Rationale for Recommendations

I. *Exposure information*—A. *Production/use/disposal information.* U.S. production of each one of the three carbofuran intermediates was between 10 million and 50 million pounds in 1977 (EPA, 1982). These compounds are intermediates consumed onsite in the manufacture of carbofuran, a pesticide. However, these chemicals are released to the aquatic environment in wastewater; average wastewater volume is 1.4 million gallons per day and contains 0.5–1.5 mg/L of each of the three intermediates after treatment (Fekete, 1982a). According to the manufacturer of carbofuran, these wastes are scheduled to be treated by a metropolitan waste treatment plant after a hookup in late 1982 or early 1983. Additional wastes containing the three carbofuran intermediates are present in a sludge that is incinerated or placed in a hazardous waste landfill; as a result, the sludge could also be a source of environmental exposure for the three chemicals.

The sole manufacturer of carbofuran produces these intermediates in a closed system in a single plant; thus, the opportunity for occupational exposure is minimal (FMC, 1981).

B. *Chemical fate information.* No studies on the environmental transport or persistence of the three carbofuran intermediates were found. Although these compounds are expected to biodegrade, no data on biodegradation rates have been found.

II. *Biological effects of concern to human health.* The health effects of the three carbofuran intermediates are not well characterized. However, due to the lack of significant human exposure, no health effects testing is recommended.

III. *Environmental considerations*—A. *Short-term (acute) effects.* In screening experiments with goldfish, the 48– and 96–hour LC_{50} values for the three carbofuran intermediates ranged from 6.5 to 75 mg/L (Fekete, 1982b).

B. *Long-term (subchronic/chronic) effects.* No studies on the long-term effects of the three carbofuran intermediates have been found.

C. *Other effects (physiological/behavioral/ecosystem processes).* No Studies on the physiological, behavioral, or ecosystem effects of the three carbofuran intermediates have been found.

D. *Bioconcentration and food-chain transport.* Based on their estimated octanol/water partition coefficients (see Table 1), little bioconcentration is expected for the three carbofurans.

E. *Reasons for specific environmental recommendations.* The three designated carbofuran intermediates are released at a rate of 1.4 million gallons per day in an effluent containing 0.5–1.5 mg/L of each of these chemicals. LC_{50} values for goldfish are 6.5–75 mg/L. However, goldish are not normally considered a sensitive species, and other species of fish and invertebrates may have LC_{50} values at significantly lower concentrations. Thus, the three carbofuran intermediates are being released to the environment at concentrations that may exceed anticipated environmental effects levels.

Chemical fate testing, principally environmental monitoring, is needed to better characterize the nature of the dispersion, concentration, and persistence of the three carbofuran intermediates in the environment. Acute toxicity testing to fish and invertebrates is recommended to characterize more precisely the toxicity of these carbofuran intermediates.

References

(1) EPA. 1982. Environmental Protection Agency TSCA chemical Substance Inventory (public portion). Washington, DC: Environmental Protection Agency.

(2) Fekete, TM. 1982a. Letter from FMC Corporation to Dynamac Corporation, August 12, 1982.

(3) Fekete, TM. 1982b. Letter from FMC Corporation to Dynamac Corporation, February 26, 1982.

(4) FMC. 1981. Unpublished data provided to ITC by J. Acker, March 27, 1981.

(5) Leo AE, Hansch C, Elkins D. 1971. Partition coefficients and their uses. Chem. Revs. 71(6):525–615.

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Friday
December 3, 1982

Part IV

Department of Health and Human Services

Food and Drug Administration

OTC Drug Products for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis; Establishment of a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 82N-0214]

OTC Drug Products for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

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

DATES: Written comments by March 3, 1983, and reply comments by April 4, 1983.

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

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

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

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment of the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it. After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis as a notice of proposed rulemaking.

Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

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

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis should be accompanied by appropriate documentation.

Originally the Advisory Review Panel on OTC Antimicrobial (II) Drug Products was charged with the review of ingredients for the treatment or prophylaxis (prevention) of dandruff and seborrhea, and the Advisory Review Panel on OTC Miscellaneous External Drug Products was charged with the review of ingredients used as remedies for cradle cap and psoriasis.

In a notice published in the **Federal Register** of December 16, 1972 (37 FR 26842), FRA requested submission of data and information on antimicrobial active ingredients to the Advisory Review Panel on OTC Antimicrobial (II) Drug Products.

The agency subsequently found considerable overlapping between the ingredients submitted to the Antimicrobial (II) Panel for review in response to the December 16, 1972 call for data, and the ingredients submitted to the Miscellaneous External Panel for review in response to calls for data published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). The agency concluded that a review of all ingredients submitted for the treatment or prophylaxis of dandruff, seborrhea, and psoriasis by one panel would be more efficient and that it would be appropriate for this review to be undertaken by the Miscellaneous External Panel. The members of the Antimicrobial (II) Panel were invited to serve as consultants to the Miscellaneous External Panel when ingredients with known antimicrobial actions were reviewed. In the **Federal Register** of March 6, 1979 (44 FR 12271), a notice was published announcing that the review of ingredients and data pertaining to dandruff and seborrhea was transferred from the Antimicrobial (II) Panel to the Miscellaneous External Panel.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and

Drug Administration, after January 3, 1983, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, National Center for Drug and Biologics (HFD–510) (adress above).

FDA published in the Federal Register of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorize the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. In some advance notices of proposed rulemaking previously published in the OTC drug review, the agency suggested an earlier effective date. However, as explained in the tentative final monograph for OTC topical antimicrobial drug products (published in the Federal Register of July 9, 1982; 47 FR 29986), the agency has concluded that it is more reasonable to have a final monograph be effective 12 months after the date of its publication in the Federal Register. This period of time should enable manufacturers to reformulate, relabel, or take other steps to comply with a new monograph with a minimum disruption of the marketplace thereby reducing economic loss and ensuring that consumers have continued access to safe and effective drug products.

On or after the effective date of the monograph, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date of the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the Federal Register of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the Federal Register of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients in OTC antimicrobial drug products was issued in the Federal Register of December 16, 1972 (37 FR 26842), including active ingredients for the treatment or prevention of dandruff and seborrhea, and a request for data and information on all OTC active ingredients used in miscellaneous external drug products was issued in the Federal Register of November 16, 1973 (38 FR 31697). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient' "). In the Federal Register of August 27, 1975 (40 FR 38179), a notice supplemented the November 16, 1973, notice with a detailed, but not necessarily all-inclusive, list of ingredients in miscellaneous external drug products. This list, which included cradle cap and psoriasis remedies, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of the opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC drug review to all OTC drug products.

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

William E. Lotterhos, M.D., Chairman
Rose Dagirmanjian, Ph. D.
Vincent J. Derbes, M.D. (resigned July 1976)
George C. Cypress, M.D. (resigned November 1978)
Yelva L. Lynfield, M.D. (appointed October 1977)
Harry E. Morton, Sc. D.
Marianne N. O'Donoghue, M.D.
Chester L. Rossi, D.P.M.
J. Robert Hewson, M.D. (appointed September 1978)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Marvin M. Lipman, M.D., of Consumers Union, served as the consumer liaison. Gavin Hildick-Smith, M.D., served as industry liaison from January until August 1975, followed by Bruce Semple, M.D., until February 1978. Both were nominated by the Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, also served as an industry liaison since June 1975.

Two nonvoting consultants, Albert A. Belmonte, Ph. D., and Jon J. Tanja, R.Ph., M.S., provided assistance to the Panel since February 1977.

The following FDA employees assisted the Panel: John M. Davitt served as Executive Secretary until August 1977, followed by Arthur Auer until September 1978, followed by John T. McElroy, J.D. Thomas D. DeCillis, R.Ph., served as Panel Administrator until April 1976, followed by Michael D.

Kennedy until January 1978, followed by John T. McElroy, J.D. Joseph Hussion, R.Ph., served as Drug Information Analyst until April 1976, followed by Victor H. Lindmark, Pharm. D., until March 1978, followed by Thomas J. McGinnis, R.Ph.

The Advisory Review Panel on OTC Miscellaneous External Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations on drug products for the control of dandruff, seborrheic dermatitis, and psoriasis in this document. The Panel's findings on other categories of miscellaneous external drug products are being published periodically in the **Federal Register**.

The Miscellaneous External Panel prefers the term "seborrheic dermatitis" to "seborrhea." The Panel believes that "seborrheic dermatitis" more accurately describes the condition with which the submitted products are intended to deal, and this term is therefore used throughout this document.

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topics in this document were held on August 3 and 4, September 28 and 29, October 28 and 29, December 9 and 10, 1979; January 27 and 28, March 7 and 8, April 20 and 21, June 22 and 23, August 3 and 4, October 5 and 6, November 7 and 8, and December 14 and 15, 1980.

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

The following individuals were given an opportunity to appear before the Panel, either at their own request or at the request of the Panel, to express their views on OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis:

Frank Akin
D. Anderson, Ph. D.
Alex Apostolou, Ph. D., D.V.M.
B. Bopp, Ph. D.
John Brickto, M.D.
Richard Brogle, Ph. D.
Sol Gershon, Ph. C., Ph. D.
Marty Garotalo
William Hubregs, Ph. D.
R. Janicki, M.D.
Kenneth Johannes
J. Kesterson, Ph. D., D.V.M.
James J. Leyden, M.D.
Norman Meltzer, Ph. D.
Sigfrid A. Muller, M.D.
Milos Novotny, Ph. D.
Mary Paxton, M.S.
Mark Pittelkow, M.D.
Harold O'Keefe
Stephen Schwartz
Samuel Solomon, M.D.
Arnold Winfield
Gail Zimmerman

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

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

In accordance with the OTC drug review regulations in §330.10, the Panel reviewed OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis with respect to the following three categories:

Category I. Conditions under which OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis are not generally recognized as safe and effective or are misbranded.

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

The Panel reviewed 32 active ingredients for the control of dandruff, seborrheic dermatitis, psoriasis, and cradle cap. The Panel placed 5 ingredients in Category I, 2 ingredients in Category II, and 19 ingredients in Category III for the control of dandruff. The Panel placed three ingredients in Category I (one for scalp and body use and one for scalp use only), one ingredient in Category II, and three ingredients in Category III (one for body use only) for the control of seborrheic dermatitis. The Panel placed two ingredients in Category I, four ingredients in Category II, and nine ingredients in Category III (one for body use only) for the control of psoriasis. For the control of cradle cap, the Panel placed no ingredients in Category I, no ingredients in Category II, and two ingredients in Category III. (The number of ingredient classfications does not equal the number of ingredients reviewed because some ingredients were reviewed for more than one labeled use.)

I. Submission of Data and Information

In the **Federal Register** of November 16, 1973 (38 FR 31697), a notice was published requesting the submission of data and information on product categories to be reviewed by the Miscellaneous External Panel. A subsequent notice, published in the **Federal Register** of August 27, 1975 (40 FR 38179) requested data and information on additional product categories as well as specific ingredients to be reviewed by the Panel, including drug products for psoriasis and cradle cap.

As previously stated, a notice published in the **Federal Register** of March 6, 1979 (44 FR 12271) administratively transferred the review of active ingredients for the treatment and prophylaxis of dandruff and seborrhea (seborrheic dermatitis) and all pertinent data and information from the Antimicrobial (II) Panel to the Miscellaneous External Panel.

A. Submissions

Pursuant to the above notices, the following submissions were received:

Firms	Marketed products
Abbott Laboratories, North Chicago, IL 60064.	Selsun Blue for Normal Hair, Selsun Blue for Dry Hair, Selsun Blue for Oily Hair.
Alberto-Culver Co., Melrose Park, IL 60106.	Rinse Away Dandruff Rinse.
Alcon Laboratories, Inc., Fort Worth, TX 76101.	Ionil, Ionil-T.
Armour-Dial, Inc., Phoenix, AZ 85077.	Dial Conditioning Dandruff Shampoo for Normal Hair, Dial Conditioning Dandruff Shampoo for Dry Hair, Dial Conditioning Shampoo for Oily Hair.
Avon Products, Inc., Suffern, NY 10901.	Keep-Clear Anti-dandruff Shampoo.
Block Drug Co., Inc., Jersey City, NJ 07302.	Tegrin Cream, Tegrin Foam, Tegrin Medicated Shampoo, Tegrin Medicated Soap.
Chester A. Baker Laboratories, Inc., Miami, FL 33169.	Baker's P & S Liquid.
Cooper Laboratories, Inc., Wayne, NJ 07470.	Packer's Pine Tar Liquid Shampoo, Packer's Pine Tar Soap, Sebaveen.
Colgate-Palmolive, New York, NY 10022.	Grenadier Dandruff Control Hair Groom, Look Twice Anti-dandruff Lotion Shampoo, Wildroot Dandruff Treatment Hair Groom.
Denver Chemical Mfg. Co., Stamford, CT 06904.	Siroil.
Emery Uncommon Chemicals, Linden, NJ 07036.	Ogilvie Dandruff Shampoo.
Flow Pharmaceuticals, Palo Alto, CA 94303.	Nu-Flow.
G. S. Herbert Laboratories, Irvine, CA 92664.	Vanseb Dandruff Shampoo, Vanseb-T Tar Shampoo.
H. B. Distributing Co., West Newton, MA 02165.	Hospital Brand Psoriasis Emulsion.
H. Clay Glover Co., Inc., Toms River, NJ 08753.	Glover's Imperial Medicated Ointment, Glover's Imperial Medicated Soap, Glover's Imperial Sarcoptic Mange Medicine, Rewocid SBU 185.
Hask, Inc. Toiletries, Great Neck, NY 10021.	Hask D.S.T. Treatment Shampoo, Hask Hair and Scalp Treatment.

Firms	Marketed products
Helene Curtis Industries, Inc., Chicago, IL 60639.	Enden Lotion Shampoo, Suave Dandruff Shampoo.
Hess Hair Milk Laboratories, Inc., St. Paul, MN 55117.	Hess Hair Milk.
Marion Laboratories, Inc., Kansas City, MO 64137.	Metasep Medicated Shampoo.
Max Factor, Hollywood, CA 90028.	Sebb Lotion.
Mitchum-Thayer, Inc., Tuckahoe, NY 10707.	Mazon Medicated Cream, Mazon Medicated Shampoo, Mitchum Dandruff Shampoo.
Neutrogena Corp., Los Angeles, CA 90045.	T/Gel Shampoo.
Plough, Inc., Memphis, TN 38151.	Sulfur-8 Hair and Scalp Conditioner.
Preston Pharmaceuticals, Inc., Butler, NJ 07405.	Dermakon Dandruff Shampoo.
Procter and Gamble, Cincinnati, OH 45202.	Head and Shoulders.
Purdue Frederick Co., Norwalk, CT 06856.	Betadine Shampoo.
Purex Corp., Ltd., Batavia, IL 60510.	Cuticura Ointment.
R. Schattner Co., Pharmaceuticals, Washington, DC 20016.	Chloraderm.
R. T. Vanderbilt Co., Inc., Norwalk, CT 06855.	Vancide 89 RE.
Reed and Carnrick, Kenilworth, NJ 07033.	Alphosyl Lotion Sebical Anti-dandruff Shampoo, Tarbonis.
Smith, Kline, and French Laboratories, Philadelphia, PA 19101.	Pragmatar.
Sterling Drug, Inc., New York, NY 10016.	Cradol, Double Danderine, Phisodan.
Stiefel Laboratories, Inc., Oak Hill, NY 12460.	Polytar Bath, Polytar Shampoo.
Syntex Laboratories, Inc., Palo Alto, CA 94304.	Methakote.
Texas Pharmacal Co., San Antonio, TX 78296.	Meted Cream Shampoo, Meted Lotion Shampoo, Meted-2 Cream Shampoo, Meted-2 Lotion Shampoo, Pentrax Tar Shampoo.
Warner-Lambert Co., Morris Plains, NJ 07950.	Listerine Antiseptic.
Westwood Pharmaceuticals, Inc., Buffalo, NY 14213.	Balnetar, Estar Therapeutic Tar Gel, Fostex Cream, Sebucare Scalp Lotion, Sebulex Conditioning Shampoo, Sebutone Antiseborrheic Tar Shampoo.
Whitehall Laboratories, New York, NY 10017.	Denorex Medicated Liquid Shampoo, Oxipor VHC Lotion.

The following submissions were also reviewed:

Source	Submission
American Cyanamid Co., Princeton, NJ 08540.	Bibliography of omadines.
Beecham Products, Inc., Clifton, NJ 07012.	Zinc pyrithione anti-dandruff hair groom.
Block Drug Co., Inc., Jersey City, NJ 07302.	Hydrocortisone alcohol and coal tar extract.
National Cancer Institute, Bethesda, MD 20205.	Bioassay of Selsun for Posssible Carcinogenicity.
Olin Corp., New Haven, CT 06511.	Zinc omadine.
Pennwalt Corporation, Rochester, NY 14623.	Hydrocortisone acetate and calcium undecylenate.
The Proprietary Association, Washington, DC 20006.	Coal tar products.
Whitehall Laboratories, New York, NY 10017.	Coal tar lotions.

