**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 333**

**[Docket No. 81N-0114]**

**RIN 0905-AA06**

## Topical Acne Drug Products for Over-the-Counter Human Use; Final Monograph

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) topical acne drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on OTC topical acne drug products that have come to the agency's attention. This final rule does not include final agency action on the OTC topical acne active ingredient benzoyl peroxide. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

**EFFECTIVE DATE:** August 16, 1992.

**FOR FURTHER INFORMATION CONTACT:** William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

**SUPPLEMENTARY INFORMATION:** In the **Federal Register** of March 23, 1982 (47 FR 12430), 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 topical acne drug products, together with the recommendations of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products (Antimicrobial II Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by June 21, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by July 21, 1982.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC topical acne drug products was published in the **Federal Register** of January 15, 1985 (50 FR 2172). Interested persons were invited to file by May 15, 1985 written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by May 15, 1985. New data could have been submitted until January 15, 1986, and comments on the new data until March 17, 1986.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC topical acne drug products (50 FR 2172), the agency advised that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register**. Therefore, on or after August 16, 1992, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may 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 this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule on OTC topical acne drug products, eight consumers, one drug manufacturers association, one cosmetic manufacturers association, and four drug manufacturers submitted comments. A request for oral hearing before the Commissioner was also received on one issue. Copies of the comments and the hearing request received are on public display in the Dockets Management Branch (address above). Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

The Antimicrobial II Panel in its advance notice of proposed rulemaking (47 FR 12430 at 12475) and the agency in its tentative final monograph (50 FR 2172 at 2181) proposed monograph status for the ingredient benzoyl peroxide for OTC topical use in the treatment of acne. However, following this proposal the agency became aware of a study by Slaga, et al. (Ref. 1) that raised a safety concern regarding benzoyl peroxide as a tumor promoter in mice and a study by Kurokawa, et al. (Ref. 2) that reported benzoyl peroxide to have tumor initiation potential. Neither of these studies was discussed by the Panel or by the agency in the **Federal Register** publications identified above.

Subsequently, a drug manufacturers association submitted data and information in support of the safety of benzoyl peroxide (Refs. 3 through 6). FDA has evaluated these data and information and determined that the studies show that benzoyl peroxide is a skin tumor promoter in more than one strain of mice as well as in other laboratory animals tested. To date, topical studies (which have shown only tumor promotion) have been of short duration (about 52 weeks), which the agency considers insufficient to rule out the potential for carcinogenicity. Although extensive animal data and human epidemiology data are available, the agency is unable to state that benzoyl peroxide is generally recognized as safe at this time. In the **Federal Register** of August 7, 1991 (56 FR 37622), the agency published an amended tentative final monograph for OTC topical acne drug products in which it reclassified benzoyl peroxide from Category I (as proposed in the **Federal Register** of January 15, 1985) to Category III. Opportunities for public

comment and the submission of new data in response to this reclassification are discussed in that amended tentative final monograph.

This reclassificaton of benzoyl peroxide does not relate directly to the establishment of other acceptable ingredients, labeling, and other conditions for OTC topical acne drug products. Accordingly, in order to establish a final monograph for these other conditions without undue delay, at this time the agency is issuing a final monograph that addresses all other conditions. Final agency action on all aspects of the OTC topical acne drug product rulemaking except issues related to benzoyl peroxide occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC topical acne drug products.

In proceeding with this final monograph, the agency has considered all objections, the request for oral hearing, and the changes in the procedural regulations. Based on the discussion in comment 15 below, the agency considers the request for a hearing to be moot.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of December 16, 1972 (37 FR 26842) or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

**References**

(1) Slaga, T. J., et al., Skin-Tumor Activity of Benzoyl Peroxide, A Widely Used Free Radical-Generating Compound, Science, 213:1023–025, 1981.

(2) Kurokawa, Y., et al., Studies on the Promoting and Complete Carcinogenic Activities of Some Oxidizing Chemicals in Skin Carcinogenesis, Cancer Letters, 24:299–304, 1984.

(3) Comment No. RPT, Docket No. 81N–0114, Dockets Management Branch.

(4) Comment No. RPT00002, Docket No. 81N–0114, Dockets Management Branch.

(5) Comment No. SUP00002, Docket No. 81N–0114, Dockets Management Branch.

(6) Comment No. SUP00003, Docket No. 81N–0114, Dockets Management Branch.

## I. The Agency's Conclusions on the Comments

### *A. General Comments on OTC Topical Acne Drug Products*

1. One comment stated its continuing position that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464 at 9471 to 9472); in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260); and in paragraph 1 of the preamble to the tentative final monograph in the present proceeding (50 FR 2172 at 2173). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–698 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. Several comments agreed with the agency's proposed rulemaking for OTC topical acne drug products. In particular, support was noted for (1) the proposed labeling in § 333.350, in which the agency consolidated the numerous claims recommended by the Panel into a few concise statements in order to improve clarity and reduce repetition; (2) the categorization of active ingredients in § 333.310, which would require each OTC acne drug product to contain one of the approved ingredients or the specific combination of sulfur and resorcinol included under permitted combinations in § 333.320; and (3) the proposed warning in § 333.350(c)(1)(ii) regarding the use of more than one topical acne medication at the same time, which the agency believed necessary in order to alert consumers using more than one acne product about the increased potential for dryness and irritation because all of the Category I acne ingredients are keratolytic and tend to dry out the skin. Another comment specifically stated its support for the agency's proposed Category I classification of the combination of 8 percent sulfur and 2 percent resorcinol. The comment pointed out that this combination has a long history of safe and effective use as an OTC topical acne drug product.

3. One comment disagreed with the Panel's decision not to classify adjunctive treatment products (i.e., wash-off medicated cleansers, soaps, and washes) in its review of topical acne drug products. The comment maintained that these adjunctive therapies are effective for their antiseborrheic and keratolytic properties in the self-treatment of acne. The comment stated that the usefulness of these cleansers has been widely accepted by dermatologists, and washing the skin with medicated acne cleansers or soap as an adjunct to other acne treatment has been highly recommended. The comment requested that these products be recognized as adjuncts to acne treatment for the purpose of "promoting drying and peeling," "alleviating oiliness," and "removing/reducing sebum."

Although the Panel discussed adjunct therapies in its review of ingredients for the treatment of acne (Ref. 1), it did not classify adjunct therapies for the treatment of acne because of the lack of specific information regarding such treatments (e.g., abrasive scrubs, cleansers, and soaps). The Panel did not consider an ingredient unless it actually treated acne, i.e., actually reduced lesion count. The Panel noted that some consumers may prefer acne products that are formulated as abrasive scrubs. For this reason, the Panel included a short discussion of abrasive scrubs (physical abradents) in its report (47 FR 12430 at 12441). The Panel did state its belief that it is unlikely that superficial epidermabrasion will remove the tightly adherent comedo. The Panel discussed a study by Mills and Kligman (Ref. 2) in which the authors concluded there was no evidence showing that abradents could effectively remove comedones.

The agency has not received any submissions of data regarding adjunct therapies in treating acne in response to either the Panel's report or the tentative final monograph for OTC topical acne drug products. The comment did not submit any data on the safety and efficacy of these therapies. Therefore, the agency has no basis upon which to grant the comment's request. Data on the safety and effectiveness of these products, from controlled clinical studies, are needed before such therapies can be considered generally recognized as safe and effective as an adjunct in the treatment of acne. In addition, the agency points out that products that contain only claims for cleansing of the skin or removing oil are considered cosmetic products and are not subject to this OTC drug monograph. For the above reasons, the agency is not including in this final monograph either adjunctive therapies or the labeling claims suggested by the comment.

**References**

(1) Minutes of the 49th Meeting of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products, March 21 and 22, 1980, pp. 46–56.

(2) Mills, O. H., Jr., and A. M. Kligman, Evaluation of Abrasives in Acne Therapy, *CUTIS; Cutaneous Medicine for the Practitioner*, 23:704–705, 1979.

*B. Comments on OTC Topical Acne Ingredients*

4. One comment contended that the agency's proposed classifications of various active drug ingredients do not establish requirements for the cosmetic uses of those ingredients. The comment gave several examples of ingredients that the Panel and agency have found lack effectiveness as active anti-acne drug ingredients, but which have other uses in cosmetic products (e.g., preservative, emulsifier, stabilizer, viscosifier, fragrance, and antioxidant) and could be used for these purposes in acne drug products. The comment requested that the agency include a statement in this final rule similar to statements that appeared in the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6822 to 6823). These statements were that this monograph "covers only the drug use of the active ingredients listed therein," and "the concentration range, limitations, warnings, and directions established for these ingredients in the monograph do not apply to the use of the same ingredients in products intended solely as cosmetics."

