FDA Regulation of Sunscreens

FDA U.S. FOOD & DRUG ADMINISTRATION

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Drug or Cosmetic??

Drug FD&C Act, Section 201(g)(1)*

Articles intended for disease:

- Diagnosis
- Cure
- Mitigation
- Treatment
- Prevention
- **Intended to Affect the Structure or Any Function of the Body of Humans or Animals**

Cosmetic FD&C Act, Section 201(i)*

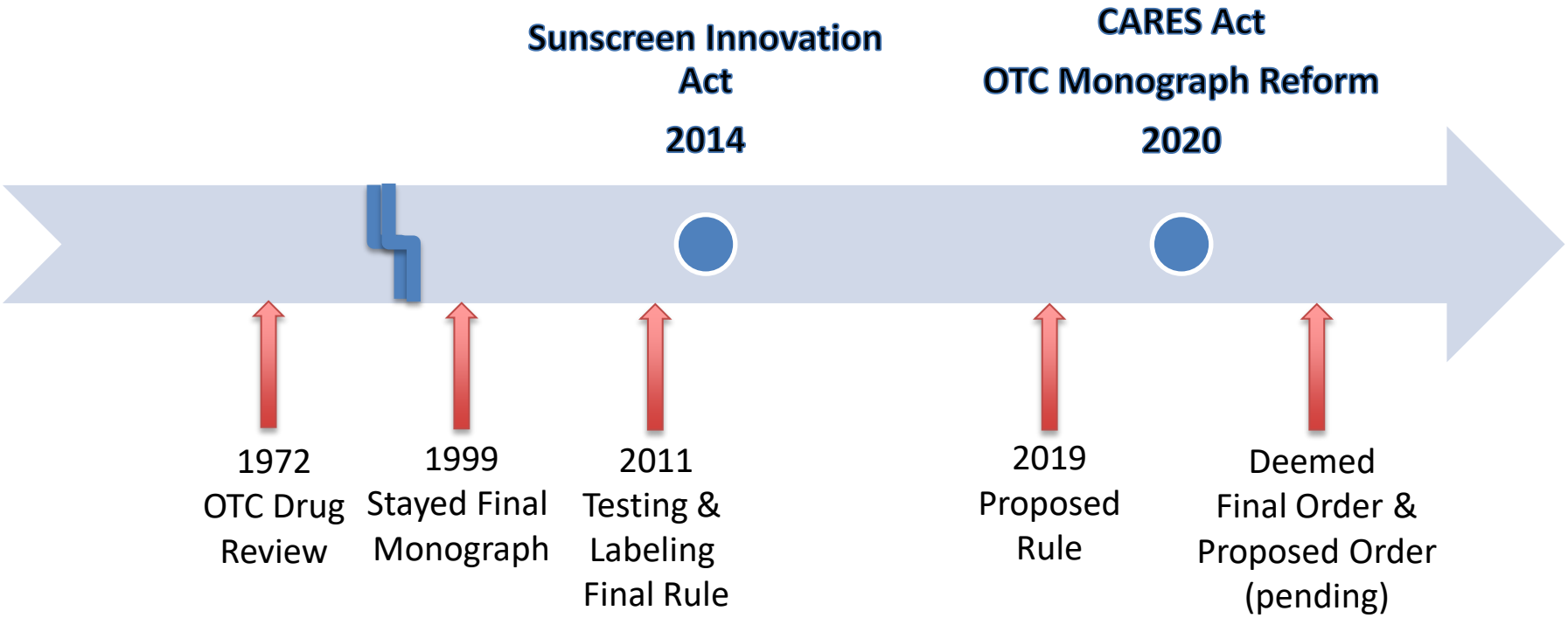
Articles intended for:

- Cleansing
- Beautifying
- Promoting Attractiveness
- Altering Appearance

Products meeting both definitions must meet requirements for BOTH drugs and cosmetics

*Most relevant provisions

Statutory Provisions Impacting Sunscreens: Abbreviated Timeline



Regulatory Pathway for Marketing Nonprescription Drugs

- New Drug Application/Abbreviated New Drug (NDA/ANDA)
  - Application submitted to FDA for premarket approval
- OTC Drug Review (OTC Monograph)
  - Marketed without an approved drug application if the drug complies with statutory and regulatory requirements
  - Began in 1972 to evaluate the safety and effectiveness of OTC drug products marketed in the United States before May 11, 1972
  - Established conditions under which an OTC drug is generally recognized as safe and effective (GRASE) in the form of OTC monographs

