Proposed Rules

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This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

NUCLEAR REGULATORY COMMISSION

10 CFR Part 34

[Docket No. PRM–34–5]

Amersham Corporation, Receipt of a Petition for Rulemaking: Extension of Comment Period

AGENCY: Nuclear Regulatory Commission.

ACTION: Petition for rulemaking: extension of comment period.

SUMMARY: On June 18, 1996 (61 FR30837), the Nuclear Regulatory Commission (NRC) published for public comment a petition for rulemaking filed by Amersham Corporation. The petitioner requested that the NRC amend its regulations by removing the reference to "associated equipment" from the radiography equipment regulations. The petitioner believes that this amendment would clarify the licensing reviews of sealed sources and radiographic exposure devices to meet the applicable requirements. The comment period for this petition for rulemaking was to have expired on September 3, 1996.

A public workshop was held by NRC on August 29, 1996, concerning the issues raised in the petition, and many of the attendees were planning to follow up their public comments with letters on the petition. The petitioner believes that the issues raised in the petition require significant input from the affected licensees in order that the most effective regulations can be put in place. Therefore, Amersham Corporation has requested that the comment period be extended until September 30, 1996.

DATES: The comment period has been extended and now expires on September 30, 1996. Comments received after this date will be considered if it is practical to do so, but assurance of consideration cannot be given except for comments received on or before this date.

ADDRESSES: Send written comments to: Secretary, U.S. Nuclear Regulatory Commission, Washington, DC 20555–0001, Attention: Docketing and Service Branch.

Deliver comments to 11555 Rockville Pike, Rockville, Maryland, between 7:45 am and 4:15 pm on Federal workdays.

For a copy of the petition, write: Rules Review Section, Rules Review and Directives Branch, Division of Freedom of Information and Publications Services, Office of Administration, U.S. Nuclear Regulatory Commission, Washington, DC 20555–0001.

FOR FURTHER INFORMATION CONTACT: Michael T. Lesar, Office of Administration, U.S. Nuclear Regulatory Commission, Washington, DC 20555–0001. Telephone 301–415–7163 or Toll Free: 800–368–5642.

Dated at Rockville, Maryland, this 10th day of September 1996.

For the Nuclear Regulatory Commission.

John C. Hoyle,

Secretary of the Commission.

[FR Doc. 96–23632 Filed 9–13–96; 8:45 am]

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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

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 avobenzone (Parsol® 1789) 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 sunscreen ingredients cinoxate, diethanolamine methoxycinnamate, dioxybenzone, homosalate, octocrylene, octyl methoxycinnamate, octyl salicylate, oxybenzone, sulisobenzone, and/or trolamine salicylate. OTC marketing pursuant to this amendment may not begin until FDA publishes a subsequent notice in a future issue of the **Federal Register**. This proposal is in response to a citizen petition and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by October 16, 1996; written comments on the agency's economic impact determination by October 16, 1996. The agency is requesting comments within a 30-day period, instead of the normal 90 days, so that the marketing status of OTC avobenzone-containing sunscreen drug products can be determined in an expeditious manner (see section II.E. of this document). 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, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Desk copies of these written comments to Debra L. Bowen, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–105), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2304.

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. Avobenzone was not included in § 352.10 at that time. Subsequently, a manufacturer petitioned the agency to reopen the administrative record for OTC sunscreen drug products and to include avobenzone, an ultraviolet A (UVA)

radiation-absorbing sunscreen ingredient, in the monograph based upon avobenzone's history of use in several countries other than the United States since 1981 (Ref. 1).

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. Although the petition to include avobenzone in the monograph was discussed in the proposal (58 FR 28194 at 28210 and 28211), the agency stated that it had not reached a decision concerning the use of foreign marketing data as the sole basis to support the inclusion of an ingredient in the OTC drug review. The agency stated that it would not be in the public interest to unduly delay publication of the proposed rule for OTC sunscreen drug products and noted that a decision concerning the petition would be announced in a future issue of the **Federal Register**.

In the proposed rule, the agency also discussed the public health significance of 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, one cosmetic manufacturers' association, one professional association, one consumer, one U.S. Senator, two health care professionals, and seven manufacturers submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above).

On March 3, 1993, FDA received a petition (Ref. 2) requesting the agency to: (1) Reopen the rulemaking for OTC sunscreen drug products to include avobenzone as an active ingredient in the proposed rule for OTC sunscreen drug products; (2) permit broad spectrum combination sunscreen products containing avobenzone to be marketed with a range of sun protection factor (SPF) values; and (3) permit interim marketing of such products. The petitioner also made several subsequent submissions of data and other information (Refs. 3 through 8).

Following publication of the proposed rule for OTC sunscreen drug products on May 12, 1993, the agency responded to the petition in letters dated August 19, 1993, October 27, 1993, May 9, 1994, and May 9, 1996, and during meetings on May 11, 1994, March 6, 1995, and August 11, 1995 (Refs. 9 through 15). The petitioner subsequently clarified and modified its requests (Ref. 3): (1) To include avobenzone alone and in combination with all of the proposed monograph sunscreen ingredients except the aminobenzoates; (2) to limit the concentration of avobenzone to 1 to 3 percent (if data do not support up to 5 percent); and (3) to utilize approved new drug application (NDA) labeling and proposed monograph labeling as guides in proposing labeling for avobenzone-containing sunscreen drug products. Following the August 11, 1995 meeting, a manufacturer, in support of the petition, publicly released safety data from its NDA (approved by the agency in December 1992) for an OTC sunscreen drug product (Shade UVAGuard® SPF 15 lotion containing avobenzone, octyl methoxycinnamate, and oxybenzone) along with additional data and information concerning avobenzone (Refs. 16 and 17). The first NDA for a sunscreen drug product (Photoplex® containing avobenzone with padimate O) was approved in September 1988.

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

A. General

1. The petition requested that the agency reopen the rulemaking for OTC sunscreen drug products to include avobenzone as an active ingredient in the proposed rule for OTC sunscreen drug products. Several comments requested that the agency include avobenzone in the final monograph for these products. The petition and comments expressed concern about the potential hazards of UVA radiation and the need for making broad spectrum sunscreens widely available so that consumers can protect themselves from UVA as well as ultraviolet B (UVB) radiation. The petition contended that avobenzone has been marketed in the United States (and abroad) to a material extent and for a material time under generally safe and effective conditions.

The agency has determined that avobenzone has been marketed in OTC sunscreen drug products for a material time and to a material extent. Avobenzone has been continuously marketed in the United States under NDA's for approximately 8 years and subject to the adverse event reporting requirements. Over 5,000,000 units of avobenzone containing products have been sold in the United States. Accordingly, the agency has determined that avobenzone can be considered in this rulemaking for OTC sunscreen drug products. This document amends the proposed rule to include avobenzone. Accordingly, the agency has determined that avobenzone can be included in the monograph for OTC sunscreen drug products. This document amends the proposed rule to include avobenzone.

