[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 347]

[Docket No. 78N-0021]

SKIN PROTECTANT DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Establishment of a Monograph; Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions for the safety, effectiveness, and labeling of over-the-counter (OTC) skin protectant drug products (drugs used as aids in the temporary relief of minor skin irritations). The proposed rule, based on the recommendations of the Advisory Review Panel on Over-the-Counter (OTC) Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, is part of the Food and Drug Administration's ongoing review of OTC drug products.

DATES: Comments by November 2, 1978, and reply comments by December 4, 1978.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: Pursuant to part 330 (21 CFR part 330), the Commissioner of Food and Drugs received on December 14, 1977, a report of the Advisory Review Panel on Over-the-Counter (OTC) Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products. In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC skin protectant drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel 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 on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration (address given above).

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report; the Panel's findings are being issued as a formal proposal to obtain full public comment before the Agency reaches any decision on the Panel's recommendations. The report has been prepared independently of the Food and Drug Administration (FDA). It represents the best scientific judgment of the Panel members but does not necessarily reflect the agency position on any particular matter contained in it. After careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC skin protectant drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC skin protectant drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before September 5, 1978, except to the extent that the person submitting it demonstrates that it still 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 given above).

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (category I), be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph because they would cause the drug to be not generally recognized as safe and effective or to be misbranded (category II), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph because the available data are insufficient (category III) to classify such conditions either as category I or category II be permitted to remain on the market, or to be introduced into the market after the date of publication of the final monograph in the FEDERAL REGISTER: *Provided,* That FDA receives notification of testing in accordance with § 330.10(a)(13) (21 CFR 330.10(a)(13)). The Panel recommended that a period of 2 years be permitted for the completion of studies to support the movement of category III conditions to category I. The Commissioner will review that recommendation as well as all comments on this document, and will determine what time period to permit for category III testing after that review is completed.

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels. In the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), the Commissioner published the final regulations providing for the OTC drug review under § 330.10 which were made effective immediately. Pursuant to these regulations, the Commissioner issued in the FEDERAL REGISTER of December 12, 1972 (37 FR 26456) a request for data and information on all active ingredients utilized in topical analgesic, including antirheumatic, otic, burn, sunburn treatment, and prevention drug products.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report pursuant to § 330.10(a)(1) on the safety, effectiveness, and labeling of those products:

Thomas G. Kantor, M.D., Chairman; John Adriani, M.D.; Col. William A. Akers, M.D.; Maxine Bennett, M.D.; Minerva S. Buerk, M.D.; Walter L. Dickison, Ph. D.; and Jerry Mark Shuck, M.D.

The Panel was charged to review submitted data and information for OTC topical analgesic ingredients, including antirheumatic, otic, burn, and sunburn prevention and treatment active ingredients. For purposes of this review, the Panel grouped the active ingredients and labeling into four major pharmacologic groups, i.e., external analgesics, skin protectants, topical otics, and sunscreens.

The Panel presents its conclusions and recommendations for skin protectant active ingredients in this docu-

ment. The Panel's conclusions for topical otic active ingredients were published in the FEDERAL REGISTER of December 16, 1977 (42 FR 63556). The Panel's conclusions and recommendations for external analgesic and sunscreen active ingredients will be presented in a later issue of the FEDERAL REGISTER.

The Panel was first convened on March 6, 1973, in an organizational meeting. Working meetings were held on May 8 and 9, July 12 and 13, September 27 and 28, November 3 and 4, November 26 and 27, 1973; January 30 and 31, March 6 and 7, April 10 and 11, May 8 and 9, June 10 and 11, July 17 and 18, September 24 and 25, October 22 and 23, November 26 and 27, 1974; January 21 and 22, March 13 and 14, April 17 and 18, May 21 and 22, July 15 and 16, September 30 and October 1, November 12 and 13, 1975; March 4 and 5, May 19 and 20, June 22 and 23, September 27 and 28, November 18 and 19, 1976; February 23 and 24, May 25 and 26, August 22, 23, and 24, October 25, and December 13, 14, and 15, 1977.

Six nonvoting liaison representatives served on the Panel. Mrs. Jacqueline Pendleton (at the initial meeting), Mrs. Valerie Howard (from May 8, 1973 to September 28, 1973), Lynn Berry (from November 3, 1973 to April 27, 1976), Kathleen A. Blackburn (from July 6, 1976 to August 24, 1977), and Emily Londos (from October 25, 1977), each nominated by an ad hoc group of consumer organizations, served as the consumer liaison, and Joseph L. Kanig, Ph. D., nominated by the Proprietary Association, and Ben Marr Lanman, M.D., nominated by the Cosmetic, Toiletry, and Fragrance Association, served as the industry liaisons.

The following FDA employees served: C. Carnot Evans, M.D., served as Executive Secretary. Lee Geismar, served as Panel Administrator. Lee Quon, R. Ph., served as Drug Information Analyst until July 1973, followed by Thomas H. Gingrich, R. Ph., until July 1975, followed by Timothy T. Clark, R. Ph., until July 1976, followed by Victor H. Lindmark, Pharm. D.

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

Joseph P. Armellino, M.D.; Charles Bluestone, M.D.; Stuart Ericksen, Ph. D.; Alexander A. Fisher, M.D.; Thomas Fitzpatrick, M.D., Ph. D.; J.M. Glassman, M.D.; Peter Hebborn, Ph. D.; George E. Heinze; Kenneth R. Johannes; Albert M. Kligman, M.D.; Howard Maiback, M.D.; Edward Marlowe, Ph. D.; Kenneth L. Milstead, Ph. D.; John Parrish, M.D.; Madhue Pathak, M.D.; Robert Sayre, Ph. D.; Joseph P. Soyka, M.D.; Garrett Swenson, Esq.; Stephen M. Truitt, Esq.; and Frederick Urbach, 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 data and information submitted through December 14, 1977, in arriving at its conclusions and recommendations for OTC skin protectants drug products.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to skin protectant drug products are set out in three categories:

Category I. Conditions under which OTC skin protectant drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC skin protectant 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.

I. SUBMISSION OF DATA AND INFORMATION

Pursuant to the notice published in the FEDERAL REGISTER of December 12, 1972 (37 FR 26456) requesting the submission of data and information on OTC skin protectants drugs, the following firms made submissions related to the indicated products:

A. SUBMISSIONS BY FIRMS

Firms and Marketed Products

Beecham Products (formerly Calgon Consumer Products Co., Inc.) Rahway, N.J. 07065—S.T. 37.

Bowman Pharmaceuticals, Inc., Canton, Ohio 44702—Almophen Ointment, Calamine Compound Paste, Caloxal Lotion, Petrozin Ointment.

Calhoun's Laboratory, Baxley, Ga. 31513—Burn-O-Jel.

Carbisulphoil Co., Dallas, Tex. 75204—Foille Liquid, Foille Ointment, Foille Spray.

Cheesebrough-Pond's, Inc., Trumbull, Conn. 06611—Vaseline Pure Petroleum Jelly, Vaseline White Petroleum Jelly, Vaseline Ultra White Petroleum Jelly, Vaseline Sterile Ultra White Petroleum Jelly.

Church & Dwight Co., Inc., Syracuse, N.Y. 13201—Arm & Hammer Baking Soda.

Otis Clapp and Sons, Inc., Cambridge, Mass. 02139—Obtundia Calamine Cream.

Gebauer Chemical Co., Cleveland, Ohio 44104—Gebauer's Tannic Spray.

Medical Supply Co., Rockford, Ill. 61101—MSCo Burn Compound, MSCo Burn Spray, Telephone Ointment.

Norwich Pharmacal Co., Norwich, N.Y. 13815—Unguentine Aerosol with Benzocaine, Unguentine Ointment, Unguentine Plus, Unguentine Spray.

Noxell Corp., Baltimore, Md. 21203—Noxzema Skin Cream.

Pfizer Pharmaceuticals, New York, N.Y. 10017—Un-Burn.

Plough, Inc., Memphis, Tenn. 38101—Coppertone Lipkote Lip Balm, Mexsana Medicated Powder.

Resinol Chemical Co., Baltimore, Md. 21201—Resinol Medicated Cream, Resinol Medicated Ointment.

The R. Schattner Co., Washington, D.C. 20016—Chloraderm, Oraderm Lip Lotion.

E. R. Squibb & Sons, Inc., New Brunswick, N.J. 08903—Zinc Oxide Ointment.

Whitehall Laboratories, Inc., New York, N.Y. 10017—Digene Chafing Ointment, Sperti Healing Ointment.

B. LABELED INGREDIENTS CONTAINED IN MARKETED PRODUCTS SUBMITTED TO THE PANEL

Alcohol, allantoin, aluminum hydrate, aluminum hydroxide, anhydro parahydroxymercuri metacresol, benzalkonium chloride, benzethonium chloride, benzocaine, benzoic acid, benzyl alcohol, bicarbonate of soda, bismuth subcarbonate, bismuth subnitrate, boric acid, calamine, calamine lotion, camphor, carbolic acid, chlorbutanol [sic], chlorobutanol, chloroxylenol, citric acid, clove oil, cornstarch, dimethylpolysiloxane, ethyl alcohol, eucalyptol, eucalyptus oil, eugenol, glycerin, gum tragacanth, hexylresorcinol, homosalate, 8-hydroxyquinoline, ichthammol, kaolin, lanolin, lidocaine hydrochloride, lime water, live yeast cell derivative, menthol, methylcellulose, methyl parben [sic], oil of cade, oil eucalyptus, oil thyme, oleostearin, oxyquinoline base, parachlorometaxylenol, petroleum jelly, petrolatum, phenol, polysorbate 20, prepared calamine, propylene glycol, propyl parben [sic], red petrolatum, resorcin, resorcinol, shark liver oil, sodium borate, sodium citrate, sodium phenolate, sulfur, tannic acid, thyme oil, water, zinc acetate, zinc carbonate, and zinc oxide.

In addition to the submitted ingredients, the Panel reviewed cocoa butter.

C. CLASSIFICATION OF INGREDIENTS

1. Active Ingredients

Allantoin, aluminum hydroxide gel (alumunim hydrate, aluminum hydroxide), bismuth subnitrate, boric acid, calamine (calamine lotion, prepared calamine), cocoa butter, corn starch (cornstarch), dimethicone (dimethyl polysiloxane), glycerin, kaolin, live yeast cell derivative, petrolatum (petroleum jelly, white petrolatum), shark liver oil, sodium bicarbonate (bicarbonate of soda), sulfur, tannic acid, zinc acetate, zinc carbonate, and zinc oxide.

2. Inactive Ingredients

Alcohol, benzyl alcohol, bismuth subcarbonate, citric acid, clove oil, ethyl alcohol, gum tragacanth, lanolin, lime water, methylcellulose, oleostearin, polysorbate 20, propylene glycol, propyl paraben, sodium borate, sodium citrate, and water.

3. Ingredients Deferred to Other OTC Advisory Review Panels or Other Experts

Anhydro parahydroxymercuri metacresol, benzalkonium chloride, benzethonium chloride, chloroxylenol, 8-hydroxyquinoline, ichthammol, methyl paraben, oxyquinoline base, and parachloro- metaxylenol.

4. Ingredients Considered by This Panel in Separate Pharmacologic Groups

(a) Sunscreens

Homosalate, and red petrolatum.

(b) External analgesics

Benzocaine, camphor, chlorobutanol (chlorbutanol), eucalyptol, eucalyptus oil, eugenol, hexyresorcinol, menthol, oil of cade, phenol (carbolic acid), resorcinol (resorcin), sodium phenoxide (sodium phenolate), and thyme oil.

D. REFERENCED OTC VOLUME SUBMISSIONS

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of December 12, 1972 (37 FR 26456). The volumes will be put on public display on or before September 5, 1978, in the office of the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

II. General Statements and Recommendations

A. General Discussion

1. *Introduction.* For centuries, the topical application of medicaments to minor burns, abraded skin, irritated areas, and minor wounds has frequently produced salutary temporary results. The Panel has designated these agents as skin protectants. Skin protectants include various types of compounds, which are chemically inert and are used to cover and thus to protect skin surfaces against drying and other irritation. These agents are also pharmaceutic necessities and are familiar components of drug and cosmetic vehicles. Applied to irritated skin, skin protectants act as mechanical barriers that physically alter the superficial wound environment by excluding air, removing wetness, preventing drying, and protecting from continuous intertriginous contact.

The Panel recognizes that the action of these agents is almost entirely physical or mechanical, but also recognizes that in many cases, the use of these products confers a therapeutic benefit to persons who have superficial wounds by making the wound area more comfortable. In addition to the purely mechanical protection against friction and rubbing, protectants also decrease the irritation that is caused by drying of the stratum corneum (Refs. *1, 2,* and *3*). Rehydrating the stratum corneum relieves the symptoms of irritation, and permits the normal healing processes to continue. Skin protectants provide symptomatic relief only and do not stop the underlying disease processes.

Wounds for which skin protectants are appropriate include those with superficial loss of skin layers (epidermal surface) such as scrapes, abrasions, and minor scratches. Irritation or epidermal loss due to physical effects of sun, wind, and rubbing are often relieved of their mninor discomforts by application of skin protectants. In addition, the fluids from weeping rashes or toxic dermatoses (poison ivy, poison sumac, intertriginous moisture, prickly heat, insect bites, and eczema) are absorbed or adsorbed by many of these drugs. Often itching is ameliorated. Burns are specifically discussed below.

Wounds must be seen by a physician if any evidence of infection, such as increasing pain, redness, swelling, fever, pustules, red streaks leading from the wound, or swollen regional lymph nodes is noted. Also, if no benefit is provided, lesions worsen, exudation increases, or the problem persists for more than 7 days, a physician should be consulted.

Skin protectants such as the adsorbent powders and oleaginous ointments are inert, are not absorbed, and are nontoxic. For these reasons, these agents can be applied liberally, as often as necessary. Exceptions will be dealt with in the discussions of the individual ingredients, below.

For most of the skin protectant ingredients, the Panel is not aware of any well-controlled clinical studies that have been conducted. However, the Panel recommends that the requirement for such studies be waived, on the grounds that clinical studies are not necessary to support the use of mechanical barriers such as these to protect the skin from further injury. Protectants have been widely used and are included in all standard drug compendia. Their usefulness in providing a mechanical barrier is recognized in standard drug reference texts (Refs. *4, 5,* and *6*). There are data that support the role of protectants in preventing water loss from the stratum corneum (Refs. *1, 2,* and *3*). The Panel concludes that these data are sufficient to validate the effectiveness of the skin protectant ingredients.

The Panel has classified various agents as skin protectants. The following definitions have been adopted by the Panel to clarify terminology.

