# Modeling and Simulation Approaches of Topically Applied Drugs to Support Formulation Optimization, Clinical Development and Regulatory Assessment

## *Case Studies Discussion*

CRCG Workshop, September 31st, 2021

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Certara UK

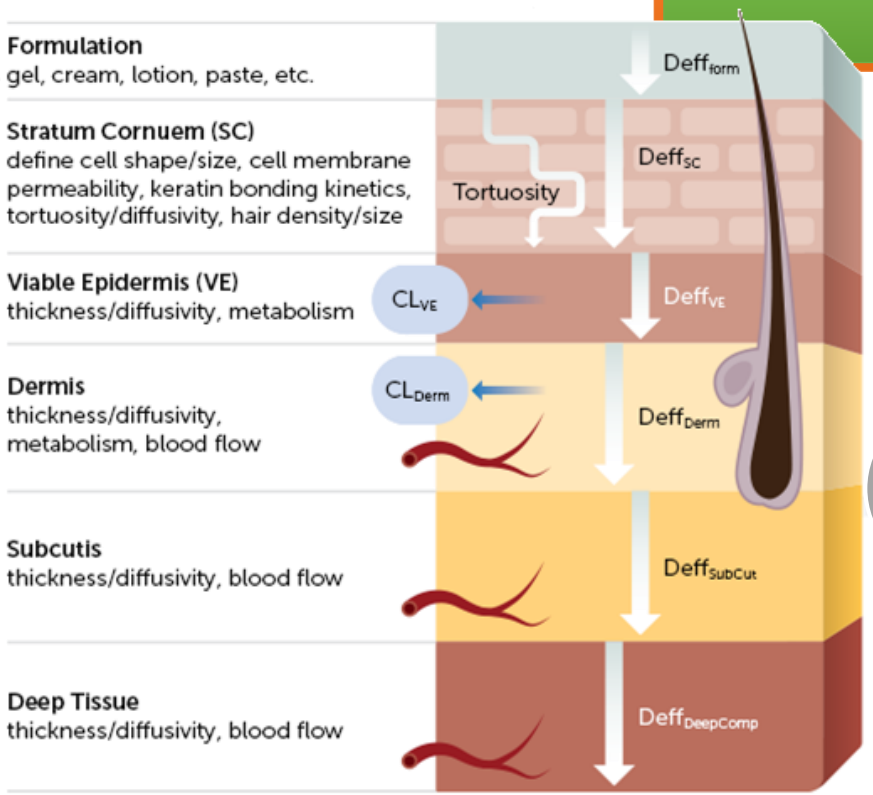
# IVIVE with the use of PBPK – dermal absorption

phys-chem + ADME/PK

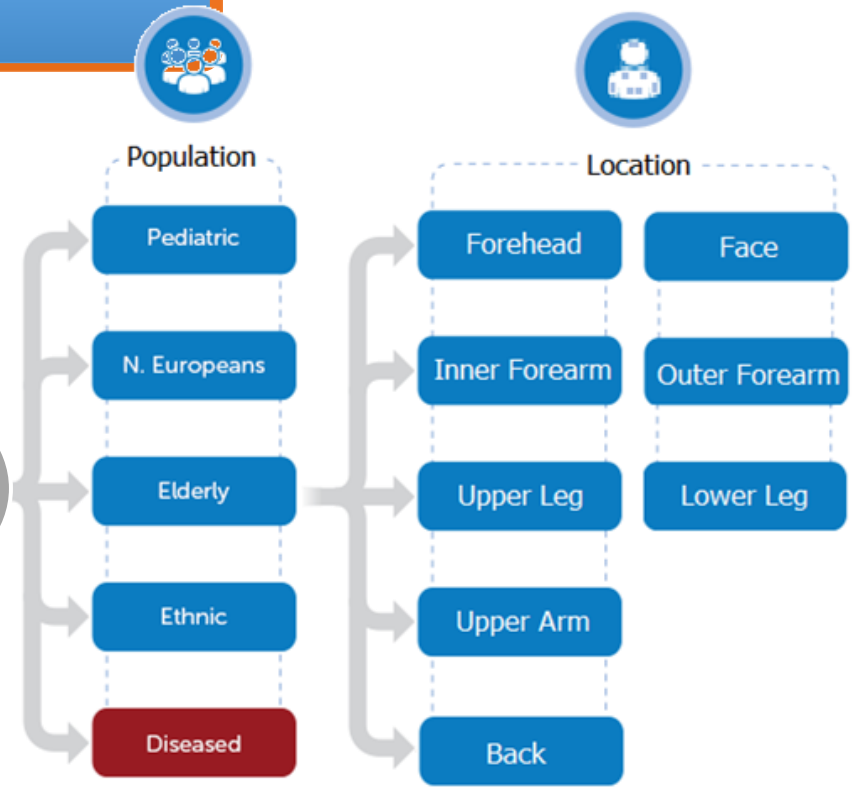
TRIAL DESIGN

DRUG DATA ⟷ SYSTEMS DATA

physiological parameters




MECHANISTIC IVIVE & PBPK/PD




Population PK (/PD)
Covariates, Parameters, Profiles





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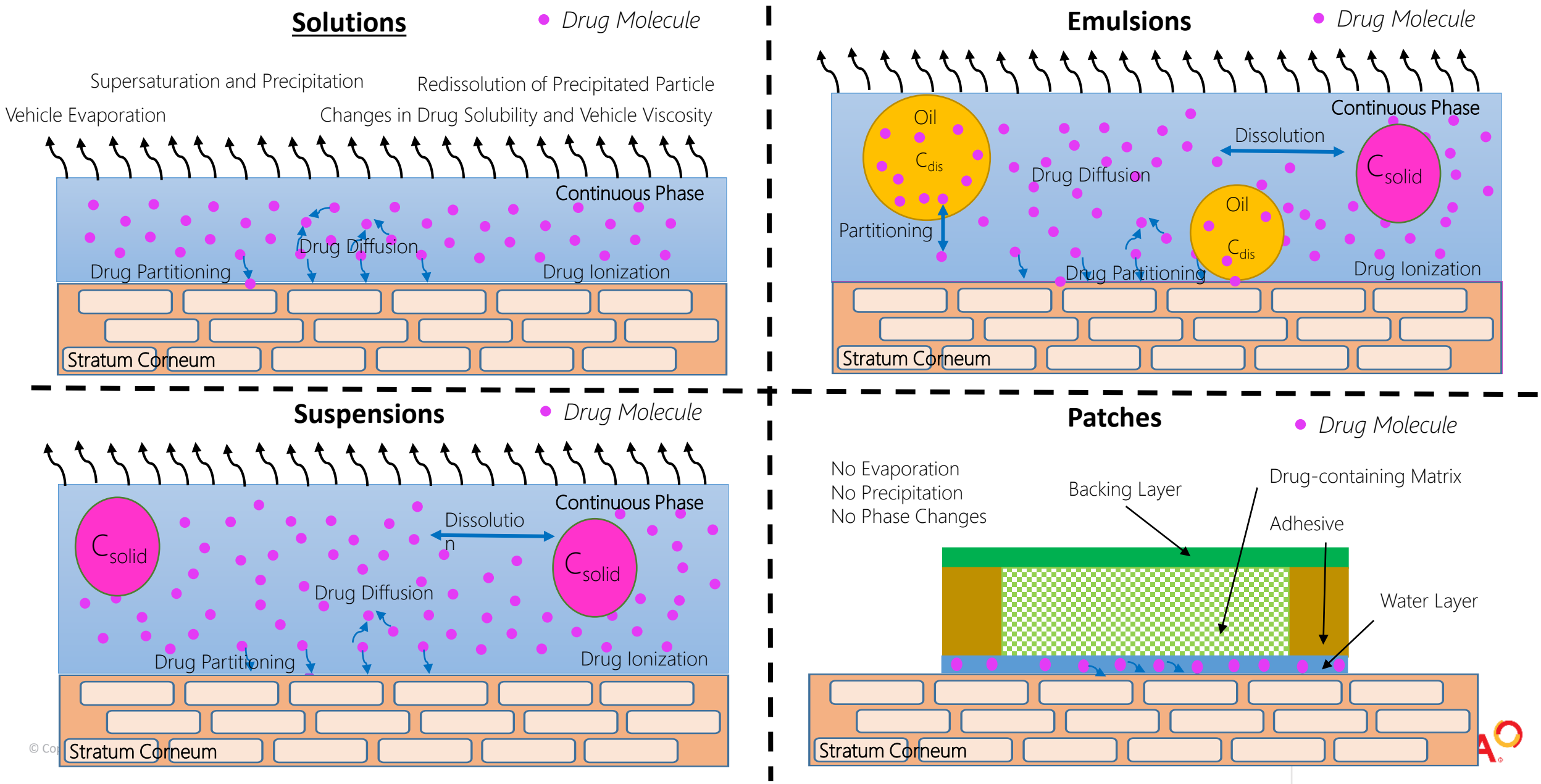
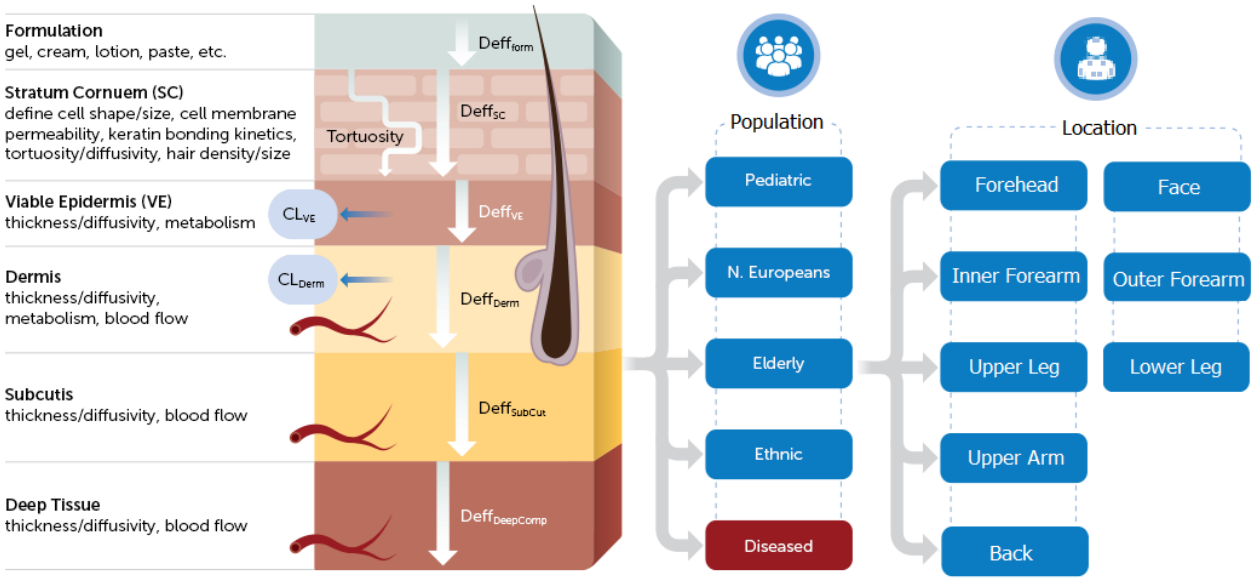
# Modeling Metamorphosis of Topical/Transdermal Formulations

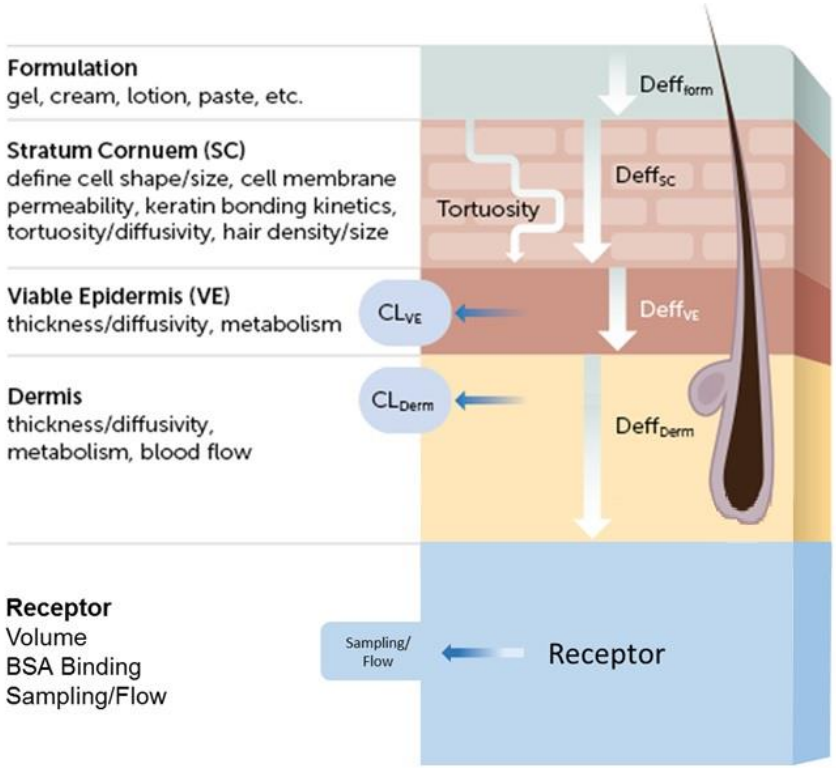


# Simcyp's Multi-Phase Multi-Layer (MPML) MechDermA Model – IVPT

## Multi-Phase Multi-Layer (MPML) MechDermA Model




## MPML MechDermA IVPT Module





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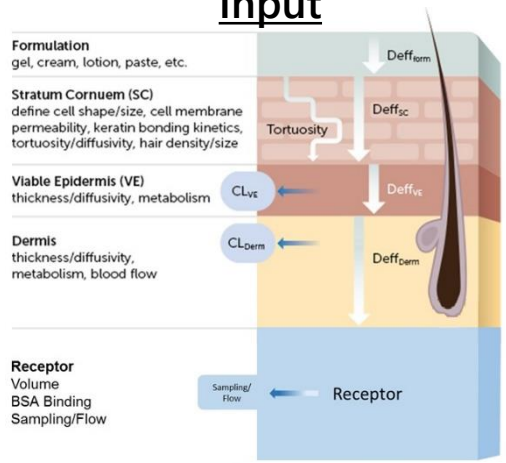
# Dermal *In Vitro – In Vivo* Extrapolation (IVIVE) with MPML MechDermA

