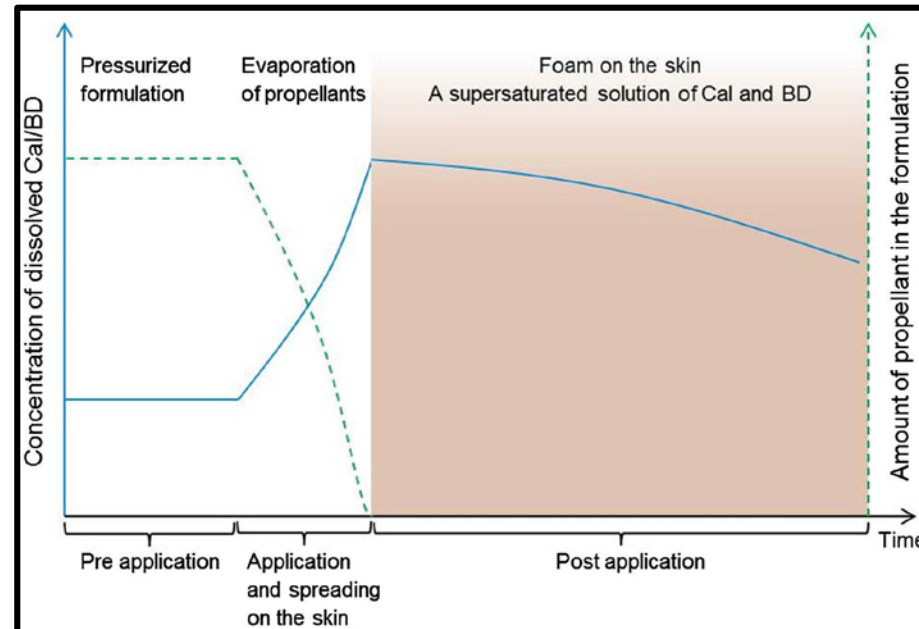
Modeling Metamorphosis of Topical/Transdermal Formulations – Even Simple Formulations Are Not That Simple !!!
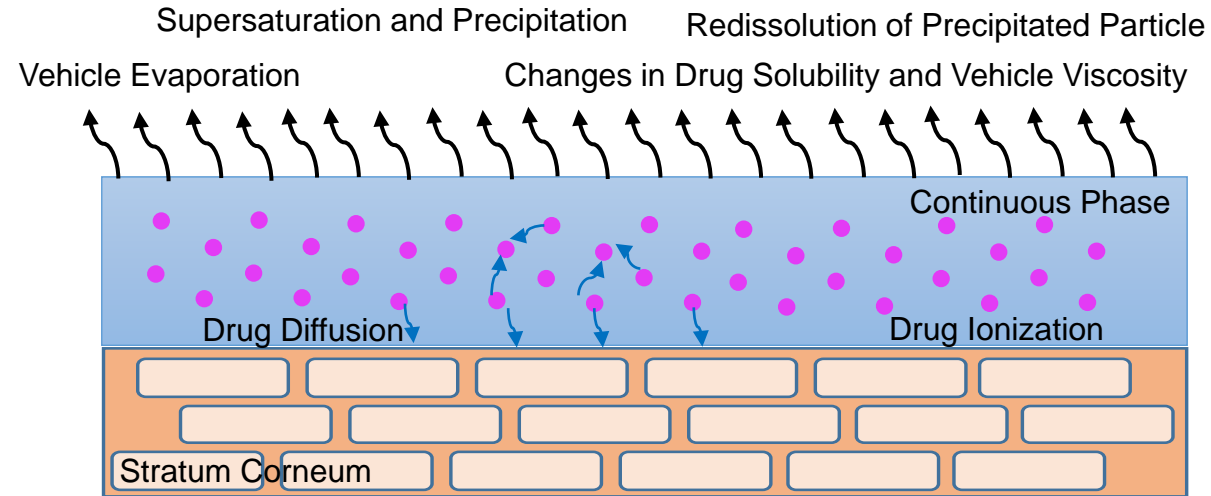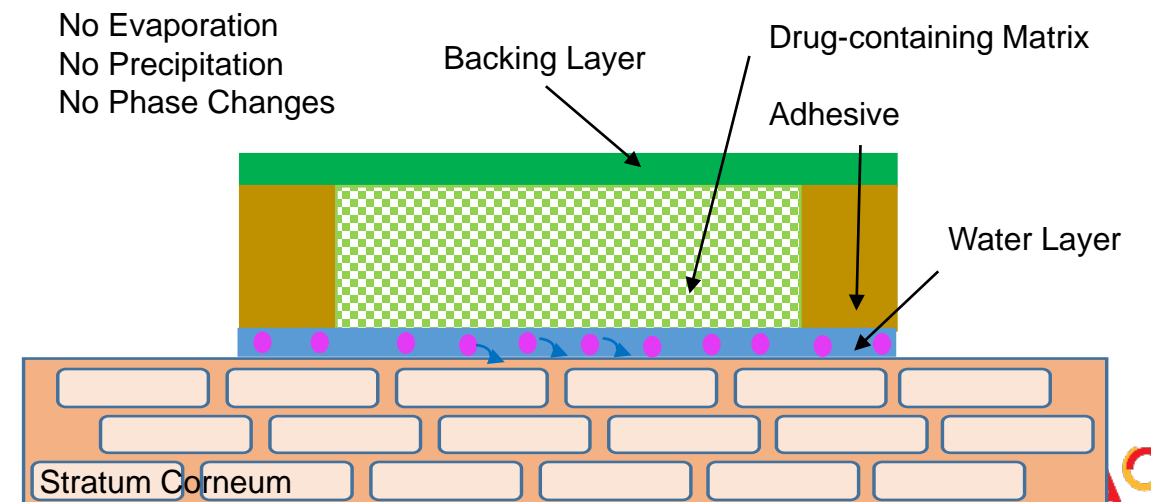
Simcyp's Multi-Phase Multi-Layer (MPML) MechDermA Model
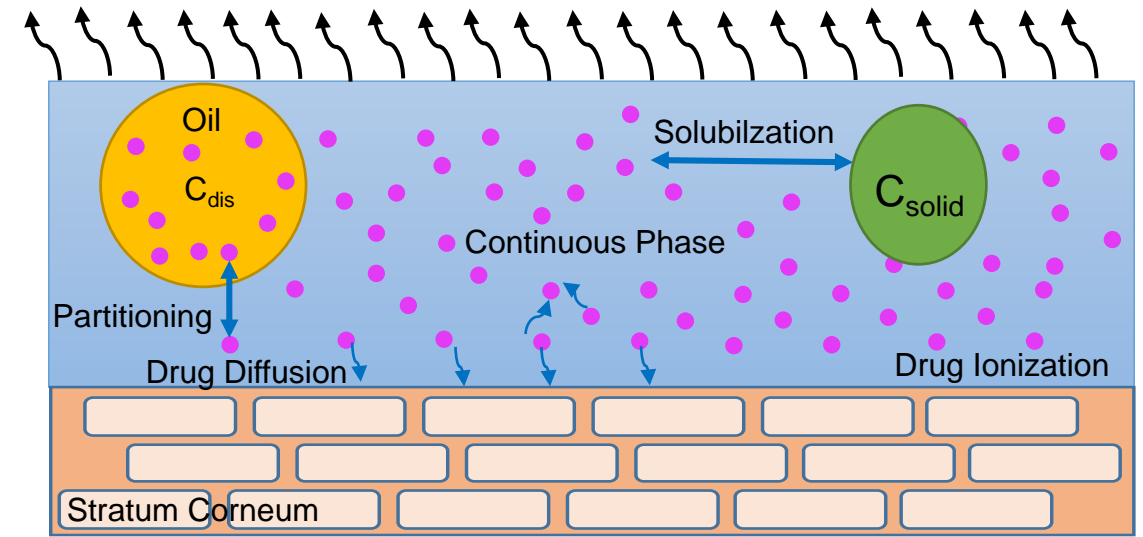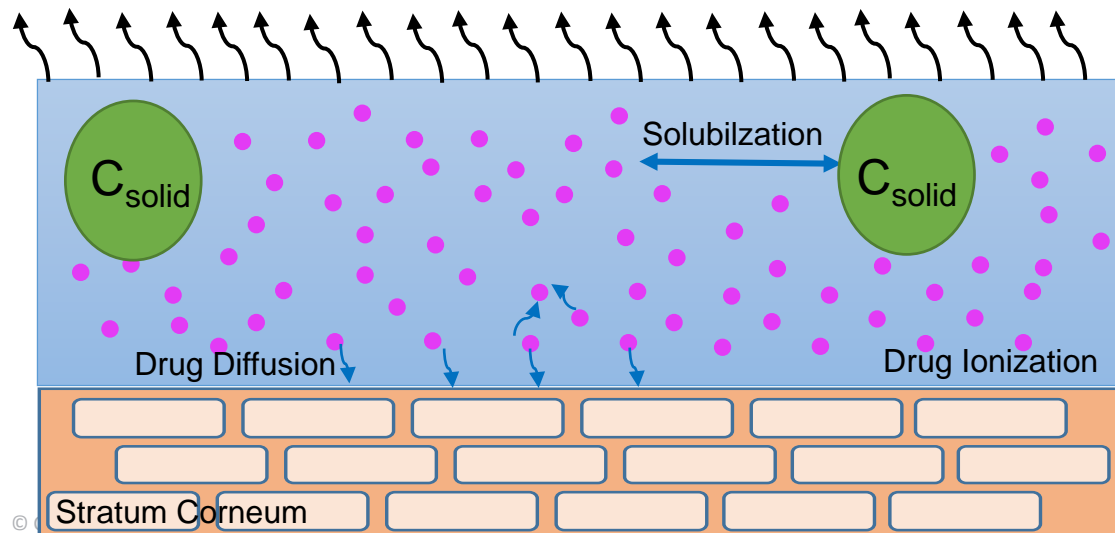
Martins et al. GRC - Barrier Function of Mammalian Skin, NH, USA, August 13 - 18, 2017.
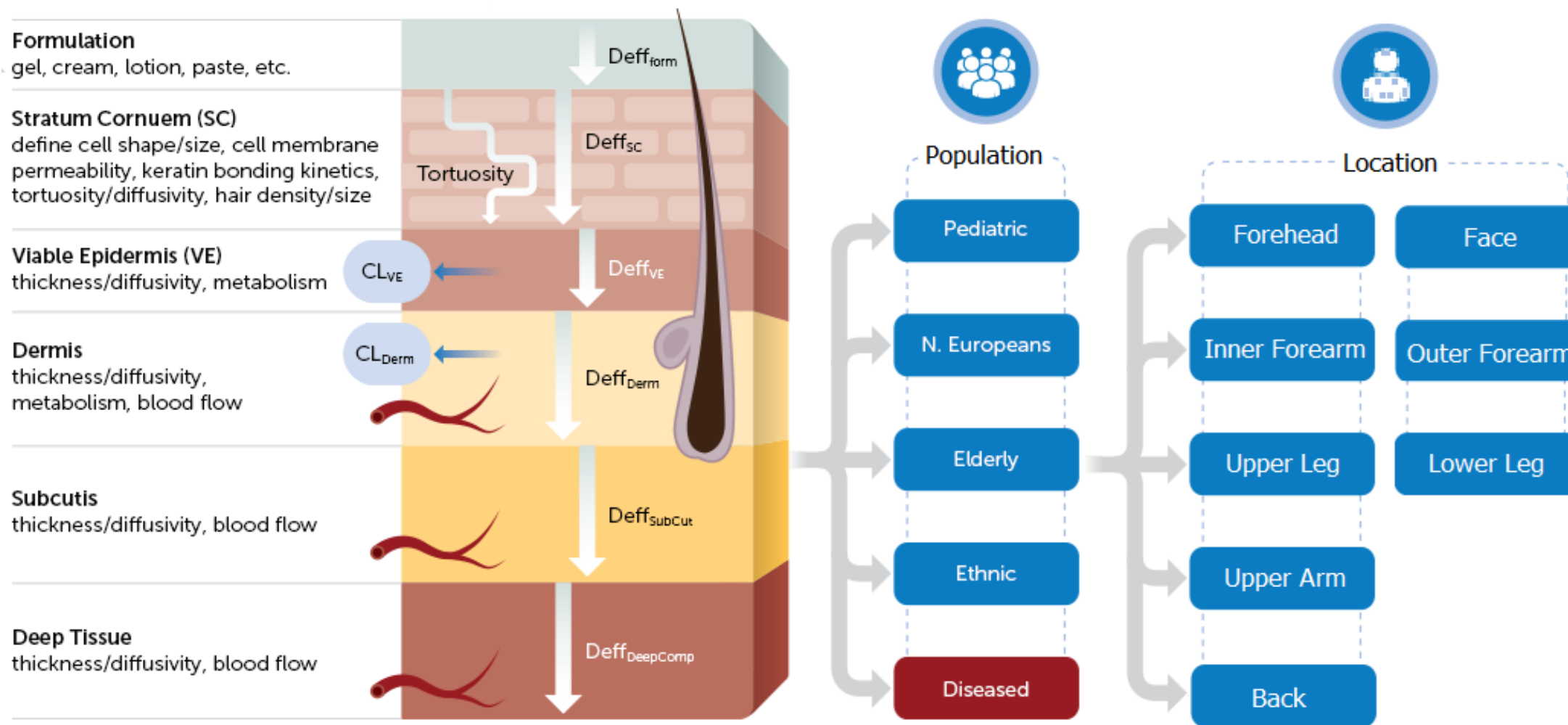
Input Parameters Needed to Parameterize the Model

Systems Data	Trial Design	Drug Data	Formulation

Systems Parameters

In vitro Simulation

- Static or flow through
- Anatomical region
- Type of skin sample
- Thickness of skin sample
- Area of diffusion cell
- Volume of receptor fluid

In vivo Simulation

- Site of application
- Physiology is then populated from database generated from meta-analysis (can be modified by the user)

Trial Design

- Number of subjects
- Demographics (age range, gender)
- Dose and volume of formulation applied
- Duration of simulation

Drug Parameters

- MW
- Log P
- pKa
- f_u (QSAR)

## Skin Model Inputs (Partition and Diffusion Coefficient)

- $K_{SClip:Water}$ (QSAR)
- $K_{SC:VE}$ (QSAR)
- $K_{Dermis:VE}$ (QSAR)
- $K_{Dermis:Blood}$ (QSAR)
- D_{SClip} (QSAR)
- D_{VE} (QSAR)
- D_{Dermis} (QSAR)
- fu_{SC} (QSAR)

