Current Regulatory Perspectives for Dermal Absorption Under the OTC Monograph

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2019 Topical Drug Development
July 29, 2019

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
- Sunscreen
  - Sunscreen Innovation Act (SIA)
  - Dermal absorption of sunscreen
  - Regulatory action and advice
  - Maximal usage trial (MUsT)
- Antiseptic
  - Regulatory actions
  - Health care professional use and Consumer use
  - MUsT
- Summary & conclusion

Changes of dermal absorption under OTC monograph

- In 1970s,
  - Little awareness of dermal absorption of OTC drugs (i.e. sunscreen and antiseptic) by public.
  - No bioanalytical methods available to measure systemic concentration.
  - Public use of sunscreen and antiseptic was much less frequent.
- Recently,
  - An increase in public awareness of a potential safety related to dermal absorption of OTC drugs.
  - Highly sensitive validated bioanalytical methods became available.
  - Notable changes in public use of sunscreen and antiseptic.

Sunscreen

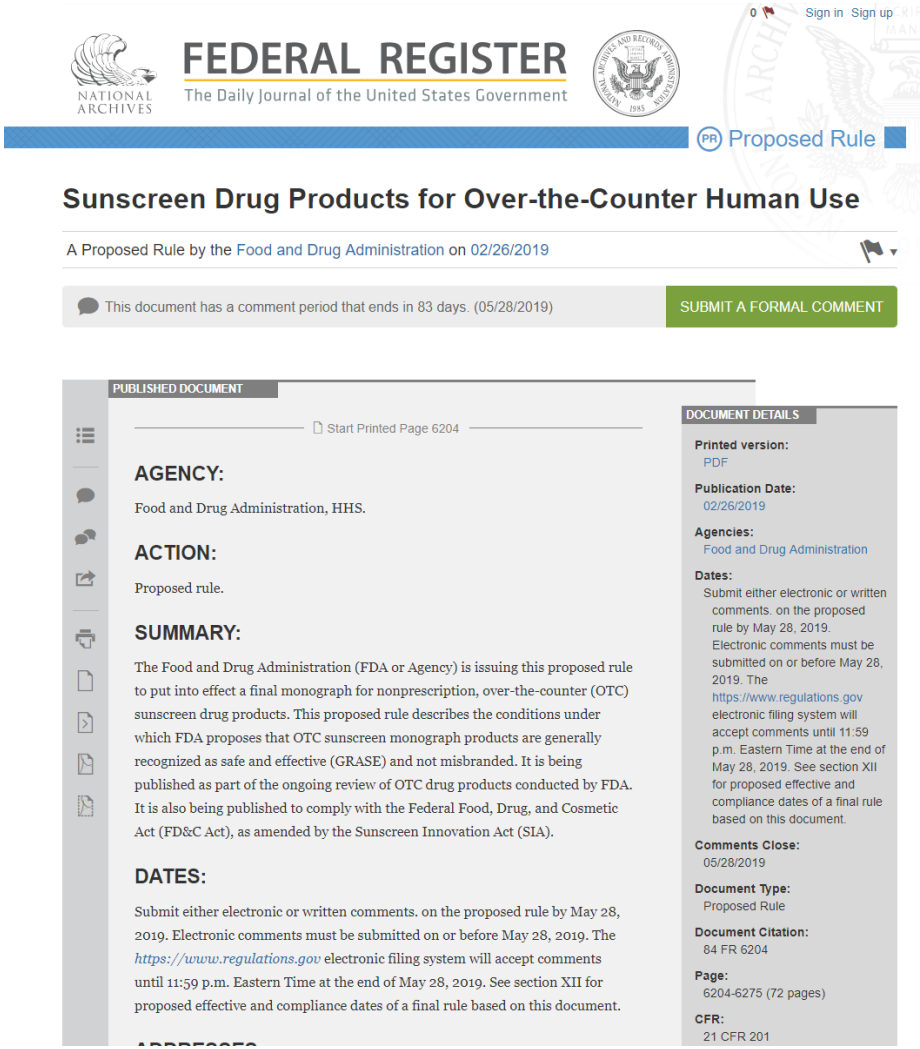
Sunscreen Innovation Act (SIA)

- Enacted on 11/26/2014
- Deadline: 11/26/2019
- The bill requires the FDA to review and determine whether over-the-counter (OTC) sunscreens are generally recognized as safe and effective (GRASE) and ensure that any sunscreens marketed in the U.S. are appropriately labeled.

