

FDA PROPOSAL PART II: NO, THE WAIT IS NOT OVER!

THE NEW US Food and Drug Administration (FDA) Sunscreen Regulations Proposal is a “well written” and “comprehensive” document.¹ It is, however, at least five years too late, as the long wait and the uncertainty in regulations have put a major damper on our efforts to seek newer, safer and more effective UV filters. It has also caused a lot of anxiety among scientists, health advocates, manufacturers, regulators and, more importantly, consumers as to the future of sun care protection that would allow cosmetic and sunscreen chemists to create superior formulations to better protect consumers.

Today we have a “rag-tag” collection of UV filters. The current FDA proposal has deemed all but two, zinc oxide and titanium dioxide, as Category I Generally Regarded As Safe and Effective (GRASE) filters to use. Two others, trolamine salicylate and para-aminobenzoic acid, were banned and relegated to Category II (non-GRASE items) and the remaining Category I filters were classified as Category III filters requiring extensive safety data before



Not all UV filters are the same—as seen with a variety of sunscreen options in today's marketplace.

being reapproved. Fortunately, the FDA allows their use in current formulations until the Final Regulations become effective on Nov. 26, 2019. However, the FDA released a second document which explained their evaluation of the economic impact of the proposed regulation and indicated that if industry was willing to provide the safety data required they would implement a five-year stay on the organic UV filters which have been proposed to be listed as category III. The FDA expects that industry will defend six of the 12 filters (oxybenzone, octinoxate, avobenzone, octisalate, homosalate and octocrylene). This is unlikely to happen but is under debate within the industry.

In my April column, I clearly outlined the FDA's proposal for future sunscreen regulations in the US. In this month's column, I will comment on the salient features of that proposal. I contacted many of my industry friends for their opinions on this far-reaching document, and the responses that I received ranged from comments that “the FDA has gone wild!”

to “the FDA threw a monkey-wrench into the regulations of sunscreens” to “it's about time.” Some even praised the FDA for acknowledging the need for more, and safer, UV filters and for finally acknowledging that the current list of UV filters is inadequate. These new filters will require extensive safety data before they are approved as Category I GRASE items. The deadline that the FDA set, Nov. 26, 2019, was imposed by the Sunscreen Innovation Act (SIA) that the Public Access to Sunscreens (PASS) Coalition successfully lobbied for in Congress, and the law was signed by President Barack Obama on November 26, 2014. The SIA set a five-year maximum timeline for Final Regulations in sunscreens to be enacted.

I would have preferred that sunscreens not be treated as OTC drugs but rather as special cosmetics as they are regulated in most of the rest of the world. If sunscreens were regulated as cosmetics, we would have had by now an efficient set of safe and effective ultraviolet filters



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that would have afforded our consumers much better protection particularly from the now well-documented harmful UVA radiation. That decision, apparently, is not forthcoming soon and, unfortunately, the FDA is reluctant to allow the reclassification of sunscreens as “cosmetics” even though they are mandated to enforce cosmetic regulations.

This new FDA proposal failed to comment on the status of the six Time and Extent Application (TEA) UV filters that we sorely need. The majority of those TEA ingredients are excellent UVA filters with great safety and repeated use records, and these ingredients were designed in compliance with the Dalton 500 Rule that minimizes skin penetration. But the FDA is requesting the same type of additional safety data for the TEA candidates as well—so we are years away from getting these approved.

The new FDA proposal has a multitude of new regulations that have been thrust upon the industry with major consequences for the future of the sunscreen industry and that of skin cancer prevention. Due to space limitations, let me review a few of the important issues in the new FDA Proposal for Sunscreen Regulations in the US.

Proposed GRASE Status

At a time that the industry has been fending off the barrage of criticism leveled on oxybenzone (and I am not a fan of this ingredient) for destroying coral reefs, the FDA clearly questioned the “human safety” profile of this ingredient, citing excessive permeability into the skin and even its endocrine disrupting potential. As reported, Hawaii, the island of Palau, Key West, FL and others have passed ordinances banning oxybenzone and octinoxate from use in sunscreen products, mostly for environmental concerns. Questioning their “human safety,” however, by the FDA, has nailed the coffin shut for their approval as Category I ingredients in the future.

