U.S. FOOD & DRUG ADMINISTRATION

In Vitro Testing of Sunscreens for Dermal Absorption

Yang Yang, PhD, BPharm

Division of Product Quality Research, Office of Testing and Research

Office of Pharmaceutical Quality, CDER, FDA

Yang.yang@fda.hhs.gov

Topical Drug Development Workshop

07.23-24.2020

This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Sunscreens are no different.

People expect safe and effective sunscreens.

Outline

- ❑ Introduction
- ❑ Study Design
- ❑ Materials and Methods
- ❑ Results
- ❑ Conclusions
- ❑ References
- ❑ Acknowledgements

Introduction

- Sunscreens are OTC drugs indicated for the prevention of sunburn and skin damage following chronic exposure to UV radiation.

- Sunscreens contain UV filters as active ingredients. They are supposed to act locally on the skin surface following dermal application.

- UV filters have been detected in systemic circulation.

Introduction

- In 2019, FDA issued a proposed sunscreen rule identified the need for additional safety data for UV filters, including dermal absorption data that can be obtained from MUsT studies.

- FDA guidance recommends conducting *in vitro* skin permeation test (IVPT) to: 1) select products for MUsT studies, and 2) be used as an alternative approach to test the final product formulation composed of GRASE ingredients only.

- Case studies were conducted by FDA.

Study Designs

Study I. Product Selection for MUsT Studies using IVPT

- Formulations: 1 cream, 2 lotions, 2 sprays.
- Skin model: Dermatomed human skin
- Dosing: Single infinite dose (to reflect maximal usage conditions)

Study II. Further IVPT Method Development for formulation testing

- Formulations: 1 cream, 1 lotion, 4 sprays.
- Skin model: Heat-separated human epidermis (HSE)
- Dosing: Single finite dose (to match with the 2nd clinical study with one application on Day 1 at 2 mg/cm^2)

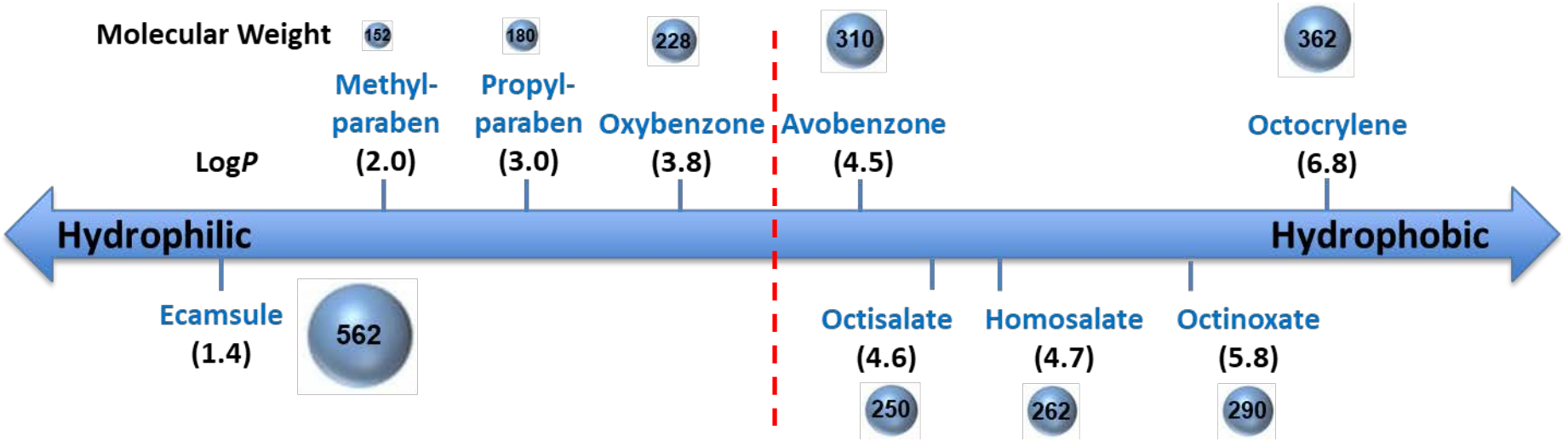
Active ingredients in 8 commercial formulations

Product names in IVPT studies	UV Filters in Sunscreen Formulations	Product names in Clinical studies
Cream	*Avobenzone 2%, Octocrylene 10%, Ecamsule 2%*	Cream (Study I)
A-lotion	*Avobenzone 3%, Octocrylene 6%, Oxybenzone 4%*	Lotion (Study I & II)
B-lotion	*Avobenzone 3%, Octocrylene 6%, Oxybenzone 4%*	-
A-spray	*Avobenzone 3%, Octocrylene 8%, Oxybenzone 6%*	-
B-spray	*Avobenzone 3%, Octocrylene 10%, Oxybenzone 5%*	Spray-2 (Study I)
C-spray	*Avobenzone 3%, Octocrylene 10%, Oxybenzone 6%, Homosalate 15%, Octisalate 5%*	Spray-1 (Study II)
D-spray	*Avobenzone 3%, Octocrylene 10%, Homosalate 10%, Octisalate 5%, Octinoxate 7.5%*	Spray-2 (Study II)
D-oil spray	*Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octinoxate 7.5%*	Spray-3 (Study II)

Physiochemical properties of UV filters affect skin permeation

	Ecamsule	Oxybenzone	Avobenzone	Octisalate	Homosalate	Octinoxate	Octocrylene
Log*P*	1.4	3.8	4.5	4.6	4.7	5.8	6.8
Molecular Weight	562.7	228.2	310.4	250.3	262.3	290.4	361.5
Melting Point	255°C	62°C	83.5°C	<25°C	<20°C	-25°C	14°C
TPSA	160 Å^2	46.5 Å^2	43.4 Å^2	46.5 Å^2	46.5 Å^2	35.5 Å^2	50.1 Å^2
pKa	2.0	7.6	9.7	8.1	8.1	-4.8	-

LogP, octanol-water partition coefficient; TPSA, topological polar surface area in Å^2; pKa, acid dissociation constant at log scale.



 SCCS "Scientific Advice on US FDA questions regarding the safety assessment of UV filters in the EU." 2015.

