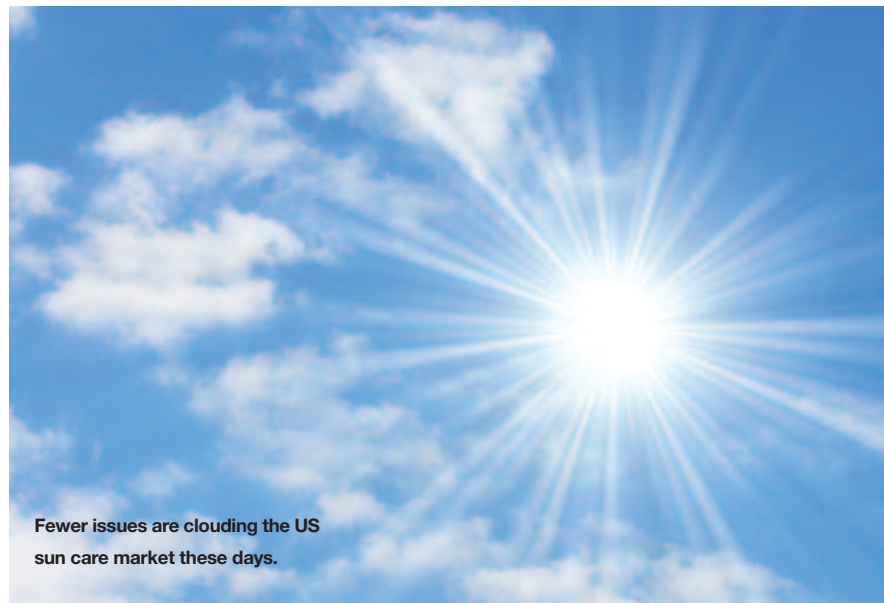


FDA: NOW YOU'RE TALKING!

AFTER YEARS OF SILENCE, indecision and conflicting regulations, the FDA has finally begun proposing Final Rules in sunscreens. More importantly, a new image has appeared in strong contrast to the once reticent FDA. We have rarely had an FDA spokesperson appear in our meetings and they are scarcely forthcoming with responses in debates. Skin cancer rates are still on the rise yet no clear regulations were available to arbitrate and offer guidelines for safe and effective products, rules and control. Now things are changing!

In the most recent round of regulations that started on June 14, the FDA issued four detailed documents, namely: Labeling and Effectiveness Testing; Sunscreen Drug Products for over-the-counter Human Use—Final Rule (174 pages); Proposed Rule (26 pages); Advanced Notice of Proposed Rule Making (14 pages) and a Guide for Industry.¹⁻⁴ FDA also held a press conference attended by Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research, FDA, Reynold Tan, Ph.D, inter-



Fewer issues are clouding the US sun care market these days.

disciplinary scientist CDER/FDA, and Ronald L. Moy, M.D., president of the American Academy of Dermatology (AAD). In addition, FDA released a very informative video for the consumer and those interested in hearing more and getting clarification about the new Final Rule.⁵ Since then, I have personally communicated with Dr. Tan on a number of issues. His answers and responses were extremely forthcoming, open and helpful. He also agreed to participate in a HAPPI open forum webinar as well as a round table panel at the upcoming Florida Sunscreen Symposium.

The question that could be asked is why now? Did the FDA finally feel the heat from Congress, all those politicians who tossed their hat into the ring? The consumer advocacy groups? Other international regulatory organizations? The Personal Care Product Council? Or the American Academy of Dermatology (AAD)? Or was it the consumers and scientists who voiced their concern? Was our focused attention on their slow-as-molasses process inspirational? Regardless

of whose influence proved most effective at generating results, action on these issues has been of top importance for years and, finally, we see some movement.

Starting a Dialogue

On Aug. 11, Happi hosted both FDA's Dr. Tan FDA and me for a 70-minute discussion of the recently announced Final Rule. The response was overwhelming, attracting more than 1,200 registrants who called in hundreds of questions. I continue to receive feedback and inquiries, which is a great sign that we are all feeling the weight of responsibility as well as feeling collectively empowered to see the regulations through to a successful conclusion.

