Utility of Quantitative Pharmacology and Pharmacometrics in Investigating Active Sunscreen Ingredients Absorption

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Topical Drug Development - Evolution of Science and Regulatory Policy II

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Disclaimer

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Overview

- FDA Sunscreen Clinical Trial
  - Substantial systemic exposures were observed from the tested commercially available sunscreens
  - Key Research Objectives:
    - Establish QPP platforms to estimate/predict sunscreen absorption
    - Assess any potential toxicity with regard to the observed exposure
- QPP Roles on Sunscreen Research Roadmap
  - PBPK Modeling
  - PPK Modeling
  - Other Feasible and Supportive Approaches

FDA Sunscreen Clinical Trial (NCT03582215)

➢ Objectives

- To assess the systemic exposure of sunscreen active ingredients upon single and multiple dose/application when sunscreen product is applied under maximal use conditions.

➢ Study Design

Part 1

- Four formulations
- Four arm study in 24 subjects (1:1; M:F, Age: 18-60 y)
- Dose: application every 2 hours, four times per day for 4 days (approx. 2 mg/cm2, 75% of body surface area)
- PK samples (30 points): Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 9, 10, 12, 14, 23, 28, 33, 47, 52, 57, 71, 73, 74, 76, 78, 81, 82, 84, 86, 95, 120 and 144 h

(Ref: Matta, M. K., et al. JAMA 2019)

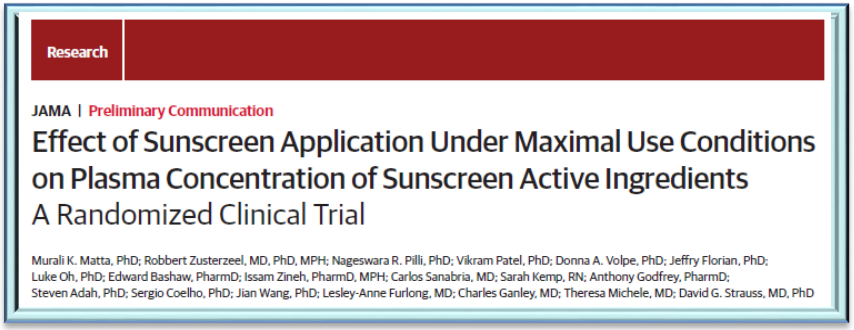
Part 2

- Four formulations
- Four arm study in 48 subjects (1:1; M:F, Age: 18-60 y)
- Dose: application once on day 1, and every 2 hours, four times per day for days 2 to 4 (approx. 2 mg/cm2, 75% of body surface area)
- PK samples (30 points): Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 9, 10, 12, 14, 23, 28, 33, 47, 52, 57, 71, 73, 74, 76, 78, 81, 82, 84, 86, 95, 120, 144, 216, 312 and 480 h

(Ref: Matta, M. K., et al. JAMA 2020)

FDA Sunscreen Clinical Trial (NCT03582215)

- Part 1 Results
  - Substantial systemic exposure of four active sunscreen ingredients were observed from the investigated commercially available sunscreens