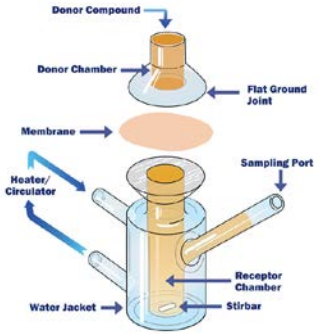
Analytical methods

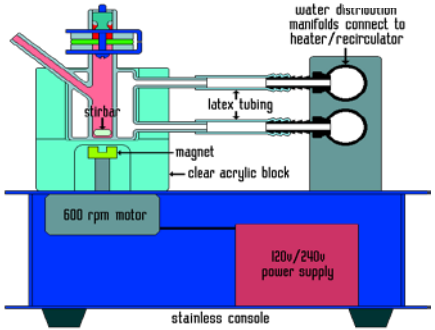
Agilent RapidFire-MS/MS system

SciEx UHPLC-Qtrap 6500 MS/MS

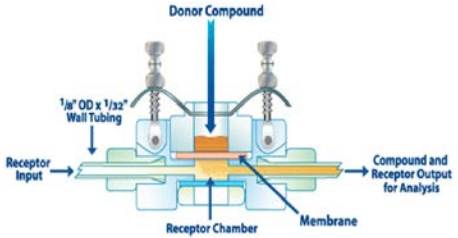
Devices for *in vitro* skin permeation test

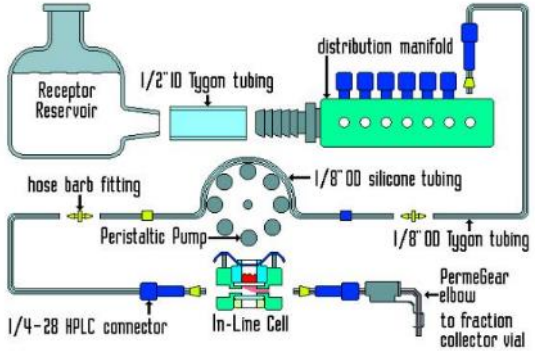
Franz Diffusion System





Flow-Through Diffusion System

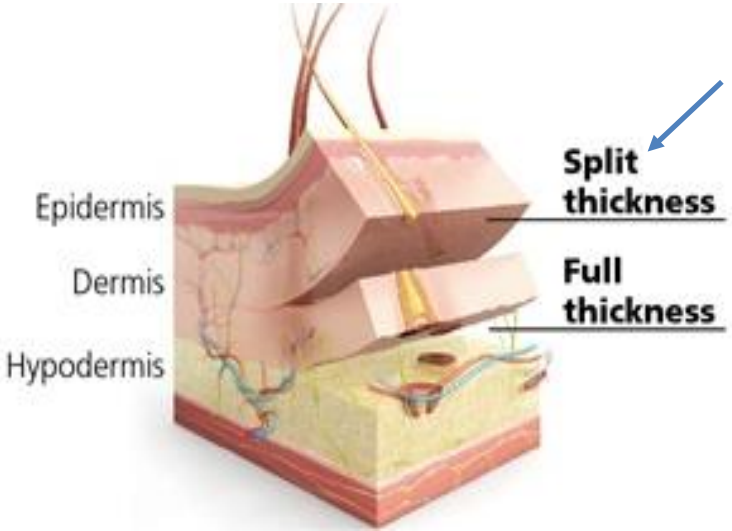




Receiver solution:
4% BSA in PBS
Temperature: 32°C
Duration: 24 h.

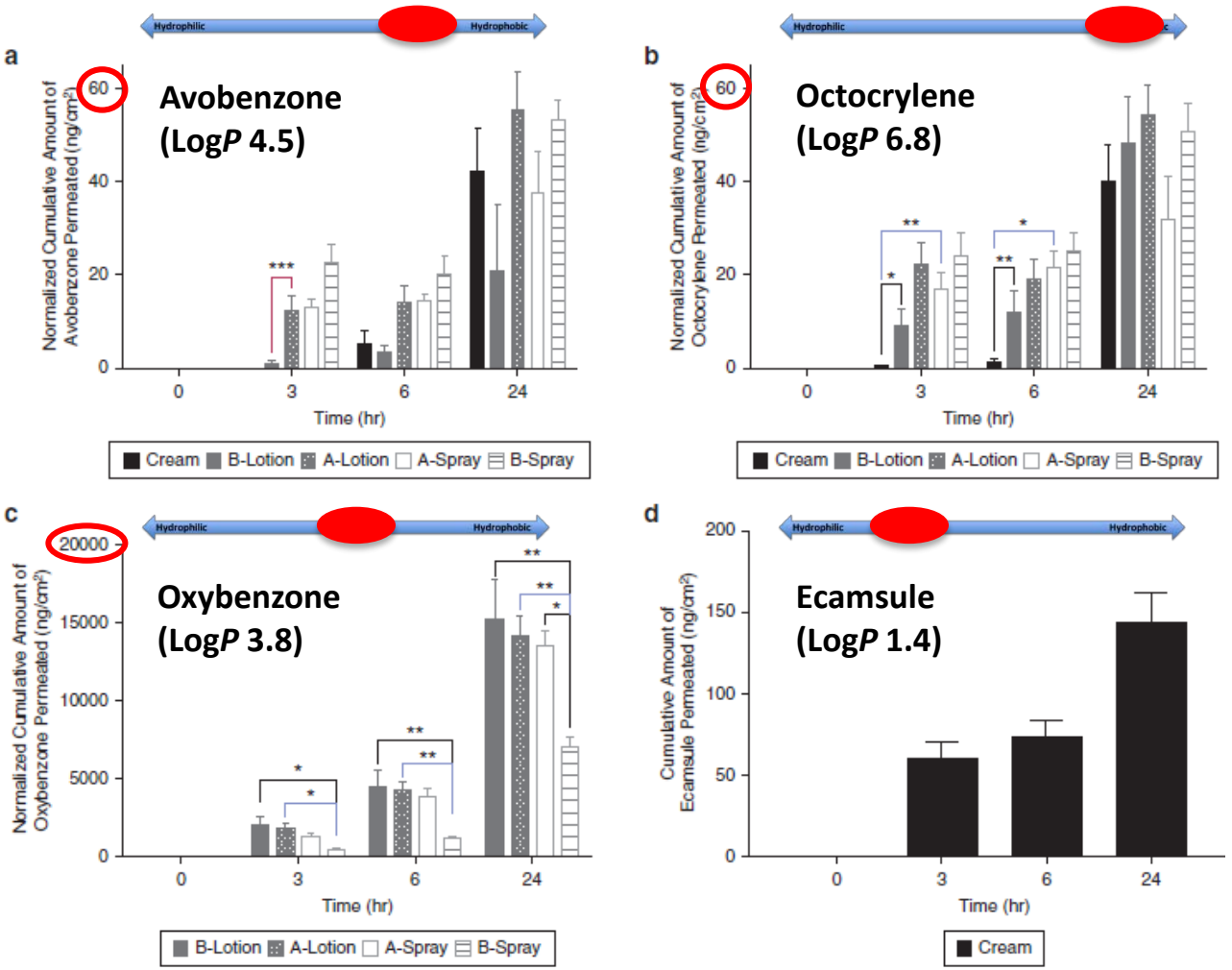
PermeGear, Inc.