- **Time and Extent Application (TEA):** The bill allows sunscreens that have been marketed for five continuous years in the United States or other countries and in sufficient quantity eligible for review under this Act.

- The SIA bill:
  1. Establishes a framework for the review and approval by the FDA of OTC sunscreens with new active ingredients.
  2. Sets forth timeframe requirements for review.
  3. Requires applications for review to include safety and efficacy data as well as adverse drug experience information.

Sunscreen Proposed Rule



FEDERAL REGISTER
The Daily Journal of the United States Government

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Proposed Rule

Sunscreen Drug Products for Over-the-Counter Human Use

A Proposed Rule by the Food and Drug Administration on 02/26/2019

This document has a comment period that ends in 83 days. (05/28/2019)

SUBMIT A FORMAL COMMENT

PUBLISHED DOCUMENT

Start Printed Page 6204

AGENCY:

Food and Drug Administration, HHS.

ACTION:

Proposed rule.

SUMMARY:

The Food and Drug Administration (FDA or Agency) is issuing this proposed rule to put into effect a final monograph for nonprescription, over-the-counter (OTC) sunscreen drug products. This proposed rule describes the conditions under which FDA proposes that OTC sunscreen monograph products are generally recognized as safe and effective (GRASE) and not misbranded. It is being published as part of the ongoing review of OTC drug products conducted by FDA. It is also being published to comply with the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Sunscreen Innovation Act (SIA).

DATES:

Submit either electronic or written comments. on the proposed rule by May 28, 2019. Electronic comments must be submitted on or before May 28, 2019. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of May 28, 2019. See section XII for proposed effective and compliance dates of a final rule based on this document.

DOCUMENT DETAILS

Printed version:
PDF

Publication Date:
02/26/2019

Agencies:
Food and Drug Administration

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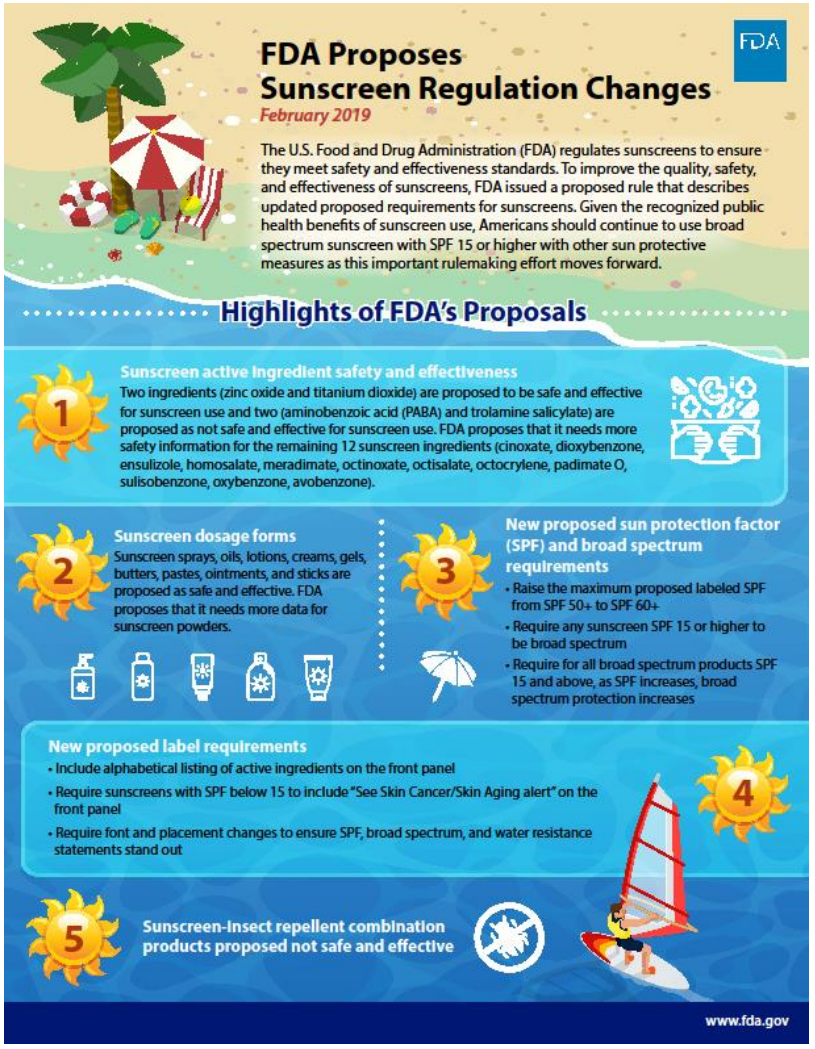
Comments Close:
05/28/2019

