U.S. FOOD & DRUG ADMINISTRATION

Master MUsT elements

Luke Oh, Ph.D.

Clinical Pharmacology Reviewer, DIIP
Office of Clinical Pharmacology, CDER, FDA

Topical Drug Development – Evolution of Science and Regulatory Policy II
July 23 - 24, 2020

Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Agenda

- Background
- MUsT key elements
- MUsT program for Sunscreen
- Master protocol
- Regulatory action & advice
- Summary

Background

- What is MUsT?
  - Maximal Use Trial program enables the assessment of systemic concentrations of a topically applied drug product under maximal use conditions.

- Why is MUsT important?
  - For topical OTC products such as sunscreens and antiseptics, safety concerns are critical as OTC drug products are used by a large population with a wide age range.
  - Once an active ingredient is included in the monograph category I (GRASE), many different formulations can be developed and marketed without additional studies.

- Why do we need Master protocol?
  - Consistency and clarity in data interpretation.
  - Time and resource effective for drug development

“Standard Design Elements” of MUsT under OTC monograph*

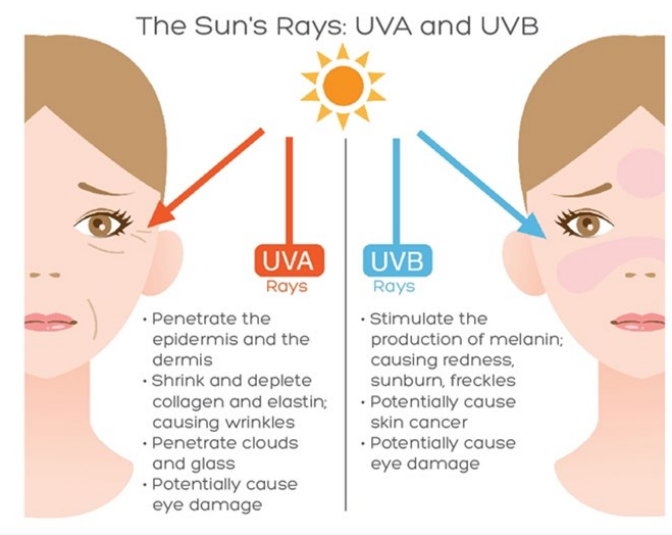
- ✓ Frequency of dosing
- ✓ Duration of dosing
- ✓ Use of highest proposed strength
- ✓ Total involved surface area to be treated at one time
- ✓ Amount applied per square centimeter (area)
- ✓ Method of application/site preparation

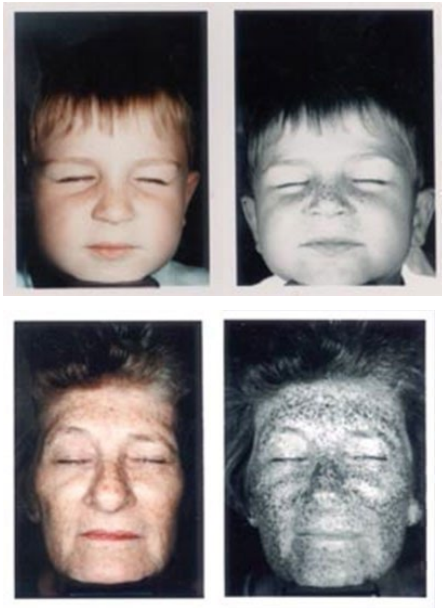
** Final Guidance for Industry: Maximal usage trials for topically applied active ingredients being considered for inclusion in an Over-The-Counter monograph: Study elements and consideration (May 2019)*

Common Key Elements

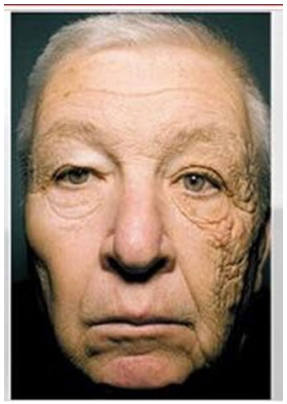
- Demographics of subjects
  - Number of subjects representing general US demographics across sex, ages, and races.
- Body surface area
  - Maximal body surface area per topical application that is consistent with proposed use.
- Frequency of application
  - Maximal number of uses per day (over an 8-hour period)
- Treatment duration
  - Maximal duration of usage or time to reach steady state