B. Ingredients Reviewed by the Panel

1. *Ingredients contained in marketed products submitted to the Panel.*

Alcohol
Alkyl isoquinolinium bromide
Allantoin
Amino acid mix "B"
Beeswax
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Boric acid
Captan (*N*-trichloromethylthio-4-cyclohexene-1, 2-dicarboximide)
Cetyl alcohol
Cetyl alcohol-coal tar distillates [1]
Cholesterol
Coal tar
Coal tar extract
Coal tar solution
Colloidal oatmeal
Colloidal sulfur
Cresol
Crude coal tar extract
Crude tar extract
L-cysteine hydrochloride
Entsufon
Eucalyptol
Extract of coal tar
Extract of coal tar solution
Glycerin
Isopropyl palmitate
Juniper tar
Lanolin
Lanolin cholesterols
Lauryl isoquinolinium bromide
Liquid paraffin oil
Liquor carbonis detergens
Menthol
Mercuric oleate
D,L-Methionine
Methylbenzethonium chloride
Methyl salicylate
Micropulverized sulfur
Mineral oil
Mineral wax
N-trichloromethylmercapto-4-cyclohexene-1,2-dicarboximide
Oil of violet
One, three-dihydroxy, two-ethyl hexane
Oxyquinoline
Parachlorometaxylenol
Petrolatum
Phenol
Pine oil
Pine tar
Polyoxyethylene ethers
Povidone iodine
Precipitated sulfur
Rectified tar oil
Refined extract of coal tar
Resorcinol
Rose geranium oil
Salicylic acid
Selenium sulfide
Sodium borate
Sodium chloride
Sodium phenolate
Sodium salicylate
Solubilized coal tar extract
Solubilized crude coal tar
Standardized extract of coal tar
Standardized tar extract
Sublimed sulfur
Sugar of lead
Sulfur
Thymol
Vegetable oil
Zinc pyrithione
Zinc 2-pyridinethiol 1-oxide

2. *Other ingredients reviewed by the Panel.*

Benzyl benzoate
Calcium undecylenate
Hexachlorophene
Hydrocortisone acetate
Hydrocortisone alcohol
Lanolin oil
Polyethylene glycol derivatives
Undecylenic acid monoethanolamide sulfosuccinate, sodium salt
White petrolatum

C. Classification of Ingredients

1. *Active ingredients.*

Alkyl isoquinolinium bromide
Allantoin
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Borate preparations (boric acid and sodium borate)
Captan (*N*-trichloromethylmercapto-4-cyclohexene-1, 2-dicarboximide)
Chloroxylenol (parachlorometaxylenol)
Coal tar preparations (coal tar, coal tar distillate, coal tar extract, coal tar solution) (crude coal tar extract, crude tar extract, extract of coal tax, extract of coal tar solution, liquor carbonis detergens, refined extract of coal tar, solubilized coal tar extract, solubilized crude coal tar, standardized extract of coal tar, and standarized tar extract).
Colloidal oatmeal
Cresol
Ethohexadiol (2-ethyl-3-propyl-1, 3-propanediol)
Eucalyptol
Hydrocortisone preparations (hydrocortisone acetate and hydrocortisone alcohol)
Juniper tar
Lauryl isoquinolinium bromide
Menthol
Mercury oleate (mercuric oleate)
Methylbenzethonium chloride

[1] For the purpose of this document, these ingredients will be considered separately as cetyl alcohol and coal tar distillate.

Methyl salicylate
Phenol
Phenolate sodium (sodium phenolate)
Pine tar preparations (pine tar and rectified tar oil)
Povidone-iodine (providone iodine)
Resorcinol
Salicylic acid
Selenium sulfide
Sodium salicylate
Sulfur (colloidal sulfur, micropulverized sulfur, precipitated sulfur, and sublimed sulfur)
Thymol
Undecylenate preparations (calcium undecylenate and undecylenic acid monoethanolamide sulfosuccinate, sodium salt)
Zinc pyrithione (zinc 2-pyridinethiol 1-oxide)

2. *Inactive ingredients.*
Alcohol
Beeswax
Benzoic acid
Cetyl alcohol
Cholesterol
Entsufon sodium (entsufon)
Glycerin
Isopropyl palmitate
Lanolin
Lanolin cholesterols
Lanolin oil
Lead acetate (sugar of lead)
Mineral oil (liquid paraffin oil)
Mineral wax
Oil of violet
Oxyquinoline
Petrolatum
Pine oil
Polyethylene glycol derivatives
Polyoxyethylene ethers
Rose geranium oil
Sodium chloride
Vegetable oil
White petrolatum

3. *Other ingredients.* Amino acid mix "B," *D,L*-methionine, and cysteine hydrochloride (*L*-cysteine) are contained in a combination product submitted to this Panel for review as a result of the calls for data published in the Federal Register of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) that requested information on products to be reviewed as miscellaneous external drug products. The labeling of this product contained indications for "the treatment of, and as an aid in the prevention of diaper rash, cradle cap, and chafing of the infant skin."

The Panel is unaware of any evidence to demonstrate effectiveness of these ingredients in preventing or treating cradle cap. Therefore, the Panel concludes that these ingredients are Category II for this use and has not further discussed them in this document. The Panel's conclusions on these ingredients for use in diaper rash are included in a statement on OTC diaper rash drug products published in the Federal Register of September 7, 1982 (47 FR 39406, 39412, 39436, and 39464).

Benzyl benzoate and hexachlorophene were included in the call-for-data notice published on August 27, 1975 (40 FR 38179) as ingredients used in the treatment of cradle cap. The agency is aware of no data to demonstrate safety and effectiveness of benzyl benzoate for this use. Although hexachlorophene has been used in treatment of cradle cap in the past, present FDA regulations at 21 CFR 250.250 limit this ingredient to preservative use in concentrations no higher than 0.1 percent in OTC products because of safety considerations. Benzyl benzoate and hexachlorophene are placed in Category II by the Panel and will not be discussed further in this document.

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the Federal Register of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All the submitted information included in these volumes, except for those deletions which are made in accordance with confidentiality provisions as set forth in § 330.10(a)(2), will be put on public display after January 3, 1983, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Discussion

A. Anatomy and Physiology of the Skin and Scalp

The skin accounts for approximately 16 percent of the body weight of the average adult. It acts as a barrier, protecting against invasion of the body by outside organisms and preventing the escape of essential body fluids and electrolytes. It protects against damaging corrosives, cushions the effect of external injury, and resists the passage of electrical currents. The skin is composed of two mutually dependent layers, the epidermis and the dermis, which are cushioned on fat-containing subcutaneous tissue.

The conditions dealt with in this document involve the epidermis or outer skin layer—in particular epidermal cellular development and the shedding rate of dead epidermal cells. It is therefore important to examine the structure of the epidermis and the development of epidermal cells.

Epidermal cells are continuously formed in the basal layer (stratum germinativum) of the epidermis. From the stratum germinativum the columnar basal cell reproduces by mitotic division to form daughter cells, one or both of which begin an outward migration to the skin surface. The next layer of cells makes up the bulk of the epidermis and is called the prickle cell layer (stratum spinosum) because when a section of skin is prepared for viewing under a microscope, the cells shrink, but the intercellular attachments persist so that they appear to have prickles or spines. In the course of about 14 days, the mature epidermal cell flattens and acquires granules of keratohyalin that justify the name of the next layer, the granular layer (stratum granulosum) (Ref. 1). As the cell approaches the surface, it slowly dies. Its keratohyalin granules change to keratin, and it loses its nucleus to become part of the horny layer (stratum corneum), the outermost layer of the epidermis. As a result of wear and replacement from underneath, the dead epidermal cell is finally shed. Normally, this slough of skin is continuous and imperceptible. However, in dandruff, seborrheic dermatitis, and psoriasis, the rate of epidermal cell development is accelerated, and the shedding rate of these cells is excessive. The Panel's standard of effectiveness for OTC medications to control these conditions is the ability to permeate the skin barrier and control this excessive shedding or flaking.

The stratum corneum is not a completely unbroken surface, but is marked at intervals with openings to the pilosebaceous units and the eccrine glands (Ref. 1). Sweat is secreted through the eccrine glands located in the dermis, while the sebaceous glands, which along with hair follicles make up the pilosebaceous units, secrete sebum onto the skin. Sebum is a fatty substance that lubricates the skin and is thought to enhance the skin's function as a protective barrier.

Although the skin's function as a barrier has been stressed, it is not an impenetrable barrier. It is possible for external substances to be absorbed through the skin.

Several factors affect the absorption of substances through the skin:

1. *Skin thickness.* The skin on the scalp, the palms, and soles is thicker than that on other parts of the body and therefore less permeable. Eyelid and scrotal skin is generally the thinnest and most permeable (Ref. 2).

2. *Blood circulation to the skin.* The amount of blood circulating directly under the skin surface affects absorption. A person can absorb more of a chemical through cheek skin with its bed of underlying blood vessels than from the skin on the tips of the fingers or toes which have a smaller vascular bed.

3. *Temperature of the skin.* The higher the skin temperature, the greater the absorption through the skin.

4. *Hydration of the skin.* Accumulation of moisture on the skin seems to "open" the compactness of the stratum corneum, facilitating penetration of the barrier (Ref. 3).

The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, hereinafter referred to as the Topical Analgesic Panel, concluded in its report published in the **Federal Register** of December 4, 1979 (44 FR 69773) that the skin of a child older than 6 months of age is similar to that of an adult with respect to absorptive properties. That Panel also stated that it was unaware of any data demonstrating differences between geriatric skin and the skin of younger adults, but concluded that the skin of a geriatric patient may warrant special considerations. The Advisory Review Panel on Miscellaneous External Drug Products concludes that, to provide a margin of safety, the ingredients it reviewed—with the exception of those proven safe for use in treating cradle cap—are not to be used on children under the age of 2 years except under the advice and supervision of a doctor. This is because in very young children the amount of skin surface in proportion to body weight is greater than in older children and adults. Also, children under the age of 2 do not have fully developed hepatic enzyme systems for handling toxic substances that might be absorbed.

The scalp is the covering of the cranial part of the head. It is a five-layer structure consisting of the skin, connective tissue, aponeurotic layer (expanded tendon), loose connective tissue, and periosteal layer (fibrous membrane covering the entire surface of the bone). The skin is the outermost layer, with the connective tissue located immediately underneath.

The skin of the scalp is among the thickest found on the body. It contains numerous sweat and sebaceous glands and is held firmly to the layer beneath it by fibrous bands. The hair follicles extend deeply into the second layer of the scalp and are set close together (Refs. 4 and 5).

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B. Skin Disorders Involving Excessive or Abnormal Shedding of Dead Epidermal Cells From the Scalp and Body

The Panel provides the following table to summarize the basic similarities and differences between the four skin conditions discussed in this section:

DISTINGUISHING FEATURES OF DANDRUFF, SEBORRHEIC DERMATITIS, PSORIASIS, AND CRADLE CAP

Characteristic	Dandruff	Cradle cap	Seborrheic dermatitis	Psoriasis
Site	Scalp	Scalp	Scalp, face, and body (especially hairy areas, body folds, and behind ears.	Scalp and body (especially knees, elbows, low back, nails).
Borders	Indistinct	Indistinct	Indistinct	Very sharp.
Inflammation (Redness)	No	Yes	Yes	Yes.
Appearance of scales	Dry, grayish-white	Yellowish-brown, greasy	Greasy	Silvery scales which flake off in layers like mica.
Age of onset	Puberty	1 to 2 weeks after birth, up to termination of infancy.	Puberty	Young adulthood, as a rule, but can occur at any age.
Itching	Variable	Not known	Usual	Variable.
External factors that worsen condition.	Cold weather	Improper cleansing	Stress, poor health	Stress, mechanical irritation.
Rate of epidermal turnover	2X above the norm [1]	Not demonstrated	More than 2X above the norm [1]	Greatly increased above the norm (10–20X). [2]
Duration	Can persist for life—diminishing in middle and old age.	Usually clears in 3–4 weeks; can last up to 2 months.	Can persist for life—frequent exacerbations and remissions.	Can persist for life—exacerbations and remissions.

[1] Ackerman, A. B., and A. M. Kligman, "Some Observations on Dandruff", *Journal of the Society of Cosmetic Chemists*, 20:81–101, 1969.
[2] Goldschmidt, H., and A. M. Kligman, "Quantitative Estimation of Keratin Production by the Epidermis", *Archives of Dermatology*, 88:709–712, 1963.

1. *Dandruff.* The entire surface of the human skin sheds dead cells continuously at a rate which varies from site to site. Dandruff is a condition involving an increased rate of shedding from the scalp of dead epidermal cells. The scales are shed in large clumps. Normally the stratum corneum on the scalp consists of fully keratinized, closely packed cells, which have lost their nuclei, arranged in a orderly pattern. In dandruff, the increased shedding of skin causes this layer to have fewer cells, some of which still have nuclei, and these are in a disordered pattern. The scales appear dry, white, or grayish and are usually seen in small round patches especially on the crown of the head (Ref. 1). In some cases, these round patches may extend to cover the entire scalp. Occasionally itching is felt, but usually a person with dandruff complains only of unsightly scales (Refs. 2, 3, and 4).

The one visible manifestation of dandruff is scaling. Dandruff appears to be seasonal, being milder in the summer months and most severe from October through December. Cleaning the hair and scalp on a regular basis is often sufficient to control the symptoms of mild cases of dandruff.

Few cases of dandruff are seen betweeen the ages of 2 and 10 years, but the condition is common with the onset of puberty. The shedding of cornfied scales increases rapidly, peaking in the early twenties. Thereafter, the occurrence of dandruff diminishes in middle and old age. Dandruff occurs with the same frequency in both sexes (Refs. 3 and 5).

The cause of dandruff has not been clearly defined, but it is known to involve an increase in the rate of epidermal turnover. This rapid transit of cells to the surface does not allow for complete keratinization of new cells (Ref. 1). Older theories attribute the cause of dandruff to improper diet, hormone imbalance, or a vitamin B-complex deficiency (Ref. 5). One theory frequently discussed in the literature is that dandruff is caused by *Pityrosporum ovale*, a yeast-like fungus resident to the scalp (Refs. 5 through 9). Proponents of this theory support the use of

antimicrobials in controlling dandruff, but the Panel has concluded that there is not a definite correlation between the presence of *Pityrosporum ovale* and the development of dandruff. (See part II. paragraph C.1. below—*Antiseptics (antimicrobials).*)

Dandruff usually responds to treatment, but tends to relapse if treatment is discontinued. If dandruff is left untreated, the resulting problems are problems of appearance; no medical disability will result.

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2. *Seborrheic dermatitis.* In seborrheic dermatitis there is a greater increase in the turnover rate of skin cells than is seen with dandruff. This condition is also marked by inflammation and retention of nuclei in the skin cells (Ref. 1). While dandruff is strictly a disease of the scalp, seborrheic dermatitis occurs in other hairy areas of the body and inskin folds. This condition can be found on the scalp, eyebrows and eyelashes, in the external ear canal, behid the ears, in the nasal folds, midchest, armpits, between the shoulder blades, and in the pubic area and groin (Refs. 2, 3, and 4). These areas have the largest concentrations of sebaceous glands and the largest concentrations of bacteria and yeasts.

One theory is that excessive secretion of sebum (seborrhea) causes seborrheic dermatitis, possibly by providing a substrate of oil which bacteria and yeasts can metabolize into irritating substances such as free fatty acids. It has not been demonstrated, however, that seborrheic dermatitis is always accompanied by increased sebum production. In fact, according to Leyden, seborrheic dermatitis patients do not produce more sebum than age-matched controls (Ref. 5).

Cradle cap may be a form of infantile seborrheic dermatitis, which can involve the scalp, the skin behind the ears, the nasolabial fold, neck, armpits, unbilicus, and especially the diaper area (Refs. 6 and 7). It may also represent an accumulation of vernix caseosa (fatty substance covering the fetus) and scales that result from the mother's fear of washing the head over the fontanels. Cradle cap is a scaly inflammation of the scalp which is very common in the first week or two of life, but can occur any time during infancy. Cradle cap usually clears in a month and does not recur (Ref. 7). Some cases evolve into atopic dermatitis with itching, papulovesicles, and oozing, which spreads to the cheeks, forehead, and extensor surfaces of the extremities, as well as the scalp (Ref. 8). Obviously, conditions of this severity are not amenable to OTC therapy and require prompt treatment by a doctor.

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3. *Psoriasis.* Psoriasis is a chronic inflammatory disease of the skin characterized by well-defined pink or dull red lesions that are covered with silvery scales. The lesions may remain indefinitely, or the patient may experience frequent exacerbations and remissions (Refs. 1 through 8).

Approximately 1 to 3 million Americans are afflicted with psoriasis. The disease occurs more commonly in Caucasians than in Blacks.

Psoriasis is characterized by alterations in the epidermis which shows accelerated cellular turnover and swelling of the capillaries underneath. These alterations include an increase in thickness of the epidermis, retention of nuclei of the epidermal cells, and the absence of a granular layer (stratum granulosum). The rate of turnover of the cells in the epidermis is increased; that is, a basal cell may take only 3 to 4 days to keratinize and reach the stratum corneum instead of the normal 25 to 30 days.

Like seborreheic dermatitis, psoriasis occurs on the scalp and the body. A large amount of research has been devoted to this disease, but its cause is still unknown. It is a condition which may be genetically transmitted (Ref. 9). This condition is more apt to appear in both members of a set of identical twins than in both members of a set of fraternal twins. However, not everyone who inherits the genetic predisposition for psoriasis will develop the disease. If the disease does develop, it may manifest itself in a single lesion on the scalp, stubborn lesions on the elbows and knees, or redness and scaling of the entire body.

Environmental stimuli can provoke psoriatic eruptions in persons with a predisposition to psoriasis. Spread of a skin disease in response to external trauma is referred to as the Koebner reaction. As a result of a Koebner reaction, a psoriatic lesion will often appear at the site of a cut, burn, sunburn, or pre-existing rash. The lesion appears between 3 and 18 days (usually 10 to 14) after the initial trauma and is preceded or accompanied by changes in the capillaries. Internal streptococcal infections are also known to cause psoriasis, and certain medications taken orally such as antimalarials, lithium, and propranolol may exacerbate psoriasis (Ref. 9). Endocrine factors sometimes appear to play a role; for example, psoriasis often clears or improves during pregnancy, but may recur or appear for the first time after birth of the child. Emotional stress may also provoke psoriasis.

A questionnaire was circulated among individuals suffering from psoriasis to evaluate the factors they perceived as important in the behavior of the disease (Ref. 10). Of 1,000 persons, 77 percent

said that hot weather improved their condition, while 23 percent said that hot weather worsened it. Twelve percent indicated that cold weather made their psoriasis better, while 88 percent said cold weather made their psoriasis worse. In 14 percent, trauma was said to initiate the disease.

