DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 333

[Docket No. 81N-0114]

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

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Adminstration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish 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 notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by May 15, 1985. New data by January 15, 1986. Comments on the new data by March 17, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10).

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

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, which was the advisory review panel responsible for evaluating date 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 put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, eight drug manufacturers, one drug manufacturer association, one counsulting firm, three physicians, and one consumer submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on March 23, 1982 (47 FR 12430), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tenative final monograph." Its legal status, however, is that of a proposed rule. In this tenative final monograph (proposed rule) to establish Part 333, Subpart D, FDA states for the first time its position on the establishment of a monograph for OTC topical acne drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC topical acne drug products.

This proposal constitutes FDA's tenative adoption of the Panel's conclusions and recommendations on OTC topical acne drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panels report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the **Federal Register** of September 29, 1981; 46 FR 47730). The Court in *Cutler* held that the OTC drug review regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Acccordingly, this provision has been deleted from the regulations, which 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.

Although it was not required to do so under *Cutler*, FDA will no longer use 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 will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions 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 they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to this monograph that are 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 the advance notice of proposed rulemaking for OTC topical acne drug products (published in the **Federal Register** of March 23, 1982 (47 FR 12430)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the

monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The Agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited through 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 advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments

1. One comment contended 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 paragraph 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) and 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). FDA reaffirms the conclusions stated there. Subsequent 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, 696–98 (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. One comment pointed out an error in the Panel's report under part II. paragraph A.1.b.(2) regarding the statement that "Clinical response was evaluated after 2 weeks by lesion counts. . . ." (See 47 FR 12448.) The comment believed that it should read 12 weeks instead of 2 weeks.

This was a printing error; the sentence should have read "Clinical response was evaluated after 12 weeks. . . ."

3. Noting the statement under part II. paragraph I.2., Criteria for Evaluating Effectiveness, that "studies in induced or experimental acne were similarly not considered as proof of effectiveness" (47 FR 12442), one comment stated that comedolytic studies are important in making a preliminary determination of effectiveness of some active ingredients and urged the agency to add the following sentence: "However, animal and human comedolytic studies can be used as corroborative and supporting evidence of effectiveness."

The agency agrees with the comment that animal and human comedolytic studies can be useful as supporting evidence of effectiveness. Even though the Panel did not consider studies in induced acne as sole proof of effectiveness, FDA does not believe that the Panel's statement precludes manufacturers from using this type of study as preliminary or supporting evidence of effectiveness.

4. One comment stated that acne responds favorably to the application of mouthwash to the infected area once or twice daily. The comment specifically mentioned a mouthwash containing thymol, eucalyptol, methyl salicylate, and menthol in alcohol as an effective acne remedy. The comment suggested that mouthwashes be considered as the initial treatment for acne because they are less expensive and "just as effective" as OTC acne drug products.

Because the comment did not submit any data to support its contention that mouthwashes are effective acne treatments, the agency cannot agree with the comment's conclusion. Thymol, one of the ingredients in the mouthwash mentioned by the comment, was classified Category II as an active acne ingredient by the Panel and has been reclassified Category III by the agency. (See comment 7 below.) No data were submitted on eucalyptol, and it was not contained in any acne drug products. Therefore, this ingredient was not reviewed by the Panel. The Panel identified methyl salicylate, menthol, and alcohol as inactive ingredients.

It appears that the effectiveness of mouthwashes as acne remedies would likely be due to the alcohol present in the products. The product mentioned by the comment contains 26.9 percent alcohol. Alcohol was classified as an antiseptic at a concentration of 60 to 95 percent by the Advisory Review Panel on OTC Miscellaneous External Drug Products in its report published in the **Federal Register** of May 21, 1982 (47 FR 22324). However, the Advisory Review Panel on OTC Antimicrobial (II) Drug Products did not review alcohol as an active ingredient for the treatment of acne, and the agency is not aware of adequate data that support the use of alcohol as an acne drug product.

B. Comments on Active Ingredients

5. One comment submitted data (Ref. 1) addressing two of the Panel's concerns on povidone-iodine: availability of elemental iodine from the complex and the stability of povidone-iodine (47 FR 12465). The comment stated that substantial data were submitted to the OTC Antimicrobial (I) Panel and other panels showing that iodine is freely released from the complex and the rate of iodine release is controlled by tissue demand. The comment contended that at equilibrium any iodine that is removed from the complex is replaced within less than 25 milliseconds (Refs. 2 and 3). The comment pointed out that chemical titration studies were submitted to the antimicrobial rulemaking, and these

studies show that povidone-iodine provides the same amount of available iodine as tincture of iodine (Ref. 4). Regarding the stability of the complex, the comment contended that even if a stability issue existed, it would be outside the scope of the review, as stability is covered by the current good manufacturing practice regulations (CGMP) (21 CFR Parts 210 and 211). The comment stated that, under the CGMP regulations, minimum standards have been set to ensure product stability for finished drug products (21 CFR 211.166), and the manufacturer of the finished dosage form is responsible for complying with these stability standards. The comment added that expiration dating as well as appropriate storage conditions are determined through required written testing programs.

