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

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Topical Drug Development Workshop
July 30, 2019

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- 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.
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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Ref: FDA Draft Guidance for Industry (May 2018), *'Maximal usage trial (MUsT) for Topical Active ingredients being considered for inclusion in an over-the-counter monograph: Study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'*

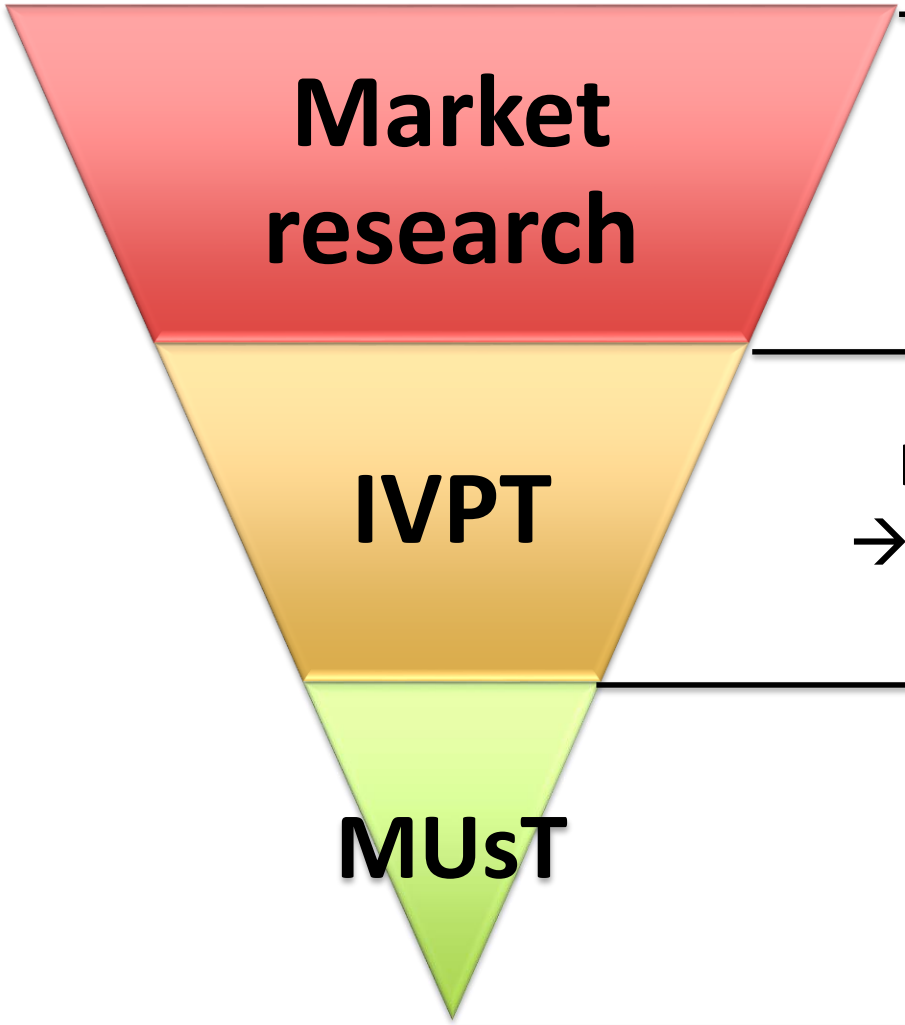
The usage of IVPT to evaluate formulation effects on dermal absorption for OTC monograph

- 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)



Research of marketed products (% of active ingredient, permeation enhancer)