Skin damage by ultra-violet (UV) rays and Benefits of sunscreen

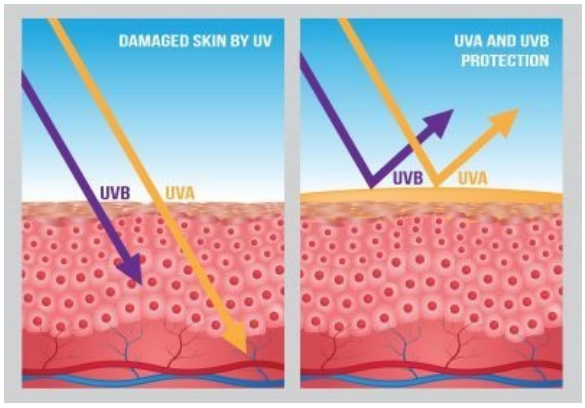




(Photos from website of Inside Outside wellness center)



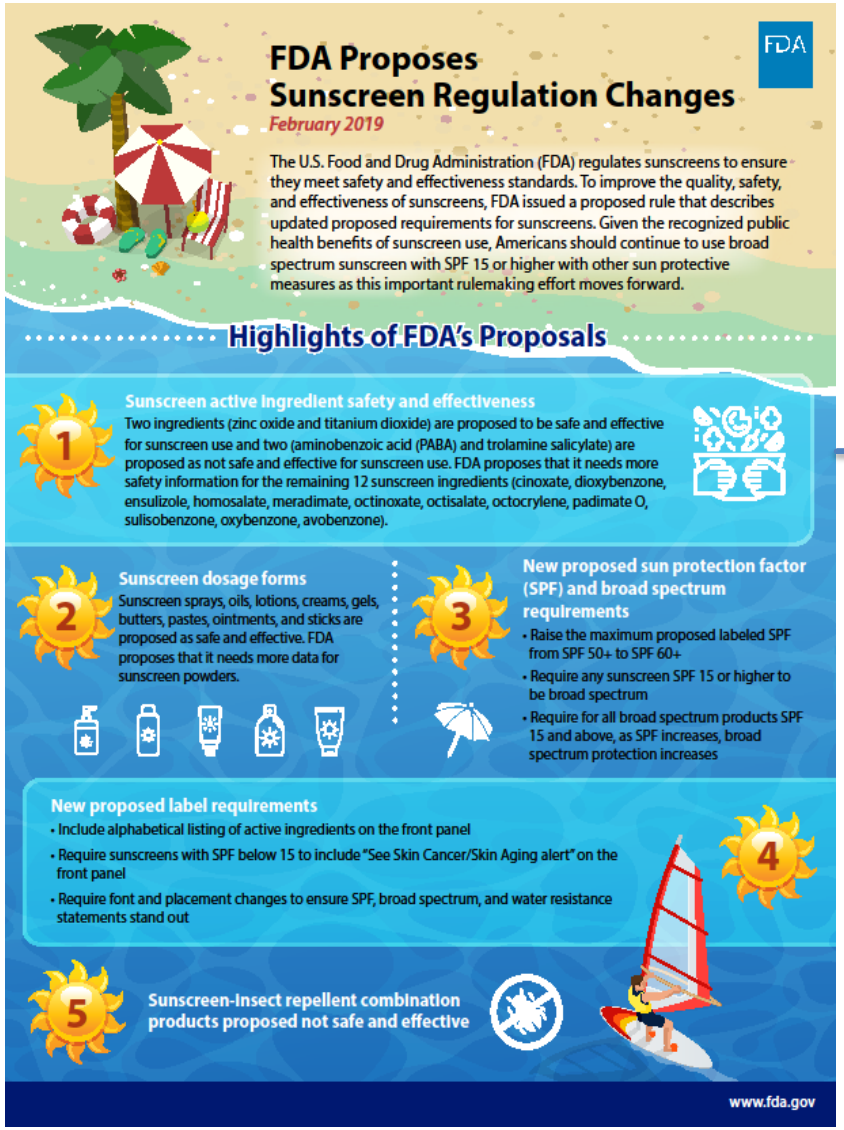
(Gordon and Brieva, Unilateral Dermatoheliosis, N Engl J Med 2012; 366:e25)



Benefits of Sunscreen

- Decrease in skin aging
- Decrease in sunburn
- May reduce potential risks of skin cancer

Sunscreen Active Ingredients



Category I (GRASE)
- Zinc Oxide
- Titanium Dioxide

Category II (Non-GRASE)
- Aminobenzoic acid (PABA)
- Trolamine salicylate

Category III (Insufficient data for GRASE determination)