As noted by the comment, the agency discussed this subject in the tentative final monograph for OTC skin protectant drug products. The same principles are applicable in this final monograph. Because this final rule covers only the drug use of the active ingredients listed herein, the concentration range, limitations, warnings, and directions established for these ingredients in the monograph do not apply to the use of the same ingredients for non-drug effects in products intended solely as cosmetics. Those products intended for both drug and cosmetic use must conform to the requirements of the final monograph, the cosmetic labeling requirements of section 602 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 362), and the provisions of 21 CFR part 701, especially 21 CFR 701.3(d) regarding label declarations where a cosmetic product is also a drug.

5. One comment objected to the agency's placement of borates (boric acid and sodium borate) in Category II in products used for the treatment of acne. The comment noted that it did not know the actual concentrations or functions of borates in the acne preparations evaluated because it did not have access to the proprietary formulations submitted to the rulemaking for OTC acne drug products. However, the comment maintained that because the ingredients were referred to as "active," their inclusion in the products must serve an efficacious purpose. The comment stated its belief that borax and/or boric acid were acting as pH control agents, preservative additives, or astringent and/or surface tension reducing additives, and that the concentration used in these products is relatively low—probably at a maximum of 5 percent by weight. The comment argued that, considering these functions, a Category II classification of borates based on efficacy was questionable.

Regarding safety, the comment maintained that the data bases used in evaluating borates were an inadequate series of literature reviews and did not include an evaluation of the only controlled clinical study on humans or long-term chronic animal studies. The comment stated that borax and boric acid have a long history of safe use in cosmetics, cleaning products, bath preparations, and pharmaceuticals. The comment added that a report by the Cosmetic Ingredient Review (CIR) Panel indicated that a level of borates up to 5 percent in cosmetics was safe for topical use. The comment included a summary of acute as well as chronic toxicity data, which had been generated over a period of years, to support the safety of borates. The comment stated that a closer examination of the criteria for classifying borates as Category II ingredients was justified considering the data cited as well as the long history of safety associated with borax and boric acid.

The Antimicrobial II Panel reviewed borates for safety and effectiveness in topical acne and topical antifungal drug products. The Panel concluded that borate preparations with a concentration of 5 percent or less were safe for topical application. However, there were very little data available for the Panel to evaluate the effectiveness of borates for the treatment of acne. There were no reports of clinical trials that showed definitive activity of borates in treating acne. The Panel found only one study that addressed borates as single ingredients in the treatment of acne. The study included 22 individuals treated with 50 percent sodium borate (present as small abrasive particles) in a vehicle of soapless cleansers. The rationale for the preparation's use was oil removal (the soapless cleansers) and gentle abrasion of the skin (the abrasive particles). The Panel noted that the study was neither controlled nor double-blind, lesion counts were not used as the method of evaluation, and concomitant therapy was administered. The Panel concluded that borates had not been conclusively shown to be effective in treating acne.

Regarding the comment's belief that borates were acting as pH control agents, preservative additives, or astringent and/or surface-tension reducing additives in topical acne drug products, the comment did not submit any data to support this position. If the borate were functioning as a pH control agent, preservative additive, or surface tension reducing additive, it would be an inactive ingredient as defined in 21 CFR 220.3(b)(7) and (8). Borates as active/inactive ingredients in OTC astringent drug products were discussed in an amendment of the notice of proposed rulemaking for OTC skin protectant drug products (54 FR 13490 at 13491 to 13492). The acceptability of boric acid as a buffering agent or stabilizer in OTC drug products was discussed there. However, neither the data submitted to the Panel, nor the information provided by the comment, are sufficient to alter the nonmonograph classification of borates as active ingredients for the treatment of acne.

*C. Comments on Labeling of OTC Topical Acne Drug Products*

6. One comment noted its continuing opposition to the agency's exclusivity policy. The comment contended that FDA should not prescribe exclusive lists of terms from which indications for use for OTC drugs must be drawn, thereby prohibiting alternative OTC drug labeling terminology which is truthful, not misleading, and intelligible to the consumer. The comment subsequently requested clarification whether the proposed modifications in FDA's exclusivity policy (published in the **Federal Register** of April 22, 1985; 50 FR 15810) were intended to supersede the labeling policy on indications proposed in the tentative final monograph for OTC topical acne drug products (published in the **Federal Register** of January 15, 1985; 50 FR 2172 at 2177).

The general labeling policy proposed in the tentative final monograph for OTC topical acne drug products has been superseded. In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a rule finalizing the April 22, 1985 proposal and changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated

APPROVED USES; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated APPROVED USES; or (3) the approved monograph language on indications, which may appear within a boxed area designated APPROVED USES, plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The indications (§ 333.350(b)) in this final monograph for OTC acne drug products specifically refer to the general labeling policy stated in 21 CFR 330.1(c)(2).

7. Three comments disagreed with the agency's not including an antibacterial labeling claim for any topical acne ingredient in the tentative final monograph (50 FR 2172 at 2177 to 2178). The comments requested that the agency place an antibacterial claim in Category I in the final monograph for OTC topical acne drug products. Two of the comments specifically requested that products containing either benzoyl peroxide or the combination of 8 percent sulfur and 2 percent resorcinol be allowed to use the antibacterial claim in their labeling. These comments stated that the agency was in error regarding the statement in the tentative final monograph that no in vivo data were submitted in support of an "antibacterial" claim following publication of the Panel's report. The comments mentioned the presentations (and submissions) of data and literature (Ref. 1) addressing the antibacterial effectiveness of benzoyl peroxide and the combination of sulfur and resorcinol that had been made to the Panel. The comments contended that because the Panel had classified the antibacterial claim in Category I at its final meeting and included the claim as an indication in the labeling in its recommended monograph (47 FR 12430 at 12474 to 12476), there appeared to be no need for additional data submissions following publication of the Panel's report. One comment urged the agency to require an active acne ingredient to meet the in vivo testing criteria of both the free fatty acid reduction, as well as the *Propionibacterium acnes* log-reduction tests, in order to use the antibacterial indication on the product labeling. The comment also suggested that the definitional testing methodologies be subject to modification or substitution by suitably equivalent test procedures.

One comment (Ref. 2) included two studies and selected literature previously presented to the Panel in support of the antibacterial effectiveness of benzoyl peroxide against the *P. acnes* organisms commonly associated with acne. Another comment (Ref. 3) included two studies that utilized the Panel's recommended *P. acnes* reduction technique and an optional free fatty acid reduction assay to determine in vivo antimicrobial activity of benzoyl peroxide. The comment also included an antibacterial study on *P. acnes* and fatty acid reduction previously provided to the Panel for the combination of 8 percent sulfur and 2 percent resorcinol (Ref. 1). The third comment (Ref. 4) included three clinical studies that assessed the effectiveness of benzoyl peroxide in reducing *P. acnes* and free fatty acids. The comment also resubmitted four presentations that had been made to the Panel on *P. acnes* and free fatty acid reduction by the combination of 8 percent sulfur and 2 percent resorcinol as well as several concentrations of benzoyl peroxide.

The agency has reviewed these studies and determined that no single study satisfies the Panel's in vivo testing criteria recommended in § 333.340 of its monograph (47 FR 12430 at 12475). One study (Ref. 5) was a 30-day, double-blind, half-face comparison of a 5-percent benzoyl peroxide wash with its vehicle in 20 subjects with facial acne. Nonblinded arms of the study consisted of Ivory soap washes compared with the 5-percent benzoyl peroxide wash or its vehicle in 40 subjects. During the first 15 days, subjects washed only with tap water. During the next 15 days, twice-daily washings of contralateral sides of the face were done by ancillary personnel using 2 of 3 treatments (5-percent benzoyl peroxide wash, the vehicle, or Ivory soap) in each subject to one or the other side of the face. Quantitative *P. acnes* cultures were performed using a modified Williamson scrub technique at baseline and on days 15, 22, and 29. Twenty subjects in the benzoyl peroxide-placebo group demonstrated a reduction in *P. acnes* counts of 16 percent on the benzoyl peroxide side and 2 percent on the placebo side ($p<0.01$). In the total of 40 subjects treated with benzoyl peroxide, there was a reduction in *P. acnes* counts of greater than 0.75 log ($p<0.01$) on the side of the face washed with benzoyl peroxide. Although the only apparent deviation in this study from the Panel's recommended guidelines (47 FR 12430 at 12473 to 12474) was the determination of a single (instead of the preferred three separate) *P. acnes* baseline count, insufficient information was provided regarding microbiological techniques, sample sites utilized, and individual *P. acnes* counts. The study satisfies a majority of the in vivo testing criteria set forth by the Panel in its recommended monograph; however, as presented, it does not support the antibacterial claim. The data that were provided could not be appropriately, statistically analyzed because the original data were not included with the submission.

