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

Da Zhang, Ph.D.
Division of Clinical Pharmacology III, OCP, CDER, FDA

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FDA Sunscreen Clinical Trial

- Substantial systemic exposures were observed from the tested commercially available sunscreens
- Key Research Objectives:
  - Assess any potential toxicity with regard to the observed exposure
  - Establish QPP platforms to estimate/predict sunscreen absorption

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**

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<th>Part 1</th>
<th>Part 2</th>
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  | - 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) | - An open-label, randomized, 4-arm study with 48 healthy adult subjects to evaluate 6 active sunscreen ingredients (Manuscript in preparation)  
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)
Sunscreen Key Research Objectives:

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

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

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
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

Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

www.fda.gov
Mechanistic IVIVE Prediction of drug PK in population of interest

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

Phys-chem
- MW
- Density
- LogP
- LogD
- pKa

Systems Data

Mechanistic IVIVE
Prediction of drug PK in population of interest

Trial Design
- Dose
- Administration route
- Frequency
- Co-administered drugs
- Populations
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
Other Feasible and Supportive QPP Approaches?
In Vitro Permeability Test (IVPT)

- IVPT plays an important role in topical dermatological drug development
- IVPT measures relative permeability and provides potential systemic exposure of topically applied drugs

Static (Franz) diffusion cell used in IVPT

(Images from PermeGear, Inc.)
Utility of IVPT in Sunscreen Monograph Qualification Process and Formulation Testing Process

Draft not for implementation

Monograph Qualification Process

Proposed Ingredient X

Dermal Safety

MUsT

IVPT

Same formulation
Dermal Safety/MUsT/IVPT

Pre-Clinical

Safety Multiple

Added to Monograph

Monograph

Added as Release Test

Formulation Testing Process

Equal or Lesser Permeation Confirms Safety Multiple

New Formulation

Repeat IVPT

Permeation Same or Less Than

To Market

Permeation LARGER Than in Monograph

Options:
1. Reformulate & Repeat Study
2. Petition FDA that observed difference does not present a safety risk
3. Repeat Monograph Qualification process
4. Submit an NDA for the specific formulation

Control Formulation
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

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