1	**Avobenzone**
2	**Oxybenzone**
3	**Ensulizole**
4	**Homosalate**
5	**Meradimate**
6	**Octinoxate**
7	**Octisalate**
8	**Octocrylene**
9	Padimate O
10	Sulisobenzone
11	Dioxybenzone
12	Cinoxate

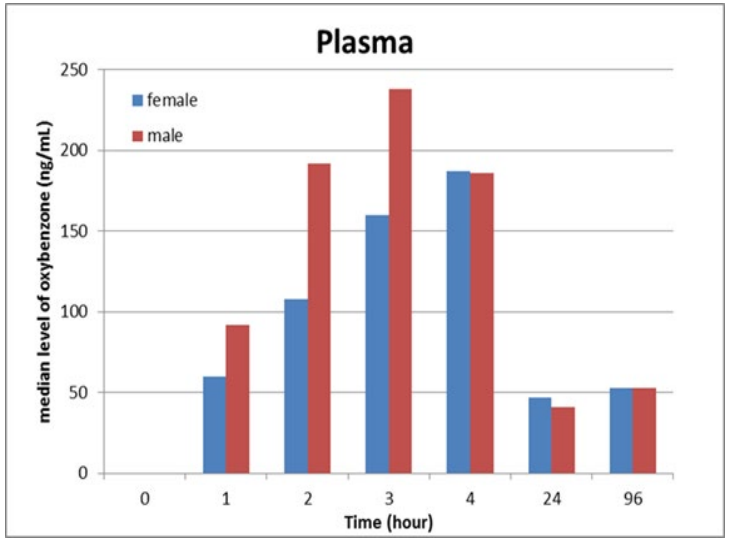
Not deferred

Sunscreen Final Rule Deferral

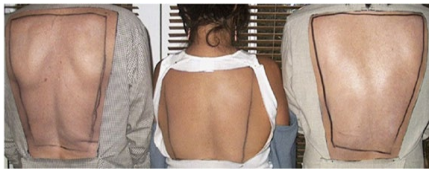
- Sunscreen final rule has been deferred till Nov. 29. 2020
- The sunscreen industry has submitted the deferral request of 8 active ingredients in Category III.
  - The industry needs to provide a pharmacokinetic (PK) assessment of active ingredients following repeated topical applications under maximal use conditions.
  - Depending on the level of systemic exposure of active ingredients, additional nonclinical studies may be necessary to support the systemic safety of the active ingredients.
  - The FDA is working with the industry to set the Master protocol with standardization of key elements.

Dermal absorption of sunscreen

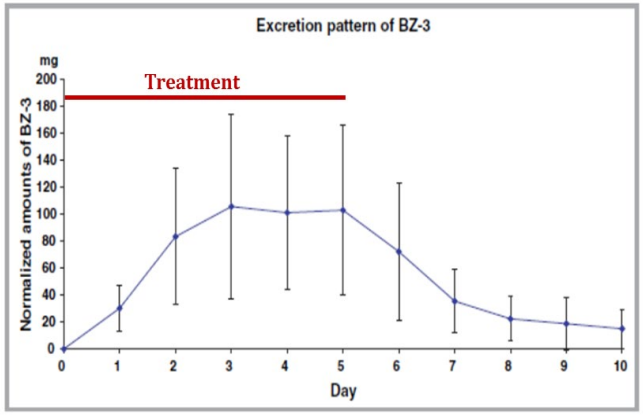
- Sunscreen ingredients were found in systemic circulation and tissue in humans (Schlumpf, 2010; Krause, 2012, …,etc)
- In vivo permeation studies show detectable systemic exposure of a sunscreen ingredient following topical application of sunscreen (Janjua, 2008; Gonzalez, 2006; Gulson, 2012, …,etc)



(adapted from Janjua et al., 2008)



(Gulson et al, 2012)



(Gonzalez et al., 2006)

