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Shielding Our Future: The Need for Innovation in Sunscreen Active Ingredients and Safety Testing in the United States

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ABBREVIATIONS BEMT, bemotrizinol; CARES, Coronavirus Aid Relief and Economic Security; FDA, US Food and Drug Administration; GRASE, Generally Recognized as Safe and Effective; MUST, maximal usage trial; NDA, new drug application; OTC, over-the-counter; SPF, sun protection factor; TEA, Time and Extent Application; UVA, ultraviolet A radiation; UVB, ultraviolet B radiation

KEYWORDS broad spectrum; cosmetic; over-the-counter drug; skin cancer; SPF (sun protection factor); sunscreen

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Effective and safe sunscreens play a crucial role in prevention of skin cancers.[1–3] Compared with adults, children and adolescents typically spend more time outdoors, increasing their exposure to sun and consequently elevating their risk of sunburn and sun-related skin damage. By incorporating sunscreen into a child's routine, along with other sun protection measures like protective clothing and seeking shade, we can help establish lifelong sun-safe habits that will benefit children's skin health well into adulthood.[4] However, its widely known and reported in the news that the United States is lagging behind other regions of the world when it comes to the active ingredients in our sunscreens, especially when it comes to broad spectrum ingredients that offer stable ultraviolet A radiation (UVA) protection.[5–7] Initially governed by a time-consuming rulemaking process, sunscreens have had and continue to face challenges in keeping pace with scientific advancements and emerging safety concerns.

Early commercial sunscreen products produced in the 1930s and 40s were beach products marketed with single digit sun protection factor (SPF) values. These products primarily provided protection from UVB rays that resulted in obvious and painful sunburns. Coppertone's memorable advertisements featuring a dog playfully exposing a child's tan lines featuring headlines that read "Tan, don't burn" or "Get the fastest tan" appeared in the 1950s. The regulatory status of sunscreens underwent a significant shift in the 1970s when the US Food and Drug Administration (FDA) reclassified sunscreens from cosmetics to nonprescription drugs, more commonly referred to as over-the-counter (OTC) drugs. The reclassification brought sunscreens under more stringent regulatory oversight, requiring manufacturers to comply with specific OTC drug regulations that included labeling standards and efficacy testing requirements. As part of this transition, the FDA was to list and set standards for permitted active ingredients. This change reflected the evolving understanding of sunscreen's importance in public health, moving beyond mere cosmetic purposes to a recognized role in cancer prevention.

Around the 1990s research demonstrated that UVA wavelengths (315–400 nm) could be effective in inducing melanoma in animal models, shifting attention from solely UVB protection to the need for broad-spectrum sunscreens that protect against both UVA and UVB radiation.[8,9] Continued research into the harmful effects of UVA spurred development of new sunscreen active ingredients like avobenzone that could expand the range of protection.[10] Concurrently, consumer awareness about the potential dangers of UVA radiation led to increased demand for broad-spectrum sunscreens. This prompted manufacturers to reformulate their products in order to offer more comprehensive protection. New UVA filters were first introduced in Europe where sunscreens are considered cosmetics and subject to a less challenging regulatory framework.[11] Avobenzone, approved in 1988, remains the only UVA absorptive molecule listed by the FDA that can be broadly used by the industry. Unfortunately, a major short coming of avobenzone is its lack of photostability, that is, its tendency to degrade when exposed to sunlight.[12] In 2006 ecamsule (also known as Mexoryl SX) was approved, but for use only in specific products through the New Drug Application (NDA) process.[13]

The regulation of sunscreens in the United States has continued to undergo significant changes. The Time and Extent Application (TEA) process was introduced by the FDA in 2002 as a pathway for approving

new OTC sunscreen active ingredients that had been used extensively in other countries. However, the TEA process proved to be slow and ineffective. A 2011 FDA Final Rule for sunscreens introduced new labeling and testing requirements, including a broad-spectrum designation. The Sunscreen Innovation Act in 2014 aimed to expedite the review and approval of new sunscreen ingredients but did not yield measurable success either. In 2019, the FDA proposed major revisions to sunscreen regulations, addressing concerns about the safety of synthetic organic active ingredients (sometimes referred to as chemical filters). Then the Coronavirus Aid, Relief, and Economic Security (CARES) Act of 2020 fundamentally altered the regulatory framework for OTC drugs, replacing the rulemaking process with an administrative order system. This led to the 2021 Deemed Final Order for OTC sunscreen products which essentially maintained the status quo, followed by a concurrent proposed order suggesting further changes, including reclassification of active ingredients based on the need for additional safety data. If you are confused reading this, you can imagine the challenges sunscreen ingredient manufacturers and sunscreen formulators face in trying to anticipate the future when developing new ingredients and products in the United States.

