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; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would establish conditions under which over-the-counter (OTC) acne drug products are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by June 21, 1982 and reply comments by July 21, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on November 15, 1980 a report on OTC acne drug products from the Advisory Review Panel on OTC Antimicrobial (II) Drug Products. FDA regulations (21 CFR 330.10 (a)(6)) provide that the agency issue in the **Federal Register** a proposed order containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC acne drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgement of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC acne drug products as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC acne drug products will be stated initially when the tentative final monograph is published in the **Federal Register** as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC acne drug products. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC acne drug products should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC acne drug products submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after April 22, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations 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," "Category II," and "Category III" at the final monograph stage in favor of 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 because that was the framework in which the Panel conducted its evaluation of the data.

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 6 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 which 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. Further, any OTC drug products subject to this monograph which 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.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all antimicrobial active ingredients for the treatment and prevention of specific disorders such as seborrhea, dandruff, acne, athlete's foot, vaginitis, and otitis externa (swimmer's ear) was issued in the **Federal Register** of December 16, 1972 (37 FR 26842). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the durg product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.'")

A subsequent request for data and information on topical antibiotic active ingredients used in OTC products for treatment and prevention of infections in minor skin wounds was published in the **Federal Register** of September 7, 1973 (38 FR 24391). The Panel's conclusions and recommendations for topical antibiotic drug products were published in the **Federal Register** of April 1, 1977 (42 FR 17642).

Products for the treatment of swimmer's ear were referred for review to the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products. Products for the intravaginal treatment of vaginitis were referred for review to the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products. Products for the treatment of dandruff and seborrhea were referred for review to the Advisory Review Panel on OTC Miscellaneous External Drug Products.

In this document the Panel presents its conclusions and recommendations for acne drug products. The Panel's conclusions and recommendations for topical antifungal drug products are published elsewhere in this issue of the **Federal Register.**

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients contained in antimicrobial products:

Wallace Guess, Ph. D., Chairman
Frank B. Engley, Jr., Ph. D.
Paul D. Stolley, M.D., M.P.H. (resigned June 1977)
William F. Schorr, M.D. (resigned July 1977)
W. Kenneth Blaylock, M.D.
E. Dorinda Shelley, M.D.
Margaret Hitchcock, Ph. D. (resigned September 1974)
David R. Brown Sc. D. (appointed March 1975, resigned March 1976)
Eula Bingham, Ph. D. (appointed July 1976, resigned June 1977)
James E. Rasmussen, M.D. (appointed October 1976)
George B. Youngstrom, M.D. (appointed June 1977, resigned October 1979)
Anne Tucker, Ph. D. (Panel consultant from July 1978 to March 1979; appointed as a Panel member March 1979)
Zenona W. Mally, M.D. (appointed October 1979)

The Panel first convened on July 26 and 27, 1974 in an organizational meeting. Working meetings which dealt with the topic in this document were held on June 9 and 10, 1978; March 23 and 24, April 27 and 28, July 20, August 17 and 18, October 12 and 13, November 16 and 17, 1979; February 22 and 23, March 21 and 22, April 25 and 26, June 6 and 7, July 18 and 19, September 21 and 22, and November 14 and 15, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

The following nonvoting liaison representatives served on the Panel. Sarah Newman, nominated by an ad hoc group of consumer organizations, served as the consumer liaison. Gavin Hildick-Smith, M.D., nominated by the Cosmetic, Toiletry and Fragrance Association, served as an industry liaison until April 1978. Michael Winrow, Ph. D., nominated by the Proprietary Association, also served as an industry liaison until April 1979, followed by Kenneth R. Johannes until January 1980, followed by C. Elizabeth McKinivan, M.D.

The following FDA employees served: Mary K. Bruch served as Executive Secretary; Michael Kennedy served as Panel Administrator in July 1974, followed by Armond M. Welch, R.Ph., until August 1978, followed by Lee Geismar. Melvin Lessing, R.Ph., M.S., served as Drug Information Analyst until October 1974, followed by Joseph Hussion, R.Ph., until July 1976, followed by Anne W. Eggers, R.Ph., M.S., until June 1978, followed by Elaine G. Euchner, R.Ph.

The following individuals were given an opportunity to appear before the Panel to express their views on acne drug products either at their own or at the Panel's request:

Eugene A. Conrad, Ph. D.
Richard Dobson, M.D.
Charles A. Evans, M.D., Ph. D.
Carol Farhi
Samuel B. Frank, M.D.
Arnold Friede
David Fulgham, M.D.
Eugene Gans, Ph. D.
George Hoffnagle, Sc. D.
Albert M. Kligman, M.D., Ph. D.
William H. Lederer, Ph. D., J.D.
James J. Leyden, M.D.
Zenona W. Mally, M.D. (before becoming a Panel member)
Philip Merker, Ph. D.
Sergio Nacht, Ph. D.
Albert Packman, D. Sc.
Peter Pochi, M.D.
Sirje M. Puhvel, Ph. D.
Alan Shalita, M.D.
Vithal Shetty, Ph. D.
John Strauss, M.D.
Harold Upjohn, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through November 15, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC acne drug products with respect to the following three categories:

Category I. Conditions under which OTC acne drug products are generally

recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC acne drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 27 active ingredients in topically applied acne products and classified 2 ingredients in Catefory I, 23 ingredients in Category II, and 2 ingredients in Category III.

I. Submission of Data and Information

A. Submissions by Firms

Firms and Marketed Products

AHC Pharmacal, Miami, FL 33125.
bp Gel Medication, bp Gel Medication Strong.
Barnes-Hind Pharmaceuticals, Inc., Sunnyvale, CA 94086.
Komed Acne Lotion, Komed Mild Acne Lotion, Komex Acne Scrub.
Bowman Pharmaceuticals, Inc., Canton, OH 44702.
Bowman Drawing Paste.
Campana Corp., Batavia, IL 60510.
Cuticura Acne Cream (Cutitone).
Carter Products, Inc., Cranbury, NJ 08512.
Persol.
Chattem Drug and Chemical Co., Chattanooga, TN 37409.
Mudd.
Dermik Laboratories, Inc., Fort Washington, PA 19034.
Vlemasque.
Dome Laboratories, West Haven, CT 06516.
Acne-Dome Creme, Acne-Dome Lotion, Acne-Dome Medicated Cleanser, Vlem-Dome Wet Dressing.
Flow Pharmaceuticals, Inc., Palo Alto, CA 94303.
d-SEB.
Fox Pharmacal, Inc., North Miami, FL 33161.
Aktex.
H. B. Distributing Co., West Newton, MA 02165.
Hospital Brand Acne Cream.
Helena Rubinstein, Inc., New York, NY 10022.
Bio-Clear Medicated Cream.
Ketchum Laboratories, Inc., Amityville , NY 11701.
Propoa pH Super Cleanser.
Laboratory Robaina, Inc., Hialeah, FL 33010.
Acetolia Robaina.
Norcliff Thayer, Inc., Tuckahoe, NY 10707.
Oxy-5 Lotion, Oxy-10 Lotion.
Pennwalt Corp., Rochester, NY 14603.
Bare Face Acne Skin Medicine, Ting Antiseptic Medicated Cream.
Poythress, Willian P., & Co., Inc., Richmond, VA 23261.
Bensulfoid Lotion.
Press Chemical & Pharmaceutical Laboratories, Inc., Columbus, OH 43206.
Epsal Ointment.
Preston Pharmaceutics, Inc., Butler, NJ 07405.
Dermakon Dandruff Shampoo, Dermakon Medicated Cream.
Purdue Frederick Co., Norwalk, CT 06856.
Betadine Skin Cleanser, Betadine Skin Cleanser Foam.
Rorer, William H., Inc., Fort Washington, PA 19034.
Loroxide Lotion, Vanoxide Lotion.
Schattner, R., Co., Washington, DC 20016.
Chloraderm.
Smith, Kline, & French Laboratories, Philadelphia, PA 19101.
Acnomel Acne Cake, Acnomel Acne Cream.
Squibb, E. R., & Sons, Inc., New Brunswick, NJ 08903.
Epi*Clear Acne Lotion, Epi*Clear Acne Scrub Cleanser, Epi*Clear Acne Soap, Epi*Clear Antiseptic Lotion 5%, Epi*Clear Antiseptic Lotion 10%, Epi*Clear Squibb Acne Kit.
Sterling Drug, Inc., New York, NY 10016.
Campho-Phenique Liquid, pHisoAc, Stridex Medicated Pads.
Stiefel Laboratories, Inc., Oak Hill, NY 12460.
SAStid Soap, Sulfoxyl Cream Strong, Sulfoxyl Lotion Regular, Sulfoxyl Lotion Strong.
Syntex Laboratories, Inc., Palo Alto, CA 94304.
Microsym Acne Lotion.
Texas Pharmacal Co., San Antonio, TX 78296.
Contrablem, Liquimat, Persadox Cream, Persadox Lotion, Sulforcin Base 4%, Sulforcin Lotion.
Upjohn Co., Kalamazoo, MI 49001.
Plexion, Zinc Sulfide Compound Lotion, Improved.
Vick Divisions Research and Development, Division of Richardson-Merrell, Inc., Wilton, CT 06897.
Clearasil Regular Tinted, Clearasil Stick Medication, Clearasil Vanishing Formula.
Warner-Lambert Co., Morris Plains, NJ 07950.
Listerex Antibacterial Scrub Gel, Listerex Antibacterial Scrub Lotion, Listerex Herbal Scrub.
Westwood Pharmaceuticals, Inc., Buffalo, NY 14213.
Fostex Cake, Fostex Cream, Fostril, Pernox, Transact.

In addition, the following firms or groups provided related information:

Avon Products, Inc., Suffern, NY 10901.
Sulfur-resorcinol combinations.
Herbert Laboratories, Irvine, CA 92715.
Benzoyl peroxide 2.5 percent.
Koppers Co., Inc., Pittsburgh, PA 15219.
Resorcinol.
Miranol Chemical Co. Inc., Irvington, NJ 07111.
Miranol C2M.
Procter & Gamble Co., Cincinnati, OH 45247.
Tetracycline hydrochloride.
Proprietary Association, Washington, DC 20006.
Benzoyl peroxide safety, labeling recommendations.
Schuylkill Chemical Co., Philadelphia, PA 19132.
Alcloxa, allantoin.
Sterling Drug, Inc., New York, NY 10016.
Salicylic acid.
Stiefel Laboratories, Inc., Oak Hill, NY 12460.
Antibacterial data on benzoyl peroxide-sulfur combinations.
Vick Divisions Research and Development, Division of Richardson-Merrell, Inc., Wilton, CT 06897.
Benzoyl peroxide absorpotion, in vitro protocol for determining antibacterial activity, in vivo protocol for testing antibacterial activity, prevention of new acne lesions by topical therapeutic ingredients, resorcinol safety.
Westwood Pharmaceuticals Inc., Buffalo, NY 14213.
Laureth-4 safety, polyethylene safety.

B. Labeled Ingredients Contained in OTC Marketed Products Submitted to the Panel

The Panel has identified the following labeled ingredients in marketed products:

Alcloxa
Alcohol
Alkyl isoquinolinium bromide
Allantoin
Alpha tocopheryl acetate
Aluminum chlorhydroxide complex
Aluminum chlorhydroxy allantoinate
Aluminum hydroxide
Aluminum magnesium silicate
Aluminum oxide
Bentonite
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Benzoyl peroxide
Boric acid
Calcium phosphate
Calcium polysulfide
Calcium thiosulfate
Camphor
Carbomer 940
Carboxyvinyl polymer
Cetyl alcohol
Chlorhydroxyquinoline
Cholesterol
Citric acid
Coal tar
Colloidal alumina
Colloidal sulfur
Cosmetic colors
Dibenzothiophene
Dioctyl sodium sulfosuccinate
Edetate disodium
Epsom salts
Estrone
Glycerin
Glycerol monostearate
Glyceryl monostearate
Hexachlorophene
Hydrocarbon hydrotropes
Isopropyl
Isopropyl alcohol
Isopropyl palmitate
Magnesium sulfate
Menthol
Methylbenzethonium chloride
Methylparaben
Methyl parasept
Methyl salicylate
Micropulverized sulfur
Parachlorometaxylenol
Phenol
Phenyl salicylate
Polyethylene
Polyethylene glycol monostearate
Polyethylene glycol 1000 monostearate
Polyoxyethylene lauryl ether

Povidone-iodine
Precipitated sulfur
Propylene glycol
Propyl parasept
Purified water
Pyrilamine maleate
Rescorcijol
Resorcinol
Resorcinol monoacetate
Salicylic acid
Soapless cleansers
Sodium borate
Sodium hydroxide
Sodium lauryl sulfate
Sodium phenolate
Sodium tetraborate decahydrate
Sodium thiosulfate
Stearic acid
Sulfated surfactants
Sulfonated alkyl benzenes
Sulfur
Sulfur precipitated
Tetracaine hydrochloride
Thymol
Water
Wetting agents
Zinc oxide
Zinc stearate
Zinc sulfide

C. Classification of Ingredients

1. *Ingredients identified by the Panel as active ingredients.* The Panel has adopted the following nomenclature for the active ingredients reviewed in this document. Other nomenclature, where needed for clarification, has been included in parentheses.

Alkyl isoquinolinium bromide
Aluminum salts
  Alcloxa (aluminum chlorhydroxy allantoinate)
  Aluminum chlorohydrex (aluminum chlorhyaroxide complex)
  Aluminum hydroxide
  Magnesium aluminum silicate (aluminum magnesium silicate)
Benzocaine
Benzoic acid
Benzoyl peroxide
Borates
  Boric acid
  Sodium borate (sodium tetraborate decahydrate)
Calcium polysulfide
Calcium thiosulfate
Camphor
Chlorhydroxyquinoline
Chloroxylenol (parachlorometaxylenol)
Coal tar
Dibenzothiophene
Estrone
Magnesium sulfate (epsom salts)
Phenolates
  Phenol
  Phenolate sodium (sodium phenolate)
Phenyl salicylate
Povidone-iodine
Pyrilamine maleate
Resorcinol (rescorcijol)
Resorcinol monoacetate
Salicylic acid
Sodium thiosulfate
Sulfur (colloidal sulfur, micropulverized sulfur, precipitated sulfur, sulfur precipitated)
Tetracaine nydrochloride
Thymol
Vitamin E (alpha tocopheryl acetate)
Zinc salts
  Zinc oxide
  Zinc stearate
  Zinc sulfide

2. *Ingredients identified by the Panel as inactive or pharmaceutically necessary ingredients.* Based on the available literature and in some cases based on concentrations reported in a submission, the Panel considers the following to be inactive ingredients when used for the treatment of acne. In general, most are used as pharmaceutical aids (solvent, vehicle, dispersant, or preservative,) or as product identification materials.

Alcohol
Allantoin
Aluminum oxide
Bentonite
Benzalkonium chloride
Benzethonium chloride
Calcium phosphate
Carbomer 940
Carboxyvinyl polymer
Cetyl alcohol
Cholesterol
Citric acid
Colloidal alumina
Cosmetic colors
Dioctyl sodium sulfosuccinate
Edetate disodium
Glycerin
Glycerol monostearate
Glyceryl monostearate
Hexachlorophene
Hydrocarbon hydrotropes
Isopropyl alcohol (isopropyl)
Isopropyl palmitate
Laureth-4 (polyoxyethylene lauryl ether)
Menthol
Methylbenzethonium chloride
Methylparaben (methyl parasept)
Methyl salicylate
Polyethylene
Polyethylene glycol monostearate
Polyethylene glycol 1000 monostearate
Propylene glycol
Propylparaben (propyl parasept)
Purified water
Soapless cleansers
Sodium hydroxide
Sodium lauryl sulfate
Stearic acid
Sulfated surfactants
Sulfonated alkyl benzenes
Water
Wetting agents

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document includes submissions made by interested persons in response to the call-for-data notice published in the **Federal Register** of December 16, 1972 (37 FR 26842). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after April 22, 1982, in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Background

Acne affects about 80 percent of the population to some extent during adolescence (Ref. 1). Because this skin condition is common and readily recognizable by consumers, the Panel believes that safe and effective OTC acne medications should be available to the consumer.

Although much has been learned about acne in the past 30 years, much still remains unknown. Even the exact origin of the word "acne" is unknown, Some scholars believe it is a corruption of the Greek word "akne," meaning the highest point or stage (including the peak of growth in humans) (Ref. 2). Another theory is that "acne" comes from another Greek word, "aknesis," which means a rash that does not itch (Ref. 2). In fact, according to Plewig and Kligman (Ref. 3), the only undisputed fact about acne is that it does exist.

The Panel believes that the myths or misconceptions about acne need to be dispelled, including those concerning diet, sexual habits, and the belief that acne can be washed away with soap and water (Ref. 4). For years, people suffering from acne believed that eating chocolates, fatty foods, and "junk foods" either caused acne or made it worse and that abstaining from these foods would cure their acne. Unfortunately, they were often disappointed.

The role of diet is still being studied. For example, a double-blind study tested the effects of large amounts of chocolate on 65 acne patients (Ref. 5). Two kinds of candy bars that looked identical were used. One contained no chocolate; the other was an enriched chocolate bar containing 10 times the amount of chocolate as an average candy bar. The subjects ate one kind of chocolate bar daily for 4 weeks, and for the next 3 weeks they ate no candy. Then they ate the other kind of bar once daily for 4 weeks. Chocolate was found to have no effect on the clinical course of acne.

Another study was conducted with acne patients who believed that certain foods (chocolate, peanuts, milk, or cola) were causing their acne to flare (Ref. 6). These patients were fed large amounts of the suspected food for several days, but no significant change was noted in

the number or character of their acne lesions during the next several days.

According to Cunliffe and Cotterill (Ref. 2), "Iodides have also been blamed for aggravating acne but the evidence for this is rather poor * * *."

Myths about the relationship between sexual habits and the development of acne go far back in history. MacKenna cited Jonston who wrote in 1648 that acne, called "vari," infected young people who were sexually mature but who remained chaste (Ref. 7). More than a century later, according to Cunliffe and Cotterill (Ref. 2), Plenck wrote that marriage could cure acne, but Hebra disagreed. Although some sexual myths may still persist today, there is no evidence to show that they are any more than myths (Ref. 4).

Another misconception is that acne will go away if it is ignored. Although many people no longer have significant acne by the time they are in their early twenties, a number of people still suffer from acne in their forties. The Panel believes it is particularly important that consumers realize that the treatment of acne may have to be continued for several years.

The following discussion summarizes the findings of several surveys on skin conditions.

The most recent report was published by the National Center for Health Statistics and covers the period from 1971 to 1974 (Ref. 8). The data were collected by direct physical examinations, tests, and measurements performed on samples of the population aged 1 to 74 years. Participants were chosen from the civilian noninstitutionalized population.

This report shows that significant skin disease increases rapidly with age. In children aged 1 to 5 years the rate was 142.3 per 1,000. In youths aged 12 to 17 years the rate was 362.0 per 1,000. In young adults aged 18 to 24 years the rate was 365.1 per 1,000. The rapid increase was attributed to acne vulgaris, which, as noted earlier, is common during adolescence and young adulthood. Among the individual types of skin disease that were diagnosed, acne was the most prevalent (68.1 per 1,000 population). The survey also showed that youths aged 12 to 17 years with skin problems are more likely to consult someone who is a "nonprofessional" rather than a dermatologist or other physician.

The Health Examination Survey of 1966 to 1970 (Ref. 9) presented national estimates on the prevalence of facial acne and other skin conditions among noninstitutionalized youngsters aged 12 to 17 by age, sex, geographic region, population, size of place of residence, family income, education of parents, overall health, indication of stress, selected health habits, and physiological development. It was estimated that 28.3 per 100 youths had moderate to severe facial acne. Major findings included the following:

Facial acne (all grades combined) is about as prevalent among girls as boys in the 12–17 year age range. However, such conditions start somewhat earlier and tend to be less severe in girls than boys.

Among youths reporting they had acne, more than half (51 percent) were bothered some or a lot by the condition and (58 percent) were using some treatment for it but only 11 percent had seen a doctor about it.

White youths are slightly more likely than Negro youth to have moderate to severe facial acne but less likely to have mild conditions limited to comedones with little or no inflammatory reaction.

Facial acne is somewhat more prevalent among youths living in the South and West than those in the Northeast or Midwest. However, no consistent urban-rural differences in prevalence rates were found.

Some direct or indirect association is evident between acne prevalence in youths and the education of their parents but not their family income level. The acne prevalence rates decrease consistently with increasing education level of parents.

Facial acne is slightly more prevalent among youths whose health was rated fair-poor than among those considered in good-excellent health by either themselves or their parents.

Facial acne prevalence increases with the degree of nervousness of the youth, the association being stronger and more consistent when based on the youth's own rating of nervousness than that given by his or her parent.

The amount of food eaten particularly among boys appears to be related, directly or indirectly, to the prevalence of facial acne. Acne rates are higher among those who are said, by their parents, to eat too much than those who eat too little.

The prevalence and severity of facial acne increases with the degree of development of secondary sex characteristics among boys 12–16 years and girls 12–15 years of age.

Among girls acne tends to start after the onset of menarche for girls who reach this stage of physiological development before 13 years of age but to precede this point of development for those whose menarche onset is 14 years or later.

A report on a questionnaire survey published in 1972 stated that out of 1,023 high school students whose questionnaires were evaluated, 85.1 percent reported that they had acne (Ref. 10). Of this group, 87.7 percent had not consulted a doctor. The most frequently given reason was that the acne was not severe enough. A few students felt the treatment was too costly; the rest did not specify a reason.

About half of the students surveyed reported a seasonal change in their acne. Among those students reporting a seasonal change, statistically significant improvement was shown during summer.

Most of the students with acne were using some kind of treatment, with girls starting treatment a little sooner than boys. However, the authors reported that only 33.4 percent of the students reported that they never missed their treatment. Statistically, the girls were significantly better than the boys in following a regular treatment schedule.

A total of 117 products was used, with 93.6 percent of the students using one or more products and only 6.4 percent using none. The products included soaps, astringents (which did not claim anti-acne properties), anti-acne preparations, complexion products, and miscellaneous products. Soaps were the most widely used (49.7 percent); anti-acne preparations were the next most widely used (28.8 percent).

People suffering from acne spend millions of dollars yearly for OTC acne preparations as well as prescription drugs (Ref. 11). "Cosmetically" accepted medications are important. In fact, dermatologists say that patient acceptance is as important as effectiveness in acne treatment. They also say that consumers want therapeutic products that work but are not too harsh or unpleasant smelling. Consumers like a product that can be easily applied, feels good, and perhaps may even have a lathering property which enhances the sense of feeling clean and leaves the skin feeling soft.

Dermatologists are often asked questions about the causes of acne, including what foods are responsible. Patients are also concerned about the possibility of scarring. They also ask what they are doing wrong, if makeup can harm the skin, and, in some cases, why they are getting acne at age 30 after having had flawless skin in adolescence. Probably the most difficult question of all to answer is: "When will the acne disappear?"

There are certain aspects of acne therapy that patients most dislike. These include the odor and the stinging and itching of acne products; the staining effect; and dryness and peeling, which to many patients means premature wrinkling. This dryness also makes it difficult to apply a water-base makeup. Patients also dislike the ashy grayness, which is produced by benzoyl peroxide products and cryotherapy and is seen mainly in black skin. Other adverse effects of acne therapy may include vaginal yeast infections as a result of taking systemic antibiotics. A less serious complaint is that having to

remember to apply or take the medication a certain number of times a day is a nuisance. Finally, patients dislike acne surgery, i.e., the comedone extraction and opening up of pustular lesions which many dermatologists routinely do at each office visit.

It has been known since the early 1970's that certain cosmetics and hair pomades can cause blackheads and whiteheads (comedogenic). It has been estimated that up to 50 percent of the popular cosmetic creams will produce comedones when tested on the inner surface of the rabbit ear once daily for 2 weeks (Ref. 3).

The term "acne cosmetica" was coined in 1972 by Kligman (Ref. 12) and refers to acneform eruptions of a low-grade, persistent nature occurring in adult women. These eruptions are caused mainly by prolonged use of cosmetics containing the offending ingredients.

The Panel agrees with the following statement by Sulzberger (Ref. 13): "There is probably no single disease which causes more psychic trauma, more maladjustments between parents and children, more general insecurity and feelings of inferiority, and greater sums of psychic suffering than does acne vulgaris."

References

(1) "Stubborn and Vexing, That's Acne," *FDA Consumer,* 14:14–17, 1980.

(2) Cunliffe, W. J., and J. A. Cotterill, "The Acnes: Clinical Features, Pathogenesis and Treatment," W. B. Saunders Co. Ltd., London, pp. 2–3 and 14, 1975.

(3) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, Berlin, pp. 1 and 227, 1975.

(4) Fardal, R. W., "The Myths and Magic of Acne Care," *Hawaii Medical Journal,* 35:333–335, 1976.

(5) Fulton, J. E., Jr., G. Plewig, and A. M. Kligman, "Effect of Chocolate on Acne Vulgaris," *Journal of the American Medical Association,* 210:2071–2074, 1969.

(6) Anderson, P. C., "Foods as the Cause of Acne," *American Family Physician,* 3:102–103, 1971.

(7) MacKenna, R. M. B., "Acne Vulgaris," *Lancet,* 1:169–176, 1957.

(8) U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, "Skin Conditions and Related Need for Medical Care Among Persons 1–74 Years," DHEW Publication No. (PHS) 79–1660, Series 11, No. 212, pp. 1–72, 1978.

(9) U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, "Skin Conditions of Youths 12–17 Years," DHEW Publication No. (HRA) 76–1639, Series 11, No. 157, 1976.

(10) Emerson, G. W., and J. S. Strauss, "Acne and Acne Care. A Trend Survey," *Archives of Dermatology,* 105:407–411, 1972.

(11) Shalita, A. R., "Acne Vulgaris: Not Curable but Treatable," *Modern Medicine,* 43:66–76, 1975.

(12) Kligman, A. M., and O. H. Mills, Jr., "Acne Cosmetica," *Archives of Dermatology,* 106:843–850, 1972.

(13) Sulzberger, M. B., and S. H. Zaidens, "Psychogenic Factors in Dermatologic Disorders," *Medical Clinics of North America,* 32:669–685, 1948.

B. Definitions

The Panel adopted the following definitions related to the use of acne drug products:

1. *Comedones (whiteheads and blackheads).* Comedones are the primary lesions of acne and consist of dead cell (keratinous) debris, bacteria, sebum, and hair fragments which plug up the opening of the pilosebaceous unit. The development of the comedo is associated with an increased turnover rate of the epithelial cells lining the sebaceous follicle. The follicle becomes distended with horny material and at this early stage is known as a microcomedo, a microscopic comedo. Further distention of the sebaceous follicle results in the closed comedo.

a. *Whiteheads.* Whiteheads or closed comedones are small, whitish, firm nodules which may be difficult to see. The opening to the comedo is not visible to the naked eye. Closed comedones either rupture and become inflammatory lesions, such as papules, pustules, and nodules, or develop into open comedones. When horny material accumulates in the closed comedo, it causes the opening in the comedo to dilate, pushing horny material to the skin surface. This marks the beginning of the open comedo or blackhead.

b. *Blackheads.* Blackheads are long-lasting lesions that do not usually develop into inflammatory lesions. The tip of the blackhead appears black because of melanin, a pigment.

2. *Lesion.* In this document a lesion is considered as a characteristic area of a skin condition. Acne lesions include open and closed comedones, papules, pustules, and nodules.

3. *Nodule.* A large, red, often painful inflammatory acne lesion that contains pus and leads to scarring. Nodules are deep-seated lesions which affect the dermis. They develop from the rupture of closed comedones and are characteristic of acne conglobata. Nodules may fuse to form odd-shaped lesions. The term "cystic acne" refers to nodular inflammatory lesions and not to true cysts, which are large, round, flesh-colored, noninflammatory lesions with smooth surfaces.

4. *Papule.* A small, inflammatory lesion that appears red and raised. Papules develop from closed comedones. They may develop into pustules and nodules, or they may resolve spontaneously after 2 to 3 weeks.

5. *Pilosebaceous unit.* Consists of a hair follicle and the associated sebaceous gland. These are connected to the surface of the skin by a duct through which the hair passes.

6. *Pustule.* A small, raised, inflammatory lesion that is filled with pus and arises from a papule. Superficial pustules resolve after a few days and rarely cause visible scarring. A deep-seated pustule takes 2 to 6 weeks to resolve, and scarring may result.

7. *Sebum.* A secretion of the sebaceous glands consisting of a mixture of fats and waxes. The severity of acne parallels the degree of sebum secretion.

C. Types of Acne

Kligman (Ref. 1) uses two major classificatioins of acne—true acne and drug-induced acne. The Panel has adapted these classifications to this document, citing other references when appropriate.

1. *True acne*—a. *Acne vulgaris.* A common skin disorder, acne vulgaris is characterized by comedones, papules, pustules, and nodules. Typically, a person with acne will have a variety of acne lesions, although in some individuals one lesion type may predominate. Acne vulgaris primarily occurs on the face, shoulders, back, and chest, but occasionally may be more widespread.

Open and closed comedones are usually the first acne lesions to occur. In the early stages, comedones are generally found on the forehead and chin. Later, papules and pustules appear on the cheeks as well. Although usually a disease of adolescence, acne does not always clear spontaneously when maturity is reached. It may persist into the third or fourth decades of the patient's life (Refs. 2 and 3). In fact, acne may even begin after the teenage years or at any age.

b. *Acne conglobata.* Acne conglobata is a severe and chronic form of acne vulgaris. The lesions tend to be particularly severe on the face, chest, and back. Lesions may also occur on the buttocks, thighs, upper arms, and neck. Most of the lesions are large, painful, and cystic and may be characterized by abscesses and scarring. Males are affected more frequently than females. The disease, which usually begins between the ages of 18 and 30 years, often continues for many years, resulting in severe disfigurement (Ref. 4).

c. *Acne fulminans.* Also termed "acute febrile ulcerative conglobate acne with polyarthralgia," acne fulminans is a

rare, severe form of acne. The main lesions are nodules that become ulcerated. Systemic effects include fever, anemia, and painful, swollen joints (Ref. 5).

d. *Acne tropicalis.* This type of acne occurs when a susceptible person is exposed to excessive heat and humidity. It resembles severe acne conglobata and is unchanged as long as the patient remains in a tropical climate, but clears completely when the patient returns to a cool, dry climate (Ref. 1). Military personnel that are stationed in tropical climates are particularly at risk for developing this type of acne.

e. *Infantile acne.* This is an acne-like rash of unknown cause. Comedones and papules usually occur on the cheeks of male infants under 1 year of age, but the disease generally subsides completely in 2 to 3 years (Ref. 4).

f. *Premenstrual flares of acne.* Many women suffer from premenstrual flares of acne characterized by the rapid appearance of papulo-pustules. The precise cause is still unknown, but is presumed to be related to cyclical hormone fluctuation (Ref. 1).

g. *Gram-negative acne or folliculitis.* This type of acne usually occurs during long-term treatment of acne with antibiotics which specifically act on gram-positive bacteria, thereby permitting gram-negative bacteria to flourish. The invading organisms are usually *Enterobacter, Klebsiella,* or *Proteus.* A change in the characteristics of the facial acne of a previously well-controlled case of acne may be a sign of gram-negative acne (Ref. 1).

h. *Acne venenata or acne caused by external contactants.* Topical agents or exposure to certain chemicals can cause this type of acne (Ref. 5). "Acne cosmetica" is a mild eruption mainly consisting of closed comedones. It is usually caused by facial creams and is seen in women beyond the age of adolescence (Ref. 1). "Pomade acne" is caused by greases and oils applied to the scalp or face. The lesions are usually small, closed comedones concentrated on the forehead and temples (Ref. 5). "Acne detergicans" is a mild form of acne consisting of closed comedones, apparently induced by excessive scrubbing and washing with certain soaps (Ref. 1).

The most extensive cases of acne venenata are caused by industrially used compounds such as chlorinated hydrocarbons, cutting oils, petroleum oil, coal tars, and pitches. This condition is often referred to as "chloracne." The initial treatment in all forms of acne venenata is to stop the exposure to the causative agent (Ref. 5).

i. *Acne caused by radiation.* Both untraviolet light and ionizing radiation may be associated with the development of special types of acne. Excessive exposure to the sun may induce comedones, usually large blackheads, around the eyes and cheeks of elderly people. Ionizing radiation, such as cobalt and X-rays, can cause a comedonal acne. Acne aestivalis (mallorca acne) is a rare seasonal acne which flares up in the summer months and regresses in winter. It usually affects women beyond adolescence, with papules developing on the lower back. These forms of acne generally subsides when the causative agent is eliminated (Ref. 5).

j. *Acne mechanica.* Aggravation of existing acne can develop from localized pressure or friction. For example, resting the chin on the hand can aggravate acne on the chin (Ref. 1).

2. *Drug-induced acne.* Drug-induced acne is not a true acne, but an acne-like eruption caused by drugs. The eruption subsides when the drug is discontinued. The lesions are generally papules and pustules. The condition is usually characterized by a sudden onset after adolescence and an unusual localization (forearm, buttock). Systemic signs of drug toxicity may also be present (Ref. 1). The drugs that are often involved in these kinds of eruptions include steroids, certain anticonvulsants (phenobarbital, phenytoin, and trimethadione), and certain halogenated drugs. Isoniazid, a drug used in long-term therapy of tuberculosis, may also be involved in some acne-like conditions (Refs. 4 and 5).

References

(1) Kligman, A. M., "Classification of Acne," *CUTIS; Cutaneous Medicine for the Practitioner,* 17:520–522, 1976.

(2) Moschella, S. L., D. M. Pillsbury, and H. J. Hurley, Jr., "Dermatology," Volume II, W. B. Saunders, Co., Philadelphia, pp. 1129–1131, 1975.

(3) Shalita, A., et al., "Acne," *Journal of Investigative Dermatology,* 73:434–442, 1979.

(4) Cunliffe, W. J., and J. A., Cotterill, "The Acnes: Clinical Features, Pathogenesis and Treatment," Edited by A. Rook, W. B. Saunders Co. Ltd., London, pp. 25–28, 33–35, and 38–40, 1975.

(5) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, pp. 106, 196–198, 226, 230, 233, 238–239, and 257, 1975.

D. Development of Acne

Acne generally begins at puberty when substantial androgen secretion takes place. Androgen is the male sex hormone and comes mainly from the testes in the male and from the ovaries and adrenal glands in the female. Although male adrenals also produce androgens, they play only a small role in acne. The most potent androgen is testosterone, the circulating androgen. Testosterone is converted in the skin by the enzyme 5-*alpha*-reductase to dihydrotestosterone, the tissue-active androgen (Ref. 1).

Dihydrotestosterone stimulates the cells of the sebaceous glands to increase protein synthesis and accelerate cell division and cell turnover. Thus the sebaceous glands become larger until they surround and completely dominate the hair follicles. Sebaceous follicles (pilosebaceous units) like these produce large amounts of sebum which cause the characteristic oily skin of acne (Ref. 1). Acne usually occurs on the face, upper chest, and back because there are more pilosebaceous units there than on other areas of the body (Ref. 2).

The size of the sebaceous gland usually varies inversely with the size of the hair follicle associated with it (Ref. 3). The kind of hair in the follicle can also affect the development of acne. A thin, small hair may be unable to keep the duct open and the hair is trapped in the plug. However, heavier facial or scalp hair may push the plug to the surface of the skin and prevent a comedo from forming (Ref. 2).