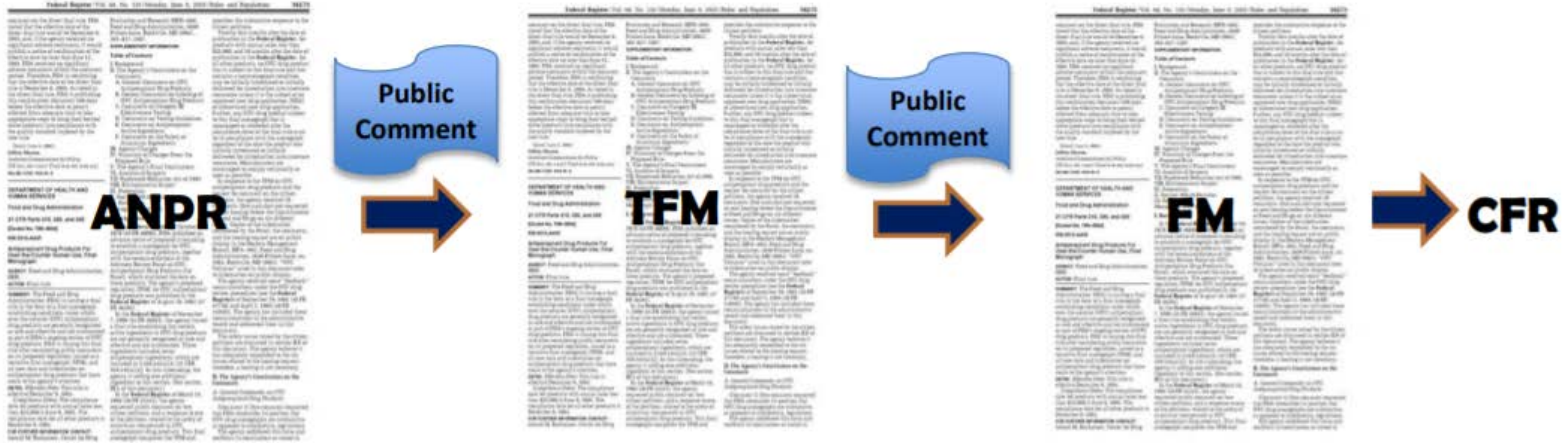
OTC Monograph

- A “rule book” for each therapeutic category establishing conditions, such as active ingredients, uses (indications), doses, route of administration, labeling, and testing under which an OTC drug is generally recognized as safe and effective (GRASE)
- OTC monographs cover ~ 800 active ingredients for over 1,400 different uses, authorizing over 100,000 drugs

OTC Monograph Rulemaking Process

Under OTC Drug Review Prior to OTC Monograph Reform

- Three-phase public notice-and-comment rulemaking process
  - Phase 1: Advance Notice of Proposed Rulemaking (ANPR)
  - Phase 2: Tentative Final Monograph (TFM)
  - Phase 3: Final Monograph → Code of Federal Regulations (CFR)



Generally Recognized as Safe and Effective

- Standard for OTC monograph drugs is GRASE [FD&C 201(p)]
  - GRASE conditions for an OTC drug relate to manufacture, labeling, human safety and efficacy, and benefit of the drug in humans versus risk in humans
  - If a drug meets GRASE conditions, FDA is required to find it GRASE
- Active ingredients and other conditions evaluated in the OTC Drug Review were categorized in an ANPR and TFM as
  - Category I: GRASE
  - Category II: not GRASE
  - Category III: insufficient data available to determine if GRASE
  - In a final monograph regulation, conditions were either ‘in’ or ‘out’ of the monograph

Sunscreen Monograph Final Rules

- 1999 Stayed Final Monograph
  - Found 16 active ingredients GRASE for use in sunscreens
  - Stayed to address UVA and broad spectrum
- 2011 Labeling and Effectiveness Testing Rule
  - Specified labeling and testing methods for SPF, broad spectrum, and water resistance claims
  - Included other labeling requirements such as directions for use and warnings