## A tool for Virtual Bioequivalence for Complex Topical Products

### Input



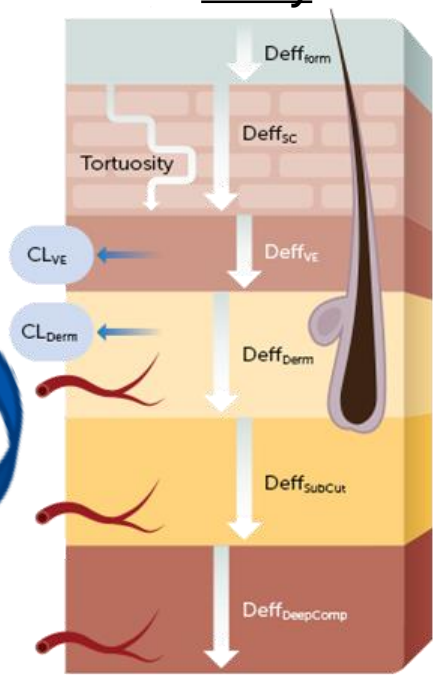

*In vitro* Release/Permeation Studies

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

- Composition
- Drug Solubility in various phases
- Drying Rate (evaporation – weight loss)
- Specific gravity
- Particle size (solid particles/droplets)
- Rheology
- Precipitation characterization
- Excipients penetration

**Confirm & Learn Approach**

### Verify

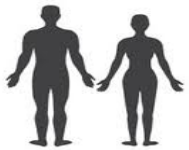



Mechanistic Dermal Absorption Model

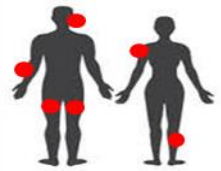
- Confirm key drug/formulation parameters: partition and diffusion coefficients
- Verify model performance with challenge formulations (different strengths, non-Q1, Q2, Q3 formulation)

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



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



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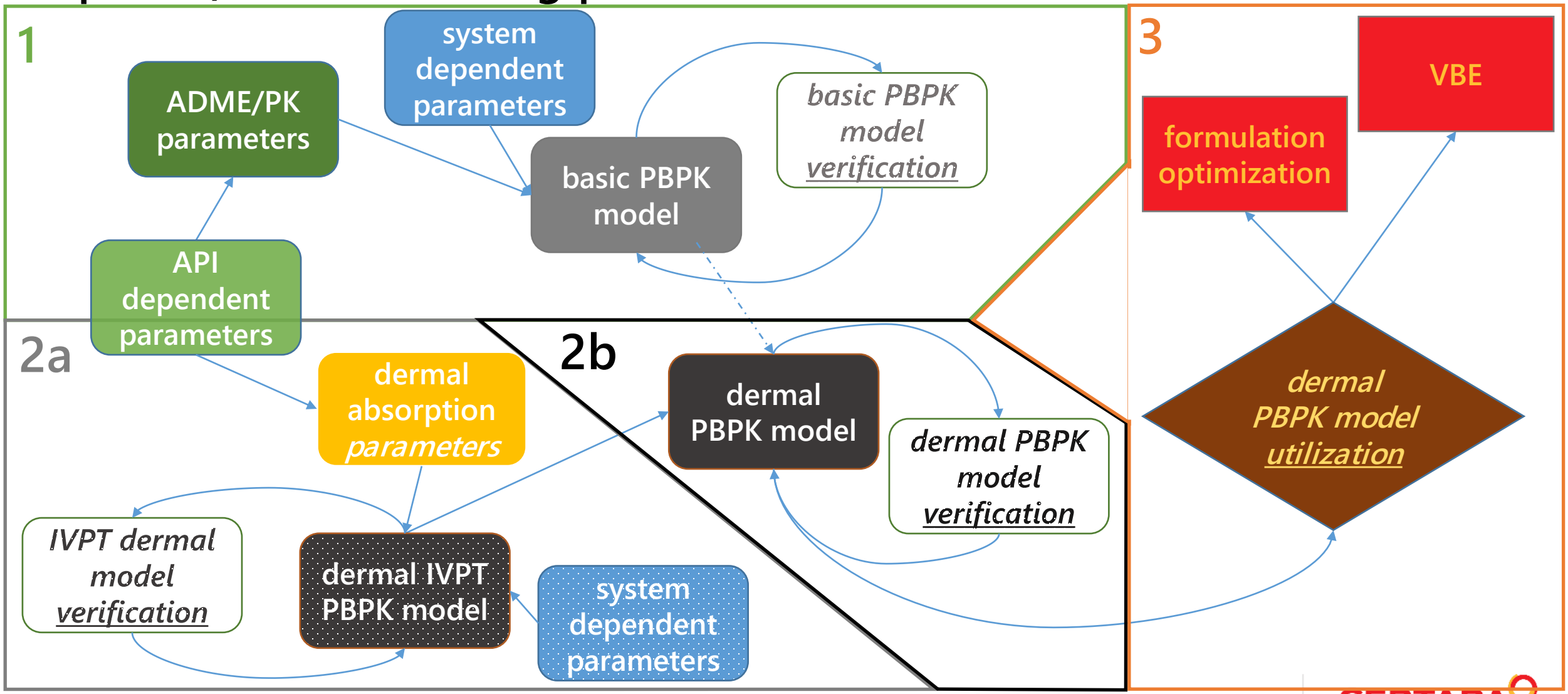
# Case study – Nimesulide

## (Simplified) model building plan





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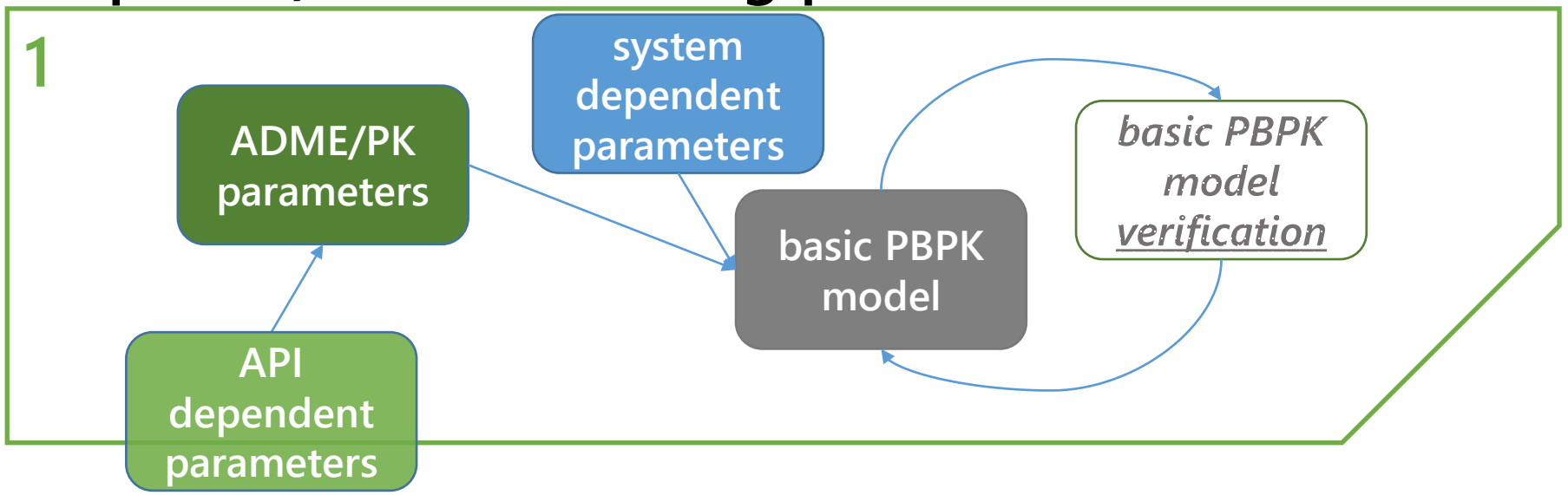
# Case study – Nimesulide

## (Simplified) model building plan




**Step 1: Development of a Nimesulide PBPK model**





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# Nimesulide compound file development

| Group | Parameter | Value [unit] | Source |
|---|---|---|---|
| P-Ch | MW | 308.3 | https://pubchem.ncbi.nlm.nih.gov/compound/4495 |
| | logP | 2.6 | https://pubchem.ncbi.nlm.nih.gov/compound/4495 |
| | compound type | monoprotic acid | https://pdfs.semanticscholar.org/27d0/6d0407aa235dc84c468c4a38055ec965a8bb.pdf |
| | pKa | 6.5 | https://www.ncbi.nlm.nih.gov/pubmed/27325447 |
| | PSA / HBD | 110 / 1 | https://pubchem.ncbi.nlm.nih.gov/compound/4495 |
| B | B/P | 0.55 | assumed |
| | fu plasma | 0.02 | https://www.drugbank.ca/drugs/DB04743 |
| D | Vss | 0.156 [L/kg] - calculated<br>Vd/F [L/kg] 0.18-0.39* | https://www.ncbi.nlm.nih.gov/pubmed/9812177 |
| M/E | Cliv | 1.6 [L/h] - calculated; CV 30% (assumed)<br>3A4 contr – negligible<br>CL/F [ml/h/kg] - 31.02-106.16 | https://www.ncbi.nlm.nih.gov/pubmed/9812177 |
| A (po) | fa<br>ka | 0.71<br>0.4 | extrapolated based on PSA/HBD |





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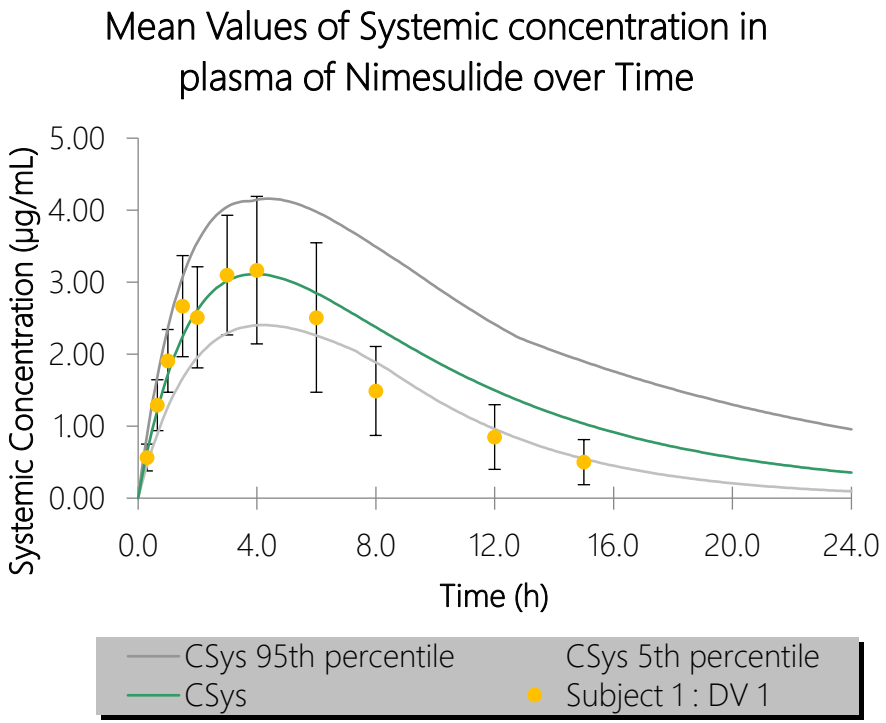
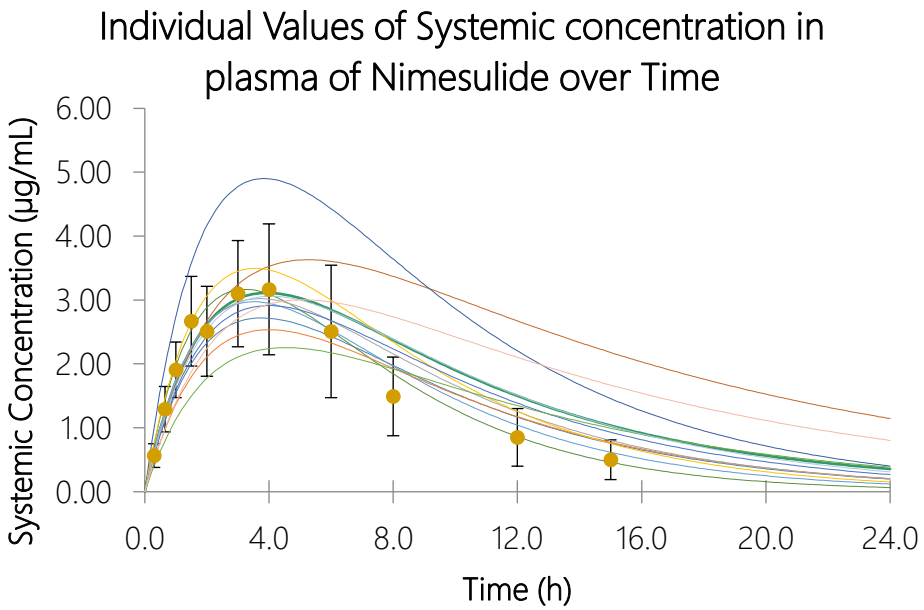
# Clinical studies – po administration

| no | source | source | dose | formulation | n | m/f | age av | age sd | age range | population | end points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Jovanovic 2005 | Vojnosanit Pregl 2005; 62(12): 887–893. | 100 mg po | tablet | 12 | 9/3 | 37.2 | 2.7 (SE) | 21-49 | HV | plasma PK |
| 2 | Erdogan 2006 | International Journal of Clinical Pharmacology and Therapeutics, Vol. 44 – No. 6/2006 (270-275) | 100 mg po BID; Administration started at least 4 days (4 – 7 days) before the last dose (1 – 2 hours before the arthroscopic knee examination) | tablet | 17 plasma 16 synovium | | | | 18-65 | patients who were scheduled to have an arthroscopic knee examination | plasma, synovial fluid |
| 3 | Gandini 1991 | Il Farmaco, 46 (9), 1071-1079, 1991 | 200 mg single dose<br><br>100 mg twice daily for 7 days | tablet | 12 | 6/6 | 29 | | 25-34 | HV | Plasma PK |

# Compound file verification

| no | source | source | dose | formulation | n | m/f | age av | age sd | age range | population | end points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Jovanovic 2005 | Vojnosanit Pregl 2005; 62(12): 887–893. | 100 mg po | tablet | 12 | 9/3 | 37.2 | 2.7 (SE) | 21-49 | HV | plasma PK |

