US Sunscreen Landscape - Shaping the future

Carl D’Ruiz

The Sunscreen E-Summit
June 7, 2022

Agenda

1. *Overview of how sunscreens are regulated in US and abroad*
2. *History of FDA OTC Sunscreen monograph and ingredients*
3. *Overview of 2021 Sunscreen Monograph Proposed Order*
4. *PCPC Sunscreen Consortium activities related to supporting safety of 7 Category III ingredients*
5. *Innovation incentives under 2021 PO*
6. *New Sunscreen Innovation activities and FDA GRASE status new FDA sunscreen UV-filters: Bemotrizinol*

Regulatory Overview:

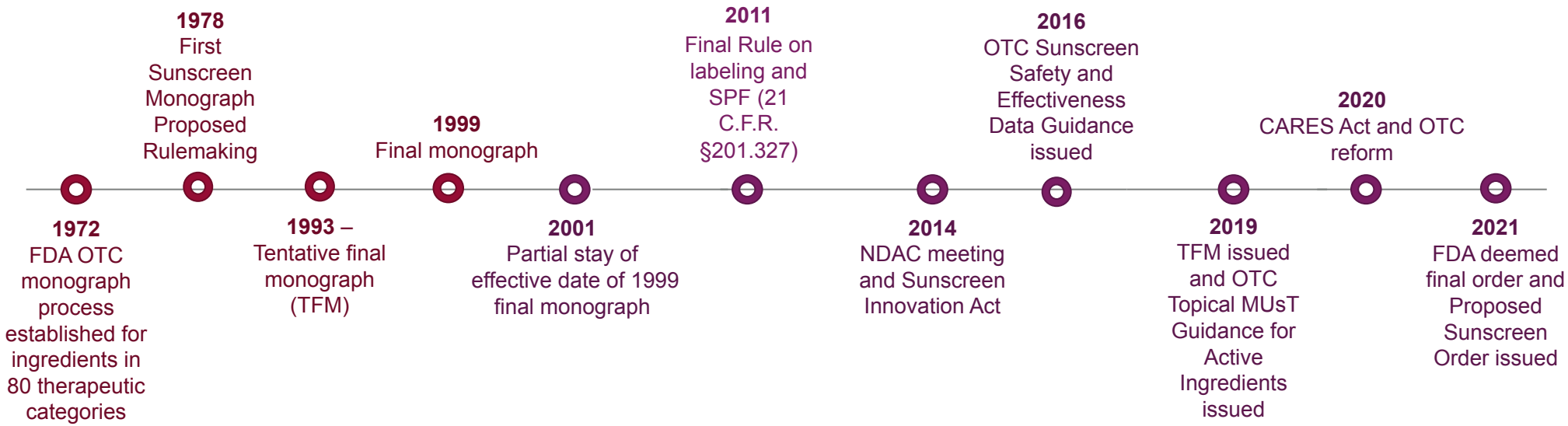
UV Filters Are Regulated as Drugs in the US

- In the US, UV-filters are regulated as drugs because they fall under the legal definition of “drug” per the Federal Food, Drug and Cosmetic Act
  - "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" [FD&C Act, sec. 201(g)(1)]
- Intended use:
  - *To help prevent sunburn or to decrease the risks of skin cancer and early skin aging caused by the sun*
- Primarily regulated under FDA’s OTC Sunscreen Drug Products Monograph
- In other regions of the world, sunscreen products and UV filters are primarily regulated as Cosmetics

Country	Classification
USA	OTC Drug
Canada	Natural Health Products or OTC Drugs
Australia	Cosmetic / Therapeutic Product
China	Special Cosmetic
Taiwan	Specific Purpose Cosmetic
Korea	Functional Cosmetic
Europe	Cosmetic
Japan	Cosmetic
UK	Cosmetic
New Zealand	Cosmetic
Mercosur	Cosmetic
South Africa	Cosmetic
ASEAN	Cosmetic
India	Cosmetic
Israel	Cosmetic
Russia	Cosmetic
Mexico	Cosmetic

FDA OTC Sunscreen Drug Monograph (M020)

Key Milestones

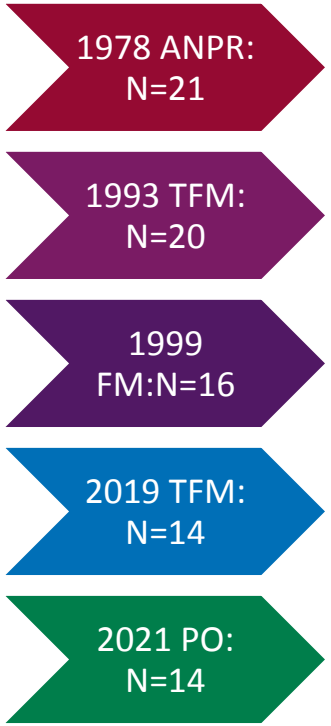


Full history:
https://www.fda.gov/drugs/historical-status-otc-rulemakings/rulemaking-history-otc-sunscreen-drug-products#Original

NDAC, Nonprescription Drugs Advisory Committee
TFM – Tentative Final Monograph
MUsT- Maximum Usage Trials

Number of Available UV Filters in US

Has decreased over time!