Document Type:
Proposed Rule

Document Citation:
84 FR 6204

Page:
6204-6275 (72 pages)

CFR:
21 CFR 201

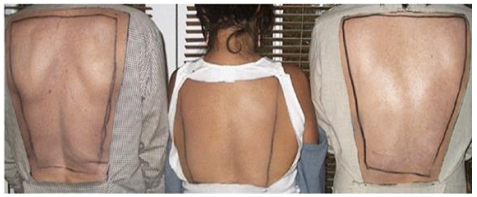


16 sunscreen ingredients in the Proposed Rule

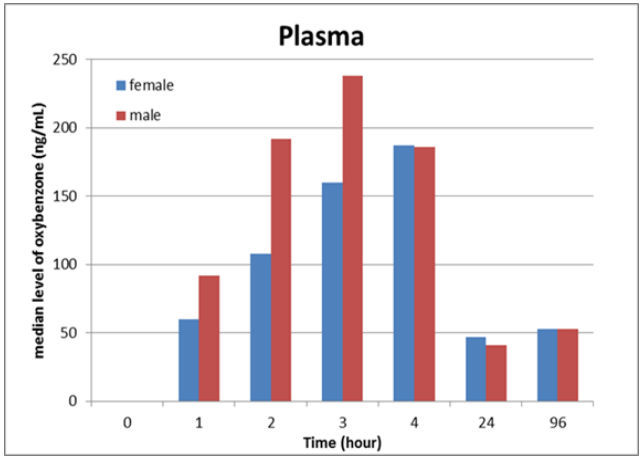
- Category I (GRASE)
  - Zinc Oxide
  - Titanium Dioxide
- Category II (Non-GRASE)
  - Aminobenzoic acid (PABA)
  - Trolamine salicylate
- Category III (Insufficient data for GRASE determination)
  - The remaining current 12 sunscreen ingredients: cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzone, oxybenzone, and avobenzone.

Dermal Absorption of Sunscreen

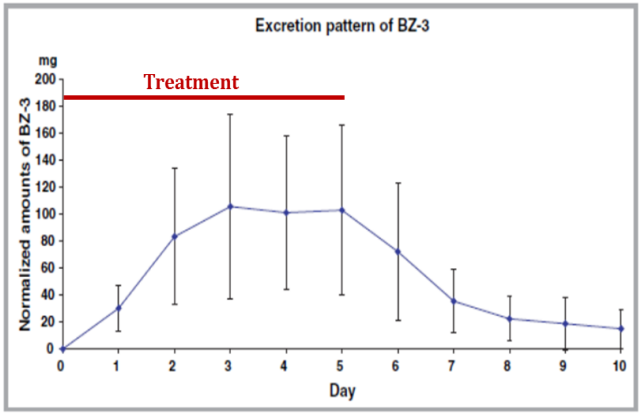
- Sunscreen ingredients were found in systemic circulation and tissue in humans (Schlumpf, 2010; Krause, 2012)
- In vivo permeation studies show detectable systemic exposure of a sunscreen ingredient following topical application of sunscreen (Janjua, 2008; Gonzalez, 2006; Gulson, 2012)



(Gulson et al, 2012)



(adapted from Janjua et al., 2008)



(Gonzalez et al., 2006)