Formulation Data

- Type of Formulation
  - ✓ Solution
  - ✓ Emulsion (w/wo particles)
  - ✓ Suspension
  - ✓ Patch
- Composition
- Drug solubility in different phases
- Drying rate (weight loss)
- Specific gravity
- Particle size (solid particles/droplets)
- Rheology
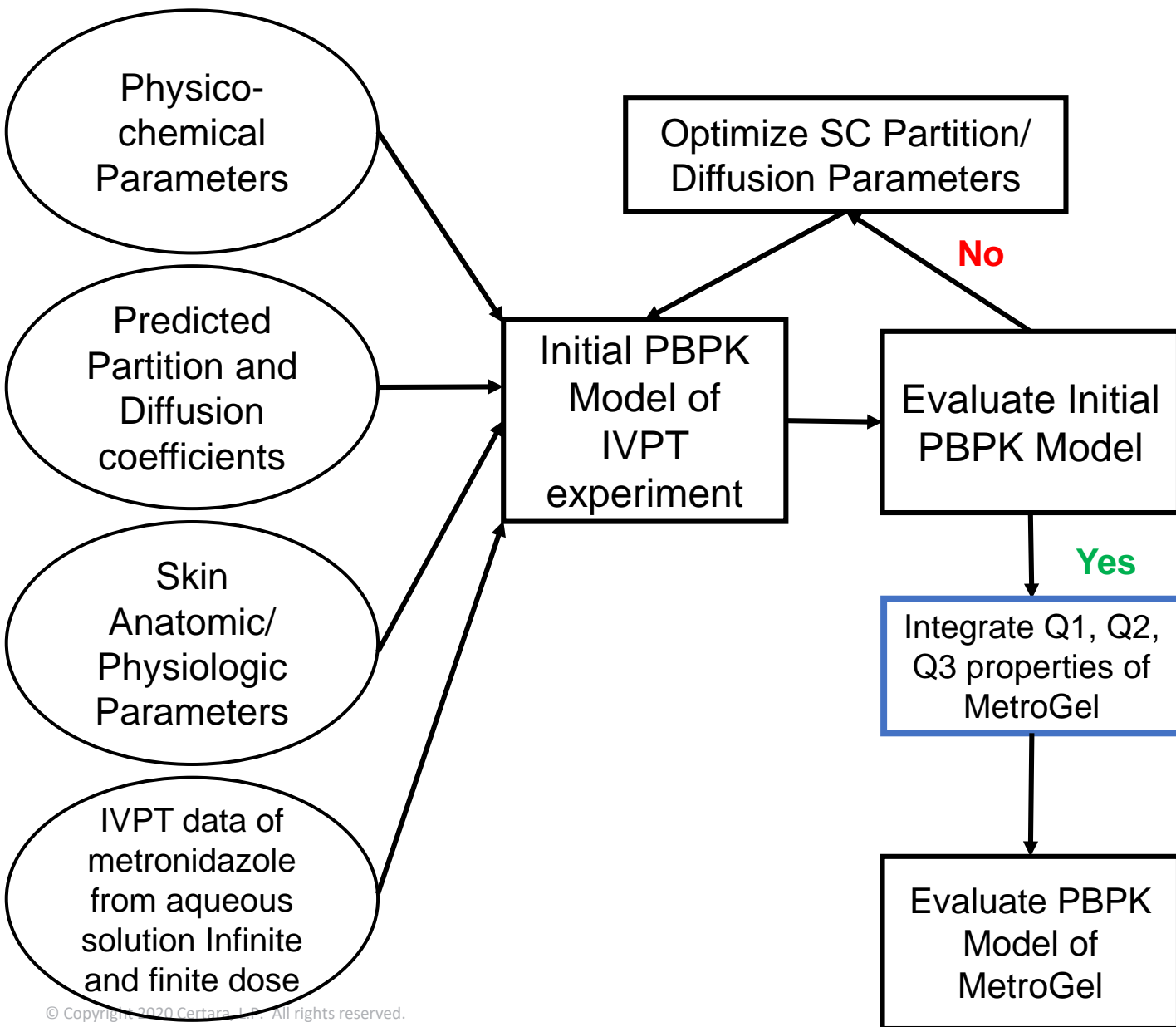- Precipitation characterization

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Case Example 1 – Modeling *In Vitro* and *In Vivo* Skin Permeation of Metronidazole Commercial Formulations (MetroGel®️ and MetroCream®️)

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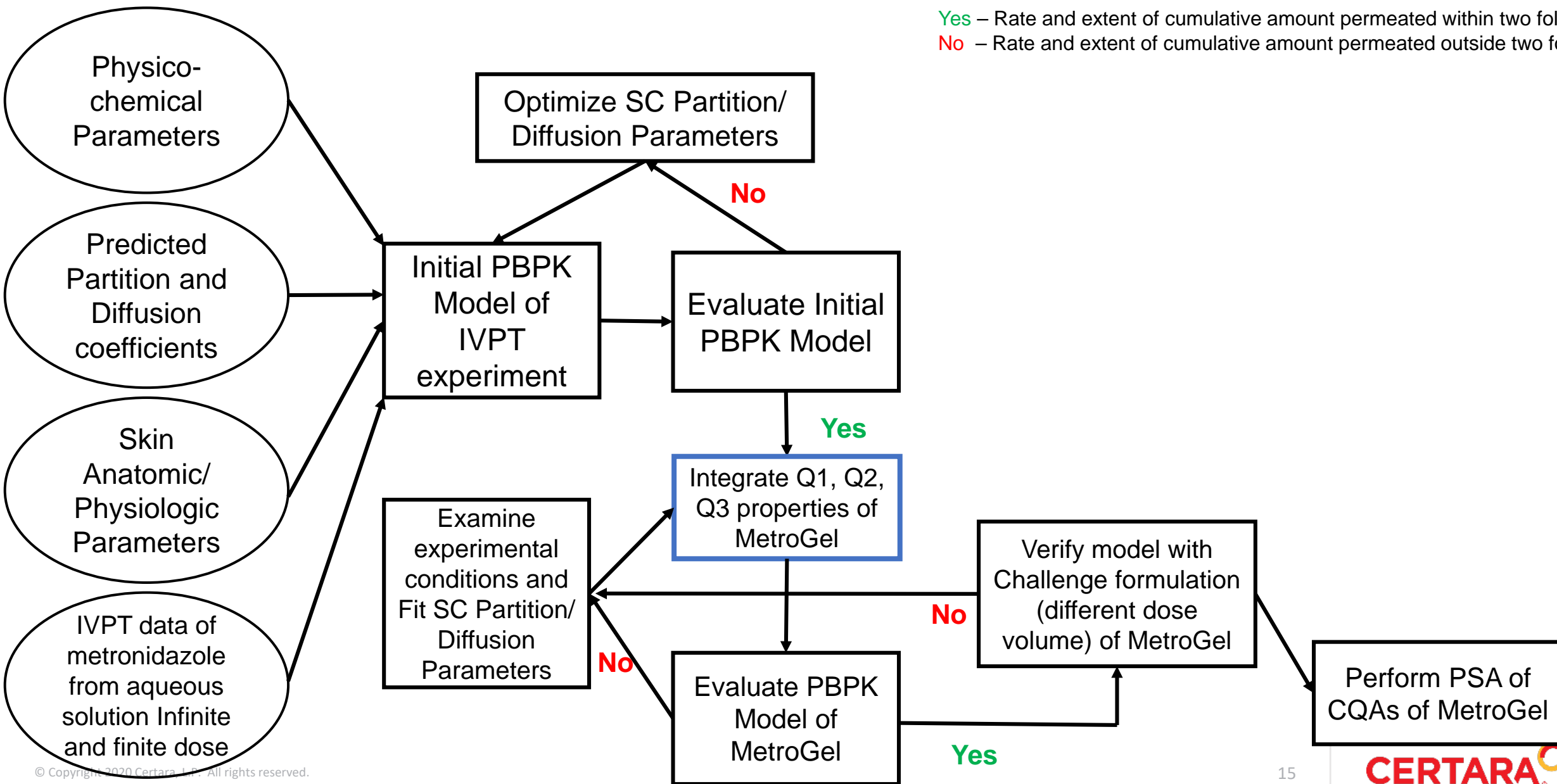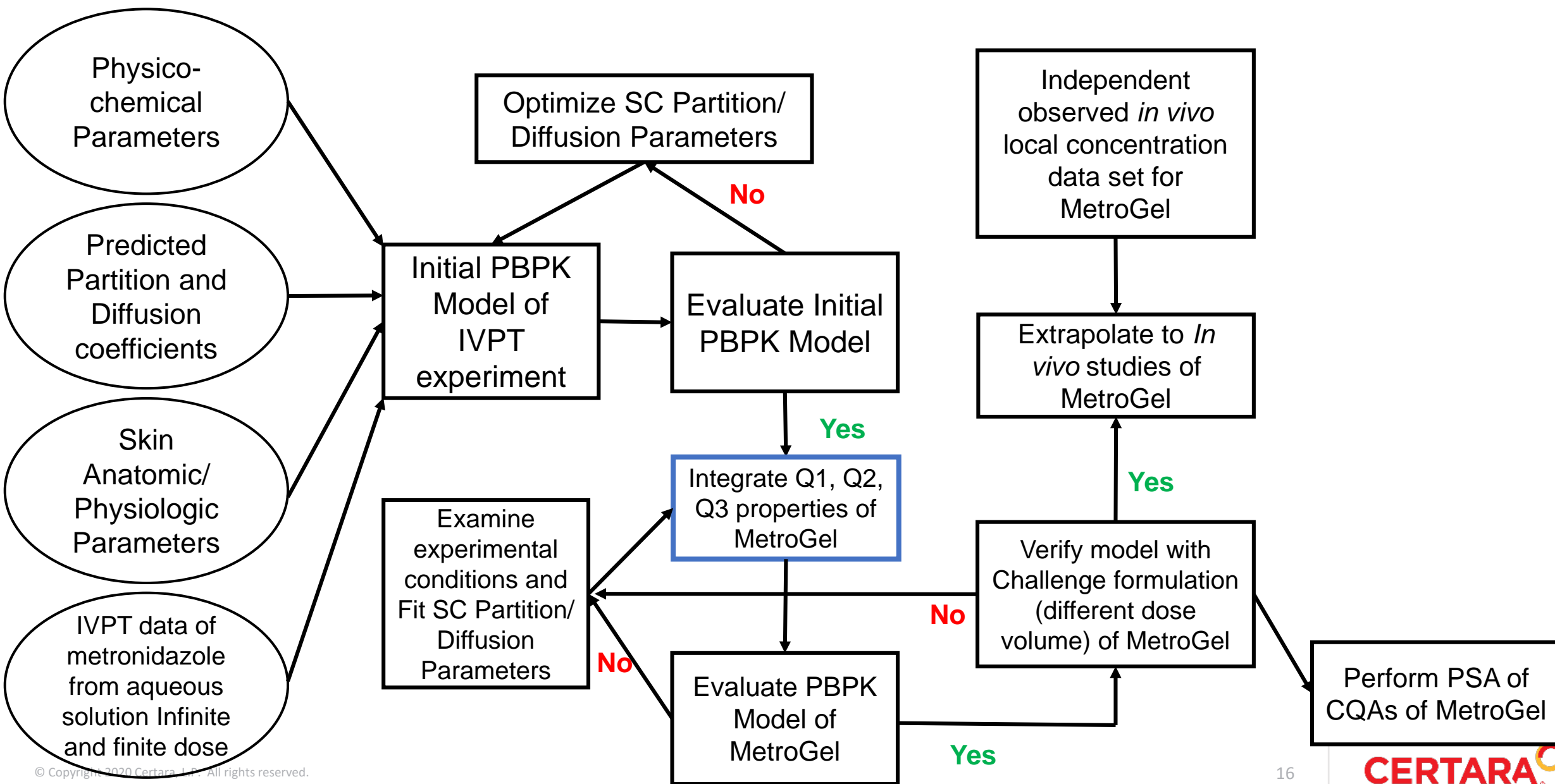# Experimental Data and a Modeling Plan for Metronidazole
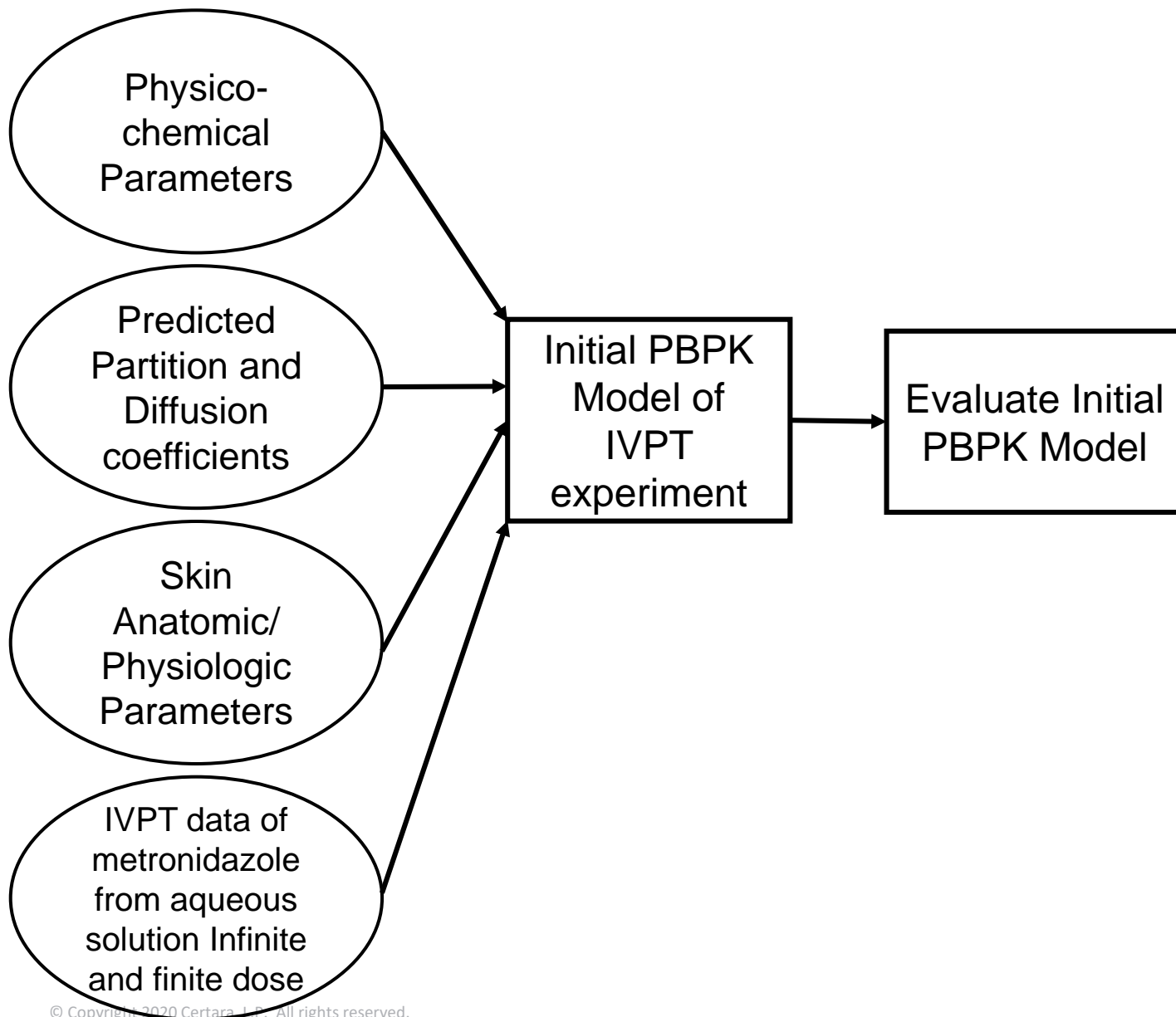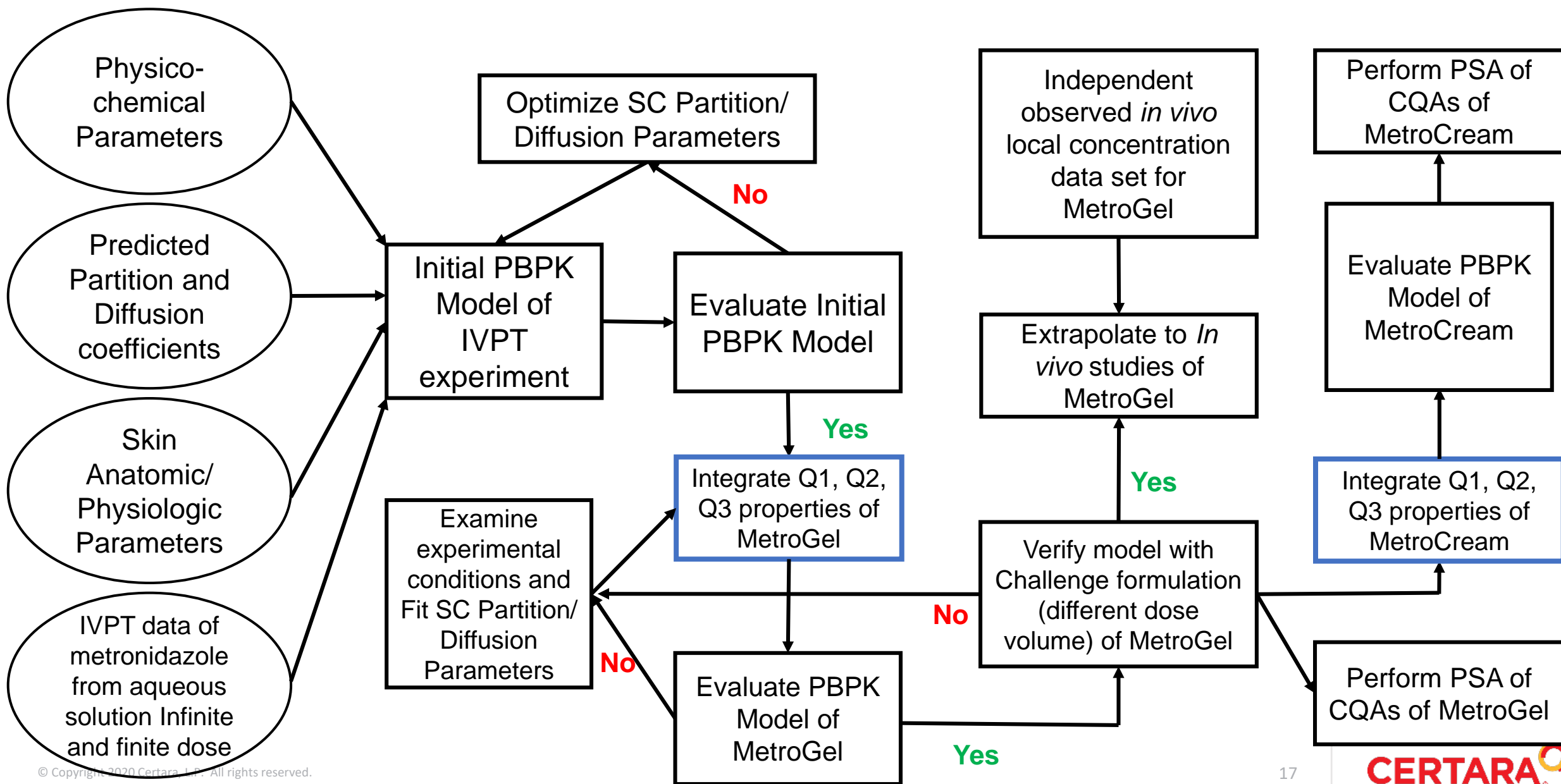
Experimental Data and a Modeling Plan for Metronidazole