Since the mid-1990s, new drug applications for topical products have included a Maximal Usage Trial (MUST) as part of the clinical pharmacology/bioavailability assessment. Beginning in 2019 the FDA has requested additional safety data, including MUST studies, on 12 active sunscreen ingredients that are currently available in marketed OTC drug products. A MUST is designed to capture the effect of maximal use conditions on absorption into the blood with standard pharmacokinetic assessments.[14] Two inorganic particulate sunscreens, titanium dioxide and zinc oxide, are currently permitted without MUST testing because they do not penetrate the skin to any appreciable amount. For other sunscreen actives this testing involves applying a formulated sunscreen to 75% of the body surface area 4 times a day for 4 days, then measuring blood concentrations of active ingredients.[14,15] The FDA recommends further toxicology testing for active ingredients that exceed a plasma of 0.5 ng/mL, but this threshold is arbitrary as the health significance of this level is unknown. Sunscreen active ingredients are often used in combinations to provided broad-spectrum protection, in a variety of forms (sprays, sticks, lotions, oils), and marketed to specific populations such as babies and children which adds difficulty in design, interpretation, and extrapolation of data from these safety studies.

There is no question that MUST testing is crucial as sunscreens and sunscreen usage patterns have changed dramatically. People are applying sunscreens with much higher SPF values (combinations of actives ingredients used in greater concentrations) and with much greater frequency. The time expense and time to conduct MUST and prepare other extensive toxicological data assessments that could potentially require animal testing—which would create an immense barrier to use in the European Union where animal testing of cosmetics and cosmetic ingredients is banned—often stands as an impediment to producers of ingredients intended to be widely used in affordably priced products. To date, it seems several firms pursuing approval of UVA protective ingredients started under the TEA process in the 2000s have mostly abandoned efforts. Only approval of bemotrizinol (BEMT) is still being actively pursued, with nearly two decades of effort and expense.[6,16]

Bemotrizinol protects against both UVB and UVA rays, with absorption peaks at 310 nm and 340 nm, respectively providing more comprehensive protection.[10] BEMT, if approved, would be one of the most thoroughly tested sunscreen active ingredient in the United States. Like other modern sunscreen active ingredients used in other regions, BEMT was designed for improved photostability and boasts a molecular weight of 627.81 g/mol which exceeds the 500 Dalton rule and indicates low potential for skin penetration.[11,17]

As you can tell, the issues around sunscreens ingredients in the United States are complex. From the perspective of a cosmetic formulator, there is an urgent need for better sunscreen active ingredients in the United States to address the growing demand for safe and effective broad-spectrum protection. But the current regulatory landscape has left formulators with limited options. Only zinc oxide and titanium dioxide are currently considered Generally Recognized as Safe and Effective (GRASE) by the FDA. While these inorganic ingredients offer good protection, only zinc oxide provides some UVA coverage and both result in products with less-than-ideal aesthetics, such as white cast and heavy textures which discourage consistent use by consumers, especially those with darker skin tones. The lack of approved active ingredients that provide robust UVA protection hampers our ability to create elegant, high-SPF formulations that offer comprehensive broad-spectrum defense.

There is also a need for new methodologies in the rigorous evaluation of sunscreen active ingredients to ensure optimal public health protection while keeping pace with scientific advancements in photoprotection. It is critically important that we as scientists and consumers engage with legislators to advocate for expedited review of new sunscreen actives and determine how we can incentivize sunscreen innovation. By vetting and approving innovative sunscreen ingredients, we could create more diverse, cosmetically appealing, and highly protective products that encourage regular use across all demographics that ultimately contribute to better public health outcomes in sun protection and skin cancer prevention.

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