Proposed Order 2021 GRASE Status	
Active Ingredient	**Category***
Aminobenzoic acid (PABA)	II
Trolamine salicylate	II
Zinc oxide	I
Titanium dioxide	I
Avobenzone	III
Ensulizole	III
Homosalate	III
Octinoxate	III
Octisalate	III
Octocrylene	III
Oxybenzone	III
Meradimate	III
Sulisobenzone – BZ-4	III
Dioxybenzone – BZ-8	III
Cinoxate	III

7 PCPC Consortium supported UV-Filters

Independently being supported

Not marketed and not industry supported

* **Category I** – Generally regarded as safe and effective (GRASE) and not misbranded
Category II – Not GRASE and/or misbranded
Category III – Insufficient data to classify as either Category I or Category II

2021 Proposed Order GRASE Status and Testing Requirements

For Category III Sunscreen Actives[1]

Human Clinical Studies

- Dermal irritation and sensitization
- Dermal photosafety
- **Human absorption studies/maximum usage trials (MUsT)**[2]

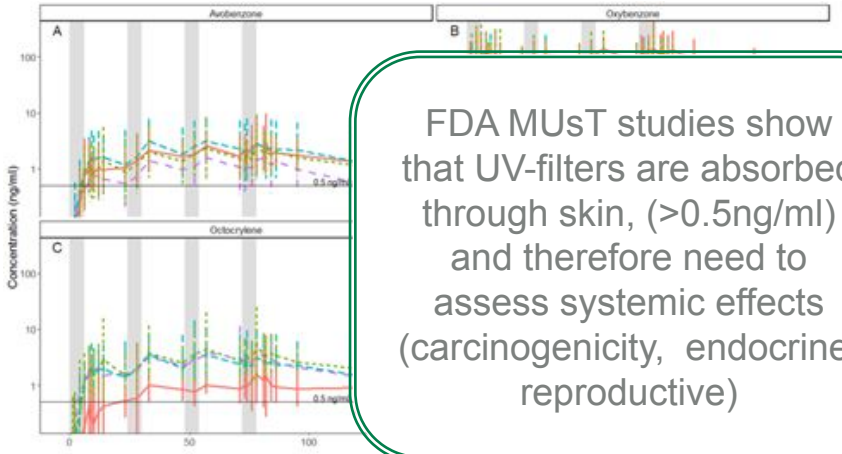
Nonclinical (Animal) Studies

- Dermal carcinogenicity
- Systemic carcinogenicity
- Developmental and reproductive toxicity (DART)
- Toxicokinetics (ADME)
- Hormonal Effects

Other

- In vitro permeation tests (IVPT)
- Pediatric data (case-by-case basis – depending on MOS)
- Postmarketing Safety Data

FDA's Rationale for Proposed Order Data Requests



FDA MUsT studies show that UV-filters are absorbed through skin, (>0.5ng/ml) and therefore need to assess systemic effects (carcinogenicity, endocrine, reproductive)

Proposed safety framework is supported per Sept 2014 NDAC meeting

Aligns and extends SIA GRASE determination requirements for new ingredients to current TFM Cat III active ingredients

Changing patterns of sunscreen use – indicate more frequent and longer use

Evolving scientific knowledge

Highly sensitive validated bioanalytical methods are now available

NDAC, Nonprescription Drugs Advisory Committee
SIA, Sunscreen Innovation Act

FDA Pharmacokinetic (PK) Maximal Usage Trials (MUsT)

Why is the MUsT a must[1]?

Clinical Significance

MUsT is the FDA's standard approach for assessing the in vivo bioavailability of topical drug products and measuring the systemic absorption potential of topically applied active ingredients that are under consideration for inclusion in an OTC monograph.

FDA absorption threshold value of 0.5 ng/mL = the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100,000 after a single dose.[2]

Regulatory Utility

Results from pilot and pivotal MUsT studies, together with data from other long-term nonclinical studies help FDA estimate a safety margin for systemic exposure to the active ingredient and determine whether additional safety data are needed to support a GRASE finding for an active ingredient.

If MUsT shows that a sunscreen active is not absorbed systemically, some aspects of toxicology testing may not be needed.

For example, A systemic carcinogenicity study would not be needed if:

(1) PK MUsT results in a steady state blood level < 0.5 ng/mL and

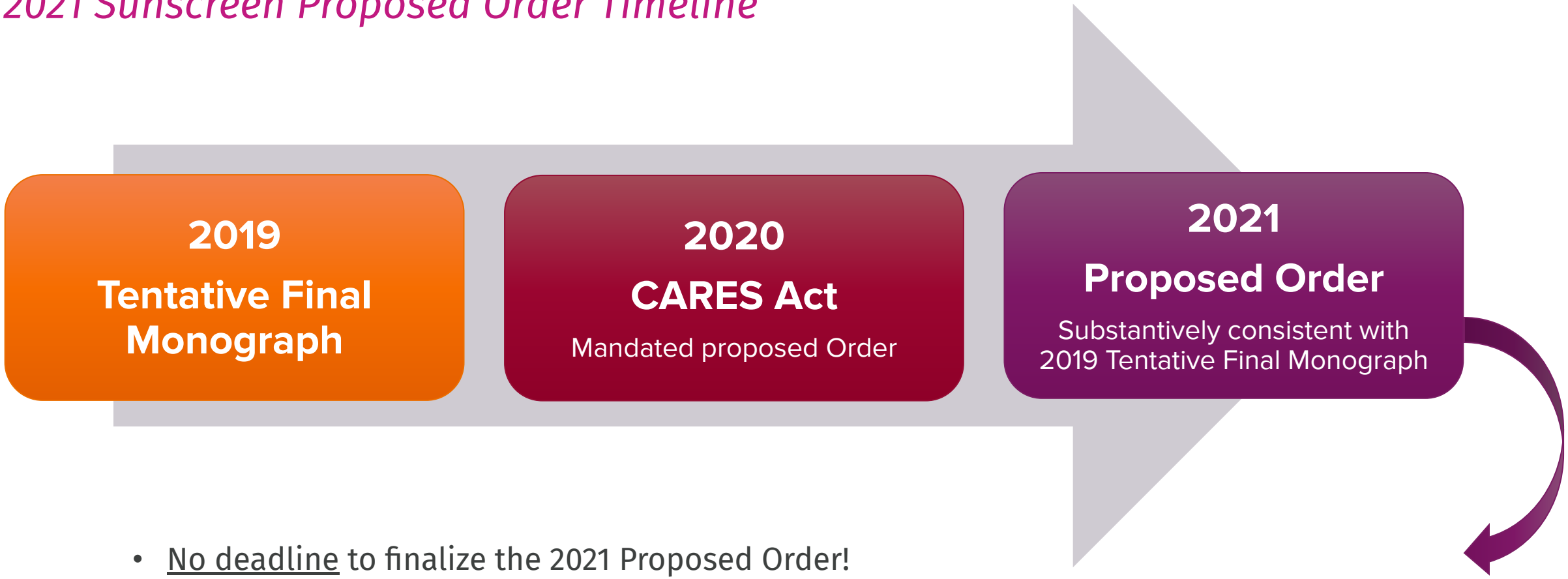
(2) Toxicology data does not reveal any other safety signals for the ingredient or for any known structurally similar compound indicating the potential for adverse effects at lower levels

[1]FDA (2016). Nonprescription Sunscreen Drug Products Safety and Effectiveness Data: Guidance for Industry

[2] Threshold value is consistent with the Threshold of Toxicological Concern concept applied to impurities in the ICH guidance for industry M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

OTC Sunscreen Monograph regulation

2021 Sunscreen Proposed Order Timeline



- No deadline to finalize the 2021 Proposed Order!
- When final order ***is*** issued, it must have an effective date of at least 1-year after publication

FDA Active Ingredient Deferrals

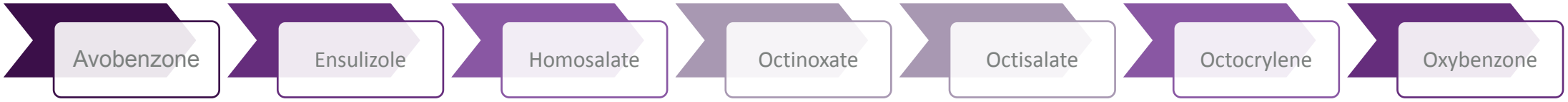
For Category III ingredients

FDA has indicated that if it receives "satisfactory indication of timely and diligent progress on the necessary studies for a specific ingredient," then it would be prepared to initially ***defer issuance of a revised final order*** *regarding the status of sunscreens containing that ingredient – renewed annually*

PCPC Sunscreen Consortium

PCPC sunscreen consortium

- Established in 2019 to support safety and deferral from rulemaking of 7 Sunscreen Ingredients:



- Clinical and Non-clinical Workplans have been developed to address FDA data requests

- Currently engaging with FDA on proposed data request approaches

2021 PO New Sunscreen Innovation Incentives

Industry initiated OTC Monograph Order Requests (OMORs)

- **Tier 1** – Fee based review of new ingredients/indications/monograph therapeutic categories
  - 18 mo. exclusivity innovation incentive
  - 2023 fee: $517,381
  - Require GRASE and MUsT Guideline data submissions
- **Tier 2** – Drug fact label or condition of use changes
  - No exclusivity
  - 2023 fee: $103,476
- OMOR Format and Content Draft Guidance for Industry issued April 10, 2023
  - 60-day comment period

	Tier 1 - GRASE Finalization	Tier 1[1]	Tier 2	Tier 1 - Specified Safety Labeling Change
Filing determination	60 calendar days after receipt of OMOR	60 calendar days after receipt of OMOR	60 calendar days after receipt of OMOR	60 calendar days after receipt of OMOR
Proposed Order Issued	12 months after receipt of OMOR	12 months after receipt of OMOR	10 months after receipt of OMOR	6 months after receipt of OMOR
Public Comment Period	45 calendar days	45 calendar days	45 calendar days	45 calendar days
Assessment of comments	60 calendar days	60 calendar days	60 calendar days	60 calendar days
Comment review extension[2]	6 months[2]	5 months[2]	3 months[2]	3 months[2]
Final Order Issued	17.5 months after receipt of OMOR (or 23.5 months[3])	17.5 months after receipt of OMOR (or 22.5 months[3])	15.5 months after receipt of OMOR (or 18.5 months[3])	11.5 months after receipt of OMOR (or 14.5 months[3])

Current Status of FDA Sunscreen Active Ingredients

Summary

- FDA's 2021 Final Deemed Order effectively maintains the "status quo" in the OTC sunscreen space by utilizing the previously stayed monograph from 1999 as the current applicable monograph until FDA issues a finalized order
- Sunscreen products that comply with the 2021 Final Deemed Order do not need to be removed from the market
- Manufacturers who want to continue marketing sunscreen products that contain active ingredients for which insufficient data exist (based on the Proposed Order – Category III) are requested to submit additional data to FDA
- New OMOR Ingredient Innovation requests – data requirements are like NDAs
- No deadline For FDA to finalize the 2021 Proposed Order!