In another study (Ref. 6), 15 subjects with a high facial density of *P. acnes* were treated with a 5-percent benzoyl peroxide lotion and assessed for the suppression of *P. acnes* over a 24-hour period. The test lotion was applied 3 times over a 12-hour period. A modified Williamson and Kligman procedure was used for test site preparation, sample collection, and culturing. Samples for quantitative cultures of *P. acnes* were taken from each subject at baseline and 12 and 24 hours after the last treatment. A statistically significant ($p=0.001$) reduction in *P. acnes* counts was reported at both 12 and 24 hours after treatment (34 percent and 22 percent, respectively). There was a greater than 0.75 log reduction in the *P. acnes* counts at both time periods. The agency finds that this study deviated from the Panel's recommended in vivo criteria for antibacterial activity in two key ways: The uncontrolled design and the very short duration of the study. In addition, appropriate statistical analysis was not possible because the original data were not provided with the submission.

In another study (Ref. 7), 20 subjects with Pillsbury Grades II and III acne were enrolled in this single blind, randomized, parallel group comparison of 10 percent benzoyl peroxide lotion (applied to the face twice daily) with oral tetracycline hydrochloride (250 milligrams (mg) three times per day) for 8 weeks. The Williamson and Kligman scrub technique was used to quantify the skin-surface bacteria at baseline, at 8 weeks at the end of treatment, and 4 weeks after treatment ended. Ten subjects in the test-lotion group and 7 subjects in the tetracycline group completed the treatment period. *P. acnes* Type I and Type II reductions occurred in 78 percent ($p=0.001$) and 100 percent ($p=0.12$), respectively, of the benzoyl peroxide subjects and in 43 percent and 83 percent, respectively, of the tetracycline subjects.

In another study (Ref. 8), 8 subjects with acne were involved in a double-blind, half-face comparison of a 10-percent benzoyl peroxide cream with 5 and 10 percent benzoyl peroxide lotions. Each subject received 2 applications per day of the cream to one side of the face, and the 5- or 10-percent lotion to the opposite side of the face, 6 days a week for 2 weeks. Beginning at day 1, a significant ($p<0.1$) reduction from baseline of *P. acnes* Type I and Type II counts was seen in both the cream and lotion groups. The median reduction in *P. acnes* Type I and Type II counts at day 11 was 99.8 and 93.3 percent, respectively, in the cream group.

The two studies (Refs. 7 and 8) differ significantly from the Panel's recommended in vivo criteria for antibacterial activity. Neither study included a vehicle control or the recommended number of subjects for a full-face (minimum of 30 subjects) or a half-face (minimum of 15 subjects) study design. It was not clear in either study whether the same skin site (in each subject) was sampled at each of the different time points. In addition, while the two baseline bacteria counts reported in one study (Ref. 8) appeared adequate, the other study (Ref. 7) reported only a single baseline count.

Finally, the preferred baseline *P. acnes* density ($1\times10^5$ to $1\times10^6$ organisms per square centimeter) was not satisfied by all the subjects in one study (Ref. 7), and only the mean counts for the subjects in the other study (Ref. 8) were reported.

The agency notes that, although a dramatic reduction in organisms was reported in three of the four studies discussed above, these studies all have flaws. Although the results of these studies make it difficult to rule out the possibility of antimicrobial activity for benzoyl peroxide, these studies, because of their flaws, cannot be used to support general recognition of an antibacterial claim for topical acne drug products containing benzoyl peroxide.

Three clinical studies (Ref. 4) published after the Panel ceased its deliberations assessed the effectiveness of benzoyl peroxide in reducing *P. acnes* and free fatty acids. A study by Leyden et al. (Ref. 9) was a controlled, parallel-group comparison of gel and lotion formulations of benzoyl peroxide (2.5 percent, 5 percent, and 10 percent concentrations). A reduction in *P. acnes* counts of approximately 1.5 log was reported with all benzoyl peroxide formulations (with no significant difference between the formulations). An 8-week, double-blind study by Cunliffe and Holland (Ref. 10) compared 5-percent benzoyl peroxide gel and lotion in 48 subjects (paired according to sex, grade of acne, and lesion count). A reduction in both *P. acnes* counts and free fatty acids was shown throughout the treatment period. Nacht et al. (Ref. 11) compared a 3-percent hexachlorophene suspension with a 5-percent benzoyl peroxide lotion in a half-face study in 9 subjects with high-density *P. acnes* baseline counts. A reduction in mean *P. acnes* counts of 98 percent (1.6 log) and a 52-percent reduction in free fatty acid/triglyceride ratios was reported for benzoyl-peroxide treated areas.

The agency has determined that further information on the design and conduct of the Leyden et al. study (Ref. 9) would be needed to reach a definite conclusion regarding antibacterial activity. The details provided for the Cunliffe and Holland study (Ref. 10) and the Nacht et al. study (Ref. 11) were insufficient for appropriate evaluation; further, neither of these studies included vehicle control groups. Therefore, neither of these studies (Refs. 10 and 11) are adequate to establish general recognition of an antibacterial claim for OTC topical acne products containing benzoyl peroxide.

The agency has determined that all of the studies described above either differ significantly from the guidelines recommended by the Panel or do not provide sufficient detail of the study design, conduct, or data to allow for an appropriate evaluation. One critical deviation, in almost every study, was the lack of a vehicle control. The agency considers the vehicle control group essential in order to rule out any activity which might be attributable to the vehicle. In addition, inclusion of a vehicle control is necessary because the antimicrobial effectiveness of the acne drug product may be contingent upon the contact time permitted by the vehicle. Further, with one exception, it is impossible to determine whether the active ingredient produced the recommended minimum reduction of 0.75 log in *P. acnes* count from the baseline measurement, because the original data were not provided in the submissions.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (address above) (Ref. 12).

The submitted data do not support inclusion in this final monograph of the antibacterial labeling that the Panel proposed in § 333.350(b)(3). Therefore, the Panel's recommended testing criteria under § 333.340 of its proposed monograph, which support use of the antibacterial labeling proposed in § 333.350(b)(3), are not being included in this final monograph. However, the agency believes that an OTC topical acne ingredient should meet specific testing criteria in order to be allowed to make an antibacterial claim.

The Panel recommended an optional in vivo test in § 333.340(e)(2) of its monograph using a reduction in free fatty acids on the skin surface to confirm antibacterial activity (47 FR 12430 at 12475). Although one comment urged the agency to require an active acne ingredient to meet this test to use the antibacterial indication in labeling, the agency concludes that such a test should continue to be optional if, based on the studies submitted and other information, the following modification is made to the criterion for in vivo testing for antibacterial activity that was recommended by the Panel in § 333.340(e)(1):

* * * A reduction of *P. acnes* counts of 0.75 log by the active ingredient must be demonstrated using an appropriate statistical test at an alpha error of less than or equal to 0.05. The *P. acnes* count in the active drug post treatment specimens must be at least 0.75 log lower than the corresponding baseline specimens and must be at least 0.75 log lower than the lesser of the vehicle baseline or vehicle post treatment *P. acnes* counts.

Regarding one comment's suggestion that the definitional testing methods be subject to modification or substitution by suitably equivalent test procedures, the agency notes that alternate methods would be acceptable so long as they have been evaluated and accepted by the agency. Such methods should be submitted to the agency for review. If found acceptable, they could be included in the monograph in the future as an alternate method. However, adequate data need to be submitted to the agency to support the testing procedures that would support antibacterial labeling for OTC acne drug products.

**References**

(1) OTC Volumes 070234, 070235, and 070236.

(2) Comment No. C00025, Docket No. 81N-0114, Dockets Management Branch.

(3) Comment No. C00021, Docket No. 81N-0114, Dockets Management Branch.

(4) Comment No. C00026, Docket No. 81N-0114, Dockets Management Branch.

(5) Unpublished Study, The Effect of Oxy Wash 5% on the Cutaneous Population of Propionibacterium Acnes, Report No. NTI-004, Comment No. C00025, Docket No. 81N-0114, Dockets Management Branch.

(6) Unpublished Study, Quantitative Determination of Suppression of Propionibacterium Acnes Over a 24 Hour Period by 5% Benzoyl Peroxide (Oxy 5), Report No. MA-00112, Comment No. C00025,

Docket No. 81N-0114, Dockets Management Branch.

(7) Unpublished protocol, IR Number 61-77, Comment No. C00021, Docket No. 81N-0114, Dockets Management Branch.