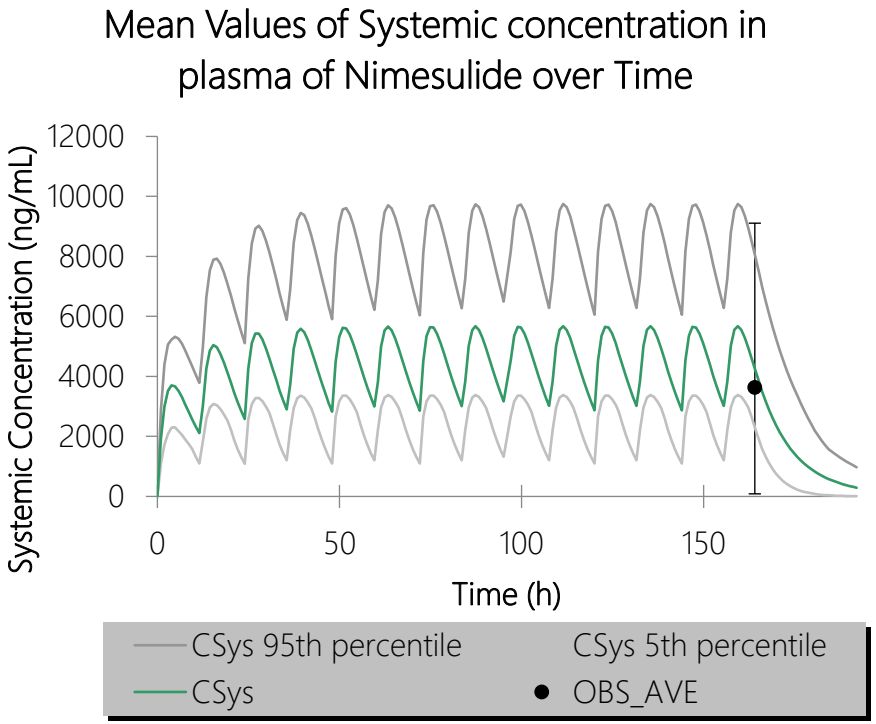


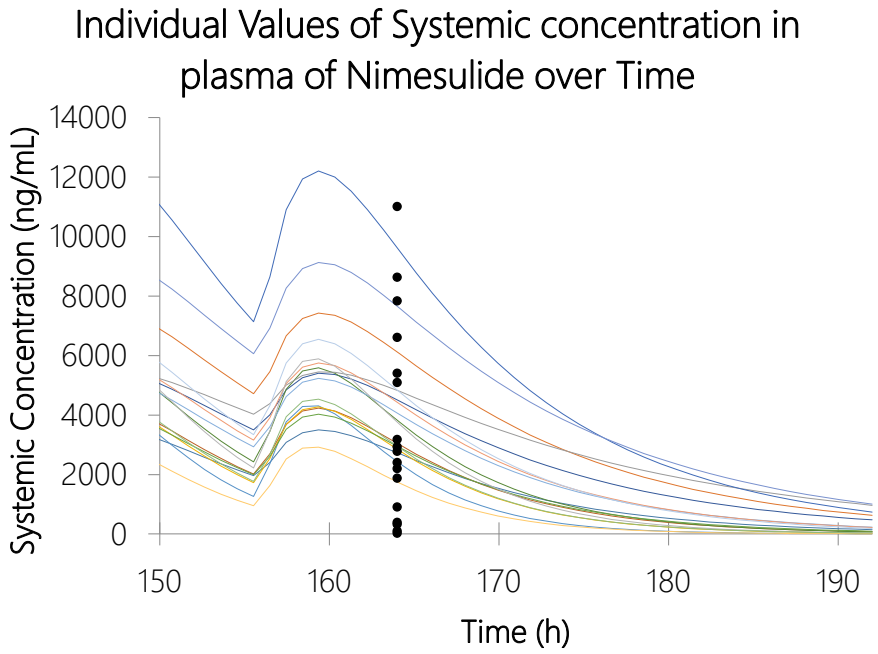




Cmax underpredicted yet well within 2 fold; the calculated Cliv from this study was used for all other simulations

# Compound file verification

| no | source | source | dose | formulation | n | m/f | age av | age sd | age range | population | end points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | Erdogan 2006 | International Journal of Clinical Pharmacology and Therapeutics, Vol. 44 – No. 6/2006 (270-275) | 100 mg po BID; Administration started at least 4 days (4 – 7 days) before the last dose (1 – 2 hours before the arthroscopic knee examination) | tablet | 17 plasma 16 synovium | | | | 18-65 | patients who were scheduled to have an arthroscopic knee examination | plasma, synovial fluid |

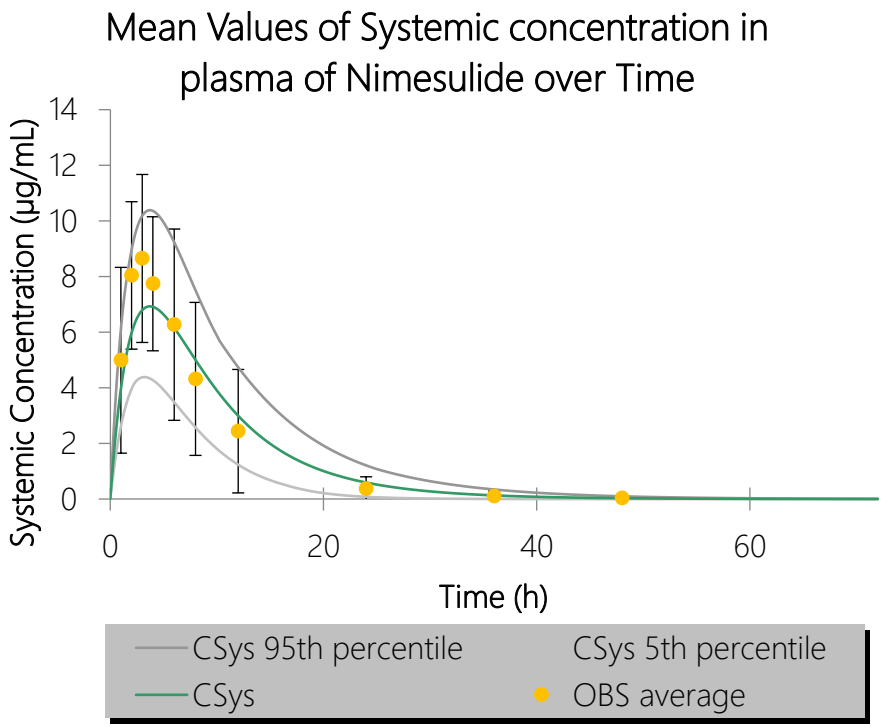


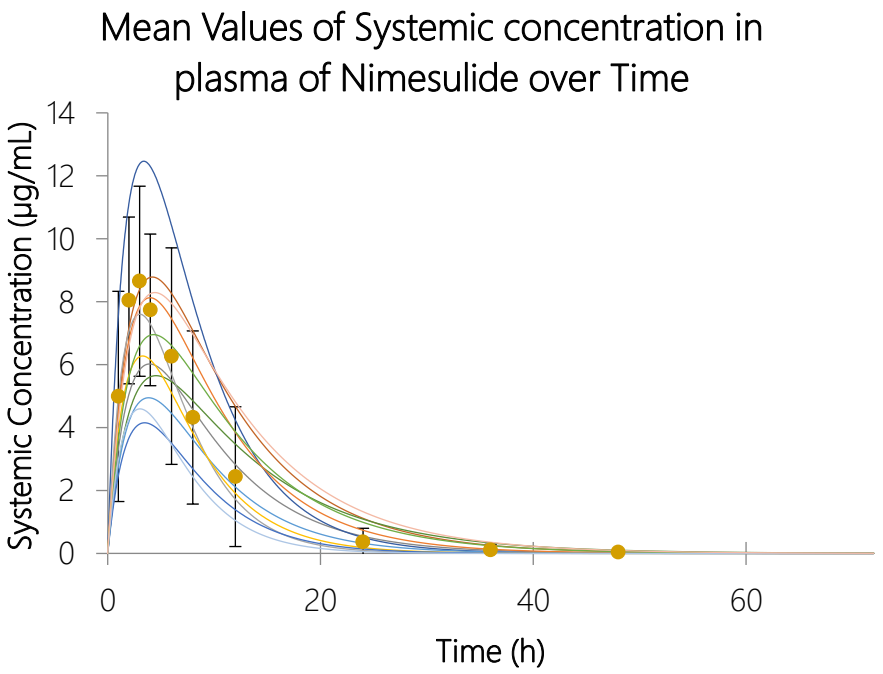



# Compound file verification

| no | source | source | dose | formulation | n | m/f | age av | age sd | age range | population | end points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | Gandini 1991 | Il Farmaco, 46 (9), 1071-1079, 1991 | 200 mg single dose<br>100 mg twice daily for 7 days | tablet | 12 | 6/6 | 29 | | 25-34 | HV | Plasma PK |

200 mg single dose

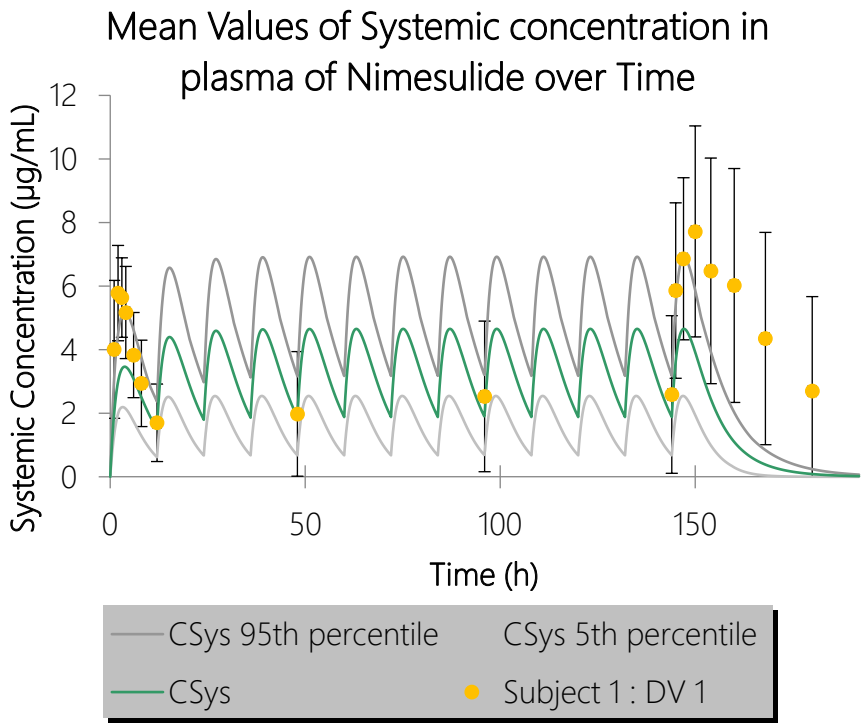


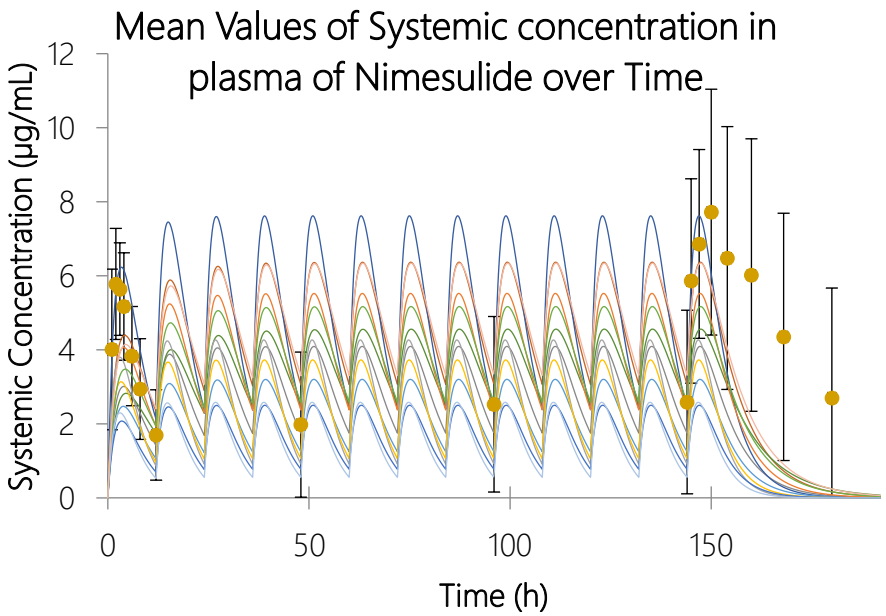



# Compound file verification

| no | source | source | dose | formulation | n | m/f | age av | age sd | age range | population | end points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | Gandini 1991 | Il Farmaco, 46 (9), 1071-1079, 1991 | 200 mg single dose<br>100 mg twice daily for 7 days | tablet | 12 | 6/6 | 29 | | 25-34 | HV | Plasma PK |