The Panel considered povidone-iodine to be safe. However, it believed that further studies were needed on availability and stability and to determine effectiveness of the drug in the treatment of acne (47 FR 12465). The agency has reviewed the data submitted regarding availability (Refs. 2 and 3) and agrees with the comment that iodine is rapidly released from the povidone-iodine complex. According to the references that were submitted, a povidone-iodine solution at a concentration of 1 to 10 percent contains over 99 percent complexed iodine (Ref. 2). The concentration of free iodine in the solution reaches a maximum of 8×10^{-5} moles/liter. At equilibrium, the povidone-iodine complex is self-monitoring. Based on an iodine-starch reaction as a biological model, it has been shown that any iodine that is removed from the complex would be replaced within less than 25 milliseconds (Ref. 3). In addition, povidone-iodine is recognized in the United States Pharmacopeia/National Formulary (USPXXI/NFXVI) and subject to the requirements contained therein.

The agency also agrees with the comment that issues regarding stability can be resolved by the CGMP regulations (21 CFR Parts 210 and 211). These regulations require a written testing program to assess the stability of finished products and to determine appropriate storage conditions and an expiration date. Section 211.137(a) requires that drug products bear an expiration date supported by appropriate stability testing. Where an expiration date is not necessary under the provisions of § 211.137(g), manufacturers must have appropriate data to show that the drug products are stable for at least 3 years. Therefore, FDA concludes that further submissions of data on the stability of povidone-iodine are not needed for purposes of this rulemaking proceeding.

The agency believes that the issues of availability of iodine from the povidone-iodine complex and stability of the complex have been resolved for this ingredient. However, the agency believes that a double-blind, vehicle-controlled study is still needed to resolve the Panel's concerns regarding povidone-iodine's effectiveness in the treatment of acne. Thus, povidone-iodine remains in Category III for use in the treatment of acne.

References

(1) Comment No. C00012, Docket No. 81N-0114, Dockets Management Branch.

(2) Schenck, H. U., et al., "Structure of Povidone-Iodine," *in* "Current Chemotherapy and Infectious Disease," Volume I, American Society for Microbiology, Washington, pp. 477–478, 1980.

(3) Ditter, W., D. Horn, and E. Luedekke, "Thermodynamic and Kinetic Examinations Concerning the Complex Binding State and the Rate of Liberation of Iodine from Aqueous Iodine-PVP-Solutions," included in Comment No. C00012, Docket No. 81N-0114, Dockets Management Branch.

(4) Comment No. C00108, Docket No. 75N-0183, Dockets Management Branch.

6. Several comments requested that the agency reclassify salicylic acid 0.5 to 5 percent from Category III to Category I. The comments pointed out that the Panel reviewed several well-designed studies supporting the effectiveness of salicylic acid (47 FR 12466), but none of these studies used the vehicle as the control as was required by the Panel. One comment submitted two vehicle-controlled studies (Refs. 1 and 2) which it believed met the Panel's criteria and demonstrated the effectiveness of salicylic acid in the treatment of acne. In one study, 2 percent salicyclic acid was tested against the vehicle and an active control (5 percent benzoyl peroxide) in 180 subjects (Ref. 1). In the second study, salicylic acid 0.5 and 2 percent were compared to the vehicle control in 187 subjects (Ref. 2).

The agency has reviewed the submitted studies (Refs. 1 and 2) and concludes that they meet the Panel's criteria for well-designed studies (47 FR 12472) and demonstrate the effectiveness of salicylic acid in the treatment of acne. In a 12-week study of 180 subjects, good or excellent results (for total lesions) were obtained by 40 percent of the subjects using 2 percent salicylic acid. Such results were obtained for only 5 percent of the subjects using the vehicle and 2 percent of the subjects using benzoyl peroxide (Ref. 1). Salicylic acid was particularly effective on inflammatory lesions (papules and pustules), where 86 percent of the subjects treated with salicylic acid had good or excellent results, compared with 11 percent for the vehicle and 15 percent for benzoyl peroxide. Although there was no statistically significant difference between the three treatments in their effect on closed comedones, salicylic acid was significantly more effective than the vehicle or benzoyl peroxide in the reduction of total lesions, inflammatory lesions, and open comedones ($p<0.001$).

In the second study, in which 0.5 and 2 percent salicylic acid were tested against the vehicle in 187 subjects, both concentrations of salicylic acid were found to be superior to the vehicle control in reducing inflammatory lesions, open and closed comedones, and total lesion count ($p<0.001$) (Ref. 2). At the end of the treatment, 98 percent of the subjects using 2 percent salicylic acid showed good or excellent results compared with 91 percent using 0.5 percent salicylic acid and 11 to 12 percent of the subjects in the two control groups. Based on these studies and the data cited by the Panel (47 FR 12466), the agency is proposing to classify salicylic acid 0.5 to 2 percent in Category I for the treatment of acne.

Although the Panel considered salicylic acid to be safe in concentrations up to 5 percent, the agency is proposing to limit the upper concentration to 2 percent. The only safety data discussed by the Panel were on the 0.5- to 2-percent concentration, which was judged to be a mild irritant when applied to either normal or abraded skin of rabbits. The Panel also reported results of the application of a lotion containing 2 percent salicylic acid to normal and abraded rabbit skin and to the eyes of rabbits (47 FR 12465–6). In part, the Panel based its acceptance of the 5-percent concentration as safe on a theoretical calculation of systemic absorption (47 FR 12466). The studies submitted to the agency following publication of the advance notice of proposed rulemaking used 2 percent salicylic acid, and adverse reactions reported were minimal (Refs. 1 and 2). The agency is concerned that there is an increased potential for irritation from concentrations greater than 2 percent and that adequate data have not been submitted to establish general recognition of the safety of concentrations above 2 percent in treating acne. In its topical antifungal report, the Panel had recommended a safe concentration of 3 percent for topical antifungal use, but stated that