Yes – Rate and extent of cumulative amount permeated within two folds
No – Rate and extent of cumulative amount permeated outside two folds

Physico-chemical Parameters

Predicted Partition and Diffusion coefficients

Skin Anatomic/ Physiologic Parameters

IVPT data of metronidazole from aqueous solution Infinite and finite dose

Optimize SC Partition/ Diffusion Parameters

Initial PBPK Model of IVPT experiment

Evaluate Initial PBPK Model

No

Yes

Integrate Q1, Q2, Q3 properties of MetroGel

Evaluate PBPK Model of MetroGel

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Experimental Data and a Modeling Plan for Metronidazole

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Experimental Data and a Modeling Plan for Metronidazole

Physico-chemical Parameters

Predicted Partition and Diffusion coefficients

Skin Anatomic/ Physiologic Parameters

IVPT data of metronidazole from aqueous solution Infinite and finite dose

Optimize SC Partition/ Diffusion Parameters

Initial PBPK Model of IVPT experiment

Evaluate Initial PBPK Model

No

Independent observed *in vivo* local concentration data set for MetroGel

Extrapolate to *In vivo* studies of MetroGel

Yes

Integrate Q1, Q2, Q3 properties of MetroGel

Yes

Examine experimental conditions and Fit SC Partition/ Diffusion Parameters

No

Evaluate PBPK Model of MetroGel

Yes

Verify model with Challenge formulation (different dose volume) of MetroGel

No

Perform PSA of CQAs of MetroGel

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Experimental Data and a Modeling Plan for Metronidazole

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Data Available

a. IVPT data - Infinite and Finite dose from aqueous metronidazole solution.

b. A battery of Q3 characterization data such as pH of formulation, viscosity, evaporation profile, drug solubility in continuous phase from two different laboratories.[a,b]

c. IVPT data – three doses 3, 10 and 30 mg/cm^2 from Ajjarapu et al.[c]

d. IVPT data – one dose 10 mg/cm^2 from Roberts et al.[b]

e. *In vivo* data from two studies reported in literature.

[a]Murthy SN. et al. AAPS 2015; [b]Roberts et al. (unpublished); [c]Ajjarapu et al. Poster Presentation. AAPS 2019

Simulation of *in vitro* skin permeation of metronidazole from aqueous solution – Infinite Dosing Conditions

- MW – 171.56, log P -0.02, Compound type – Monoprotic Base, pKa 2.38
- Compound is non-ionized at skin surface pH
- Back as skin site, Dose = 10 mg, Dose Volume = 2 mL, Trial Design = 10 trials X 6 individuals

Partition and diffusion coefficient of metronidazole across various tissue layers predicted by QSAR

Parameter	Value	Unit of measure	Method
$K_{lip/water}$	1.279	NA	Hansen 2013
$K_{sebum/water}$	0.816	NA	Yang 2019
$K_{SC/VE}$	0.995	NA	Shatkin and Brown QSAR
$K_{Dermis/VE}$	0.729	NA	Modified Chen 2015
$K_{Dermis/Sebum}$	0.891	NA	Modified Chen 2015
$K_{Receptor:Dermis}$	1	NA	Assumed
$P_{corneocyte}$	1E-05	cm/h	Default
D_{sclip}	7.7E-04	cm^2/h	Johnson QSAR
Tortousity	2336.06	NA	Johnson QSAR
D_{Dermis}	0.0102	cm^2/h	Modified Chen 2015
D_{ve}	0.0102	cm^2/h	Modified Chen 2015
$D_{Receptor}$	1	cm^2/h	
Fraction unbound in SC	0.488		Polak et al. 2016

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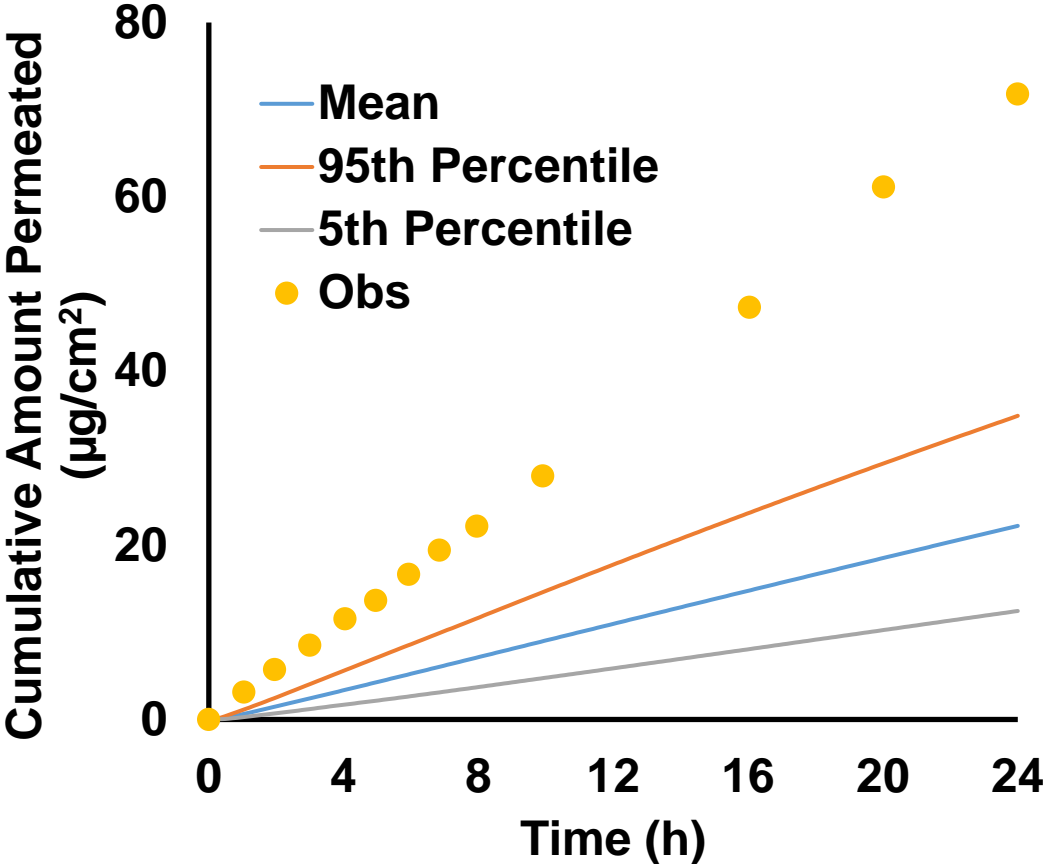# Simulation of *in vitro* skin permeation of metronidazole from aqueous solution – Infinite Dosing Conditions
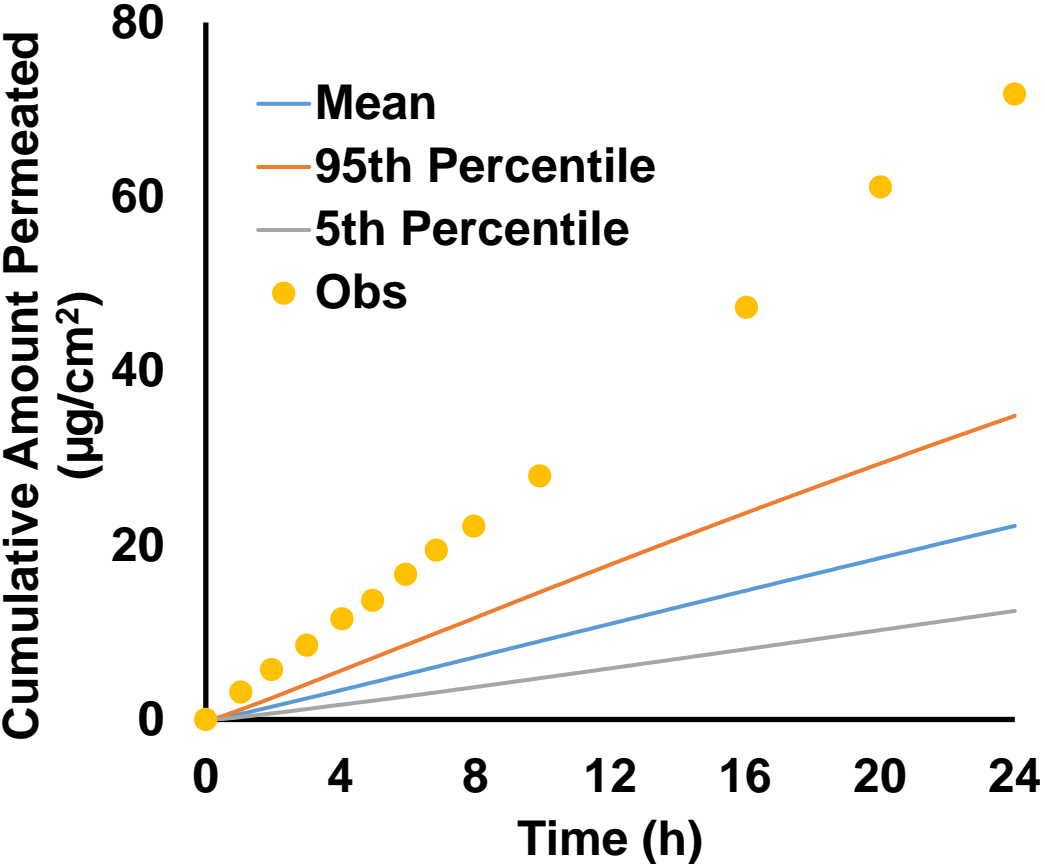
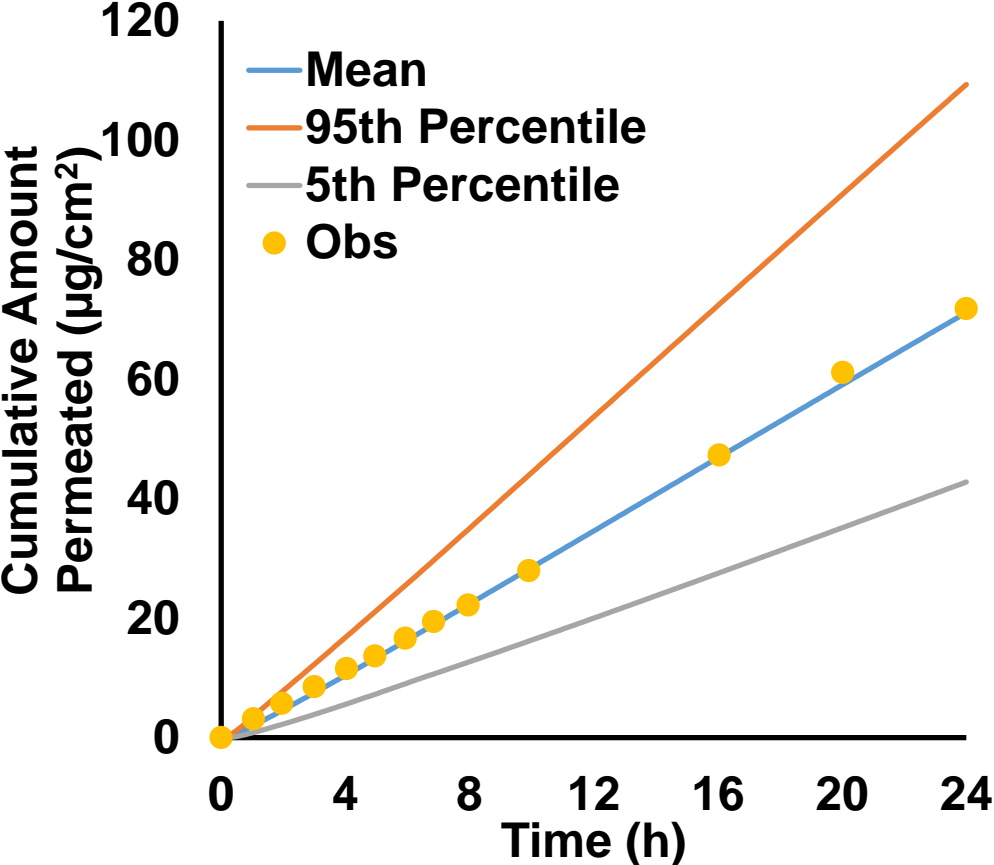Bottom-up predictions led to nearly four fold under prediction of the extent of permeation