Other skin diseases may coexist or alternate with psoriasis, including seborrheic dermatitis. Lesions resembling psoriasis are not uncommon in seborrheic dermatitis, and differentiation between the two may be difficult (Refs. 11 and 12).

The diagnosis of psoriasis is aided by examining the fingernails and toenails. The hyperproliferation of the nail bed and disordered growth of the nail plate produce a distorted, thick, opaque, and crumbly nail. Pits and ridges of the nail are often found. Separation of the free end of the nail from its bed becomes marked.

Complications are uncommon in patients with psoriasis, but some have been reported. These include infection, sometimes as a result of occlusive corticosteroid therapy; eczematization, as a result of sensitization to topically applied agents; pustulation, including a pustular form of psoriasis associated with high fever and severe systemic symptoms; and arthritis.

There is no cure for psoriasis, but it is possible to reduce its severity. The various stages of the disease are treated by different methods. Because the barrier that normally prevents drug penetration to the skin is disrupted, psoriatic skin is more permeable to many medications than normal skin. In the early stages of treatment, the patient may therefore respond rapidly to topically-applied medications, but the improvement rate will slow as the skin barrier approaches a normal state (Ref. 13).

The Panel recommends that only mild cases of psoriasis be self-treated. Individuals with severe cases involving large areas of the body should seek professional treatment.

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C. Agents Marketed for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis

There are no definitive cures for dandruff, seborrheic dermatitis, and psoriasis. OTC drugs at best can only control these conditions with regular use. OTC agents submitted to the panel for control of dandruff, seborrheic dermatitis, and psoriasis can be generally classified into the following therapeutic categories: antiseptics (antimicrobials), keratolytics, cytostatics, corticosteroids, antipruritics, and tar preparations. Categorization is made somewhat complex, however, by the fact that two or more therapeutic effects may be attributed to some ingredients.

1. *Antiseptics (antimicrobials).* Since the origin of the germ theory of disease, microorganisms have been proposed frequently as causal factors in various scalp disorders. The hair is an efficient trap for particles, and conditions of the scalp are quite favorable for the growth of microorganisms. There are numerous sweat glands to supply moisture and sebaceous glands to secrete a variety of lipids.

The microbiology of dandruff was reviewed in a 1976 article by Priestley and Savin (Ref. 1), who stated that "Modern investigative techniques * * * have only scratched the surface of our understanding of dandruff, raising a cloud of conflicting ideas and reports." According to these authors, the question of microbial involvement in dandruff is still unsettled. The Panel agrees. Over 100 years ago, Malassez (Ref. 2) identified the yeast *Pityrosporum ovale* as a suspect in the mystery of dandruff etiology. Priestley and Savin pointed out that today there is general agreement that *Pityrosporum ovale* can be recovered from most, if not all scalps, normal or otherwise; thus it would not appear limited to occurrence in scalps with dandruff. They noted that, of the studies they had reviewed, all but one agreed that the aerobic bacterial flora of the scalp is dominated by coagulase negative micrococci (Ref. 1). The dissenting study was by Roia and Vanderwyk (Ref. 3), who found that only 57 percent of those with dandruff had any scalp bacteria at all, compared with 25 percent of those without dandruff. They found that the most prevalent bacterial species was *Bacillus subtilis* and that micrococci were virtually absent. McGinley et al. (Ref. 4) were baffled by these findings because their studies and most other studies with which they were familiar showed that aerobic cocci occur on all scalps, both normal and diseased.

In another 1976 article, Leyden, McGinley, and Kligman (Ref. 5) discussed the role of microorganisms in dandruff. Using quantitiative techniques, they examined the scalps of over 100 subjects, with and without dandruff. The following organisms were consistently found without regard to the presence or absence of dandruff: *Pityrosporum*, mainly *Pityrosporum ovale;* aerobic goagulase negative cocci; and *Propionibacterium acnes*. These comprise the majority of the resident microflora of the scalp. The quantity of *Pityrosporum ovale* in subjects with dandruff was almost twice that found in subjects free of dandruff. These authors also reported that there were no quantitative or qualitative differences in the number of coagulase negative cocci observed in the two groups. However, the anaerobic diphtheroid *Propionibacterium acnes* was significantly decreased in scalps with dandruff.

The authors concluded that to the best of their knowledge "* * * this is the first study in which the relationship between microorganisms and dandruff has been systematically investigated with quantitative techniques. The evidence implicates neither any particular organism nor any combination of organisms in the production of dandruff. In dandruff there was no change in the composition of the microflora; the only noteworthy difference is a greater quantity of *Pityrosporum ovale*." The authors did not find this greater quantity

meaningful. Leyden (Ref. 6) has suggested that the increased numbers of *Pityrosporum ovale* may be related to sebum materials trapped in the dandruff scales on which the microorganisms feed. He concludes that this yeast has no causal relationship to dandruff or seborrheic dermatitis.

The Panel recommends that antimicrobial agents be judged on their own merit with respect to control of dandruff. If such agents are shown in well-controlled double-blind clinical studies to be effective in the control of dandruff, they should be placed in Category I. Such classification should not in itself be taken as proof of any particular causal relationship in dandruff, however, because an ingredient may be capable of acting in more than one therapeutic manner. For example, an antimicrobial might also have keratolytic or cytostatic properties.

2. *Keratolytics.* These agents cause a peeling away of the stratum corneum, thus removing scales. The Panel believes that keratolytics probably act by dissolving the cement that holds the epidermal cells together, rather than dissolving keratin. Their beneficial action in dandruff, seborrheic dermatitis, and psoriasis is to loosen scales, enabling them to be washed off more readily. They do not prevent the scales from being formed.

3. *Cytostatics.* Use of cytostatics offers a direct approach to controlling dandruff. These agents reduce the rate of cell growth and multiplication and thereby increase the time involved in epidermal turnover. The production of dead cells, which in dandruff are shed in large flakes by the scalp, is correspondingly slowed, so that there is a dramatic decline in visible dandruff flakes.

4. *Antipruritics and corticosteroids.* The sensations of pain and itching are carried by the same nerve receptors and filaments. For this reason, a number of topical anesthetics are effective as antipruritics as well, and the Panel notes that ingredients in this class are sometimes used in dandruff, seborrheic dermatitis, and psoriasis products for their action in relieving itching. Corticosteroids also act as antipruritics, but have an additional anti-inflammatory effect and so have been suggested for OTC use for dandruff, seborrheic dermatitis, and psoriasis of the body and scalp. However, additional data are needed on the safety and effectiveness of corticosteroids for use in these conditions. (See part III. paragraph C.1.j. below—*Hydrocortisone preparations.*) The Panel believes that the temporary relief of itching does not amount to effective control of dandruff, seborrheic dermatitis, and psoriasis. Effective control of these conditions should involve control of the excessive shedding of epidermal cells which characterizes them.

5. *Tar preparations.* The mode of action of tar preparations in the treatment of skin disorders is unknown. It may be that tar preparations act as cytostatics, inhibiting cell reproduction. Or they may act as keratolytics, penetrating the epidermis and removing the scales produced in these skin disorders. The most widely used tar preparations for controlling dandruff, seborrheic dermatitis, and psoriasis are those derived from coal tar.

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D. Role of Vehicles in OTC Products Marketed for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis

Products for controlling dandruff, seborrheic dermatitis, and psoriasis of the scalp are marketed in the form of preshampoo preparations, intended to be applied to the scalp and left on for 5 to 20 minutes before shampooing; medicated shampoos; after-shampoo rinses; and hair dressings. Products for controlling seborrheic dermatitis and psoriasis occurring on the body are available in the form of ointments, creams, and lotions. In all these preparations, the role of the vehicle is extremely important, as the characteristics of the vehicle affect the rate and degree of the therapeutic ingredient's absorption.

Vehicles that damage the stratum corneum, such as detergents and solvents, can increase absorption. Vehicles that simulate the physiological characteristics of the skin can also increase absorption, as can vehicles that hydrate the skin and are the appropriate pH. A change in the pH of an applied solution influences absorption indirectly by altering the ionization of the compound. Ionization decreases the passage of chemicals through the stratum corneum.

Lipids and lipid-soluble substances pass easily through the skin, but small molecules that are both water- and lipid-soluble, are more easily absorbed. Certain nonaqueous vehicles promote absorption by structurally or chemically damaging the stratum corneum. Volatile solvents of low molecular weight such as ether, methanol, ethanol, and acetone, may damage the stratum corneum by extracting lipids.

Ionic and nonionic surface active agents, widely used in shampoos as emulsifiers and detergents, can damage the barrier layer of the skin in concentrations as low as 1 percent (Ref. 1). These surface active substances, known as wetting agents, lower the surface tension of water and promote wetting. By wetting the scalp these agents emulsify the sebum. There are several types of wetting agents: cationics, such as the quaternary ammonium compounds; anionics such as sodium lauryl sulfate and dioctyl sodium sulfosuccinate; and nonionic wetting agents, such as propylene glycol, sorbitan esters of fatty acids, and polyoxyethylene sorbitan esters of fatty acids.

Seborrheic dermatitis and psoriasis are conditions that in themselves damage the skin barrier, permitting increased absorption (Ref. 2). An occlusive ointment used as a vehicle can further increase this skin absorption by preventing the evaporation of perspiration. This moisture then collects under the occlusive substance and hydrates the stratum corneum.

References

(1) Scheuplein, R. J., and I. H. Blank, "Permeability of Skin," *Physiological Reviews*, 51:702–742, 1971.

(2) Malkinson, F. D., and L. Gehlmann, "Factors Affecting Percutaneous Absorption," *in* "Cutaneous Toxicity," edited by V. A. Drill and P. Lazar, Academic Press, Inc., New York, pp. 63–81, 1977.

E. Labeling

1. *General discussion.* In reviewing the labels submitted for the various products, the Panel noted that products containing the same ingredients were often promoted for different conditions, that is, for seborrheic dermatitis and psoriasis of the body and scalp and/or dandruff.

After reviewing and evaluating the available date, the Panel notes that ingredients that are effective in

controlling scalp psoriasis are usually effective in controlling dandruff and seborrheic dermatitis. Ingredients effective in relieving the symptoms of dandruff will also relieve the symptoms of seborrheic dermatitis (Ref. 1), but they may not be effective in treating scalp psoriasis.

Misdiagnosis of seborrheic dermatitis of the scalp as dandruff is not of great consequence because treatment is generally the same for both. However, dandruff is considered a relatively stable condition, whereas seborrheic dermatitis fluctuates in severity, often as a result of stress. Psoriasis calls for different treatment methods, but if the consumer treats psoriasis with an antidandruff preparation, no harm is likely to follow. The psoriasis will not be worsened, but it will probably persist, leading the consumer to seek professional diagnosis and treatment.

The Panel believes that mild cases of body seborrheic dermatitis and psoriasis may be amenable to self-diagnosis and self-treatment by consumers, and products to treat symptoms of these conditions should be available for OTC use. However, severe and unresponsive cases of seborrheic dermatitis and psoriasis should be treated by a doctor.

It is often difficult, however, even for a professional to distinguish between these conditions. The Panel believes that misdiagnosis of a mild case of body psoriasis as seborrheic dermatitis or vice versa is not of great consequence. If the condition does not respond to treatment or worsens, the consumer should seek professional advice and should be so advised in the warnings section of the labeling. Likewise, if the condition covers large areas of the body, the consumer should be advised to consult a doctor.

The Panel concludes that a product may be labeled for use in any one or more of these conditions, so long as the active ingredient or ingredients involved have been proven safe and effective in controlling each condition included in the labeling.

2. *Indications.* The indications for use should be simply and concisely stated. They should enable the consumer to clearly understand the results that can be anticipated from the use of the product and should be restricted to the conditions for which the ingredients of the product are safe and effective. No reference should be made or implied with respect to relief of any symptoms unrelated to these conditions.

a. The Panel recommends the following indications for products for the control of dandruff, seborrheic dermatitis, and psoriasis. One or more may be used, depending on the conditions for which the therapeutic ingredients of the product are proven safe and effective.

(1) *For products used for controlling dandruff.* "Relieves the itching and scalp flaking associated with dandruff."

(2) *For products used for controlling seborrheic dermatitis. "Relieves the itching, irritation, and skin flaking associated with seborrheic dermatitis" (select one or both of the following as appropriate: "of the scalp" and/or "of the body.")*

(3) *For products used for controlling psoriasis.* "Relieves the itching, redness, and scaling associated with psoriasis" (selected one or both of the following as appropriate: "of the scalp" and/or "of the body.")

b. The Panel recommends the following indication for products intended for controlling cradle cap: "Relieves scaly inflammation of the scalp associated with cradle cap."

3. *Ingredient labeling.* These products should contain only active ingredients plus such inactive ingredients as are needed for formulation. The label should state the concentration of each active ingredient.

The Panel recommends that all inactive ingredients be listed on the label because the consumer may need to know all the ingredients in view of the potential for allergic or idiosyncratic reactions. The label should not, however, imply or claim that the product's inactive ingredients have a therapeutic benefit.

4. *Warnings.* The Panel recommends that labeling of these products include the following warnings in addition to the general warning required by 21 CFR 330.1(g) and the warnings for specific ingredients as discussed in the ingredient write-ups later in this document:

(i) "For external use only."

(ii) "Avoid contact with the eyes—if this happens, rinse thoroughly with water."

(iii) "If condition worsens or does not improve after regular use of this product as directed, consult a doctor."

d. *For products used for controlling seborrheic dermatitis or psoriasis on the body.* "If condition covers a large area of the body, consult your doctor before using this product."

e. *For products other than those used to treat cradle cap.* "Do not use on children under 2 years of age except as directed by a doctor."

5. *Directions for use.* The directions for use should be clearly stated and provide the user with sufficient information to ensure safe and effective use of the product. The Panel believes that the labeling directions for products intended to control seborrheic dermatitis and psoriasis should state whether the product is to be applied to the scalp or to the affected area of the body. (See part III. paragraph A.2. below—*Category I labeling.*)

6. *Labeling describing product performance.* The Panel finds it unacceptable to use any claims related to product performance unless they can be substantiated by scientific data. Any claims such as, "fast," "quick," "long acting," "remarkable," etc. are considered to be misleading and may be confusing to the consumer unless they can be supported by adequate scientific data.

7. *Labeling descriptive of product attributes.* The Panel accepts the use of terms describing certain physical and chemical qualities of OTC products for controlling dandruff, seborrheic dermatitis, and psoriasis, as long as these terms do not imply that any therapeutic effort occurs. These terms should only pertain to product attributes or to the pharmaceutical elegance of the formulation.

The Panel believes that certain labeling claims are reasonable and informative to the consumer when they accurately reflect inherent characteristics of the marketed product. Terms such as "nongreasy," "does not stain," "does not soil clothes," "pleasantly scented," are acceptable.

In addition, the Panel recognizes that, depending on the ingredient, products also have been promoted to control the "oiliness" or "dryness" associated with dandruff, seborrheic dermatitis, and psoriasis. However, the Panel emphasizes that these terms should not be identified as indications for use. They are to be used in addition to the appropriate indications specified above.

Reference

(1) Kligman, A. M., K. J. McGinley, and J. J. Leyden, "The Nature of Dandruff," *Journal of the Society of Cosmetic Chemists*, 27:111–139, 1976.

III. Categorization of Data

For the convenience of the reader, the Panel provides the following summary of the categorization of active ingredients reviewed in this document:

CATEGORIZATION OF INGREDIENTS

Ingredient	Category	Uses [1]
Alkyl isoquinolinium bromide.	III	D
Allantoin	III	D, S, P
Benzalkonium chloride	III	D
Benzethonium chloride	III	D, C
Benzocaine	II	P
Borate preparations	II	D, S
Captan	III	D

CATEGORIZATION OF INGREDIENTS—Continued

Ingredient	Category	Uses [1]
Chloroxylenol	III	D, S
Coal tar preparations	I, III [2]	D, S, P
Colloidal oatmeal	II	D
Cresol	II	P
Ethohexadiol	III	D
Eucalyptol	III	D
Hydrocortisone preparations.	III	D, S, P
Juniper tar	III	D, S, P
Lauryl isoquinolinium bromide.	III	D
Menthol	III	D, S, P
Mercury oleate	II	P
Methylbenzethonium chloride.	III	C
Methyl salicylate	III	D
Phenol and phenolate sodium.	III	S, P
Pine tar preparations	III	D, S, P
Povidone-iodine	III	D, S
Resorcinol	II	P
Salicylic acid	I	D, S, P
Selenium sulfide	I	D
Sodium salicylate	III	D, S
Sulfur	I	D
Thymol	III	D
Undecylenate preparations.	III	D, S, P
Zinc pyrithione	I	D, S

[1] C=Cradle cap, D=Dandruff, S=Seborrheic dermatitis, P=Psoriasis.
[2] Category I for use in a shampoo only. Category III for other uses.

A. Category I Conditions

These are conditions under which active ingredients used for controlling dandruff, seborrheic dermatitis, and psoriasis are generally recognized as safe and effective and not misbranded.

1. *Category I active ingredients.*

Coal tar preparations (in shampoos)
Salicylic acid
Selenium sulfide
Sulfur
Zinc pyrithione

a. *Coal tar preparations (coal tar USP, coal tar distillate, coal tar extract, coal tar solution).* The panel concludes that coal tar preparations are safe and effective for OTC use as shampoos for controlling dandruff and seborrheic dermatitis and psoriasis of the scalp.

