



Utilizing Mechanistic Dermal Absorption Models to Assess Virtual BE

James F Clarke PhD

Senior Research Scientist

simCYP



CERTARA®



CENTER FOR RESEARCH ON
**COMPLEX
GENERICS**

at the University of Maryland,
Baltimore and the
University of Michigan



Reuse of Models and Modelling Strategy

Mechanistic and PBPK Models – Unique advantages for Model Reuse

Mechanistic PBPK Modelling - Separation of system/drug data

**Systems
Data**

**Trial
Design**

**Drug
Data**

**Formulation
Data**

Mechanistic PBPK Modelling - Separation of system/drug data

**Systems
Data**

**Trial
Design**

**Drug
Data**

**Formulation
Data**

Age
Weight
Tissue Volumes
Tissue Composition
Cardiac Output
Tissue Blood Flows
[Plasma Protein]

Mechanistic PBPK Modelling - Separation of system/drug data

Systems Data

Age
Weight
Tissue Volumes
Tissue Composition
Cardiac Output
Tissue Blood Flows
[Plasma Protein]

Trial Design

Drug Data

MW
LogP
pKa
Protein binding
BP ratio
In vitro Metabolism
Permeability
Solubility

Formulation Data

Mechanistic PBPK Modelling - Separation of system/drug data

Systems Data

Age
Weight
Tissue Volumes
Tissue Composition
Cardiac Output
Tissue Blood Flows
[Plasma Protein]

Trial Design

Drug Data

MW
LogP
pKa
Protein binding
BP ratio
In vitro Metabolism
Permeability
Solubility

Formulation Data

Particle Size
Excipients
Release
Disintegration
Viscosity
Evaporation

Mechanistic PBPK Modelling - Separation of system/drug data

Systems Data

Age
Weight
Tissue Volumes
Tissue Composition
Cardiac Output
Tissue Blood Flows
[Plasma Protein]

Trial Design

Dose
Administration route
Frequency
Co-administered drugs
Populations
No of male/female

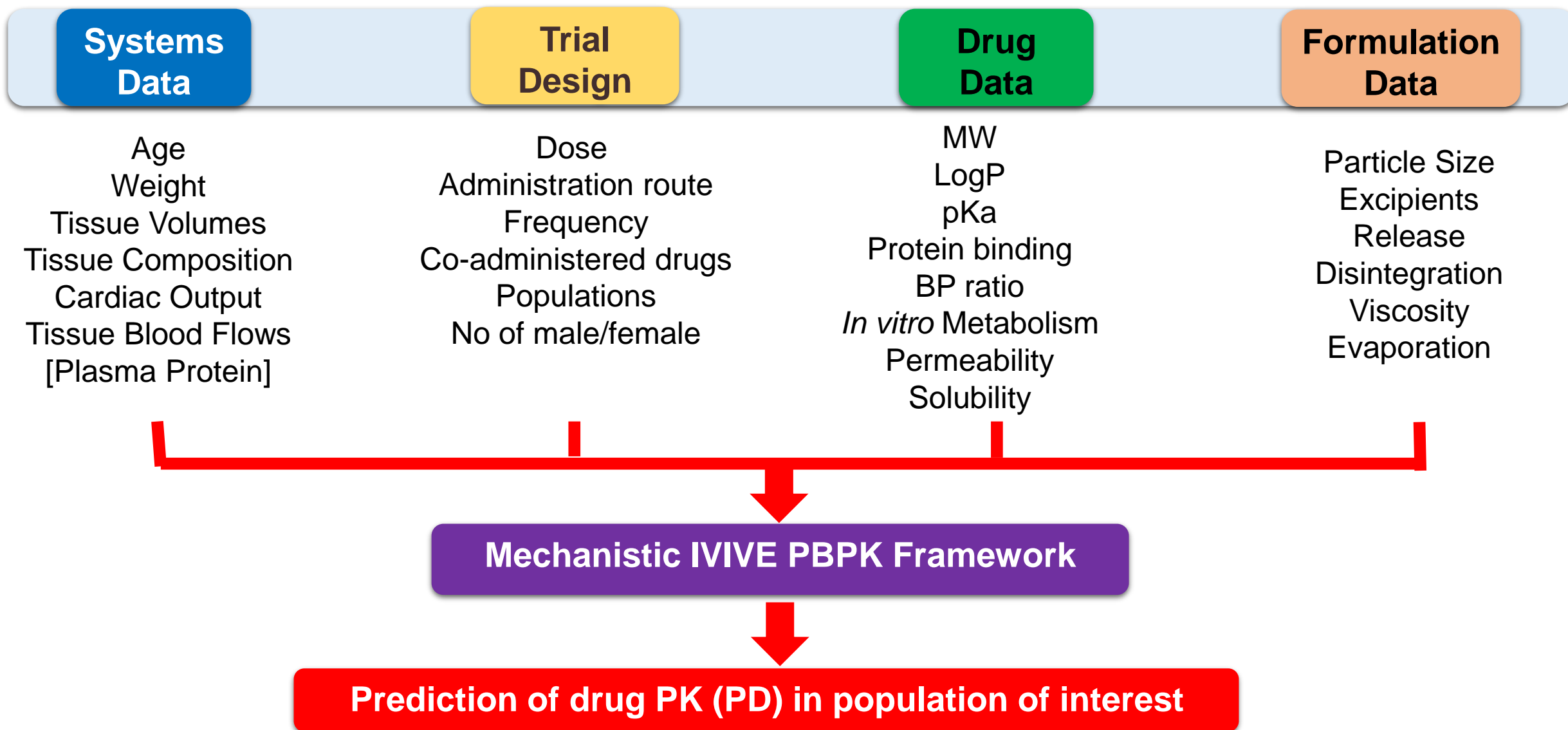
Drug Data

MW
LogP
pKa
Protein binding
BP ratio
In vitro Metabolism
Permeability
Solubility

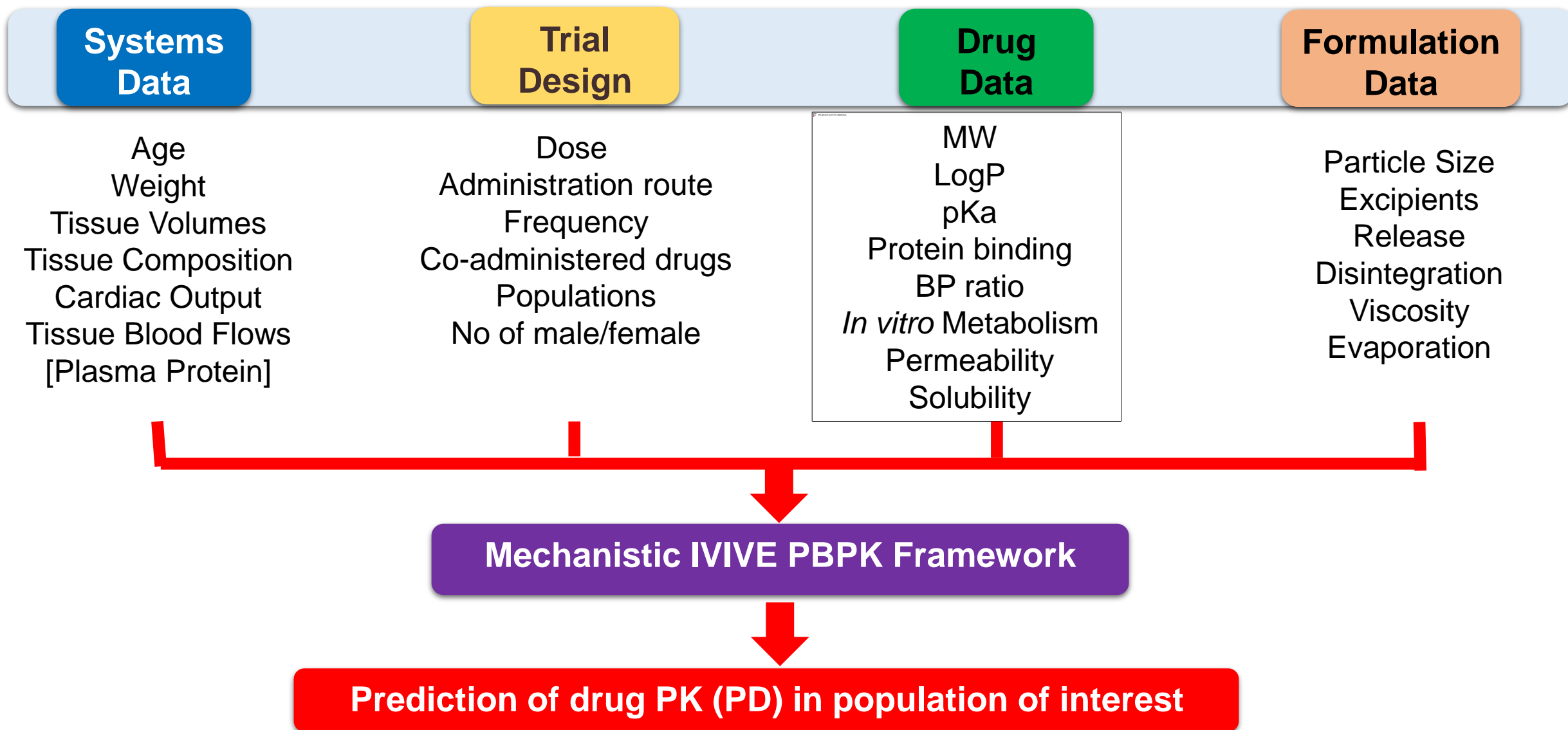
Formulation Data

Particle Size
Excipients
Release
Disintegration
Viscosity
Evaporation

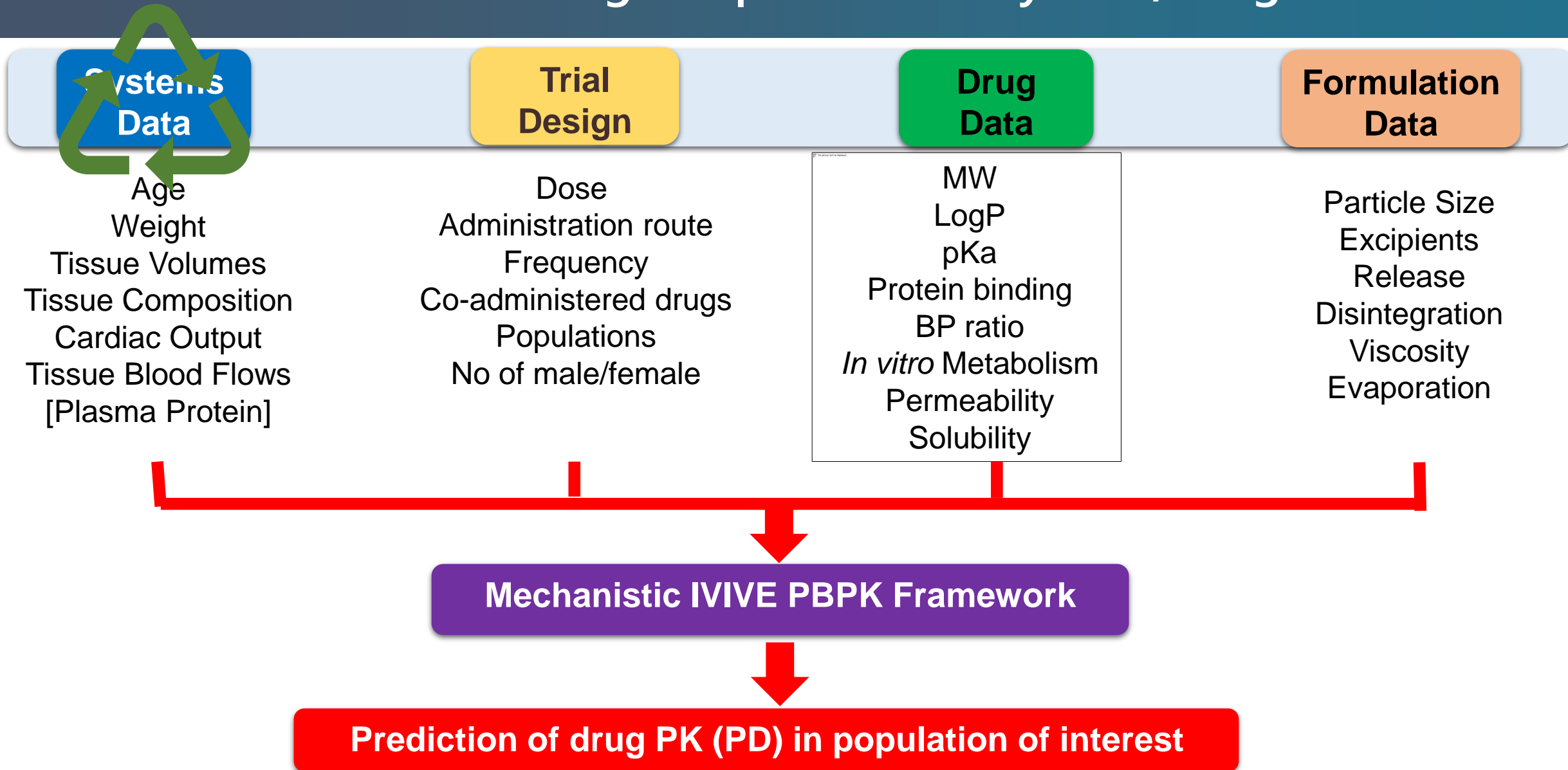
Mechanistic PBPK Modelling - Separation of system/drug data



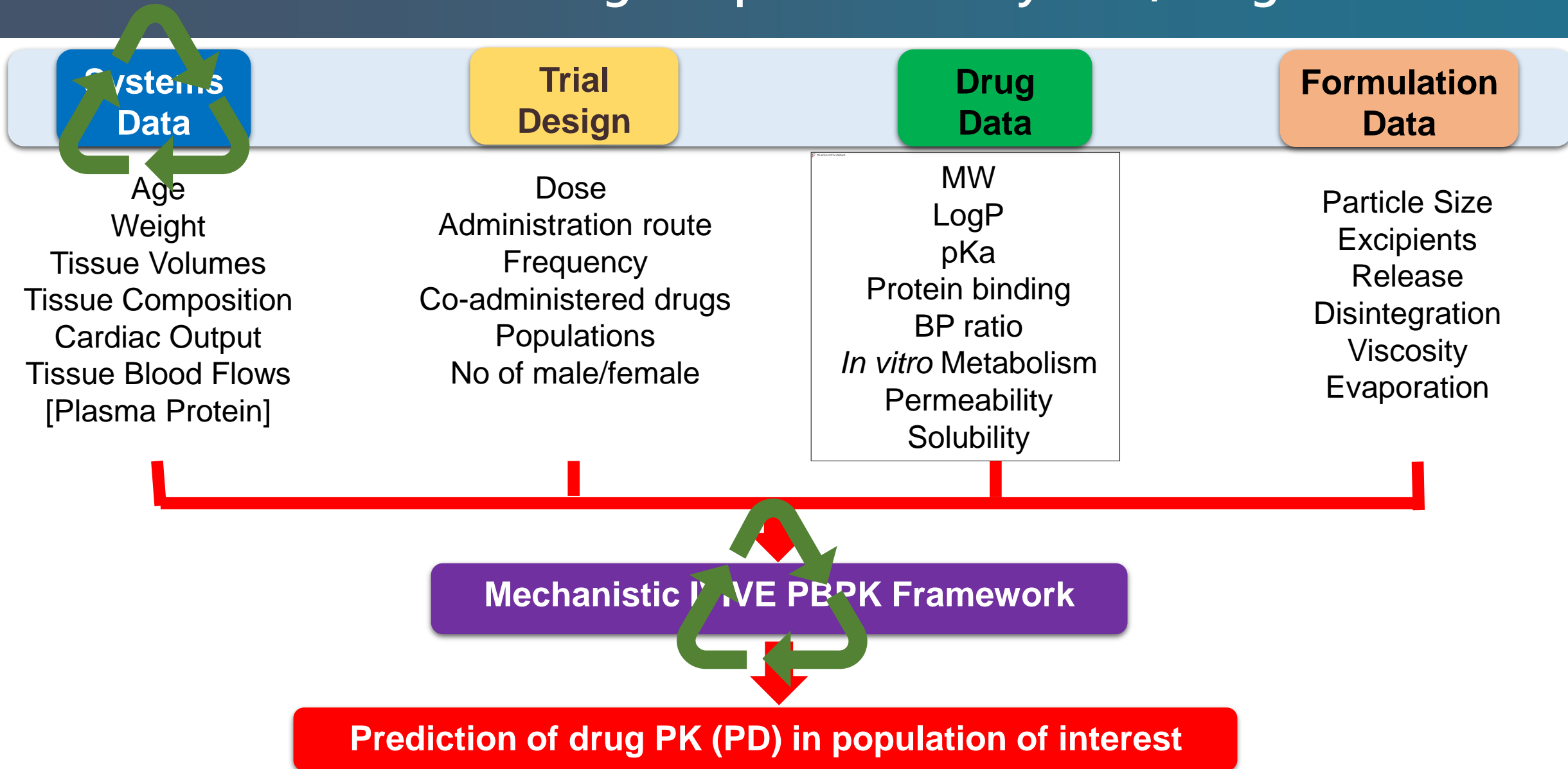
Mechanistic PBPK Modelling - Separation of system/drug data



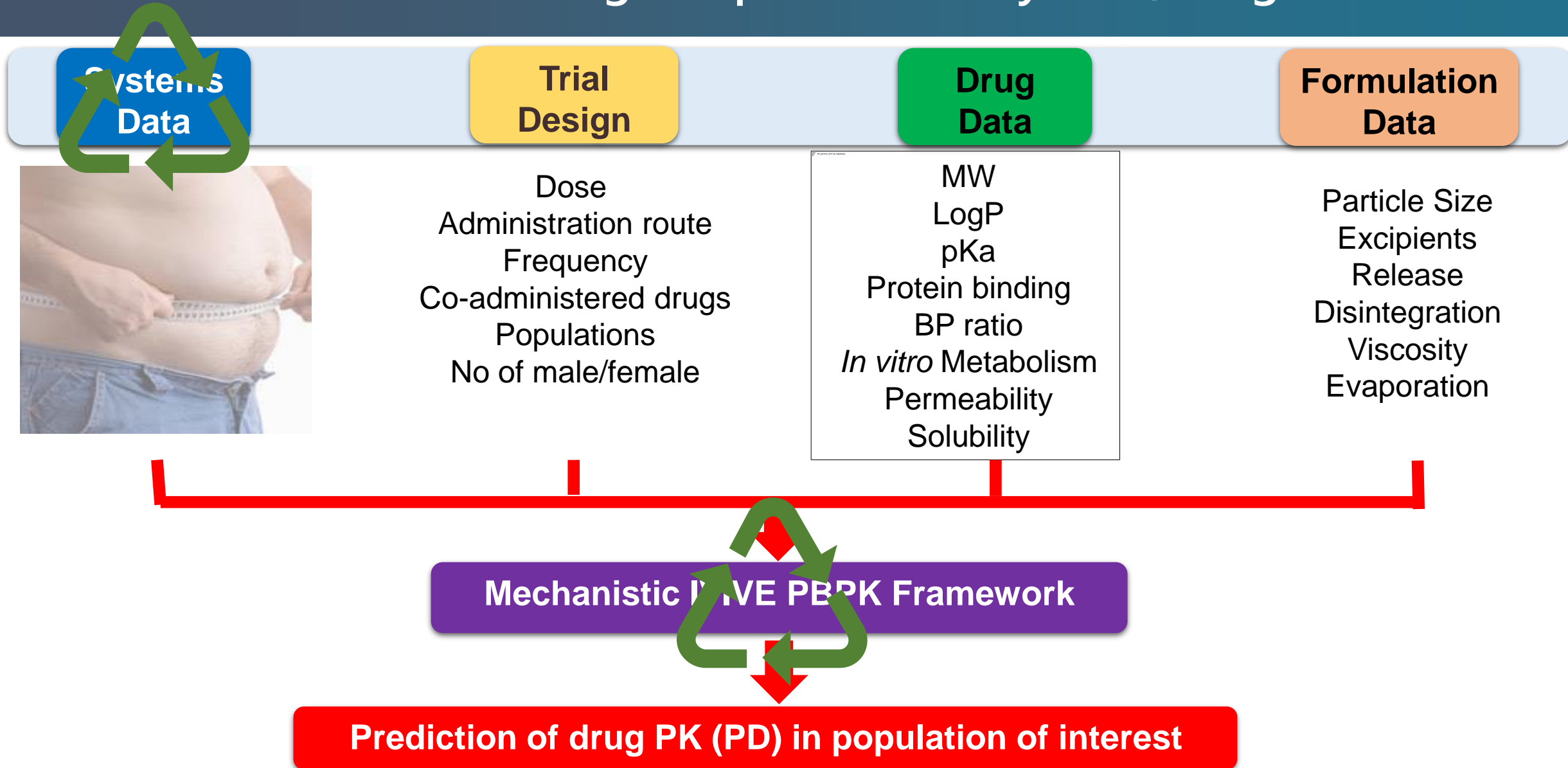
Mechanistic PBPK Modelling - Separation of system/drug data



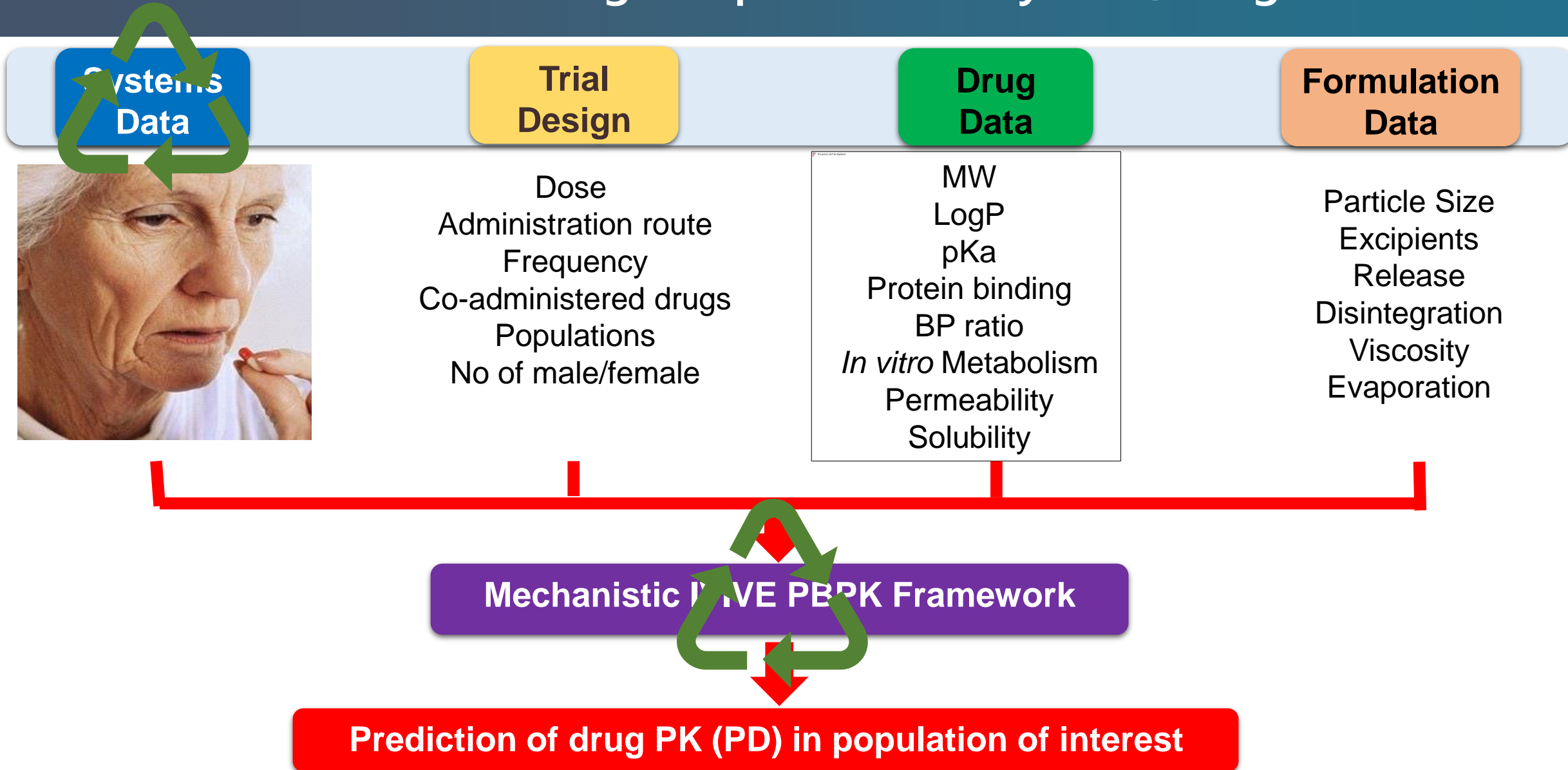
Mechanistic PBPK Modelling - Separation of system/drug data



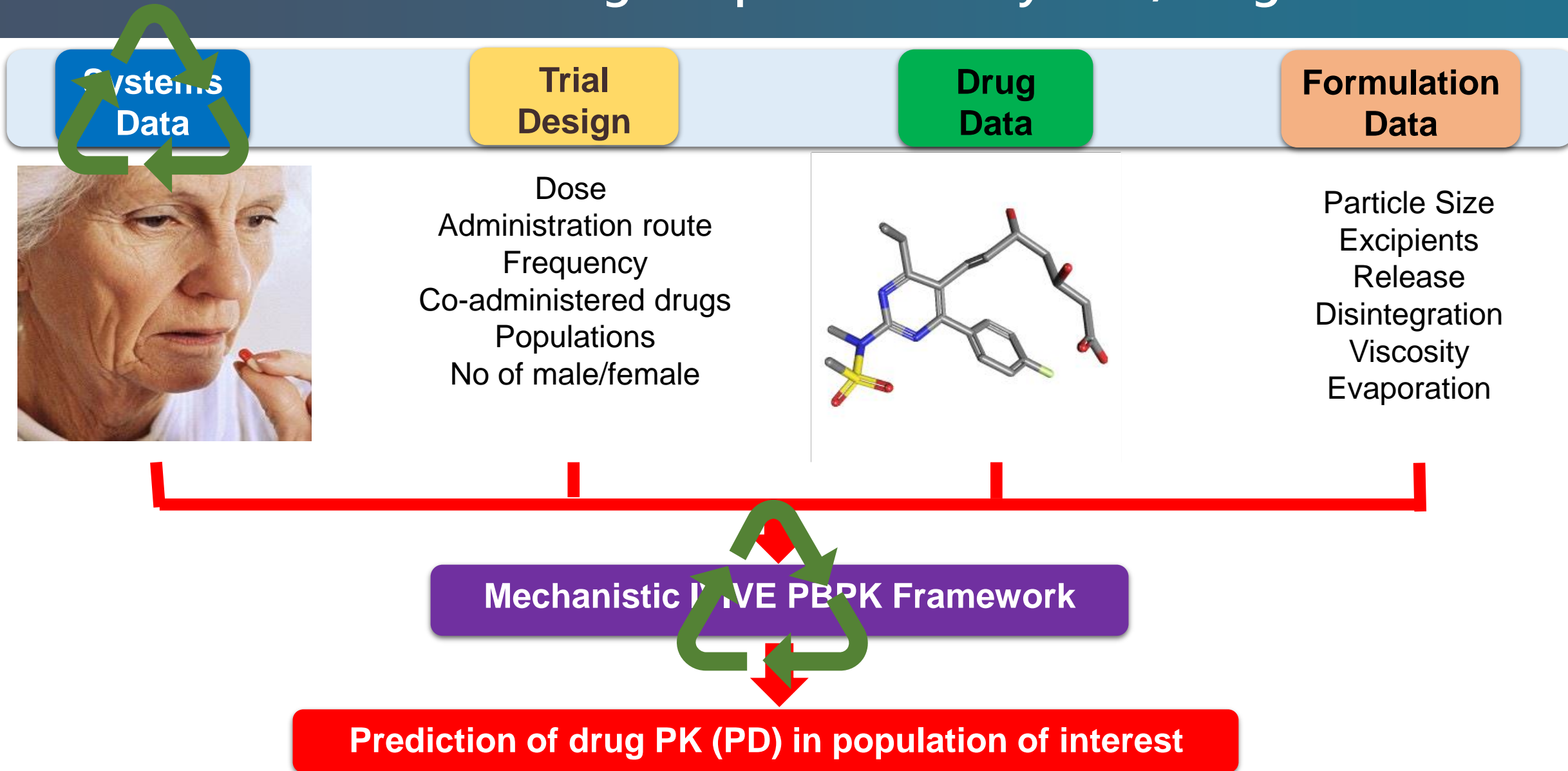
Mechanistic PBPK Modelling - Separation of system/drug data



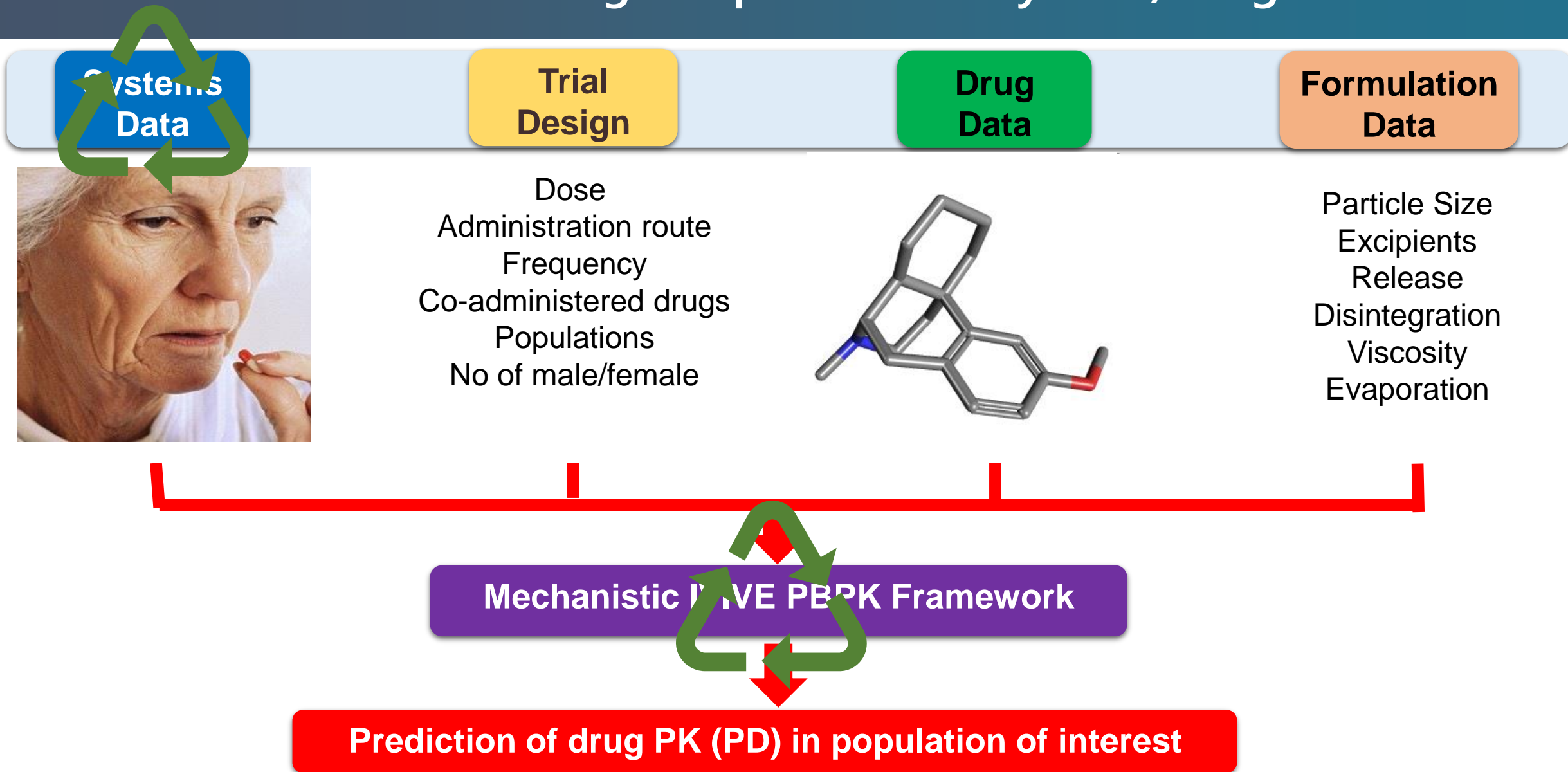
Mechanistic PBPK Modelling - Separation of system/drug data



