

at the FAA, Central Region, Office of the Regional Counsel, Room 1558, 601 E. 12th Street, Kansas City, Missouri 64106.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 352

[Docket No. 78N-0038]

RIN 0910-AA01

Sunscreen Drug Products for Over-the-Counter Human Use; Amendment to the Tentative Final Monograph; Enforcement Policy

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that amends the tentative final monograph (proposed rule) for over-the-counter (OTC) sunscreen drug products. This amendment would establish conditions under which products containing zinc oxide as a sunscreen active ingredient are generally recognized as safe and effective and not misbranded at concentrations of up to 25 percent alone and 2 to 25 percent in combination with any proposed Category I sunscreen active ingredient except avobenzone. OTC marketing of such drug products is being permitted pending establishment under the OTC drug review of a final monograph covering sunscreen drug products. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Submit written comments by January 20, 1999; written comments on the agency's economic impact determination by January 20, 1999. FDA is proposing that any final rule based on this proposal become effective 12 months after its date of publication in the **Federal Register**.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Donald Dobbs, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of August 25, 1978 (43 FR 38206), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC sunscreen drug products. Proposed § 352.10 listed the active ingredients to be generally recognized as safe and effective for use in these products. The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (the Panel) reviewed zinc oxide as both a sunscreen and skin protectant. The Panel classified zinc oxide at concentrations of 1 to 25 percent as a Category I skin protectant (43 FR 34628 at 34648, August 4, 1978). Although zinc oxide was a labeled ingredient in a marketed sunscreen product, the Panel classified zinc oxide as an inactive ingredient (43 FR 38206 at 38208).

In the **Federal Register** of May 12, 1993 (58 FR 28194), FDA published a notice of proposed rulemaking (tentative final monograph) for OTC sunscreen drug products. The agency discussed a study submitted to the Panel using zinc oxide alone and in combination with phenyl salicylate, another sunscreen ingredient (58 FR 28194 at 28213). The study was designed to measure the ability of zinc oxide (15 to 33.3 percent) to absorb ultraviolet (UV) radiation over a broad range of wavelengths. The agency concluded that the data were not adequate to determine the effectiveness of zinc oxide because the effectiveness data for zinc oxide used alone were limited to one subject. Therefore, the agency classified zinc oxide in Category III (available data are insufficient to determine safety or effectiveness) (58 FR 38213) and requested data to support

the effectiveness of zinc oxide as a sunscreen ingredient.

In the proposed rule, the agency also discussed the public health significance of ultraviolet A (UVA) radiation and the characteristics and proposed labeling of OTC sunscreen drug products that claim to provide protection from UVA radiation (58 FR 28194 at 28232 and 28233). Testing procedures for sunscreen drug products with UVA radiation protection claims were discussed in the proposed rule (58 FR 28194 at 28248 to 28250) and at a public meeting on May 12, 1994 (as noted in the **Federal Register** of April 5, 1994 (59 FR 16042)).

In response to the proposed rule, four manufacturers submitted data to support the effectiveness of zinc oxide as an OTC sunscreen active ingredient for both ultraviolet B (UVB) and UVA protection. Copies of the comments received are on public display in the Dockets Management Branch (address above). The four comments requested that the agency reclassify zinc oxide from Category III to Category I status.

II. The Agency's Evaluation of the Comments and Other Data

A. Effectiveness of Zinc Oxide

1. Several comments evaluated the effectiveness of zinc oxide as a sunscreen active ingredient in various formulations utilizing the sun protection factor (SPF) test method in the Panel report (43 FR 38206 at 38265 and 38266). Using the testing procedures in the proposed rule (58 FR 28194 at 28298), the agency recalculated the SPF test results (as stated in the tables in section II.A of this document) after eliminating those results where the homosalate control was out of range.