Skin protectant. A skin protectant is any agent that isolates the exposed skin or mucous membrane surface from harmful or annoying stimuli. In common practice only those substances which protect by mechanical or other physical means are considered to be skin protectants. Generally, substances in this category are inert, insoluble, finely subdivided, and adsorb some moisture. The different types of skin protectants and their mode of action are defined below:

a. *Absorbent.* An absorbent is an skin protectant having the power to absorb, suck up, incorporate, and take into itself gases, liquids, or rays of light. Absorption differs from adsorption in that the former involves a penetration of one substance into another so that a molecular intermingling results.

b. *Adsorbent.* An adsorbent is a skin protectant which attracts and holds to its surface a gas, liquid, or substance in solution or fine suspension. Adsorption is a surface interface phenomenon. Adsorbent agents may attach atoms or molecules to their surfaces by means of unsatisfied valence bonds, e.g., finely divided carbon, clay, magnesia, zinc oxide, activated charcoal.

c. *Astringent.* An astringent is a topically applied protein precipitant which has a low cell penetrability. Its action is essentially limited to the cell surface and the interstitial spaces. The permeability of the cell membrane is reduced but the cells remain viable.

d. *Demulcent.* A demulcent is a protective agent employed primarily to alleviate irritation, particularly of mucous membranes or abraded tissue. It is frequently applied to intact skin.

e. *Emollient.* An emollient is a bland, fatty, or oleaginous substance which may be applied locally, particularly to the skin, or to mucous membranes or abraded areas. The skin is rendered softer and more pliable.

f. *Lubricant.* A lubricant is any substance that lessens friction.

g. *Wound-healing aid.* A wound-healing aid is a protective agent that augments or promotes the healing of wounds.

REFERENCES

(1) Berube, G. R., M. Messinger, and M. Berdick, "Measurement in Vivo of Transepidermal Moisture Loss," *Journal of the Society of Cosmetic Chemists,* 22:361-368, 1971.

(2) Berube, G. R., and M. Berdick, "Transepidermal Moisture Loss. II. The Significance of the Use Thickness of Topical Substances," *Journal of the Society of Cosmetic Chemists,* 25:497-506, 1974.

(3) Blank, I. H., "Factors which Influence the Water Content of the Stratum Corneum," *Journal of Investigative Dermatology,* 18:433-440, 1952.

(4) "The Pharmacopeia of the United States of America," 18th ed., The United States Pharmacopeial Convention, Inc., Bethesda, Md., 1970.

(5) Sollmann, T., "A Manual of Pharmacology and Its Applicatioans to Therapeutics and Toxicology," 8th ed., W. B. Saunders Co., Philadelphia, pp. 121-136, 1957.

(6) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th ed., Macmillan Co., New York, pp. 946-949, 1975.

2. *Burns.* Included among active ingredients that this Panel evaluated were those for use on burns. Such agents tend to fall within the classification of skin protectants. The exclusion of air and the prevention of drying provide comfort to persons with superficial burns. When OTC

products are applied to superficial burn wounds occupying less than 1 percent of the body surface, relief of pain can be dramatic. No skin protectants, however, have been proven to promote healing, reduce blister formation, or have any special beneficial effects other than providing comfort. Skin protectant active ingredients with wound-healing aid claims are discussed below. Because ingredients for preventing infection are the consideration of another OTC Advisory Review Panel, they have not been considered in that role by this Panel.

The Panel reviewed the definition of burn wounds and has accepted the traditional classification of first degree, second degree, third degree, and fourth degree. A first degree burn wound displays erythema, and if any loss of tissue occurs, it is superficial, usually a late "flaking" of the outermost epithelial layers. Such wounds heal spontaneously with no scarring.

A second degree or partial-thickness burn wound has varying destruction of the layers of the epidermis and dermis but allows residual epithelium and/or skin appendages (hair follicles, sebaceous glands, sweat glands) to eventually grow and coalesce to resurface the wound. Such wounds are often characterized by blistering. A partial-thickness burn wound does not require grafting.

The Panel recommends that OTC products should be applied only to first and minor second degree burns.

A third degree or full-thickness burn wound is one that destroys all layers of epithelium, including the skin appendages. The wounds are generally charred and anesthetic, and usually require skin grafting. A fourth degree burn is one that involves the underlying fat, fascia, muscle, and even bone. The deeper burns (third and fourth degree) should be treated by a physician.

The first aid of minor burns should include immediate removal of the offending agent and cooling of the affected surface. Since tissue damage during a burn is related both to the temperature of the offending agent and the duration of contact, the more rapidly the tissue temperature itself returns to normal, the less damage will be inflicted. After the contact has ceased, the tissue temperature may remain above the critical level at which tissue injury occurs for several minutes. Tissue temperature reduction is the desired result of cool water therapy. The sooner the tissue is cooled, the better. This is best done by immersion of the burned area into cold tap water, or by the application of cool compresses to areas that are difficult to immerse. Running water will increase the pain. Iced water or iced compresses are too cold. They create pain and possibly further injury. If pain is relieved by such cold therapy in the early period, the wounds generally will require little topical treatment. Beyond 30 minutes after injury, the cold treatment is of little value in preventing destruction. After washing such a wound, the application of a protective covering will relieve pain.

No topical agent has as yet been conclusively demonstrated to increase the rate of healing of minor burns, abrasions, and wounds as discussed below. Agents are available, however, that will protect the wound, provide an optimum environment for healing, and control infection. Agents for control of infection are being considered by another OTC Advisory Review Panel. Skin protectants classified as category I are generally appropriate for minor, superficial burn wounds. Butter, lard, goose grease, and nonsterile oleaginous substances cannot be recommended despite the fact that such agents will make the wound feel better. A physician should be consulted for more extensive burns.

It is not appropriate to apply OTC drugs to extensive burns because the agents will have to be removed prior to examination by a physician. This will result in unnecessary pain. Topical medicaments that help relieve pain, other than by physically altering the wound environment, will be discussed in a separate document.

3. *Wound healing.* Claims have been made that some OTC active ingredients submitted to the Panel aid in wound healing (i.e., allantoin, live yeast cell derivative, and zinc acetate) when the drugs are placed directly upon the wound. Such wounds might be superficial burns, minor cuts, scratches, scrapes, and abrasions.

No controlled studies of aids in wound healing conclusively prove that minor wounds under OTC consideration heal in an accelerated fashion. The Panel concludes that an agent that is capable of aiding wound healing in well-controlled experimental wounds will probably have some effect on the healing process. The degree of this effect remains to be demonstrated in clinical trials. Therefore, skin protectant active ingredients for OTC use with labeling claims as a wound-healing aid are classified as category III.

The process of wound healing can be divided into three general phases:

a. Substrate phase (0 to 5 days)—Cellular infiltration and inflammation occurs;

b. Cellular phase (5 to 15 days)—A fibroblastic phase follows, characterized by proliferation of collagen fibers to form a matrix support for the wounds; and

c. Remodeling phase (1 to 36 months)—A maturation phase results in which the collagen matrix is mechanically strengthened by the formation of collagen cross-linkages (Refs. *2* and *3*).

Epithelization is required to resurface open wounds to complete their healing. Cuts, abrasions, and burns close by the growth of epithelial cells from the margins of the wound, and also from residual epidermal remnants (hair follicles, sebaceous glands) that remain scattered within the affected area. Wound contraction reduces the surface defect by dynamically "shrinking" the wound in size. The fibroblastic phase is concurrent with both wound epithelization and wound contracture. Considerable overlap of the restorative events happens especially during the first 15 days after injury.

Agents affecting wound healing can act at one or more of these phases and in a complex manner. Corticosteroids, as anti-inflammatory agents, can act primarily in the first two phases and can retard some wound healing (as in surgical wounds), but can promote it in other cases such as ulcerative proctitis and related disorders (Ref. *4*). Vitamin A, which promotes collagen production, can counteract the retardant effect of steroids in some cases (Refs. *2* and *5*).

Collagen production and cross-linkages have been experimentally quantified by measurements of collagen production and wound tensile strength (Refs. *2*, *5*, and *6*). Most agents promoting experimental wound healing, such as oxygen, oral ascorbic acid, and oral vitamin A appear to act primarily to promote collagen synthesis (Ref. *3*).

REFERENCES

(1) Summary Minutes of the 30th Meeting of the Panel on Review of Topical Analgesic, Antirheumatic, Otic, Burn, Sunburn Treatment and Prevention Drug Products, August 22-24, 1977.

(2) Van Winkle, W., "The Tensile Strength of Wounds and Factors that Influence It," *Surgery, Gynecology and Obstetrics*, 129:819, 1969.

(3) Brooks, M. P., "Wound Healing: A Review," *Journal of the Mississippi State Medical Association*, 9:385-390, 1973.

(4) Spiro, H. N., "Clinical Gastroenterology," Collier-Macmillan, Ltd., London, p. 597, 1970.

(5) Ehrlich, H. P., T. Tarver and K. Hunt, "Effects of Vitamin A in Glucocorticosteroid on Inflammation in Collagen Synthesis," *Annals of Surgery*, 177:222-228, 1973.

(6) Forrester, J. C., "Mechanical, Biochemical and Architectural Features of Surgical Repair," *Advances in Medical and Biological Physics*, 14:1-39, 1972.

4. *Combinations of skin protectants.* The Panel has reviewed the submitted data and finds that there need be no limit to the number of skin protectants that may be combined. The Panel believes it reasonable to require that each ingredient make a contribution to the designated product in order to be deemed an active ingredient.

The Panel concludes that two or more skin protectant active ingredients may be combined provided that:

a. Each is present in sufficient quantity to act additively or by summation to produce the claimed therapeutic effect when the ingredients are within the effective concentration range specified for each ingredient in the monograph.

b. The ingredients do not interact with each other and one or more do not reduce the effectiveness of the other or others, by precipitation, change in acidity or alkalinity, or in some other manner that reduces the claimed therapeutic effect.

c. The petition of the active ingredients between the skin and the vehicle in which they are incorporated is not impeded and the therapeutic effectiveness of each remains as claimed or is not decreased.

5. *Combinations of skin protectants and other nonskin protectant active ingredients.* The Panel is cognizant of the fact that by their very nature skin protectants are also suitable vehicles for use in delivering active ingredients classified in other categories such as topical analgesics and sunscreens. In such a situation, the skin protectant may serve a different purpose and will be expected to meet the criteria established for such other purpose. Accordingly, the Panel concludes that skin protectants must either meet the criteria established in this document or those for external analgesics or sunscreens.

III. Skin Protectants

A. General Comments

The Panel is aware that by their nature, skin protectants are ideally suited to be the vehicle for applying ingredients classified in other categories (topical analgesics, sunscreens) to the skin. However, in this discussion, the Panel will address only the skin protectant use of these ingredients.

As stated earlier in this document, the Panel has concluded that there need be no limit on combining skin protectant ingredients, as long as the general aspects of good pharmaceutical practice are observed and products retain their integrity under conditions of general use.

The Panel has carefully considered the anatomy and physiology of the skin and concludes that generally there need be no limitation on the use of skin protectants by any age group, including infants under 6 months, except as specifically limited in the individual ingredient monographs.

A detailed discussion of skin anatomy, physiology, penetration, percutaneous absorption and photosensitization is contained in a separate document regarding topical sunscreens which is to be published separately. The same discussion is pertinent with regard to skin protectants.

The Panel has considered the use of skin protectants for three distinct purposes, namely for skin conditions of dryness, wetness, or to provide lubricity. In this regard the following table was established:

Dryness	Wetness	Lubricity
A. Ingredients		
Allantoin	Aluminum hydroxide gel	Starch
Cocoa butter	Calamine	Cocoa butter
Dimethicone	Corn starch	Dimethicone
Glycerin	Dimethicone	Petrolatum
Petrolatum	Kaolin	Shark liver oil
Shark liver oil	Zinc acetate	Zinc oxide
	Zinc oxide	
B. Claims		
Chapping	Poison ivy	Intertrigo
Peeling	Poison oak	Chafing
Scaling	Contact dermatitis	Galling
Cracked lips		Rubbing
Windburn		Friction
First degree burns		
Scrapes		
Abrasions		

On further evaluation, the Panel decided that to associate these skin conditions with specific ingredients is not helpful in view of the overlapping functions of some of the ingredients. In addition, since the Panel has placed no limitation on which ingredients may be combined, most combination products will be suitable for use in more than one of these skin conditions.

The Panel recognized that OTC drug products generally have not been recommended for use in children under 2 years of age. However, the Panel concluded that this 2 year lower age limit should be waived for the majority of skin protectants with the exception of zinc acetate, shark liver oil, and live yeast cell derivative. For the labeling of drug products containing these three ingredients, the Panel recommended the following: "There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician."

In addition, the Panel considered a 6 month lower age limit sufficient for glycerin and aluminum hydroxide gel. For these two skin protectant ingredients, the Panel recommended the following labeling: "There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician."

The Panel made these recommendations on the basis of safety considerations.

B. Categorization of Data

1. *Category I conditions under which skin protectant ingredients 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.

Category I Active Ingredients

The panel has classified the following skin protectant active ingredients as generally recognized as safe and effective and not misbranded:

Allantoin, aluminum hydroxide gel, calamine, cocoa butter, corn starch, dimethicone, glycerine, kaolin, petrolatum preparations—petrolatum, and white petrolatum, shark liver oil, sodium bicarbonate, zinc acetate, zinc carbonate, and zinc oxide.

a. *Allantoin.* The Panel concludes that allantoin is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below. The Panel has also evaluated allantoin as a protectant for use as a wound-healing aid. (See part III. par. B.3.a. below—Allantoin.)

Allantoin (5-ureidohydantoin) in the racemic form appears as monoclinic plates or prisma. Allantoin forms many salts, including the sulfonamide and aluminum hydroxy derivatives (Refs. *1* and *2*).

Allantoin is a product of purine metabolism. It is prepared synthetically by the oxidation of uric acid with alkaline potassium permanganate, or by heating urea with dichloroacetic acid (Ref. *3*).

(1) *Safety.* Clinical and marketing experience have confirmed that allantoin is safe in the OTC dosage range used as a skin protectant.

A search of the literature has not produced any reports of adverse reactions to the topical use of allantoin (Refs. *4* and *5*).

The Schwartz patch test on 200 individuals has shown allantoin to be nontoxic, nonirritating, and nonallergenic. The Draize technique, in rabbits, has shown allantoin to be nonirritating even when applied to the conjunctival sac of the eye and the repeated insult test on 12 individuals has not shown allantoin to be a primary skin irritant or primary sensitizer (Ref. *6*).