Let me share with you the highlights of what transpired during and after that webinar. Dr. Tan gave an excellent presentation on the Final Rule in sunscreens, the Proposed Rule for capping the allowed SPF to 50+ and the Advanced Notice of Rule Making (ANPR) for regulating sprays and other dosage forms. He also spoke about the intended follow-up by the FDA and measures to enforce the



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Final Rule in the US. As it has been the case for the past 30 years, my presentation dealt with the problems with regulations and specifically for what was not “Final” in the Final Regulations.

Here are the issues that were not addressed in the Final Rule:

1. No decision was made on the eight TEA ingredients.
2. No decision was made on the combination of avobenzone with zinc oxide, titanium dioxide, ensulizole, meradimate, PABA and padimate O. All are still not allowed combinations with avobenzone.
3. The decision to allow SPFs higher than 50 has been relegated to the Proposed Rule, until a Final Rule is issued in the future. SPFs higher than 50 will still be allowed despite the FDA’s stated position of not favoring their inclusion in the Final regulations.
4. The decision to disallow sprays and other dosage forms has been consigned to the ANPR. Sprays are still allowed during

this interim period.

5. No action has been taken concerning labeling sun care products as “natural” or the practice of using photostabilizing ingredients or quenchers that are also UV absorbers.
6. Despite their assurances that all the current ingredients in sunscreens have a clean bill of health, a study of their safety has yet to be completed—this includes the issue of nanoparticles. See Dr. Tan’s comments on nanoparticles of zinc and titanium oxides that follow.
7. Harmonization with other international organizations (eg. EU, Japanese, Australian, etc.) has not been accomplished.
8. The testing parameters still require debate as many in the industry are voicing their concerns related to the application dose, the roughness of the substrate, the input optics bandwidth, the wavelength interval, and other issues that are not clearly defined.

The questions called in to the webinar reflected the genuine concern that practi-

tioners in our field feel concerning the specifics of the Rule, its application and its enforcement. Here are some of the key questions that were fielded by Dr. Tan:

Q: Can you clarify if the drug facts have to go on both inner package or just on outer package?

A: The Drug Facts panel must appear on the outer package label. Requirements for inner package labeling are described in 21 CFR 201.10(h)(2)(i). In summary, the inner container label must include the proprietary name, established name, lot/control number, and the manufacturer, packer or distributor.

Q: Can we manufacture products before June 2012 and sell the current formula or does the new formula have to be done before June 2012?

A: The effective date for the final rule is June 18, 2012. All OTC sunscreen drug products marketed under the OTC monograph system and introduced into interstate commerce after that date must comply with requirements in the June 17, 2011 final rule.

Q: If a sunscreen has been tested and on the market since prior to 1999, does it have to be retested?

A: By June 17, 2013, all OTC sunscreen drug products marketed under the OTC monograph system must be SPF tested according to the SPF test procedure parameters in the 2011 sunscreen final rule.

Q: Is “sweat resistant” an allowed claim?

A: Under the 2011 final rule, “sweat resistant” is not an allowed claim. Sunscreen products that are tested according to the water-resistant test can label as “water resistant (40 or 80 minutes).”

Q: Are pull out or outsert labels allowed on products that have small cartons? What about products that are being used as “testers or samples” specifically lipstick with 0.01oz in each tester bullet?

A: Pullout and outsert labels are allowed on



With the FDA's recent rulings, consumers may better understand sun protection.

OTC drug products that have limited labeling space (e.g., small cartons). This type of labeling is one way to include the required labeling information for small size products, like lipsticks that contain sunscreens.

Q: Since sunscreen products make cosmetic claims, should the inactive ingredients be listed in descending order or are we allowed to choose?

A: If the product is an OTC drug product that is not also a cosmetic product, then the inactive ingredients shall be listed in alphabetical order. If the product is an OTC drug product that is also a cosmetic product, then the inactive ingredients shall be listed in descending order of concentration (see 21 CFR 701.3).