2. Several comments objected to the definition of a sunscreen active ingredient in proposed § 352.3(c) (58 FR 28194 at 28295) which states: "An active ingredient that absorbs at least 85 percent of the radiation in the UV range at wavelengths from 290 to 320 nanometers, but may or may not transmit radiation at wavelengths longer than 320 nanometers." The comments contended that the proposed definition is inadequate because it fails to include safe and effective ingredients whose absorption maxima are in the UVA wavelength range of 320 to 400 nanometers (nm).

The agency is aware that avobenzone's maximum absorbance is in the UVA wavelength range and agrees with the comments that the proposed definition of a sunscreen active ingredient needs to be modified to represent ingredients that sufficiently absorb, reflect, or scatter radiation in the UVA wavelengths. As the proposed definition impacts other sunscreen ingredients, the agency intends to address this issue in a future issue of the **Federal Register**.

B. Safety of Avobenzone

3. The petition (Ref. 2) requested that FDA include avobenzone as an active ingredient in the proposed monograph and permit broad spectrum combination sunscreen drug products with avobenzone to be marketed with a range of SPF values. The petition contended that avobenzone is generally recognized as safe based on substantial evidence consisting of the results of adequate and well-controlled published studies, unpublished data, safe domestic OTC marketing of two sunscreen drug products that are the subjects of approved NDA's, and several years of foreign marketing. The petition provided numerous published and unpublished studies in humans and animals (Refs. 2, and 3 through 8) in support of the safety of avobenzone.

An Australian clinical study (Ref. 6) evaluated the frequency of reactions to a SPF 15 broad spectrum sunscreen formulation containing 2 percent avobenzone in combination with 8 percent octyl methoxycinnamate and another formulation containing only the cream base without the sunscreen active ingredients. This randomized, longitudinal, double-blinded study involved 603 adults who were directed

to apply either the sunscreen or the cream based formulation daily for 7 months.

At the end of the 7-month study, 114 participants (18.9 percent) reported adverse skin reactions; 90 (14.9 percent of the 603 adults) had inflammatory skin reactions. Further testing confirmed that 45 of these 90 subjects had a history of allergic reactions. Patch testing of 22 of these 45 subjects indicated that 4 who had positive patch-test reactions gave a history of cosmetic intolerance. A majority of the adverse responses were consistent with irritant reactions to both the sunscreen preparation and the cream base control. However, the data indicated that none of the participants who were patch tested because of reported inflammatory skin reactions tested positive to the sunscreen active ingredients alone. The agency finds this study provides additional support for the safety of 2 percent avobenzone with octyl methoxycinnamate and suggests that avobenzone is not a potent photosensitizer.

The cumulative irritation potential of 8 test products was compared in an occlusive repeat insult patch test evaluation procedure on 25 healthy adult volunteers (Ref. 6). Each test product contained 1 to 3 percent avobenzone with various combinations of 2 to 7.5 percent octyl methoxycinnamate, 2 percent phenylbenzimidazole sulfonic acid, and/or 5 percent micronized titanium dioxide. Patches were applied 3 times a week over a 2-week period and were removed after 48 hours (when applied on Monday and Wednesday) or 72 hours (when applied on Friday). Skin sites were evaluated on a scale of 0 to 4 (increasing severity) for skin irritation and sensitization reaction. The test product containing 2 percent avobenzone in combination with 7.5 percent octyl methoxycinnamate was the only test product to demonstrate noticeable levels of irritation. However, a report included with the study indicated that these results were due to the emulsification system. Although only low levels of cumulative irritancy were observed with all but one formulation, the agency believes that additional subjects should have been tested in order to assess cumulative irritation potential in this study.

Four clinical occlusive skin patch tests involving 199 subjects were conducted using 4 test formulations containing combinations of 0.075 to 0.5 percent avobenzone and 7.5 to 8.0 percent octyl methoxycinnamate (Ref. 6). Each subject was patch tested with the test formulations for 48 and 72 hours, followed by an immediate and 24-hour observation reading for skin reactivity. No control group was included. The results of the study indicated that avobenzone was not a primary irritant and elicited no significant immediate or delayed skin reaction at the site of application. These data are supportive of the safety of low (0.075 to 0.5 percent) concentrations of avobenzone in combination with 7.5 to 8.0 percent octyl methoxycinnamate.

A Canadian company provided a certification describing the number of consumer complaints of skin irritancy and sensitivity reactions associated with a sunscreen drug product containing 2 percent avobenzone, 8.5 percent octyl methoxycinnamate, and 2.2 percent phenylbenzimidazole sulfonic acid (Ref. 6). The company reported only four complaints of skin reactions related to the use of this product from January 1993 to June 1994, noting that over 180,000 liters (L) were marketed during this time period. Although the agency considers the very low number of complaints (based on the number of L sold) as supportive of the safety of 2 percent avobenzone in this combination product, the reported marketing history only covers an 18-month period.

Skin sensitization potential of 4 percent avobenzone in combination with 7 to 7.5 percent octyl methoxycinnamate and 4.5 to 6.5 percent titanium dioxide was assessed in a study on the albino guinea pig (Ref. 6). No sensitization reactions to either formulation were reported. A study (Ref. 6) on hairless mice compared and demonstrated the protective effect of two commercially available broad-spectrum sunscreens against chronic exposure to UVA irradiation (340 to 400 nm). One sunscreen product contained 3 percent avobenzone (the other active ingredients were not given) and the other contained 3 percent oxybenzone. The study also emphasized the importance of assessing the safety of the vehicle or base of the sunscreen product to minimize skin irritation or photodamage. The agency considers the preclinical safety data for avobenzone submitted by the comments to be adequate.

The comment (Ref. 6) also included the following: (1) A statement from a company certifying that avobenzone had been used for 10 years in a wide variety of skin creams and sunscreen products (in combination with octyl methoxycinnamate and oxybenzone) without any material adverse biological effects, and (2) a table of sunscreen products marketed and sold in Canada that contain 2 to 5 percent avobenzone in combination with other active sunscreen ingredients. However, no other supporting data were provided with these documents.

A clinical study (Ref. 7) assessed the cumulative dermal irritancy and allergic potential of a sunscreen product containing 2 percent avobenzone, 7.5 percent octyl methoxycinnamate, and 3.0 percent titanium dioxide. In this study, the sunscreen product was applied to the back of 50 adults under occlusive cutaneous test plasters. After 48 hours (or 72 hours at the weekend), the plasters were removed and the test sites were evaluated 6 hours later to assess irritancy. The test sunscreen product was again applied to the same areas under cutaneous test plasters. This repetitive process covered a period of 3 weeks, followed by a 6-day pause, and then a challenge phase during which the sunscreen was reapplied to untreated areas of the back and removed 72 hours after application. The test sites were examined 6 hours after removal of the plaster. The agency considers the cumulative irritancy and allergic potential assessment data from this study as supportive of the safety of 2 percent avobenzone.

