Adrian, MI, Lenawee County, NDB RWY 5, Amdt 7
Springfield, MO, Springfield Regional, VOR or GPS RWY 20, Amdt 17 Cancelled
Springfield, MO, Springfield Regional, VOR RWY 20, Amdt 17
Jefferson City, MO, Jefferson City Memorial, NDB or GPS RWY 30, Amdt 8A Cancelled
Jefferson City, MO, Jefferson City Memorial, NDB RWY 30, Amdt 8A
Sidney, MT, Sidney-Richland Muni, NDB or GPS RWY 1, Amdt 2 Cancelled
Sidney, MT, Sidney-Richland Muni, NDB RWY 1, Amdt 2
Sidney, MT, Sidney-Richland Muni, NDB or GPS RWY 19, Amdt 3 Cancelled
Sidney, MT, Sidney-Richland Muni, NDB RWY 19, Amdt 3
Columbus, NE, Columbus Muni, NDS or GPS RWY 14, Amdt 12 Cancelled
Columbus, NE, Columbus Muni, NDS RWY 14, Amdt 12
Roswell, NM, Roswell Industrial Air Center, RNAV RWY 35, Amdt 2 Cancelled
Roswell, NM, Roswell Industrial Air Center, VOR/DME RNAV RWY 35, Amdt 3
Roswell, NM, Roswell Industrial Air Center, NDB RWY 21, Amdt 15 Cancelled
Roswell, NM, Roswell Industrial Air Center, NDB RWY 21, Amdt 16
Columbus, OH, Ohio State University, VOR/DME RNAV or GPS RWY 27L, Amdt 6 Cancelled
Columbus, OH, Ohio State University, VOR/DME RNAV RWY 27L, Amdt 6
Columbus, OH, Ohio State University, NDB or GPS RWY 9R, Amdt 6 Cancelled
Columbus, OH, Ohio State University, NDB RWY 9R, Amdt 6 Cancelled
Newark, OH, Newark-Heath, VOR/DME RNAV or GPS RWY 27, Amdt 6 Cancelled
Newark, OH, Newark-Heath, VOR/DME RNAV RWY 27, Amdt 6
Tiffin, OH, Seneca County, NDB or GPS RWY 24, Amdt 7 Cancelled
Tiffin, OH, Seneca County, NDB RWY 24, Amdt 7
Wooster, OH, Wayne County, VOR or GPS RWY 10, Orig-A Cancelled
Wooster, OH, Wayne County, VOR RWY 10, Orig-A
Wooster, OH, Wayne County, NDB or GPS RWY 28 Amdt 7A Cancelled
Wooster, OH, Wayne County, NDB RWY 28 Amdt 7A
Antlers, OK, Antlers Muni, NDB or GPS RWY 35, Amdt 2A Cancelled
Antlers, OK, Antlers, Muni, NDB RWY 35, Amdt 2A
Aurora, OR, Aurora State, NDB or GPS RWY 17, Amdt 1 Cancelled
Aurora, OR, Aurora State, NDB RWY 17, Admt 1
Roseburg, OR, Roseburg Regional, VOR or GPS–A, Amdt 5 Cancelled
Roseburg, OR, Roseburg Regional, VOR–A, Amdt 6
Aguadilla, PR, Rafael Hernandez, VOR/DME or GPS RWY 8, Amdt 1 Cancelled
Aguadilla, PR, Rafael Hernandez, VOR/DME RWY 8, Amdt 1
Newberry, SC, Newberry Muni, NDB or GPS RWY 22, Amdt 4 Cancelled
Newberry, SC, Newberry, Muni, NDB RWY 22, Amdt 4
Andrews, TX, Andrews County, NDB or GPS RWY 15, Amdt 2 Cancelled
Andrews, TX, Andrews County, NDB RWY 15, Amdt 2
Conroe, TX, Montgomery County, VOR/DME RNAV or GPS RWY 32, Amdt 1 Cancelled
Conroe, TX, Montgomery County, VOR/DME RNAV RWY 32, Amdt 1
Fort Stockton, TX Fort Stockton-Pecos County, VOR or GPS RWY 12, Amdt 7A Cancelled
Fort Stockton, TX Fort Stockton-Pecos County, VOR RWY 12, Amdt 7A
Houston, TX, Ellington Field, VOR/DME or TACAN or GPS RWY 4, Amdt 3 Cancelled
Houston, TX, Ellington Field, VOR/DME or TACAN RWY 4, Amdt 3
Houston, TX, Houston Intercontinental, VOR/DME or GPS RWY 14L, Amdt 15A Cancelled
Houston, TX, Houston Intercontinental, VOR/DME RWY 14L, Amdt 15A
Hereford, TX, Hereford Muni, NDB or GPS RWY 21, Amdt 2 Cancelled
Hereford, TX, Hereford Muni, NDB RWY 21, Amdt 2
St George, UT, St George Muni, VOR/DME or GPS RWY 34, Amdt 2A Cancelled
St George, UT, St George Muni, VOR/DME RWY 34, Amdt 2A
Richmond/Ashland, VA, Hanover County Muni, NDB or GPS RWY 16, Orig Cancelled
Richmond/Ashland, VA, Hanover County Muni, NDB RWY 16, Orig
Richmond, VA, Richmond Intl, VOR or GPS RWY 34, Amdt 20 Cancelled
Richmond, VA, Richmond Intl, VOR RWY 34, Amdt 21
Bellingham, WA, Bellingham Intl, NDB or GPS RWY 16 Orig Cancelled
Bellingham, WA, Bellingham Intl, NDB RWY 16 Orig

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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; Marketing Status of Products Containing Avobenzone; Enforcement Policy

AGENCY: Food and Drug Administration, HHS.