Q. Will the FDA be testing safety of ALL ingredients including inactives?

A: FDA will be evaluating the safety of all sunscreen active ingredients. It is the manufacturer's responsibility to ensure that its products' inactive ingredients are safe in amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality and purity (21 CFR 330.1(e)).

Q. Does the FDA have any research on nanomaterial safety? Is vitamin A carcinogenic in sunscreens?

A: FDA is currently reviewing the safety of nanoparticles. For nanoparticles, we are typically talking about ZnO and TiO₂. Based upon data we have on TiO₂ nanoparticles, there seem to be no significant permeation into the outer layers of the skin. So at this point we do not have any reason to be concerned about the safety of nanoparticles of TiO₂. (Note: An FDA study by N. Sadrieh et. al was cited as evidence.⁶ Also, *C&E News* has an interesting write up on nanoparticles in sunscreens that should be consulted.)⁷ The purported carcinogenicity concern with vitamin A in sunscreens is a result of a study of retinyl palmitate, a vitamin A derivative. That study does not definitively demonstrate that retinyl palmitate is a carcinogen for humans. It is a study in mice predisposed to developing tumors. The control arm of the study (i.e., the mice administered the drug vehicle without retinyl palmitate) also developed a high number of tumors. FDA will continue to monitor safety data, and if a safety signal becomes apparent, FDA will take the necessary corrective action. Note: A recent report on retinyl palmitate by S. Wang et.al has been published and should be consulted.⁸

Many other questions were posted but the time ran out. I will tackle the important questions in a future column.

Addressing Vital Issues

During the Florida Sunscreen Symposium, which will be held in Orlando Sept. 14-17, a roundtable discussion moderated by Den-

nis Lott will address the following vital issues.⁹ A panel has been selected that will address the point and the counterpoint for each of the following questions and issues:

1. Are in vitro SPF methods viable? The Sun Protection Factor (SPF) method has been around since the 1970s with very little actual change except perhaps the initiation of specifications for the solar simulator device. Is this SPF number really realistic? Is it, in fact, better than in vitro methods? Dr. Robert Sayre will comment on the SPF method, specifically the spectra of the solar simulators used for testing and how it differs from the sun's spectra, and how this would make SPFs under realistic sun conditions as compared to SPFs predicted by solar simulators. Joe Stanfield will talk about the various efforts throughout the world including the ISO directive to develop in vitro methods and the problems associated with.

2. Does a Critical Wavelength (CW) of 370nm or higher provide adequate UVA protection? UVA protection has been a subject for so long in the US, long after other entities have decided on a method for testing. The FDA appeared to settle on methods and labeling in 2007, and then, on June 14 of this year, dropped a bomb on us. Whereas in 2007 the Administration stated that a Persistent Pigment Darkening in vivo method and an in vitro method were necessary to establish the UVA ranking and labeling, the June 14 Final Rule only required a CW of 370nm or higher. The 370nm CW is much weaker than the earlier 2007 requirement. Dr. Tan will get the discussion started by enlightening us as to the reasoning behind the FDA's decision, and he will explain the FDA's rationale behind the 370nm UVA requirement. Dominique Moyal (L'Oréal) will explain that a CW of 370 is very weak. The EU system of 1/3 UVA PF to SPF requires more UVA protection. In fact, a 370 CW has less UVA protection than most high SPF products on the market today. The 370

CW will ultimately cause manufacturers to weaken the protection afforded in the UVA spectra.

3. SPF must be labeled as tested. The Final Rule stated that "FDA's general approach to combination drugs prohibits the inclusion of additional active ingredients if they do not provide additional benefit." What FDA is really saying is if the tested value is SPF 39, then SPF 39 is how the product must be labeled. Dr. Tan will explain the rationale: SPF should be labeled as tested per the monograph. That is, the labeled SPF is the next integer below the tested value. If this rule is not followed, products could be over formulated, and violate FDA's approach to combination drugs. I will argue that this will cause confusion if the shelf is stocked with SPFs of all numbers. How will consumers know the difference between SPF 44 and 46? If SPFs exceeding 50 are not allowed, then it would be incredibly difficult to obtain a product that ended up with an SPF of between 50 and 51.