Two studies evaluated the ability of zinc oxide-containing sunscreen drug products to block sunburning radiation (Ref. 1). In both studies, formulations containing either 4 percent or 25 percent zinc oxide, 2 percent oxybenzone (a proposed Category I sunscreen ingredient (58 FR 28194 at 28295)), and a placebo were tested. The vehicles consisted of commonly utilized oils and emulsifiers and varied only in the concentration of the active ingredients and the amount of purified water. The results of these studies were as follows:

TABLE 1.—SPF TEST DETERMINATIONS FOR FOUR FORMULATIONS

Sunscreen	Anticipated SPF	Test SPF (Study 1)	Test SPF (Study 2)
4% Zinc oxide	SPF 2.5	SPF 3.01	2.79
25% Zinc oxide	SPF 15.0	SPF 16.74	16.14

TABLE 1.—SPF TEST DETERMINATIONS FOR FOUR FORMULATIONS—Continued

Sunscreen	Anticipated SPF	Test SPF (Study 1)	Test SPF (Study 2)
2% Oxybenzone	SPF 3.0	SPF 3.98	3.39
Placebo	SPF 1.5	SPF 1.46	1.33

These results indicate that the 4-percent zinc oxide formulation provides more protection against sunburning radiation than does the placebo. However, as expected, the 25-percent zinc oxide formulation provides the most protection against sunburning radiation. The agency believes that these results demonstrate the effectiveness of zinc oxide (up to 25 percent) as an OTC

sunscreen active ingredient in providing protection against sunburning radiation. Formulations containing 15 percent and 20 percent zinc oxide were tested against a control containing no zinc oxide (Ref. 2). The 3 formulations contained the same 12 ingredients at the same concentrations except for the active ingredient, two inactive ingredients (octyl palmitate and volatile silicone DC-245), and deionized water. The 15-percent zinc oxide formulation

contained 11 percent octyl palmitate, 7.5 percent volatile silicone DC-245, and 53.3 percent deionized water; the 20-percent zinc oxide formulation contained 9 percent octyl palmitate, 6.5 percent volatile silicone DC-245, and 51.3 percent deionized water; and the placebo contained 17 percent octyl palmitate, 7.5 percent volatile silicone DC-245, and 62.3 percent deionized water. The results were as follows:

TABLE 2.—SPF TEST DETERMINATIONS FOR THREE FORMULATIONS

Sunscreen	Test SPF
15% Zinc oxide	15.29
20% Zinc oxide	16.57
Placebo	3.57

The agency believes these data also support the effectiveness of zinc oxide as a sunscreen active ingredient.

Five studies, done at two different laboratories, were designed to demonstrate the effectiveness of zinc oxide as a sunscreen active ingredient in different formulations (Ref. 3). In three studies, zinc oxide (2 percent in one formulation and 6 percent in two formulations) was the only active ingredient. In two studies, zinc oxide (2.5 percent or 7.5 percent) was combined with titanium dioxide (2.5 percent), a proposed Category I sunscreen ingredient (58 FR 28194 at 28295). The vehicle formulations without zinc oxide were not tested. The results of the SPF testing were as follows:

TABLE 3.—SPF TEST DETERMINATIONS FOR FIVE FORMULATIONS

Sunscreen	Test SPF
2% Zinc oxide	2.99
6% Zinc oxide	6.16
6% Zinc oxide	5.91
2.5% Zinc oxide and 2.5% titanium dioxide	11.77
7.5% Zinc oxide and 2.5% titanium dioxide	20.52

Although these studies did not include a placebo, the agency believes that the data support the effectiveness of 2 percent zinc oxide as a sunscreen active ingredient.

The SPF of two formulations containing 5 and 10 percent fine particle size (10 to 70 nanometer (nm), average 30 nm), pH neutral (7.3) zinc oxide was studied using testing procedures that were slightly modified by the addition of a range-finding technique (Ref. 4). The two formulations contained the same inactive ingredients at slightly different concentrations to account for the difference in concentration of zinc oxide. The results of this study were as follows:

TABLE 4.—SPF TEST DETERMINATIONS FOR TWO FORMULATIONS

Sunscreen	Anticipated SPF	Test SPF
5% Zinc oxide	SPF 5	SPF 5.01
10% Zinc oxide	SPF 10	SPF 9.10

Although the vehicle formulations without zinc oxide were not tested, the agency believes that these results and

consistent with the effectiveness of zinc oxide as a sunscreen active ingredient.