*Observed data is n = 6

Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2019

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Simulation of *in vitro* skin permeation of metronidazole from aqueous solution – Infinite Dosing Conditions

Bottom-up predictions led to nearly four fold under prediction of the extent of permeation

Simulated cumulative amount permeated (µg/cm²) captured the observed profile

$Kp_{sclipid:water}$ = Partition coefficient between SC lipids:water

*Observed data is n = 6

Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2019

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Simulation of *in vitro* skin permeation of metronidazole from aqueous solution – Finite Dosing Conditions

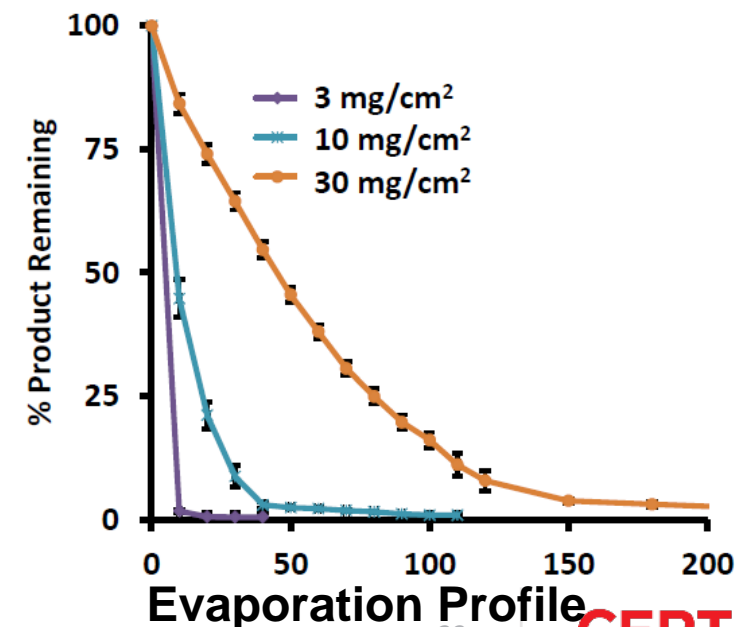- Back as skin site, Dose = 1.5 mg, Dose Volume = 300 µL, Trial Design = 10 trials X 6 individuals
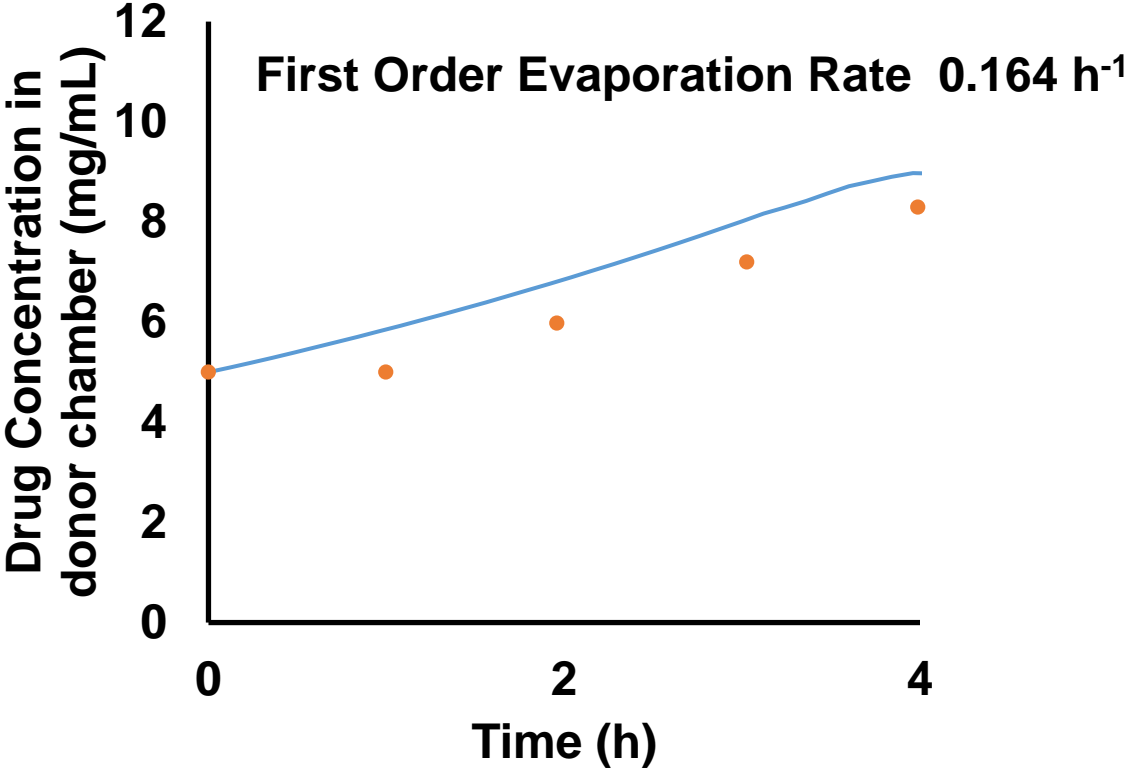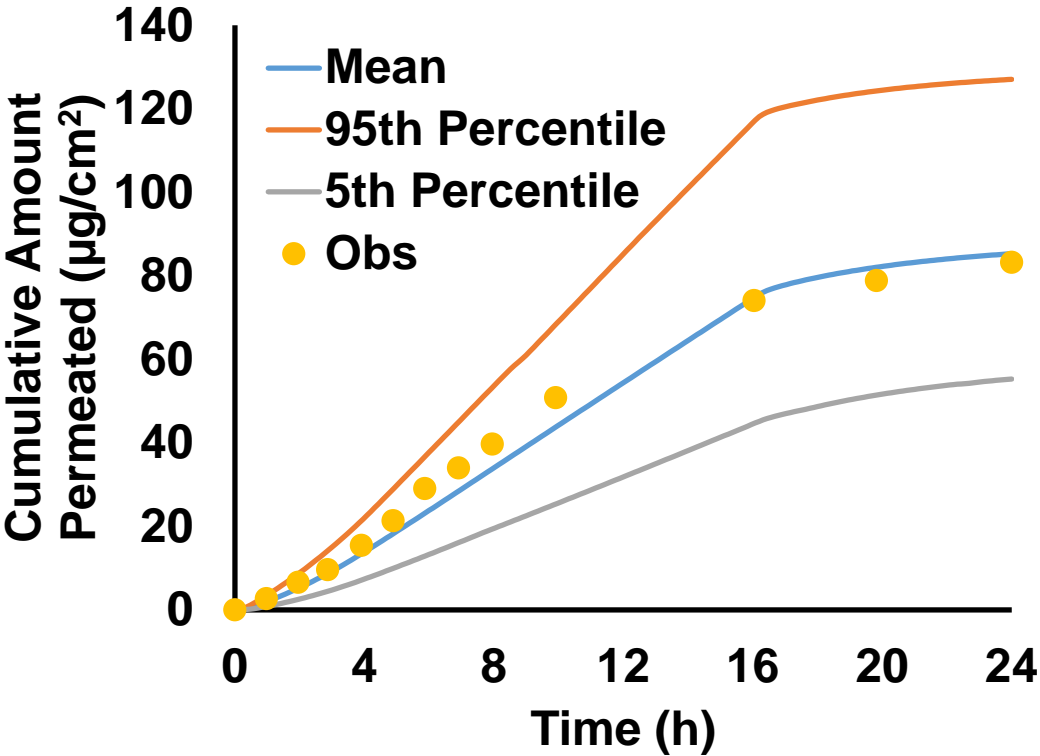
Predicted profile closely matches to the observed data. This steps serve to verify the fitting of $Kp_{sclipid:water}$

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Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2019

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MetroGel® (0.75%) Structural and Physical Characterization Data – Murthy et al. 2015

Parameter	MetroGel®
Formulation Simulation Option	Solution
Dose of Cream Applied (mg/cm²)	10
Density of formulation (g/cm³)	1.01
Dose of Drug Applied (µg)	74
Volume of Formulation (mL)	0.01
Thickness of Formulation (cm)	0.01
Viscosity (cP)	12779
pH of formulation	5.23
Drug Solubility in Continuous Phase (mg/mL)	8.7
Evaporation Profile	User Input Profile
Precipitation Model	Empirical
CSR	1
PRC (h⁻¹)	11

Product	Initial Viscosity (@0.01/S⁻¹)	Yield Stress
MetroCream®	9541 ± 284	94 ± 0.00
Generic cream	6830 ± 1166	70 ± 3.00
MetroGel®	12779 ± 1215	50 ± 4.04
Generic gel-1	10534 ± 263	50 ± 0.00
Generic gel-2	12489 ± 1692	49 ± 5.20

Viscosity Measurements

Evaporation Profile

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Murthy SN. et al. AAPS Annual Meeting. Orlando, Florida, USA, 25-29 October 2015

Parameterization of Formulation Parameters for MetroGel® in MPML MechDermA Model

Metronidazole

SIM

Formulation Options and Parameters

✓ Formulation pH is skin surface pH Formulation pH `5.23` CV (%) `0`

Fraction non-ionised at skin surface fni skin surface 🔒 `0.998589`

Formulation drug liberation lag time (h) `0` CV (%) `0` ☐ Apply lag time to vehicle evaporation

✓ Consider Vehicle Evaporation

				Mean	CV (%)
Temperature of skin (°C)	`32`	Vapour pressure of vehicle at skin temperature (mm Hg)		`43`	`30`
MW of vehicle (g/mol)	`18`	Air velocity (m/sec)		`0.5`	`30`
Density of vehicle (g/ml)	`1.0238`	Maximum % (v/v) vehicle evaporated		`99`	`0`

○ (Zero Order) Evaporation rate (ml/h) 🔒 `1.25073` CV (%) `30`

○ First Order Evaporation Rate Constant K$_{ER}$ (1/h) `0.1234` CV (%) `10`

◉ Vehicle Evaporation Profile

❌ Custom Dermal - Drug/Formulation Parameter(s)

✓ Allow drug to precipitate

○ Mechanistic Growth Model (only suspensions and emulsions with particles)
◉ Empirical Model (only solutions and emulsions without particles)

Critical Supersaturation Ratio `1`

Precipitation Rate Const. (1/h) `11`

❌ Apply Secondary PRC Secondary PRC (1/h) `100`

Reference Concentration ◉ Total Concentration in continuous phase (unionized + ionized)
○ Unionized Concentration in continuous phase

◉ Solution

Diffusion Coeff (cm^2/h) 🔒 `1.84346E-06` Vehicle molar volume (mL/mol) `18`

Drug solubility in vehicle (mg/mL) `8.7` Viscosity (centipose) `12779`

Particle Count for Precipitation 🔒 `354916`
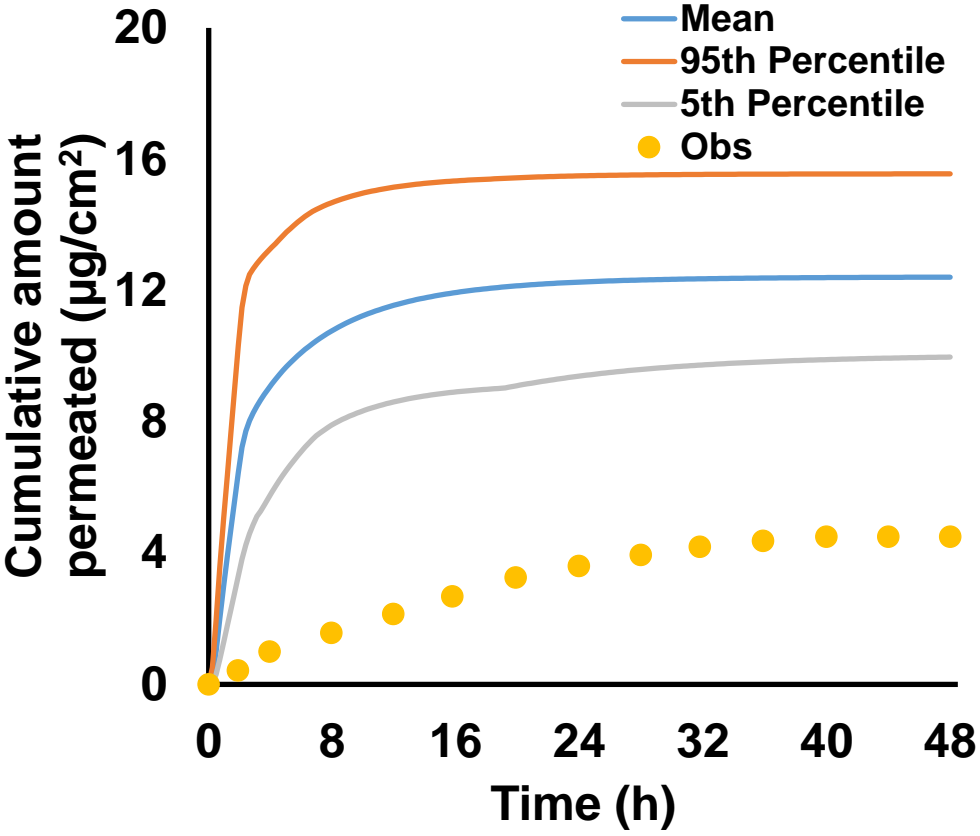
Formulation pH Input

Input of Evaporation Profile

Precipitation Model *CSC* (*CSR* x Eq.Sol)

$$DR(t) = \sum_{NBINs}^{i=1} -N_i \, S_{DR} \frac{D_{eff}(t)}{h_{eff,i}(t)} 4\pi a_i(t) \left(a_i(t) + h_{eff,i}(t) \right) \left(S_{surface}(t) - C_{bulk}(t) \right)$$

Wang Flanagan Equations (Diffusion layer model for particle dissolution)

Physical and Structural Characterization Data of Topical Formulations

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Simulation of *in vitro* skin permeation of metronidazole from MetroGel® - Murthy et al. Q3 Characterization - Dose 10 mg/cm²

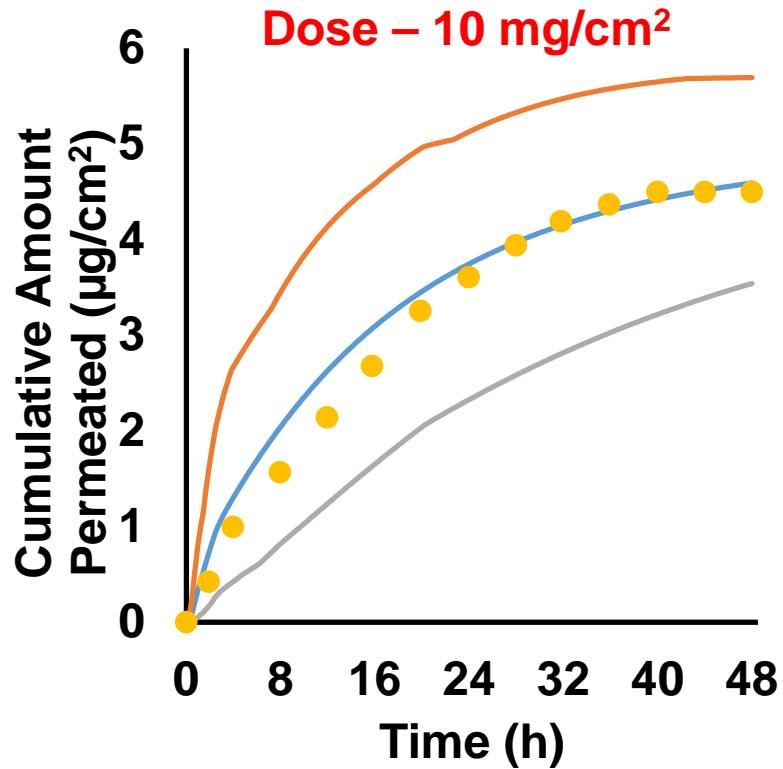Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2017; Murthy SN. et al. AAPS 2015

