**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 in combination with the OTC sunscreen ingredients cinoxate, diethanolamine methoxycinnamate, dioxybenzone, homosalate, octocrylene, octyl methoxycinnamate, octyl salicylate, oxybenzone, sulisobenzene, 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 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 (address above) may be filed with the docket.

**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.

**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 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.

**Conroe, TX, Montgomery County, VOR/DME RNAV or GPS RWY 32, Amdt 1 Cancelled**

**Fort Stockton, TX, Fort Stockton-Pecos County, VOR or GPS RWY 12, Amdt 7A Cancelled**

**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**

**Newport, KY, Newport, Muni, VOR/DME RNAV or GPS RWY 6, Amdt 2 Canceled**

**Paterson, NJ, Passaic County, VOR/DME RNAV or GPS RWY 24, Amdt 4 Canceled**

**Tampa, FL, Tampa Intl, VOR/DME RNAV or GPS RWY 28, Amdt 7 Cancelled**

**Fort Worth, TX, Will Rogers Field, VOR/DME or GPS RWY 23, Amdt 17 Canceled**

**Dallas, TX, Dallas-Fort Worth International, VOR/DME RNAV or GPS RWY 24, Amdt 9 Cancelled**

**Minneapolis, MN, Minneapolis St Paul International, VOR/DME RNAV or GPS RWY 21, Amdt 7 Cancelled**

**Saint Paul, MN, Minneapolis St Paul International, VOR/DME RNAV or GPS RWY 9L, Amdt 15A Cancelled**

**San Antonio, TX, San Antonio Intl, VOR/DME RNAV or GPS RWY 17, Amdt 2 Cancelled**

**Big Spring, TX, Franklin County, VOR/DME RNAV or GPS RWY 10, Amdt 1 Cancelled**

**Brownsville, TX, Brownsville Muni, VOR/DME RNAV or GPS RWY 10, Amdt 1 Cancelled**

**Kingman, AZ, Kingman Muni, VOR/DME RNAV or GPS RWY 28, Amdt 1 Cancelled**

**Newark, NJ, Newark Liberty International, VOR/DME RNAV or GPS RWY 24, Amdt 7 Cancelled**

**Tiffin, OH, Seneca County, NDB or GPS RWY 24, Amdt 7 Cancelled**

**Wooster, OH, Wayne County, VOR or GPS RWY 10, Amdt 7 Cancelled**

**Antlers, OK, Antlers Muni, NDB or GPS RWY 35, Amdt 2A Cancelled**

**Aurora, OR, Aurora State, NDB or GPS RWY 17, Amdt 1 Cancelled**

**Roseburg, OR, Roseburg Regional, VOR or GPS-A, Amdt 5 Cancelled**

**Aguadilla, PR, Rafael Hernandez, VOR/DME or GPS RWY 8, Amdt 1 Cancelled**

**Newbury, SC, Newbury Muni, NDB or GPS RWY 22, Amdt 4 Cancelled**

**Newbury, SC, Newbury Muni, NDB or GPS RWY 22, Amdt 4**

**Andrews, TX, Andrews County, NDB or GPS RWY 15, Amdt 2 Canceled**

**Conroe, TX, Montgomery County, VOR/DME RNAV or GPS RWY 32, Amdt 1 Canceled**

**Fort Stockton, TX, Fort Stockton-Pecos County, VOR or GPS RWY 12, Amdt 7A Cancelled**

**Roseburg, OR, Roseburg Regional, VOR/DME RNAV or GPS RWY 15, Amdt 2 Cancelled**

**Newark, OH, Newark-Heath, VOR/DME RNAV or GPS RWY 27, Amdt 6 Cancelled**

**Newark, OH, Newark-Heath, VOR/DME RNAV or GPS RWY 27, Amdt 6 Cancelled**

**Richmond/Victoria, VA, Hanover County Muni, NDB or GPS RWY 16, Orig Cancelled**

**Richmond, VA, Richmond Intl, VOR or GPS RWY 34, Amdt 20 Cancelled**

**Richmond, VA, Richmond Intl, VOR or GPS RWY 34, Amdt 21**

**Bellingham, WA, Bellingham Intl, NDB or GPS RWY 16 Orig Cancelled**

**Bellingham, WA, Bellingham Intl, NDB or GPS RWY 16 Orig Cancelled**

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**BILLING CODE 4910–13–M**
II. The Agency’s Conclusions on the Comments

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.

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 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 photoallergic reactions, and that the proposed warning statement in §352.2(c)(1)(ii) (“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, Bilisland, 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

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).
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 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. 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 photoalergenic potential” of avobenzone. Moreover, the comment did not submit any data to support such a contention.

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 photoalergenic potential” of avobenzone. Moreover, the comment did not submit any data to support such a contention.

In summary, the agency 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 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 69765, 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.

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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 photo-stability 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 photo-stability of avobenzone (61 FR 48645 at 48651 and 48652). The agency also continues to evaluate photo-stability 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 photo-stability of all OTC sunscreen active ingredients in a future issue of the Federal Register.

Reference

(1) Comment No. LET138, Docket No. 78N-0036, 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 sunscreen ingredients). One 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. Another comment contended that by using the synergies of various sunscreen active ingredients in combination with avobenzone, manufacturers should not be allowed because of photo-stability 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 expressed the 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; (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.

- 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 28154 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 UV 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 713.2b.15 and 713.2b.16," in OTC Vol. 06ATFM, Docket No. 78N-0038, Dockets Management Branch.
- (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. Additionally, 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 avobenzone-containing OTC sunscreen drug products be combined with titanium dioxide, zinc oxide, and/or phenylbenzimidazole sulfinic 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 sulfinic 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, allergic sensitization, phototoxicity, and phototoxic potential of 2 to 3 percent avobenzone in combination with the proposed Category I 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 agency were: (1) Ref. 4, (2) Ref. 5, and (3) Ref. 6) that utilized combinations of avobenzone with titanium dioxide and/or phenylbenzimidazole sulfinic 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

5. Comment No. LET130, Docket No. 78N–0038, Dockets Management Branch.

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 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 28295 to 28296) 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.
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 Phoenix Scientific, Inc. The ANADA provides for use of sulfadimethoxine oral solution for chickens, turkeys, and cattle for treatment of certain bacterial infections.


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 read:}

§ 520.2220a Oral Dosage Form New Animal Drugs; Sulfadimethoxine Oral Solution

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


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.

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