In animal sensitization studies, two aluminium salts of allantoin were tested without occlusion on guinea pigs. A 25-percent alcloxa (aluminum chlorhydroxy allantoinate) suspension and a 25-percent aldioxa (aluminum dihydroxy allantoinate) suspension were used. Also, two antiperspirant creams were formulated with 0.25-percent alcloxa and 0.75-percent aldioxa. Each of the 4 test formulations was rubbed into a 4-inch square, dorsal area of 3 guinea pigs (total of 12 guinea pigs) for 1 minute on alternating days for 8 days. The vehicle without the allantoin salt was applied in the same manner as a control. After the fourth treatment, the animals received no further applications for 1 week. A fifth sensitizing dose was then applied. During the experimental period, the animals were observed for any changes in the appearance of the skin. Their weight and general health exhibited no change. There were no immediate or delayed reactions noted after the fifth sensitizing dose. The concentrations used are 30 to 100 times those in commercial prepara-

tions and would indicate that allantoin is safe in OTC topical drug products (Ref. 7).

Acute oral toxicity tests were performed on male Webster, Swiss albino mice. Aqueous suspensions of aldioxa were administered in dosages of 5 to 23 grams per kilogram (g/kg) over a 2-week observation period. There was no evidence of toxicity under the conditions of the test. Food and water intake appeared normal over the duration of the study (Ref. 7).

(2) *Effectiveness.* Due to its wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that allantoin is effective for use as an OTC skin protectant.

Allantoin has been used as a protectant. Because allantoin forms complexes with a variety of sensitizing agents rendering them nonsensitizing, it is especially useful for individuals sensitive to topical products, including sulfonamides (Refs. *1, 2,* and *5*). Allantoin has been claimed to be an effective protectant as the aluminum hydroxide salt (Ref. *5*). When combined with aminobenzoic acid (PABA), fewer sensitivity reactions are noted than with PABA alone (Ref. *8*). Allantoin is known to possess a keratolytic (skin softening) action (Ref. *9*). Flesch (Ref. *10*) demonstrated the keratolytic action by incubating psoriatic scales in solutions of 0.2-percent allantoin and 0.2-percent aluminum chlorhydroxy allantoinate. The allantoin preparations dispersed the scales into solution.

The allantoin layer extracts sulfhydril compounds from the keratin of the horny (most superficial) part of the skin. Since this is the major barrier to water, the application of allantoin will allow transpiration of water vapor as well as moisture absorption (Ref. *6*).

Although allantoin does not possess germicidal or antiseptic properties, it does act as a debrider and cleansing agent (Ref. *11*).

Most published studies are not well-controlled with the exception of an investigation in the use of allantoin for treatment of diaper rash (Ref. *12*). In this three part study, glyoxyl diureide (allantoin) was incorporated into an ethanolamine stearate base at a concentration of 0.2 percent along with silicones (Dow Corning 200 or 555) at a 3-percent concentration and hexachlorophene at 0.25 percent. In the first part of the study, 726 newborn infants were divided into 2 groups. The test group, consisting of 429 subjects, was treated daily with the preparation. The control group consisted of 297 subjects. Both groups received routine hospital care and were examined daily. The results are summarized in the table below:

	Number of cases studied	Number of cases free from eruption	Skin reactions noted	Percentage of reactors
Test products	429	408	21	4.8
Controls	297	265	32	14.1

In the second part of the study, 110 infants ranging from 1 to 18 months of age were followed for a period of 6 months. Mothers in this group were warned not to make any changes in the general care of the infant, to avoid the use of all medicaments other than the prescribed emulsion, and to cleanse the diaper area with lukewarm water after urination or defecation. They were to report, immediately, any evidence of a dermatitis or other untoward reaction. Their results are summarized below:

Number of cases	Appearance of diaper area on initial examination	Results	Remarks
83	Clear	Clear	
5	Clear	Mild erythema	1 lost to study; 4 stopped emulsion until cleared, then reused it and remained clear.
22	Erythema, intertrigo, mild papulovesicular eruption.	20 cleared completely; 1 cleared partially, 1 unchanged.	No complications.

The third part of the study included subjects who presented dermatoses common to infants. The emulsion was applied to the involved areas three times daily. No other medication was used. Rubber and plastic panties were avoided. The results are summarized below:

Diagnosis	Number of patients	Clear	Partially clear	Unchanged
Intertrigo	16	16		
Diaper area erythema	17	15	2	
Atopic eczema	2	1		1
Contact dermatitis	2	1	1	
Bedsores	1	1		
Total	38	34	3	1

The investigators concluded that the medication was efficacious and relatively free from side reactions.

(3) *Dosage.* Adult, children, and infants topical dosage is the application of a 0.5 to 2.0 percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the category I labeling for skin protectant active ingredients. (See part III, paragraph B.1. below—Category I labeling.)

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(2) "The Dispensatory of the United States of America," 26th ed., edited by Osol, A. R. and M. D. Altschule, J.B. Lippincott Co., Philadelphia, pp. 43-44, 1973.

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(4) Mecca, S. B., "The Function and Applicability of the Allantoins," *Proceedings of the Scientific Section—The Toilet Goods Association,* 39:7-15, 1963.

(5) Mecca, S. B., "Allantoin: A Review of its History and Therapeutic Properties," *Philadelphia Medicine,* 41:1109-1113, 1946.

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b. *Aluminum hydroxide gel.* The Panel concludes that aluminum hydroxide as a gel is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Aluminum hydroxide gel is effective as a skin protectant due to its adsorbent and astringent properties. Aluminum hydroxide gel is also known as aluminum hydroxide and aluminum hydrate. It is a white amorphous powder that is practically insoluble in water and forms a gel when in prolonged contact with water. The hydrated oxide and aluminum hydroxide make a suspension, the equivalent of 3.6 to 4.4 percent weight in weight (w/w) of aluminum oxide. Different methods of preparation produce gels with different physical properties (Refs. *1* and *2*).

(1) *Safety.* Clinical and marketing experience has confirmed that aluminum hydroxide gel is safe in the currently marketed dosage range as a skin protectant.

Aluminum hydroxide gel is practically insoluble in water and is physiologically inert. Evaluation of local or systemic reactions to the topical application of aluminum hydroxide gel is important. Friedman, in his report on treatment of skin erosion in patients with bowel fistulas, states that no patient exhibited adverse skin reactions, nor had any dermatitis been reported in workers preparing or applying the aluminum hydroxide gel (Ref. *3*). Further study was made to investigate aluminum salt penetration into human skin when applied topically (Ref. *4*). the results show very little aluminum reaches the dermal area through excised skin. In patients with normal skin, penetration even into the stratum corneum in minimal. Local irritation appears to be absent in regard to topical application of aluminum salts. Based on the penetration information, systemic toxicity is not expected. The material has been marketed for almost a century with positive consumer acceptance (Ref. *5*). As an antacid, aluminum hydroxide gel has been found to be safe for oral use by the FDA Advisory Review Panel on OTC Antacid Products (see the FEDERAL REGISTER of April 5, 1973) (38 FR 8717)). An animal study conducted by Eyerle and Breuhaus supports this conclusion. The experimental animal received 2 ounces (oz) (56.7 grams (g)) of aluminum hydroxide daily for 6 days over a 3-month period. Observation during treatment and after autopsy showed no changes in health or internal structure (Ref. *6*).

(2) *Effectiveness.* There are controlled studies documenting the effectiveness of aluminum hydroxide gel as a skin protectant. Aluminum ion, a trivalent cation, can bind strongly with many proteins and, therefore, can act as an antibacterial agent (Ref. *7*). Aluminum does not adsorb most amino acids, ascorbic acid, glucose, or fats (Ref. *8*).

Aluminum hydroxide gel is reported to afford relief in a variety of skin conditions, including miliaria rubra (prickly heat), certain fungal disorders, such as tinea cruris (jock itch), tinea (ringworm) and other epidermophytoses, weeping eczematous lesions, and impetigo (Refs. *1, 2,* and *3*).

In a study on treatment of gangrene with aluminum hydroxide gel, Newman, as cited by Spiesman, concludes that the hastening of appearance of the line of demarcation was due to the protective power of the substance and its ability to neutralize acids and other toxins (Ref. *9*).

Howard (Ref. *2*) employed colloidal aluminum hydroxide gel topically for a variety of skin diseases in the tropics. Patients received almost immediate relief of the distressing symptoms of miliaria rubra on first application. He concluded that aluminum hydroxide gel was the most useful of a number of drugs tested in the treatment of skin problems of afflicted military personnel in tropical climates.

Friedman and associates (Ref. *10*) treated 134 patients suffering from pruritis ani with a thick paste of aluminum hydroxide gel which had been prepared by evaporation from a commercial gel. In the moist type of pruritis ani, 93 of 98 patients experienced prompt sustained relief of itching, irritation, and discomfort. Results in the dry type of pruritis ani were poor.

In a study of application of aluminum hydroxide to wound areas of 23 colostomy patients, Friedman reports the successful arrest of pain and spread of infection. The aluminum hydroxide can inactivate the trypsin and prevent damage to the external area, and will also adsorb bacterial toxins arresting the spread of infection over surface skin (Ref. *3*).

In the Panel's opinion, aluminum hydroxide gel is useful as both an astringent and a protectant. Based on the various studies presented, and the numerous types of skin conditions treated, the Panel concludes that aluminum hydroxide gel is both safe and effective for OTC use.

(3) *Dosage.* Adult and children 6 months of age and older topical dosage is the application of a 0.15 to 5.0 percent preparation to the affected area as needed. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for skin protectant active ingredients. (See part III. paragraph B.1.—category I Labeling.) In addition, the Panel, based upon the discussion above, recommends the following specific labeling: *Warning.* "Do not use on children under 6 months of age without consulting a physician.

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(9) Spiesman, M. G., "Colloidal Kaolin and Aluminum Hydroxide Gel (Kalum) in Management of Lower Bowel Conditions," *Review of Gastroenterology*, 10:191-200, 1943.
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c. *Calamine.* The Panel concludes that calamine is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Calamine is effective as a skin protectan due to its absorbent properties. Calamine, also known as prepared calamine, is a mixture containing not less than 98 percent zinc oxide and 0.5 percent ferrous oxide. Zinc oxide has been evaluated to be safe and effective as a skin protectant. (See part III. paragraph B.1.n. below—Zinc oxide.) Due to the ferrous oxide, calamine has a pink color. It is an odorless, fine powder that is insoluble in water and nearly completely soluble in mineral acids (Refs. *1, 2,* and *3*).

(1) *Safety.* Clinical and marketing experience has confirmed that calamine is safe in the OTC dosage range used as a skin protectant.

The toxicity of this substance is the same as that of zinc oxide. (See part III. paragraph B.1.n.(1) below—Safety.) The ferrous oxide acts as a coloring agent and has no pharmacologic effect (Ref. *4*).

(2) *Effectiveness.* Due to its wide use and clinical acceptance the Panel concludes that calamine is effective for use as an OTC skin protectant.

Calamine is an effective skin protectant because of its close chemical identity with zinc oxide (Refs. *1, 2,* and *3*). (See part III. paragraph B.1.n.(2) below—Effectiveness.)

(3) *Dosage.* Adult, children, and infants topical dosage is the application of a 1 to 25 percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the category I labeling for skin protectant active ingredients. (See part III. paragraph B.1. below—category I labeling.)

REFERENCES

(1) "The Merck Index," 8th ed., Merck and Co., Inc., Rahway, N.J., p. 189, 1968.
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(4) Gleason, M. N. et al., "Clinical Toxicology of Commercial Products: Acute Poisoning," 3d ed., Williams and Wilkins, Baltimore, Md., p. 29, 1969.

d. *Cocoa butter.* The Panel concludes that cocoa butter is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Cocoa butter is effective as a skin protectant due to its emollient properties. Cocoa butter is the fat obtained from the roasted seed of Theobroma cacao. It is a mixture of stearin, palmitin, olein, laurin, linolein, and traces of other glycerides. It is a yellowish-white solid with a faint, agreeable odor and a bland chocolate-like taste. It is a brittle solid below 25° C. Cocoa butter possesses the remarkable property of maintaining its firmness within a few degrees of body temperature. It readily melts at body temperature without passing through an appreciable softening stage (Refs. *1* and *2*).

Cocoa butter is recognized as an emollient by Goodman and Gilman (Ref. *3*) when applied externally to the skin and mucous membrances. They also recognize its wide acceptance as a suppository and an ointment base. "The United States Pharmacopeia" (Ref. *4*) recognizes cocoa butter as a pharmaceutical aid, specifically as a suppository base. "Merck Index" (Ref. *5*) states that cocoa butter is used as a lubricant in massage and as a base for suppositories and ointments.

(1) *Safety.* Clinical and marketing experience has confirmed that cocoa butter is safe in the dosage range used as a skin protectant.

No reports regarding the safety of cocoa butter have been specifically identified. However, the Panel recognizes that its safety has been established by its wide and continuous use in pharmaceutical products and cosmetics (Refs. *1, 2,* and *6*).

(2) *Effectiveness.* Due to its wide use and clinical acceptance the Panel concludes that cocoa butter is effective for use as an OTC skin protectant.

Due to its bland nonirritating properties, cocoa butter is used as a skin protectant on abraded or irritated tissue, especially in the anorectal area. Cocoa butter provides a physical barrier against against further contact by possible irritants (Ref. *3*). These properties, combined with the fact that it is a vehicle for other drugs, accounts for its acceptability in suppositories and emollient preparations (Ref. *7*).

(3) *Dosage.* Adult, children, and infants topical dosage is the application of a 80 to 100 percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the category I labeling for skin protectant active ingredients. (See part III. paragraph B.1. below—Category I labeling.)

REFERENCES

(1) "The Dispensatory of the United States of America," 27th ed., edited by Osol, A., and R. Pratt, J. B. Lippincott Co., Philadelphia, p. 1179, 1972.
(2) "Remington's Pharmaceutical Sciences," 14th ed., Mack Publishing Co., Easton, Pa., p. 1376, 1970.
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(4) "The United States Pharmacopeia," 19th ed., United States Pharmacopeial Convention, Rockville, Md., pp. 555-556, 1975.
(5) "The Merck Index," 8th ed., Merck and Co., Inc., Rahway, N.J., p. 1033, 1968.
(6) Griffenhagen, G., "A History and Evolution of the Suppository Mold," *American Journal of Pharmacy*, 125:135-142, 1953.
(7) Mezey, G., "Der Einfluss Lipophiler Emulgatoren auf die Arzneiabgabe aus mit Kakaobutter Hergestellten Suppositorien," *Pharmazie*, 26:166-169, 1971.

e. *Corn starch.* The Panel concludes that corn starch is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Corn starch is effective as a skin protectant due to its absorbent properties. Corn starch is described as granules from the mature grain of Zea mays. Corn starch is recognized by the "United States Pharmacopoeia" (Ref. *1*). Corn starch consists of irregular, angular white masses of fine powder. It is insoluble in cold water and alcohol (Refs. *1* and *2*).

(1) *Safety.* Clinical and marketing experience has confirmed that corn starch is safe in the OTC dosage range used as a skin protectant.