ACTION: Announcement of Enforcement Policy.

SUMMARY: The Food and Drug Administration (FDA) is announcing an enforcement policy allowing over-the-counter (OTC) marketing of sunscreen drug products containing avobenzone (Parsol® 1789) at concentrations of up to 3 percent alone and 2 to 3 percent avobenzone in combination with the OTC sunscreen ingredients cinoxate, diethanolamine methoxycinnamate, dioxybenzone, homosalate, octocrylene, octyl methoxycinnamate, octyl salicylate, oxybenzone, sulisobenzone, and/or trolamine salicylate. OTC marketing of such drug products is being permitted pending establishment under the OTC drug review of a final monograph covering sunscreen drug products. FDA anticipates that sunscreen drug products containing up to 3 percent avobenzone alone and 2 to 3 percent avobenzone in combination with the proposed Category I cinnamate, benzophenone, salicylate, and/or diphenylacrylate sunscreen ingredients will be determined to be generally recognized as safe and effective and not misbranded.

EFFECTIVE DATE: The enforcement policy is effective April 30, 1997.

ADDRESSES: Written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: John D. Lipnicki, 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 an amendment to the tentative final monograph for OTC sunscreen drug products, published in the **Federal Register** of September 16, 1996 (61 FR 48645), FDA proposed conditions under which products containing avobenzone are generally recognized as safe and effective and not misbranded at concentrations of up to 3 percent alone and 2 to 3 percent avobenzone in combination with the proposed Category I cinnamate, benzophenone, salicylate, and/or diphenylacrylate sunscreen ingredients. This proposal was based on an evaluation of available safety and effectiveness data, which have been placed on display in the Dockets Management Branch (address above).

Because no OTC drug advisory review panel had considered avobenzone or avobenzone-containing combination drug products, the agency stated that these products could not be marketed until the agency stated by notice in the **Federal Register** that the products have been tentatively determined to be generally recognized as safe and effective and that OTC marketing will be permitted under specified conditions (61 FR 48645 at 48653). Before marketing could begin, the comment period for the proposal must have ended

and another **Federal Register** notice must have been published setting forth the agency's determination concerning interim marketing before publication of the final rule for OTC sunscreen drug products. The agency requested written comments by October 16, 1996.

In response to the proposed rule, seven commercial organizations, one international organization, one professional organization, and one individual consumer submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above).

II. The Agency's Conclusions on the Comments

1. Several comments discussed issues that impact all OTC sunscreen drug products or all such products that provide ultraviolet A (UVA) radiation protection, e.g., the definition of a sunscreen active ingredient, a maximum sun protection factor (SPF) of 30, and UVA testing methodology.

Following publication of the proposed rule for OTC sunscreen drug products on May 12, 1993 (58 FR 28194), the agency received numerous, similar comments. Because these issues impact other OTC sunscreen drug products, the agency intends to address all of the comments in future issues of the **Federal Register**. The agency does not find it necessary to resolve these issues now to allow interim marketing of OTC sunscreen drug products containing avobenzone under the proposed monograph.

2. One comment suggested that FDA should clarify the implication that its failure to rely explicitly on available foreign marketing data in determining that avobenzone is generally recognized as safe and effective for use in certain OTC sunscreen formulations does not mean that such data are unreliable, irrelevant, or inadequate compared to analogous U.S. marketing data or that foreign data would not have supported the agency's ultimate determination. The comment maintained that FDA can use foreign marketing data alone to establish that an OTC sunscreen active ingredient is generally recognized as safe and effective. The comment recommended that FDA should promptly review citizen petitions for all proposed OTC sunscreen ingredients and not only those that provide protection against UVA radiation. The comment referred to the agency's advance notice of proposed rulemaking on eligibility criteria for considering additional conditions in the OTC drug monograph system (61 FR 51625, October 3, 1996) and hoped that it would be expedited with issuance of a final rule within 12 months.

Another comment urged the agency to grant two other citizen petitions to include methylbenzylidene camphor (Ref. 1) and isoamyl-p-methoxycinnamate (Ref. 2) as Category I sunscreen active ingredients. In addition to foreign marketing data contained in the petitions, the comment stated that the agency already has supportive data for the combination of avobenzone with methylbenzylidene camphor (61 FR 48645 at 48647). The comment contended that FDA had grandfathered other cinnamates based on supportive data concerning octyl methoxycinnamate in combination with avobenzone and that this should be extended to isoamyl-p-methoxycinnamate.

The agency's reliance on information other than the available foreign marketing data in the amendment to the proposed rule for OTC sunscreen drug products is not intended to reflect an ultimate agency conclusion about the potential usefulness of foreign marketing data. As discussed in the advance notice of proposed rulemaking on eligibility criteria for considering additional conditions in the OTC drug monograph system, marketing of an OTC drug in a foreign country (but never in the United States) has in the past not been considered sufficient to satisfy the requirements of marketing to a material extent and for a material time which is necessary to make the drug eligible for consideration in the OTC drug monograph system (61 FR 51625 at 51627). Any possible changes to that approach will be considered under that rulemaking. The agency notes that avobenzone has been marketed for a material time and extent in the United States, and thus differs from other ingredients that do not have this marketing history.

