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Simcyp

Development and validation of Dermal PBPK model towards Virtual Bioequivalence Assessment

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&

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BE challenges and solution for complex locally acting drug products

- **BE challenges for complex and locally acting drug products**
  - costly and time consuming
  - challenging for the PD endpoints
- **New paradigm potentially useful**
  - include mechanistic in silico models
  - therefore allows for the virtual scenarios testing
  - bridging the clinical knowledge gap or reduce the clinical testing burden

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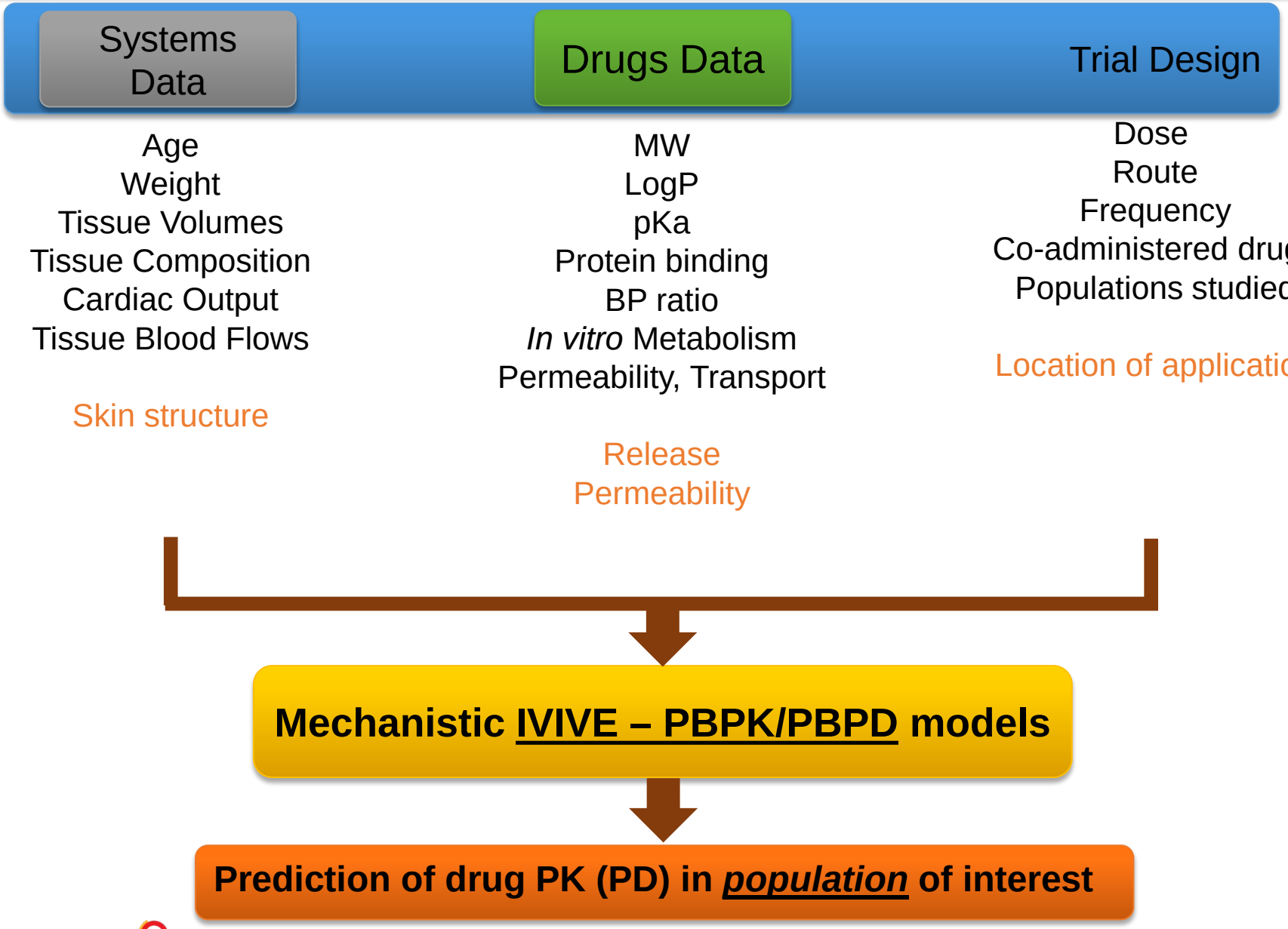
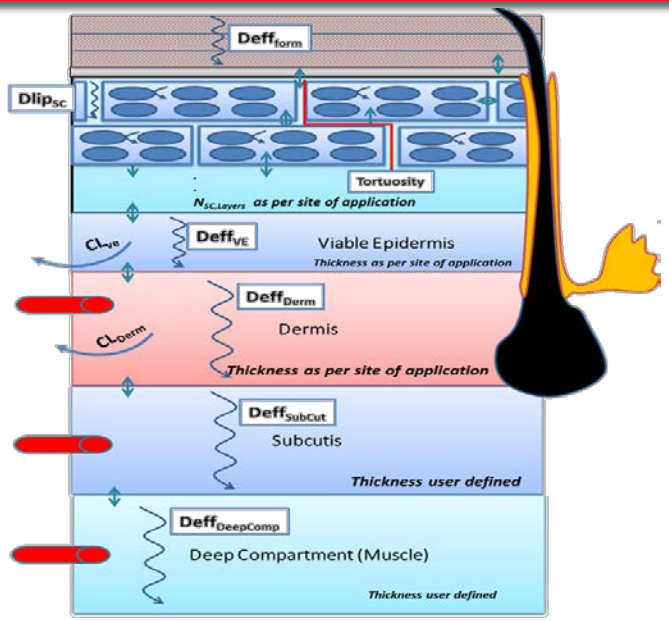
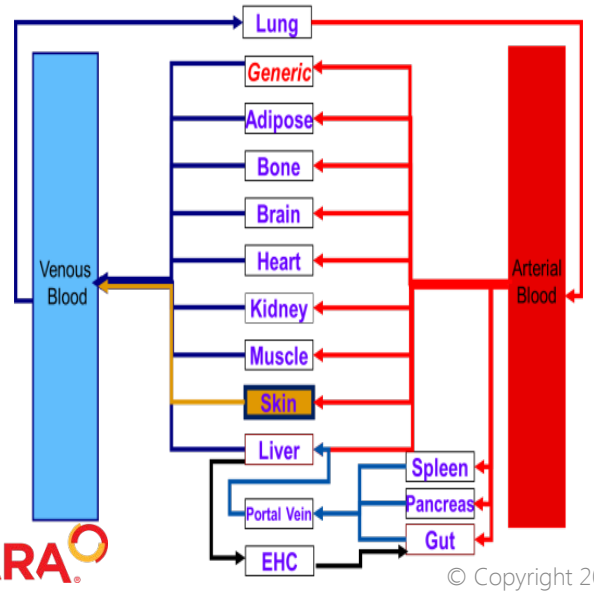
Advantage of mechanistic PBPK modelling