A Draize eye irritation study was conducted with 100 milligrams (mg) of a powdered preparation containing 71 percent corn starch on nine white rabbits. At the end of the 24-hour observation period, all animals exhibited chemosis and discharge. All evidence of irritation resolved in 48 hours. The same preparation was tested for dermal sensitivity under open patch conditions in rabbits. The powder showed no evidence of dermal irritation when applied to either normal or

abraded skin. This test was repeated in 50 randomly selected human subjects. Corn starch exhibited no evidence of being allergenic, photoallergenic, a sensitizer, or a primary irritant. There was an absence of reactions throughout the study (Ref. *3*).

Corn starch administered orally to rats required daily doses as large as one-tenth of the animal body weight for 2 to 7 weeks before eliciting any adverse effects such as inhibition of growth (Ref. *4*). Intraperitoneal and intramuscular injection of surgical powders containing corn starch were found to exert a weak and temporary irritation in rabbits in contrast to the strong protracted effect of talc (Ref. *5*).

Corn starch is of known nutritive value and is included in the diet in sizable amounts. Although in its raw state it is digested slowly, its metabolism is well understood. Its safety is supported by the use of corn starch orally for years as a tablet disintegrant in pharmacy and its recognition for this purpose by the official compendia (Refs. *1* and *2*).

While the practice of eating large quantities of corn starch present in certain laundry starch products has been common among sizable numbers of people in this country for many years, very few incidents of untoward effects have been reported that are directly attributable to the corn starch. The primary problem recognized in these cases has been deficiency of essential nutrients in the diet of these individuals who have consumed laundry starch instead of more nourishing foods (Ref. *6*). Starch gastrolith has been reported in one individual who consumed three to four boxes of starch daily for 1 year (Ref. *7*).

The only other adverse effects reported to be caused by corn starch have been foreign body granulomas inside the peritoneum resulting from surgical glove powder consisting primarily of corn starch and magnesium oxide being transferred to surgical sites (Refs. *8* and *9*). Although several cases of such granulomas have been reported, the incidence of starch granulomas is uncommon (Ref. *9*).

Corn starch is an organic substance which has been shown to support bacterial growth in the presence of moisture (Ref. *10*). Corn starch is sometimes used in combination with other absorbent powders. When used on open and/or discharging wounds, an antiseptic agent may help discourage bacterial growth (Ref. *11*).

There are no reported incidents of adverse effects to the topical application of corn starch (Ref. *3*).

(2) *Effectiveness.* Due to its wide use and clinical acceptance the Panel concludes that cornstarch is effective for use as an OTC skin protectant.

Powdered cornstarch is widely recommended in the medical literature as a common and important ingredient in protective dusting powders. It is bland to the skin and affords protection to the skin by absorbing moisture, perspiration, and noxious secretions, and by lubricating particularly those surfaces that are in continuous apposition. It also allows for enhanced evaporation of moisture from the skin by increasing the surface area available for this process (Ref. *2*). In addition, it soothes and allays dermal irritation and itching. Gases, toxins, and microorganisms are absorbed and suspended by cornstarch. Many authorities consider cornstarch superior to talc since it is virtually free of chemical contaminants and it does not tend to produce granulomatous reactions in wounds as readily as talc (Ref. *5*). Finally, cornstarch is many times as absorbent as talc. On exposing cornstarch and talc to moisture saturated air, it was found that cornstarch absorbed more than 25 times more moisture than did the talc (Ref. *3*). Absorption by cornstarch probably surpasses that of any powder described in the official compendia (Ref. *3*). Because cornstarch is so absorptive of water, a sticky mass may form when it is used alone. Therefore, another finely dispersed dessicant is usually incorporated in a formulation for use as an absorbent.

(3) *Dosage.* Adult, children, and infants topical dosage is the application of a 10 to 85 percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the Category I labeling for skin protectant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

REFERENCES

(1) "The United States Pharmacopeia," 19th ed., United States Pharmacopeial Convention, Rockville, Md., p. 575, 1975.

(2) "The Dispensatory of the United States of America," 27th ed., edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, p. 1091, 1972.

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(11) Lesser, M. A., "Medicated Dusting Powders," *Drug and Cosmetic Industry,* 62:183, 1948.

f. *Dimethicone.* The Panel concludes that dimethicone is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Dimethicone is effective as a skin protectant due to its demulcent properties. Dimethicone, also known as dimethycone and dimethyl polysiloxane, is a complex silicone compound with an approximate molecular weight of 14,000 to 21,000. It is a light gray translucent liquid of greasy consistency which is immiscible with water and alcohol, but miscible with ether and most hydrocarbon solvents (Refs. *1* and *2*). Dimethicone is one of many silicone compounds with the general formula $O\text{-}Si(R_1R_2)\text{-}O\text{-}Si(R_1R_2)\text{-}O\text{-}etc.$ By manipulating the R_1 and R_2 groups and the degree of cross-linking, silicone compounds of different properties may be produced. In dimethicone, the R_1 and R_2 groups are methyl radicals. The water-repellant properties of silicones have many applications in medicine, commerce, and industry (Ref. *3*).

(1) *Safety.* Clinical and marketing experience has confirmed that dimethicone is safe in the OTC dosage range used as a skin protectant.

Dimethicone is remarkably free of irritancy or adverse reactions to the skin (Refs. *4*, *5*, and *6*). This is also supported by marketing data. Toxicity has not been documented (Ref. *5*).

The Advisory Review Panel on OTC Antacid Products (see the FEDERAL REGISTER of June 4, 1974) (39 FR 19877) found the use of simethicone (4.0 to 4.5 percent silica aerogel in dimethicone (Ref. *7*)) safe for internal use at a dosage of 500 mg daily. Topically, dimethicone is relatively inert (Ref. *3*).

The occlusive nature of dimethicone is detrimental to inflamed, traumatized, abraded, and excoriated skin, and to lesions that require free drainage. Dimethicone is not sensitizing but does cause a temporary irritation to the eyes (Refs. *3* and *8*).

(2) *Effectiveness.* Due to its wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that dimethicone is effective for use as an OTC skin protectant.

Dimethicone is used as a protective agent. It almost completely seals the wound and prevents further drying of lesions such as windburn, cracked and chapped skin, and chapped lips (Refs. *4* and *6*). However, cuts, infected lesions, and puncture wounds may

become macerated and further inflamed under the seal.

Dimethicone possesses skin adherent and water-repellant properties. It is found in such dosage forms as an ointment (30 percent), cream (30 percent), and a spray (33.33 percent) (Ref. *3*). It is useful as a prophylactic against exposure to water soluble substances to which the patient may be sensitive or which may aggravate a preexisting eczema. It may prevent the ammonia, produced by bacterial decomposition of urine, from coming into contact with the skin resulting in dermatitis (Ref. *9*).

The substantivity of dimethicone is excellent. When dimethicone is incorporated into a nonwashable base, several surgical washings are required for its removal (Ref. *7*).

Dimethicone is used internally as a protectant for the gastro-intestinal mucosa. Birtley et al. conducted a study in which 10 male Wistar rats were deprived of food but not water for 18 hours before gastric intubation of 0.25 to 2.0 milliliters (ml) dimethicone. Ten minutes later, 1 ml of a suspension of aspirin (45 milligrams/milliliter (mg/ml)) in 1 percent carboxymethylcellulose (CMC) in water was gastricly intubated. Two control groups of 10 rats each received either 1 ml of a 1 percent weight in volume (w/v) CMC with aspirin suspension or dimethicone alone. All animals were sacrificed 2 hours after administration of the test substance. Dimethicone caused a reduction in the amount of aspirin-induced gastric irritation compared with the unprotected group receiving aspirin alone (Ref. *10*). The control group receiving dimethicone alone produced no evidence of mucosal irritation.

Kahan et al. incorporated a 3 percent silicone compound (Dow-Corning 200 or 555) into an ethanolamine stearate base that also included 0.2 percent allantoin and 0.25 percent hexachlorophene. In the first part of his three-phase study, 726 infants were divided into two groups. The test group of 429 infants was treated daily with the preparation. The control group of 297 infants received products normally employed in routine newborn nursing care. Both groups received routine hospital care. The control group presented more dermatoses than did the test group. Indicating that the silicone preparation afforded some degree of protection. In the second part of the study, 110 infants ranging from 1 to 18 months of age were followed for a period of 6 months. Mothers in this group were warned not to make any changes in the general care of the infant, to avoid the use of all other medications except the prescribed emulsion, and to cleanse the area with lukewarm water after urination of defecation. They were to report immediately any evidence of dermatitis or other untoward reaction. Over the 6-month period, there were 22 cases of erythema, intertrigo, and mild papulovesicular eruption. Twenty cases cleared completely and one case cleared partially. The results of this part of the study, again, indicate that the silicone preparation afforded protection. In the third part of the study, subjects presented dermatoses common to infants. The emulsion was applied to the involved area three times daily and no other medication was used. The results are summarized below:

Diagnosis	Number of patients (with dermatoses)	Dermatoses cleared	Dermatoses partially cleared	Unchanged
Intertrigo	16	16	.....	.....
Diaper erythema	17	15	2	.....
Atopic eczema	2	1	.....	1
Contact dermatitis	2	1	1	.....
Bedsores	1	1	.....	.....
Total	38	34	3	1

The investigators concluded that the preparation afforded topical protection and was relatively free of side reactions (Ref. *9*).

(3) *Dosage.* Adult, children, and infants topical dosage is the application of a 1 to 30 percent preparation to the affected area as needed.

(4) *Labeling.* The panel recommends the Category I—Labeling for skin protectant active ingredients. (See part III, paragraph B.1. below—Category I—Labeling.) In addition the panel, based on the discussion above, recommends the following specific labeling: *Warning.* "Not to be applied over puncture wounds, infections, or lacerations."

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g. *Glycerin.* The panel concludes that glycerin is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Glycerin is effective as a skin protectant due to its absorbent, demulcent, and emollient properties. Chemically, glycerin, also known as glycerine and glycerol (propane 1,2,3-triol), is the simplest of the trihydric alcohols. The chemical formula is CH_2OH-CHOH-CH_2OH. It is a clear, colorless, syrupy liquid with a sweet taste and characteristic odor. Glycerin has a molecular weight of 92.10 and is hygroscopic, taking up and retaining water. Glycerin is miscible with water and alcohol, but insoluble in chloroform, ether, and fixed and volatile oils. Solutions of glycerin are neither acidic nor alkaline (Refs.*1* and *2*).

(1) *Safety.* Clinical and marketing experience has confirmed that glycerin is safe in the dosage range used as a skin protectant.

Glycerin has been in use for over 100 years. When taken internally, glycerin is almost completely innocuous. Humans have taken 100 g daily for 50 days with no ill effects (Ref. *3*). Osmotic effects such as hypovolemia and diarrhea occur following massive oral doses. The topical effects of glycerin have been investigated utilizing a variety of techniques. In one such study, the tails of rats were soaked in undiluted glycerin 4 hours daily for 4 days,

1 hour daily for 6 days, and 2 hours daily for 6 days. Under none of these regimens were any changes produced in the skin. In another study, undiluted glycerin was applied to the conjunctiva of rabbits, cats, and dogs. There were no visible changes. Undiluted glycerin was also applied to the buccal mucosa of rats, rabbits, and dogs with no discernable pathology either topically or systemically.

Studies of the skin irritant properties of natural and synthetic glycerin applied dorsally (30 percent of the body surface) to rabbits gave no indication of irritation or other dermatitis. It was concluded that glycerin is not absorbed percutaneously in amounts sufficient to produce a pharmacologic effect (Refs. *4* and *5*).

However, in another study, undiluted glycerin and a 50 percent aqueous solution were repeatedly and extensively applied to the skin of rabbits. This produced a mild irritation but did not produce other significant toxicity (Refs. *6* and *7*).

It has been reported that undiluted glycerin absorbs water and is somewhat dehydrating and irritative to mucous membranes and particularly to inflamed or sunburned skin (Refs. *6* and *8*). When used in undiluted form, water can be extracted from wounds where the vapor barrier (keratin layer) has been altered. This drying effect can cause discomfort in open wounds (Refs. *2* and *9*). However, in aqueous concentrations of 20 to 45 percent, glycerin is relatively nonirritating and safe as a skin protectant.

(2) *Effectiveness.* Due to its wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that glycerin is effective for use as an OTC skin protectant.

Glycerin is a valuable product in the pharmacy because of its solvent properties, sweet taste, and nonfermentability. It is a widely employed vehicle for internally and externally used medicinal substances. Glycerin keeps substances moist by holding water and is valuable as a protectant in many skin conditions (Refs. *1* and *2*).

The dehydrating and osmotic properties of glycerin have been used in preparations for local application to various dermatoses (Refs. *1, 9, 10,* and *11*). This dehydration action is at its maximum when glycerin is used in the undiluted form. In one study, a keratinous mass (a callous) was soaked in a solution of glycerin for 48 hours with no decrease in brittleness. At that time, 0.1 ml of water was added and still there was no decrease in brittleness. Water alone reduced brittleness by 25 percent in 1 hour (Refs. *12*). The application of glycerin has not been shown to effect the ability of keratin to absorb water (Refs. *13*). The Panel believes that undiluted glycerin is not effective as a skin protectant but that a solution of 20 to 45 percent glycerin in water will lose water to the epidermis and act to soften the skin (Refs. *1, 9, 10, 14, 15,* and *16*).

Glycerin is discussed in a separate document as an ingredient for otic use (see the FEDERAL REGISTER of December 16, 1977 (42 FR 63556)).

(3) *Dosage.* Adult and children 6 months of age and older topical dosage is the application of a 20 to 45 percent preparation to the affected area as needed. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for skin protectant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

In addition, the Panel based upon the discussion above recommends the following specific labeling: *Warning.* "Do not use on children under 6 months of age without consulting a physician."

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h. *Kaolin.* The Panel concludes that kaolin is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Kaolin is effective as a skin protectant due to its absorbent properties. Kaolin is a native hydrated aluminum silicate, powdered and freed from gritty particles by elutriation. Kaolin is also known as China clay, white bole, argilla, and porcelain clay. Its absorbing and water-binding qualities vary widely (Ref. *1*). It is a white or yellowish-white, earthy mass or white powder (Ref. *2*).

(1) *Safety.* Clinical and marketing experience has confirmed that kaolin is safe in the OTC dosage range used as a skin protectant.

Kaolin produced no adverse effects on oral administration to rats in doses less than 50 g/kg. Death was produced, however, by kaolin suspension in rats due to bowel obstruction at doses of 149 g/kg (Ref. *3*). Dogs fed 60 g kaolin suspension daily by stomach tube 5 days weekly for 3 months showed no evidence of adverse effects (Ref. *4*). Injected into the gastric mucosa of rabbits, kaolin will produce a silicosis-like granuloma, but not when administered by mouth (Ref. *5*).