The petitions mentioned by the comments are referred to in that advance notice of proposed rulemaking (61 FR 51625 at 51627). Final resolution of those petitions will depend upon the outcome of that rulemaking. In the meantime, manufacturers may seek marketing approval for their products having only foreign marketing experience via a new drug application (NDA).

References

(1) Comment No. CP1, Docket No. 78N–0038, Dockets Management Branch.

(2) Comment No. CP3, Docket No. 78N–0038, Dockets Management Branch.

3. Eight comments agreed with the agency's proposal to include avobenzone in §§ 352.10 and 352.20 of the proposed monograph for OTC sunscreen drug products. Although agreeing with the agency's proposal, one comment stated that avobenzone has not been adequately tested for safety in children. The comment contended that children may be at greater risk than adults for contact irritation and photoallergenic reactions, and that the proposed warning statement in § 352.52(c)(1)(iii) (''Discontinue use if signs of irritation or rash appear * * *'') may not be adequate for children. The comment provided an abstract (Ref. 1) that reported the results of photopatch testing using UV absorbers on 387 patients with dermatitis of the sun-exposed areas of the body. Isopropyl dibenzoylmethane was reported to induce 26 allergic and 35 photoallergic reactions and butyl methoxydibenzoylmethane (avobenzone) was reported to induce 10 allergic and 17 photoallergic reactions in these photopatch tests. The abstract stated that the production of isopropyl dibenzoylmethane was stopped in 1993 because of ''frequent (photo)sensitization'' to this ingredient. The comment requested that the agency do the following for an initial period of at least 2 years: (1) Restrict the general use of avobenzone-containing OTC sunscreen drug products to use by adults with labeling warnings to physicians and parents concerning its use on children, and (2) request companies to monitor all adverse reactions from avobenzone-containing products, especially those in children.

The agency is aware of several European studies and case reports (Refs. 2 and 4 through 8) involving patch/photopatch testing of isopropyl dibenzoylmethane and avobenzone on people suspected of having photodermatoses. With regard to this population, Buckley, O'Sullivan, and Murphy (Ref. 6) noted that ''Many cases of sensitization have occurred in subjects with pre-existing photodermatoses, where sunscreen use is frequent; contact and photocontact dermatitis are more likely to develop in injured or inflamed skin.'' Parry, Bilsland, and Morley (Ref. 7) observed that suggested cross-sensitivity to isopropyl dibenzoylmethane and avobenzone has previously been reported. Motley and Reynolds (Ref. 8) stated that primary sensitization to avobenzone is thought to be unusual compared to sensitization to isopropyl dibenzoylmethane. Trevisi et al. (Ref. 2) reported that their study seems to confirm that avobenzone could be a weaker sensitizer than the isopropyl derivative. Urbach (Ref. 9) and

Dromgoole and Maibach (Ref. 10) noted that some allergic reactions to avobenzone may have been cross-reactions as a result of prior exposure to the isopropyl derivative. However, Buckley, O'Sullivan, and Murphy (Ref. 6) pointed out that although combined sensitivity to isopropyl dibenzoylmethane and avobenzone has been documented previously, it is generally impossible to attribute it to cross-sensitivity between dibenzoylmethanes, as people may unknowingly have previously been exposed through cosmetic or sunscreen use. According to White (Ref. 3), isopropyl dibenzoylmethane was voluntarily removed from the European market due to frequent reports of contact and photocontact allergy, whereas avobenzone was classified by the European Commission as Category A, i.e., ''no further evidence needs to be submitted to support its safety.''

The agency believes that, overall, medical literature reports of allergic reactions to avobenzone appear to be few in comparison to the scope of its usage and to the number of allergic reactions associated with isopropyl dibenzoylmethane, a sunscreen ingredient that has never been approved for use in the United States and that has been removed from the European market. Neither a 10-year (1982 to 1992) French study of 283 people (5 to 85 years of age) with suspected photodermatosis (Ref. 5) nor a 3-year (1990 to 1993) Italian study of 108 people (10 to 79 years of age) with suspected photodermatosis (Ref. 2) reported any positive photopatch reactions to avobenzone. The two studies reported a total of seven positive photopatch reactions to isopropyl dibenzoylmethane. Several reports (Refs. 6 through 10) suggest that some allergic reactions to avobenzone may be related to prior sensitization to isopropyl dibenzoylmethane. None of the studies or reports (including the abstract provided by the comment) described any special relationships between sensitivity to dibenzoylmethanes and age.

One comment reported that an avobenzone-containing OTC sunscreen drug product has been marketed in the United States since 1993 (under an approved NDA) with a total adverse event rate of 0.0067 percent. The product is marketed for the general population (with the exception of children under 6 months of age) and contains 3 percent avobenzone, 3 percent oxybenzone, and 7.5 percent octyl methoxycinnamate. The agency previously discussed the adverse event information submitted by this comment and adverse event reports contained in the agency's Spontaneous Reporting System (SRS) in the amendment to the proposed rule for OTC sunscreen drug products (61 FR 48645 at 48650 and 48651). These data reveal that 6 of the 59 adverse drug experience (ADE) reports in the SRS concerned reactions in children 12 years of age and under. Three of these reports mention ''no drug effect'' and/or ''rash'' (one report noted multiple preexisting allergies), two mention ''itching,'' and one mentions ''burning.'' Thus, although ADE incidence rates or drug safety comparisons cannot be made using SRS data alone, the agency believes that the data support the safe use of avobenzone on children.