this ingredient should be restricted to "relatively small body areas" (47 FR 12549). As the Panel pointed out, "the major difference in the use of salicylic acid in acne as opposed to its use in fungal infections of the foot and groin is the very large surface area over which acne may be involved" (47 FR 12465). Letters from Dr. Leyden (Ref. 3) and Dr. Shalita (Ref. 4) submitted as comments to the advance notice of proposed rulemaking support general recognition of this 0.5- to 2-percent concentration, but do not indicate general recognition of higher concentrations. As another comment pointed out (Ref. 5), many of the studies reviewed by the Panel utilized salicylic acid at a 0.5-percent concentration. Based on the submitted data, the agency proposes that salicylic acid 0.5 to 2 percent be classifed in Category I but that concentrations greater than 2 percent up to 5 percent remain in Category III pending receipt of data to establish general recognition of safety at these concentrations.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 6).

References

(1) Shalita, A. R., "Double-blind Investigation of 2% Salicylic Acid Solution Versus Vehicle Solution and Active Control (Benzoyl Peroxide 5%) in the Treatment of Acne Vulgaris Pillsbury Grades I to III," included in Comment No. C00002, Docket No. 81N-0114, Dockets Management Branch.

(2) Leyden, J., "Double-blind Investigation of 0.5% and 2% Salicylic Acid Solutions (Medicated Pads) Versus Vehicle Solutions (Pads) in the Treatment of Acne Vulgaris Pillsbury Grades I to III," included in Comment No. SUP, Docket No. 81N-0014, Dockets Management Branch.

(3) Comment No. C00009, Docket No. 81N-0114, Dockets Management Branch.

(4) Comment No. C00004, Docket No. 81N-0114, Dockets Management Branch.

(5) Comment No. C00011, Docket No. 81N-0114, Dockets Management Branch.

(6) Letter from W. E. Gilbertson, FDA, to E. J. Hiross, Sterling Drug Inc., coded LET002, Docket No. 81N-0114, Dockets Management Branch.

7. One comment objected to the Panel's Category II classification of thymol, specifically disagreeing with the Panel's assessment that there are insufficient data available to determine safety. The comment requested that the views of other panels be considered, noting that thymol was found by the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (TOPICAL Analgesic Panel) to be safe as an external analgesic at a concentration of 1 to 2 percent, not irritating when applied to the skin, and virtually unabsorbed topically (44 FR 69855). The comment added that the Advisory Review Panel on OTC Oral Cavity Drug Products found thymol (0.006 to 0.1 percent) safe for topical use on mucous membranes of the mouth and throat (47 FR 22888); and that the Antimicrobial II Panel, which evaluated antifungal drug products in addition to acne drug products, found that thymol, up to and including 0.2 percent, is safe as an inactive ingredient for use in topical antifungal formulations (47 FR 12522). The comment stated that numerous safety studies were submitted to the Panel, including clinical trials in which thymol was used on about 600 humans for up to 6½ months, and that no significant adverse effects were seen.

The comment contended that the Panel's reason for placing thymol in Category II for effectiveness, i.e., the absence of data evaluating the effectiveness of thymol in a vehicle-controlled study for the treatment of acne (47 FR 12462), was inconsistent with other Panel statements, specifically "ingredients were placed in Category II if there was no rational explanation of their mode of action, no substantial scientific evidence to suggest effectiveness, no general acceptance by consultant 'acne experts' and no supportive evidence of effectiveness in the medical literature on acne." Stating its belief that Category II should be reserved for cases where no data have been presented or where the data presented show that an ingredient has no effect, the comment maintained that placing an ingredient in Category II merely because of the absence of a vehicle-controlled study was an inappropriate course of action. The comment added that it had submitted to the Panel five clinical studies on thymol that demonstrated a statistical and clinical improvement in acne (Ref. 1). The comment also objected to the Panel's statement that thymol has questionable antibacterial activity at 0.16 to 0.5 percent concentration (47 FR 12462) and submitted new in vitro data to support antibacterial activity (Ref. 2).

The agency has reviewed the data submitted (Refs. 1, 2, and 3) and proposes to reclassify thymol from Category II to Category III. Regarding safety, the Panel stated that data are needed on absorption from small areas of application to intact and broken skin, effect on wound healing, and irritation potential (47 FR 12462). As the comment noted, the same Panel considered thymol at concentrations of 0.2 percent or less to be safe as an inactive ingredient in topical antifungal formulations (47 FR 12523), even though the Panel stated that more data were needed to determine the safety at higher concentrations. Based on the lack of adverse effects from the use of thymol (0.0162 percent) in clinical trials (Ref. 1), the lack of irritation or sensitization on animals and humans (Refs. 1 and 3), and the Panel's view that 0.2 percent (or less) thymol is safe for topical antifungal use, the agency believes that thymol in concentrations up to 0.2 percent can be considered safe for topical use in the treatment of acne. However, more data are needed on the safety of concentrations greater than 0.2 percent for the treatment of acne.

Although the agency believes that the conclusions of panels other than the initial reviewing panel should be considered when making a safety determination, a safety determination by a panel for a use other than topical application in acne cannot necessarily be applied to the topical treatment of acne. The Topical Analgesic Panel based its approval of the safety of thymol at a concentration of 1 to 2 percent on clinical use. Topical application to acne differs from topical analgesic use because a larger surface area is involved and duration of treatment is longer, usually involving several months of use. The agency does not believe that concentrations of thymol greater than 0.2 percent have been widely used in the treatment of acne to allow general recognition of safety. Thus the agency proposes that thymol only in a concentration of 0.2 percent or less be considered safe for the treatment of acne.