Insufficient dermal absorption data

- 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
  - Body surface area – minimum 75%
  - Dose per topical application: 2 mg/cm^2

Regulatory action and advice

- Publication of *Proposed Rule, Sunscreen Drug Products for Over-the-Counter Human use* (02/26/2019)
- Publication of *Final guidance, Maximal usage trial (MUsT) for Topical Active ingredients being considered for inclusion in an over-the-counter monograph: Study elements and considerations* (May, 2019)

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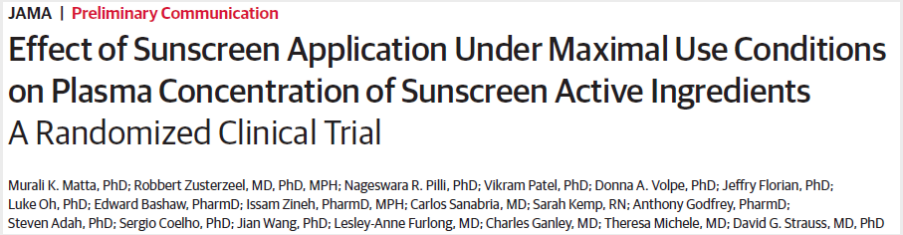
- Publication of in vitro permeation test review (Submitted)
- Publication of Sunscreen PK study (Matta et al., 2019)



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

- Publication of Maximal Usage Trial (Bashaw et al., 2014)

Article

DIA

Therapeutic Innovation & Regulatory Science
1–8
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DOI: 10.1177/2168479014539157
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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]

Maximal Usage Trial (MUsT)

- In the mid 1990s the FDA developed and implemented the use of the “maximal use” trial as part of an in vivo bioavailability program.
  - Outgrowth of the dissatisfaction with previous bioavailability assessments
  - Made possible by the refinement of analytical methodologies
- Trial design has been presented and discussed at various national meetings and workshops (AAPS, FIP-BioInternational, ASCPT, etc.)
- Over the 20 years from 1996 - 2016 a total of 66 MUsT’s were submitted as part of original NDAs. A total of 1512 subjects participated in these trials, with 887 (58.6%) male and 658 (43.4%) female. (Manuscript in preparation)

Assessment of the human systemic absorption of sunscreen ingredients

(NCT03582215)