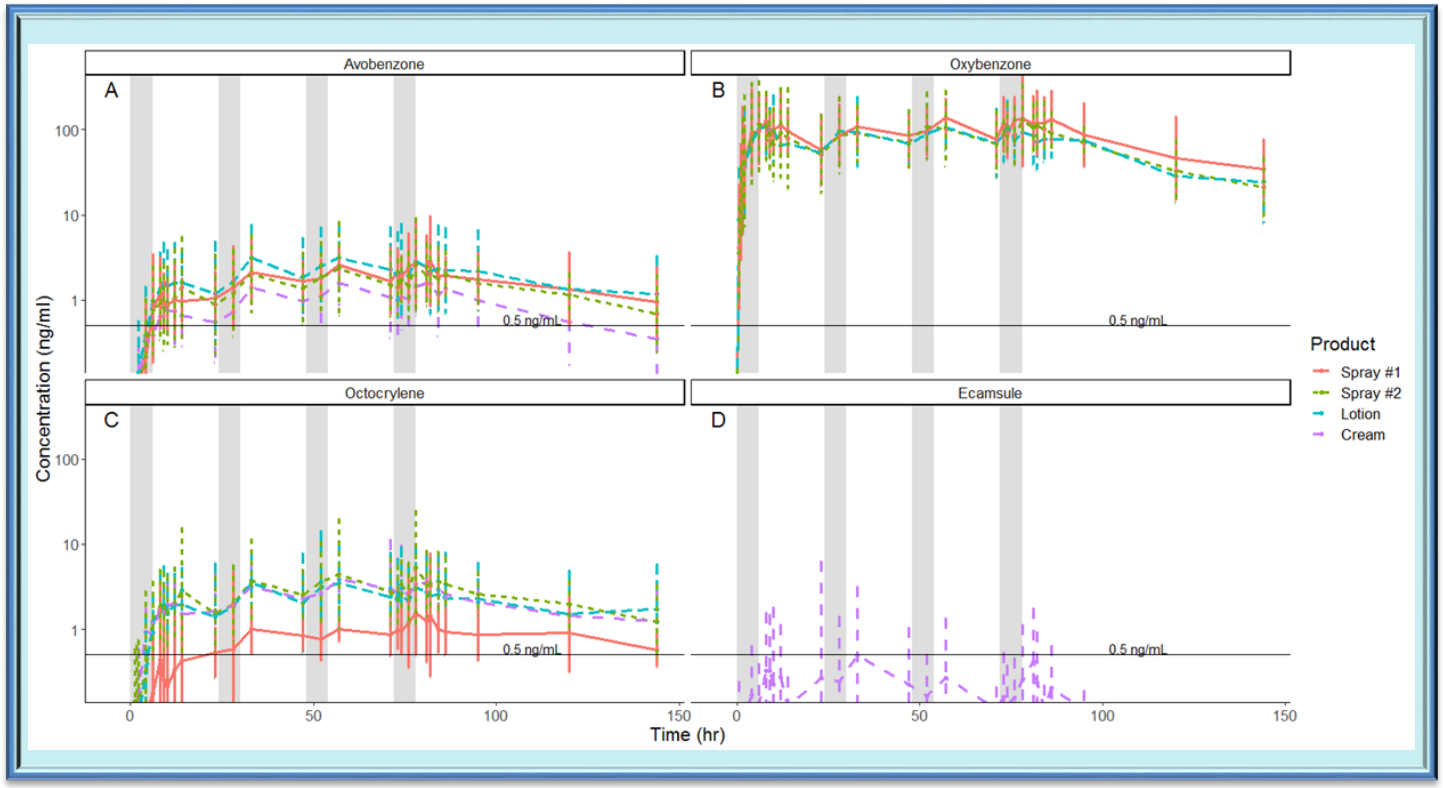
Research

JAMA | Preliminary Communication

Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients

A Randomized Clinical Trial

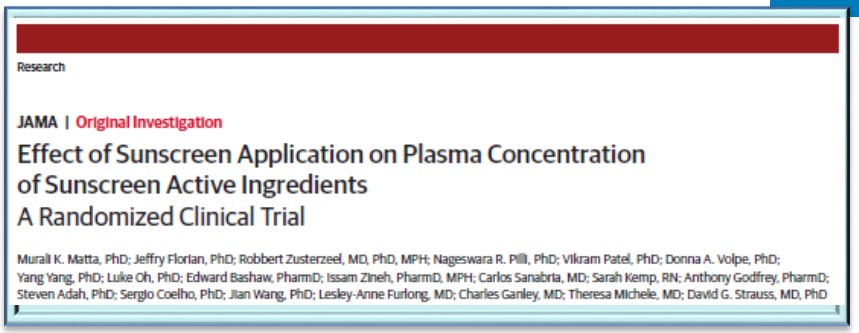
Murali K. Matta, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Jeffry Florian, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD



(Ref: Matta, M. K., et al. JAMA 2019)

FDA Sunscreen Clinical Trial (NCT03582215)

- Part 2 Results
  - Substantial systemic exposure of four active sunscreen ingredients were observed from the investigated commercially available sunscreens



Research

JAMA | Original Investigation

Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

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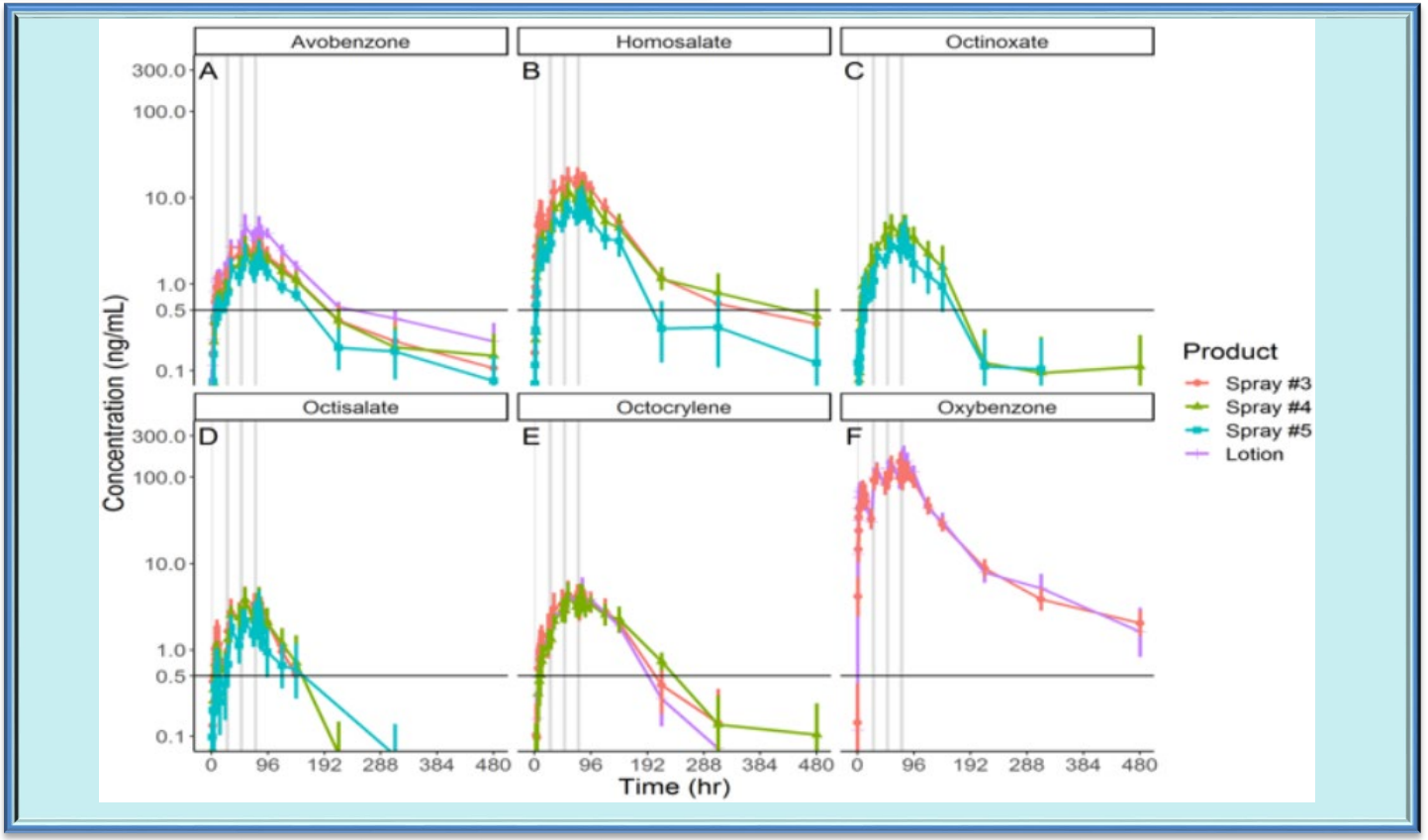