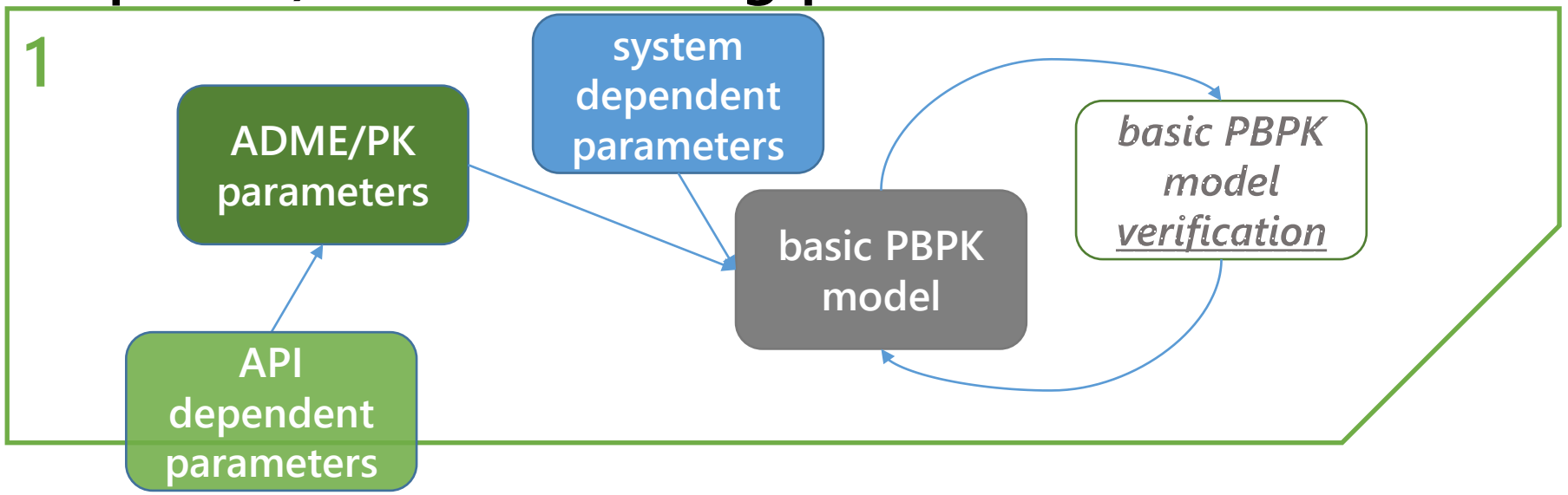
100 mg BID dose 7 days



# Case study – Nimesulide

## (Simplified) model building plan




**Step 1: Development of a Nimesulide PBPK model**

**The developed Nimesulide PBPK model described Nimesulide systemic disposition well**





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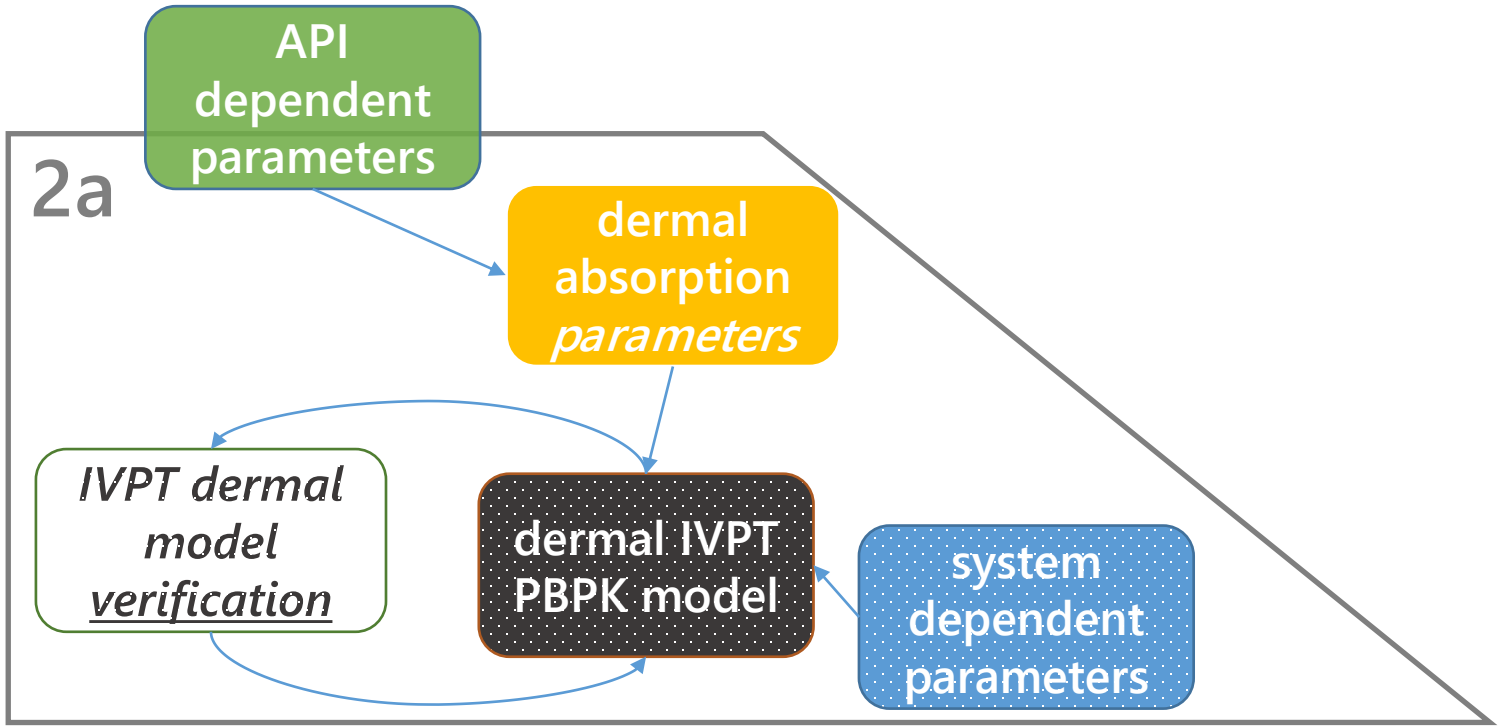
# Case study – Nimesulide

## (Simplified) model building plan

## Step 2a: Development of a Nimesulide dermal IVPT PBPK model





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# Dermal compound and formulation file development

2a

| Group | Parameter | Value [unit] | Source |
|---|---|---|---|
| A | $Kp_{sc\_lip:water}$ | 72.87 | predicted – Hansen 2013 |
| | $Kp_{sc\ lip:ve}$ | 6.17 | predicted – Chen 2015 |
| | $Kp_{dermis:ve}$ | 0.92 | predicted – Chen 2015 |
| | $Kp_{sebum:water}$ | 796.97 | predicted – Valiveti 2008 |
| | $Kp_{dermis:blood}$ | 2.37 | predicted – Shatkin&Brown 1991 |
| | $Kp_{sebum:dermis}$ | 0.015 | calculated – $Kp_{lip:vehicle}/Kp_{sebum:vehicle}$ |
| | $D_{sc\_lip}$ | 0.00045 [$cm^2/h$] | predicted – Johnson 1996 |
| | $D_{ve}$ | 0.00036 [$cm^2/h$] | predicted – Chen 2015 |
| | $D_{dermis}$ | 0.00036 [$cm^2/h$] | predicted – Chen 2015 |
| | $D_{sebum}$ | 0.00057 [$cm^2/h$] | predicted – Johnson 1996 |
| | fu sc | 0.092 | predicted – Polak 2016 |
| | fu muscle | 1 | assumed |
| | fu subcutis | 1 | assumed |
| | $f_{ni,\ corneocytes}$ | 0.33 | calculated (H-H) |
| | $P_{corn}$ | 1E-05 [cm/s] | assumed |

F

*Table 1 – Solubility of nimesulide in various solvents*

| Solvent(s) | | | Solubility mg/ml | Dielectric Constant (ε) of Solvent(s) |
|---|---|---|---|---|
| Water | | | 0.014 | 78.36 |
| Glycerol | | | 0.218 | 42.5 |
| Methanol | | | 8.812 | 32.63 |
| Ethanol | | | 3.320 | 24.3 |
| Butanol | | | 2.120 | 17.1 |
| n-Octanol | | | 0.970 | 9.72 |
| Ethylene Glycol | | | 0.510 | 37.7 |
| Propylene Glycol | | | 1.760 | 32.0 |
| Polyethylene Glycol (PEG) 400 | | | 63.120 | 12.4 |
| Glycerol | 80% + Ethanol | 20% | 0.691 | 38.86 |
| | 60% | 40% | 1.693 | 35.22 |
| | 10% | 90% | 4.040 | 26.12 |
| PEG 400 | 80% | 20% | 9.900 | 21.92 |
| | 60% | 40% | 24.640 | 19.54 |
| | 90% | 10% | 65.600 | 13.59 |
| Water | 80% | 20% | 0.101 | 67.55 |
| | 60% | 40% | 0.125 | 56.74 |
| | 90% | 10% | 3.320 | 24.30 |
| Glycine-NaOH buffer | pH | 7 | 0.034 | – |
| | | 7.9 | 0.081 | – |
| | | 8.84 | 0.807 | – |
| | | 9.42 | 3.886 | – |
| | | 9.52 | 6.914 | – |
| | | 10.17 | 34.639 | – |

*Partition coefficient in n-octanol/water = 1.788, pKa = 6.4–6.8 [18, 30–32]. The pKa varies according to different solvents/system. From: Seedher & Bhatia (2003) [34].*





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# Dermal IVPT studies

2a

| no | source | source | dose | formulation | n | m/f | endpoints | skin type | type | area [cm2] | occlusion | addiitonal settings |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Dajal 2002 | Drug Dev Ind Pharm (2002) 28(3) | Nimulide 1%<br>Orthobid 1%<br>Nisegel 1% | gel | 1(7-14) | 0/1 | receptor fluid | cryopreserved<br>dermatomed | flow through | 0.636 | yes | |
| 2 | Pereira 2017 | Current Drug Delivery, 2017, 14, 516-520 | Nimesulide 2% | gel | 1(6) | 0/1 | S.C. total amount<br>VE+D total amount<br>receptor fluid (BLQ) | cryopreserved<br>full thickness | static | 1.86 | yes | |





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# Dermal IVPT studies

2a

| no | source | source | dose | formulation | n | m/f | endpoints | skin type | type | area [cm2] | occlusion | addiitonal settings |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
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Drug Development and Industrial Pharmacy, 28(3), 297–304 (2002)

## Comparison of the Transdermal Absorption of Nimesulide from Three Commercially Available Gel Formulations

Pankaj Dayal,[1] Narayanasamy Kanikkannan,[1] Amarjit Singh,[2] and Mandip Singh[1,*]

### Skin Permeation Studies

All epidermal preparations were mounted onto an automated, temperature-controlled, continuous flow-through diffusion cell system maintained at 32°C (PermeGear, Riegelsville, PA). An infinite dose of nimesulide gel (~300 mg) was applied to the skin over a 0.636 $cm^2$ area. A phosphate buffer solution (pH 7.4) was passed through the receptor chamber at a controlled rate using an Ismatec IP multi-channel peristaltic pump. Samples were collected at 1, 2, 4, 6, 8, 12, 18, and 24 hr using a retriever IV fraction collector (Gilson, Inc., Middleton, WI) operated by an index controller (PermeGear, Riegelsville, PA). The samples were analyzed by HPLC.

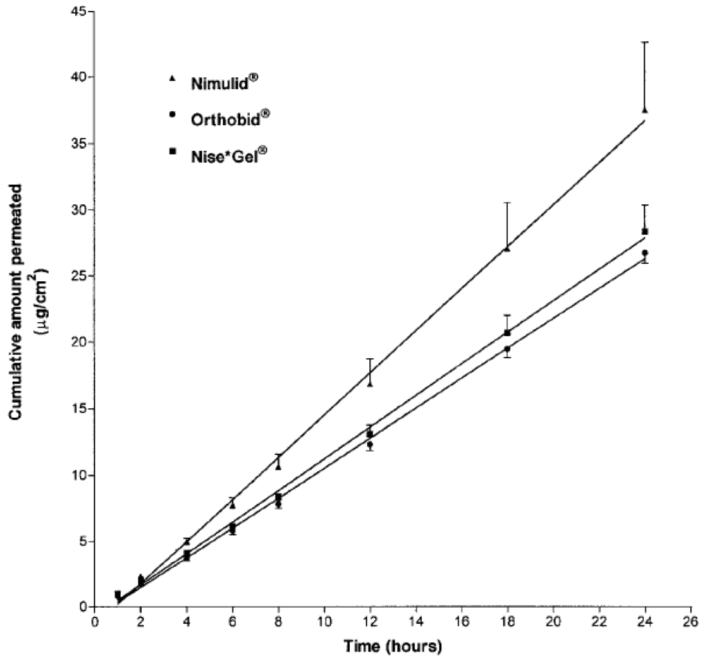


Figure 3. Permeation profiles of nimesulide from commercial gels across human skin. Each data point represents the mean and SD ($n$=7–14).

## RU2593777C1

The drug Nise ® gel for external use 1% contains the following components, mg / g:

| Components | Mg / g |
|---|---|
| Nimesulide | 10.0 |
| N-methyl-2-pyrrolidone | 250,0 |
| Propylene glycol | 100.0 |
| Macrogol | 315.5 |
| Isopropanol | 100.0 |
| Purified water | 200,0 |
| Carbomer 940 | 20,0 |
| Butylhydroxyanisole | 0.2 |
| Thiomersal | 0.1 |
| Potassium dihydrogen phosphate | 0.2 |
| Fragrance (Narcissus-938) | 4.0 |



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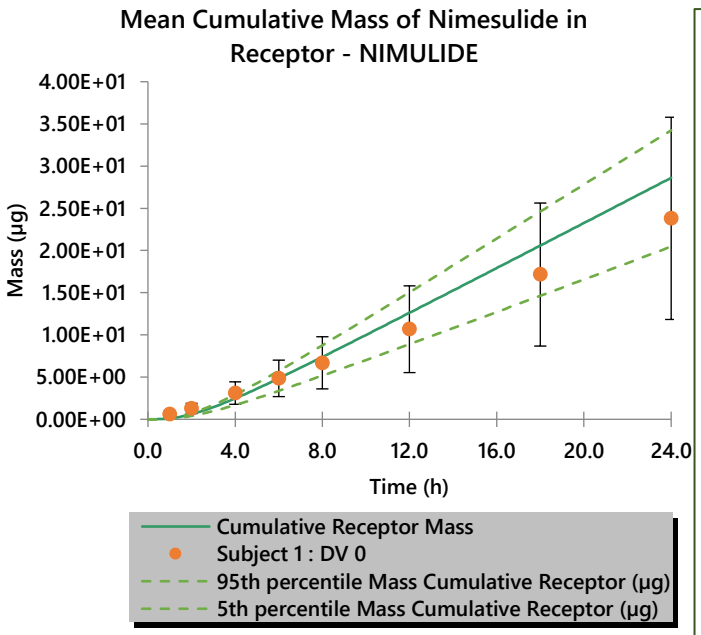
# Dermal formulation understanding/development/optimization

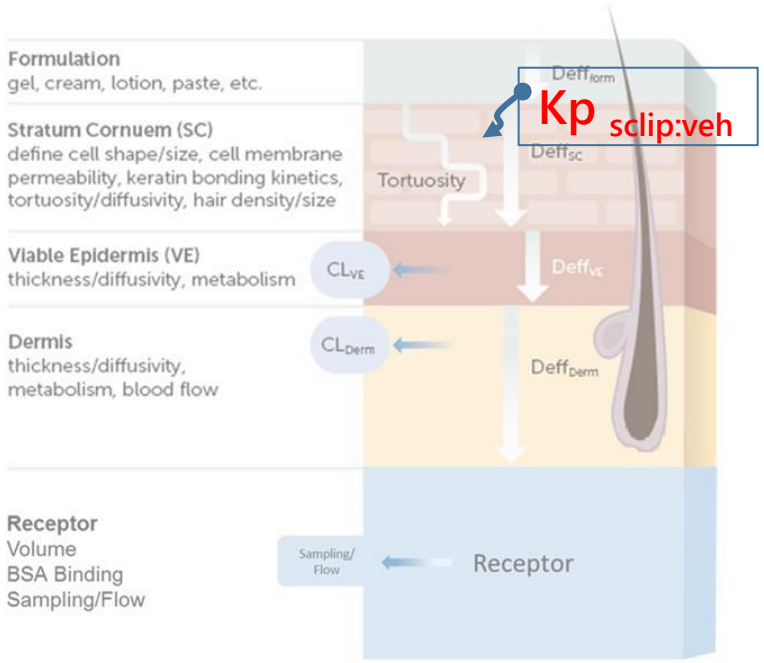
2a

## INTERPLAY BETWEEN

### DRUG/FORMULATION DATA + SYSTEMS DATA




- Q1 based
- Sensitivity Analysis
  - measurable parameters – preferrable
  - to help understand excipients effect
  - to allow accounting for various formulations




abdomen skin sex specific differences

M/F optimization give different results --> needs to be considered!