Results for Study I.
Product selection for MUsT studies using IVPT



Dermatomed skin
(Avg. 250 µm)

IVPT using Dermatomed Human Skin (infinite dose)

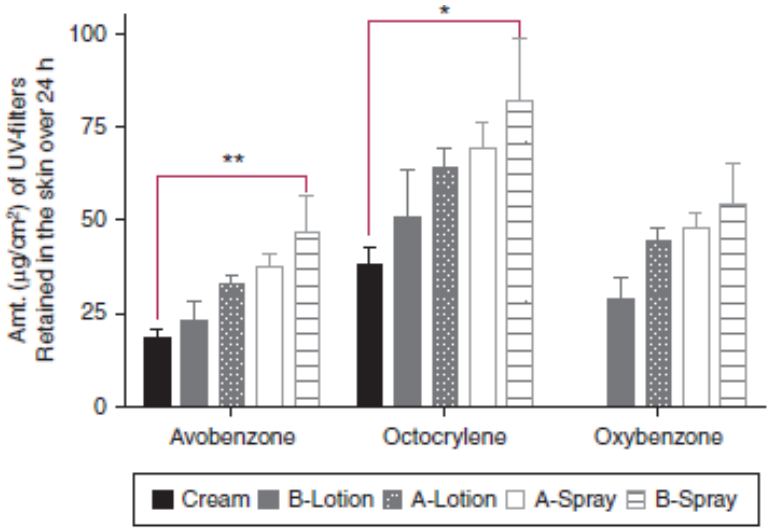


Rank orders of cumulative skin permeation of UV filters (infinite dose)

Product Type	Rank order of UV filters permeated through cadaver skin (1→5: Highest → Lowest)			
	Avobenzone	Octocrylene	Oxybenzone	Ecamsule
B-lotion	5	3	1 [1]	-
A-lotion	1	1	2 [2]	-
A-spray	4	5	3 [3]	-
B-spray	2	2	4 [1, 2, 3]	-
Cream	3	4	-	1
Statistical Difference	No	No	$P < 0.005$[1, 2], $P < 0.05$[3]	-

(One-way ANOVA with Tukey's multiple comparisons test was used for all data analysis.)

Skin retention of UV filters (infinite dose)

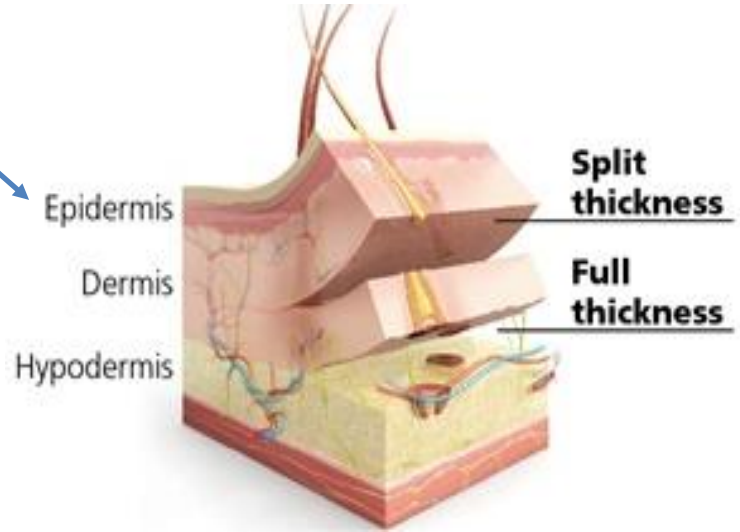


Product Type	Rank order of UV filters retained in cadaver skin* (1→5: Highest → Lowest)			
	Avobenzone	Octocrylene	Oxybenzone	Ecamsule
B-lotion	4	4	4	-
A-lotion	3	3	3	-
A-spray	2	2	2	-
B-spray	1 [1]	1 [3]	1	-
Cream	5 [1]	5 [3]	-	1
Statistical Difference	$P < 0.005$[1]	$P < 0.05$[3]	No	-

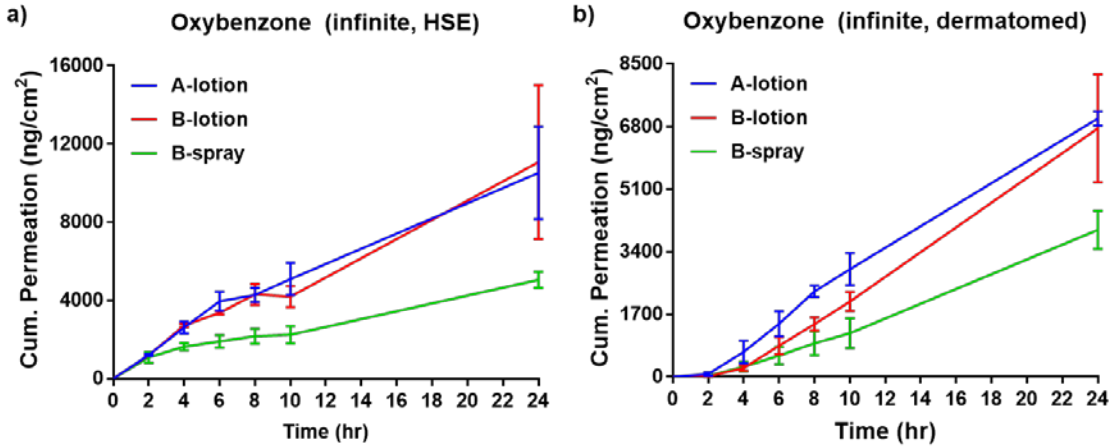
Results for Study II. Further IVPT Method Development to better reflect *in vivo* situations