Utilizing a similar protocol, six clinical studies (Ref. 7) assessed the cumulative dermal irritancy and allergic potential of sunscreen products containing 0.2 to 1.5 percent avobenzone in combination with 1.5 to 7.5 percent octyl methoxycinnamate, 8 percent titanium dioxide, 0.6 to 3.45 percent methylbenzylidene camphor, and/or 3.5 to 4.5 percent phenylbenzimidazole sulfonic acid. The investigators found no evidence that any of these sunscreen products caused cumulative irritation. The cumulative irritancy data are supportive of the safety of low (0.2 to 1.5 percent) concentrations of avobenzone. Phototoxicity assessments were reported for two products (containing 1.0 and 1.5 percent avobenzone). However, two study summaries noted that the phototoxicity/photoallergenicity test protocols did not involve multiple applications of the products or multiple irradiation exposures of the test sites and can only be considered a phototoxicity assay. The agency concludes that the results from the two phototoxicity/photoallergenicity studies do not adequately address the phototoxicity or photoallergenicity of the test products.

Six studies (Ref. 8) assessed the safety of the following four sunscreen drug products: (1) A gel containing 3 percent avobenzone in combination with 8.5 percent octyl methoxycinnamate, 3 percent oxybenzone, and 5 percent octyl salicylate; (2) a gel containing 3 percent

avobenzone in combination with 8.5 percent octyl methoxycinnamate, 6 percent oxybenzone, and 6 percent octyl salicylate; (3) a cream containing 3 percent avobenzone in combination with 8.5 percent octyl methoxycinnamate, 3 percent oxybenzone, and 5 percent octyl salicylate; and (4) a cream containing 3 percent avobenzone in combination with 8.5 percent octyl methoxycinnamate, 6 percent oxybenzone, and 6 percent octyl salicylate. The studies included the following tests: (1) A 21-day cumulative irritation test, (2) a phototoxicity test, (3) a photocontact allergy test, (4) a comedogenic potential test, (5) an in-use irritation potential test in children, and (6) an in-use irritation potential test in adults.

Results of the 21-day cumulative irritancy test (Ref. 8) indicated that the most frequently observed response to the cream and gel sunscreen formulations was minimally visible erythema. The agency notes that 3 of 23 subjects recorded a moderate erythema in response to the second sunscreen formulation, and 4 of 23 subjects recorded a moderate erythema reaction in response to the fourth formulation.

The phototoxicity potential of these 4 products was assessed in 11 adults (Ref. 8). Each product was applied to two skin sites with a third test site used as an untreated control. One set of treated test sites was covered with nonwoven cotton cloth and not irradiated. The second set of treated sites was irradiated first with 10 times the predetermined minimal erythema dose (MED) of UVA irradiation, then with 0.5 times the predetermined MED of UVA/UVB irradiation. Both the untreated and treated test sites were later evaluated for any observable skin reactions at 5 minutes, 3 hours, and 24 hours after irradiation. Results indicated that all samples induced mild cutaneous responses at the 24-hour time period in several subjects. The authors of the study reported that the minimal erythema responses were considered to represent irritation to the test material, to the test procedure of tape stripping, or to the procedure of covering the sites between evaluation. The agency believes that additional subjects should have been tested in order to assess phototoxicity potential in this study.

Photocontact allergy testing showed that the second and third products reacted at the 48-hour reading of the irradiated challenge sites with mild erythema. The study report concluded that there was no clinically identifiable evidence of photocontact allergic responses to any of the materials tested, although mild erythema reactions were reported with two products at the 48-hour readings.

Two randomized, parallel-group, evaluator-blind, noncontrolled in-use studies (Ref. 8) evaluated the irritation potential of 2 sunscreen formulations in 20 children and 20 adults. Each product contained 3 percent avobenzone, 8.5 percent octyl methoxycinnamate, 6 percent octyl salicylate, and 6 percent oxybenzone (each in a different vehicle). The subjects applied the assigned product to their face/neck, arms, and legs at least twice a day for 2 weeks. A nine-point scale was used to grade the signs and symptoms of irritation at weeks 0 (before and after the first test product application), 1, and 2. Adverse events included itching and facial erythema. No serious treatment-related events were reported. Although these studies provided useful information concerning adverse events experienced during short-term actual use, the agency believes that additional subjects should have been tested in order to assess the in-use irritation potential of the test products.

The primary irritation potential of a test product containing 2 percent avobenzone, 8.5 percent octyl methoxycinnamate, and 2.2 percent phenylbenzimidazole sulfonic acid was evaluated in 15 adult subjects (Ref. 8). Negative (saline solution), mild positive (1 percent sodium lauryl sulfate in saline), and vehicle controls were included. Each subject received a single, approximately 24-hour contact application of each test material to the upper back area. Only 2 of the 15 subjects were reactive to the positive control. No clinically identifiable skin reactions were reported for the test product or vehicle. Another small study of primary irritation potential (Ref. 8) on 10 subjects tested a product containing 2 percent avobenzone, 7.5 percent octyl methoxycinnamate, and 4.5 percent oxybenzone and reported no primary irritant effect on the skin. The agency believes additional subjects should have been tested in these studies in order to assess the primary irritation potential of the test products.

A well-controlled occlusive patch study of 106 adults (Ref. 8) assessed the primary irritation potential (contact sensitization) and allergenic sensitization potential of the following test and control products: (1) 3 percent avobenzone in combination with 7.5 percent octyl methoxycinnamate, (2) 3 percent avobenzone, (3) 7.5 percent octyl methoxycinnamate, and (4) cream vehicle for 3 percent avobenzone. The data indicated that no subjects experienced primary irritation or allergenic sensitization to any of the test products. The agency considers this study as supportive of the safety of the sunscreen formulation containing 3 percent avobenzone in combination with 7.5 percent octyl methoxycinnamate.

Three studies (Ref. 8) assessed the protective effect of sunscreen drug products containing 1 percent avobenzone in patients diagnosed with atopic dermatitis and in patients receiving photochemotherapy for psoriasis. Without a concurrent vehicle control, it is unclear whether protection and/or improvement of the disease was related to sunscreen ingredients. Further, isolated use of steroids and salicylic acid-containing topical products may have interfered with the photocontact potential of the sunscreen formulation tested in the patients receiving photochemotherapy for psoriasis.

Three clinical studies (Ref. 8) evaluated the allergic contact dermatitis potential, contact irritancy potential, or phototoxicity/photoallergenicity potential, respectively, of test products containing 1 to 3 percent avobenzone. The agency does not find these studies useful. The first two studies did not adhere to standard contact irritancy and allergenicity protocol as occlusive applications were not made on a daily basis. The third study did not adhere to the standard photomaximization test protocol as application of the test material was followed by exposure to non-erythemogenic UV radiation of 10 Joules per square centimeter (J/cm^2) (instead of 3 MED's), and 24-hour skin patching of the test material followed rather than preceded irradiation.