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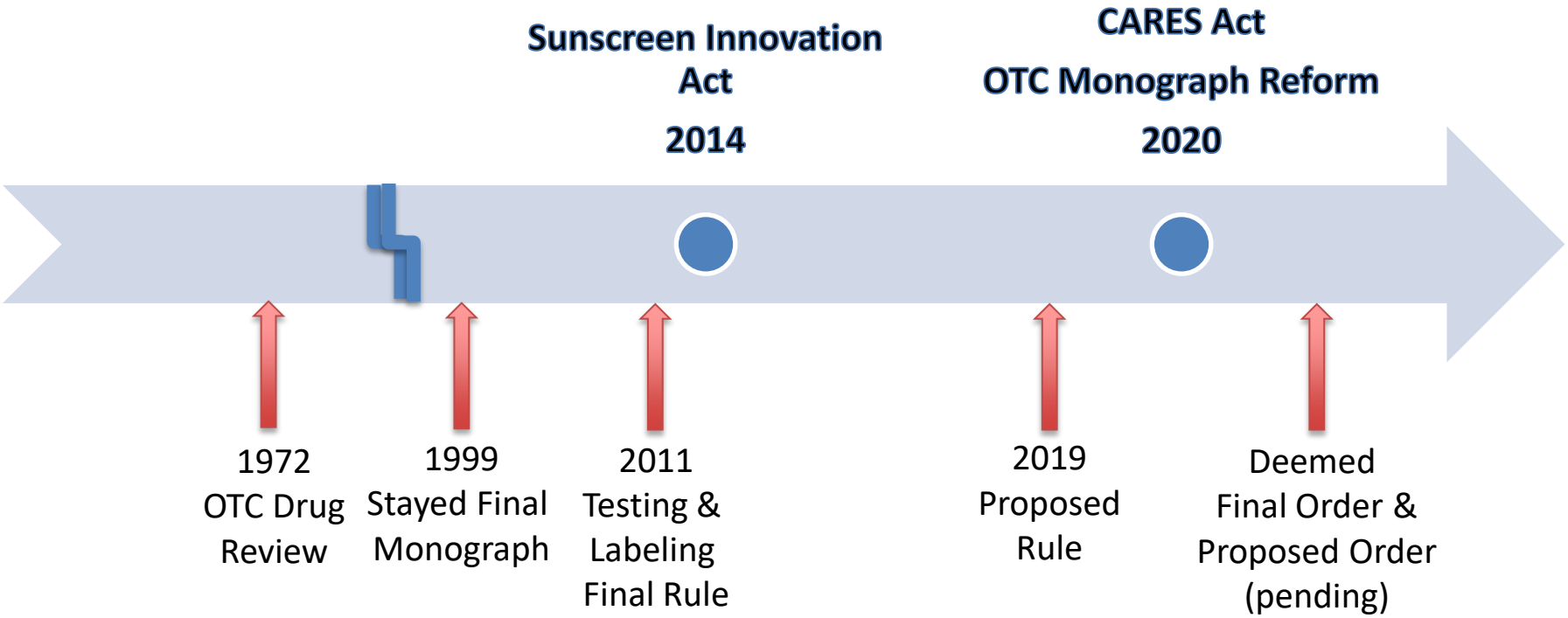


Sunscreen Innovation Act

P.L. 113-195

- Enacted November 26, 2014 with the following key provisions for sunscreens
  - Established a new administrative order process for review of active ingredients not already included in the monograph
  - Required publication of guidances
  - Required FDA to finalize the sunscreen monograph

- If the sunscreen monograph regulations do not include maximum SPF and dosage forms, FDA must report to Congress on the reasons why not and include a plan to address in rulemaking

What the SIA Did NOT Do

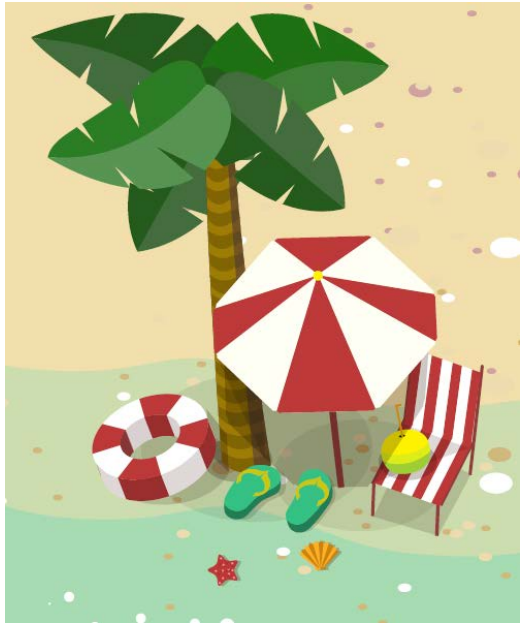
- Guarantee new sunscreen ingredients would be on the market soon after enactment of SIA
- Change Generally Recognized as Safe and Effective (GRASE) standards
- Change FDA's scientific review
- Change rulemaking process for monographs or the overall monograph system
- Provide additional FDA resources for monograph, time and extent application (TEA), or SIA review