Heat-separated epidermis (HSE)

(avg. 60 µm)
TEWL <10 g/cm^2·h



Intra-donor variability (CV%) can be very different between HSE and dermatomed human skin

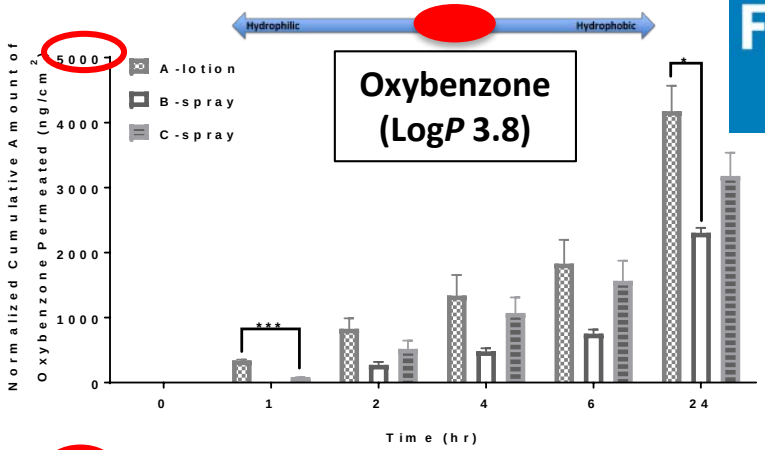


	Time Points (h)	B-lotion		A-lotion		B-spray	
		HSE	Dermatomed	HSE	Dermatomed	HSE	Dermatomed
CV% of Cumulative Oxybenzone Permeation	0	-	-	-	-	-	-
	2	3.0	34.3	5.2	55.2	25.1	62.0
	4	3.2	29.4	11.7	45.1	11.1	48.5
	6	2.5	27.4	12.3	23.4	17.2	40.5
	8	12.5	12.6	8.6	6.8	17.6	35.1
	10	12.8	12.8	16.3	15.1	20.1	34.4
	24	35.6	21.7	22.5	2.7	8.3	13.1

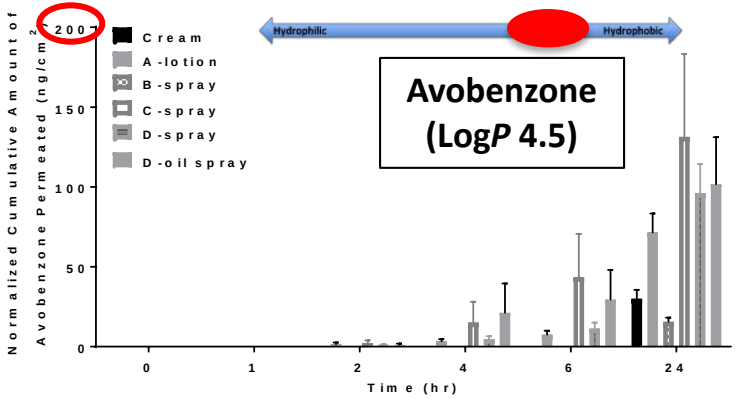
IVPT using Heat-separated human epidermis (finite dose)

Less oxybenzone permeation due to reduced dosing.

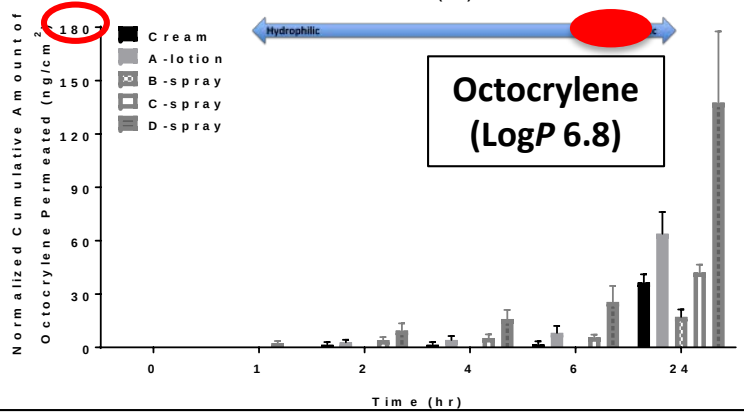
a)



b)