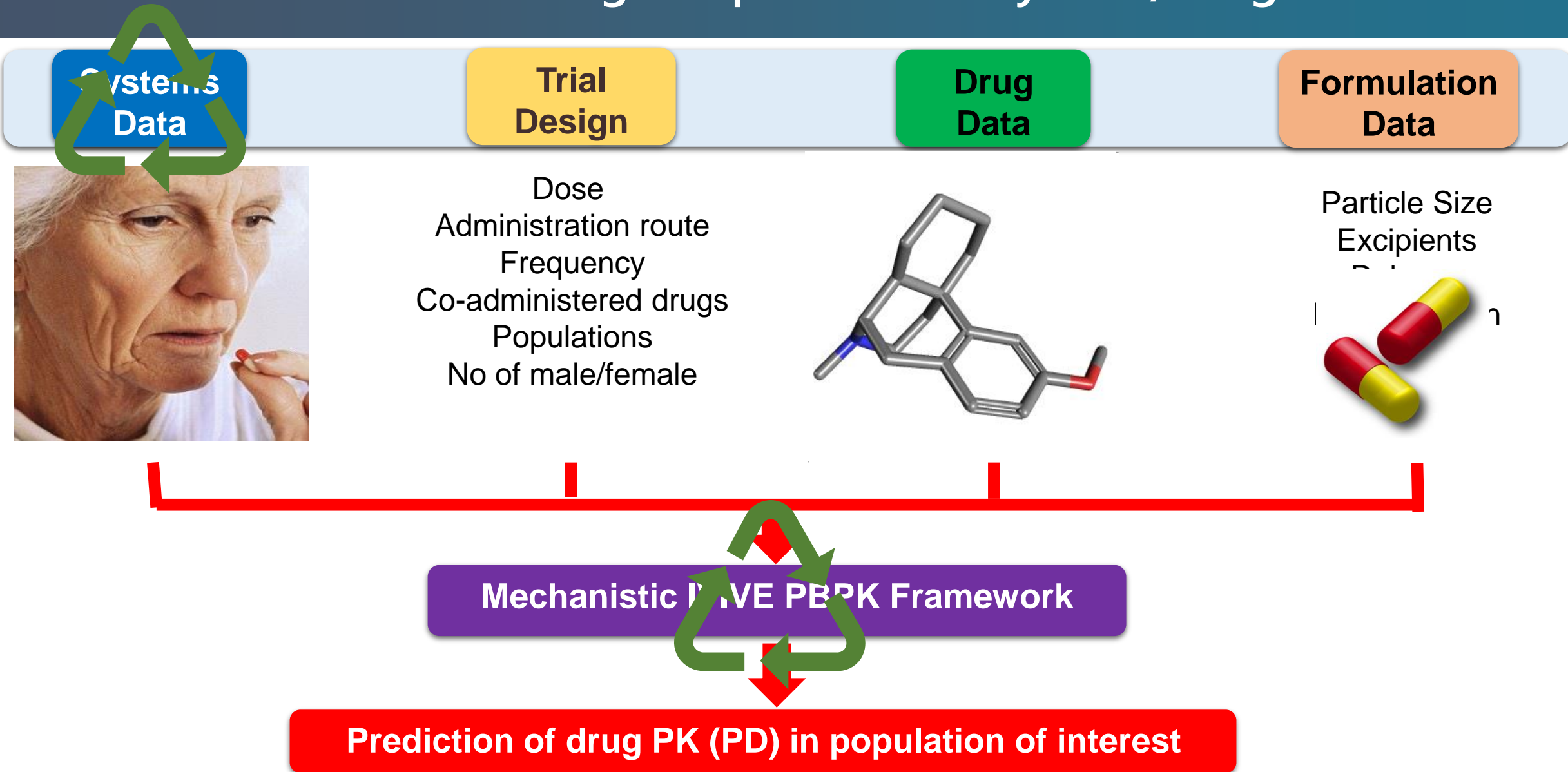
Mechanistic PBPK Modelling - Separation of system/drug data



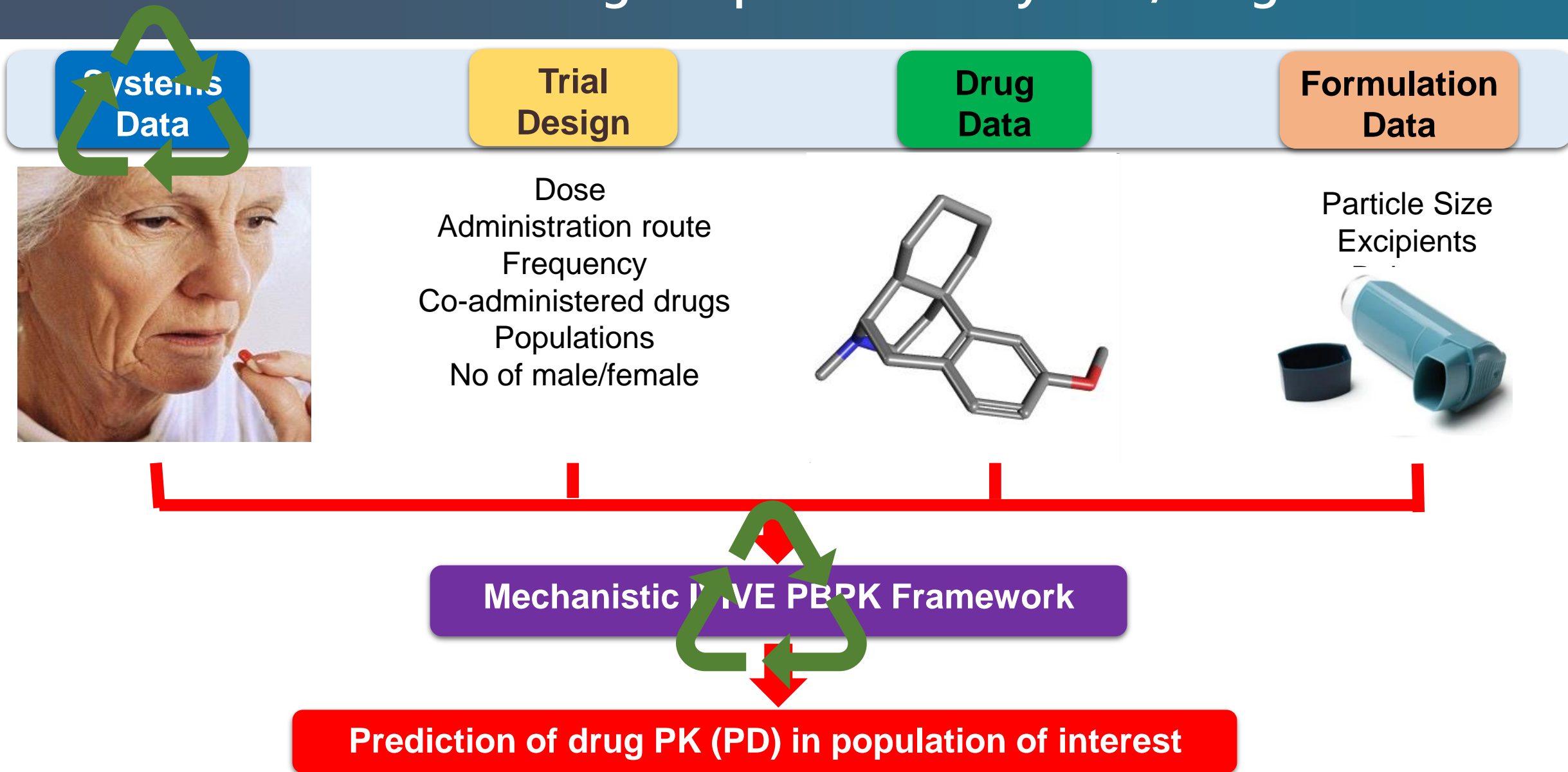
Mechanistic PBPK Modelling - Separation of system/drug data



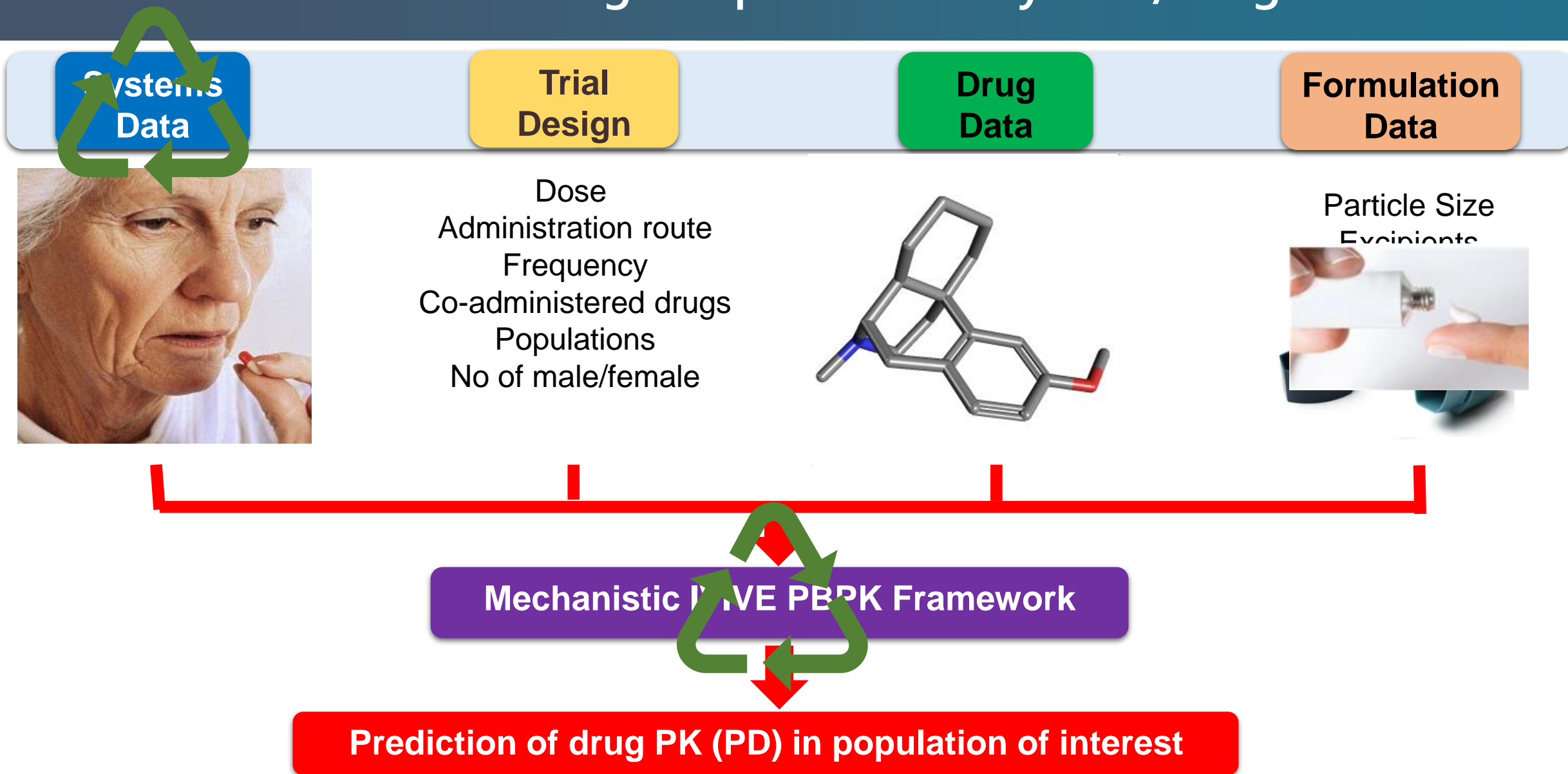
Mechanistic PBPK Modelling - Separation of system/drug data



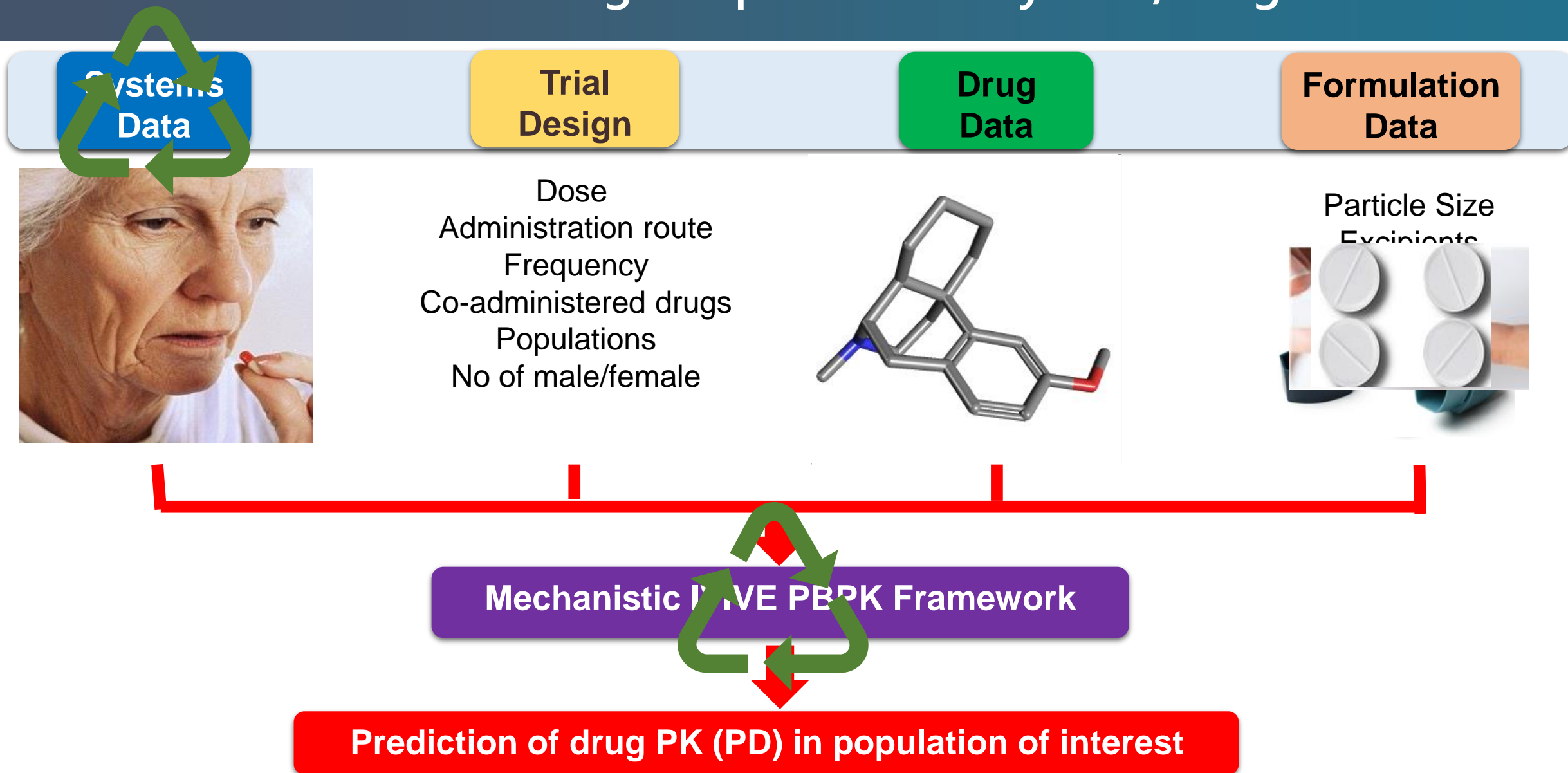
Mechanistic PBPK Modelling - Separation of system/drug data



Mechanistic PBPK Modelling - Separation of system/drug data

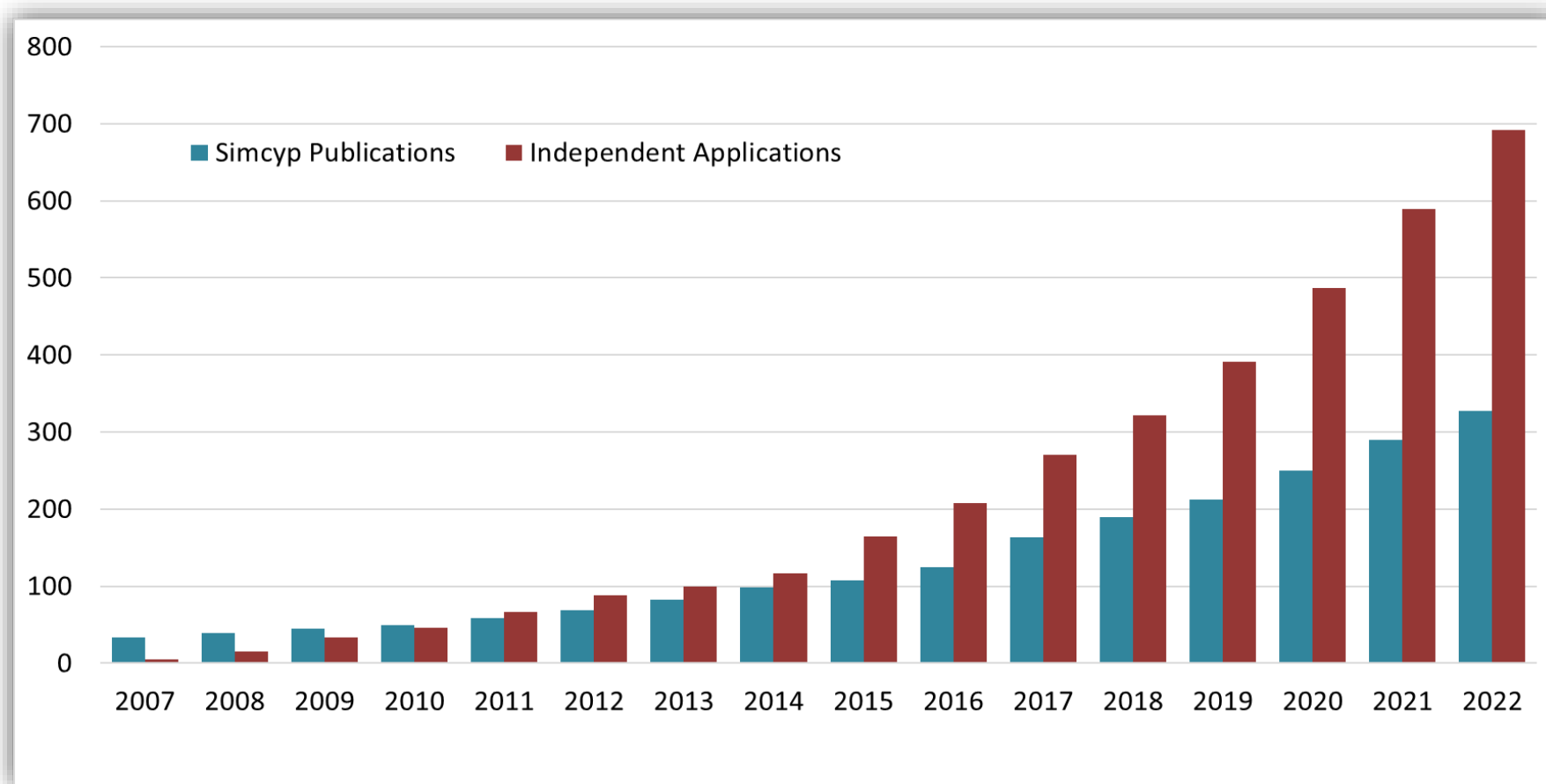


Mechanistic PBPK Modelling - Separation of system/drug data

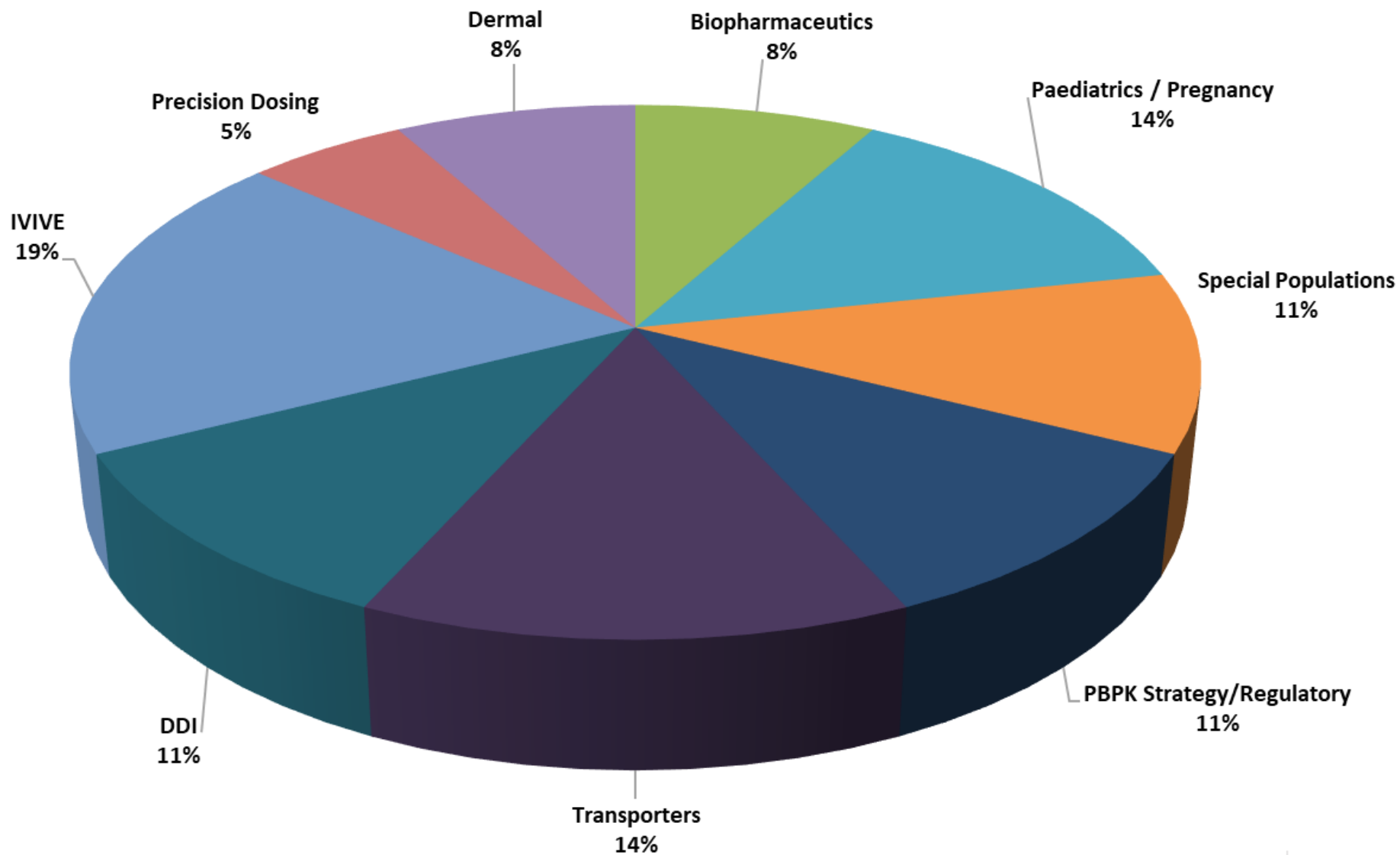


Verification of the platform - Open Science

Cumulative number of publications over years 2007 - 2022

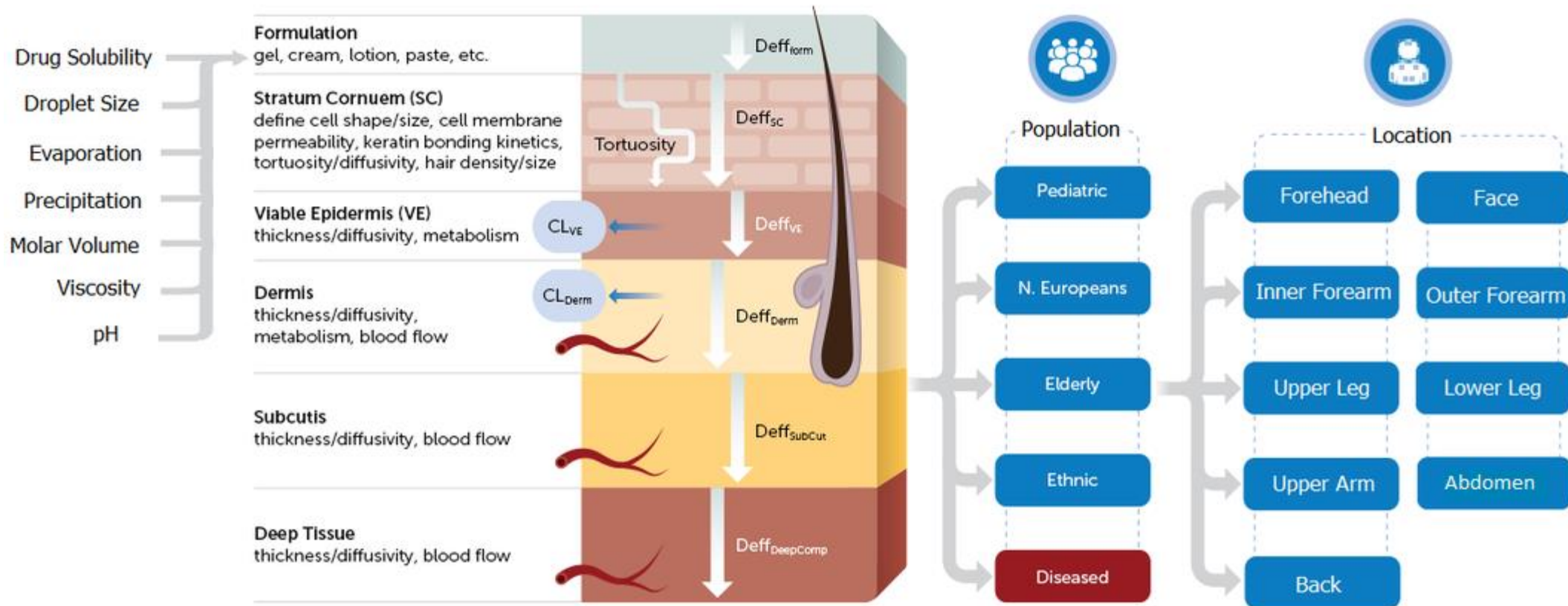


Topics of Simcyp publications in 2021-2022



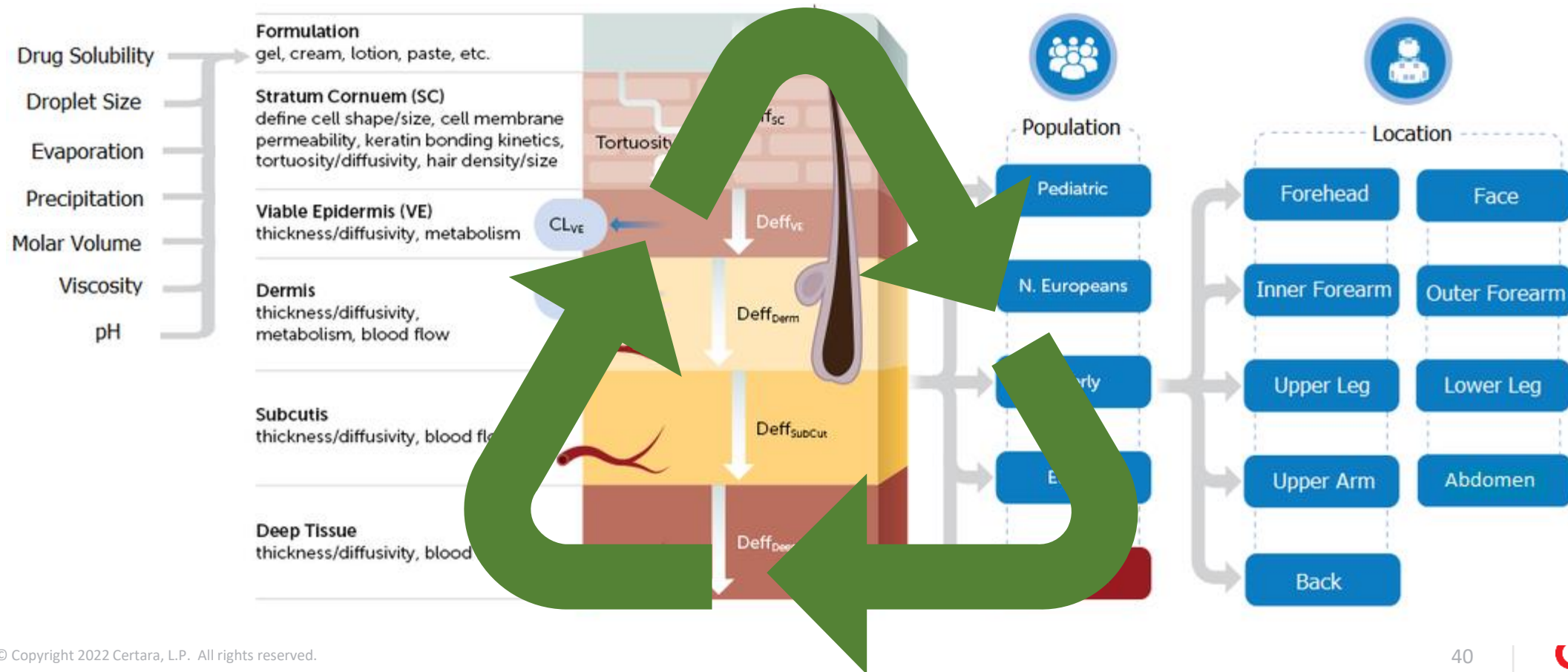
Dermal PBPK Modelling – MPML MechDermA

Built over the past 8 years, funded by various FDA grants in collaboration with OGD:



Dermal PBPK Modelling – MPML MechDerma

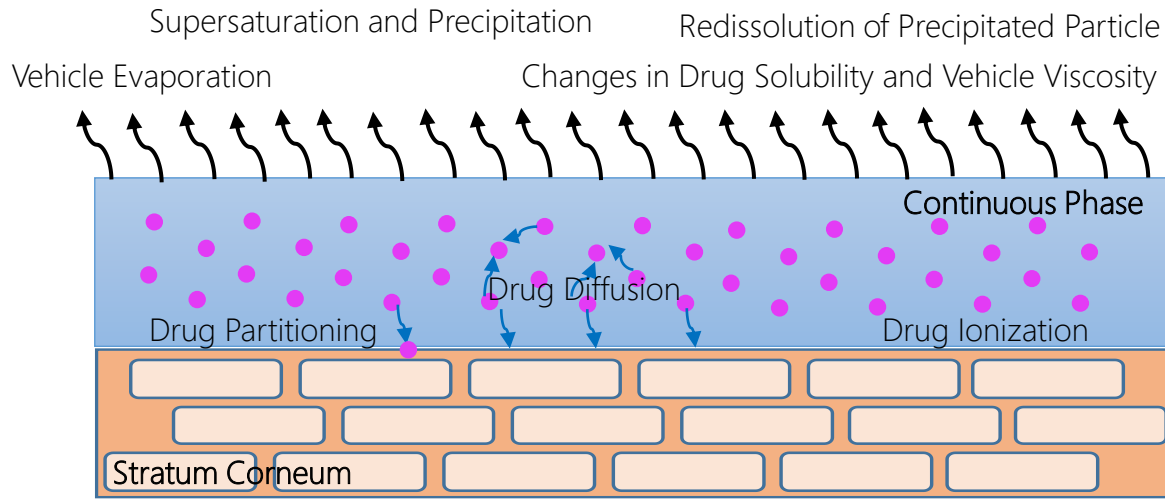
Built over the past 8 years, funded by various FDA grants in collaboration with OGD:



Modeling Metamorphosis of Topical/Transdermal Formulations

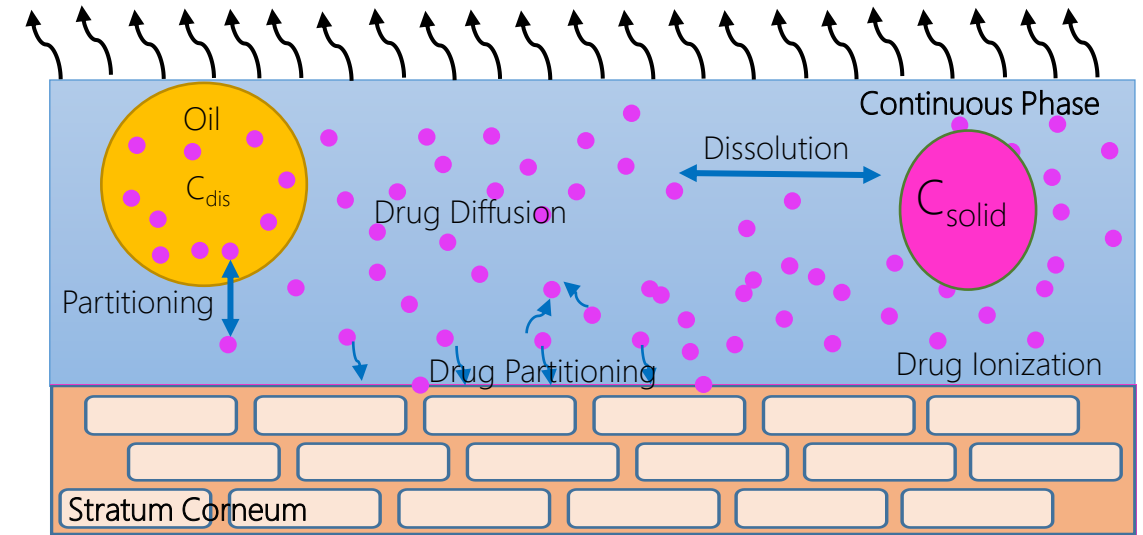
Solutions

● Drug Molecule



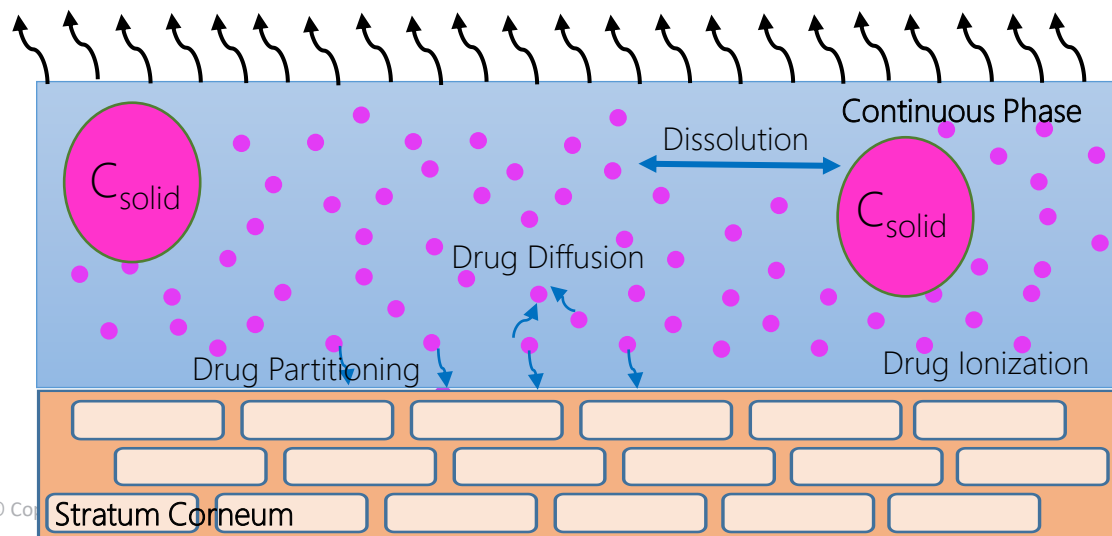
Emulsions

● Drug Molecule



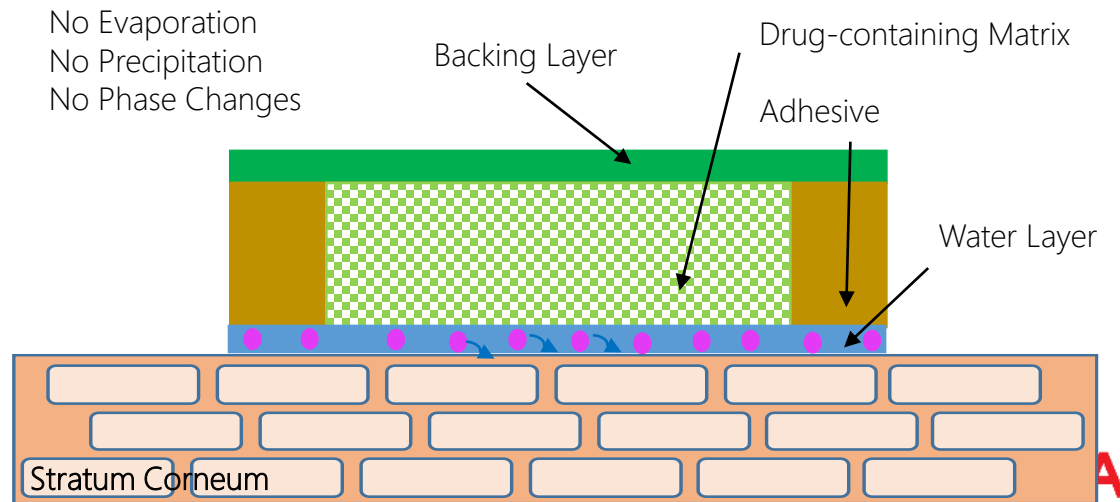
Suspensions

● Drug Molecule



Patches

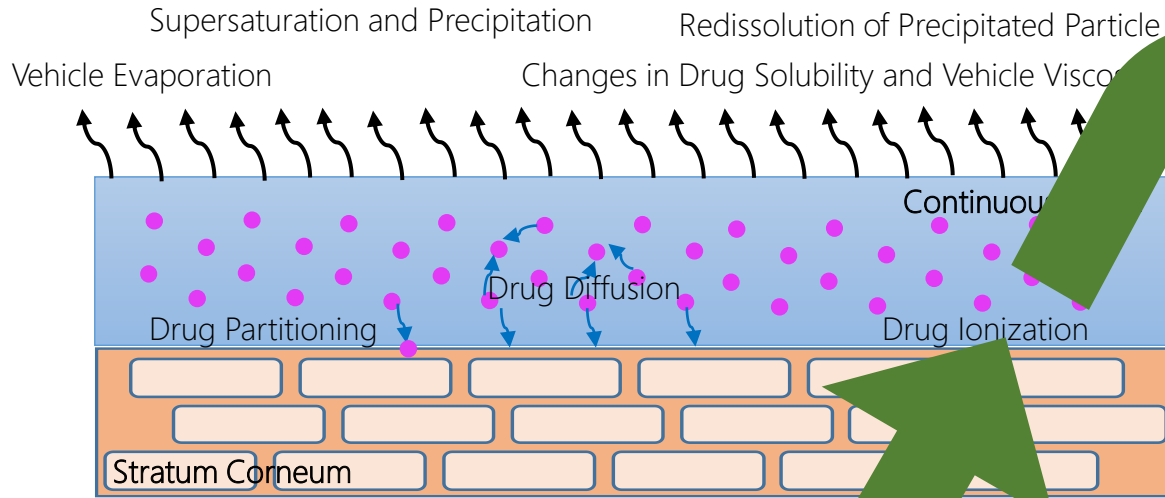
● Drug Molecule



Modeling Metamorphosis of Topical/Transdermal Formulations

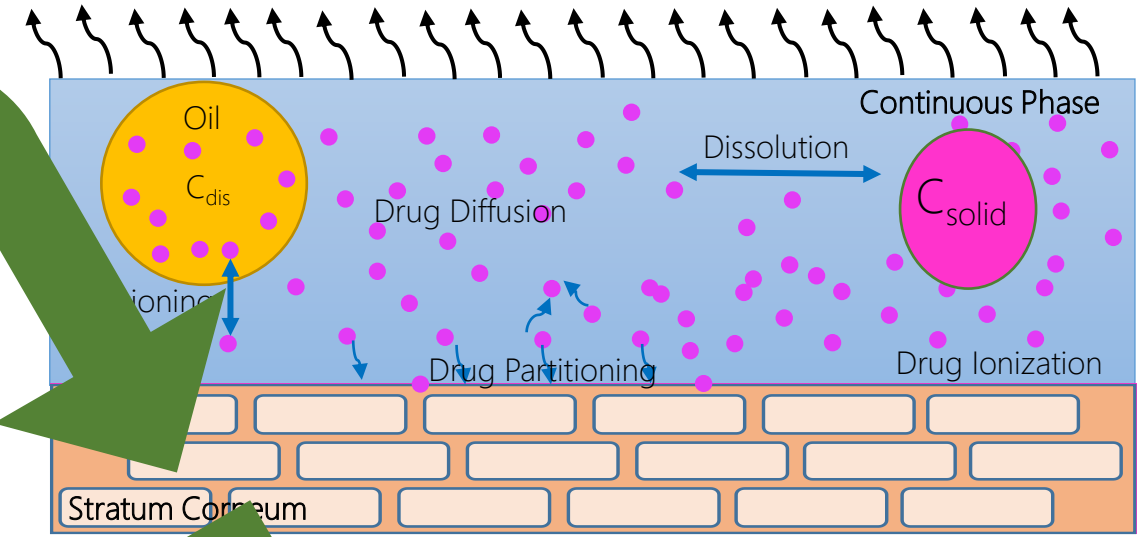
Solutions

● Drug Molecule



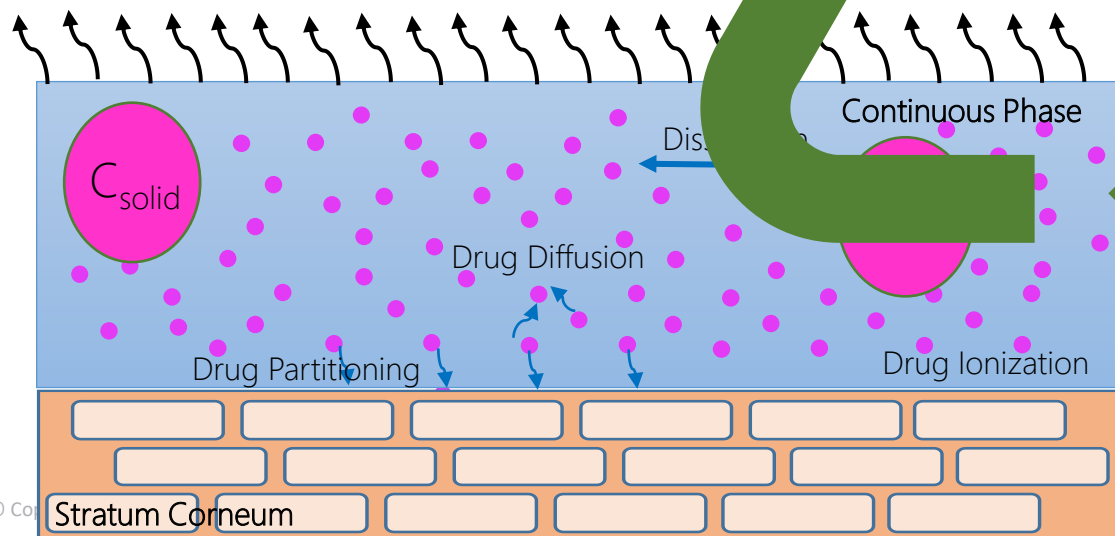
Emulsions

● Drug Molecule



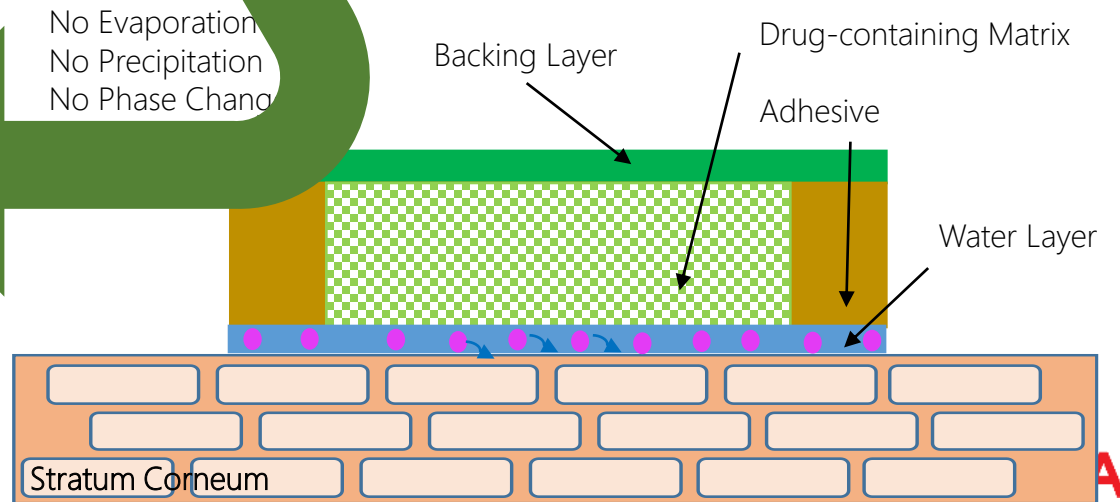
Suspensions

● Drug Molecule



Patches

● Drug Molecule



MPML MechDermA Publications

Papers and Posters

MPML MechDermA Publications

Papers and Posters

Development of a PBPK model for topical lidocaine in order to predict systemic absorption in healthy volunteers, geriatrics and paediatrics

CERTARA
Simcyp

Farzaneh Salem, Nikunj Kumar Patel and Sebastian Polak. Simcyp Division, Certara UK Limited, Sheffield, UK

MPML MechDermA Publications

Papers and Posters

Development of a PBPK model for topical lidocaine in order to predict systemic absorption in healthy volunteers, geriatrics and paediatrics

CERTARA
Simcyp

Farzaneh Salem, Nikunj Kumar Patel and Sebastian Polak. Simcyp Division, Certara UK Limited, Sheffield, UK

Quantitative description of the physiological changes in diseased skin and their incorporation into Physiologically Based Pharmacokinetic Models.

CERTARA
Simcyp

James Clarke¹, Nikunj Kumar Patel¹, Sebastian Polak^{1,2}

¹Certara, Simcyp-Division, Level-2 Acero, 1 Concourse way, Sheffield, United Kingdom.

²Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland

MPML MechDermA Publications

Papers and Posters

Development of a PBPK model for topical lidocaine in order to predict systemic absorption in healthy volunteers, geriatrics and paediatrics

CERTARA
Simcyp

Farzaneh Salem, Nikunj Kumar Patel and Sebastian Polak. Simcyp Division, Certara UK Limited, Sheffield, UK

Quantitative description of the physiological changes in diseased skin and their incorporation into Physiologically Based Pharmacokinetic Models.

CERTARA
Simcyp

James Clarke¹, Nikunj Kumar Patel¹, Sebastian Polak^{1,2}

¹Certara, Simcyp-Division, Level-2 Acero, 1 Concourse way, Sheffield, United Kingdom.

²Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland

Predicting Diffusion in the Dermis: a Physiologically Based, Bottom-up Approach

CERTARA
Simcyp

James Clarke¹, Nikunj Kumar Patel¹, Sebastian Polak^{1,2}

¹Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom, ²Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland

MPML MechDermA Publications

Papers and Posters

Modeling *in vitro* skin permeation experiments to mechanistically understand *in vivo* dermal absorption: Application of *in vitro-in vivo* extrapolation (IVIVE) and physiological based pharmacokinetic (PBPK) modeling using testosterone as model drug

CERTARA
Simcyp

er to predict systemic
S

CERTARA
Simcyp

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

Quantitative description of the physiological changes in diseased skin and their incorporation into Physiologically Based Pharmacokinetic Models.

CERTARA
Simcyp

James Clarke¹, Nikunj Kumar Patel¹, Sebastian Polak^{1,2}

¹Certara, Simcyp-Division, Level-2 Acero, 1 Concourse way, Sheffield, United Kingdom.

²Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland

Predicting Diffusion in the Dermis: a Physiologically Based, Bottom-up Approach

CERTARA
Simcyp

James Clarke¹, Nikunj Kumar Patel¹, Sebastian Polak^{1,2}

¹Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom, ²Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland

MPML MechDermA Publications

Papers and Posters

Modeling *in vitro* skin permeation experiments to mechanistically understand *in vivo* dermal absorption: Application of *in vitro-in vivo* extrapolation (IVIVE) and physiological based pharmacokinetic (PBPK) modeling using testosterone as model drug

CERTARA
Simcyp

er to predict systemic
S

CERTARA
Simcyp

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

Development of the dermal absorption model for the ketoprofen local and systemic exposure prediction

CERTARA
Simcyp

ed skin and their
els.

CERTARA
Simcyp

Sebastian Polak^{1,2}, Nikunj Kumar Patel¹

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland



Predicting Diffusion in the Dermis: a Physiologically Based, Bottom-up Approach

CERTARA
Simcyp

James Clarke¹, Nikunj Kumar Patel¹, Sebastian Polak^{1,2}

¹Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom, ²Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland

MPML MechDermA Publications

Papers and Posters

Modeling *in vitro* skin permeation experiments to mechanistically understand *in vivo* dermal absorption: Application of *in vitro-in vivo* extrapolation (IVIVE) and physiological based pharmacokinetic (PBPK) modeling using testosterone as model drug



er to predict systemic
S



Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

Development of the dermal absorption model for the ketoprofen local and systemic exposure prediction



ed skin and their
els.



Sebastian Polak^{1,2}, Nikunj Kumar Patel¹

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland



Predicting Diffusion in the Dermis: a Physi

Assessing Formulation Attributes' Impact On Local And Systemic Exposure Of Clindamycin After Topical Application Of Pro-Drug Clindamycin Phosphate Using PBPK Modelling



James Clarke¹, Nikunj Kumar Patel¹, Sebastian Polak^{1,2}

¹Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, U

Sebastian Polak^{1,2}, Nikunj Kumar Patel¹, Karen Rowland-Yeo¹, Masoud Jamei¹

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

MPML MechDermA Publications

Papers and Posters

Modeling *in vitro* skin permeation experiments to mechanistically understand *in vivo* dermal absorption: Application of *in vitro-in vivo* extrapolation (IVIVE) and physiological based pharmacokinetic modeling using testosterone as model drug

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University

CERTARA
Simcyp

er to predict systemic

CERTARA
Simcyp

Mechanistic Physiologically-Based Pharmacokinetic Modelling for Prediction of Dermal Absorption in Psoriatic Patients

F. MARTINS¹, N. PATEL¹, M. JAMEI¹ and S. POLAK^{1,2}

¹Simcyp Limited, UK; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

Email: Frederico.martins@certara.com

Development of the dermal absorption model for the ketoprofen local and systemic exposure prediction

CERTARA
Simcyp

ed skin and their
els.

CERTARA
Simcyp

Sebastian Polak^{1,2}, Nikunj Kumar Patel¹

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland



Predicting Diffusion in the Dermis: a Physiologically-Based Pharmacokinetic Modelling

Assessing Formulation Attributes' Impact On Local And Systemic Exposure Of Clindamycin After Topical Application Of Pro-Drug Clindamycin Phosphate Using PBPK Modelling

CERTARA
Simcyp

James Clarke¹, Nikunj Kumar Patel¹, Sebastian Polak^{1,2}

¹Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, U

Sebastian Polak^{1,2}, Nikunj Kumar Patel¹, Karen Rowland-Yeo¹, Masoud Jamei¹

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

MPML MechDermA Publications

Papers and Posters

Modeling *in vitro* skin permeation experiments to mechanistically understand *in vivo* dermal absorption: Application of *in vitro-in vivo* extrapolation (IVIVE) and physiological based pharmacokinetic modeling using testosterone as model drug

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University



er to predict systemic
S



Mechanistic Physiologically-Based Pharmacokinetic Modelling for Prediction of Dermal Absorption in Psoriatic Patients

F MARTINS¹, N PATEL¹, M. JAMEI¹ and S POLAK^{1,2}

¹Simcyp Limited, UK; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

Email: Frederico.martins@certara.com



Development of the dermal absorption model for the ketoprofen local and systemic exposure

Sebastian Polak^{1,2}, Nikunj Kumar Patel¹

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University

Predicting local tissue concentrations after topical drug application with a physiologically-based pharmacokinetic model

James Clarke, Sebastian Polak, Nikunj Kumar Patel

Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom



Predicting Diffusion in the Dermis: a Physiologically-Based Pharmacokinetic Model

Assessing Formulation Attributes' Impact On Local And Systemic Exposure Of Clindamycin After Topical Application Of Pro-Drug Clindamycin Phosphate Using PBPK Modelling

James Clarke¹, Nikunj Kumar Patel¹, Sebastian Polak^{1,2}

¹Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, U

Sebastian Polak^{1,2}, Nikunj Kumar Patel¹, Karen Rowland-Yeo¹, Masoud Jamei¹

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland



MPML MechDermA Publications

Papers and Posters

Modeling *in vitro* skin permeation experiments to mechanistically understand *in vivo* dermal absorption: Application of *in vitro-in vivo* extrapolation (IVIVE) and physiological based pharmacokinetic modeling using testosterone as model drug

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University

Certara logo
er to predict systemic

Mechanistic Physiologically-Based Pharmacokinetic Modelling for Prediction of Dermal Absorption in Psoriatic Patients

F. MARTINS¹, N. PATEL¹, M. JAMEI¹ and S. POLAK^{1,2}

¹Simcyp Limited, UK; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

Email: Frederico.martins@certara.com

Certara logo

Development of the dermal absorption model for the ketoprofen local and systemic exposure

Sebastian Polak^{1,2}, Nikunj Kumar Patel¹

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University

Predicting local tissue concentrations after topical drug application with a physiologically-based pharmacokinetic model

James Clarke, Sebastian Polak, Nikunj Kumar Patel

Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom

CERTARA logo
Simcyp

CERTARA logo
Simcyp

CERTARA logo
Simcyp

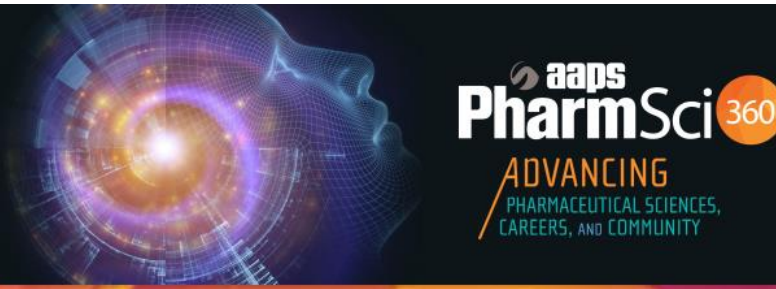


#T1230-05-037
Predicting Depth Resolved Concentrations in the Dermis using PBPK modelling: Design, development and verification of the model with five drugs

James Clarke, Nikunj Kumar Patel, Sebastian Polak

Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom

CONTACT INFORMATION: James.Clarke@Certara.com



CERTARA logo
Simcyp

MPML MechDerma Publications

Papers and Posters

**Mechanistic modelling of dermal drug absorption using the Simcyp Multi-phase Multi-layer MechDerma model:
Case study of a transdermal patch formulation of weak base drug timolol**

N. Patel^a, S. Cristea^a, R. Rose^a, F. Salem^a, K. Abduljalil^a, T. Johnson^a, M. Jamei^a, S. G. Raney^b, X. Zhang^b,
H.-P. Lin^b, B. Newman^b, E. Chow^b, P. Ghosh^b, J. Fan^b, L. Fang^b, S. Polak^{a,c}

^a Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ^b Office of Generic Drugs, US FDA, Silver Spring, Maryland, USA; ^c Faculty of Pharmacy, Jagiellonian University Medical College, Poland.



Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian U



er to predict systemic
S

d Pharmacokinetic
mal Absorption in



PSORITIC PATIENTS

F MARTINS¹, N PATEL¹, M. JAMEI¹ and S POLAK^{1,2}

¹Simcyp Limited, UK; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

Email: Frederico.martins@certara.com

Development of the dermal absorption model for the
ketoprofen local and systemic expo

**Predicting local tissue concentrations after topical
drug application with a physiologically-based
pharmacokinetic model**

Sebastian Polak^{1,2}, Nikunj Kumar Patel¹

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian Univ

James Clarke, Sebastian Polak, Nikunj Kumar Patel

Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom



#T1230-05-037

**Predicting Depth Resolved Concentrations in the Dermis using
PBPK modelling: Design, development and verification of the
model with five drugs**

James Clarke, Nikunj Kumar Patel, Sebastian Polak

Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom

CONTACT INFORMATION: James.Clarke@Certara.com



MPML MechDerma Publications

Papers and Posters

**Mechanistic modelling of dermal drug absorption using the Simcyp Multi-phase Multi-layer MechDerma model:
Case study of a transdermal patch formulation of weak base drug timolol**

N. Patel^a, S. Cristea^a, R. Rose^a, F. Salem^a, K. Abduljalil^a, T. Johnson^a, M. Jamei^a, S. G. Raney^b, X. Zhang^b,
H.-P., Lin^b, B. Newman^b, E. Chow^b, P. Ghosh^b, J. Fan^b, L. Fang^b, S. Polak^{a,c}

^a Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ^b Office of Generic Drugs, US FDA, Silver Spring, Maryland, USA; ^c Faculty of Pharmacy, Jagiellonian University Medical College, Poland.



Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian U



er to predict systemic
S
d Pharmacokinetic
mal Absorption in
PSORITIC PATIENTS

F MARTINS¹, N PATEL¹, M. JAMEI¹ and S POLAK^{1,2}

Add your Assigned Poster Number by replacing this text

Multi-Phase Multi-Layer Mechanistic Physiologically based Pharmacokinetic Dermal Absorption Model verification including inter and intra individual variability assessment using nicotine as a model drug

Frederico Severino Martins¹, Nikunj Kumar Patel¹, James Clarke¹, Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

aaps PharmSci 360
ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

CONTACT INFORMATION: NikunjKumar.Patel@certara.com

James Clarke, Sebastian Polak, Nikunj Kumar Patel

Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom



#T1230-05-037

Predicting Depth Resolved Concentrations in the Dermis using PBPK modelling: Design, development and verification of the model with five drugs

James Clarke, Nikunj Kumar Patel, Sebastian Polak

Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom

CONTACT INFORMATION: James.Clarke@Certara.com

aaps PharmSci 360
ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

MPML MechDerMA Publications

Papers and Posters

**Mechanistic modelling of dermal drug absorption using the Simcyp Multi-phase Multi-layer MechDerMA model:
Case study of a transdermal patch formulation of weak base drug timolol**

N. Patel^a, S. Cristea^a, R. Rose^a, F. Salem^a, K. Abduljalil^a, T. Johnson^a, M. Jamei^a, S. G. Raney^b, X. Zhang^b,
H.-P. Lin^b, B. Newman^b, E. Chow^b, P. Ghosh^b, J. Fan^b, L. Fang^b, S. Polak^{a,c}

^a Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ^b Office of Generic Drugs, US FDA, Silver Spring, Maryland, USA; ^c Faculty of Pharmacy, Jagiellonian University Medical College, Poland.



Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

PSORITIC PATIENTS

F. MARTINS¹, N. PATEL¹, M. JAMEI¹ and S. POLAK^{1,2}

Add your Assigned Poster Number by replacing this text

CONTACT INFORMATION: N

Multi-Phase Multi-Layer Mechanistic Physiologically based Pharmacokinetic Dermal Absorption Model verification including inter and intra individual variability assessment using nicotine as a model drug

Frederico Severino Martins¹, Nikunj Kumar Patel¹, James Clarke¹, Sebastian Polak^{1,2}

Performance verification of mechanistic dermal physiological based pharmacokinetic (PBPK) model for enhanced understanding of dermal absorption: prediction of local tissue exposure after topical application of acitretin

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

Predicting Depth Resolved Concentrations in the Dermis using PBPK modelling: Design, development and verification of the model with five drugs

James Clarke, Nikunj Kumar Patel, Sebastian Polak

Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom

CONTACT INFORMATION: James.Clarke@Certara.com

#T1230-05-037



MPML MechDerMA Publications

Papers and Posters

**Mechanistic modelling of dermal drug absorption using the Simcyp Multi-phase Multi-layer MechDerMA model:
Case study of a transdermal patch formulation of weak base drug timolol**

N. Patel^a, S. Cristea^a, R. Rose^a, F. Salem^a, K. Abduljalil^a, T. Johnson^a, M. Jamei^a, S. G. Raney^b, X. Zhang^b,
H.-P. Lin^b, B. Newman^b, E. Chow^b, P. Ghosh^b, J. Fan^b, L. Fang^b, S. Polak^{a,c}

^a Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ^b Office of Generic Drugs, US FDA, Silver Spring, Maryland, USA; ^c Faculty of Pharmacy, Jagiellonian University Medical College, Poland.



Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian U

PSORITIC PATIENTS

F MARTINS¹, N PATEL¹, M. JAMEI¹ and S POLAK^{1,2}

Add your Assigned Poster Number by replacing this text

CONTACT INFORMATION:

Multi-Phase Multi-Layer Mechanistic Physiologically based Pharmacokinetic Dermal Absorption Model verification including inter and intra individual variability assessment using nicotine as a model drug

Frederico Severino Martins¹, Nikunj Kumar Patel¹, James Clarke¹, Sebastian Polak^{1,2}

Performance verification of mechanistic dermal physiological based pharmacokinetic (PBPK) model for enhanced understanding of dermal absorption: prediction of local tissue exposure after topical application of acitretin

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

#T1230-05-037

CONTACT INFORM

Predicting Depth Resolved Concentrations in the Dermis using PBPK modelling: Design, development and verification of the model with five drugs

Development and Validation of a Dermal PBPK Model for Prediction of the Hair Follicular Absorption of Caffeine: Application of the Simcyp MPML MechDerMA model

Frederico S Martins¹, Nikunj Kumar Patel¹, Masoud Jamei¹ and Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

MPML MechDermA Publications

Papers and Posters

Mechanistic modelling of dermal drug absorption using the
Case study of a transdermal patch form

N. Patel^a, S. Cristea^a, R. Rose^a, F. Salem^a, K. Abduljalil^a, T. J.
H.-P., Lin^b, B. Newman^b, E. Chow^b, P. Ghosh^b



^a Simcyp Limited (a Certara Company), Sheffield
Spring, Maryland, USA; ^c Faculty of Pharmacy, Jagiellonian

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian U

Multi-phase Multi-layer MechDermA model: Development,
verification and application of a PBPK-PD model of dermal
absorption for transdermal product assessment

Frederico Martins¹, Nikunj Kumar Patel¹, Farzaneh Salem¹, Masoud Jamei¹, Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

simulator | consultancy | education

PSORITIC PATIENTS

F MARTINS¹, N PATEL¹, M. JAMEI¹ and S POLAK^{1,2}



Simcyp

Simcyp

Add your
Assigned
Poster
Number by
replacing
this text

CONTACT INFORMATION: N

Multi-Phase Multi-Layer Mechanistic Physiologically based Pharmacokinetic Dermal Absorption Model
verification including inter and intra individual variability assessment using nicotine as a model drug

Frederico Severino Martins¹, Nikunj Kumar Patel¹, James Clarke¹, Sebastian Polak^{1,2}

¹Sim

Performance verification of mechanistic dermal physiological
based pharmacokinetic (PBPK) model for enhanced
understanding of dermal absorption: prediction of local tissue
exposure after topical application of acitretin

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

#T1230-05-
037

CONTACT INFORM

Predicting Depth Resolved Concentrations in the Dermis using
PBPK modelling: Design, development and verification of the
model with five drugs

Development and Validation of a Dermal PBPK Model for
Prediction of the Hair Follicular Absorption of Caffeine:
Application of the Simcyp MPML MechDermA model

Frederico S Martins¹, Nikunj Kumar Patel¹, Masoud Jamei¹ and Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland



Simcyp



Simcyp



Simcyp



Simcyp



MPML MechDermA Publications

Papers and Posters

Mechanistic modelling of dermal drug absorption using the
Case study of a transdermal patch form

N. Patel^a, S. Cristea^a, R. Rose^a, F. Salem^a, K. Abduljalil^a, T. J.
H.-P., Lin^b, B. Newman^b, E. Chow^b, P. Ghosh^b



^a Simcyp Limited (a Certara Company), Sheffield
Spring, Maryland, USA; ^c Faculty of Pharmacy, Jagiellonian University Medical College, Poland.