People with acne have larger sebaceous follicles than those without acne (Ref. 3). Studies have shown a correlation between the severity of acne (as measured by the degree of inflammation) and the rate of sebum excretion (Refs. 4, 5, and 6). In general, from the studies one can conclude that people with acne produce more sebum than those without acne.

Kligman and Katz (Ref. 7) conducted tests on the ears of albino rabbits and demonstrated that sebum can induce comedones. The components of sebum that have been shown to be most comedogenic are squalene and free fatty acids (Ref. 8). Because subjects with acne produce more sebum than subjects with no acne (controls), it is possible that excessive sebum production is the initiating event in comedogenesis. Research has been done on changes that apparently involve increased turnover of the cells that are shed into the canal of the follicle (Ref. 9). The resulting increased cohesiveness of the cells could explain the formation of a comedo. Although the factors involved in the initiation of this abnormality are not entirely known, one factor appears to be sebum.

Because the sebaceous gland is clearly an androgen-sensitive organ, several investigators have searched for differences in circulating levels of testosterone in acne patients. These

studies showed no significant differences in testosterone in males with or without acne and suggest that females with acne may have somewhat elevated levels (Refs. 10, 11, and 12). However, these studies were conducted when there were no techniques for assessing free versus bound testosterone, and little attention was paid to the possibility of excessive production of adrenal androgens.

Lee's studies (Ref. 13) offer another possibility. In a small group of patients, those who developed acne demonstrated an early onset of testosterone production, suggesting that a "hormone abnormality" may exist. The current evidence favors the conclusion that acne patients do not suffer from exessive production of androgens, but have a hypersensitivity of the end-organ sebaceous gland to normal circulating levels of androgens (Ref. 14).

Certain species of microorganisms including *Staphylococcus, Propionibacterium acnes (P. acnes),* and *Pityrosporum* produce lipases (fat-splitting enzymes). These microorganisms live on the surface of the skin and in the horny layer. They also accumulate in the sebum within the opening and the neck of the sebaceous follicles. *P. acnes* appears to be the most important of these microorganisms in the development of acne (Refs.15 and 16).

P. acnes produces cellular products other than lipases which may play some part in the pathogenesis of acne. These products include esterases, proteases, and hyaluronidase. However, the action of lipases is best known. The bacteria produce lipases. The lipases break down triglycerides contained in the sebum into free fatty acids and glycerol, which the bacteria may then use as nutrients. Some researchers believe that the free fatty acids are the irritating, inflammatory, and comedogenic components of sebum (Refs. 8 and 16).

The evidence implicating *P. acnes* in the pathogenesis of inflammation includes the following:

(1) Increasing numbers of *P. acnes* are seen at the light and electron microscopic level with the onset of abnormal keratinization characteristics of acne (Refs. 17 and 18).

(2) Significantly higher densities of *P. acnes* are recoverable from the skin of teenage acne patients than from age-matched controls (Ref. 19).

(3) Successful suppression of *P. acnes* by systemic or topical antibiotics or antimicrobials is accompanied by clinical improvement (Refs. 16 and 20).

(4) *P. acnes* antibody titers tend to parallel the clinical severity of acne (Ref. 21).

(5) Intradermal injection of *P. acnes* produces intense inflammation in subjects with acne and minimal reactions in control subjects who do not have acne (Ref. 22).

(6) Injection of *P. acnes* attracts polymorphonuclear leukocytes to the follicle and results in the release of hydrolase (Ref. 23).

The significance of free fatty acids has been questioned because of the minimal inflammation which develops after a single intradermal injection of amounts of fatty acid comparable to those found in single sebaceous follicles. However, repeated intradermal injections through ruptured follicles can reasonably be expected to contribute to the inflammatory response (Ref. 9).

Some studies suggest that free fatty acids are not the only inflammatory agents in acne. According to Puhvel and Sakamoto (Ref. 22), "the effect of antibiotics in acne is more likely to depend on direct suppression of *P. acnes* as inflammatory agents rather than on indirect reduction of intrafollicular lipase, as the free fatty acid theory of acne therapy had previously supposed."

It is thought that *P. acnes* produces substances that are chemotactic for polymorphonuclear leukocytes (Ref. 24). Chemotactic refers to inducing movement of cells or organisms.

These authors also found that accumulations of polymorphonuclear leukocytes along the periphery of the walls of closed comedones may be the first change marking the transition from noninflamed lesions into inflammatory ones. Furthermore, lipids within comedones have demonstrated chemotactic activity for polymorphonuclear leukocytes (Ref. 24).

More recent studies by the same authors have demonstrated differences in the cytotactic activity of the same microbial strain grown in different media. This varied movement and arrangement, called cytotaxis, may explain why comedones may differ in inflammatory potential (Ref. 25).

Another possible triggering or aggravating factor in acne that should be mentioned is stress. Shalita (Ref. 8) reported that acne becomes worse in many people during times of emotional stress. However, controlled studies to support this view are lacking because of the difficulty in designing studies that can accurately measure these effects.

References

(1) Shalita, A. R., "Acne Vulgaris: Current Concepts in Pathogenesis and Treatment," *International Journal of Dermatology,* 15:182–187, 1976.

(2) "Stubborn and Vexing, That's Acne," *FDA Consumer,* 14:14–17, 1980.

(3) Cunliffe, W. J., and J. A. Cotterill, "The Acnes: Clinical Features, Pathogenesis and Treatment," W. B. Saunders Co., London, pp. 62, 66–67, 1975.

(4) Pochi, P. E., and J. S. Strauss, "Sebum Production, Casual Sebum Levels, Titratable Acidity of Sebum, and Urinary Fractional 17-Ketosteroid Excretion in Males with Acne," *Journal of Investigative Dermatology,* 43:383–388, 1964.

(5) Burton, J. L., and S. Shuster, "The Relationship Between Seborrhoea and Acne Vulgaris," *British Journal of Dermatology,* 84:600–602, 1971.

(6) Cunliffe, W. J., and S. Shuster, "Pathogenesis of Acne," *Lancet,* 1:685–687, 1969.

(7) Kligman, A. M., and A. G. Katz, "Pathogenesis of Acne Vulgaris. 1. Comedogenic Properties of Human Sebum in the External Ear Canal of the Rabbit," *Archives of Dermatology,* 98:53–57, 1968.

(8) Kligman, A. M., V. R. Wheatley, and O. H. Mills, Jr., "Comedogenicity of Human Sebum," *Archives of Dermatology,* 102:267–275, 1970.

(9) Shalita, A. R., "Acne Vulgaris: Not Curable but Treatable," *Modern Medicine,* 43:66–76, 1975.

(10) Pochi, P. E., et al., "Plasma Testosterone and Estrogen Levels, Urine Testosterone Excretion, and Sebum Production in Males with Acne Vulgaris," *Journal of Clinical Endocrinology and Metabolism,* 25:1660–1664, 1965.

(11) Forstrom, L., et al., "Plasma Testosterone Levels and Acne." *Acta Dermato Venereologica,* 54:369–371, 1974.

(12) Mauvais-Jarvis, P., G. Charransol, and F. Bobas-Masson, "Simultaneous Determination of Urinary Androstanediol and Testosterone as an Evaluation of Human Androgenicity," *Journal of Clinical Endocrinology and Metabolism,* 36:452–459, 1973.

(13) Lee, P. A., "Acne and Serum Androgens During Puberty," *Archives of Dermatology,* 112:482–484, 1976.

(14) Sansone, G., and R. M. Reisner, "Differential Rates of Conversion of Testosterone to Dihydroterstosterone in Acne and in Normal Human Skin—A Possible Pathogenic Factor in Acne," *Journal of Investigative Dermatology,* 56:366–372, 1971.

(15) Marples, R. R., D. T. Downing, and A. M. Kligman, "Control of Free Fatty Acids in Human Surface Lipids by *Corynebacterium Acnes," Journal of Investigative Dermatology,* 56:127–131, 1971.

(16) Mills, O. H., Jr., R. R. Marples, and A. M. Kligman, "Acne Vulgaris. Oral Therapy with Tetracycline and Topical Therapy with Vitamin A," *Archives of Dermatology,* 106:200–203, 1972.

(17) Kligman, A. M., "An Overview of Acne," *Journal of Investigative Dermatology,* 62:268–287, 1974.

(18) Knutson, D. D., "Ultrastructural Observations in Acne Vulgaris: The Normal Sebaceous Follicle and Acne Lesions,"

Journal of Investigative Dermatology, 62:288–307, 1974.

(19) Leyden, J. J., et al., "Propionibacterium Levels in Patients With and Without Acne Vulgaris," *Journal of Investigative Dermatology*, 65:382–384, 1975.

(20) Marples, R. R., and A. M. Kligman, "Ecological Effects of Oral Antibiotics on the Microflora of Human Skin," *Archives of Dermatology*, 103:148–153, 1971.

(21) Puhvel, S. M., et al., "Study of Antibody Levels to *Corynebacterium Acnes*," *Archives to Dermatology*, 90:421–427, 1964.

(22) Puhvel, S. M., and M. Sakamoto, "An In Vivo Evaluation of the Inflammatory Effect of Purified Comedonal Components in Human Skin," *Journal of Investigative Dermatology*, 69:401–406, 1977.

(23) Webster, G. F., et al., "Polymorphonuclear Leukocyte Lysosomal Release in Response to *Propionibacterium Acnes* In Vitro and its Enhancement by Sera from Inflammatory Acne Patients," *Journal of Investigative Dermatology*, 74:398–401, 1980.

(24) Puhvel, S. M., and M. Sakamoto, "The Chemoattractant Properties of Comedonal Components," *Journal of Investigative Dermatology*, 71:324–329, 1978.

(25) Puhvel, S. M., and M. Sakamoto, "Cytotaxin Production by Comedonal Bacteria (*Propionibacterium acnes, Propionibacterium granulosum* and *Staphylococcus epidermidis*)," *Journal of Investigative Dermatology*, 74:36–39, 1980.

E. Classifying the Severity of Acne

The lack of an internationally accepted method of classifying or grading the severity of acne has long been a source of confusion and controversy. For many years, morphologists had classified skin disorders according to the predominant lesion. With acne the lesions included comedones, papules, pustules, and nodules. But simply using these words served little purpose except to indicate the extent of the disease process. Consequently, dermatologists have established many different systems in an attempt to classify acne (Ref. 1). The biggest problem with so many different systems is that data originating in different places cannot be easily compared because the criteria may differ widely (Ref. 2).

One classification system has evolved that grades acne according to the number of lesions. For example, Grade I comedonal acne would be defined as less than 10 comedones on one side of the face (Ref. 2). Acne is often classified by using the terms "mild," "moderate," or "severe." Acne that is primarily comedonal is considered mild; papular and pustular, moderate; and nodular, severe (Ref. 2).

Frank (Ref. 3) classified acne into seven types but using no grading scale. Examples of these types are noninflammatory comedonal acne, inflammatory comedonal acne, and mild papular acne of early adolescence.

Recently a clinical system was devised that uses photographic standards to grade acne on a scale of 0 to 8 (Ref. 4).

Another system, the Pillsbury grading scale, is described here in some detail because it has been widely used by dermatologists. Many studies described later in this document have used this system of classification. Pillsbury (Ref. 5) developed a method of classifying acne by using Roman numerals to grade the severity of the condition. The scale begins with Grade I acne, the mildest type, and ends with Grade IV acne, which is most severe and requires the most aggressive treatment plan. This grading scale is used primarily for acne vulgaris. Other types of acne are generally not graded.

In Grade I acne, comedones are the main lesions with only an occasional small, inflamed pustule. In Grade II acne the inflammatory state becomes more evident. Papules and pustules are more numerous than in Grade I, but the lesions generally remain confined to the face. Grade III acne is a moderately servere acne manifested by numerous small pustules and an occasional larger lesion and usually affects the upper shoulders, back, and chest as well as the face. Grade IV acne is the most severe and is usually called acne conglobata (Ref. 5). (For more details on acne conglobata, see part II. paragraph C.1.b. above—Acne conglobata.)

One problem with Pillsbury's classification is that it does not take into account the number of acne lesions. Most dermatologists would consider a person with hundreds on comedones as having a more severe case of acne compared to an individual with only three or four pustules. Using Pillsbury's classification, the person with the comedones would be considered as having a less severe case of acne. For this reason, other systems of classification have been developed.

Because of the numerous classification systems that have evolved and the various types of lesions present in acne, the Panel believes it is essential that the system used for grading acne in clinical trials be clearly defined.

References

(1) Witkowski, J. A., and L. C. Parish, "Acne: A New Emphasis," *International Journal of Dermatology*, 14:425–426, 1975.

(2) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, pp. 162–163, 1975.

(3) Frank, S. B., "An Update on Acne Vulgaris," *International Journal of Dermatology*, 16:409–412, 1977.

(4) Cook, C., R. L. Centner, and S. E. Michaels, "An Acne Grading Method Using Photographic Standard," *Archives of Dermatology*, 115:571–575, 1979.

(5) Pillsbury, D. M., "A Manual of Dermatology," W. B. Saunders Co., Philadelphia, pp. 173–174, 1971.

F. Treatment of Acne

Acne cannot be cured, but it can be treated successfully. The Panel believes that more than three-fourths of the people suffering from acne can be effectively treated, with visible improvement even in the most severe case. However, treatment may be long and costly in severe cases because many effective medications are available only by prescription and require a physician's supervision. Treatment must be adapted to the individual because no single ideal treatment exists for all types of acne.

Dermatologists generally believe that early treatment can reduce the severity of the disease and, to some degree, also reduce scarring. Nevertheless, many people with severe acne do not see a doctor because they believe there is no satisfactory treatment available or because they cannot afford prescription treatment. Conversely, dermatologists sometimes see patients who are convinced they have acne even though it is barely visible or almost nonexistent.

There is no evidence that any treatment program prevents the onset of acne. However, the Panel believes 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. Clinical studies show that individual papules and pustules will resolve without treatment within 14 days (Refs. 1 and 2). Studies reviewed by the Panel have used a conservative estimate of 4 weeks as the natural resolution time of acne pimples (Ref. 3). Using this estimate, any acne therapy that significantly reduces lesion counts over the first 4 weeks of treatment is effective in treating existing lesions. Any treatment that continues to reduce lesion counts beyond 4 weeks is actually preventing the development of new acne lesions. 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.

The Panel has reviewed several studies showing that both benzoyl peroxide and sulfur reduce lesion counts over 8 to 12 weeks. (See part III. paragraph A.1.a. below—Benzoyl peroxide and part III. paragraph A.1.b. below—Sulfur.) The Panel concludes that any ingredient that is shown to be effective in treating acne, by reducing lesion counts over at least 8 weeks, will

also be effective in preventing the development of new acne lesions.

The effect of both mild and severe acne can be significant. The active lesions and resulting scarring may produce emotional distress and social withdrawal. Adolescents suffering from acne may have a particularly difficult time because they are trying to cope with other physical and emotional changes along with the added problem of acne. Cohen and Nadelson (Ref. 4) wrote the following on this subject.

> Physicians are often perplexed by the adolescent's paradoxical behavior. The child who appears most preoccupied with his skin may manipulate his lesions, disregard sensible personal hygiene, or apply harmful medication, in spite of his physician's instructions. At other times, he may impose on himself ascetic, and equally self-destructive, programs of abstinence from foods, overzealous washing, or overuse of prescribed medication. These extremes are at times related to the normal drives in adolescence, painfully magnified by the skin disease. Also, just as eczema may deflect parental attention from other family problems, the child with acne may use his blemishes as an excuse for avoiding social situations which arouse anxiety.

Some of the various available treatments (OTC and prescription) are as follows:

1. *Topical OTC products.*
   a. Benzoyl peroxide 2.5 to 10 percent.
   b. Salicylic acid 0.5 to 5 percent.
   c. Abrasives—soaps, granules; epidermabrasion—polyester fiber sponges.
   d. Sulfur-resorcinol combinations.
   e. Sulfurated lime topical solution (Vleminckx' solution).
   f. Sulfur 3 to 10 percent.
   g. Povidone-iodine 7.5 percent.
2. *Topical prescription products.*
   a. Benzoyl peroxide 2.5 to 10 percent.
   b. Tretinoin (vitamin A acid) 0.05 to 0.1 percent
   c. Antibiotics—clindamycin, erythromycin, tetracycline.
   d. Aluminum chloride 6.25 percent.
   e. Benzoyl peroxide and sulfur combinations.
3. *Systemic prescription products.*
   a. Antibiotics by mouth (tetracycline, erythromycin, minocycline).
   b. Corticosteroids.
   c. Estrogens.
   d. Investigational drugs, including 13-cis-retinoic acid and cimetidine.
4. *Local therapies.*
   a. Cryotherapy, carbon dioxide solid or slush, liquid nitrogen.
   b. Acne surgery, especially for comedones.
   c. Intralesional steroids for cysts.
   d. Dermabrasion.
   e. Fibrin injections for scars.

References

(1) Kligman, A. M., "An Overview of Acne," *Journal of Investigative Dermatology,* 62:268–287, 1974.

(2) Orentreich, N., and N. P. Durr, "The Natural Evolution of Comedones into Inflammatory Papules and Pustules," *Journal of Investigative Dermatology,* 62:316–320, 1974.

(3) OTC Volume 070280.

(4) Cohen, D. J., and T. Nadelson, "The Impact of Skin Disease on the Person," *in* "Dermatology in General Medicine," McGraw-Hill Book Co., New York, pp. 5–8, 1962.

G. Use of Oral Zinc in the Treatment of Acne

Although oral zinc was not submitted to the Panel for review, the Panel chose to include a discussion of this ingredient because of its increasing popularity and current availability as an OTC medication in pharmacies and health food stores. The Panel did not include oral zinc under the ingredient statements in this document because the Panel's review was officially limited to topical products. However, the Panel considered it appropriate to bring this use of oral zinc to the agency's attention.

Zinc is a trace element with an atomic weight of 65.38; thus zinc sulfate 220 milligrams (mg) corresponds to 50 mg elemental zinc (Zn^{++}). It is an essential nutrient required by animals and humans. The recommended dietary allowance is set at 15 mg and can be supplied by dietary solids containing 25 parts per million (ppm) (Ref. 1).

The rate at which zinc is absorbed from the small intestine is influenced by the level of zinc in the blood. There is a wide margin of safety between the required intake and the toxic dose. Laboratory animals can tolerate up to 2,000 ppm in the diet. Above this level, growth depression and anemia result. The anemia appears to result from an induced copper deficiency, but the growth depression results from reduced food intake (Ref. 2). Toxic levels must be defined cautiously because the levels of other metals greatly influence zinc toxicity. For instance, if copper is present in a limited concentration, zinc is toxic at lower levels. The effects of zinc on copper and iron metabolism can be found in a review of metal toxicities (Ref. 3). Zinc does not appear to accumulate when administered orally (Ref. 2).

The maximum recommended dose for zinc deficiency is 220 mg zinc sulfate three times daily. Nausea may be a problem, but it may be avoided by taking zinc sulfate in capsules after meals (Ref. 4). The emetic dose of zinc sulfate is 1 to 2 grams (g) or 225 to 450 mg zinc. The usual symptoms of toxicity are fever, nausea, vomiting, stomach cramps, and diarrhea (Ref. 2). An adult died from an oral dose of 28 g zinc sulfate (Ref. 5).

Zinc sulfate has been administered therapeutically for leg ulcers and acne in oral doses of 200 mg taken three times daily. This regimen generally caused the serum zinc level to increase by about 25 to 30 percent above the normal range of 70 to 125 micrograms per 100 milliliters (μg/100 mL). The serum level reached a plateau within 10 weeks (Refs. 6 and 7).

A 4-month study of 27 patients (ref. 8) and a 3-month study of 21 patients (Ref. 9) showed no adverse effects from the use of oral zinc. Greaves and Skillen (Ref. 10), however, reported nausea in 3 out of 18 patients in a 4-month study, but hematology studies were normal.

Weimer et al. (Ref. 11) conducted a 12-week study on 28 patients and noted that half of the patients receiving 220 mg zinc sulfate had nausea, vomiting, or diarrhea. Six of these patients could not tolerate the nausea and had to withdraw from the study. In another 12-week study, 5 out of 20 patients reported side effects after treatment with 200 mg zinc sulfate (Ref. 12).

There are reports of gastric bleeding after the ingestion of zinc sulfate monohydrate capsules (Refs. 13 and 14). These studies suggest that the salt form may be an important factor. The studies described earlier, in which no ill effects were reported, used the heptahydrate (citrate) salt dissloved in water (effervescent dosage form) before ingestion.

Zinc oxide ointment has been used extensively without adverse effects (Ref. 2). Considering the poor absorption of metals from the skin, topical use of zinc salts can be considered safe. However, ingesting amounts higher than the recommended dietary allowance may cause adverse effects and should not be encouraged unless supervised by a physician. Furthermore, the consequences of long-term administration of zinc salts are unknown.

Metabolically, zinc is important in many essential enzyme systems, in protein synthesis, and in the stabliization of membranes and macromolecules. Zinc depletion has been observed in malnutrition and malabsorption states. It may also be induced by diets that depend on food grown in soil that is poor in minerals (Ref. 4). In the skin, zinc deficiency has been associated with poor wound healing (Ref. 15), inflammation of the skin of the hands or feet (Ref. 16), and acrodermatitis enteropathica, a severe

gastrointestinal and skin disease of early childhood (Ref. 17). The relationship between acne and zinc deficiency remains uncertain (Ref. 18).

A possible connection between zinc deficiency and acne vulgaris was observed in a patient with acne and acrodermatitis enteropathica. When this patient was treated with oral zinc, the acne cleared "almost completely" (Ref. 19).

Baer et al. (Ref. 20) reported that a zinc depletion diet (0.2 mg elemental zinc daily) in six young men resulted in the development of acne in four of the men. An acute exacerbation of cystic acne developed in one man after 22 days of zinc depletion, when his serum zinc level had decreased from 78 to 28 μg per 100 mL. Most of the acne lesions disappeared within 4 days of restarting 44 mg elemental zinc (as zinc sulfate) in the diet. Milder acne appeared in other subjects who were on the zinc-depletion diet, but whose serum zinc levels remained normal. The researchers believed that serum zinc levels probably did not reflect the tissue zinc levels of these patients in the early stages of zinc depletion.

This echoed the feeling of Fitzherbert (Ref. 21), who postulated that acne might be associated with deficiencies of zinc not detectable in serum, and that plasma zinc levels were "of little use in assessing whether anyone with acne vulgaris can benefit from zinc replacement therapy." Fitzherbert suggested that zinc levels in hair would be a more accurate method of investigating zinc levels in the skin. He also pointed out that zinc deficiency in rats produces abnormal keratinization of skin and hypertrophy of sebaceous gland cells, causing the sebaceous glands to become more prominent. He further postulated that reversal of these histopathological changes might require administration of daily zinc over periods of 3 to 4 months or longer (Ref. 22). Fitzherbert suggested a dosage of zinc sulfate of 100 mg/day to be taken by teenagers at night, to meet their daily requirement of zinc (Ref. 23).

Several double-blind, controlled studies comparing oral zinc to other medications in the treatment of acne have had conflicting results. Michaelsson, Juhlin, and Ljunghall (Ref. 24) compared oral zinc sulfate 200 mg with oral tetracycline, a well-accepted drug in the treatment of acne, in a 12-week study. No difference was seen between the two drugs in 37 patients with moderate and severe acne. The acne score of each group of patients decreased an average of 70 percent. Serum zinc levels were measured before treatment and after 12 weeks of treatment. There was no correlation between serum zinc levels and clinical response. Although the investigators felt that zinc was more effective than oral tetracycline in treating papular and pustular acne and less effective on comedones, this was not confirmed statistically.

In 64 patients, the same group of investigators also compared the effects of effervescent tablets of zinc sulfate 200 mg three times daily, with placebo, vitamin A 300,000 to 400,000 International Units per day (I.U./day), or a combination of the same doses of zinc and vitamin A (Ref. 19).

After 12 weeks of treatment the total "acne score" in patients treated with zinc was reduced from 100 percent to 13 percent. The pustules and papules had disappeared in most patients after 8 to 12 weeks, and comedones had decreased to 44 percent. The improvement was about the same in patients given zinc and vitamin A. After only 4 weeks of treatment, the two groups receiving zinc showed a mean decrease of 100 percent to 35 percent, but the placebo and vitamin A groups only decreased from 100 percent to 75 percent and 70 percent, respectively. Then zinc was added to the treatment of all but two patients in both the placebo and vitamin A groups. The researchers switched the medication for "ethical" reasons, based on their belief that most patients' acne improved within 4 weeks and that they could not justify placebo treatment for longer than 4 weeks. Their study was later criticized for this position (Ref. 25). The authors concluded that the effect of zinc plus vitamin A was no better than treatment with zinc alone (Ref. 19).

Goransson, Liden, and Odsell (Ref. 26) conducted a randomized, double-blind investigation of 200 mg oral zinc sulfate three times daily versus effervescent placebo tablets in 54 patients with acne. The trial was performed between October and the end of April to minimize natural ultraviolet radiation and included a 6-week active treatment period. Patients were examined and photographed before treatment, after 3 weeks of treatment, and again 6 weeks after treatment. Each type of lesion was counted and multiplied by a "severity index," so that the sums of all lesion types yielded a score of overall "acne load." After both zinc and placebo treatment, a statistically significant reduction in numbers of lesions was evident. Lesion reduction continued during both the first and second 3-week treatment periods in the zinc treatment group, but no statistically significant reduction occurred in the placebo group after the first 3 weeks of treatment. Zinc sulfate therapy was statistically significantly better than placebo, when patients showing 25 percent improvement were compared ($p<0.01$). No statistically significant difference was found when the patients in each group who showed 50 percent improvement were compared.

Overall, the authors concluded that the acne improved "about one-third" after 6 weeks of treatment with zinc. They speculated that the treatment period was probably not long enough to see the full effect of zinc therapy, and that a trial period of 3 months would have been more desirable. According to Fitzherbert (Ref. 23), even 12 weeks is too short a time to see maximal biological changes induced by zinc, as structural changes in the swollen hypertrophic cells of sebaceous glands are only slowly reversed.

A randomized, double-blind trial of 39 patients showed that zinc was not superior to placebo in the treatment of acne (Ref. 12). Patients with papular and pustular acne were given either oral zinc sulfate effervescent tablets 200 mg three times daily or placebo effervescent tablets. Only 25 patients were treated for 12 weeks; the remaining 14 were treated for either 4 or 8 weeks. There was a significant reduction in papules and pustules in both groups, but no statistically significant difference between the groups. Serum zinc levels, which were originally normal in both groups, rose considerably in both groups, although the increase in the zinc group was significantly higher than the placebo group. The researchers thought that the increased zinc levels were possibly caused by seasonal variations in zinc metabolism. They concluded that the negative therapeutic results might have been attributed to the small number of patients or to natural seasonal improvement in acne, as the study was conducted in the spring.

Another double-blind study compared zinc sulfate monohydrate capusles (137 mg three times daily) to placebo (Ref. 7). The use of the monohydrate salt was unique to this study and accounts for the lower dosage. Twelve patients were included in the active treatment group and 10 patients in the placebo group. Patients were evaluated by lesion counts. After 8 weeks of treatment, both groups had decreases in the mean values of papules, pustules, and closed comedones; open comedones remained about the same in the zinc group. No statistically significant differences were seen between the groups in any type of acne lesion. Positive zinc absorption was well documented by rises in zinc levels in serum and urine. The

investigators speculated that the divergent results in their study might have reflected differences in characteristics of their patient population.

In a randomized, double-blind trial involving 40 patients, zinc sulfate capsules (220 mg three times daily) were compared with placebo (Ref. 11). During the 12-week treatment period, patients were seen at 0, 2, 4, 6, 8, and 12 weeks and evaluated with lesion counts. After 12 weeks there was a 37-percent decrease in the pustule counts of the group receiving zinc compared to no change in the placebo group. Comedones and papules decreased 47 percent in the zinc group compared to 37 to 38 percent in the placebo group. This difference was not significant. The researchers concluded that zinc "Appeared to have a slightly beneficial effect on pustules after at least 6 weeks of treatment" but was not helpful for comedones or papules.

From these studies zinc appears to be valuable in the treatment of papular and pustular acne. However, the Panel is concerned that there seems to be unexplained wide variation in the results of double-blind studies with zinc conducted in different geographical areas. Investigators in Sweden believe that zinc is valuable in the treatment of acne (Refs. 19, 24, and 26), but investigators in Denmark (Ref. 12) and the United States (Refs. 7 and 11) remain unconvinced of its efficacy. In general, the Swedish studies, done by three different groups of investigators, involved larger numbers of patients than the other studies and the use of an effervescent dosage form. These patients, because they had fewer gastrointestinal side effects, also appeared to tolerate the zinc better than other groups of patients. The contrasting results between studies from various countries suggest to the Panel that environmental factors such as seasonal variation in ultraviolet light exposure, the amount of zinc in the natural diet, and the dosage form may have influenced the studies.

The Panel concludes that more double-blind, controlled trials could be useful in establishing the effectiveness of zinc sulfate in treating acne. As stated earlier, the Panel is not recommending the OTC use of oral zinc in the treatment of acne, but has included it in this document only for discussion.

References

(1) National Nutrition Consortium, Inc., "Vitamin-Mineral Safety, Toxicity, and Misue," The American Dietetic Association, Chicago, pp. 34–35, 1978.

(2) Van Reen, R., "Zinc Toxicity in Man and Experimental Species," *in* "Zinc Metabolism," Edited by A. S. Prasad, Charles C. Thomas, Springfield, IL, pp. 411–425, 1966.

(3) Bremner, I., "Heavy Metal Toxicities," *Quarterly Reviews of Biophysics,* 7:75–124, 1974.

(4) Hartoma, R., "Zinc Deficiency—A Disease With Diverse Symptoms," *International Medicine,* 1:9–11, 1979.

(5) Cowan, G. A. B., "Unusual Case of Poisoning by Zinc Sulphate," *British Medical Journal,* 1:451–452, 1947.

(6) Halsted, J. A., J. C. Smith, Jr., and M. I. Irwin, "A Conspectus of Research on Zinc Requirements of Man," *Journal of Nutrition,* 104:347–378, 1974.

(7) Orris, L., et al., "Oral Zinc Therapy of Acne. Absorption and Clinical Effect," *Archives of Dermatology,* 114:1018–1020, 1978.

(8) Hallbook, T., and E. Lanner, "Serum Zinc and Healing of Venous Leg Ulcers," *Lancet,* 2:780–782, 1972.

(9) Vahlquist, A., G. Michaelsson, and L. Juhlin, "Acne Treatment with Oral Zinc and Vitamin A: Effects on the Serum Levels of Zinc and Retinol Binding Protein (RPB)," *Acta Dermato Venereologica,* 58:437–442, 1978.

(10) Greaves, M. W., and A. W. Skillen, "Effects of Long-Continued Ingestion of Zinc Sulfate in Patients with Venous Leg Ulceration," *Lancet,* 2:889–891, 1970.

(11) Weimar, V. M., et al., "Zinc Sulfate in Acne Vulgaris," *Archives of Dermatology,* 114:1776–1778, 1978.

(12) Weismann, K., S. Wadskov, and J. Sondergaard, "Oral Zinc Sulphate Therapy for Acne Vulgaris," *Acta Dermato Venereologica,* 57:357–360, 1977.

(13) Cunliffe, W. J., "Unacceptable Side-Effects of Oral Zinc Sulphate in the Treatment of Acne Vulgaris," *British Journal of Dermatology,* 101:363, 1979.

(14) Moore, R., "Bleeding Gastric Erosion after Oral Zinc Sulphate," *British Medical Journal,* 1:754, 1978.

(15) Pories, W. J., et al., "Acceleration of Healing with Zinc Sulfate," *Annals of Surgery,* 165:432–436, 1967.

(16) Weismann, K., et al., "Acquired Zinc Deficiency Dermatosis in Man," *Archives of Dermatology,* 114:1509–1511, 1978.

(17) Moynahan, E. J., "Acrodermatitis Enteropathica: A Lethal Inherited Human Zinc-Deficiency Disorder," *Lancet,* 1:399–400, 1974.

(18) "Zinc Again," unsigned editorial, *British Medical Journal,* 1:1493, 1977.

(19) Michaelsson, G., L. Juhlin, and A. Vahlquist, "Effects of Oral Zinc and Vitamin A in Acne," *Archives of Dermatology,* 113:31–36, 1977.

(20) Baer, M. T., et al., "Acne in Zinc Deficiency," *Archives of Dermatology,* 114:1093, 1978.

(21) Fitzherbert, J. C., "Acne Vulgaris—Zinc Deficiency?", *Medical Journal of Australia,* 2:273, 1976.

(22) Fitzherbert, J. C., "Acne Vulgaris—Zinc Deficiency?", *Medical Journal of Australia,* 1:848, 1976.

(23) Fitzherbert, J. C., "Zinc Deficiency in Acne Vulgaris," *Medical Journal of Australia,* 2:685–686, 1977.

(24) Michaelsson, G. L. Juhlin, and K. Ljunghall, "A Double-Blind Study of the Effect of Zinc and Oxytetracycline in Acne Vulgaris," *British Journal of Dermatology,* 97:561–566, 1977.

(25) Glover, S. C., and M. I. White, "Zinc Again," *British Medical Journal,* 2:640–641, 1977.

(26) Goransson, K., S. Liden, and L. Odsell, "Oral Zinc in Acne Vulgaris: A Clinical and Methodological Study," *Acta Dermato Venereologica,* 58:443–448, 1978.

H. Abrasive Scrubs

The Panel realizes that some consumers may prefer acne products that are formulated as abrasive scrubs. For this reason, even though the Panel believes it unlikely that superficial epidermabrasion will remove the tightly adherent comedo, the Panel has included the following discussion on physical abradents.

Saperstein (Ref. 1) reported on a 10-year study of 1,000 acne patients who were treated with abrasives along with other forms of topical and systemic treatment for acne. Saperstein found that fused synthetic aluminum oxide in a soap paste was the most effective abradent of all that were tested. However, no lesion counts were included in this report. According to this researcher, the purpose of epidermabrasion is to keep the sebum washed off the skin and to keep the pores open. Saperstein noted that during this treatment the patients stopped picking and squeezing their acne lesions, "for the abrasion routine apparently replaces the emotional need to scrutinize and express each lesion."

Mills and Kligman (Ref. 2) also studied abrasives for the treatment of acne. They wrote that abrasives "are popular with patients, possibly because the patient is lead (sic) to believe that conscientious scrubbing will clean out 'clogged pores' and that his deliverance is therefore in his own hands." These researchers studied five abradents including one containing aluminum oxide and one containing polyethylene granules to see whether they were effective in helping to remove comedones. Each test group consisted of 10 patients with "moderate acne and conspicuous comedones." Treatment was twice daily for 8 weeks; no other medication was used during this time. Global clinical assessments were done biweekly. Lesion counts were taken before the study and at the end of the study. Mills and Kligman found that "none of the test materials had a clinically significant effect in eliminating comedones." Open comedones were reduced no more than 20 percent; closed comedones were not reduced at all.

Early in the study, all of the treatments reduced the number of papules and pustules to some extent, but in some patients the reduction was followed by an increase in the number of papules and pustules.

Mills and Kligman (Ref. 2) concluded that there was no evidence showing that abradents could effectively remove comedones. They stated that, because skin affected by acne is vulnerable to chemical and physical trauma, they "do not advise the use of abradents as adjuncts in acne treatment."