2. One comment (Ref. 1) measured the UVA protection factor (PFA) for three formulations: (1) 4 percent zinc oxide, (2) 2 percent oxybenzone, and (3) a placebo. The vehicles consisted of commonly utilized oils and emulsifiers and varied only in the concentration of the active ingredients and the amount of purified water. The PFA values were determined using a modified test method similar to the Panel's proposed SPF test (43 FR 38206 at 38265 to 38266). For the PFA test method, the light source was modified to emit only UVA radiation (>99.2 percent). The biological endpoint used in this test method was a change in skin color, either erythema (redness) or tanning (browning) of the skin observed 16 to 24 hours after the UV exposure. The lowest dose of UVA radiation that caused a minimally perceptible response was defined as the minimal response dose (MRD), which was determined for unprotected skin (MRD_u) and for the sunscreen protected skin (MRD_p). The PFA was the ratio of (MRD_p) divided by the (MRD_u). The UVA determinations for the three formulations were as follows:

TABLE 5.—PFA TEST DETERMINATIONS FOR THREE FORMULATIONS

Sunscreen	Anticipated PFA	Test PFA
4% Zinc oxide	2.00	2.36
2% Oxybenzone	2.00	2.27
Placebo	1.25	1.11

Although the PFA value reported for the 4 percent zinc oxide formulation was low, these results indicate that zinc oxide blocks radiation (320 to 340 nm) in the UVA II range.

3. Several comments submitted results of in vitro testing data. One comment (Ref. 1) used a Cary 2300 Spectrophotometer to measure the spectral absorbance of three formulations: (1) 4 percent zinc oxide, (2) 25 percent zinc oxide, and (3) 2 percent oxybenzone. The vehicles consisted of commonly utilized oils and emulsifiers and varied only in the concentration of the active ingredients and the amount of purified water.

Albino hairless mouse stratum corneum/epidermis samples were prepared by mechanical removal of the dermis using a dulled razor blade. The samples were cut into 1-inch circles and maintained in a hydrated state by floating the samples (dermal side down) on a water bath. The absorbance of each skin sample was measured and recorded. Ten microliters (μL) of sunscreen were applied to the skin substrate, allowed to dry for 15 minutes, and the absorbance measured. The absorbance of each sunscreen treated sample was subtracted from the absorbance of the skin (without sunscreen) to yield the absorbance of the sunscreen. Five replicate measurements for each sunscreen formula were averaged and plotted with standard deviations at each 10 nm.

The spectral absorbance plots showed that zinc oxide has a relatively flat and broad absorbance curve from 250 nm through 370 nm with a sharp drop in absorbance beyond 370 nm and extending into the visible spectrum. Comparison of the measurements of the 4 percent zinc oxide with 25 percent zinc oxide showed that the magnitude of absorbance is related to the amount of zinc oxide in the formulation. The spectral absorbance plot of the 2 percent oxybenzone showed an absorbance peak at 250 nm, another at approximately 280 nm, followed by a gradual drop in absorbance throughout the UVA wavelengths (320 to 400 nm). These measurements adequately demonstrated that zinc oxide absorbs radiation between 290 and 380 nm and, thus, support effectiveness.

Another comment (Ref. 2) included the results of in vitro testing ("Diffey method") of a formulation containing 15 percent zinc oxide in a stable emulsion. The transmittance data indicated UV radiation blockage from 290 to 380 nm and support the premise that zinc oxide can protect against UV radiation, including both UVB and UVA.

One comment (Ref. 3) included a spectral profile of attenuation for zinc oxide alone in a cosmetic formulation and from 1:1 and 3:1 combinations of zinc oxide and titanium dioxide. These spectral profiles of zinc oxide in various formulations demonstrated that zinc oxide as a single ingredient can provide protection in both the UVB and UVA spectral regions.

