Maximal Use Pharmacokinetic Trial Design for Topical Dermatological Products

By

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Disclaimer

The opinions and views expressed in this presentation are my own and do not reflect US Food and Drug Administration policy or official guidance.
Outline

- Topical dermatological products
- The skin barrier and dermatological diseases
- Maximal use pharmacokinetic (PK) trial design
- Application of systemic PK data
Topical dermatological products

- Topically applied products
  - Intended for local action
  - May have unintended systemic absorption
  - Variety of dosage forms: cream, lotion, ointment, gel, foam, etc.
The skin barrier
Altered skin barrier

Atopic dermatitis
Atopic dermatitis
Severe acne vulgaris

Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. Fitzpatrick’s Dermatology in General Medicine, 8th Edition: www.accessmedicine.com

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Mild and severe papulopustular rosacea
Chronic plaque psoriasis


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Potential for systemic absorption

Luliconazole cream for tinea pedis and tinea cruris.

Reference: Clinical Pharmacology and Biopharmaceutics review.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204153Orig1s000ClinPharmR.pdf
Potential for systemic absorption

Tavaborole topical solution, 5% for onychomycosis

Regulatory requirement

- Code of Federal Regulations (21 CFR 320.21)
  - Evidence measuring the in vivo bioavailability of the drug product that is the subject of the application, or
  - Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability
Determinants of Topical Bioavailability
Maximal use PK trial

A maximal use pharmacokinetic (PK) trial is conducted by obtaining adequate number of PK samples following administration of your to-be-marketed formulation. This trial should be conducted in a suitable number of subjects with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

• Frequency of dosing
• Duration of dosing
• Use of highest proposed strength
• Total involved surface area to be treated at one time
• Amount applied per square centimeter
• Method of application/site preparation

Steps should be taken to ensure that the target patient population (age, gender, race, etc.) is properly represented in the maximal use PK trial.
Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products

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Healthy versus diseased skin

Diseased skin has compromised barrier properties which could affect the amount of drug absorbed through the skin.

Healthy skin  Atopic dermatitis


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Change in disease states affects drug absorption

Luliconazole cream 1%

Reference: Adapted from raw data in NDA 204153 - Clinical Pharmacology and Biopharmaceutics review.  
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204153Orig1s000ClinPharmR.pdf
Total involved surface area

- Example: For acne indication, drug should be applied to the entire face, shoulders, upper chest and upper back in order to capture the worst case

Severe acne vulgaris
Study duration

• Effects of improvement in skin barrier with treatment

• Duration should be sufficient to reach steady state but not too long that the skin is healed and reduces drug absorption
Study duration

- Topical corticosteroid formulation X
  - Drug was applied for either 15 days or 29 days to subjects with plaque psoriasis
  - HPA axis suppression was seen at Day 15 (about 20%) but not seen at Day 29
  - Likely reason is due improvement in skin conditions (i.e., skin barrier function) with the longer treatment duration
Higher systemic drug concentrations in pediatric subjects might be observed due to larger surface area to body weight ratio and/or ontogenic differences in physiological processes affecting ADME.
Pediatric subjects

- HPA axis suppression rate for Diprolene AF Cream, 0.05% in subjects with atopic dermatitis

<table>
<thead>
<tr>
<th>Age Group</th>
<th>3mo-1yr n=4</th>
<th>2yr-5yr n=16</th>
<th>6yr-8yr n=28</th>
<th>9yr-12yr n=12</th>
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<td># suppressed</td>
<td>2</td>
<td>6</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>%</td>
<td>50</td>
<td>38</td>
<td>32</td>
<td>17</td>
</tr>
</tbody>
</table>

- Rates appear higher with lower age
  - Caveat: not statistically significant, not all cases show this trend

Adapted from presentation by Denise Cook, MD at the Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee on March 24, 20015
Method of application and site preparation

- Debridement procedure removes dead tissue from the surface and thus may alter drug absorption.

- Occluded conditions might alter drug absorption compared to non-occluded conditions.
Impact of excipient change on drug bioavailability

• Surfactant system was changed in the formulation

• The bioavailability (BA) of clindamycin increased by ~ 1.6 fold while that of tretinoin remained unchanged

Reference: NDA 50803- Clinical Pharmacology and Biopharmaceutics review.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/050803Orig1s000ClinPharmR.pdf
Formulation

- To-be-marketed formulation should be used
- In case when there is a change in the excipient system, an additional maximal use PK trial may be needed
Amount applied in the maximal use PK trial should be recorded and compared with that used in the Phase 3 safety and efficacy trials and proposed for clinical use.
Impact of Maximal Use PK Trial

- Systemic safety evaluation
  - Comparing the systemic exposure to animal toxicity threshold data
  - Correlating systemic levels to systemic safety signals
  - Comparing to data from other formulation or route of administration to assess relative risk
  - Comparing to data from in vitro enzyme inhibition/induction studies to assess risk for drug interactions
Impact of Maximal Use PK Trial

• Support waiver for Pharm/Tox studies when submitting a 505(b)(2) NDA application

• Support establishment of a clinical bridge when submitting a 505(b)(2) NDA application

• Support waiver of TQT trial if systemic exposures are low (e.g., Cmax below 1nM)

• HPA axis suppression for topical corticosteroids
  – Requires empirical data currently
  – Potential for exposure-response in future?
Other considerations

• Maximal use PK trial design is flexible
  – Discuss with FDA if there are unique circumstances

• May be used in conjunction with other techniques
  – Microdialysis to assess local concentrations
Summary

• Topical drug products can lead to systemic absorption and adverse effects
• Systemic bioavailability assessment should be conducted under maximal use conditions
• Study design should be discussed with the FDA
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