(8) Unpublished Protocol, IR Number 90-79, Comment No. C00021, Docket No. 81N-0114, Dockets Management Branch.

(9) Leyden, J., et al., Topical Antibiotics and Topical Antimicrobial Agents in Acne Therapy, *Acta Dermatovener*, Supplement 89:75-82, 1980.

(10) Cunliffe, W. J., and K. T. Holland, The Effect of Benzoyl Peroxide on Acne, *Acta Dermatovener*, 61(3):267-269, 1981.

(11) Nacht, S., et al., Comparative Activity of Benzoyl Peroxide and Hexachlorophene, *Archives of Dermatology*. 119:577-579, 1983.

(12) Letter from W. E. Gilbertson, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET11, Docket No. 81N-0114, Dockets Management Branch.

8. One comment contended that the proposed definition of acne in § 333.303(a) (i.e., "An inflammatory skin disease involving the oil glands and hair follicles of the skin") is incomplete because it fails to recognize the noninflammatory lesions that are also characteristic of acne. The comment cited three references (Refs. 1, 2, and 3) to support its position. The comment stated that mild acne can be caused by either noninflammatory or inflammatory lesions and recommended that the definition of acne be expanded as follows: "A skin disease, involving the oil glands and hair follicles of the skin. This disease includes noninflammatory lesions (comedones, whiteheads, and blackheads) as well as inflammatory lesions, also called pimples (papules and pustules)."

A standard medical dictionary defines acne as "an inflammatory disease of the pilosebaceous unit" (Ref. 4). However, other authors define acne based on the clinical manifestations of the disease. Moschella, Pillsbury, and Hurley (Ref. 3) note that the interaction of many factors leads to the production of clinical lesions which are either noninflammatory (i.e., open and closed comedones) or inflammatory. The closed comedones (whiteheads) are the first visible lesions of acne and suffer one of two fates, either they rupture and incite an inflammatory lesion or they transform into open comedones (blackheads) (Ref. 2). Although many clinicians regard blackheads as the hallmark of acne, their absence by no means negates the diagnosis, because many acne sufferers have few or no blackheads (Ref. 1). Hurwitz (Ref. 5) noted that acne usually appears as a variety of lesions with the comedones being characteristic of the disease. Gossell (Ref. 6) also described comedones as being the typical lesions of acne. In its mildest form, acne consists of open (blackheads) and closed (whiteheads) comedones. Tunnessen (Ref. 7) noted that while there exists great variation in the number and type of lesions in each person, comedones are usually the predominant lesions present in early adolescence. The comedones have been referred to as the noninflammatory lesions of acne (Refs. 8 and 9). Acne consisting primarily of blackheads and whiteheads has been designated as mild or noninflammatory acne (Refs. 10 through 13). Although individuals usually have a combination of noninflammatory and inflammatory lesions, one or the other type may predominate (Ref. 8).

The Panel designated the comedo the primary lesion of acne (47 FR 12430 at 12435). The comedo has been considered by many (as noted above) to be a sign or symptom on which a diagnosis of acne can be made. Because the comedo may be the predominant lesion of acne in some individuals, the agency agrees with the comment and concludes that it would be appropriate to include the noninflammatory lesions of acne in the monograph definition of acne. However, the definition section of the monograph only includes those terms that are necessary for the information that appears in the monograph. The agency does not believe that consumers differentiate between inflammatory or noninflammatory lesions, or use the terms inflammatory or noninflammatory to describe their lesions. Likewise, consumers do not use the terms comedo or comedones to describe their blackheads or whiteheads. Therefore, the agency is not including the terms inflammatory, noninflammatory, or comedones in the monograph definition of acne. Consumers do use the terms "blackheads," "whiteheads," "pimples," and "blemishes" to describe their acne. The terms "blackheads," "pimples," and "blemishes" were proposed in the tentative final monograph to appear in the indications for OTC acne drug products. These terms plus the term "whiteheads" describe the inflammatory and noninflammatory appearances of acne in consumer terms. (See discussion of definitions for these terms in comment 9 below.) Accordingly, the agency is revising the definition of acne in § 333.303(a) of this final monograph to read as follows: "Acne. A disease involving the oil glands and hair follicles of the skin which is manifested by blackheads, whiteheads, acne pimples, and acne blemishes."

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(4) Dorlands' Illustrated Medical Dictionary 27th Ed., W. B. Saunders Co., Philadelphia, 1988, s.v. acne.

(5) Hurwitz, S., Acne Vulgaris, *American Journal of Diseases of Children*, 133:536-544, 1979.

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(8) Spector, R., The Topical and Systemic Treatment of Acne Vulgaris, *Iowa Medicine*, 76:280-283, 1986.

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(11) Quan, M. and R. A. Strick, Management of Acne Vulgaris, *American Family Physician*, 38:207-218, 1988.

(12) Commens, C., Management of Acne, *Australian Family Physician*, 15:893-894, 1986.

(13) Stubborn and Vexing, That's Acne, *FDA Consumer*, 14:14-17, 1980.

9. One comment requested that the following definitions, some of which the Panel adopted in the advance notice of proposed rulemaking (47 FR 12430 at 12435), be included in the final monograph for OTC acne drug products:

Comedo. The primary lesion of non-inflammatory acne.

Whitehead. A noninflammatory acne lesion, also called a closed comedo, characterized by a small, whitish, firm nodule.

Blackhead. A noninflammatory acne lesion, also called open comedo, characterized by a black tip.

Pimples. A small prominent inflamed elevation of the skin, including papules and pustules.

Papules. A small inflammatory lesion that appears red and raised.

Pustules. A small, raised inflammatory lesion that is filled with pus and arises from a papule.

The comment maintained that the terms, as defined above, should be included in the definition section of the monograph because they would provide clarity and consistency in referring to

the lesions that characterize acne. In addition, the comment disagreed with the agency's deleting the terms "follicle" and "lesion" from the definition section of the proposed monograph. The comment stated that the definition section will frequently be used by professionals involved with OTC acne drug products. The comment requested the agency to reinstate the terms "follicle" and "lesion" in the final rule, because they are correct medical terms. Two comments urged the agency to allow the use of such terms as "comedones," "whiteheads," "papules," and "pustules" in addition to the proposed terms of "blackheads," "acne pimples," and "acne blemishes" in § 333.350(b)(2) "other allowable indications" for OTC topical acne drug products. One comment stated that the different types of acne lesions are often defined and/or discussed in articles and books written for the general public; thus, the public is well-advised and continually exposed to the meanings of these terms. Both comments believed that including these terms in the monograph would provide more accurate and meaningful descriptions of the various types of acne lesions and thus would be appropriate for use in the indications section and other parts of the labeling.

The Panel's definitions relating to the use of acne drug products included "comedo," "whitehead," "papule," and "pustule" (47 FR 12430 at 12435). However, the Panel did not include these terms in the definitions in § 333.350(b) of its recommended monograph (47 FR 12475). Further, in the tentative final monograph the agency did not propose any of these terms for use in the labeling of OTC acne drug products.

The Panel proposed the terms "blackhead," "pimple," and "lesion" in § 333.350(b) of its recommended monograph (47 FR 12475) because it considered these terms to be more meaningful to consumers. However, the Panel defined a lesion generally (i.e., a characteristic area of a skin condition), and stated that lesions in acne include blackheads and pimples. The agency considers the terms "blackheads" and "pimples" appropriate for the labeling of OTC acne drug products, but does not consider the terms "comedo," "papule," "pustule," "lesion," and "follicle" as being widely used or understood by the majority of consumers who use OTC acne drug products. As discussed in comment 8 above, none of these terms has been included in the definition of acne that appears in this final monograph. The agency agrees with the comment that allowing the term "whiteheads" in the indications for use is appropriate, because a whitehead is both the initial, and a primary, lesion of acne (see comment 8 above). In addition, the agency believes that consumers understand the meaning of the term and commonly use it to describe their acne lesions. However, the agency does not believe that many consumers use the terms "comedo" or "comedones" to refer to "whiteheads" or "blackheads" (closed and open comedones, respectively). Thus, the agency concludes that the terms "comedo" or "comedones" in the labeling of OTC acne drug products would be confusing to consumers.