The sunscreen industry has been supporting the archaic Category I filters (12 of the remaining 16 filters are now Category III requiring extensive safety

testing before they can be classified as Category I) to formulate all of their sunscreen products. The FDA’s intransigence by not allowing any new filters to be introduced into the US market and setting unrealistic barriers and standards, has discouraged basic research for the creation of new filters. Today, the sunscreen industry does not have one patented active ingredient on this list of 12 filters, that a single company can afford to spend the money and time required to establish its safety and satisfy the FDA’s requirements for approval. Which company today is going to submit data that include the Maximum Usage Trial (MUS_T) test for skin permeability, the Developmental and Reproductive Toxicity (DART) tests for endocrine disrupting activities and any other FDA requests to satisfy the drug requirements of those filters? These filters are currently sold by numerous vendors, not just one, and their sale to the industry is, at best, only in the millions to low tens of millions of dollars annually. They are not cancer-treatment drugs or blood pressure reducing medicines or cholesterol modifying drugs that sell for hundreds of millions or billions of dollars a year. The Return On their Investment (ROI) for UV filter suppliers is simply not there.

Though I personally agree with the premise that dermal permeability testing (MUS_T test or equivalent) should be performed on all current and future UV filters, all 12 ingredients currently characterized as Category III ingredients would fail this test as they are low molecular weight compounds that would inevitably permeate the skin to one degree or another. The solution? Approve the TEA ingredients that have high molecular weights (based on the Dalton 500 rule) and encourage the introduction of other novel filters emanating from academia and industry.

If you read the new proposed monograph, the FDA approved as GRASE (Category I) only zinc oxide and titanium dioxide. It focused on two other Category III ingredients, namely oxybenzone and avobenzone. In both cases, the FDA is requiring extensive MUS_T and DART testing

at a minimum. I presume the remaining items, namely cinoxate, dioxybenzone, sulisobenzone, padimate O, meradimate, ensulizole, homosalate, octisalate, octinoxate and octocrylene would be rendered useless or unapproved if no company in our industry has the will, the courage, the time and the money to go through with the proposed extensive testing for approval as GRASE UV filters. If this, still unidentified gallant company, comes forward and submits the necessary FDA safety data, what will prevent another supplier that did not foot that huge bill from selling those ingredients on the market once approved by the FDA for a much lower price and gain a competitive advantage?

So, it is my belief, that the FDA has jumped-the-gun by throwing this “monkey-wrench” into industry regulations without at least approving alternative filters (such as the TEA, or other new ingredients) that would fill in the gap temporarily to achieve the desired solar protection today. The consumer is bound to question the safety of those 12 filters, as the FDA has, and calls for their removal from our current formulations will undoubtedly be heard soon.

Proposed SPF Requirements

The FDA has acquiesced to the demands made by industry sunscreen manufacturers to increase the upper limit of labeled SPF on sunscreen products. It is ironic, but the FDA has doubled the SPF cap exactly every 20 years. In 1978 the upper limit was 15 and was doubled in 1999 to 30+. Now, in 2019, the cap has been raised to 60+. In fact, the FDA has indicated that it will consider the marketing of sunscreen products as high as 80! The justification is based, among other considerations, upon the fact that when testing for the SPF 60 cap, the error in the calculations is about 30%, hence the value of 80! FDA has reported several studies that justified its call for higher SPF products. FDA cites several studies for “at-risk” populations. These included Ulrich et al.’s research on protection for organ transplant recipients who are susceptible to non-melanoma skin cancers,² Kuhn et al. showing



Sunscreens with a higher level of SPF will soon be the norm in our industry.

prevention of skin lesions in topical lupus erythematosis patients,³ Faurschou et al.'s reporting the prevention of urticarial reactions in subjects with idiopathic solar urticarial,⁴ and Fourtanier et al.'s work showing lower levels of polymorphous light eruption.⁵ Thus, the vast majority of sunscreen users—those that are not transplant recipients, do not have lupus erythematosus or idiopathic solar urticaria or polymorphous light eruptions—will now be able to use SPF products up to a value of 80, loaded with possibly re-approved Category III ingredients or simply formulations with only zinc or titanium oxides, if they can find them mass-marketed at a reasonable price with that high SPF value!

All the previous arguments we heard for not raising the cap to more than 50+ were not considered, including international harmonization (the majority of the world has set 50+ as the cap), insufficient data warranting products higher than 50+, the false sense of protection for using SPFs higher than 50 and staying much longer in the sun, and the unnecessary exposure to more UV active ingredients, especially the now dreaded so-called chemical UV filters. Those arguments have unfortunately been ignored!

The FDA acknowledges "variability in SPF values is exacerbated at High SPF"

yet it looks like higher than 50+ will be the norm in the future of sunscreens. In response, the FDA has introduced the so-called stricter requirements for measuring broad spectrum and UVA protection (see below).

My last question that I pose in defense of lower SPF caps, rather than higher caps, is "How on earth are we to achieve aesthetically pleasing, low cost, mass-marketed beach products of mandated higher SPFs and more efficient UVA protection with only zinc oxide and titanium dioxide?"