The agency notes that the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products (the Panel) discussed ''adult skin'' and ''infant skin'' in its reports on OTC external analgesic drug products (44 FR 69768 at 69773, December 4, 1979) and OTC sunscreen drug products (43 FR 38206 at 38217, August 25, 1978). The Panel thoroughly discussed the absorptive characteristics of infant and adult skin and defined adult human skin to be that of individuals older than 6 months of age. The agency continues to concur with the Panel's recommended age limitations concerning the use of sunscreens because biological systems that metabolize and excrete drugs absorbed through the skin may not be fully developed in children under the age of 6 months.

Thus, the agency believes that at this time the data do not support the contention that children 1 to 12 years of age ''may be at a greater risk than adults with respect to contact irritation reaction and photoallergenic potential'' of avobenzone. Moreover, the comment did not submit any data to support such a contention.

FDA considers protection against UVA radiation an important public health benefit. As the agency stated in the amendment to the proposed rule for OTC sunscreen drug products (61 FR 48645 at 48653), the addition of avobenzone to the proposed monograph would provide for wide availability of new combination sunscreen products that will provide consumers with broad spectrum protection. The agency is also aware that some individuals can have moderate or acute adverse reactions to active ingredients that cause no reactions in most people. FDA currently considers the warnings proposed in § 352.52(c)(1)(iii) (''Discontinue use if signs of irritation or rash appear. If irritation or rash persists, consult a doctor.'') sufficient to alert consumers to the possibility of an allergic reaction to avobenzone or any other sunscreen active ingredient. At this time, the agency does not believe there is a sufficient basis for a warning to restrict use of avobenzone-containing sunscreen drug products to adults only, as one comment suggested. Avobenzone-containing sunscreen drug products will need to bear the directions in proposed § 352.52(d)(1) or (d)(2), which include the statements: ''Children under 2 years of age should use sunscreen products with a minimum SPF of 4'' and ''Children under 6 months of age: consult a doctor.''

Regarding the comment's request that FDA ask companies to monitor all adverse reactions from avobenzone-containing products, especially those in children, the agency's current good manufacturing practice regulations for finished pharmaceuticals (21 CFR 211.198) include requirements for handling all written and oral complaints regarding a drug product. However, while FDA encourages OTC drug manufacturers to report adverse events under the agency's Medwatch program, manufacturers are not required to do so. At this time, the agency's adverse experience reporting requirements only apply to those OTC drugs subject to approved NDA's or abbreviated NDA's (ANDA's). The agency is considering a proposed regulation that would, among other things, require manufacturers, packers, and distributors of marketed OTC drug products that are not the subject of approved applications to report ADE information to FDA. In the meantime, the agency will continue to monitor ADE's for sunscreen drug products reported to its Medwatch program and in the medical literature.

References

(1) Schauder, S., ''UV Absorber Allergy and Photoallergy: A 14–Year Experience,'' abstract in Comment No. C518, Docket No. 78N–0038, Dockets Management Branch.

(2) Trevisi, P. et al., ''Sunscreen Sensitization: A Three-Year Study,'' *Dermatology*, 189:55–57, 1994.

(3) White, I. R., ''Risk of Contact Dermatitis from UV-A Sunscreens'' (reply letter), *Contact Dermatitis*, 29:221, 1993.

(4) Comment No. CP5, Docket No. 78N–0038, Dockets Management Branch.

(5) Szczurko, C. et al., ''Photocontact Allergy to Oxybenzone: Ten Years of Experience,'' *Photodermatology, Photoimmunology, and Photomedicine*, 10:144–147, 1994.

(6) Buckley, D. A., D. O'Sullivan, and G. M. Murphy, ''Contact and Photocontact Allergy to Dibenzoylmethanes and Contact Allergy to Methylbenzylidene Camphor,'' *Contact Dermatitis*, 28:47, 1993.

(7) Parry, E. J., D. Bilsland, and W. N. Morley, ''Photocontact Allergy to 4-tert.butyl-4'-methoxy-dibenzoylmethane (Parsol 1789),'' *Contact Dermatitis*, 32:251, 1995.

(8) Motley, R. J., and A. J. Reynolds, ''Photocontact Dermatitis Due to Isopropyl and Butyl Methoxy Dibenzoylmethanes (Eusolex 8020 and Parsol 1789),'' *Contact Dermatitis*, 21:109, 1989.

(9) Urbach, F., ''Risk of Contact Dermatitis from UV–A Sunscreens'' (letter), *Contact Dermatitis*, 29:220, 1993.

(10) Dromgoole, S. H., and H. I. Maibach, ''Sunscreening Agent Intolerance: Contact and Photocontact Sensitization and Contact Urticaria,'' *Journal of the American Academy of Dermatology*, 22:1068–1078, 1990.