Although a standard medical dictionary (Ref. 1) defines a pimple as a papule or pustule most often due to acne vulgaris, the agency does not believe that the terms "papule" or "pustule" are widely understood by consumers. The agency considers the term "acne pimples" to be more informative and less confusing to consumers. The terms "blackhead" and "pimple" were defined in the tentative final monograph. The term "acne blemish," which appeared in the labeling proposed in § 333.350(b)(2), was not. Therefore, the agency is clarifying the definition of the word "pimple" that was proposed in § 333.303(d) of the tentative final monograph by adding the word "acne" before "pimple" and by adding the words "resulting from acne" at the end of the definition. The agency is also adding a definition for "acne blemish" that reads: "A flaw in the skin resulting from acne." The agency is revising the definition for "blackhead" to read: "A condition of the skin that occurs in acne and is characterized by a black tip." Finally, the agency is adding a definition for "whitehead," which reads: "A condition of the skin that occurs in acne and is characterized by a small, firm, whitish elevation of the skin." The agency is not using the term "nodule" in defining a whitehead, as suggested by the comment, because this type of acne lesion is usually macular or papular but rarely nodular. The Panel defined a "nodule" as a deep-seated lesion that develops from the rupture of closed comedones (whiteheads) (47 FR 12430 at 12435). Nodular lesions are more characteristic of acne conglobata, while the whiteheads in acne vulgaris are a more superficial type lesion (i.e., papular) (Ref. 2).

The above changes and addenda to the definitions require some editing of the definition section proposed in the tentative final monograph. Also, based on the amended definitions appearing in this final monograph, the indications section of this final monograph (§ 333.350(b)) now includes the terms "acne blemishes," "acne pimples," "blackheads," and "whiteheads."

References

(1) Dorlands' Illustrated Medical Dictionary 27th Ed., W. B. Saunders Co., Philadelphia, 1988, s.v. pimple.

(2) Dorlands' Illustrated Medical Dictionary 27th Ed., W. B. Saunders Co., Philadelphia, 1988, s.v. papule.

10. One comment contended that the statement of identity (i.e., "acne medication") proposed in § 333.350(a), although accurate, was limiting as it did not distinguish between types of topical acne products. As an example, the comment cited a lack of distinction made between products intended to remain on the skin and those which are rinsed off after being applied. The comment suggested the agency allow other statements of identity which it felt would be appropriate for acne drug products, such as "acne treatment," "medicated acne cleanser," and "antibacterial acne medication (or cleanser or treatment)." The comment also asked that the product form, e.g., lotion, cream, gel, foam, etc., be allowed to be added, where appropriate, to more fully inform consumers.

The agency agrees with the comment that the term "acne treatment" would be an appropriate alternative statement of identity for OTC acne drug products because this term is as informative to consumers as the proposed statement of identity "acne medication." The agency also concurs with the comment's request to allow the dosage form to be added, following the product's statement of identity. Such information could be helpful to consumers in comparing and selecting topical acne drug products. The United States Pharmacopeia (U.S.P.) lists a number of dosage forms that might be used for OTC topical drug products, e.g., aerosol, cream, emulsion, gel, lotion, ointment, solution, or suspension (Ref. 1). The agency notes however that a foam, which the comment cited as an example, is not defined as a pharmaceutical dosage form in the U.S.P. (Ref. 1). In addition, although an aerosol is a defined pharmaceutical dosage form in the U.S.P., the agency determined from a marketplace survey of topical acne drug products (Refs. 2, 3, and 4) and from reviewing the submissions made to the Panel that there are only two aerosol drug products promoted as a "foam." However, neither product contains monograph ingredients. The agency is not aware of any topical acne

ingredients included in this final monograph having been marketed in an aerosol or foam dosage form. Therefore, the agency is not including "aerosol" or "foam" in the monograph as a part of the statement of identity.

The dosage forms listed in the monograph are examples only and are not intended to be all inclusive. Section 333.301(a) of the monograph states that an OTC acne drug product is in a form "suitable" for topical administration. The agency's marketplace survey shows that the most widely used dosage forms for OTC topical acne drug products are lotions, creams, and gels. Therefore, the agency is selecting these dosage forms to appear as examples in the statements of identity in § 333.350(a) of this final monograph as follows: "acne treatment," "acne medication," "acne treatment" (insert dosage form, e.g., "cream," "gel," or "lotion"), and "acne medication" (insert dosage form, e.g., "cream," "gel," or "lotion"). Other dosage forms would also be acceptable for OTC topical acne drug products based on their previous marketing history for this type of product. Examples include pads and ointments.

The agency believes that the other terms suggested by the comment, which included "antibacterial acne medication (or cleanser or treatment)" and "medicated acne cleanser," are not appropriate terms for the labeling of OTC acne drug products. Regarding the term "antibacterial," although several submissions were made in support of reinstating the "antibacterial claim" to Category I status, the agency has determined that the studies were not adequate; therefore, the term "antibacterial" is nonmonograph in this final rule (see comment 7 above). The agency considers the term "medicated" to be unnecessary because all OTC topical acne drug products contain medication. In addition, the agency notes that while "medicated acne cleanser" may be a term associated with adjunctive acne therapies, the agency is not including such products in this final monograph (see comment 3 above). Accordingly, the agency is not including these other terms in this final monograph.

**References**

(1) The United States Pharmacopeia XXII—The National Formulary XVII, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 1688–1697, 1989.

(2) Physicians Desk Reference for Nonprescription Drugs, 10th Ed., Medical Economics Co., Inc., Oradell, NJ, p. 209, 1989.

(3) Billows, J. A., Acne Products, *in* Handbook of Nonprescription Drugs, 8th Ed., American Pharmaceutical Association, Washington, pp. 583–591, 1988.

(4) Acne Products, *in* Facts and Comparisons, J. B. Lippincott Co., New York, pp. 544a–545a, 1989.

11. Two comments requested that the agency reinstate to Category I status the following labeling claims that had been recommended by the Panel: "loosens blackheads," "helps remove blackheads," and "unclogs (or unplugs) pores to help clear acne." The comments stated that the agency did not include these claims in the tentative final monograph because it believed that they were not clear or would be misleading to the consumer. The comments stated that Category I acne ingredients cause exfoliation of the stratum corneum, which causes an increased rate of turnover of the cells lining the duct walls of the comedo (blackhead). The comments added that peeling agents can also reduce the cohesiveness of these cells lining the duct. The comments stated that "the net effect of this topical treatment reduces the tendency of forming new comedones and loosens the structure of the formed comedones to help their extrusion" (Refs. 1, 2, and 3). The comments concluded that based on these mechanisms of action, the above claims are accurate, meaningful, and truthful statements that should be permitted in the monograph.

The agency does not agree with the comments that these statements should be included in the final monograph. In the tentative final monograph for OTC topical acne drug products (50 FR 2172 at 2179), the agency stated its belief that the Panel's recommended phrases "loosens blackheads," "helps remove blackheads," and "unclogs (or unplugs) pores to help clear acne," do not meaningfully or accurately describe the action of topical acne drug products. The agency has reviewed the three references cited by the comments and determined that they primarily describe the effectiveness of acne ingredients in terms of sebum removal and a mild peeling action. The agency notes that one of these references (Ref. 1) attributes some of the activities, as discussed by the comments, to topical acne ingredients which cause mild irritation and desquamation. However, a number of other sources in the literature (Refs. 4 through 9) present a different viewpoint. Accordingly, the agency concludes that there is insufficient basis to make the requested changes.

The agency considers the claims requested by the comments as accurately describing the action of comedolytic agents (i.e., agents which cause the unseating and expelling of comedones) (Refs. 4 and 10). A comedo (or blackhead, which is the term used in the labeling claims requested by the comment) is a plug of keratin and sebum within the dilated orifice of a hair follicle (Ref. 11). A comedolytic agent acts by preventing infrainfundibulum horny cells from sticking together and by causing an increased turnover of epithelial cells lining the pilosebaceous canal. This rapid turnover of loose horny cells causes the unseating and expulsion of existing comedones (Refs. 7, 8, and 9). The agency notes that benzoyl peroxide is the only OTC ingredient for the treatment of acne which has known comedolytic activity (Refs. 4 through 7). However, as discussed above, this final rule does not include final agency action on benzoyl peroxide.

As pointed out by the comments, certain Category I ingredients (i.e., sulfur and resorcinol) have exfoliating activity (i.e., agents which evoke a superficial peeling) (Refs. 4 and 10). The agency notes, however, that exfoliating agents do not necessarily function as a comedolytic. A comedolytic can be described as an exfoliant of the follicular infundibulum. However, an exfoliating agent, in general, is not specific for pilosebaceous epithelium. In addition, an exfoliating agent does not attack fibrous proteins (keratin) or cause loss of horny substance, does not dissolve comedones, and acts primarily on the epidermis (Refs. 4 and 5). Because most pustular acne lesions are quite superficial, an exfoliating agent (through its surface peeling action) can unroof these lesions and produce spontaneous drainage (Ref. 7). However, most of the agents that induce exfoliation, e.g., sulfur and resorcinol, are not a comedolytic. Although salicylic acid at concentrations of 5 to 10 percent is an effective comedolytic, the concentrations included in this final monograph (i.e., 0.5 to 2 percent) work primarily as a peeling agent, produce desquamation by hydrolyzing the intracellular substances of surface squames (exfoliants), and have less comedolytic activity (Refs. 7, 8, and 9). None of the active ingredients included in this portion of the final monograph are effective as a comedolytic agent at OTC concentrations (Refs. 4 and 5).