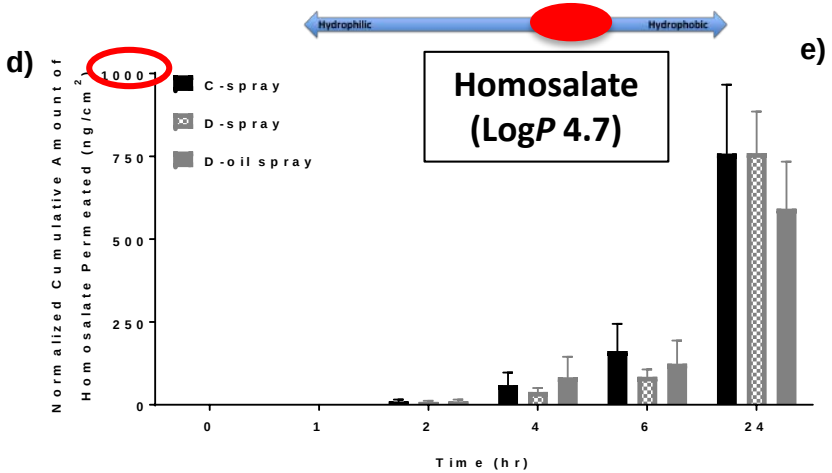


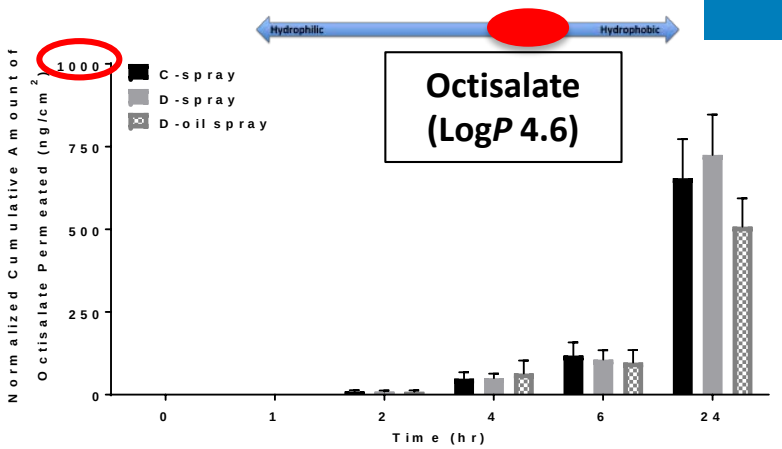
c)

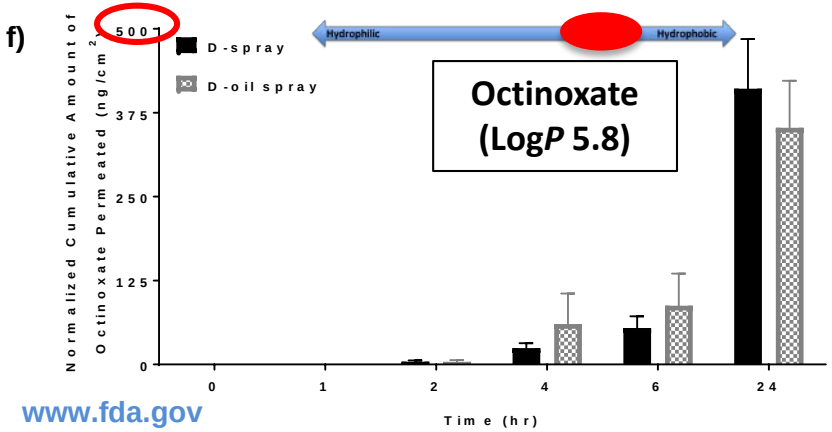


Higher *permeation of avobenzone and octocrylene observed through HSE than dermatomed skin → these two UV filters have greater dermal affinity than oxybenzone.*

IVPT using heat-separated human epidermis (finite dose) Cont.







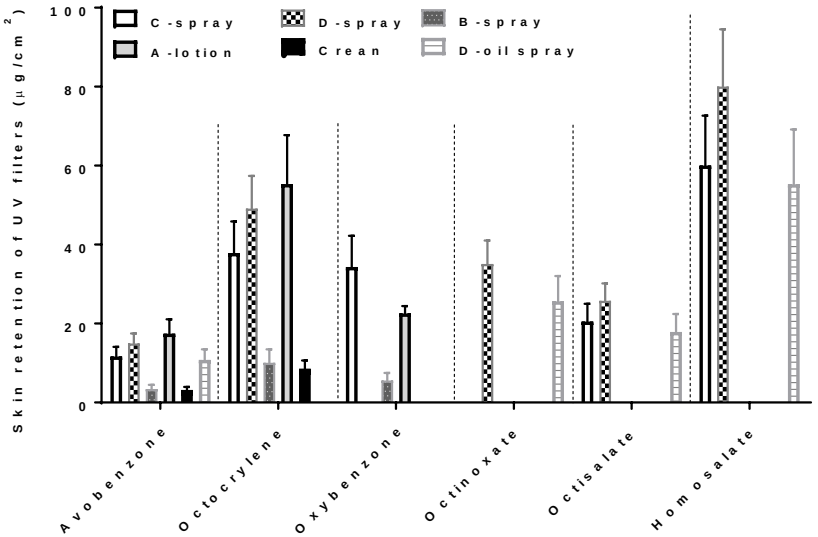
Significantly higher permeation than avobenzone (logP 4.5) was observed, may be due to higher concentration and lower MW of these UV filters.

Rank orders of cumulative permeation of UV filters in IVPT vs. clinical AUC

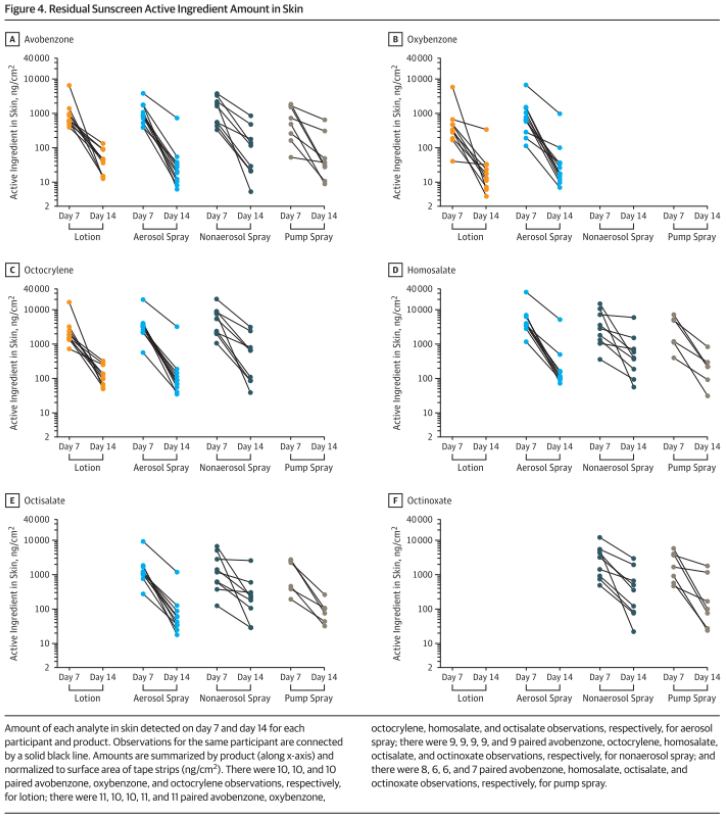
Product names in IVPT	Oxybenzone			Octocrylene			Avobenzone			Product names in Clinical Study
	IVPT	Clinical AUC		IVPT	Clinical AUC		IVPT	Clinical AUC		
		day 1	day 4		day 1	day 4		day 1	day 4	
A-lotion	2	1	1	3	1	1	4	1	1	Lotion
C-spray	1	2	2	2	3	3	1	2	2	Spray-1
D-spray	-	-	-	1	2	2	3	3	3	Spray-2
D-oil spray	-	-	-	-	-	-	2	4	4	Spray-3