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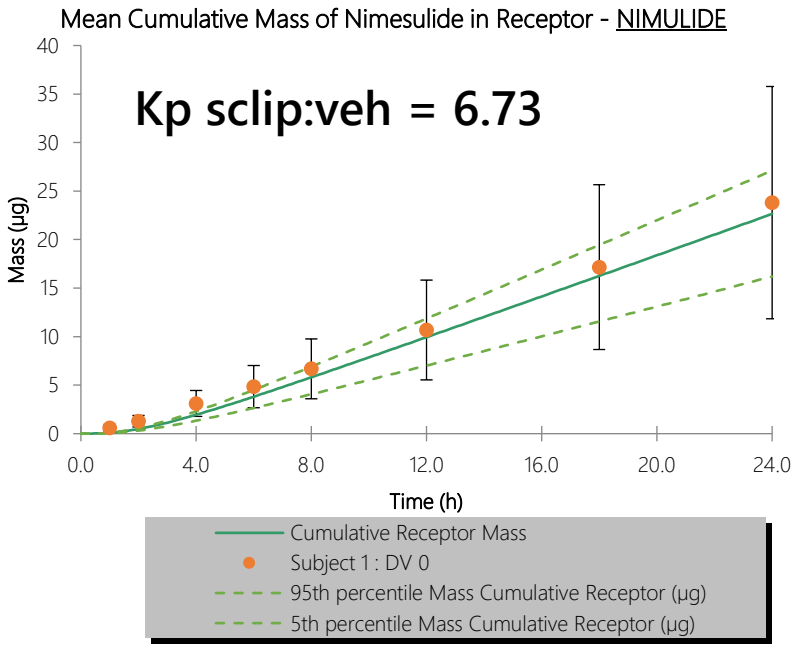
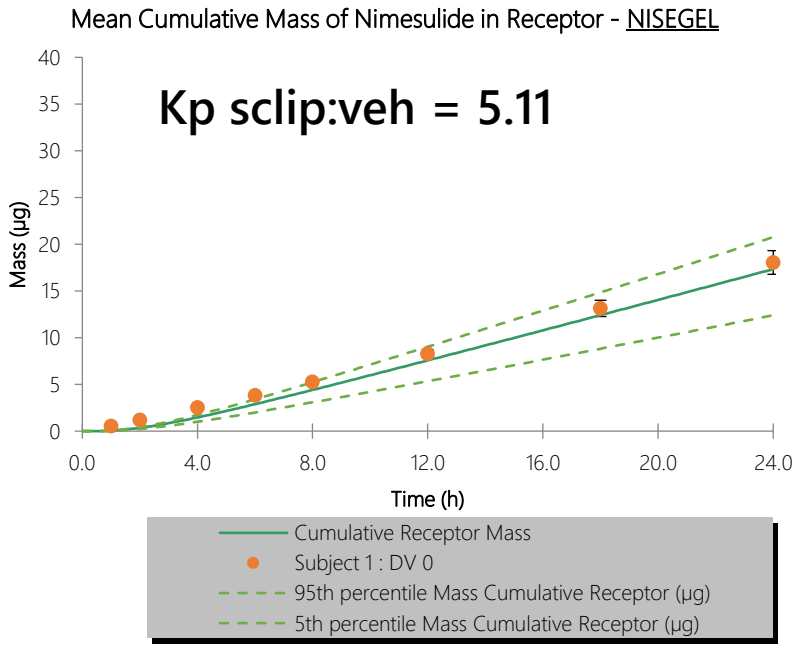
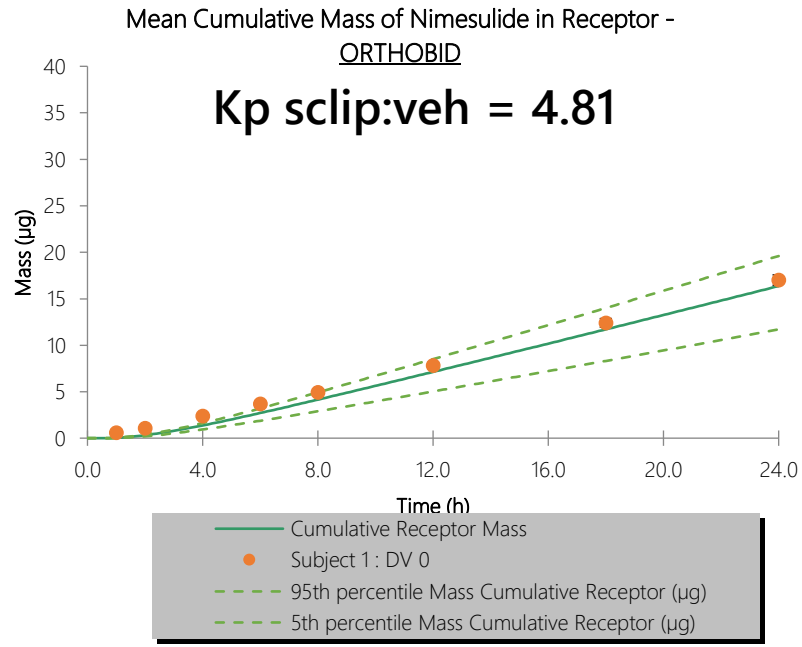
# Dermal formulation understanding/development/optimization

2a

| no | source | source | dose | formulation | n | m/f | endpoints | skin type | type | area [cm2] | occlusion | addiitonal settings |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Dajal 2002 | Drug Dev Ind Pharm (2002) 28(3) | Nimulide 1%<br>Orthobid 1%<br>Nisegel 1% | gel | 1(7-14) | 0/1 | receptor fluid | cryopreserved<br>dermatomed | flow through | 0.636 | yes | |




**Vehicle:water solubility ratio = 10.8**

**Vehicle:water solubility ratio = 14.26**

**Vehicle:water solubility ratio = 15.15**





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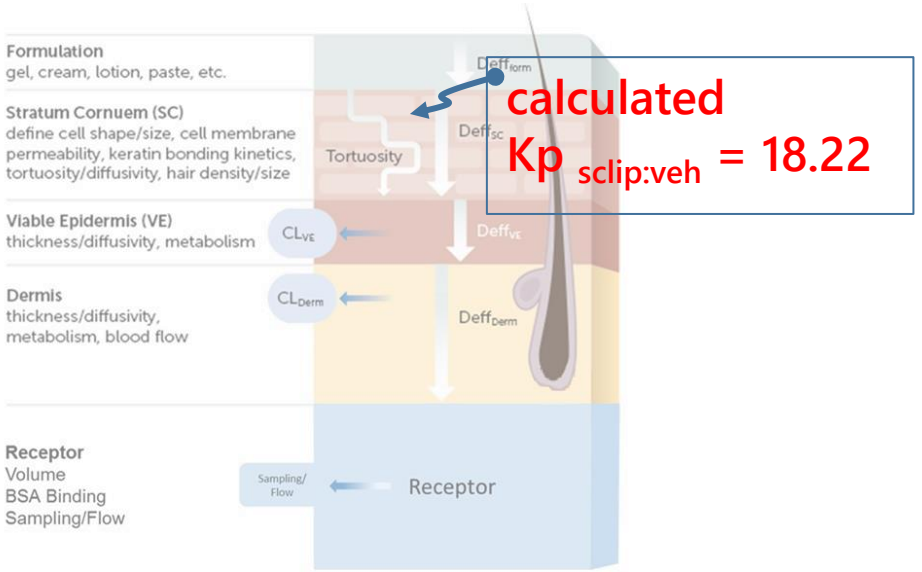
# Dermal formulation understanding/development/optimization

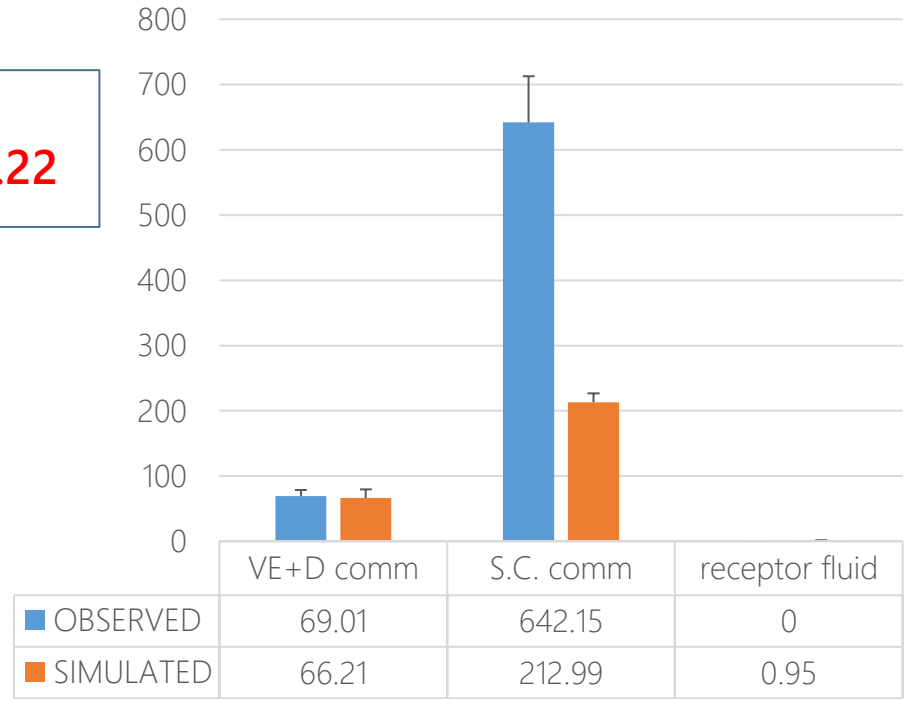
2a

| no | source | source | dose | formulation | n | m/f | endpoints | skin type | type | area [cm2] | occlusion | addiitonal settings |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | Pereira 2017 | Current Drug Delivery, 2017, 14, 516-520 | Nimesulide 2% | gel | 1(6) | 0/1 | S.C. total amount<br>VE+D total amount<br>receptor fluid (BLQ) | cryopreserved<br>full thickness | static | 1.86 | yes | |

| Product | Excipients |
|---|---|
| Commercial Nimesulide (gel 2%) | Propylene glycol, isopropyl alcohol, castor oil, carbomer, trolamine, phenoxyethanol, parabens and water. |

**NO ethanol**
**-->**
**assumed**
**vehicle:water solubility ratio = 4**




| | VE+D comm | S.C. comm | receptor fluid |
|---|---|---|---|
| OBSERVED | 69.01 | 642.15 | 0 |
| SIMULATED | 66.21 | 212.99 | 0.95 |





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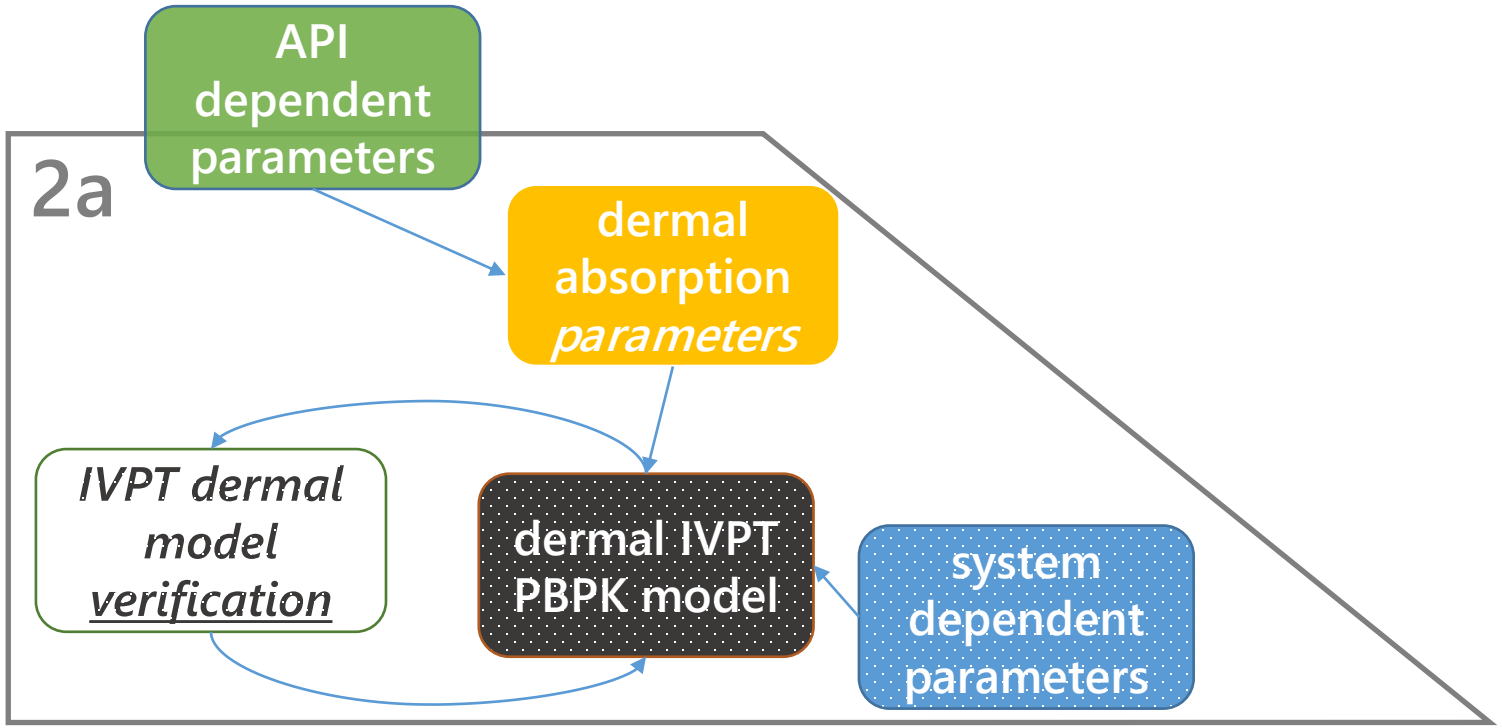
# Case study – Nimesulide