Accordingly, the agency concludes that the claims requested by the comments do not apply to the primary activity of the current monograph ingredients. The agency is not including these claims in the final monograph at this time.

**References**

(1) Hopponen, R. E., Acne Products, *in* "Handbook of Nonprescription Drugs," 5th

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(2) Montagna, W., and P. F. Parakkal, The Structure and Function of Skin, 3rd Ed., Academic Press, Inc., New York, pp. 321–331, 1974.

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(4) Schachner, L., The Treatment of Acne: A Contemporary Review, The Pediatric Clinics of North America, 30:501–510, 1983.

(5) Plewig, G., and A. M. Kligman, Acne. Morphogenesis and Treatment, Springer-Verlag, New York, pp. 277–311, 1975.

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(7) Reisner, R. M., Acne Vulgaris, *in* Current Dermatologic Therapy, W. B. Saunders Co., Philadelphia, pp. 3–6, 1982.

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(9) Quan, M., and R. A. Strick, Management of Acne Vulgaris, American Family Physician, 38:207–218, 1988.

(10) Melski, J. W., and K. A. Arndt, Current Concepts: Topical Therapy for Acne, New England Journal of Medicine, 302:503–506, 1980.

(11) Dorlands' Illustrated Medical Dictionary, 27th Ed., W. B. Saunders Co., Philadelphia, 1988, s.v. comedo.

12. One comment recommended that the agency delete the term "entire" from the proposed directions for using topical acne drug products in § 333.350(d)(1), which read: "Cleanse the skin thoroughly before applying medication. Cover the entire affected area with a thin layer one to three times daily * * *."

Believing that the term "entire" in these directions might encourage overuse of topical acne drug products, the comment provided an example how the directions could be misread by consumers. A person with pimples speckling the back or shoulders might cover the whole back or shoulder area with an acne medication one to three times daily. The comment maintained that such application could result in overdrying of large areas of the skin. Therefore, the comment recommended that the directions simply read "Apply to the affected area."

In the advance notice of proposed rulemaking for OTC topical acne drug products, the Panel stated that the aim of acne therapy is not only to clear up existing acne lesions but also to prevent the formation of new acne lesions (47 FR 12430 at 12438). Studies reviewed by the Panel used a conservative estimate of 4 weeks as the natural resolution time of acne pimples. A person who has not been treated for acne will have a natural cyclical rise and fall in the number of acne lesions over this time period. Using this estimate, the Panel concluded that any acne therapy that significantly reduced lesion counts over the first 4 weeks was effective in treating existing lesions. Also, any ingredient shown to be effective by reducing lesion counts beyond 4 weeks was also effective in preventing the development of new acne lesions.

The Panel discussed the fact that if individuals are instructed to cover the whole area where they have acne (i.e., the general area where they have the disease, rather than spot treatment), the medication will treat the existing acne lesions as well as prevent the development of new lesions (Refs. 1 and 2). Treating only the existing lesions will not provide successful long-term management of the disease due to its cyclical nature. Tunnessen (Ref. 3) emphasized the importance of covering all of the skin with the acne medication, not just the active lesions, to prevent new pimples from beginning. Quan and Strick (Ref. 4) recommended that patients using topical preparations be specifically instructed to apply the medication to all the affected areas (not just the individual lesions).

The agency believes, as did the Panel, that the purpose of acne therapy is to clear existing lesions and prevent the formation of new ones. In order to be as effective as possible, acne medications must be left on the skin for a finite period of time to penetrate into the follicle and dermis. Accordingly, they should be applied directly to areas of the skin with active lesions as well as to surrounding areas which have the potential for developing lesions. The directions to cover the entire affected area are intended to inform the user to apply the acne medication to all areas of the skin where existing lesions are visible as well as the surrounding areas where new acne lesions are likely to occur. Accordingly, the agency does not agree with the comment's recommendation that the term "entire" be deleted from the directions for use of topical acne drug products in § 333.350(d)(1).

**References**

(1) Minutes of the 41st Meeting of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products, April 27 and 28, 1979, pp. 165–168.

(2) Minutes of the 51st Meeting of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products, June 6 and 7, 1980 p. 74–75.

(3) Tunnessen, W. W., "Acne: An Approach to Therapy for the Pediatrician," Current Problems in Pediatrics. 14(5):1–36, 1984.

(4) Quan, M., and R. A. Strick, Management of Acne Vulgaris, American Family Physician, 38(2):207–218, 1988.

13. One comment objected to the proposed elimination of the term "caution(s)" in the labeling of OTC drug products. The comment asserted that while the terms "warning" and "caution" are both usually used to call attention to potential danger, there is a distinction between the terms that is important, especially when products contain long lists of warnings. The comment contended that the word "warning" is significantly harsher than "caution." A warning precludes the use of a product under certain conditions, e.g., "Warning: For external use only. Avoid contact with the eyes." The word "caution" on the other hand, does not preclude the use of the product but may alert the user to a potential problem, e.g., "Caution: If irritation develops discontinue use and consult a physician." Because the same phrases may be warnings with regard to one class of products and merely cautions with regard to another, the comment maintained that the flexibility of both terms is essential in order to prepare accurate and comprehensible labeling.

Section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(f)(2)) states, in part, that a drug must bear in its labeling "* * * such adequate warnings * * * as are necessary for the protection of users." Section 330.10(a)(4)(v) of the OTC drug regulations provides that labeling of OTC drug products should include "* * * warnings against unsafe use, side effects, and adverse reactions * * *."

The agency notes that historically there has not been consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances, either of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. The agency considers the word "warning" alone to be the simplest, clearest signal to consumers. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC

drug labeling that is intended to alert consumers to potential safety problems.

14. One comment contended that the labeling statements included in a final monograph for OTC acne drug products can create no inferences for cosmetics or for the cosmetic aspects of acne drug products intended for both drug and cosmetic use. The comment stated that in other OTC drug rulemaking proceedings, such as in the tentative final monograph for OTC skin bleaching drug products (47 FR 39108 at 39115), the agency acknowledged that OTC drug monographs apply only to the active ingredients that fall within the statutory definition of "drugs." Maintaining that this same principle applies to OTC topical acne drug products, the comment requested that the agency include in the preamble to the final monograph the following statement: "The agency emphasizes that OTC drug monographs contain appropriate drug labeling claims to be used on OTC drug products and do not preclude the use of acceptable cosmetic claims if the product is both a drug and a cosmetic."

The agency agrees with the ideas expressed in this statement. While this monograph does not include any cosmetic labeling, such labeling may also appear on appropriate products along with the required drug labeling. (See comment 15 below for a discussion of where cosmetic labeling may appear.) Products labeled for both drug and cosmetic use must conform to the pertinent final OTC drug monograph(s), the cosmetic labeling requirements of section 602 of the act (21 U.S.C. 362), and 21 CFR 701.

15. One comment disagreed with the agency's position of prohibiting cosmetic claims from appearing in any portion of the labeling that is required by the monograph. The comment stated that so long as the labeling is truthful and not misleading, information about both the cosmetic and drug properties of a product should be permitted anywhere on the labeling. The comment contended that although acne is a medical condition treated with drug products, it is also a "cosmetic" problem because it "afflicts" the appearance. Therefore, the goal of therapy is a cosmetic one (i.e., to achieve a better appearance). Pointing out that the agency included the instructions "Cleanse the skin thoroughly before applying medication" in the directions proposed in § 333.350(d)(1), the comment argued that because the directions require an acne medication to be applied after the skin has been cleansed (a cosmetic claim), the agency should permit an acne product to bear unified, truthful cosmetic/drug claims. The comment requested that the agency reconsider its position regarding segregating cosmetic labeling information from monograph information, and requested a hearing on this policy before the Commissioner.

The agency does not agree with the comment that the directions for use for OTC topical acne drug products contain a cosmetic claim. The consumer is instructed to cleanse the skin before applying the topical acne drug product. The act of cleansing is not done with the topical acne drug product, and this cleansing is intended to enhance the effectiveness of the topical acne drug product. The agency also does not agree with the comment that a statement about cleansing in the directions of these products supports an integrated drug-cosmetic labeling approach.