Multi-phase Multi-layer MechDermA model: Development,
verification and application of a PBPK-PD model of dermal
absorption for transdermal product assessment

Frederico Martins¹, Nikunj Kumar Patel¹, Farzaneh Salem¹, Masoud Jamei¹, Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

simulator | consultancy | education



Simcyp

Multi-phase Multi-layer MechDermA model: Development,
verification and application of PBPK-PD model of dermal
absorption for topical product assessment

Frederico Martins¹, Nikunj Kumar Patel¹, Farzaneh Salem¹, Masoud Jamei¹, Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

CONTACT INFORMATION: N

Performance verification of mechanistic dermal physiological
based pharmacokinetic (PBPK) model for enhanced
understanding of dermal absorption: prediction of local tissue
exposure after topical application of acitretin

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

#T1230-05-
037

Predicting Depth Resolved Concentrations in the Dermis using
PBPK modelling: Design, development and verification of the
model with five drugs

Development and Validation of a Dermal PBPK Model for
Prediction of the Hair Follicular Absorption of Caffeine:
Application of the Simcyp MPML MechDermA model

Frederico S Martins¹, Nikunj Kumar Patel¹, Masoud Jamei¹ and Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland



Simcyp



Simcyp



Simcyp



Simcyp



Simcyp

MPML MechDerMA Publications

Papers and Posters

Mechanistic modelling of dermal drug absorption using the
Case study of a transdermal patch form

N. Patel^a, S. Cristea^a, R. Rose^a, F. Salem^a, K. Abduljalil^a, T. J.
H.-P., Lin^b, B. Newman^b, E. Chow^b, P. Ghosh^c



^a Simcyp Limited (a Certara Company), Sheffield
Spring, Maryland, USA; ^c Faculty of Pharmacy, Jagiellonian University Medical College, Poland.

Multi-phase Multi-layer MechDerMA model: Development,
verification and application of a PBPK-PD model of dermal
absorption for transdermal product assessment

Frederico Martins¹, Nikunj Kumar Patel¹, Farzaneh Salem¹, Masoud Jamei¹, Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

simulator | consultancy | education



Simcyp

Multi-phase Multi-layer MechDerMA model: Development,
verification and application of PBPK-PD model of dermal
absorption for topical product assessment

Frederico Martins¹, Nikunj Kumar Patel¹, Farzaneh Salem¹, Masoud Jamei¹, Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

CONTACT INFORMATION: N

Performance verification of mechanistic dermal physiological
based pharmacokinetic (PBPK) model for enhanced
understanding of dermal absorption: prediction of local tissue
exposure after topical application of acitretin

Sumit Arora¹, Nikunj Kumar Patel¹ and Sebastian Polak^{1,2}

¹Certara UK Ltd, Simcyp Division, Sheffield; ²Faculty of Pharmacy, Jagiellonian University Medical College, Poland

#T1230-05-
037

Predicting Depth Resolved Concentrations in the Dermis using
PBPK modelling: Design, development and verification of the
model with five drugs

Development and
Prediction of
Application of

Development and Validation of a Dermal PBPK Model for
Prediction of the Hair Follicular Absorption of Caffeine:
Application of the Simcyp MPML MechDerMA model

CONTACT INFORM

Frederico S Martins¹, Nikunj Kumar Patel¹

¹Simcyp (a Certara company), Sheffield, United Kingdom

Frederico S Martins¹, Nikunj Kumar Patel¹, Masoud Jamei¹ and Sebastian Polak^{1,2}

¹Simcyp (a Certara company), Sheffield, United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland

MPML MechDerMA Publications

Papers and Posters

Mechanistic modelling of dermal drug absorption using the Certara Simcyp MechDerMA model: Case study of a transdermal patch formulation

N. Patel^a, S. Cristea^a, R. Rose^a, F. Salem^a, K. Abduljalil^a, T. J.

H.-P., Lin^b, B. Newman^b, E. Chow^b, P. Ghosh^c

^a Simcyp Limited (a Certara Company), Sheffield

Spring, Maryland, USA; ^c Faculty of Pharmacy, Jagiellonian University Medical College, Poland.



Multi-phase Multi-layer MechDerMA model: Development, verification and application of a PBPK-PD model of dermal absorption for transdermal product assessment

Frederico Martins¹, Nikunj Kumar Patel¹, Farzaneh Salem¹, Masoud Jamei¹, Sebastian Polak^{1,2}

¹ Simcyp (a Certara company), Sheffield, United Kingdom, ² Jagiellonian University Medical College, Kraków, Poland

simulator | consultancy | education



Simcyp

Multi-phase Multi-layer MechDerMA model: Development, verification and application of PBPK-PD model of dermal absorption for topical product assessment

Frederico Martins¹, Nikunj Kumar Patel¹, Farzaneh Salem¹, Masoud Jamei¹, Sebastian Polak^{1,2}

¹ Simcyp (a Certara company), Sheffield, United Kingdom, ² Jagiellonian University Medical College, Kraków, Poland



Simcyp



Simcyp

Performance verification of mechanistic dermal physiological based pharmacokinetic (PBPK) model for enhanced understanding of dermal absorption: prediction of local tissue exposure after topical application of acitretin

CONTACT INFORMATION: N



Simcyp



Development and validation of Dermal PBPK model towards virtual bioequivalence assessment: Prediction of dermal drug absorption of various Ibuprofen formulations using Simcyp MechDerMA model

Frederico S. Martins^{1*}, Nikunj Kumar Patel¹, Sinziana Cristea^{1#} and Sebastian Polak^{1,2}

¹ Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ² Faculty of Pharmacy, Jagiellonian University Medical College, Poland; [#] currently at Leiden Academic Centre for Drug Research

*Frederico.Martins@Certara.com



Simcyp

Frederico S Martins¹, Nikunj Kumar Patel¹

¹ Simcyp (a Certara company), Sheffield, United Kingdom

Frederico S Martins¹, Nikunj Kumar Patel¹, Masoud Jamei¹ and Sebastian Polak^{1,2}

¹ Simcyp (a Certara company), Sheffield, United Kingdom, ² Jagiellonian University Medical College, Kraków, Poland

MPML MechDerMA Publications

W2073 **Quantitative Prediction of Dermal Drug Absorption using MPML-MechDerMA model: Relative Effects of Application Site on Rivastigmine Pharmacokinetics from a Transdermal Delivery System**

T. Abdulla¹, N. K. Patel¹, S. Polak^{1,2}, F. Martins¹, A. Rostami-Hodjegan^{1,3}, M. Jamei¹

¹ Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ² Faculty of Pharmacy, Jagiellonian University Medical College, Cracow, Poland; ³ Centre for Applied Pharmacokinetic Research, The University of Manchester, U.K.

2017

AAPS ANNUAL MEETING & EXPOSITION



DEVELOPING SCIENCE. IMPACTING HEALTH.

CERTARA

Simcyp

Poland

Simcyp

CONTACT INFORMATION: tariq.abdulla@certara.com

Multi-phase Multi-layer MechDerMA model: Development, verification and application of PBPK-PD model of dermal absorption for topical product assessment

CERTARA

Simcyp

Frederico Martins¹, Nikunj Kumar Patel¹, Farzaneh Salem¹, Masoud Jamei¹, Sebastian Polak^{1,2}

¹ Simcyp (a Certara company), Sheffield, United Kingdom, ² Jagiellonian University Medical College, Kraków, Poland

Performance verification of mechanistic dermal physiological based pharmacokinetic (PBPK) model for enhanced understanding of dermal absorption: prediction of local tissue exposure after topical application of acitretin

CONTACT INFORMATION: N

CERTARA

Simcyp

aaps PharmSci 360

CERTARA

Simcyp

Skin Forum

Development and validation of Dermal PBPK model towards virtual bioequivalence assessment: Prediction of dermal drug absorption of various Ibuprofen formulations using Simcyp MechDerMA model

Frederico S. Martins^{1*}, Nikunj Kumar Patel¹, Sinziana Cristea^{1#} and Sebastian Polak^{1,2}

¹ Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ² Faculty of Pharmacy, Jagiellonian University Medical College, Poland; [#] currently at Leiden Academic Centre for Drug Research

*Frederico.Martins@Certara.com

CERTARA
Implementing Translational Science

simcyp
simulator | consultancy | education

CERTARA

CERTARA

Simcyp

Frederico S Martins¹, Nikunj Kumar Patel¹

¹ Simcyp (a Certara company), SI

Frederico S Martins¹, Nikunj Kumar Patel¹, Masoud Jamei¹ and Sebastian Polak^{1,2}

¹ Simcyp (a Certara company), Sheffield, United Kingdom, ² Jagiellonian University Medical College, Kraków, Poland

MPML MechDerMA Publications

W2073 **Quantitative Prediction of Dermal Drug Absorption using MPML-MechDerMA model: Relative Effects of Application Site on Rivastigmine Pharmacokinetics from a Transdermal Delivery System**

T. Abdulla¹, N. K. Patel¹, S. Polak^{1,2}, F. Martins¹, A. Rostami-Hodjegan^{1,3}, M. Jamei¹

¹ Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ² Faculty of Pharmacy, Jagiellonian University Medical College, Cracow, Poland; ³ Centre for Applied Pharmacokinetic Research, The University of Manchester, U.K.

2017

AAPS ANNUAL MEETING & EXPOSITION



DEVELOPING SCIENCE. IMPACTING HEALTH.

CERTARA

Simcyp

Poland

Simcyp

CONTACT INFORMATION: tariq.abdulla@certara.com

Multi-phase Multi-layer MechDerMA model: Development, verification and application of PBPK-PD model of dermal absorption for topical product assessment

CERTARA

Simcyp

Frederico Martins¹, Nikunj Kumar Patel¹, Farzaneh Salem¹, Masoud Jamei¹, Sebastian Polak^{1,2}

¹ Simcyp (a Certara company), Sheffield, United Kingdom, ² Jagiellonian University Medical College, Kraków, Poland

Performance verification of mechanistic dermal physiological based pharmacokinetic (PBPK) model for enhanced

Development and verification of PBPK model for a topical cream formulation of Trifarotene to simulate local and systemic exposure and model application to simulate potential CYP-mediated drug-drug interactions

Poster Number

W4060

N. Patel¹, K. Benkali², H. Osman-Ponchet², S. Neuhoff¹, S. Polak¹, N. Wagner³

¹ Simcyp Ltd. (a Certara Company), Sheffield (United Kingdom); ² Galderma R&D, Sophia Antipolis (France); ³ Galderma R&D, Fort Worth (USA)

CONTACT INFORMATION: Nathalie.wagner@galderma.com



2017

AAPS ANNUAL MEETING & EXPOSITION

DEVELOPING SCIENCE. IMPACTING HEALTH.

CERTARA

Simcyp

CERTARA
Implementing Translational Science

¹ Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ² Faculty of Pharmacy, Jagiellonian University Medical College, Poland; [#] currently at Leiden Academic Centre for Drug Research

*Frederico.Martins@Certara.com

simcyp
simulator | consultancy | education

CERTARA

Simcyp

Frederico S Martins¹, Nikunj Kumar Patel¹

¹ Simcyp (a Certara company), Sheffield, United Kingdom

Frederico S Martins¹, Nikunj Kumar Patel¹, Masoud Jamei¹ and Sebastian Polak^{1,2}

¹ Simcyp (a Certara company), Sheffield, United Kingdom, ² Jagiellonian University Medical College, Kraków, Poland

MPML MechDerMA Publications

W2073 **Quantitative Prediction of Dermal Drug Absorption using MPML-MechDerMA model: Relative Effects of Application Site on Rivastigmine Pharmacokinetics from a Transdermal Delivery System**

T. Abdulla¹, N. K. Patel¹, S. Polak^{1,2}, F. Martins¹, A. Rostami-Hodjegan^{1,3}, M. Jamei¹

¹ Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.; ² Faculty of Pharmacy, Jagiellonian University Medical College, Cracow, Poland; ³ Centre for Applied Pharmacokinetic Research, The University of Manchester, U.K.

2017
AAPS ANNUAL
MEETING & EXPOSITION



DEVELOPING SCIENCE. IMPACTING HEALTH.

CERTARA

Simcyp

Poland

Simcyp

CONTACT INFORMATION: tariq.abdulla@certara.com

Multi-phase Multi-layer MechDerMA model: Development, verification and application of PBPK-PD model of dermal absorption for topical product assessment

CERTARA

Simcyp



Article

Physiologically Based Pharmacokinetic Modeling of Transdermal Selegiline and Its Metabolites for the Evaluation of Disposition Differences between Healthy and Special Populations

Santosh Kumar Puttrevu^{1,*}, Sumit Arora¹, Sebastian Polak^{1,2} and Nikunj Kumar Patel¹

¹ Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield S1 2BJ, UK; Sumit.Arora@certara.com (S.A.); sebastian.polak@certara.com (S.P.); nikunj.kumar.patel@certara.com (N.K.P.)

² Pharmacoepidemiology and Pharmacoeconomics Unit, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, str., 30-688 Krakow, Poland

* Correspondence: santoshkumar.puttrevu@certara.com; Tel.: +44 (0) 114 460 0165

Received: 11 August 2020; Accepted: 28 September 2020; Published: 30 September 2020

2

College, Kraków, Poland

Physiologically Based Pharmacokinetic (PBPK) model for a topical cream formulation of selegiline: Systemic exposure and model application to drug-drug interactions

S. Polak^{1,2}, S. Neuhoff¹, S. Polak¹, N. Wagner³

¹ Sheffield Hallam University, Sheffield, United Kingdom; ² Galderma R&D, Sophia Antipolis, France; ³ University of Applied Sciences, Applied Sciences, Applied Sciences (A)



2017
AAPS ANNUAL
MEETING & EXPOSITION

DEVELOPING SCIENCE. IMPACTING HEALTH.

CERTARA

Simcyp

Faculty of Pharmacy, Jagiellonian University Medical College, Cracow, Poland; ² Centre for Drug Research, Jagiellonian University Medical College, Cracow, Poland

simcyp
simulator | consultancy | education

CERTARA

Simcyp

*, Masoud Jamei¹ and Sebastian Polak^{1,2}

¹ Sheffield Hallam University, Sheffield, United Kingdom, ² Jagiellonian University Medical College, Kraków, Poland

MPML MechDerMA Publications

ARTICLE

Multi-phase multi-layer mechanistic dermal absorption (MPML MechDerMA) model to predict local and systemic exposure of drug products applied on skin

Nikunj Kumar Patel¹ | James F. Clarke¹ | Farzaneh Salem¹ | Tariq Abdulla¹ | Frederico Martins¹ | Sumit Arora¹ | Eleftheria Tsakalozou² | Arran Hodgkinson¹ | Omid Arjmandi-Tash¹ | Sinziana Cristea¹ | Priyanka Ghosh² | Khondoker Alam² | Sam G. Raney² | Masoud Jamei¹ | Sebastian Polak^{1,3}



Article

Physiologically Based Pharmacokinetic Modeling of Transdermal Selegiline and Its Metabolites for the Evaluation of Disposition Differences between Healthy and Special Populations

Santosh Kumar Puttrevu^{1,*}, Sumit Arora¹, Sebastian Polak^{1,2} and Nikunj Kumar Patel¹

¹ Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield S1 2BJ, UK; Sumit.Arora@certara.com (S.A.); sebastian.polak@certara.com (S.P.); nikunj.kumar.patel@certara.com (N.K.P.)

² Pharmacoepidemiology and Pharmacoeconomics Unit, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, str., 30-688 Krakow, Poland

* Correspondence: santoshkumar.puttrevu@certara.com; Tel.: +44 (0) 114 460 0165

Received: 11 August 2020; Accepted: 28 September 2020; Published: 30 September 2020



College, Kraków, Poland

BPK model for a topical cream formulation of systemic exposure and model application to drug-drug interactions

onchet², S. Neuhoff¹, S. Polak¹, N. Wagner³
field (United Kingdom); ²Galderma R&D, Sophia Antipolis (A)

of Pharmacy, Jagiellonian University Medical Centre for Drug Research
om

, Masoud Jamei¹ and Sebastian Polak^{1,2}

United Kingdom, ²Jagiellonian University Medical College, Kraków, Poland



MPML MechDerMA Publications

ARTICLE

Multi-phase multi-layer mechanistic dermal absorption (MPML MechDerMA) model to predict local and systemic exposure of drug products applied on skin

Nikunj Kumar Patel¹ | James F. Clarke¹ | Farzaneh Salem¹ | Tariq Abdulla¹ | Frederico Martins¹ | Sumit Arora¹ | Eleftheria Tsakalozou² | Arran Hodgkinson¹ | Omid Arjmandi-Tash¹ | Sinziana Cristea¹ | Priyanka Ghosh² | Khondoker Alam² | Sam G. Raney² | Masoud Jamei¹ | Sebastian Polak^{1,3}



Article

Physiologically Based Pharmacokinetic Modeling of Transdermal Selegiline and Its Metabolites for the Evaluation of Disposition Differences between Healthy and Special Populations

Santosh Kumar Puttrevu^{1,*}, Sumit Arora¹, Sebastian Polak^{1,2} and Nikunj Kumar Patel¹

¹ Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield S1 2BJ, UK; Sumit.Arora@certara.com (S.A.); sebastian.polak@certara.com (S.P.); nikunj.kumar.patel@certara.com (N.K.P.)

² Pharmacoepidemiology and Pharmacoeconomics Unit, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, str., 30-688 Krakow, Poland

* Correspondence: santoshkumar.puttrevu@certara.com; Tel.: +44 (0) 114 460 0165

Received: 11 August 2020; Accepted: 28 September 2020; Published: 30 September 2020



College, Kraków, Poland

molecular
pharmaceutics

pubs.acs.org/molecularpharmaceutics

Article

Mechanistic Modeling of In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model

Sumit Arora,* James Clarke, Eleftheria Tsakalozou, Priyanka Ghosh, Khondoker Alam, Jeffery E. Grice, Michael S. Roberts, Masoud Jamei, and Sebastian Polak



Cite This: *Mol. Pharmaceutics* 2022, 19, 3139–3152



Read Online

United Kingdom, Jagiellonian University Medical College, Kraków, Poland



MechDerMA
Pharmacokinetics

2017

AAPS ANNUAL
MEETING & EXPOSITION



DEVELOPING SCIENCE. IMPACTING HEALTH.

CERTARA

Simcyp

Simcyp

CERTARA

Simcyp

aaps
PharmSci 360

CERTARA

Multi-phase multi-layer mechanistic dermal absorption (MPML MechDerma) model to predict local and systemic exposure of drug products applied on skin

Nikunj Kumar Patel¹ | James F. Clarke¹ | Farzaneh Salem¹ | Tariq Abdulla¹ | Frederico Martins¹ | Sumit Arora¹ | Eleftheria Tsakalozou² | Arran Hodgkinson¹ | Omid Arjmandi-Tash¹ | Sinziana Cristea¹ | Priyanka Ghosh² | Khondoker Alam² | Sam G. Raney² | Masoud Jamei¹ | Sebastian Polak^{1,3}



Article

Physiologically Based Pharmacokinetic Modeling of Transdermal Selegiline and Its Metabolites for the Evaluation of Disposition Differences between Healthy and Special Populations

Santosh Kumar Puttrevu^{1,*}, Sumit Arora¹, Sebastian Polak^{1,2} and Nikunj Kumar Patel¹

¹ Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield S1 2BJ, UK; Sumit.Arora@certara.com (S.A.); sebastian.polak@certara.com (S.P.); nikunj.kumar.patel@certara.com (N.K.P.)

² Pharmacoepidemiology and Pharmacoeconomics Unit, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, str., 30-688 Krakow, Poland

* Correspondence: santoshkumar.puttrevu@certara.com; Tel.: +44 (0) 114 460 0165

Received: 11 August 2020; Accepted: 28 September 2020; Published: 30 September 2020



Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Development and Qualification of a Physiologically Based Pharmacokinetic Model of Finasteride and Minoxidil Following Scalp Application

Arpar Ngampanya^a, Udomsak Udomnilobol^b, Pakawadee Sermsappasuk^c, Natapol Pornputtpong^d, Boonsri Ongpipattanakul^d, Nikunj Kumar Patel^e, Suree Jianmongkol^{a,*}, Thomayant Prueksaritanont^{b,**}

^a Faculty of Pharmaceutical Sciences, Department of Pharmacology and Physiology, Chulalongkorn University, Bangkok, Thailand

^b Chulalongkorn University Drug Discovery and Drug Development Research Center (ChulaDDR), Chulalongkorn University, Bangkok, Thailand

College, Krakó



pubs.acs.org/molecularpharmaceutics

Article

Mechanistic Modeling of In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model

Sumit Arora,^{*} James Clarke, Eleftheria Tsakalozou, Priyanka Ghosh, Khondoker Alam, Jeffery E. Grice, Michael S. Roberts, Masoud Jamei, and Sebastian Polak



Cite This: *Mol. Pharmaceutics* 2022, 19, 3139–3152



Read Online

United Kingdom, ¹Jagiellonian University Medical College, Kraków, Poland

Multi-phase multi-layer mechanistic dermal absorption (MPML MechDerma) model to predict local and systemic exposure of drug products applied on skin

Nikunj Kumar Patel¹ | James F. Clarke¹ | Farzaneh Salem¹ | Tariq Abdulla¹ | Frederico Martins¹ | Sumit Arora¹ | Eleftheria Tsakalozou² | Arran Hodgkinson¹ | Omid Arjmandi-Tash¹ | Sinziana Cristea¹ | Priyanka Ghosh² | Khondoker Alam² | Sam G. Raney² | Masoud Jamei¹ | Sebastian Polak^{1,3}



Article

Physiologically Based Pharmacokinetic Modeling of Transdermal Selegiline and Its Metabolites for the Evaluation of Disposition Differences between Healthy and Special Populations

Santosh Kumar Puttrevu^{1,*}, Sumit Arora¹, Sebastian Polak^{1,2} and Nikunj Kumar Patel¹

¹ Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield S1 2BJ, UK; Sumit.Arora@certara.com (S.A.); sebastian.polak@certara.com (S.P.); nikunj.kumar.patel@certara.com (N.K.P.)

² Pharmacoepidemiology and Pharmacoeconomics Unit, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, str., 30-688 Krakow, Poland

* Correspondence: santoshkumar.puttrevu@certara.com; Tel.: +44 (0) 114 460 0165

Received: 11 August 2020; Accepted: 28 September 2020; Published: 30 September 2020



Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Development and Qualification of a Physiologically Based Pharmacokinetic Model of Finasteride and Minoxidil Following Scalp Application

Received: 24 September 2020 | Revised: 8 December 2020 | Accepted: 29 December 2020

DOI: 10.1002/psp4.12600

REVIEW



Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: A case for diclofenac sodium topical gel, 1%

Eleftheria Tsakalozou | Andrew Babiskin | Liang Zhao

Mechanistic Modeling of In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model

Sumit Arora,* James Clarke, Eleftheria Tsakalozou, Priyanka Ghosh, Khondoker Alam, Jeffery E. Grice, Michael S. Roberts, Masoud Jamei, and Sebastian Polak



Cite This: *Mol. Pharmaceutics* 2022, 19, 3139–3152



Read Online

United Kingdom, Jagiellonian University Medical College, Kraków, Poland



md
makol Thailand

Article

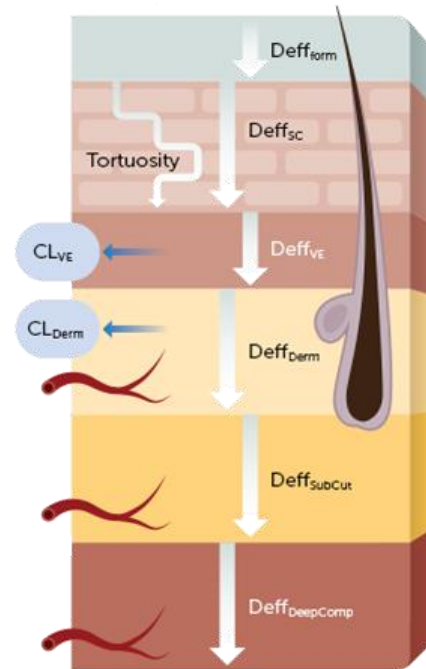


Integrating Mechanistic Modelling within the Generic Topical Drug Product Development Process

Workflow for maximising the impact of mechanistic models

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

Dermal *In Vitro* - *In Vivo* Extrapolation (IVIVE) with MPML MechDerma

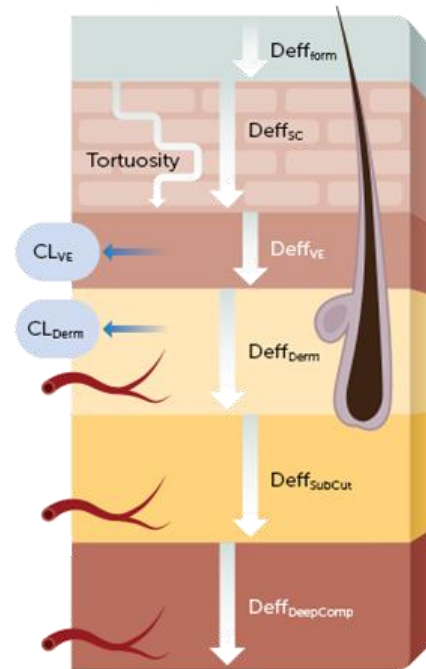


Dermal *In Vitro* - *In Vivo* Extrapolation (IVIVE) with MPML MechDermA

Input

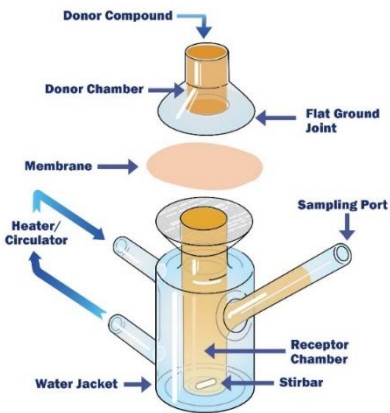
Understanding Q1, Q2 and Q3 properties of topical products

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



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

Input

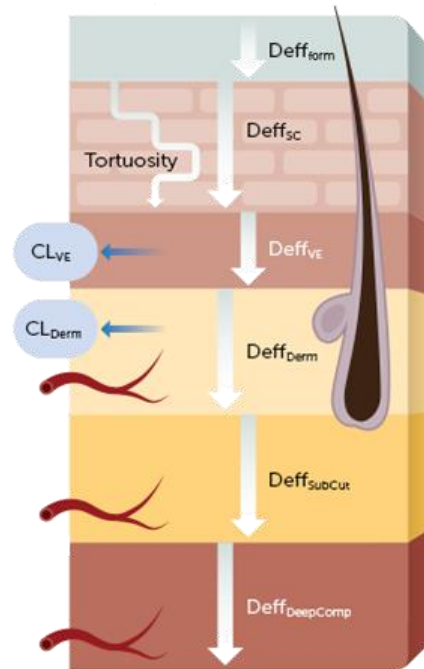


In vitro Release/Permeation Studies



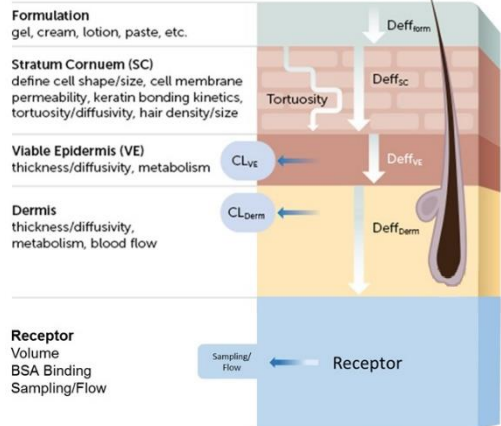
Understanding Q1, Q2 and Q3 properties of topical products

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



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

Input

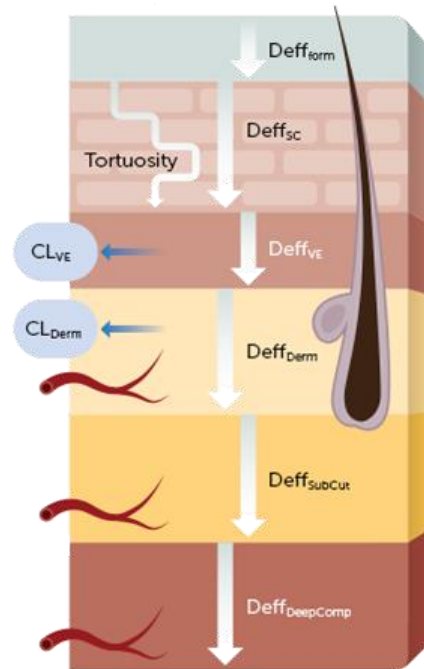


In vitro Release/Permeation Studies

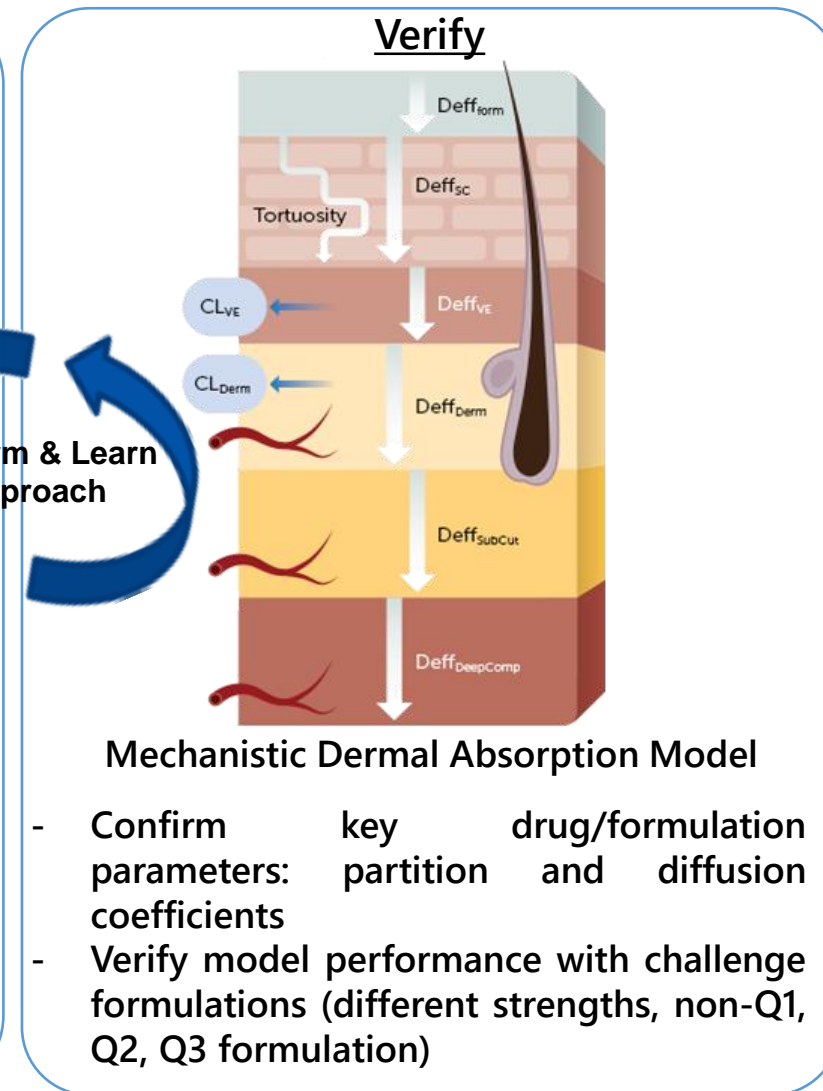
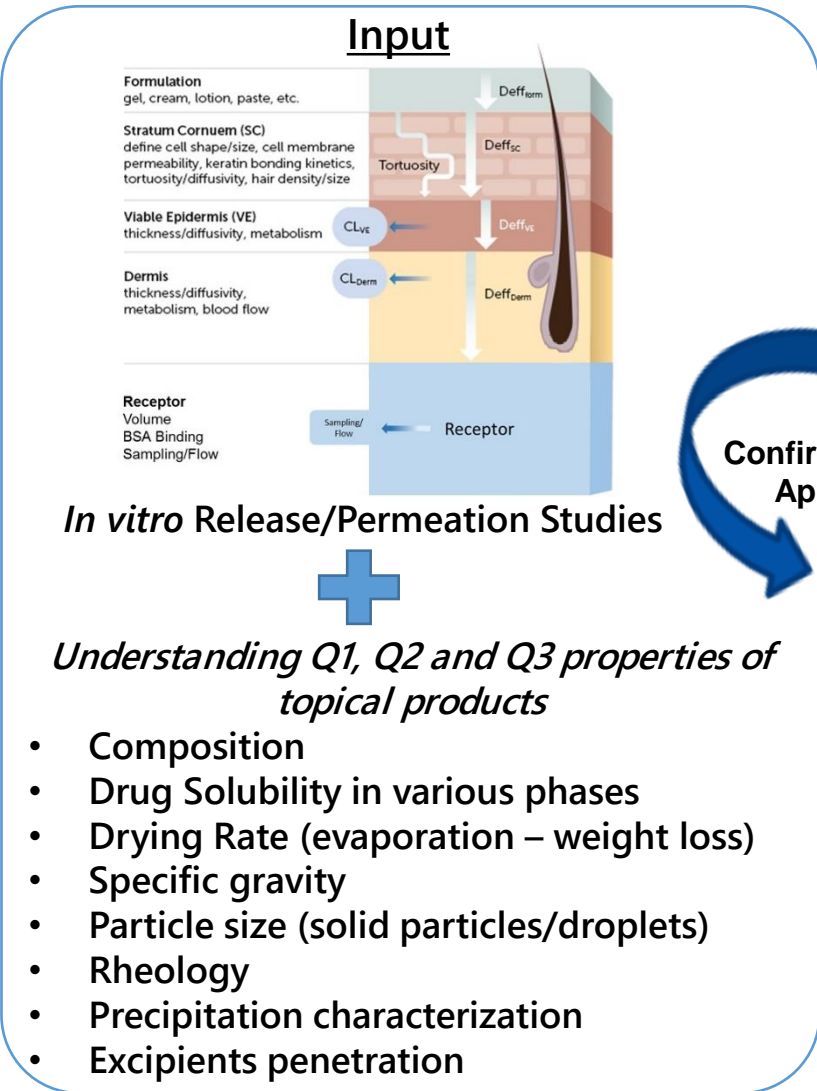


Understanding Q1, Q2 and Q3 properties of topical products

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



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



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

Input

Formulation
 gel, cream, lotion, paste, etc.