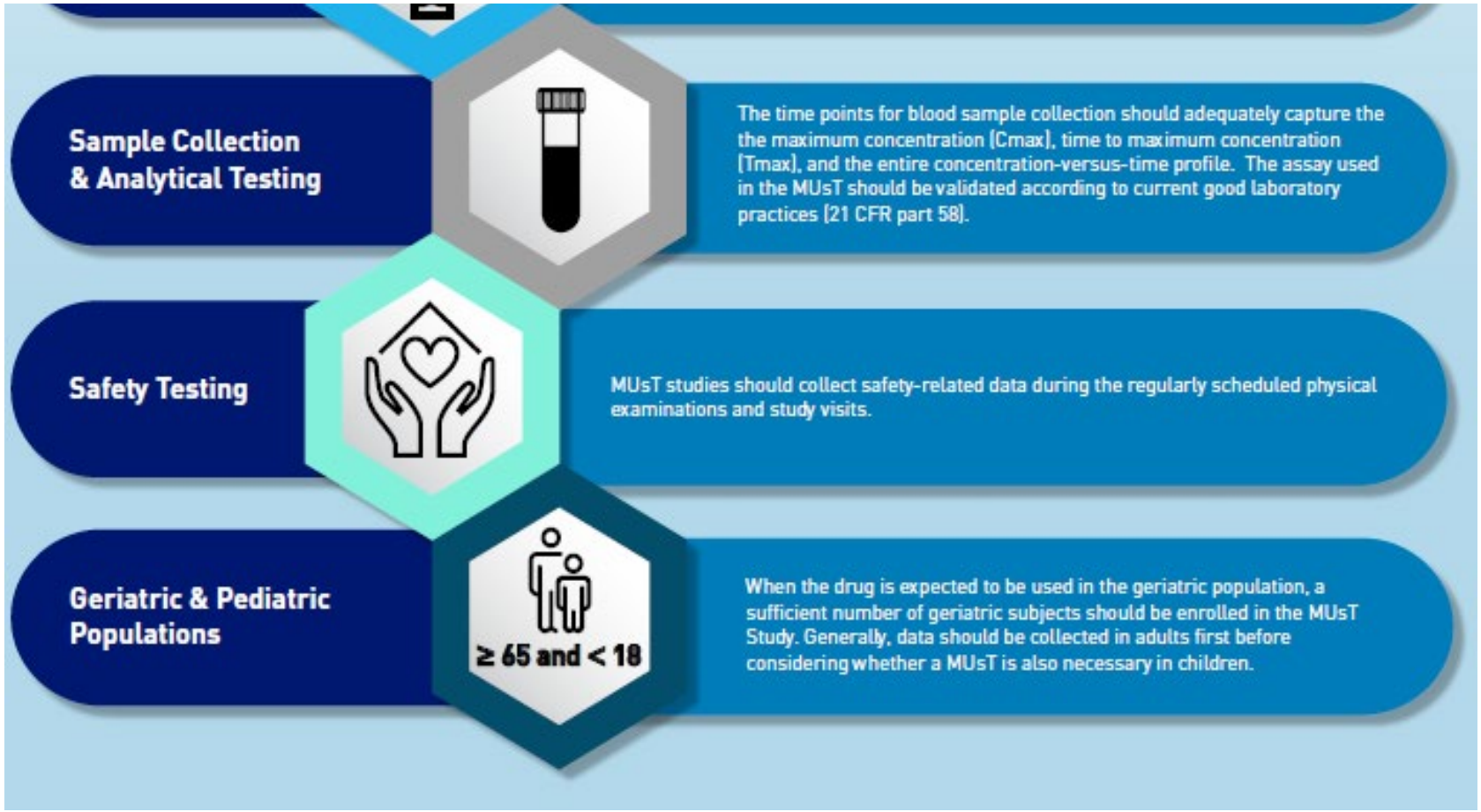
Insufficient dermal absorption data in literature

- Common issues in publication
  - Extemporaneous formulations
  - Sub-maximal use conditions

- Recommended criteria of maximal use conditions
  - Application every 2 hours 4 times a day
  - Duration to reach steady state (to be informed by a pilot study)
  - Body surface area – minimum 75%
  - Dose per topical application: 2 mg/cm^2

Considerations for MUsT

Considerations for MUsT



Sunscreen Pilot MUsT study design

Pilot MUsT study design	
Population	Healthy subjects
Dosing regimen	Every 2 hours (4 times per day)
Dose	2 mg/cm^2
BSA	75%
PK sample collection	To-be-determined based on characteristics of ingredient

- A pilot study is to obtain initial PK data to design the confirmatory pivotal study.
- The subject number should be able to address the anticipated inter-subject and intra-subject variability.
- At least 4 market-image formulations should be tested including one formulation with permeation enhancer.
- PK sample collection needs to adequately capture the Cmax, Tmax, and the entire concentration-versus-time profile.