An unpublished report discussed a half-face study in which 53 subjects were treated either with a combination of polyethylene, 2 percent sulfur, and 1.5 percent salicylic acid or a combination of sulfur and salicylic acid without polyethylene (Ref. 3). Both treatments significantly decreased open comedones, closed comedones, and papules. However, neither formulation decreased pustules significantly over baseline. There was no difference in the results between the combination with polyethylene and the one without polyethylene.

The Panel concludes that aluminum oxide and polyethylene do not have an effect on acne lesions and therefore considers them inactive ingredients.

References

(1) Saperstein, R. B., "Treatment of Acne with Long-Term Continuous Graded Abrasion," *Archives of Dermatology*, 81:601, 1960.

(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.

(3) OTC Volume 070268.

I. Evaluation of Safety and Effectiveness

1. *Criteria for evaluating safety.* The Panel has developed flexible criteria for assessing the safety of the many chemical agents used in acne treatment products. This flexibility was needed to accommodate the differences between chemical agents. It should be noted that although some data did not meet all of these criteria, the Panel considered other assessments adequate to allow a safety evaluation for a particular ingredient. Some products had been marketed long before this review began. The Panel's evaluation in those instances was based on limited historical data, new data obtained from various sources, and the Panel's own knowledge and judgment.

Influencing factors in the data assessment were the surface area and the site of application, the frequency and length of application, and the vehicle. The degree of occlusion from clothing was also considered because acne may affect the upper torso as well as the face. The Panel also recognizes that because of acne the stratum corneum may not be intact and inflammation may be severe. These conditions could greatly influence the degree of absorption through the skin.

To avoid needless repetition, these safety evaluation criteria are detailed later in this document. (See part III. paragraph E.1. below—Safety guidelines.)

After the Panel evaluated the safety of an ingredient, it placed that ingredient in Category I, II, or III. When an ingredient was classified Category III for safety, the Panel concluded that the data base was inadequate to fully assess safety. In these cases the safety guidelines discussed below could be used by a manufacturer to move an ingredient from Category III to Category I by generating data where there are none or where existing data are inadequate.

The actual criteria for the movement to Category I are obviously judgmental and have to be examined in their totality. Although in such cases a benefit-to-risk concept may seem desirable, the Panel attempted to assess safety per se rather than by benefit-to-risk.

The Panel is concerned about the safety of certain ingredients or combinations of ingredients when the single ingredient or combination product has a keratolytic or "peeling" effect on the skin. It has long been known that the stratum corneum protects underlying skin areas against irritants and damage from ultraviolet radiation. Research on the effect of reducing the thickness of the stratum corneum by the use of keratolytic agents has not resolved the Panel's concerns, particularly on absorption, irritation, sensitization, or the possibility of carcinoma from exposure to ultraviolet light.

2. *Criteria for evaluating effectiveness.* The Panel required each ingredient to have at least one well-designed clinical trial demonstrating its effectiveness in the treatment of acne in order to be classified as Category I. In evaluating data, the Panel also considered the study design and how it conformed to the following description of a well-designed trial.

The trial should be a multi-center study involving more than one investigator using the same protocol in different geographic locations, thus helping to eliminate geographic influence and investigator bias. The trial should be double-blind, i.e., the investigators and patients should not know the identity of the drugs. The drugs should be randomly assigned. The trial should also be controlled, with the control being the vehicle minus the active ingredient or ingredients. The vehicle may be modified or altered if needed to ensure blinding. No additional treatment other than soap and water should be allowed. The investigators should state which calendar months were included in the study because acne lesions generally clear up somewhat in the summer. A well-designed study should last at least 8 to 12 weeks. Patients should be evaluated once before treatment and at least twice during the study, including the final examination.

The Panel preferred lesion counts, grouped by type of lesion, as a method of evaluating acne ingredients. A lesion count is usually taken before treatment, during treatment, and after treatment. The final results show the percentage of reduction in the number of each type of lesion after treatment, compared to before treatment. Global assessments were also considered acceptable as long as they were on a numbered scale (such as 1 to 6) with a rigidly defined numerical system that could be reliably reproduced.

Active ingredients should be significantly more effective in reducing lesion count than the vehicle. Results should be statistically analyzed.

Studies that showed a statistically significant decrease in free fatty acid content or sebum excretion rate as proof of effectiveness were not acceptable as sole evidence of effectiveness. Studies in induced or experimental acne were similarly not considered as proof of effectiveness. The Panel did not evaluate adjunctive therapies. An ingredient was not considered unless it actually treated acne, i.e., actually reduced lesion count. The Panel did not consider ingredients that reduce inflammation but do not act on the comedone, such as, topical steroids.

If a clinical trial did not meet all of the Panel's criteria, some other supporting evidence was necessary to place an ingredient in Category I. However, the Panel did not intend to be too rigid in setting up criteria for proof of effectiveness. The Panel recognized that not all studies would meet each criterion for a single "best study." Each submission and ingredient was analyzed according to the above criteria, but the final categorization depended upon the total information available at the time.

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 the consultant "acne experts," and no supportive evidence of effectiveness in

the medical literature on acne. All of these factors were considered in the Panel's decision on final categorization. The ultimate decision did not rest on any single one of them but on the Panel's general recognition of effectiveness of the ingredient.

3. *Vehicles.* The Panel believes that a proper vehicle is one that will deliver the drug to the site of action at a rate that will allow maximum benefit without causing or allowing toxic effects. However, the Panel recognizes that choosing an appropriate vehicle for adquate drug delivery without contributing to the whole acne problem can be quite difficult. Many drug delivery systems are used today in OTC preparations, ranging from solutions, gels, lotions, and creams, to solid sticks, mascara-like creams, and cosmetic touch-up type formulations. The Panel was unable to accurately assess the influence of such a variety of vehicles on the effectiveness of the therapeutic ingredient.

III. Acne Drug Products

A. Category I Conditions

These are conditions under which OTC acne drug products are generally recognized as safe and effective and are not misbranded. The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

1. *Category I active ingredients.*

Benzoyl peroxide
Sulfur

a. *Benzoyl peroxide.* The Panel concludes that benzoyl peroxide is safe and effective for OTC topical use in the treatment of acne.

(1) *Safety.* The stability of a given preparation of benzoyl peroxide is especially dependent upon the vehicle (Ref. 1). The potential for irritation or other toxic manifestations are undoubtedly affected by stability.

The intraperitoneal LD_{50} of benzoyl peroxide in mice has been reported to be from 75 to 210 milligrams per kilogram (mg/kg) (Refs. 2 through 5). Because most deaths following intraperitoneal administration occur after 24 hours, it is important to note that the 75-mg/kg value was calculated after a 7-day observation (Ref. 2). Several factors may account for differences in the LD_{50} values reported, including vehicle, the length of observation, and the strain of mouse. One study reported the intraperitoneal LD_{50} in mice as 17.1 plus or minus 2.1 micromoles (μmol) or 180 mg/kg per mouse. According to this study, 26 μmol per mouse will result in 100 percent mortality (Ref. 4).

Although benzoyl peroxide is much less toxic orally than intraperitoneally, death occurs faster by the oral route following a lethal dose. To illustrate, the oral LD_{50} in mice in one study was reported as 2,127 mg/kg, but a lethal oral dose caused central nervous system depression and death within hours (Ref. 5). Following oral administration to Swiss mice (7-day observation), an LD_{50} or 1.4 g/kg was calculated (Ref. 6). The animals were lethargic and prostrate, and exhibited labored respiration prior to death.

In another study a lotion containing 10 percent benzoyl peroxide was administered orally to male rats at a dose of 3 g/kg. During the following 2-week observation period there were no deaths. No effects on appearance, behavior, or weight gain were noted (Ref. 6). In rats the LD_{50} is reported as 373 mg/kg intraperitoneally and 6,400 mg/kg orally (Ref. 5).

The difference in intraperitoneal versus oral LD_{50} values suggests that orally administered benzoyl peroxide is not readily absorbed. In fact, the cause of death could be due to the metabolite benzoic acid because the oral LD_{50}'s of the two compounds are nearly identical in the mouse. There is, however, indirect evidence to suggest that benzoyl peroxide can be absorbed by the gut. Oral administration in mice produces central nervous system depression (Ref. 5), which is not characteristic of benzoic acid.

There is some evidence that benzoyl peroxide can be absorbed following dermal application to guinea pigs. When benzoyl peroxide was applied to the shaved backs of guinea pigs at doses up to 1 g/kg and occluded for 24 hours, a dose-related weight loss was observed (Ref. 7). This was probably an effect of the metabolite rather than the parent compound.

Holzmann, Morsches, and Benes (Ref. 8) reported the plasma levels at benzoic acid in 20 patients on benzoyl peroxide therapy. The level peaked 3 days after application of 20 percent benzoyl peroxide lotion and was never higher than 610 micrograms per liter (μg/L). These investigators measured benzoic acid on the assumption that benzoyl peroxide itself does not penetrate the skin.

Two other studies also suggest that benzoyl peroxide does not penetrate the skin. One study consisted of applying benzoyl peroxide to human forearms, waiting 4 hours, then washing the arm with chloroform. Both benzoyl peroxide and benzoic acid were recovered in the chloroform wash in a ratio of 1.5 to 1, indicating conversion to benzoic acid(Ref. 9).

Nacht et al. (Refs. 10 and 11) reported on an in vitro study in which excised human skin was used to measure penetration of C^{14}-benzoyl peroxide. After 8 hours, 1.9 percent of the labeled drug was recovered as benzoic acid on the dermal side. Extraction from the skin itself yielded 2.6 percent of the labeled drug, half benzoyl peroxide and half benzoic acid.

These investigators also applied C^{14}-benzoyl peroxide to the forearms of monkeys and measured radioactivity in the urine. The output peaked between 6 and 30 hours. Forty-five percent of the administered dose was recovered, 98 percent of which was benzoate. Nacht et al. (Ref. 11) concluded that benzoyl peroxide penetrates the skin layers where it is converted to benzoic acid and then absorbed into the systemic circulation. They also concluded that benzoic acid was quickly eliminated through the kidneys without passing through the liver. In the liver, benzoic acid would have conjugated with glycine and formed hippuric acid, but no hippuric acid was recovered in the urine.

In a subchronic study in rats, benzoyl peroxide was administered intragastrically five times weekly for 3 months (Ref. 2). Two control groups of 10 animals, male and female, were used. One group was given the vehicle, 0.1 percent polysorbate 80; the other group was given 2 g/kg benzoic acid. Two other groups were treated with benzoyl peroxide. These groups consisted of 40 animals each, male and female, dosed with either 0.5 or 2 g/kg benzoyl peroxide. The benzoic acid-treated group was removed from the study after 1 week because most of the group developed aspiration pneumonia. During the experiment a hematologic evaluation was done monthly. Gross and histological examination of tissues was done at the end of 3 months.

The following signs were observed near the end of the experiment in the group that was given 2 g/kg benzoyl peroxide: poor appetite, weakness, weight loss (prominent in males), urinary incontinence, intermittent irritability, and transient twisting of the muscles. One striking patholgical change was bladder distension due to blockage of the urinary passage by cartilaginous material. Localized lymphangitis (inflammation of the lymph vessels) of the salivary gland was also noted. The urinary effect was most frequent in the high dose group, whereas the lymphagitis occurred in the control group as well. In the high dose group,

tubular destruction was noted in the kidneys.

Feeding studies were conducted in mice, rats, and dogs (Ref. 12 and 13). These studies used flour treated with benzoyl peroxide and are of little value, because benzoyl peroxide is converted to benzoic acid in flour (Ref. 12).

Benzoyl peroxide is not considered to be carcinogen (a cancer-producing substance). In one study in rats and mice, benzoyl peroxide was given orally, painted on the skin, or injected subcutaneously without evidence of carcinogenicity (Ref. 12). In another study, Swiss mice painted three times weekly with 100 mg benzoyl peroxide did not have a tumor index greater than the controls which had been painted with a solvent (Ref. 14). A report by Heuper (Ref. 15) further supports benzoyl peroxide's lack of carcinogencity.

Benzoyl peroxide was found to be negative in the dominant lethal assay in the mouse when tested at 62 mg/kg intraperitoneally (Ref. 16). The dominant lethal assay is a frequently used method of testing the effect of a chemical substance on spermatogenesis (the maturation of sperm). In another study, benzoyl peroxide was extensively screened for mutagenicity (Ref. 17). The screen consisted of three *Salmonella* mutants and one strain of yeast and was carried out with and without metabolic activation systems. A 0.37-percent concentration of benzoyl peroxide, the highest dose used in the mutagenicity tests, gave 50 percent survival of the test organisms. Results were clearly negative in all tested strains.

A number of subchronic studies have been conducted in rabbits using dermal application of benzoyl peroxide. In one of these, a 10-percent benzoyl peroxide gel was applied to the ears of four rabbits five times weekly for 2 weeks (Ref. 1). The observed irritation in the animals consisted of desquamation and erythema. None of the animals was visibly sick.

A 30-day controlled study was conducted on 16 rabbits, divided into two groups of 8 rabbits each (Ref. 18). The skin was abraded in four rabbits in each group. A lotion containing 5 percent benzoyl peroxide was applied to one group of rabbits five times weekly. The area of application was about 10 percent of the total body surface. Based on the information that 4 to 5 g of lotion was applied, the calculated dose averaged 98 mg/kg. No effects could be detected on body weight, hematology, organ weight, gross pathology, or histopathology. One treated rabbit died from respiratory infection before the end of the study.

A similar study was conducted for 43 days with both 5 and 10 percent benzoyl peroxide lotion (Ref. 6). A group consisted of five rabbits with half of the shaved area abraded on each animal. Based on estimated application, the two test doses were 120 and 240 mg/kg. No effects of benzoyl peroxide were detected other than some reddening of the skin, particularly following application of the 10-percent lotion.

A 12-week study using an ointment containing 10 percent benzoyl peroxide was conducted on rabbits of both sexes (Ref. 2). No adverse effects were noted. Another report contains results of a 3-month study in which 1.9 g of ointment was applied to rabbits five times a week (83 mg/kg estimated dose). The only adverse effect was a slight reddening of the skin during the first few weeks which lessened as the study progressed.

Primary skin irritation was assessed by patch tests on intact and abraded rabbit skin (Ref. 6). The exposure period was 4 hours, after which the reaction was graded immediately and at 24 and 48 hours. Slight erythema was noted only at 4 hours on 5 of 12 sites with 10 percent benzoyl peroxide and 3 of 12 sites with 5 percent benzoyl peroxide. Application of 5 or 10 percent benzoyl peroxide to rabbit eyes produced only a mild, transient erythema (Refs. 6 and 18).

Some irritation occurs when benzoyl peroxide is applied to human skin. This consists of mild burning and itching in most subjects and moderate drying and peeling in all subjects (Refs. 1, 2, and 18).

Complete hematological studies and urinalysis were conducted on 20 out of 147 patients following topical therapy with 5.5 percent benzoyl peroxide (Ref. 19). Results showed no evidence of systemic effects. Also, no sign of sensitivity was noted in any of the 147 patients treated with benzoyl peroxide.

The Panel is particularly interested in the cutaneous toxicity (irrigation and contact sensitization) of benzoyl peroxide on human skin. This is important because the effectiveness of benzoyl peroxide is partly due to its mild peeling action on the skin during the early phase of treatment, and peeling may enhance irritation and sensitization.

The sensitization of the skin to this ingredient is well known among physicians (Ref. 20). Sensitization may be related to the genetic makeup of the individual. Certain types of complexion are highly sensitive to environmental factors as well as topical drugs. People who have an atopic background (an inherited tendencey to develop allergy) and who have allergies will be more easily irritated by certain topical preparations. In general, the concentration of the medicine, the vehicle, and the degree of occlusion should be considered in determining sensitization rates. The skin type, individual immunologic background, and other variables should also be considered.

Repeated patch tests with benzoyl peroxide may produce an experimental contact dermatitis (Ref. 21). However, in clinical use sensitization is low, usually between 1 and 2 percent of users (Ref. 22).

Benzoyl peroxide will produce a primary irritant dermatitis in a person with sensitive skin. Light-complexioned individuals may be easily irritated by a benzoyl peroxide preparation as well as other medications. Skin dryness also makes skin vulnerable to irritations. It is well known to the Panel that skin type (ruddy compared with olive) relates to the ease with which the skin is irritated.

There is evidence that the higher the concentration of benzoyl peroxide, the greater the irritation. For that reason, ideally the lowest effective concentration of benzoyl peroxide should be used in the management of acne.

The Panel appreciates that an increase in concentration and the use of drying vehicles may produce more irritation and desquamation in some people but does not believe this represents a substantial hazard. The Panel concludes that benzoyl peroxide in concentrations of 2.5 to 10 percent is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Benzoyl peroxide has antimicrobial properties attributed to its capacity to slowly release oxygen. The oxygen acts on certain kinds of bacteria, called anaerobes, which do not live in its presence. *P. acnes* is an anaerobic bacteria.

Another action of benzoyl peroxide is as an exfoliant, i.e., it causes peeling of the outer layers of the skin. Benzoyl peroxide is formed by the reaction of alkaline sodium hydrogen peroxide with benzoyl chloride in water. Benzoyl peroxide has been used since the 1920's for ulcers and burns. Concentrations of benzoyl peroxide in submissions reviewed by the Panel ranged from 2.5 to 10 percent.

The mechanism of action of benzoyl peroxide was studied by using a 5-percent benzoyl peroxide gel applied twice daily. This preparation was associated with a significant depression of the surface bacterial count and a decrease in the concentration of fatty acid formation. The researchers

theorized that the antibacterial activity of benzoyl peroxide reduced the population of *C. acnes (P. acnes)* with a subsequent decrease in free fatty acids. The investigators also believed that benzoyl peroxide is a mild keratolytic, but this was not firmly established (Ref. 23). Although benzoyl peroxide has antibacterial activity, none of the antibacterial studies on this ingredient have met the Panel's in vivo criteria. (See part III. paragraph E.2.c. below—In vivo testing of acne ingredients.)

Vasarinsh (Ref. 24) studied the effects of 5 percent and 10 percent benzoyl peroxide lotions on epidermis and dermis. He was unable to find any microscopic epidermal changes when there was no peeling. Biopsies showed that dermal changes, however, were common in all patients regardless of whether they had clinical signs of erythema and desquamation. These changes mainly consisted of mild dilatation (expansion) of the blood vessels in the upper portions of the dermis and lymphocytes (white blood cells) surrounding the blood vessels, the hair follicles, and the small lobules of the sebaceous glands. Vasarinsh was unable to quantify any keratolytic effect.

Ede (Ref. 19) studied the effectiveness of 5.5 percent benzoyl peroxide in a randomized, controlled, double-blind trial of 196 patients. Patients who entered the study had Grade II or III acne (system of classification unspecified). Four treatment groups were used. One group consisted of 48 patients treated with 5.5 pecent benzoyl peroxide. Another group consisted of 54 patients treated with 5.5 percent benzoyl peroxide-0.25 percent chlorhyaroxyquinoline. In the third group, 45 patients were treated with 5.5 percent benzoyl peroxide-0.25 percent chlorhyaroxyquinoline-0.5 percent hydrocortisone. In the fourth group, 49 patients were treated with the vehicle as a control.

Frequency of application varied from one to four times daily depending upon "therapeutic response and upon the extent of skin peeling and erythema." At least one of the daily applications was made under direct medical supervision. The patients used soap before each application, but no other therapy was allowed. They were evaluated by lesion counts at 0, 14, and 28 days. Statistical analysis showed no statistically significant differences in the number of patients in the groups or in the distribution of patients with regard to sex, age, complexion, skin type (normal, dry, oily), pores, (normal or enlarged), grade of acne, or frequency of application.

After 4 weeks of treatment, the lesion count of patients treated with benzoyl peroxide alone decreased from 10.5 to 6.6. The count increased in the vehicle group from 10.4 to 11.1. Statistical analysis of results showed that all three active treatments were significantly more effective than the vehicle in reducing lesion counts at 2 and 4 weeks ($p<0.001$).

Clinical evaluation showed that 65 percent of the patients treated with benzoyl peroxide improved; 29 percent remained the same; and 6 percent were worse. In the vehicle group, 33 percent improved; 37 percent were the same; and 30 percent became worse. Benzoyl peroxide (along and in combination) was found to be significantly more effective than vehicle when overall clinical response was evaluated.

In another double-blind, controlled, randomized study, 28 patients were treated with 5 percent benzoyl peroxide lotion, and 27 patients were treated with the vehicle used as a control (Ref. 25). Patients entered the study only if they had Grade II or III acne based on Pillsbury's classification (Ref. 26). Patients were treated two or three times daily depending upon the evaluator's initial appraisal of the severity of the acne. Comparison of the makeup of the groups showed no significant differences between age, sex, frequency of therapy, or severity of acne.

Patients were evaluated by lesion counts and global impressions before treatment and after 6 weeks of treatment. The benzoyl peroxide group had a 39.7-percent improvement in lesion counts compared to 7.7 percent improvement for the vehicle group. This difference was statistically significant ($p<0.001$). The investigator rated 68 percent of the patients treated with benzoyl peroxide as excellent or good, 18 percent fair, and 14 percent poor at the conclusion of the study. In the vehicle group, no patients were rated as excellent or good; 30 percent were considered fair; and 70 percent poor. The investigator found treatment with benzoyl peroxide superior to vehicle when evaluated by global impression ($p<0.001$).

Another randomized, controlled, and double-blind study was done on 92 patients to determine the effectiveness of benzoyl peroxide (Ref. 27). Patients were treated twice daily with either 5 percent benzoyl peroxide, 3 percent sulfur, a combination of 10 percent benzoyl peroxide and 3 percent sulfur, or vehicle. Soap and water was the only other treatment allowed. Treatment lasted 12 weeks. Patients were evaluated by lesion counts and clinical impression.

Patients were given a satisfactory rating if continued improvement in lesion counts was noted over 12 weeks or if they were discharged in less than 12 weeks with greater than 50 percent improvement in lesion counts. In the benzoyl peroxide group, 41.7 percent (10 patients) were satisfactory and 58 percent (14 patients) were unsatisfactory at the end of the treatment period. Ten percent of the vehicle group (20 patients total) were rated satisfactory and 90 percent unsatisfactory. For the benzoyl peroxide-treated patients rated as satisfactory, treatment averaged 6.8 weeks with a decrease in lesion count of 71.2 percent.

Good and excellent results in clinical impressions were seen in 58.3 percent of patients treated with the benzoyl peroxide-sulfur combination; 41.7 percent of the benzoyl peroxide group; 29.1 percent of the sulfur group; and 10 percent of the vehicle group.

Although a statistical analysis of results was not presented, the researchers stated that the three active preparations were "demonstrably more effective than the placebo." They also stated that the 5-percent benzoyl peroxide treatment "produced the greatest improvement of acne symptoms in the shortest period of time," but that the benzoyl peroxide-sulfur combination "proved somewhat better than the other formulae."

Two unpublished, randomized, double-blind trials comparing 5 and 10 percent benzoyl peroxide followed nearly identical protocols (Refs. 26 and 28). Each treatment group contained 25 patients with Grade II or III acne (Pillsbury classification). The patients had had no systemic therapy for 1 month before entering the study and no topical therapy for 2 weeks. Each patient was treated one to three times daily, depending upon the severity of acne and tolerance to benzoyl peroxide. No vehicle controls were used. The patients were evaluated by lesion counts and global impression when the study began and at intervals of 2 to 4 weeks for the next 12 weeks. The results were expressed as follows: excellent was 75 to 100 percent improvement; good was 50 to 75 percent improvement; fair was 25 to 50 percent improvement; poor was less than 25 percent improvement.

In one study, good to excellent results were reported in 36 percent of the patients who had used 5 percent benzoyl peroxide and 56 percent of the patients who had used the 10-percent

lotion. The second study showed good to excellent results in 54 percent of the group treated with 5 percent benzoyl peroxide and in 72 percent of the group treated with 10 percent benzoyl peroxide. This report also gave the results of the lesion counts. Overall, 5 percent benzoyl peroxide reduced the count from 17.7 to 11.2, and 10 percent benzoyl peroxide decreased the count from 28.0 to 17.9. Although it appears that 10 percent benzoyl peroxide may be more effective than 5 percent benzoyl peroxide in reducing the number of acne lesions, no statistical analysis of the results was presented.

Belknap (Ref. 29) conducted a parallel comparison of 5 percent benzoyl peroxide gel and 0.05 percent retinoic acid cream. (Retinoic acid, also known as tretinoin or vitamin A acid, is a prescription drug for acne.) Patients with Grade II and Grade III acne (Pillsbury classification) were randomly assigned to treatment with either of the active drugs. They had had no topical or systemic medications for 2 weeks before entering the study. The benzoyl peroxide group (29 patients) was treated twice daily and the retinoic acid group (31 patients) was treated once daily. No topical or systemic therapy was allowed other than soap and water. Length of treatment was 8 weeks. Patients were evaluated with lesion counts grouped by type (papules, open comedones, etc.). Results were considered excellent if improvement was greater than 75 percent.

When overall ratings of the two treatment groups were compared, 16 patients who had used benzoyl peroxide showed excellent results compared to 8 patients who had used retinoic acid. This difference was significant ($p<0.025$).

Both drugs were "extremely effective" for all lesion types, but Belknap (Ref. 29) stated that "it appears that the benzoyl peroxide gel produced a more rapid effect on inflammatory lesions (papules and pustules) than did the vitamin A acid." Both treatments also significantly reduced the number of open and closed comedones after 2 weeks of treatment, although Belknap again reported that "the extent of reduction was greater in the benzoyl peroxide group." The Panel has stated that a Category I acne treatment should be effective against all types of acne lesions and believes this study gives evidence of that effectiveness for benzoyl peroxide.

Several investigators have studied 2.5 percent benzoyl peroxide for effectiveness. One investigator treated 10 males with a 2.5-percent benzoyl peroxide water-based gel twice daily for 28 days (Ref. 30). Ten males were treated with the control. No other significant topical or systemic therapy was allowed. *P. acnes* and free fatty acid/triglyceride ratios were measured. In the group treated with 2.5 percent benzoyl peroxide, the pretreatment level of *P. acnes* (in millions/square centimeter (cm^2)) was 6.0. On the 28th day of treatment the *P. acnes* level was 4.2. In the control group the pretreatment level of *P. acnes* was 5.9; on the 28th day of treatment the level was 5.7. The free fatty acid/triglyceride ratio in the control group was 0.75. On the 28th day the ratio was 0.71. In the group treated with benzoyl peroxide the pretreatment ratio was 0.88. On the 28th day the ratio was 0.36. Reduction of *P. acnes* and the free fatty acid/triglyceride ratio was significantly greater with 2.5 percent benzoyl peroxide than with the control.

In another unpublished study, 50 acne patients were treated with either 2.5 percent or 10 percent benzoyl peroxide twice daily for 8 weeks (Ref. 31). This study was randomized and double-blind, but not controlled. Patients were examined biweekly. Evaluation was made by measuring the reduction in the number of specific lesion types and in the total of these lesion types. Patients were also evaluated by global impression.

At 8 weeks, the percent reduction of total lesions from baseline was 46.7 percent for 2.5 percent benzoyl peroxide and 44.3 percent for 10 percent benzoyl peroxide. Statistical analysis showed that there was no significant difference between the effectiveness of the two concentrations. Also, both treatments significantly decreased the total number of papules and pustules ($p<0.001$). No difference was noted between the two treatments in global evaluation. Good to fair results were noted in 46 percent of patients in each treatment group. In this study, side effects from 2.5 percent benzoyl peroxide were found to be less severe and occurred less frequently than with the 10-percent benzoyl peroxide.

Yong (Ref. 32) conducted an open clinical trial with 2.5 percent and 5 percent benzoyl peroxide gel. He treated 200 patients twice daily. Each concentration was given to 100 patients. No significant other topical or systemic therapy was permitted except soap and water. Treatment lasted 4 to 18 weeks. If the lesion count decreased by greater than 75 percent, improvement was considered excellent. Forty-six patients who had been treated with 5 percent gel compared to 36 patients who had been treated with 2.5 percent gel were rated as excellent. Twenty-eight patients in each group were given a good rating (lesions decreased by 50 to 75 percent). Yong concluded that there was no significant difference in effectiveness between the two different strengths of benzoyl peroxide gel.

Numerous adequately controlled, double-blind, and randomized studies have documented the effectiveness of benzoyl peroxide. The Panel recognizes that acne represents a spectrum of severity ranging from comedones to nodules and pustules. No one concentration of benzoyl peroxide or any other ingredient will be suitable for the wide range of this disease even when the frequency of application is varied. The Panel feels that higher concentrations of benzoyl peroxide may be suitable for severe acne or for mila acne lesions that have not responded to lower concentrations. The Panel concludes that benzoyl peroxide 2.5 to 10 percent is effective for OTC use in the treatment of acne.

(3) *Dosage*—(i) *Concentration.* Benzoyl peroxide 2.5 to 10 percent.

(ii) *Directions for use.* See part III. paragraph A.2. below—Category I labeling.

(4) *Labeling.* The Panel recommends the Category I labeling for OTC products used in the treatment of acne and in the prevention of new acne lesions. (See part III. paragraph A.2. below—Category I labeling.)

References

(1) OTC Volume 070207.

(2) OTC Volume 070168.

(3) Horgan, V. J., et al., "Toxicity of Autoxidized Squalene and Linoleic Acid, and of Simpler Peroxides, in Relation to Toxicity of Radiation," *Biochemical Journal,* 67:551–558, 1957.

(4) Philpot, J., and D. B. Roodyn, "A Comparison between the Effects in Mice of Injected Organic Peroxides and of Whole-Body X-Irradiation," *International Journal of Radiation Biology,* 4:372–382, 1959.

(5) Antonyuk, O. K., "Experimental Data on Toxicity of Benzoyl Peroxide and Triphenyl Phosphate," *Gigiena Primeneniya Polimernykh Materialov i Izdelii iz Nikh,* 1:311–313, 1969.

(6) OTC Volume 070199.

(7) Sharp, R. L., Eastman Kodak Co., letter to Richard Daily, Informatics, Inc., December 14, 1977, included in OTC Volume 070294.

(8) Holzmann, H., B. Morsches, and P. Benes, "The Absorption of Benzoyl Peroxide from Leg Ulcers," *Arzneimittel-Forschung,* 29:1180–1183, 1979.

(9) OTC Volume 070097.

(10) Nacht, S., et al., "Benzoyl Peroxide: In Vitro and Vivo Skin Penetration and Metabolic Disposition," *Clinical Research,* 27:533A, 1979.

(11) Nacht, S., et al., "Benzoyl Peroxide: Percutaneous Penetration and Metabolic Disposition," draft of unpublished paper, included in OTC Volume 070264.

(12) Sharratt, M., A. C. Frazer, and O. C. Forbes, "Study on the Biological Effects of

Benzoyl Peroxide," *Food and Cosmetics Toxicology*, 2:527–538, 1964.
(13) Radomski, J. L., G. Woodward, and A. J. Lehman, "The Toxicity of Flours Treated with Various 'Improving' Agents," *Journal of Nutrition*, 36:15–25, 1948.
(14) Van Duuren, B. L., et al., "Carcinogenicity of Epoxides, Lactones, and Peroxy Compounds," *Journal of the National Cancer Institute*, 31:41–55, 1963.
(15) Hueper, W. C., "Cancer Induction by Polyurethan and Polysilicone Plastics," *Journal of the National Cancer Institute*, 33:1005–1022, 1964.
(16) Epstein, S. S., et al., "Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse," *Toxicology and Applied Pharmacology*, 23:288–325, 1972.
(17) Litton Bionetics, Mutagenic Evaluation of Benzoyl Peroxide, submitted to FDA, June 1975, included in OTC Volume 070294.
(18) OTC Volume 070048.
(19) Ede, M., "A Double-Blind, Comparative Study of Benzoyl Peroxide, Benzoyl Peroxide-Chlorhydroxyquinoline, Benzoyl Peroxide-Chlorhydroxyquinoline-Hydrocortisone, and Placebo Lotions in Acne," *Current Therapeutic Research*, 15:624–629, 1973.
(20) Eaglstein, W. H., "Allergic Contact Dermatitis to Benzoyl Peroxide," *Archives of Dermatology*, 97:527, 1968.
(21) Poole, R. L., J. F. Griffith, and F. S. K. MacMillan, "Experimental Contact Sensitization with Benzoyl Peroxide," *Archives of Dermatology*, 102:635–639, 1970.
(22) Leyden, J. J., and A. M. Kligman, "Contact Sensitization to Benzoyl Peroxide," *Contact Dermatitis*, 3:273–275, 1977.
(23) Fulton, J. E., Jr., A. Farzad-Bakshandeh, and S. Bradley, "Studies on the Mechanism of Action of Topical Benzoyl Peroxide and Vitamin A Acid in Acne Vulgaris," *Journal of Cutaneous Pathology*, 1:191–200, 1974.
(24) Vasarinsh, P., "Benzoyl Peroxide-Sulfur Lotions. A Histological Study," *Archives of Dermatology*, 98:183–187, 1968.
(25) OTC Volume 070098.
(26) Pillsbury, D. M., "A Manual of Dermatology," W. B. Saunders Co., Philadelphia, pp. 173–174, 1971.
(27) OTC Volume 070099.
(28) OTC Volume 070238.
(29) Belknap, B. S., "Treatment of Acne with 5 Percent Benzoyl Peroxide Gel or 0.05 Percent Retinoic Acid Cream," *CUTIS; Cutaneous Medicine for the Practitioner*, 23:856–859, 1979.
(30) OTC Volume 070263.
(31) OTC Volume 070270.
(32) Yong, C. C., "Benzoyl Peroxide Gel Therapy in Acne in Singapore," *International Journal of Dermatology*, 18:485–488, 1979.

b. *Sulfur.* The Panel concludes that sulfur is safe and effective for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel reviewed the toxicology of sulfur in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Although the studies usually conducted to establish a toxicological profile were not done on sulfur, the Panel concluded that sulfur is safe for use in antifungal preparations because of its long history of oral and topical use without serious toxic effects.

Sulfur has been used in acne preparations in concentrations ranging from 2 to 10 percent. Although as much as 50 percent of the body surface area could be exposed to sulfur, there is no indication that absorption occurs, at least not to an extent that could approximate oral doses which have been administered to humans. For this reason, the Panel has focused its attention on the local effects of topically applied sulfur.

Scott (Ref. 1) reported that radioactive sulfur was absorbed by normal skin in 8 hours and disappeared from the dermis within 24 hours. The extent of absorption and the chemical form of the absorbed drug were not discussed. In acne patients, the rate of penetration through the epidermis was the same as for normal skin, but the accumulation of radioactive sulfur in the undischarged contents of the sebaceous glands was 10 times greater than in normal skin and remained in high concentrations for up to 3 weeks.

An unspecified number of rabbits were studied after applications of either a 10-percent sulfur ointment (vehicle not specified) or a combination of 2.5 percent sulfur and 10 percent benzoyl peroxide for a period of 12 weeks (Ref. 2). The only reaction was a redness attributed to mild irritation of the skin. This occurred during the first 3 weeks of the study. No signs of toxicity were noted in the hematological examination, urinalysis, or organ analysis.

Another experiment used a 20-percent sulfur cream or a 20-percent sulfur-20 percent benzoyl peroxide cream on the shaved backs of rabbits for a 2-hour exposure period. No reactions to these materials were noted (Ref. 3).