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Simulation of *in vitro* skin permeation of metronidazole from MetroGel® - Murthy et al. Q3 Characterization - Dose 10 mg/cm²
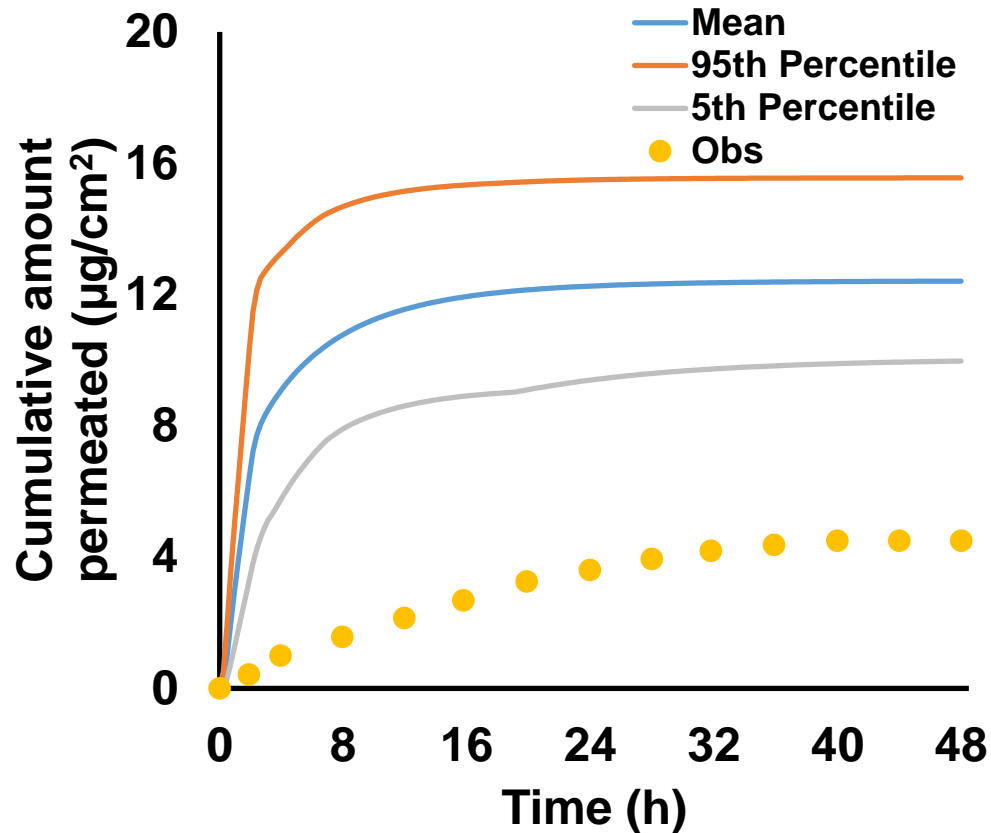
- Significant overprediction was observed both for the rate and extent of metronidazole permeation from Metrogel®

- Clearly, the translation of model parameters from simple aqueous based infinite and finite dosing conditions to complex formulation was not straight forward

- A closer look at the experimental conditions revealed differences in hydration conditions between the aqueous IVPT experiments where large dose volume was used (around 2mL in infinite dosing conditions) vs IVPT experiments for gel where 10μL dose volume was applied in the experiment.

- **Skin hydration is known to effect the diffusion of the drug through stratum corneum[a] and thus, we decided to optimize diffusion coefficient of metronidazole using IVPT data for 10 mg/cm² for MetroGel formulation.**

Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2017; [a]Yuosef et al. AAPS J . 2017 Jan;19(1):180-190.
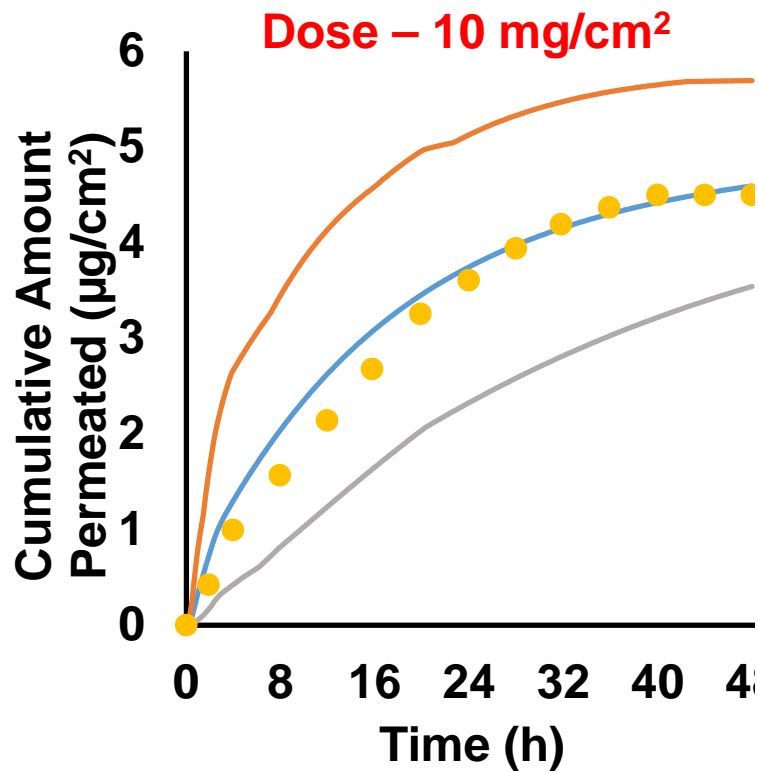
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Simulation of *in vitro* skin permeation of metronidazole from MetroGel® - Murthy et al. Q3 Characterization - Dose 10 mg/cm²

- Optimized $D_{sclipid}$ using 10 mg/cm² IVPT data
- 3 mg/cm² and 30 mg/cm² IVPT dataset serves as model verification

Dose – 10 mg/cm²

Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2017

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- Optimized $D_{sclipid}$ using 10 mg/cm² IVPT data
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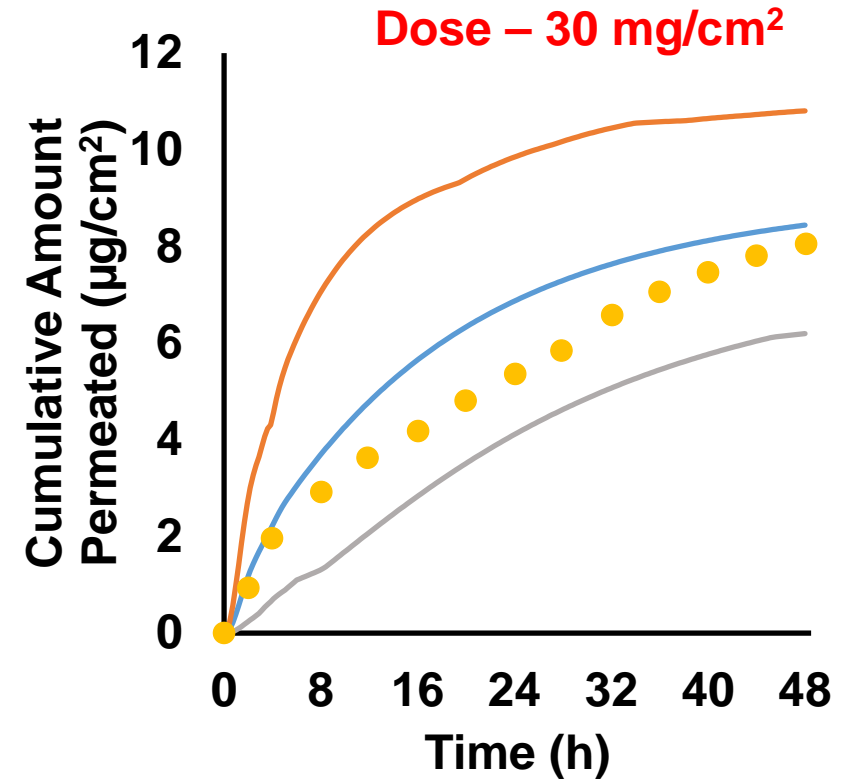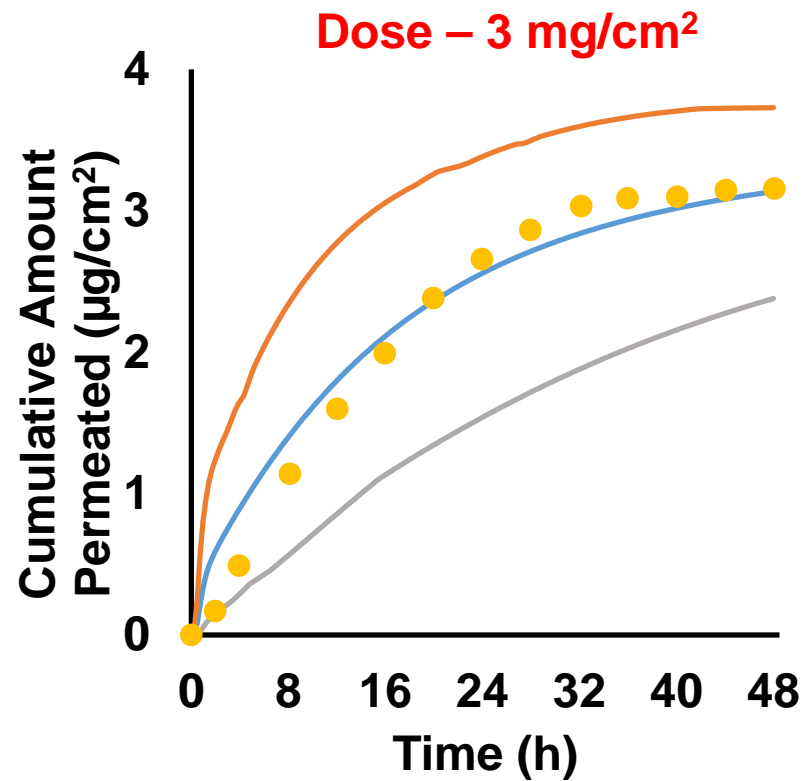
Optimized PBPK model was able to **predict** cumulative amount permeated (µg/cm²) observed from the challenge formulation (different dose volumes).

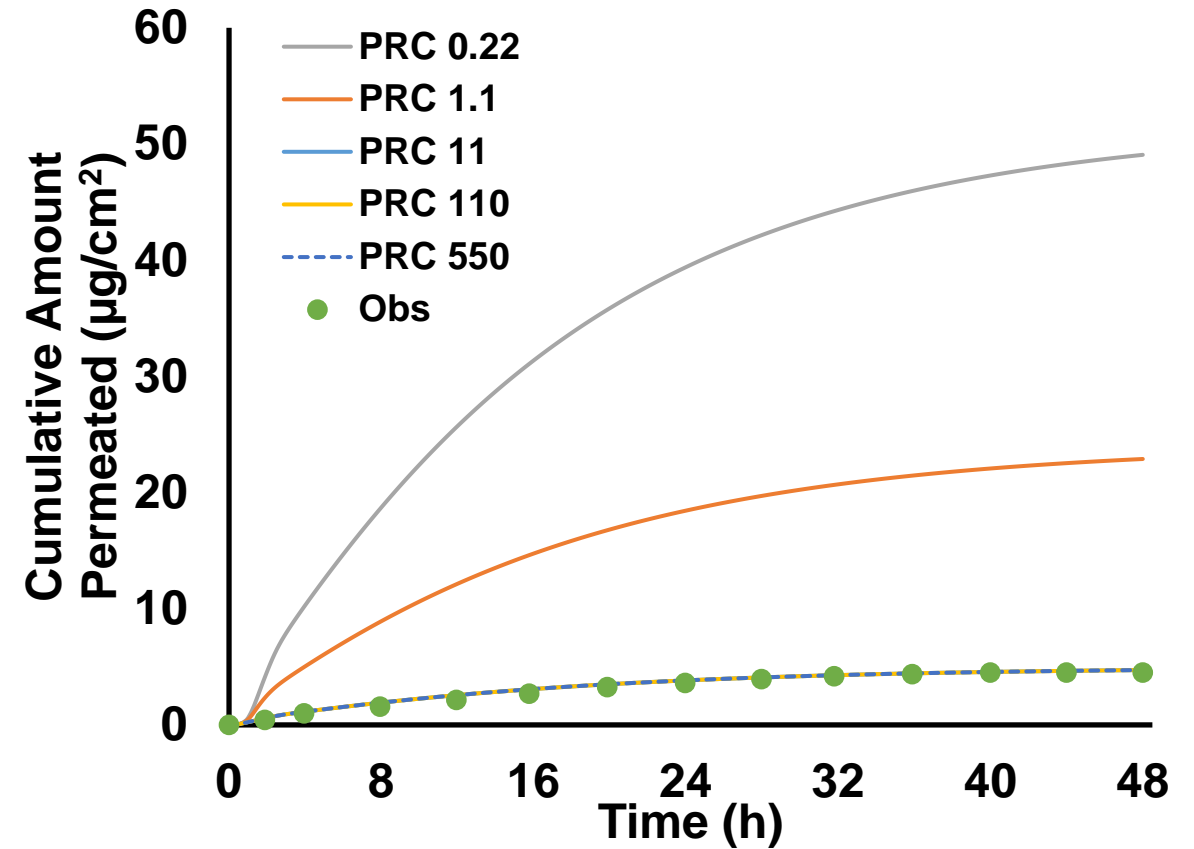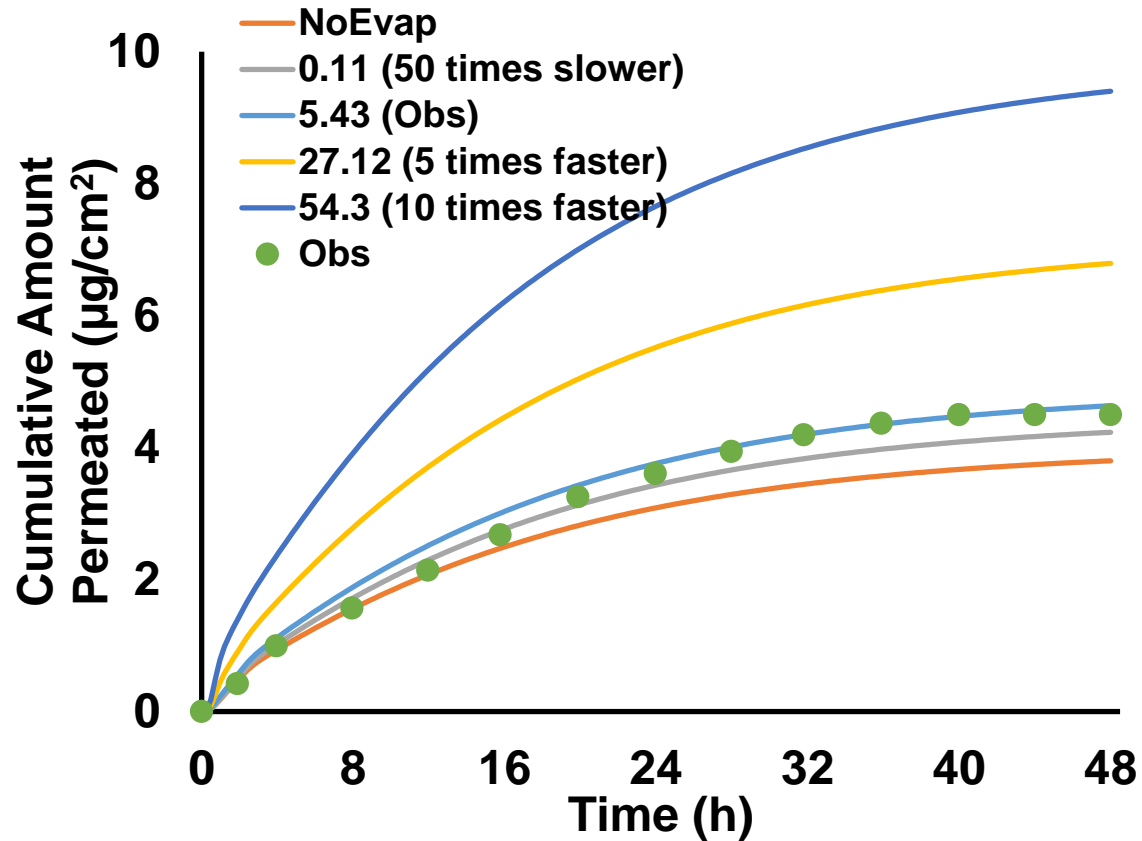Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2017