Regarding effectiveness, the Panel reviewed the clinical studies mentioned by the comment in which thymol 0.0162 percent was tested (Ref. 1) and stated that none of the studies tested thymol against a vehicle control (47 FR 12462). The Panel recommended, and the agency concurs, that thymol should be evaluated by a double-blind, vehicle-controlled clinical trial. The comment submitted data on antibacterial activity in which the minimal inhibitory concentration of thymol against one strain of *Corynebacterium acnes* was found to be between 62.5 micrograms/milliliter (μg/ml) and 125 μg/mL (Ref. 2). Although this study indicates that thymol has antibacterial activity in vitro, it is not adequate evidence to move thymol to Category I or to allow the antibacterial labeling recommended by the Panel. The Panel recommended that in vivo testing is necessary in order for a Category I ingredient to use antibacterial labeling (47 FR 12473).

The agency believes that even though the data do not meet the Panel's criteria, they are supportive evidence that thymol may have an effect on acne.

Thus, the agency proposes that thymol in a concentration of 0.2 percent or less be considered safe for the treatment of acne, but that further data are needed on effectiveness (Category III). For concentrations greater than 0.2 percent up to 0.5 percent, data are needed on both safety and effectiveness (Category III).

The agency's detailed comments and evaluation of the submissions and the references cited by the comment are on file in the Dockets Management Branch (Ref. 4).

References

(1) OTC Volume 070156.
(2) Comment No. C00010, Docket No. 81N-01114, Dockets Management Branch.
(3) OTC Volume 070155.
(4) Letter from W. E. Gilbertson, FDA, to J. D. Clark, Warner-Lambert Co., coded LET003, Docket No. 81N-0114, Dockets Management Branch.

C. Comments on Combination Products

8. One comment urged the agency to place the combination of sulfur and salicylic acid in Category I without requiring additional testing. The comment compared this combination to the combination of sulfur and resorcinol, which the Panel had placed in Category I. Although not submitting any data, the comment stated that salicylic acid is superior to resorcinol as a keratolytic agent. In addition, the comment pointed out that salicylic acid is less likely to be systemically absorbed than resorcinol because it is less soluble and that the occasional pigmemtation problems that may occur with topical use of resorcinol are not seen with salicylic acid.

The Panel concluded that data on the effectiveness of sulfur-salicylic acid combinations were inadequate (47 FR 12471). The agency has reviewed the data submitted to the Panel (Refs. 1 through 4) and agrees with the Panel's assessment. The agency is aware of two clinical studies on the combination (Refs. 5 and 6) that were reviewed by the Panel (47 FR 12466), but neither study met the Panel's criteria. No new data on this combination have come to the agency's attention. As discussed in comment 6 above, the agency proposes to classify salicylic acid 0.5 to 2 percent as Category I as a single ingredient. Sulfur 3 to 10 percent is also in Category I as a single ingredient (47 FR 12447). However, the Panel did not provide for a combination of two Category I acne ingredients, stating that each ingredient's contribution to the efficacy of the combination should be demonstrated in a clinical trial (47 FR 12468).

The combination policy in § 330.10(a)(4)(iv), as supplemented by the agency's general guidelines for OTC drug combination products (Ref. 7), specifies the criteria for OTC combination drug products. The agency's guidelines state that ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or conditions if the combination meets the OTC combination policy in 21 CFR 330.10(a)(4)(iv) in all respects and the combination is, on a benefit-to-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. The guidelines also state that Category I active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredient in terms of enhancing effectiveness, safety, patient acceptance, or quality of formulation.

According to the Panel, the exact mechanisms of action for salicylic acid and sulfur are unknown, although both ingredients have keratolytic activity (47 FR 12447 and 12466). Although the mechanisms of action are unknown, under either aspect of the combination policy described above, data must be submitted demonstrating that the combination of ingredients is equal to or better than the individual ingredients alone. For the sulfur-resorcinol combination, the Panel discussed a study in which the combination was found to be superior to sulfur and placebo in the reduction of papules and whiteheads (47 FR 12469). The combination was not compared with resorcinol; however, the Panel had concluded that resorcinol is not effective as a single ingredient (47 FR 12459). In addition, the Panel cited several other studies that support the effectiveness of the sulfur-resorcinol combination (47 FR 12468). Because sulfur and salicylic acid are both considered effective as single ingredients, data are needed showing that the combination is equal to or better than the single ingredients. The comment, however, did not submit any such data for the sulfur-salicylic acid combination. Combinations containing ingredients from the same therapeutic category, such as sulfur and salicylic acid, will be permitted if adequate data are presented to the agency.

References

(1) OTC Volume 070090.
(2) OTC Volume 070092.
(3) OTC Volume 070261.
(4) OTC Volume 070268.
(5) Riley, K. A., "Therapeutic Skin Washing in Seborrhea and Acne Vulgaris," *Medical Times*, 86:973–977, 1958.
(6) Baird, J. W., "Acne. A New Approach to an Old Problem," *Journal of Pediatrics*, 52:152–157, 1958.
(7) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D-0322, Dockets Management Branch.