Reported adverse effects of kaolin are at least as rare as those for starch. Kaolin has been used for hundreds of years in both external and internal preparations (Ref. *1*). Currently, one oral kaolin preparation (kaolin and pectin) is recognized as an official preparation by the "National Formulary" (Ref. *6*). Kaolin is classified by recognized standard clinical toxicology references as practically nontoxic with the probable lethal human dose suggested as greater than 15 g/kg (Ref. *7*). It has been prescribed orally for intestinal disorders at doses of 100 g several times daily with no ill effects. Cholera patients have been fed 600 g kaolin over a 12-hour period without ill effects (Ref. *7*). Epidemiologic studies performed over a 5-year period have demonstrated that the general health of kaolin workers does not differ significantly from that of the general population (Ref. *8*). One report of granuloma due to excessive ingestion of kaolin for gastrointestinal disorders has been reported (Ref. *5*). There is a report of rare intestinal obstruction due to ingested kaolin (Ref. *9*). There have been no reports of adverse effects to the topical application of kaolin (Ref. *10*).

(2) *Effectiveness.* Due to its wide use and clinical acceptance, the Panel con-

cludes that kaolin is effective for use as an OTC skin protectant.

Kaolin is considered an effective skin protectant that helps to absorb excessive moisture and perspiration (Refs. *11* and *12*). While it is recognized as an effective water absorbent, it is also an excellent adsorbent of dissolved or suspended substances such as gases, toxins, and bacteria (Refs. *4* and *13*). It has been recommended as a desiccant dusting powder for use in weeping eczemas, discharging ulcers, and similar conditions (Ref. *1*).

Kaolin and a kaolin mixture with pectin are recognized as adsorbents by the "National Formulary" (Ref. *14*). Goodman and Gilman (Ref. *9*) state that kaolin is used for the treatment of diarrhea and dysentery, and is also used in the treatment of chronic ulcerative colitis to adsorb toxins and bacteria in the colon. The "Merck Index" defines the medical use of kaolin as a gastrointestinal adsorbent and a topical adsorbent. In veterinary medicine, it is also used as a poultice (Ref. *2*).

(3) *Dosage.* Adult, children and infants topical dosage is the application of a 4.0 to 20 percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the Category I labeling for skin protectant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

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i. *Petrolatum preparations (petrolatum, white petrolatum).* The Panel concludes that petrolatum and white petrolatum are safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Petrolatum is effective as a skin protectant due to its emollient and lubricant properties. Protrolatum is also known as amber petrolatum, base petrolatum, pure petrolatum jelly, and pure ultra white petrolatum jelly. Petrolatum is an unctuous yellow to light amber mass. It is a purified mixture of semisolid hydrocarbons obtained from petroleum and may contain a suitable stabilizer (Ref. *1*). White petrolatum is the same semisolid hydrocarbon, but it has been wholly or nearly decolorized (Ref. *2*). Both products (petrolatum and white petrolatum) are essentially the same except for color. For purposes of this report, they will be considered together as petrolatum (Refs. *1* and *2*).

Petrolatum melts between 38° and 60° C and has a specific gravity of 0.815 to 0.880 at 60° C. It is insoluble in water, slightly soluble in alcohol, freely soluble in benzene and chloroform, and soluble in ether and in most fixed and volatile oils. Petrolatum is an oleaginous ointment base and topical protectant. It is also described in the "United States Pharmacopeia" (Ref. *2*) under petrolatum gauze, hydrophilic ointment, white ointment, and hydrophilic petrolatum. The "National Formulary" and "Merck Index" list petrolatum as an ointment base (Refs. *1* and *3*). The "Merck Index" (Ref. *3*) also recognizes the use of petrolatum as a protective dressing. Petrolatum has been identified as one of the important emollient hydrocarbons by Goodman and Gilman (Ref. *4*).

(1) *Safety.* Clinical and marketing experience has confirmed that petrolatum is safe in the OTC dosage range used as a skin protectant.

Studies on animals show no adverse effect on healing of burns. Superficial burns and abrasions on humans also healed with no complications. Petrolatum is not absorbed through intact or injured skin and is neither sensitizing nor irritating (Ref. *5*). Extensive burns, however, are at risk for infection under a sealed, greasy cover. Cuts, infected lesions, and puncture wounds also may become macerated and further inflamed under the seal.

Large amounts are essentially nontoxic when ingested in liquid laxative preparations (Ref. *5*).

(2) *Effectiveness.* Due to their wide use and clinical acceptance, the Panel concludes that petrolatum preparations are effective for use as OTC skin protectants.

Petrolatum (usually white petrolatum) has been utilized in burn wound management as a dressing of lightly impregnated fine mesh gauze. Most data are compiled from patients admitted to hospitals for care of major thermal injury. The dressings were used until the dead burned tissue separated. Skin grafting followed (Ref. *5*). Such uses are not appropriate for OTC consideration. For superficial burns of minimal extent, petrolatum and petrolatum gauze exclude air, prevent evaporation, and reduce pain.

The use of petrolatum as an emollient has been well accepted for dry skin conditions, especially with flaking skin such as sunburn, and chapping. Evaporation and drying are curtailed. In addition, the substance is a soothing topical lubricant. As a skin protectant, this substance can be applied to prevent irritating materials from contacting the normal skin, such as in preventing diaper rash (Ref. *5*).

(3) *Dosage.* Adult, children, and infants topical dosage is the application of a 30- to 100-percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the Category I labeling for skin protectant active ingredients. (See part III, paragraph B.1. below—Category I Labeling.) In addition, the Panel, based on the discussion above, recommends the following specific labeling: *Warning.* "Not to be applied over puncture wounds, infections, or lacerations."

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(5) OTC Volume 060109.

j. *Shark liver oil.* The Panel concludes that shark liver oil is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Shark liver oil is effective as a skin protectant due to its emollient properties. Shark liver oil is an amber to brown oily liquid and is extracted from the livers of the shark, principally from the lemon shark, *Hypoprion brevirostris,* although many other spe-

cies of shark may be the source. The oil is a source of vitamins A and D. Shark liver oil is reported to have a potency not less than 16,500 U.S.P. units of vitamin A and not less than 40 U.S.P. units vitamin D per g (Ref. *1*).

(1) *Safety.* Clinical and marketing experience has confirmed that shark liver oil is safe in the OTC dosage range used as a skin protectant.

Although shark liver oil is not officially recognized in U.S. compendia, several formulations are recognized in foreign compendia, e.g., dilute shark liver oil, shark liver oil emulsion, shark liver oil emulsion for infants, and shark liver oil with vitamin D (Ref. *2*). Shark liver oil is used in preference to cod liver oil orally as a source of vitamin A when large amounts of vitamin D are not required (Ref. *2*).

(2) *Effectiveness.* Due to its wide use and clinical acceptance, the Panel concludes that shark liver oil is effective for use as an OTC skin protectant.

Shark liver oil provides temporary relief of skin irritations by its soothing and protective effect. The effect continues as long as this oleaginous substance remains in contact with the affected areas (Refs. *3, 4,* and *5*).

(3) *Dosage.* Adult and children 2 years of age and older topical dosage is the application of a 3-percent preparation to the affected area as needed. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for skin protectant active ingredients. (See part III, paragraph B.1. below—Category I Labeling.)

In addition, the Panel, based upon the discussion above recommends the following specific labeling: (1) *Warning.* "Do not use on children under 2 years of age without consulting a physician."

REFERENCES

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k. *Sodium bicarbonate.* The Panel concludes that sodium bicarbonate is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Sodium bicarbonate is effective as a skin protectant due to its absorbent properties. Sodium bicarbonate is also known as bicarbonate of soda or baking soda. Sodium bicarbonate is a white crystalline powder with a chemical formula of $NaHCO_3$. It is soluble in 10 parts of water at 25° C and insoluble in alcohol. The powder is odorless with a saline and slightly alkaline taste. It forms alkaline solutions. In dry air, the powder is stable but slowly decomposes in moist air releasing carbon dioxide and water, leaving a residue of sodium carbonate (Ref. *1*).

(1) *Safety.* Clinical and marketing experience has confirmed that sodium bicarbonate is safe in the dosage range used as a skin protectant.

Sodium bicarbonate is relatively nontoxic and no adverse reactions have been noted on topical application. The Panel emphasizes that this agent is not to be used for neutralization of acid burns over large surfaces of the body. The exothermic neutralization reaction can cause deepening of the burn and can allow excessive absorption of sodium from the altered body surface in such extensive burns (Ref. *2*). The treatment of choice for acid burns is copious flooding of the affected area with cold water as discussed elsewhere in this document. (See part II, paragraph A.2. above—Burns.) Sodium bicarbonate is nontoxic when taken internally.

(2) *Effectiveness.* Due to its wide use and clinical acceptance, the Panel concludes that sodium bicarbonate is effective for use as an OTC skin protectant. Application of topical sodium bicarbonate has a long history of market acceptability and is popular as folk remedy for insect stings and minor burns.

Sodium bicarbonate soothes irritated skin (Ref. *3*), relieves pain of minor acid burns, and when used in a bath or as a dusting powder, reduces the odor of sweat. Prompt application of moistened bicarbonate as a paste has helped relieve itching from nonpoisonous insect stings and bites.

Sodium bicarbonate has been used in tepid baths for relief of pruritis due to sunburn. In addition, such baths have been recommended for hives (urticaria), the treatment of exfoliative dermatitis, and eczema (Refs. *3* and *4*). Beckman (Ref. *5*) recommended local applications of sodium bicarbonate solutions for mild itching. As a topical protectant, sodium bicarbonate is effective in the symptomatic relief of minor irritations, insect bites, and stings.

Bicarbonates and other mild alkalis combine with the tissue elements to form alkaline albuminates or with cutaneous fats to form soaps. In this way, the epithelium is softened. They were used in a variety of skin diseases to facilitate the penetration of antiseptic remedies into the skin (Refs. *3* and *6*).

Sodium bicarbonate when used locally on the skin in the form of a moist paste or a solution is an effective antipruritic (Refs. *7* and *8*).

(3) *Dosage.* Adult, children and infants topical dosage is the application of a 1- to 100-percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the Category I labeling for skin protectant active ingredients. (See part III, paragraph B.1. below—Category I Labeling.) In addition, the Panel, based on the discussion above recommends the following specific labeling: *Warning.* "Do not apply to extensive acid burns. Flood acid burns with cold tap water and consult a physician."

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1 *Zinc acetate.* The Panel concludes that zinc acetate is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below. The Panel has also evaluated zinc acetate as a skin protectant for use as a wound-healing aid below. (See part III. paragraph B.3.c. below—Zinc acetate.)

Zinc acetate is effective as a skin protectant due to its astringent properties. Zinc acetate is a salt of a weak acid and is crystalline with a sharp metallic taste. If effloresces slowly to form a basic salt. Zinc acetate is freely soluble in water and soluble in alcohol (Refs. *1* and *2*).

(1) *Safety.* Clinical and marketing experience has confirmed that zinc acetate is safe in the OTC dosage range used as a skin protectant.

There is no evidence of toxicity upon topical application of zinc acetate to either the skin or mucous membranes (Ref. *3*). A long marketing experience has produced no untoward reactions (Ref. *3*).

(2) *Effectiveness.* Due to its wide use and clinical acceptance, the Panel concludes that zinc acetate is effective for use as an OTC skin protectant.

Zinc compounds which ionize have protective, astringent, and mild antiseptic properties (Refs. *1*, *3*, and *4*). The zinc ion precipitates protein and is sometimes used in deodorants because of this astringent property (Ref. *2*). Zinc acetate, zinc sulfate, and zinc chloride have been used in the treatment of skin infections and with certain fatty acids as fungicidal and fungistatic agents (Refs. *3* and *4*).

(3) *Dosage.* Adult and children over 2 years of age topical dosage is the application of a 0.1 to 2.0 percent preparation to the affected area as needed. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for skin protectant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

In addition, the Panel, based upon the discussion above, recommends the following specific labeling: *Warning.* "Do not use on children under 2 years of age without consulting a physician."

REFERENCES

(1) "The Extra Pharmacopeia," 25th Ed., Edited by Todd, R. G., The Pharmaceutical Press, London, p. 1489, 1967.

(2) Wilson, C. O. and O. Gisvold, "Textbook of Organic and Medicinal Chemistry," 3d Ed., J.B. Lippincott Co., Philadelphia, p. 553, 1966.

(3) OTC Volume 060042.

(4) OTC Volume 060043.

m. *Zinc carbonate.* The Panel concludes that zinc carbonate is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Zinc carbonate is an effective skin protectant due to its absorbent properties. Zinc carbonate, $ZnCO_3$, is an inert white powder which is insoluble in water (ref. *1*).

(1) *Safety.* Clinical and marketing experience has confirmed that zinc carbonate is safe in the OTC dosage range used as a skin protectant.

When applied topically as a paste or in an ointment, there have been no reports of toxicity (refs. *2* and *3*).

(2) *Effectiveness.* Due to its wide use and clinical acceptance, the Panel concludes that zinc carbonate is effective for use as an OTC skin protectant. Its use has been similar to zinc oxide as a protectant which is discussed below. (See part III. B.1.n. below—Zinc oxide.)

The Panel has been unable to document the effectiveness of zinc carbonate and attribute its effectiveness to the properties of zinc salts in general—most notably, zinc oxide, chloride, calamine, zinc stearate, zinc gelatin, etc. Zinc salts are recognized in the official compendia and standard reference texts as effective topical protectants, astringents, and demulcents (refs. *4*, *5*, and *6*).

The Panel, on the basis of wide clinical use and acceptance, concludes that zinc carbonate is safe and effective as a skin protectant.

(3) *Dosage.* Adult, children and infants topical dosage is the application of a 0.2 to 2.0 percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the Catagory I labeling for skin protectant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

REFERENCES

(1) "The Merck Index," 8th Ed., Merck and Co., Inc., Rahway, New Jersey, p. 1128, 1968.

(2) OTC Volume 060042.

(3) OTC Volume 060043.

(4) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., The Macmillan Co., New York, p. 948, 1975.

(5) "Remington's Pharmaceutical Sciences," 14th Ed., Mack Publishing Co., Easton, Pa; p. 768, 1970.

(6) "The United States Pharmacopeia," 19th Ed., The United States Pharmacopeial Convention, Rockville, MD; 1975.

n. *Zinc oxide.* The Panel concludes that zinc oxide is safe and effective for OTC use as a skin protectant as specified in the dosage section discussed below.

Zinc oxide is effective as a skin protectant due to its absorbent and lubricant properties. Zinc oxide is also known as flowers of zinc and zinc white. Zinc oxide (ZnO) is a fine, odorless, amorphous white or yellowish white powder. It is practically insoluble in water or alcohol and is relatively inert chemically. Zinc oxide reacts slowly with fatty acids to form insoluble soaps. It is mildly astringent and has skin protectant properties (Ref. *1*).

(1) *Safety.* Clinical and marketing experience has confirmed that zinc oxide is safe in the OTC dosage range used as a skin protectant.