B. Photochemistry and Photobiology of Sunscreens

Recent scientific advances in understanding the photochemistry and photobiology of sunscreen drug products have raised many issues regarding sunscreen active ingredients, including zinc oxide and titanium dioxide. Because zinc oxide and titanium dioxide have many similar physical characteristics and may be used in combination in OTC sunscreen drug products, the following discussion addresses both ingredients.

There has been renewed interest in using physical sunscreens, i.e., zinc oxide and titanium dioxide, in sunscreen formulations because these ingredients may confer protection for a broad range of the UV radiation spectrum. Some manufacturers have developed ultra fine forms of these ingredients in the range of 0.02 to 0.10 microns that are transparent on the skin, may offer both UVA and UVB protection, and are esthetically pleasing (Refs. 5, 6, and 7).

Sunscreens have been generally classified as chemical (organic) or physical (inorganic) depending on whether they absorb specific UV radiation wavelengths or reflect and scatter UV radiation. Zinc oxide and titanium dioxide have been described as physical sunscreen ingredients that provide protection from UV radiation through reflection and scattering. However, new data and information indicate that they also absorb UV radiation as well as scatter visible light

(Refs. 8 and 9). Various authors (Refs. 8 and 10 through 13) have shown that these ingredients exhibit a semiconductor optical absorption gap. They absorb most radiation at wavelengths shorter than the gap (approximately 380 nm) and scatter radiation at wavelengths longer than the gap. When zinc oxide and titanium dioxide are irradiated with light containing energy greater than the band gap (approximately 3 electron volts), an electron from the valence band can be excited to the conduction band, thus creating an electron-hole pair. Because of these semiconductor properties, zinc oxide and titanium dioxide have been used as photocatalysts to degrade organic substances and pesticides in the environment (Refs. 14 through 18). In addition, titanium dioxide is being currently developed as a photooxidative self-cleaning and/or biocidal coating for industrial surfaces (Ref. 19).

There are many formulation variables that may affect the photocatalytic capability of zinc oxide and titanium dioxide. Such variables include mineral components, particle size, surface area, crystalline structure, particle coatings, pH of the medium, differences in the refractive index of the medium, and other components in the formulation (Refs. 5 through 8 and 10 through 23). These formulation variables are not mentioned in the United States Pharmacopeia (USP) compendial monograph for zinc oxide. In fact, the USP treats zinc oxide as a pure compound, without consideration of trace ions that may affect the absorption band gap between the valence and conduction bands or electronic energy levels, i.e., the range of wavelengths that are absorbed.

On September 19 and 20, 1996, the agency held a public meeting on the photostability, photochemistry, and photobiology of sunscreens in order to gather more information related to the issues discussed previously (Ref. 24). As a result of this public meeting, in the **Federal Register** of August 15, 1996 (61 FR 42398), the administrative record for the rulemaking for OTC sunscreen drug products was reopened until December 6, 1996, to allow for additional data and comment. The agency is evaluating all data and information received as a result of the workshop and may discuss

these recent scientific advances in future issues of the **Federal Register**.

C. Conclusion

The agency believes that the results of the studies using the SPF test to demonstrate the effectiveness of zinc oxide adequately demonstrate that at a 2 to 25 percent concentration it provides protection against UVB radiation.

In the proposed rule for OTC sunscreen drug products, the agency stated that a sunscreen ingredient must have an absorption spectrum extending to 360 nm or above in order for a product containing that ingredient to display UVA radiation protection claims in its labeling (58 FR 28194 at 28233). The agency also stated that the product would have to demonstrate meaningful UVA radiation protection by satisfying "yet to be established" UVA radiation testing procedures that would be included in the monograph. The agency described suggested interim UVA radiation test procedures in the proposed rule (58 FR 28194 at 28248 to 28250) and in a notice of public meeting (59 FR 16042, April 5, 1994) to discuss such testing procedures.