9. Several comments urged the agency to broaden the range of acceptable concentrations for sulfur-resorcinol combinations beyond the Panel's recommendation of 8 percent sulfur combined with either 2 percent resorcinol or 3 percent resorcinol monoacetate. One comment, noting that the Panel had placed 3 to 10 percent sulfur in Category I as a single ingredient (47 FR 12447), requested that 3 to 10 percent sulfur be allowed in combination with 2 percent resorcinol or 3 percent resorcinol monoacetate. Noting the Panel's statement that resorcinol enhances the activity of sulfur (47 FR 12469), the comment asserted that "There simply is no basis for assuming that resorcinol enhances the activity of eight percent sulfur, but not of other concentrations of sulfur within the Category I range."

Other comments requested that 2 percent sulfur be allowed in combination with 1 percent resorcinol to make available the widest possible choice of safe and effective medications. One of the comments stated that there should be no question about safety as the Panel judged the combination to be safe at the highest concentrations. Pointing out the Panel's statement that "consumer interests are best served by exposure to the fewest ingredients possible at the lowest possible dosage regimen that is consistent with a satisfactory level of effectiveness" (47 FR 12468), another argued that lowering the concentration of this combination would be consistent with the Panel's statement. Both comments mentioned a study that was reviewed by the Panel (47 FR 12469), comparing the effectiveness of a combination containing 2.66 percent colloidal sulfur (equivalent to 2 percent sulfur) and 1 percent resorcinol with a combination of 8 percent sulfur and 2 percent resorcinol, sulfur alone, and placebo (Ref. 1). The comments contended that this study met the Panel's criteria and showed that the combination of 2 percent sulfur and 1 percent resorcinol was "equivalent" to the combination of 8 percent sulfur and 2 percent resorcinol and was superior to the placebo and to sulfur alone in reducing papules and whiteheads.

The agency is proposing to allow a combination of 3 to 8 percent sulfur with either 2 percent resorcinol or 3 percent

resorcinol monoacetate. The Panel concluded that 3 to 10 percent sulfur is safe and effective in the treatment of acne (47 FR 12447) and that resorcinol enhances the activity of sulfur (47 FR 12469). Because the Panel approved a combination of 8 percent sulfur and 2 percent resorcinol, the agency believes it would be reasonable to allow lower concentrations of sulfur (3 to 8 percent) that safe and effective to be combined with resorcinol. As both sulfur and resorcinol have keratolytic activity and may prove to be too irritating to the skin when combined in higher concentrations and because resorcinol enhances the activity of sulfur, the agency would require safety studies prior to allowing a combination of sulfur greater than 8 percent with resorcinol.

FDA agrees with the comments that there would be no safety problems for sulfur-resorcinol combinations in lower concentrations that proposed above, but the agency does not agree that data are adequate to determine effectiveness. The agency has reviewed the study cited by the comments (Ref. 1) and the Panel's criteria for evaluating effectiveness (47 FR 12442). The study did not meet the criteria of being a multi-center study involving more than one investigator, and it did not use the vehicle as the control. The Panel stated that although a clinical trial did not meet all of its criteria, an ingredient could still be considered for Category I provided there is supporting evidence of effectiveness. The agency is not aware of any other data supporting the effectiveness of a sulfur-resorcinol combination at the low concentrations requested by the comment; nor is the agency aware of any marketed products at this concentration. As discussed by the Panel, the two sulfur-resorcinol creams were superior to placebo and sulfur alone in the reduction of papules and whiteheads. However, no difference was found between the four treatment groups in overall complexion, pustules, blackheads, and oiliness (47 FR 12469). While the study is supportive of effectiveness, and the agency is aware that resorcinol enhances the activity of sulfur, the agency believes that further study is needed to establish the effectiveness of the combination of sulfur 2 percent and resorcinol 1 percent.

Reference

(1) OTC Volume 070256.

D. Comments on Labeling

10. Noting its continuing opposition to the exclusivity policy, one comment stated that FDA should not prohibit the use of alternative OTC labeling terminology to describe indications, if that terminology is truthful, not misleading, and intelligible to the consumer. The comment stated that existing statutory provisions (15 U.S.C. 1453(a) and sections 502(e) and 503 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(e) and 353)) and 21 CFR 201.61 do not show a congressional intent to authorize FDA to legislate the exact wording of OTC drug claims to the exclusion of other equally accurate and truthful claims for these products, and that section 502(c) (21 U.S.C. 352(c)) of the act demonstrates a congressional intent to the contrary.

During the course of the OTC drug review, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under § 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received.

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. In a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002), FDA announced that a hearing would be held to asist the agency in resolving this issue. On September 29, 1982, FDA conducted an open public forum at which interested parties presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monographs for nighttime sleep-aids and stimulants (published in the **Federal Register** of June 13, 1978; 43 FR 25544). The agency's decision on this matter will be announced in the **Federal Register** following conclusion of its review of the material presented at the hearing.

11. One comment requested that the agency add the following two labeling statements, which the comment contended are truthful and not misleading, to the Panel's recommended § 333.350(b)(1): "Dermatologist tested" and "One of the most effective acne pimple medications you can buy without a prescription." The comment also requested the addition of the claim "Antibacterial (or antimicrobial) action against *P. acnes*, the organism commonly associated with acne" to the Panel's recommended § 333.350(b)(3).

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

Because the first two claims suggested by the comment, "Dermatologist tested"' and "One of the most effective acne pimple medications you can buy without a prescription," are not directly to the safe and effective use of acne drug products, the agency considers these claims to be outside the scope of the monograph. Such statements or terms will be evaluated by the agency on a product-by-product basis, unde the provisions of section 502 of the act (21 U.S.C. 352) relating to labeling that is false and misleading. Moreover, any term that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, statements and terms outside the scope of the monograph may be included elsewhere in the labeling provided they are not false or misleading.