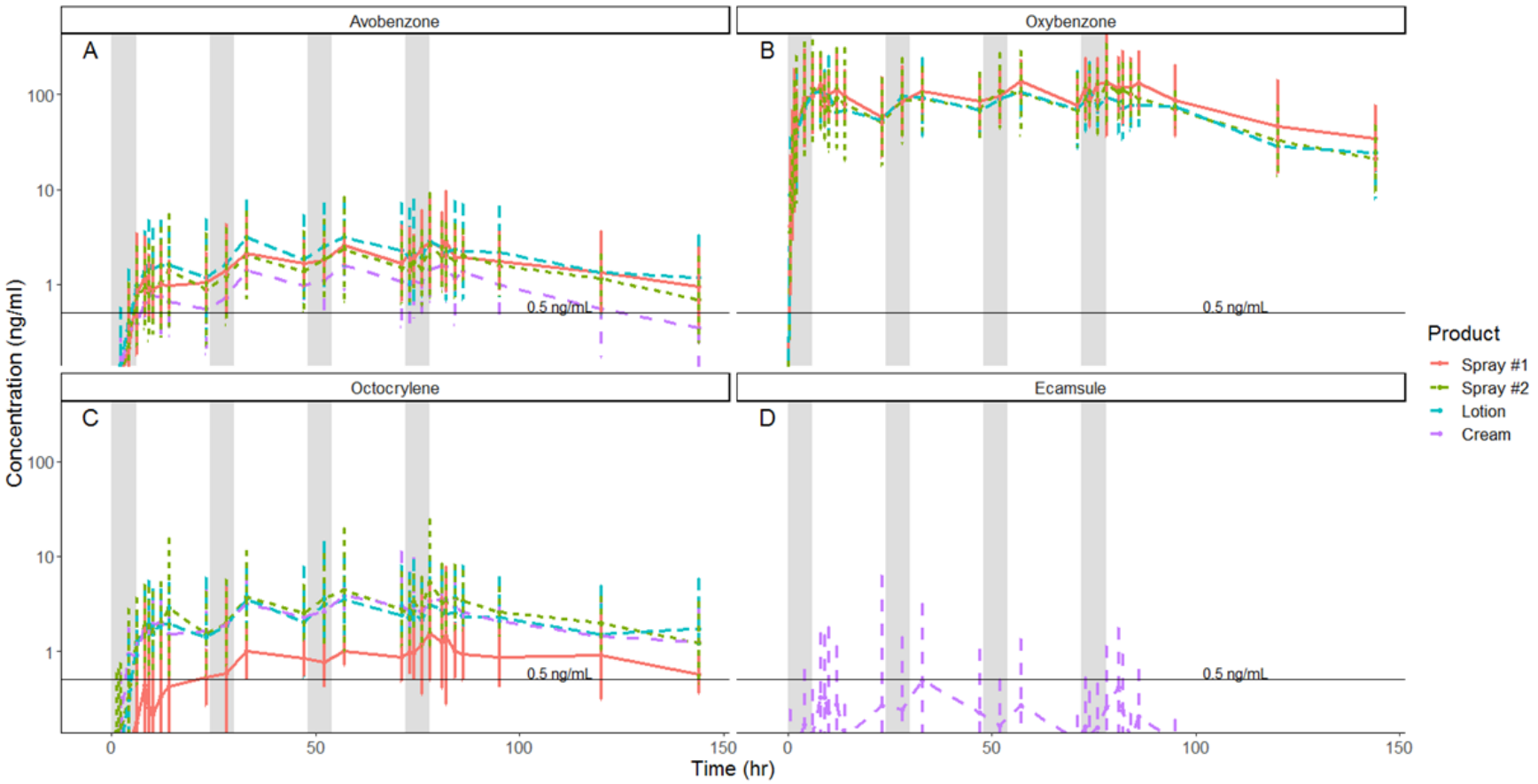
- Objective: To assess the systemic exposure of sunscreen active ingredients when sunscreen product is applied under maximal use conditions.
- Part 1: An open-label, randomized, 4-arm study with 24 healthy adult subjects to evaluate 4 ingredients in 4 sunscreen products (published in JAMA)

	Avobenzone (%)	Oxybenzone (%)	Octocrylene (%)	Ecamsule (%)
Maximum allowed on U.S. Market	3%	6%	10%	2%
Spray # 1	3%	6%	2.35%	-
Spray # 2	3%	5%	10%	-
Lotion	3%	4%	6%	-
Cream	2%	-	10%	2%

- Part 2: An open-label, randomized, 4-arm study with 48 healthy adult subjects to evaluate 6 ingredients (Manuscript in preparation)
  - Homosalate, Octisalate, and Part 1 ingredients
  - Lotion and spray formulations
- Methods
  - Subject received topical application of sunscreen product to 75% BSA every 2 hours, 4 times a day, for 4 days (3 days for Part 2)
  - Serial PK sample collections on Days 1 and 4. additional PK sample collections on Days 2, 3, and 21*.

* Day 21 is only for Part 2 study

Plasma concentrations of sunscreen ingredients (Part 1)*



*Matta, M. K., et al. (2019). "Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial." JAMA.

Topical Antiseptic

OTC topical antiseptics: Regulatory actions

- Topical antiseptics are intended to reduce the risk of infection by killing or inhibiting the growth of microorganisms on the skin.
  - Health Care Antiseptics [2017 Final Rule (FR)]
    - Hand washes, hand rubs, surgical scrubs for health care personnel
    - Products for patient preoperative skin preparation
    - 24 active ingredients in the 2015 Proposed Rule (PR) were found ineligible for monograph
    - Actions on 6 active ingredients are deferred

Regulatory actions

- Consumer Antiseptic Rub (2019 FR)
  - Consumer hand rubs, wipes (leave-on products)
  - 27 in the 2016 PR were excluded and 3 are deferred.