The toxicity of zinc oxide powder to animals was found to be extremely low. In one study, a daily diet consisting of 0.5 percent zinc oxide fed to rats elicited no toxic symptoms attributable to zinc even in the third generation (Ref. *2*). In another study, cats fed a daily diet containing 250 to 300 mg zinc oxide daily for 12 to 16 weeks showed excessive fibrosis of the pancreas and an increased zinc content of the liver and pancreas (Ref. *3*). A further study demonstrated that after oral daily doses of 175 to 1,000 mg zinc oxide in cats and dogs for 3 to 53 weeks, histological examinations were negative except for some fibrous change in the pancreas of cats fed 188 to 267 mg/kg (Ref. *4*).

Generally, zinc compounds are relatively nontoxic with approximately 10 to 15 mg ingested daily in the average diet. Zinc is too poorly absorbed to cause acute systemic intoxication, although the ingestion of large quantities may cause emesis and purgation (Ref. *5*). No estimates of the acute oral toxicity of zinc oxide were located in the literature, and it is assumed that no human fatalities have resulted from ingestion of zinc oxide (Ref. *5*). Studies of workers exposed to zinc oxide powder and dust over many years showed no evidence of acute or chronic illness due to zinc (Ref. *5*). The only siginificant reported toxicity directly attributable to zinc oxide is associated with the freshly formed oxide. Influenza-like symptoms have been reported among workers who inhaled the freshly formed fumes of zinc oxide. However, the disease has an acute onset, a duration of 12 to 24 hours, and rarely causes permanent damage (Refs. *6* and *7*). In addition to its wide use as a topical drug in baby ointments and numerous other dermatologic medications over the years, zinc oxide has been prescribed orally as a antispasmodic in cholera, epilepsy, and whooping cough. It has also been used for its protective action in diarrhea. A dose of 120 to 300 mg has been suggested when zinc oxide is administered orally (Ref. *8*). The probable human lethal dose of zinc oxide has been estimated at 0.5 to 5 g/kg (Ref. *9*). Zinc oxide is not irritating to the skin and is therefore recommended for use in cosmetic face powders. No reports of topical toxicity were found in the literature (Ref. *9*).

(2) *Effectiveness.* Due to its wide use and clinical acceptance, the Panel concludes that zinc oxide is effective for use as an OTC skin protectant.

Zinc oxide is either the sole active ingredient or one of the principal ingredients of a variety of formulations sold OTC and by physicians' prescriptions for the treatment of many cutaneous conditions (Refs. *1* and *8*). Formerly, it was perhaps the most frequently used agent in topical dermatotherapy (Ref. *10*). While having a low range of sensitization, zinc oxide has a cooling, slightly astringent, antiseptic, antibacterial, and protective action (Ref. *10*). It has been found particularly effective in the treatment of diaper rash and prickly heat and is also used in such skin diseases and infections as eczema, impetigo, ringworm, ulcers, pruritus, and psoriasis (Refs. *1*, *8*, and *10*). Zinc oxide is widely recognized as a skin protectant (Ref. *9*).

(3) *Dosage.* Adult, children and infants topical dosage is the application

of a 1 to 25 percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the Category I labeling for skin protectant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

REFERENCES

(1) "Remington's Pharmaceutical Sciences," 14th Ed., Mack Publishing Co., Easton, Pa., p. 771, 1970.

(2) Heller, V. G. and A. D. Burke, "Toxicity of Zinc," *Journal of Biological Chemistry,* 74:85-93, 1927.

(3) Scott D. A. and A. M. Fisher, "Studies on the Pancreas and Liver of Zinc Fed Cats," *American Journal of Physiology,* 121:253-260, 1938.

(4) Drinker, K. R., P. K. Thompson and M. Marsh, "An Investigation of the Effect of Long-Continued Ingestion of Zinc Oxide by Cats and Dogs, Together with Observations Upon the Excretion and Storage of Zinc," *American Journal of Physiology,* 80:31-64, 1927.

(5) Batchelor, R. P., J. W. Fehnel, R. M. Thompson and K. R. Drinker, "A Clinical and Laboratory Investigation of the Effect of Metallic Zinc, of Zinc Oxide and of Zinc Sulphide Upon the Health of Workmen," *Journal of Industrial Hygiene,* 8:322-363, 1926.

(6) Sollman, T., "A Manual of Pharmacology," 8th Ed., W. B. Saunders, Philadelphia, pp. 1302-1305, 1957.

(7) Sayres, R. R., "Metal Fume Fever and Its Prevention," *Public Health Reports,* 53:1081-1086, 1938.

(8) "The Dispensatory of the United States of America," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, pp. 1255-1256, 1972.

(9) OTC Volume 060137.

(10) Appel, B., L. M. Ohmart and R. F. Sterner, "Zinc Oxide," *Archives of Dermatology,* 73:318-324, 1956.

CATEGORY I LABELING

The Panel recommends the following Category I labeling for skin protectant active ingredients to be generally recognized as safe and effective and not misbranded, as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* The indications should be limited to one or more of the following phrases:

(1) "Aids in the temporary relief of minor skin irritations."

(2) "For the temporary protection of minor skin irritations."

(3) "Soothes minor skin irritations."

(4) "Gives comfort to minor skin irritations."

(5) For skin protectant active ingredients for symptoms of dryness: "For symptoms of chapping, peeling or scaling '(optional, any or all of the following)' due to minor burns, sunburn, windburn, scrapes, abrasions, or cracked lips."

(6) For skin protectant active ingredients for symptoms of wetness: "For symptoms of oozing or weeping '(optional, and or all of the following)' due to contact dermatitis, poison oak or poison ivy."

(7) For skin protectant active ingredients for symptoms of friction:

(i) "For symptoms of" (optional, one or more of the following) "intertrigo, chafing, galling, rubbing or friction."

(ii) "For the temporary protection and lubrication of minor skin irritations."

b. *Warnings.* (1) "For external use only."

(2) "Avoid contact with the eyes."

(3) "Discontinue use if symptoms persist for more than 7 days and consult a physician."

c. *Directions for use.* "Apply liberally as often as necessary."

2. *Category II conditions under which skin protecant active ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the category II conditions be eliminated from OTC skin protectant drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

CATEGORY II ACTIVE INGREDIENTS

The Panel has classified the following skin protectant active ingredients not generally recognized as safe and effective or as misbranded:

Bismuth subnitrate.
Boric acid.
Sulfur.
Tannic acid.

a. *Bismuth subnitrate.* The Panel concludes that bismuth subnitrate is not safe and there are no data to show that it is effective for OTC use as a skin protectant.

Bismuth subnitrate is also known as basic bismuth nitrate, bismuth oxynitrate, bismuthyl nitrate, white bismuth, Spanish white. It is a white, slightly hydroscopic powder which is practically insoluble in organic solvents and water, but slowly hydrolyzes, liberating nitric acid. It is odorless and tasteless, and has been promoted as an antiseptic and protectant.

(1) *Safety.* Bismuth subnitrate powder has been used in human therapy as an astringent and skin protectant. Because of toxicity, its use has fallen into disrepute (Ref. *1*). Fatalities in infants have have reported due to oral ingestion of bismuth subnitrate. In the intestinal tract, bacteria convert the nitrate to nitrite which is then absorbed systemically, leading to the formation of methemoglobinemia. Although adults are also affected, infants are more susceptible (Ref. *2*). Toxicity due to the bismuth ion has been demonstrated in animals. Symptoms include nephritis, hepatotoxicity, and circulatory collapse. symptoms of human toxicity to bismuth include anorexia, weakness, rheumatic pain, and fever (Ref. *3*). Pastes containing bismuth subnitrate were once injected into fistulae and abscess cavities which has led to bismuth poisoning. Symptoms ranged from mild darkening of gums, tongue, and pharynx to ulcerative stomatitis, nephritis, and vomiting, occasionally leading to death (Ref. *4*). In addition, when used in surgical procedures, the drug has caused toxicity (Ref. *5*).

(2) *Effective.* There are no data to support bismuth subnitrate as effective for skin application. Only its astringent properties would be useful in a topical product (Ref. *6*) and the data available do not consistently support this claim. The Panel concludes that bismuth subnitrate as a dusting powder and in an anhydrous ointment base for application to intact skin is not effective.

(3) *Evaluation.* Because bismuth subnitrate is unsafe and has no proved effectiveness as a skin protectant, the Panel concludes that the benefit to risk ratio is unfavorable to allow it to continue as an OTC skin protectant.

REFERENCES

(1) Swinyard, E. A., and S. C. Harvey, "Topical Drugs," in "Remington's Pharmaceutical Sciences," 14th ed., Mack Publishing Co., Easton, Pa., p. 771, 1970.

(2) "Remington's Pharmaceutical Sciences," 15th ed., Mack Publishing Co., Easton, Pa., p. 733, 1975.

(3) "Drill's Pharmacology in Medicine," 2d ed., edited by DiPalma, J. R., McGraw-Hill, New York, p. 781, 1958.

(4) "The Dispensatory of the United States of America," 27th ed., edited by Osol, A., and R. Pratt, J. B. Lippincott Co., Philadephia, p. 197, 1972.

(5) "The Dispensatory of the United States of America," 27th ed., edited by Osol, A., and R. Pratt, J. B. Lippincott Co., Philadephia, pp. 43-44, 1972.

(6) "The Extra Pharmacopeia," 26th ed., edited by Todd, R. G., the Pharmaceutical Press, London, p. 321, 1972.

b. *Boric acid.* The Panel concludes that boric acid is not safe and there are no data to show that it is effective for OTC use as a skin protectant.

Boric acid also known as boracic acid, or orthoboric acid, is a colorless, odorless material which is in the form of scales, crystals, or white powder. When dry, it is 99.5 percent boric acid (Refs. *1* and *2*). One g dissolves in 18 ml water or alcohol and in 4 ml glycerin.

(1) *Safety.* In experimental animals, a 10-percent boric acid ointment was absorbed through abraded skin under continual treatment, resulting in deposition of considerable boron in the brain, liver, body fat, and kidneys (Ref. *3*). Studies of the same material applied to third-degree burns also showed considerable uptake in all the tissues.

Boric acid has been shown to be absorbed in toxic quantities from ointment applied to abraded and burned

skin. A fatal dose of boric acid of less than 20 g in adults and less than 5 g in infants has been recorded. "As little as one-third the median lethal dose or treatment of a burn involving only 4 percent of the surface area of the body with 10 percent ointment U.S.P. will produce pathologic changes in central nervous system" (Ref. *3*).

Cope found that a 10-percent boric acid ointment used to treat burn patients of the Coconut Grove fire resulted in excretion of 2 g boric acid daily (Ref. *4*). A saturated solution of boric acid used as an irrigant to a granulating burn resulted in excretion of as much as 2.5 g boric acid daily (Ref. *4*). Such excretion suggests blood levels via absorption that are near the toxic level.

The absorption studies of borated talc powder applied to the diaper area and other areas of infants and children for a year failed to show significant concentrations of boron in the urine. It was later found that boric acid absorption was decreased in the presence of talc since calcium metaborate, an insoluble salt, was formed. Fatal cases of poisonings in infants showed a range of 52 to 296 mg percent of boric acid in the blood. The fatal range is 100 to 200 mg percent of boric acid blood levels (Ref. *5*). Boric acid has also been shown to be absorbed from weak solutions through normal skin (Ref. *5*).

Lord Lister used boric acid as an antiseptic solution in 1895. The material enjoyed great popularity in the form of powder, lotions, ointments, and pastes. Solutions for irrigation of bladder, rectum, and serous cavities had also been used. Within a few years after the use of boric acid became established in medicine, reports of poisonings began to appear in the literature. Many of the intoxications were from the application of boric acid containing medicaments to burns or wounds in solution, powder, ointment, or compresses. Most resulted from deliberate medication rather than from accidental ingestion (Ref. *5*).

Goldbloom et al. (Ref. *5*) described four deaths in infants and reviewed the world literature showing 109 cases of boric acid poisoning, 27 of which included quantitative analyses. There were 34.9 percent infants in the overall group, with a mortality of 70.2 percent.

(2) *Effectiveness.* The Panel concludes that boric acid has no specific therapeutic value for skin application. Boric acid has very weak local anti-infective activity. Its only officially recognized use, as noted in the "National Formulary," is as a buffer. It is for this reason that use of the substance occurs in ophthalmic preparations. The substance can also be used as a dusting powder, but only if combined with specific inert materials, such as talc. In this combination insoluble calcium metaborate is formed, and percutaneous absorption is reduced (Ref. *6*). There are no data to support the effectiveness of boric acid as a protectant.

The nontherapeutic value of boric acid, in addition to the fact that boric acid is absorbed through the skin, a situation particularly hazardous to children, is validated by the fact that many hospital pharmacies have already removed the material from their shelves. Its use is obsolete.

(3) *Evaluation.* Boric acid is not safe because of the risk of poisoning. In addition, there are no data to demonstrate its effectiveness as a skin protectant. The Panel concludes that the benefit to risk ratio is unfavorable to allow boric acid to continue as an OTC skin protectant.

REFERENCES

(1) "The Dispensatory of the United States of America," 27th ed., edited by Osol, A., and R. Pratt, J. B. Lippincott Co., Philadelphia, p. 199, 1972.

(2) "Remington's Pharmaceutical Sciences," 13th ed., Mack Publishing Co., Easton, Pa., pp. 1230-1231, 1965.

(3) Fisher, R. S. et al., "Boron Absorption from Borated Talc," *Journal of the American Medical Association*, 157:503-505, 1955.

(4) Pfeiffer, C. C., L. F. Hallman, and I. Gersh, "Boric Acid Ointment: A Study of Possible Intoxication in the Treatment of Burns," *Journal of the American Medical Association*, 128:266-274, 1945.

(5) Goldbloom, R. B., and A. Goldbloom, "Boric Acid Poisoning: A Report of Four Cases and a Review of 109 Cases form the World Literature," *Journal of Pediatrics*, 43:631-643, 1953.

(6) "Remington's Pharmaceutical Sciences," 15th ed., Mack Publishing Co., Easton, Pa., p. 1250, 1975.

c. *Sulfur.* The panel concludes that sulfur is not safe and not effective for OTC use as a skin protectant.

Sulfur is a nonmetallic element existing in several allotropic forms (Ref. 1). The three types of sulfur that are recognized pharmaceutically are precipitated sulfur, sublimed sulfur, and washed sulfur. A fourth type, colloidal sulfur, has been claimed to be more active than other types because of its very small particle size (Ref. 2). Sulfur is both keratoplastic (stimulates keratin formation) and keratolytic (dissolves keratin) when applied topically (Ref. 3). In low concentration, sulfur is reduced to a sulfide. The SH groups of cell proteins are oxidized to S-S groups, a transformation important in the formation of keratin and accounting for its keratoplastic action. The keratolyic effect of high concentrations results from reduction of the S-S bridges of the keratin molecule, leading to the disintegration of epidermis.