Stratum Corneum (SC)
 define cell shape/size, cell membrane permeability, keratin bonding kinetics, tortuosity/diffusivity, hair density/size

Viable Epidermis (VE)
 thickness/diffusivity, metabolism

Dermis
 thickness/diffusivity, metabolism, blood flow

Receptor
 Volume, BSA Binding, Sampling/Flow

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

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

Healthy NEurCaucasian

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

Diseased Population

Elderly Subjects

Paediatric Population

Integrated Mechanistic Modelling

Key:

ITEM

PROCESS

DATA

Integrated Mechanistic Modelling

Key:

ITEM

PROCESS

DATA

Formulation
Development

Model Development

Integrated Mechanistic Modelling

Key:

ITEM

PROCESS

DATA

Formulation
Development

Model Development

Preliminary PBPK
Model

Integrated Mechanistic Modelling

Key:

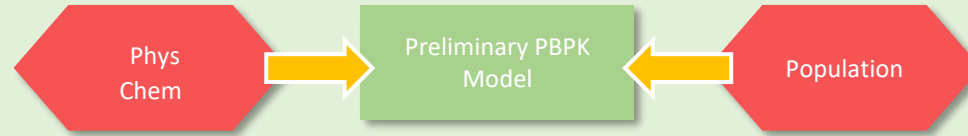
ITEM

PROCESS

DATA

Formulation
Development

Model Development



Integrated Mechanistic Modelling

Key:

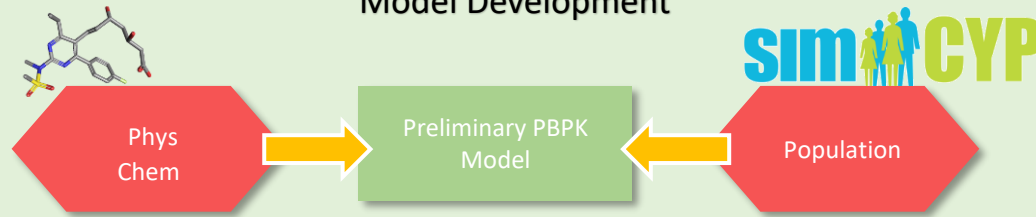
ITEM

PROCESS

DATA

Formulation
Development

Model Development



Integrated Mechanistic Modelling

Key:

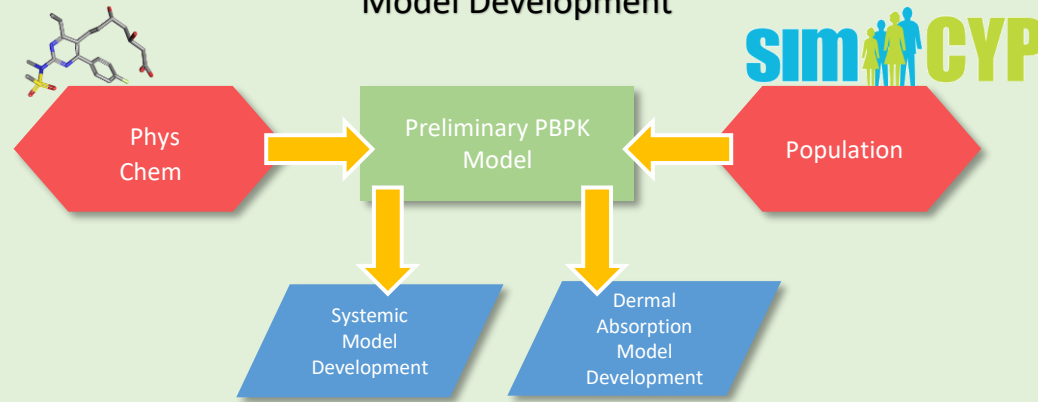
ITEM

PROCESS

DATA

Formulation
Development

Model Development



Integrated Mechanistic Modelling

Key:

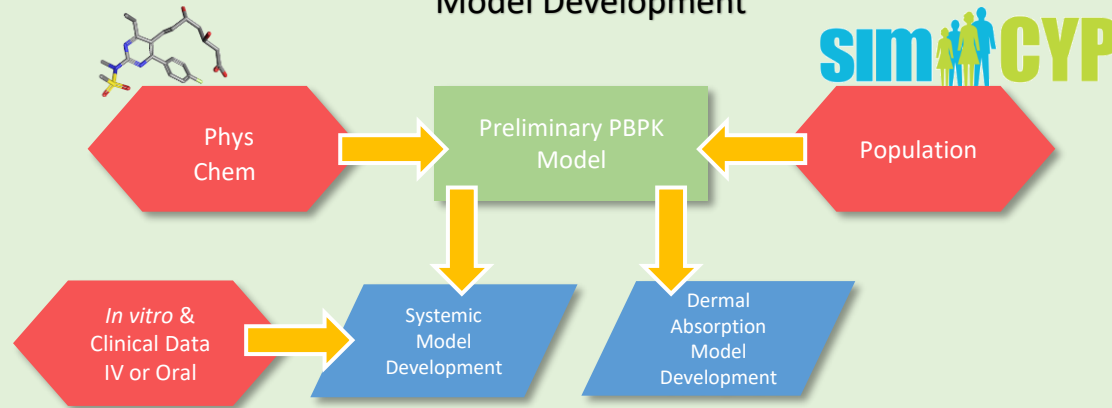
ITEM

PROCESS

DATA

Formulation
Development

Model Development



Integrated Mechanistic Modelling

Key:

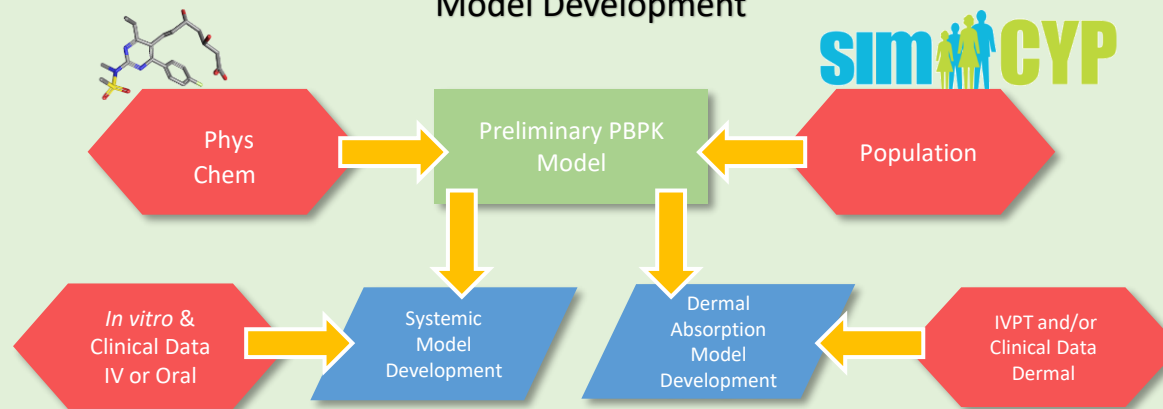
ITEM

PROCESS

DATA

Formulation
Development

Model Development



Integrated Mechanistic Modelling

Key:

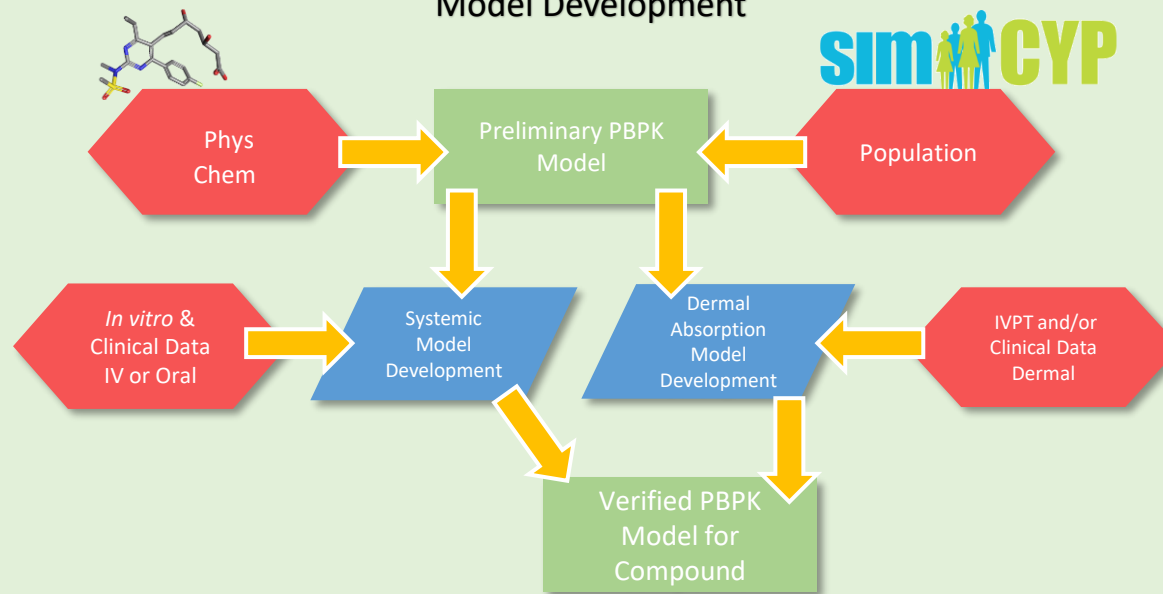
ITEM

PROCESS

DATA

Formulation
Development

Model Development



Integrated Mechanistic Modelling

Key:

ITEM

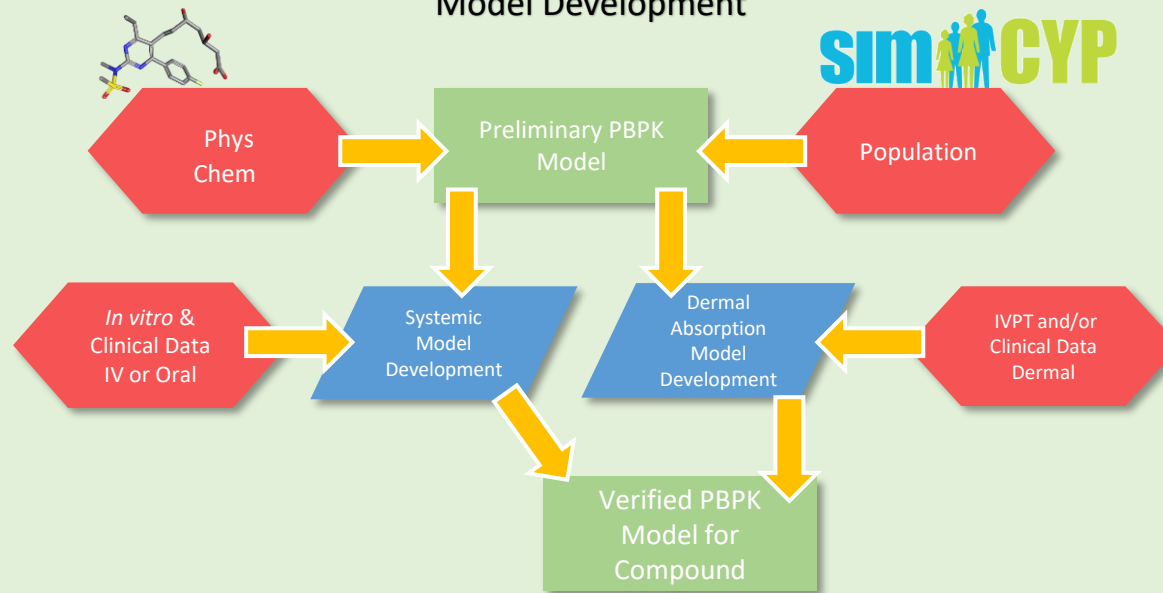
PROCESS

DATA

Formulation Development

Q1, Q2, Q3 Information for RLD

Model Development



Integrated Mechanistic Modelling

Key:

ITEM

PROCESS

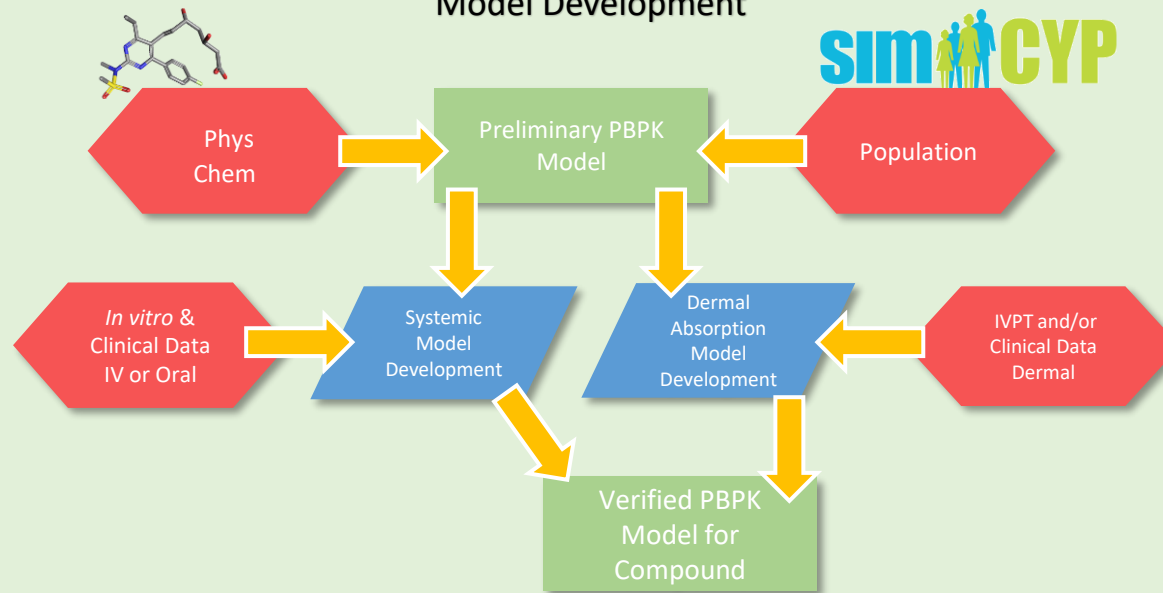
DATA

Formulation Development



Q1, Q2, Q3
Information
for RLD

Model Development



Integrated Mechanistic Modelling

Key:

ITEM

PROCESS

DATA

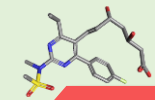
Formulation Development



Q1, Q2, Q3
Information
for RLD

Model Development

simCYP



Phys
Chem

Preliminary PBPK
Model

Population

In vitro &
Clinical Data
IV or Oral

Systemic
Model
Development

Dermal
Absorption
Model
Development

IVPT and/or
Clinical Data
Dermal

Verified PBPK
Model for
Compound

Preliminary PBPK
model for RLD
Formulation

Integrated Mechanistic Modelling

Key:

ITEM

PROCESS

DATA

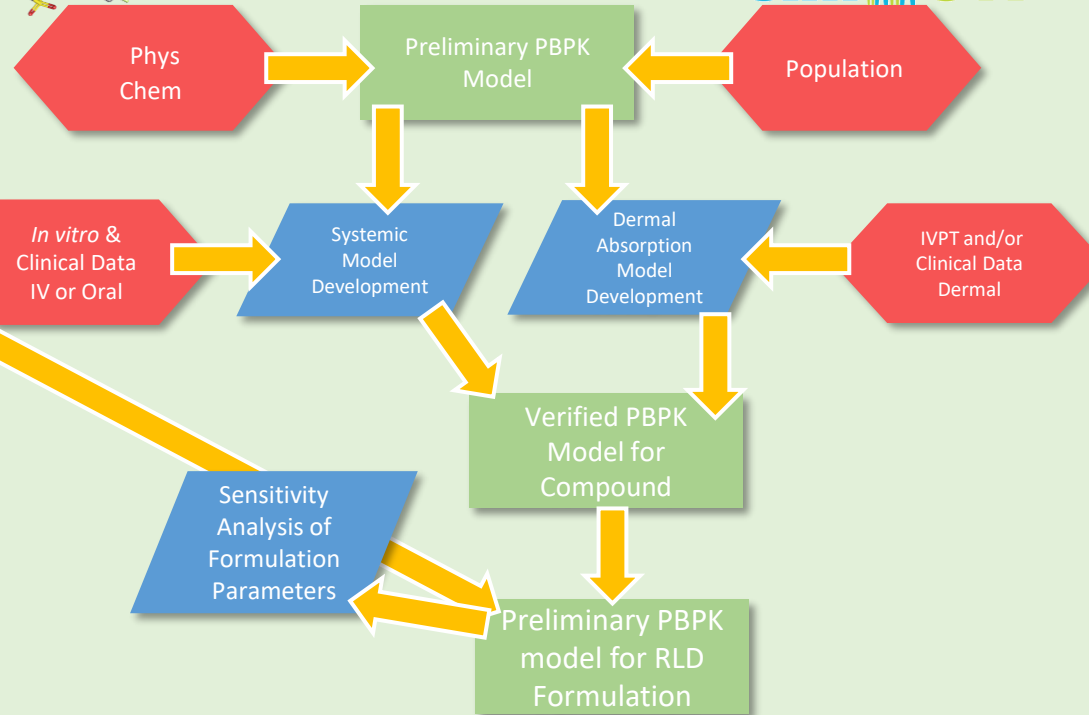
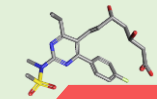
Formulation Development



Q1, Q2, Q3 Information for RLD

Model Development

simCYP



Integrated Mechanistic Modelling

Key:

ITEM

PROCESS

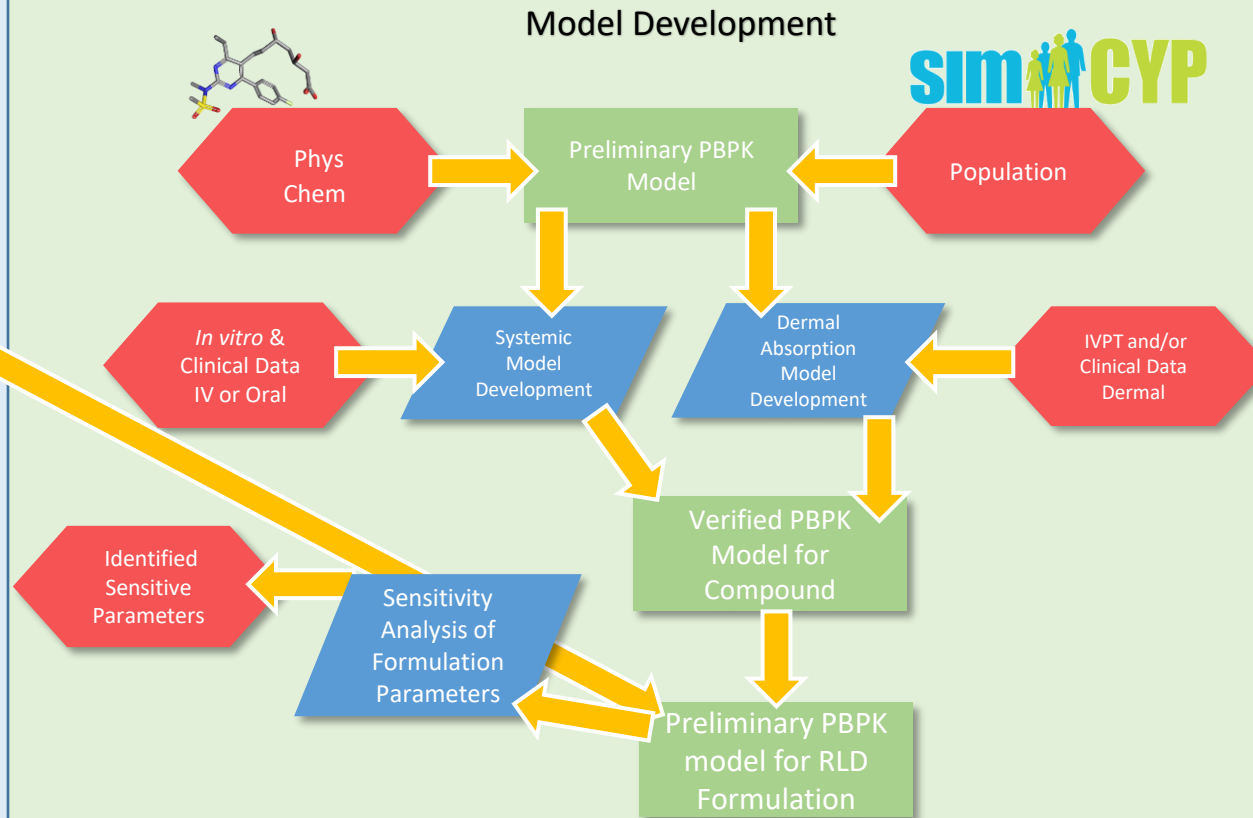
DATA

Formulation Development



Q1, Q2, Q3 Information for RLD

Model Development



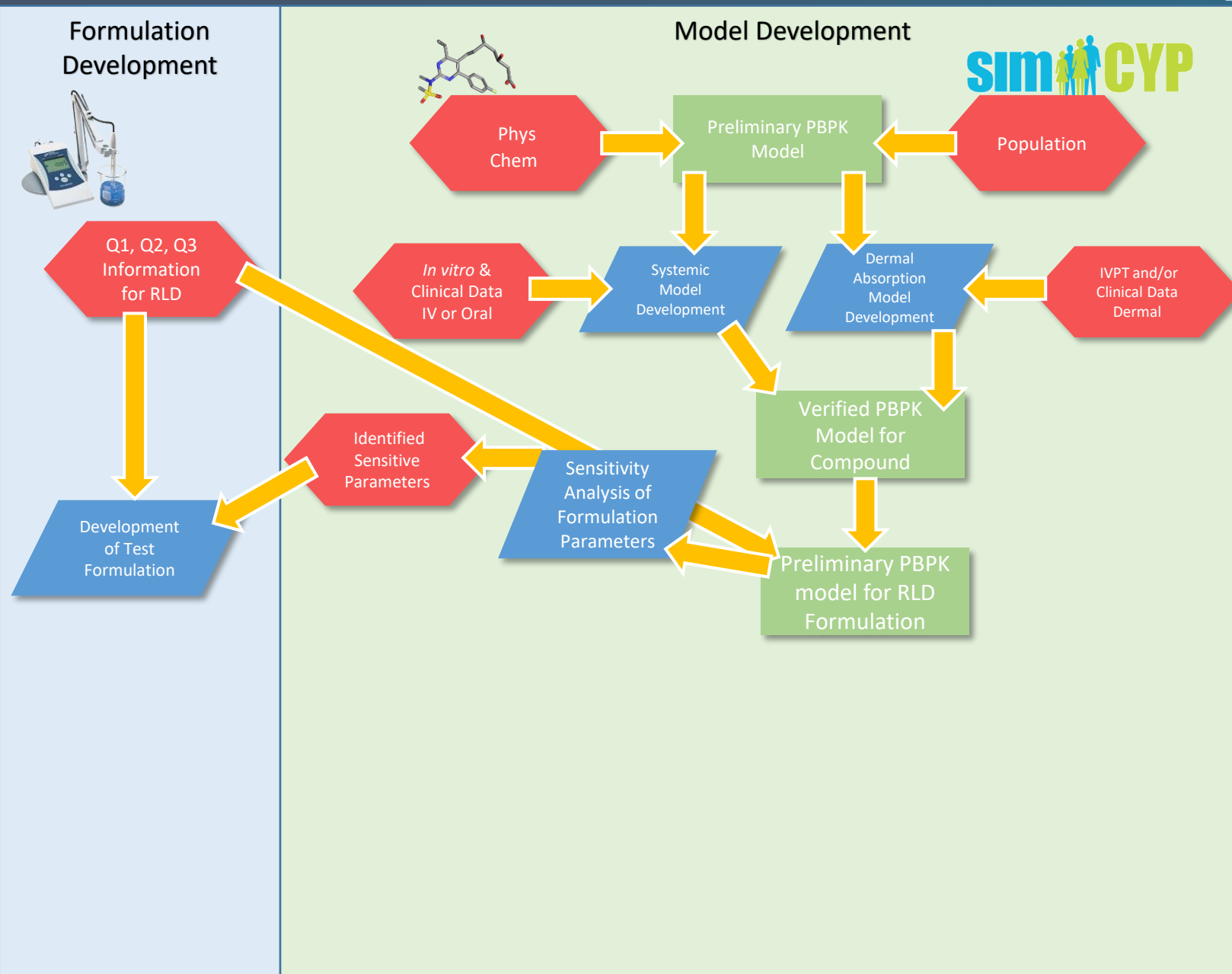
Integrated Mechanistic Modelling

Key:

ITEM

PROCESS


DATA



Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA

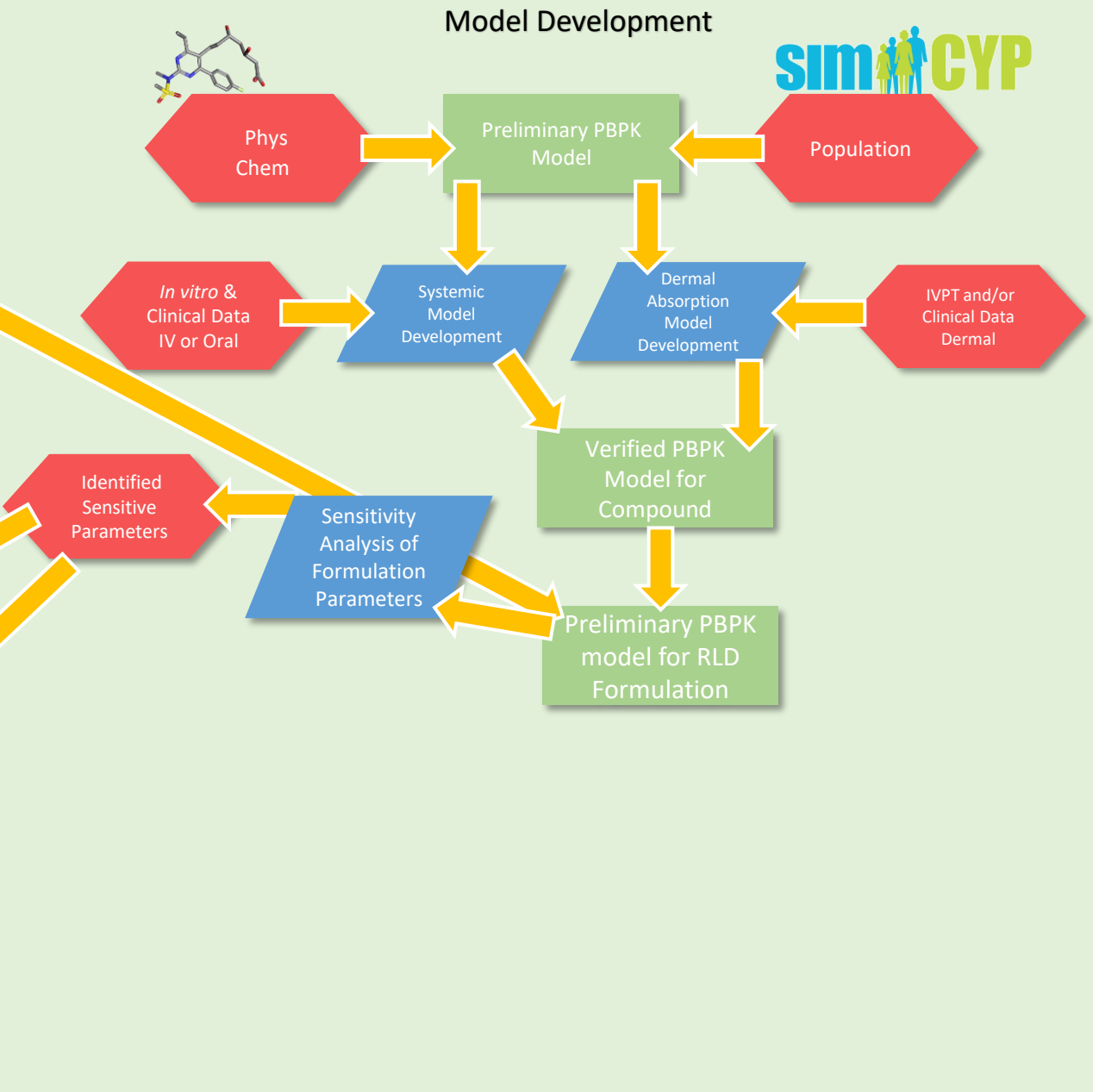
Formulation Development



Q1, Q2, Q3 Information for RLD

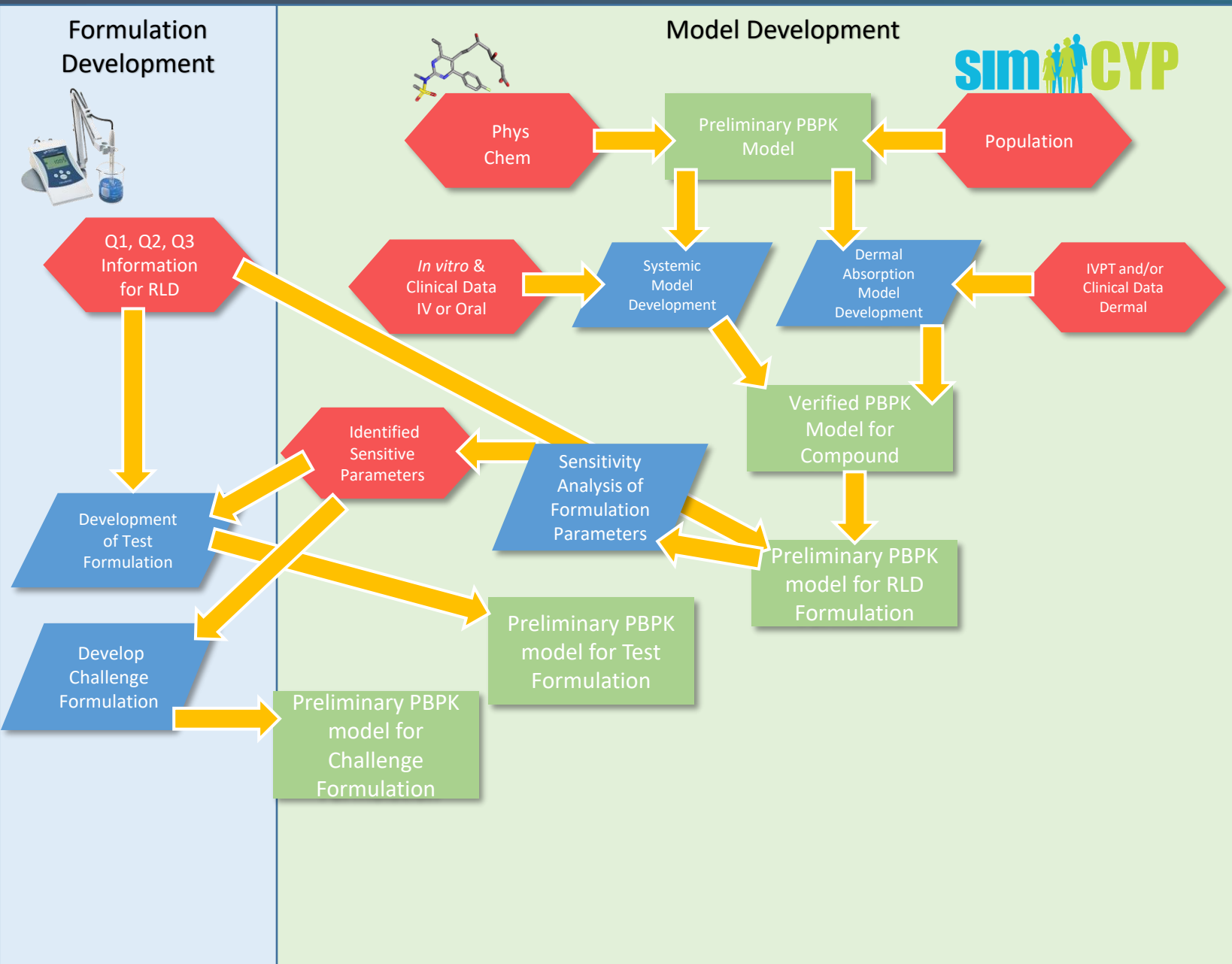
Development of Test Formulation

Develop Challenge Formulation



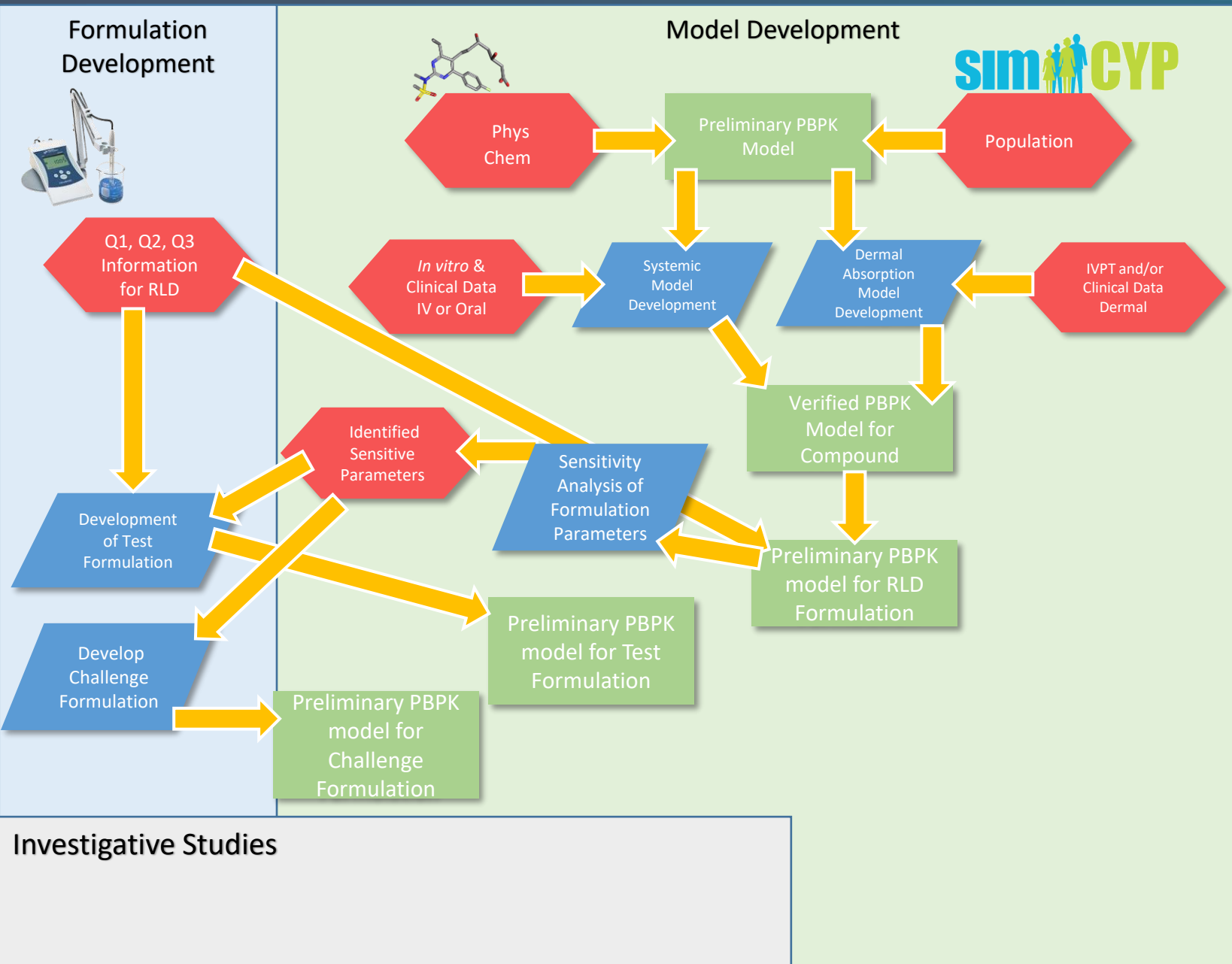
Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA



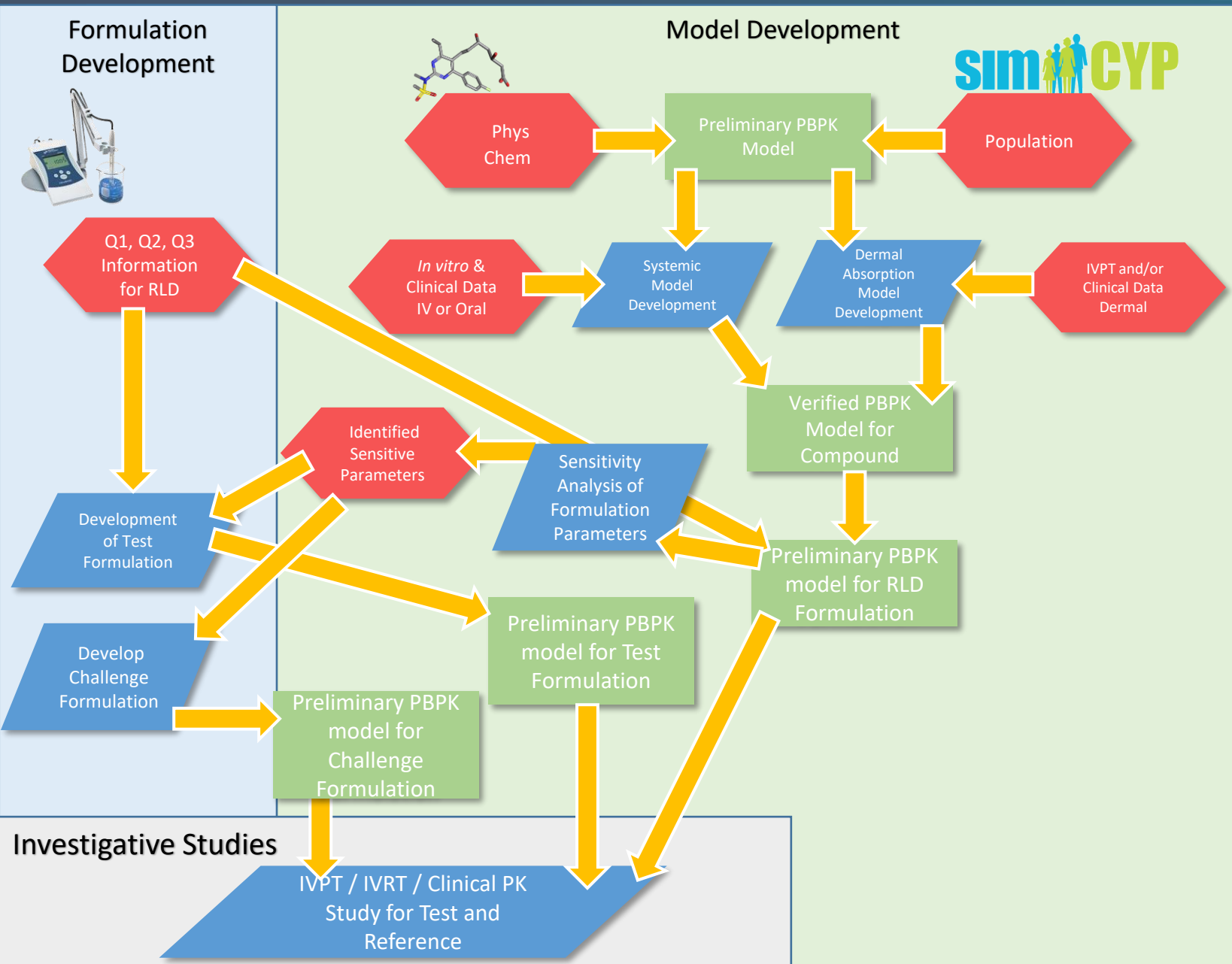
Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA



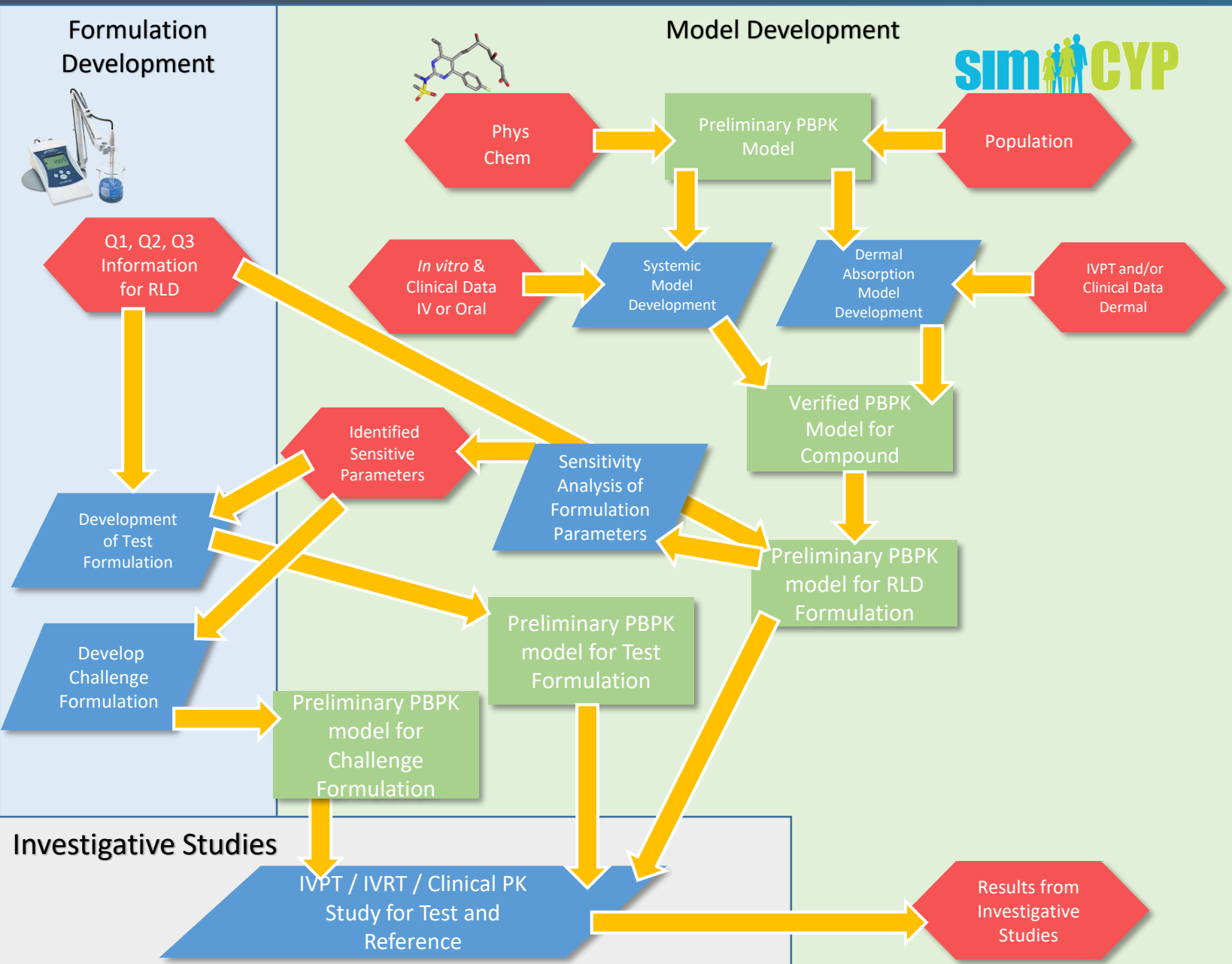
Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA



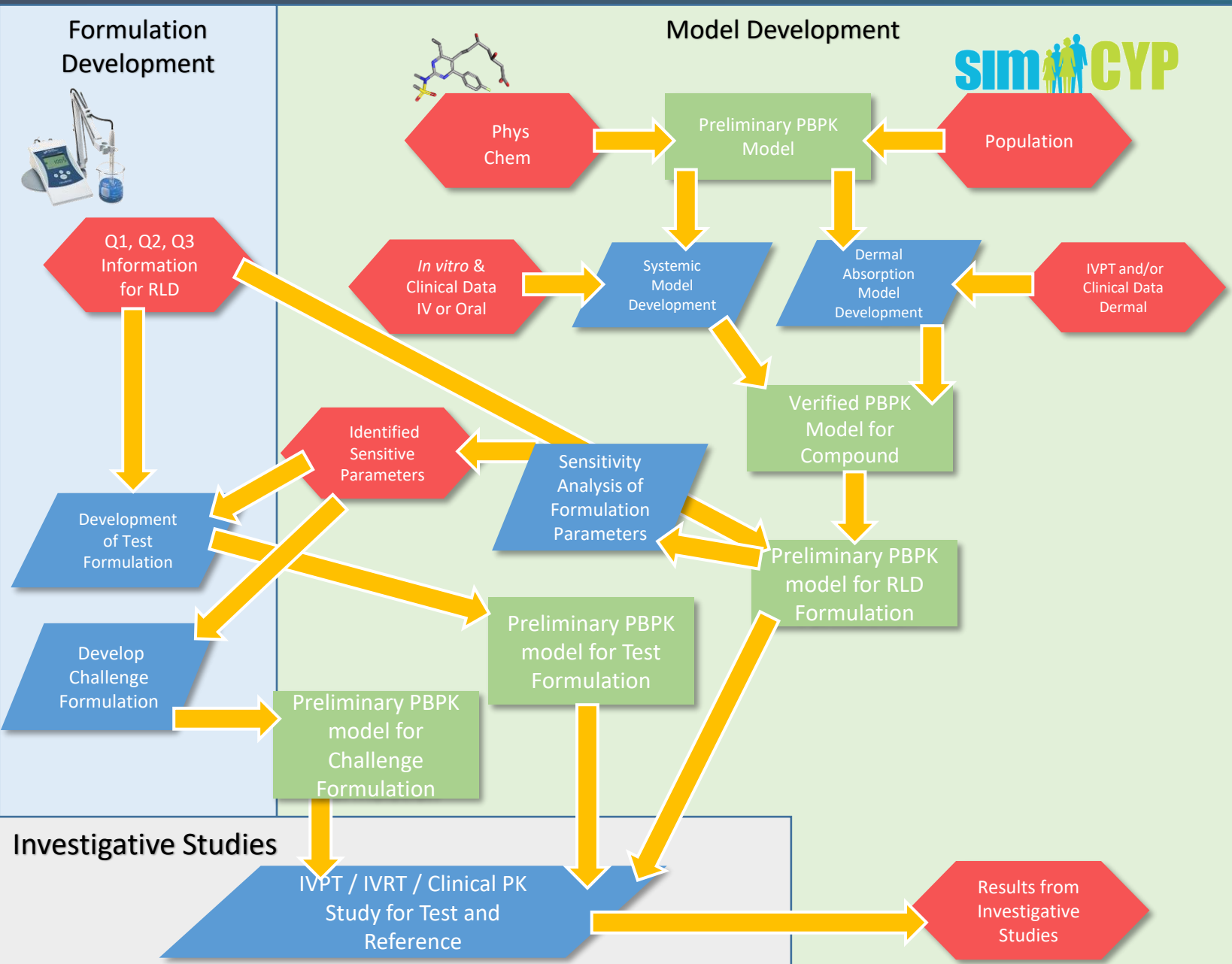
Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA



Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA




Model Verification

This section is currently blank, representing the final stage of the modelling process.

Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA

Formulation Development


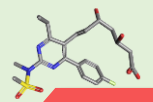


Q1, Q2, Q3 Information for RLD

Development of Test Formulation

Develop Challenge Formulation

Model Development



Phys Chem

Preliminary PBPK Model

Population

In vitro & Clinical Data IV or Oral

Systemic Model Development

Dermal Absorption Model Development

IVPT and/or Clinical Data Dermal

Verified PBPK Model for Compound

Sensitivity Analysis of Formulation Parameters

Identified Sensitive Parameters

Preliminary PBPK model for RLD Formulation

Preliminary PBPK model for Test Formulation

Preliminary PBPK model for Challenge Formulation

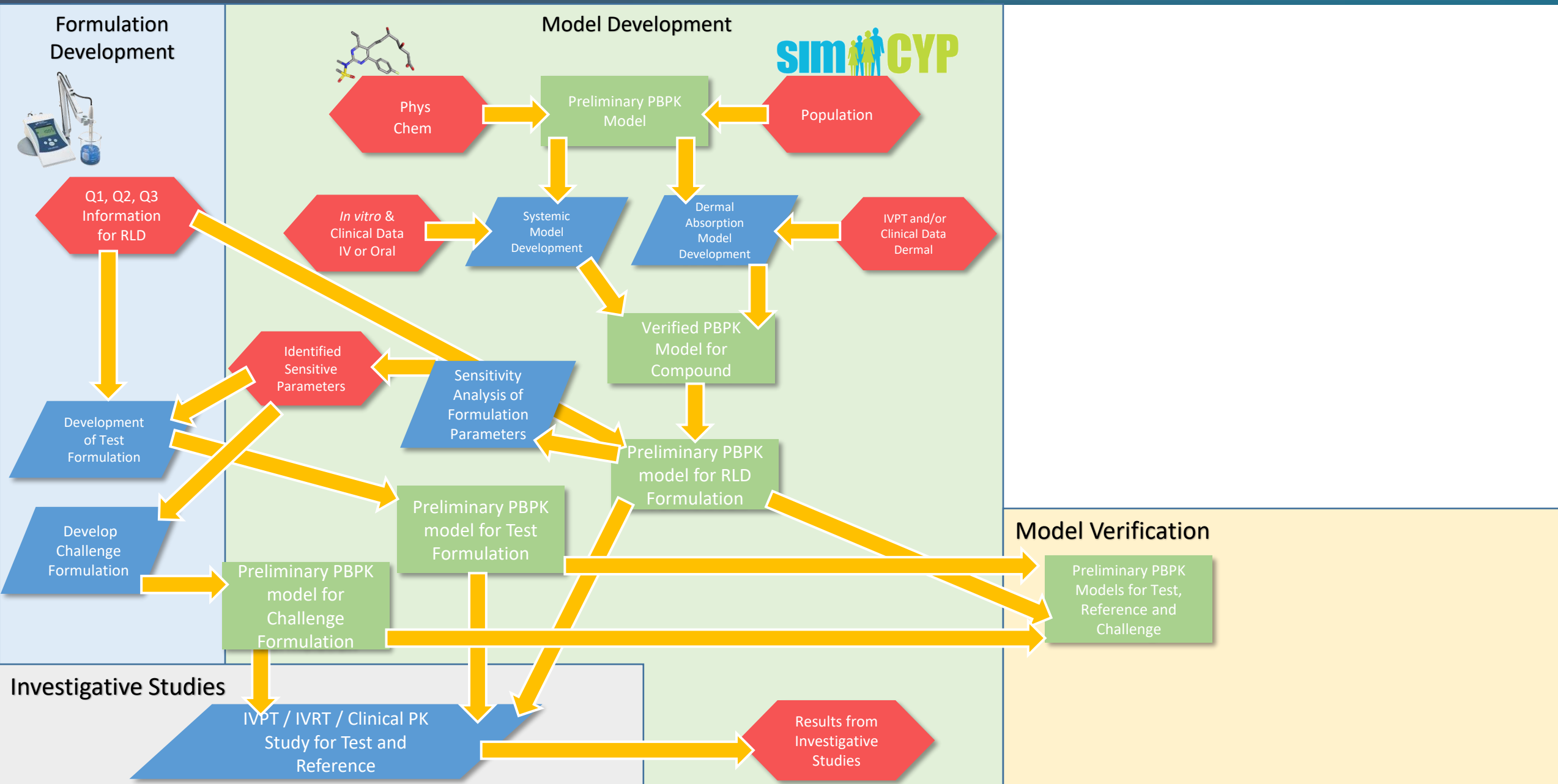
Model Verification

Preliminary PBPK Models for Test, Reference and Challenge

Investigative Studies

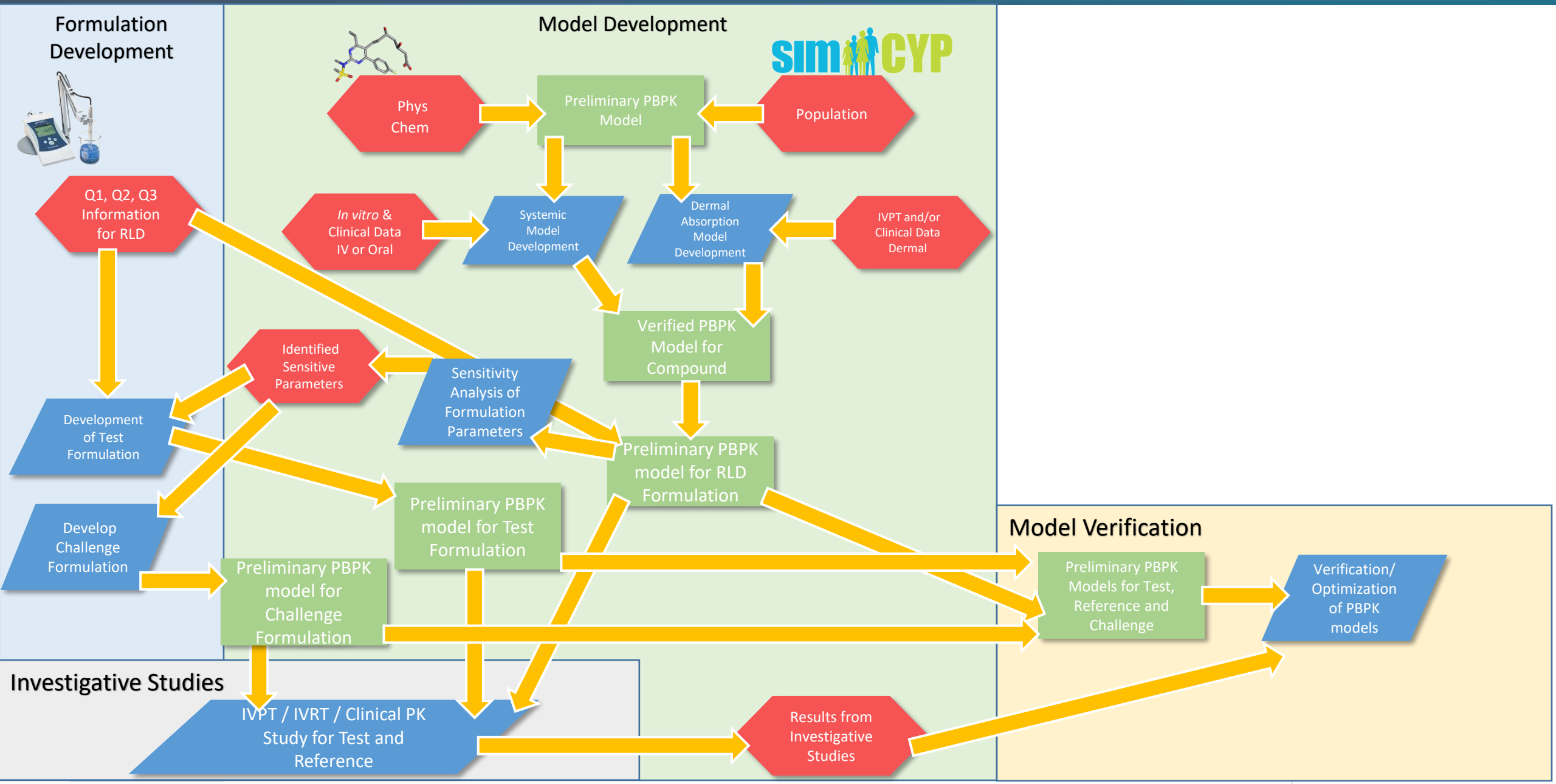
IVPT / IVRT / Clinical PK Study for Test and Reference

Results from Investigative Studies



Integrated Mechanistic Modelling


Key: ITEM PROCESS DATA



Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA

Formulation Development


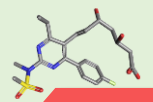


Q1, Q2, Q3 Information for RLD

Development of Test Formulation

Develop Challenge Formulation

Model Development



Phys Chem

Preliminary PBPK Model

Population

In vitro & Clinical Data IV or Oral

Systemic Model Development

Dermal Absorption Model Development

IVPT and/or Clinical Data Dermal

Verified PBPK Model for Compound

Sensitivity Analysis of Formulation Parameters

Identified Sensitive Parameters

Preliminary PBPK model for RLD Formulation

Preliminary PBPK model for Test Formulation

Preliminary PBPK model for Challenge Formulation

Virtual Bioequivalence

Investigative Studies

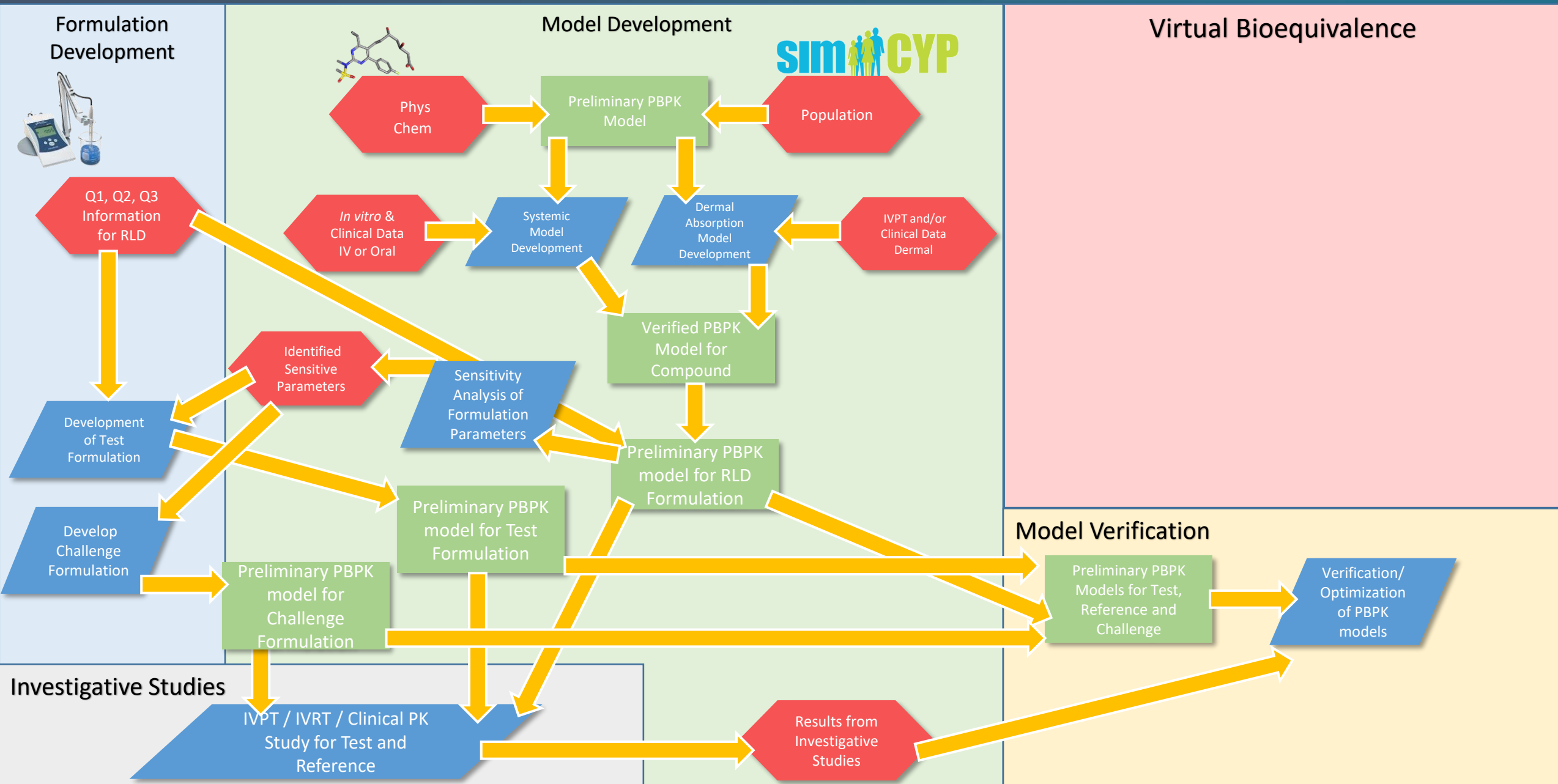
IVPT / IVRT / Clinical PK Study for Test and Reference

