FDA Issues Recommendations for Sunscreen Safety Studies

Recent draft guidance from the US Food and Drug Administration (FDA) outlines data the agency needs to determine whether a proposed active ingredient for over-the-counter (OTC) sunscreen products is "generally recognised as safe and effective" (GRASE), and not misbranded, when used under certain conditions. Active ingredients deemed GRASE may be added by the FDA to the OTC sunscreen drug monograph, becoming eligible for wide use in non-prescription sunscreen products.

Released in November 2015, *Over-the-Counter Sunscreens: Safety and Effectiveness Data* represents partial implementation of the 2014 Sunscreen Innovation Act (SIA), which established new procedures and review timelines for FDA GRASE determinations. The processes and timelines set forth in the SIA are intended to facilitate the evaluation of new sunscreen active ingredients, speeding their addition to the US market. To date, there are just 16 active ingredients listed in the sunscreen monograph; sunscreen products marketed in the US without a new drug application (NDA) may contain only those 16 active ingredients. The list has not changed since 1999.

Marketing Sunscreens in the US

All sunscreens marketed in the US are regulated by the FDA as OTC drugs; they reach the US market by one of two processes: 1) an approved NDA or abbreviated NDA (ANDA), or 2) the OTC drug monograph process. Most sunscreen products are sold under the monograph process.

As noted in the draft guidance, the monograph process evaluates individual active ingredients, not specific products or formulations. The FDA has likened OTC drug monographs to "rule books" for formulating OTC products. A monograph specifies the "conditions of use" under which a category of products (e.g., sunscreens) is considered GRASE and not misbranded. If the FDA adds an active ingredient to the OTC sunscreen monograph, it can be used in any future sunscreen, regardless of the product's vehicle or formulation.

In contrast, the NDA process focuses on individual product formulations. For NDA approval, a sponsor must demonstrate that a specific, final-formulation sunscreen product is safe and effective for its specified use, based on data presented in the application. The FDA reviews

and approves NDAs; following initial approval, changes to approved specifications (e.g., a product's formulation or manufacturing process) typically require additional FDA review and approval.

Currently, there are four sunscreen products marketed in the US under approved NDAs: Anthelios 20, Anthelios 40, and Anthelios SX, by La Roche-Posay, and Capital Soleil, by Vichy Laboratories. (L'Oréal is the parent company of both La Roche-Posay and Vichy.) Each of the four contains ecamsule, a non-monograph sunscreen active ingredient, in combination with other sunscreen active ingredients that are subject to the OTC sunscreen monograph.

The New Draft Guidance

As detailed in *Over-the-Counter Sunscreens: Safety and Effectiveness Data*, for GRASE determinations of sunscreen active ingredients, the FDA recommends that sponsors perform both clinical and non-clinical safety tests:

Dermal safety studies typically include two sets, both performed in humans: studies without specific exposure to light, and photosafety studies assessing skin response to ultraviolet exposure. Skin safety studies usually consist of irritation patch testing, sensitisation patch testing, phototoxicity testing, and photoallergenicity testing. Sensitisation studies and photoallergenicity studies are designed to detect immunologically mediated reactions. Irritation studies assess whether an ingredient causes direct skin toxicity, and phototoxicity studies are designed to detect acute light-induced tissue responses to photoreactive chemicals.

When making GRASE determinations, the FDA "generally" relies on data from human dermal safety studies in conjunction with data on post-marketing adverse events (AEs), according to the guidance. At times, however, AE data are sufficiently rigorous to cancel the need for one or more of the skin safety studies.

Absorption studies in humans evaluate whether a proposed active ingredient penetrates the skin and results in systemic exposure. As noted in the guidance, systemic exposure could cause AEs; it could also reduce a sunscreen's efficacy. For GRASE determinations, the FDA recommends that sponsors provide data from a maximal usage trial (MUsT) designed to evaluate how the maximal use of an active ingredient affects its blood absorption. Such studies rely on standard pharmacokinetic assessments, such as C_{max}, T_{max}, AUC, half-life, clearance, and volume of distribution. A MUsT should assess at least four formulations in which the proposed sunscreen active ingredient is the only active ingredient. Sponsors should prepare the formulations using vehicle/formulation systems appropriate for topical sunscreens and that are expected to induce the highest *in vivo* absorption. The study protocol should justify the chosen formulations.

Carcinogenicity studies include both dermal and systemic studies in animals. They are intended to help characterise any potential risk for tumours, as well as to identify tumour types, the level of exposure at which tumours occur, and the "no observed adverse effect level" (NOAEL). Animal carcinogenicity studies also help identify potential systemic or organ toxicities.

The FDA recommends conducting a dermal carcinogenicity study in which mice or rats are administered the product for two years. If human bioavailability data suggest the ingredient could penetrate skin and cause systemic exposure, the FDA recommends a second carcinogenicity study (in a different species than the one used for the dermal study) using a route that produces systemic exposure. All carcinogenicity studies should assess a full panel of tissues.

The FDA recommends **developmental and reproductive toxicity (DART) studies** in animals to evaluate the potential effects of exposure on a developing foetus, on young animals up to sexual maturation, and on the reproductive capability of sexually mature animals. Recommended endpoints include vaginal patency, preputial separation, anogenital distance, and nipple retention. The agency also suggests that offspring behaviour be assessed (e.g., mating behaviour) for potential neuroendocrine effects.

Animal toxicokinetic data for sunscreen active ingredients can help to bridge toxic levels observed in animal studies to potential human AEs associated with systemic exposure. Unique studies are unnecessary, however, since carcinogenicity, DART, and other non-clinical toxicity studies typically provide toxicokinetic measures.

Note: In addition to safety data, the new draft guidance briefly discusses effectiveness data needed for a GRASE determination, and describes the FDA's anticipated approach to final formulation testing to ensure the effectiveness of OTC sunscreen products.

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