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Simulation of *in vitro* skin permeation of metronidazole from MetroGel® - Roberts et al. Q3 Characterization - Dose 10 mg/cm²

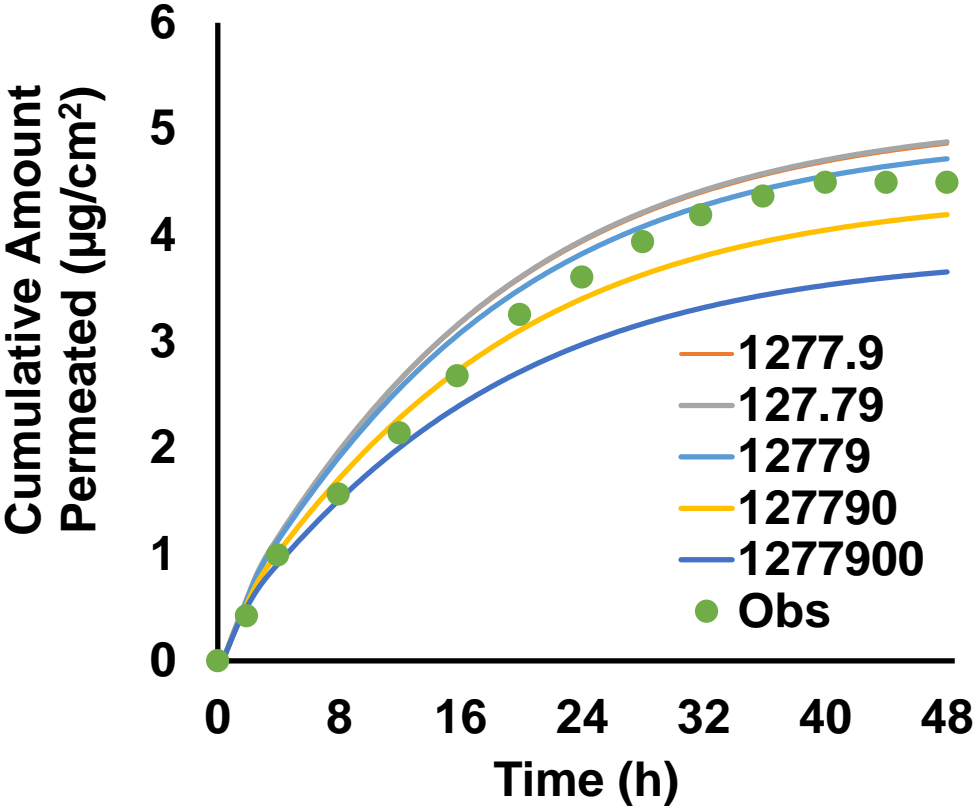All the parameters are similar except pH of formulation (pH 4.8) and evaporation profile
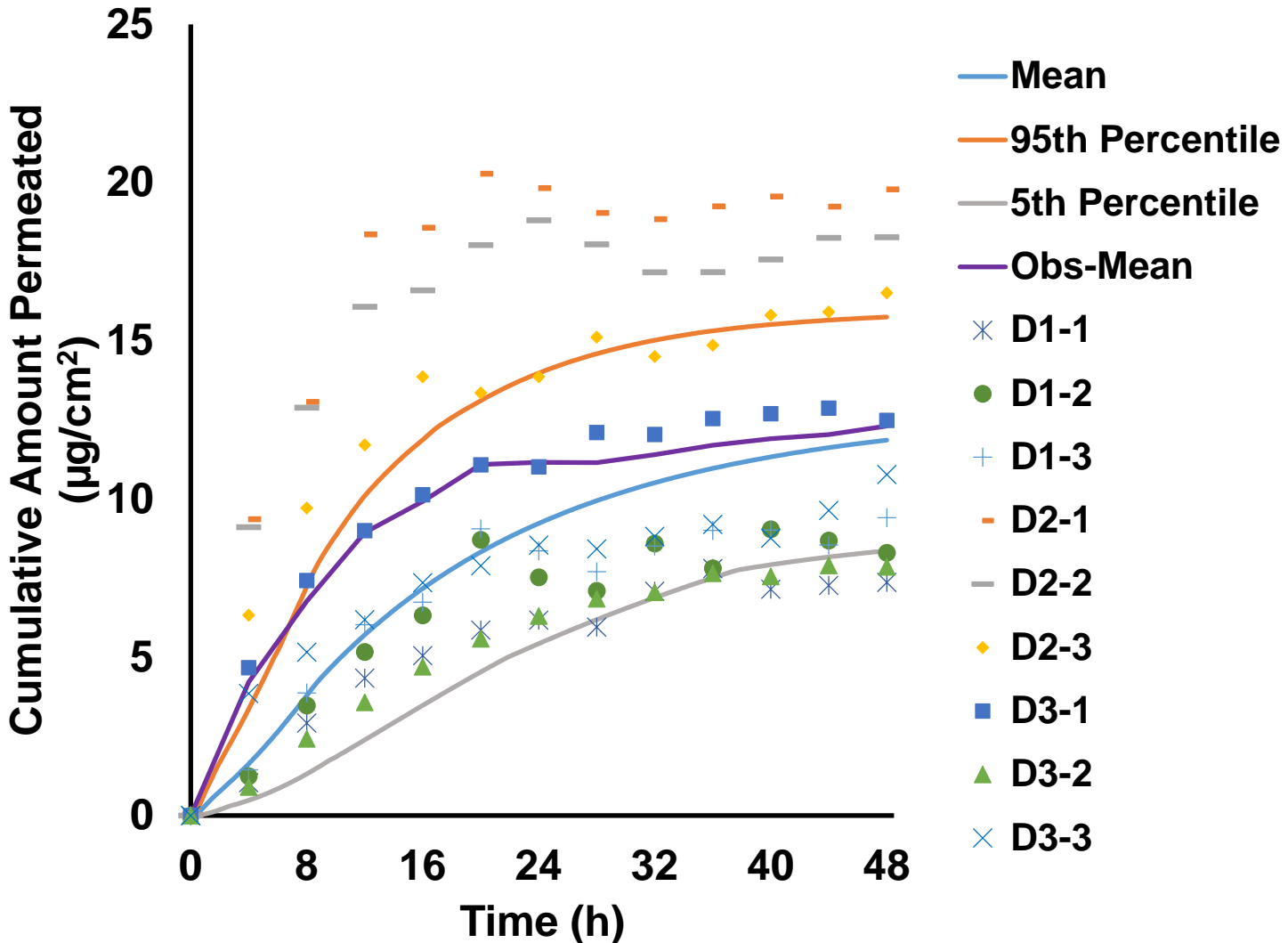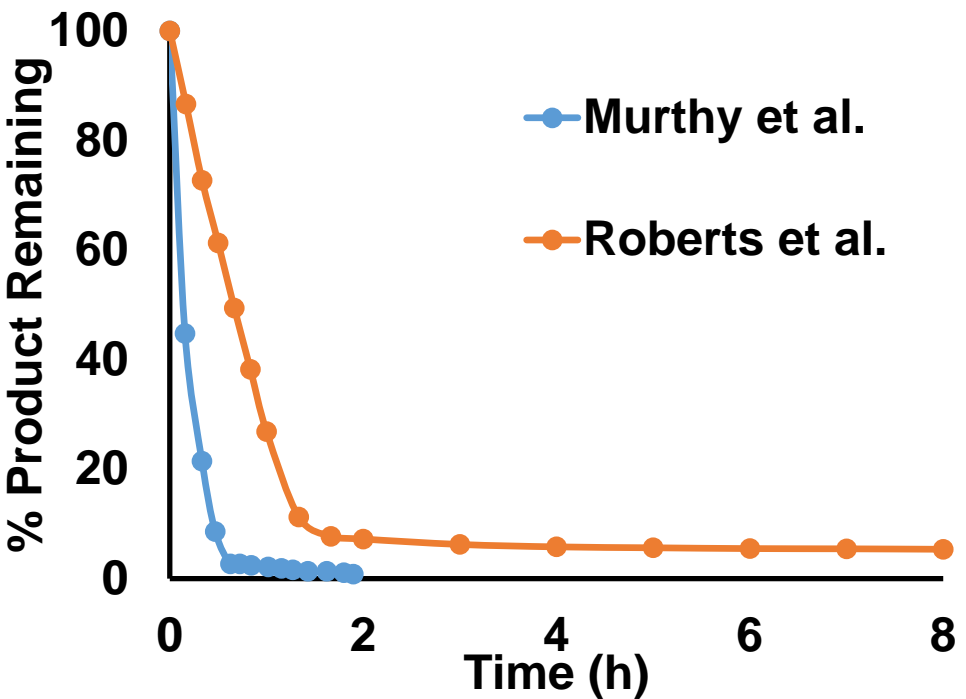
The model was able to **predict** mean cumulative amount permeated (µg/cm²) as well as variability from 10mg/cm² dose determined by another lab.
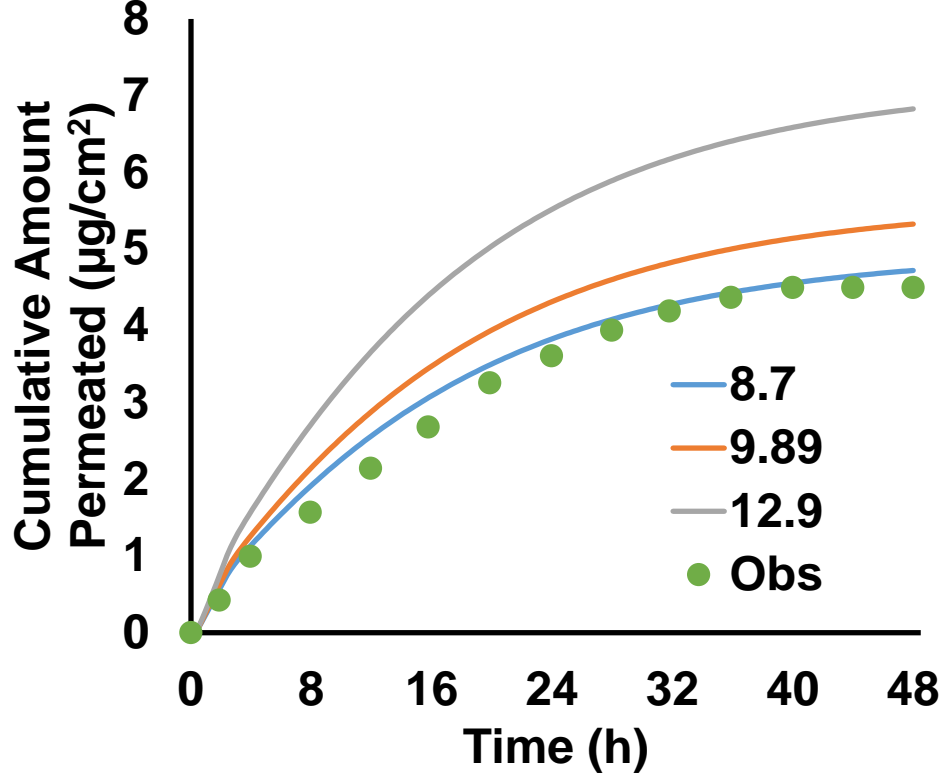
Murthy SN. et al. AAPS 2015; Roberts et al. (unpublished)

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Evaporation Rate Constant

Precipitation Rate Constant

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# Parameter Sensitivity Analysis of Critical Formulation Parameters of MetroGel®
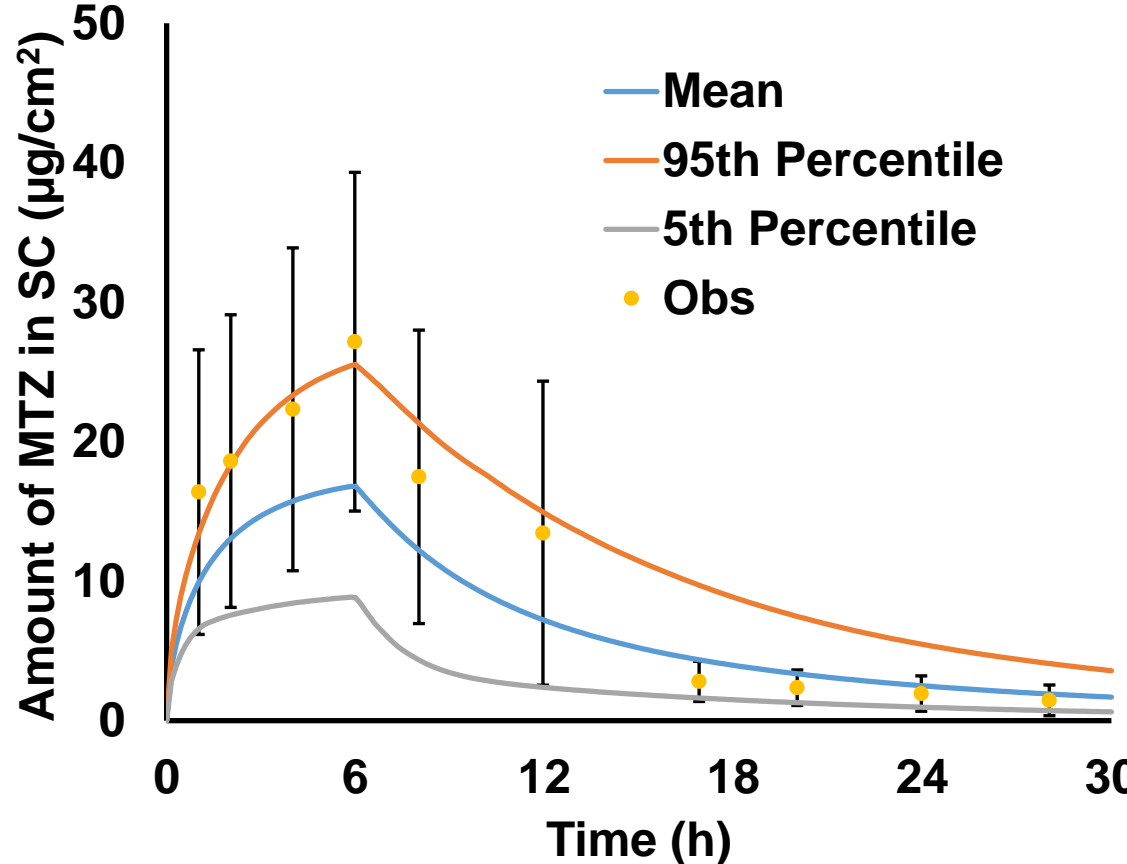
Vehicle Viscosity