- Consumer Antiseptic Washes (2016 FR)
  - Consumer body washes, hand washes (rinse-off products)
  - 19 in the 2013 PR were excluded and 3 are deferred.

Active ingredient	2017 Health Care Antiseptics FR	2016 Consumer Antiseptic Wash FR	2019 Consumer Antiseptic Rub FR
Ethanol (60-95%)	O	Not eligible	O
Benzalkonium chloride	O	O	O
Benzethonium chloride	O	O	Not eligible
Chloroxylenol	O	O	Not eligible
Isopropyl alcohol (70-91.3%)	O	Not eligible	O
Povidone iodine 5-10%	O	Not eligible	Not eligible

A maximal-use condition of antiseptics

- Hand washes and hand rubs tend to be chronically used; particularly health care workers use it extensively on a daily basis.
  But, there is no certain limitation to the extent of use (e.g., *use no more than XX times/day*)

- In order to support "a maximal use condition" for the intended indication, the sponsor needs to provide adequate justifications (e.g., literature or observational studies).
  - The patterns of use of these agents have changed over the last 20 - 30 years with an increase in nosocomial infections and a rise in antibiotic resistant organisms. So, older use data may not be relevant today.

A maximal-use condition of antiseptics

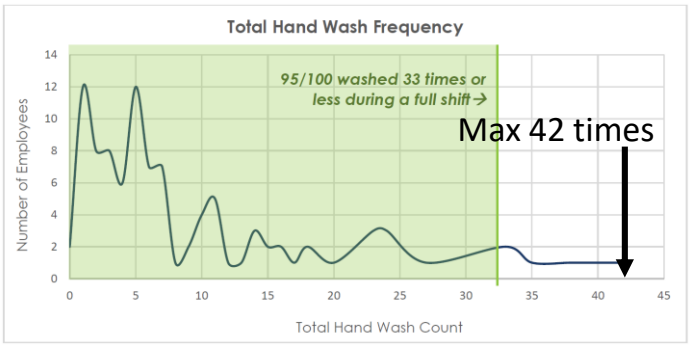
- Health care use >> consumer use
  → MUsT program to support health care indication will also meet the requirements of MUsT for the consumer indication which represents a lower intensity of use than the health care indication.

Examples of maximal use conditions expected by indications

	Health Care Hand rub	Consumer Hand rub
Dosing frequency	**~100 times/day** *(Evans et al. 2012)*	**~50 times/day** *(Kinnula et al. 2009.)*
Dosing duration	**12 hours/day**	**8 hours/day**
Study duration	**5 days**	**5 days**

Observational studies for consumer hand washes

- Study 1
  - 100 workers in 11 day-care sites for 8 hours



(FDA Docket No. FDA-2015-N-0101)

- Study 2
  - 20 workers in 7 day-care sites, 8 hours per day for 3 days

Total hand wash frequency (times/a work shift)

	Day 1	Day 2	Day 3	Total Day 1 to 3
Maximum	46	61	41	144 **(48 per day)**
95% Upper (the second most frequent)	42	29	41	113 **(37.6 per day)**

(Data source: FDA Docket No. FDA-1975-N-0012)

"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

The elements were selected to evaluate the potential for systemic drug absorption at the upper limit of use covered by the clinical trials and allowed for in the label.

** 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)*

Summary & Conclusion

- Despite the conventional wisdom of the 1970s, sunscreens and antiseptics are absorbed and the question of long term safety has not yet been answered.
- To attain a dermal absorption profile for active ingredient, proper MUsT program needs to be planned with consideration of MUsT design elements:
  - Sunscreen: BSA, frequency, and duration
  - Antiseptic: BSA, and high frequency
- Proper MUsT program evaluating systemic exposure of active ingredients of sunscreen or antiseptic may provide key data to establish an absorption profile for topical OTC products.

Acknowledgements

Office of Clinical Pharmacology
Edward D. Bashaw, PharmD
Sojeong Yi, PhD
Soo Hyeon Shin, PhD
Da Zhang, PhD
Donny Tran, PhD
Shirley Seo, PhD

Division of Applied Regulatory Science
Matta Murali, PhD
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Division of Nonprescription Drug
Sergio Coelho, PhD
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