4. Three comments expressed concern about the photostability of avobenzone-containing sunscreen drug products, especially when used in a formulation without any other sunscreen active ingredients. Two comments stated that OTC sunscreen drug products with avobenzone as their only sunscreen active ingredient may not provide effective protection against ultraviolet B (UVB) radiation and that, even when combined with other sunscreen active ingredients, the UVA radiation tests (61 FR 48645 at 48652) do not stress the formulation enough to determine if the product will remain effective after receiving higher doses of UV radiation. One comment stated that because no official method has yet been established to test for protection from UVA radiation, broad marketing of avobenzone-containing sunscreen drug products should not be allowed because of photostability concerns related to avobenzone. One of the comments also questioned whether avobenzone photoproducts are photoallergenic. None of the comments supplied any data to support their contentions.

The agency is aware that avobenzone's maximum absorbance is in the UVA radiation spectrum (i.e., 340 to 350 nanometers (nm)) and that most of the data discussed in the amendment to the proposed rule for OTC sunscreen drug products concerns combinations of avobenzone with other Category I sunscreen active ingredients. However, data submitted to the agency (Ref. 1) reported a mean SPF of 2.4 for avobenzone alone in an appropriate vehicle. In its conclusions about the safety and effectiveness of OTC avobenzone-containing sunscreen drug products (61 FR 48645 at 48652), the agency stated that it considered the submitted data as supportive of the safety and effectiveness of up to 3 percent avobenzone alone ''if the finished product provides at least an SPF 2.'' An SPF of 2 indicates that the ingredient provides some UVB protection.

The agency agrees with the comment concerning the need for a monograph method for determining UVA radiation protection and believes that such a method should also address the photostability of sunscreen active ingredients. However, FDA has determined that adequate and well-controlled studies using currently accepted methods provide sufficient evidence of the effectiveness of 2 to 3 percent avobenzone in protecting against UVA radiation (61 FR 48651 and 48652). The agency continues to evaluate data and information and plans to propose a monograph method for determining UVA radiation protection in a future issue of the **Federal Register**.

One of the comments also questioned whether avobenzone photoproducts are photoallergenic. Agency review of adverse drug experience data for an OTC 3 percent avobenzone combination product marketed under an NDA since 1993 revealed no serious outcomes or alarming trends in numbers or types of reactions. The agency previously stated that, although more information will ultimately be required before the nature and safety profiles of avobenzone photodegradation products can be thoroughly assessed, it is presently not aware of any safety or effectiveness problems associated with the photostability of avobenzone (61 FR 48645 at 48651 and 48652). The agency also continues to evaluate photostability information recently submitted following the September 19 and 20, 1996, public meeting (61 FR 42398, August 15, 1996) on the photochemistry and photobiology of sunscreens. The agency plans to address the photostability of all OTC sunscreen active ingredients in a future issue of the **Federal Register**.

Reference

(1) Comment No. LET138, Docket No. 78N–0038, Dockets Management Branch.

5. Three comments disagreed with the proposed requirement for a minimum concentration of avobenzone when it is used in combination OTC sunscreen drug products (i.e., a minimum of 2 percent when used in a combination OTC sunscreen drug product with one or more of the proposed Category I cinnamate, benzophenone, diphenylacrylate, and/or salicylate sunscreen active ingredients). One comment stated that the minimum concentration requirement is inappropriate and unnecessarily restrictive. The comment stated that: (1) Meaningful and appropriate UVA radiation protection can be provided by using avobenzone at concentrations below 2 percent; (2) if a lower concentration of avobenzone still provides effective UVA radiation protection, it will be more cost effective for the consumer; (3) lower avobenzone concentrations may provide for products with better aesthetics and thus better usage compliance; and (4) Canada, the European Union, and Australia have no minimum concentration requirement for avobenzone in combination sunscreen products. The comment recommended that the proposed minimum concentration be revised to permit use of alternative efficacy-based minimums provided that supporting data are generated showing that each ingredient in a combination drug product provides a significant contribution to overall product effectiveness.

Two comments stated that the same rationale the agency used in determining that OTC sunscreen drug products with only one active sunscreen ingredient do not require minimum concentrations (i.e., finished product testing) should also apply to combination products. Another comment contended that by using the synergies of various sunscreen active ingredients in combination with avobenzone, manufacturers will be able to fine tune active levels based on total product efficacy. According to the comment, the combination of 1 percent avobenzone and 6 percent oxybenzone provides at least as much protection as 3 percent avobenzone alone, while the combination of 1 percent avobenzone and 10 percent octocrylene provides more UVA radiation protection than 2 percent avobenzone. The comment concluded that minimum concentration requirements encourage overmedicating the consumer without the benefit of increased UVA radiation protection.

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 tentatively concluded that minimum concentration requirements are necessary for combination sunscreen products (i.e., until a method is developed that can demonstrate the contribution of each OTC sunscreen ingredient in a combination product) because of its concern that each ingredient in a combination drug product contributes to the overall effectiveness of the product. The agency further stated:

> To require no minimum contribution at all could allow the use of amounts so small as to be misleading and deceptive to the consumer and could permit the inclusion of ingredients solely for promotional purposes. In addition, this could result in the

consumer's exposure to an additional ingredient or ingredients with minimal additional benefit being provided.

Following publication of the proposed rule for OTC sunscreen drug products on May 12, 1993, the agency received several comments concerning minimum concentrations for OTC sunscreen active ingredients. Because this issue impacts other OTC sunscreen active ingredients, the agency intends to address all of the comments in a future issue of the **Federal Register**.