A final OTC drug monograph covers only the drug use of the active ingredients listed therein. The concentration range limitations, statements of identity, indications, warnings, and directions established for these ingredients in the monograph do not apply to the use of the same ingredients in products intended solely as cosmetics. However, if a product is intended for both drug and cosmetic use, it must conform to the requirements of the final OTC drug monograph. In addition, such products may also bear appropriate labeling for cosmetic uses provided the labeling complies with section 602 of the act (21 U.S.C. 362) and the provisions of 21 CFR part 701.

The labeling requirements for products covered by OTC drug monographs were being revised at the time of publication of the OTC topical acne tentative final monograph. The revised regulations in § 330.1(c)(2) set out three alternatives for stating an OTC drug product's indications for use in OTC drug labeling, as discussed in comment 6 above. If the labeling uses the APPROVED USES and boxed area designations provided in the regulations, cosmetic labeling may not appear within the boxed area. Such terminology is not reviewed and approved by FDA and, therefore, cannot appropriately be included in the APPROVED USES boxed area. However, cosmetic claims may appear elsewhere in the labeling (but not in the box), should manufacturers choose the labeling alternative provided in § 330.1(c)(2) (i) or (iii). If the APPROVED USES and boxed area options are not used, drug and cosmetic labeling may be commingled. However, the drug labeling must contain the information set out in the monograph and be presented in such a manner that consumers will readily be able to differentiate the drug aspects from the cosmetic aspects of such labeling. Otherwise, commingled drug and cosmetic labeling claims may be confusing or misleading and thereby subject the product to regulatory action under the act.

Because drug and cosmetic labeling may appear together, in the circumstances described above, the request for a hearing on this issue is moot.

16. One comment stated that manufacturers should be allowed to use one or more of the three alternatives included in § 330.1(c)(2), provided that each labeling is complete and in compliance with all other labeling requirements. As an example, the comment stated that a manufacturer might wish to use the first alternative by listing APPROVED USES or FDA APPROVED USES in a boxed area on the outer container and also use the third alternative by presenting the same FDA approved indications under APPROVED USES or FDA APPROVED USES together with alternative truthful and nonmisleading terminology outside the boxed area on the immediate container. The comment requested that the final rule provide this labeling flexibility.

This comment was submitted before FDA issued a final rule in the **Federal Register** of May 1, 1986 (51 FR 16258) in which it changed its policy to allow such labeling. (See § 330.1(c)(2)(iv).) The indications (§ 333.350(b)) in this final rule contain a cross-reference to the labeling provisions in § 330.1(c)(2).

17. One comment recommended allowing manufacturers the option to include in the labeling under § 333.350(d) "Directions," an appropriate "directions for sensitivity test" to determine possible consumer sensitivity to the active ingredient(s) in topical acne drug products. The comment maintained that instructions on sensitivity testing would be informative as well as helpful in minimizing possible reactions for new users of acne medications. The comment proposed the following example for sensitivity test labeling:

SENSITIVITY TEST FOR NEW USER

1. Apply cream sparingly with finger-tips to one or two small affected areas during the first three days. If no discomfort occurs, apply up to two times daily, wherever pimples are a problem.

2. If bothersome dryness or peeling occurs, reduce dosage to one application per day or every other day.

The Panel, in its review of topical acne drug products, discussed whether

or not to include in the monograph labeling for a "sensitivity test" (Ref. 1). The directions for this test would advise individuals, especially those with unusually dry or sensitive skin, to pretest an acne medication on a small area of the skin before applying the product over a large area. The Panel believed that while it is common for mild irritation to occur with the use of OTC topical acne drug products, in particular products containing benzoyl peroxide, a greater degree of irritation is usually associated with excess use or improper application of the acne medication. The Panel considered the warning it recommended in § 333.350(c)(2), which advises consumers that there exists potential for irritation with the use of benzoyl peroxide, along with the directions for general use of topical acne drug products it recommended in § 333.350(d)(1), as including the information which would be conveyed to consumers in directions for a "sensitivity test." Although, the Panel did not propose to require such labeling in the monograph, the Panel had no objections to including a sensitivity test as optional labeling.

The agency notes that benzoyl peroxide is reported to be the most potentially irritating of OTC acne ingredients. However, as discussed above, benzoyl peroxide and labeling for products containing benzoyl peroxide are not included in this final rule. The active ingredients included in this final monograph act primarily as exfoliating agents (i.e., agents which evoke a superficial peeling) (Refs. 2 and 3) and thus their potential to cause irritation is greatly reduced. However, there are some individuals with sensitive skin who may benefit from labeling for a sensitivity test. Therefore, as requested by the comment, in this final monograph the agency is including "directions for a sensitivity test" as optional labeling. Manufacturers who believe this information is necessary can convey it to consumers in the labeling of their products. Section 333.350(d) is revised to include a new paragraph (3) to read as follows:

"*Optional directions.* In addition to the required directions in paragraphs (d)(1) and (2) above, the product may contain the following optional labeling: '*Sensitivity Test for a New User.* Apply product sparingly to one or two small affected areas during the first three days. If no discomfort occurs, follow the directions stated' (select one of the following: 'elsewhere on this label,' 'above,' or 'below.')"

The agency has determined that the second sentence of the sensitivity test suggested by the comment should be included as part of the regular directions for all OTC acne drug products. Accordingly, the directions in § 333.350(d)(1) are being revised to read as follows: "Cleanse the skin thoroughly before applying medication. Cover the entire affected area with a thin layer one to three times daily. Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor. If bothersome dryness or peeling occurs, reduce application to once a day or every other day."

**References**

(1) Minutes of the 51st Meeting of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products, June 6 and 7, 1980, pp. 93–96.

(2) Melski, J. W., and K. A. Arndt, Current Concepts: Topical Therapy for Acne, New England Journal of Medicine, 302:503–506, 1980.

(3) Schachner, L., The Treatment of Acne: A Contemporary Review, The Pediatric Clinics of North America, 30:501–510, 1983.

**II. Summary of Significant Changes to the Proposed Rule**

1. The definition of acne proposed in § 333.303(a) is being revised by adding the terms "blackheads," "whiteheads," "acne pimples," and "acne blemishes." These terms are commonly used by consumers in describing acne. In addition, the agency is deleting the term "inflammatory" because it believes that consumers do not differentiate between the "inflammatory" and "noninflammatory" types of lesions that occur in acne. Also, consumers do not use these terms to describe their lesions. Accordingly, the agency is including the following definition of acne in § 333.303(a): "Acne. A disease involving the oil glands and hair follicles of the skin which is manifested by blackheads, whiteheads, acne pimples, and acne blemishes." Likewise, the agency is revising the definition of "acne drug product" in § 333.303(b) (redesignated § 333.303(c)) to delete the term "lesions" at the end of the definition and replace it with the terms "acne blemishes," "acne pimples," "blackheads," and "whiteheads," as follows: "Acne drug product. A drug product used to reduce the number of acne blemishes, acne pimples, blackheads, and whiteheads." (See comment 8 above.)

2. Based on these definitions of acne and acne drug product, the agency is adding the term "whiteheads" to the proposed terms "blackheads," "acne pimples," and "acne blemishes" in the indications for use in § 333.350(b)(2). The agency believes that consumers understand these terms and commonly use them to describe their acne lesions. (See comment 9 above.)

3. The agency is including a definition of the term "whitehead" in § 333.303(f) as follows: "A condition of the skin that occurs in acne and is characterized by a small, firm, whitish elevation of the skin." (See comment 9 above.)

4. The agency is revising the definition of "blackhead" proposed in § 333.303(c) (redesignated § 333.303(e)) as follows: "A condition of the skin that occurs in acne and is characterized by a black tip." (See comment 9 above.)

5. The agency is clarifying the definition of the word "pimple" proposed in § 333.303(d) by adding the word "acne" before "pimple" and by adding the words "resulting from acne" at the end of the definition as follows: "Acne pimple. A small, prominent, inflamed elevation of the skin resulting from acne." (See comment 9 above.)

6. The term "acne blemish" which appeared in the labeling proposed in § 333.350(b)(2) was not defined in the tentative final monograph. Therefore, the agency is adding a definition for "acne blemish" in § 333.303(b) of this final monograph as follows: "Acne blemish. A flaw in the skin resulting from acne." (See comment 9 above.)

7. The agency is adding the term "acne treatment" as an alternate statement of identity in § 333.350(a). The agency is also including several representative examples of dosage forms that may appear in the statement of identity as follows: "acne treatment" (insert dosage form, e.g., "cream," "gel," "lotion," or "ointment") and "acne medication" (insert dosage form, e.g., "cream," "gel," "lotion," or "ointment"). (See comment 10 above.)