Although "tars" have been used for thousands of years to treat skin disorders, downing and Bauer (Ref. 1) cite Becher and Serle as being credited with the discovery and description of coal tar in 1681. The United States Pharmacopeia (USP) defines coal tar as "The tar obtained as a by-product during the destructive distillation of bituminous coal" (Ref. 2). A blackish-brown viscous liquid with a characteristic naphthalene odor, it is a mixture of tar acids and hydrocarbons which polymerize at high temperatures to form some 10,000 different compounds (Ref. 3). Coal tar consists generally of 2 to 8 percent light oils (benzene, toluene, and xylene), 8 to 10 percent middle oils (phenols, cresols, and naphtalene), 8 to 10 pecent heavy oils (naphthalene and derivatives), 16 to 20 percent anthracene oils (predominantly anthracene), and about 50 percent pitch (Ref. 4). The physical and chemical composition of coal tar varies depending on the geographical source of the coal and the temperature and efficiency of the coke ovens (Ref. 5).

The specifications for coal tar in the official compendia are not particularly selective in that they permit coal tar to be used in medicine regardless of source. The reason for the omission in the selectivity of the monograph is that it has not yet been shown that there is any difference in the therapeutic activity of the different coal tars that meet the required specifications (Ref 1). The Panel is aware of a Joint Industry Coal Tar Project the objective of which is to develop a standard of quality that will lead to an effective, uniform coal tar product with the smallest quantity of undesirable components. The panel commends the industry's efforts in this regard and urges continued research in this area.

Crude coal tar is often further modified or refined into coal tar extract, coal tar solution, and coal tar distillate. Although differences in therapeutic activity have not been demonstrated when crude coal tars from various sources have been used, it is believed that the degree of refinement of coal tar is responsible for variation in therapeutic effectiveness of the different coal tar products (Ref. 6). Because of the differences in therapeutic activity between the various coal tar preparations, the Panel has reviewed and made recommendations on each specific coal tar preparation.

When crude coal tar, which is of complex and unknown composition, is refined by various methods, with the aim of obtaining a more acceptable esthetic and pharmaceutically practical product, the pharmacologically active components in the final product may be altered qualitatively and quantitatively.

It was pointed out by Obermayer and Becker (Ref. 7) that one should not lose sight of the possibility that none of the constituents of coal tar exist as such in coal and that tar is not, in the true sense, distilled from coal. Tar actually results from condensation of the liquid products of decomposition of coal by heat. These investigators redistilled crude coal tar (that had been previously distilled at 800° F) under vacuum and collected fractions at three different temperatures as well as the pitch that remained after distillation. They also separated crude coal tar by extraction with dibutyl ether into ether-soluble and ether-nonsoluble portions. When tested on psoriasis patients, each of these fractions from crude coal tar had an effect similar to that of crude coal tar, but was less effective than that produced by the whole coal tar. Steam distillation was employed by Nelson and Osterberg (Ref. 8) to fractionate crude coal tar, and the distillate was extracted with ether. When the ether-soluble material was employed in an ointment to treat 12 cases of infantile eczema, it was found to be as effective as the ointment made with the original crude coal tar. In addition, the purified product did not produce folliculitis. On the other hand, Jaffrey (Ref. 9) fractionated crude coal tar by distillation and reported that some fractions seemed to have no therapeutic value.

Coal tar distillate can also be obtained by distilling tar with an aromatic hydrocarbon solvent and consists of all the volatile products of the tar freed from the pitch. It is a dark, brownish-red, fairly mobile liquid with a penetrating odor (Ref. 3).

A coal tar solution is obtained by mixing coal tar with washed sand, polysorbate 80, and alcohol, and macerating the mixture for 7 days, then filtering (Ref. 10). Coal tar solution is often referred to as liquor carbonis detergens.

Coal tar extract is similar to coal tar solution except that other solvents are used to extract the various components from coal tar.

(1) *Safety.* Several acute oral toxicity studies have been conducted in mice using various forms of coal tar (Refs. 11, 12, and 13). For crude coal tar and coal tar extract, the oral LD_{50} was reported to be between 5 to 10 milliliters per kilogram of body weight (mL/kg). The oral LD_{50} of coal tar solution was estimated to be 14.5 mL/kg (Ref. 14).

In an ocular irritation study using 0.1 mL of coal tar in the eyes of rabbits, coal tar was shown to produce only minimal irritation (Ref. 11). The results of a dermal irritation study in rabbits showed that coal tar produced a primary irritation index of 2.8 out of a maximum of 8. The irritation consisted of redness with little or no swelling. These studies are consistent with the reports of Muller and Kierland (Ref. 15) and Sax (Ref. 16) who reported coal tar to be only slightly irritating. Muller and Kierland (Ref. 17) considered 2 percent crude coal tar with 1 percent polysorbate 20 in petrolatum to be only slightly toxic when applied to the body. Long-tern use of strong coal tar preparations may produce a painless, chronic folliculitis (tar acne), which is reversible when the coal tar is discontinued (Ref. 18) and may be avoided by leaving the treated area exposed, not using the product on hairy

areas, and avoiding the use of coal tar for extended periods of time.

Adverse reactions to coal tar are more frequently seen with crude coal tar than with its derivatives (extracts, fractionates, distillates, and spirits). The adverse reactions consist mainly of the folliculitis described above and an allergic or irritant contact dermatitis. Coal tar has an odor, frequently stains the skin and hair (especially in patients with blonde, bleached, or gray hair), and should be applied carefully to the affected area only.

Coal tar has also been shown to produce photosensitivity reactions (Refs. 19 and 20). Because of this tendency, it should not be used to treat such disorders as lupus, erythematosis, polymorphous light eruptions, etc., and the patient should be cautioned about sun exposure up to 24 hours after using a coal tar product.

Adverse effects following the application of a crude coal tar ointment to 95 percent or more of the body surface were studied in 12 patients, 9 of whom had severe atopic dermatitis and 3 of whom had psoriasis (Refs. 11 and 17). The age range was 20 to 67 years. Treatment consisted of applications of the ointment twice daily, together with gradually increasing ultraviolet exposure from a quartz lamp. Liver and kidney functions tests were performed before application of the ointment and 2 to 3 weeks after treatment. A urinalysis was done twice a week. Ten patients tolerated the ointment well and had excellent clinical response. There was no evidence of renal or hepatic injury, and no phenolic substances could be found in the urine. Temporary mild diarrhea in one patient on the second and third day of treatment was the only adverse effect noted. Two of the patients did not tolerate the ointment and were dropped from the study.

One of the major concerns regarding the topical use of coal tar is its potential for causing cancer. It is generally accepted that coal tar contains carcinogenic substances. Recent biochemical studies indicate that medicinal coal tars contain different carcinogens but in uneven concentrations. The carcinogens are produced in coking ovens during the heating of the coal which liberates organic free radicals, the cancer-causing entities (Ref. 5). The higher the temperatures in the coking ovens (1,000° C and above), the greater and more varied is the production of free radicals. The smaller free radicals combine to produce polynuclear hydrocarbons, which are generally recognized as the primary carcinogens in coal tar. At least 75 polynuclear hydrocarbons have been identified in coal tar (Ref. 21).

Skin cancer has been linked to chronic exposure to concentrated solutions of topical coal tar in industrial settings. It is important to note that the average exposure time in these cases has been measured to be from 20 to 24 years.

A number of animal studies confirm the carcinogenic potential of coal tar. Horton (Ref. 22) applied 10, 50, or 100 milligrams (mg) of crude coal tar to the skin of mice twice weekly. Almost all of the surviving mice developed skin carconomas in direct proportion to the quanitity of tar applied.

Wallcave et al. (Ref. 23) evaluated coal tars with known polynuclear hydrocarbon content in a study done with ICR Swiss mice. Thirty-one carcinomas and 22 benign tumors developed in the 58 mice studied. Hilfrich and Mohr (Ref. 24) applied two drops of 5 percent crude coal tar in dimethylsulfoxide to mice twice weekly. All animals that survived for 12 months developed carcinomas. Rasmussen (Ref. 5) concluded that the animal studies "suggest that tar contains carcinogens and that these noxae [poisons] are present in commercially used products in sufficient concentrations to cause benign and malignant neoplasia when applied to the skin of test animals in a fashion that parallels human medicinal uses."

Sir Percivall Pott (Ref. 25) is generally credited with the first recorded observation of environmental carcinogenesis. In 1775 he published his findings that chimney sweeps who started working at a very early age and continued working through puberty developed scrotal cancer. The cancer-causing ingredients were attributed to the soot and coal tar that lodged in their clothes. Further discussion in the published literature of cancer induced by occupational exposure to coal tar has been reported by Hoffman (Ref. 21).

In 1966 Greither, Gisbertz, and Ippen (Ref. 26) reviewed the literature for the possible occurrence of cancer in patients treated with coal tar since 1900. Only 13 cases of skin cancer attributable to coal tar use were reported, and, of these 13 patients, 2 had also been treated with arsenic. The majority of these patients developed cancer in the anogenital area, however, and for this reason, in addition to Pott's observations, the Panel believes it important to require a warning against application to this area for coal tar products that may be marketed for control of psoriasis on the body.

Data, reported and included as part of the Third National Cancer Survey on patients using coal tar, indicate that the incidence of skin cancer in patients treated with coal tar ointment is not significantly increased above the expected incidence of skin cancer for the general population (Ref. 27). Farber (Ref. 28) suggests that it is possible that psoriasis selectively protects against cancer of the skin.

After a review of all available data, the Panel concludes that coal tar preparations are safe for topical use when formulated in shampoos for use on the scalp. The Panel recognizes the concern regarding carcinogenic potential of topically-applied coal tar preparations, but believes that the contact time of a shampoo is of such short duration that this concern should not prevent such use of coal tar on the scalp. However, because in the treatment of body seborrheic dermatitis and psoriasis the coal tar preparation is intended to remain on the skin for prolonged periods of time and to be used chronically, the risk of cancer development cannot be dismissed. Although the available information, including followup studies on patients treated with a combination of crude coal tar ointment and ultraviolet light, does not indicate an increased incidence of skin cancer in psoriatic patients treated with coal tar, the Panel concludes that more studies are needed to determine the risk. (See part III. paragraph C.l.g. below—*Coal tar preparations (coal tar USP, coal tar distillate, coal tar extract, coal tar solution).)* The Panel recommends that coal tar preparations remain available for OTC use while these studies are in progress and regular reports are being provided by industry and the scientific community to the agency. The Panel also believes that the pharmaceutical industry should strive to develop safer tars that are still therapeutically active.

(2) *Effectiveness.* Coal tar and coal tar preparations have long been considered rational therapy for many skin disorders, including dandruff, seborrheic dermatitis, and psoriasis, as coal tar reduces the number and size of epidermal cells produced (Ref. 29). However, the actual mechanism by which coal tar exerts this therapeutic effect is still unknown. Several theories have been proposed. It may be that, once applied, coal tar takes oxygen from the skin, thereby inhibiting cell reproduction and resulting in a decrease in size and number of cells. It may also be that coal tars formulated in various soaps and shampoos have value in treating dandruff, seborrheic dermatitis,

and psoriasis, by penetrating the epidermis and removing the scales produced in these skin disorders (Ref. 30). Possibly some of the polyphenolic substances and perioxides in coal tar react with epidermal sulfhydryl groups to produce an effect on the skin similar to that resulting from exposure to the sun (Ref. 31). This theoretically decreases epidermal proliferation and dermal infiltration.

In addition to decreasing the number and size of cells produced, coal tar also has vasoconstrictive, astringent, antibacterial, and antipruritic properties.

Patient acceptance of crude coal tar is very poor because it is extremely messy, smelly, and stains skin and hair. In order to reduce these cosmetically troublesome properties, coal tar was initially compounded into lotions, shampoos, bath oils, and liniments. More recently manufacturers have tried to refine crude coal tar into more cosmetically acceptable fractionates, distillates, liquors, filtrates, or tinctures, which exhibit a wide range of therapeutic activity (Ref. 32). Another modification of crude coal tar is an emulsion colloid of coal tar in an emollient vehicle equivalent to about 5 percent crude coal tar. The tar gel not only appears to deliver the beneficial elements of crude coal tar, but does so in a form that is convenient to apply and that is cosmetically acceptable (Ref. 33).

Another approach to an acceptable product for the treatment of dandruff, seborrheic dermatitis, and psoriasis of the scalp has been the employment of crude coal tar derived from anthracite coal. It was first employed by Combes in 1947 (Ref. 34) for the treatment of a variety of dematoses including seborrheic dermatitis and psoriasis. Satisfactory results in the treatment of seborrheic dermatitis and psoriasis were claimed also by Silver, Bereston, and Scham in 1955 (Ref. 29) with a preparation containing crude coal tar produced from anthracite under standardized conditions. The tar was micronized during the manufacturing process, which permits a stabilized colloidal solution to be prepared. Additional satisfactory results were published in 1980 by Olansky (Ref. 33) who found the preparation cosmetically acceptable for use in shampoos and baths for the treatment of dandruff, seborrheic dermatitis, and psoriasis. This coal tar preparation contains 1 percent micronized whole crude coal tar that is water-dispersible in addition to possessing all of the components of the crude coal tar.

It is generally accepted that the more coal tar is refined, the less effective it is. There are no data in the literature to show that there is a refined coal tar superior to or even equal in clinical effect to crude coal tar (Ref. 32). The diversity of composition of fractions of crude coal tar prepared by official methods and suggested methods for quality assurances were described by Gruber, Klein, and Foxx (Ref. 35).

Although coal tar preparations are widely prescribed and used, there are few well-controlled studies documenting the effectiveness of coal tar in dandruff, seborrheic dermatitis, and psoriasis. Many of the studies that have been done used products containing coal tar in addition to other active ingredients, and most were not placebo-controlled.

One study compared a shampoo containing a 5-percent coal tar solution to an identical shampoo without the coal tar solution for use in dandruff (Ref. 36). One hundred subjects were examined to obtain baseline scores for severity of dandruff. Half of the subjects were then instructed to use the shampoo without coal tar and the other half the coal tar shampoo once a week for 8 weeks. The subjects then returned for a reevaluation of their dandruff conditions. Statistical analysis showed no significant difference between the two shampoos (Ref, 37).

In one study, a 5-percent coal tar extract shampoo was compared to a placebo shampoo vehicle without coal tar for effectiveness (Ref. 38). A pretrial baseline was established by using a detergent shampoo. The products were compared in the treatment of common dandruff and "dandruff associated with seborrheic dermatitis of the scalp." Subjects were chosen because they felt they has a significant amount of dandruff. A detergent shampoo was used for a period of 2 weeks after which subjects were evaluated for adherent and loose dandruff on five scalp areas. A total of 105 subjects with moderate to severe dandruff was examined and assigned to treatment groups. The subjects were instructed to shampoo twice weekly and return for scoring at 2 and 4 weeks after the baseline visit. They received written directions to wet the hair thoroughly, rub the product liberally into hair and scalp, rinse thoroughly, briskly massage a second application of the product into a rich lather, and rinse thoroughly. The actual amount of product used in each shampooing or duration of contact of the scalp with the shampoo, was not specified. Five days after the fourth (2 weeks) shampooing, the subjects were scored for dandruff severity by a technician and after the eighth (4 weeks) shampooing, the subjects were scored by a technician and a dermatologist. The data provided in the report stated that the technician found the placebo preparation caused a decrease in dandruff score of 10.5 percent, whereas the dermatologist rated this figure at 28 percent. The technician found the shampoo containing the coal tar extract caused an average decrease of 32 percent, and the dermatologist found a 47-percent decrease. Statistical analysis of the differences between the median scores was carried out by nonparametric methods. The product containing the coal tar was statistically more effective in reducing total dandruff scores than the placebo preparation at a 99.9-percent confidence level, whether scored by the technician or the dermatologist. During the study, subjects were observed for evidence of primary irritation, allergic contact dermatitis, and phototoxicity. Adverse reactions for both preparations were limited to subjective descriptions of mild stinging of the skin. No objective adverse reactions were noted.

The results of the study were examined by an independent statistician (Ref. 37) who concluded that while the scoring by the technician indicated that the shampoo containing the coal tar extract was significantly better than its vehicle, the scoring of the same results by a dermatologist did not indicate a significant difference.

A randomized, doubler-blind, placebo-controlled study was conducted to evaluate a product containing 7.5 percent coal tar solution and 1.5 percent menthol in the treatment of scalp psoriasis (Ref. 39). Fifty-three subjects were instructed to use an assigned shampoo (25 used a nonmedicated shampoo, and 25 used the coal tar shampoo) every other night for the first 2 weeks and twice a week thereafter for the next 4 weeks. Three subjects did not follow the prescribed course of treatment and were dropped from the evaluation. The results of the study indicated that the coal tar and menthol product provided statistically significant relief of the redness, itching, and scaling associated with the scalp psoriasis. The Panel notes that coal tar was used on the more severe cases of psoriasis. The placebo group demonstrated a worsening of all symptoms except for scaling, which remained stable throughout the course of the study. While this study indicates the combination of coal tar and menthol to be effective in relieving scalp psoriasis, the contribution of the individual ingredients was not assessed.

Submissions containing crude coal tar solution in various concentrations were submitted to the Panel (Refs. 40 through 47). The concentration of coal tar

solution varied from 0.01 to 48.5 percent. In no instance was it shown that the coal tar solution was effective in controlling dandruff or psoriasis of the scalp. It was pointed out by Gruber, Klein, and Foxx (Ref. 35) that the coal tar solution does not contain 20 percent coal tar, as an undetermined amount of insoluble components of the tar are filtered out of the suspension in preparing the solution. It was emphasized that none of the coal tar solution and extract samples actually contained the labeled amount of 20 percent coal tar. The 20-percent figure is based on the amount of crude coal tar initially added to the ethanol, sand, and polysorbate 80, and not the amount of coal tar remaining in the extract after filtration. Approximately 7 percent tar "fractions" are found in coal tar solution after extraction.

Olansky (Ref. 33) conducted a 16-month clinical study to evaluate the effectiveness of a 1-percent colloidal crude coal tar shampoo in the treatment of dandruff, seborrheic dermatitis, and scalp psoriasis.