FDA Proposed Rule: Sunscreens

- Proposed rule issued February 21, 2019
  - Because the rule is proposed not final, it did not go into effect
  - Docket No. FDA-1978-N-0018: more than 15,000 comments received
- Proposed conditions under which OTC sunscreen monograph products are generally recognized as safe and effective
- Part of ongoing effort to ensure sunscreens are safe and effective for regular, life-long use
- FDA continuing to work with industry and stakeholders to make sure consumers have access to safe and effective sunscreens

Key Elements of the Proposed Rule

- **Active Ingredients**
- Dosage Forms
- **Sun Protection Factor (SPF) and Broad Spectrum**
- Sunscreen-Insect Repellant Combinations
- **Labeling**
- Final Formulation Testing and Record Keeping



Proposed GRASE Status for Sunscreen Active Ingredients

GRASE* for use in sunscreens	Not GRASE** for use in sunscreens	***Insufficient data for use in sunscreens
Zinc oxide and titanium dioxide	Aminobenzoic acid (PABA) and trolamine salicylate	Cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzone, oxybenzone, avobenzone

*GRASE= Generally Recognized as Safe and Effective **These ingredients are not currently marketed. ***For those ingredients in the "insufficient data" category, FDA proposes that it needs additional data to determine that sunscreens with these ingredients would be GRASE.

- Request for additional data does not mean FDA has concluded that 12 ingredients are unsafe
- Manufacturers requested additional time to provide data for 8 ingredients
- **Consumers should continue to use broad spectrum sunscreens with SPF 15 or higher in conjunction with other sun protective measures to reduce the risk of sunburn, skin cancer, and early skin aging caused by the sun**

Sunscreen Safety Data Framework

- Rationale
  - Changing patterns of use
    - Used as preventive drugs, over a lifetime period of exposure, in a population spanning all age groups
  - Evolving scientific knowledge
    - Different formulations with greater SPF and broad-spectrum protection
    - Ingredients may be absorbed through the skin→

      Need to consider systemic effects (carcinogenicity, endocrine, reproductive)
- FDA's proposed safety framework supported by an independent Advisory Committee as a good starting point (September 2014)

Safety Data Requested for Sunscreens

Clinical Studies	Nonclinical Studies
Human Irritation and Sensitization study whether the ingredient causes skin irritation or an allergic reaction	**Dermal Carcinogenicity** study the long-term effect of dermal administration of the ingredient to see if it causes tumors of the skin or the rest of the body
Human Photosafety study whether the ingredient causes skin irritation or an allergic reaction when exposed to light	**Systemic Carcinogenicity** study the long-term effect of the ingredient in the body to see if it causes tumors
Human Absorption/Maximal Usage Trial (MUsT) evaluate whether and the extent to which an ingredient is absorbed into the body	**Developmental and Reproductive Toxicity (DART)** study developmental and reproductive risks, which can include endocrine effects
Pediatric Considerations additional studies may be needed to ensure that a sunscreen active ingredient would be GRASE for use in pediatric populations if results from other studies suggest a narrow margin of safety	**Toxicokinetic** study whether and to what extent the ingredient is absorbed in animals to help calculate a safety margin for human use

MUsT Pilot Study: Part I

JAMA Network

QUESTION What is the maximum plasma concentration of active ingredients of various types of sunscreen formulations under maximal use conditions?

CONCLUSION Application of 4 commercially available sunscreens resulted in plasma concentrations exceeding the FDA-established threshold for potentially waiving some nonclinical toxicology studies for sunscreens.

POPULATION

12 Men
12 Women

Healthy adults aged 18 to 60 years with a body mass index of 18.5-29.9 and no allergies or sensitivities to components of the sunscreen formulations

Mean age: 35.5 years

LOCATIONS

1
Pharmacology unit

INTERVENTION

PRIMARY OUTCOME

Systemic absorption of avobenzone measured as geometric mean maximum plasma concentration

FINDINGS

Geometric mean plasma concentration of avobenzone, ng/mL (coefficient of variation, %)