Product names in IVPT	Homosalate			Octisalate			Octinoxate			Product names in Clinical Study
	IVPT	Clinical AUC		IVPT	Clinical AUC		IVPT	Clinical AUC		
		day 1	day 4		day 1	day 4		day 1	day 4	
A-lotion	-	-	-	-	-	-	-	-	-	Lotion
C-spray	1	1	1	2	2	2	-	-	-	Spray-1
D-spray	2	2	2	1	1	1	1	1	1	Spray-2
D-oil spray	3	3	3	3	3	3	2	2	2	Spray-3

Skin retention of UV filters



Tape stripping method (6 strips):



Matta et. al. JAMA 2020

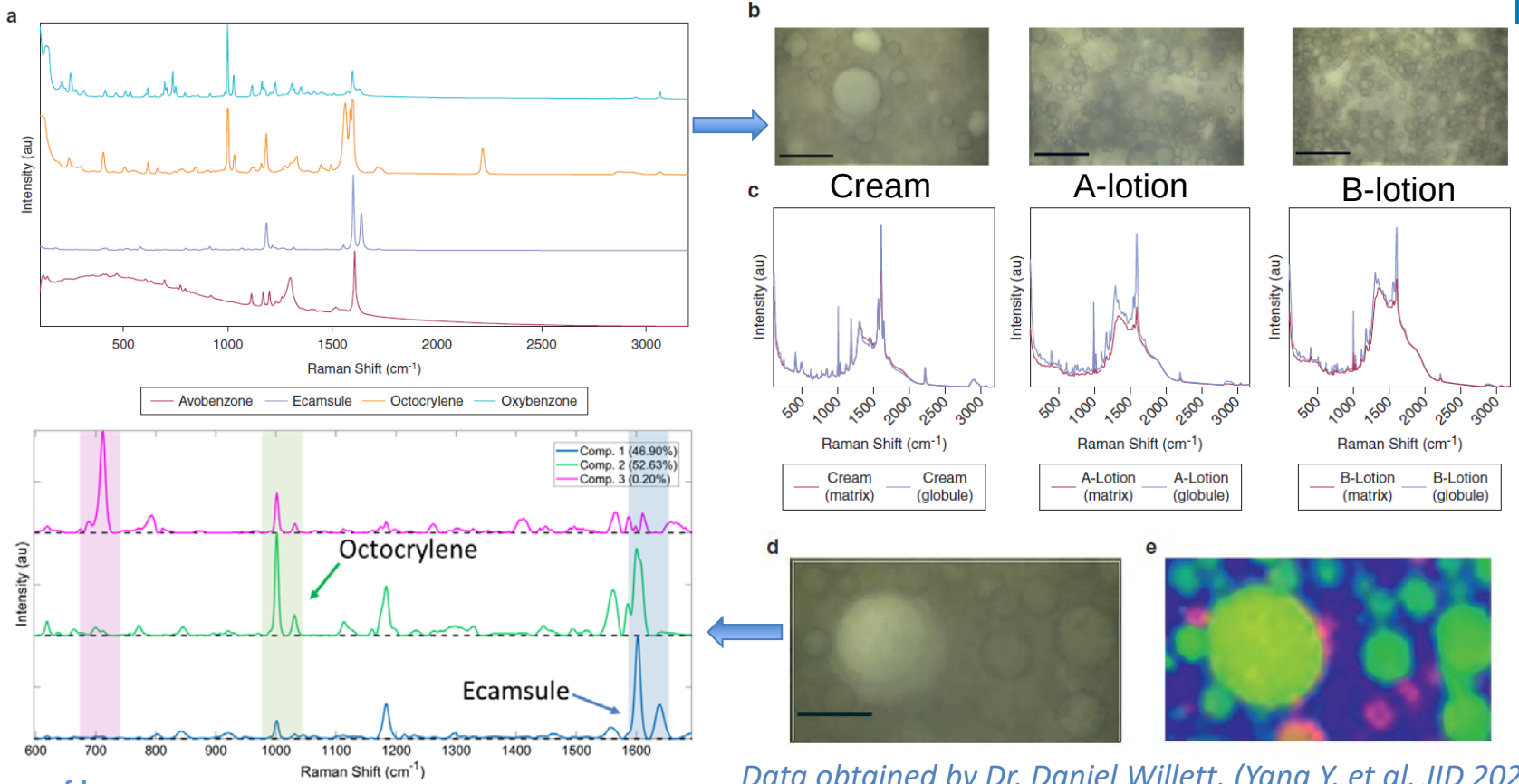
Rank orders of skin retention of UV filters

	Oxybenzone			Octocrylene			Avobenzone			
Product names in IVPT	IVPT	Clinical		IVPT	Clinical		IVPT	Clinical		Product names in Clinical Study
		day 7	day 14		day 7	day 14		day 7	day 14	
A-lotion	2	2	2	3	3	3	1	3	3	Lotion
C-spray	1	1	1	2	2	2	3	2	4	Spray-1
D-spray	-	-	-	1	1	1	2	1	1	Spray-2
D-oil spray	-	-	-	-	-	-	4	4	2	Spray-3
	Homosalate			Octisalate			Octinoxate			
Product names in IVPT	IVPT	Clinical		IVPT	Clinical		IVPT	Clinical		Product names in Clinical Study
		day 7	day 14		day 7	day 14		day 7	day 14	
A-lotion	-	-	-	-	-	-	-	-	-	Lotion
C-spray	1	1	1	2	3	3	-	-	-	Spray-1
D-spray	2	2	2	1	1	1	1	1	1	Spray-2
D-oil spray	3	3	3	3	2	2	2	2	2	Spray-3