Although the agency continues to evaluate data and information for the purpose of proposing a monograph method for determining UVA radiation protection, it nevertheless finds there is ample data demonstrating that zinc oxide provides protection against UVA radiation. The agency plans to propose a monograph method for determining UVA radiation protection (both without and following water immersion or perspiration) in a future issue of the **Federal Register**. Until the agency proposes a monograph UVA radiation testing method, the agency considers testing procedures similar to the UVA protection factor method described above (Ref. 1), and those methods described by R. W. Gange et al. (Ref. 25) and N. J. Lowe et al. (Ref. 26) as adequate for determining the UVA radiation protection potential of a finished OTC sunscreen drug product.

Based upon the Panel's evaluation of zinc oxide as a skin protectant and the long history of use of zinc oxide in various drug and cosmetic products, the agency continues to believe that there are no safety concerns regarding the use of zinc oxide as a sunscreen active ingredient in concentrations up to 25 percent. In addition, the agency believes at this time that zinc oxide can be combined with any one or more of the other Category I sunscreen ingredients in § 352.10 of the proposed rule with the exception of avobenzone. The agency is currently reviewing data and information in support of the use of zinc

oxide and avobenzone in combination (Ref. 27) and will make a decision when its review is completed.

In the notice of proposed rulemaking for OTC sunscreen drug products, the agency discussed minimum concentration requirements for OTC sunscreen ingredients (58 FR 28194 at 28214). The agency concluded that effectiveness requirements (i.e., final product testing) make the use of minimum concentration requirements unnecessary for single ingredient products. However, because of its concern that each ingredient in a combination drug product contributes to the overall effectiveness of the product, the agency tentatively concluded that minimum concentration requirements are necessary for combination sunscreen drug products (i.e., until a method is developed that can demonstrate the contribution of each OTC sunscreen ingredient in a combination product). The agency received a number of comments on this position. The agency is currently evaluating these comments and will address them in the final monograph.

At this time, the agency considers the data submitted by the comments as supportive of the safety and effectiveness of up to 25 percent zinc oxide alone (if the finished product provides at least an SPF 2) and 2 to 25 percent zinc oxide in combination with any one or more of the other Category I sunscreen ingredients (except avobenzone) at the concentrations for permitted combinations of sunscreen active ingredients in proposed § 352.20 (58 FR 28194 at 28295). Accordingly, the agency is proposing to amend the proposed monograph for OTC sunscreen drug products to include zinc oxide in §§ 352.10 and 352.20.

D. Enforcement Status

The Panel did not consider zinc oxide as a sunscreen active ingredient alone or in combination products. The agency is not aware of any OTC sunscreen drug products currently marketed with zinc oxide as the sole sunscreen ingredient. The agency is aware that there are a number of combination sunscreen drug products that contain zinc oxide.

An FDA Compliance Policy Guide (CPG) (Ref. 28) addresses the marketing of OTC drug products containing combinations of ingredients. Under this guide, FDA's stated policy is that OTC drug combinations that were commercially marketed in the United States on or before May 11, 1972, and that are not subject to a final monograph, should not be considered for regulatory action on the basis of suspected labeling deficiencies unless

the deficiency constitutes a potential hazard to health. For OTC combination drug products that were not marketed on or before May 11, 1972, and have not been considered by an OTC advisory review panel, the CPG states that the agency may propose to include the combination in a final monograph. However, marketing of such a product generally may not proceed until after the comment period has ended on the proposal and a subsequent notice is published in the **Federal Register** setting forth the agency's determination concerning interim marketing.