The photosensitization potential of 2 percent avobenzone alone and in combination with 7.5 percent octyl methoxycinnamate was assessed in a panel of 25 adult subjects (Ref. 8). Dimethylsulfoxide (DMSO) was incorporated in both test formulations. As it is not clear what effect DMSO may have had on the study results, the agency has not considered these data in assessing the safety of avobenzone.

Data and other information submitted by another comment (Refs. 16 and 17) consisted of summaries of preclinical safety studies, reports from clinical safety studies of various formulations containing avobenzone, adverse drug experience data, and photostability information. The reports included six clinical safety studies from an approved NDA for a sunscreen lotion that contains 3 percent avobenzone, 3 percent oxybenzone, and 7.5 percent octyl methoxycinnamate. Four of the studies evaluated irritation/

sensitization, photoallergenicity, and phototoxicity potential. The other two studies were outdoor use tests. These data support the safety of 3 percent avobenzone alone and in combination with Category I cinnamates and benzophenones.

The comment (Ref. 17) also included reports from six clinical safety studies concerning a prior formulation that contained 2 percent avobenzone, 2 percent oxybenzone, and 7.5 percent octyl methoxycinnamate. One report included a repeat insult patch test (protocol HST–1–84–25) designed to evaluate the primary irritation and sensitization potential of the formulation, the lotion vehicle, 4 percent avobenzone in a petrolatum base, and 8 percent homosalate lotion. The study evaluated the test products under occlusive patch conditions during an initial 3-week induction phase, a 2-week rest (no treatment) phase, and a 1-week challenge phase. During the induction phase, occlusive patches impregnated with the test products were applied to the upper back of each subject and evaluated 24 to 48 hours after patch removal. During the challenge phase, occlusive patches were applied to the original induction phase sites and evaluated after 48 hours (patches were applied and evaluated twice during this phase). Of the 162 healthy adults enrolled in the study, 154 (mean age 39.8) completed the study (individual data were not provided). Mean irritation scores for the avobenzone formulation ranged from 0.05 to 0.24 during the nine induction phase observations and were 0.10 and 0.18 during the two challenge phase observations. One subject exhibited a possible allergic reaction to the tape and all four test products. Application of the avobenzone formulation and a control product under home use conditions by this subject resulted in no reported adverse reactions. The investigator noted that this subject experienced "non-specific, multiple reactions, including to test tape."

Another report (Ref. 17) included a clinical study (protocol HST–5–84–33) designed to evaluate the photoallergenicity potential of the 2 percent avobenzone formulation, its lotion vehicle, and a product containing 3 percent oxybenzone plus 7 percent Padimate O. The study consisted of the determination of each subject's MED, a 3-week induction phase, a 10-day rest (no treatment) phase, and a 4-day elicitation phase. During the induction phase, two test sites for each product were outlined on the subject's back, the products were applied, and the sites remained under occlusive patches for 24 hours. After the 24-hour period, the patches were removed and the sites were irradiated with three MED's of UVA/UVB radiation. The sites were evaluated 48 hours later for reactions on an increasing severity scale of 0 to 3+. This process was repeated twice weekly for a total of six exposures. During the elicitation phase, test materials were applied to two sites adjacent to the induction sites and occluded for 24 hours. After 24 hours, one of each set of elicitation test sites (the corresponding site in each set was shielded) and an untreated control site received 4 J/cm^2 of UVA radiation. All sites were evaluated at 48 and 72 hours after irradiation.

Six male and 19 female adults (all Caucasian and in good health) between 20 and 39 years of age (mean age 29.2) enrolled in and completed the study. No positive responses were reported at either 48 or 72 hours. The investigator concluded that no detectable contact photosensitization potential was associated with any of the test materials. The agency considers this study as supportive of the safety of 2 percent avobenzone in combination with oxybenzone and octyl methoxycinnamate.

Another report (Ref. 17) included a clinical study (protocol HST–7–84–32) designed to evaluate the phototoxicity potential of the 2 percent avobenzone formulation and 4 percent avobenzone in petrolatum. Seven female and three male adults (all Caucasian and in good health) between 18 and 63 years of age (mean age 29) enrolled in and completed the study. After the determination of each subject's MED, each test product was applied to two test sites on each subject's back, occluded for 24 hours, and then reapplied. Within 5 minutes after reapplication, one site for each product was shielded, and the other sites were irradiated with 1 MED of UVA/UVB radiation followed by 12 minutes of UVA radiation. One additional untreated test site was irradiated to serve as a control. Test sites were evaluated at 15 minutes, 24 hours, and 48 hours after irradiation on an increasing severity scale of 0 to +++. No positive reactions were reported for either test product. The agency considers this study as supportive of the safety of 2 percent avobenzone in combination with oxybenzone and octyl methoxycinnamate.

Three clinical studies (protocols 92–8, 92–7, and 92–45) (Ref. 17) evaluated the safety of a formulation identified as H03–146, which contained a combination of 4 percent avobenzone, 5 percent oxybenzone, 5 percent octyl salicylate, and 10 percent octocrylene in a lotion vehicle. Each study included other unidentified sunscreen products as comparative controls.

Protocol 92–8 evaluated the irritation and sensitization potential of H03–146 in a modified Draize human repeat insult patch test (Ref. 12). The 6-week study involved induction and challenge phases separated by a 14-day rest (notreatment) period. During the 3-week induction phase, an occlusive patch impregnated with H03–146 was applied to the upper back of subjects on each Monday, Wednesday, and Friday (a total of nine applications). The patches were removed by the subjects 24 hours after application and evaluated 24–48 hours after patch removal. Responses were evaluated on a scale of 0 to 4 (increasing severity). After a 14-day period in which no patches were applied, a patch was then applied for 48 hours to a site adjacent to the original induction site on each subject and then evaluated. Although the protocol called for only one challenge patch, the procedure was repeated with an additional 48-hour patch.

Of the 217 subjects who began the study, 205 (90 percent female and 10 percent male) completed the study. Subjects were between 18 and 65 years of age with 83 percent between 18 and 49 years of age. Irritation scores of 1 (macular, faint erythema involving at least 25 percent of the test area) were reported for 1 to 5 subjects after the second through ninth induction applications and for one subject after the first challenge application only. No test formulation-induced allergies or irritation scores above 1 were reported. The investigator concluded that the test formulation had very low irritation potential and induced no allergies. The comment's statistical analysis of results from the four lotions used in the study (using Friedman tests) noted that no significant differences were found between the lotions in regard to irritation at any time point. The agency considers this study as supportive of the safety of 4 percent avobenzone in combination with oxybenzone, octyl salicylate, and octocrylene.

Protocol 92–7 evaluated the photoallergenicity potential of H03–146 using a four-phase protocol. During the first phase, the MED was determined by administering a series of five doses of UV radiation, using a xenon arc solar simulator, to determine the lowest UV radiation dose that produced minimally perceivable erythema 16 to 24 hours later. During the induction phase, occlusive patches were applied to each subject for 24 hours followed by three times the MED in irradiation (UVA plus

UVB). This procedure was repeated twice weekly for 3 weeks, followed by a 10-day rest (notreatment) phase. The fourth phase consisted of a challenge phase involving the application of duplicate 24-hour occlusive patches to a different site followed by 4 J/cm² UVA irradiation to one of the patched sites (the other served as an unirradiated control) plus an untreated site (an irradiated control). Responses were scored 48 and 72 hours later using a scale of 0 to 3 (increasing severity).