–The minimum and maximum concentrations for avobenzone proposed in § 352.20 were based upon the agency's review of safety and effectiveness data and other information. Adequate and well-controlled studies using currently accepted methods have demonstrated the effectiveness of 2 to 3 percent avobenzone (alone and in combination with some proposed monograph sunscreen ingredients) in providing protection against UVA radiation. None of the comments submitted any data to support the effectiveness of avobenzone at concentrations lower than 2 percent. In the absence of any data, the agency is unable to address the overmedication/benefits issue raised by one comment.

6. Two comments asserted that all of the ''claims'' that can be made for avobenzone-containing OTC sunscreen drug products can also apply and should be allowed for such products containing titanium dioxide and/or zinc oxide. One comment stated that titanium dioxide or zinc oxide can enhance the UVA radiation protection effectiveness of avobenzone, allow for formula flexibility and cost competition for avobenzone, and promote usage compliance by consumers because titanium dioxide and zinc oxide are nonirritating and nongreasy. The comment added that consumers should not be misled into believing that only avobenzone can provide broad spectrum protection.

In the proposed rule for OTC sunscreen drug products (58 FR 28194 at 28232 to 28233), the agency discussed UVA radiation protection claims and proposed labeling that would apply to proposed Category I sunscreen active ingredients (e.g., titanium dioxide) that met certain criteria. Until the agency proposes a method for the determination of UVA radiation protection, sunscreen drug products may bear UVA claims provided that they: (1) Contain sunscreen active ingredients that absorb UVA radiation, and (2) meet the agency's enforcement policy which allows claims that were available in labeling prior to the beginning of the OTC drug review to appear in labeling of currently marketed products until the rulemaking for OTC sunscreen drug products is completed, and the regulation for this class of products becomes effective (Ref. 1). The agency is aware that some currently marketed OTC sunscreen drug products that contain titanium dioxide are promoted with claims pertaining to UVA radiation and/or broad spectrum protection (Ref. 2). The agency has recently (Refs. 3 through 6) discussed conditions under which OTC sunscreen drug products containing 2 to 25 percent zinc oxide would be generally recognized as safe and effective with labeling claims for UVA radiation protection. Sunscreen drug products containing zinc oxide that meet such conditions may be marketed before the establishment of a final monograph in accordance with the agency's longstanding policy regarding ingredients or combinations of ingredients and uses being evaluated in the OTC drug review (Ref. 1). Thus, the agency does not believe that consumers have been misled into believing that only avobenzone-containing sunscreen products can provide broad spectrum protection. The agency also plans to address UVA radiation claims and testing procedures further in a future issue of the **Federal Register**.

–References

(1) ''Food and Drug Administration Compliance Policy Guides 7132b.15 and 7132b.16,'' in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(2) ''Physicians' Desk Reference for Nonprescription Drugs,'' 17th ed., Medical Economics Co., Montvale, NJ, 1996, pp. 629 and 760.

(3) Comment No. LET150, Docket No. 78N–0038, Dockets Management Branch.

(4) Comment No. LET151, Docket No. 78N–0038, Dockets Management Branch.

(5) Comment No. LET152, Docket No. 78N–0038, Dockets Management Branch.

(6) Comment No. LET153, Docket No. 78N–0038, Dockets Management Branch.

7. One comment recommended that FDA issue a ''call-for-data'' to allow equal and ample opportunity for all interested parties to develop and submit additional data that may be needed to support combinations of avobenzone with other sunscreen active ingredients. Alternatively, the comment suggested that the agency should allow other avobenzone combinations provided that supporting safety data (i.e., clinical phototoxicity, photoallergenicity, repeat insult patch testing) are generated for products prior to marketing.

Several comments recommended that the agency allow avobenzone to be combined with titanium dioxide, zinc oxide, and/or phenylbenzimidazole sulfonic acid to provide for maximum flexibility in formulating effective OTC sunscreen drug products. Some of the comments referenced data presented at the September 19 to 20, 1996, Public Meeting to Discuss the Photochemistry and Photobiology of Sunscreens (Ref. 1) concerning products that contained avobenzone with either titanium dioxide or zinc oxide. Three comments added that studies evaluated in the amendment to the tentative final monograph were determined to be supportive of the safety of avobenzone and that these studies utilized combination test products that contained titanium dioxide and/or phenylbenzimidazole sulphonic acid.

The agency has previously stated (Refs. 2 and 3) that data from clinical studies are necessary to establish the safety and effectiveness of combinations of avobenzone with proposed Category I sunscreen active ingredients. In the amendment to the tentative final monograph (61 FR 48645 at 48650), the agency concluded that data submitted to the agency provide sufficient evidence to demonstrate the low irritation, allergenic sensitization, photoallergenic, and phototoxic potential of 2 to 3 percent avobenzone in combination with the proposed Category I cinnamate, benzophenone, diphenylacrylate, and/or salicylate sunscreen active ingredients. The agency further stated, however, that it does not consider the submitted data adequate to allow avobenzone to be combined with any and all proposed monograph sunscreen ingredients. The clinical studies referenced by the comment (Refs. 4, 5, and 6) that utilized combinations of avobenzone with titanium dioxide and/or phenylbenzimidazole sulfonic acid only assessed the irritation and/or contact allergy potential of the products. Two of the studies (Refs. 4 and 6) assessed irritation potential in study populations of only 25 and 15 individuals, respectively. One cumulative irritancy study (Ref. 5) utilized test products containing only low concentrations of avobenzone (0.2 to 1.5 percent). Another study (Ref. 5), noted by the agency as being supportive of the safety of 2 percent avobenzone, only assessed the cumulative irritancy and allergic potential of an avobenzone-containing combination sunscreen product containing 7.5 percent octyl methoxycinnamate and 3 percent titanium dioxide. Until complete and adequate data are submitted, the agency has no basis to allow other avobenzone combinations.