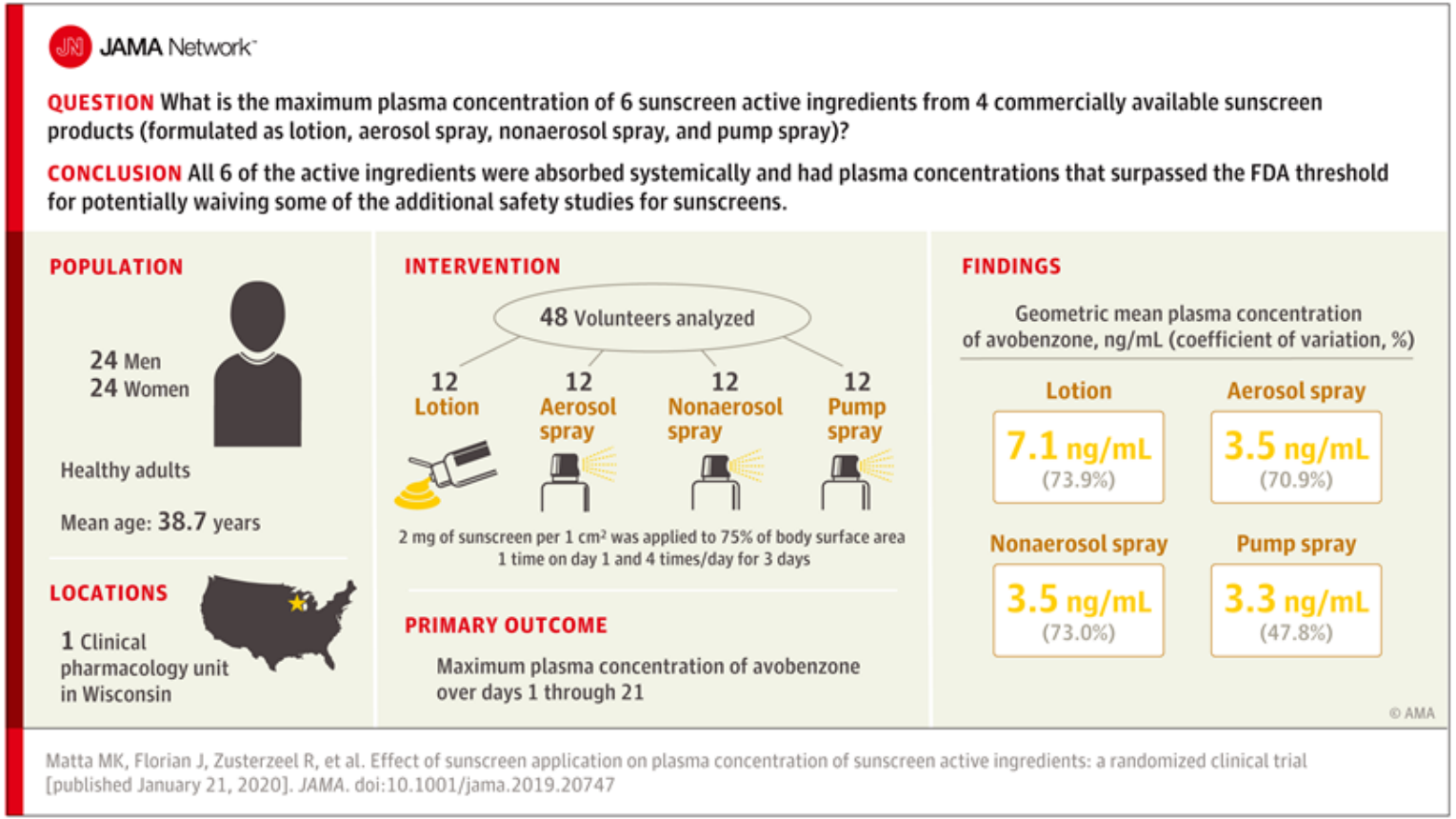
Spray 1	Spray 2
4.0 ng/mL (60.9%)	3.4 ng/mL (77.3%)

Lotion	Cream
4.3 ng/mL (46.1%)	1.8 ng/mL (32.1%)

The systemic absorption of sunscreen ingredients supports the need for further studies to determine the clinical significance of these findings

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 [published May 6, 2019]. *JAMA*. doi:10.1001/jama.2019.5586

MUsT Pilot Study: Part II



Conclusions from the MUsT Pilots

- All active ingredients tested were systemically absorbed
  - Study I: avobenzone, oxybenzone, octocrylene, ecamsule
  - Study II: avobenzone, oxybenzone, octocrylene, homosalate, octisalate, and octinoxate
- Absorption occurred even after a single use
- Sunscreen active ingredients can remain in the body for an extended period (systemic exposure and skin)
- Pivotal MUsT data and information on relevant metabolites needed to determine full absorption profile
- Absorption does not mean the ingredients are unsafe. Nonclinical studies are needed to determine the clinical significance of systemic exposure