Of the 27 subjects who began the study, 26 (69 percent male and 31 percent female) completed the study. Subjects were between 18 and 37 years of age with 96 percent between 18 and 29 years of age. One out of the 26 subjects received a score of 1 (mainly erythema with little or no edema) during the challenge phase (no other reactions were reported). The reactive subject was rechallenged (with scores of 1 at 48 hours and 2 at 72 hours) and subsequently patched to the test formulation vehicle and the vehicle plus each (singly) of the active ingredients in common with the two products tested in this study (avobenzone, oxybenzone, and octyl salicylate). Octocrylene (present in only one of the formulations) was not individually tested. Although no reactions were reported with any of the components, rechallenge with the original test products again elicited a reaction in this subject in both irradiated and control sites. The observed response in this subject was reported to be an allergic contact dermatitis and not a photocontact allergy. The investigator concluded that the test formulation was not photoallergenic. The agency considers the photoallergenicity data in this study as supportive of the safety of 4 percent avobenzone in combination with oxybenzone, octyl salicylate, and octocrylene.

Protocol 92–45 evaluated the photoirritation/phototoxicity potential of H03–146. The test formulation was applied to duplicate sites on the lower or mid-back of subjects, allowed to dry, and covered with an occlusive dressing (an adjacent control site was occluded without any application). After 24 hours, one test formulation patch and the untreated control patch (the irradiated control) were removed and immediately exposed to 20 J/cm² of UVA irradiation. The other test formulation patch served as an unirradiated control. The presence of a wheal-and-flare response or erythema 5 to 10 minutes after irradiation was recorded. Delayed erythema and edema were evaluated 24 and 48 hours after irradiation using a scale of 0 to 4 (increasing severity).

Six male and 14 female subjects began and completed the study. Subjects ranged from 18 to 48 years of age with 95 percent between 18 and 29 years of age. No immediate or delayed reactions suggestive of phototoxicity were reported. The investigator concluded that, under the conditions of the study, the test formulation did not possess a detectable phototoxicity potential in humans. The agency considers this study as supportive of the safety of 4 percent avobenzone in combination with oxybenzone, octyl salicylate, and octocrylene.

Preclinical tests (Ref. 16) on a 3 percent avobenzone formulation included studies of skin and eye irritation in the rabbit, oral and subcutaneous acute toxicity in the mouse and rat, skin penetration in the pig, mutagenicity (Ames test), and photocarcinogenicity in the mouse. Preclinical tests on avobenzone (in the rabbit, rat, mouse, guinea pig, excised human skin, bacteria, or yeast) included five acute toxicity studies, three subchronic toxicity studies, three sensitization studies, six skin penetration studies, three mutagenicity studies, a phototoxicity study, a photoallergy study, and a teratology study. The preclinical data report concluded that no adverse effects were observed other than slight to moderate species specific dermal irritations. The citizen petition (Ref. 2) also included several preclinical studies previously reviewed by the agency, an additional mutagenicity study involving chromosome analysis of human peripheral blood lymphocytes, and two photomutagenicity studies. The agency considers the preclinical safety data for avobenzone to be adequate.

The agency considers the safety data as providing sufficient evidence to demonstrate the low irritation, allergenic sensitization, photoallergenic, and phototoxic potential of 2 to 3 percent avobenzone alone and in combination with the proposed monograph cinnamate, benzophenone, salicylate, and/or diphenylacrylate sunscreen ingredients. However, the agency does not consider the data adequate to allow avobenzone to be combined with any and all proposed monograph sunscreen ingredients without similar supportive data.

4. The petition maintained that avobenzone has extensive marketing experience in the United States based on the products marketed under approved NDA's. The petition also noted that avobenzone has been marketed "as a safe and effective UV–A sunscreen filter" throughout the world since 1981.

The comment (Refs. 16 and 17) provided a summary of adverse drug experience (ADE) data for its 3 percent avobenzone product covering the period from January 1993 through December 31, 1995. The comment estimated a total complaint rate of 0.0067 percent for this period (based on reported sales of "more than one million packages"). Annual percentages of the total ADE reports received during this period were reported as 44, 29, and 27 percent for the years 1993, 1994, and 1995, respectively. The majority of these complaints were typical of a topical sunscreen drug product. The highest "percent of total complaints" was reported in the categories of "lack of efficacy" (24 percent), "dermatitis/erythema/pruritus/edema" (19 percent), and "rash" (18 percent). "Urticaria" and "allergic reaction" accounted for 6.6 percent, and "all other" accounted for 22 percent. None of the reported ADE's was deemed serious in nature or confirmed as a causal relationship following complaint investigation. The actual number of complaints and an explanation of the "all other" category were not provided.

The agency's Spontaneous Reporting System (SRS) has 59 reports of ADE's associated with this 3 percent avobenzone product from 1993 through March 8, 1996 (all from domestic sources) (Ref. 18). These 59 reports represented the following 107 reactions (more than one reaction per report):

TABLE 1.—ADVERSE DRUG EXPERIENCE REPORTS

Reaction	Total	Reaction	Total
Rash	26	Eye pain	2
No drug effect	19	Vesicles, bullae	2
Application site reaction	10	Abnormal vision	2
Pruritus	8	Acne	1
		Arthrosis	1

TABLE 1.—ADVERSE DRUG EXPERIENCE REPORTS—Continued

Reaction	Total	Reaction	Total
Paresthesia	5	Chloasma	1
Skin discoloration	4	Conjunctivitis	1
Allergic reaction	3	Maculopapular rash	1
Facial edema	3	Peripheral edema	1
Pain	3	Lacrimation	1
Photosensitivity	3	Lymphadenopathy	1
Urticaria	3	Vasodilation	1
Contact dermatitis	2	Exfoliative dermatitis	1
Hyperesthesia	2		

The agency finds that these ADE reports do not signal any alarming trend in numbers or types of reactions. No serious outcomes were reported.

As discussed in section A., comment 1, of this document, avobenzone has been continuously marketed in the United States under NDA's for approximately 8 years. Although ADE incidence rates or drug safety comparisons cannot be made using SRS data alone, the agency believes the reports covering these approximately 8 years of OTC use support general recognition of the safety of avobenzone.

5. The comment contended that the studies of effectiveness, phototoxicity, and photosensitization contained in its approved NDA show that its 3 percent avobenzone product remains effective and safe after exposure to UVA/UVB radiation and/or UVA radiation alone. The comment stated that clinical testing demonstrated that neither avobenzone nor any potential photodegradation products exhibited any phototoxic or photosensitization potential. The comment concluded that no performance or safety issues were identified relative to potential negative effects of photodegradation and that outdoor tests further confirm that performance was maintained despite any minor potential photodegradation or photolability.