4. Limiting SPFs by limiting the amount of sunscreen allowed in the product. The FDA suggested that one way to limit SPFs would be to limit the amount of sunscreen allowed. We solicit comment on whether FDA should address this issue through a direct limit on product formulation rather than through labeling. We also solicit comment and data on how to establish the maximum SPF value as a formulation limit (if one were to be set). This is how sunscreens should be regulated. A standard formula should be established for each SPF. This is how most OTCs are regulated. I will offer an opinion as to why this is a good approach. For example, most, if not all, of the OTC drugs have ranges for the actives which allows claims to be made with no further testing required. Why should sunscreens not be the same? Joe Stanfield will counter that, based on years and years of testing, it is impossible to predict an

SPF based on the amount of sunscreen in a product. "The inactive ingredients can have a profound effect on the SPF of a product. Also, this would probably eliminate further research. There would simply be no incentive to conduct research in an attempt to make better, more effective products."

5. SPF should be capped at 50? Stanfield will state that the FDA has basically capped SPFs at 50+, yet millions of consumers annually buy products over SPF 50. It is estimated that 50% of the market is now SPF 50 or above. Dr. Tan will explain the FDA's position on this sensitive subject. SPF should be capped at 50. There is no measureable increased performance beyond SPF 50. An SPF 50 would theoretically protect a user against 50 MEDs. Nowhere on earth would a user ever receive 50 MEDs and, in fact, 30 MEDs is routinely published in the literature as the maximum amount that can be received on earth. Additionally, the FDA states in the monograph that data has been supplied to prove that the SPF test is adequate to test SPFs of 80, but there is no data to show that SPFs of over 80 can be adequately tested. Dennis Lott will offer a counter opinion. He will argue that consumers need more protection for the following reasons:

- A. Studies show that consumers never use the tested amount; thus, they never receive the full labeled SPF. The "30 MEDs" is a theoretical number based on the amount of erythemally effective energy needed to create mild sunburn on the average skin Type II individual. There exists a large population group that react much faster than that; thus, there would be more than 30 "MEDS."
- B. Lott will show slides of actual outdoor studies that show a clinical difference between SPF 50 and SPFs 70-85.

6. Must sprays supply more data to show they are acceptable dosage forms? The FDA has requested more data concerning

sprays. In particular, there seems to be a concern about amount used, uniformity of the spray, and the difference in SPF if sprayed rather than rubbed. Dr. Tan will explain the FDA's position arguing that sprays must have more data submitted to be allowed. Specifically, they must address the following:

1. Sprays must provide data showing consumers how to use enough of the product. Anyone watching a user apply a spray product knows that only a fraction of the product actually hits the user.
2. The Monograph states to apply "fifteen minutes before sun exposure," yet this product is typically used as an easily applicable product that is sprayed on at the beach, pool, etc.
3. Data should be supplied showing the product is equally effective if rubbed or sprayed. For example, the FDA is suggesting labeling that instructs the consumer to spray in the hand and then rub on the face.

How do SPFs vary when a user does not apply as much as used in the laboratory tests? Dr. Olga Dueva-Kogonov will offer insights and recent data concerning sprays. Sprays are no different than lotions and creams where every study ever performed shows consumers do not use enough product. If it is known that for accepted dosage forms of lotions and creams are not applied and used correctly, why should sprays be held to a different and more rigorous standard? Also, sprays hold about a 30% market share in the US mass market sun care arena. It is obvious that sprays enjoy a tremendous following from consumers. It is unreasonable for the FDA to not allow this dosage form and risk alienating consumers. This could only exacerbate the real problem with sun care users do not use sunscreen often enough.

A slew of new questions have been generated by the recent FDA announcements of the planned final rules for sunscreens. This is an exciting time where the potential to resolve outstanding issues is finally within sight. The FDA has, at long last, responded to the pressure from concerned interests. Our persistent attention is still required to carry these new plans through to a successful completion. The fact that there is genuine discussion and participation from the industry and the FDA, is a good sign. Future product developments are on the horizon, and the reduction of preventable skin cancers will occur in the near future.

Let's keep moving in that direction! And let's keep talking. ●

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