## (Simplified) model building plan

### Step 2a: Development of a Nimesulide dermal IVPT PBPK model

### The developed IVPT PBPK model allows for formulation differentiation





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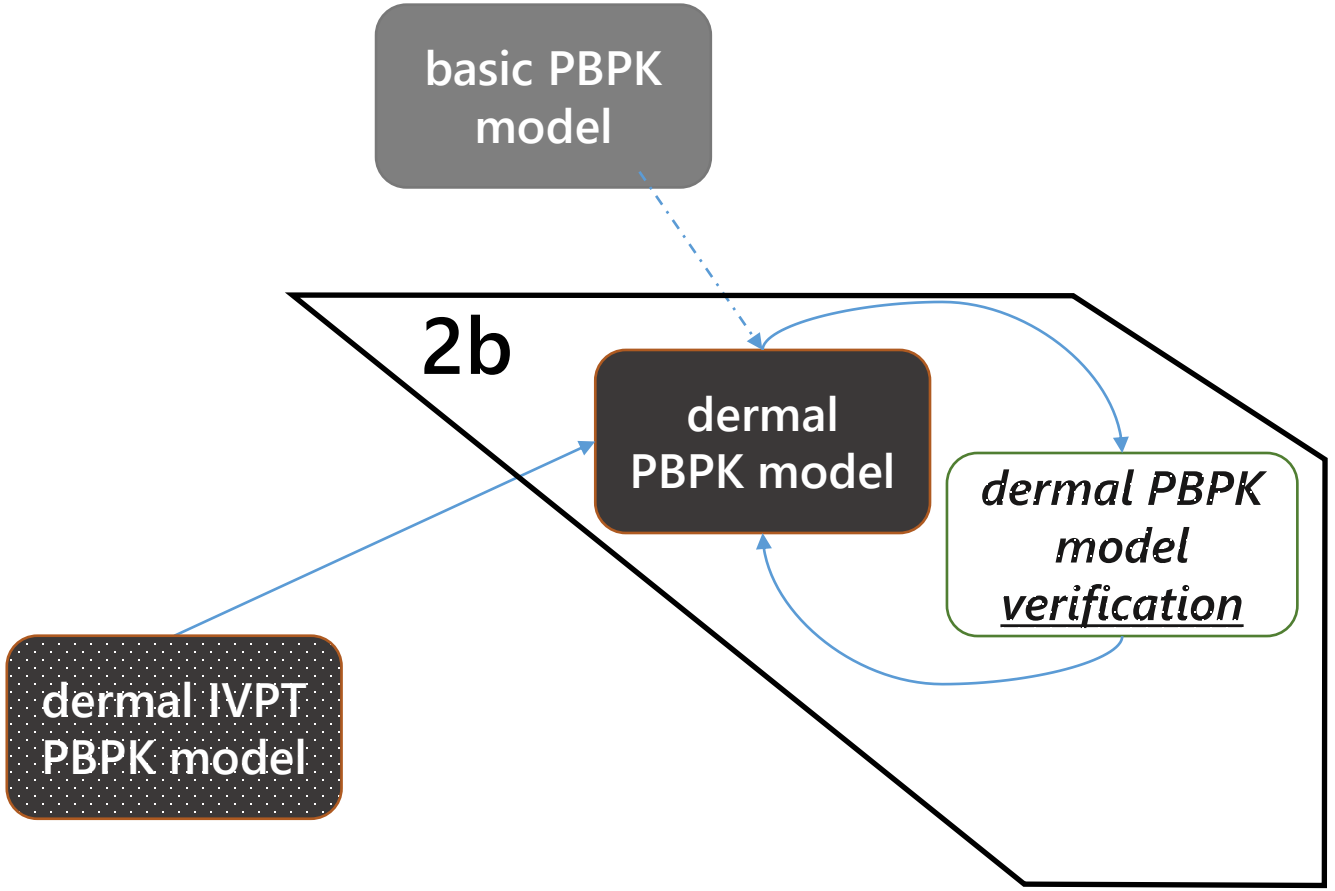
# Case study – Nimesulide

## (Simplified) model building plan

## Step 2b: Development of a Nimesulide dermal in vivo PBPK model





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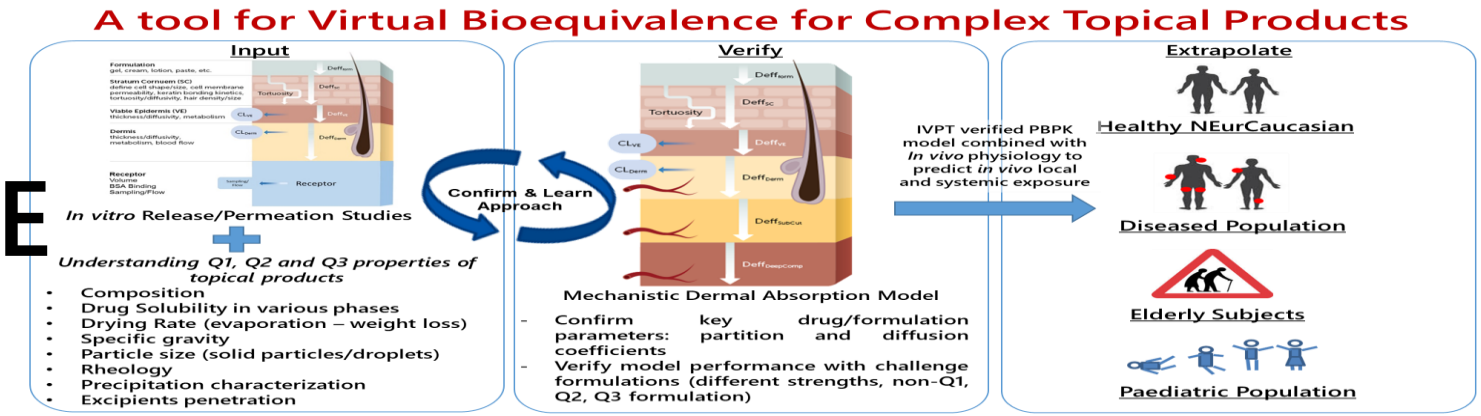
# Clinical studies – dermal administration / IVIVE and model verification 2b

| no | source | source | dose | formulation | n | m/f | age av | age sd | age range | population | end points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Sengupta 1998 | Eur J Clin Pharmacol (1998) 54: 541-547 | Nimesulide gel 1% w/w as Nimulid transgelTM (dose of 10 mg of pure drug) were applied as a thin uniform film on the right forearm (12 cm x 8 cm) | gel (water-soluble gel base, alcohol content 66% v/v) | 12 | 12/0 | 20.5 | | 18-23 | HV | PK plasma |
| 2 | Erdogan 2006 | International Journal of Clinical Pharmacology and Therapeutics, Vol. 44 – No. 6/2006 (270-275) | 1-week administration of nimesulide gel, applied on the knee 3 times a day and the amount was described as "the size of a single lentil" of gel (approximately 0,4 mg/10 $cm^2$) to be applied on the knee skin 3 times a day and to be rubbed for no longer than 1 minute | gel (Sulidin) | 17 plasma 13 SF | | | | 18-65 | patients who were scheduled to have an arthroscopic knee examination | plasma, synovial fluid |

IVIVE





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# Clinical studies – dermal administration / IVIVE and model verification 2b

| no | source | source | dose | formulation | n | m/f | age av | age sd | age range | population | end points |
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| 1 | Sengupta 1998 | Eur J Clin Pharmacol (1998) 54: 541-547 | Nimesulide gel 1% w/w as Nimulid transgelTM (dose of 10 mg of pure drug) were applied as a thin uniform film on the right forearm (12 cm x 8 cm) | gel (water-soluble gel base, alcohol content 66% v/v) | 12 | 12/0 | 20.5 | | 18-23 | HV | PK plasma |

**Nimulid gel**

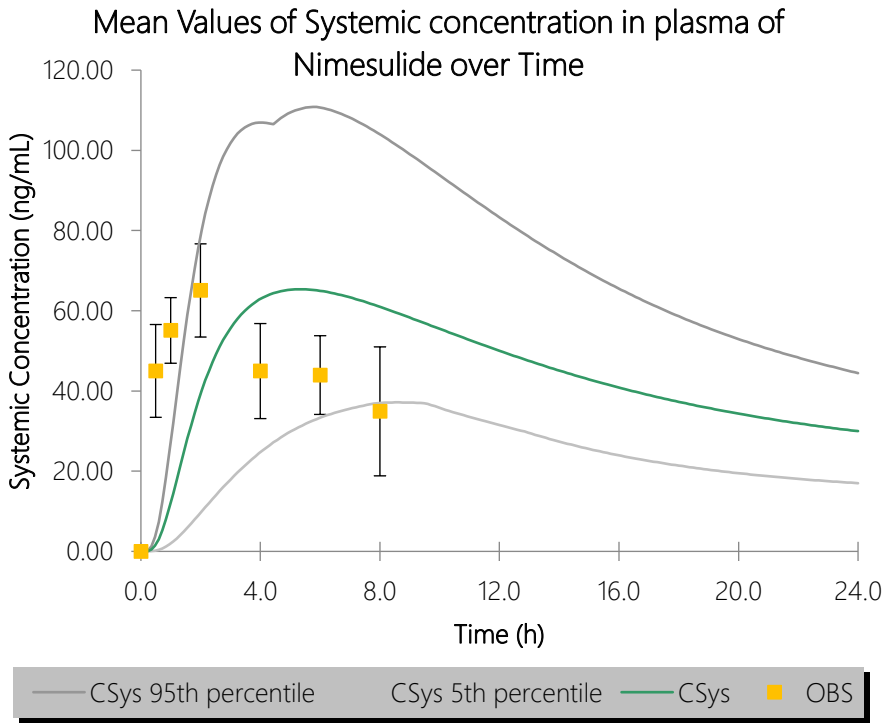
↓

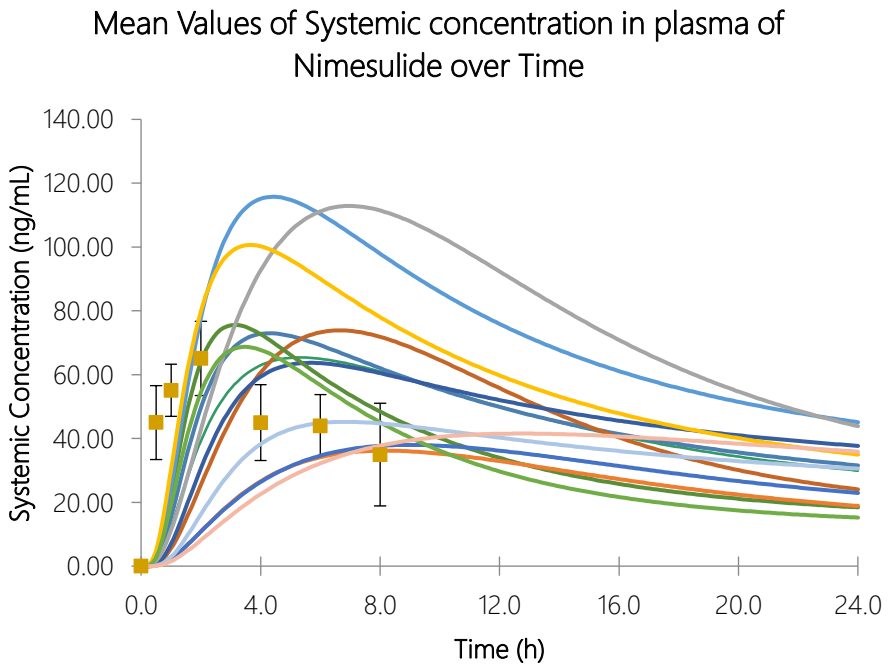
**Vehicle:water solubility ratio = 10.8**

↓

**Kp sclip:veh = 6.73**

→





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# Clinical studies – dermal administration / IVIVE and model verification 2b

| no | source | source | dose | formulation | n | m/f | age av | age sd | age range | population | end points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | Erdogan 2006 | International Journal of Clinical Pharmacology and Therapeutics, Vol. 44 – No. 6/2006 (270-275) | 1-week administration of nimesulide gel, applied on the knee 3 times a day and the amount was described as "the size of a single lentil" of gel (approximately 0,4 mg/10 $cm^2$) to be applied on the knee skin 3 times a day and to be rubbed for no longer than 1 minute | gel (Sulidin) | 17 plasma 13 SF | | | | 18-65 | patients who were scheduled to have an arthroscopic knee examination | plasma, synovial fluid |

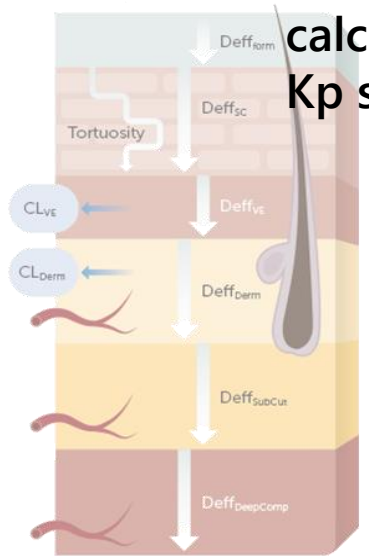
**Sulidin gel**

**6.1. List of excipients**

**Diethylene Glycol Monoethyl Ether**
**Buthylated Hydroxytoluene**
**Hydroxypropylcellulose**
**Glyceryl Monooleate**
**Methyl Paraben**
**Propyl Paraben**