The comment included the results from an in vitro assessment of the photostability of four avobenzone-containing formulations (Table 2) (Ref. 17).

TABLE 2.—AVOBENZONE FORMULATIONS

Ingredient	H03–084	H03–087	H03–088	H03–089
Avobenzone	4.0%	4.0%	4.0%	4.0%
Octocrylene	0.0%	5.0%	3.0%	3.0%
Octyl methoxycinnamate	7.5%	7.5%	7.5%	7.5%
Octylsalicyulate	5.0%	5.0%	5.0%	5.0%
Oxybenzone	5.0%	4.0%	4.0%	4.0%

The assessment evaluated the amount of absorbance retained at three wavelengths (305 nm, 335 nm, and 355 nm) in thin films of each test formulation after exposure to direct sunlight in Memphis, TN, from approximately 10 am to 3 pm during the month of March. Measurements were made after 0, 1, 2.5, and 5 hours of exposure. After 5 hours of exposure, the following amounts of absorbance (percent recovered) were reported (Table 3):

TABLE 3.—PERCENT ABSORBANCE RECOVERED

Formula	308nm	335nm	355nm
H03–084	63.1	56.0	40.8
H03–087	70.4	61.3	44.0
H03–088	68.5	60.8	44.9
H03–089	68.0	60.0	43.8

The photostability assessment report concluded that combinations of these five ingredients are sufficiently stable during sunlight exposure so that, even after 5 hours of exposure, the majority of the total original absorbance (and sunscreen effectiveness) is maintained. The report also noted that appropriate formulation techniques using monograph sunscreen ingredients can result in photostable formulations.

As with other sunscreen ingredients, the agency has concerns related to the photostability of avobenzone alone and in combinations, the safety of photodegradation products, and the effect of photodegradation on product effectiveness (Refs. 12 and 15). FDA believes that the in vitro photostability assessment (which did not utilize the marketed formulation) may indicate a significant amount of photodegradation in the test formulations after 5 hours. No information was provided concerning the nature of the photodegradation products or their specific short-term or long-term safety profiles. Although these questions remain, the agency is presently not aware of any safety or effectiveness problems associated with the photostability of avobenzone alone or in combinations with the proposed monograph cinnamate, benzophenone, salicylate, or diphenylacrylate sunscreen ingredients. The agency intends to address the issue of photostability of all OTC sunscreen active ingredients in a future issue of the **Federal Register**.

C. Effectiveness of Avobenzone

6. The petition asserted that avobenzone is generally recognized as an effective UVA radiation sunscreen ingredient, both alone and in combination with other UVA and UVB radiation sunscreen ingredients, based on published and unpublished studies and marketing experience with NDA-approved avobenzone-containing sunscreen drug products. The petitioner provided published studies in support of the effectiveness of avobenzone (Refs. 2 and 3).

J. M. Menter (Ref. 19) stated that avobenzone has good blocking throughout the UVA region, with maximum absorbance at 340 to 350 nm. Gange, et al. (Ref. 20) and Lowe, et al. (Ref. 21), assessed the UVA radiation protection provided by a combination of 3 percent avobenzone plus 7 percent padimate O in humans photosensitized

with 8-methoxsalen (8–MOP). Both studies demonstrated that the combination was effective in providing protection against UVA radiation and provided significantly greater UVA radiation protection than either avobenzone alone or the other tested sunscreen formulations that did not contain avobenzone. Kaidbey and Barnes (Ref. 22) assessed the UVA radiation protection provided by various sunscreen formulations by evaluating immediate pigment darkening in humans. Products tested included a combination of avobenzone and oxybenzone and a combination of avobenzone, octyl salicylate, oxybenzone, and octocrylene (ingredient concentrations were not given). The study demonstrated that test formulations containing avobenzone plus oxybenzone provided more effective UVA radiation protection than the formulations without avobenzone, and that the multi-ingredient avobenzone-containing combination product appeared to be significantly more effective than the tested marketed products.

Urbach (Ref. 23) and Lowe (Ref. 24) assessed the UVA radiation protection of 3 percent avobenzone alone and in combination with 7.5 percent octyl methoxycinnamate in humans photosensitized with 8–MOP. Urbach also tested 2 percent avobenzone alone and in combination with 7.5 percent octyl methoxycinnamate. The studies demonstrated that 2 to 3 percent avobenzone (alone and in combination with octyl methoxycinnamate) was effective in providing protection against UVA radiation and that the combination product was significantly more effective than octyl methoxycinnamate alone in reducing UVA erythema. The petition also noted the agency's previous approval of NDA's for a sunscreen product containing 3 percent avobenzone and 7 percent padimate O, and a sunscreen product containing 3 percent oxybenzone, and 7.5 percent octyl methoxycinnamate.

In the notice of proposed rulemaking for OTC sunscreen drug products, the agency proposed that an OTC 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) to discuss such testing procedures.

Although the agency continues to evaluate data and information relative to a monograph method for determining UVA radiation protection, it finds that the submitted studies provide sufficient evidence of the effectiveness of 2 to 3 percent avobenzone in protecting against UVA radiation. The agency also finds that the studies demonstrate that 2 to 3 percent avobenzone in combination with appropriate proposed monograph sunscreen ingredients can provide "broad spectrum" protection (58 FR 28194 at 28232 and 28233). Any avobenzone-containing sunscreen drug product bearing this claim requires both UVA radiation protection testing and SPF testing of the finished product. 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 those described by R. W. Gange, et al. (Ref. 20) and N. J. Lowe, et al. (Ref. 21) as adequate for determining the UVA radiation protection potential of a finished OTC sunscreen drug product.

D. Conclusions

The agency considers the safety studies discussed in section B., comment 3 of this document as providing sufficient evidence to demonstrate the low irritation, allergenic sensitization, photoallergenic, and phototoxic potential of 2 to 3 percent avobenzone alone and in combination with the proposed Category I cinnamate, benzophenone, diphenylacrylate, and/or salicylate sunscreen ingredients. ADE data have not revealed any alarming trends in the numbers or types of reactions nor any serious outcomes with this combination of sunscreen ingredients. The agency considers the warning statements proposed in § 352.52(c)(1) as adequate for OTC sunscreen drug products that contain avobenzone (e.g., "Discontinue use if signs of irritation or rash appear. If irritation or rash persists, consult a doctor."). In addition, adequate and well-controlled studies using currently accepted methods 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. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 12).

FDA recognizes that the photostability of any topical product, particularly a sunscreen drug product, is an important safety and effectiveness consideration. Although more information will ultimately be required before the nature and safety profiles of avobenzone photodegradation products can be thoroughly assessed, the agency is presently neither aware of any known toxic breakdown product(s) for avobenzone formulations combined with proposed monograph sunscreen ingredients, nor is the agency aware of any systemic toxicity for avobenzone from a photodegradation product. FDA intends to further address the issue of photostability (and other aspects of final formulation safety testing) of all OTC sunscreen active ingredients in a future issue of the **Federal Register**.