Results from Investigative Studies

Model Verification

Preliminary PBPK Models for Test, Reference and Challenge


Verification/Optimization of PBPK models



Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA

Formulation Development

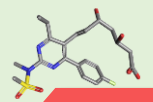



Q1, Q2, Q3 Information for RLD

Development of Test Formulation

Develop Challenge Formulation

Model Development

Phys Chem

Preliminary PBPK Model

Population

In vitro & Clinical Data IV or Oral

Systemic Model Development

Dermal Absorption Model Development

IVPT and/or Clinical Data Dermal

Verified PBPK Model for Compound

Sensitivity Analysis of Formulation Parameters

Identified Sensitive Parameters

Preliminary PBPK model for RLD Formulation

Preliminary PBPK model for Test Formulation

Preliminary PBPK model for Challenge Formulation

Virtual Bioequivalence

Verified PBPK model for Test Formulation

Verified PBPK model for RLD Formulation

Model Verification

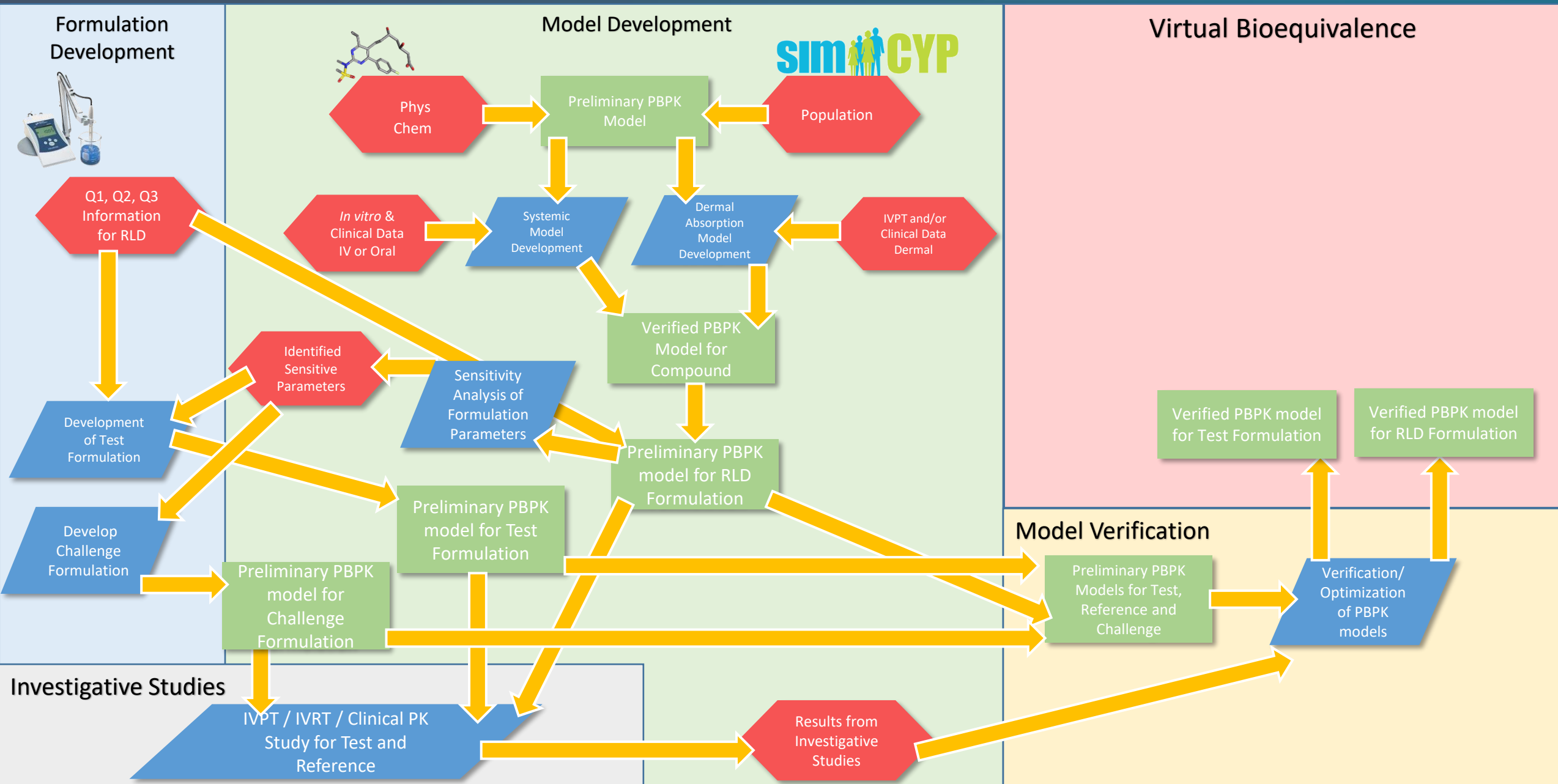
Preliminary PBPK Models for Test, Reference and Challenge

Verification/Optimization of PBPK models

Investigative Studies

IVPT / IVRT / Clinical PK Study for Test and Reference


Results from Investigative Studies



Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA

Formulation Development

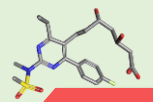



Q1, Q2, Q3 Information for RLD

Development of Test Formulation

Develop Challenge Formulation

Model Development

Phys Chem

Preliminary PBPK Model

Population

In vitro & Clinical Data IV or Oral

Systemic Model Development

Dermal Absorption Model Development

IVPT and/or Clinical Data Dermal

Verified PBPK Model for Compound

Sensitivity Analysis of Formulation Parameters

Identified Sensitive Parameters

Preliminary PBPK model for RLD Formulation

Preliminary PBPK model for Test Formulation

Preliminary PBPK model for Challenge Formulation

Virtual Bioequivalence

In vitro – in vivo Extrapolation

Verified PBPK model for Test Formulation

Verified PBPK model for RLD Formulation

Model Verification

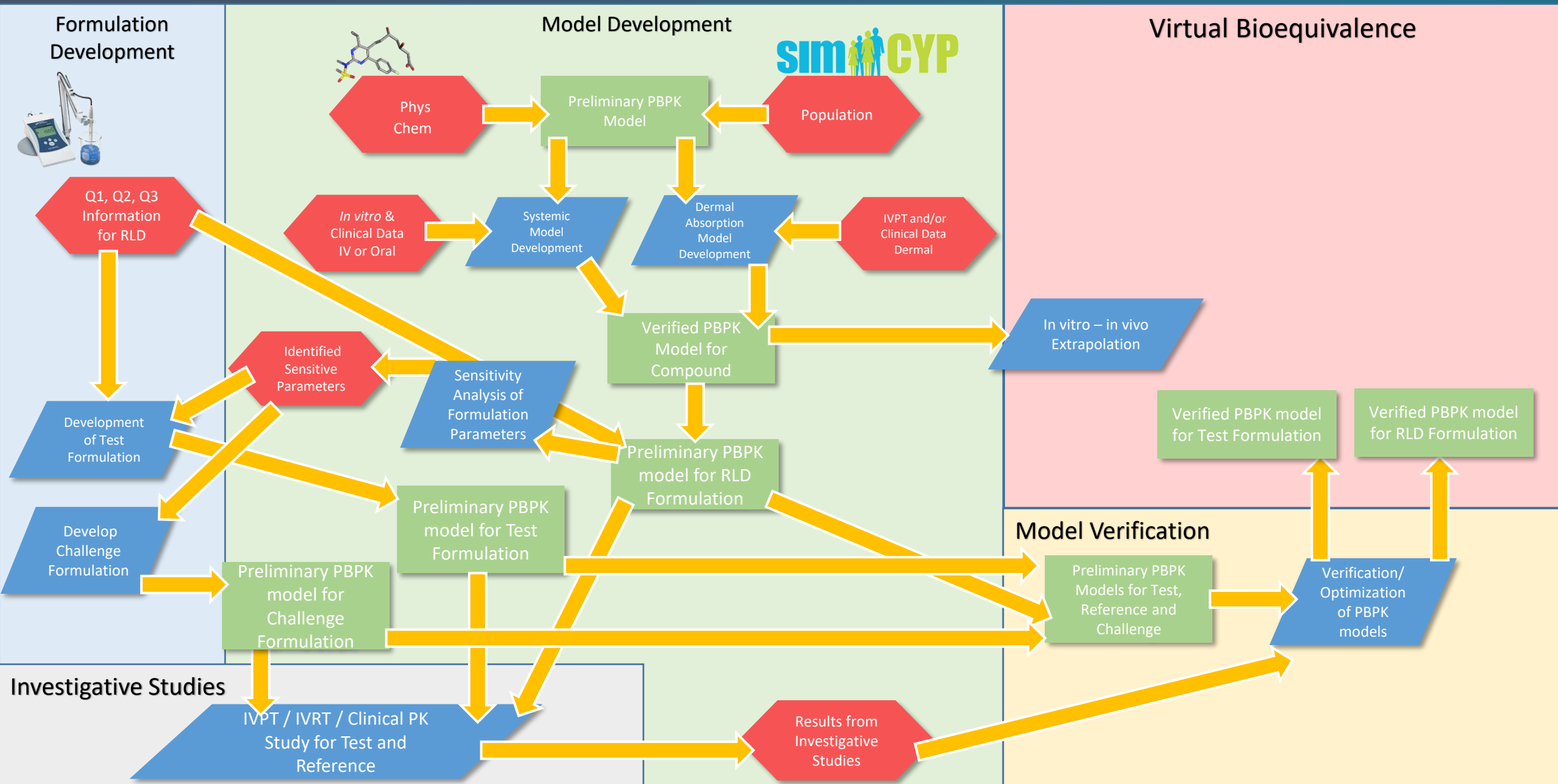
Preliminary PBPK Models for Test, Reference and Challenge

Verification/Optimization of PBPK models

Investigative Studies

IVPT / IVRT / Clinical PK Study for Test and Reference


Results from Investigative Studies



Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA

Formulation Development

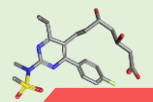



Q1, Q2, Q3 Information for RLD

Development of Test Formulation

Develop Challenge Formulation

Model Development

Phys Chem

Preliminary PBPK Model

Population

In vitro & Clinical Data IV or Oral

Systemic Model Development

Dermal Absorption Model Development

IVPT and/or Clinical Data Dermal

Verified PBPK Model for Compound

Sensitivity Analysis of Formulation Parameters

Identified Sensitive Parameters

Preliminary PBPK model for RLD Formulation

Preliminary PBPK model for Test Formulation

Preliminary PBPK model for Challenge Formulation

Virtual Bioequivalence

In vitro – in vivo Extrapolation

Virtual Bioequivalence Assessment

Verified PBPK model for Test Formulation

Verified PBPK model for RLD Formulation

Model Verification

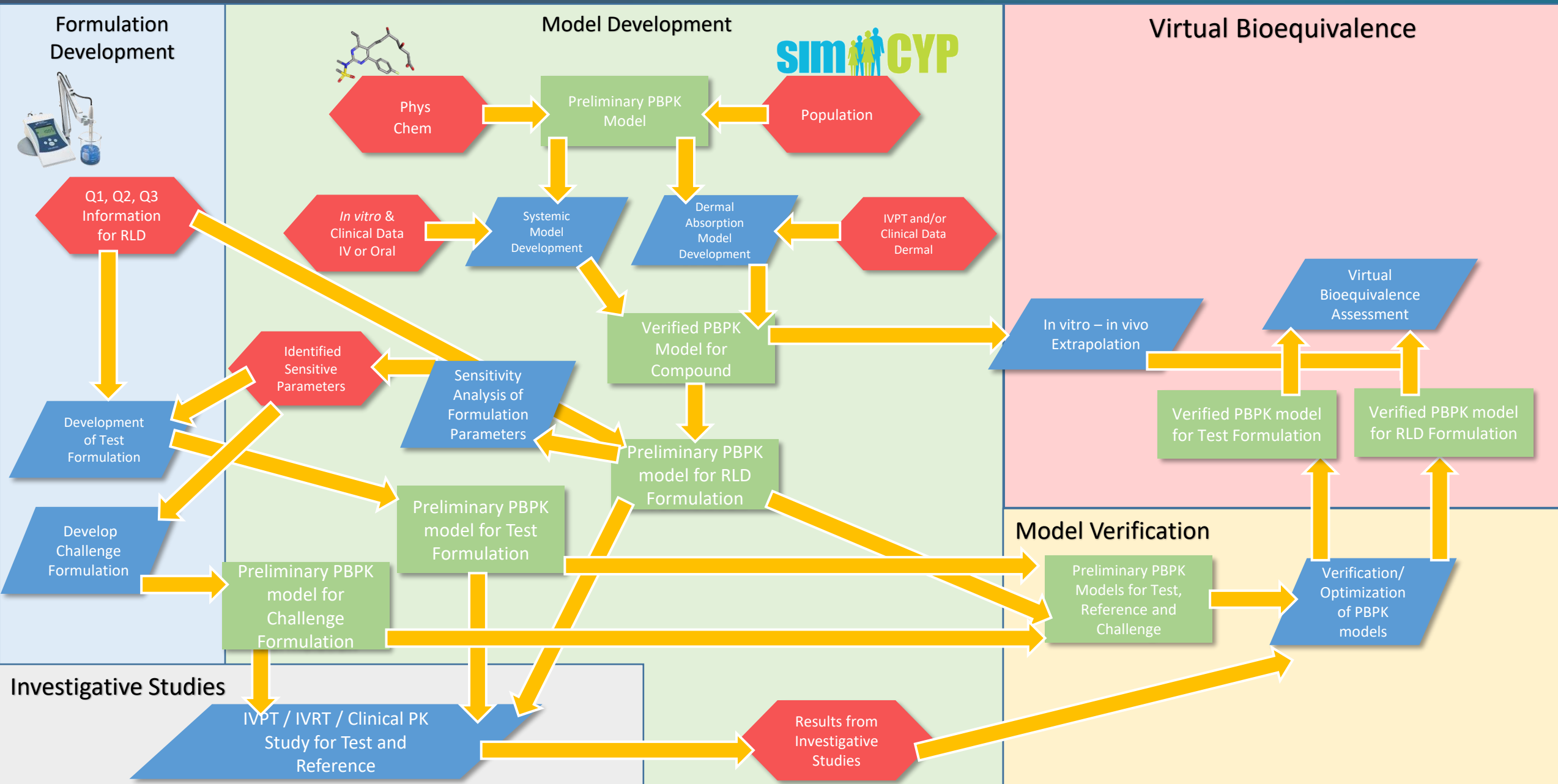
Preliminary PBPK Models for Test, Reference and Challenge

Verification/Optimization of PBPK models

Investigative Studies

IVPT / IVRT / Clinical PK Study for Test and Reference


Results from Investigative Studies



Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA

Formulation Development

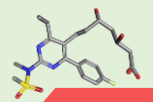



Q1, Q2, Q3 Information for RLD

Development of Test Formulation

Develop Challenge Formulation

Model Development

Phys Chem

Preliminary PBPK Model

Population

In vitro & Clinical Data IV or Oral

Systemic Model Development

Dermal Absorption Model Development

IVPT and/or Clinical Data Dermal

Verified PBPK Model for Compound

Sensitivity Analysis of Formulation Parameters

Identified Sensitive Parameters

Preliminary PBPK model for RLD Formulation

Preliminary PBPK model for Test Formulation

Preliminary PBPK model for Challenge Formulation

Virtual Bioequivalence

Bioequivalence Results

Virtual Bioequivalence Assessment

In vitro – in vivo Extrapolation

Verified PBPK model for Test Formulation

Verified PBPK model for RLD Formulation

Model Verification

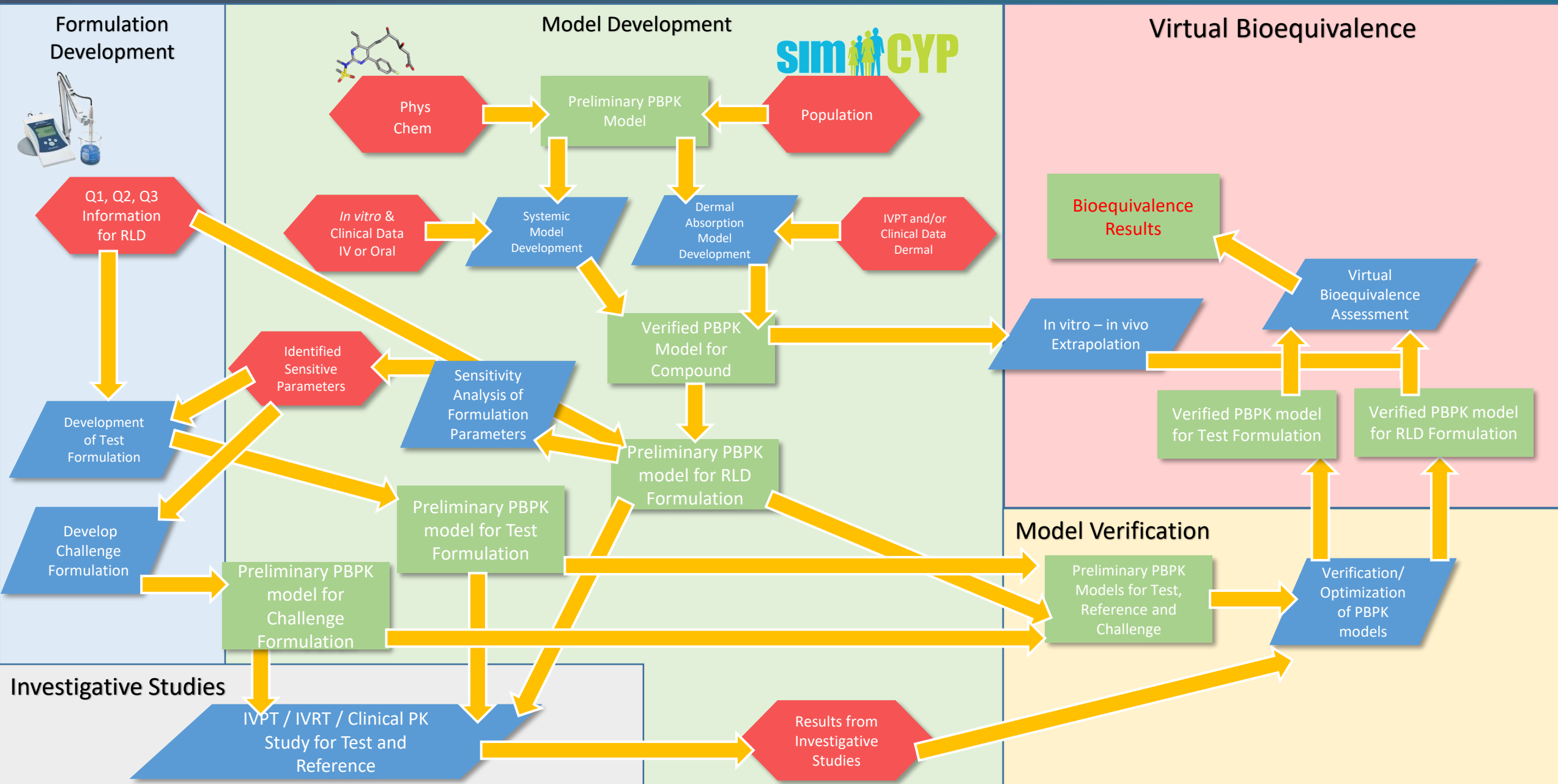
Preliminary PBPK Models for Test, Reference and Challenge

Verification/Optimization of PBPK models

Investigative Studies

IVPT / IVRT / Clinical PK Study for Test and Reference


Results from Investigative Studies



Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA

Formulation Development

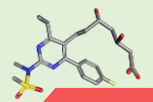



Q1, Q2, Q3 Information for RLD

Development of Test Formulation

Develop Challenge Formulation

Model Development

Phys Chem

Preliminary PBPK Model

Population

In vitro & Clinical Data IV or Oral

Systemic Model Development

Dermal Absorption Model Development

IVPT and/or Clinical Data Dermal

Verified PBPK Model for Compound

Sensitivity Analysis of Formulation Parameters

Identified Sensitive Parameters

Preliminary PBPK model for RLD Formulation

Preliminary PBPK model for Test Formulation

Preliminary PBPK model for Challenge Formulation

Virtual Bioequivalence

'Safe Space' for formulation attributes

Bioequivalence Results

Sensitivity Analysis

Virtual Bioequivalence Assessment

In vitro – in vivo Extrapolation

Verified PBPK model for Test Formulation

Verified PBPK model for RLD Formulation

Model Verification

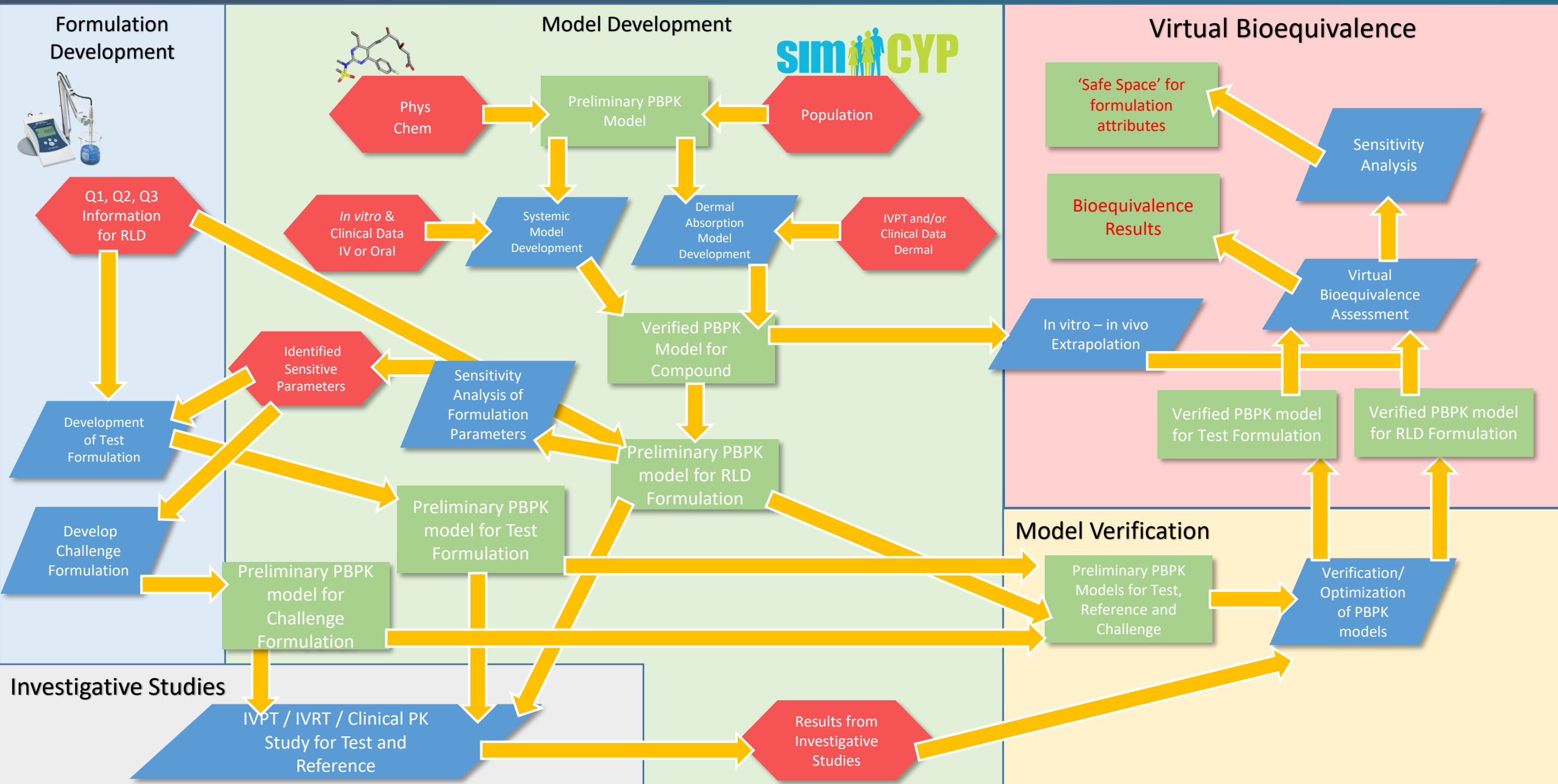
Preliminary PBPK Models for Test, Reference and Challenge

Verification/Optimization of PBPK models

Investigative Studies

IVPT / IVRT / Clinical PK Study for Test and Reference


Results from Investigative Studies



Integrated Mechanistic Modelling

Key: ITEM PROCESS DATA

Formulation Development

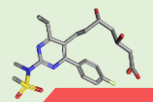



Q1, Q2, Q3 Information for RLD

Development of Test Formulation

Develop Challenge Formulation

Model Development

Phys Chem

Preliminary PBPK Model

Population

In vitro & Clinical Data IV or Oral

Systemic Model Development

Dermal Absorption Model Development

IVPT and/or Clinical Data Dermal

Verified PBPK Model for Compound

Sensitivity Analysis of Formulation Parameters

Identified Sensitive Parameters

Preliminary PBPK model for RLD Formulation

Preliminary PBPK model for Test Formulation

Preliminary PBPK model for Challenge Formulation

Virtual Bioequivalence

'Safe Space' for formulation attributes

Bioequivalence Results

Sensitivity Analysis

Virtual Bioequivalence Assessment

In vitro – in vivo Extrapolation

Verified PBPK model for Test Formulation

Verified PBPK model for RLD Formulation

Model Verification

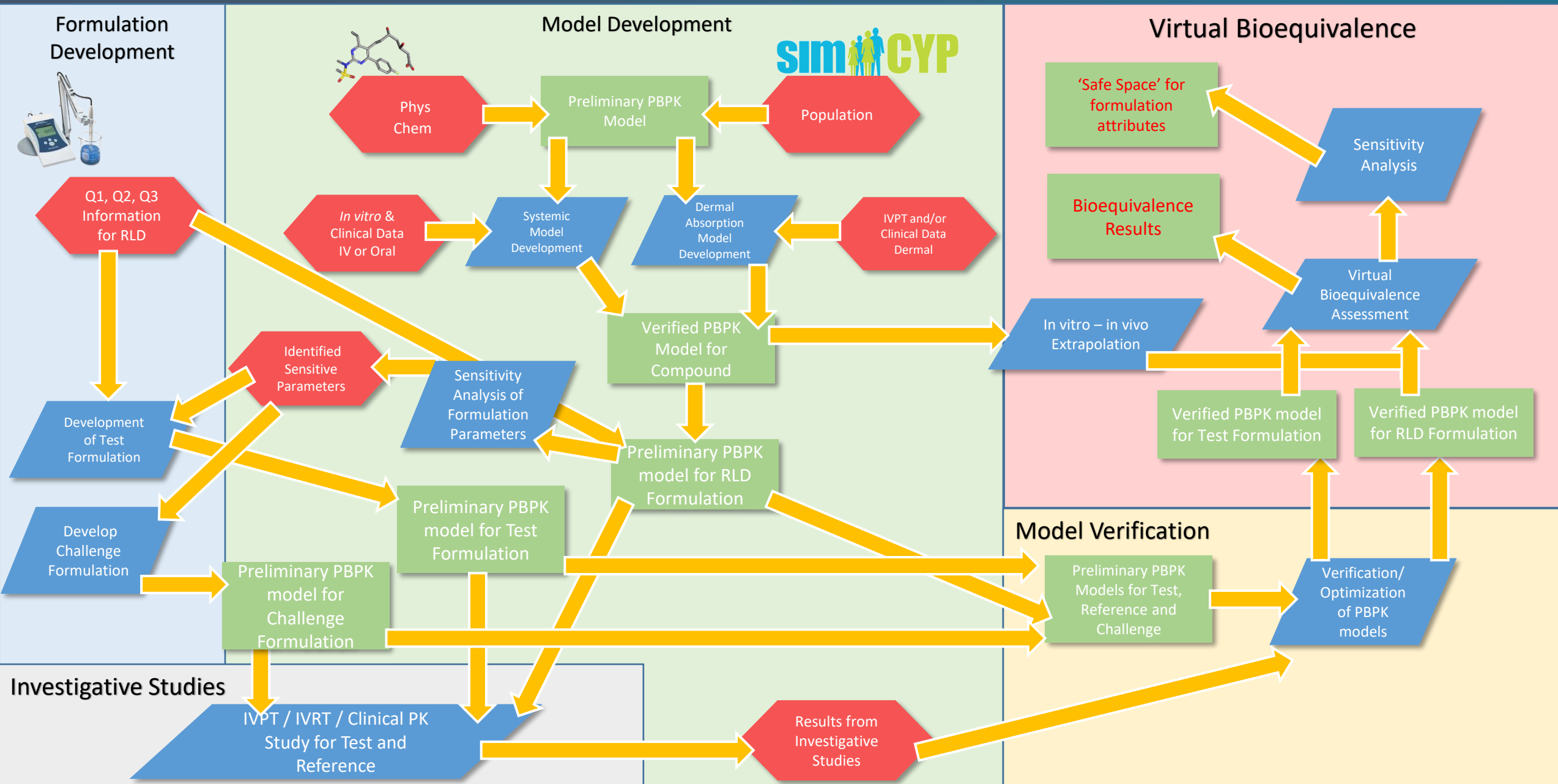
Preliminary PBPK Models for Test, Reference and Challenge

Verification/Optimization of PBPK models

Investigative Studies

IVPT / IVRT / Clinical PK Study for Test and Reference

Results from Investigative Studies





Desoximetasone Topicort Spray Example

Generic Drug Development Process and Investigative Virtual Bioequivalence

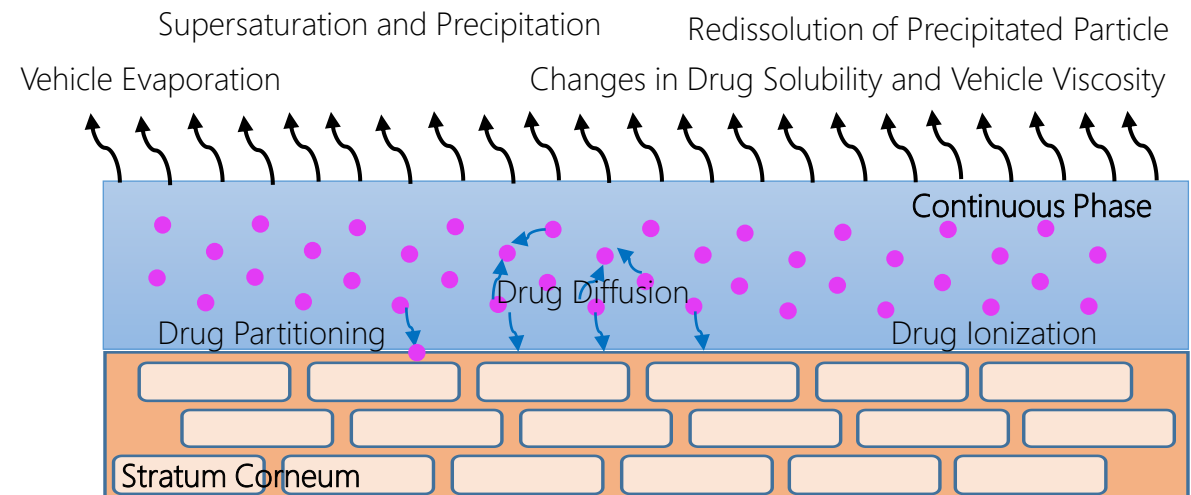
Desoximetasone - Topicort Spray Example

Upcoming Publication – in peer review

- Topicort Spray 0.25% - Information on Q2 taken from patent *
- Mechanistic formulation model uses Q2 as input
 - Evaporation rate of Isopropyl alcohol can be predicted
- No information publicly available on Q3 parameters
 - Viscosity
 - Solubility
 - pH
 - Evaporation rate

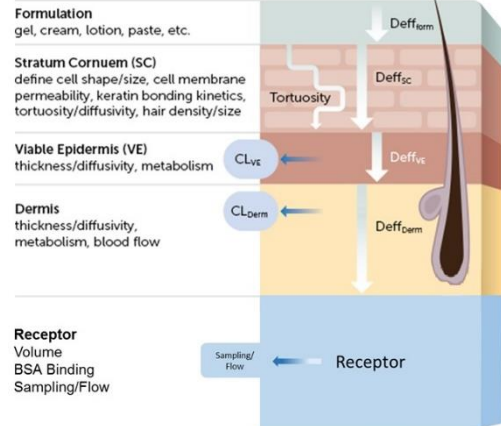
Component	Primary/Secondary (% w/w)	Tertiary (% w/w)
Desoximetasone	0.25	0.33
Glyceryl oleate	0.9	1.17
Isopropyl alcohol	23.4	0.00
Isopropyl myristate	31.38	40.96
L-menthol	0.05	0.07
Mineral oil	44.03	57.47

● Drug Molecule



Desoximetasone - Topicort Spray Example

Input



In vitro Release/Permeation Studies

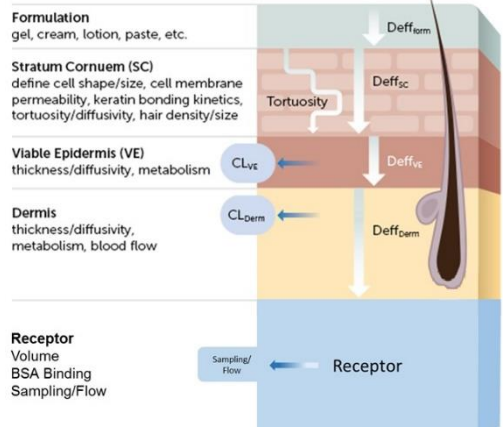


Understanding Q1, Q2 and Q3 properties of topical products

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

Desoximetasone - Topicort Spray Example

Input



In vitro Release/Permeation Studies



Understanding Q1, Q2 and Q3 properties of topical products

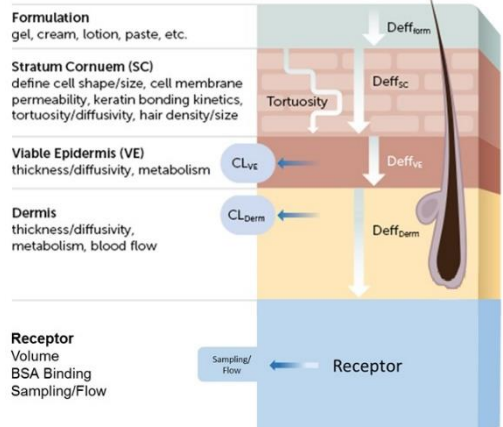
- Composition
- Drug Solubility in various phases
- Drying Rate (evaporation – weight loss)
- Specific gravity
- Particle size (solid particles/droplets)
- Rheology
- Precipitation characterization
- Excipients penetration

Component	Tertiary (% w/w)
Desoximetasone	0.33
Glyceryl oleate	1.17
Isopropyl alcohol	0.00
Isopropyl myristate	40.96
L-menthol	0.07
Mineral oil	57.47

*

Desoximetasone - Topicort Spray Example

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

Component	Tertiary (% w/w)
Desoximetasone	0.33
Glyceryl oleate	1.17
Isopropyl alcohol	0.00
Isopropyl myristate	40.96
L-menthol	0.07
Mineral oil	57.47

Dermal Formulation Options (Solution)

Continuous Phase Constituents*

	% (v/v)	± Density ρ	Molar Mass	Molar Volume	Viscosity	Intrinsic Solubility (mg/mL)*
Vehicle Component 1	Water	0	1	18.02	18.11	0.0421
Vehicle Component 2	Custom	58.38	0.85	452.36	532.19	
Vehicle Component 3	Custom	41.62	0.85	270.45	319.35	
Total	Solution	100	0.85	443.61	100	0.5

Formulation Diffusion Coefficients (cm²/h)

Diffusion Coeff in Vehicle

Method Predicted Dveh (cm²/h)

Solubility

Formulation fni**

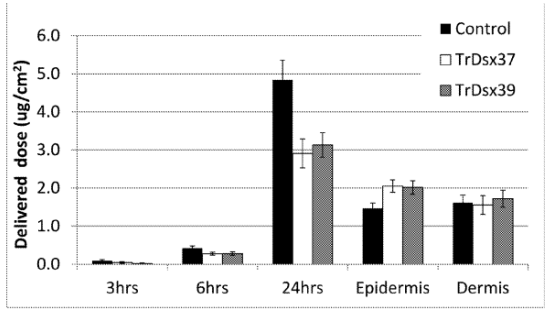
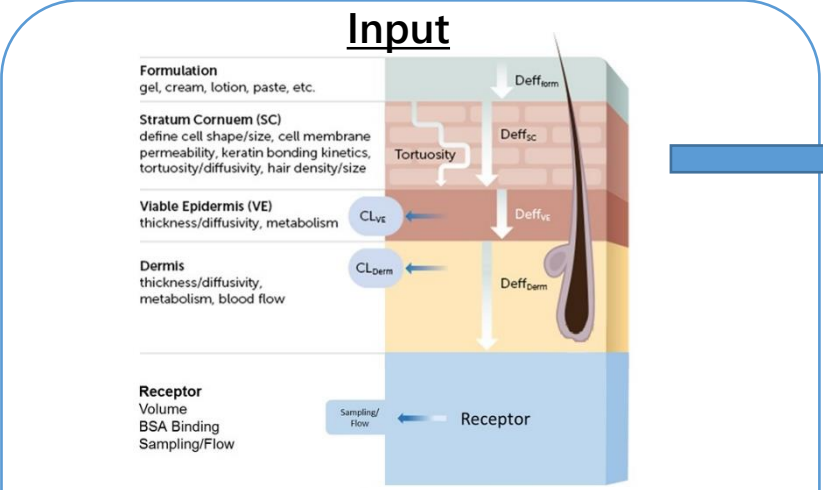
Drug solubility in continuous Phase (mg/mL)

Vehicle: Water Solubility Ratio†

* Constituents of the continuous phase of the selected formulations.
 ** fni is calculated from the formulation pH assuming Henderson Hasselback, Caution should be used when simulation non-aqueous vehicles as HH may not apply.
 † Density of the entire vehicle must be defined in order to calculate Molar Volume.
 ‡ Applied as a scalar to K_{sc} and K_{seb} .

