Current Program Update

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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 discussion/Q&A 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.
WELCOME TO THE GREAT ROOM AT THE FDA
The Current State of Dermal Absorption Assessment

Physiologically Based Pharmacokinetic Models

Patient Factors

Characterization Based Approaches

Open Flow Microperfusion

IVPT/IVRT

Clinical Pharmacokinetics

Master MUsT Protocol Development

Pharmacogenetics

Collaboration

Biomarker

DPK

Big Data

Microdialysis

Translational Medicine

Scientific Outline

FDA
Update on Dermal Absorption Activities

• COVID 19 has had a dramatic impact on the FDA
• The last “full staff” day at the FDA was March 16th
• Large amounts of FTE resources are being allocated regards to support of COVID-19 related priorities
  – For the Office of Clinical Pharmacology’s Monograph Group this has revolved (not surprisingly) around hand sanitizers and related issues

• Despite the difficulties in collaboration, the FDA staff working in the dermal absorption area, across all offices, have accomplished a lot that I will summarize and you will hear more about from the later speakers.
The FDA’s and CDER’s “DUAL” Role

Regulations

Conservative

FDA

Science

Innovation
The FDA’s and CDER’s “DUAL” Role

Regulations

Conservative

FDA

Science

Innovation
The term “Activates” is used here as often the “actions and activities” of the FDA drive other research and the science at large

*Not a typo
External Outreach

• Complicated by COVID-19
• Presentations cancelled (selected)
  – AAD
  – The Photodermatology Society
  – This workshop (twice)
  – 9th International Symposia on Microdialysis
• In early 2020 a series of talks were given at the New York Society for Cosmetic Chemists meeting at the end of January speakers included:
  – Myself
  – Dr. Raney
  – Dr. Stinchcomb
  – Dr. Yi
External Outreach

• In 2021 the FDA hopes to again be able to engage with the scientific community in person rather than via webex, zoom, or emails.

• For this reason, your feedback about this workshop, its pluses and minuses from an educational and scientific content delivery standpoint is very important.

• Following the conference we will reach out and make available an opportunity for you to provide feedback and encourage you to do so.
In Vitro Permeation Testing (IVPT)

- IVPT is a key element in formulation selection but has historically had some issues with acceptance.
- Since the last workshop the FDA has published two articles on the use of IVPT in topical drug development and evaluation.
- The first article was focused as a “best practices strawman” for developing a consistent test that can be of regulatory use.
- The second article was focused on the permeation of sunscreen and the data from that article will be discussed by the lead author Dr. Yang.
In Vitro Permeation Testing (IVPT)

- Topics covered include
  - System selection
    - Static vs Flow-Thru
  - Skin selection for use
    - Donor
    - Skin site
    - Skin Integrity
    - Thickness
    - Preparation and storage
  - Receptor fluid
    - Temperature
    - Agitation
    - Duration
  - Study Design
    - Duration
    - Sampling time intervals
    - Replicates

https://doi.org/10.1177/2168479019875338
In Vitro Permeation Testing

The purpose of the paper was to be a true “strawman” to advance the conversation to begin to move a laboratory test into a regulatory test.

The biggest issue facing the migration of any test from an experimental basis, to regulatory use is reproducibility and validation across different sites.

Validation will be the key to acceptance.

General Test Characteristics

- Well defined procedures
  - Validation
  - Standardized Training
- Be reproducible
  - Run to Run
  - Site to Site
- Be predictable
- Be relevant clinically

Relevant in that it MUST inform the development process
In Vitro Permeation Testing (IVPT)

In Vitro Testing of Sunscreens for Dermal Absorption: A Platform for Product Selection for Maximal Usage Clinical Trials