The agency sees no need to issue a ''call-for-data'' for all interested parties to develop and submit additional data to

support combinations of avobenzone with other sunscreen active ingredients. The agency is currently reviewing all data and information received as a result of the September 19 to 20, 1996, Public Meeting to Discuss the Photochemistry and Photobiology of Sunscreens and will address this information in a future issue of the **Federal Register**. Interested parties may submit additional data to support combinations of avobenzone with other sunscreen active ingredients in an appropriate citizen petition to amend the proposed monograph for OTC sunscreen drug products. (See 21 CFR 10.30.)

References

(1) Comment No. TR3, Docket No. 78N–0038, Dockets Management Branch.
(2) Comment No. LET118, Docket No. 78N–0038, Dockets Management Branch.
(3) Comment No. MM11, Docket No. 78N–0038, Dockets Management Branch.
(4) Comment No. LET127, Docket No. 78N–0038, Dockets Management Branch.
(5) Comment No. LET130, Docket No. 78N–0038, Dockets Management Branch.
(6) Comment No. SUP18, Docket No. 78N–0038, Dockets Management Branch.

8. One comment requested clarification of the Category I sunscreen active ingredients proposed as permitted combinations with avobenzone. The comment stated that the list of Category I sunscreen active ingredients in the summary section of the amendment to the proposed tentative final monograph (61 FR 48645) did not coincide with the combinations listed by alphabetical letters in proposed § 352.20(a)(2) (61 FR 48645 at 48654).

The agency corrected this discrepancy in the **Federal Register** of February 26, 1997 (62 FR 8663). Section 352.20(a)(2) now states:

> Two or more sunscreen active ingredients identified in § 352.10(b), (c), (d), (f), (i), (l), (m), (n), (o), (s), and (u) 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.

9. One comment asked whether clinical testing of avobenzone-containing OTC sunscreen drug products prior to marketing would be permitted without an approved investigational new drug application (IND). The comment urged the agency to allow clinical testing without an approved IND of avobenzone concentrations and active ingredient combinations not specified in the amendment.

Section 312.2(b)(1) (21 CFR 312.2(b)(1)) exempts the clinical investigation of a drug product that is lawfully marketed in the United States from the procedures and requirements contained in part 312 (21 CFR part 312) (which governs the use of IND's) if, among other things, the investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug. Because this notice allows the lawful OTC marketing of certain avobenzone-containing sunscreen drug products without an approved NDA, an exemption from the requirements of part 312 would be allowed for those products specified in this notice if all of the conditions in § 312.2(b)(1) are met. However, OTC sunscreen active ingredient concentrations and combinations not specified in this notice may not be lawfully marketed at this time without an approved NDA. Such products, therefore, would not be exempted from the procedures and requirements of part 312 on the basis of this notice. An IND would be needed to study the safety and effectiveness of such products.

III. Enforcement Status

After carefully reviewing all of the comments received, the agency is issuing a notice of enforcement policy permitting OTC marketing of drug products containing up to 3 percent avobenzone alone and 2 to 3 percent avobenzone in combination with the following proposed Category I sunscreen active ingredients: Cinoxate, diethanolamine methoxycinnamate, dioxybenzone, homosalate, octocrylene, octyl methoxycinnamate, octyl salicylate, oxybenzone, sulisobenzone, and/or trolamine salicylate. The agency addressed the safety and effectiveness of such avobenzone-containing drug products in the proposed amendment to the tentative final monograph for OTC sunscreen drug products (61 FR 48645 at 48646 through 48652). Based on a comment received in response to the proposal, the agency has reevaluated the use of OTC avobenzone-containing sunscreen drug products on children and believes that the need for the warning suggested by the comment regarding use on children between 6 months and 12 years of age has not been established. Most of the other comments concerned requests for other avobenzone-containing sunscreen product combinations and/or concentrations, or issues similar to those submitted in response to the proposed rule that apply to all OTC sunscreen drug products and that will be addressed in future issues of the **Federal Register**. Accordingly, the agency has tentatively determined that it is appropriate at this time to allow the interim marketing of the OTC avobenzone-containing products identified in proposed §§ 352.10 and 352.20.

The agency's enforcement policy in Compliance Policy Guide 7132b.16, relating to OTC marketing of combination drug products that are under consideration in FDA's OTC drug review, makes it clear that FDA may by notice in the **Federal Register** permit interim marketing of products such as the sunscreen drug products discussed in this notice. The agency advises that sunscreen drug products containing up to 3 percent avobenzone alone and 2 to 3 percent avobenzone in combination with the proposed Category I cinnamate, benzophenone, salicylate, and/or diphenylacrylate sunscreen ingredients as proposed in §§ 352.10 and 352.20 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. Products containing avobenzone require both UVA radiation protection testing and SPF testing of the finished product, as discussed in the amendment to the proposed rule for OTC sunscreen drug products (61 FR 48645 at 48652). Until the agency proposes a monograph UVA radiation testing method, the agency considers testing procedures similar to those described by R. W. Gange et al. and N. J. Lowe et al. as adequate for determining the UVA radiation protection potential of a finished OTC sunscreen drug product. Products containing avobenzone require SPF testing of the finished product in accordance with proposed §§ 352.10 and 352.20 (58 FR 28194 at 28295 and 28296) and as amended in §§ 352.10 and 352.20 (61 FR 48645 at 48654). The products must be marketed with the labeling proposed in §§ 352.50 through 352.60 (58 FR 28194 at 28296 to 28298) and as amended in § 352.52 (61 FR 48645 at 48655). Marketing of such products with labeling not in accord with the labeling in these sections 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.