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 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).

Thus, the agency considers the data submitted by the petition and the comment as supportive of the safety and effectiveness of up to 3 percent avobenzone alone (if the finished product provides at least an SPF 2) and 2 to 3 percent avobenzone in combination with cinoxate, diethanolamine methoxycinnamate, dioxybenzone, homosalate, octocrylene, octyl methoxycinnamate, octyl salicylate, oxybenzone, sulisobenzone, and/or trolamine salicylate (at concentrations for permitted combinations of sunscreen active ingredients in § 352.20 of the proposed rule for OTC sunscreen drug products). Accordingly, the agency is proposing to amend the proposed rule for OTC sunscreen drug products to include avobenzone in §§ 352.10 and 352.20.

E. Enforcement Status

No OTC drug advisory review panel considered avobenzone or avobenzone-containing combination drug products. In accordance with the agency's Compliance Policy Guide 7132b.16 (which describes the agency's enforcement policy regarding the marketing of OTC combination drug products not reviewed by an OTC drug advisory review panel) (Ref. 25), these combinations may not be marketed until the agency states by notice in the **Federal Register** that the combinations have been tentatively determined to be generally recognized as safe and effective and that OTC marketing of the combinations will be permitted under specified conditions. Before marketing may begin, the comment period for this proposal must end and then another **Federal Register** notice must be published setting forth the agency's determination concerning interim marketing before publication of the final rule. Any such interim marketing that might be allowed, pending issuance of the final monograph, is subject to the risk that the agency may adopt a different position in the final monograph that could require relabeling, recall, or other regulatory action.

One comment maintained that there is a real and significant public health need for widely available avobenzone-containing sunscreen products that provide protection against the hazards associated with UVA and UVB radiation. To provide manufacturers with the extensive lead time necessary to make avobenzone-containing sunscreen products available by the 1997 summer season, the comment requested that the agency complete its determination concerning interim marketing no later than October 1, 1996.

The agency considers it in the public interest to proceed with a determination of the marketing status of avobenzone as soon as possible because the addition of this ingredient to the proposed monograph would provide for wide availability of new combination sunscreen products that will provide consumers with broad spectrum protection. Accordingly, the agency is requesting comments regarding this proposed amendment in a period of 30 days (shorter than the normal 90 days) so that the marketing status of OTC avobenzone-containing sunscreen drug products can be determined in an expeditious manner.

F. Labeling

The petition recommended using approved NDA labeling, which addresses both the UVA and UVB protection of the product, as appropriate for OTC sunscreen drug products containing avobenzone. Accordingly, 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 avobenzone may include under "Indications" 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") "throughout 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) Comment No. CP4, Docket No. 78N–0038, Dockets Management Branch.

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

(3) Comment No. C234, Docket No. 78N–0038, Dockets Management Branch.

(4) Comment No. LET96, Docket No. 78N–0038, Dockets Management Branch.

(5) Comment No. LET101, Docket No. 78N–0038, Dockets Management Branch.

(6) Comment No. LET127, Docket No. 78N–0038, Dockets Management Branch.

(7) Comment No. LET130, Docket No. 78N–0038, Dockets Management Branch.

(8) Comment No. SUP18, Docket No. 78N–0038, Dockets Management Branch.

(9) Comment No. LET95, Docket No. 78N–0038, Dockets Management Branch.

(10) Comment No. LET105, Docket No. 78N–0038, Dockets Management Branch.

(11) Comment No. LET118, Docket No. 78N–0038, Dockets Management Branch.

(12) Comment No. LET141, Docket No. 78N–0038, Dockets Management Branch.

(13) Comment No. MM11, Docket No. 78N–0038, Dockets Management Branch.

(14) Comment No. MM12, Docket No. 78N–0038, Dockets Management Branch.

(15) Comment No. MM13, Docket No. 78N–0038, Dockets Management Branch.

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

(17) Comment No. SUP20, Docket No. 78N–0038, Dockets Management Branch.

(18) Food and Drug Administration, Center for Drug Evaluation and Research, Adverse Drug Event Line Listing for Shade UVAGuard® SPF 15 Lotion for the years 1993 through March 1996, Docket No. 78N–0038, Dockets Management Branch.

(19) Menter, J. M., "Recent Developments in UVA Photoprotection," *International Journal of Dermatology*, 29:389–394, 1990.

(20) Gange, R. W., et al., "Efficacy of a Sunscreen Containing Butyl Methoxydibenzoylmethane Against Ultraviolet A Radiation in PhotosensitizedSubjects," *Journal of the American Academy of Dermatology*, 15:494–499, 1986.

(21) 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.

(22) Kaidbey, K. H., and A. Barnes, "Determination of UVA Protection Factors by Means of Immediate Pigment Darkening in Normal Skin," *Journal of the American Academy of Dermatology*, 25:262–266, 1991.

(23) Urbach, F. D., "Protocol #HPT–670," unpublished report in C234, Docket No. 78N–0038, Dockets Management Branch.

(24) Lowe, N. J., "Protocol #GL/87–1," unpublished report in C234, Docket No. 78N–0038, Dockets Management Branch.

(25) "Food and Drug Administration Compliance Policy Guide 7132b.16," in OTC vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

IV. Effective Date

The agency advises that any final rule for OTC sunscreen drug products resulting from this proposed rule will be effective 12 months after its date of publication in the **Federal Register**. Any notice of enforcement policy allowing interim marketing will state its effective date. On or after the stated dates, any OTC drug product that is not in compliance with the notice of enforcement policy or the final rule may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to the final rule that is repackaged or relabeled after the effective date of the rule must be in compliance with the rule regardless of the date that the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the final rule at the earliest possible date.

V. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). 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). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order.

Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of a rule on small entities. This proposed rule would allow manufacturers to market avobenzone-containing sunscreen drug products without having to obtain an approved NDA, as is currently required, and thus 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. Thus, this proposed rule will not impose a significant economic burden on affected entities. Therefore, under the Regulatory Flexibility Act (5 U.S.C. 605(b)), the Commissioner of Food and Drugs certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on manufacturers of OTC sunscreen drug products. Comments regarding the impact of this rulemaking on such manufacturers should be accompanied by appropriate documentation. The agency is providing a period of 30 days from the date of publication of this proposed rulemaking in the **Federal Register** for comments to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

VI. 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)).

VII. Environmental Impact

The agency has determined under 21 CFR 25.24(c)(6) 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.

VIII. Public Comment

Interested persons may, on or before October 16, 1996, submit written comments to the Dockets Management Branch (address above). Desk copies of these written comments should be submitted to Debra L. Bowen, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Written comments on the agency's economic impact determination may be submitted on or before October 16, 1996. 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 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) be amended as follows:

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

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

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. Section 352.10 is amended by redesignating paragraphs (b) through (t) as paragraphs (c) through (u) and by adding new paragraph (b) to read as follows:

§ 352.10 Sunscreen active ingredients.