Sulfur can cause slight skin irritation and irritates the eyes if allowed to remain in them. Neither irritation is serious, however. Also, the Panel is unaware of any systemic toxicity from topically applied sulfur. For these reasons the Panel concludes that sulfur is safe for the treatment of acne. The Panel recommends an upper limit of 10 percent. Although sulfur is safe at higher concentrations, 10 percent is the highest concentration contained in currently marketed acne products. The Panel notes that even though sulfur is a safe, mild, peeling agent for the skin, some data suggested that sulfur may enhance the sensitization potential of benzoyl peroxide. (See part III. paragraph D. below—Combination Products Used in the Treatment of Acne.)

(2) *Effectiveness.* Sulfur has been used medically for centuries and although the rationale for its use in acne is presumed to be its keratolytic and antibacterial effects, the exact mechanism of action remains unknown. There are no studies available on this ingredient that meet the Panel's in vivo criteria for antibacterial claims. (See part III. paragraph E.2.c. below—In vivo testing of acne ingredients.) Strakosch (Ref. 3) indicated that the keratolytic action of sulfur was actually due to its conversion to hydrogen sulfide when in contact with tissue. The degree of tissue conversion of sulfur to hydrogen sulfide is unknown, and there are no additional data available on this subject.

One study showed that sulfur may have a comedogenic effect. Mills and Kligman (Ref. 4) were able to induce comedones in rabbits after applying concentrations of sulfur from 2 to 8 percent to the external ear canal. They also induced comedones in humans by applying from 2.5 to 5 percent concentrations of sulfur in a closed patch test. Strauss et al. (Ref. 5), however, were unable to reproduce these results. They used identical methods in 52 patients who were treated with 5 percent sulfur in either octoxynol 9 or a carbomer 934P base. Either the octoxynol 9 vehicle or a dry patch was used as a control. The researchers used multiple biopsies of the test sites which were sectioned serially to detect the presence of comedones. Only the octoxynol 9 vehicle was associated with the production of comedones.

A single-blind, half-face evaluation of the effectiveness of a 10-percent sulfur lotion was conducted on 29 patients who had Pillsbury Grade II to III acne (Ref. 6). They had had no topical therapy for 2 weeks before the study and no systemic therapy for 4 weeks before the study. Each patient used a soap control on half of the face. The other half of the face was treated with an aluminum oxide scrub and the sulfur lotion at night, and a soap washing followed by the sulfur lotion in the morning. Treatment lasted for 6 weeks with evaluation by lesion counts at 0, 2, 4, and 6 weeks. Both total lesion and specific lesion counts were reduced by treatment with sulfur and aluminum oxide. However, open comedones were the only specific lesion count significantly reduced more by sulfur and aluminum oxide than by the soap treatment.

Sulfur is frequently combined with resorcinol in acne preparations. Numerous studies have established the effectiveness of this combination. (See part III. paragraph D. below—Combination Products Used in the Treatment of Acne.)

In a double-blind, randomized trial (Ref. 7), 92 patients were treated twice daily with one of the following treatments: (1) 3 percent sulfur, (2) 5 percent benzoyl peroxide, (3) 3 percent sulfur-10 percent benzoyl peroxide, or (4) vehicle lotion. Clinical response was evaluated after 2 weeks by lesion counts and clinical evaluation. In order to merit a satisfactory rating, the patients must have had a 50-percent or greater decrease in lesions if treated for less than 12 weeks or have shown continued improvement over a 12-week period.

Of the 24 patients treated with sulfur, 33 percent were rated as satisfactory. This compared to satisfactory ratings of 54 percent for the sulfur-benzoyl peroxide combination, 41.7 percent for benzoyl peroxide, and 10 percent for the vehicle. Clinical assessment of patients treated with sulfur showed 29.2 percent good to excellent, 50 percent fair to no change, and 20.8 percent worse. This compared to vehicle results of 10 percent good to excellent, 45 percent fair to no change, and 45 percent worse. Although the results were not analyzed statistically, it was concluded that the active treatments (sulfur, benzoyl peroxide, and the sulfur-benzoyl peroxide combination) were "demonstrably more effective" than vehicle.

One submission contained a compilation of five half-face studies conducted by different investigators using the same protocol (Ref. 2). The studies were randomized and double-blind. Patients were treated for 8 weeks and evaluated by lesion counts. Treatment consisted of a base cream on one side of the face. On the other side of the face, a cream containing 5 percent sulfur or 10 percent benzoyl peroxide or a combination of the two ingredients was applied.

Treatment results on the 42 patients treated with sulfur showed a 42.8-percent decrease in comedones and a 36.3-percent decrease in other lesions. For the 123 patients using the vehicle the reduction was 28 percent for comedones and 18.3 percent for other lesions. Overall results showed a reduction in lesions of 52 percent for benzoyl peroxide-sulfur combination; 41 percent for sulfur; 40 percent for benzoyl peroxide; and 25 percent for vehicle.

Not all of the studies were statistically analyzed. Some researchers found the combination of benzoyl peroxide and sulfur superior to either ingredient used alone. In other studies, no significant difference was seen between sulfur, benzoyl peroxide, or the combination of sulfur and benzoyl peroxide.

The Panel concludes that sulfur is effective for OTC use in the treatment of acne.

(3) *Dosage*—(i) *Concentration.* Sulfur 3 to 10 percent.

(ii) *Directions for use.* See part III. paragraph A.2. below—Category I labeling.

(4) *Labeling.* The Panel recommends the Category I labeling for OTC products used in the treatment of acne and in the prevention of new acne lesions. (See part III. paragraph A.2. below—Category I labeling.)

References

(1) Scott, A., "The Behaviour of Radioactive Sulphur After its External Application to the Skin," *British Journal of Dermatology,* 69:39–49, 1957.

(2) OTC Volume 070168.

(3) Strakosch, E. A., "Studies on Ointments. III. Ointments Containing Sulphur," *Archives of Dermatology and Syphilology,* 47:216–225, 1943.

(4) Mills, O. H., and A. M. Kligman, "Is Sulphur Helpful or Harmful in Acne Vulgaris?, *British Journal of Dermatology,* 86:620–627, 1972.

(5) Strauss, J. S., et al., "A Re-examination of the Potential Comedogenicity of Sulfur," *Archives of Dermatology,* 114:1340–1342, 1978.

(6) OTC Volume 070126.

(7) OTC Volume 070099.

2. *Category I labeling.* The Panel reviewed all submitted labels of preparations used for the treatment of acne and recommends the following labeling. The Panel realizes that there may be many similar phrases and terms that can be used in labeling to convey the same information to consumers. However, to ensure conformity to required standards, variations from the labeling recommended below must be obtained through the procedures to amend the monograph in § 330.10(a)(12) (21 CFR 330.10(a)(12)).

a. *Acne treatment labeling.* The Panel recommends that one or a combination of the following phrases be used as labeling for products effective in the treatment of acne.

(1) "For the management of acne."
(2) "For the treatment of acne."
(3) "Anti-acne formula."
(4) "Anti-acne medication."
(5) "Anti-acne formulation."
(6) "Dries and clears acne blemishes."
(7) "Dries and clears acne pimples."
(8) "Dries acne blemishes and allows skin to heal."
(9) "Dries acne pimples and allows skin to heal."
(10) "Dries up acne pimples."
(11) "Helps clear acne pimples."
(12) "Clears up most acne pimples."
(13) "Clears up most acne blemishes."
(14) "Reduces the number of acne lesions."
(15) "Reduces the severity of acne lesions."
(16) "Reduces blackheads."
(17) "Clears up most blackheads."
(18) "Loosens blackheads."
(19) "Helps clear up blackheads."
(20) "Helps clear up acne pimples."
(21) "Helps remove blackheads."
(22) "Helps remove acne pimples."
(23) "Dries up blackheads."
(24) "Dries up acne blemishes."
(25) "Unclogs pores to help clear acne."
(26) "Unplugs pores to help clear acne."
(27) "Penetrates follicles to eliminate most blackheads and acne pimples."
(28) "Penetrates pores to eliminate most blackheads and acne pimples."
(29) "Penetrates follicles to control blackheads and acne pimples."
(30) "Penetrates pores to control blackheads and acne pimples."
(31) "Penetrates follicles to clear most blackheads and acne pimples."
(32) "Penetrates pores to clear most blackheads and acne pimples."
(33) "Penetrates follicles to reduce blackheads or acne pimples."
(34) "Penetrates pores to reduce blackheads or acne pimples."

b. *Acne prevention labeling.* Acne prevention labeling may be used in addition to acne treatment labeling for acne drug products that are effective in preventing the development of new acne lesions. These products should not be used to prevent acne in the person who has never had acne. The Panel believes that ingredients that are effective in treating acne are also effective in preventing new lesions. (See part II. paragraph F. above—Treatment of Acne.) The Panel recommends that one of a combination of the following phrases be used as labeling for products effective in the prevention of new acne lesions.

(1) "Helps keep skin clear of new acne lesions."
(2) "Helps keep skin clear of new acne pimples."
(3) "Helps prevent new blackheads or acne pimples."
(4) "Helps prevent new acne pimples."
(5) "Helps prevent new acne pimples from forming."
(6) "Helps prevent new acne lesions."
(7) "Helps prevent the development of new acne lesions."
(8) "Helps prevent new acne blemishes from forming."

Prevention labeling is to be used only in conjunction with treatment labeling. Examples of acceptable labeling are:

"Clears up most acne pimples and reduces blackheads. Helps prevent new acne blemishes from forming."

"Dries and clears acne blemishes and reduces blackheads. Helps prevent the development of new acne lesions."

c. *Antibacterial claims.* Products containing ingredients which are in Category I for the treatment of acne may also be labeled with one or more of the following antibacterial claims, provided that the product as formulated meets the in vivo effectiveness testing criteria recommended by the Panel. (See part III. paragraph E.2.c. below—In vivo testing of acne ingredients.)

(1) "Antibacterial."

(2) "Kills acne bacteria."

(3) "Kills the bacteria that can cause acne."

(4) "Kills acne bacteria on the skin."

(5) "Kills acne bacteria in the skin."

(6) "Kills acne bacteria and helps clear acne pimples."

(7) "Works to kill bacteria that may cause pimple redness to spread."

(8) "Works to kill bacteria that may cause inflammation to spread."

(9) "Penetrates follicles to kill bacteria associated with acne."

(10) "Penetrates pores to kill bacteria associated with acne."

(11) "Penetrates follicles to reduce bacteria associated with acne."

(12) "Penetrates pores to reduce bacteria associated with acne."

(13) "Reduces *P. acnes,* bacteria associated with acne."

(14) "Reduces the bacterial products associated with the inflammation of acne."

(15) "Reduces the bacterial products associated with the irritation of acne."

d. *Product attributes.* The Panel accepts the use of terms describing certain physical and chemical qualities of OTC topical acne drug products, as long as these terms do not imply any therapeutic effect and are distinctly separated from labeling indications.

These product attributes pertain to the inherent characteristics or the pharmaceutical elegance of the formulation. These properties are usually due to specific inactive, and in some cases active, ingredients included in the final product formulation. Product characteristics appear in the labeling for consumer information or product appeal and involve terms relating to the product's color, odor, and feel. The Panel considers the following list and similar terms acceptable:

(1) "Greaseless."

(2) "Nonstaining."

(3) "Odorless."

(4) "Colorless."

(5) "Nontinted."

(6) "Blends easily with skin."

(7) "Disappearing foam."

(8) "Drying."

(9) "Dries excess skin oils."

(10) "Skin-softening."

(11) "Cools and comforts hot, irritated skin areas."

(12) "Cleans the skin and helps to remove oil."

e. *Warnings*—(1) *For all acne products.* (i) "For external use only."

(ii) "Other topical acne medications should not be used at the same time as this medication."

(2) *For products containing benzoyl peroxide.* "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."

(3) *For products containing sulfur.* "Do not get into eyes. If excessive skin irritation developes or increases, discontinue use and consult a doctor or pharmacist."

(4) *For sulfur-resorcinol products.* "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body."

f. *Directions for use.* The Panel suggests the following directions for acne products that are applied and left on the skin:

"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."

Other products, such as soaps or masks, may be applied and removed and should have appropriate directions.

B. Category II Conditions

These are conditions under which OTC acne drug products are not generally recognized as safe and effective or are misbranded. The Panel recommends that the Category II conditions be eliminated from OTC acne drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

1. *Category II active ingredients.*

Alkyl isoquinolinium bromide
Aluminum salts
  Alcloxa
  Aluminum chlorohydrex
  Aluminum hydroxide
  Magnesium aluminum silicate
Benzocaine
Benzoic acid
Borates
  Boric acid
  Sodium borate
Calcium polysulfide
Calcium thiosulfate
Camphor
Chlorhydroxyquinoline
Chloroxylenol
Coal tar
Dibenzothiophene
Estrone
Magnesium sulfate
Phenolates
  Phenol
  Phenolate sodium
Phenyl salicylate
Pyrilamine maleate
Resorcinol and resorcinol monoacetate (as single ingredients)
Sodium thiosulfate
Tetracaine hydrochloride
Thymol
Vitamin E
Zinc salts
  Zinc oxide
  Zinc stearate
  Zinc sulfide

a. *Alkyl isoquinolinium bromide.* The Panel concludes that alkyl isoquinolinium bromide is not effective and that there are insufficient data available to permit final classification of its safety for OTC topical use in the treatment of acne.

(1) *Safety.* Alkyl isoquinolinium bromide is a surface-acting agent and is active against bacteria, molds, and fungi (Ref. 1).

The oral LD_{50} is 230 mg/kg in rats and 200 mg/kg in guinea pigs. Rats that were fed 12.5 mg/kg for 2 years continued to grow normally. Guinea pigs tolerated 1:5,000 alkyl isoquinolinium bromide in drinking water for 6 months (Ref. 2). Normal skin showed no irritation or sensitization from the use of 0.1 percent solutions of this ingredient. Solutions of 0.5 percent can be considered safe for use where accidental contact with the eye may occur (Ref. 1).

The Panel has found the safety data on alkyl isoquinolinium bromide insufficient and therefore considers this ingredient of questionable safety when used topically for the treatment of acne.

(2) *Effectiveness.* Alkyl isoquinolinium bromide is contained in only one product submission reviewed by the Panel (Ref. 1). No data on the effectiveness of this ingredient in the treatment of acne are available in the submission or in the medical literature. For this reason the Panel concludes that alkyl isoquinolinium bromide is not

effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed alkyl isoquinolinium bromide in category II because there are no data available on the effectiveness of this ingredient in the treatment of acne.

References

(1) OTC Volume 070009.

(2) Gloxhuber, C., "Review Articles. Toxicological Properties of Surfactants," *Archives of Toxicology,* 32:245–270, 1974.

b. *Aluminum salts (alcloxa, aluminum chlorohydrex, aluminum hydroxide, and magnesium aluminum silicate).* The panel concludes that the aluminum salts (alcloxa, aluminum chlorohydrex, aluminum hydroxide, and magnesium aluminum silicate) are safe but are not effective for OTC use in the treatment of acne.

(1) *Safety.* The Panel determined alcloxa to be safe for topical use in concentrations of 0.25 to 10 percent as described in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** The Panel has reviewed additional data (Refs. 1, 2, and 3) which support this finding.

Aluminum chlorohydrex was found safe at concentrations up to 25 percent for topical use in nonaerosol formulations in a report by the Advisory Review Panel on OTC Antiperspirant Drug Products published in the **Federal Register** on October 10, 1978 (43 FR 46719). Although intradermal injections of aluminum chlorohydrex produced granulomas in guinea pigs (Ref. 4), the Panel believes that this ingredient is safe for topical use, particularly because it is a protein precipitant. With protein precipitants, absorption through the skin is probably minimal.

Aluminum hydroxide and magnesium aluminum silicate are widely used antacids and were found safe for that use by the Advisory Review Panel on OTC Antacid Drug Products in a report published on April 4, 1973 (37 FR 8717). Aluminum hydroxide, like aluminum chlorohydrex, produced granulomas in guinea pigs following intradermal injection (Ref. 4), but again the Panel sees no problem when it is used topically. Patch test and primary skin irritation studies showed tht magnesium aluminum silicate does not irritate or sensitize the skin (Ref. 5). The Panel concludes that the four aluminum salts discussed above are safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Alcloxa apparently works by dissociating into allantoin and aluminum chloride at skin pH. Its mechanism of action in the treatment of acne is presumed to depend upon the astringency of the aluminum chloride as well as the soothing and healing properties of the allantoin. Alcloxa has been used for over 50 years for the treatment of a wide variety of skin problems, such as eczema, sunburn, itching, athlete's foot, impetigo, acne, diaper rash, and psoriasis. Its reputation is based upon "skin softening and tissue-building actions" (Ref. 2).

Submissions reviewed by the Panel (Refs. 1, 2, 3, and 6) contained no clinical trials on alcloxa in the treatment of acne, and there is no information in the gneral medical literature on the effectiveness of this ingredient in treating acne.

Warshaw (Ref. 7) studied an aqueous solution of 20 percent aluminum chlorohydrex on 66 acne patients. She believed the aluminum preparation inhibits sweating and decreases overactivity of the sebaceous gland. All patients in this study were treated with a combination of sulfur and resorcinol. Half of the subjects also used the aluminum chlorohydrex solution. Treatment time varied from 3 weeks to 6 months. The author reported that 32 of the 33 patients treated with aluminum chlorohydrex showed decreased comedones, pustules, and oiliness. The group treated only with sulfur and resorcinol showed "less rapid improvement" and the improvement was not as well maintained.

This study was not randomized, vehicle-controlled, or double-blind. The Panel cannot draw conclusions from this study on the effectiveness of aluminum chlorohydrex as a single ingredient because it was used with the sulfur-resorcinol combination.

Several randomized, blinded, and controlled trials have been conducted on a combination of aluminum chlorohydrex and sulfur (Ref. 8). No statistically significant differences were found between the aluminum chlorohydrex combination, a sulfur-resorcinol combination, and placebo. However, because these studies did not use aluminum chlorohydrex as a single ingredient, they will not be discussed in detail.

The Panel has seen no data in the submissions or in the medical literature to support the use of aluminum hydroxide in acne.

The Panel has received one submission on magnesium aluminum silicate which states that this ingredient is metabolically inert. Magnesium aluminum silicate works by absorbing oils and superficially debriding the skin (Ref. 5).

In an unpublished study of 12 patients, half of the face was treated with magnesium aluminum silicate and the other half of the face served as the control. After 1 month of treatment, "there appeared to be an improvement in the treated area vs. the control in the clearing of comedones" in six subjects. No change was noted in the other six patients (Ref. 5).

In another unpublished study, 55 patients applied magnesium aluminum silicate nightly for 1 week and then twice weekly for the next 3 to 5 weeks. Controls were not used, and criteria for evaluation were not explained. At the end of the study, 45 patients were considered improved, 8 were unchanged, and 2 were worse (Ref. 5).

Neither of the above two studies meets the Panel's criteria for effectiveness and neither study particularly supports the effectiveness of magnesium aluminum silicate. (See part II. paragraph I.2. above—Criteria for evaluating effectiveness.)

The Panel concludes that the aluminum salts are not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel believes that the aluminum salts are not effective ingredients for the treatment of acne. Either no effectiveness data were available on the single active ingredients, or the available studies did not support the effectiveness of aluminum salts.

References

(1) OTC Volume 070030.

(2) OTC Volume 070100.

(3) OTC Volume 070124.

(4) Turk, J. L., and D. Parker, "Granuloma Formation in Normal Guinea Pigs Injected Intradermally with Aluminum and Zirconium Compounds," *Journal of Investigative Dermatology,* 68:336–340, 1977.

(5) OTC Volume 070172.

(6) OTC Volume 070230.

(7) Warshaw, T. G., "A New Approach to the Control of Acne Vulgaris," *New York State Journal of Medicine,* 57:3999–4000, 1957.

(8) OTC Volume 070053.

c. *Benzocaine.* The Panel concludes that benzocaine is not safe and is not effective for OTC use in the treatment of acne.

(1) *Safety.* Benzocaine has been used widely as a local anesthetic, especially in ointments and dusting powders for wounds, burns, and ulcers. The range of concentrations used is from 5 percent to 50 percent. It has been injected subcutaneously once a week in 3 percent solutions and is said to be almost devoid of local irritant action (Ref. 1).

The Canadian government listed the maximum single oral dose limits for an adult at 195 mg and the maximum oral daily intake at 585 mg. It also limits benzocaine to 8 percent concentrations

in pharmaceuticals for external use (Ref. 2). Dreisbach (Ref. 3) lists the maximum amount safe for surface use as 5,000 mg or 25 mL of a 20-percent solution. Gosselin et al. (Ref. 4) report that benzocaine is a local anesthetic of low toxicity. Despite its low water solubility and its reportedly poor absorption from many sites, there are instances of severe methemoglobinemia in infants from the use of either a benzocaine ointment or suppository.

Benzocaine is a common sensitizing agent which can produce allergic contact dermatitis. Approximately one-fourth of the people who are sensitive to benzocaine react when *para*-phenylenedamine, a component of hair dyes, comes in contact with their skin. Cross-reactivity is also noted with the sulfonamides and with sunscreens that contain *para*-aminobenzoic acid or its esters or both. Benzocaine-sensitive patients may also cross-react with injectable local anesthetics, such as procaine and tetracaine (Ref. 5).

Fisher, Pelzig, and Kanof (Ref. 6) studied the ability of *para*-phenylenediamine to act as a sensitizer on the skin to produce an allergic edematous contact type of dermatitis. The authors noted that allergic hypersensitivity to benzocaine and *para*-phenylenediamine may happen repeatedly even years after the initial sensitization. They found that in a group of 50 patients sensitive to *para*-phenylenediamine, 46 were still sensitive when tested 3 to 10 years later. Of these 46 patients, 18 were found to be sensitive to benzocaine. In a separate study, they also found that 10 of 24 patients sensitized to benzocaine were also sensitive to *para*-phenylenediamine.

In a similar study, Gaul (Ref. 7) used a patch test and found that, in a group of 580 dermatologic patients, 50 were sensitive to *para*-phenylenediamine, and 16 were sensitive to benzocaine. Of the benzocaine-sensitive patients, 3 were sensitive only to benzocaine. The rest were sensitive to other drugs such as *para*-phenylenediamine, procaine, and penicillin in addition to benzocaine. The Panel notes that benzocaine is chemically dissimilar from *para*-phenylenediamine,.

In the North American Contact Dermatitis Group's study (Ref. 8), the incidence of allergic sensitivity to benzocaine was 5 percent, equal to some other commonly used drugs, and less than the more frequent sensitizers such as neomycin. This study was on 1,200 patients seeking treatment for skin diseases. These patients were considered high risks for developing alllergy.

The routine topical patch test does not reveal immediate sensitivity, such as an urticarial reaction (hives), to benzocaine. Nasal testing, eye testing, scratch tests, or intradermal testing can be used to screen patients for hypersensitivity (Ref. 9). However, there is concern that scratch testing and intradermal skin testing to detect this type of hypersensitivity may give false-negative results.

Benzocaine is a moderate sensitizer when applied topically over a long period to normal or diseased skin. When used for short periods on noninfected skin, it is only a weak sensitizer. The use of benzocaine should be avoided by people known to be sensitive and by those with skin infections.

(2) *Effectiveness.* Benzocaine is a local anesthetic which may alleviate itching, burning, and pain.

Currently marketed OTC acne products contain benzocaine in a concentration of 0.5 percent. A concentration of 5 to 10 percent is considered useful in relieveing itching (Ref. 1). Ointments containing less than 5 percent benzocaine and acidic preparations of benzocaine are generally ineffective (Ref. 10).

No effectiveness data are available on benzocaine in the treatment of acne. The Panel sees no need for including a local anesthetic in an acne remedy. The Panel concludes that the use of benzocaine is irrational in acne therapy.

(3) *Evaluation.* The Panel has placed benzocaine in Category II for the treatment of acne because this ingredient's sensitizing potential and because there is no acceptable rationale for the use of this ingredient in treating acne.

References

(1) Osol, A., and R. Pratt, "United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 186, 1973.

(2) OTC Volume 070138.

(3) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 8th Ed., Lange Medical Publications, Los Altos, CA, p. 274, 1974.

(4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 142, 1976.

(5) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, pp. 42 and 312–313, 1973.

(6) Fisher, A. A., A. Pelzig, and N. B. Kanof, "The Persistence of Allergic Exzematous Sensitivity and the Cross-Sensitivity Pattern to Paraphenylenediamine," *Journal of Investigative Dermatology*, 30:9–12, 1958.

(7) Gaul, L. E., "Types of Sensitization Disclosed by Positive Patch Testing to Paraphenylenediamine and Benzocaine," *Annals of Allergy*, 18:738–745, 1960.

(8) North American Contact Dermatitis Group, "Epidemiology of Contact Dermatitis in North America: 1972," *Archives of Dermatology*, 108:537–540, 1973.

(9) Eyre, J., and F. Nally, "Nasal Test for Hypersensitivity, Including a Positive Reaction to Lignocaine," *Lancet*, 1:264–265, 1971.

(10) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 269, 1977.

d. *Benzoic acid.* The Panel concludes that benzoic acid is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Free and combined forms of benzoic acid occur in nature. Most berries contain appreciable amounts of this acid.

The acute toxicity of benzoic acid is similar in all species. The oral LD_{50} is 2.53 g/kg in the rat, 2.37 g/kg in the mouse, and 2 g/kg in the cat, dog, and rabbit. Benzoic acid given by other routes yielded these LD_{50}'s: 1.46 g/kg intraperitoneally in mice; 2 g/kg subcutaneously in rabbits; and 1.71 g/kg intravenously in rats (Refs. 1 and 2). After the intravenous injection, rats had tremors and convulsions before death. The surviving rats had excessive salivation, vomiting, and diarrhea (Ref. 2).

Benzoic acid is rapidly absorbed, conjugated with glycine, and excreted in the urine as hippuric acid (Ref. 3). In most species, the liver is the primary site of conjugation. Because there is no accumulation, symptoms of chronic administration are like those seen in acute studies. When rats were fed benzoic acid for 28 days, animals fed 5 percent in the diet died within 2 weeks, showing hyperexcitability, urinary incontinence, and convulsions. Males fed 2 percent benzoic acid exhibited a decrease in body weight (Ref. 4). Dogs can be fed up to 1 g/kg for long periods without effect, but epileptic convulsions and death occur above this amount (Ref. 3).

Benzoic acid was once administered as a 6–g oral dose or a 2–g intravenous dose in humans in a liver function test (Ref. 3). Within 6 hours, 80 percent of the dose is usually eliminated, the remainder being eliminated within 14 hours. Ingestion of 4 to 6 g benzoic acid produces only mild gastric irritation (Ref. 5). "Large oral doses" cause severe gastric pain, nausea, and vomiting (Ref. 6).

Benzoic acid 6 percent is contained in Whitfield's ointment, which has been used as a topical antifungal agent for many years. In view of the use of this ointment for over 50 years without toxic manifestations, the Panel concludes that

benzoic acid is safe for topical use in the treatment of acne.

(2) *Effectiveness.* Benzoic acid is generally considered to be an antifungal agent. It is also widely used as a food preservative. But the Panel has seen only one study (Ref. 7) on the use of benzoic acid in acne treatment and this was not as a single ingredient.

(3) *Evaluation.* The Panel has placed benzoic acid in Category II because it is not generally recognized as an anti-acne agent and because there are no controlled studies on benzoic acid as a single ingredient for the treatment of acne.

References

(1) Fairchild, E. J., "Registry of Toxic Effects of Chemical Substances," Vol. II. U.S. Department of Health, Education, and Welfare, Cincinnati, p. 179, 1977.

(2) Hager, G. P., C. W. Chapman, and E. B. Starkey, "The Toxicity of Benzoic Acid for White Rats," *Journal of the American Pharmaceutical Association (Scientific Edition),* 31:253–255, 1942.

(3) "Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents," 17th Report of the Joint Food and Agriculture Organization of the United Nations/World Health Organization, Expert Committee on Food Additives, World Health Organization, Geneva, Switzerland, pp. 34–42, 1974.

(4) Fanelli, G. M., and S. L. Halliday, "Relative Toxicity of Chlortetracycline and Sodium Benzoate after Oral Administration to Rats," *Archives Internationales de Pharmacodynamie et de Therapie,* 144:120–125, 1963.

(5) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasitides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 994 and 1012, 1975.

(6) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins Co., Baltimore, p. 137, 1976.

(7) Milberg, I. L. "Clinical Evaluation of an Antiseptic Medicated Cream in the Treatment of Acne Vulgaris," *New York State Medical Journal,* 58:2674–2675, 1958.

e. *Borates (boric acid and sodium borates).* The Panel concludes that borates (boric acid and sodium borate) are safe but are not effective for OTC topical use in the treatment of acne.

(1) *Safety.* The toxicology of borates was summarized by this Panel in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** The Panel concluded that borates were safe in concentrations of 5 percent of less. Rather than repeat that data here, the Panel will summarize only the data it has received since completing its recommendations on antifungal drug products.

One preparation used for acne contains boric acid in a concentration of just over 12 percent. For sodium borate, all of the submitted acne preparations contain less than 5 percent except for one which contains 50 percent sodium borate. However, because this preparation is a scrub, which is rinsed off a few minutes after application, exposure time would be relatively short.

In the antifungal recommendations mentioned above, the greatest concern about the use of sodium borate was its irritation potential because so little data had been submitted on this potential, However, two submissions to the acne review added information on irritation potential (Refs. 1 and 2). Both of these submissions suggest that 50 percent sodium borate preparations are irritating to the eye and have recommended warnings to this effect on the label.

Single applications to normal and abraded rabbit skin have shown different results, but most of the evidence shows that 50 percent sodium borate preparations are mildly irritating. Repeated applications over a period of 2 to 3 weeks, however, are severely irritating (Refs. 1 and 2). When used according to labeled directions (i.e., "wet skin with water, apply, and rinse off after 60 seconds,") over a 20-day period, the 50-percent preparation did not irritate either normal or abraded rabbit skin. Blood levels of boron in the treated group were not significantly different from the controls.

In a 30-day study, however, twice-daily application under the same conditions resulted in such severe skin reactions that the study was ended after 8 days. Although the blood boron levels of the treated group were about five times as high at the end of the study, they were still within the normal values for rabbits. Within 4 or 5 days after the study was discontinued, the rabbits' skin returned to normal (Ref. 1).

In a separate study (Ref. 1) a combination product containing 98 percent borax (sodium borate) was used to evaluate percutaneous absorption and irritation potential in rabbits. Doses of 1.0 g/kg and 5.0 g/kg of the product were used after adding enough saline to form a paste. Sodium borate was applied 5 days a week for 3 weeks with daily exposures of 6 hours to both normal and abraded skin. The treated area was covered with polyethylene wrap.

No rabbits died as a result of the treatment. However, weight gain in the test animals was less than in the control animals. Mild to moderate redness, edema, and mild fissuring indicated irritation. The skin also became slightly to noticeably leathery. There were no significant differences from controls in hematologic values, urinalysis findings, organ/body weight ratios, or gross pathological tissue changes.

In a similar experiment using mostly the same conditions, the rabbits treated with 5.0 g/kg sodium borate showed emaciation, depressed righting reflex, and impaired muscular coordination (Ref. 1). Several animals also developed acne-like lesions during the latter part of the application period.

The Panel recognizes that this kind of experiment does not approximate the labeled directions for use of the 50-percent sodium borate product. Such data, however, indicate potentially serious problems when high concentrations of sodium borate preparations remain on the skin for long periods and may be under occlusion.

Contrasted with these results, a 4-hour patch test using a 50-percent sodium borate suspension resulted in no primary irritation (Ref. 1).

A study by Weir and Fisher (Ref. 3) was very helpful in calculating the risk of topical applications of 12 percent boric acid if certain assumptions are made. In this study, definite signs of toxicity were noted when 1,170 ppm boron equivalent was fed to rats or dogs. For example, rats that were fed 1,170 ppm boron equivalent of either boric acid or sodium borate became sterile. Dogs that were fed 1,750 ppm boron equivalent developed atrophy of the testicles. In rats, degeneration of the gonads occurred as well as desquamation of the skin on the paws and tail.

If 1,170 ppm boron equivalent is converted, this would represent 6,685 ppm boric acid in the diet and 10,300 ppm sodium borate in the diet. At the 1,750 ppm boron equivalent level of feeding, this would convert to 10,000 ppm boric acid and 15,400 ppm sodium borate in the diet.

If the average mongrel dog weighs 30 lb or 13.6 kg and consumes 500 g of dry food daily (Ref. 4), it can be calculated that the total daily intake in this experiment would have been 5 g boric acid or 7.5 g sodium borate. The average blood volume of a dog is 35.4 mL per lb body weight (Ref. 4). Therefore, a 30-lb dog would have a blood volume of approximately 1 L. If 5 g boric acid were instantaneously distributed in 1 L of blood, there would be a blood concentration of 5,000 ppm. In a similar calculation, the blood sodium borate concentration would be 7,500 ppm. These concentrations of 1,170 ppm and 1,750 ppm boron equivalent are toxic

levels. About one-fourth of this dose, or 350 ppm, was found to be a "no effect" level by this test. This would amount to 2,500 ppm boric acid or 3,850 ppm sodium borate as the "no effect" level. These calculations were derived from the paper by Weir and Fisher (Ref. 3), but it should be noted that assumptions were made that are probably not the actual case.

If one makes the same assumptions about topical absorption in humans, one can approximate a safety evaluation. Assuming a worst-case type of application of the 12-percent boric acid product to the upper torso of a human and again assuming total rapid absorption into the blood, one arrives at a blood concentration similar to that assumed for the dog above. If 15 g of the 12-percent preparation were applied to the back and chest area twice daily, there would be 3.6 g boric acid available for absorption. If this were distributed into 7 L of blood (the blood volume of a person), the blood concentration would be 0.0005 g/mL or 500 ppm. This blood concentration is below the 2,500 ppm calculated above as the possible "no effect" level in dogs.

Although the Panel believes that high concentrations of borates may be irritating to abraded skin, it concludes that boric acid and sodium borate are safe for OTC topical use in concentrations up to 5 percent.

(2) *Effectiveness.* The Panel has found only one study (Ref. 1) evaluating the effectiveness of borates as single ingredients in the treatment of acne. In this clinical trial, 22 patients (13 females and 9 males) with acne and oily skin were treated with 50 percent sodium borate in a vehicle of soapless cleansers. The sodium borate was present as small abrasive particles that dissolved after 30 to 60 seconds of gentle rubbing on the skin. The rationale for its use was oil removal (the soapless cleansers) and gentle abrasion of the skin (the abrasive particles).

The patients were treated one to four times daily with this gritty scrub. They were also given other topical and systemic agents, including antibiotics and prednisone. At the beginning of the study, 18.2 percent of the patients had mild acne, 72.7 percent had moderate acne, and 9.1 percent had severe acne. After 4 weeks of treatment, half of the patients had mild acne and half had moderate acne.

At the final examination (8 weeks), the results were as follows: no acne in 4.8 percent, very mild acne in 14.3 percent, mild acne in 57.1 percent, and moderate acne in 23.8 percent. The oiliness of the patients' skin was also evaluated. Before treatment, oiliness was mild in 31.8 percent and moderate in 68.2 percent. At the conclusion of the trial, oiliness was absent in 27.8 percent, very mild in 5.6 percent, mild in 50.0 percent, and moderate in 16.7 percent.

The Panel notes that the study was not controlled or double-blind. Lesion counts were not used as a method of evaluation. Concomitant therapy was given. Statistical analysis of results was not presented.