Forty-nine subjects, men and women aged 10 to 70, were directed to wash their hair and scalp twice weekly for 8 weeks. Examinations by a physician were recorded initially and after 1, 2, 4, and 8 weeks.

The results showed that each dermatosis treated with this coal tar shampoo responded well, with either substantial improvement, control, or complete clearing at the end of 8 weeks.

A tar shampoo containing 8.75 percent special crude coal tar extract was evaluated to determine its effectiveness in the treatment of seborrheic dermatitis (Ref. 48). Fifty-six subjects were used in the uncontrolled study. They were instructed to shampoo three times a week for 2 weeks. The shampoo was rinsed out after the first shampooing, reapplied, lathered in again, and allowed to remain on the scalp for 5 minutes. This was followed by a thorough rinsing. No other topical treatments were used.

The study showed that 51 of the 56 subjects had good to excellent results. Two subjects had fair results; three showed no improvement.

The Panel reviewed four submissions containing extracts of crude coal tar. One product (Ref. 11) contained 5.7 percent crude coal tar extract said to be equivalent to 2.5 percent crude coal tar. No data were presented to show that the tar extract was better than its vehicle in the treatment of psoriasis. Two submissions for the same product (Refs. 12 and 49) contained a tar extract prepared by double extraction of crude coal tar using a nonionic emusifier solvent followed by an aqueous alcohol solvent. The insoluble carbon particles and pitch are filtered out. A concentration of 0.3 percent of these crude coal tar components in the finished products was estimated to be equivalent to at least 5 percent crude coal tar. The effectiveness of these two products in controlling dandruff was not tested and no data were presented to show that these tar components were significantly better than the vehicle for self treatment of psoriasis. A third product (Ref. 13) contained 1.5 percent of a tar extract said to be a polyoxyethylene lauryl ether extract of coal tar equivalent to 0.5 percent crude coal tar. No data were presented to show that this tar extract was more effective than its vehicle in controlling dandruff and psoriasis.

Cetyl alcohol-coal tar distillate represents another attempt to use a more acceptable portion of crude coal tar. It was contained in one submission made to the Panel (Ref. 14) but was in combination with sulfur and salicylic acid. No controlled studies were presented to show that this component of coal tar is effective in the control of dandruff, seborrheic dermatitis, and psoriasis.

Still another attempt to use a more acceptable fraction of crude coal tar was a "refined fraction." One submission (Ref. 47) was received by the Panel but the "refined fraction" in a concentration of 0.3 percent was one of four tar preparations in the shampoo and no evidence was presented to show that this fraction of crude coal tar was effective in controlling dandruff.

It was concluded that this tar preparation was clinically effective in the treatment of seborrheic dermatitis; that is, it reduced the clinical manifestations of seborrheic dermatitis and substantially reduced corneocyte and yeast counts. No adverse reactions were reported, although five patients found the tar odor offensive. No patients reported discoloration or staining of the hair.

Young (Ref. 50) conducted a double-blind, paired-comparison study to evaluate various coal tar preparations in treating body psoriasis. All patients were treated in a hospital for at least 2 weeks, and an evaluation was then made. In 14 patients, a 20-percent coal tar solution in a zinc oxide paste was compared with the zinc oxide paste alone. The results showed that in four patients the coal tar ointment was superior. In 10 patients the effects of the coal tar ointment and the ointment base alone were equal. The author concluded that the 20-percent coal tar in zinc oxide paste was better than zinc oxide paste alone in treating psoriasis.

In the same study, 20 percent coal tar zinc oxide paste was compared with 5 percent coal tar in zinc oxide paste in 17 patients; in 14 patients, 20 percent coal tar in a vehicle of lanolin and soft paraffin was compared with 5 percent coal tar in the same vehicle. It was concluded that the 20-percent coal tar preparations and the 5-percent coal tar preparations were equal in therapeutic effect, regardless of vehicle (Ref. 50).

A comparison in 11 patients of a 5-percent coal tar solution and a 1-percent coal tar solution, both formulated in zinc oxide paste, showed that the 1-percent solution gave superior results in one patient. No difference between the two concentrations was seen in 10 patients. When the same percentages of coal tar were formulated in a lanolin and soft paraffin base and used on seven patients, the test preparations showed equal effects. A final comparison between the 1-percent coal tar solution formulated in zinc oxide, in lanolin and soft paraffin, and the bases alone showed that the 1-percent coal tar in each of these bases was statistically no better than the bases alone (Ref. 50).

The Panel concludes that the coal tar preparations identified below are effective in controlling dandruff, seborrheic dermatitis, and psoriasis. The Panel concludes that these preparations are safe when applied as shampoos for use on the scalp, but data are insufficient to demonstrate safety of coal tar when applied to the scalp for a longer period of time than shampooing requires or when applied on the body. Therefore, the Panel classifies coal tar in Category III for any use other than shampooing the scalp.

(3) *Dosage.* For topical use as a shampoo in the following concentrations: Coal tar distillate, 4 percent; Coal tar extract, 2 to 8.75 percent; Coal tar solution, 2.5 to 5 percent; Coal tar USP 0.5 to 5 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described below. (See part III. paragraph A.2. below—*Category I labeling.)*

In addition, the Panel suggests that manufacturers include in labeling a cautionary statement to the effect that products containing coal tar may stain light-colored hair.

The Panel also recommends the following warnings for coal tar-containing products for use on the body in the event that such products are reclassified in Category I:

(a) "Use caution in exposing skin to sunlight after applying this product. It

may increase your tendency to sunburn for up to 24 hours after application."

(b) "Do not use this product in or around the rectum or in the genital area or groin except on the advice of a doctor."

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b. *Salicylic acid.* The Panel concludes that salicylic acid is safe and effective for OTC topical use for controlling seborrheic dermatitis of the body and scalp, psoriasis of the body and scalp, and dandruff.

Salicylic acid (2-hydroxybenzoic acid) occurs as acicular crystals or as a crystalline powder. It is found principally in wintergreen leaves and in the bark of sweet birch, can be made synthetically, and gradually discolors in sunlight. One gram (g) is soluble in 460 mL water, 3 mL acetone, 2.7 mL alcohol, 42 mL chloroform, 3 mL ether, about 60 mL glycerol, and 52 mL oil of turpentine. The pH of a saturated aqueous solution is 2.4. It is used topically mainly for its keratoplastic activity (correction of abnormal keratinization) in low concentrations, its keratolytic activity (causing peeling of the skin) in higher concentrations, and its antifungal and antibacterial activities (Ref. 1).

(1) *Safety.* Salicylic acid and its derivatives are used as analgesics, antipyretics, fungistatics, keratolytics, rubefacients, and anti-inflammatory agents.

Salicylic acid softens and destroys the stratum corneum by increasing water concentration, probably as a result of lowering the pH, which causes the horny layer of the skin to swell, soften, and then shed. Damage to normal skin has been associated with its overuse.

Systemically, salicylic acid and its compounds produce a variety of reactions in man which are collectively called "salicylism." The early symptoms of salicylism, which may begin when the plasma salicylate level is as low as 12.2 mg/100 mL, are erythema, ringing in the ears, deafness, nausea, and vomiting. The more severe reactions, which may appear when the plasma salicylate levels range from 40 to 50 mg/100 mL, include severe drowsiness, confusion,

euphoria, difficulty in breathing, and hemorrhage (Ref. 2).

The Panel notes that OTC products containing salicylic acid for the control of dandruff, seborrheic dermatitis, and psoriasis are marketed in concentrations varying from 1.8 to 3 percent. The Panel concludes that, because of the relatively weak concentration and the method of use of these products, there is no potential for toxic effects to occur from percutaneous absorption.

(2) *Effectiveness.* Most salicylic acid products on the OTC market for topical use contain this ingredient in combination with other ingredients (Refs. 3 through 21). Consequently, few studies have been conducted on salicylic acid as a single ingredient for topical use.

The Panel is aware of a recent double-blind study in which 2 percent salicylic acid, 2 percent sulfur, and a combination of sulfur and salicylic acid (2 percent each) were tested against a vehicle for controlling dandruff (Ref. 3). Forty-eight subjects were included in the 5-week study. The products were used under supervision twice a week. Clinical grading of dandruff was on a scale from 0 to 10, and weekly corneocyte counts were made. A significant reduction in both the clinical grade of scaling and corneocyte count was reported for salicylic acid as compared to the vehicle control.

The Panel is aware of only one other study in which salicylic acid was evaluated as a single ingredient in the control of dandruff (Ref. 4). Four different preparations were included in the study: 2 percent sulfur in combination with 2 percent salicylic acid, 2 percent sulfur in combination with 2 percent salicylic acid in a protein formulation, 2 percent sulfur combined with 2 percent salicylic acid and 0.5 percent coal tar, and 1.8 percent salicylic acid in a lotion vehicle intended for daily application. Ten subjects with a minimum degree of scaling (score of 5 or greater on a 10-point scale) were assigned to each formulation. Evaluations were made at 3 and 6 weeks. The study demonstrated that the salicylic acid lotion preparation showed statistically significant reductions in both clinical grade and corneocyte counts at both 3 and 6 weeks.

All other studies reviewed by the Panel were conducted using salicylic acid in combination with other ingredients (Refs. 5 through 21). The Panel's evaluations of combination products are discussed elsewhere in this document. (See part III. paragraph D. below—Combination Products.) Although the studies mentioned above were limited to concentrations of 2 percent salicylic acid, the agency recognizes that products submitted to the Panel for review contained from 1.8 to 3 percent salicylic acid. The Panel previously reviewed salicylic acid in its report on OTC corn and callus remover drug products published in the **Federal Register** of January 5, 1982 (47 FR 522) and concluded that at concentrations above 1 percent this ingredient has keratolytic action on the skin. Because the effect of salicylic acid in dandruff, seborrheic dermatitis, and psoriasis is due to its keratolytic action in removing scales, the Panel concludes that salicylic acid is effective for controlling seborrheic dermatitis and psoriasis of the body and scalp and dandruff.

(3) *Dosage.* For topical use in concentrations of 1.8 to 3 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described below. (See part III. paragraph A.2. below—*Category I labeling.*)

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c. *Selenium sulfide.* The Panel concludes that selenium sulfide is safe and effective for OTC topical use for controlling dandruff.

Selenium sulfide, also referred to as selenium disulfide, is a bright orange powder prepared from selenious acid and hydrogen sulfide (Ref. 1). It is practically insoluble in water and organic solvents, but soluble in carbon disulfide and benzene (Refs. 1 and 2). Selenium is an essential trace element for man and is contained in the enzyme glutathione peroxidase (Ref. 3).

Selenium sulfide is used in OTC detergent suspension shampoos in a 1-percent concentration for controlling dandruff (Ref. 4). Presently this ingredient is marketed for control of seborrheic dermatitis only in a 2.5-percent concentration that is restricted to prescription use. The Panel knows of no studies that have been done to demonstrate the effectiveness of a 1-percent concentration in controlling seborrheic dermatitis, but suggests that manufacturers might wish to consider performing such studies to determine whether the lower concentration is in fact effective for controlling seborrheic dermatitis as well as dandruff.

(1) *Safety.* Because selenium sulfide is practically insoluble in water and organic solvents, its toxicity contrasts sharply with the highly toxic water-soluble selenium compounds and with elemental selenium. The oral LD_{50} for selenium sulfide in rats is 136 mg/kg, as compared to 7 mg/kg for highly soluble sodium selenite. Available evidence indicates that there is little danger of absorbing toxic amounts when selenium sulfide is applied to normal intact skin or hair (Ref. 5). This ingredient has been used in an OTC antidandruff shampoo in a concentration of 1 percent for several years with very few reported incidences of toxicity.

A series of four studies was done to determine whether selenium was absorbed through intact skin on the scalp as a result of shampooing under normal conditions with a 1-percent selenium sulfide shampoo (Ref. 4). The first two studies were designed to determine when peak blood levels would occur if any selenium were absorbed. In the first study, blood samples were drawn from four subjects 12 hours after shampooing, and urinary excretion of selenium was measured over a period of 24 hours following use of the shampoo. In the second study, blood samples were drawn from four subjects 4 hours after shampooing, 8 hours after shampooing, and at intervals in between. Measurements of selenium excreted in urine were made five times over a 24-hour period. Apparently no selenium was absorbed because there appeared to be no change in blood selenium levels other than slight variations that were within the standard deviation of the analytical method.

The third study was conducted on four subjects who shampooed with the 1-percent selenium sulfide preparation twice a week for 8.5 weeks. Simultaneously, a control group of four subjects used a shampoo that did not contain selenium sulfide, and blood and urine selenium levels were measured in both groups. The difference in blood selenium levels and urine selenium levels between control and experimental subjects was neither statistically nor

clinically significant (Ref. 4). In the fourth study, urinalysis of samples collected each month showed no selenium absorption after shampooing weekly with the 1-percent preparation for 6 months (Ref. 4).

When selenium is applied to damaged skin, it can be absorbed, and toxicity may occur (Ref. 5). The Panel therefore recommends that selenium sulfide products be labeled with a warning against use on damaged skin such as open sores. Ransone, Scott, and Knoblock (Ref. 6) described symptoms of selenium intoxication in a woman who had been using a selenium sulfide suspension shampoo two or three times a week for 8 months to treat a scalp eruption and who had developed an open lesion on her scalp. She developed tremors, followed by severe perspiration, garlicky breath, and a pain in the lower abdomen. Over the next 3 days, she became increasingly weak, lethargic, had no appetite, and vomited occasionally. Use of the shampoo was discontinued, and within 10 days after the onset of the symptoms, the patient felt completely well. One month later she was still without symptoms.

It has been noted that preparations containing selenium sting the mucosa of the eyes on contact (Ref. 5). Labeling of selenium sulfide products should include a warning to avoid contact of the products with the eyes and to rinse the eyes immediately with water should this occur.

Because of concern over possible carcinogenicity of selenium sulfide, a bioassay of a shampoo containing this ingredient in a 2.5-percent concentration was recently done under the supervision of the National Cancer Institute (Ref. 7). Under conditions of this bioassay, topical application of the shampoo was not shown to cause cancer in ICR Swiss mice. The official report of the study points out, however, that the study was limited by the relatively short life span of this strain of mice.

In a study using a modified Draize-Shelanski human patch test, a 1-percent concentration of selinium sulfide was shown to cause no photosensitization reactions. The reactions that were seen indicated irritation due to occulsive patching rather than sensitivity. A 2.5-percent selenium sulfide suspension was also reported to cause a contact dermatitis. Investigators believe that prolonged contact with skin, e.g., overnight application, of both 1 and 2.5 percent concentrations may produce irritation (Ref. 4).

Selenium sulfide suspensions can cause rebound oiliness of the scalp. Long-term studies showed increased scalp oiliness in 13 of 104 subjects using a 1-percent selenium sulfide suspension. Short-term studies showed increased scalp oiliness in 5 of 50 of the subjects using a 2.5-percent selenium sulfide suspension, in 1 of 370 subjects using a 1-percent selenium sulfide suspension, and in 2 of 50 subjects using a 0.5-percent suspension (Ref. 4).

Discoloration of various shades of natural and dyed hair by selenium sulfide suspension shampoos has been recorded. However, studies indicate that this is not a common occurrence and is most likely to occur, if at all, when shampooing with a selenium suspension is followed by poor rinsing or no rinsing at all (Ref. 4).

Six cases of diffuse hair loss after using a 2.5-percent selenium sulfide shampoo were reported by Grover (Ref. 8). The hair loss stopped 1 to 2 weeks after use of the product was discontinued. Later studies showed no significant effect on the percentages of growing and resting hairs after both a single application and prolonged use of a selenium sulfide suspension shampoo and use of the same preparation without selenium sulfide (Ref. 9).

The Panel concludes that selenium sulfide is safe for use in a concentration of 1 percent in a shampoo for controlling dandruff.

(2) *Effectiveness.* There are several theories regarding the mechanism of action of selenium sulfide. Spoor (Ref. 10) found a 2.5-percent selenium sulfide suspension to be one of the most active agents tested in inhibiting the growth of *Pityrosporum ovale.* It is possible that selenium sulfide, when absorbed, is converted into selinide and sulfide ions, and the selinide ions block the enzyme systems involved in the growth of epithelial tissue (Ref. 11). In any event, selenium sulfide is a demonstrated cytostatic, slowing the rate of cell turnover, whether the turnover rate is normal or higher than normal (Ref. 12).

Four studies were conducted to demonstrate the effectiveness of 1 percent selenium sulfide in controlling dandruff (Ref. 4). The first study was conducted on 19 adults with moderate to severe dandruff. For the first 4 weeks, the dandruff was treated by continuous use of a 2.5-percent selenium sulfide suspension. At the end of this period, the subjects were given a 1-percent selenium sulfide suspension to use for 4 weeks. The subjects rated the effectiveness of the 1- and 2.5-percent suspensions as equal.

The second study was double-blinded and used 6 comparable groups of 50 to 53 individuals with moderate to very severe dandruff. Each group shampooed with one of the following six test solutions: 2.5 percent selenium sulfide suspension shampoo, 1 percent selenium sulfide suspension shampoo, 0.5 percent selenium sulfide suspension shampoo, the detergent vehicle for the selenium sulfide suspensions, 2 percent zinc pyrithione shampoo, and a combination 2-percent sulfur and 2-percent salicylic acid shampoo. The three selenium sulfide suspension shampoos were found to be more effective than the detergent vehicle in controlling dandruff and attendant itching. The 2.5-percent selenium sulfide suspension shampoo and the 1-percent selenium sulfide suspension shampoo were equal in effectiveness and superior to the 0.5-percent selenium sulfide suspension shampoo, the 2-percent zinc pyrithione shampoo, and the combination 2-percent sulfur and 2-percent salicylic acid shampoo.