Sunscreen products contain UV filters as active ingredients for the protection of the skin against UV. The US Food and Drug Administration (FDA) issued a new proposed rule in 2019 (84 FR 2864) for sunscreens and identified the need for additional safety data for certain UV filters including their dermal absorption data. Dermal absorption data reveal systemic exposure of UV filters in humans, which can be obtained from clinical maximal usage trials. FDA guidance recommends conducting in vitro skin permeation tests (IVPT) to help select formulations for maximal usage clinical trials as IVPT results may be indicative of in vivo absorption. This case study reports in vitro methodologies used for the selection of sunscreen products for an FDA-sponsored proof-of-concept maximal usage clinical trial. An IVPT method was developed using human cadaveric skin. Conventionally available sunscreen products were tested to determine the skin absorption potential of consensus UV filters using the IVPT. All studied sunscreen products demonstrated a certain degree of skin absorption of UV filters using IVPT and a formulation rank order was obtained. These sunscreen products were also characterized for several formulation properties including the globule size in emulsions, which was found to be an indicator for the rank order.

INTRODUCTION

In Vitro Testing of Sunscreens for Dermal Absorption: A Platform for Product Selection for Maximal Usage Clinical Trials


Sunscreen products contain UV filters as active ingredients for the protection of the skin against UV. The US Food and Drug Administration (FDA) issued a new proposed rule in 2019 (84 FR 2864) for sunscreens and identified the need for additional safety data for certain UV filters including their dermal absorption data. Dermal absorption data reveal systemic exposure of UV filters in humans, which can be obtained from clinical maximal usage trials. FDA guidance recommends conducting in vitro skin permeation tests (IVPT) to help select formulations for maximal usage clinical trials as IVPT results may be indicative of in vivo absorption. This case study reports in vitro methodologies used for the selection of sunscreen products for an FDA-sponsored proof-of-concept maximal usage clinical trial. An IVPT method was developed using human cadaveric skin. Conventionally available sunscreen products were tested to determine the skin absorption potential of consensus UV filters using the IVPT. All studied sunscreen products demonstrated a certain degree of skin absorption of UV filters using IVPT and a formulation rank order was obtained. These sunscreen products were also characterized for several formulation properties including the globule size in emulsions, which was found to be an indicator for the rank order.

INTRODUCTION

UV filters are active ingredients in sunscreen products. They function to protect the skin from sunburns and UV-related skin damage. These small molecules protect the skin by absorbing, scattering, or reflecting UV. Ideally, UV filters are intended to work on the skin surface without penetrating the skin and thereby mitigating the systemic circulation. However, UV filters such as chemicals have been detected in the systemic circulation. In vitro, UV filters are used to determine the skin absorption potential of sunscreen products. Several studies have investigated the in vitro skin permeation of UV filters and have demonstrated varying degrees of skin absorption. Therefore, application of sunscreen ingredients may lead to systemic exposure in a single daily application.

https://doi.org/10.1016/j.jid.2020.04.009
FDA In Vivo MUsT Study #2

THE WALL STREET JOURNAL.

ARTICLES

THE NUMBERS

Sunscreen Chemicals Accumulate in Body at High Levels

July 17, 2020 05:30 am ET

For the second time in less than a year, a study of common sunscreen ingredients has established that the chemicals are absorbed into the bloodstream at concentrations far greater than the Food and Drug Administration’s safety threshold.
FDA MUSt Publications on Sunscreen Absorption

May 2019

Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial

March 2020

Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial
Non-FDA MUsT Sunscreen Absorption

- Article published August 2019 from Friedrich-Alexander University Erlangen-Nürnberg
- 20 subjects received topical application of a commercially available sunscreen containing avobenzone and octocrylene
- Dosing was for 1 day with an initial dose of 2mg/cm² followed by 1mg/cm² reapplied at 2 and 4 hours to approximately 75-80% BSA.
- Subjects were exposed to the sun for 9hrs.

https://doi.org/10.1016/j.envint.2019.105068
Even though the study was only a one day study and was dosed at a lower level than in the FDA studies, significant levels of avobenzone, octocrylene, and octocrylene’s primary metabolite (CDAA) were seen in the plasma and urine.
### Table 2

<table>
<thead>
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<th>Key figures and toxicokinetic parameters for plasma data.</th>
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Guidance Issuance

FDA Activates*

- IVPT
- In Vivo MUST Trials
- Guidance Issuances
- External Outreach

Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations

Final Guidance

What is recommended in this guidance?