New Sunscreen Actives on the Horizon: PARSOL® Shield (Bemotrizinol- BEMT)

New UV-filters: PARSOL® Shield (Bemotrizinol - BEMT)

- A generally recognized as safe and effective (GRASE) determination is being sought by DSM for the inclusion of a new broad-spectrum UV sunscreen active ingredient called Bemotrizinol (BEMT - PARSOL® Shield) 6% on FDA's OTC Sunscreen Monograph
- BEMT is the first new US sunscreen active ingredient ('*new molecular entity*') to be evaluated under FDA's revised GRASE and new Maximum Usage Trial (MUsT) PK test guidelines for OTC drug substances
- Currently, all BEMT clinical studies requested by FDA have been completed
- Preliminary results from Pivotal MUsT study are supportive of a GRASE determination for BEMT

CAS number: 187393-00-6

Chemical formula: $C_{38}H_{49}N_3O_5$

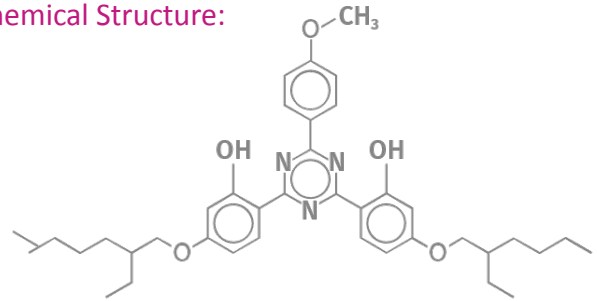
Molecular Weight: 627.801 g/mol

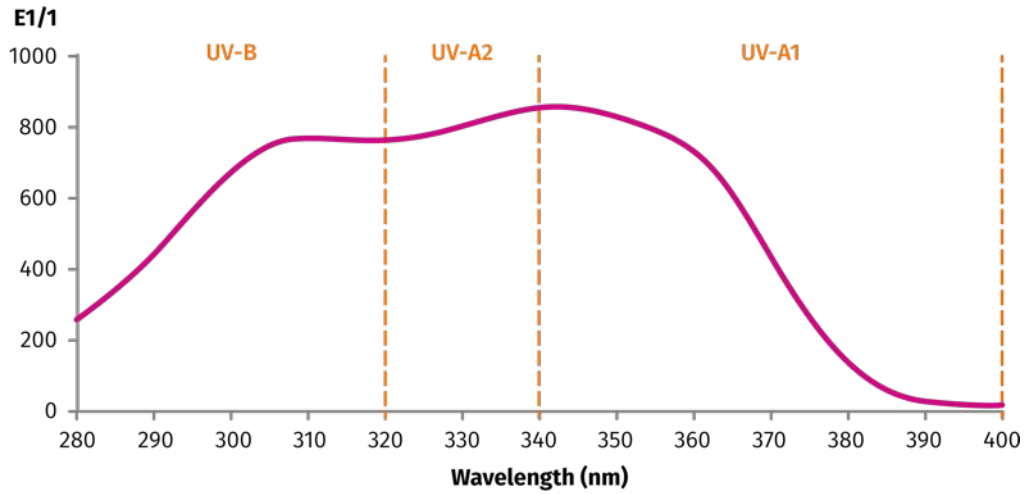
Po/w: > 5.7

Color: Pale yellow

Texture: Powder

Chemical Structure:





Studies required to support GRASE determination for BEMT[1,2,3]

Chemistry
- ✔ Manufacturing and Quality Information
- ✔ USP Monograph

Human Clinical Studies
- ✔ Human absorption studies/maximum usage trials (MUsT)
  - ✔ Pilot
  - ✔ Pivotal (in progress)
- ✔ Dermal irritation/CIT, sensitization and phototoxicity

Nonclinical Studies
- ✔ In vitro permeation tests (IVPT)
- ▪ Systemic carcinogenicity - TBD
- ✔ Toxicokinetics (ADME)

Effectiveness data
- ✔ SPF Studies (two @ ≤ 6% + combinations of monograph UV filters)

Other
- Human Safety Data to Establish Adverse Event (AE) Profile
  - ✔ Available documented cases
  - ✔ Human study or medical literature AE data

[1] As agreed with FDA on 6/2019 and per FDA 11/13/2014, Proposed Sunscreen Order (PSO).