New Proposed Sun Protection Factor (SPF) Requirements

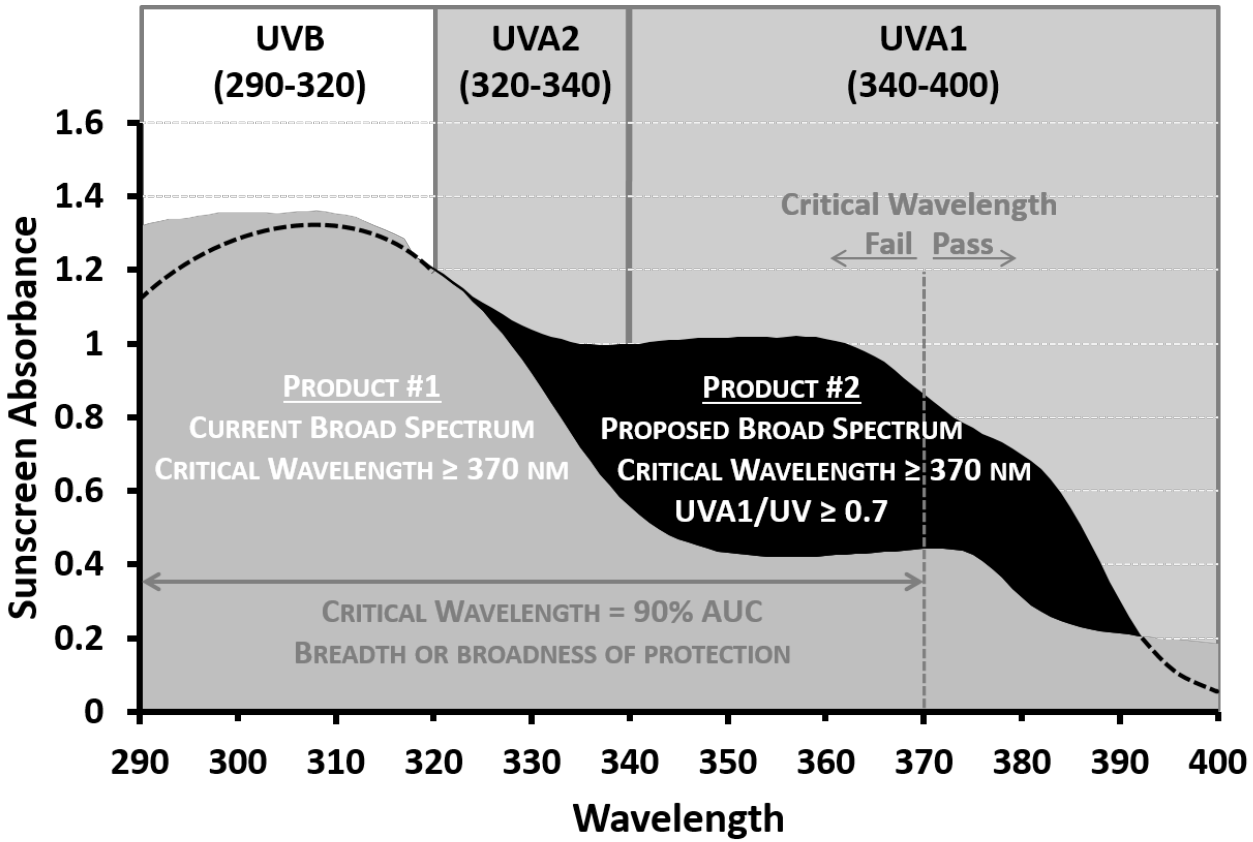
- Raise maximum proposed labeled SPF from SPF 50+ to SPF 60+
- Permit marketing of sunscreen products formulated up to SPF 80
- SPF labeling indicates lowest number in a range of tested results

Determined SPF	Labeled SPF	Determined SPF	Labeled SPF
2-14	Determined SPF	30-39	30
15-19	15	40-49	40
20-24	20	50-59	50
25-29	25	60-80	60+

New Proposed Broad Spectrum Requirements

- Require any sunscreen SPF 15 or higher to be broad spectrum
- Require for all broad spectrum products SPF 15 and above, as SPF increases, broad spectrum protection increases
- Require that broad spectrum products provide adequate protection against UVA
  - UV absorbance critical wavelength of 370 nm (90% AUC)
  - UVA1/UV ratio at least 0.7

Proposed Broad Spectrum Criteria



New Proposed Label Requirements

- Include alphabetical listing of active ingredients on the front panel
- Require sunscreens with an SPF below 15 to include “See Skin Cancer/Skin Aging alert” on the front panel
- Require font and placement changes to ensure SPF, broad spectrum, and water resistance statements stand out