The agency is aware that a number of sunscreen combination drug products containing zinc oxide have entered the market place during the pendency of the rulemaking for OTC sunscreen drug products. Based upon the Panel's favorable evaluation of zinc oxide as a skin protectant and zinc oxide's long history of safe use at comparable levels in various drug and cosmetic products. Because these products are currently being marketed and provide a significant health benefit to consumers, the agency sees no reason to restrict other products from entering the marketplace until the agency publishes a subsequent **Federal Register** notice to permit interim marketing. Accordingly, the agency, by this notice, has determined that it is appropriate at this time to allow the interim marketing of the OTC zinc oxide-containing products identified in proposed §§ 352.10 and 352.20. The agency is considering amending the CPG (Ref. 28) in the future to address special situations such as this one.

Products containing zinc oxide require both UVA radiation protection testing (as discussed in section II. C. of this document) and SPF testing of the finished product, as proposed in subpart D of the proposed monograph for OTC sunscreen drug products (58 FR 28194 at 28298 to 28301). If the products contain UVA claims in their labeling, then they must be marketed with the labeling proposed in § 352.52 in this document. Products covered by this monograph amendment may be marketed pending issuance of the final monograph for this drug class, subject to the risk that the agency may adopt a different position in the final monograph that could require reformulation and/or relabeling, recall or other regulatory action. Marketing of such products with UVA labeling claims not in accord with the labeling proposed in this document may also result in regulatory action against the product, the marketer, or both. The final monograph for OTC sunscreen drug products will establish the final

formulation, labeling, and testing requirements for such products.

E. Labeling

In addition to applicable labeling proposed in §§ 352.50 through 352.60 (58 FR 28194 at 28296 to 28298), the agency is proposing that the labeling for sunscreen drug products containing zinc oxide may include under their "Indications" or "Uses" any of the following phrases: (1) "Broad spectrum sunscreen," (2) "Provides" (select one of the following: "UVB and UVA" or "broad spectrum") "protection," (3) "Protects from UVB and UVA" (select one of the following: "rays" or "radiation"), (4) (Select one of the following: "Absorbs," "Protects," "Screens," or "Shields") "within the UVA spectrum," (5) "Provides protection from the UVA rays that may contribute to skin damage and premature aging of the skin."

III. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comments No. RPT5 and CR7, Docket No. 78N-0038, Dockets Management Branch.
2. Comments No. C131, C352, and SUP21, Docket No. 78N-0038, Dockets Management Branch.
3. Comments No. C140, C350, C513, and LET145, Docket No. 78N-0038, Dockets Management Branch.
4. Comment No. C351, Attachment III, Docket No. 78N-0038, Dockets Management Branch.
5. Catlow, B., "Formulating with Ultrafine TiO₂," *Seifen Oele Fette Wachse*, 119:497-500, 1994.
6. Alexander, P., "Ultrafine Titanium Dioxide Makes the Grade," *Manufacturing Chemist*, 62:21,23, 1991.
7. Brown, M. W., and E. Galley, "Testing UVA and UVB Protection from Microfine Titanium Dioxide," *Cosmetics and Toiletries*, 105:69-73, 1990.
8. Sayre, R. et al., "Physical Sunscreens," *Journal of the Society of Cosmetic Chemists*, 41:103-109, 1990.
9. Fox, M. A., "Mechanistic Photocatalysis in Organic Synthesis," in *Photocatalysis: Fundamentals and Applications*, John Wiley & Sons, New York, pp. 421-455, 1989.
10. Russell, J. et al., "The Assessment of the OH Scavenging Action of Therapeutic Agents," *Journal of Pharmaceutical and Biomedical Analysis*, 12:863-866, 1994.
11. Harbour, J. H., J. Tromp, and M. L. Hair, "Photogeneration of Hydrogen Peroxide in Aqueous TiO₂ Dispersions," *Canadian Journal of Chemistry*, 63:204-208, 1985.
12. Rao, M. V. et al., "Photosynthesis Production of H₂ and H₂O₂ on Semiconducting Oxide Grains in Aqueous Solutions," *Journal of Physical Chemistry*, 84:1987-91, 1980.

13. Schwitzgebel, J. et al., "Role of Oxygen Molecule and the Photogenerated Electron in TiO₂-Photocatalyzed Air Oxidation Reactions," *Journal of Physical Chemistry*, 99:5633-38, 1995.