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

Pilot and Pivotal MUsT

Example of market research

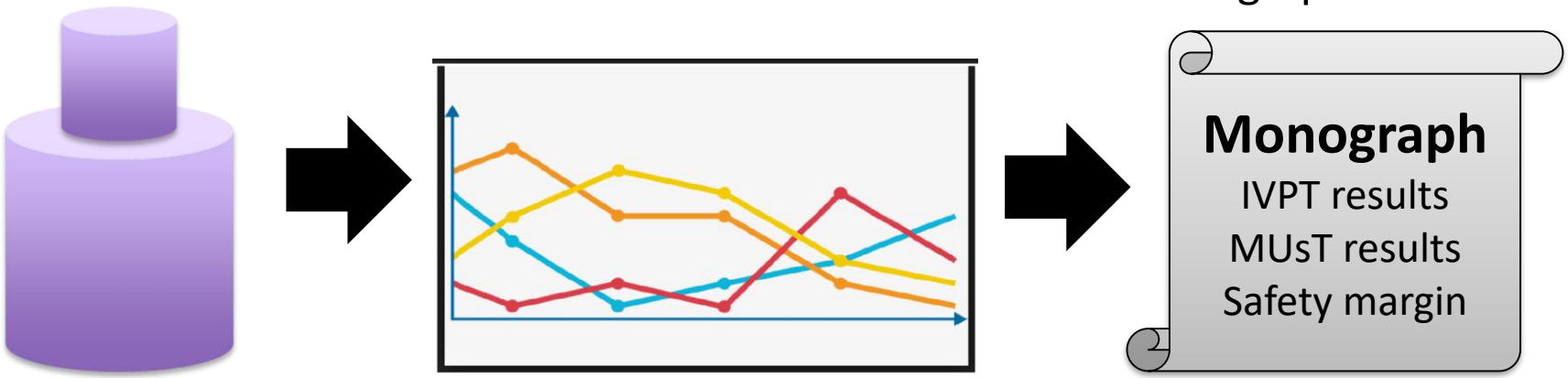
Product	Formulation Type	Active ingredient Strength	Permeation Enhancers
A	Lotion	2%	Not Includes
B	Lotion	2%	Includes (X, Y, Z)
C	Lotion	5%	Not includes
D	Gel	2%	Not includes
E	Gel	2%	Includes (X, Y)
F	Spray	1%	Includes (Z)
G	Spray	2%	Includes (X, Y, Z)
H	Spray	2%	Includes (Y, Z)

Final Formulation Testing (after GRASE determination)

New formulation

IVPT

Comparison with monograph conditions



- 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

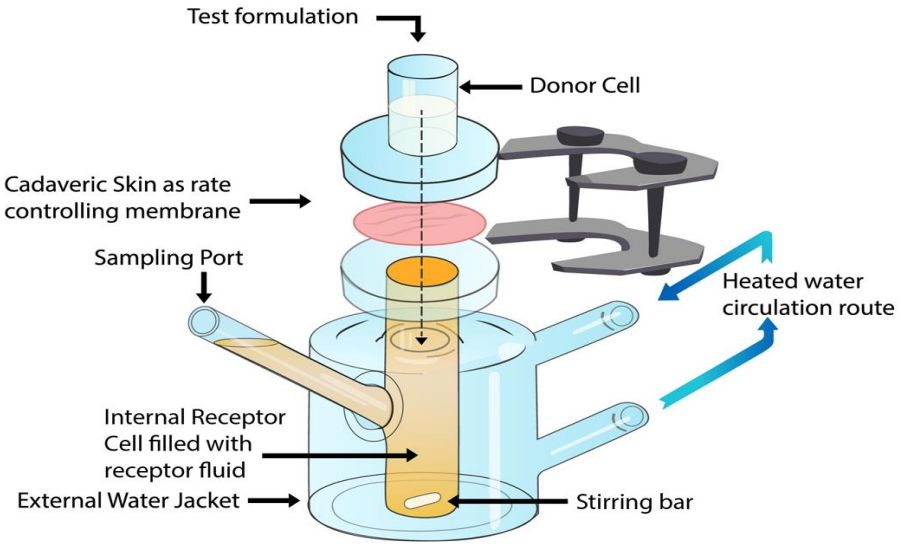
- In the literature, IVPT results showed high variability and low reproducibility.

  → 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.