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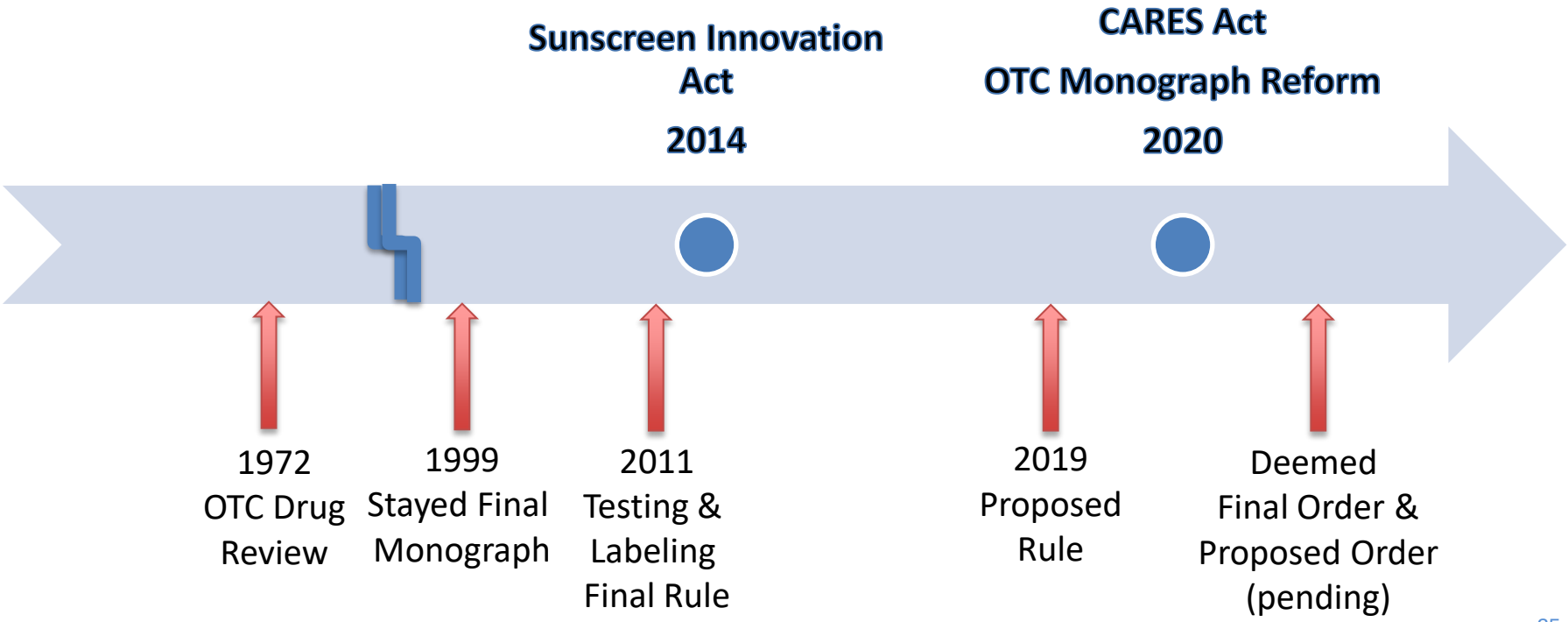


OTC Monograph Reform

- On March 27, 2020, the “Coronavirus Aid, Relief, and Economic Security Act” (CARES Act) was signed into law
- The CARES Act includes an important legislative initiative that reforms and modernizes the way OTC monograph drugs are regulated in the United States
- For simplicity, we refer to the regulatory framework under the CARES Act as OTC Monograph Reform
- The new legal framework is located at section 505G of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355h)