Note: All other required studies previously submitted under TEA (FDA Docket 2005-N-0453A)

[2]FDA (2016). Nonprescription Sunscreen Drug Products Safety and Effectiveness Data: Guidance for Industry

[3]FDA (2019) Maximal usage trial (MUsT) for topical active ingredients being considered for inclusion in an OTC monograph

BEMT Pivotal MUsT Study Recently Completed

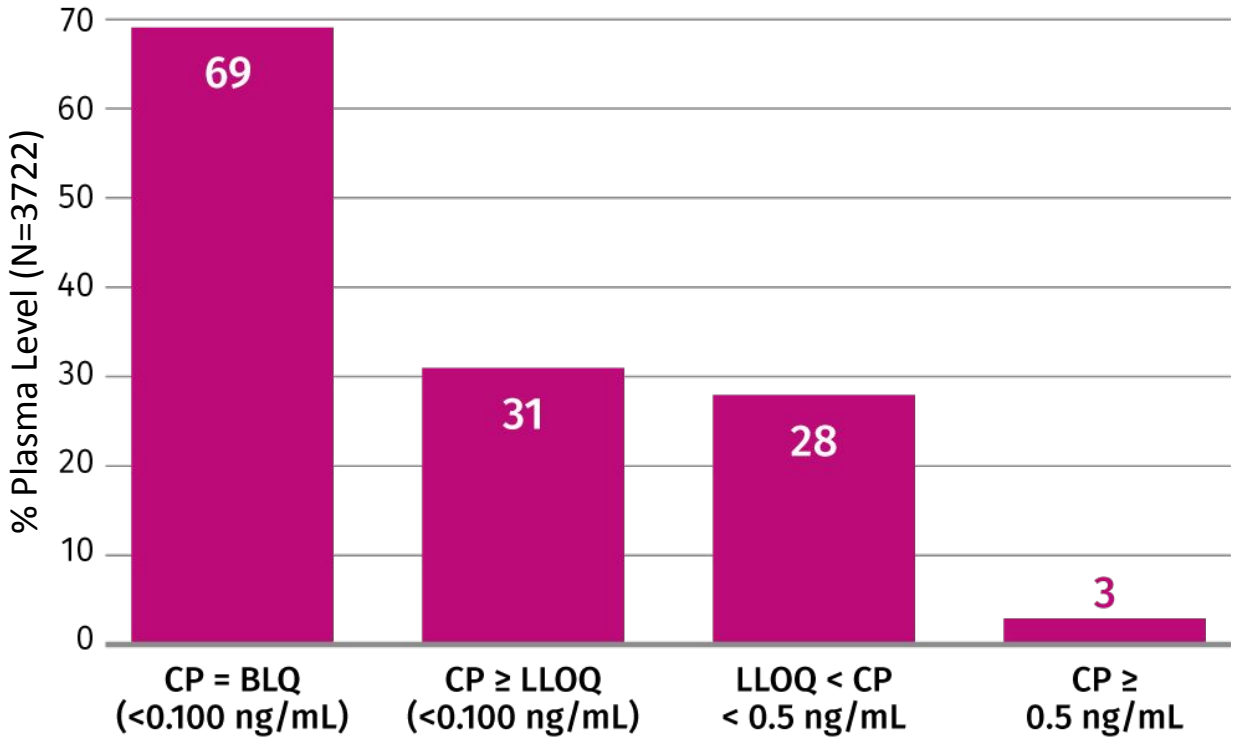
- Open-label, randomized, 3-arm, 162 subject, 4-day pivotal Phase 3 PK clinical trial
- PK and Systemic absorption of BEMT was assessed with 3 market image sunscreen formulations containing 6% BEMT in oil + 10% ethanol permeation enhancer, Oil-Water and Water-Oil excipient phases
- Daily applications represented maximal-use conditions in healthy adult participants (≥ 18 yrs.)
- Subjects received 4 topical applications/day: on the morning of Days 1 through 4, between 07:00 and 10:00 hours followed by 3 more applications each day at 2, 4, and 6 hours after the first application, resulting in study drug application at 0, 2, 4, 6, 24, 26, 28, 30, 48, 50, 52, 54, 72, 74, 76, and 78 hours relative to the first application (16 applications total)
- For each "dose," approximately 2 mg of a sunscreen formulation (about 0.12 mg BEMT) per 1 cm^2 of body surface area was applied to at least 75% of the body surface area (105g sunscreen/d for an average 60kg person!)
- 23 blood samples per subject were collected at pre-specified times through 96 hours after the first application
- A validated lower limit of quantification (LLOQ) threshold of 0.100 ng/mL was used to improve the study's ability to determine to what extent, if any, systemic exposure to BEMT exceeds 0.5 ng/mL
- Plasma concentrations below the lower limit of quantitation (BLQ) were set to 0.050 ng/mL (½ LLOQ) and treated as "missing" for PK parameter calculations
- Safety evaluations included adverse event (AE) monitoring, vital sign measurements, and physical examinations (including skin examinations)

Pivotal MUsT Preliminary Results

Number of Analyzed Plasma BEMT Samples, by Treatment

Treatment		T2	T3	T4
N		55	53	54
Number of Samples	Total	1263 (100.0)	1218 (100.0)	1241 (100.0)
	Cp = BLQ	906 (71.7)	790 (64.9)	857 (69.1)
	Cp ≥ LLOQ < 0.1 ng/mL	357 (28.3)	428 (35.1)	384 (30.9)
	LLOQ < Cp < 0.5 ng/mL	325 (25.7)	389 (31.9)	342 (27.6)
	Cp ≥ 0.5 ng/mL	32 (2.5)	39 (3.2)	42 (3.4)