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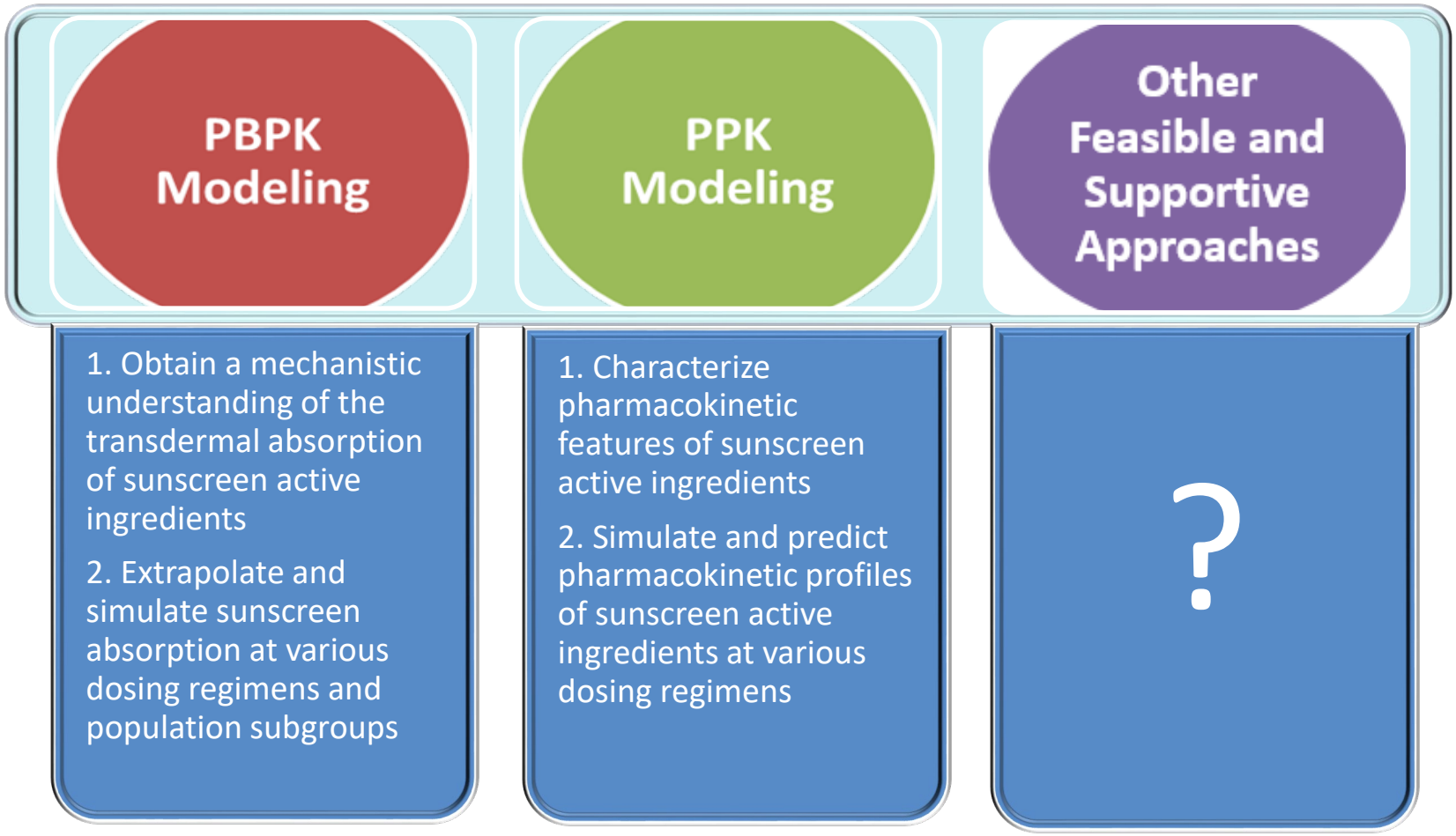
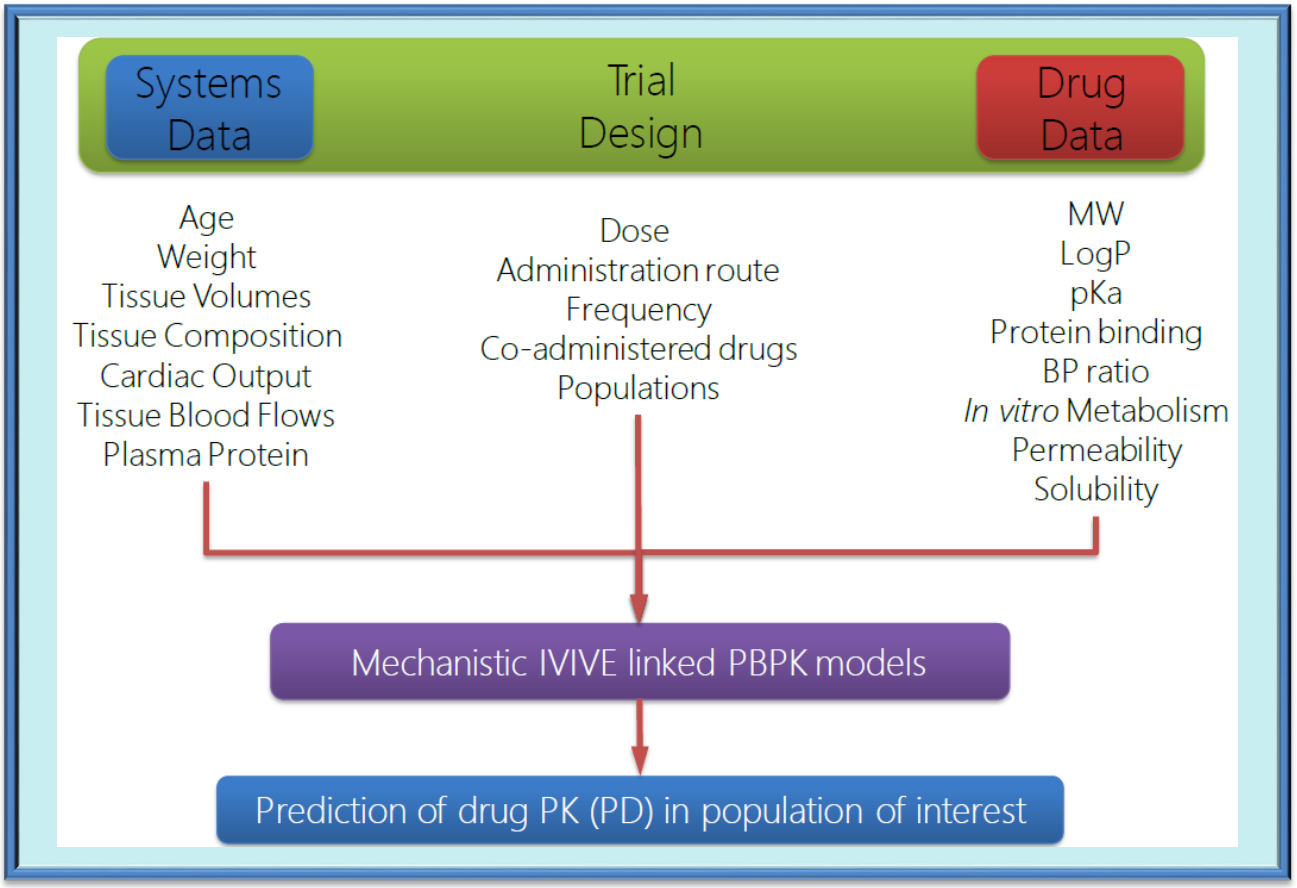
Sunscreen Key Research Objectives:

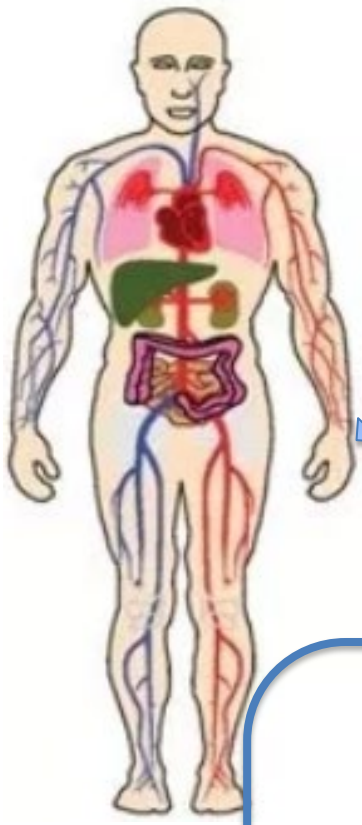
- Establish QPP platforms to estimate/predict sunscreen absorption
- Assess any potential toxicity with regard to the observed sunscreen active ingredient exposure

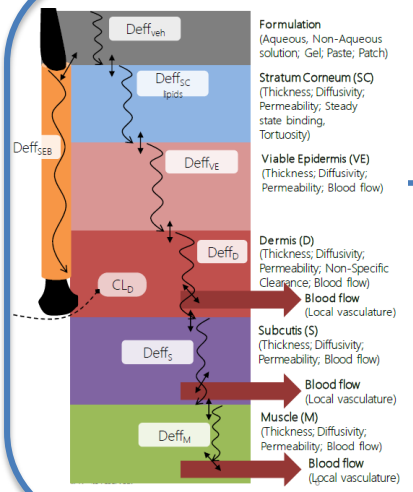
QPP Sunscreen Projects Roadmap

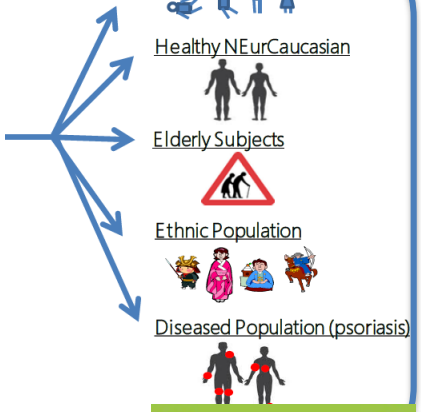


Physiologically Based Pharmacokinetic (PBPK) Modeling



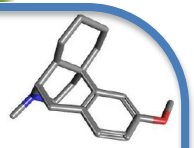






Systems Data

Drug Data



Phys-chem
1. MW
2. Density
3. LogP
4. LogD
5. pKa

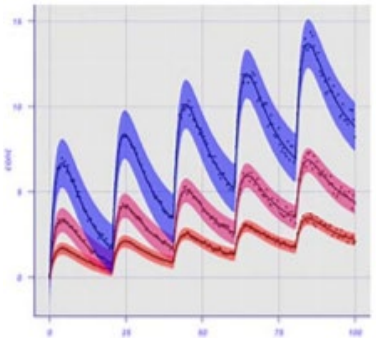
- ADME parameters
  1. BP / fu
  2. CL
  3. ....