Although the Panel recommended labeling for antibacterial activity (47 FR 12476), none of the Category I

ingredients met the Panel's in vivo criteria for antibacterial activity (47 FR 12473). Thus, no ingredients were recommended to use the antibacterial claims. None of the comments received following publication of the Panel's report submitted in vivo data relating to antibacterial activity. Therefore, because there are no ingredients that can use the antibacterial labeling, the agency is not proposing antibacterial labeling claims, including the claim suggested by the comment, in this tentative final monograph.

12. Several comments objected to the warning recommended by the Panel for all acne products in § 333.350(c)(1)(ii), "Other topical acne medications should not be used at the same time as this medication." The comments noted that dermatologists frequently prescribe the concomitant or sequential use of benzoyl peroxide with retinoic acid or salicylic acid, and one comment cited a reference to this effect (Ref. 1). One comment stated that the combined use of a comedolytic agent with an antimicrobial or antibiotic is rational, safe, and routine therapy; while other comments were concerned that the warning would preclude the use of non-drug acne cleansers and medicated soaps. According to one comment, market research has shown that many consumers think of non-drug cleansers as "medications," and therefore the warning could cause confusion. Another comment believed the warning would prevent consumers from using a medicated acne wash product containing a Category I ingredient before applying an acne product intended to remain on the skin.

The comments either suggested deleting the warning or provided alternate warnings. One comment recommended the following warning: "Do not use other topical medications at the same time or immediately following application of this medicine." Another comment believed it would be more appropriate to warn the consumer about the potential for increased dryness and irritation when more than one acne medication is used. Two comments believed that specific safety concerns should be addressed only in the warnings for the ingredients in question. One of these comments pointed out that the Panel's real concern was that the use of sulfur with benzoyl peroxide would enhance the sensitization potential of benzoyl peroxide (47 FR 12469). This comment suggested deleting the general warning at § 333.350(c)(1)(ii) and revising the warning for sulfur in § 333.350(c)(3) to include the statement "Topical acne medications containing benzoyl peroxide should not be used at the same time as this medication" or a similarly worded warning.

The agency agrees with the comments that the warning proposed in § 333.350(c)(1)(ii) could be confusing to consumers who use a medicated or nonmedicated acne cleanser prior to applying an acne medication intended to remain on the skin. As pointed out by the comments, the warning also contradicts the common practice among dermatologists of prescribing more than one acne medication for a patient. The Panel's original concern was that using benzoyl peroxide and sulfur at the same time could increase irritation or cause a sensitization problem. However, the Panel expanded this concept into a broad warning that would cover all ingredients because it believed that the use of any two keratolytic agents may result in an adverse effect (Ref. 2).

All of the Category I acne ingredients are keratolytic and tend to dry out the skin. The agency believes that some type of warning is necessary to alert consumers using more than one acne product about the increased potential for dryness and irritation. Thus, the agency is proposing, instead of the warning recommended by the Panel, the following warning for all acne drug products in § 333.350(c)(1)(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."

References

(1) Frank, S.B., "Acne-Update for the Practitioner," Yorke Medical Books, New York, pp. 141, 145, 150–158, 250, and 253–254, 1979.

(2) Summary Minutes of the 54th Meeting of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products, November 14 and 15, 1980, p. 10, included in OTC Volume 07BPA2.

13. One comment requested that the words "pharmacist" and "sensitive areas of the neck" be deleted from the warning for benzoyl peroxide recommended by the Panel in § 333.350(c)(2), which reads as follows:

Do not use this medication if you have very sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possibly swelling. More frequent use or higher concentrations may aggravate such irritation. Mild irritation may be reduced by using the product less frequently or in a lower concentration. If irritation becomes severe, discontinue use; if irritation still continues, consult a doctor or pharmacist. Keep away from eyes, lips, mouth, and sensitive areas of the neck. This product may bleach hair or dyed fabrics.

The comment objected to the word "pharmacist" because the training and experience of most pharmacists does not qualify them to diagnose or treat dermatological conditions. The comment believed that in the situation described in the warning most pharmacists would refer the consumer to a physician.

The comment objected to the phrase "sensitive areas of the neck" stating it would be confusing to the consumer because it implies that a "greater sensitivity exists in certain unspecified areas of the neck." The comment noted that the consumer is already forewarned about using the product on very sensitive skin and thus the warning regarding the neck is redundant. The agency agrees with the comment. Although the pharmacist is an important member of the health care team, FDA believes that the situation covered by the warning, where the patient may have an allergic reaction to benzoyl peroxide, is more appropriately handled by the physician. It is likely in such a case that the physician will treat the patient with a prescription medication, particularly if the reaction is severe. Thus, the agency is not including the word "pharmacist" in the warning proposed in this tentative final monograph. The agency also agrees with the reasons cited by the comment for not including the phrase "sensitive areas of the neck" in the warning. Thus, the benzoyl peroxide warning proposed in § 333.350(c)(2) of this tentative final monograph reads as follows: "* * * If irritation becomes severe, discontinue use; if irritation still continues, consult a doctor. Keep away from eyes, lips, and mouth. This product may bleach hair or dyed fabrics.