(1) *Safety.* Sulfur when applied to the skin in the usual topical preparations has been considered nontoxic. More recent information seems to point toward a toxic hazard involving the topical use of sulfur. Prolonged application over a period of weeks can produce a primary irritant dermatitis because of sulfur's keratolytic and keratoplastic effects (Ref. 3). Irritation to eyes and respiratory tract have also been shown to occur when sulfur preparations are used topically (Ref. 4).

The keratoplastic characteristic suggests a healing property of this substance. The true mechanism is one of injury. First the sulfur will break down the epidermis, then it will help stimulate repair. At higher concentration, above 2 percent, the keratolytic process surpasses the keratoplastic action and only epithelial injury is expressed. It is important to realize that these two properties do not operate independently, even at low concentrations. Therefore, use on previously damaged skin areas, as burns, lesions, and open surface wounds, may interfere with the healing process (Ref. 5).

Once sulfur is absorbed into the systemic circulation, a significant portion will be converted to hydrogen sulfide. The ingestion of 10 to 23 g or high percutaneous absorption may lead to hydrogen sulfide poisoning. These symptoms include hydrogen sulfide odor of the breath, vomiting, difficulty in swallowing, fever, headache, excitement or depression, and possible prostration. The higher level of the dose range can cause abdominal pain, diarrhea, and possible kidney injury (Ref. 6).

The information reviewed supports the conclusion that sulfur is unsafe for use as a skin protectant.

(2) *Effectiveness.* The claim that sulfur is effective in the local treatment of burns, sunburns, wounds, abrasions, and other surface injuries cannot be substantiated. The Panel concludes that there is no therapeutic rationale for the use of sulfur in the burn wound. Its keratolytic and keratoplastic activity are contraindications in the treatment of burns or in any other lesion which heals by epithelialization (Ref. 7). As noted under the safety section, these two properties cannot be separated even at low concentrations (Ref. 5). Such inappropriate treatment could result in destruction of freshly healing surface epithelium.

Sulfur has been used therapeutically for a variety of other indications, such as a fungicide and bactericide and for seborrheic dermatitis.

(3) *Evaluation.* The panel has found no evidence that sulfur is effective in the management of burns, abrasions, or other surface injuries. The keratolytic activity of sulfur contraindicates the drug for such healing wounds, since the drug may further destroy

young epitheliae cells. The benefit to risk ratio of sulfur as a skin protectant for minor skin injury is unacceptable.

REFERENCES

(1) "The Merck Index," 8th ed., Merck and Co., Inc., Rahway, N.J. p. 1005, 1968.
(2) "The Dispensatory of the United States of America," 25th ed., edited by Osol, A. and G. Farrar, J. B. Lippincott Co., Philadelphia, p. 1368, 1955.
(3) Beckman, H., "Pharmacology—The Nature, Action and Use of Drugs," 2d ed., W. B. Saunders, Philadelphia, p. 693, 1961.
(4) Gleason, M. N. et al., "Clinical Toxicology of Commercial Products," 2d ed., Williams and Wilkins, Baltimore, Md., p. 113, 1963.
(5) Lorenc, E. and R. K. Winkelman, "Evaluation of Dermatologic Therapy," *Archives of Dermatology*, 83:103, 1961.
(6) Von Oeltingen, W. F., "Poisoning: A Guide to Clinical Diagnosis and Treatment," W. B. Saunders, Philadelphia, p. 314, 1963.
(7) Goodman, L. S. and A. Gilman, "The Pharmacologic Basis of Therapeutics," 4th ed., The Macmillan Co., New York, p. 1058, 1970.

d. *Tannic acid.* The panel concludes that tannic acid is not safe and not effective for OTC use as a skin protectant.

Tannic acid, also known as tannin and gallotannic acid, is obtained from nutgalls gathered from the young twigs of *Quercus infectoria* (Oaks). It is an amorphous, fluffy or dense, yellowish white to light brown powder. It is acidic in water, essentially odorless, with a strong astringent taste. The drug precipitates protein and also forms insoluble complexes with many heavy metal ions, alkaloids and glycosides. It has little action on intact skin. However, when applied to abraded tissue, it precipitates a protein-tannate film that serves as a mechanical cover (Refs. *1*, *2*, and *3*).

(1) *Safety.* In 1942, Wells et al. (Ref. *4*) reported that tannic acid poisoning from the treatment of severe burns following the use of sprays, jellies, or solutions resulted in toxic hepatitis within 36 hours. Death from central necrosis of the liver occurred from 80 to 130 hours later. The following year, Barnes (Ref. *5*) showed that tannic acid or sodium tannate when injected was fatal to mice and guinea pigs in a dose of 40 mg/kg. Guinea pigs with 25 percent body burns treated with the 20 percent solution had a higher mortality rate as opposed to those untreated. Depression of liver function has been shown when tannic acid was injected in relatively low doses. Several authors concluded that repeated topical applications of burn preparations containing 10 percent tannic acid to large body areas cause hepatic damage (Refs. *4*, *5*, and *6*). Tannic acid is deposited in the muscle, lungs, and kidney, in addition to the liver.

(2) *Effectiveness.* The desired effect of tannic acid originally was to produce a protein precipiate which would act as a protective coating. The local effect of the coalgulum was supposed to be benefical (Ref. *2*). The benefit of the protein coalgulum in the use of tannic acid may be its exclusion of air and relief of pain. However, the great disadvantage of this type of treatment is the formation of an outer crust under which bacterial growth may flourish.

Tannic acid has been used in the form of a powder, glycerite, ointment, gargle, spray, lozenge, and suppository. In radiology, it is used as a cleansing enema (Ref. *3*). In the past, tannic acid has been used as an astringent and protective coating over mucous membranes. From 1925 to 1942, tannic acid was used as a 2.5 to 5.0 percent aqueous solution for treating burns (Ref. *7*). However, the panel recognizes that "* * * there are few legitimate medical uses for this drug" (Ref. *1*).

(3) *Evaluation.* The panel concludes that the documented hepatotoxicity and the obsolete indications for the use of tannic acid make this drug not safe or effective for burn therapy, and not suitable as an OTC skin protectant.

REFERENCES

(1) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 4th ed., The Macmillan Co., New York, p. 992, 1970.
(2) "The Dispensatory of the United States of America," 27th ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, p. 1140, 1972.
(3) Krezanoski, J. Z., "Tannic Acid: Chemistry, Analysis and Toxicology," *Radiology*, 87:655–657, 1966.
(4) Wells, D. B., H. D. Humphrey and J. J. Coll, "Relation of Tannic Acid to Liver Necrosis Occuring in Burns," *New England Journal of Medicine*, 226:629–636, 1942.
(5) Barnes, J. M. and R. J. Rossiter, "Toxicity of Tannic Acid," *Lancet*, 2:218–222, 1943.
(6) McClure, R. D., C. R. Lan and H. Romence, "Tannic Acid and Treatment of Burns: An Obsequy," *Annals of Surgery*, 120:387–398, 1944.
(7) Davidson, E. G., "Tannic Acid in the Treatment of Burns," *Surgery, Gynecology and Obstetrics*, 41:202–221, 1925.

CATEGORY II LABELING.

The Panel has examined the submitted labeling claims for OTC products containing skin protectant ingredients and has placed certain claims into Category II. The following Category II labeling statements are unsupported by scientific data or by sound theoretical reasoning or are misleading: "cures * * *" any irritation, and "prevents formation of blisters".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

CATEGORY III ACTIVE INGREDIENTS.

Allantoin, Live yeast cell derivative, and Zinc acetate.

a. *Allantoin.* The Panel concludes that allantoin is safe, but there are insufficient data available to permit final classification of its effectiveness as a skin protectant for OTC use as a wound-healing aid. Allantoin has been described and evaluated to be safe and effective as a skin protectant for OTC use other than as a wound-healing aid. (See part III. paragraph B.1.a. above—Allantoin.)

(1) *Safety.* The safety of allantoin has been discussed elsewhere in this document. (See part III. paragraph B.1.a.(1) above—Safety.)

(2) *Effectiveness.* There is insufficient evidence to establish the effectiveness of allantoin as a wound-healing aid. However, it has been suggested that allantoin has properties that aid in wound healing. The Panel concludes that such studies are anecdotal, poorly designed, and inconclusive.

Allantoin has been used topically in granulating wounds and resistant ulcers to stimulate the growth of healthy tissue (Ref. *1*). The rationale for this use began in World War I when it was noted that wounds infested with maggots healed with unexpected promptness (Refs. *1* and *2*). In 1935, evidence was presented that showed that the beneficial effects of maggots were due to the allantoin in their excretions (Ref. *1*). Thus, allantoin was widely employed by surgeons to accelerate cell proliferation of sluggish wounds, especially osteomyelitis.

Terms such as cell proliferant, epithelization stimulant, and chemical debrider have been used to describe the wound-healing claims made for allantoin in such texts as the "British Pharmaceutical Codex," "United States Dispensatory," "Remington's Pharmacuetical Sciences," "Martindale's Extra Pharmacopeia," and "Merck Index" (Refs. *3* through *7*). In a survey article, Mecca published a summary of the available literature to 1960 on the wound-healing capabilities of allantoin (Ref. *8*). The Panel has reviewed this article and others. Nearly all allude to this property but none offer any evidence or are able to describe this property with any degree of acceptable detail (Refs. *9* through *13*).

It has been suggested that allantoin, by virtue of its debriding properties, will cleanse away necrotic tissue, hastening the granulation phase of wound healing (Ref. *12*). It has yet to be demonstrated that allantoin stimulates epithelization or creates an environment favorable to epithelization.

As previously noted, evidence must be produced by scientific study in man demonstrating that allantoin stimulates the wound-healing process. Until such time, allantoin will be classified as Category III for such claims.

(3) *Proposed dosage.* Adult, children and infants topical dosage is the application of a 0.5 to 2.0 percent preparation to the affected area as needed.

(4) *Labeling.* The Panel recommends the Categroy III labeling for skin protectant active ingredients as wound-healing aids. (See part III. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstate effectiveness as a wound-healing aid will be required in accordance with the guidelines set forth below for testing skin protectant ingredients as wound-healing aids. (See part III. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The Dispensatory of the United States of America," 27th ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, p. 197, 1972.

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(9) Anonymous, "Today's Drugs—Allantoin," *British Medical Journal,* 4:535, 1967.

(10) Flesch, P., "New Approaches to the Study of Human Horny Layers," *Proceedings of the Scientific Section—The Toilet Goods Association,* 29:27-31, 1958.

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b. *Live yeast cell derivative.* The Panel concludes that live yeast cell derivative (LYCD) is safe but there are insufficient data available to permit final classification of its effectiveness as a skin protectant for OTC use as a wound-healing aid.

Live yeast cell derivative is also known as skin respiratory factor (SRF). It is an alcoholic extract of live baker's yeast, *Saccharomyces cerevisiae,* obtained by refluxing cakes of live yeast with ethanol. The filtered, straw-yellow solution is concentrated by evaporation, removing the alcohol and most of the water. A final filtration step yields a clear brown viscous aqueous solution with a soluble nonvolatile content of 45 to 55 percent. A unit of activity is calculated as the amount of LYCD which is required to increase the oxygen uptake of 1 mg of dry weight rat abdominal skin by 1 percent at the end of a 1-hour testing period in a Warburg apparatus. This is reported for each lot of LYCD as million units per pound (lb) or units per g. The Warburg assay potency for each lot of LYCD before formulation must fall between 8,000 and 12,000 units per g (Ref. *1*).

The Panel received three submissions from the same manufacturer for marketed products with the same ingredients with healing claim(s). The product contains LYCD and 3 percent shark liver oil. The 3 percent shark liver oil is claimed to contain 855 U.S.P. units of vitamin A per g of the product and 2.25 U.S.P. units of vitamin D per g of the product. The manufacturer declared LYCD to be the major active ingredient in the products and the shark liver oil as an emollient ointment base in which the products are formulated.

The LYCD supplies 2,000 units SRF per oz of ointment and is claimed as "an effective agent in accelerating the healing of wounds." The effective range of LYCD is stated to be 2,000 to 3,000 units. The LYCD is made from baker's yeast and is claimed to increase the oxygen utilization of dermal tissue, to increase collagen formation, and to increase the rate of healing of controlled wounds.

The Panel has evaluated the claims made for LYCD as a wound-healing aid below.

(1) *Safety.* The Panel concludes that LYCD is safe. LYCD is made from baker's yeast which is generally recognized as safe. Baker's yeast and brewer's yeast are very similar, and both are known under the same technical name, *Saccharomyces cerevisiae* (Ref. *1*). The official "National Formulary XIII" dosage of brewer's yeast as a vitamin supplement is 10 g orally four times daily (Ref. *2*). This dose has been used for many years. No toxic reactions are recorded for this foodstuff.

(2) *Effectiveness.* There are no adequately well-controlled clinical studies to establish the effectiveness of LYCD as a wound-healing aid. Animal and in vitro studies were submitted to support a positive influence of LYCD on wound healing. However, an in vivo clinical study in human subjects, submitted by the manufacturer, was inadequately controlled and inconclusive (Ref. *3*).

The laboratory data obtained from animal and in vitro studies show that LYCD has the characteristics expected of a wound-healing aid, i.e., increased oxygen uptake, hydroxyproline formation which is associated with collagen biosynthesis, tissue growth, and epithelization (Ref. *4*). However, corroboration of these effects by LYCD on wound healing in human subjects is not available.

(i) *Laboratory data from animal and in vitro studies.* The most sophisticated studies to show that LYCD has characteristics expected of a wound-healing aid have been performed by Goodson et al. (Ref. *4*). The in vitro oxygen utilization by cultured human fibroblasts was studied by a method adapted from polymorphonuclear leukocyte methods (Ref. *5*). Oxygen consumption in cultured fibroblasts was increased by 137 percent with the addition of LYCD (p is less than 0.01). The addition of potassium cyanide to LYCD decreased oxygen uptake by one-half, suggesting a relation to the cytochrome system. The oxygen uptake by polymorphonuclear leukocytes was similarly increasee by LYCD in vitro.

The effect of LYCD on in vitro incorporation of proline into hydroxyproline was studied by the method of Uitto (Ref. *6*). Since all the radioactivity in the study was added as proline, the radioactivity of hydroxyproline is a direct measure of the oxidation of proline to hydroxyproline and thus the incorporation into collagen. The results showed an average increase of labeled ^{14}C proline uptake of 70 percent into LYCD-incubated human skin samples obtained at excisional surgery on three patients.