Cp: plasma concentration
Maximum steady-state concentration = 0.5 ng/mL
BLQ: Below the lower limit of quantitation (ie <0.100 ng/mL);
LLOQ: lower limit of quantitation (ie 0.100 ng/mL) N: Number of subjects



BEMT Study Findings and Conclusions

- All FDA required clinical pharmacokinetic (PK), human dermal safety, nonclinical and efficacy studies for BEMT have been completed.
- The *preliminary* analysis of results from pivotal MUsT gave 3722 plasma samples from 162 subjects indicate:
  - 70% of samples were below 0.1 ng BEMT/mL plasma (BLQ)
  - 97% of samples did not exceed FDA's threshold of 0.5ng/mL
- Adverse events were moderate to mild, and plasma did not show evidence of BEMT accumulation or steady-state BEMT concentrations above FDA's target threshold of 0.5 ng/mL plasma
- The results of these studies indicate that maximal topical applications of 6% BEMT are safe and do not contribute to meaningful systemic exposure.
- Results appear to be supportive of an FDA GRASE Determination

Summary of BEMT's journey towards acceptance under the monograph

2002

- FDA creates time and extent application (TEA) regulatory process for accepting new foreign actives on OTC monographs

2005

- Bemotrizinol TEA submitted to FDA
- FDA determines that BEMT is eligible for review

2006

- Additional data submitted to FDA by Sponsor to support BEMT TEA data requirements

2014

- Sunscreen Innovation Act (SIA) introduces new process for determining GRASE of TEA ingredients
- Nonprescription Drugs Advisory Committee (NDAC) advises FDA re: scope of safety testing that should be conducted to support GRASE determinations for active ingredients in OTC sunscreens
- FDA issues a Proposed Sunscreen Order (PSO) for BEMT indicating it is eligible to be considered for inclusion on the OTC sunscreen monograph pending the submission of additional data needed to support a GRASE determination

2016

- FDA amends TEA process review timelines per SIA mandates
- FDA issues guidance on sunscreen safety and effectiveness data, identifying the data needed to support long-term use of sunscreen actives and support FDA GRASE determinations
- FDA issues guidance on the format and content of information submitted by a sponsor in support of a TEA/SIA request
- No further activity on BEMT TEA by Sponsor

2019

- FDA issues final guidance for conducting maximum usage trials (MUsT) for assessing the dermal absorption of topical sunscreen active ingredients
- **DSM meets with FDA** to indicate that it is an Interested Party to the OTC listing of BEMT (6%) and obtains feedback re: approach for addressing the data gaps that will support FDA's amending its initial determination that BEMT has not been shown to be GRASE

2019 – Current

- FDA advice / recommendations re: remaining studies to be completed obtained
- New BEMT USP monograph drafted
- FDA clinical, nonclinical and SPF studies completed and will be submitted to FDA in Q2/'23
- GRASE petition expected to be filed in Q3'23 following FDA feedback
- Precedent setting - NDAC meeting likely required
- Final GRASE determination expected Q1-Q2 '24

BEMT: Bemotrizinol
TEA: time and extent application
SIA: Sunscreen Innovation Act

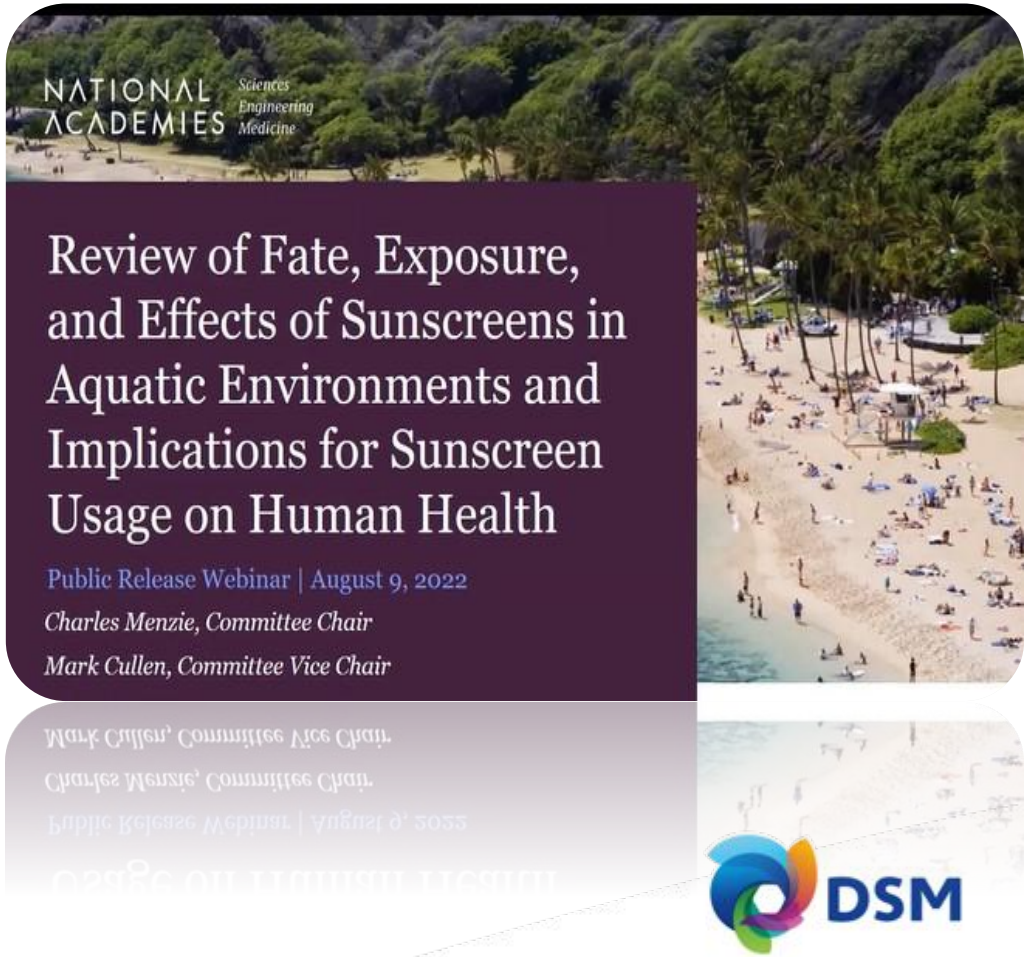
NDAC: Nonprescription Drugs Advisory Committee
GRASE: Generally recognized as safe and effective
MUsT: maximum usage trials