14. Hidaka, H. et al., "Photodegradation of Surfactants. XV: Formation of SO₄²⁻ Ions in the Photooxidation of Sulfur-Containing Surfactants," *Chemosphere*, 29:2619-2624, 1994.

15. Minero, C. et al., "Photocatalyzed Transformation of Nitrobenzene on TiO₂ and ZnO," *Chemosphere*, 28:1229-1244, 1994.

16. Dieckmann, M. S., K. A. Gray, and P. V. Kamat, "Photocatalyzed Degradation of Adsorbed Nitrophenolic Compounds on Semiconductor Surfaces," *Water Science Technology*, 25:277-279, 1992.

17. Mak, M. K. S., and S. T. Hung, "Degradation of Neat and Commercial Samples of Organophosphate Pesticides in Illuminated TiO₂ Suspensions," *Toxicology and Environmental Chemistry*, 36:155-168, 1992.

18. Borello, R. et al., "Photocatalytic Degradation of DDT Mediated in Aqueous Semiconductor Slurries by Simulated Sunlight," *Environmental Toxicology and Chemistry*, 8:997-1002, 1989.

19. Heller, A., "Chemistry and Applications of Photocatalytic Oxidation of Thin Organic Films," *Accounts of Chemistry Research*, 28:503-508, 1995.

20. Anonymous, "Formulators Fine-Tune TiO₂-Based Screens," *Manufacturing Chemist*, 64:26-29, 1993.

21. Tichy, S., "Transparent TiO₂ for UV Protection," *Seifen Oele Fette Wachse*, 118:612-620, 1992.

22. Ortyl, T. T., and G. E. Peck, "Surface Charge of Titanium Oxide and Its Effect on Dye Adsorption and Aqueous Suspension Stability," *Drug Development and Industrial Pharmacy*, 17:2245-2268, 1991.

23. Macleod, T. M., and W. Fran-Bell, "Study of Physical Light Screening Agents," *British Journal of Dermatology*, 92:149-156, 1975.

24. Comment No. TR3, Docket No. 78N-0038, Dockets Management Branch.

25. Gange, R. W. et al., "Efficacy of a Sunscreen Containing Butyl Methoxydibenzoylmethane Against Ultraviolet A Radiation in Photosensitized Subjects," *Journal of the American Academy of Dermatology*, 15:494-499, 1986.

26. Lowe, N. J. et al., "Indoor and Outdoor Efficacy Testing of a Broad Spectrum Sunscreen Against Ultraviolet A Radiation in Psoralen-sensitized Subjects," *Journal of the American Academy of Dermatology*, 17:224-230, 1987.

27. Comment No. CP8, Docket No. 78N-0038, Dockets Management Branch.

28. "Food and Drug Administration Compliance Policy Guide 7132b.16," in OTC Vol. 06ATFM, Docket No. 78N-0038, Dockets Management Branch.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory

alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities.

Title II of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the principles set out in the Executive Order and these two statutes. The purpose of this proposed rule is to add a new ingredient, combinations of ingredients, and labeling for OTC sunscreen drug products that contain zinc oxide and to allow manufacturers to market zinc oxide-containing sunscreen drug products under the OTC drug monograph system, which would be beneficial to small entities. The proposed rule would also have a positive impact on the availability and marketing of broad spectrum OTC sunscreen drug products by allowing additional products to be marketed.

Some manufacturers of currently marketed products may incur costs to relabel their products should they wish to include the new labeling information. Such information may increase product sales because of the broader uses information being allowed. The agency has been informed that relabeling costs of the type required by this proposed rule generally average about \$2,000 to \$3,000 per stock keeping unit (SKU) (individual products, packages, and sizes). The agency is aware of 16 manufacturers that together produce less than 100 SKU's of OTC sunscreen drug products containing zinc oxide. There may be a few additional small manufacturers or products in the marketplace that are not identified in the sources FDA reviewed. Manufacturers who wish to include the new labeling may elect to relabel their products at the next scheduled labeling printing. Assuming that there are about 100 affected OTC SKU's in the marketplace, total one-time costs of relabeling would be \$200,000 to \$300,000 if all of the products were

re-labeled. The agency believes the actual cost could be lower because some manufacturers may not elect to relabel their products at this time and some of the label changes will be made by private label manufacturers that tend to use simpler and less expensive labeling. In addition, there should be minimal waste of existing labeling for any manufacturer who elects to relabel at this next labeling printing.