Trial Design

Dose
Administration route
Frequency
Co-administered drugs
Populations

Mechanistic IVIVE

Prediction of drug PK in population of interest



PBPK Modeling of Avobenzone

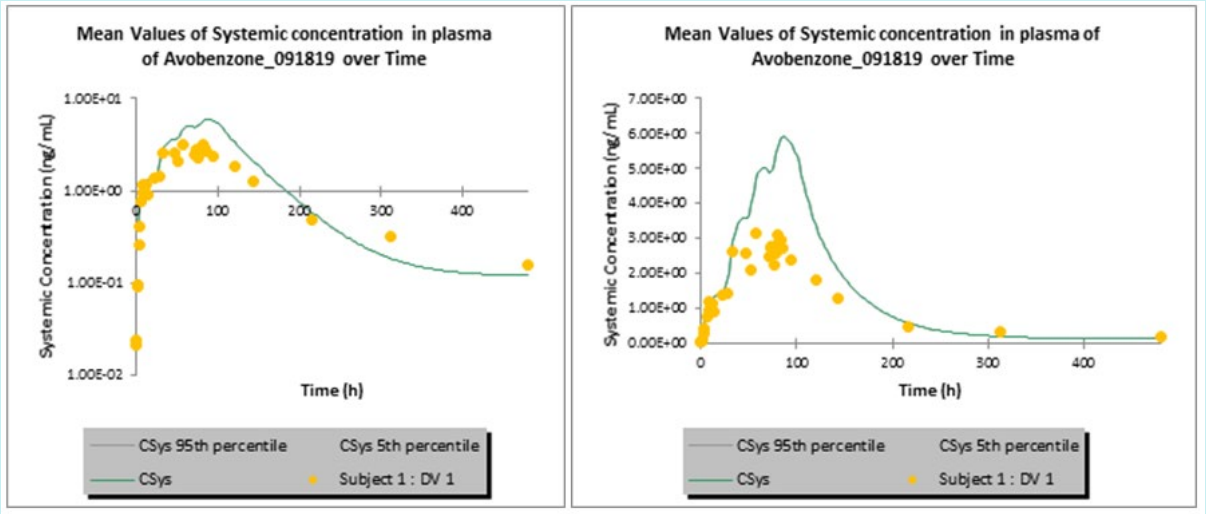
➢ Limitations and Related Assumptions

ADME Characteristics Unknown

- Protein binding and blood to plasma ratio are unknown
- Volume of distribution is unknown
- Clearance is unknown
  - Executed with assumptions

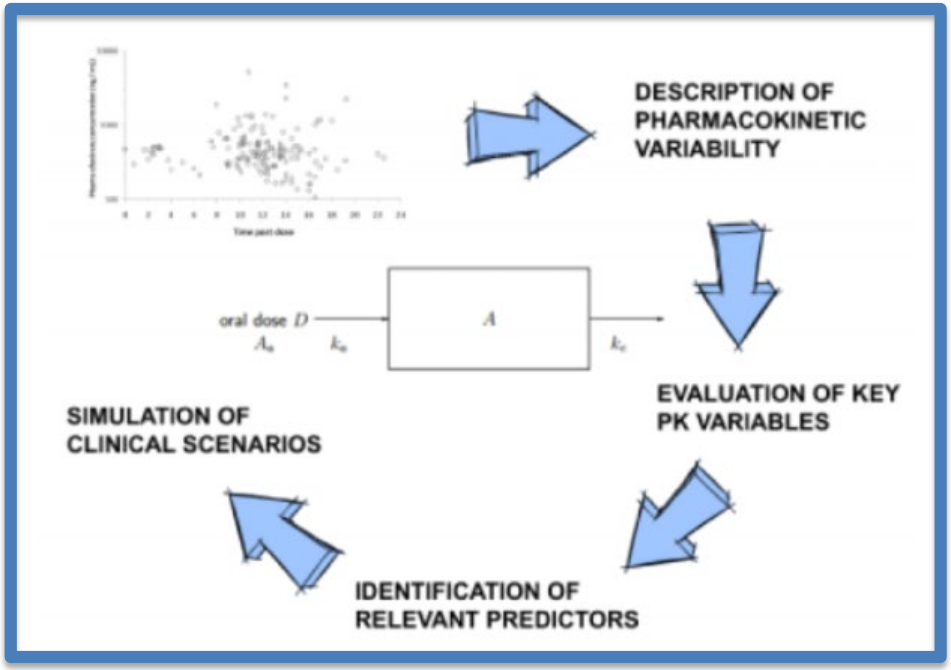
Formulation Attributes Unknown

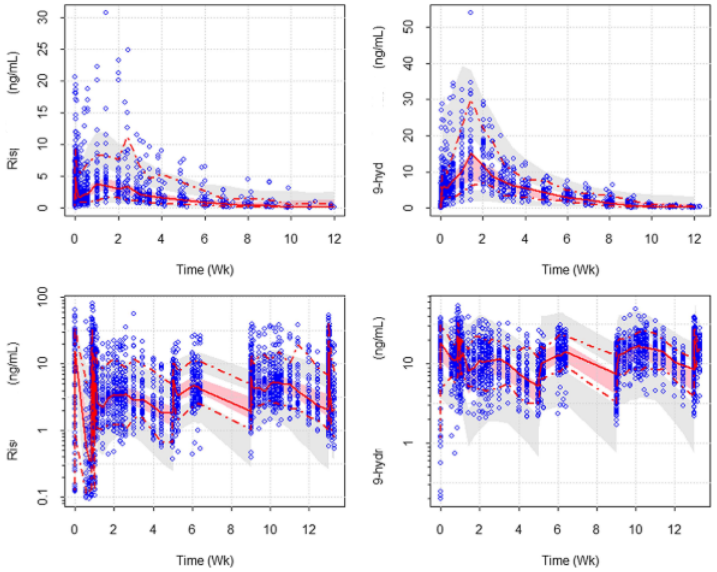
- Formulation composition, formulation pH, evaporation, viscosity
  - Executed based on characteristics of typical dosage forms and tested via sensitivity analysis
- Excipient effects
  - Justified and performed in an empirical manner



Population PK (PPK) Modeling

- Build population PK models for clinically tested active sunscreen ingredients
- Simulate PK profiles/exposures at various sunscreen dosing regimens





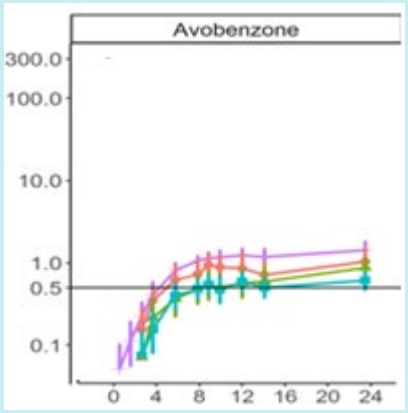
http://pktk.co.uk/services/mathematical-modelling