updated 4/10/23

Thank you!

US National Academy of Sciences

- **Reinforces the public health benefits** associated with the use of broad-spectrum sunscreens and the importance of formulation flexibility to drive consumer use
- Confirms PCPC's and DSM's long-held position that:
  - There is currently **insufficient** relevant and reliable **scientific data** to conduct realistic ERAs (ecological risk assessment),
  - There is **not enough scientific data to support sunscreen ingredient bans** and
  - **Policymakers, regulators and legislators should not make any decisions** that impact consumers' access to FDA-approved sunscreen UV filters until the scientific community reaches an informed consensus



A more modern UV filter - PARSOL® SHIELD (Bemotrizinol or BEMT)

Testing demonstrates that it is eco-friendly: With regards to Persistence, Bioaccumulation and Toxicity (PBT) measures[1], BEMT has a Favorable Eco-Profile

No adverse effects were observed in 5 other aquatic eco-tox concerns:

Short term fish / Acute

Short term aquatic invertebrates / Acute

Long term aquatic invertebrates / Chronic

Algae

Aquatic Microorganisms

US only has **9 ingredients approved** - other regions have **more than 30**

ANTICIPATED US FDA GRASE DETERMINATION

2024

USA

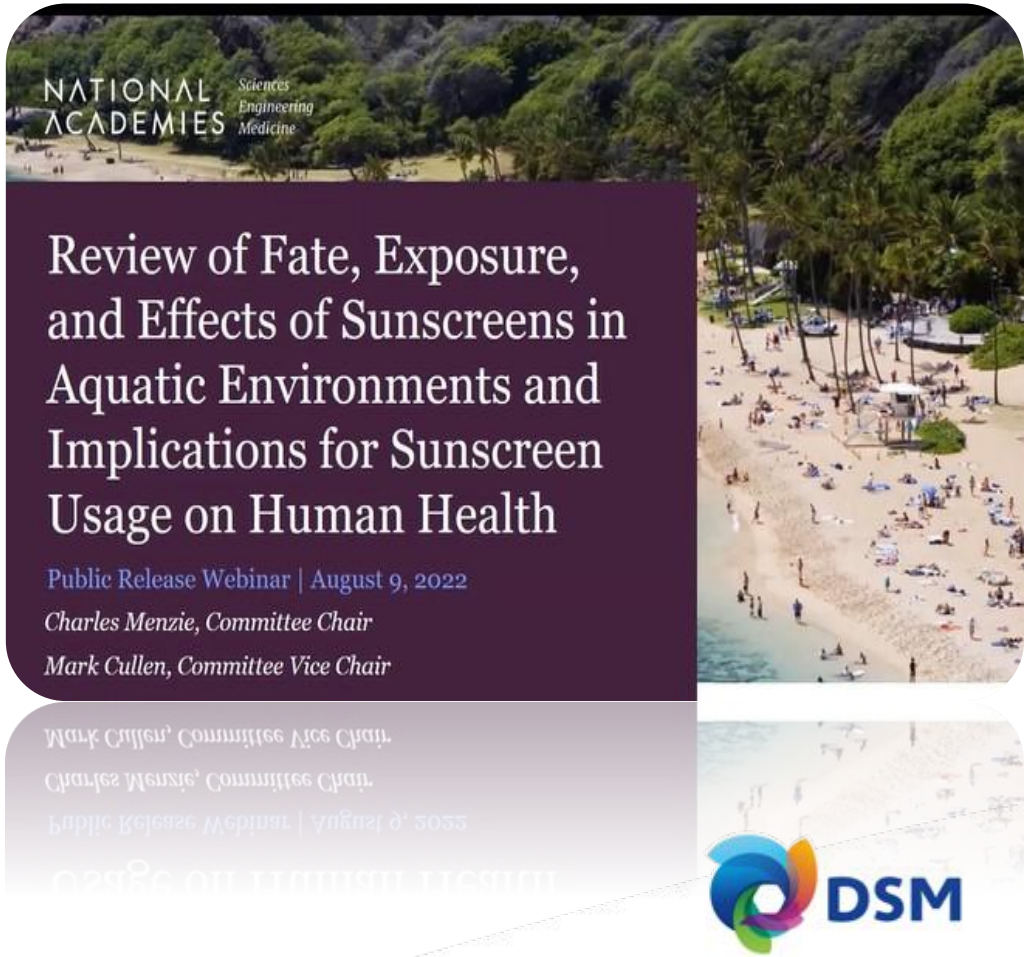
1. EU Reach* PBT Regulation

BRIGHT SCIENCE. BRIGHTER LIVING.™

US National Academy of Sciences

On 9 Aug 2022 released a report entitled: **Review of Fate, Exposure, and Effects of Sunscreens in Aquatic Environments and Implications for Sunscreen Usage and Human Health**