Manufacturers who wish to enter the marketplace with a new zinc oxide sunscreen combination product will incur the standard costs that all manufacturers have when introducing a new product.

The agency considered but rejected several alternatives: (1) A delayed marketing period, and (2) an exemption from coverage for small entities. The delayed marketing period was rejected because similar products currently exist in the marketplace. The agency does not consider an exemption for small entities appropriate because consumers who use these manufacturers' products would not have appropriate products for safe and effective use.

This analysis shows that this proposed rule is not economically significant under Executive Order 12866 and that the agency has undertaken important steps to reduce the burden to small entities. Nevertheless, some entities could incur some impacts, especially private label manufacturers that provide labeling for a number of affected products. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act. Finally, this analysis shows that the Unfunded Mandates Reform Act does not apply to the proposed rule because it would not result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements proposed in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed amendment to the tentative final monograph for OTC sunscreen drug products is a "public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

The agency has determined under 21 CFR 25.31(c) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Public Comment

Interested persons may, on or before January 20, 1999, submit written comments to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before January 20, 1999. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 352

Labeling, Over-the-counter drugs. Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 352 (proposed in the **Federal Register** of May 12, 1993 (58 FR 28194) and amended in the **Federal Register** of September 16, 1996 (61 FR 48645)) be amended as follows:

PART 352—SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 352 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 352.10 is amended by adding paragraph (v) to read as follows:

§ 352.10 Sunscreen active ingredients.

* * * * *

(v) Zinc oxide up to 25 percent.

3. Section 352.20 is amended by revising paragraphs (a)(1) and (a)(3)(xxi) to read as follows:

§ 352.20 Permitted combinations of active ingredients.

(a) * * *

(1) Two or more sunscreen active ingredients identified in § 352.10(a), and (c) through (v) may be combined when used in the concentrations established for each ingredient in paragraph (a)(3) of this section and the finished product has a minimum sun protection factor

value of not less than 2 as measured by the testing procedures established in subpart D of this part.

* * * * *

(3) * * *

(xxi) Zinc oxide 2 to 25 percent.

* * * * *

4. Section 352.52 is amended by adding paragraph (b)(2)(vii) to read as follows:

§ 352.52 Labeling of sunscreen drug products.

* * * * *

(b) * * *

(2) * * *

(vii) For products containing the active ingredient identified in § 352.10(v), the following labeling statements may be used—(A) "Broad spectrum sunscreen."

(B) "Provides" (select one of the following: "UVB and UVA" or "broad spectrum") "protection."

(C) "Protects from UVB and UVA" (select one of the following: "rays" or "radiation").

(D) (Select one of the following: "Absorbs," "Protects," "Screens," or "Shields") "within the UVA spectrum."

(E) "Provides protection from the UVA rays that may contribute to skin damage and premature aging of the skin."

Dated: October 10, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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PANAMA CANAL COMMISSION

35 CFR Part 117

RIN 3207-AA48

Marine Accidents: Investigations; Control; Responsibility

AGENCY: Panama Canal Commission.

ACTION: Notice of proposed rulemaking; request for comments.

SUMMARY: The Panama Canal Commission (Commission) proposes to amend its regulations to limit its liability in marine accidents. The new regulations will require potential claimants to carry insurance against marine accidents in an amount of \$1 million to cover damages sustained by their vessels at the Canal when transiting the waterway or navigating in waters adjacent thereto.

DATES: The agency must receive written comments on or before November 30, 1998.