IV. Opportunity for Comments

Interested persons may submit written comments to the Dockets Management Branch (address above). Such comments will be considered in determining whether further amendments or revisions to this policy are warranted. 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.

(Secs. 201, 501, 502, 503, 505, 510, and 701 of the Federal Food, Drug, and Cosmetic Act and under authority of the Commissioner of Food and Drugs)

Dated: April 22, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–11116 Filed 4–29–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 520

Oral Dosage Form New Animal Drugs; Oxytetracycline Hydrochloride Soluble Powder

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of an abbreviated new animal drug application (ANADA) filed by the Pennfield Oil Co. The ANADA provides for the use of a generic oxytetracycline hydrochloride soluble powder for the drinking water of cattle, swine, sheep, chickens, and turkeys.

EFFECTIVE DATE: April 30, 1997.

FOR FURTHER INFORMATION CONTACT: Dianne T. McRae, Center for Veterinary Medicine (HFV–102), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1623.

SUPPLEMENTARY INFORMATION: Pennfield Oil Co., 14040 Industrial Rd., Omaha, NE 68137, filed ANADA 200–026, which provides for use of 102.4-gram (g) oxytetracycline hydrochloride per 4.78-ounce (135.5-g) packet for making medicated drinking water for cattle, swine, sheep, chickens, and turkeys for control and treatment of bacterial infections caused by oxytetracycline susceptible organisms.

ANADA 200–026 for Pennfield Oil Co.'s oxytetracycline hydrochloride water soluble powder is approved as a generic copy of Pfizer's NADA 8–622 Terramycin-343 (oxytetracycline hydrochloride) soluble powder. The ANADA is approved as of March 13, 1997, and the regulations are amended in 21 CFR 520.1660d by adding new paragraphs (a)(8) and (b)(6) to reflect the approval. The basis for approval is discussed in the freedom of information summary.

In accordance with the freedom of information provisions of 21 CFR part 20 and 514.11(e)(2)(ii), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

The agency has determined under 21 CFR 25.24(d)(1)(i) 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.

List of Subjects in 21 CFR Part 520

Animal drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 520 is amended as follows:

PART 520—ORAL DOSAGE FORM NEW ANIMAL DRUGS

1. The authority citation for 21 CFR part 520 continues to read as follows:

–Authority: Sec. 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b).

2. Section 520.1660d is amended by adding new paragraphs (a)(8) and (b)(6) to read as follows:

§ 520.1660d Oxytetracycline hydrochloride soluble powder.

(a) * * *

(8) Each 135.5-gram packet (4.78 ounce) contains 102.4 grams of OTC HCl.

(b) * * *

(6) No. 053389 for use of OTC HCl concentrations in paragraph (a)(8) of this section in chickens, turkeys, swine, cattle, and sheep.

* * * * *

Dated: April 2, 1997.

Michael J. Blackwell,

Deputy Director, Center for Veterinary Medicine.

[FR Doc. 97–11079 Filed 4–29–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 520

Oral Dosage Form New Animal Drugs; Sulfadimethoxine Oral Solution

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of an abbreviated new animal drug application (ANADA) filed by Phoenix Scientific, Inc. The ANADA provides for use of sulfadimethoxine oral solution for chickens, turkeys, and cattle for treatment of certain bacterial infections.

EFFECTIVE DATE: April 30, 1997.

FOR FURTHER INFORMATION CONTACT: Lonnie W. Luther, Center For Veterinary Medicine (HFV–102), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1623.

SUPPLEMENTARY INFORMATION: Phoenix Scientific, Inc., 3915 South 48th Street Ter., P.O. Box 6457, St. Joseph, MO 64506–0457, filed ANADA 200–192, which provides for use of sulfadimethoxine 12.5 percent oral solution for chickens, turkeys, and cattle. The oral solution is used to make medicated drinking water for broiler and replacement chickens for the treatment of outbreaks of coccidiosis, fowl cholera, and infectious coryza; meat-producing turkeys for disease outbreaks of coccidiosis and fowl cholera; dairy calves, dairy heifers, and beef cattle (in drinking water and as a drench) for shipping fever complex, bacterial pneumonia associated with *Pasteurella* spp. sensitive to sulfadimethoxine, calf diphtheria and foot-rot associated with *Sphaerophorus necrophorus* sensitive to sulfadimethoxine.

Approval of Phoenix's ANADA 200–192 for sulfadimethoxine oral solution is as a generic copy of Pfizer's NADA 31–205 for Albon® (sulfadimethoxine) 12.5 percent concentrated solution. The ANADA is approved as of March 24, 1997, and the regulations are amended by revising 21 CFR 520.2220a(b) to