E. Comments on Testing Procedures

14. Several comments suggested revision or requested clarification of the Category III testing guidelines. One comment stated that the safety guidelines are too detailed and are more appropriate for new chemical entities than for ingredients that have a long history of use, but are in Category III because of specific safety questions. Another comment recommended deleting the safety guidelines because there are no ingredients in Category III for safety reasons.

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and

final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. The revised procedures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also part II. paragraph A.2. below—Testing of Category II and Category III conditions.)

15. Two comments disagreed over how to interpret the criterion of a 0.75 log reduction of *P. acnes* that the Panel recommended in the in vivo test to determine antibacterial activity (47 FR 12474). One comment urged the agency to make the testing for the reduction of free fatty acids a mandatory rather than an optional confirmatory test. The comment contended that the free fatty acid determination should be required to ensure that the antibacterial agent has penetrated and is acting at the follicular level. The comment stated that it is possible for a drug to reduce a number of *P. acnes* on the surface of the skin but be ineffective in the treatment of acne.

None of the ingredients reviewed by the Panel met the requirement for antibacterial labeling, and no new antibacterial data have been submitted to FDA. Therefore, any questions regarding antibacterial testing will be addressed when in vivo test data are submitted to the agency. In addition, the testing procedures to determine antibacterial activity recommended by the Panel in § 333.340 have not been included in the proposed monograph.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and is proposing to reclassify salicylic acid (0.5 to 2 percent) from Category III to Category I and thymol (up to 0.2 percent) from Category II to Category III. For the convenience of the reader, the following table is included as a summary of the categorization of topical acne active ingredients by the Panel and the proposed classification by the agency.

Topical acne active ingredients	Panel	Agency
Alkyl isoquinolinium bromide.	II	II
Aluminum salts (alcloxa, aluminum chlorohydrex, aluminum hydroxide, and magnesium aluminum silicate.	II	II
Benzocaine	II	II
Benzoic acid	II	II
Benzoyl peroxide	I	I
Borates (boric acid and sodium borate).	II	II
Calcium polysulfide	II	II
Calcium thiosulfate	II	II
Camphor	II	II
Chlorhydroxyquinoline	II	II
Chloroxylenol	II	II
Coal tar	II	II
Dibenzothiophene	II	II
Estrone	II	II
Magnesium sulfate	II	II
Phenolates (phenol and phenolate sodium).	II	II
Phenyl salicylate	II	II
Povidone-iodine	III	III
Pyrilamine maleate	II	II
Resorcinol and resorcinol monoacetate (as single ingredients).	III	III
Salicylic acid (0.5 to 2 percent).	III	I
Salicylic acid (over 2 up to 5 percent).	III	III
Sodium thiosulfate	II	II
Sulfur	I	I
Tetracaine hydrochloride	II	II
Thymol	II	III
Vitamin E	II	II
Zinc salts (zinc oxide, zinc stearate, and zinc sulfide).	II	II

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for topical acne drug products at 47 FR 12471. The agency's position regarding the Panel's testing guidelines is discussed in comment 14 above. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any topical acne ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency is proposing to classify salicylic acid 0.5 to 2 percent in Category I. Concentrations of salicylic acid greater than 2 percent up to 5 percent remain in Category III pending receipt of data to establish general recognition of safety. (See comment 6 above.)

2. The agency is proposing to reclassify thymol from Category II to Category III. (See comment 7 above.)

3. The agency is proposing to broaden the range of acceptable concentrations of sulfur-resorcinol combinations. The Panel recommended that 8 percent sulfur can be combined with 2 percent resorcinol or 3 percent resorcinol monoacetate, and the agency is proposing to allow 3 to 8 percent sulfur to be combined with 2 percent resorcinol or 3 percent resorcinol monoacetate. (See comment 9 above.)

4. The definitions proposed in § 333.303 include only those definitions considered necessary for this tentative final monograph. The Panel's recommended definitions for "follicle" and "lesion" have been deleted because they are not used in the labeling proposed in the tentative final monograph. Also, as discussed in paragraph 5 below, these words are not widely understood by consumers.

5. The agency has reviewed the indications statements recommended by the Panel in § 333.350(b)(1) and (2) and does not believe that some of the words or phrases are appropriate for consumer labeling. The agency has not included the words "lesion" or "follicle" in the proposed labeling because it does not believe that most consumers would understand these words. Other phrases recommended by the Panel that the agency believes are not clear or would be misleading to the consumer include "Reduces blackheads," "Loosens blackheads," "Helps remove blackheads," "Helps remove acne pimples," "Unclogs pores to help clear acne," and "Unplugs pores to help clear acne." The agency believes that the phrase "Reduces blackheads" is more clearly and accurately stated as "Reduces the number of blackheads" and has included the latter in the labeling proposed below. "Loosens blackheads" would not be helpful to consumers because it does not meaningfully describe the action of acne drug products. The agency also believes that the phrase "Helps remove" does not accurately describe the action of these drug products and could be misleading to consumers. Although acne drug products work by penetrating pores, and

this fact is indicated in the proposed labeling, phrases such as "Unclogs pores" and "Unplugs pores" do not provide accurate descriptions of the drugs' activity.

Other terms recommended by the Panel, such as "Anti-acne formula," "Anti-acne medication," and "Anti-acne formulation," are not indications for use, but would be more appropriately considered statements of identity. The statement of identity recommended by the Panel in § 333.350(a) for acne drug products is "acne medication," which the agency is adopting and proposing in this tentative final monograph. The agency finds no reason to retain the other three terms identified above.