In vitro skin permeation testing systems

Static (Franz) system



Flow-through (Bronaugh) system

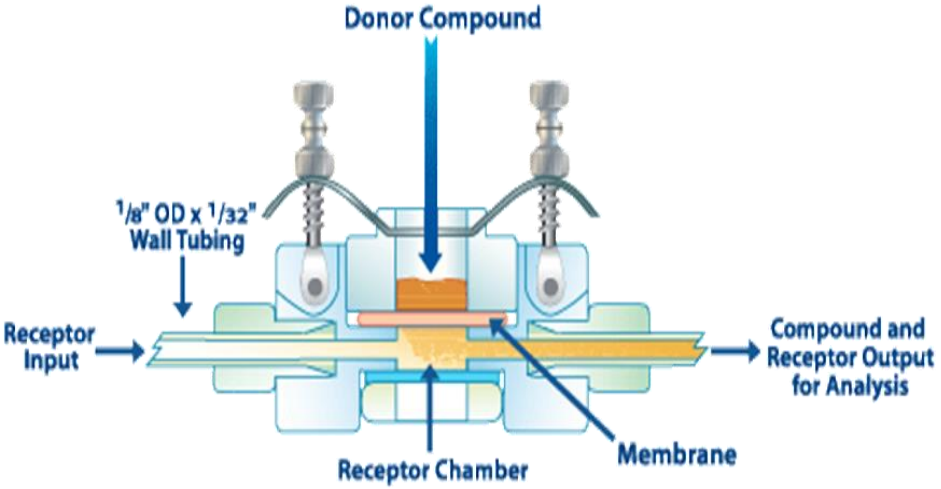


Figure from Finnin et al, In Vitro Skin Permeation Methodology (2012)

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

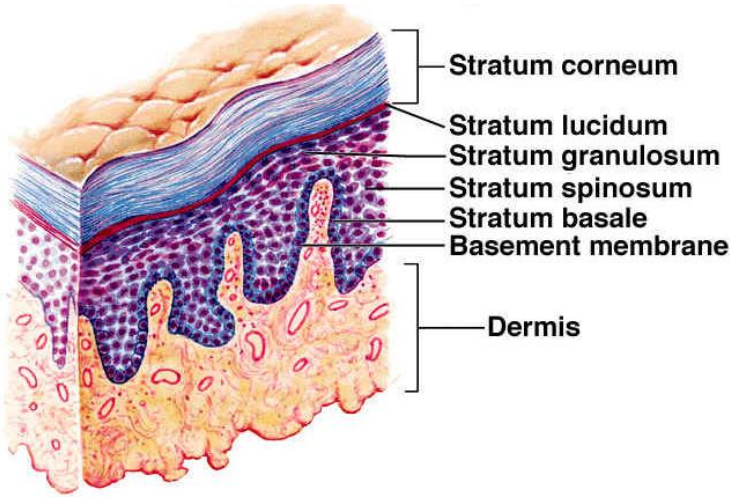


Figure from http://pmuinternational.com/skin-structure-permanent-makeup

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

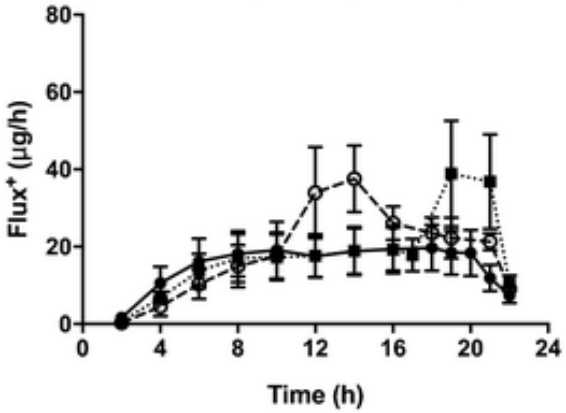


Figure from Shin et al, Pharmaceutical Research (Sep 2017)

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)

Acknowledgements

Office of Clinical Pharmacology

Edward D. Bashaw, PharmD

Division of Clinical Pharmacology III

Special Monograph Team

Luke Oh, PhD, Soo Hyeon Shin, PhD, Da Zhang, PhD

Shirley Seo, PhD

Doanh Tran, PhD

Division of Nonprescription Drug Products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