FDA Sunscreen Study: Totality of the Data

Jeffry Florian, Ph.D.
Division of Applied Regulatory Science
Office of Clinical Pharmacology
OTS/CDER/OMTP/FDA
Disclaimer

- The opinions expressed in this presentation are the presenter’s and do not necessarily reflect the official views of the United States Food and Drug Administration (FDA).
Overview

• Background

• Lessons learned from FDA sunscreen studies

• Areas of ongoing learning

• Summary
Background

• FDA published a proposed rule in February 2019
  – update regulatory requirements for certain sunscreen ingredients
• A key data gap for these active sunscreen ingredients is understanding whether, and to what extent, the ingredient is absorbed into the body after topical application
• Many questions around how this information gap could be addressed
• FDA conducted two **PILOT** studies to gather initial data on the systemic absorption
  – a maximal usage trial following maximal usage trial guidance
  – a study evaluating exposure after a single application and a longer duration
FDA Sunscreen Studies

Study 1:
- 4 products / 6 subjects
- Multiple applications per day
- Sample plasma out to Day 7

Clinical Study: NCT03582215

Study 2:
- 4 products / 12 subjects
- Single application Day 1
  - Multiple applications Day 2, 3, and 4
- Sample skin (Day 14) and plasma (Day 21)
Trials Successfully Conducted

JAMA | Preliminary Communication
Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

Murali K. Matta, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Jeffry Florian, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

JAMA | Original Investigation
Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

Murali K. Matta, PhD; Jeffry Florian, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Yang Yang, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

Clinical Study: NCT03582215
### Active Ingredients Are Absorbed and Can Be Detected

<table>
<thead>
<tr>
<th>Geometric Mean (ng/mL)</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avobenzone</td>
<td>1.8-4.3</td>
<td>3.3-7.1</td>
</tr>
<tr>
<td>Oxybenzone</td>
<td>169-210</td>
<td>180-258</td>
</tr>
<tr>
<td>Octocrylene</td>
<td>2.9-7.8</td>
<td>6.6-7.8</td>
</tr>
<tr>
<td>Homosalate</td>
<td>40.3</td>
<td>13.9-23.1</td>
</tr>
<tr>
<td>Octisalate</td>
<td>10.0</td>
<td>4.6-5.8</td>
</tr>
<tr>
<td>Ecamsule</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>Octinoxate</td>
<td>-</td>
<td>5.2-7.9</td>
</tr>
</tbody>
</table>
Active Ingredients Were Absorbed After One Day, Multiple Applications (Study 1)
Active Ingredients Absorbed After One Day, One Application (Study 2)

![Graph showing concentration over time for different active ingredients after sunscreen application.](image)
Active Ingredients Accumulate With Repeat Administration (Study 1)

Similar $C_{\text{max}}$ between Day 3 to 4 but still increasing

Sunscren applied
Active Ingredients Were Detectable Out to Day 7 (Study 1)
Some Active Ingredients Were Detectable Out to Day 21 (Study 2)
## Multiple Day Terminal Half-life – Skin Depot?

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Avobenzone</strong></td>
<td>33-55</td>
<td>24-31</td>
</tr>
<tr>
<td><strong>Oxybenzone</strong></td>
<td>48-79</td>
<td>79</td>
</tr>
<tr>
<td><strong>Octocrylene</strong></td>
<td>43-84</td>
<td>48-79</td>
</tr>
<tr>
<td><strong>Homosalate</strong></td>
<td>41</td>
<td>47-78</td>
</tr>
<tr>
<td><strong>Octisalate</strong></td>
<td>26</td>
<td>54-77</td>
</tr>
<tr>
<td><strong>Octinoxate</strong></td>
<td>-</td>
<td>51-157</td>
</tr>
</tbody>
</table>
Tape Stripping Results – Likely Skin Depot

- Lotion
  - Avobenzone
  - Oxybenzone
  - Octocrylene

- Pump Spray
  - Homosalate
  - Octisalate
  - Octinoxate

Active ingredient in skin (ng/cm²)
Lessons Learned/Remaining Questions

We Now Know

• Studies are feasible to conduct
• Active ingredients
  • are absorbed
  • can be measured
  • accumulate with repeat application
  • remains in system for extended period of time
• Skin serving as a depot
Remaining Questions – Safety

➢ Conducted studies do not answer questions about safety *but*

JAMA publications

**CONCLUSIONS AND RELEVANCE** In this preliminary study involving healthy volunteers, application of 4 commercially available sunscreens under maximal use conditions resulted in plasma concentrations that exceeded the threshold established by the FDA for potentially waiving some nonclinical toxicology studies for sunscreens. The systemic absorption of sunscreen ingredients supports the clinical significance of these findings from the use of sunscreen.

CONCLUSIONS AND RELEVANCE

examining sunscreen absorption of ingredients administered in 4 different sunscreen formulations were systematically absorbed and had plasma concentrations that surpassed the FDA threshold for potentially waiving some of the additional safety studies for sunscreens. These findings do not indicate that individuals should refrain from the use of sunscreen.

JCO Oncology Practice

**Interpreting the Findings and the Need for More Data**

The fact that the sunscreen active ingredients are absorbed systemically does not mean they are unsafe. Rather, this finding sheds new light on the safety of sun protection over time. The fact that an ingredient is absorbed through the skin and into the body does not mean that the ingredient is unsafe, nor does the FDA seeking further information indicate such. Rather, this finding calls for further industry testing to determine the safety and effect of systemic exposure of sunscreen ingredients, especially with chronic use.”

Results to date do not alter benefit/risk of sunscreen use

1 DG Strauss and TM Michele, 2020 – JCO Oncology Practice


Remaining Questions – Study Design

- Substantial information learned from both FDA studies but
- Different designs may be needed for different products
  - number of subjects
  - length of study
  - amount applied
  - population

- Considerations in implementing a Master Protocol for sunscreens will be presented this afternoon
Remaining Questions – Metabolite Exposure

• Potential for metabolites to be absorbed
  – Similar or even greater exposure than parent compound

• Separate study quantified metabolite exposures

• 20 healthy volunteers

• Analytes
  – 2-cyano-3,3-diphenylacrylic acid (CDAA)
    • octocrylene metabolite

• Additional information is needed

Hiller et al, 2019 *Environmental International*
Summary

• FDA completed two PILOT clinical studies on sunscreen absorption
• Studies demonstrated all active ingredients from seven products
  – were absorbed, accumulated with repeat administration, and could be detected in circulations for an extended period of time
• When designing your own studies, the design may vary by product
  – FDA encourages conversations before beginning pilot studies

• The fact than an ingredient is absorbed through the skin and into the body does not mean that the ingredient is unsafe
Acknowledgements

Division of Applied Regulatory Science
David Strauss, MD, PhD
Murali Matta, PhD
Nageswara Pilli, PhD
Robbert Zusterzeel, MD, PhD, MPH
Vikram Patel, PhD
Donna Volpe, PhD

Office of Clinical Pharmacology
Dennis Bashaw, PharmD
Issam Zineh, PharmD, MPH

Division of Immune and Inflammation Pharmacology
Luke Oh, PhD
Da Zhang, PhD

Division of Nonprescription Drug Products
Steven Adah, PhD
Sergio Coelho, PhD
Theresa Michele, MD

Division of Pharmaceutical Quality and Research
Yang Yang, PhD
Ashraf Muhammad, PhD
Celia Cruz, PhD

Spaulding Clinical Research
Sarah Kemp, RN
Anthony Godfrey, PharmD
Carlos Sanabria, MD
Monjot Kang, PharmD
THANK YOU