Drug Solubility in Continuous Phase (mg/mL)

Simulation of *in vivo* skin permeation of metronidazole from MetroGel® and Rosex®

Rosex was assumed to be similar to the Metrogel. Both are 0.75% w/w gels of metronidazole with similar Q1 properties

Assumed metronidazole freely permeates through corneocyte
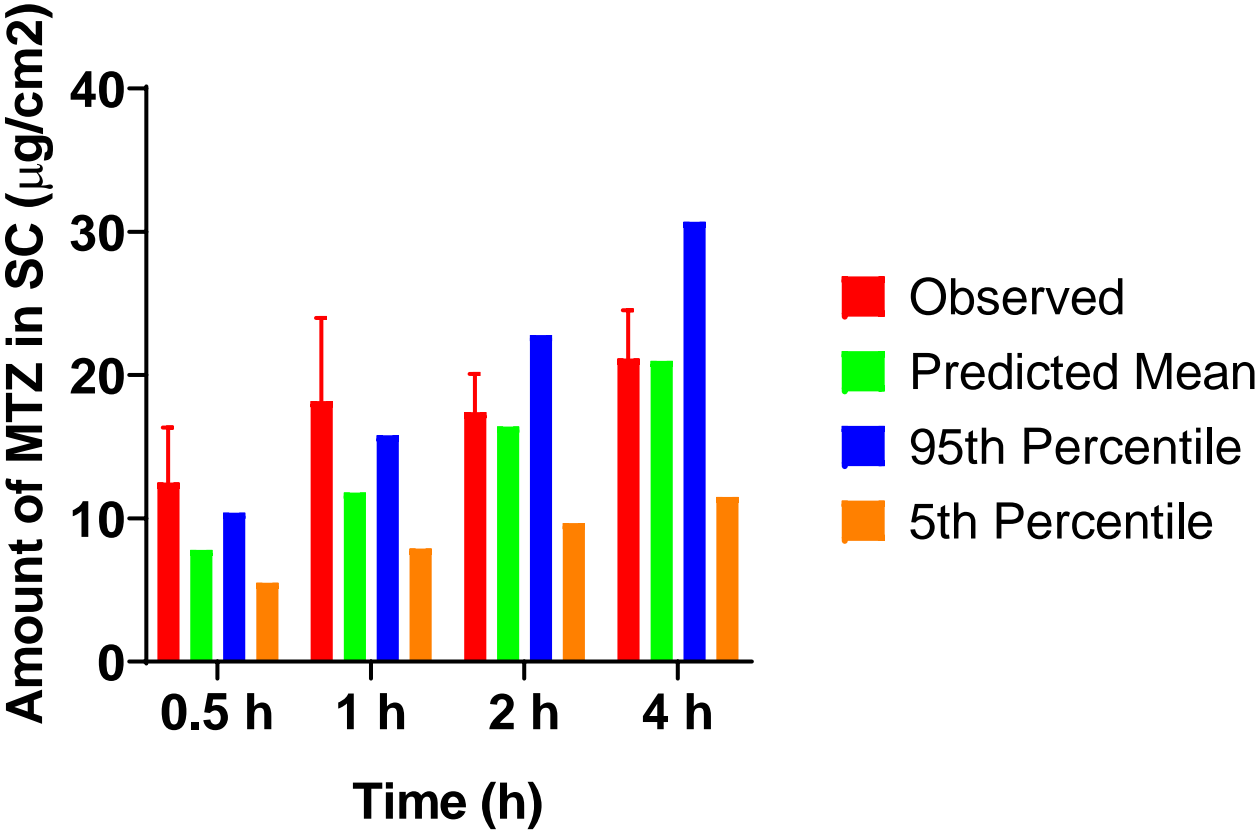
Dykes et al. 1997

Araujo et al. 2018

The model was able to **predict** metronidazole amount permeated (µg/cm^2) in the stratum corneum observed *in vivo* demonstrating successfully IVIVE in this case.
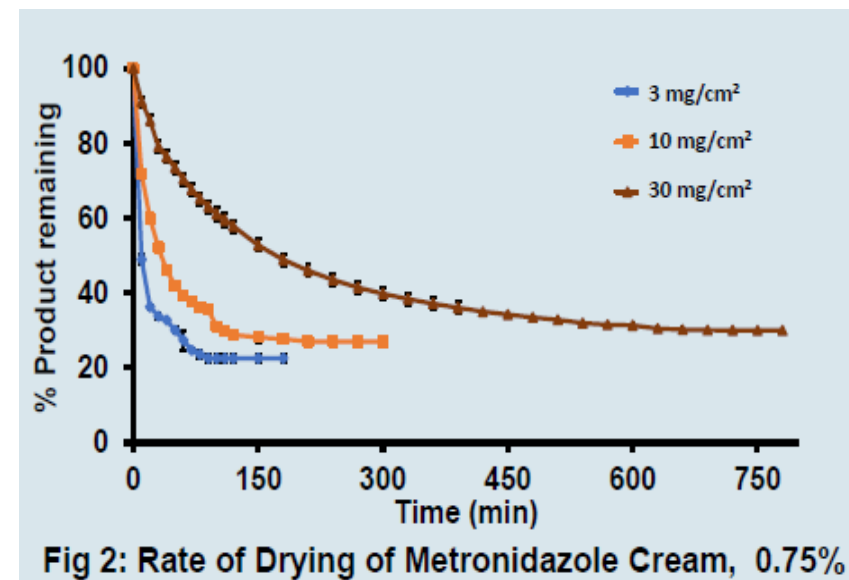
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Data Available

a. A battery of Q3 characterization data such as pH of formulation, viscosity, evaporation profile, drug solubility in continuous phase from two different laboratories.[a,b]

b. IVPT data –10 mg/cm^2 from three different laboratories.[a,b,c]

[a]Murthy SN. et al. AAPS 2015; [b]Roberts et al. (unpublished), [c]Zhang et al. Poster Presentation. AAPS 2019

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MetroCream® (0.75%) Structural and Physical Characterization Data – Murthy et al. 2015

Parameter	MetroCream
Formulation Simulation Option	Emulsion
Dose of Cream Applied (mg/cm^2)	10
Density of formulation (g/cm^3)	1.02
Dose of Drug Applied (µg)	73
Volume of Formulation (mL)	0.01
Thickness of Formulation (cm)	0.01
Viscosity (cP)	9541
pH of formulation	4.82
Drug Solubility in Continuous Phase (mg/mL)	8.7
Ratio Dispersed/Aqueous	0.614
% Volume fraction of Aqueous Phase	73*
% Volume fraction of Dispersed Phase	27
D50 (globule size, µm)	2.88
Evaporation Profile	User Input Profile
Precipitation Model	Empirical
CSR	1
PRC (h^{-1})	11

Fig 2: Rate of Drying of Metronidazole Cream, 0.75%

Observed data taken from Ajjarapu et al. Poster Presentation. AAPS 2017

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*Taken from plateau phase of the evaporation profile

Murthy SN. et al. AAPS Annual Meeting. Orlando, Florida, USA, 25-29 October 2015

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Simulation of *in vitro* skin permeation of metronidazole from MetroCream® - Dose 10 mg/cm²

- Back as skin site, Dose = 0.074 mg, Dose Volume = 10 µL, Trial Design = 10 trials X 6 individuals
- Diffusion and partition parameters are same as MetroGel

[a]Murthy SN. et al. AAPS 2015; [b]Roberts et al. (unpublished), [c]Zhang et al. Poster Presentation. AAPS 2019

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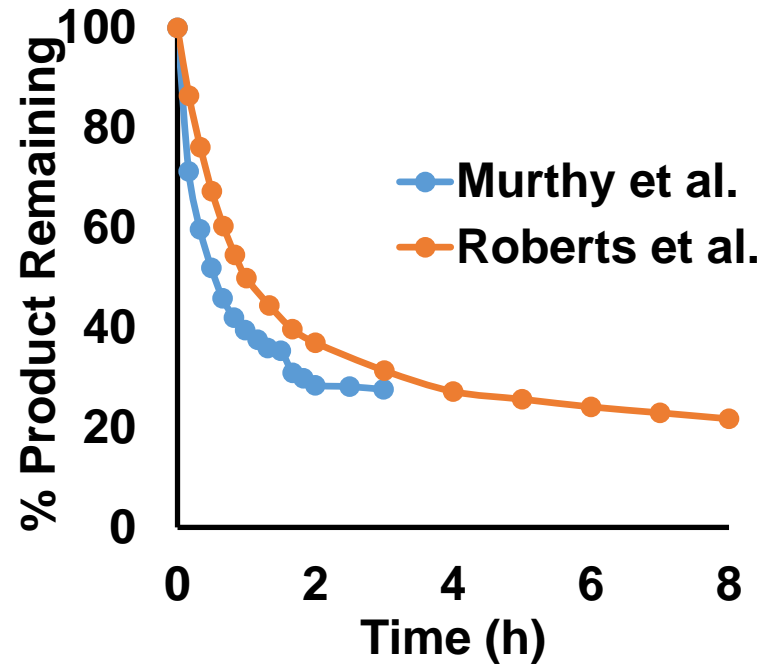
Simulation of *in vitro* skin permeation of metronidazole from MetroCream ® (10 mg/cm2)

- Back as skin site, Dose = 0.074 mg, Dose Volume = 10 µL, Trial Design = 10 trials X 6 individuals
- Diffusion and partition parameters are kept same as that for MetroGel
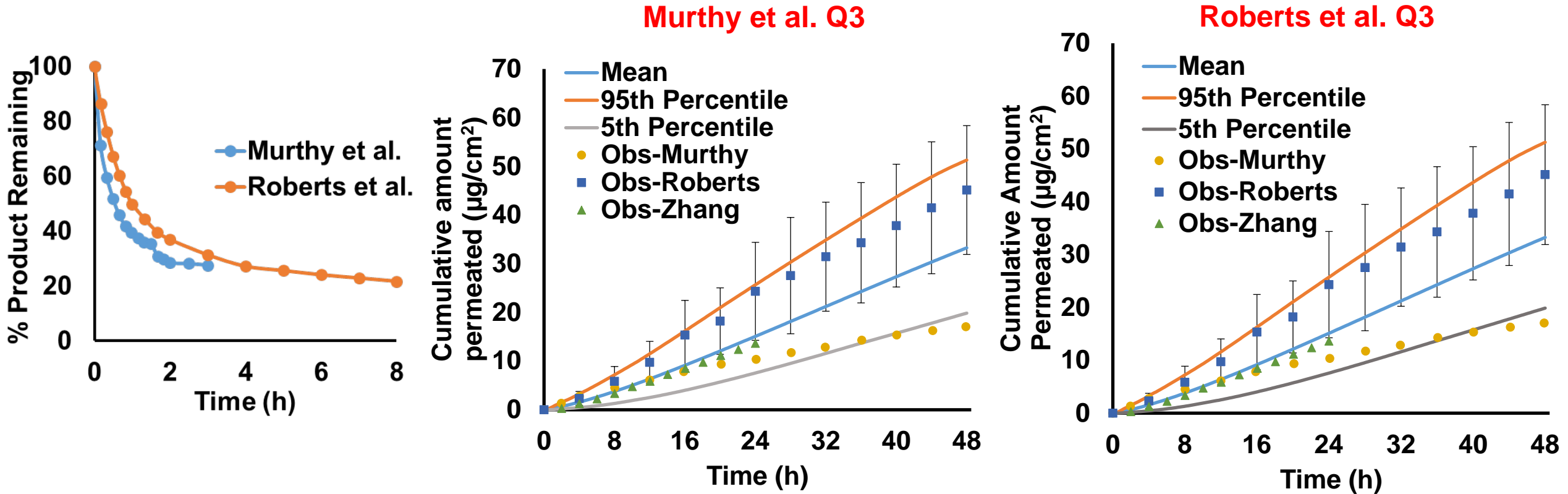
Murthy et al. Q3

Roberts et al. Q3

Simulated cumulative amount permeated (µg/cm^2) was able to successfully **predict** the observed data from three different laboratories **bottom up**

*Note – Simulations are done using Franz diffusion setup based on Murthy et al. and Roberts et al. Q3 properties, Data from Zhang et al. is obtained using flow through setup, It is overlayed on the same graph for comparison purpose only

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[a]Murthy SN. et al. AAPS 2015; [b]Roberts et al. (unpublished), [c]Zhang et al. Poster Presentation. AAPS 2019

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**Case Example 2 – Modeling *In Vitro* Skin Permeation of Acyclovir Commercial Formulations (Zovirax and Aciclostad)**