- Study was **mandated by Congress** under the direction of the US Environmental Protection Agency (EPA) due to concerns raised about the **potential toxicity of sunscreens** to a variety of **marine and freshwater aquatic organisms**, particularly corals and **concerns that people will use less sunscreen** rather than substituting sunscreens with UV filters that are considered environmentally safe
- Bottom line: recommends that **EPA conduct an ecological risk assessment of UV filters** to characterize the **possible risks to aquatic ecosystems** and the species that live in them and describes the **role of sunscreens in preventing skin cancer** and what is known about how human health could be affected by potential changes in usage

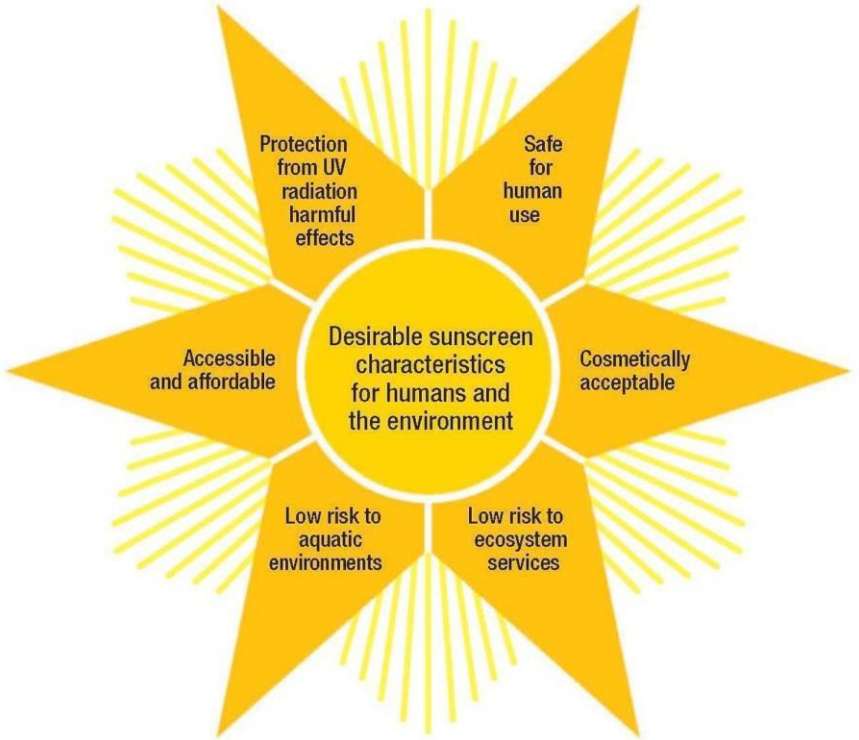


US National Academy of Sciences

Recommendation 1: The U.S. Environmental Protection Agency should conduct an ecological risk assessment (ERA) for all currently marketed UV filters and any new ones that become available

Recommendation 2: "Call For Data" The U.S. Environmental Protection Agency, partner agencies (e.g., Centers for Disease Control and Prevention, U.S. Department of the Interior, U.S. Food and Drug Administration, National Institutes of Health, National Oceanic and Atmospheric Administration, National Science Foundation), and sunscreen formulators and UV filter manufacturers should conduct, fund or support, and share research and data on sources, fate processes, environmental concentrations, bioaccumulation studies, modes of action, and ecological and toxicity testing for UV filters alone and as part of sunscreen formulations.

Additionally, epidemiological risk modeling and behavioral studies related to sunscreen usage should be conducted to better understand human health outcomes from changing availability and usage



FDA new Proposed Order for sunscreens
What's new and what's not?

Active ingredients

GRASE: zinc oxide and titanium dioxide

NOT GRASE:

- aminobenzoic acid and trolamine salicylate
- **cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzone, oxybenzone, and avobenzone**
  - inadequate data to support a safety finding
  - one year renewable "deferrals" possible if progress made to support their safety
  - clinical and non-clinical safety studies required

Maximum SPF

Maximum labeled SPF of 60+ and permits the marketing of products formulated with SPF value up to 80

Broad spectrum requirements

To address the growing evidence of significant harms associated with UVA exposure, the proposed order states that all sunscreens with SPF values of 15 and above should satisfy broad spectrum requirements

New requirement that broad spectrum products meet a UVA I / UV ratio of 0.7 or higher

Dosage Forms

Oils, lotions, creams, gels, butters, pastes, ointments, sticks, sprays, or powders are allowed

GRASE status for spray sunscreens, subject to testing and labeling requirements, and additional data are needed to determine that powders are GRASE

Nano - Not proposing to categorically classify sunscreen products manufactured using nanotechnology (or containing nanomaterials) as GRASE or not GRASE, but invites public comments

DSM