The Panel concludes that borates have not been conclusively shown to be effective in treating acne. Sodium borate may act as a mild physical abrasive to remove superficial pustules, but it probably does not effectively remove the primary lesions of acne (blackheads and whiteheads) because they are deeply rooted in the follicles.

(3) *Evaluation.* Because there is no controlled clinical trial evaluating the effectiveness of boric acid and sodium borate in the treatment of acne, the Panel has placed these ingredients in Category II.

References

(1) OTC Volume 070206.
(2) OTC Volume 070218.
(3) Weir, R. J., Jr., and R. S. Fisher, "Toxicological Studies on Borax and Boric Acid," *Toxicology and Applied Pharmacology,* 23:351–364, 1972.
(4) Siegmund, O. H., "The Merck Veterinary Manual," 4th Ed., Merck and Co., Rahway, NJ, pp 35 and 1270, 1973.

f. *Calcium polysulfide.* The Panel concludes that calcium polysulfide is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Calcium polysulfide releases hydrogen sulfide and elemental sulfur when placed in contact with water (Ref. 1), such as might be present on the skin. The amount of hydrogen sulfide released is unknown but is thought to be below toxic levels when sulfide compounds are used externally. Neither of the submissions to the Panel (Refs. 2 and 3) contained any toxicity data on calcium polysulfide. However, because the Panel considers calcium polysulfide to be essentially elemental sulfur, it does not consider that the external use of this ingredient would present any systemic toxicological hazard. (See part III. paragraph A.1.b. above—Sulfur.) Also, local effects of calcium polysulfide would probably be the same as for elemental sulfur. The Panel concludes that calcium polysulfide is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Calcium polysulfide is one of the components of a sulfurated lime solution (Vleminckx' solution) which has been used for about 100 years (Ref. 4). In the past, there was no standardized definition of sulfurated lime solution, but it always contained high concentrations of sulfides and sulfates (25 to 35 percent) (Refs. 2 and 3). According to the "United States Pharmacopeia," sulfurated lime solution contains 25 percent sublimed sulfur and 16.5 percent lime (calcium oxide) (Ref. 5).

The product described in the submissions to the Panel (Refs. 2 and 3) contains calcium thiosulfate along with calcium polysulfide. Four mL of this combination added to 1 pint of water produces a sulfurated lime solution for use as a wet dressing. When used as directed, a substantial amount of hydrogen sulfide is liberated, giving off an obnoxious odor. Drying of the skin is also quite pronounced with sulfurated lime solution.

No controlled clinical trials on effectiveness are contained in the submissions and Panel is not aware of such studies in the medical literature. In addition, the Panel does not believe that calcium polysulfide is intended to be used as a single active ingredient.

The Panel concludes that calcium polysulfide is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* Although calcium polysulfide has been used for many years for the treatment of acne, in the absence of controlled clinical trails demonstrating effectiveness, the Panel concludes that it is not effective for this use.

References

(1) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 9th Ed., Lange Medical Publications, Los Altos, CA, p. 246, 1977.
(2) OTC Volume 070248
(3) OTC Volume 070250.
(4) Schmitt, C. L., "Topical Agents Used in Treatment of Acne," *Clinical Medicine,* 70:1473–1476, 1963.
(5) "United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 450, 1980.

g. *Calcium thiosulfate.* The Panel concludes that calcium thiosulfate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* No safety data on this ingredient were contained in the submissions (Refs. 1 and 2). But calcium thiosulfate or calcium hyposulfite (CaS_2O_3) decomposes to elemental sulfur and therefore presents the same safety considerations as sulfur. (See part III. paragraph A.1.b. above—Sulfur.) The Panel concludes that calcium thiosulfate is safe for OTC topical use.

(2) *Effectiveness.* No controlled clinical trials demonstrating effectiveness in acne are available on

this ingredient. Calcium thiosulfate is a component of sulfurated lime solution, which also contains calcium polysulfide. (See part III. paragraph B.1.f. above—Calcium polysulfide.)

The Panel concludes that calcium thiosulfate is not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel has placed calcium thiosulfate in Category II because there are no clinical studies demonstrating that this ingredient is effective in the treatment of acne.

References

(1) OTC Volume 070248
(2) OTC Volume 070250.

h. *Camphor.* The Panel concludes that camphor is safe but is not effective for OTC topical use in the treatment of acne. The Panel also concludes that at concentrations less than or equal to 0.2 percent, camphor is an inactive ingredient that can be used in formulations for product identification.

(1) *Safety.* The Panel considers camphor to be safe as discussed in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.**

(2) *Effectiveness.* Camphor has been submitted for the treatment of acne in concentrations of 2 to about 11 percent. No effectiveness data were contained in any of the submissions (Refs. 1, 2, and 3), nor is such data available in the medical literature. Depending on the concentration, camphor is considered either a local anesthetic to relieve itching (up to 3 percent) or a counterirritant (3 to 11 percent). The Panel sees no rationale for the use of such an ingredient in treating acne and concludes that this ingredient is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed camphor in Category II because there are no clinical studies available demonstrating effectiveness. Also there is no rationale for the use of this ingredient in treating acne.

References

(1) OTC Volume 070247.
(2) OTC Volume 070249.
(3) OTC Volume 070004.

i. *Chlorhydroxyquinoline.* The Panel concludes that chlorhydroxyquinoline is not safe and is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Chlorhydroxyquinoline (5-chloro-8-hydroxyquinoline) is an antifungal agent structurally similar to oxyquinoline (8-hydroxyquinoline) (Ref. 1). The latter compound was evaluated by this Panel in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register** and further studies were recommended to define the safety of oxyquinoline. There is even less information available on the toxicology of chlorhydroxyquinoline. Available data on the carcinogenicity of quinoline and oxyquinoline (Refs. 2 through 5), coupled with the mutagenicity of quinoline, 8-hydroxyquinoline, and 5-hydroxyquinoline in the Ames test (Refs. 6 and 7) make carcinogenicity tests on chlorhydroxyquinoline imperative. These tests should be carried out in a system using a tumor-promoting agent as well.

The Panel conclude that chlorhydroxyquinoline is not safe because there are no safety data available on this ingredient.

(2) *Effectiveness.* The Panel found only one study that evaluated chlorhydroxyquinoline as a single ingredient in the treatment of acne. Witkowski and Parish (Ref. 8) treated 100 patients with Grade II acne (Pillsbury's classification) with either 5 percent benzoyl peroxide-0.25 percent chlorhydroxyquinoline lotion (50 patients) or 0.25 percent chlorhydroxyquinoline lotion (50 patients). Patients were randomly assigned to either treatment group. They were instructed to wash the affected areas daily with "a commercially available soap used at home." Frequency of application was not explicity defined but apparently varied from patient to patient and with the patient's response to therapy. No other systemic or local therapy was allowed. Patients were examined at 2-week intervals using lesion counts to evaluate responses.

The results shown as percentage of reduction in lesion count after 6 weeks of treatment are as follows: 75 to 100 percent in 4 patients treated with chlorhydroxyquinoline and 10 treated with chlorhydroxyquinoline-benzoyl peroxide; 50 to 74.9 percent in 4 patients treated with chlorhydroxyquinoline and 17 treated with the combination; 25 to 49.9 percent in 5 patients treated with chlorhydroxyquinoline and 3 treated with the combination; 0 to 24.9 percent in 11 patients treated with chlorhydroxyquinoline and 9 treated with the combination. Eleven patients in the chlorhydroxyquinoline-benzoyl peroxide group became worse compared to 26 patients in the chlorhydroxyquinoline group. The combination product was found to be more effective than chlorhydroxyquinoline used alone ($p < 0.0005$). Chlorhydroxyquinoline does not appear to be effective in the treatment of acne, but it is difficult to draw conclusions because the trial was not vehicle controlled.

Chlorhydroxyquinoline is generally combined with benzoyl peroxide in marketed OTC products. The Panel believes that chlorhydroxyquinoline is not intended to be used as the sole active ingredient for the OTC topical treatment of acne. Because there is no vehicle-controlled trial evaluating the effectiveness of chlorhydroxyquinoline, the Panel concludes that this ingredient is not effective in the treatment of acne.

(3) *Evaluation.* The Panel has placed chlorhydroxyquinoline in Category II because there are no safety data available, particularly carcinogenicity studies. Also, there is not vehicle-controlled clinical trial evaluating the effectiveness of chlorhydroxyquinoline as a single ingredient for the treatment of acne.

References

(1) Windholz, M., "The Merck Index," (9th Ed., Merck and Co., Rahway, NJ, p. 276, 1976.
(2) Yamamoto, R. S., et al., "8-Hydroxyquinoline: Chronic Toxicity and Inhibitory Effect on the Carcinogenicity of N-2-Fluorenylacetamide," *Toxicology and Applied Pharmacology,* 19:687–698, 1971.
(3) Hirao, K., et al., "Carcinogenic Activity of Quinoline on Rat Liver," *Cancer Research, 36:329–335, 1976.*
(4) Hueper, E. C., "Experimental Studies on 8-Hydroxyquinoline in Rats and Mice," *Archives of Pathology,* 79:245–250, 1965.
(5) "World Health Organization, International Agency for Research on Cancer Monographs of Evaluation of Carcinogenic Risk of Chemicals to Man," Vol. 13, World Health Organization, Lyons, France, pp. 101–112, 1976.
(6) Talcott, R., M. Hollstein, and E. Wei, "Mutagenicity of 8-Hydroxyquinoline and Related Compounds in the *Salmonella Typhimurium* Bioassay," *Biochemical Pharmacology,* 25:1323–1328, 1976.
(7) Hollstein, M., R. Talcott, and E. Wei, "Quinoline: Conversion to a Mutagen by Human and Rodent Liver," *Journal of the National Cancer Institute,* 60:405–410, 1977.
(8) Witkowski, J. A., and L. C. Parish, "Chlorhydroxyquin-Benzoyl Peroxide Lotion in the Treatment of Acne—An Objective Evaluation," *CUTIS: Cutaneous Medicine for the Practitioner,* 5:1481–1484, 1969.

j. *Chloroxylenol.* The Panel concludes that chlorozylenol is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel considers chloroxylenol to be safe in concentrations up to 3.75 percent as discussed in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.**

(2) *Effectiveness.* Chloroxylenol is active in vitro against fungi and gram-positive and gram-negative bacteria.

The Panel has received one submission on 2 percent chloroxylenol (Ref. 1) which did not contain any clinical studies on effectiveness. To the Panel's knowledge, this ingredient has not been clinically studied for effectiveness in treating acne. Standard dermatology reference texts do not list chloroxylenol as an active ingredient for the treatment of acne. The Panel concludes that chloroxylenol is not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel has placed chloroxylenol in Categoy II because no controlled clinical trials are available evaluating the effectiveness of this ingredient.

Reference

(1) OTC Volume 070060.

k. *Coal tar.* The Panel concludes that coal tar is not safe and not effective for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel thoroughly reviewed the toxicology of coal tar in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Coal tar was placed in Category II because of substantial data indicating that it has a carcinogenic potential. Since that time, no other safety data were submitted to the Panel.

The Panel concludes that coal tar is not safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Crude coal tar 0.4 percent in an alcohol base was submitted as an active ingredient in one combination product used to treat acne (Ref. 1). The submission stated that coal tar USP "is a local irritant used topically in lotions and ointments in a range of 1 to 20% concentrations," but no data were included pertaining to the rationale for including the 0.4-percent concentration.

In its earlier review of crude coal tar for use in fungal infections, the Panel found references stating that coal tar 0.1 percent is astringent (Ref. 2); 2 to 4 percent is antipruritic; and 6 to 20 percent is keratoplastic, causing thickening of the upper layers of the skin (epidermis and stratum corneum) (Ref. 3). The Panel is unaware of any studies documenting the effect of 0.4 percent coal tar on skin.

In a letter referring to a presentation before the Panel on coal tar, Cullen (Ref. 4) stated: "There is no evidence in the medical literature that topical tar is of any value in the therapy of pruritus, chafing, tinea pedis, acne vulgaris, or soft corns."

The Panel was able to find only one other mention of the use of coal tar in acne in a book by Plewig and Kligman (Ref. 5). They wrote that "virtual cures (of acne) have been claimed for the combination of ultraviolet light and crude coal tar. The latter is a potent acneigen; moreover, its capacity to induce comedones is enhanced by sunlight."

The ability of coal tar to photosensitize the skin is well known. It is used therapeutically in the Goeckerman treatment of psoriasis and other skin diseases (Ref. 6).

The principal photosensitizing ingredients of coal tar are the acridine compounds in the anthracene oil fraction. Presumably, after absorption by the cells of the epidermis, these compounds become intimately associated with oxidizable substances in the cell. They are then activated by capture of a quantum (a unit of energy) of radiant energy of a specific wave length and react with oxygen, causing damage to the cell structure. The resulting oxygen deficiency then retards the development of keratin in the epidermis (Ref. 6).

Although exposure to sunlight alone is sometimes beneficial in treating acne, and photosensitization caused by coal tar might be theoretically beneficial in increasing the effects of sun exposure, no evidence of this is known to the Panel. On the contrary, Plewig and Kligman (Ref. 5) state that phototoxic reactions induced by coal tar may complicate acne in workers exposed to coal tar.

The Panel is aware of many reports stating that coal tar can induce acne and is a "potent comedogenic agent" (Ref. 5). Occupational "tar acne" is a common skin problem in road builders, roofers, and conduit makers exposed to coal tar, heavy coal tar distillates, or coal tar pitch (Ref. 7). Such workers develop extensive eruptions, comedones, and small yellowish cysts, which are most prominent on skin surfaces touched by soiled clothing. Hyperpigmentation of skin is also marked on the sun-exposed skin areas of these workers. Tar acne is probably caused by hydrocarbons, especially chloronaphthalene, deposited in the skin. The lesions resolve slowly, probably due to high tissue concentrations of the insoluble acnegenic substances (Ref. 5).

Coal tar induces hyperkeratosis in all keratinizing epithella, including the upper part of the pilosebaceous duct, which is usually not involved in comedo formation (Ref. 8). The first comedones which become visible in tar acne are of the open type, as the pilosebaceous canal orifice becomes distended with retained keratin (Ref. 9). The follicular horny papules are often black and surrounded by erythema (Ref. 10), and there is usually uniform involvement of most of the follicles within a certain area of the skin (Ref. 11). The tar comedones usually do not rupture to create papulopustules typical of acne vulgaris. The tar comedones also differ from the comedones of acne vulgaris by the virtual absence of *P. acnes* bacteria, probably due to bacteriostatic substances in the tar. The absence of inflammation in the tar comedones may be due to the lack of bacteria, which are thought to produce follicular irriation (Ref. 9).

A human model of coal tar acne was developed by Kaidbey and Kligman (Ref. 9) using a continuous occlusive application of crude coal tar to the backs of young adult males. A 25-percent concentration of coal tar distillate regularly induced an acneiform eruption after 3 weeks, but a 10-percent concentration produced only a mild follicular thickening in a few subjects.

The Panel concludes that coal tar is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel concludes that coal tar should be placed in Category II for the following reasons: (i) There are no clinical studies supporting the effectiveness of coal tar for the treatment of acne. (ii) Coal tar has been observed to induce acne in human models and in people exposed to it in their occupations. (iii) There are abundant data demonstrating a carcinogenic potential of crude coal tar and preparations derived from crude coal tar containing aromatic hydrocarbons.

References

(1) OTC Volume 070004.

(2) Combes, F. C., "The Use of Coal Tar in the Treatment of Skin Diseases," *New England Journal of Medicine,* 228:384–386, 1943.

(3) Pusey, W. A., "The Principles and Practice of Dermatology Designed for Students and Practitioners," 4th Ed., D. Appleton and Co., New York, pp. 132–135, 1924.

(4) Letter from Cullen, S. I. to A. M. Welch, Summary of proposed presentation to the Panel, included in OTC Volume 07BPA3.

(5) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, pp. 59, 239, and 276, 1975.

(6) Cole, H. N., Jr., "Goeckerman Therapy in the Management of Common Dermatoses," *Archives of Dermatology and Syphilology,* 80:788–791, 1959.

(7) Ormsby, O. S., and H. Montgomery, "Diseases of the Skin," 7th Ed., Lea and Febiger, Philadelphia, p. 1330, 1948.

(8) Cunliffe, W. J., and J. A. Cotterill, "The Acnes: Clinical Features, Pathogenesis and Treatment," W. B. Saunders and Co., Philadelphia, p. 82, 1975.

(9) Kaidbey, K. H., and A. M. Kligman, "A Human Model of Coal Tar Acne," *Archives of Dermatology*, 109: 21–215, 1974.

(10) Domonkos, A. N., "Andrews' Diseases of the Skin," 6th Ed., W. B. Saunders Co., Philadelphia, p. 88, 1971.

(11) Rook, A., D. S. Wilkinson, and F. J. G. Ebling, "Textbook for Dermatology," Vol. II, F. A. Davis Co., Philadelphia, pp. 1350–1351, 1968.

1. *Dibenzothiophene.* The Panel concludes that dibenzothiophene is not safe and that there are insufficient data available to permit final classification of its effectiveness for OTC topical use in the treatment of acne.

(1) *Safety.* Very little safety data are available on dibenzothiophene. The Panel received only one submisson (Ref. 1) which contained two animal studies.

Acute oral toxicity was tested in rats using dibenzothiophene suspended in olive oil. Twelve dose levels ranging from 0.25 to 4.0 g/kg were included in the study. Although there were 32 animals in the study, many dose groups consisted of only one animal. The "approximate" LD_{50} was 0.5 g/kg. All deaths were delayed, and some animals remained comatose for several days. Other signs of toxicity were a rough coat, weakness, diarrhea, and a red crust above the eyes.

From this study, a level of 0.05 g/kg/day was chosen for administration to dogs in a chronic study. Four male beagles were dosed five times a week for 3 months. None of the dogs exhibited any signs of toxicity, including gross pathology and histopathology.

The Panel notes that derivatives of benzothiophene are highly toxic and many are carcinogenic. Because there are not enough toxicity data available to evaluate this ingredient, the Panel concludes that dibenzothiophene is not safe for OTC topical use in the treatement of acne.

(2) *Effectiveness.* The mechanism of action of debenzothiophene is thought to be the liberation of organic sulfur (Ref. 1), although this has not been well studied. In vitro testing of dibenzothiophene was done using the plate diffusion method (cup plate) with *Staphylococcus aureus (S. aureus)* and "a casual mixed culture or organisms found inhabiting normal skin" (Ref. 1). The site was not specified. Falcon plastic assay spiders were inserted into cups filled with 5.0 percent dibenzothiophene cream or lotion and then placed in wells in sterile agar. After 24 hours' incubation at 37° C, the zone of inhibition was measured. The zone of inhibition against *S. aureus* was 22 millimeters (mm) for the lotion and 21 mm for the cream. With the mixed culture, the zone was 40 mm for the lotion and 32 mm for the cream.

There are several unpublished clinical trials on the effectiveness of dibenzothiophene. One study of 82 patients used 5 percent dibenzothiophene in 10 different creams and lotions (Ref. 1). Some also contained hexachlorophene, sulfur, neomycin, and a cosmetic pigment. Twelve patients has excellent results; 57 had fair results and 13 had results rated as "minimal." However, this study did not meet the Panel's criteria. The specifics of the study were not given. The study was not double-blind or controlled. No definitions of how acne was measured or of treatment results were included. In addition, patients used many other treatments including soaps, systemic antibiotics, "something to relieve premenstrual tension and irregularity," superficial X-ray therapy, ultraviolet light, and staphylococcal vaccine. The length of time necessary to achieve the results was also not specified.

In another study (Ref. 1), 16 patients with Grade I to III acne (based on number of acne lesions) were treated with 5 percent dibenzothiophene cream and lotion. The patients were given no other therapy and used the cream or lotion three or four times daily. Results showed nine patients excellent, three much improved, three improved, and one worse. There was no control in this trial. Also, it was not clear how long it took to achieve the results.

A study on 51 patients treated with 5 percent dibenzothiophene for 3 months showed the following results: 13 excellent, 20 good, 8 fair, and 9 poor. No explanation was given for the one patient who apparently dropped out of the study. Some patients with cystic acne were treated concurrently with superficial X-ray therapy and vaccines. No specific information was given on frequency of application or definition of results (Ref. 1).

Another unpublished study was conducted on over 100 patients treated with 5 percent dibenzothiophene cream or lotion (Ref. 1). No details were given on the frequency of application, other medications used, or the length of the trial. Although no specific results were given, the investigators noted "it is an effective topical agent with good patient acceptance."

Although dibenzothiophene appears useful in the treatment of acne, there are no controlled clinical trials that meet the effectiveness criteria established by the Panel. The Panel concludes that this ingredient is of questionable effectiveness for OTC use in the treatment of acne.

(3) *Evaluation.* Dibenzothiophene has been placed in Category II because the safety data are quite limited. The compound was fairly toxic when given in an acute study. There was no suggestion of a mechanism of action. Also, the Panel considered the only chronic study poorly designed (only four dogs, no controls). The Panel is also concerned about toxicity because many derivatives of benzothiophene are highly toxic.

Reference

(1) OTC Volume 070096.

m. *Estrone.* The Panel concludes that estrone is not safe and is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Estrone is a metabolite of estradiol, an ovarian hormone. Generally the estrogens used in therapy are readily absorbed through the skin and can have systemic effects. During enterohepatic circulation, they are gradually oxidized and conjugated to less active products. Normally, up to 100 μg of estrogens are excreted daily by females at the midcycle ovulating maximum, up to 25 μg per day by males, and 30 mg per day in pregnant females who are near term. The usaul prescription dose of oral estrone given for various uses is 5 mg. Nausea is the most frequent symptom associated with oral estrogen therapy. In addition, it has been suggested that there is an increased risk of thromboembolism and cancer as a result of long-term estrogen therapy (Ref. 1).

The use of creams containing estrone 2.5 mg/g, which results in a daily does of 5 mg, had not caused obvious side effects (Refs. 2, 3, and 4). However, it is generally agreed that, to achieve local efficacy, estrone must be absorbed in sufficient quantity to cause systemic effects (Refs. 5 and 6). The Panel notes that these studies were not looking specifically for side effects. The studies were short term and included small numbers of patients. The panel concludes that estrone is not safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Estrogens were first reported as being used topically in the treatment of acne in the late 1940's. Acne was thought to be primarily caused by an endocrine disturbance affecting the pilosebaceous unit (Refs. 2, 3, and 7). Acne patients were shown to have an increased ratio of androgens to estrogens, the androgens being responsible for pilosebaceous gland activity. It was believed that topical application of estrogens would result in a more normal androgen-estrogen ratio,

resulting in reduction of sebum secretion and subsequent reduction of acne lesions. The substance most commonly used in these studies was a water-soluble, conjugated equine estrogen, sodium estrone sulfate. One mg estrone is equal to 10,000 I.U.

Shapiro (Ref. 7) treated 30 patients with acne that had not responded to the usual treatments with 2.5 to 5 mg estrone applied two to four times daily. Within 6 weeks he noticed improvement shown by a decrease in papules, pustules, and oiliness. The applications were then gradually reduced to once daily or once every other day. After 16 weeks of treatment, Shapiro reported that 20 of the 30 patients showed a satisfactory clinical remission. He stated that treatment with estrone offered "a promising approach to therapy-resistant acne vulgaris." The Panel notes that Shapiro expressed the patients' comedones during the treatment period. (The word "express," as used in dermatology, means to remove contents by squeezing or pressing.) The Panel considers this study not well controlled because expression is also a type of therapy.

In a later study, Shapiro (Ref. 3) tested the effectiveness of estrone in 25 patients. Again he chose patients who had not responded to the methods of treatment usually used then, including X-ray therapy, ultraviolet irradiation, dietary regimens, and various peeling agents. The total daily application of estrone was 5 mg. Treatment was continued for 1 to 7 months (average 4 months). The estimated total amount of estrogenic substances applied in this time ranged from 150 to 700 mg.

As in the previous study by Shapiro (Ref. 7), lesions were not counted. Evaluation was based on clinical judgment, i.e., whether there was an apparent decrease in skin oiliness or a reduction of pustules, papules, comedones, and cysts. Shapiro reported that excellent results were obtained in 15 patients (60 percent). Results were good in four patients and fair in three. Three patients could not tolerate the cream and were dropped from the study.

Shapiro (Ref. 3) also monitored changes in menstrual cycle, breasts, and libido to determine any systemic effects. He found no adverse effects from the use of estrone.

Sawicky, Danto, and Maddin (Ref. 2) evaluated the effectiveness of estrone in a half-face study of 26 patients. Half of the face was treated with 2.5 mg estrone daily. The vehicle control was applied to the other half of the face. The patients were unaware of which side of the face received the active treatment. Patients were treated for 2 to 16 weeks with the total amount of hormone applied ranging from 38 to 204 mg.

The investigators found estrone to be more effective on cystic lesions than on papules and pustules. Three male patients with cystic acne showed great improvement on the side of the face treated with estrone. Patients with papules and pustules were reported to have moderate, slight, or no improvement.

The clinical data from several researchers (Refs. 8, 9, and 10) indicate that perhaps males benefit more from topical estrogen therapy than females. For example, Whitelaw (Ref. 8) used a cream containing 0.625 mg estrone/g and found that 55 percent of his male patients (76 patients) were much improved after treatment for 6 months or more, but that only 21 percent of the female cases (23 patients) responded satisfactorily.

Using diethylstilbestrol dilaurate (a synthetic estrogen) lotion on 84 patients, Philip (Ref. 9) came to a similar conclusion. Patients applied 3.5 to 7 mg diethylstilbestrol daily. The dosage was gradually reduced after 6 weeks of treatment. The length of treatment, however, is unclear. Of the 36 males in the study, 33 (92 percent) showed good or excellent improvement. Ten (21 percent) of the 48 females were reported as good or excellent at the conclusion of the trial. Philip concluded that estrogen therapy "appears to be effective and desirable only in the management of acne vulgaris in the adolescent male."

Peck, Klarmann, and Spoor (Ref. 10) reported good or excellent results in 55 of 69 patients treated with a lotion containing estrone. The lotion also contained numerous other ingredients including zinc oxide, zinc sulfide, sulfur, salicylic acid, aluminum hydroxide, and oxyquinoline. The authors believed the lotion to be somewhat more effective in males than in females. They stated that natural estrone was more satisfactory than synthetic estrogenic hormones such as diethylstilbestrol.

The researchers also stated that the optimal concentration of estrone is 50,000 I.U./ounce (5 mg/ounce). This is considerably lower than the concentrations used in the studies described above (150,000 to 600,000 I.U./ounce). Concentrations above 50,000 I.U. would produce undesirable systemic effects. Peck, Klarmann, and Spoor (Ref. 10) found no effect of topical estrogen on blood estrogen level, menstrual cycle, or vaginal cornification after 1 month of applications to 12 subjects.

Estrone was contained in only one product submission to the Panel (Ref. 11). The concentration of estrone in this product is quite low—0.333/mg ounce (3,333 I.U./ounce).

Damrau (Ref. 12) tested the estrone cream described above (which also contains salicylic acid) on 45 subjects. He reported that the action of the cream is hyperemizing, meaning that it causes an increased blood flow to a part of the body. It is keratolytic and "produces an unusual degree of absorption and effectiveness of estrone."

A control group of 16 subjects used a "leading acne product" (ingredients not specified). Both groups were instructed to apply a thin layer of cream over the affected area of the face twice daily. The total amount was one-half teaspoonful. After 5 minutes the cream was washed off with soap and water.

The total amount of estrogenic hormone applied in 1 month was under 2 mg (20,000 I.U.). Length of treatment was 6 months in the estrone group and 3 months in the control group.

The results showed 80 percent of the estrone-treated patients improved after 1 month, with 2 percent of the patients completely cleared. After 6 months, 73 percent of the patients were completely cleared, and the remaining patients were improved. In the control group after 3 months, 75 percent were improved and the rest showed no change.

Overall acne counts decreased from 6.2 to 0.6 in the treated group and from 6.2 to 4.8 in the controls. The acne count was not specified as to lesion type. Although the results were not analyzed statistically, Damrau (Ref. 12) concluded that the estrone cream was a superior product.

Most of the studies reviewed by the Panel reported favorable results for estrone in the treatement of acne. Several authors in medical journals (Refs. 13, 14, and 15), however, held that local estrogen therapy was of limited value.

It is apparent from the review of the literature that there has been little work done in the last 20 years to indicate that topically applied estrogen is an effective ingredient to treat acne. None of the studies reviewed met the standards the Panel has recommended to determine effectiveness. None of the studies were randomized or double-blind and most did not use a vehicle control. Methods of evaluating patients were not rigidly defined and in some cases were difficult to determine. Results were not statistically analyzed.

The effectiveness of topical estrogens in acne is not attributed to a local effect on the skin (Ref. 16). Theoretically, estrongens may affect the sebaceous glands by inhibiting androgen

production. The Panel believes, however, that very high concentrations of estrone would have to be applied topically for sufficient amounts to be absorbed systemically to produce this effect.

The Panel notes that in the only submission on estrone, this ingredient occurs in such a small concentration (3,333 I.U./ounce) that a systemic effect is unlikely. The panel concludes the estrone is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed estrone in Category II because it is toxic at the high concentrations needed to produce an effect on acne lesions.

References

(1) Murad, F., and A. G. Gilman, "Estrogens and Progestins," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 1423–1450, 1975.

(2) Sawicky, H. H., J. L. Danto, and W. S. Maddin, "Clinical Evaluation of Topically Applied Estrogen Cream in Acne Vulgaris," *Archives of Dermatology and Syphilology,* 68:17–20, 1953.

(3) Shapiro, I., "Estrogens by Local Application in Treatment of Acne Vulgaris," *Archives of Dermatology and Syphilology,* 63:224–227, 1951.

(4) Holbrook, A. A., "The Treatment of Acne Vulgaris in Teen-age Males with Oral and Topical Administration of Estrogenic Hormone," *Wisconsin Medical Journal,* 52:425–428, 1953.

(5) Cunliffe, W. J., and J. A. Cotterill, "The Acnes: Clinical Features, Pathogenesis and Treatment," W. B. Saunders Co., Philadelphia, p. 226, 1975.

(6) Dickerson, J., et al., "Efficacy of Estradiol Vaginal Cream in Postmenopausal Women," *Clinical Pharmacology and Therapeutics,* 26:502–507, 1979.

(7) Shapiro, I., "Estrogenic Treatment of Acne Vulgaris. A Preliminary Report," *Journal of the Medical Society of New Jersey,* 46:128–129, 1949.

(8) Whitelaw, M. J., "The Treatment of Adolescent Acne with Topical Application of Estrogens," *Journal of Clinical Endocrinology and Metabolism,* 11:487–491, 1951.

(9) Philip, A. J., "Tropical Estrogens in Acne Vulgaris," *New York State Journal of Medicine,* 51:1313–1314, 1950.

(10) Peck, S. M., E. G. Klarmann, and H. J. Spoor, "Treatment of Acne Vulgaris with Estrone," *Archives of Dermatology,* 70:452–467, 1954.

(11) OTC Volume 070106.

(12) Damrau, F., "Acne Vulgaris (Evaluation of a New Estrogenic Cream)," *Medical Record and Annals,* 54:219–220, 1961.

(13) Kline, P. R., "Modern Treatment of Acne Vulgaris," *Journal of the Medical Society of New Jersey,* 51:97–101, 1954.

(14) "Acne Vulgaris," unsigned reply to letter to the editor, *Journal of the American Medical Association,* 155:1547–1548, 1954.

(15) "Oestrogen Ointment and Acne," unsigned reply to letter to the editor, *British Medical Journal,* 1:1450, 1954.

(16) Pochi, P. E., and J. S. Strauss, "Sebaceous Gland Suppression with Ethinyl Estradiol and Diethylstilbestrol," *Archives of Dermatology,* 108:210–214, 1973.

n. *Magnesium sulfate.* The Panel concludes that magnesium sulfate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Magnesium sulfate is also known as epsom salts. One gram is equivalent to 4.06 millimoles or 8.12 milliequivalents (meq) of magnesium (Ref. 1). The primary use of this salt is as a cathartic, where the usual dose is 15 g. Although the mechanism of action may be fluid retention due to an osmotic gradient, absorption of up to 20 percent does occur and can result in symptoms of magnesium intoxication in persons with kidney failure (Ref. 2). A study of five patients with kidney insufficiency who received high doses of magnesium described symptoms of hypermagnesemia (an abnormally large magnesium content in the blood plasma) as nausea, vomiting, malaise, hypotension, and drowsiness (Ref. 3).

In evaluating magnesium sulfate for OTC use as a laxative, one Panel suggested that a warning label for people with kidney disease be included on products in which a daily dose would be more than 50 meq (40 FR 12910). In evaluating this drug as an antacid, the Advisory Review Panel on OTC Antacid Drug Products suggested a similar warning in its recommendations published in the **Federal Register** on April 5, 1973 (38 FR 8719).

Other therapeutic uses of magnesium sulfate include treatment of eclampsia (convulsions and coma occurring in pregnancy or after childbirth) and hypomagnesemia (an abnormally low magnesium content in the blood plasma). For eclampsia magnesium sulfate can be given intramuscularly or intravenously. Magnesium sulfate functions as a sedative and anticonvulsant (Ref. 4). For treatment of hypomagnesemia, magnesium sulfate can be given as intramuscular doses of 2 g four times daily, or as intravenous doses of 2 to 4 g daily (Ref. 1).

Magnesium sulfate has also been extensively used topically to alleviate local inflammatory conditions. No adverse effects were noted (Ref. 5). Because magnesium is poorly absorbed through the skin (Ref. 6), it is unlikely that, even in patients with impaired kidney function, topical use could result in absorption of magnesium in sufficient quantities to cause systemic toxicity. The Panel concludes that magnesium sulfate is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* The Panel received one product submission containing magnesium sulfate at concentrations of 40 to 43 percent (Ref. 7). The Panel notes that this ingredient is formulated in a hydrophilic ointment base, a known comedolytic agent. According to the submission (Ref. 7), the mechanism of action of magnesium sulfate is "drawing inflammation to the surface of the skin by osmotic pressure." Another submission included a report of a study in which magnesium sulfate was used to treat a dermatological condition (Ref. 8). However, no information on the use of magnesium sulfate in the treatment of acne was included.

There are no studies in the submission or in the medical literature indicating that magnesium sulfate is of value in treating acne. The Panel concludes that magnesium sulfate is not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel has placed magnesium sulfate in Category II because there are no studies that demonstrate that this ingredient is effective in the treatement of acne.

References

(1) Peach, M. J., "Cations: Calcium, Magnesium, Barium, Lithium, and Ammonium," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 790–791, 1975.

(2) Fingl, E., "Laxatives and Cathartics," *in* "The Pharacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, p. 980, 1975.

(3) Randall, R. E., Jr., et al., "Hypermagnesemia in Renal Failure. Etiology and Toxic Manifestations," *Annals of Internal Medicine,* 61:73–88, 1964.

(4) Taylor, E. S., "Beck's Obstetrical Practice and Fetal Medicine," 10th Ed., Williams and Wilkins Co., Baltimore, pp. 369–371, 1976.

(5) Chernick, W. S., "The Ions: Potassium, Calcium, Magnesium, Fluoride, Iodide, and Others" *in* "Drill's Pharmacology in Medicine," Edited by J. DiPalma, McGraw-Hill, New York, p. 948, 1971.