PPK Modeling of Avobenzone

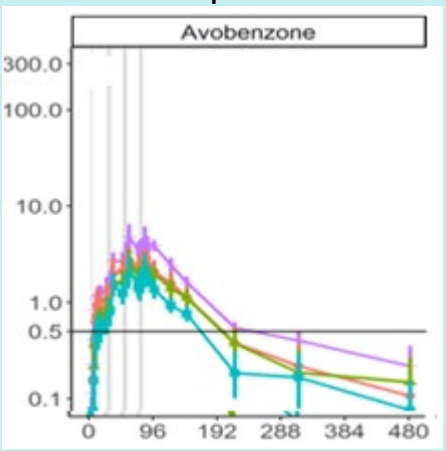
FDA

FDA Sunscreen Trial 2

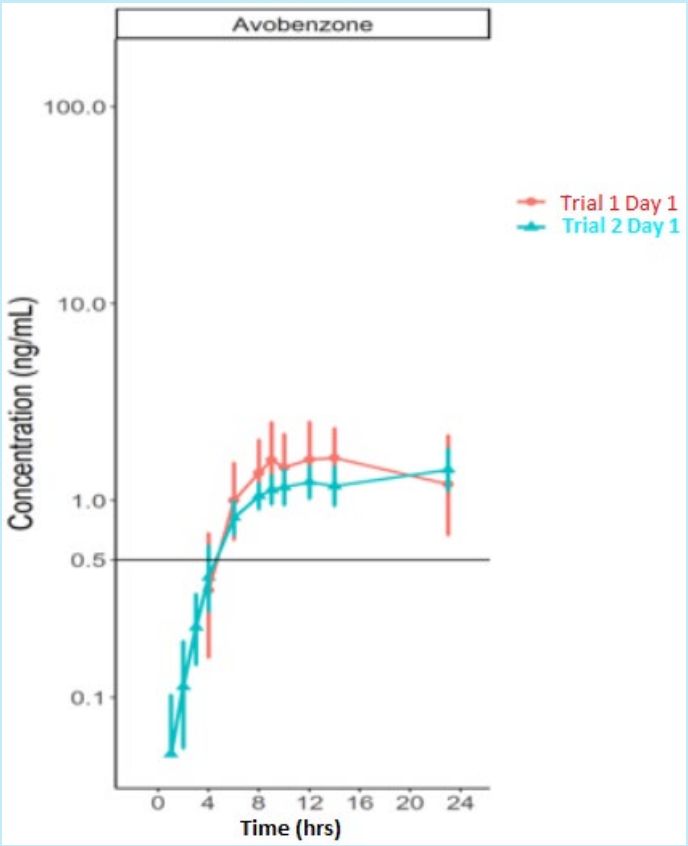
Single-dose PK



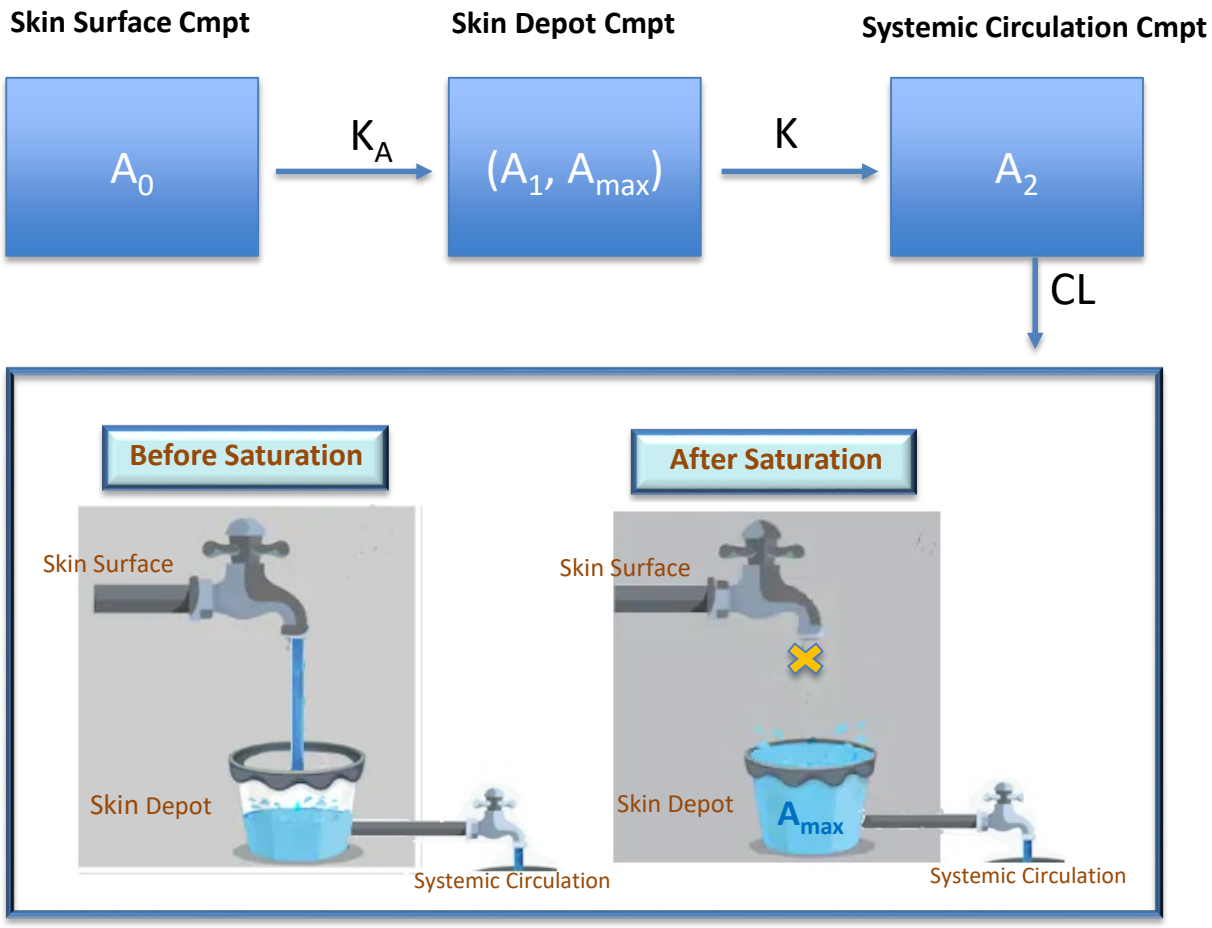
Multiple-dose PK



FDA Sunscreen Trial 1 vs. Trial 2 on Day 1



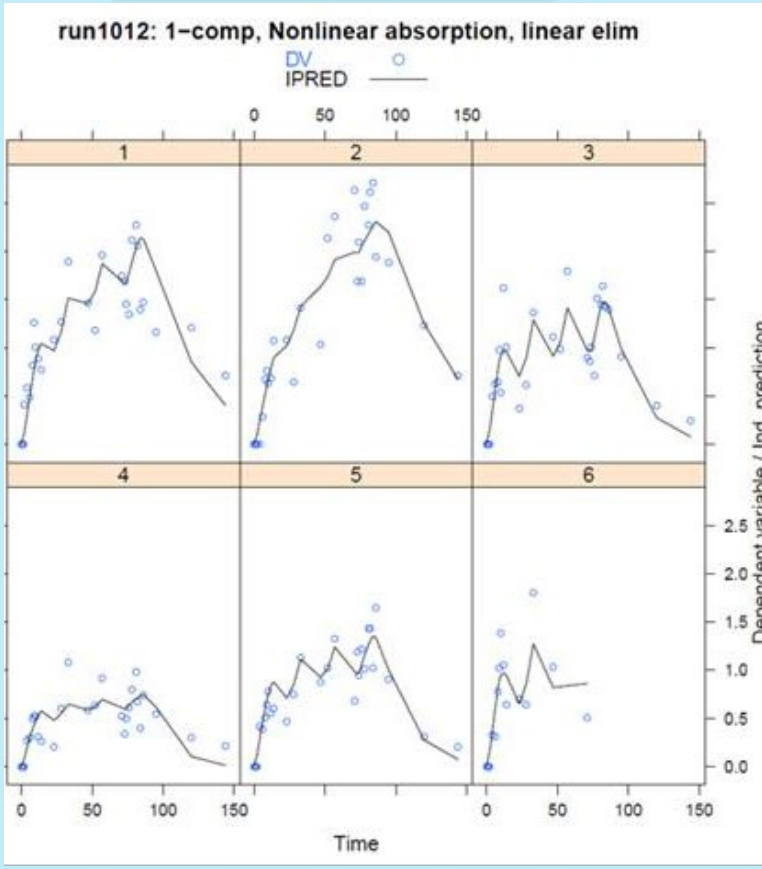
PPK Modeling of Avobenzone



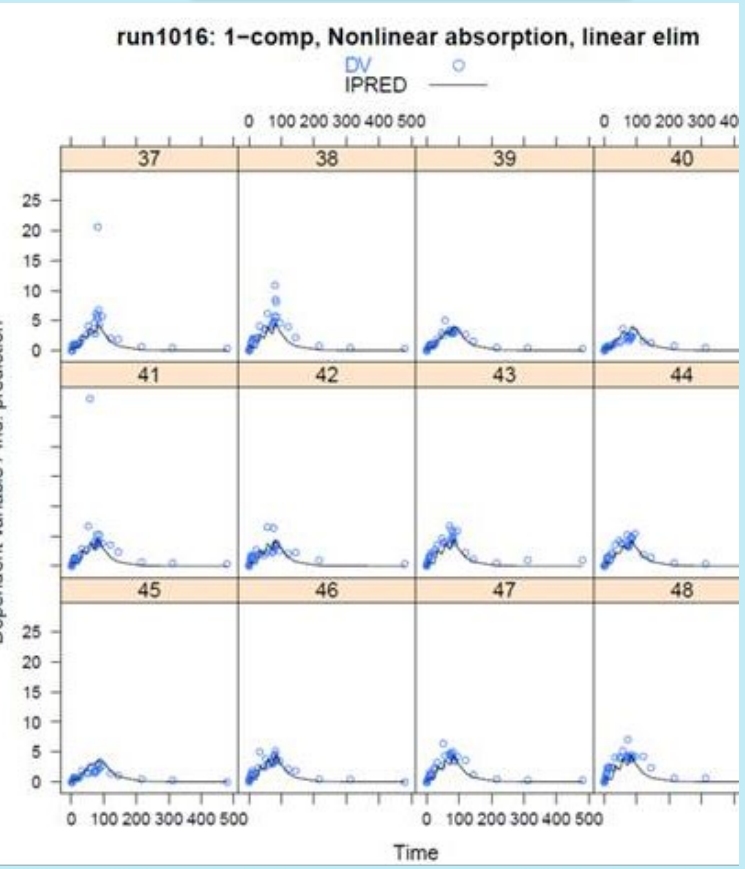
PPK Modeling of Avobenzone

FDA

FDA Sunscreen Trial 1



FDA Sunscreen Trial 2