A third study conducted over a 3-month period compared a 1-percent selenium sulfide shampoo with its detergent vehicle (Ref. 4). All subjects used the detergent vehicle the first month. During the second month, 47 subjects used a 1-percent selenium sulfide shampoo, while 48 subjects used the detergent. During the third month, all subjects used the 1-percent selenium sulfide shampoo. At the end of the second month of the study, the dandruff severity decreased in 45 of the 47 subjects using the 1-percent selenium sulfide shampoo, remained unchanged in 1 subject, and increased in 1 subject. Of the 48 subjects using the detergent vehicle, dandruff severity decreased in 23, increased in 11, and remained the same in 14.

At the end of the third month, subjects who used the 1-percent selenium sulfide shampoo for that month only showed significant improvement: 43 subjects had a decrease in dandruff severity, while 1 had an increase. Those who used the 1-percent selenium sulfide shampoo for 2 months had less dandruff at the end of the study than those who used it for only 1 month. It was concluded that 1 percent selenium sulfide was effective in controlling dandruff. No effect on oiliness was demonstrated.

The fourth study was conducted on 370 subjects using a 1-percent selenium sulfide suspension and its detergent vehicle (Ref. 4). The study was performed in a double-blind crossover fashion. The selenium sulfide suspension and the detergent vehicle were both labeled as test shampoos. The subjects were instructed to shampoo for 4 weeks with one test shampoo. The following 4 weeks they used the other test shampoo. At the end of the study, both the examining physician and subjects rated the 1-percent selenium

sulfide suspension superior to the vehicle in controlling dandruff. The vehicle, however, still produced significant improvement of the scalp condition when compared with the scalp condition at the beginning of the study.

The Panel concludes that selenium sulfide in a concentration of 1 percent is effective in controlling dandruff.

(3) *Dosage.* For topical use in a concentration of 1 percent.

4. *Labeling.* The Panel recommends the Category I labeling described below. (See part III. paragraph A.2. below—*Category I labeling.*) In addition, the Panel recommends the following warning for labeling of products containing selenium sulfide: "Do not use if you have open sores on your scalp."

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d. *Sulfur.* The Panel concludes that sulfur is safe and effective for OTC topical use for controlling dandruff.

Sulfur has long been used in medicine as a parasiticide, fungicide, and to treat certain cutaneous disorders unassociated with infection (Ref. 1). Elemental sulfur can exist in several different crystalline forms as well as an amorphous or polymeric form. In general, sulfur is insoluble in water, sparingly soluble in alcohol, and soluble in organic solvents (Ref. 2).

Four forms of elemental sulfur are used in dermatology: sublimed sulfur (flowers of sulfur) a fine, yellow, crystalline powder; washed sulfur, made by washing sulfur with ammonia; precipitated sulfur (milk of sulfur), a fine yellowish-white, amorphous, odorless powder with smooth texture; and colloidal sulfur, in which minute particles of elemental sulfur are stabilized in an aqueous medium containing a colloid such as egg albumin or gelatin (Ref. 3). Precipitated sulfur and colloidal sulfur are the forms most commonly used.

(1) *Safety.* Sulfur is an ancient remedy, which is still popular as a treatment for acne, dandruff, and seborrheic dermatitis. Allergic reactions to it are rare. Basch (Ref. 4) reported in 1926 that the application of a 10-percent sulfur ointment for 3 days to infants with scabies resulted in poisoning and death in some cases. He also reported earlier cases of poisoning from the application of precipitated sulfur powder or sulfur ointment to eczematous patients, manifested by headache, vomiting, muscle cramps, dizziness, and collapse, followed by recovery in several hours. Basch applied a 25-percent sulfur ointment to rabbits and guinea pigs and detected symptoms of sulfur poisoning and sulfuric acid in the blood of the animals with abraded skin but not those with intact skin. However, sulfur in 2 to 5 percent concentrations applied topically is well tolerated by humans, and there have been no reports of toxicity from application of these concentrations. Sulfur taken orally may have a laxative or cathartic effect. Sax (Ref. 5) rated the toxicity of sulfur as very low.

Sulfur may cause irritation to the skin, eyes, and respiratory tract (Ref. 6). Labeling of sulfur-containing products should include a warning to avoid contact of the products with the eyes and to rinse the eyes immediately should this occur. In concentrations above 15 percent, it is very irritating to the skin, and concentrations below 15 percent may cause severe topical irritation to some people when applied for prolonged periods. Prolonged local use may result in a characteristic dermatitis venenata (Ref. 7).

Lorenc and Winkelmann (Ref. 8) found only three references in the literature that attempt to describe the histologic effects of sulfur on the skin. These researchers studied the histologic effects of concentrations of 5, 20, and 40 percent sulfur in petrolatum on hairless mouse skin over a 4-week period of exposure. With the 5 percent concentration there was increasing edema of the epidermis during the first week, followed by thickening of the prickle cell layer. This reaction reached a maximum at 2 weeks, resulting in nonadherent cells in the stratum corneum which retained their nuclei. With the 20 percent sulfur, the reactions were the same, but occurred more rapidly and with greater severity. The 40 percent preparation produced a severe epidermal reaction. The stratum corneum was almost completely absent at the end of 4 weeks, and intercellular and intracellular edema were seen to the point of separation of epidermis from dermis. Lorenc and Winkelmann concluded that sulfur injures the epidermis and that the injury is followed by a reparative process when lower concentrations are applied. However, when concentrations of sulfur above 5 percent are used, the injury exceeds the reparative process, and peeling results in severity proportionate to the concentration. Thus, the terms "keratoplastic" (correcting of abnormal keratinization) and "keratolytic" (causing peeling of the skin) describe different phases of the same reaction. Lorenc and Winkelmann also reported that the sequence of events after the application of various concentrations of sulfur to the skin of hairless mice was essentially the same as the sequence reported when sulfur was applied to the skin of the human thigh, abdomen, and scrotum.

Rossoff (Ref. 9) reported that sulfur in 5 to 10 percent concentrations is keratolytic. Rossoff did not suggest that lower concentrations were used primarily to correct abnormal keratinization, although he noted that a 2-percent sulfur concentration in combination with salicylic acid is popular in antiseborrheic preparations.

The Panel concludes that sulfur is safe for topical use in concentrations of 2 to 5 percent.

(2) *Effectiveness.* The majority of the 20 sulfur submissions received for review for controlling dandruff contained this ingredient in combination with other active ingredients (Refs. 10 through 30). Formulated as shampoos, conditioning lotions, and ointments, these preparations contain sulfur in concentrations ranging from 2 to 5 percent. Few studies have evaluated sulfur as a single active ingredient in controlling dandruff. One 6-week double-blind study compared a lotion shampoo containing 2 percent sulfur with its base and a cream shampoo containing 2 percent sulfur with its base in treating dandruff in four groups of 50 men and women (Ref. 25). The subjects

were each assigned to use one of the four preparations twice a week for the first 2 weeks and once weekly thereafter. They were examined at the second, fourth, fifth, and sixth weeks, 5 days after shampooing.

Statistical analysis of the results showed that each sulfur-containing shampoo produced a significant decrease in the amount of dandruff, compared to its vehicle control, at the sixth week examination. The Panel points out that, because the research laboratory that conducted the study has been under a grand jury investigation for mishandling data, these data cannot stand alone.

In another double-blind study, a 2-percent sulfur shampoo was compared to its vehicle in the control of dandruff (Ref. 25). Forty-nine patients used the sulfur shampoo, and 50 used the vehicle for a period of 2 months. Subjects were instructed to shampoo twice weekly for the first 2 weeks and once weekly thereafter until completion of the study. Clinical evaluations of the dandruff condition were made initially and weekly thereafter. Thirty of the 49 subjects using the sulfur shampoo showed improvement in their dandruff conditions as compared to 23 of 50 using the vehicle. This difference is not statistically significant. It was noted by the investigators that 10 of 50 subjects using the vehicle shampoo refused to shampoo only once weekly and were given permission to shampoo twice a week. Seven of these 10 showed improvement. The investigators concluded that these seven subjects could be considered failures under the one-shampoo-a-week terms of the study. If considered failures, the differences between the sulfur and control groups would be significant. These data suggest that sulfur may be effective and are supported by an additional double-blind study that compared the activity of 2 percent sulfur, 2 percent salicylic acid, and a combination of sulfur and salicylic acid (2 percent each) against a vehicle control (Ref. 26). The specifics of this study are discussed under salicylic acid above. (See part III. paragraph A.1.b. above—*Salicylic acid.*) The differences in clinical grading between the sulfur and vehicle groups were statistically significant. However, the differences in corneocyte counts were statistically indistinguishable.

The Panel is aware of one other study in which 2 and 5 percent sulfur shampoos were compared against their shampoo vehicle as a control (Ref. 31). This 8-week study had been completed through the fifth week when the data were presented to the Panel. Beginning at the second week, statistically significant differences in both corneocyte counts and the clinical grade of dandruff were seen between both test shampoos and the vehicle. There was no significant difference between the 2- and 5-percent sulfur shampoos. The Panel concludes that preparations containing 2 to 5 percent sulfur are effective in controlling dandruff.

(3) *Dosage.* For topical use in concentrations of 2 to 5 percent.

(4) *Labeling.* the Panel recommends the Category I labeling described below. (See part III. paragraph A.2. below—*Category I labeling.*)

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(26) OTC Volume 160414.

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(28) OTC Volume 160401.

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(31) Meltzer, N., Presentation to Panel, 42nd Meeting of the Advisory Review Panel on Miscellaneous External Drug Products, November 7, 1980.

e. *Zinc pyrithione (pyrithione zinc).* The Panel concludes that zinc pyrithione is safe and effective for OTC topical use for controlling dandruff and seborrheic dermatitis of the scalp.

Zinc pyrithione is also known as zinc pyridine-2-thiol-1-oxide. It has a molecular weight of 318. It is virtually insoluble in water (15 to 20 parts per million (ppm)), but its solubility is increased by complex formation with certain organic amines. For example, in a detergent shampoo base, soluble levels of zinc pyrithione average about 300 ppm.

The compound *N*-hydroxy-2-pyridinethione and its metal salts were synthesized by Shaw et al. (Ref. 1) in 1950 and were subsequently discovered to be potent, broad-spectrum antimicrobial and antifungal agents.

The original work with zinc pyrithione as an antidandruff agent was done using a 2-percent suspension. With careful formulation, selecting the proper surfactant, it was possible to cleanse the hair and scalp of dirt and oil while depositing fine particles of zinc pyrithione on the skin (Ref. 2). Enhancing the solubility of zinc pyrithione in shampoos by adding high molecular weight polyethylenimine polymers at a level of 0.5 percent allowed zinc pyrithione to be decreased to a concentration of 1 percent without loss of antidandruff efficacy (Ref. 3). Rutherford and Black (Ref. 4) found that zinc pyrithione was soluble in sebum, and its presence could be demonstrated in the hair follicles by autoradiography although there was no evidence of epidermal penetration. Follicular residues of zinc pyrithione may be a source of its sustained activity after most of the active material has been rinsed off during shampooing. When zinc pyrithione in varying dilutions was left on the scalp from 1 to 32 minutes, the residual deposits were shown to be approximately 1 percent of the amount applied (Ref. 5); these deposits of zinc pyrithione resist rinsing off with water.

(1) *Safety.* Because zinc pyrithione is relatively insoluble in water, it is not easily absorbed through the skin when topically applied or easily absorbed through the mucous membranes if swallowed.

Animal toxicology data were summarized in several submissions (Refs. 3, 6, 7, and 8), and zinc pyrithione was shown to be minimally toxic to rats and a potent emetic (Ref. 7). Eye irritation from zinc pyrithione powder or shampoo was extreme, but when a shampoo formulation containing 2 percent zinc pyrithione was instilled into the eyes of rabbits or monkeys was rinsed out after 4 seconds, only mild irritation resulted. There was no permanent damage. Zinc pyrithione was not found to be mutagenic in mice or teratogenic in rabbits (Ref. 7). A 2-year exposure of dogs to a 0.25-percent zinc pyrithione hairgroom in doses of 0.05, 1.5, and 2.5 mg/kg a day (representing 1, 30, and 50 times the estimated dosage levels in humans) showed only slight skin thickening at the application site of the 2 higher doses. Otherwise the dogs receiving the zinc pyrithione exhibited no differences from the dogs in the control group.

Human systemic toxicity from zinc pyrithione has not been reported. Accidental poisoning from oral ingestion is apparently prevented by the ingredient's emetic effect.

Human percutaneous absorption of zinc pyrithione formulations has been measured, and safety factors have been calculated (Refs. 5, 8, and 9). Data from these studies indicate that topically applied zinc pyrithione has a high safety margin.

Human skin irritation and sensitization to zinc pyrithione is low (Refs. 5, 10, and 11). A 5-month repeated insult closed-patch test study using a 0.5 percent zinc pyrithione hairgroom on 100 human volunteers gave no evidence of primary skin irritation or sensitization. Draize tests with 1 percent aqueous dilutions of three shampoos formulated with 1 percent zinc pyrithione showed no contact sensitization and no photosensitization. One percent aqueous dilutions of two shampoos formulated with 2 percent zinc pyrithione and their vehicles were used in repeated insult closed-patch tests. No sensitization resulted. More irritation was seen with the zinc pyrithione-containing shampoos than with their vehicles, but the level of irritation was still low. Zinc pyrithione was also shown not to be phototoxic.

A double-blind, placebo-controlled test was conducted to confirm the safety of 0.1 percent zinc pyrithione formulated in a hairgroom. Fifty volunteers, all previous hairgroom users, massaged a small amount of the product into the scalp daily for 2 months, shampooing as needed with a nonmedicated shampoo provided by the researchers. The test results confirmed that scalp irritation did not occur following daily use of the zinc pyrithione preparation for 60 days (Ref. 12).

Shampoos containing zinc pyrithione have been marketed since 1964, but only 3 cased of allergic contact dermatitis resulting from their use have been reported (Refs. 13 and 14). Of 1,223 people participating in 13 clinical trials using a 1-percent zinc pyrithione shampoo, only 4 showed slight cutaneous irritation (Ref. 15). This may be due to the fact that zinc pyrithione has the potential to cross-react with the commonly prescribed drugs ethylenediamine, piperazine, and hydroxyzine hydrochloride.

(2) *Effectiveness.* Shampoos containing 1 percent zinc pyrithione have been shown in many double-blind studies to be effective in controlling the clincially evident scaling of dandruff. Shampoos containing 2 percent zinc pyrithione have also been shown to be effective for treatment of seborrheic dermatitis. Three shampoos containing 1 percent zinc pyrithione were evaluated in 13 clinical trials conducted by 5 investigators at different test sites. One shampoo was formulated for normal hair, one for oily hair, and one for dry hair (Ref. 15). All tests were double-blinded. Following 1 to 3 weeks of shampooing with a nonmedicated commercial shampoo, subjects with at least moderate dandruff were accepted into the study. Subjects were classified as having either excessively oily, normal, or dry scalps and hair and were tested with the appropriate shampoo. Duration of the test period varied from 6 to 10 weeks. Subjects with the same hair type were divided into two groups with an approximately equal distribution of severity of dandruff. One group used the test product and the other vehicle control, shampooing once or twice a week for the entire test period. Subjects were evaluated by a dermatologist 3 to 7 days following each shampooing for severity of dandruff which was rated according to a numerical scoring system. Results showed that all three medicated shampoos were effective in reducing dandruff.

Thirty-one of 33 double-blind clinical studies using a 2-percent zinc pyrithione lotion shampoo and a 2-percent zinc pyrithione cream shampoo showed that both formulations were significantly more effective in controlling dandruff than a placebo shampoo (Ref. 16). One of these studies was published by Orentreich (Ref. 17).

Use of shampoo base alone showed some improvement in scalp scaling in the above studies. Thus frequent shampooing has been suggested as a treatment for dandruff. However, the 2-percent zinc pyrithione shampoo used three times a week was significantly more effective than an unmedicated shampoo, just as it was more effective with once-a-week use.

Two clinical studies were conducted to determine if a 2-percent zinc pyrithione shampoo maintained its antidandruff effectiveness with long-term use (Ref. 5). The results showed that the zinc pyrithione shampoos were significantly more effective than the respective placebo shampoos throughout 3 months of one study and 6 months of the other study.

In a double-blind study of a 2-percent zinc pyrithione shampoo, a sulfur-salicylic acid-hexachlorophene shampoo, and an unmedicated shampoo control in the treatment of seborrheic dermatitis of the scalp, the 2-percent zinc pyrithione shampoo was found to be significantly more effective than the sulfur-salicylic acid-hexachlorophene shampoo, which was significantly more effective than the placebo after both 4 and 8 weeks of use (Ref. 18).

Approximately 5 percent of subjects with dandruff do not respond to zinc pyrithione shampoos (Ref. 16).

Four controlled studies on over 400 men with dandruff, testing a 0.25-percent zinc pyrithione hairgroom against its base, showed significantly greater improvement in "severity of dandruff, condition of scalp, and itching" in subjects using the zinc pyrithione preparation (Ref. 11).

Five double-blind, placebo-controlled studies were conducted to determine the effectiveness of 0.1 percent zinc pyrithione formulated in a hair groom to control dandruff (Ref. 12). The testing prodcedure was the same in all five studies. Volunteers for each study were previous hairgroom users with at least moderate dandruff. Baseline scores were established prior to initiating the studies. In each test, volunteers were instructed to massage a small amount of the test material (hairgroom or placebo) into the scalp daily and shampoo as needed with a nonmedicated shampoo. Tests were conducted for 2 months, with dandruff assessments made by a trained observer after 1 and 2 months' use of the test samples. Assessments were done by dividing the scalp into four sections and parting the hair in each section to observe the amount of adherent dandruff; loose scales were ignored. Scores from each of the four sections were added to give a total score for the scalp.

The results of each of the five studies demonstrated that at no time did the placebo produce a statistically significant reduction in dandruff level. The use of the hairgroom with 0.1

percent zinc pyrithione reduced the dandruff level, clinically and statistically, at the end of the both 1 and 2 months. Additionally, one study evaluated the efficacy of 0.05 percent zinc prithione in a hairgroom. This lower concentration also reduced the dandruff level but not as significantly as the 0.1 percent concentration.