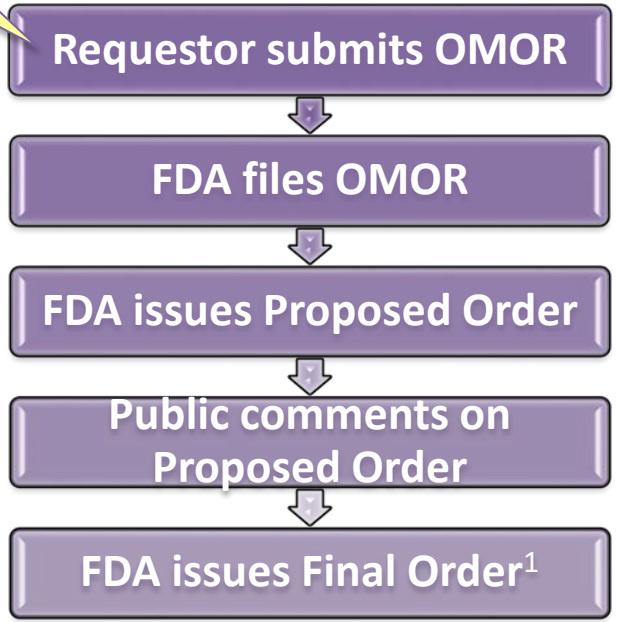
Administrative Order Process

- Replaces the rulemaking process with an administrative order process
- Gives FDA the authority to issue an administrative order that adds, removes or changes GRASE conditions for an OTC drug monograph
- Establishes an expedited process to address safety issues
- Either industry or FDA can initiate the administrative order process

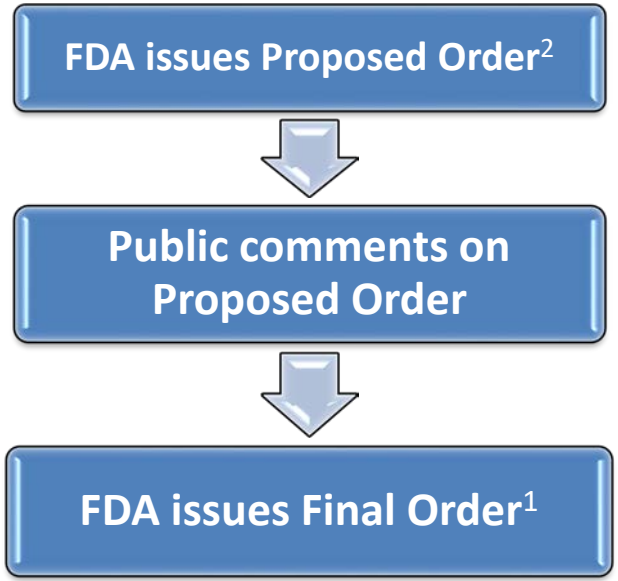
Administrative Order Process

OMOR = OTC Monograph Order Request

Industry-Initiated Order



FDA-Initiated Order



[1] Final orders are final Agency actions subject to dispute resolution, administrative hearings, and judicial review.
[2] Or interim final order under an expedited procedure

Deemed Final Orders (DFOs)

- Established legislatively by CARES Act
- Effective on March 27, 2020
- Establishes current monograph “baseline” for each therapeutic category
- DFO for sunscreens [FD&C Act s. 505G(a)(2)]
  - *the requirements specified in [21 CFR 352], as published on May 21, 1999, . . . except that the applicable requirements governing effectiveness and labeling shall be those specified in [21 CFR 201.327]*

Addresses the Sunscreen Innovation Act (SIA)

- OTC Monograph Reform sunsets the SIA on September 30, 2022
- Requires FDA to issue a proposed order revising the sunscreen deemed final order no later than 18 months after enactment

FDA Actions on Sunscreens After Monograph Reform

- On May 13, 2021, FDA published a Notice of Intent (NOI) to prepare an Environmental Impact Statement (EIS) for a future sunscreen order to comply with the National Environmental Policy Act (NEPA)
  - An EIS is a detailed written statement that analyzes the environmental impacts of a proposed action and any reasonable alternatives
  - NEPA requires federal agencies to assess the environmental effects of their proposed major actions prior to making decisions
    - Mandates a process for reviewing environmental issues
    - Enhances awareness of environmental implications of agency actions
    - Does not mandate a particular result
    - Does not give an agency the ability to take an action outside of its existing statutory authority

Next Steps for Sunscreens

- Post deemed final order
- Issue proposed order revising the deemed final order for sunscreens by September 27, 2021

FDA Resources

- For Questions on
  - OTC Monograph Reform druginfo@fda.hhs.gov
- Resources
  - OTC Monograph Reform in the CARES Act https://www.fda.gov/drugs/over-counter-otc-nonprescription-drugs/over-counter-otc-drug-review-otc-monograph-reform-cares-act
  - Sunscreen 2019 Proposed Rule https://www.federalregister.gov/d/2019-03019
  - Sunscreen Landing Page https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm239463.htm
  - Sunscreen Innovation Act Landing Page https://www.fda.gov/drugs/guidance-compliance-regulatory-information/sunscreen-innovation-act-sia
  - Environmental Impact Statement (EIS) for Certain Sunscreen Drugs https://www.fda.gov/drugs/guidance-compliance-regulatory-information/environmental-impact-statement-eis-certain-sunscreen-drug-products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