8. The agency is expanding the directions for use of all OTC acne drug products in § 333.350(d)(1) by adding an additional sentence at the end of the directions as follows: "Cleanse the skin thoroughly before applying medication. Cover the entire affected area with a thin layer one to three times daily. Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor. If bothersome dryness or peeling occurs, reduce application to once a day or every other day." (See comment 17 above.)

9. The agency is including "directions for a sensitivity test" as optional labeling. A new paragraph (3) in § 333.350(d) provides as follows: "*Optional directions.* In addition to the

required directions in paragraphs (d) (1) and (2) above, the product may contain the following optional labeling: 'Sensitivity Test for a New User. Apply product sparingly to one or two small affected areas during the first three days. If no discomfort occurs, follow the directions stated' (select one of the following: 'elsewhere on this label,' 'above,' or 'below.')" (See comment 17 above.)

10. Although the in vivo testing criterion for antibacterial activity (as recommended by the Panel in § 333.340(e)(1)) is not being included in this final monograph, the agency believes that the following standards should apply:

A reduction of *P. acnes* counts of 0.75 log by the active ingredient must be demonstrated using an appropriate statistical test at an alpha error of less than or equal to 0.05. The *P. acnes* count in the active drug post treatment specimens must be a least 0.75 log lower than the corresponding baseline specimens and must be at least 0.75 log lower than the lesser of the vehicle baseline or vehicle post treatment *P. acnes* counts. (See comment 7 above.)

### III. The Agency's Final Conclusions on OTC Topical Acne Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC topical acne drug products are generally recognized as safe and effective and not misbranded. Specifically, the agency has determined that the only ingredients that meet monograph conditions are salicylic acid, sulfur, and resorcinol and resorcinol monoacetate (in combination products). With the exception of benzoyl peroxide (see amended tentative final monograph for OTC topical acne drug products published in the **Federal Register** of August 7, 1991 (56 FR 37622), all other ingredients considered in this rulemaking have been determined to be nonmonograph conditions for use in a topical acne drug product. These ingredients are: alcloxa, alkyl isoquinolinium bromide, aluminum chlorohydrex, aluminum hydroxide, benzocaine, benzoic acid, boric acid, calcium polysulfide, calcium thiosulfate, camphor, chlorhydroxyquinoline, chloroxylenol, coal tar, dibenzothiophene, estrone, magnesium aluminum silicate, magnesium sulfate, phenol, phenolate sodium, phenyl salicylate, povidone-iodine, pyrilamine maleate, resorcinol (as single ingredient), resorcinol monoacetate (as single ingredient), salicylic acid (over 2 up to 5 percent), sodium borate, sodium thiosulfate, tetracaine hydrochloride, thymol, vitamin E, zinc oxide, zinc stearate, and zinc sulfide. In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule in 21 CFR part 310 establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule included in § 310.545(a)(1) all of the OTC topical acne ingredients listed above and was effective on May 7, 1991. This final rule does not result in the addition of any other ingredients to those already listed in § 310.545(a)(1). Accordingly, any drug product labeled, represented, or promoted for use as an OTC topical acne drug product that contains any of the ingredients listed in § 310.545(a)(1) or that is not in conformance with the monograph (21 CFR part 333), except for benzoyl peroxide as discussed above, may be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352) and may not be marketed for this use unless it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314). An appropriate citizen petition to amend the monograph may also be submitted under 21 CFR 10.30 in lieu of an application. Any OTC topical acne drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of the final rule mentioned above or this final rule that is not in compliance with the regulation or the amended tentative final monograph for OTC topical acne drug products (56 FR 37622) is subject to regulatory action.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 2172 at 2180 to 2181). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC topical acne drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96-354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC topical acne drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has determined that 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.

### List of Subjects in 21 CFR Part 333

Labeling, Over-the-counter drugs, Topical acne drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act, Part 333 of Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

## PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 333 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. Subpart C is added and reserved, and Subpart D consisting of §§ 333.301 to 333.350 is added to read as follows:

### Subpart C—[Reserved]

### Subpart D—Topical Acne Drug Products

Sec.



### Subpart D—Topical Acne Drug Products

#### § 333.301 Scope.

(a) An over-the-counter acne drug product in a form suitable for topical application is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this

subpart and each general condition established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to chapter I of title 21 unless otherwise noted.

**§ 333.303 Definitions.**

As used in this subpart:

(a) *Acne.* A disease involving the oil glands and hair follicles of the skin which is manifested by blackheads, whiteheads, acne pimples, and acne blemishes.

(b) *Acne blemish.* A flaw in the skin resulting from acne.

(c) *Acne drug product.* A drug product used to reduce the number of acne blemishes, acne pimples, blackheads, and whiteheads.

(d) *Acne pimple.* A small, prominent, inflamed elevation of the skin resulting from acne.

(e) *Blackhead.* A condition of the skin that occurs in acne and is characterized by a black tip.

(f) *Whitehead.* A condition of the skin that occurs in acne and is characterized by a small, firm, whitish elevation of the skin.

**§ 333.310 Acne active ingredients.**

The active ingredient of the product consists of any of the following when labeled according to § 333.350.

(a) Resorcinol 2 percent when combined in accordance with § 333.320(a).

(b) Resorcinol monoacetate 3 percent when combined in accordance with § 333.320(b).

(c) Salicylic acid 0.5 to 2 percent.

(d) Sulfur 3 to 10 percent.

(e) Sulfur 3 to 8 percent when combined in accordance with § 333.320.

**§ 333.320 Permitted combinations of active ingredients.**

(a) Resorcinol identified in § 333.310(a) when combined with sulfur identified in § 333.310(e) provided the product is labeled according to § 333.350.

(b) Resorcinol monoacetate identified in § 333.310(b) when combined with sulfur identified in § 333.310(e) provided the product is labeled according to § 333.350

**§ 333.350 Labeling of acne drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "acne medication," "acne treatment," "acne medication" (insert dosage form, e.g., "cream," "gel," "lotion," or "ointment"), or "acne treatment" (insert dosage form, e.g., "cream," "gel," "lotion," or "ointment").

(b) *Indications.* The labeling of the product states, under the heading "Indications," the phrase listed in paragraph (b)(1) of this section and may contain any of the additional phrases listed in paragraph (b)(2) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraph (b) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) "For the" (select one of the following: "management" or "treatment") "of acne."

(2) In addition to the information identified in paragraph (b)(1) of this section, the labeling of the product may contain any one or more of the following statements:

(i) (Select one of the following: "Clears," "Clears up," "Clears up most," "Dries," "Dries up," "Dries and clears," "Helps clear," "Helps clear up," "Reduces the number of," or "Reduces the severity of") (select one or more of the following: "acne blemishes," "acne pimples," "blackheads," or "whiteheads") which may be followed by "and allows skin to heal."

(ii) "Penetrates pores to" (select one of the following: "eliminate most," "control," "clear most," or "reduce the number of") (select one or more of the following: "acne blemishes," "acne pimples," "blackheads," or "whiteheads").

(iii) "Helps keep skin clear of new" (select one or more of the following: "acne blemishes," "acne pimples," "blackheads," or "whiteheads").

(iv) "Helps prevent new" (select one or more of the following: "acne blemishes," "acne pimples," "blackheads," or "whiteheads") which may be followed by "from forming."

(v) "Helps prevent the development of new" (select one or more of the following: "acne blemishes," "acne pimples," "blackheads," or "whiteheads").

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 333.310.* (i) "For external use only."

(ii) "Using other topical acne medications at the same time or immediately following use of this product may increase dryness or irritation of the skin. If this occurs, only one medication should be used unless directed by a doctor."

(2) *For products containing sulfur identified in §§ 333.310 (d) and (e).* "Do not get into eyes. If excessive skin irritation develops or increases, discontinue use and consult a doctor."

(3) *For products containing any combination identified in § 333.320.* "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) "Cleanse the skin thoroughly before applying medication. Cover the entire affected area with a thin layer one to three times daily. Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor. If bothersome dryness or peeling occurs, reduce application to once a day or every other day."

(2) The directions described in paragraph (d)(1) of this section are intended for products that are applied and left on the skin. Other products, such as soaps or masks, may be applied and removed and should have appropriate directions.

(3) *Optional directions.* In addition to the required directions in paragraphs (d)(1) and (d)(2) of this section, the product may contain the following optional labeling: "*Sensitivity Test for a New User.* Apply product sparingly to one or two small affected areas during the first 3 days. If no discomfort occurs, follow the directions stated: (select one of the following: 'elsewhere on this label,' 'above,' or 'below.')"

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

Dated: June 4, 1991.

**David A. Kessler,**

*Commissioner of Food and Drugs.*

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