Are you submitting a topical active ingredient being considered for inclusion in an OTC monograph?

MUst Can Help Answer the Following Questions:

- Does the active ingredient have dermal penetration and systemic exposure and if it is in what extent?
- If there is systemic exposure, does the exposure change in different physiologies or conditions?
- When considered with other appropriate safety and effectiveness data, do the plasma tests support that the ingredient is generally recognized as safe and effective under the intended conditions of use?
FDA Pilot Guidance Snapshot

Guidance Snapshots are a communication tool that provide highlights from guidance documents using visuals and plain language to support transparent communication and dissemination of FDA guidance documents. During the Pilot, Guidance Snapshots will contain a *subset* of the following key features:

- Explanation of why the guidance document is important
- Highlights from the guidance document
- Educational background about the guidance topic
- Link to the full guidance document
- Drug development timeline for when to apply the guidance recommendations
- Guidance Recap Podcast that describes highlights and background the guidance document explained directly from the authors
- Twitter hashtags to create a platform for discussing views on the guidance
- Link to the FDA docket for providing official comments to the Agency (for applicable draft guidances)

https://www.fda.gov/drugs/guidances-drugs/guidance-snapshot-pilot
MUsT Snapshot

• The MUsT Snapshot is the fourth one prepared as part of the FDA pilot program.
• Previous snapshots have been issued for:

<table>
<thead>
<tr>
<th>Guidance Document</th>
<th>Guidance Snapshot</th>
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<tbody>
<tr>
<td>In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions Final Guidance</td>
<td>In Vitro DDI Guidance Snapshot</td>
</tr>
<tr>
<td>Clinical Drug Interaction Studies - Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions Final Guidance</td>
<td>Clinical DDI Guidance Snapshot</td>
</tr>
<tr>
<td>Developing Targeted Therapies In Low-Frequency Molecular Subsets of a Disease Final Guidance</td>
<td>Targeted Therapies Guidance Snapshot</td>
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https://www.fda.gov/media/140321/download
• In comparison, in the actual Guidance document, the MUsT Study Elements and Consideration section is over 5 pages and has specific verbiage on these elements and how to address them.
• The snapshot provides a concise overview of the issues and why it is an element to be evaluated.
• Each page of the snapshot also contains the weblink to the actual guidance.
MUuST Snapshot

• A short background is included along with an explanation, and an example as to why the guidance is important.

• This information is provided to put the document into the context of drug development (in this case dermal drug development).

• As noted this is the fourth snapshot to be issued in the pilot program and it was posted at the FDA on July 21st, 2020.
PUTTING THE PIECES TOGETHER
• COVID-19 has impacted the FDA and regulated industry in ways that could not have been imagined at the end of the workshop last August

• Even so the FDA has continued to move forward in developing the science and in communicating with industry using the tools we have available to us

• The development of the tests and the standards has moved on and will continue to do so
The Goal

Science Based Regulatory Policy

Clinical Pharmacology
Pharmacogenetics
Master MUsT Protocol Development
Biomarker Qualification
Big data
Physiologically Based Pharmacokinetic Models
IVPT/IVRT
Collaboration
Open Flow Microperfusion
Microdialysis
Patient Factors
Translational Medicine
Characterization Based Approaches
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Physiologically Based Pharmacokinetic Models
IVPT/IVRT
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Open Flow Microperfusion
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The Goal

Policy Based Regulatory Policy

Clinical Pharmacology

Pharmacogenetics

Physiologically Based Pharmacokinetic Models

IVPT/IVRT

Translational Medicine

Patient Factors

Master MUsT Protocol Development

Biomarker Qualification

Open Flow Microperfusion

DPK

Collaboration

Characterization Based Approaches

Translational Medicine

Science Based Regulatory Policy

Collaboration is the KEY To success
• Developing a Science Based Regulatory Policy can only be done with the input of all stakeholders.
  – The FDA cannot do it alone
  – The Industry cannot do it alone
  – Academia, Clinicians, and the Public cannot do it alone.
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