On a side note:
Formulation properties may affect skin absorption of UV filters

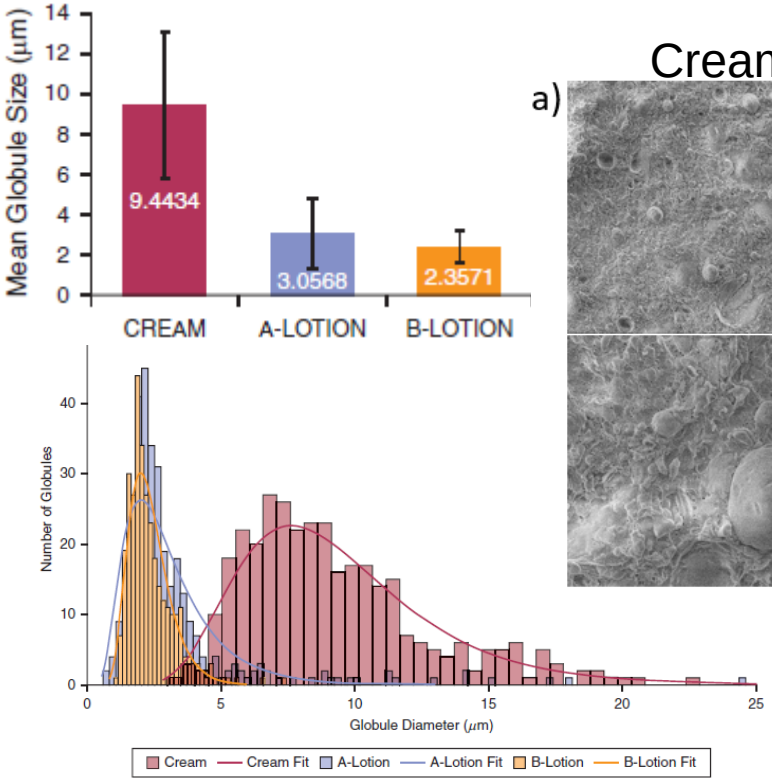
- Formulation type
- Globule size distribution
- pH
- Rheological properties (yield stress, viscosity)
- In-use weight loss (evaporation rate)

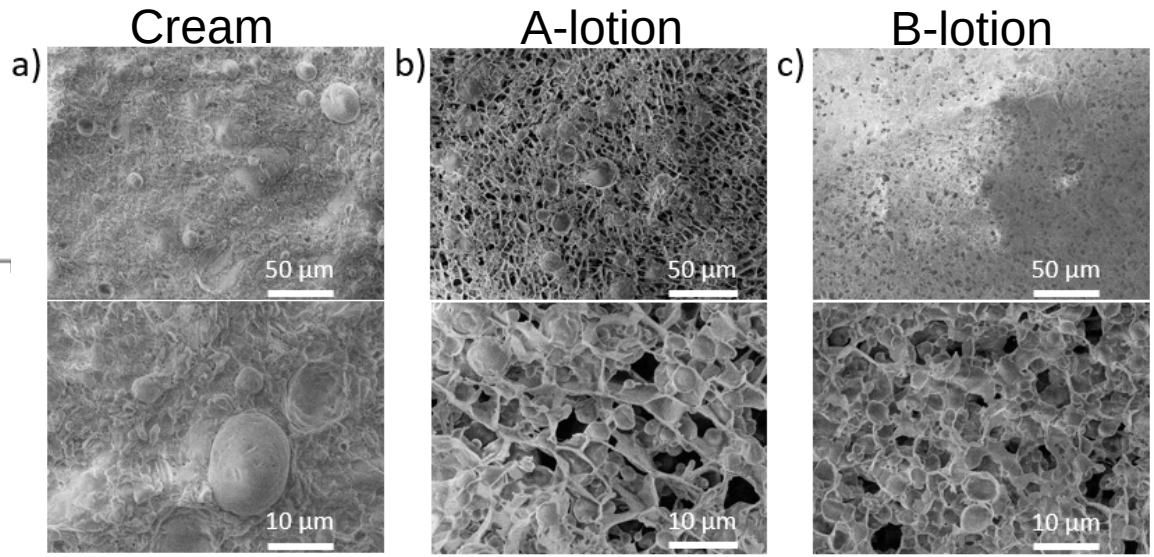
Raman microscopy, mapping, and multivariate analysis of globules and matrices



Data obtained by Dr. Daniel Willett. (Yang Y. et al. JID 2020.)

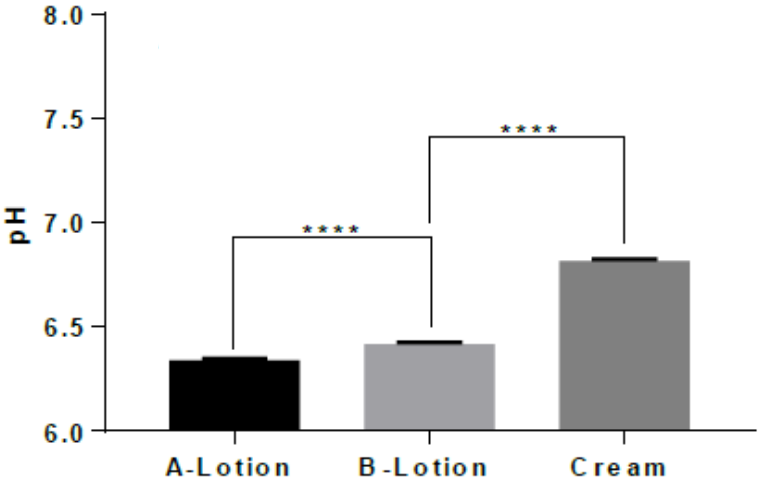
Cryo-SEM characterization of the semisolid sunscreens