(6) Birmingham, D. J., "Cutaneous Absorption and Systemic Toxicity," *in* "Cutaneous Toxicity," Edited by V. A. Drill and P. Lazar, Academic Press, New York, p. 53, 1977.

(7) OTC Volume 070245.

(8) OTC Volume 070276.

o. *Phenolates (phenol and phenolate sodium).* The Panel concludes that the phenolates (phenol and phenolate sodium) are not effective and that there are insufficient data available to permit final classification of their safety in concentrations of 1.5 percent or less for OTC topical use in the treatment of acne.

The Panel considers phenol and phenolate sodium as a single ingredient when both are contained in a product

formulation. The total level of phenol equals the sum of the phenol and phenolate sodium concentrations.

(1) *Safety.* The potential toxicity of phenol in concentrations greater than 1.5 percent was described by the Advisory Review Panel on OTC Antimicrobial I Drug Products elsewhere in the **Federal Register** (39 FR 33121) published September 13, 1974. This Panel agreed with that assessment and further described the toxicity of phenol in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Phenol was considered of questionable safety for OTC topical use in concentrations less than 1.5 percent. The Panel has received no new data that leads it to change this evaluation.

The Panel concludes that there are insufficient data to adequately determine the safety of phenol in concentrations less than or equal to 1.5 percent. The reason for this decision is the lack of controlled studies evaluating (1) the absorption from small areas of application to either broken or intact skin, (2) the local effects on wound healing, and (3) the potential for hypersensitivity or idiosyncratic reactions.

(2) *Effectiveness.* Phenol has anesthetic, bactericidal, and fungicidal properties (Ref. 1). Apparently, the anesthetic effect of phenol is the reason for its inclusion in acne products.

Phenol has been studied in a variety of inflammatory diseases, athlete's foot, and infected eczema (Refs. 1, 2, and 3). However the Panel could find no clinical trials examining the effectiveness of phenol in treating acne.

Plewig and Kligman (Ref. 4) state that most "traditional exfoliants turned out to be surprisingly weak or ineffective: phenol, resorcinol, beta-naphthol, sulfur, Vleminckx's solution and sodium thiosulfate. Hence, only a few agents which cause peeling are in fact comedolytic. The probable explanation is that most 'peelers' affect only the epidermis and not the follicular infrainfundibulum."

The Panel concludes that there are no data to show that the phenolates are clinically effective in the treatment of acne.

(3) *Evaluation.* In the absence of clinical trials demonstrating effectiveness in the treatment of acne, the Panel has placed phenolates (phenol and phenolate sodium) in Category II.

References

(1) Freeman, C. W., J. G. Gathings, and T. Gopinathan, "Evaluation of Chloraderm as a Dermatologic Agent. A Study of Bacteriologic, Fungicidal and Antipruritic Properties," *Medical Annals of the District of Columbia,* 30:213–215, 1960.

(2) OTC Volume 070101.

(3) OTC Volume 070247.

(4) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, p. 278, 1975.

p. *Phenyl salicylate.* The Panel concludes that phenyl salicylate is not effective and that there are insufficient data available to permit final classification of its safety for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel reviewed the safety of phenyl salicylate in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Since the Panel made those recommendations, no additional safety data were submitted. In the absence of data on irritation, sensitization, and effects on broken skin, the Panel concludes that phenyl salicylate is of questionable safety for topical use in the treatment of acne.

(2) *Effectiveness.* The Panel received only one product submission on phenyl salicylate (Ref. 1). This submission contained no data and the Panel could not find mention in the medical literature of phenyl salicylate for the treatment of acne. The Panel concludes that phenyl salicylate is not effective in the OTC topical treatment of acne.

(3) *Evaluation.* The Panel has placed phenyl salicylate in Category II because there are no effectiveness data available. The Panel believes there is no rationale for the use of this ingredient in the treatment of acne.

Reference

(1) OTC Volume 070004.

q. *Pyrilamine maleate.* The Panel concludes that pyrilamine maleate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Pyrilamine maleate is a widely used antihistamine. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products reviewed pyrilamine for that use and considered it safe in its recommendations published in the **Federal Register** of September 9, 1976 (41 FR 38391). The recommended oral dose is 25 to 50 mg three to four times daily.

Submissions to the Panel indicated no toxic effects or irritation from the topical use of pyrilamine maleate (Refs. 1 and 2). Patch tests on a combination product containing 1 percent pyrilamine maleate showed no cutaneous sensitivity (Refs. 1 and 2), although this ingredient is known to be a mild sensitizer when used topically.

In the Panel's view, pyrilamine maleate is safe for topical use.

(2) *Effectiveness.* The Panel is not aware of any clinical trials demonstrating the effectiveness of pyrilamine maleate in treating acne. According to the submissions received by the Panel (Refs. 1 and 2), pyrilamine maleate is used in acne treatment products as an antipruritic and is effective in treating wheals which are flat or raised lesions that may itch or burn and are typical of hives. The Panel believes it is irrational to use an antihistamine or antipruritic to treat acne. The Panel concludes that pyrilamine maleate is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed pyrilamine maleate in Category II because there is no rationale for the inclusion of an antihistamine in acne treatment products.

References

(1) OTC Volume 070046.

(2) OTC Volume 070047.

r. *Resorcinol and resorcinol monoacetate.* The Panel concludes that resorcinol and resorcinol monoacetate are safe but are not effective as single ingredients for OTC topical use in the treatment of acne.

(1) *Safety.* Resorcinol is a phenolic compound which was reviewed by this Panel in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** The Panel considered resorcinol in high concentrations (10 percent) to be unsafe for topical use. As discussed in the publication mentioned above, resorcinol resembles phenol in its systemic actions but causes more prominent central stimulation. Acne preparations contain up to 2 percent resorcinol or 3 percent resorcinol monoacetate.

Patty (Ref. 1) reported that the cutaneous application of solutions or salves containing from 3 to 25 percent resorcinol could result in local toxicity including edema, itching, dermatitis, or peeling. Systemic toxicity could also occur. Some signs of systemic toxicity include restlessness, methemoglobinemia, convulsions, or death. The Panel recognizes that the severity of the signs would be related to the dose.

Patty also noted that ingestion of 4 g resorcinol caused dizziness and sleepiness in a 4-year-old child. In another case after ingestion of 8 g resorcinol the signs and symptoms included fall in blood pressure and low

body temperature. Both patients recovered.

A combination of 8 percent sulfur and 1 percent resorcinol was used in an eye irritation study conducted in rabbits. This study confirmed the potential for irritation if the sulfur-resorcinol combination was allowed to remain in the eye. Washing the eyes after 30 seconds of exposure greatly reduced the irritation (Refs. 2 and 3).

Acute dermal irritation studies in rabbits confirmed the mild irritation potential of this combination (Refs. 2 and 3).

Subacute studies (Refs. 2 and 3) of the above combination were conducted in rabbits on both normal and abraded skin. Some of the studies were done over 20-day periods and others over 30-day periods. Dose levels of 0.1, 0.3, and 1.0 g/kg body weight were applied daily to the shaved backs of rabbits (both males and females). At the end of these studies, hematology studies, urinalysis, gross pathology, and histopathological evaluations were done. In general, all values within normal limits, except that skin changes of an irritant nature were noted for the higher dose levels.

Although these studies appeared to be comprehensive, well-controlled, and well-conducted, the Panel noted several deficiencies. For example, in the dermal exposure of rabbits about 6 to 7 percent of the body surface area was exposed to the sulfur-resorcinol combination. However, in actual human use for acne, the area of application includes the face, shoulders, chest, and back and represents about one-half of the body surface area. In addition, the study indicated the material was applied once daily. But in the treatment of acne in humans the recommended application is three times daily. Also, at the highest dose used, 1 g/kg/day, the total exposure of the rabbit to resorcinol amounted to 20 mg/kg/day with a limited surface area for absorption. This study did not address the Panel's major concern about the absorption potential when large amounts of resorcinol are applied to large surface areas, particularly when it is applied three times daily.

In subchronic studies, resorcinol used alone was administered by various routes to rats and rabbits. The only noteworthy toxicological finding was an increase in the weight of the thyroid. In the rat a no-effect level was reported as 154 mg/kg given twice daily subcutaneously for up to 38 days (Ref. 4).

The results of the micronucleus test in rats and a modified Ames test using *Salmonella typhimurium* showed that resorcinol was not mutagenic (Refs. 5 and 6). Following application to the skin of mice for 368 days or to the skin of the rabbit ear for up to 160 weeks, resorcinol was not found to be carcinogenic (Refs. 7 and 8).

The Panel also received limited data on human exposure to airborne resorcinol in the work place. Workers were exposed for 10 years or longer to an "inhaled threshold limit value" of 10 ppm. This equals a total inhaled dose of about 6.43 mg/kg/day. Workers did not complain of irritations or discomfort, nor did they display abnormal clinical signs referrable to the thyroid gland, central nervous system, or hematological system. Blood determinations for thyroid-stimulating hormone (TSH) and thyroid hormone (T_4) showed that values were within the normal range (Refs. 9 and 10).

In vitro skin penetration studies were done using excised human skin to determine the percutaneous absorption of resorcinol applied as a 2-percent resorcinol-8 percent sulfur cream (Ref. 11). Data indicated a lag time of about 3 hours followed by a maximum rate of skin penetration of 6.1 $\mu g/cm^2/h$. This would yield a pharmacokinetically calculated steady-state blood level of resorcinol of 19 $\mu g/100$ mL in persons with acne. (Pharmacokinetics is the study of the action of a drug over a period of time. Steady state refers to the point at which the amount of drug absorbed is equal to the amount eliminated.) This level is reported to be 1/161 to 1/653 of the blood levels estimated to have been reached in leg-ulcer subjects who had systemic toxicity (ref. 11).

Plasma, tissue distribution, and excretion data indicated that resorcinol (containing trace amounts of ^{14}C-resorcinol) was rapidly eliminated from the rat following a single subcutaneous injection of 10, 50, or 100 mg/kg (Ref. 12). Resorcinol was also rapidly eliminated after repeated dosing with a total daily dose of 100 mg/kg given daily over 14 days. The amount of the resorcinol dose eliminated in the urine was 85.7 percent in about 3 hours and 93.6 percent in 24 hours. Between 1 hour and 24 hours following injection, plasma levels decreased from 0.32 percent to 0.01 percent of the administered dose. One hour after administration, the amount of the administered dose contained in potential target organs was 0.005 percent in the thyroid, 0.02 percent in the brain, and 0.03 percent in the spleen. Plasma half-life was determined using doses of 50 and 100 mg/kg. The half-life was 0.5 hour during the first 2 hours after treatment and about 4 hours thereafter. No significant difference in plasma elimination rates were observed between the single dose and the repeated doses of resorcinol. Organ disposition data showed that vital and potential target organs did not accumulate resorcinol during the time in which plasma levels were declinng (Ref. 12).

Resorcinol excreted in rat urine was about 75 percent glucuronide and 25 percent sulfate ester. No free resorcinol was detected (Ref. 12).

The percutaneous absorption and metabolic disposition of resorcinol were investigated in three human volunteers. Resorcinol 2 percent in a hydroalcoholic vehicle was applied to the face, neck, shoulders, back, and chest (about 30 percent of the available skin area). Blood samples were collected 1 week after this first drug application and weekly for 3 more weeks. No resorcinol was detected at the limit of the assay (0.5 $\mu g/mL$).

After 2 weeks of continuous application (800 mg/subject/day), an average of 1.64 percent of the administered dose was excreted in the urine at 24 hours. The excreted resorcinol was in the form of either the glucuronide or the sulfate ester. Thyroid function was assessed at 2, 3, and 4 weeks and found to be normal. Blood chemistries were also normal in all subjects throughout the study (Ref. 12).

The Panel concludes that 2 percent resorcinol or 3 percent resorcinol monoacetate is safe for OTC topical use in the treatment of acne. However, the Panel is concerned about the potentially large surface area of the body that could be available for absorption if an acne preparation were applied to the entire upper torso (about 1 square meter of absorption area through broken skin). For this reason the Panel recommends the following warning for acne combinations containing resorcinol: "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body." (See part III. paragraph A.2. above—Category I labeling.)

(2) *Effectiveness.* The concentration of resorcinol generally used in acne products is 1 to 2 percent. Resorcinol monoacetate 3 percent is equivalent to 2 percent resorcinol. Resorcinol has antibacterial, antifungal, and mild keratolytic activity. Resorcinol monoacetate slowly liberates resorcinol, producing a milder, but longer-lasting effect (Ref. 13).

As mentioned above, sulfur and resorcinol are often used together in the treatment of acne, but it is difficult to document the historical origin of this combination. The precise mechanism of action of these combinations has never

been proven, but may depend on keratolysis or on the ingredients' ability to produce erythema and desquamation with enhanced resolution of comedones, papules, and pustules. (For a review of sulfur-resorcinol combinations, see part III. paragraph D.1. below—Category I combination product—sulfur-resorcinol.)

No study has examined the effectiveness of resorcinol used as a single ingredient in the treatment of naturally occurring acne. The Panel concludes that resorcinol is not effective for OTC topical use as a single ingredient in the treatment of acne.

(3) *Evaluation.* In the absence of data documenting the effectiveness of resorcinol and resorcinol monoacetate used alone in the treatment of acne, the Panel has placed these ingredients in Category II.

References

(1) Patty, F., "Industrial Hygiene and Toxicology," 2d Ed., Vol. 2, Interscience Publishing Co., New York, p. 1379, 1963.

(2) OTC Volume 070234.

(3) OTC Volume 070235.

(4) OTC Volume 070284.

(5) Hossack, D. J. N., and J. C. Richardson, "Examination of the Potential Mutagenicity of Hair Dye Constituents Using the Micronucleus Test," *Experientia,* 33:377–378, 1977.

(6) McCann, J., et al., "Detection of Carcinogens as Mutagens in the *Salmonella*/Microsome Test: Assay of 300 Chemicals," *Proceedings of the National Academy of Sciences,* 71:5135–5139, 1975.

(7) Van Duuren, B. L., and B. M. Goldschmidt, "Cocarcinogenic and Tumor-Promoting Agents in Tobacco Carcinogenesis," *Journal of the National Cancer Institute,* 56:1237–1242, 1976.

(8) Stenback, F., "Local and Systemic Effects of Commonly Used Cutaneous Agents: Lifetime Studies of 16 Compounds in Mice and Rabbits," *Acta Pharmacologica et Toxicologica,* 41:417–431, 1977.

(9) OTC Volume 070287.

(10) OTC Volume 070288.

(11) OTC Volume 070271.

(12) OTC Volume 070290.

(13) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasitides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, p. 991, 1975.

s. *Sodium thiosulfate.* The Panel concludes that sodium thiosulfate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Sodium thiosulfate, $Na_2O_3S_2$, is a water-soluble reducing agent used in veterinary medicine to treat ringworm and mange (Ref. 1). It has also been used extensively as an antidote for cyanide posioning in humans (Ref. 2). In this treatment, the stomach contents are washed out with a solution of 5 percent sodium thiosulfate, leaving 10 g of the solution in the stomach.

The lowest subcutaneous dose known to cause death in the rabbit is reported as 4 g/kg (Ref. 3). The intravenous LD_{50} in the rat is greater than 2.5 g/kg (Ref. 1). One study used oral gavage and determined the minimal lethal dose in the rat to be greater than 5 g/kg (Ref. 4). At this dose, labored breathing and panting were the only symptoms observed. Sodium thiosulfate at concentrations up to 22 percent was found to be nonirritating to intact or abraded rabbit skin occluded for 24 hours and read at 24 and 72 hours (Ref. 4).

The Panel concludes that sodium thiosulfate is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Sodium thiosulfate is contained in marketed acne products in concentrations of 2 to 8 percent. The apparent rationale for the use of this ingredient is a potential keratolytic and antibacterial activity either by sodium thiosulfate itself or by sulfur that is liberated when the compound comes in contact with the skin.

Numerous unpublished studies have evaluated the effectiveness of sodium thiosulfate (Ref. 4). However, none of these studies met the effectiveness criteria set by the Panel. All involved a combination product containing sodium thiosulfate, resorcinol, and salicylic acid. None used a vehicle control. The method of patient evaluation and treatment results were usually not explained. In one study, the combination product mentioned above was tested on 74 patients with acne vulgaris. The results were as follows: 46 percent very good, 39 percent good, 8 percent "medium," and 7 perent poor. No other details were given.

In an uncontrolled clinical trial, Sewell (Ref. 5) evaluated 224 patients who had mild to severe acne. No mention was made of randomization or blinding. A sodium thiosulfate combination product was applied four times daily for 2 to 50 weeks. The patients also washed with a soap containing salicylic acid and sulfur. Of the 28 subjects using a 2-percent sodium thiosulfate-1 percent salicylic acid-1 percent resorcinol lotion, 64.3 percent showed marked improvement and the rest were improved by the end of the study. The other 196 patients applied an 8-percent sodium thiosulfate-2 percent salicylic acid-2 percent resorcinol lotion. Of these patients, 33.7 percent were improved and 65.8 percent were markedly improved. Sewell concluded that the sodium thiosulfate combinations were effective in the treatment of acne, although it is difficult to determine the contribution made by sodium thiosulfate as a single ingredient.

Hall and Lupton (Ref. 6) studied 44 patients with acne in a double-blind, half-face trial. One-half of each patient's face was treated with 8 percent sodium thiosulfate-2 percent salicylic acid-2 percent resorcinol. An alcohol-water vehicle was applied to the other half of the face. Treatment was twice daily for 8 weeks. Patients were allowed to continue medications they were previously using including abrasive cleansers and tetracycline. At the final evaluation, the researchers determined which side of the face showed greater improvement. In 19 patients, the treated side showed more improvement. Five patients were more improved on the placebo side. In the remaining patients, no difference was noted between the combination product and the placebo.

Although the effectiveness of sodium thiosulfate has been studied extensively, none of the studies have evaluated sodium thiosulfate as a single active ingredient. For this reason the Panel concludes that sodium thiosulfate is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* In the absence of data demonstrating effectiveness as a single ingredient in the treatment of acne, the Panel has placed this ingredient in Category II.

References

(1) Windholz, M., et al., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 1122–1123, 1976.

(2) Thienes, C. H., and T. J. Haley, "Clinical Toxicology," 5th Ed., Lea and Febiger, Philadelphia, p. 205, 1972.

(3) Fairchild, E., "Registry of Toxic Effects of Chemical Substances," Vol. II, United States Department of Health, Education, and Welfare, Cincinnati, p. 907, 1977.

(4) OTC Volume 070088.

(5) Sewell, J. W., Jr., "Therapeutic and Cosmetic Advantages of a Nonpigmented Acne Lotion," *CUTIS; Cutaneous Medicine for the Practitioner,* 1:473–476, 1965.

(6) Hall, J. H., and E. S. Lupton, "Topical Acne Therapy: A Double-Blind Study," *CUTIS; Cutaneous Medicine for the Practitioner,* 9:545–547, 1972.

t. *Tetracaine hydrochloride.* The Panel concludes that tetracaine hydrochloride is not safe and is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Tetracaine hydrochloride is a derivative of *p*-aminobenzoic acid similar to benzocaine. (For a discussion of benzocaine, see part III. paragraph B.1.c. above—Benzocaine.)

The aminobenzoic acid derivatives are known to cause allergic sensitivity reactions. Also, cross-sensitivity

between members of this group is frequently reported. Sensitivity tests such as skin, conjunctival, and patch tests are not considered reliable for predicting the possibility of allergic reactions (Ref. 1).

Tetracaine hydrochloride is used as a 0.5-percent solution for the topical anesthesia of the eye. On mucous membranes of the nose and throat, a 2-percent solution is used (Ref. 2). However, considering the large surface area of application and the possibility of long-term use in acne, the Panel concludes that tetracaine hydrochloride is not safe for OTC topical use in the treatment of acne because of the potential for sensitization.

(2) *Effectiveness.* According to a submission to the Panel, tetracaine hydrochloride, a local anesthetic, is included in acne preparations to help "relieve the irritation and discomfort usually associated with acne vulgaris" (Ref. 3).

Tetracaine hydrochloride was found to be one of the most effective and longest lasting drugs in a series of topical anesthestics studied by Adriani and Zepernick (Ref. 4). These researchers reported the maximum effective concentration as 1 percent. The concentration of tetracaine hydrochloride currently marketed in acne products is 0.25 percent.

There are no clinical trials establishing the effectiveness of tetracaine hydrochloride in treating acne. The Panel believes the use of a local anesthetic in acne treatment is irrational therapy and concludes that tetracaine hydrochloride is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed tetracaine hydrochloride in Category II because it is a recognized sensitizer and there is no rationale for the use of a local anesthetic in the treatment of acne.

References

(1) Swinyard, E. A., "Local Anesthetics," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, pp. 986–987, 1975.

(2) Ritchie, J. M., and P. J. Cohen, "Cocaine; Procaine and Other Synthetic Local Anesthetics," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 379–400, 1975.

(3) OTC Volume 070046.

(4) Adriani, J., and R. Zepernick, "Clinical Effectiveness of Drugs Used for Topical Anesthesia," *Journal of the American Medical Association,* 188:711–716, 1964.

u. *Thymol.* The Panel concludes that thymol is not effective and that there are insufficent data available to determine its safety for OTC topical use in the treatment of acne.

(1) *Safety.* The toxicology of thymol was discussed in the Panel's recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** The Panel determined that this ingredient is of questionable safety because of inadequate data evaluating the absorption of thymol from small areas of application to intact and broken skin. Data on the local effects of thymol on wound healing and thymol's irritation potential were also lacking. Acne submissions on thymol (Refs. 1 and 2) were reviewed and found to contain no new information. The Panel concludes that thymol is of questionable safety for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Thymol, an ingredient with antibacterial and antifungal properties, is used in acne preparations in concentrations of about 0.16 to 0.5 percent. At these low concentrations thymol has questionable antibacterial activity.

Several affectiveness studies (Ref. 3) have been reviewed by the Panel, but none evaluated thymol against a vehicle control. In one study, 60 subjects applied a 0.16-percent thymol scrub once or twice daily for 3 months. The patients were evaluated on a scale of 0 to 4 for comedones, papules, pustules, and oiliness at the pretreatment examination and at the conclusion of the study. Results showed that the subjects had significantly fewer acne lesions and less oiliness after 3 months than at the beginning of the trial ($p < 0.01$).

Thymol was also evaluated in an 8-week trial of 139 patients (Ref. 3). Forty-seven subjects applied a thymol gel; 44 subjects used a thymol lotion. The remaining patients used soap and water. Again, acne lesions were not counted. Evaluation of blackheads, whiteheads, papules, pustules, and oiliness was based on a severity scale (1 to 5). Analysis of results showed that the thymol gel and lotion were significantly more effective than soap and water in the overall evaluation at 8 weeks ($p < 0.05$ and 0.01, respectively). Treatment with soap only, however, also showed a statistically significant improvement over the initial examination ($p < 0.01$).

The Panel doubts that thymol is effective as a single active ingredient for treating acne. This ingredient has little or no antibacterial activity in the concentrations currently used in OTC acne products. To the Panel's knowledge, the effectiveness of this ingredient for treating acne has never been established in a vehicle-controlled clinical trial. Thymol is not listed in standard medical texts as beneficial in acne therapy. The Panel concludes that thymol is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* In the absence of data evaluating the effectiveness of thymol in a vehicle-controlled study for the treatment of acne, the Panel has placed thymol in Category II for effectiveness.

References

(1) OTC Volume 070002.

(2) OTC Volume 070155.

(3) OTC Volume 070156.

v. *Vitamin E.* The Panel concludes that vitamin E is not effective and that there are insufficient data available to determine its safety for OTC topical use in the treatment of acne.

(1) *Safety.* Vitamin E (*alpha*-tocopherol acetate) is a naturally occurring oil found primarily in plant materials (Ref. 1). The highest concentrations are found in wheat germ, sunflower seeds, soybean oils, and other plant sources. Deficiency of this vitamin in animals results in symptoms which closely resemble various conditions in the human that allegedly benefit from vitamin E therapy. These include disorders of the reproductive, muscular, cardiovascular, and hematopoietic systems (Ref. 2). (Hematopoietic refers to the production of blood cells.)

There are no notable pharmacological or toxicological effects of oral vitamin E, nor any explanation of its mode of action. Presumably, it exerts its effect by virtue of its properties as an antioxidant (Ref. 2). This concept is supported by observations on the protective effect of vitamin E against the lethality of carbon tetrachloride, mediated by lipid peroxidation (Ref. 3).

Vitamin E is absorbed like other fat-soluble vitamins, entering the blood stream by way of the lymph, and is distributed to all tissues. It is excreted primarily by the liver. Some metabolic derivatives, though, are found in the urine (Ref. 2). Numerous experiments indicate that high dietary intakes of vitamin E are apparently without toxic side effects (Ref. 4). Up to 800 I.U. (about 600 mg) per day for 3 years has been consumed in these studies.

Topical vitamin E is rated 0 to 1 as an irritant and 3 to 4 as a sensitizer. According to Fisher (Ref. 5), vitamin E was a sensitizer when used in an antiperspirant. Sensitization is more of a problem when the ingredient is occluded but also occurs when vitamin E is applied to the face. The risk of sensitization increases when vitamin E is used with a second preparation which causes peeling.

Because this vitamin accumulates in the body, has an unknown mechanism of action, and has some potential for sensitization, the Panel concludes that vitamin E used topically is of questionable safety.

(2) *Effectiveness.* The effectiveness of vitamin E used as a single ingredient in treating acne has never been established in a well-controlled clinical trial.

Nikolowski (Ref. 6) stated that acne vulgaris responds to combined vitamin E and vitamin A treatment. However, he was referring to systemic and not topical use of these drugs. In a later publication, Nikolowski (Ref. 7) stated that "alone and in combination with vitamin A and nicotinamide it (vitamin E) is helpful in treating kraurosis, purpuras, roentgen therapy, acne vulgaris * * *"

Schuppener (Ref. 8) successfully treated 93 acne patients with a combination of 0.1 percent vitamin E, 1 percent sulfur, 0.003 percent estradiol, 0.3 percent prednisolone, and vitamin A 50,000 I.U./100 mL in an ointment base. It is not clear which of the ingredients in the combination was responsible for the results.

The Panel believes there is no rationale for using vitamin E in topical acne therapy. The Panel concludes that vitamin E is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed vitamin E in Category II because the effectiveness of this ingredient in acne has not been demonstrated in a controlled clinical trial.

References

(1) Windholz, M., et al., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1290, 1976.

(2) Cohn, V. H., "Fat Soluble Vitamins: Vitamin K and Vitamin E," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 1595–1598, 1975.

(3) Plaa, G. L., "Toxicology of the Liver," *in* "Toxicology: The Basic Science of Poisons," Edited by L. J. Casarett and J. Doull, MacMillan Publishing Co., New York, p. 181, 1975.

(4) Scott, M. L., "Vitamin E," *in* "The Fat-Soluble Vitamins," Edited by H. DeLuca, Plenum Press, New York, p. 195, 1978.

(5) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, p. 419, 1973.

(6) Nikolowski, W., "Vitamin E in Dermatology and Related Fields," *Parfumerie und Kosmetik*, 37:65–68, 1956.

(7) Nikolowski, W., "Vitamin E and its Indication for the Treatment of Skin Disease," *Medizinische Klinik*, 55:415–418, 1960.

(8) Schuppener, H. J., "On the Clinical Aspects and Modern Therapy of Acne. Experience with a New Anti-Acne Agent," *Deutsches Medizinisches Journal*, 17:711–714, 1966.

v. *Zinc salts (zinc oxide, zinc stearate, and zinc sulfide).* The Panel concludes that the zinc salts (zinc oxide, zinc stearate, and zinc sulfide) are safe but are not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Zinc oxide, zinc stearate, and zinc sulfide are insoluble compounds of zinc. It is recognized that a small amount of zinc sulfide may be converted into the soluble zinc sulfate.

Several submissions were reviewed by the Panel, but none contained any toxicity data on the zinc compounds. It has long been recognized that the soluble zinc salts (zinc sulfate and zinc chloride) can cause toxicity when ingested and are somewhat corrosive on the skin. These salts have not been used topically in acne treatment and will not be discussed here. Oral zinc was discussed earlier in this document. (See part II. paragraph G. above—Use of Oral Zinc in the Treatment of Acne.)

Zinc stearate has a relatively long history of use in baby powders. Upon ingestion, it has "a low order of toxicity" (Ref. 1). Topically, salts of zinc have been used as astringents and mild "antiseptics," probably through the precipitation of protein by the zinc ion. Zinc salts have been incorporated into ointments, powders, and pastes and used as absorbents and protectives on epithelial surfaces, ulcers, and wounds (Ref. 2).

Gosselin et al. (Ref. 3) gave the insoluble zinc salts an estimated toxicity rating of 3, meaning that they are "moderately toxic" with a probable oral lethal dose of 0.5 to 5 g/kg. However, this was only an estimate, because, according to Gosselin et al., acute oral toxicity data could not be located. Aspiration of zinc stearate powder has produced fatal pneumonitis in infants. Powdered zinc oxide, however, does not cause a pulmonary reaction. Heat volatilization of zinc produces fine airborne particles of zinc oxide. Inhalation of freshly formed fumes may cause "fume fever," an influenza-like illness (Ref. 3).

McNally (Ref. 4), in a review on zinc toxicity, pointed out that zinc is normally found in the tissues of the human body and plants as well as being a common constituent in many foods. As much as 200 mg zinc was excreted by a human who had been fed a zinc-enriched meal the previous day.

Zinc sulfide lotion, an official topical preparation in Great Britain for many years, has been used in acne treatment (Ref. 5). This lotion is a mixture of various zinc sulfides, including polysulfides, and probably exerts its action on the skin as an astringent zinc salt. Zinc sulfide is reported to liberate hydrogen sulfide and elemental sulfur when placed in contact with water such as might be present on the skin (Ref. 6). The amount of hydrogen sulfide released is unknown but is thought to be below toxic levels. The Panel views this compound as elemental sulfur and considers it safe. (See part III. paragraph A.1.b. above—Sulfur.)

Despite the scarcity of toxicity data on zinc compounds, their long history of topical use without reported ill effect has led the Panel to conclude that these ingredients are safe for the treatment of acne.

(2) *Effectiveness.* The zinc salts have been used as astringents, protectives, and antiseptics.

In the past, white lotion (lotio alba) containing zinc sulfate, sulfurated potash, and water was frequently prescribed for the treatment of mild acne (Ref. 7). This lotion should be freshly compounded because it is unstable. It has an unpleasant odor and may cause excessive drying and redness of the skin.

It appears that any beneficial effect of white lotion in dermatologic conditions results primarily from the sulfur content of the lotion. Guth and Mansour (Ref. 8) stated that when it was freshly prepared, white lotion contained zinc monosulfide, zinc polysulfide, zinc hydroxide, and free sulfur suspended in a solution of sulfate, thiosulfate, and potassium ions. Exposure of the lotion to ultraviolet light or sunlight resulted in the formation of hydrogen peroxide which oxidized sulfides to sulfites and sulfates. When the lotion ages, there is a marked increase in free sulfur in its contents.

No effectiveness data on zinc salts were contained in the submissions to the Panel. To the Panel's knowledge, these ingredients have never been studied in a clinical setting for the treatment of acne.

The Panel concludes that there are no data to show that zinc salts are effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed the zinc salts (zinc oxide, zinc stearate, and zinc sulfide) in Category II because the effectiveness of these ingredients in treating acne has not been established in a controlled clinical trial.

References

(1) Deichmann, W. B., and H. W. Gerarde, "Toxicology of Drugs and Chemicals," Academic Press, New York, p. 639, 1969.

(2) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th

Ed., MacMillan Publishing Co., New York, pp. 948 and 1000–1001, 1975.

(3) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, pp. 69–70 and 99, 1976.

(4) McNally, W. D., "Medical Jurisprudence and Toxicology," W. B. Saunders Co., Philadelphia, pp. 192–196, 1939.

(5) Blacow, N. W., "Martindale. The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 455, 1972.

(6) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 9th Ed., Lange Medical Publications, Los Altos, CA, p. 246, 1977.

(7) Lubowe, I. I., "Modern Drugs in Dermatology," *Clinical Medicine*, 78:31–35, 1971.

(8) Guth, E. P., and Z. Mansour, "Photochemical Formation of Hydrogen Peroxide in White Lotion U.S.P.," *Journal of Pharmaceutical Sciences*, 56:376–379, 1967.

2. *Category II labeling.* The Panel concludes that certain labeling claims related to safety or effectiveness of an ingredient are unsupported by scientific data or, in some instances, by sound theoretical reasoning. The Panel therefore concludes that such labeling should be removed from the market.

Many claims from current labels have been placed in Category II either because they are vague, too broad, incomplete, modified incorrectly, or do not specifically indicate that the product effectively treats acne. Such labels mislead the lay person.

Many claims would appear to be acceptable; however, certain modifying words can make these claims unclear or even imprecise. For this reason, modifiers such as "fast" are not allowed. Examples of labels with vague modifers include the following:

"Clears up more pimples faster."

"Fights blemishes fast."

"Works fast against surface pimples."

"Clinically proven for prompt effective relief of acne."

"Instantly active medicated cream for acne pimples."

"Speeds up gentle, natural peeling of acne pimples."

Because the following labeling claims do not specifically indicate that the product effectively treats acne or imply that the product treats conditions other than acne, the Panel considers them misleading to the lay person:

"Helps prevent skin infections."

"Degerming."

"For temporary relief of minor soreness, irritations, and itching."

"Anesthetic."

"Pain-relieving antiseptic for the skin."

"Designed to protect against infection while it relieves local soreness, irritations, and dryness."

"Temporary relief of surface pain and discomfort."

"Helps clear up complexion problems."

"It not only goes to work drying out your pimples and blackheads, it does much more."

"Promotes healing."

"Aids healing."

"Helps heal acne and other minor skin conditions."

"Helps clear acne and related skin blemishes."

"Makes externally caused skin flare-ups look better while they're getting better."

The Panel believes that the following labeling claims are either inaccurate or not clear or may be meaningless to the consumer:

"Helps pull loosened oils from pores."

"Helps prevent the reinfection of pimples."

"Minimizes redness and itching."

"Aids in removing greasy oils from your skin. This can prevent the pores from becoming clogged again."

"Hypoallergenic."

"Bactericide."

"Hypoacnegenic."

"An effective antimicrobial against a wide variety of both gram positive and gram negative bacteria and fungi."

"Scientific treatment (or formula)."

"Vitaminized."

"Antiseptic."

"Special ingredients help dry the acne pimple."

"Special medicated skin cleanser."

"Erases worn out cells."

"Dermatologist-tested."

"Dries quickly to give long-term medication."

"Helps heal and clear acne by molecular action."

"100% medication, not a cosmetic."

"Continues to work over a longer period of time."

"Fights acne pimples."

"Kills facial germs."

"Kills germs commonly associated with acne."

"Strips away oils and waxy buildup that can lead to pimples and blackheads."

"Drinks up excess oils."

"Benefits oily and acne-blemished skin."

"Aids in the removal of superficial dry skin."

"Produces a soft, light peeling of the skin."

"Allows healthy new skin to grow."

"Helps normalize underlying tissue."

"Minimizes scarring."

"Anti-irritant."

"Helps involute inflamed pustules."

"Promoted involution of acne lesions and stimulates healing of the underlying tissues after effectively debriding any necrotic tissue which may be present."

"Bacteriostatic action, especially against Staph bacteria usually present in cases of infected acne lesions."