Sunscreen Pivotal MUsT study design

Pivotal MUsT study design	
Population	N healthy subjects
Dosing regimen	Every 2 hours (4 times per day)
Dose	2 mg/cm^2
Treatment duration	5 days or to reach steady-state
BSA	75%
PK sample collection	To-be-determined based on pilot study results

- Pivotal MUsT study should be conducted in a sufficiently large number of subjects given the large target population and variation in skin permeation within it
- Elements including dose, dosing regimen, and BSA are standardized. The current label recommends the application of sunscreen 2 mg/cm^2 every 2 hours.
- At least 4 market-image formulations should be tested including one formulation with permeation enhancer.

Master Key Elements for Sunscreen

- Demographics of subjects
  - Pilot study: To understand inter-subject and intra-subject variability
  - Pivotal study: Sufficient number of subjects representing general US demographics across sex, ages, and races.
- Body surface area
  - 75% body surface area is considered as the maximal skin area for sunscreen.
- Frequency of application
  - Every 2 hours per day (4 applications per 8 hours)
- Treatment duration
  - 5 days or to achieve steady state

Regulatory action and advice

- Publication of *Proposed Rule, Sunscreen Drug Products for Over-the-Counter Human use* (02/26/2019)

- Publication of *guidance, Maximal usage trial (MUsT) for Topical Active ingredients being considered for inclusion in an over-the-counter monograph: Study elements and considerations* (Draft 05/21/2018, Final 02/2019)

Article

Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products

Edward Dennis Bashaw, Pharm. D[1], Doanh C. Tran, Ph.D[1], Chinmay G. Shukla, Ph.D[1], and Xiaomei Liu, Pharm. D[1]

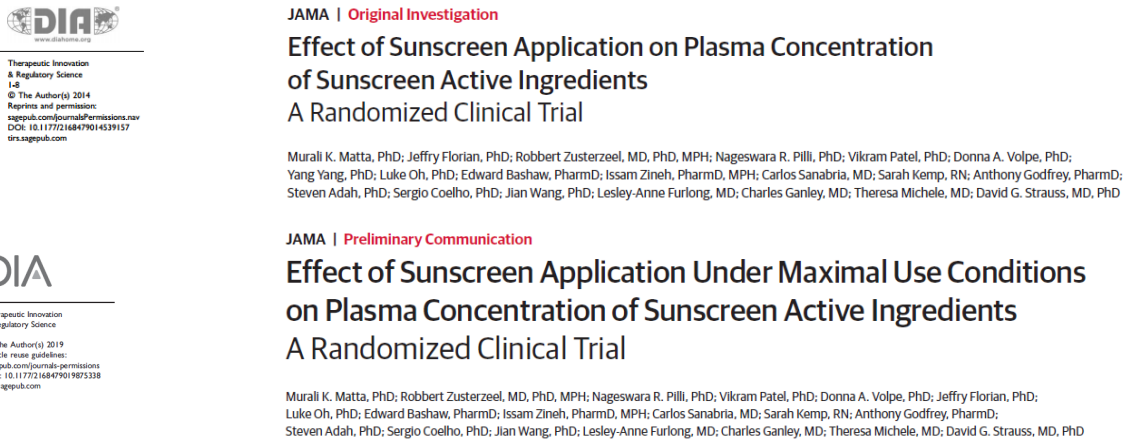
Therapeutic Innovation & Regulatory Science 1-8
© The Author(s) 2014
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/2168479014539157
tirs.sagepub.com

DIA

In Vitro Skin Permeation Methodology for Over-The-Counter Topical Dermatologic Products

Luke Oh, PhD[1], Sojeong Yi, PhD[1], Da Zhang, PhD[1], Soo Hyeon Shin, PhD[1], and Edward Bashaw, PharmD[1]

Therapeutic Innovation & Regulatory Science 1-8
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2168479019875338
tirs.sagepub.com



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

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

Summary

- With the final rule deferral, 8 sunscreen active ingredients have been proposed for evaluation within a MUsT program by an industry trade group.
- Master MUsT protocol is
  - To standardize the MUsT study design elements.
  - To develop topical OTC product in a time- and budget- efficient manner.
- There are key elements for Sunscreen Master protocol: dose and dosing regimen, BSA, and treatment duration.
- The FDA encourages the industry to discuss both pilot and pivotal study design with the FDA prior to the initiation of the study.

Acknowledgements

Office of Clinical Pharmacology
Edward D. Bashaw, PharmD

Division of Inflammatory and Immune Pharmacology
Sojeong Yi, PhD
Soo Hyeon Shin, PhD
Da Zhang, PhD
Chinmay Shukla, PhD
Suresh Doddapaneni, PhD
Chandrahas Sahajwalla, PhD