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

Da Zhang, Ph.D.
Division of Inflammation and Immune Pharmacology, OCP, CDER, FDA

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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

(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

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

PBPK Modeling
1. Obtain a mechanistic understanding of the transdermal absorption of sunscreen active ingredients
2. Extrapolate and simulate sunscreen absorption at various dosing regimens and population subgroups

PPK Modeling
1. Characterize pharmacokinetic features of sunscreen active ingredients
2. Simulate and predict pharmacokinetic profiles of sunscreen active ingredients at various dosing regimens

Other Feasible and Supportive Approaches

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Physiologically Based Pharmacokinetic (PBPK) Modeling

- **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

- **Drug Data**
  - MW
  - LogP
  - pKa
  - Protein binding
  - BP ratio
  - In vitro Metabolism
  - Permeability
  - Solubility

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**Mechanistic IVIVE linked PBPK models**

**Prediction of drug PK (PD) in population of interest**
Mechanistic IVIVE Prediction of drug PK in population of interest

Systems Data

Drug Data

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

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

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**Graphs**

- Mean Values of Systemic concentration in plasma of Avobenzone_091819 over Time
  - CSys 95th percentile
  - CSys 5th percentile
  - CSys
  - Subject 1: DV 1

- Another graph showing similar data.
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 Sunscreen Trial 2

Single-dose PK

FDA Sunscreen Trial 1 vs. Trial 2 on Day 1

Multiple-dose PK
PPK Modeling of Avobenzone

Skin Surface Cmpt: $A_0$ 

Skin Depot Cmpt: $A_1, A_{\text{max}}$ 

Systemic Circulation Cmpt: $A_2$

$K_A$: $A_0 \rightarrow (A_1, A_{\text{max}})$

$K$: $(A_1, A_{\text{max}}) \rightarrow A_2$

Before Saturation

After Saturation

Skin Surface

Skin Depot

Systemic Circulation

$A_{\text{max}}$

$CL$
PPK Modeling of Avobenzone

FDA Sunscreen Trial 1

FDA Sunscreen Trial 2
PPK Modeling of Avobenzone
Other Feasible and Supportive QPP Approaches?
IVPT and IVIVC

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

Animal IVIVC Platform

- In vivo absorption rate
- % Permeation

Pig IVPT

- Deconvolution
- In vivo absorption rate

Skin PK

IV PK

Human IV PT

Human skin absorption

Animal IVIVC Platform

- Human IV PK

Ref: Tang and Mayersohn, DMD, 2018
Yamamoto et al., Pharm Res 34, 2017
Yang et al., Journal of Controlled Release, 210, 2015

- 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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