"Combines the same type of medications prescribed by many leading skin specialists for external application to pimples and blemishes associated with acne."

"Contains time-proved ingredients."

"For mild acne or maintenance therapy."

"Unique base keeps the medication in close contact to the skin all day long."

C. Category III Conditions

These are conditions for which the available data are insufficient to permit final classification at this time.

The safety and efficacy of the following ingredients were classified on the basis of activity and use as ingredients for the treatment of acne. Ingredients for which no acne claim is made, including ingredients that have been reviewed by the Panel and are ultimately placed in Category II for efficacy, may still be included in formulations for purposes other than the treatment of acne providing these ingredients are safe at the concentrations used.

1. *Category III active ingredients.*

Povidone-iodine
Salicylic acid

a. *Povidone-iodine.* The Panel concludes that povidone-iodine is safe but that there are insufficient data available to determine its effectiveness for OTC topical use in the treatment of acne.

(1) *Safety.* Povidone-iodine is a complex of iodine with a carrier agent, povidone (polyvinylpyrrolidone), which liberates free iodine in solution. The Panel reviewed the safety of povidone-iodine in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Povidone-iodine is considered safe for topical antifungal use in concentrations up to 10 percent. However, because the Panel concluded that in some instances iodine may be an irritant or sensitizer, particularly with long-term use and under occlusion, a caution label was recommended.

Povidone-iodine was submitted for the treatment of acne at a concentration of 7.5 percent in a detergent vehicle. The Panel concludes that providone-iodine is safe for OTC topical use in the treatment of acne. Again, a caution on irritation is recommended.

(2) *Effectiveness.* Povidone-iodine is an antimicrobial agent that has been

widely used on wounds, burns, and abrasions to treat or prevent surface infection. It has also been used as a scrub before and after surgery. Povidone-iodine contains about 10 percent available iodine.

Millikan (Ref. 1) evaluated the effectiveness of 7.5 percent povidone-iodine in two studies on acne patients. In the first study, providone-iodine was compared to its vehicle control in a double-blind fashion. Patients with mild acne washed two or three times daily with one of the treatments for 3 to 4 months. Evaluation was based on global impression. At the time of the study, 9 of the 10 patients using povidone-iodine were considered improved or much improved. In the control group, three out of seven patients were rated as improved.

Millikan (Ref. 1) also studied 27 patients with Grade II to IV acne (grading system based on type and location of lesions). Povidone-iodine was compared to the vehicle control, but in this study all patients also received systemic tetracycline concomitantly. There was no significant difference in effectiveness between the vehicle and providone-iodine. The author concluded that the oral tetracycline was responsible for this result.

Brown (Ref. 2) used a 7.5-percent povidone-iodine foam to treat 32 patients who had mild to moderate acne. The patients used the preparation twice daily for at least 6 months. Methods of evaluating patients were not defined. Of the 10 subjects using only povidone-iodine, 8 were good or fair at the conclusion of the trail. The remaining 22 patients used concomitant therapy including oral tetracycline, oral contraceptives, topical agents, and ultraviolet light. In this group, 19 patients showed a favorable response, but it is impossible to determine which ingredient produced this result.

In an uncontrolled study, Hudson (Ref. 3) evaluated the effectiveness of 7.5 percent povidone-iodine in 500 patients with moderate to severe acne. Patients washed with povidone-iodine one to three times daily for 3 months to more than 1 year. Tetracycline and sulfur lotions were used in addition to povidone-iodine. Hudson reported that the skin looked and felt less oily and that patient reaction was not defined and specific treatment results were not reported.

In an unpublished study (Ref. 4), 10 patients with Grade III acne (grading system was not defined) were treated twice daily with 7.5 percent povidone-iodine. A vehicle control was not used in this study. Patients were assessed by global impression 2 weeks after treatment and 4 weeks after treatment. All patients showed good or fair improvement. Lesion counts at the final visit compared to baseline showed decreases of 79 percent for pustules, 28 percent for open comedones, 18 percent for closed comedones, and 20 percent for papules.

The studies described above indicate that povidone-iodine may be an effective acne treatment; however, none of the studies met the Panel's effectiveness criteria. Deficiencies in study design included one or more of the following: (1) Lack of vehicle control, (2) concomitant therapy used, and (3) method of evaluating patients and treatment results not well defined. Also, none of the studies included a statistical analysis of results. Other studies were reviewed by the Panel (Ref. 4), but are not detailed here because they were not controlled and included concomitant therapy. The Panel concludes that povidone-iodine is of questionable effectiveness in the treatment of acne.

(3) *Proposed dosage*—(i) *Concentration.* Povidone-iodine 7.5 percent.

(ii) *Directions for use.* See part III. paragraph A.2. above—Category I labeling.

(4) *Labeling.* The Panel recommends the Category I labeling for products used in the treatment of acne. (See part III. paragraph A.2. above—Category I labeling.)

Cautions should include the following statement: "If redness or itching occurs or persists, discontinue use and consult a doctor or pharmacist."

(5) *Evaluation.* The Panel recommends that studies be conducted to determine the stability of povidone-iodine and availability of elemental iodine from the complex. The Panel also recommends one double-blinded, vehicle-controlled clinical trial to determine the effectiveness of povidone-iodine in the treatment of acne. These studies should be conducted in accordance with the guidelines set forth below for OTC topical acne ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

(1) Millikan, L. E., "A Double-Blind Study of Betadine Skin Cleanser in Acne Vulgaris," *CUTIS; Cutaneous Medicine for the Practitioner,* 17:394–398, 1976.

(2) Brown, E. J., "A Povidone-Iodine Skin Cleanser Foam in the Management of Acne Vulgaris," *British Journal of Clinical Practice,* 31:218–219, 1977.

(3) Hudson, A. L., "Betadine Skin Cleanser in Acne Vulgaris. Skin pH Determinations," *Clinical Trials Journal,* 10:23–25, 1973.

(4) OTC Volume 070239.

Salicylic acid. The Panel concludes that salicylic acid is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical use in the treatment of acne.

(1) *Safety.* Salicylic acid and its derivatives are a widely used group of compounds. Whether the salicylates are administered orally, rectally, intravenously, or cutaneously, systemic absorption occurs. Whatever the mode of administration, the toxic effects from overdosage are essentially the same, i.e., nausea, decreased ability to hear, tinnitus (ringing in the ears), confusion, metabolic disturbances, hallucinations, and death. The possible toxic reactions are collectively known as salicylism.

The Panel reviewed the toxicity of salicylic acid in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register**. Those data will not be repeated here. This discussion will include data dealing with salicylic acid in the treatment of acne or data received by the Panel since it completed its recommendations on topical antifungal drug products.

The major difference in the use of salicylic acid in acne as opposed to its use in fungal infections of the foot or groin is the very large surface area over which acne may be involved. In fact, roughly half of the body surface could be afflicted with acne. In adult humans, this would amount to close to 1 square meter of absorptive surface area.

Salicylic acid has been applied to relatively small areas of skin or in concentrations of less than 10 percent without apparent ill effects as a keratolytic agent in the treatment of various skin disorders. Salicylic acid for topical use on acne will be considered in concentrations ranging form 0.5 to 5 percent.

Most of the reports submitted for the use of salicylic acid in acne evaluated combination ingredient products. However, the following new data on salicylic acid as a single ingredient were contained in two submissions (Refs. 1 and 2). The acute oral LD_{50} of salicylic acid in male Sprague-Dawley rats was 800 mg/kg. When concentrations of 0.5 to 2 percent were applied to either normal or abraded skin of rabbits, salicylic acid was judged to be a mild irritant.

A lotion containing salicylic acid 2 percent was applied to normal and abraded rabbit skin at a rate of 2 mL/kg and held under occlusion for 24 hours (Ref. 3). If a rabbit weighed 2 kg, then it received 4 mL of the 2-percent lotion, amounting to a total of 80 mg salicylic

acid. There were no signs of acute toxicity in any of the test animals.

When an undiluted 2-percent salicylic acid lotion was applied to the eyes of rabbits and allowed to remain in the eye, the lotion was found to be an eye irritant. When the lotion was immediately washed out after application, there was no irritation (Ref. 3).

Five mL/kg of the lotion administered by oral gavage to female rats caused no toxic symptoms (total salicylic acid dose, 100 mg per 200 g rat). In mice the acute oral LD_{50} of the lotion was 32 mL/kg, or a total dose of approximately 666 mg/kg (Ref. 3).

In humans, a blood concentration of 30 to 50 mg salicylic acid per 100 mL is considered to be toxic (Ref. 4). If a human applied 15 g of a 5-percent salicylic acid preparation to the entire upper torso, the amount of salicylic acid available for absorption would be 750 mg. If all of this were instantly absorbed and distributed into 7 L of blood, the blood concentration would be approximately 10 mg/100 mL. Blood concentrations of 6.5 mg to 15 mg/100 mL have been reported to be nontoxic (Refs. 4 and 5). Based on this calculation and the data submitted, the Panel concludes that preparations containing up to 5 percent concentrations of salicylic acid would be safe for use in treating acne.

(2) *Effectiveness.* Salicylic acid has been used for over 100 years in the treatment of acne and various keratinizing diseases. It is used alone or often in combination with sulfur or resorcinol. Despite its long history of use, the exact mechanism of action has never been determined and, in fact, no study has documented the efficacy of salicylic acid used as a single ingredient in the therapy of acne.

An extensive review of the medicinal uses and pharmacologic properties of salicylic acid was published in a series of three articles co-authored by Weirich, Longauer, and Kirkwood (Refs. 6, 7, and 8). Weirich and his associates described 10 specific pharmacological properties of salicylic acid and offered many reference sources to document their viewpoints. These properties included action such as germicidal, photoprotector, astringent, antipruritic, and anti-inflammatory. Other properties discussed were a deep keratolytic action at concentrations greater than 5 percent, a superficial surface keratolytic action at 1 to 4 percent, and an acidifying effect at 0.1 percent and above. The ability to produce an increase in penetration of topical drugs was also described. It is not certain which, if any, of these qualities is responsible for the clinical responses noted in acne. It is usually assumed, however, that salicylic acid is working as a keratolytic agent and possibly as a substance which promotes the penetration of other active ingredients. Shalita (Ref. 9), Leyden (Ref. 10), and Plewig and Kligman (Ref. 11) believe that salicylic acid, in addition to its keratolytic and anti-inflammatory action, has a comedolytic effect; that is, it causes an increased turnover of follicular ephithelial cells and an apparent decrease in the cohesiveness of these cells when they are shed into the cavity of the follicle.

A commercial product containing 2 percent sulfur and 2 percent salicylic acid in a cream base has been studied in numerous investigations (Refs. 12, 13, and 14). One study was conducted to show the effectiveness of this preparation in seborrhea associated with acne. Robinson (Ref. 12) treated 120 patients using either a cake or cream containing 2 percent sulfur and 2 percent salicylic acid. Although the specific details of the study were not given, the investigator noted, "* * * (the) cake and cream quickly dried the skin and were particularly helpful in cleansing comedones."

In another study, Riley (Ref. 13) treated 150 acne patients with a salicylic acid-sulfur combination. Depending upon the severity of the acne condition, the treatment also included a restricted diet, ultraviolet light, acne surgery, astringents, colloidal sulfur, oral vitamin A, oral antibiotics, or X-ray therapy. All patients were instructed to wash their faces with ordinary soap for the first 2 weeks. At the end of the 2-week preliminary phase, patients showing little improvement were continued on the same therapeutic routine except for washing with a 2-percent salicylic acid-2 percent sulfur cream or cake instead of soap. The patients used the salicylic acid-sulfur combination one to four times daily for 4 to 12 months. The method of evaluating patients was not explained. Results showed a good response in 147 patients. The salicylic acid-sulfur combination was helpful in one patient, but two others had a poor response. Riley concluded that the cream or cake containing salicylic acid and sulfur did contribute to the improvement of acne vulgaris. However, the study made no mention of blinding or randomization, and the results were not evaluated statistically.

Baird (Ref. 14) treated 371 patients with acne vulgaris, with 133 cases classified as severe and 238 as moderate. All patients followed a simple, restricted diet, washed their faces with the 2-percent salicylic acid-2 percent sulfur cream, and were treated with acne surgery. In addition, the severe cases may have been treated with X-rays, oral antibiotics, staphylococcus vaccines, or estrogenic hormones. In conclusion, the investigator stated that the simplified treatment plan improved all the mild to moderate cases of acne. In the severe cases, the author believed that scrubbing with the cream shortened the course of therapy. However, the study made no mention of vehicle control, blinding, randomization, or statistical analysis.

In another study, using a randomized but not blinded method, 109 patients were treated once or twice daily with a 2-percent salicylic acid lotion or a commercially available soap (Ref. 3). Patients included in the study had mild to moderate acne. They were evaluated by global assessment after 4, 7, and 14 days. After 14 days the lotion proved to be significantly superior to the soap for reducing blackheads ($p = 0.029$). There were no statistically significant differences between the two products in the frequency of "breaking out" in acne blemishes, in improvement in overall condition, or in reduction of blemishes (inflammatory lesions). The researchers considered 14 days inadequate to evaluate the frequency of "breaking out." Consequently, a somewhat similar study of 117 patients with mild to very severe acne was conducted for 3 months. The study was blinded.

In this 3-month study, patients were untreated for 2 weeks before enrollment in the study (Ref. 3). After evaluation, they were randomly assigned to the 2-percent salicylic acid lotion (57 patients) or the commercially available soap (60 patients). Patients were treated once or twice daily depending upon the severity of their acne and the oiliness of their skin. The severity of blackheads, pimples, and oiliness was measured as 0=absent, 1=mild, 2=moderate, 3=severe, and 4=very severe. The overall clinical evaluation showed good to excellent results in 72.2 percent of the patients treated with salicylic acid compared with 10.5 percent of those who had used the soap. The group using the salicylic acid lotion had a statistically significant greater improvement than the group using the soap ($p < 0.001$). More importantly, fewer blackheads and pimples were observed in the lotion-treated group. The average reduction in "severity units" at 3 months compared with baseline for salicylic acid was 1.28 for blackheads and 1.41 for pimples. For soap the average reduction was 0.37 for blackheads and 0.19 for pimples. These results were statistically significant at

the $p < 0.001$ level. This was a well-designed study; however, lesion counts were not used and the control was not the vehicle used in the 2-percent salicylic acid lotion.

Another study was conducted using a lotion containing 2.2 percent salicylic acid and 2.2 percent resorcinol in an ethyl alcohol vehicle (Ref. 15). Sixteen patients were treated for 2 months using a twice-daily regimen. Evaluation was by lesion counts. After 2 months, reduction in lesion counts was 42.9 percent for blackheads, 43.8 percent for whiteheads, 66.2 percent for pustules, and 31.0 percent for cysts. Slight to marked improvement was noted in 81 percent of the patients. However, there were no controls or randomization and the study was not blinded.

In another study (Ref. 16), 44 adolescent males with mild to moderate acne were treated twice daily for 2 weeks with a preparation containing 0.5 percent salicylic acid. There was no mention of other treatments, how the evaluations were done, whether the study was blinded, or whether a vehicle control was used. At the end of the study, 57 percent of the patients showed improvement in overall severity of acne. A decrease in facial oiliness was noted in 77 percent. Seventy-three percent of the patients showed a decrease in the amount of pressure needed to express comedones. The investigator concluded that 0.5 percent salicylic acid was effective in the treatment of mild acne.

The effectiveness of 0.5 percent salicylic acid was also evaluated in an unpublished, single-blind trial of 120 patients. Patients with mild to moderate acne were treated with either 0.5 percent salicylic acid, a commercial product containing 6 percent sulfur and 1.5 percent resorcinol, or soap. Application was made twice daily for 3 weeks. No other topical or systemic treatment was allowed. Patients were evaluated by global impression. At the end of the trial, the two active treatments were found to be significantly more effective than soap in effecting overall improvement, decreasing oiliness, and making it easier to express comedones ($p < 0.01$) (Ref. 17).

In a single-blind study, patients with Grade I to III acne (grading system was not specified) were treated with either 0.25 or 0.5 percent salicylic acid. Each treatment group contained 50 patients. Patients applied the solutions once daily for 6 weeks. The method of patient evaluation was not described. At the end of the study, improvement was noted in 70 percent of the group receiving the 0.5-percent concentration. Fifty-four percent of the patients treated with 0.25 percent salicylic acid were reported as improved. Although the results were not statistically analyzed, the investigator concluded that the 0.5-percent solution was superior to the 0.25-percent solution (Ref. 18).

In a study of 95 patients, treatment with 0.5 percent salicylic acid lasted for 1 to 8 months. Patients entered into the study had Grade I to III acne (grading system based on type of lesion). Controls were not used and methods of evaluation were undefined. Results showed good to excellent improvement in 25 percent, satisfactory improvement in 38 percent, and no improvement in 37 percent (Ref. 18).

In a double-blind, randomized trial, 49 patients with Pillsbury Grade I to II acne were studied. A medicated pad containing 0.5 percent salicylic acid in an alcoholic detergent solution was compared with placebo (pads soaked in buffered water). No systemic therapy was used, and soap and water was the only other topical treatment.

Patients were evaluated before treatment and at 4, 8, and 12 weeks by lesion counts and global evaluation. After 12 weeks, inflammatory lesions were reduced by 54 percent in the salicylic acid group and 29 percent in the placebo group. This difference was significant ($p = 0.005$). Salicylic acid also reduced open comedones by 39 percent compared with placebo, 28 percent ($p < 0.05$). There was no significant difference between treatments on closed comedones (Ref. 19). The Panel notes that this study did not use a vehicle control.

A 0.5-percent salicylic acid solution has been evaluated in five other trials involving 282 patients with mild to moderate acne (Ref. 18). Vehicle controls were not used in any of these studies. Although none of the studies included a statistical analysis of results, all indicated that 0.5 percent salicylic acid reduces the severity of acne and oiliness of the skin. Also, comedones were easier to express.

Various other submissions discussed combinations of salicylic acid but none provided any specific data; however, the general medical literature contains several pertinent articles. Kaidbey and Kligman (Ref. 20) used 50 percent crude coal tar with plastic occlusion to induce the formation of comedones on 12 subjects' backs. Comedones produced this way remain evident on the skin for months. Therefore, any reduction of comedones is considered attributable to the peeling agents and not to time.

After 2 to 4 weeks of applying the crude coal tar followed by 2 weeks of no application, the patients were treated with a wide variety of peeling agents. The comparative comedolytic activity in order of decreasing effectiveness was 0.1 percent tretinoin, 15 percent salicylic acid, 10 percent benzoyl peroxide, and 15 percent trichloroacetic acid. Neither the ethanol control nor a combination of 5 percent sulfur and 2 percent resorcinol showed comedolytic activity. A 15-percent salicylic acid preparation applied topically twice daily for 6 weeks resulted in a greater than 50 percent reduction in the number of comedones. This model is valuable only for comparing agents that are capable of dislodging or reducing the size of the comedones.

Davies and Marks (Ref. 21) studied the effects of varying concentrations of salicylic acid on normal skin of the thigh or the forearm. The strengths applied were between 2 and 12 percent in either a water-washable base or in white paraffin. Vehicle controls were applied to the opposite thigh and forearm. The patients were treated twice a day for 1 week and then biopsied. No changes were apparent except when the electron microscope was used to examine the biopsies. Using this technique, Davies and Marks noted "striking differences" in the outer layer of the skin which had been treated with 6 to 12 percent concentrations of salicylic acid. This study was undertaken in the hope of determining the exact action of salicylic acid on the skin. The authors' theory was that salicylic acid preparations enhance the shedding of the outer layer of skin by dissolving the material which holds the cells together.

The Panel concludes that salicylic acid is of questionable effectiveness as a single ingredient in the treatment of acne. Although considerable clinical experience as well as uncontrolled studies suggest that salicylic acid is an effective ingredient, there has been no vehicle-controlled, double-blind study to confirm salicylic acid's effectiveness in the treatment of acne.

(3) *Proposed dosage*—(i) *Concentration.* Salicylic acid 0.5 to 5 percent.

(ii) *Directions for use.* See part III. paragraph A.2. above—Category I labeling.

(4) *Labeling.* The Panel recommeds the Category I labeling for products used in the treatment of acne. (See part III. paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel recommends one double-blind, vehicle-controlled clinical trial to determine the effectiveness of salicylic acid in the treatment of acne. This study should be conducted in accordance with the guidelines set forth below for OTC topical acne ingredients. (See part III.

paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

(1) OTC Volume 070088.
(2) OTC Volume 070090.
(3) OTC Volume 070188.
(4) Sautter, R. D., J. A. Buckwalter, and S. E. Ziffren, "Chemicals and Enzymes in Debridement of Thermal Burns," *American Medical Association Archives of Surgery,* 76:744–748, 1958.
(5) Von Weiss, J. F., and W. F. Lever, "Percutaneous Salicylic Acid Intoxication in Psoriasis," *Archieves of Dermatology,* 90:614–619, 1964.
(6) Weirich, E. G., "Dermatopharmacology of Salicylic Acid. I. Range of Dermatotherapeutic Effects of Salicylic Acid," *Dermatologica,* 151:268–273, 1975.
(7) Weirich, E. G., J. K. Longauer, and A. H. Kirkwood, "Dermatopharmacology of Salicylic Acid. II. Epidermal Antihyperplastic Effect of Salicylic Acid in Animals," *Dermatologica,* 151:321–332, 1975.
(8) Weirich, E. G., J. K. Longauer, and A. H. Kirkwood, "Dermatopharmacology of Salicylic Acid. III. Topical Contra-Inflammatory Effect of Salicylic Acid and Other Drugs in Animal Experiments," *Dermatologica,* 152:87–99, 1976.
(9) Shalita, A., et al., "Acne," *Journal of Investigative Dermatology,* 73:434–442, 1979.
(10) Leyden, J. J., "Human Comedolytic Assay," unpublished study, included in OTC Volume 070242.
(11) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, pp. 277–278, 1975.
(12) Robinson, A. M., "A New Treatment for Seborrhea and Allied Skin Conditions (Fostex)," *Journal of the South Carolina Medical Association,* 52:253–254, 1952.
(13) Riley, K. A., "Therapeutic Skin Washing in Seborrhea and Acne Vulgaris," *Medical Times,* 86:973–977, 1958.
(14) Baird, J. W., "Acne. A New Approach to an Old Problem," *Journal of Pediatrics, 52:152–157, 1958.*
(15) OTC Volume 070191.
(16) OTC Volume 070083.
(17) OTC Volume 070181.
(18) OTC Volume 070242.
(19) OTC Volume 070286.
(20) Kaidbey, K. H., and A. M. Kligman, "Effectiveness of Peeling Agents on Experimental Open Comedones," *CUTIS; Cutaneous Medicine for the Practitioner,* 16:53–56, 1975.
(21) Davies, M., and R. Marks, "Studies on the Effect of Salicylic Acid on Normal Skin," *British Journal of Dermatology,* 95:187–192, 1976.

2. *Category III Labeling.* None.

D. Combination Products Used in the Treatment of Acne

The Panel concurs with the rationale expressed in the OTC drug combination policy regulation (21 CFR 330.10(a)(4)(iv)) as follows:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety of effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel concludes that combination products for the treatment of acne should contain the minimal number of active ingredients necessary to achieve effectiveness. In general, the fewer the ingredients, the safer and more rational the therapy. 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.

In the past, combinations of ingredients were based largely on personal experience and testimonials. The Panel believes, however, that combinations should be based on clinical trials. In order to achieve the goal of efficacy consistent with exposure to the least number of ingredients, the Panel considered only those studies that demonstrated each ingredient's contribution to the efficacy of the complete conbination. The Panel realizes that such a clinical trial for Category III combinations to move to Category I will require a substantial effort. The study should be designed so that each single active ingredient makes a statictically significant contribution to the efficacy of the combination, and the combination itself should be more effective than the vehicle control.

1. *Category I combination drug product—Sulfur resorcinol.* The Panel concludes that a conbination of 8 percent sulfur with either 2 percent resorcinol or 3 percent resorcinol monoacetate is safe and effective for OTC use in the treatment of acne. Sulfur and resorcinol are often used together in the treatment of acne, but it is difficult to document the historical origin of this combination. The precise mechanism of action of these combinations has never been proven, but it may depend on keratolysis or the ability to produce erythema and desquamation with enhanced resolution of comedones, papules, and pustules.

A half-face study was conducted on 25 males (Ref. 1). After washing the entire face with soap and water, the patients applied a cream containing 8 percent sulfur and 2 percent resorcinol to half of the face three times daily for 3 weeks. No other therapy was allowed. The weekly evaluation was based on clinical impression with acne rated as slight, moderate, or severe. The sulfur-resorcinol combination was found to significantly improve acne at 1 and 2 weeks when compared to no treatment ($p < 0.001$).

In a single-blind, half-face trial, the effectiveness of 8 percent sulfur-2 percent resorcinol cream was studied in 28 subjects (Ref. 1). The patients applied the combination to one side of the face and a placebo lotion to the other side twice daily. The only other therapy allowed during the 8-week treatment period was soap and water. Patients were evaluated by global impression. After 8 weeks, the side of the face treated with the sulfur-resorcinol cream was improved in 75 percent of the cases. Improvement on the placebo side was noted in 46.4 percent of the patients. Sulfur-resorcinol was concluded to be effective in the treatment of acne.

Another single-blind study was conducted on 79 patients with Pillsbury Grade II or III acne (Ref. 1). Patients used no topical therapy for 2 weeks and no systemic therapy for 1 month before entering the study. They were divided into three treatment groups: (1) 8 percent sulfur-2 percent resorcinol cream, (2) "phosphate-stabilized" sulfur-resorcinol cream, and (3) no treatment. The patients applied the active medications twice daily. At regular intervals during the 12-week study they were evaluated by lesion counts and global impressions.

At the end of the treatment period, good to excellent results were reported for 44 percent of the group treated with sulfur-resorcinol, 38.5 percent of the group who had used the stabilized cream, and 17.4 percent of the no-treatment group. The investigators concluded that the sulfur-resorcinol formulations gave significantly better results than no treatment in reducing the overall severity of acne. No difference was noted between the three groups in reduction of comedones. The two active treatments showed significantly better results than no treatment in reducing inflammatory lesions.

In a half-face study of 25 patients with mild to moderate acne, 8 percent sulfur-2 percent resorcinol cream was compared to a placebo cream (Ref. 2). This study was randomized and single-blind. Before treatment there was a 4-week washout period during which no systemic or topical therapy was given. The patients were evaluated weekly with lesion counts and global assessments.

After 8 weeks of treatment, 12 patients were improved on the side of the face treated with sulfur-resorcinol and 1 patient improved on the side treated with the placebo. One patient

was worse on the side of the face treated with the placebo but had no change on the side treated with the combination. Seven patients had no change on either side of the face and four patients were worse on both sides.

Inflammatory lesions decreased 30.5 percent in the group treated with sulfur-resorcinol; in the control group the lesions increased 4 percent. Open comedones decreased 20.7 percent in the combination group and 1.8 percent in the control group. The statistical analysis showed that sulfur-resorcinol significantly decreased open comedones ($p<0.05$), papules ($p<0.001$), and pustules ($p<0.005$) compared to placebo. There was no significant difference between the two groups for closed comedones, which actually increased during the course of the trial.

Another study evaluating the effectiveness of sulfur-resorcinol used four treatment groups of about 60 subjects each. The groups were as follows: (1) 2.66 percent sulfur-1 percent resorcinol, (2) 8 percent sulfur-2 percent resorcinol, (3) 2.66 percent sulfur, and (4) placebo. The patients included in the study had mild to moderate acne and were randomly assigned to a treatment group. No concurrent topical or systemic therapy was allowed. The creams were applied three times daily for 8 weeks. The patients were evaluated at 0, 2, 4, 6, and 8 weeks. Lesion counts were not used, but global assessment was based on the number of blackheads, whiteheads, papules, pustules, and on oiliness and overall complexion.

Results after 8 weeks showed that the two sulfur-resorcinol creams were equivalent and superior to the placebo and to sulfur alone in reducing papules and whiteheads. No differences in blackheads, pustules, oiliness, or overall complexion were noted between the four treatment groups. Also, there was no statistically significant difference between sulfur alone and the placebo in any category (Ref. 3).

Sulfur-resorcinol cream was compared to benzoyl peroxide in a half-face, single-blind study (Ref. 2). The vehicle of the benzoyl peroxide cream served as a control. The study included 50 institutionalized male patients with Pillsbury Grade II to III acne. The patients were allowed no other topical or systmic therapy. All medications were applied by dispensary personnel. Twenty-four patients had half of the face treated with 5 percent benzoyl peroxide and the other half treated with 8 percent sulfur-2 percent resorcinol. In the remaining patients, one side of the face was treated with benzoyl peroxide and the other side with the vehicle. Assignment of treatment and side of application were randomized. Treatment was twice daily for 8 weeks. The patients were evaluated weekly by lesion counts and global assessments.

Final results showed that there was no significant difference between sulfur-resorcinol and benzoyl peroxide. Both sulfur-resorcinol and benzoyl peroxide were more effective than the vehicle in the reduction of pustules, open comedones, the closed comedones ($p<0.01$ to $p<0.001$).

A double-blind, randomized, multiple-center trial was conducted in three European countries (Ref. 2). Patients were admitted to the study with Pillsbury Grade II to III acne. There was a 4-week washout period during which no therapy was allowed. Fifty-four patients were treated with 8 percent sulfur-2 percent resorcinol; 53 patients were treated with a sulfur-resorcinol combination plus 0.1 percent triclosan, an antibacterial agent.

The medications were applied twice daily for 8 weeks. Patients were evaluated by lesion counts every 4 weeks. Both treatments showed a statistically significant decrease in open comedones, closed comedones, total number of comedones, and inflamed lesions when the washout period was compared to the treatment period ($p<0.05$ to $p<0.01$).

Although resorcinol has been placed in Category II as a single ingredient because it is not effective, the Panel believes that resorcinol enhances the activity of sulfur. The Panel concludes that a comination of 8 percent sulfur with either 2 percent resorcinol or 3 percent resorcinol monoacetate is safe and effective in the treatment of acne but recommends that products containing this combination not be used on broken skin or over large areas of the body. The Panel recommends that sulfur-resorcinol combination products contain the following warning: "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body."

The Panel recommends that Category I combinations be labeled according to the Category I labeling for products used in the treatment of acne, as outlined elsewhere in this document. (See part III. paragraph A.2. below—Category I labeling.)

References

(1) OTC Volume 070039.
(2) OTC Volume 070236.
(3) OTC Volume 070256.

2. *Category II combination drug product—Benzoyl peroxide-sulfur.* A combination is classified by the Panel as a Category II drug product, i.e., one that is not generally recognized as safe or effective, if it contains any ingredient that is listed elsewhere in this document as a Category II ingredient for safety reasons. Although benzoyl peroxide and sulfur are Category I as single ingredients for OTC use in the treatment of acne, the Panel recommends that the benzoyl peroxide-sulfur combination be Category II because of the possibility of sensitization.

Combinations of benzoyl peroxide and sulfur are currently available by prescription only and the Panel does not recommend that these combinations be switched to OTC. However, a combination of 7.5 percent benzoyl peroxide and 5 percent sulfur was submitted for review. The Panel concludes that this combination is effective but is not safe for OTC topical use in the treatment of acne. Other concentrations of these two ingredients are used in prescription acne preparations and were submitted, but the effectiveness of these combinations has not been adequately studied in a clinical trial which meets the Panel's criteria.

a. *Safety.* Because benzoyl peroxide and sulfur are safe as single ingredients, in considering the safety of the combination one need be concerned only with the possible effect one chemical might have on the potential toxicity of the other. One such possibility is increased absorption of benzoyl peroxide due to irritation by sulfur. There is evidence, however, that benzoyl peroxide is not absorbed from rabbit skin even in the presence of 5 percent sulfur (Ref. 1). Topical studies on rabbits with a formulation containing 7.5 percent benzoyl peroxide and 5 percent sulfur showed no systemic effects (Ref. 2).

The primary concern regarding the safety of benzoyl peroxide is direct cutaneous toxicity. There is evidence that this enhanced by the presence of sulfur. Poole, Griffith, and MacMillan (Ref. 3) demonstrated a 40-percent rate of hypersensitivity to benzoyl peroxide in guinea pigs and humans who were given a patch test with an ointment containing 10 percent benzoyl peroxide and 1 percent sulfur. In the study on guinea pigs it was clearly demonstrated that sulfur was needed in addition to benzoyl peroxide to produce sensitization. Guinea pigs tested with benzoyl peroxide alone, sulfur alone, or the vehicle showed no reaction (Ref. 3). Histological alterations, particularly dermal changes, produced by benzoyl peroxide are also enhanced by sulfur (Ref. 4). In the rabbit ear assay, greater irritation was observed from the combination than from either

ingredients along (Ref. 5). Using the Draize-Shelanski test (Re. 1), true allegic responses to benzoyl peroxide-sulfur lotion were demonstrated in 19 out of 221 people, which is a higher rate than expected with benzoyl peroxide alone.

It is difficult to understand why sulfur would enhance the sensitization potential of benzoyl peroxide. Perhaps an oxidation product of sulfur is formed and this product is irritating. Because the possibility of sensitization increases when sulfur is combined with benzoyl peroxide, the Panel recommends that this combination remain available by prescription only.

b. *Effectiveness.* A double-blind, controlled, randomized trail was conducted on 80 males with moderate acne (Ref. 2). The patients applied creams containing no benzoyl peroxide or containing benzoyl peroxide in concentrations of 2.5, 5, 7.5, or 10 percent either with or without 5 percent sulfur. Half of the group was treated for 2 weeks; the other half was treated for 8 weeks. The patients were assessed by lesion counts. The statistical analysis of results showed that the most effective formulation contained 7.5 percent benzoyl peroxide and 5 percent sulfur. This combination was effective against all types of acne lesions (comedones, papules, pustules, and all lesions combined). The duration of treatment did not affect the results.

One submission contained a compilation of five half-face and five full-face studies using 10 percent benzoyl peroxide, 5 percent sulfur, a combination of these two ingredients, or a placebo base (Ref. 2). These studies were randomized and blinded. Treatment lasted 8 weeks with evaluation by lesion counts. The results of the half-face studies showed that improvement in comedones was 58.3 percent for the combination, 42.8 percent for sulfur, 49.1 percent for benzoyl peroxide, and 28 percent for the base. For inflammatory lesions the improvement was 40 percent for the combination, 36.3 percent for sulfur, 23.7 percent for benzoyl peroxide, and 18.3 percent for the base.

Most of the studies were not analyzed. However, analysis of one study showed that the benzoyl peroxide-sulfur combination was more effective than benzyol peroxide alone ($p < 0.05$).

In the full-face studies, one investigator found the combination product to be superior to sulfur used alone ($p < 0.05$). Another researcher, however, reported no significant differences between active treatments (Ref. 2).

In a double-blind, randomized study, 48 patients were treated with either a combination containing 7.5 percent benzoyl peroxide and 5 percent sulfur, 7.5 percent benzoyl peroxide, or the placebo (Ref. 2). The patients applied the lotions twice daily for 8 weeks. They were evaluated by lesion counts at 0, 2, and 8 weeks, but the numerical results of these counts were not reported. However, using a "means of slope estimate" (rate of lesion decrease) for the three treatments, the researchers found the combination product to be superior to the placebo in the treatment of comedones and in all lesions combined ($p < 0.05$ and $p < 0.025$). In treating inflammatory lesions, no significant difference was noted between the combination and the placebo. Also, no significant difference was seen between benzoyl peroxide and placebo for any lesion type.

