Integration of In Vitro Permeation Test (IVPT) and Maximal Use Trial (MUsT) into the Safety Assessment of Topical OTC Products

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Disclaimer

- The presentation today should not be considered, in whole or in part, as statements of policy or recommendation by the US Food and Drug Administration.
- Throughout the talk or the debate portion of the program representative examples of commercial products may be given to clarify or illustrate a point. No commercial endorsement is implied or intended.
Potential formulation effects on dermal absorption of topical products

• The composition of a formulation may have a significant impact on drug absorption through the skin
  – Strength of active ingredients
  – Formulation types (e.g., lotion, cream, gel, spray, etc.)
  – Other active/inactive ingredients that potentially enhance skin permeation (e.g., alcohol)

• Once active ingredients of OTC monograph are determined to be ‘generally recognized as safe and effective’ (GRASE), the active ingredients in the Over-the-Counter (OTC) monograph will be marketed in multiple diverse formulations without pre-market approval process.
Evaluation of formulation effects in a MUsT program for OTC monograph

• Per the OTC MUsT final guidance (2019), FDA recommends assessment of formulation effects on dermal absorption in a MUsT for an active ingredient using at least 4 different formulations in the absence of mitigating safety data or other bioavailability-related information.

• The tested formulations in a MUsT should include
  – the formulation with the highest potential for permeation
  – a formulation containing permeation enhancers at the high end of concentrations.

• A MUsT protocol has to include justification for the selection of formulations, e.g., in vitro skin permeation test (IVPT) results.

Ref: FDA Draft Guidance for Industry (May 2018), ‘Maximal usage trial (MUsT) for Topical Active ingredients being considered for inclusion in an over-the-counter monograph: Study elements and considerations’
The usage of IVPT to evaluate formulation effects on dermal absorption for OTC monograph

• IVPT should be coupled with a MUst program

• Before GRASE determination;
  – Screen marketed formulations using IVPT
  – Select formulations for a MUst based on IVPT results

• After GRASE determination (i.e., final formulation testing);
  – IVPT for a new formulation may inform potential dermal absorption linked to the original MUst/IVPT data
Example of Workflow
(Before GRASE determination)

- **Market research**
  - Research of marketed products (% of active ingredient, permeation enhancer)

- **IVPT**
  - IVPT with representative products
  - Select formulations for MUsT based on the results

- **MUst**
  - Pilot and Pivotal MUst
# Example of market research

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation Type</th>
<th>Active ingredient Strength</th>
<th>Permeation Enhancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Lotion</td>
<td>2%</td>
<td>Not includes</td>
</tr>
<tr>
<td>B</td>
<td>Lotion</td>
<td>2%</td>
<td>Includes (X, Y, Z)</td>
</tr>
<tr>
<td>C</td>
<td>Lotion</td>
<td>5%</td>
<td>Not includes</td>
</tr>
<tr>
<td>D</td>
<td>Gel</td>
<td>2%</td>
<td>Not includes</td>
</tr>
<tr>
<td>E</td>
<td>Gel</td>
<td>2%</td>
<td>Includes (X, Y)</td>
</tr>
<tr>
<td>F</td>
<td>Spray</td>
<td>1%</td>
<td>Includes (Z)</td>
</tr>
<tr>
<td>G</td>
<td>Spray</td>
<td>2%</td>
<td>Includes (X, Y, Z)</td>
</tr>
<tr>
<td>H</td>
<td>Spray</td>
<td>2%</td>
<td>Includes (Y, Z)</td>
</tr>
</tbody>
</table>
Final Formulation Testing (after GRASE determination)

- IVPT result for the formulation resulted in the highest dermal absorption in the MUsT will be a benchmark.
- In vitro permeability of new formulations is supposed to be similar or smaller than the established monograph condition.
- If it is greater than the monograph condition, reformulation should be considered. Otherwise, a new MUsT can address the potential for higher dermal absorption than the monograph condition.
The IVPT methodology to regulate OTC monograph products

• In the literature, IVPT results showed high variability and low reproducibility.
  → Thus, it needs to be standardized and validated to generate precise, accurate, and reproducible results.

• FDA has submitted a manuscript regarding regulatory perspectives on a standard methodology of IVPT for OTC products and will be preparing a guidance for the industry.
Despite the comparability of the two systems, the static system is the preferred system due to its wider availability and its previous acceptance by both FDA\(^1\) and USP\(^2\)

1. FDA Draft Product Specific Guidance on topical acyclovir ointment (Dec 2016)
2. USP General Chapter <1724>, Semisolid Drug Products – Performance Tests.
Human skin membrane

- **Human skin** should be used as a predictor of in vivo human PK
  - Human cadaver skin (abdominal or breast) is normally obtained as a byproduct of cosmetic surgery
- The permeation rate is highly influenced by the quality of the skin membrane.
  - Dermatomed split-thickness (200-500 µm)
  - Qualifications of skin integrity:
    - trans-epidermal water loss
    - transcutaneous electrical resistance
    - penetration of a tritiated water

Figure from http://pmuinternational.com/skin-structure-permanent-make-up
Study Design

• Study duration: ~24 hrs with regular sampling intervals
• Sampling time points: a minimum of 6 post-application
  – including one early time point (e.g., 30 min) plus baseline (i.e., pre-dose).
• Number of replicates: a minimum of 3 different skin donors with at least 3 replicates per donor for each formulation

Permeation rate over time profile

Figure from Shin et al, Pharmaceutical Research (Sep 2017)
References

• The Proposed Rule: Sunscreen Drug Products for Over-the-Counter Human Use (Feb 26, 2019)
• FDA Final Guidance - Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations (May 2019)
• FDA Draft Product Specific Guidance on topical acyclovir ointment (Dec 2016) – Section D. IVPT method development and validation
• FDA Final Guidance - Nonprescription Sunscreen Drug Products - Safety and Effectiveness Data (Nov 2016)
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