UVA & Broad-Spectrum

In all fairness, the FDA has emphasized that broad spectrum and UVA claims are paramount especially in high SPF products (SPF 15 or less products are exempt). A new testing protocol for UVA protection has been proposed. In its proposed rule, the FDA introduces UVA I/UV ratio calculation in addition to the critical wavelength requirement to address broad spectrum protection of a sunscreen product. The Proposed FDA Rule claims that all sunscreen products should have an in-vivo SPF protection 15 and above, critical wavelength 370nm and above as well as UVA I/UV ratio of at least 0.7 to provide "a more uniform amount of radiation protection across the UVA I, UVA

II and UVB ranges" (p. 6235 of the FDA Proposed Regulations). Moreover, the FDA Proposed Rule claims that introduction of UVA I/UV ratio will eliminate higher SPF value products which may provide poorer broad-spectrum protection than a product labeled as broad spectrum with a lower SPF value.

The FDA defines how ratio calculations shall be performed on p.6235. The respective numbers used to calculate UVA I/UV ratio are represented by the Area Under the Curve (AUC) per unit wavelength. Similar logic follows ratio calculations in Boots Star-Rating System used in the UK.

Does this mean that passing the FDA Proposed Rule guarantees passing in-vitro European requirements? As in the Boots Star-Rating System, the FDA does not require biologically weighted spectrum to determine its ratio. Some of the EU methods, like Colpia and ISO 24443, calculate ratios using biologically-weighted protection factors expressed by SPF and UV-PF numbers. Moreover, these ratios are calculated from in vivo (SPF) and in-vitro (UVA-PF) data! When comparing non-biologically weighted ratios, we are only left with Boots and the Proposed FDA. The FDA ratio defines relationship between UVA I (340 nm- 400 nm) and UV (290-400 nm) spectra, whereas Boots addresses the relationship between UVA (320-400nm) and UVB (290-320nm). The fact that the FDA and Boots use different spectral ranges to calculate respective ratios may result in products passing one method and failing the other.

Since ISO seems to be accepted as the "international guideline," we have attempted to compare the FDA Proposed Rule Ratio calculations against ISO 24443. Among nine formulas tested, five passed the FDA Proposed Ratio but failed ISO 24443 (contact me directly for a copy of the results). Even though the Proposed FDA protocol is an improvement over the existing critical wavelength test, it still does not guarantee conformity with international guidelines. To conclude, there are significant differences between all the in-vitro methods. Finally, if the only two

ingredients that formulators are permitted to use are zinc oxide and titanium dioxide, serious challenges are posed for producing an SPF product over 50. Also, passing these new broad spectrum claims of UVA I/UV will be extremely difficult for titanium dioxide-only formulations.

Other issues must be addressed if

sunscreen formulators are to abide by all the proposed regulations. High on this list are the challenges of formulating spray sunscreen products. They are one of the most popular methods for delivering sunscreens on the market today. Assuming that the hurdles of safety set for spray products by the

FDA (flammability risk and respiratory harm from inhalation) are passed, it will be challenging, if not impossible, to produce aesthetically-pleasing spray formulations using only ZnO and TiO₂ filters. The cost of formulating high SPF inexpensive beach products and mass-produced products is simply not possible with current inorganic filters that are far too expensive; compare the price of octyl salicylate to zinc oxide and you will see it is multifold more expensive. Of course, some of the 12 currently Category III filters must be re-approved for use, especially the only available UVA absorber, the photo-unstable avobenzone that is propped-up with UV absorbing quenchers. Otherwise, no one will have a chance of achieving broad-spectrum, high SPF aerosol propelled spray products again.

In conclusion, the FDA's goal to finalizing the Sunscreen Monograph by Nov. 26, 2019 is totally unrealistic despite my repeated calls in the past to issue a Final Monograph. I cannot perceive of a condition or of a company stepping forward to supply the necessary safety data required by the FDA to reclassify a Category III UV Filter as GRASE. Perhaps avobenzone from this list of 12 may be the only such ingredient. It goes without saying that the pending TEA ingredients, or filters resulting from the easing of the approval pathway for new, more effective UVB and UVA filters that are less permeable to the skin and offer more stable and safer broad-spectrum protection, may today be the only hope for formulating effective sunscreens in the US. •

References:

1. <https://www.federalregister.gov/documents/2019/02/26/2019-03019/sunscreen-drug-products-for-over-the-counter-human-use>. 21 CFR Parts 201, 310, 347 and 352.
2. Federal Register/Vol.84, No.38, Feb. 26, 2019 Reference 176 on page 6262.
3. Federal Register/Vol.84, No.38, Feb. 26, 2019 Reference 177 on page 6262.
4. Federal Register/Vol.84, No.38, Feb. 26, 2019 Reference 178 on page 6262.
5. Federal Register/Vol.84, No.38, Feb. 26, 2019 Reference 179 on page 6262