* * * * *

(b) Avobenzone up to 3 percent.

* * * * *

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

§ 352.20 Permitted combinations of active ingredients.

(a) Combinations of sunscreen active ingredients.

(1) Two or more sunscreen active ingredients identified in § 352.10(a), and (c) through (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.

(2) Two or more sunscreen active ingredients identified in § 352.10(b), (c), (f), (i), (k), (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.

(3) Sunscreen active ingredients shall be used within the following concentrations when used in combination with another sunscreen or when the combination is used with any other permitted active ingredient:

(i) [Reserved].

(ii) Avobenzone 2 to 3 percent.

(iii) Diethanolamine methoxycinnamate 8 to 10 percent.

(iv) Digalloyl trioleate 2 to 5 percent.

(v) Dioxybenzone 3 percent.

(vi) Ethyl .4-[bis(hydroxypropyl)] aminobenzoate 1 to 5 percent.

(vii) Glyceryl aminobenzoate 2 to 3 percent.

(viii) Homosalate 4 to 15 percent.

(ix) Lawsons 0.25 percent with dihydroxyacetone 3 percent.

(x) Menthyl anthranilate 3.5 to 5 percent.

(xi) Octocrylene 7 to 10 percent.

(xii) Octyl methoxycinnamate 2.0 to 7.5 percent.

(xiii) Octyl salicylate 3 to 5 percent.

(xiv) Oxybenzone 2 to 6 percent.

(xv) Padimate 0 1.4 to 8 percent.

(xvi) Phenylbenzimidazole sulfonic acid 1 to 4 percent.

(xvii) Red petrolatum 30 to 100 percent.

(xviii) Sulisobenzone 5 to 10 percent.

(xix) Titanium dioxide 2 to 25 percent.

(xx) Trolamine salicylate 5 to 12 percent.

(b) Sunscreen and skin protectant combinations.

(1) Any single sunscreen active ingredient when used in the

concentration established in § 347.10 may be combined with one or more skin protectant active ingredients identified in § 347.10(a), (d), (e), (f), (h), (i), and (j) of this chapter, provided the finished product has a minimum SPF value of not less than 2 as measured by the testing procedures established in subpart D of this part and provided the product is labeled according to § 352.60.

(2) Two or more sunscreen active ingredients when used in the concentrations established in § 352.20(a)(3) may be combined with one or more skin protectant active ingredients identified in § 347.10(a), (d), (e), (f), (h), (i), and (j) of this chapter, provided the finished product has a minimum SPF value of not less than 2 as measured by the testing procedures established in subpart D of this part and provided the product is labeled according to § 352.60.

* * * * *

4. Section 352.52 is amended by adding a new paragraph (b)(2)(vi) and by revising the headings of paragraphs (b)(3), (c)(2), (d)(3) and (e)(5) to read as follows:

§ 352.52 Labeling of sunscreen drug products.

* * * * *

(b) * * *

(2) * * *

(vi) *For products containing the active ingredient identified in § 352.10(b), 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") "throughout the UVA spectrum."

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

(3) *For products containing the active ingredient identified in § 352.10(t) that provide an SPF of 12 to 30, the following labeling statement may be used.* * * *

(c) * * *

(2) *For products containing the ingredient identified in § 352.10(j)*— * * *

* * * * *

(d) * * *

(3) *For products containing the ingredient identified in § 352.10(j).* * * *

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(e) * * *

(5) *For products containing the active ingredient identified in § 352.10(t) that provide an SPF of 12 to 30, the following labeling statement may be used.* * * *

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Dated: September 5, 1995.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96–23547 Filed 9–13–96; 8:45 am]

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[DEA–152P]

Schedules of Controlled Substances: Proposed Placement of Remifentanil Into Schedule II

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: This proposed rule is issued by the deputy Administrator of the Drug Enforcement Administration (DEA) to place the narcotic drug, remifentanil and salts thereof, into Schedule II of the Controlled Substances Act (CSA). The Deputy Administrator has received a recommendation from the Assistant Secretary for Health of the Department of Health and Human Services (DHHS) that remifentanil, and salts thereof, be added to Schedule II. This rule, if finalized, would require that the manufacture, distribution, dispensing, security, registration, record keeping, inventory, exportation and importation of remifentanil, and salts thereof, be subject to the CSA regulatory control mechanisms and criminal sanctions applicable to Schedule II narcotic substances.

DATES: Comments, objections and requests for a hearing must be submitted on or before October 16, 1996.

ADDRESSES: Comments, objections and requests for a hearing should be submitted in quintuplicate to the Deputy Administrator, Drug Enforcement Administration, Washington, DC 20537; Attention: DEA Federal Register Representative.

FOR FURTHER INFORMATION CONTACT: Frank Sapienza, Acting Chief, Drug and Chemical Evaluation Section, 202–307–7183.

SUPPLEMENTARY INFORMATION: The Deputy Administrator of the DEA received a letter dated August 23, 1996, from the Assistant Secretary for Health, on behalf of the Secretary of the DHHS, recommending that the substance, remifentanil, and salts thereof, be placed into Schedule II of the CSA (21 U.S.C. 801 et seq.). Remifentanil hydrochloride, a short-acting, potent μ-opioid, was approved recently by the Food and Drug Administration (FDA) for marketing as an intravenous analgesic agent for use during the induction and maintenance of general anesthesia and monitored anesthesia care.

Enclosed with the letter from the Assistant Secretary was a document prepared by the FDA entitled "Basis for the Recommendation for Controlling Remifentanil and its Salts in Schedule II of the Controlled Substances Act." The document contained a review of the factors which the CSA requires the Secretary to consider [21 U.S.C. 811(b)] and the summarized recommendations regarding the placement of remifentanil into Schedule II of the CSA.

The factors considered by the Assistant Secretary for Health with respect to the drug remifentanil were:

(1) Its actual or relative potential for abuse;

(2) Scientific evidence of its pharmacological effect;

(3) The state of current scientific knowledge regarding the drug;

(4) Its history and current pattern of abuse;

(5) The scope, duration, and significance of abuse;

(6) What, if any, risk there is to the public health;

(7) Its psychic or physiological dependence liability; and

(8) Whether the substance is an immediate precursor of a substance already controlled under the CSA.

Relying on the scientific and medical evaluation and the recommendation of the Assistant Secretary of Health, received in accordance with section 201(f) of the Act [21 U.S.C. 811(f)], the Deputy Administrator of the DEA, pursuant to sections 201(a) and 201(b) of the Act [21 U.S.C. 811(a) and 811(b)], finds that:

(1) Based on information now available, remifentanil has a high potential for abuse;

(2) Remifentanil has a currently accepted medical use in treatment in the United States; and

(3) Abuse of remifentanil may lead to severe psychological or physical dependence.

Interested persons are invited to submit their comments, objections or requests for a hearing, in writing, with regard to this proposal. Requests for a hearing should state, with particularity, the issues concerning which the person desires to be heard. All correspondence regarding this matter should be