OK Cancel

Desoximetasone - Topicort Spray Example



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

Component	Tertiary (% w/w)
Desoximetasone	0.33
Glyceryl oleate	1.17
Isopropyl alcohol	0.00
Isopropyl myristate	40.96
L-menthol	0.07
Mineral oil	57.47

Dermal Formulation Options (Solution)

Continuous Phase Constituents*

Vehicle Component	Material	% (v/v)	ρ Density	Molar Mass	Molar Volume	Viscosity	Intrinsic Solubility (mg/mL)*
Vehicle Component 1	Water	0	1	18.02	18.11		0.0421
Vehicle Component 2	Custom	58.38	0.85	452.36	532.19		
Vehicle Component 3	Custom	41.62	0.85	270.45	319.35		
Total	Solution	100	0.85		443.61	100	0.5

Formulation Diffusion Coefficients (cm²/h)

Diffusion Coeff in Vehicle

Method: Scheibel 1954 Predicted Dveh (cm²/h): 0.00051251

Solubility

Formulation fni** 1

Drug solubility in continuous Phase (mg/mL) 0.5

Vehicle: Water Solubility Ratio† 11.876

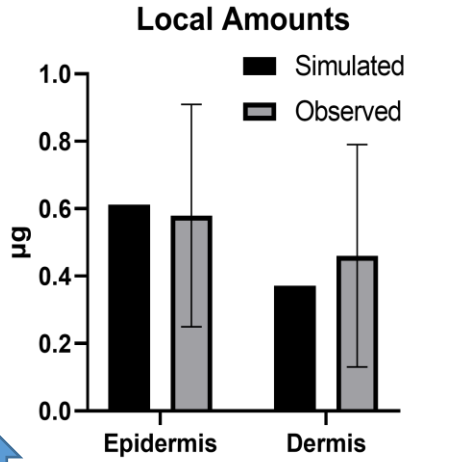
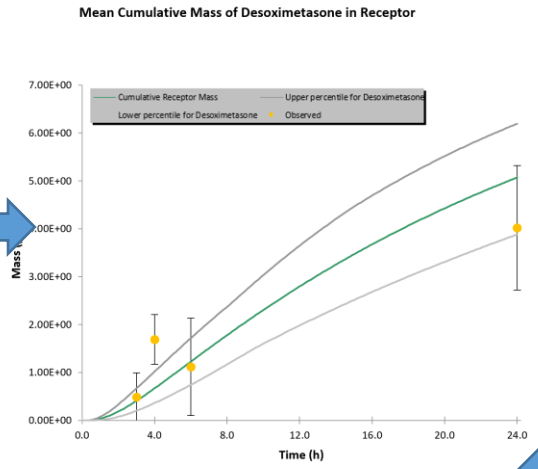
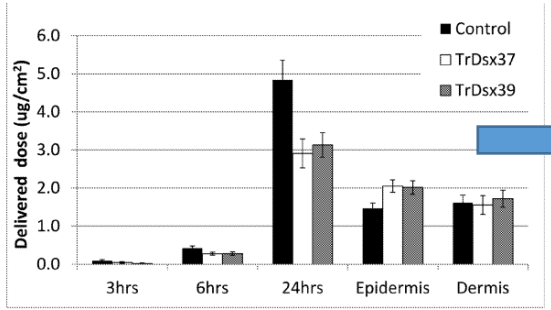
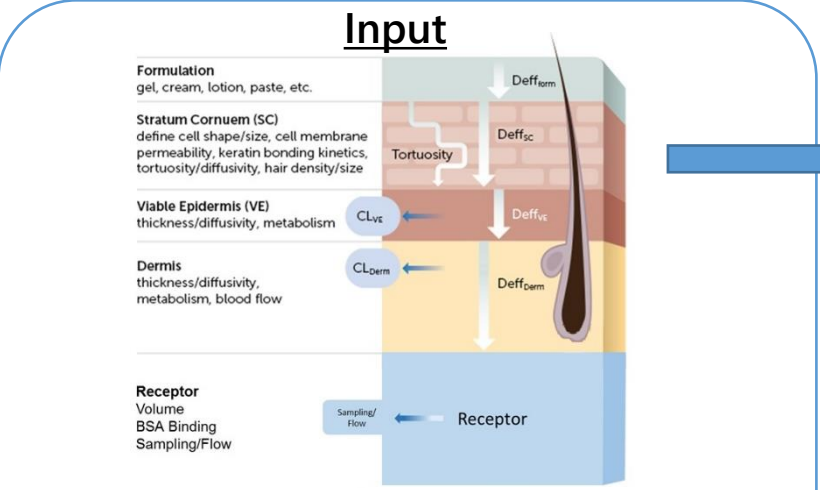
* Constituents of the continuous phase of the selected formulations.
 ** fni is calculated from the formulation pH assuming Henderson Hasselback, Caution should be used when simulation non-aqueous vehicles as HH may not apply.
 † Density of the entire vehicle must be defined in order to calculate Molar Volume.
 ‡ Applied as a scalar to K_{sc} and K_{seb}.

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

* Anissimov, Y. G. and M. S. Roberts (2011). "Modelling dermal drug distribution after topical application in human." *Pharm Res* 28(9): 2119-2129.



Desoximetasone - Topicort Spray Example



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

Component	Tertiary (% w/w)
Desoximetasone	0.33
Glyceryl oleate	1.17
Isopropyl alcohol	0.00
Isopropyl myristate	40.96
L-menthol	0.07
Mineral oil	57.47

Dermal Formulation Options (Solution)

Continuous Phase Constituents*

Vehicle Component	Material	% (v/v)	Density ρ	Molar Mass	Molar Volume	Viscosity	Intrinsic Solubility (mg/mL)
1	Water	0	1	18.02	18.11		0.0421
2	Custom	58.38	0.85	452.36	532.19		
3	Custom	41.62	0.85	270.45	319.35		
Total	Solution	100	0.85		443.61	100	0.5

Formulation Diffusion Coefficients (cm²/h)

Diffusion Coeff in Vehicle

Method: Scheibel 1954 Predicted Dveh (cm²/h): 0.00051251

Solubility

Formulation fni** 1

Drug solubility in continuous Phase (mg/mL) 0.5

Vehicle: Water Solubility Ratio† 11.876

* Constituents of the continuous phase of the selected formulations.
 ** fni is calculated from the formulation pH assuming Henderson Hasselback, Caution should be used when simulation non-aqueous vehicles as HH may not apply.
 † Density of the entire vehicle must be defined in order to calculate Molar Volume.
 ‡ Applied as a scalar to K_{sc} and K_{seb}.

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

* Anissimov, Y. G. and M. S. Roberts (2011). "Modelling dermal drug distribution after topical application in human." *Pharm Res* 28(9): 2119-2129.



Desoximetasone - Topicort Spray Example

Upcoming Publication – in peer review

Effect of **Dose Selection** on formulation parameter sensitivity

- 1) Low dose – 1 spray per 10 cm²
- 2) Middle dose – 1 spray per 2 cm²
- 3) Default dose – 1 spray per 1 cm²
- 4) IVPT dose - 3.5 sprays per 1 cm²

Viscosity:

RLD = 100 cP

Lower Bound = 1cP

Upper Bound = 100 000 cP

Solubility :

RLD = 0.55 mg/ml

Lower Bound = 0.4 mg/ml

Upper Bound = 0.7 mg/ml

Desoximetasone - Topicort Spray Example

Upcoming Publication – in peer review

Effect of **Dose Selection** on formulation parameter sensitivity

- 1) Low dose – 1 spray per 10 cm²
- 2) Middle dose – 1 spray per 2 cm²
- 3) Default dose – 1 spray per 1 cm²
- 4) IVPT dose - 3.5 sprays per 1 cm²

Viscosity:

RLD = 100 cP

Lower Bound = 1cP

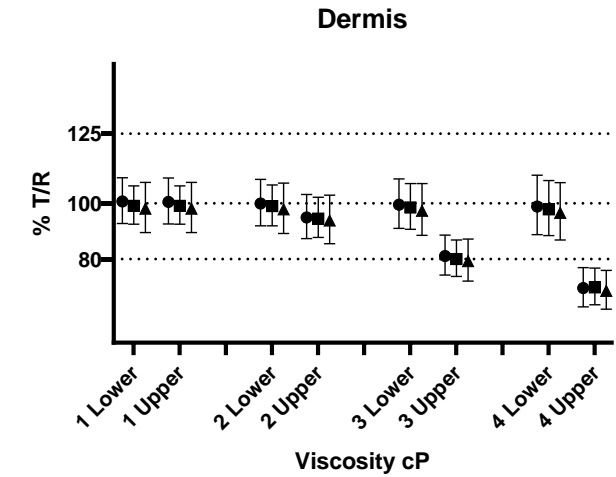
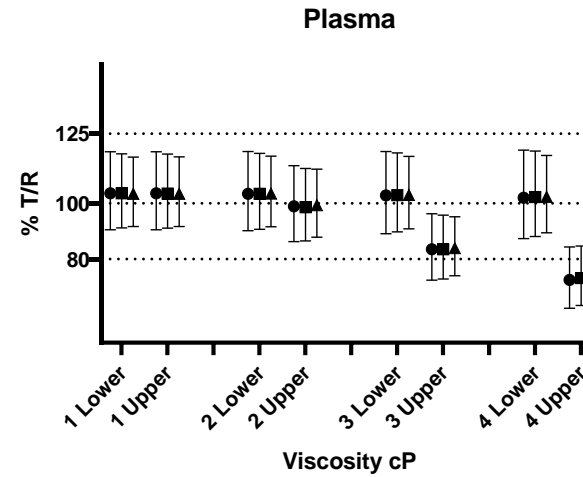
Upper Bound = 100 000 cP

Solubility :

RLD = 0.55 mg/ml

Lower Bound = 0.4 mg/ml

Upper Bound = 0.7 mg/ml



Desoximetasone - Topicort Spray Example

Upcoming Publication – in peer review

Effect of **Dose Selection** on formulation parameter sensitivity

- 1) Low dose – 1 spray per 10 cm²
- 2) Middle dose – 1 spray per 2 cm²
- 3) Default dose – 1 spray per 1 cm²
- 4) IVPT dose - 3.5 sprays per 1 cm²

Viscosity:

RLD = 100 cP

Lower Bound = 1cP

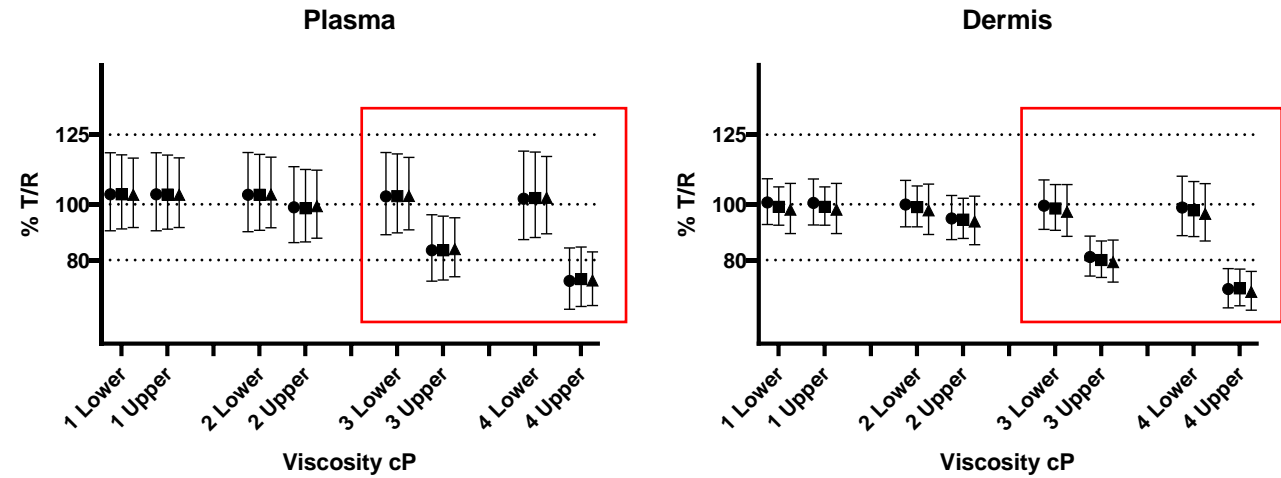
Upper Bound = 100 000 cP

Solubility :

RLD = 0.55 mg/ml

Lower Bound = 0.4 mg/ml

Upper Bound = 0.7 mg/ml



Desoximetasone - Topicort Spray Example

Upcoming Publication – in peer review

Effect of **Dose Selection** on formulation parameter sensitivity

- 1) Low dose – 1 spray per 10 cm²
- 2) Middle dose – 1 spray per 2 cm²
- 3) Default dose – 1 spray per 1 cm²
- 4) IVPT dose - 3.5 sprays per 1 cm²

Viscosity:

RLD = 100 cP

Lower Bound = 1cP

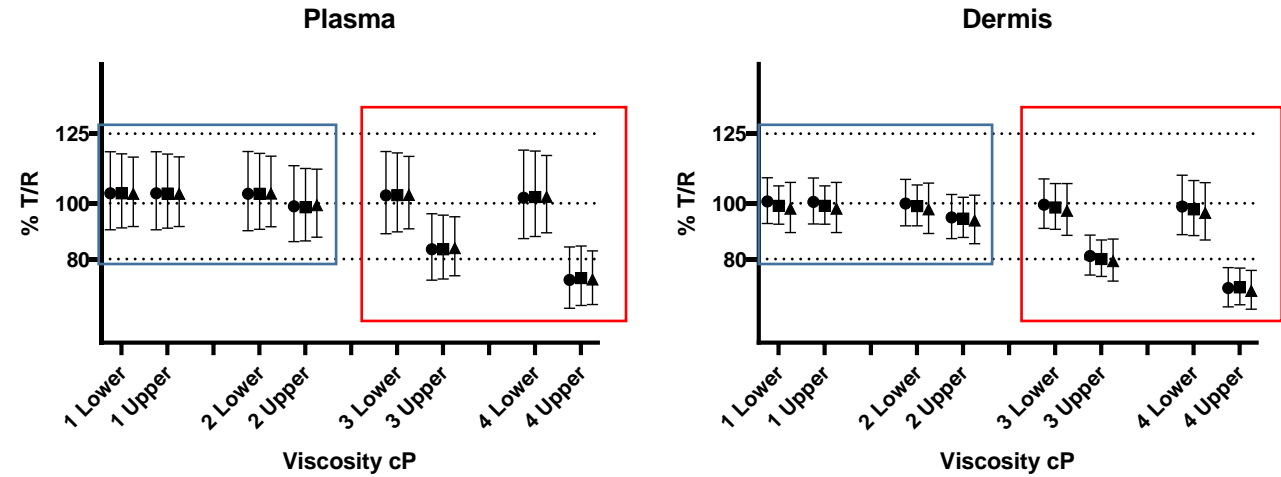
Upper Bound = 100 000 cP

Solubility :

RLD = 0.55 mg/ml

Lower Bound = 0.4 mg/ml

Upper Bound = 0.7 mg/ml



Desoximetasone - Topicort Spray Example

Upcoming Publication – in peer review

Effect of **Dose Selection** on formulation parameter sensitivity

- 1) Low dose – 1 spray per 10 cm²
- 2) Middle dose – 1 spray per 2 cm²
- 3) Default dose – 1 spray per 1 cm²
- 4) IVPT dose - 3.5 sprays per 1 cm²

Viscosity:

RLD = 100 cP

Lower Bound = 1cP

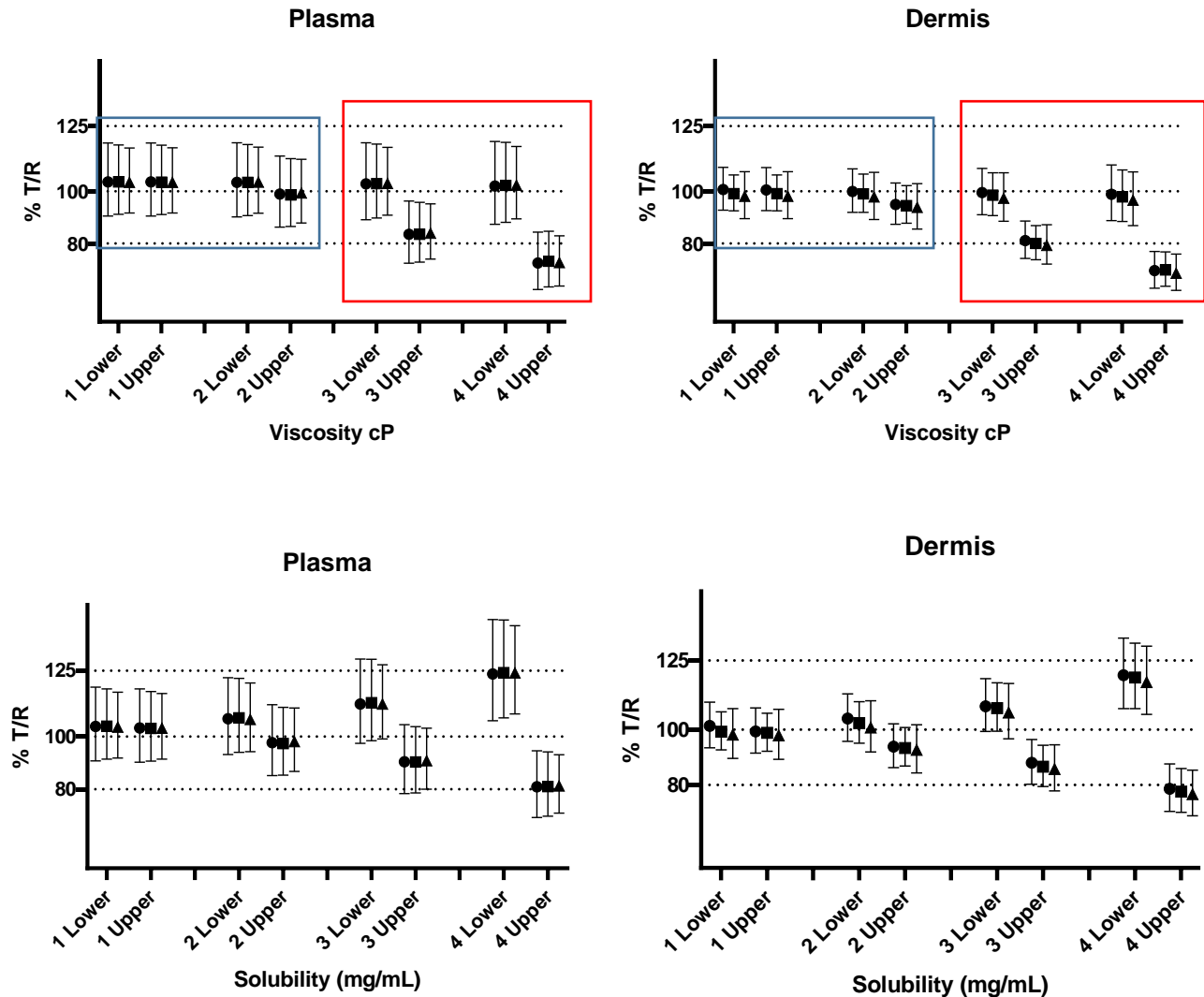
Upper Bound = 100 000 cP

Solubility :

RLD = 0.55 mg/ml

Lower Bound = 0.4 mg/ml

Upper Bound = 0.7 mg/ml



Desoximetasone - Topicort Spray Example

Upcoming Publication – in peer review

Effect of **Dose Selection** on formulation parameter sensitivity

- 1) Low dose – 1 spray per 10 cm²
- 2) Middle dose – 1 spray per 2 cm²
- 3) Default dose – 1 spray per 1 cm²
- 4) IVPT dose - 3.5 sprays per 1 cm²

Viscosity:

RLD = 100 cP

Lower Bound = 1cP

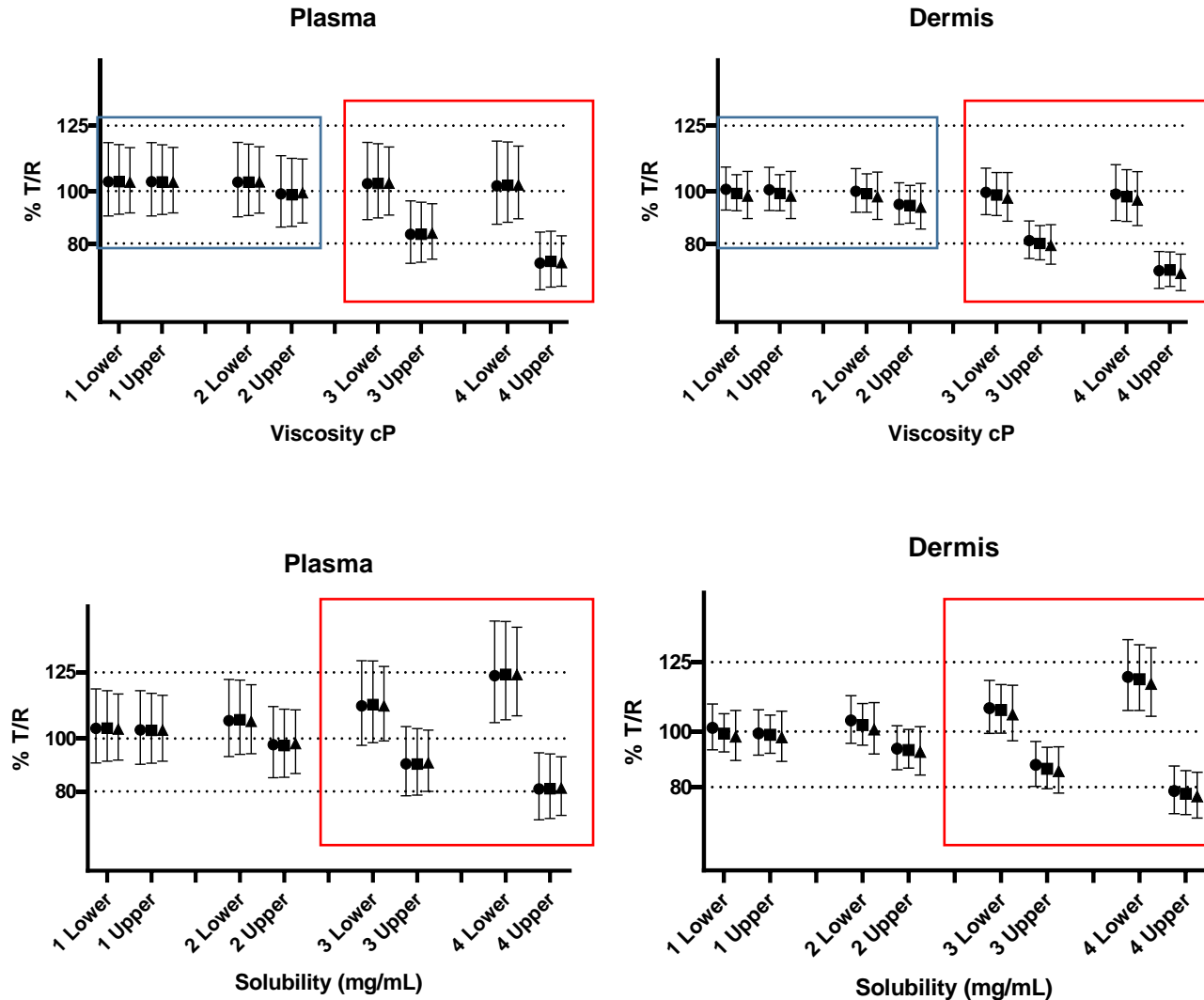
Upper Bound = 100 000 cP

Solubility :

RLD = 0.55 mg/ml

Lower Bound = 0.4 mg/ml

Upper Bound = 0.7 mg/ml



Desoximetasone - Topicort Spray Example

Upcoming Publication – in peer review

Effect of **Dose Selection** on formulation parameter sensitivity

- 1) Low dose – 1 spray per 10 cm²
- 2) Middle dose – 1 spray per 2 cm²
- 3) Default dose – 1 spray per 1 cm²
- 4) IVPT dose - 3.5 sprays per 1 cm²

Viscosity:

RLD = 100 cP

Lower Bound = 1cP

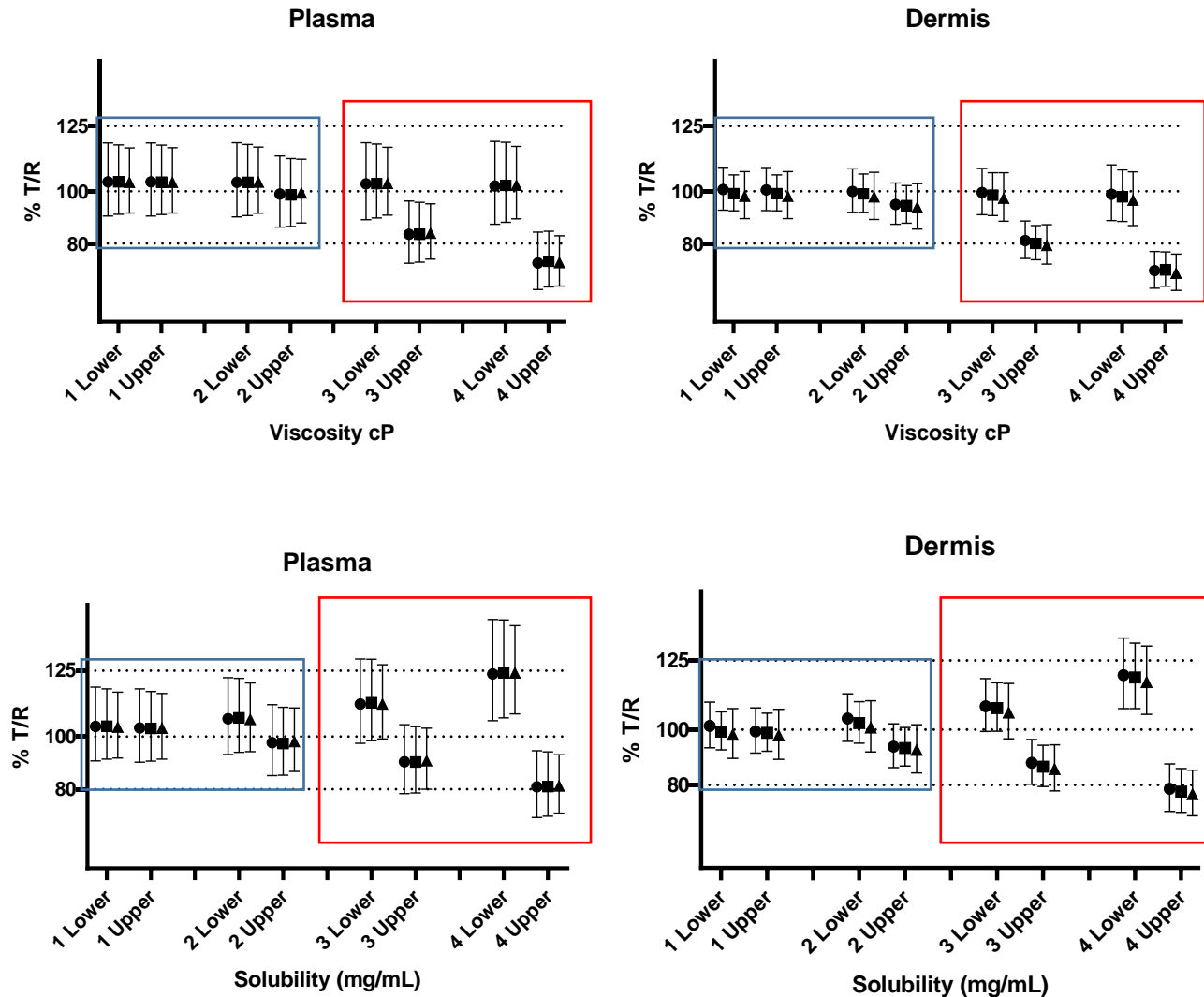
Upper Bound = 100 000 cP

Solubility :

RLD = 0.55 mg/ml

Lower Bound = 0.4 mg/ml

Upper Bound = 0.7 mg/ml





Thank you

James F Clarke PhD
Senior Research Scientist

sim  **CYP**



CERTARA 

 CENTER FOR RESEARCH ON
COMPLEX
GENERICS at the University of Maryland,
Baltimore and the
University of Michigan