FDA believes that the remainder of the statements in § 333.350(b)(1) and (2) accurately express the action of acne drug products. To improve clarity and reduce repetition, the agency has consolidated the numerous claims recommended by the Panel into a few concise statements. The agency is proposing the following indications for acne drug products under § 333.350(b):

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following:

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

(2) *Other allowable indications.* In addition to the required indication identified in paragraph (b)(1) of this section, the labeling of the product may contain additional indication statements that are limited to one or more of the following:

(i) (Select one of the following: "Dries," "Dries up," "Dries and clears," "Clears," "Clears up," "Clears up most," "Helps clear," "Helps clear up," "Reduces the number of," or "Reduces the severity of") (select one or more of the following: "blackheads," "acne pimples," or "acne blemishes") 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 both of the following: "blackheads" or "acne pimples").

(iii) "Helps keep skin clear of new acne pimples."

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

(v) "Helps prevent the development of new acne pimples."

6. The agency is not proposing the antibacterial labeling recommended by the Panel in § 333.350(b)(3) because none of the Category I ingredients were recommended to use antibacterial labeling and no in vivo data relating to antibacterial activity were submitted following publication of the Panel's report. (See comment 11 above.) In addition, the agency is not proposing the testing procedures to determine antibacterial activity recommended by the Panel in § 333.340. (See comment 15 above.)

7. The agency is not proposing the labeling for product attributes recommended by the Panel in § 333.350(b)(4). The Panel recommended that terms used to describe certain physical and chemical qualities of a drug product may be used in the labeling as long as these terms do not imply any therapeutic effect and are distinctly separated from the indications statements. These terms, such as "greaseless" or "nonstaining," are intended to provide consumer information and relate to a product's color, odor, or feel. As stated in comment 11 above, OTC drug monographs regulate only labeling information related in a significant way to those therapeutic properties of covered products having a direct bearing on their safe and effective use by lay persons. Claims concerning nontherapeutic characteristics of drugs, such as product attributes, are not dealt with in OTC drug monographs. Such terms may not appear in any portion of the labeling that is required by the monograph, but may appear elsewhere in the labeling. Labeling claims of this type are, however, subject to the drug misbranding provisions of the act.

8. The warning recommended by the Panel regarding the use of more than one topical acne medication at the same time in § 333.350(c)(1)(ii) has been revised and is being proposed as follows: "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." (See comment 12 above.)

9. The benzoyl peroxide warning recommended by the Panel in § 333.350(c)(2) has been revised and is being proposed as follows: ". . . If irritation becomes severe, discontinue use; if irritation still continues, consult a doctor. Keep away from eyes, lips and mouth. This product may bleach hair or dyed fabrics." (See comment 13 above.)

10. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

The agency advises that those parts of § 369.20 applicable to topical acne drug products will be revoked at the time that this monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking 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 proposed 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 proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC topical acne drug products. No comments were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by May 15, 1985. The agency will evaluate any comments and supporting data that are received and will reassess the economic

impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the Federal Register of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 333

OTC drugs; Topical acne drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 [21 U.S.C. 321(p), 352, 355, 371]) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended [5 U.S.C. 553, 554, 702, 703, 704]) and under 21 CFR 5.11, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 333 (which was proposed to be added in the Federal Register of January 6, 1978 (42 FR 1210)) by revising proposed Subpart D, to read as follows:

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

Subpart D—Topical Acne Drug Products

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart D—Topical Acne Drug Products

§ 333.301 Scope.

(a) An over-the-counter acne drug product in a form suitable for topical administration 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.

(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.* An inflammatory skin disease involving the oil glands and hair follicles of the skin.

(b) *Acne drug product.* A drug product used to reduce the number of acne lesions.

(c) *Blackhead.* An acne lesion characterized by a black tip.

(d) *Pimple.* A small, prominent, inflamed 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) Benzoyl peroxide 2.5 to 10 percent.

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

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

(d) Salicylic acid 0.5 to 2 percent.

(e) Sulfur 3 to 10 percent.

(f) 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(b) when combined with sulfur identified in § 333.310(f) provided the product is labeled according to § 333.350.

(b) Resorcinol monoacetate identified in § 333.310(c) when combined with sulfur identified in § 333.310(f) 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."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following:

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

(2) *Other allowable indications.* In addition to the required indication identified in paragraph (b)(1) of this section, the labeling of the product may contain additional indication statements that are limited to one or more of the following:

(i) (Select one of the following: "Dries," "Dries up," "Dries and clears," "Clears," "Clears up," "Clears up most," "Helps clear," "Helps clear up," "Reduces the number of," or "Reduces the severity of") (select one or more of the following: "blackheads," "acne pimples," or "acne blemishes") 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 both of the following: "blackheads" or "acne pimples").

(iii) "Helps keep skin clear and new acne pimples."

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

(v) "Helps prevent the development of new acne pimples."

(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 benzoyl peroxide identified in § 333.310(a).* "Do not use this medication if you have very sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possibly swelling. More frequent use or higher concentrations may aggravate such irritation. Mild irritation may be reduced by using the product less frequently or in a lower concentration. If irritation becomes severe, discontinue use; if irritation still continues, consult a doctor. Keep away from eyes, lips, and mouth. This product may bleach hair or dyed fabrics."

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

(4) *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 containing any ingredient identified in § 333.310 contains the following statements 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."

(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.

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

Interested persons may, on or before May 15, 1985, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons on or before January 15, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 17, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 17, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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