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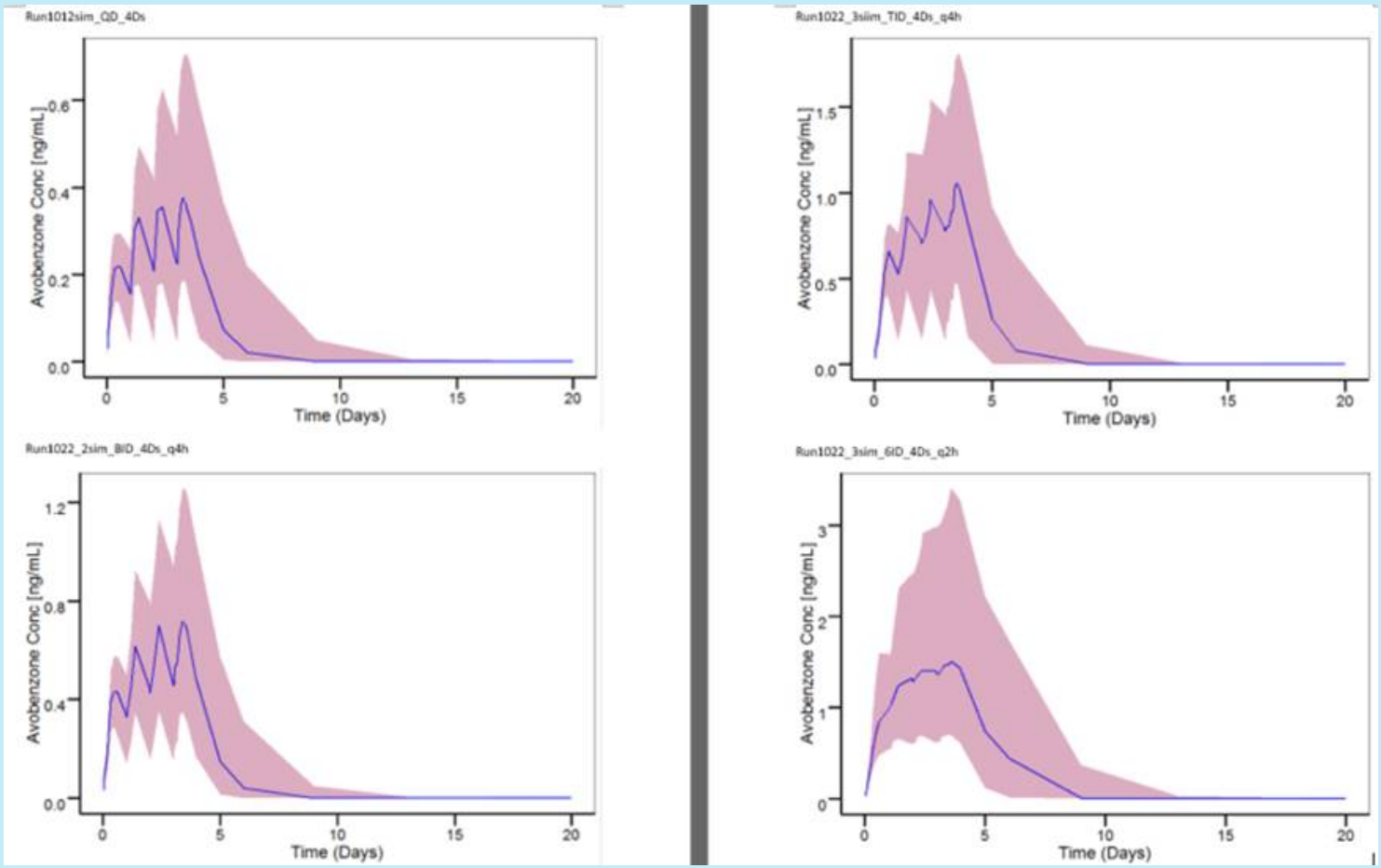
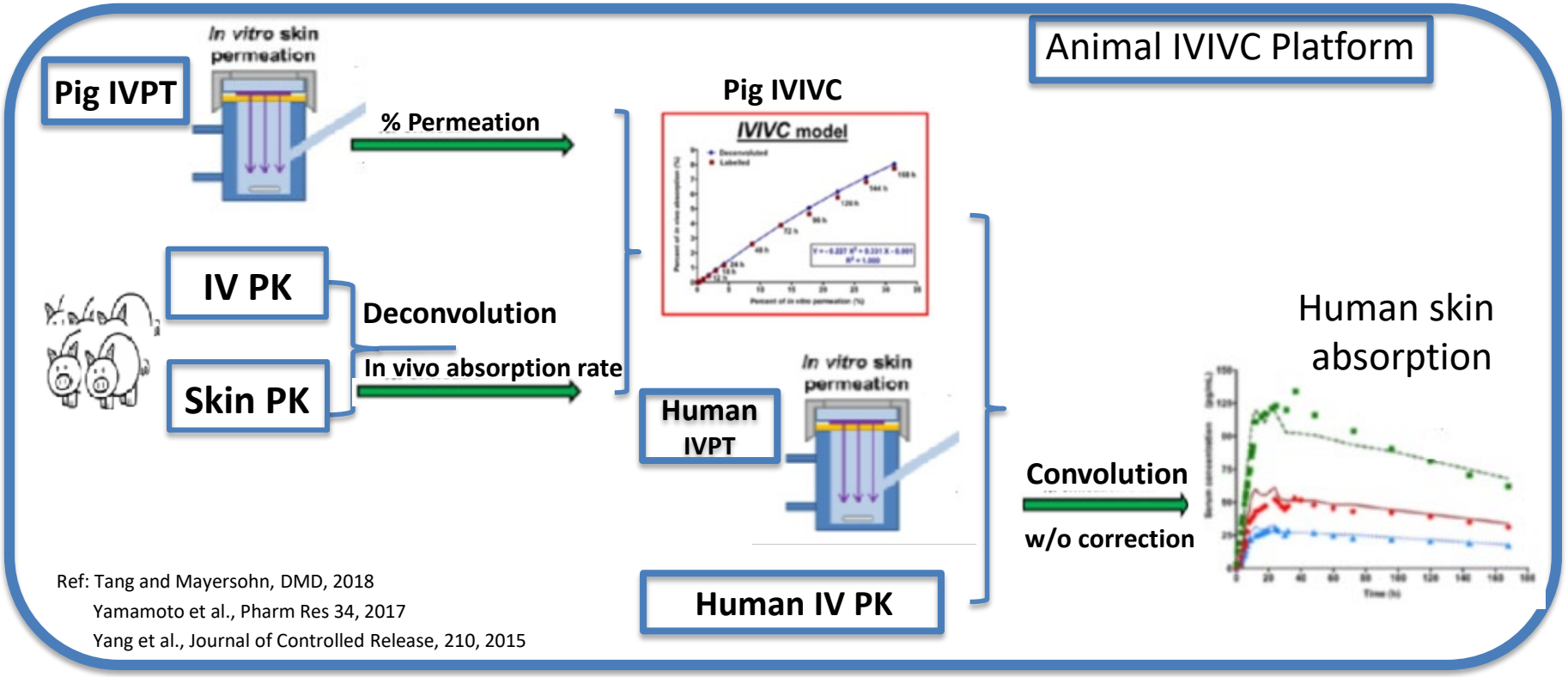


Other Feasible and Supportive QPP Approaches ?

IVPT and IVIVC

- What has been done with an established minipig transdermal IVIVC platform for human skin absorption



- Qualification of animal transdermal IVIVC platform for the prediction of human in vivo transdermal absorption

Potential Applications of QPP Platforms

- Obtain a deep understanding of the sunscreen active ingredients absorption and systemic exposure
- Simulate and predict pharmacokinetic profiles of sunscreen active ingredients at various dosing regimens
- Extrapolate and predict pediatric active sunscreen ingredients absorption and systemic exposure
- Potentially inform and impact sunscreen and other OTC skin products regulatory decision making

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