→ **NO ethanol**
**-->**
**assumed Vehicle:water solubility ratio = 4**

→




**calculated**
**Kp sclip:veh = 18.22**





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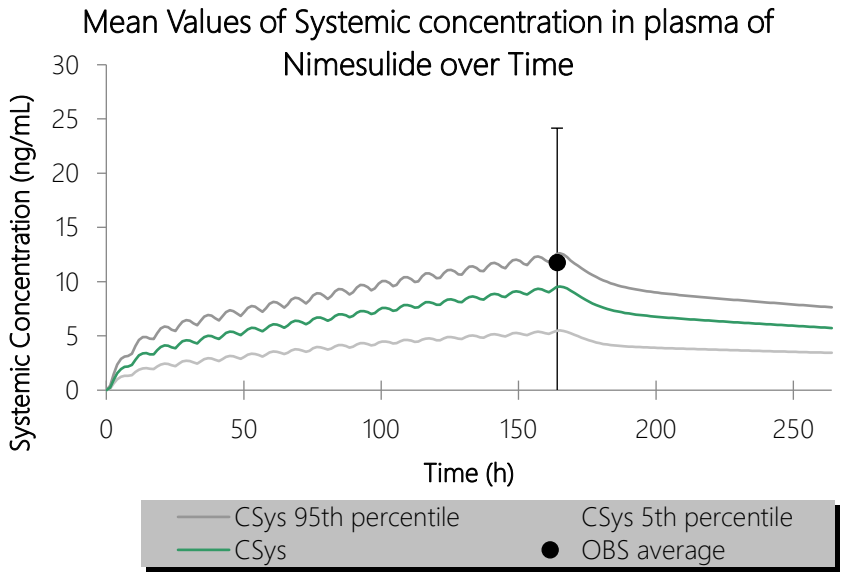
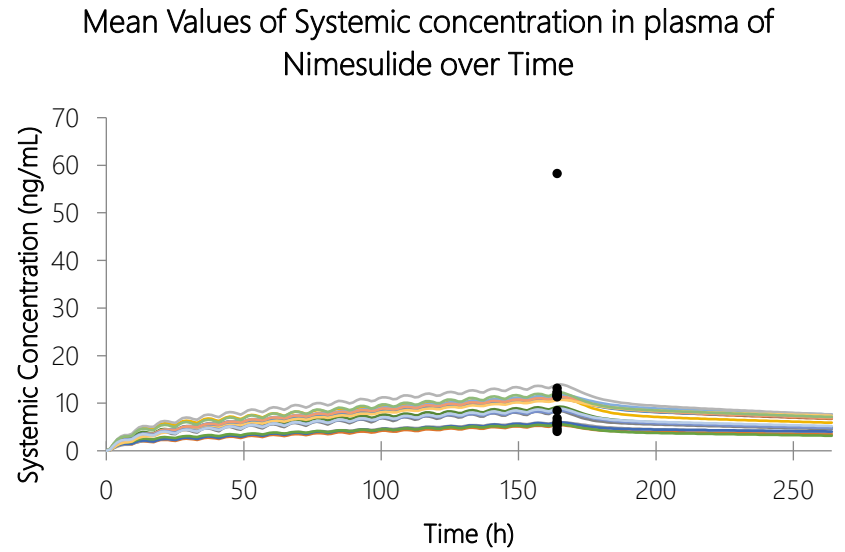
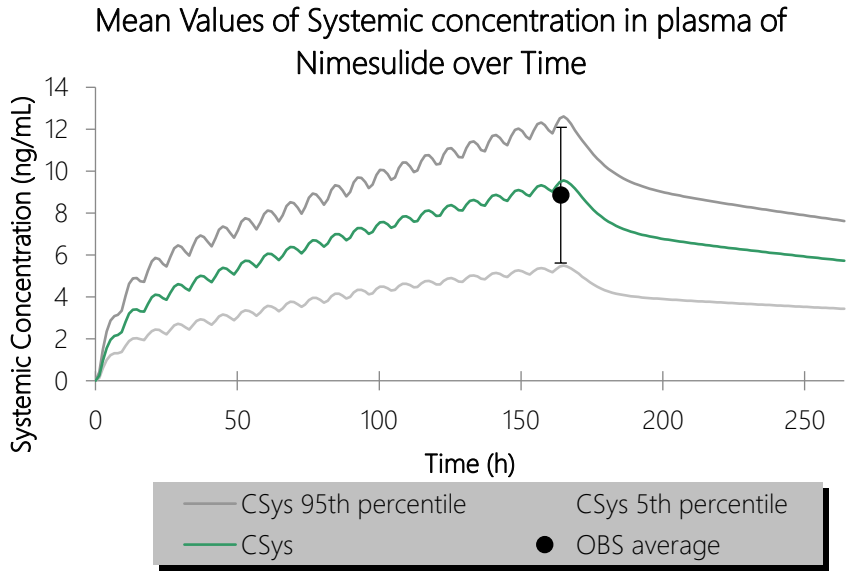
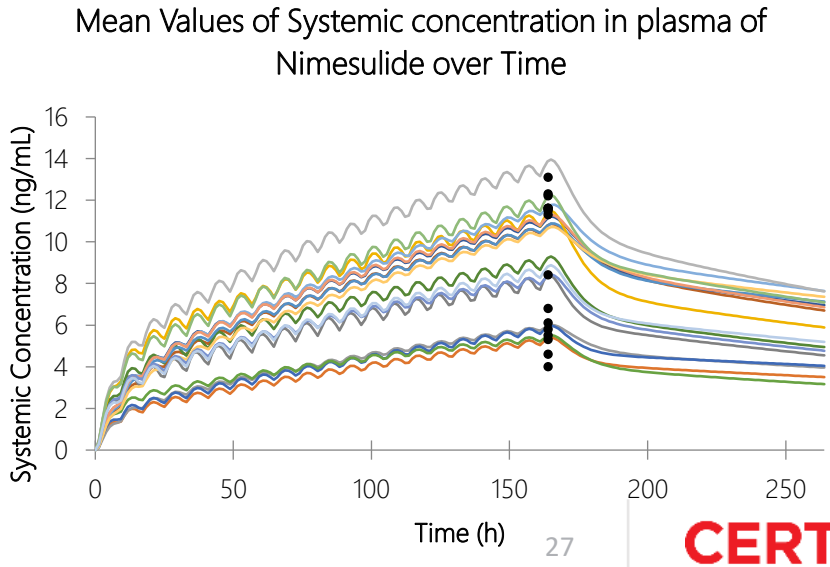
# Clinical studies – dermal administration / IVIVE and model verification 2b




NO OUTLIER





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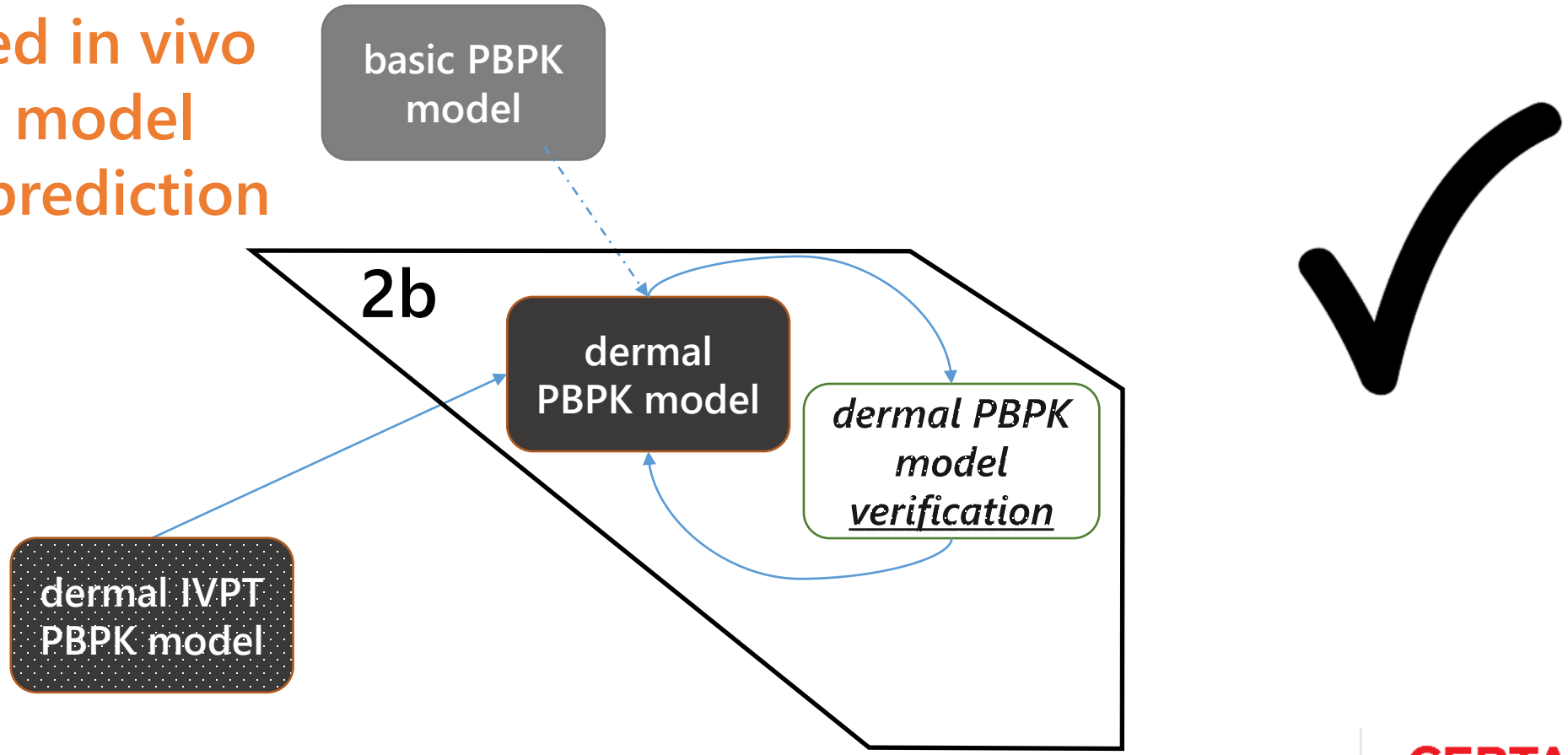
# Case study – Nimesulide

## (Simplified) model building plan

### Step 2b: Development of a Nimesulide dermal in vivo PBPK model

The developed in vivo PBPK dermal model offers good prediction quality





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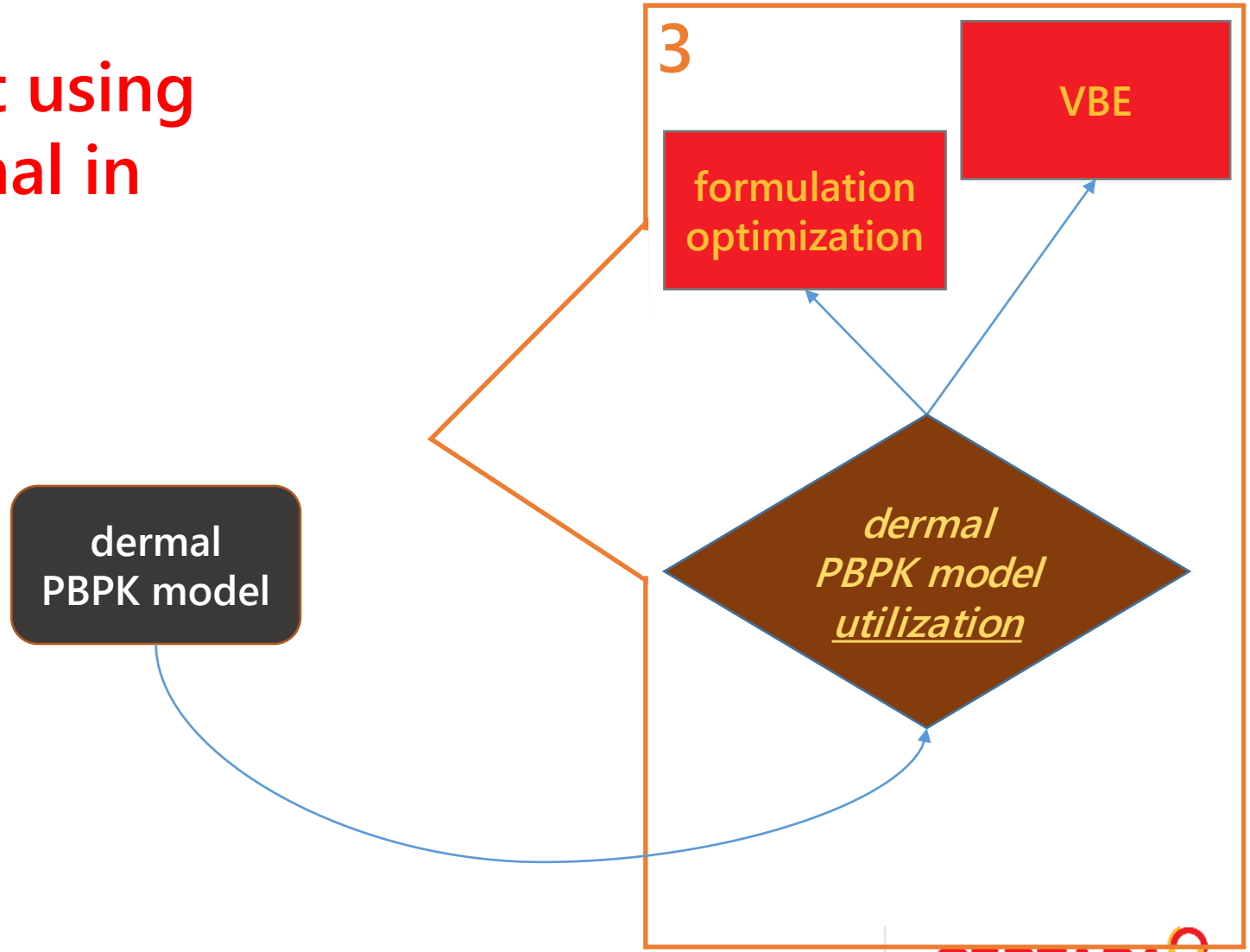
# Case study – Nimesulide