In a double-blind, randomized, half-face study (Ref. 2), 48 patients applied a combination of 7.5 percent benzoyl peroxide and 5 percent sulfur to one side of the face. On the other side of the face, they used benzoyl peroxide alone. Treatment was twice daily for 7 weeks. The patients were examined by global assessment and lesion counts at 0, 2, and 7 weeks. Both treatments reduced lesion counts, but by this method of evaluation no significant difference was noted between treatments. Analysis of global results showed that the combination product was superior to benzoyl peroxide in the treatment of comedones at 2 weeks ($p < 0.05$) and in the treatment of inflammatory lesions at 7 weeks ($p. < 0.05$).

In a multiple-center trial (Ref. 2), three investigators treated 156 patients with acne. The study was double-blind and randomized. The patients applied either a combination of 7.5 percent benzoyl peroxide and 5 percent sulfur, a placebo cream, or a commercially available cream containing sulfur and resorcinol. Treatment was twice daily. No concurrent therapy was allowed. The patients were evaluated at 0, 2, 8, and 12 weeks by lesion count.

The results of each investigator's work were statistically analyzed. One researcher reported greater improvement with the combination than with the other two treatments, but the difference was not significant. Another investigator found no significant difference between the three preparations in reducing comedones. However, benzoyl peroxide-sulfur combination was superior to sulfur-resorcinol and the placebo in reducing inflammatory lesions ($p < 0.001$). The third investigator found benzoyl peroxide-sulfur combination to be superior to the placebo for all lesion types ($p < 0.05$).

c. *Evaluation.* The Panel concludes that 7.5 percent benzoyl peroxide and 5 percent sulfur is an effective combination for topical use in the treatment of acne. However, the Panel does not recommend that this combination be made available OTC because of the potential for sensitization.

References

(1) OTC Volume 070259.

(2) OTC Volume 070168.

(3) Poole, R. L., J. F. Griffith, and F. S. K. Macmillan, "Experimental Contact Sensitization with Benzoyl Peroxide," *Archives of Dermatology*, 102:635–639, 1970.

(4) Vasarinsh, P., "Benzoyl Peroxide-Sulfur Lotions, A Histological Study," *Archives of Dermatology*, 98:183–187, 1968.

(5) OTC Volume 070207.

3. *Category III combination drug products.* A combination is classified as a Category III product if one of the following apply:

(1) The combination contains one or more ingredients listed elsewhere in this document as a Category III ingredient.

(2) The combination contains one or more ingredients listed elsewhere in this document as a Category II ingredient for effectiveness only. (An exception is sulfur-resorcinol combinations where resorcinol enhances the activity of sulfur.)

(3) The effectiveness of the combination has not been shown in a controlled clinical trial.

a. *Calcium polysulfide-calcium thiosulfate.* Calcium polysulfide and calcium thiosulfate the active ingredients in sulfurated lime topical solution (Vlieminckx' solution). This solution is most frequently used as a scabicide (Ref. 1). It has also been used in the treatment of severe pustular or cystic acne. Although sulfurated lime topical solution has been used in dermatology for over 100 years, there are no clinical trials establishing its effectiveness in treating acne.

Sulfurated lime topical solution works as a peeling agent. Plewig and Kligman (Ref. 2) stated that "only a few agents which cause peeling are in fact comedolytic." They listed sulfurated lime topical solution as one of the traditional exfoliants which is "surprisingly weak or ineffective."

Only one submission contained a clinical trial testing the effectiveness of calcium polysulfide-calcium thiosulfate combination (Ref. 3). In this double-blind, randomized study, 59 patients used either the medicated facial mask or a a nonmedicated mask (vehicle). The masks were applied once every other day and rinsed off after 15 minutes. Patients were evaluated by lesion

counts and global assessment at the initial visit and at 2, 4, 7, and 10 weeks. At each visit the patients using the combination showed a significant decrease in comedones compared to baseline ($p<0.001$). In the vehicle group the decrease in comedones was significant only at 2 and 4 weeks ($p<0.05$). The reduction of papules, however, was significant at each visit for both treatments when compared to baseline ($p<0.01$). Both groups also showed a significant decrease in the pustule counts over the 10-week course of treatment ($p<0.025$).

The Panel notes that a calcium polysulfide-calcium thiosulfate combination is generally used by dermatologists to treat severe acne that does not respond to other treatments. In this study, however, the combination was no more effective than the vehicle on papules and pustules. Although the combination was more effective than the vehicle in reducing comedones, effectiveness should be shown against all lesion types. The Panel concludes that a combination of calcium polysulfide and calcium thiosulfate is of questionable effectiveness for OTC use in the treatment of acne.

References

(1) Osol. A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1180, 1975.

(2) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, p. 278, 1975.

(3) OTC Volume 070291.

b. *Sulfur-aluminum chlorohydrex.* The Panel concludes that a combination of 5 percent sulfur and 10 percent aluminium chlorohydrex is safe but that there are insufficient data available to permit final classification of the effectiveness of this combination.

The Panel reviewed two double-blind, randomized, and controlled studies that compared the combination to the individual active components and to the vehicle (Ref. 1). However, because there was no washout period between the cross-over segments of these trials, the results were difficult to interpret.

Another study on this combination was also double-blind, randomized, and controlled. Forty-five patients with Pillsbury Grade I to III acne completed the 8 weeks of treatment. They were treated twice daily with either 5 percent sulfur-10 percent aluminum chlorohydrex, 5 percent sulfur, or the vehicle. No other treatment was allowed. Patients were evaluated by lesion counts and global assessments.

Results of global assessments showed that the combination was significantly more effective than sulfur or vehicle. Sulfur-aluminum chlorohydrex was also significantly better than sulfur and vehicle in reducing the lesion counts of papules and pustules ($p<0.05$). Reduction in the number of open comedones and cysts was greater for the combination than for the other two preparations but this was not a statistically significant difference. None of the treatments had an appreciable effect on closed comedones, difficult lesions to treat (Ref. 1).

The only side effect noted was excessive dryness. In the first 2 weeks of treatment, there were significantly more reports of this side effect with the combination product than with sulfur. At that time, the amount of drug and the frequency of administration were adjusted.

There was only one report of excessive dryness from the combination in the next 6 weeks of the trial (Ref. 1).

The Panel concludes that 5 percent sulfur-10 percent aluminum chlorohydrex is safe, but that its overall effectiveness is questionable because of its lack of effect on comedones. The Panel has stated previously that acne treatments should be effective against all lesion types to be considered as Category I. Although this combination was significantly more effective on papules and pustules, it did not have a statistically significant effect on other kinds of lesions, particularly open comedones.

Reference

(1) OTC Volume 070283.

c. *Other Category III combination products.* The Panel is unaware of any clinical trials on the following combinations which compared the combination to the individual active ingredients and to the vehicle. Although studies were submitted and reviewed by the Panel for some of these combinations, none of them met the Panel's criteria.

The Panel concludes that the following combinations are of questionable effectiveness because of inadequate data. One of these combinations contains an ingredient on which there are inadequate safety data (thymol). The safety of this ingredient must be established before the combination can move from Category III to I.

(1) Sulfur-resorcinol-alcloxa.

(2) Sulfur-resorcinol-thymol-zinc oxide.

(3) Sulfur-salicylic acid.

(4) Salicylic acid-resorcinol.

(5) Salicylic acid-resorcinol-alcloxa.

(6) Salicylic acid-resorcinol-sodium thiosulfate.

(7) Benzoic acid-boric acid-zinc oxide-zinc stearate.

E. Guidelines for Safety and Effectiveness Studies

The following guidelines are for studies that the Panel recommends be conducted in order to move a Category III topical acne drug product into Category I. These guidelines are in accord with the present state of the art but do not preclude the use of any future advances or improved technology.

The Panel's approach has been to completely study the potential toxicity of active ingredients used in topical acne products. Even though these ingredients are to be used topically, their oral toxicity should be studied first to identify the target organ or system and then to determine the safety factor which permits safe use when absorption and systemic toxicity occur.

1. *Safety guidelines.* The Panel recommends that the following studies be performed as appropriate to evaluate topical acne ingredients classified in Catogory III because of inadequate safety data.

a. *Acute studies in animals.* (1) Determine the acute oral toxicity of the total formulation in an appropriate species to define the response curve and allow determination of the LD_{10}, LD_{50}, and LD_{90}. Short-term topical toxicity tests on the total formulation should be done on both intact and abraded skin.

(2) Conduct an appropriate rabbit skin irritation study on intact and abraded skin on the vehicle and total formulation.

(3) Conduct an appropriate rabbit eye irritation study on the vehicle and total formulation.

b. *In vitro screening for carcinogenic potential.* (1) A bacterial mutagenesis assay would be a logical first step in screening for carcinogenic potential. One of the assays using the *Salmonella* histidine auxotroph back mutation, such as that described by Ames (Ref. 1) or Frantz and Malling (Ref. 2), would be suitable. Because the compounds in question are likely to be antibacterial, parallel dose-response curves for viability must be done. Where obvious antibacterial activity occurs, other cellular testing procedures should be used.

(2) Depending on the properties of the chemical tested and the results of the bacterial mutagenesis assay, other in vitro tests could be conducted for clarification. These tests should use a mammalian cell culture system designed to test either mutagenicity or transformation. Strategies for selecting

tests in this rapidly developing field can be found in current literature.

c. *Subchronic studies in animals.* (1) Conduct a 28-day dermal toxicity study in the rabbit or other appropriate species on abraded skin at suitable dose levels to ensure adequate exaggeration of normal "use" levels. At the conclusion of this study, conduct a full pathological assessment on vital organs and skin. It would be desirable to evaluate the direct effects on the skin following application for a longer period of time, but the Panel is not aware of a suitable model for such a study.

(2) Conduct a subchronic (90 days or longer) feeding study with the total formulation. Determine blood levels and conduct full pathology at termination of the study. This study should attempt to determine the "no effect" blood level of the total formulation. Determine the target organ(s) for toxic effects.

d. *Chronic studies in animals.* (1) Conduct a 1-year chronic feeding study with at least two dose levels. Monitor blood levels at 3-month intervals. Conduct a full pathology evaluation at conclusion of study.

(2) A carcinogenicity evaluation following dermal application will be necessary only if the appropriate in vitro screening assays are positive or have yielded questionable results. For example, acne agents may have antibacterial activity which can cause false-negative or misleading results in the *Salmonella* mutagenicity test because the assay procedure involves bacterial enumeration."

e. *Studies in humans.* (1) Determine the irritation potential of the vehicle and total formulation using the best current procedures.

(2) Conduct an appropriate sensitization potential study on the total formulation using the most reliable procedure for identifying both potent and weak sensitization potential(s).

(3) Because absorption studies in animals do not necessarily parallel those in humans, appropriate transepidermal studies should be conducted in humans. These studies should be conducted only where the safety of the ingredient has been adequately established in animals.

References

(1) Ames, B. N., J. McCann, and E. Yamasaki, "Methods for Detecting Carcinogens and Mutagens with the *Salmonella*/Mammalian-Microsome Mutagenicity Test," *Mutation Research,* 31:347–364, 1975.

(2) Frantz, C. N., and H. V. Malling, "The Quantitative Microsomal Mutagenesis Assay Method," *Mutation Research,* 31:365–380, 1975.

2. *Effectiveness guidelines*—a. *Guidelines for clinical trials.* To move a Category III ingredient into Category I, the ingredient must be shown to be effective in the treatment of of acne in a well-designed clinical trial that meets the following criteria:

(1) The trial should involve a sufficient number of subjects established by using accepted statistical procedures.

(2) An objective measure of the severity of acne should be decided before the study. This method should be precisely defined.

(3) Patients should be randomly assigned to total formulation or control group. The control is the vehicle (total formulation minus the active ingredient (s)). When comparing total formulation to vehicle, the use of parallel groups of patients is preferable to half-face comparisons. The comparability of groups should be established by analyzing pertinent variables, such as age, sex, severity of acne.

(4) The study should be double-blind.

(5) No concomitant therapy (other than soap and water) should be allowed.

(6) The trial should last at least 8 weeks. The investigators should state which calendar months were included in the study because acne lesions generally clear up somewhat in the summer.

(7) The patients should be evaluated at least three times: before treatment, at final examination, and at one other time. The method of evaluation should be lesion counts grouped by type of lesion (closed comedones, open comedones, papules, pustules, and total lesions). A global assessment of patients may also be helpful. Local adverse effects and patient compliance should be noted and systematically recorded.

(8) Results should be statistically evaluated. The total formulation should be significantly more effective than the placebo in reducing lesion counts.

b. *In vitro testing of acne ingredients*—(1) *Background.* The Panel has included an optional in vitro testing procedure. Before a manufacturer tests an ingredient for clinical effectiveness in acne or determines in vivo activity for an antibacterial claim, it would be helpful to determine activity against *P. acnes* in an in vitro test. With in vitro testing the minimal inhibitory concentration (MIC) of an ingredient can be determined against *P. acnes.* With this information one can determine whether the ingredient has antibacterial activity under these testing conditions. MIC determination can also be used to compare different ingredients tested against the same pure culture under the same conditions. Another use is to find whether antibacterial activity varies when an ingredient is tested against various strains of bacteria.

Ingredients often show activity in vitro which cannot be shown in vivo. Although the reverse is not so often true, it can happen when the conditions of the MIC test differ significantly from the availability of the antibacterial agent in vivo. In vitro antibacterial activity may also be affected by the interaction of the antibacterial ingredients or other components in the formulation with one of the components of the medium used to determine the MIC. Obviously this will not affect the in vivo activity.

Because the in vitro availability of the ingredient may be altered in formulation, it is often advisable to determine the MIC for the formulation as well as for the ingredient alone. The optimal multiple of the MIC of an ingredient in a topical dosage form is often very high, ranging from a hundred times to thousands of times the MIC. This high multiple is often necessary because of formulation binding, partition of the ingredients on the skin, and differential absorption into the skin. Absorption into the follicle is critical in formulations for acne treatment.

Therefore, the information derived from in vitro data may be helpful in trying to make the most effective formulations or in reaching a decision about whether to proceed with testing. Although the in vivo data ultimately determine the validity if the antibacterial claim, the MIC test is a helpful guide to potential activity and availability. In some cases it can also be useful in quality control. The following discussion illustrates how the MIC data can be used.

The MIC of benzoyl peroxide was reported as approximately 78 μg/mL against *P. acnes.* The minimal bactericidal concentration (MBC) was reported as approximately 156 μg/mL.

If these figures are applied to actual use of a formulation on the skin and some assumptions are made, useful information can be derived. The amount of drug material applied is 2 mg/cm^2 or 2,000 μg/cm^2. If an average lotion or cream product contains 10 percent benzoyl peroxide, then the amount applied could be in the range of 200 μg/cm^2.

If an average volume of a single follicle is assumed to be 2 microliters (μL) and it is estimated that there are 200 follicles/cm^2, then the total follicular volume could be estimated at 400 μL (0.4 mL) for each cm^2 of involved epidermis. Based on this estimate and assuming complete and uniform follicular penetration, the concentration of benzoyl peroxide at the site of the

organism would be 200 μg/0.4 mL or 500 μg/mL benzoyl peroxide. To obtain the multiples, the estimated concentration of benzoyl peroxide at the site is derived using the MIC or the MBC. The multiples for various concentrations of benzoyl peroxide would be as follows:

Concentration of benzoyl peroxide (percent)	MIC	MBC
10	6×	3×
7	4+×	2+×
5	3×	1.5×
2.5	1.5×	.75×

These data and calculations suggest that appropriate availability of the benzoyl peroxide from 2.5 percent formulations will be important to their effectiveness.

(2) *Testing procedures.* The Panel suggests the following procedures for testing ingredients in vitro for possible bactericidal or bacteriostatic activity against *P. acnes* (although other procedures may be used): (i) *Materials*—(*a*) Double-strength brain-heart infusion agar, containing 104 g/L.

(*b*) Single-strength brain-heart infusion agar, containing 52 g/L.

(*c*) Double-strength brain-heart infusion broth, containing 74 g/L.

(*d*) Single-strength brain-heart infusion broth, containing 37 g/L.

The brain-heart infusion agar and broth are commercial preparations to which double-distilled water is added to make the working preparations.

(ii) *Basic P. acnes culture.* An ATCC *P. acnes*-type culture or a well-characterized *P. acnes* facial isolate is reconstituted and then grown anaerobically under hydrogen/carbon dioxide or equivalent, in brain-heart infusion or a similar broth at pH 7, for 5 to 7 days, until good growth is obtained as evidenced by turbidity.

(iii) *Determination of the minimal inhibitory concentration for agents insoluble in water by the agar dilution method.* The agar dilution test is used for products that are insoluble or precipitate in broth, rendering culture media cloudy and making turbidimetric measurements of microbial growth difficult.

The test is run in duplicate. The following should be prepared and sterilized: 2 test tubes (18 mm×150 mm) with 5 mL of double-strength brain-heart infusion agar, 22 test tubes containing 5 mL of single-strength brain-heart infusion agar, and 2 test tubes containing 9 mL of brain-heart infusion broth. The agar in these test tubes is melted and kept in a 45° C water bath to prevent solidification during the test. Next, 5 mL of the concentrated test ingredient is placed into the test tubes containing the double-strength brain-heart infusion agar and mixed well for 10 seconds. Then the tubes are returned to the water bath. (This is a 1:2 dilution.)

Five mL from each one of these tubes is transferred into each of two of the single-strength brain-heart infusion agar tubes, mixed, and returned to the water bath. (This is a 1:4 dilution.) This procedure is continued until a 1:1,024 dilution has been prepared. From the last dilution tube, 5 mL is discarded so that all tubes contain a total of 5 mL of agar. The last two agar tubes will be kept undiluted and uninoculated as negative controls. The contents of each tube are mixed well and poured into 25 mm×10 mm petri dishes. The agar is allowed to solidify.

Two serial tenfold dilutions from the *P. acnes* broth culture are made using the two brain-heart infusion broth tubes. The 1:100 dilution constitutes the inoculum. The duplicate set of plates (from the 1:2 dilution to 1:1,024 dilution) is seeded with one drop of the diluted *P. acnes* culture. Two plates with inoculated brain-heart infusion agar, two plates containing a 1:2 dilution of the sample but no inoculum seeding, and two uninoculated brain-heart infusion plates serve as controls. The plates are incubated anaerobically at 35° C for 1 week and examined for growth. The end point of bacteriostatic activity is between the last plate with no growth and the first plate with growth. The titer is the dilution of the last clear plate before the first plate growth.

A piece of the agar from the plates showing no growth is subcultured in brain-heart infusion broth tubes to determine the bactericidal titer of the antimicrobial agent. An effective neutralizer should be included.

The MIC is calculated from the titer and the original concentration of the test compound in the suspending agent.

(iv) *Determination of the minimal inhibitory concentration for agents soluble in water by the broth dilution method.* The test is run in duplicate. Twenty-four test tubes (18 mm × 150 mm) are set up. Into the first four test tubes, 5 mL of a double-strength brain-heart infusion broth is pipetted. Five mL of the single-strength broth is placed into each of the other tubes.

Next, 5 mL of sterile saline is pipetted into each of the first two test tubes of double-strength broth and mixed. These will be the positive control tubes. Five mL is removed from each of these control tubes and discarded, leaving a total volume of 5 mL in each tube.

A known amount of the acne ingredient is mixed in a suspending medium and 5 mL of this dispersion is pipetted into each of the next two test tubes and mixed for 10 seconds. This is a 1:2 dilution.

Five mL of the content of each 1:2 dilution tube is transferred into the next two test tubes and mixed for 10 seconds. This is a 1:4 dilution.

This procedure is continued until a 1:1,024 dilution is obtained. Five mL from each test tube with the highest dilution is discarded, leaving a 5 mL total volume in each of the test tubes. The last two tubes will not be diluted or inoculated and will serve as negative controls. The culture of *P. acnes* in brain-heart infuson broth is mixed well to suspend the cells evenly and 1 mL is added to 9 mL of single-strength broth and mixed well. This is a 1:10 dilution.

One mL from this 1:10 diluton is added to 9 mL of single-strength brain-heart infusion broth to obtain a 1:100 dilution. This dilution constitutes the inoculum.

One-tenth mL of the inoculum is added to each of the sample dilutions and to the positive control tubes. All tubes are incubated at 35° C anaerobically for 1 week and then examined for growth.

(v) *Interpretation of the results.* The more concentrated suspensions of the test agent should completely inhibit the growth of *P. acnes*, and the broth should be clear. At higher dilutions the concentration of the active agent will be too low to completely inhibit the growth of the organism. These tubes should be turbid. The end point of activity is between the last clear and the first turbid adjacent tube. The titer is the dilution of the last clear tube.

When the test is concluded, a loopful of broth from each tube not showing turbidity should be streaked on brain-heart infusion agar plates and incubated at 35° C anaerobically for 1 week to determine whether the test compound is bacteriostatic or bactericidal at a given concentration. An effective neutralizer should be included. Knowing the titer (bacteriostatic and bactericidal) and the initial concentration of the dispersion tested, an MIC for this ingredient can be calculated by the following formula:

$$\text{Minimal inhibitory concentration } (\mu g/mL) = \text{Initial concentration } (\mu g/mL) \times \frac{1}{\text{Bacteriostatic titer}}$$

c. *In vivo testing of acne ingredients.* The Panel recommends the following testing guidelines to determine antimicrobial activity in an in vivo test. Ingredients which demonstrate in vivo activity and meet the criteria may use antibacterial claims in their labeling.

(1) *Study design.* Either parallel or half-face groups may be used. The half-

face design is permitted for drugs that are not sufficiently absorbed to result in antibacterial effects. When a drug is absorbed to a degree that systemic activity occurs, the untreated side of the face may be affected, thus invalidating the test. Reliability and extent of application are particularly important in a half-face test. For this reason, technicians should apply the drug when this study design is used. If translocation of the medication is known to occur, the half-face design should not be used.

All studies should be double-blind with the formulation containing the active ingredient compared with the vehicle control.

(2) *Subjects.* A minimum of 15 subjects for a half-face study and 30 for a parallel group study should be used. The groups should include males and females 15 years of age or older. The subjects may or may not have active acne, but they must have significant follicular fluorescence indicating an adequate density of *P. acnes* on the skin. The subjects must have a *P. acnes* baseline count of 1×10^5 to 1×10^6 organisms per cm^2.

(3) *Treatment.* The forehead and cheeks should be used as treatment sites. The method of application should be that specified in directions for use. The drug should be applied twice daily. The duration of treatment should usually be 4 weeks unless the study is intended to show that a product can meet the criteria in a shorter time. In that case the treatment time may be shortened.

(4) *Measurements.* The sample site should be specified by the investigator. To reduce error the same sample site should be used on each individual each time. The *P. acnes* count should be determined using the Williamson and Kligman scrub technique (Ref. 1). The Panel believes that the Williamson and Kligman scrub technique is the best method presently available to determine *P. acnes* counts. However, if other methods that are equivalent or superior to the Williamson and Kligman scrub technique are developed, they may be used after the agency has approved a petition to amend the monograph.

Three separate determinations of the baseline *P. acnes* count should be made. The values may be averaged to obtain a single baseline value for each subject. Measurements to determine reduction should be made weekly thereafter.

The free fatty acids determination is an optional confirmatory test. However, if it is used, the free fatty acids concentration should be carefully assessed by thin-layer chromatography, such as the method described by Downing (Ref. 2).

(5) *Criteria.* For an ingredient to be considered effective in demonstrating antibacterial activity against *P. acnes*, the following criterion must be met:

A reduction in *P. acnes* counts of 0.75 log must be shown. This reduction should be statistically significant at the $p \leq 0.1$ level. Therefore, the hypothesis test should be framed to test whether there is a 0.75-log reduction from baseline.

If it is desirable to show that the reduction is significant at the $p < 0.05$ level, the number of subjects should be increased appropriately.

To confirm antibacterial activity, an optional test to show reduction of free fatty acids may also be done. A 30-percent reduction in free fatty acids on the skin surface should be shown. The reduction should be statistically significant at the $p \leq 0.1$ level. The free fatty acid determination is included to ensure that the antimicrobial agent has penetrated and is acting at the follicular level.

(6) *Methodology*—(i) Microbiological sampling of the skin should be by the Williamson and Kligman detergent scrub technique or an equivalent technique. The following culture techinques should be observed:

a. Brain-heart infusion medium should be used to culture *P. acnes.* If another medium is developed that is shown to be equivalent or superior to brain-heart infusion, it may be used.

b. The sample retrieved from the scrub technique should be vortexed for 10 seconds prior to enumeration.

c. Anaerobic incubation should be at 35° C for 7 days.

d. A neutralizer adequate for the antimicrobial ingredient being tested should be added to the scrubbing fluid. The toxicity of the neutralizer must be determined for *P. acnes.* The presence of any residual antimicrobial agent in the sampling fluid must be investigated using adequate microbiological tests.

(ii) *Free fatty acids determination.* Samples of skin lipids should be obtained by swabbing the area with a hexane-saturated sponge (Ref. 3). Lipid analysis should be performed using a thin-layer chromatography technique, such as the one described by Downing (Ref. 2). Another method of lipid analysis that may be used is infrared spectoscopy, described by Anderson and Fulton (Ref. 4).

References

(1) Williamson, P., and A. M. Kligman, "A New Method for the Quantitative Investigation of Cutaneous Bacteria," *Journal of Investigative Dermatology,* 45:498–503, 1965.

(2) Downing, D. T., "Photodensitometry in the Thin-Layer Chromatographic Analysis of Neutral Lipids," *Journal of Chromatography, 38:91–99, 1968.*

(3) Yeung, D., and W. Smith, "Method for the In Vivo Collection of Skin Lipids," memorandum to S. Nacht, June 4, 1980, OTC Volume 070279.

(4) Anderson, A. S., and J. E. Fulton, Jr., "Sebum: Analysis by Infrared Spectroscopy," *Journal of Investigative Dermatology, 60:115–120, 1973.*

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

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)), under 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, (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding in Part 333, a new Subpart D, to read as follows:

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); (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 part:

(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) *Follicle.* A minute cavity with an opening on the surface of the skin.

(e) *Lesion.* A characteristic area of a skin condition. Lesions in acne include blackheads and pimples.

(f) *Pimple.* A small, prominent inflamed elevation of the skin.

§ 333.310 Acne active ingredients.

The active ingredients of the product consist 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.

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

(d) Sulfur 3 to 10 percent.

(e) Sulfur 8 percent when combined in accordance with § 333.320 (a) and (b).

§ 333.320 Permitted combinations of active ingredients.

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

§ 333.340 Testing procedures to determine antibacterial activity of acne active ingredients.

(a) *Study design.* Either parallel or half-face groups may be used. The half-face design is permitted for drugs that are not sufficiently absorbed to result in antibacterial effects. When a drug is absorbed to a degree that systemic activity occurs, the untreated side of the face may be affected, thus invalidating the test. Reliability and extent of application are particularly important in a half-face test. For this reason, technicians should apply the drug when this study design is used. If translocation of the medication is known to occur, the half-face design should not be used. All studies should be double-blind with the formulation containing the active ingredient compared with the vehicle control.

(b) *Subjects.* A minimum of 15 subjects for a half-face study and 30 for a parallel group study should be used. The groups should include males and females 15 years of age or older. The subjects may or may not have active acne, but they must have significant follicular fluorescence indicating an adequate density of *Propionibacterium acnes* (*P. acnes*) on the skin. The subjects must have a *P. acnes* baseline count of 1×10^5 to 1×10^6 organisms per square centimeter.

(c) *Treatment.* The forehead and cheeks should be used as treatment sites. The method of application should be that specified in directions for use. The drug should be applied twice daily. The duration of treatment should usually be 4 weeks unless the study is intended to show that a product can meet the criteria in a shorter time. In that case the treatment time may be shortened.

(d) *Measurements.* The sample site should be specified by the investigator. To reduce error the same sample site should be used on each individual each time. The *P. acnes* count should be determined using the Williamson and Kligman scrub technique (*Journal of Investigative Dermatology*, 45:498–503, 1965). Other methods of measuring *P. acnes* counts may be used if they are shown to be equivalent or superior to the Williamson and Kligman method. Such methods may be used only after the agency has approved a petition to amend the monograph. Three separate determinations of the baseline *P. acnes* count should be made. The values may be averaged to obtain a single baseline value for each subject. Measurements to determine reduction should be made weekly thereafter. The free fatty acids determination is an optional confirmatory test. However, if it is used, the free fatty acids concentration should be carefully assessed by thin-layer chromatography, such as the method described by Downing (*Journal of Chromatography*, 38:91–99, 1968).

(e) *Criteria*—(1) *Required.* For an ingredient to be considered effective in demonstrating antibacterial activity against *P. acnes*, the following criterion must be met: A reduction in *P. acnes* counts of 0.75 log must be shown. This reduction should be statistically significant at the $p<0.1$ level. Therefore, the hypothesis test should be framed to test whether there is a 0.75-log reduction from baseline. If it is desirable to show that the reduction is significant at the $p<0.05$ level, the number of subjects should be increased appropriately.

(2) *Optional.* To confirm antibacterial activity, an optional test to show reduction of free fatty acids may also be done. A 30-percent reduction in free fatty acids on the skin surface should be shown. The reduction should be statistically significant at the $p<0.1$ level. The free fatty acid determination is included to assure that the antimicrobial agent has penetrated and is acting at the follicular level.

(f) *Methodology*—(1) Microbiological sampling of the skin should be by the Williamson and Kligman detergent scrub technique or an equivalent technique. The following culture techniques should be observed:

(i) Brain-heart infusion medium should be used to culture *P. acnes*. If another medium is developed that is shown to be equivalent or superior to brain-heart infusion, it may be used.

(ii) The sample retrieved from the scrub technique should be vortexed for 10 seconds prior to enumeration.

(iii) Anaerobic incubation should be at 35° C for 7 days.

(iv) A neutralizer adequate for the antimicrobial ingredient being tested should be added to the scrubbing fluid. The toxicity of the neutralizer must be determined for *P. acnes*. The presence of any residual antimicrobial agent in the sampling fluid must be investigated using adequate microbiological tests.

(2) *Free fatty acids determination.* Samples of skin lipids should be obtained by swabbing the area with a hexane-saturated sponge as in the method by Yeung and Smith (contained in a memorandum to S. Nacht, dated June 4, 1980, in OTC Volume 070279, on file in the Dockets Management Branch, HFA–305, Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857). Lipid analysis should be performed using a thin-layer chromatography technique, such as the one described by Downing (*Journal of Chromatography*, 38:91–99, 1968). Another method of lipid anlysis that may be used is infrared spectroscopy, described by Anderson and Fulton (*Journal of Investigative Dermatology*, 60:115–120, 1973).

§ 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" and is limited to the following:

(1) *For products containing any ingredient identified in § 333.310 for the treatment for acne.* The indications consist of one or more of the following statements:

(i) "For the management of acne."

(ii) "For the treatment of acne."

(iii) "Anti-acne formula."
(iv) "Anti-acne medication."
(v) "Anti-acne formulation."
(vi) "Dries and clears acne blemishes."
(vii) "Dries and clears acne pimples."
(viii) "Dries acne blemishes and allows skin to heal."
(ix) "Dries acne pimples and allows skin to heal."
(x) "Dries up acne pimples."
(xi) "Helps clear acne pimples."
(xii) "Clears up most acne pimples."
(xiii) "Clears up most acne blemishes."
(xiv) "Reduces the number of acne lesions."
(xv) "Reduces the severity of acne lesions."
(xvi) "Reduces blackheads."
(xvii) "Clears up most blackheads."
(xviii) "Loosens blackheads."
(xix) "Helps clear up blackheads."
(xx) "Helps clear up acne pimples."
(xxi) "Helps remove blackheads."
(xxii) "Helps remove acne pimples."
(xxiii) "Dries up blackheads."
(xxiv) "Dries up acne blemishes."
(xxv) "Unclogs pores to help clear acne."
(xxvi) "Unplugs pores to help clear acne."
(xxvii) "Penetrates follicles to eliminate most blackheads and acne pimples."
(xxviii) "Penetrates pores to eliminate most blackheads and acne pimples."
(xxix) "Penetrates follicles to control blackheads and acne pimples."
(xxx) "Penetrates pores to control blackheads and acne pimples."
(xxxi) "Penetrates follicles to clear most blackheads and acne pimples."
(xxxii) "Penetrates pores to clear most blackheads and acne pimples."
(xxxiii) "Penetrates follicles to reduce blackheads or acne pimples."
(xxxiv) "Penetrates pores to reduce blackheads or acne pimples."

(2) *For products containing any ingredient identified in § 333.310 for the prevention of new acne lesions.* The indications consist of one or more of the following statements provided that the labeling also contains one or more of the indications identified in § 333.350(b)(1).
(i) "Helps keeps skin clear of new acne lesions."
(ii) "Helps keep skin clear of new acne pimples."
(iii) "Helps prevent new blackheads or acne pimples."
(iv) "Helps prevent new acne pimples."
(v) "Helps prevent new acne pimples from forming."
(vi) "Helps prevent acne lesions."
(vii) "Helps prevent the development of new acne lesions."
(viii) "Helps prevent new acne blemishes from forming."

(3) *For products that have shown antibacterial activity according to § 333.340.* The indications consist of one or more of the following provided that the labeling also contains one or more of the indications identified in § 333.350(b)(1).
(i) "Antibacterial."
(ii) "Kills acne bacteria."
(iii) "Kills the bacteria that can cause acne."
(iv) "Kills acne bacteria on the skin."
(v) "Kills acne bacteria in the skin."
(vi) "Kills acne bacteria and helps clear acne pimples."
(vii) "Works to kill bacteria that may cause pimple redness to spread."
(viii) "Works to kill bacteria that may cause inflammation to spread."
(ix) "Penetrates follicles to kill bacteria associated with acne."
(x) "Penetrates pores to kill bacteria associated with acne."
(xi) "Penetrates follicles to reduce bacteria associated with acne."
(xii) "Penetrates pores to reduce bacteria associated with acne."
(xiii) "Reduces *P. acnes,* bacteria associated with acne."
(xiv) "Reduces the bacterial products associated with the inflammation of acne."
(xv) "Reduces the bacterial products associated with the irritation of acne."

(4) *Product attributes.* Terms to describe certain physical and chemical qualities may be used, as long as these terms do not imply any therapeutic effect and are distinctly separated from the indications identified in § 333.350(b)(1), (2), and (3). These terms are intended to provide consumer information and relate to a product's color, odor, or feel.

The following or similar terms may be used:
(i) "Greaseless."
(ii) "Nonstaining."
(iii) "Odorless."
(iv) "Colorless."
(v) "Nontinted."
(vi) "Blends easily with skin."
(vii) "Disappearing foam."
(viii) "Drying."
(ix) "Dries excess skin oils."
(x) "Skin-softening."
(xi) "Cools and comforts hot, irritated skin areas."
(xii) "Cleans the skin and helps to remove oil."

(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) "Other topical acne medications should not be used at the same time as this medication."

(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 or pharmacist. Keep away from eyes, lips, mouth, and sensitive areas of the neck. This product may bleach hair or dyed fabrics."

(3) *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 or pharmacist."

(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.

Interested persons may, on or before June 21, 1982, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance

notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before July 21, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 19, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: March 16, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

[FR Doc. 82-7683 Filed 3-22-82; 8:45 am]

BILLING CODE 4160-01-M