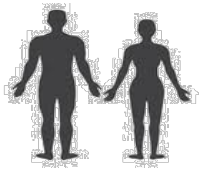
We do have tools and methods





Paediatric Population

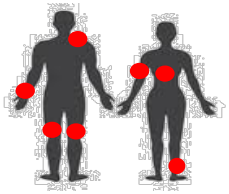
Healthy NEurCaucasian



Elderly Subjects

Ethnic Population

Diseased Population



Inter- and intra-individual variability

Different locations

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

- Various structural elements
  1. Skin surface
  2. Stratum corneum
  3. Viable epidermis
  4. Dermis
  5. Hair

- Various parameters
  1. Skin temperature
  2. Skin surface pH

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Different locations

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- Various structural elements
  1. Skin surface
  2. Stratum corneum
  3. Viable epidermis
  4. Dermis
  5. Hair

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

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Formulations

DRUG/FORMULATION SPECIFIC PARAMETERS

- Partitioning
- Diffusion
- Binding

FORMULATION SPECIFIC PARAMETERS

- Formulation type (solution, emulsion, suspension, patch)…
- … and all necessary information to characterize them
- Evaporation

CHARACTERIZED BY THE IN VITRO DATA

- Supported with the QSAR/empirical models when necessary
- Allows accounting for the excipients

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Performance verification/validation

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

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Conclusions

IVIVE in the Virtual Bioequivalence area

- USEFUL AND ALREADY AVAILABLE TOOL
- TRUST AND VALIDATION – absolutely necessary already reach and still growing
- POPULATION ANALYSIS – very important and already achievable
- PD ENDPOINTS – can be included to the validation and further analysis

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Thank you