In another study, the in vivo effect of LYCD on the formation of new tissues was studied by implanting four sterile stainless steel wound cylinders under the skin of the back of each of four Sprague-Dawley white rats (Ref. *4*). The skin incisions were closed. On the 10th day after implantation, injections of 100 microliters (μl) of 1 percent LYCD were made into two of the four rats at the site of new tissue growth for 14 days. In another group of similarily implanted rats, 50 μl of 1 percent LYCD was injected. Saline was injected into the control rats. The hydroxyproline content of the tissue adherent to the interior of the cylinders was determined at the end of the 14 days. There was a significant increase in the mean net weight of the new tissue from the rats injected with LYCD (p is less than 0.05) and a 28.9-percent increase in hydroxyproline content (p is less than 0.07).

In a study in rabbits, a marketed formulation containing LYCD in a shark liver oil ointment base was compared with petrolatum (Ref. *4*). Their effect on the epithelization of ear punch defects made on the inside of the ears of five New Zealand white rabbits was studied. The two test substances were applied to equal numbers of both left and right ears. Photographs of the wounds were taken on days 0, 5, 10, 15, and 30. Wound surfaces were measured. There was no epithelization in test or control ears on day 5. There was a 17.67-precent increase in the epithelization of the test ears on day 10 (p is less than 0.05), a 23.33-percent increase on day 15 (p is less than 0.005), and a 25.8-percent increase on day 30 (p is less than 0.005).

The laboratory data discussed above was interpreted as indicating that LYCD contains a substance or substances capable of stimulating wound oxygen consumption, epithelization, and collagen synthesis. However, in the in vivo rabbit ear-wound study, the test material, a marketed product, also contains shark liver oil. The investigators (Ref. *4*) point out that the product contains vitamin A in the form of shark liver oil and that the studies did not eliminate shark liver oil as a factor in the increased epithelization of the rabbit ear wounds. They further state: "We are not aware of published data showing that vitamin A can stimulate epithelization to the degree seen in these studies." They cite a study done by the manufacturer in which the product containing LYCD and shark liver oil was compared with the product containing shark liver oil without LYCD (Ref. *7*). The investigators evaluated the study as indicating that LYCD "is responsible for the increased oxygen utilization in skin treated with the whole formula".

The Panel has duly noted that the manufacturer's data show that LYCD alone is responsible for the increased oxygen uptake by skin treated with the whole product (LYCD and shark liver oil). It also notes that the results were, by necessity, obtained from in vitro testing, i.e., Warburg assays, and that while the association between increased oxygen utilization and epithelization is implied, clinical confirmation is needed. The Panel, therefore, concludes that corroboration of the effect of LYCD on wound healing without the presence of shark liver oil is needed in human subjects for the evaluation of LYCD as a wound-healing aid.

(ii) *Human study.* Only one human study is available for evaluation (Ref. *3*). The effect of LYCD on donor wound sites in patients with burn wounds was studied. Patients undergoing skin grafting were selected. A small number of patients (18) were entered in the study. An ointment containing shark liver oil and LYCD was applied to one-half of the donor site and the ointment without LYCD and shark liver oil was applied to the other side of the wound. The observations and recordings were made by nurses. Color, discharge, redness, epithelization, and odor were noted on days 1, 3, 6, 9, 12, and 18. In addition, photographs were obtained of the wound on those days. The wound healing time and the observations were recorded by the nurses. The conclusions drawn from the study were that both the LYCD ointment and the base ointment control tended to reduce wound healing time as compared to control donor sites, but only the ointment containing LYCD was statistically significant.

The Panel concludes that the study is insufficient to demonstrate a clinically significant effect. The study can only be considered as suggesting a potential wound-healing effect. A total of 18 patients were studied. Nine patients received the LYCD-containing ointment and another 9 patients received the base ointment. The number of control patients receiving no treatment was not given. The patients in both groups were listed in the nurses subjective index as doing "better" than the patients receiving no treatment. The number of patients are too small and the data too subjective to arrive at a conclusive interpretation. The investigators make no final conclusion on the basis of this study and only state that "based on these findings we now plan to extend our series to include an additional 15 to 20 patients."

Until an adequate well-controlled human study is done, an evaluation of LYCD as an effective wound-healing aid cannot be made. Since the wound-healing claim is made for LYCD only, the influence of shark liver oil in any preparations should be controlled.

(3) *Proposed dosage.* Adult and children 2 years of age and older topical dosage is the application of a preparation containing LYCD providing 67 units (LYCD) per g to the affected area as needed. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category III labeling for skin protectant active ingredients as wound-healing aids. (See part III, paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as a wound-healing aid will be required in accordance with the guidelines set forth below for testing protectant ingredients as wound-healing aids. (See part III, paragraph C. below—Data Required for Evaluation.)

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(6) Uitto, J., "A Method for Studying Collagen Biosynthesis in Human Skin Biopsies in vitro," Biochemica et Biophysica Acta, 201: 438-445, 1970.

(7) Summary Minutes of the OTC Panel on Hemorrhoidal Drugs, May 1, 1975. Draft of unpublished paper in OTC Volume 060150.

c. *Zinc acetate.* The Panel concludes that zinc acetate is safe, but there are insufficient data available to permit final classification of its effectiveness as a skin protectant for OTC use as a wound-healing aid. Zinc acetate has been described and evaluated to be safe and effective as a skin protectant for OTC use other than as a wound-healing aid. (See part III, paragraph B.1.1. above—Zinc acetate.)

(1) *Safety.* The safety of zinc acetate has been discussed elsewhere in this document. (See part III, paragraph B.1.1.(1) above—Safety.)

(2) *Effectiveness.* Zinc acetate was discussed for its effectiveness as a Category I skin protectant for topical application to minor skin irritations above. (See part III, paragraph B.1.1.(2) above—Effectiveness.) Considerable controversy has occurred in the literature regarding its effectiveness in promoting, enhancing, or speeding wound healing. It has been shown that zinc is excreted in the urine in high levels after surgical trauma. In addition, there are increased concentrations of zinc at the wound margin throughout most of the healing (Ref. *1*). Zinc salts have been given orally to surgical patients in an effort to enhance healing which has been shown by some investigators to be accelerated (Ref. *1*). The controlled studies showing increased wound healing have been with the oral route of administration. The data are inconclusive regarding topical absorption of zinc compounds for the benefits of wound healing. In addition, there are no other data that topical application of zinc salts to wounds will increase the healing of these wounds. The safety of topical applications of zinc salts to skin or mucous membranes is not questioned. The Panel concludes, however, that the information is insufficient to permit a definite statement that topical applications of zinc salts

do increase wound healing where applied.

(3) *Proposed dosage.* Adults and children 2 years of age and older topical dosage is the application of a 0.1- to 2.0-percent preparation to the affected area as needed. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category III labeling for skin protectant active ingredients as wound-healing aids. (See part III, paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as a wound-healing aid will be required in accordance with the guidelines set forth below for testing protectant ingredients as wound-healing aids. (See part III, paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The Extra Pharmacopeia," 25th ed., edited by Todd, R. G., The Pharmaceutical Press, London, p. 1489, 1967.

CATEGORY III LABELING

The Panel examined the submitted labeling for currently marketed OTC skin protectant products. This labeling includes claims such as "healing ointment," "aids healing of cold sores and fever blisters," etc. The marketed products were found to contain the skin protectant active ingredients discussed above. As noted earlier, the Panel has found no controlled studies which have conclusively documented that such ingredients aid in wound healing. Therefore, based upon this determination and the Panel's recommendations regarding acceptable labeling indications for skin protectants, the Panel classifies the following as a Category III labeling indication: "Aids healing of minor skin abrasions, scrapes, cuts and burns." If adequate data are not obtained within 2 years to support this claim, it should be reclassified as Category II.

C. DATA REQUIRED FOR EVALUATION

The Panel considers the protocols recommended in this document for the studies required to bring a Category III ingredient into Category I to be in agreement with the present state of the art and does not intend to preclude the use of any advances or improved methodology in the future.

1. *General comments.* It is difficult to demonstrate that the ingredients discussed above aid in the healing of minor skin abrasions, scrapes, cuts, and burns, or in any way have a salutary effect upon wound healing. Therefore, the ingredients reviewed by the Panel have been classified Category III because such data are not available. Because of the difficulties, protocols and study designs should be developed in consultation with FDA.

2. *Treatment of subjects for study.* The subjects selected for study should have wounds that are appropriate for developing and testing a Category III ingredient for efficacy in the healing of minor skin abrasions, scrapes, cuts, and burns, as would be indicated for OTC use.

The Panel has made suggestions below that are suitable as starting points in the development of a study design for testing the efficacy of ingredients as wound-healing aids.

3. *Methods of study.* The Panel concludes that in vitro experiments and animal data indicate that these ingredients may be effective as wound-healing aids. However, these topical agents must be further tested in human clinical trials. Admittedly, clinical studies of wound healing are difficult to control, gross measurements are imprecise, and wounds are not standard (i.e., abscess cavities, graft donor sites, punch biopsy defects). However, prior to attaining Category I for the claim for wound-healing aid, well-controlled human studies will be required to show no adverse effects on wound healing and no untoward local or systemic reactions to the drugs from topical application. Studies of this type should give positive data regarding wound healing.

The Panel suggests the following points for incorporation into the development of a study method:

a. At least 20 test subjects and 20 control subjects should be entered in a study.

b. The test ingredient should be applied to the wound daily for at least 14 days.

c. Urinary hydroxyproline excretion should be determined pretreatment and on selected subsequent days of treatment.

d. The wound area should be photographed pretreatment and on days 5, 7, and 14 of treatment.

e. Planimetry measurements of the wound area should be made pretreatment and on days 5, 7, and 14 of treatment.

f. The clinical charateristics of the wound such as color, discharge, redness, epithelization, etc., should be noted at appropriate intervals.

4. *Interpretation of data.* The Panel requires investigators to develop methods for human experimentation and to design studies which are well-controlled and safe. Data produced from these studies should be biologically and statistically significant and reproducible. Since the Panel is unable to recommend the precise protocols for such investigations at this time, 2 years will be allowed to develop the methodology for wound-healing studies in human subjects.

Evidence of drug effectiveness is required from a minimum of 3 positive studies based on the results of 3 different investigators or laboratories.

All data submitted to FDA must present both favorable and unfavorable results.

REFERENCES

(1) Uitto, J., "A Method for Studying Collagen Biosynthesis in Human Skin Biopsies in vitro," *Biochemica et Biophysica Acta*, 201:438-445, 1970.

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(3) Constable, J. D., "Comparative Effects of Betadine Ointment (Povidone-Iódide) and Other Topical Agents on Epidermal Regeneration in Rabbits," in "Recent Antisepsis Techniques in the Management of the Burn Wound," Purdue-Frederick Co., Norwalk, Conn., 1974.

The Food and Drug Administration has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended by adding new part 347, to read as follows:

PART 347—SKIN PROTECTANT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
347.1 Scope.
347.3 Definition.

Subpart B—Active Ingredients

347.10 Skin protectant active ingredients.
347.20 Permitted combinations of active ingredients.

Subpart C—[Reserved]

Subpart D—Labeling

347.50 Labeling of skin protectant products.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371) (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 347.1 Scope.

An over-the-counter skin protectant 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 part 347 and each of the general conditions established in § 330.1 of this chapter.

§ 347.3 Definition.

As used in this part, "skin protectant" is an agent which isolates the exposed skin or mucous membrane surface from harmful or annoying stimuli.

Subpart B—Active Ingredients

§ 347.10 Skin protectant active ingredients.

The active ingredients of the product consist of the following within the dosage limits established for each ingredient:

Allantoin, 0.5 to 2.0 percent.
Aluminum hydroxide gel, 0.15 to 5.0 percent.
Calamine, 1 to 25 percent.
Cocoa butter, 80 to 100 percent.
Corn starch, 10 to 85 percent.
Dimethicone, 1 to 30 percent.
Glycerin, 20 to 45 percent.
Kaolin, 4.0 to 20 percent.
Petrolatum preparations (petrolatum, white petrolatum), 30 to 100 percent.
Shark liver oil, 3 percent.
Sodium bicarbonate, 1 to 100 percent.
Zinc acetate, 0.1 to 2.0 percent.
Zinc carbonate, 0.2 to 2.0 percent.
Zinc oxide, 1 to 25 percent.

§ 347.20 Permitted combinations of active ingredients.

The active ingredients of the combination product consist of any two or more of the ingredients identified in § 347.10 at the dosage limit established for each ingredient.

Subpart C—[Reserved]

Subpart D—Labeling

§ 347.50 Labeling of skin protectant products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "skin protectant."

(b) *Indications.* The labeling contains a statement under the heading "Indication(s)" limited to one or more of the following phrases:

(1) "Aids in the temporary relief of minor skin irritations."

(2) "For the temporary protection of minor skin irritations."

(3) "Soothes minor skin irritations."

(4) "Gives comfort to minor skin irritations."

(5) For skin protectant active ingredients for symptoms of dryness: "For symptoms of chapping, peeling or scaling" (optional, any or all of the following) "due to minor burns, sunburn, windburn, scrapes, abrasions, or cracked lips."

(6) For skin protectant active ingredients for symptoms of wetness: "For symptoms of oozing or weeping" (optional, any or all of the following) "due to contact dermatitis, poison oak, or poison ivy."

(7) For skin protectant active ingredients for symptoms of friction:

(i) "For symptoms of" (optional, any or all of the following) "intertrigo, chafing, galling, rubbing, or friction."

(ii) "For the temporary protection and lubrication of minor skin irritations."

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

(1) "For external use only."

(2) "Avoid contact with the eyes."

(3) "Discontinue use if symptoms persist for more than 7 days and consult a physician."

(4) For products containing aluminum hydroxide gel: "Do not use on children under 6 months of age without consulting a physician."

(5) For products containing dimethicone: "Not to be applied over puncture wounds, infections, or lacerations."

(6) For products containing glycerin: "Do not use on children under 6 months of age without consulting a physician."

(7) For products containing petrolatum preparations (petrolatum, white petrolatum): "Not to be applied over puncture wounds, infections, or lacerations."

(8) For products containing shark liver oil: "Do not use on children under 2 years of age without consulting a physician."

(9) For products containing sodium bicarbonate: "Do not apply to extensive acid burns. Flood acid burns with cold tap water and consult a physician."

(10) For products containing zinc acetate: "Do not use on children under 2 years of age without consulting a physician."

(d) *Directions.* The labeling of the product contains the following statement under the heading "Directions": "Apply liberally as often as necessary."

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the hearing clerk docket number found in brackets in the heading of this document) regarding this proposal on or before November 2, 1978. Such comments should be addressed to the Office of the Hearing Clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before December 4, 1978. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday throuugh Friday.

NOTE.—The Food and Drug Administration has determined that this document will not have a major economic impact as defined by Executive Order 11821 (amended by Exective Order 11949) and OMB Circular A-107. A Copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: July 18, 1978.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

[FR Doc. 78-21164 Filed 8-3-78; 8:45 am]