Two additional studies comparing 2 percent zinc pyrithione shampoo against placebo support the effectiveness of this ingredient in controlling dandruff (Ref. 19).

Based on the above data, the Panel concludes that preparations containing 1 to 2 percent zinc pyrithione in a shampoo and 0.1 to 0.25 percent zinc pyrithione in a hairgroom are effective in controlling dandruff and seborrheic dermatitis.

(3) *Dosage.* For topical use in concentrations of 1 to 2 percent in a shampoo and 0.1 to 0.25 percent in a hairgroom.

(4) *Labeling.* The Panel recommends the Category I labeling described below. (See part III. paragraph A.2. below—*Category I labeling.*)

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2. *Category I labeling.* The Panel recommends the following labeling for Category I drug products for controlling dandruff, seborrheic dermatitis, and psoriasis. One or more of these indications may be used so long as the active ingredient or ingredients of a product have been demonstrated safe and effective for each indication used.

a. *Indications*—(1) *For products used for controlling dandruff.* "Relieves the itching and scalp flaking associated with dandruff."

(2) *For products used for controlling seborrheic dermatitis.* "Relieves the itching, irritation, and skin flaking associated with seborrheic dermatitis" (select one or both of the following as appropriate: "of the scalp" and/or "of the body.")

(3) *For products used for controlling psoriasis.* "Relieves the itching, redness, and scaling associated with psoriasis" (select one or both of the following as appropriate: "of the scalp" and/or "of the body.")

(4) *For products used for controlling cradle cap.* "Relieves scaly inflammation of the scalp associated with cradle cap."

b. *Warnings*—(1) *For all products used for controlling dandruff, seborrheic dermatitis, psoriasis, or cradle cap.*

(i) "For external use only."

(ii) "Avoid contact with the eyes—if this happens, rinse thoroughly with water."

(iii) "If condition worsens or does not improve after regular use of this product as directed, consult a doctor."

(2) *For products used for controlling seborrheic dermatitis or psoriasis on the body.* "If condition covers a large area of the body, consult your doctor before using this product."

(3) *For products that contain coal tar.*

(i) "Use caution in exposing skin to sunlight after applying this product. It may increase your tendency to sunburn for up to 24 hours after application."

(ii) "Do not use this product in or around the rectum or in the genital area or groin except on the advice of a doctor."

(4) *For all products except those used for controlling cradle cap.* "Do not use on children under 2 years of age except as directed by a doctor."

(5) *For products that contain selenium sulfide.* "Do not use if you have open sores on your scalp."

c. *Directions for use*—(1) *For shampoos.* "For best results use twice a week. Wet hair, apply to scalp and massage vigorously. Rinse and repeat."

(2) *For hairgrooms.* "Apply a small amount to scalp daily. For best results, also shampoo twice a week."

(3) *For preparations to be used on the body.* "Apply a thin layer to the affected area one to two times daily."

B. Category II Conditions

There are conditions under which active ingredients used for controlling dandruff, seborrheic dermatitis, and psoriasis are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredients:*

Benzocaine
Borate preparations
Colloidal oatmeal
Cresol
Mercury oleate
Resorcinol

a. *Benzocaine.* The Panel concludes that benzocaine is not safe or effective for OTC topical use for controlling psoriasis.

Benzocaine is the ethyl ester of aminobenzoic acid and may be prepared by reducing paranitrobenzoic acid to aminobenzoic acid and esterifying the latter with ethyl alcohol in the presence of sulfuric acid. Benzocaine is a white, crystalline, stable powder that melts at temperatures between 88° to 92° C. It is odorless and has a somewhat bitter taste. It is poorly soluble in water, but is lipid-soluble. Benzocaine has slight antiseptic and bacteriostatic properties, but these actions are not clinically significant in controlling psoriasis (Refs. 1, 2, and 3).

(1) *Safety.* The Topical Analgesic Panel in the Federal Register of December 4, 1979 (44 FR 69793) found benzocaine safe and effective for use as a topically-applied analgesic in concentrations of 5 to 20 percent. That Panel noted that the safety of benzocaine is due to the fact that it is poorly soluble in water, and the quantities absorbed through the intact skin, while sufficient to relieve pain and itching, are relatively insignificant in terms of potential toxicity. The Topical Analgesic Panel pointed out, however, that benzocaine therapy is not without hazard, and a review of the literature shows two types of adverse reactions that may occur: those that are allergic or those that may result in methemoglobinemia. In addition, the Miscellaneous External Panel notes that the salts benzocaine forms with acids may be irritating to the mucous membranes and to the skin. On weighing these risks against the fact that there is no evidence to show that benzocaine is effective in controlling psoriasis, the Panel concludes that its use is irrational for this purpose.

(2) *Effectiveness.* Reports in the medical literature attest to the long and

successful use of benzocaine as a topical analgesic, anesthetic, and antipruritic (Refs. 3 through 6). It apparently works by depressing sensory receptors in the skin. The submitted preparation that contains benzocaine (Ref. 7) also contains salicylic acid and coal tar solution, and, although no rationale is given for the inclusion of benzocaine in the product, the Panel assumes that it is included for its analgesic/antipruritic action. Such action does not amount to control of psoriasis, however. Furthermore, the Panel is unaware of any evidence to show that benzocaine is effective in controlling psoriasis, and none was submitted. The Panel therefore concludes that benzocaine is not effective for this use.

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b. *Borate preparations (boric acid and sodium borate).* The Panel concludes that borate preparations are not safe, and data are lacking to permit their final classification as effective for OTC topical use for controlling dandruff or seborrheic dermatitis.

Boric acid occurs as colorless, odorless, transparent crystals or white granules or powder. It is obtained from sodium borate and from other borates by displacement with a stronger acid. One g boric acid dissolves in 18 mL water, 18 mL alcohol, and 4 mL glycerin (Ref. 1).

Sodium borate, also known as borax, occurs as hard, odorless, colorless crystals; granules; or as a white crystalline powder. It is found in several lake waters and brines and also in minerals from which it may be obtained in commercial quantities. One g dissolves in about 16 mL water and 1 mL glycerin; sodium borate is insoluble in alcohol (Ref. 2). This ingredient has been used as a cleansing agent since ancient times (Ref. 3).

(1) *Safety.* Borate preparations are included in two products submitted to the Panel for review (Refs. 4 and 5). The submissions did not provide data on the safety of borate preparations when used as single ingredients. However, one source reports the LD_{50} of subcutaneously administered boric acid in animals as follows: 2 g/kg in mice, 1 g/kg in guinea pigs, and 1 g/kg in dogs. The oral LD_{50} for dogs was reported to be about twice that of the subcutaneous dose (Ref. 6).

The toxicity of borate preparations in humans appears to be unpredictable. For example, a 70-year-old woman died after ingesting 7.5 g boric acid powder, but a 42-year-old woman reportedly survived an intravenous dose of 15 g boric acid (Ref. 6). Locksley and Farr (Ref. 7) reported administering 20 g sodium borate intravenously over a period of 75 seconds in cancer patients receiving neutron capture therapy with no severe adverse effects. However, six infants died after receiving 3 to 6 g of this drug orally (Ref. 8).

Fisher et al. (Ref. 9) found that the blood concentration of boric acid ranged from 52 to 296 mg/100 mL in cases that were "unmistakably intoxication by boric acid." They concluded from their investigations that "there are few reliable data in the literature regarding the concentration of boric acid in the blood that is accompanied by evidence of toxic condition in the patient."

Kingma (Ref. 6) surveyed the literature from 1882 to 1957 and found 37 cases of alleged boric acid poisoning from topical application. Based on his review, Kingma recommended that pure boric acid not be used on raw surfaces and that solutions and ointments be limited to a 3-percent concentration. He concluded that a 3-percent concentration would greatly increase the safety margin of the drug, but pointed out that experiments with 5 percent borated talcum demonstrated the higher concentration in this preparation to be safe. Kingma's conclusions were substantiated by two other review articles (Refs. 9 and 10).

Pfeiffer and Jenney (Ref. 3), in discussing the passage of boric acid through skin and mucous membranes, reported that when a 10-percent boric acid ointment was applied to the torsos of two subjects no boric acid was detected in the urine. These investigators concluded that boric acid is only negligibly absorbed through intact skin. Granulating wounds or abraded surfaces, however, are rich in blood supply and permit the rapid absorption of boric acid applied in a solution, as a powder, or as an ointment. The risk factors for potential toxic absorption appear to be concentration of boric acid or sodium borate in a product, age of the patient, skin condition, and duration of exposure. Pfeiffer and Jenney (Ref. 3) suggested that the very young rank first and the very old rank second in susceptibility to borate poisoning.

Although a list of 81 references submitted to the Panel fairly well substantiates that preparations containing 5 percent borates present no great toxicity problem when applied to intact skin (Ref. 11), the Panel believes that borate preparations are not safe due to the significant amounts of borate that can be absorbed through damaged skin.

(2) *Effectiveness.* Historically boric acid has been used as a treatment for superficial fungal infections and is one of the more common components of OTC topical antifungal drugs. It is also recognized as a very weak local anti-infective and a buffering agent (Ref. 1). Sodium borate has been used as an alkalizing agent, antiseptic, and astringent for mucous membranes (Ref. 12).

The Panel reviewed an antidandruff preparation containing boric acid (Ref. 4) and another preparation containing sodium borate for controlling the itching of seborrheic dermatitis (Ref. 5). Both preparations were combinations of active ingredients, and the intended contribution of the boric acid and the sodium borate to each of the combinations was not explained.

The Panel concludes that additional data are necessary to show that borate preparations are effective for OTC topical use for controlling dandruff or seborrheic dermatitis.

References

(1) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, Mack Publishing Co., Easton, PA, p. 1257, 1980.

(2) Osol, A., and R. Pratt, "The United States Dispensatory,"; 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 199–200 and 1047, 1973.

(3) Pfeiffer, C. C., and E. H. Jenney, "The Pharmacology of Boric Acid and Boron Compounds," *Bulletin of the National Formulary Committee*, 18:57–80, 1950.

(4) OTC Volume 160321.

(5) OTC Volume 160326.

(6) Kingma, H., "The Pharmacology and Toxicology of Boron Compounds," *Canadian Medical Association Journal*, 78:620–622, 1958.

(7) Locksley, H. B., and L. E. Farr, "The Tolerance of Large Doses of Sodium Borate Intravenously by Patients Receiving Neutron Capture Therapy," *Journal of Pharmacology and Experimental Therapeutics*, 114:484–489, 1955.

(8) McNally, W. D., and C. A. Rust, "The Distribution of Boric Acid in Human Organs in Six Deaths Due to Boric Acid Poisoning," *Journal of the American Medical Association*, 90:382–383, 1928.

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

(10) Anonymous, "Boric Acid and Baby Powders," *Food and Cosmetics Toxicology*, 1:249–250–1963.

(11) OTC Volume 160355.

(12) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 1110, 1976.

c. *Colloidal oatmeal.* The Panel concludes that colloidal oatmeal is safe, but is not effective for OTC topical use for controlling dandruff.

Colloidal oatmeal is included in two preparations submitted to the Panel for use as dandruff shampoos (Refs. 1 and 2). However, there is a lack of information in the current literature regarding the use of this ingredient alone in controlling dandruff.

(1) *Safety.* Colloidal oatmeal is described as "specially processed oat grains" and labeled as a demulcent (Ref. 1). The Panel knows of no potential for toxicity in oat grains in a colloidal state when used topically and concludes that colloidal oatmeal is safe for topical use.

(2) *Effectiveness.* The Panel assumes that because of its nature and the fact that it has been used for some time in bath preparations intended to soothe itching and irritated shin, colloidal oatmeal was included in the dandruff preparations for its antipruritic/anti-irritant properties. Because the Panel knows of no data to show that colloidal oatmeal is effective in controlling dandruff, and none were submitted, it concludes that colloidal oatmeal is Category II for this indication.

References

(1) OTC Volume 160069.

(2) OTC Volume 160070.

d. *Cresol.* The Panel concludes that cresol is safe for topical use in the concentration submitted, but there are no data to show that it is effective for OTC topical use in controlling psoriasis.

Cresol is a mixture of isomeric cresols obtained from coal tar or from petroleum and may contain up to 5 percent phenol. It is soluble in about 50 parts water, and, owing to this relative insolubility in water, it is nearly always employed in combination with alkalies associated with fats or oils or soaps which render it very soluble but less effective (Refs. 1 and 2). The submitted product contained a combination of cresol oleate in a soap solution (saponated cresol solution) with mercury oleate (Ref. 3). It is used for disinfecting and has antimicrobial activity, surpassing phenol in these respects, but compared to modern antiseptics its potency is low.

(1) *Safety.* Cresol in concentrations greater than 2 percent in aqueous solutions is irritating and may cause sloughing and necrosis (Refs. 2 through 5). More highly concentrated solutions are toxic and can cause death if ingested orally (Ref. 2). The symptoms of toxicity usually develop rapidly, and death has occurred within 2 to 3 minutes after ingestion.

Because cresol, like phenol, is lipid-soluble, it is readily absorbed through intact and abraded skin (Ref. 6). The product submitted to the Miscellaneous External Panel for review contained 0.25 percent by weight of saponated cresol solution, and the Miscellaneous External Panel concludes that this concentration is safe for topical use.

(2) *Effectiveness.* The Panel is unaware of any data to show that cresol is effective in controlling psoriasis, and none were submitted. In the absence of such data, the Panel is placing this ingredient in Category II.

References

(1) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, Mack Publishing Co., Easton, PA, p. 1109, 1980.

(2) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J.B. Lippincott Co., Philadelphia, p. 355, 1973.

(3) OTC Volume 160033.

(4) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., Inc., New York, p. 991, 1975.

(5) "AMA Drug Evaluations," 4th Ed., John Wiley and Sons, Inc., p. 1023, 1980.

(6) Freeman, M. V., J. H. Draize, and E. Alvarez, "Cutaneous Absorption of Phenol," *Journal of Laboratory and Clinical Medicine*, 38:262–266, 1951.

e. *Mercury oleate.* The Panel concludes that mercury oleate is safe, but is not effective for OTC topical use for controlling psoriasis.

Mercury oleate contains the equivalent of not less than 24 percent and not more than 26 percent of mercuric oxide. It is a yellowish-brown, somewhat transparent substance, ointment-like in consistency, with the odor of oleic acid. It is slightly soluble in alcohol and in ether and is readily soluble in fixed oils (Ref. 1).

(1) *Safety.* All mercury preparations are highly toxic if absorbed in sufficient amounts. However, the absorption of mercury oleate through the skin is little better than that of metallic mercury, the quantity being too small to be significant (Ref. 2). The Panel concludes that mercury oleate is safe for limited topical application.

(2) *Effectiveness.* Mercury oleate is included in a combination product used for controlling psoriasis (Ref. 3). However, no data on the effectiveness of mercury oleate for this use were submitted, nor is the Panel aware of such data. The Panel concludes that mercury oleate is not effective in controlling psoriasis.

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 764, 1976.

(2) Sollman, T., "A Manual of Pharmacology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 1333, 1957.

(3) OTC Volume 160033.

f. *Resorcinol.* The Panel concludes that resorcinol is safe, but there are no effectiveness data available on its topical use for controlling seborrheic dermatitis or psoriasis.

Resorcinol has been used for many years in the treatment of skin diseases because of its keratolytic, bactericidal, fungicidal, exfoliative, and antipruritic properties (Ref. 1). It is used as an adjunct in the management of seborrheic dermatitis of the scalp and body and of acne. It is a white or nearly white crystalline powder of very low specific gravity, very soluble in water and alcohol, and freely soluble in glycerin and ether (Ref. 2).

(1) *Safety.* Resorcinol has been used for many years without severe toxicity, but it does cross-react with many substances and is cited as being both a sensitizer and a primary irritant. It will occasionally produce a severe allergic reaction and should be kept away from the eyes (Refs. 1 and 2). Fisher (Ref. 3) calls resorcinol a strong sensitizer and cautions against its ability to cross-react with phenol, hexylresorcinol, and hydroquinone. Andrews and Domonkos (Ref. 4) and Fisher (Ref. 3) mention it as a possible sensitizer when used in hair tonics and cosmetics. A review of the cross-sensitivity of resorcinol with other dioxybenzols was covered by Keil in 1962 (Ref. 5).

Resorcinol resembles phenol in its physiologic properties and therefore should not be used over large areas of the body. Enough can be absorbed through the skin to cause a rare systemic poisoning characterized by nausea, vomiting, diarrhea, abdominal pain, nervousness, restlessness or

drowsiness, sweating, bradycardia, and slow or labored breathing. Severe renal and cardiovascular toxicity can also result (Ref. 2). This would not present a problem when the only site of application is the scalp because of the limited size of the area and the thickness of the skin. However, the Panel does not recommend resorcinol for application to thinner skin and potentially larger areas of the body.

(2) *Effectiveness.* Use of resorcinol for seborrheic dermatitis is mentioned in textbooks and review articles (Refs. 6, 7, and 8); however, the product containing resorcinol reviewed by the Panel was for a combination of active ingredients intended for relief of the itching and scaling of psoriasis. The submissions for this product included no data or clinical studies on the effectiveness of resorcinol when used either alone or in combination for controlling psoriasis (Refs. 9 and 10).

In a review of the literature, the Panel found that resorcinol was used as an adjunct in controlling seborrheic dermatitis but not as the sole treatment. There was no reference to its use in controlling psoriasis. The Panel concludes that resorcinol has not been shown to be effective in controlling seborrheic dermatitis and psoriasis.

References

(1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1017–1018, 1973.

(2) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., A. Osol, editor, Mack Publishing Co., Easton, PA, p. 1107, 1980.

(3) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, pp. 225, 299, and 404, 1973.