## (Simplified) model building plan

**Step 3: Virtual BE assessment using the verified Nimesulide dermal in vivo PBPK model**





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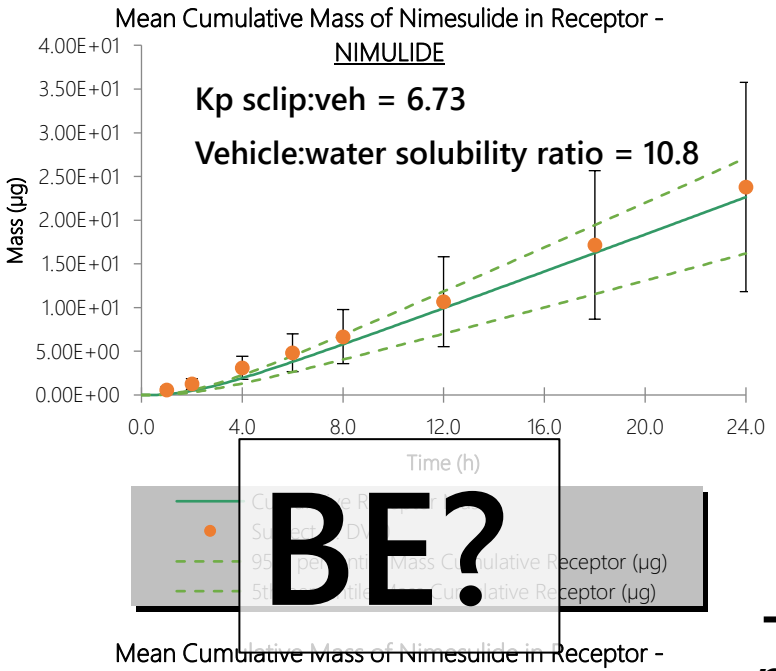
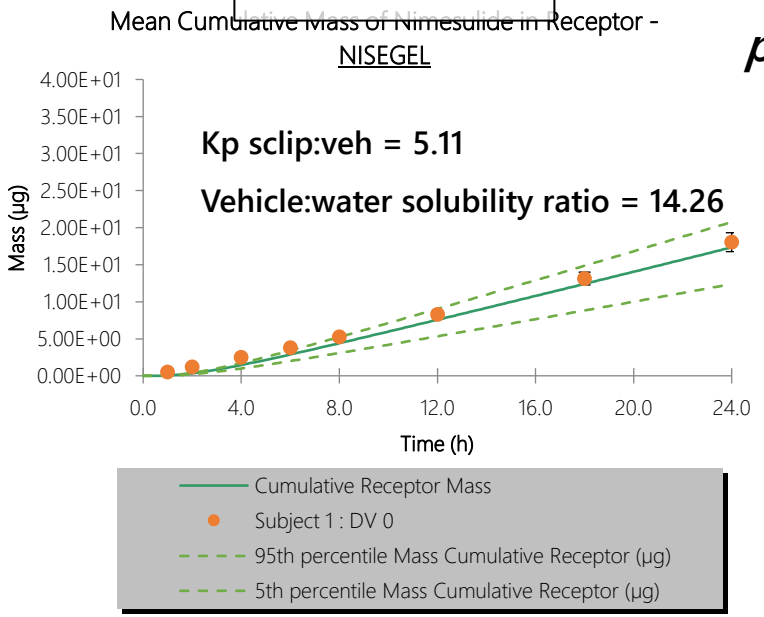
# VBE example





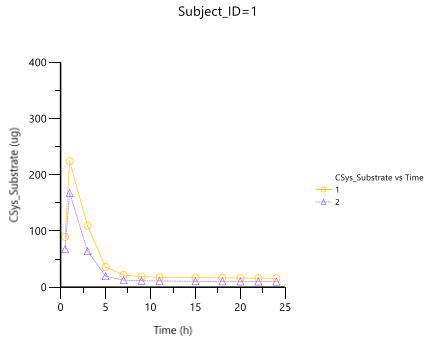

**BE?**

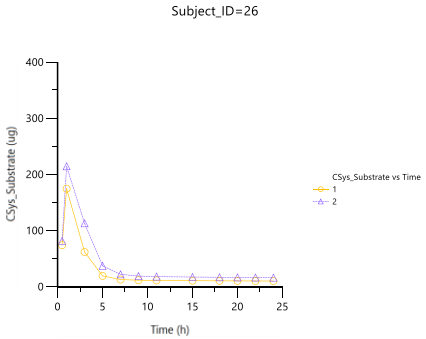


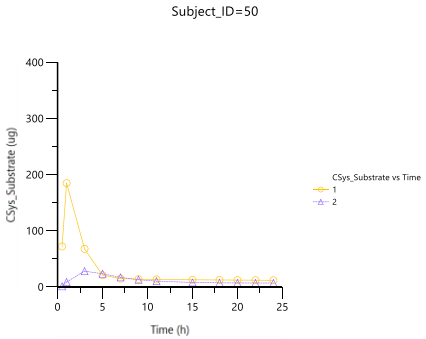

**VBE**

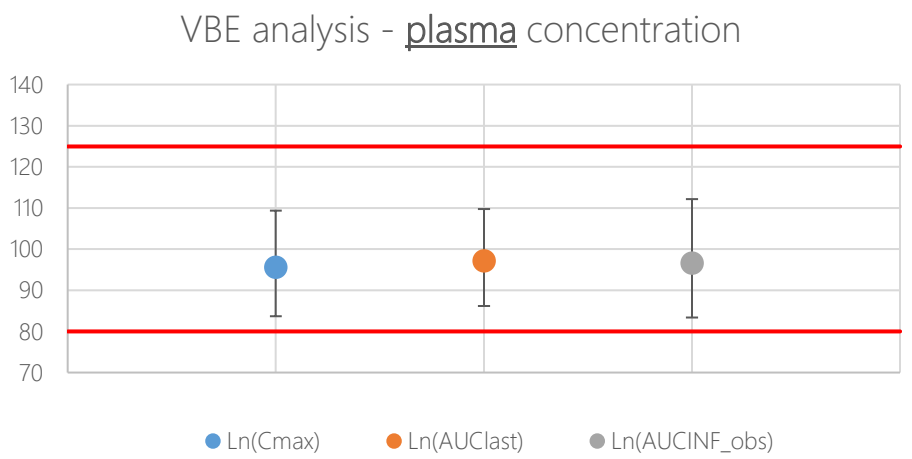
***CO/n=25***

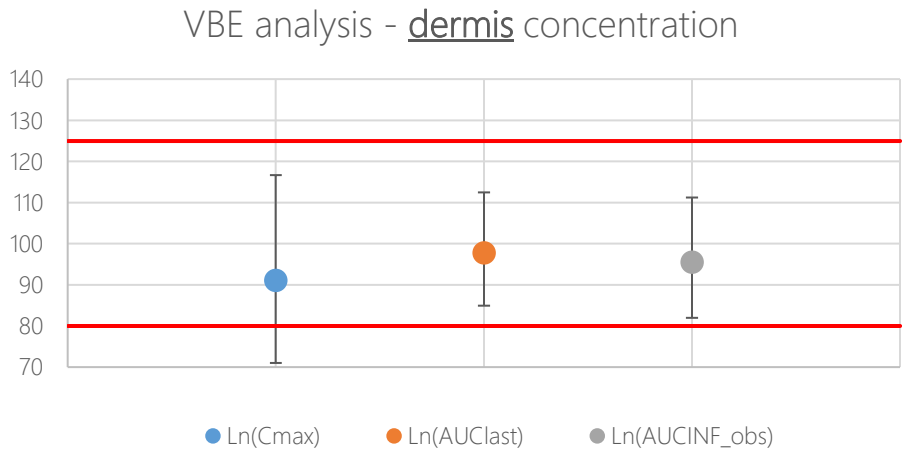
***plasma/dermis***



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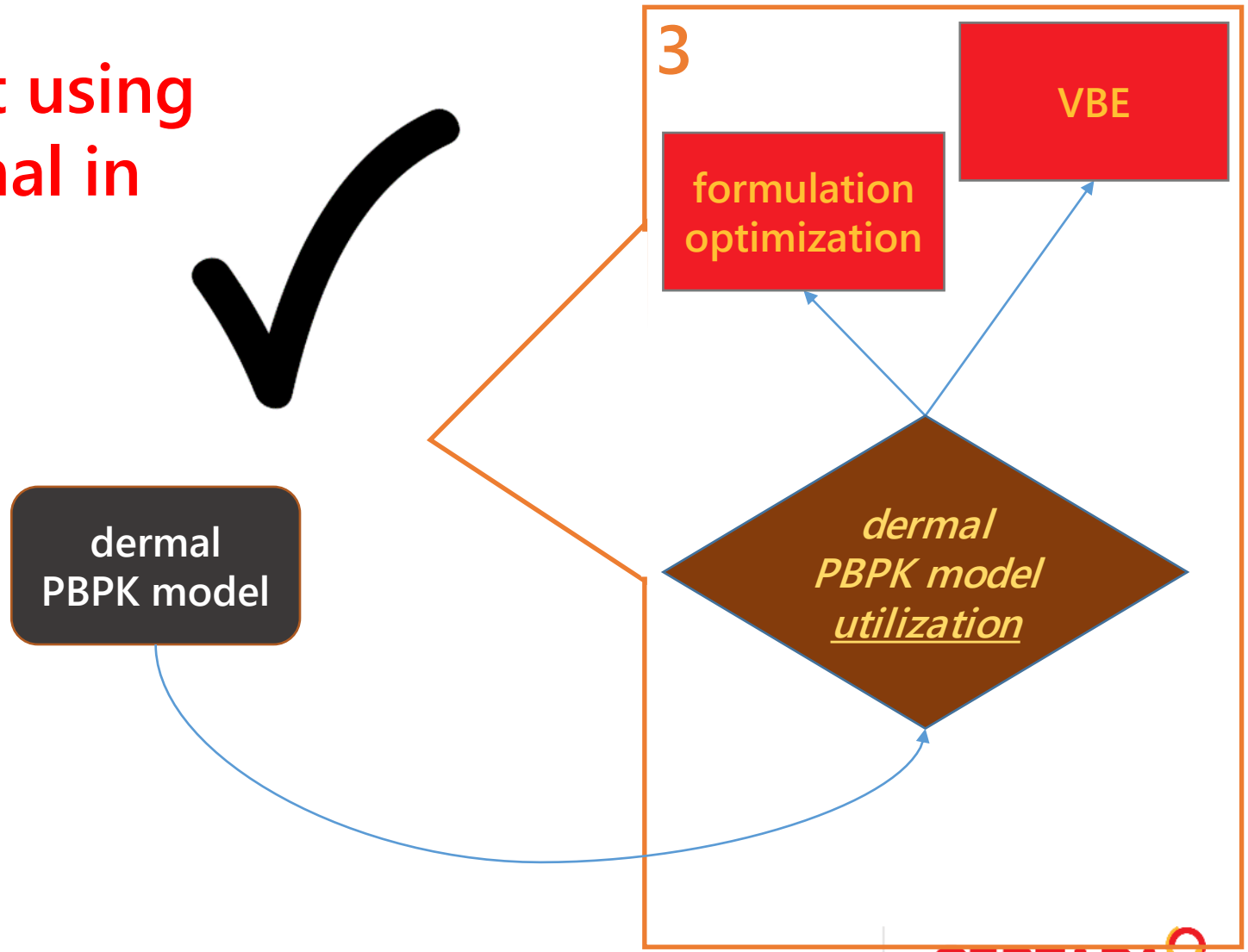
# Case study – Nimesulide

## (Simplified) model building plan

**Step 3: Virtual BE assessment using the verified Nimesulide dermal in vivo PBPK model**

The developed in vivo PBPK dermal model allowed for VBE assessment





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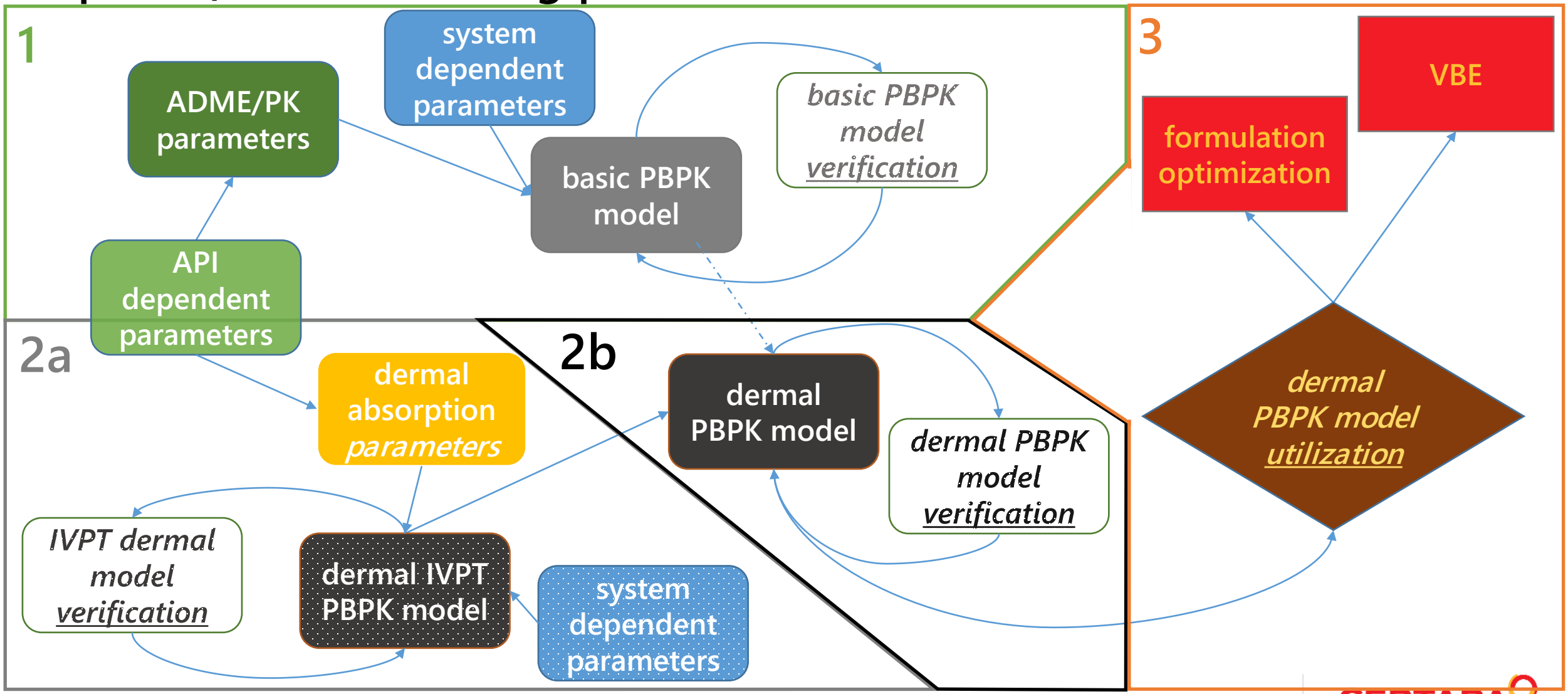
# Case study – Nimesulide

## (Simplified) model building plan





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# Take home messages

1. Physiology matters even for simulated IVPT study; important for model development
2. Sometimes simple parameters are crucial and M&S can help you to define them and thus help to understand the formulation
3. VBE and virtual formulation optimization are possible with proper tool





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