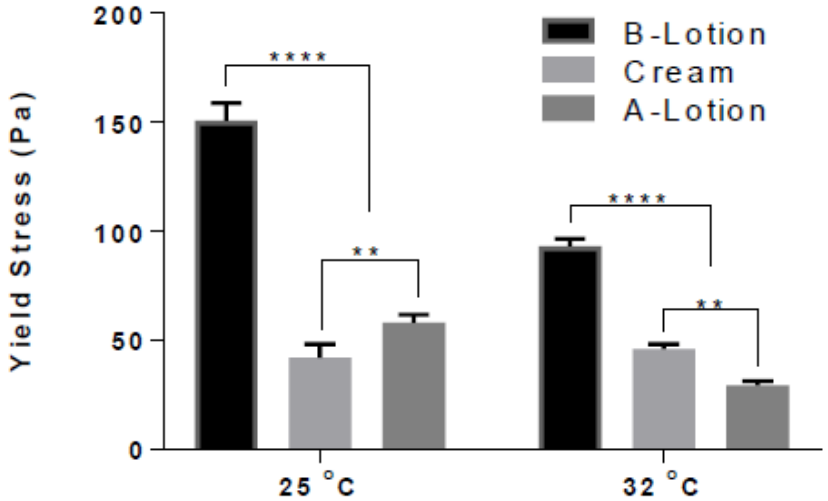




Data obtained by Dr. Huzeyfe Yilmaz.
(Yang Y. et al. JID 2020.)

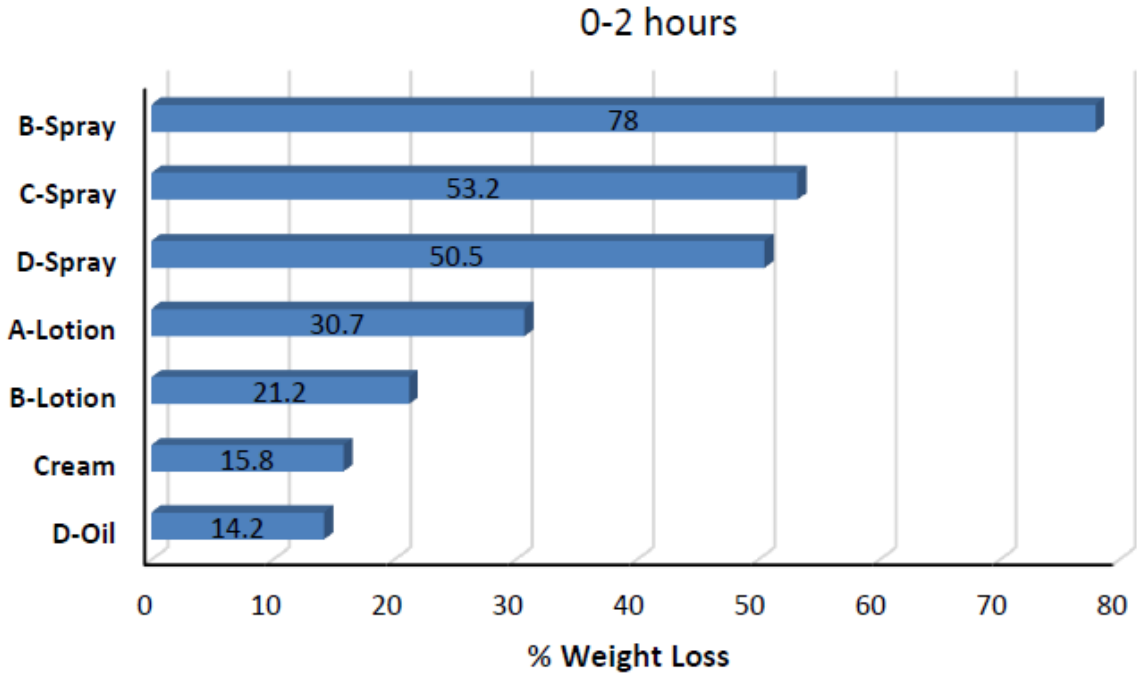
pH measurement and yield stress analysis





Data obtained by Dr. Ann-Marie Ako-Adounvo.

Differences in sunscreen weight loss reveals in-use evaporation rates vary significantly



Data obtained by Dr. Ann-Marie Ako-Adounvo.

Summary

- **Physicochemical properties affect skin permeation of UV filters**
- **Dermatomed skin was used for product selection for MUsT studies, but many improvements can still be made in the IVPT study design.**
- **IVPT using heat-separated human epidermis (HSE) showed less intra-donor variability than dermatomed skin**
- **Similar rank orders of skin content of UV filters were obtained from the IVPT and the clinical study**
- **Differences in sunscreen formulation properties may affect the absorption of UV filters**

References

1. Federal Register. Sunscreen Drug Products for Over-the-Counter Human Use - Proposed Rule. 2019

2. FDA. Guidance for Industry: Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations. 2019

3. FDA. Guidance for Industry: Nonprescription Sunscreen Drug Products - Safety and Effectiveness Data. 2016

4. Matta MK, Florian J, Zusterzeel R, et al. Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. *JAMA.* 2020;323(3):256-267.

5. Matta MK, Zusterzeel R, Pilli NR, et al. Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. *JAMA.* 2019;321(21):2082-2091.

6. Yang Y, Ako-Adounvo A-M, Wang J, et al. In Vitro Testing of Sunscreens for Dermal Absorption: A Platform for Product Selection for Maximal Usage Clinical Trials. *Journal of Investigative Dermatology.* 2020.

Acknowledgements

- ❑ **FDA intramural funding support**
- ❑ **Dr. Janet Woodcock**
- ❑ **Research group members and collaborators:**

FDA-MCERCI Workshop Committee

CDER Sunscreen Working Group

Ann-Marie Ako-Adounvo Afrifa

FDA Transdermal Working Group

Jiang Wang

Theresa Michele

Sergio Coelho

Daniel Willett

Steven Adah

Murali Matta

Huzeyfe Yilmaz

David Strauss

E. Dennis Bashaw

Muhammad Ashraf

Jian Wang

Da Zhang

Patrick Faustino

Luke Oh

Eleftheria Tsakalozou

Thomas O'Connor

Larry Lee

Soo Hyeon Shin


FDA
U.S. FOOD & DRUG
ADMINISTRATION