Data Available
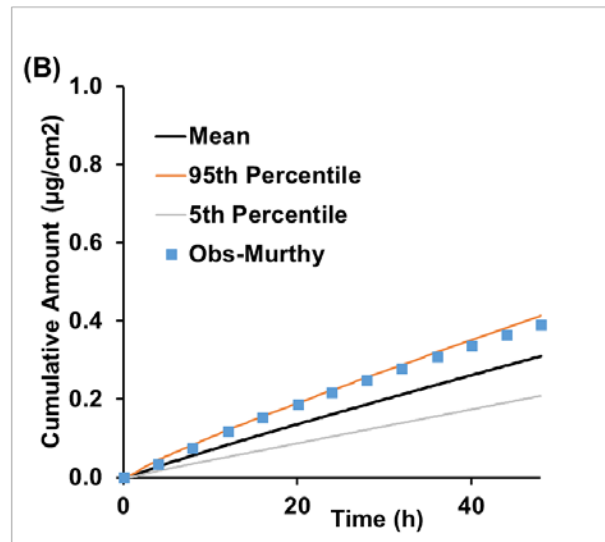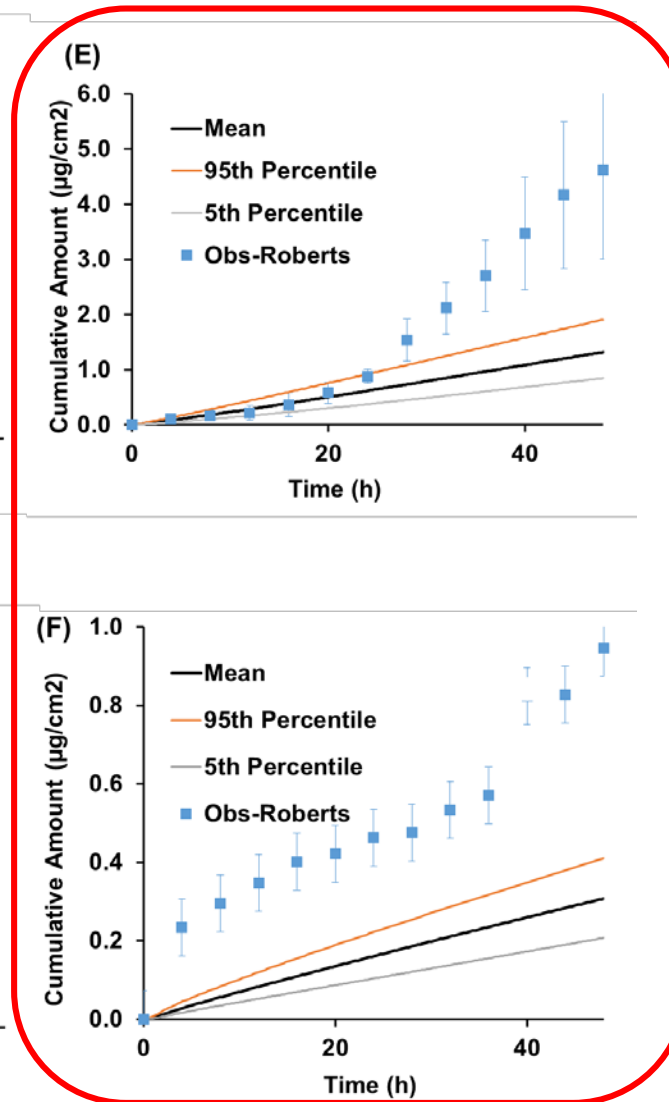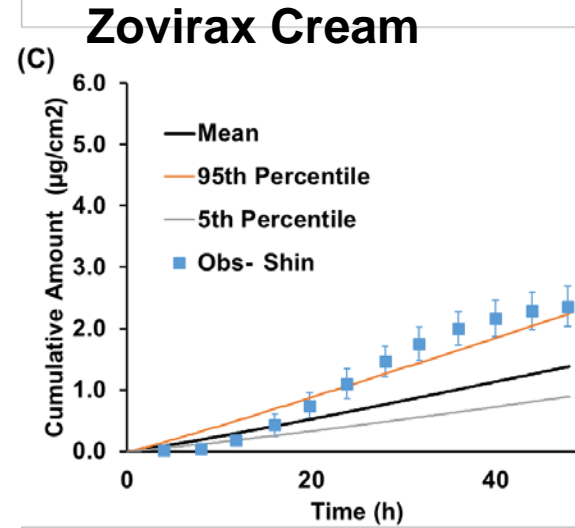
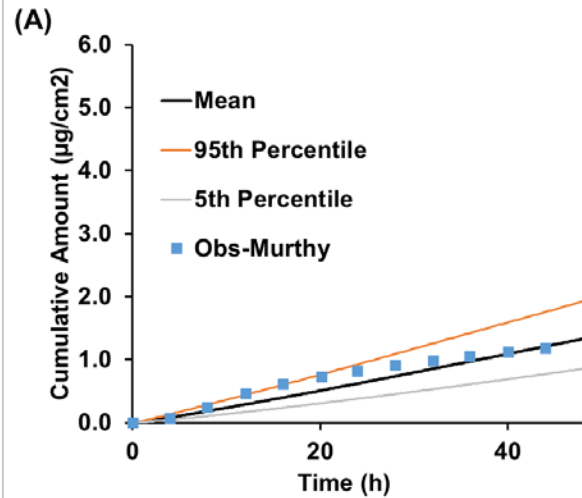a. Good understanding of Q1 and Q2 properties of both products

b. A battery of Q3 characterization data such as pH of formulation, viscosity, evaporation profile, drug solubility in continuous phase from two different laboratories.[a,c]

c. IVPT data –15 mg/cm^2 from three different laboratories.[a,b,c]

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[a]Murthy SN. et al. AAPS 2015; [b]Shin et al. Poster Presentation. AAPS 2015; [c]Roberts et al. (unpublished)

Simulation of *in vitro* skin permeation of acyclovir from Zovirax and Aciclostad

Zovirax Cream

Aciclostad Cream

Murthy SN. et al. 2015; Shin et al. Poster Presentation. AAPS 2015; Roberts et al. (unpublished)

Simulation of *in vitro* skin permeation of acyclovir from Zovirax and Aciclostad

Zovirax Cream (panels A, C, E)
Aciclostad Cream (panels B, D, F)
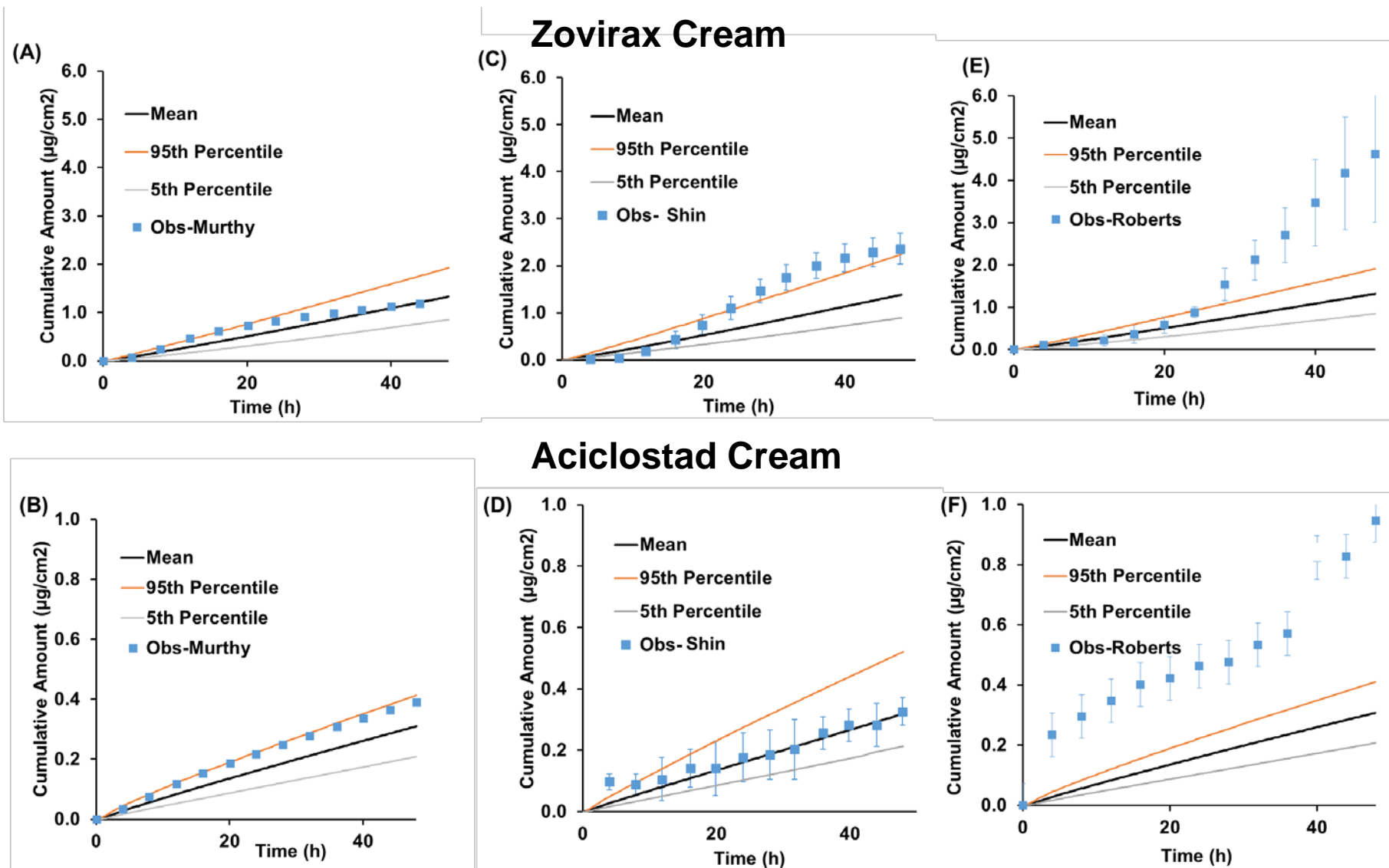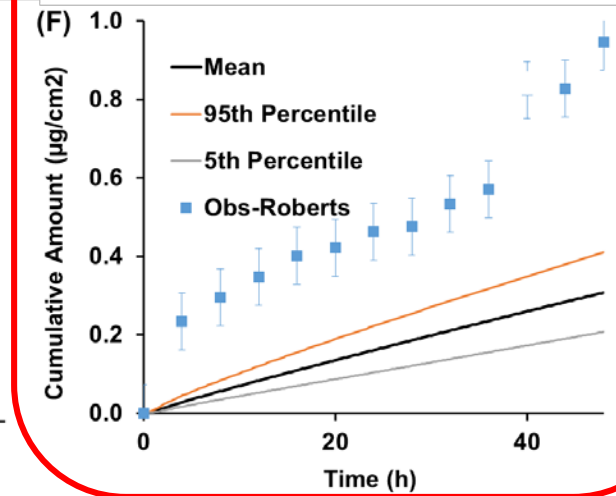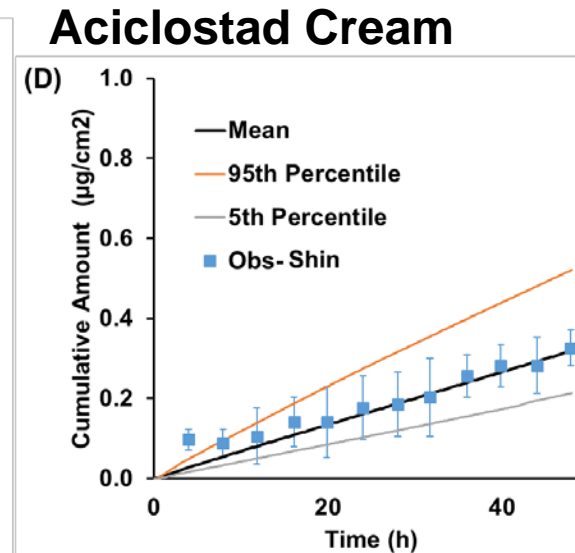
This work was presented at CRS Annual Virtual Meeting 2020 and will also be discussed as poster at upcoming AAPS PharmSci Annual Meeting 2020

Simulated cumulative amount permeated (µg/cm^2) was able to successfully **predict** the observed data from two different laboratories **bottom up**

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Murthy SN. et al. AAPS 2015; Shin et al. Poster Presentation. AAPS 2015; Roberts et al. (unpublished)

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Conclusions

- PBPK models can be immensely helpful in dermal drug development. The developed models, with limited datasets, was able to capture the *in vitro* skin permeation of drug(s) from gels and creams formulation provided these models are adequately parameterized with respect to physical and structural characterization of formulations.

- These models presents an opportunity to understand the differences between the reference and test products.

- IVIVE was demonstrated for metronidazole gel formulations – Consistent datasets in terms of dose applied and conditions of application between *in vitro* and *in vivo* scenario is needed to further understand/evaluate capability of PBPK models to predict *in vivo* exposure from *in vitro* verified models.
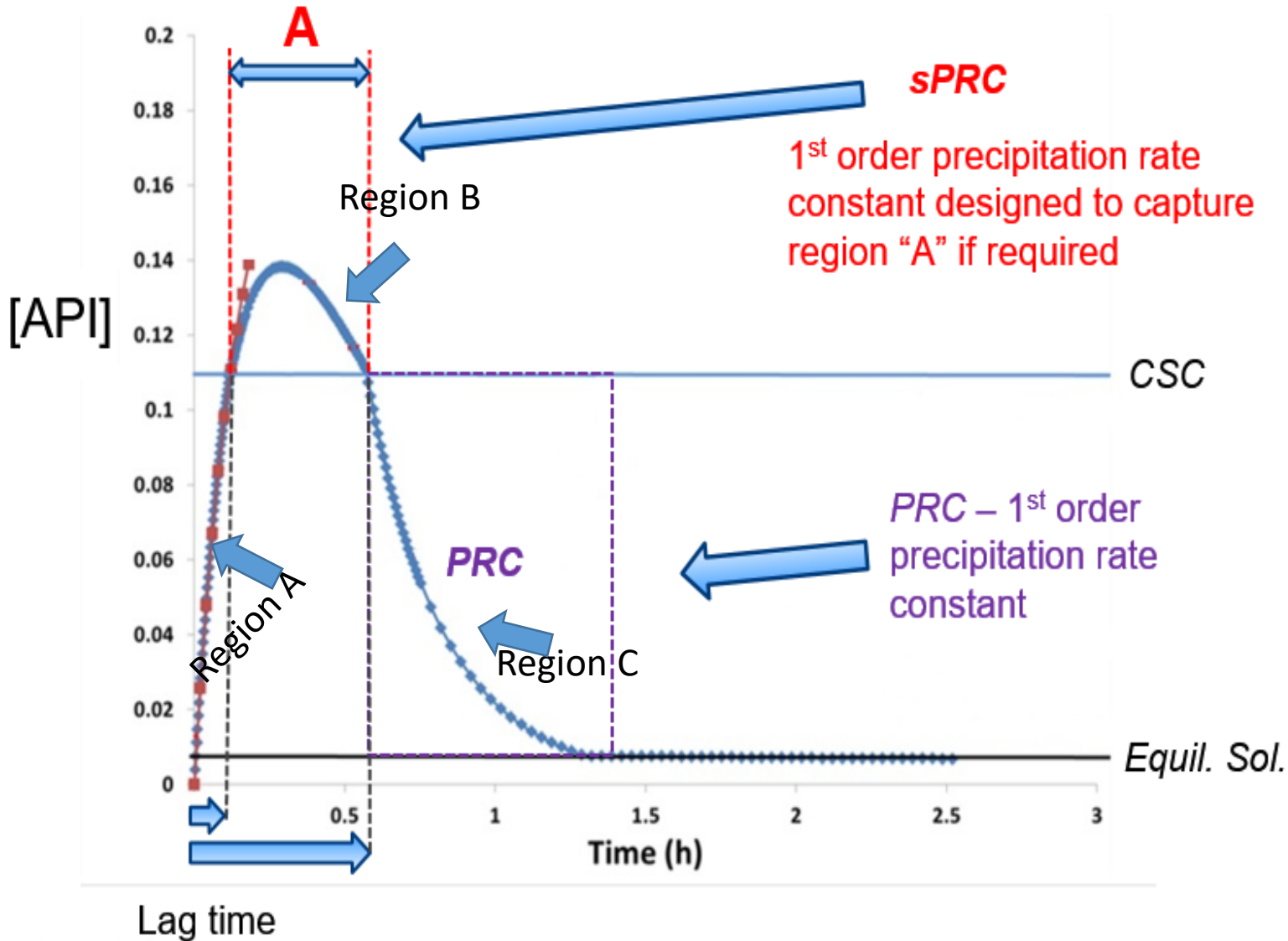
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Thank you

Email address – sumit.arora@certara.com

Back Up Slides

Empirical Supersaturation/Precipitation Model

Time Concentration Profile Receiver Compartment

Empirical Model

IF supersaturated conditions encountered THEN

Dissolution stops

Precipitation can only begin when CSC is reached

CSC **is a critical conc. at which precipitation starts**

[Drug] may continue to rise due to slow permeation of drug from skin

Supersaturated conc. may exceed *CSC* **(***CSR* **x Eq.Sol)**

CSC – Critical Supersaturation Concentration
CSR – Critical Supersaturation Ratio
PRC – Precipitation Rate Constant (1/h)
sPRC – Secondary Precipitation Rate Constant (1/h)

Metronidazole Equil.Sol = 8.7 mg/mL
CSR – 1
PRC - 11

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