(4) Andrews, G. C., and A. N. Domonkos, "Diseases of the Skin," 5th Ed., W. B. Saunders Co., Philadelphia, pp. 76 and 87, 1963.

(5) Keil, H., "Group Reactions in Contact Dermatitis Due to Resorcinol," *Archives of Dermatology*, 86:212–216, 1962.

(6) Milne, J. A., "Acne Vulgaris," *in* "Recent advances in Dermatology," edited by A. Rook, Churchill Livingstone, London, pp. 218–244, 1973.

(7) Andrews, G. C., A. N. Domonkos, and C. F. Post, "Treatment of Acne Vulgaris," *Journal of the American Medical Association*, 146:1107–1113, 1951.

(8) Andrews, G. C., "Acne Vulgaris," *The Medical Clinics of North America*, 49:737–746, 1965.

(9) OTC Volume 160237.

(10) OTC Volume 160379.

2. *Category II labeling.* The Panel concludes that certain labeling claims related to safety or effectiveness of an ingredient are unsupported by scientific data or, in some instances, by sound theoretical reasoning and should not be included in the monograph. Many claims from current labels have been placed in Category II because they are vague, too broad, or incomplete. Such labels mislead the consumer.

Many claims that would appear to be acceptable contain certain modifying words that make these claims unclear or imprecise. Modifiers such as "most" or "fast" are not allowed unless they can be substantiated by clinical data. Other examples of vague modifiers are "scientific" as in "scientific treatment" and "persistent" as in "persistent cases."

Other claims classified as Category II include; "* * * proteinized formula time proven to control dandruff," "* * * is an exclusive dandruff control formulation containing a powerful antimicrobial agent," "* * * guaranteed to control dandruff and scalp itch without shampooing."

C. Category III Conditions

1. *Category III active ingredients:*

Alkyl isoquinolinium bromide
Allantoin
Benzalkonium chloride
Benzethonium chloride
Captan
Chloroxylenol
Coal tar preparations (for prolonged application to the skin)
Ethohexadiol
Eucalyptol
Hydrocortisone preparations
Juniper tar
Lauryl isoquinolinium bromide
Menthol
Methylbenzethonium chloride
Methyl salicylate
Phenol and phenolate sodium
Pine tar preparations
Povidone-iodine
Sodium salicylate
Thymol
Undecylenate preparations

a. *Alkyl isoquinolinium bromide.* The Panel concludes that alkyl isoquinolinium bromide is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff in the dosage specified below.

Alkyl isoquinolinium bromide is a mixture of quaternary ammonium analogs of isoquinolinium containing carbon chains of varying lengths.

(1) *Safety.* Sufficient toxicological testing is available to indicate that alkyl isoquinolinium bromide is safe for use in OTC dandruff products (Ref. 1). Results of eye irritancy and dermal toxicity tests using the Draize method (Ref. 2) indicate that alkyl isoquinolinium bromide has little potential for causing irritation. It is reported that the oral LD_{50} of this igredient is 230 mg/kg in rats and 200 mg/kg in guinea pigs. An acute oral toxicity test in which 5 g/kg of a 0.15-percent concentration of alkyl isoquinolinium bromide was administered to rats indicated that at this concentration alkyl isoquinolinium bromide would not be considered a toxic substance (Ref. 1).

The Panel is not aware of any reports of irritation of sensitization occurring from the topical application of this ingredient to normal skin.

(2) *Effectiveness.* It has been demonstrated that alkyl isoquinolinium bromide has antimicrobial activity against bacteria, molds, and fungi, including yeasts (Ref. 1).

The antimicrobial effectiveness of alkyl isoquinolinium bromide as an antibacterial agent has been demonstrated, using a standard phenol coefficient test, against *Salmonella typhosa, Staphylococcus aureus, Escherichia coli,* and *Pityrosporum ovale.* In addition, agar plate zone inhibition tests have shown it to be effective in low concentrations against *Candida albicans, Cryptococcus histolytica, Aspergillus niger,* and *Trichophytan interdigitale.*

Because a definitive relationship between microbial reduction and controlling dandruff has not been established, the Panel concludes that additional data are needed to demonstrate the effectiveness of alkyl isoquinolinium bromide for this use.

(3) *Proposed dosage.* For topical use in a concentration of 0.15 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) OTC Volume 160297.

(2) Draize, J. H., and E. A. Kelley, "Toxicity to Eye Mucosa of Certain Cosmetic Preparations Containing Surface-Active Agents," *Proceedings of the Scientific Section of The Toilet Goods Association*, 17:1–4, 1952.

b. *Allantoin.* The Panel concludes that allantoin is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff, seborrheic dermatitis, and psoriasis in the dosage specified below.

Allantoin is 5-ureidohydantoin, or 2,5-dioxo-4-imidazolidinyl urea. It has a molecular weight of 158 and exists as colorless crystals with a melting point of 226° C (Ref. 1). It is the principal end product of purine metabolism in animals below man and manlike apes, resulting from oxidation of uric acid through the

action of urease (Ref. 2). One g dissolves in 190 mL of water and 500 mL alcohol. It is nearly insoluble in ether. Allantoin has been used since 1912 to stimulate tissue repair in wounds with pus or similar discharges, in skin ulcers, and in similar dermatological conditions (Refs. 1, 2, and 3).

(1) *Safety.* Allantoin appears to be free from toxic effects. No adverse effects resulting from allantoin therapy could be located in the literature, and it is not cited in customary toxicology texts. A patch test on 200 individuals confirmed the safety of allantoin for human use, demonstrating the ingredient to be nontoxic, nonirritating, and nonallergenic. In a repeated insult patch test on 12 individuals, topically applied allantoin was found not to be a primary skin irritant or primary sensitizer (Ref. 4).

One report indicated that allantoin in solution was painless when applied to wounds (Ref. 5). When large doses have been administered orally, intramuscularly, or intravenously to experimental animals and man, the only effect reported to occur is an increase in the number of white blood cells (Refs. 6 and 7).

(2) *Effectiveness.* MacAlister (Ref. 1) found that extracts of comfrey root contained relatively high percentages of allantoin. He therefore substituted solutions of allantoin for solutions of ground comfrey root for topical therapy of chronic ulcers.

The benefits of maggot therapy in healing of wounds have been reported by various investigators (Refs. 8 and 9). Robinson (Ref. 2) showed that allantoin present in the secretions of maggots was responsible for the healing of wounds. Kaplan (Ref. 10) pointed out that allantoin induced healing by stimulating formation of healthy granulations and by removing necrotic material.

Allantoin has been described as a cell proliferant, stimulant of the growth of the epithelial layer of the skin, and chemical debrider. The keratolytic action of allantoin was demonstrated by Flesch (Ref. 11). In this study, allantoin was shown to accelerate the rate of flow of oil through a standardized column of pulverized horny scales, thus indicating its ability to disperse the horny layer.

The Panel received six submissions claiming allantoin as an active ingredient for use in controlling dandruff, seborrheic dermatitis, or psoriasis (Refs. 12 through 17). Two submissions (Refs. 12 and 13) were for a liquid shampoo, and four (Refs. 14 through 17) were for lotions intended for application to psoriatic eruptions.

All the submissions were for products containing allantoin in combination with other ingredients. Of the studies reviewed, only one attempted to demonstrate the contribution of allantoin to the total product (Ref. 14). However, the details of the study were insufficient to evaluate the results conclusively.

The Panel concludes that additional data are needed to show the effectiveness of allantoin in controlling dandruff, seborrheic dermatitis, and psoriasis.

(3) *Proposed dosage.* For topical use in concentrations up to 2 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) MacAlister, C. J., "A New Cell Proliferant: Its Clinical Application in the Treatment of Ulcers," *The British Medical Journal*, 1:10–12, 1912.

(2) Robinson, W., "Stimulation of Healing in Non-healing Wounds by Allantoin Occurring in Maggot Secretations and of Wide Biological Distribution," *The Journal of Bone and Joint Surgery*, 17:267–271, 1935.

(3) Bramwell, W., "The New Cell Proliferant: A Note on the Symphytum Officinale or Common Comfrey," *The British Medical Journal*, 1:12–13, 1912.

(4) Mecca, S. B., "Allantoin and the Newer Aluminum Allantoinates," *Proceedings of the Scientific Section of The Toilet Goods Association*, 31:1–6, 1959.

(5) Robinson, W., "Allantoin, A Constituent of Maggot Excretions, Stimulates Healing of Chronic Discharging Wounds," *Journal of Parasitology*, 21:354–358, 1935.

(6) Greenbaum, F. R., "Allantoin, A Possible Leucocytosis Producing Factor," *Medical Record*, 151:285–288, 1940.

(7) Greenbaum, F. R., "The Story of Allantoin," *American Journal of Pharmacy*, 112:205–216, 1940.

(8) Wilson, E. H., C. A. Doan, and D. F. Miller, "The Baer Maggot Treatment of Osteomyelitis. Preliminary Report of Twenty-six Cases," *Journal of the American Medical Association*, 98:1149–1152, 1932.

(9) Buchman, J., "The Rationale of the Treatment of Chronic Osteomyelitis with Special Reference to Maggot Therapy," *Annals of Surgery*, 99:251–259, 1934.

(10) Kaplan, T., "The Allantoin Treatment of Ulcers," *Journal of the American Medical Association*, 108:968–969, 1937.

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

(12) OTC Volume 160050.

(13) OTC Volume 160339.

(14) OTC Volume 160047.

(15) OTC Volume 160068.

(16) OTC Volume 160255.

(17) OTC Volume 160408.

c. *Benzalkonium chloride.* The Panel concludes that benzalkonium chloride is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff in the dosage specified below.

Benzalkonium chloride is a mixture of alkylbenzyldimethylammonium chlorides (Ref. 1). It is often used as a preservative and is described as a white or yellowish-white, thick gel or gelatinous pieces and as usually having a mild, aromatic odor, and a bitter taste. It is very soluble in water and in alcohol. Mixing benzalkonium chloride in solution with ordinary soaps and with other anionic detergents may decrease or destroy the bacteriostatic activity of the solution (Refs. 1 and 2).

Benzalkonium chloride is also described as a cationic wetting agent possessing detergent and emulsifying actions. In dilutions ranging from 1:750 to 1:40,000, benzalkonium chloride has been utilized as a preoperative disinfectant, as an irrigant in the eye, vagina, and urinary bladder, and for sterile storage of metallic instruments and rubber articles (Ref. 1).

(1) *Safety.* Benzalkonium chloride has been widely used as an antimicrobial and a preservative in topically applied products. This Panel recognizes that the Advisory Review Panel on OTC Antimicrobial I Drug Products concluded that this ingredient is safe for OTC topical use in its report published in the **Federal Register** of September 13, 1974 (39 FR 33131). The data in the manufacturers' submissions (Refs. 3 through 6) serve to further support the safety of benzalkonium chloride. Results of both animal and human toxicologic studies indicate that the concentrations used in products for controlling dandruff are not irritating and do not cause allergic sensitization.

This Panel concludes that benzalkonium chloride is safe for OTC use for controlling dandruff.

(2) *Effectiveness.* The Panel recognizes that quaternary ammonium compounds are often included in shampoo formulations as wetting agents. However, several products reviewed by this Panel claimed banzalkonium chloride as an active ingredient because of its antimicrobial activity. Several studies have been conducted demonstrating the antimicrobial effectiveness of benzalkonium chloride against a variety of organisms including *Pityrosporum ovale* and *Staphylococcus aureus* (Refs. 3 and 5). However, because a definitive relationship between microbial reduction and controlling dandruff has not been established, additional data are needed to demonstrate the effectiveness of banzalkonium chloride in controlling dandruff.

None of the antidandruff studies reviewed by the Panel were conducted using benzalkonium chloride as the sole active ingredient, and the contribution of benzalkonium chloride to the activity of these combination products was not demonstrated. Therefore, the Panel concludes that data are lacking to show effectiveness of this ingredient for OTC use for controlling dandruff.

(3) *Proposed dosage.* For topical use in concentrations of 0.05 to 0.2 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) "The National Formulary," 15th Ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 1211–1212, 1980.

(2) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, Mack Publishing Co., Easton, PA, p. 1100, 1980.

(3) OTC Volume 160297.

(4) OTC Volume 160314.

(5) OTC Volume 160321.

(6) OTC Volume 160352.

d. *Benzethonium chloride.* The Panel concludes that benzethonium chloride is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff and cradle cap in the dosage specified below.

Benzethonium chloride occurs as colorless crystals, with a mild odor and a bitter taste (Ref. 1). One g dissolves in less than 1 mL water, alcohol, and chloroform. The ingredient belongs to a class of compounds identified as quaternary ammonium compounds. It was the most active of a series of related quaternary ammonium compounds studied by Rawlins et al. (Ref. 2), and was found to have antibacterial and antifungal properties.

(1) *Safety.* Benzethonium chloride is a cationic surface-active agent. One submission for a marketed OTC product containing benzethonium chloride in combination with captan was intended for controlling the scaling and itchy scalp associated with dandruff (Ref. 3). The product has been marketed under an approved new drug application since 1954, and in that time more than 5 million units have been sold with few reports of allergic sensitivity, toxicity, or injury.

Another submission was for a combination of benzethonium chloride with amino acids for cradle cap and diaper rash (Ref. 4). No data were submitted on the product's use in the control of cradle cap. However, data were submitted on the combination of ingredients in treating diaper rash. In that study, no irritation or sensitization was observed in any of the infants. As a preliminary to the study the finished product was applied to the arms and forearms of 25 children and 25 infants for up to 4 hours in some cases. No irritation or other side effects were noted.

The Panel concludes that benzethonium chloride is safe for OTC use in controlling dandruff and cradle cap.

(2) *Effectiveness.* Two clinical studies were carried out to evaluate the effectiveness of a product containing a combination of benzethonium chloride and captan in controlling dandruff (Ref. 3). Both studies were placebo-controlled.

Potential subjects were given a container of nonmedicated control shampoo and instructed to shampoo when they got home and again after 1 week and to report for another dandruff evaluation 1 week after the last shampoo. Only those subjects with a high degree of dandruff scaling were accepted in the studies.

Approximately half of those accepted in the studies used a control shampoo initially, and the other half used the test shampoo. All the subjects returned for dandruff evaluations at biweekly intervals for a total of 8 weeks. In both studies it was concluded that the test shampoo was significantly more effective than the control shampoo in controlling the scaling of dandruff.

The Panel is unaware of any data demonstrating the effectiveness of benzethonium chloride as a single active ingredient in controlling dandruff. While the available data support the effectiveness of the combination of benzethonium chloride and captan, they do not indicate the contribution of each ingredient to the combination. Therefore, the Panel concludes that the data are insufficient to permit final classification of benzethonium chloride for OTC use in controlling dandruff.

The submission on the combination of benzethonium chloride with amino acids included data on effectiveness of the product in relieving diaper rash but no data on its use in controlling cradle cap (Ref. 4). The Panel is not aware of any data to support the use of benzethonium chloride in controlling cradle cap. The Panel recognizes, however, that antimicrobials are potentially effective for this use (see part III. paragraph C.1.n. below—*Methylbenzethonium chloride*), but concludes that additional data are needed to establish such effectiveness for benzethonium chloride.

(3) *Proposed dosage.* For topical use in concentrations of 0.065 to 0.2 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 185–186, 1973.

(2) Rawlins, A. L., L. A. Sweet, and D. A. Joslyn, "Relationship of Chemical Structure to Germicidal Activity of a Series of Quaternary Ammonium Salts," *Journal of the American Pharmaceutical Association*, 43:11–16, 1943.

(3) OTC Volume 160306.

(4) OTC Volume 160042.

e. *Captan.* The Panel concludes that captan is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff in the dosage specified below.

Captan is also known chemically as *N*-trichloromethylthio-4-cyclohexene-1,2-dicarboximide or *N*-trichloromethylmercapto-4-cyclohexene-1,2-dicarboximide and is used commercially in makeup, shampoos, face masks, etc. as a preservative, particularly in formulas containing proteins (Refs. 1 and 2). Three submissions included captan in combination products for controlling dandruff (Refs. 3, 4, and 5). It is discussed as a single ingredient in two other submissions (Refs. 1 and 2).

(1) *Safety.* The ability of captan to penetrate the intact skin was studied by using the Draize Sleeve Technique (Ref. 6) on the exposed skin of rabbits (Refs. 1 and 2). Thirty mL of a 20-percent suspension of captan was applied once or twice a week to the rabbits' skin and left in place. After 2 weeks, all the rabbits had survived 100 hours of accumulated exposure with no signs of detectable poisoning. The only adverse reactions seen were redness and scaling of the skin at the site of application.

Chronic toxicity of captan was evaluated by using 2-year diet studies with albino weanling rats weighing 50 g initially (Refs. 1 and 2). The ingredient was incorporated into the diet at levels of 0.025, 0.25, and 1 percent. At the conclusion of the 2-year feeding trials, the following observations were made: (1) Weight gain was impaired only at the 1 percent level; (2) no decisive deviations were seen in the weights of internal organs; (3) the red blood cell count was within the normal range in all groups; (4) white blood cell counts, both total and differential, showed no deviation that could be associated with the treatment; (5) no gross or microscopic pathologic changes were observed.

The ability of captan to irritate the eye was evaluated by instilling 0.1-mL

samples of 0.18 to 25 percent suspensions of captan in water into the conjunctival sacs of the left eyes of each of 12 rabbits (Refs. 1 and 2). Distilled water was instilled into each right eye as a control. The results of the study showed that corneal damage occurred in only one of the treated eyes, and this was from a concentration of 25 percent captan. No injury to the irises of the treated eyes was reported, and only mild conjunctival irritation was observed. This test was repeated using diluted (0.1 percent) captan soap solutions and the soap solutions alone as the control. Mild irritation was caused by the control soap. No increased irritation was seen with the addition of captan to the soap solutions.

Patch tests using a paste containing a concentration of 50 percent captan in water were conducted on humans (Refs. 1 and 2). The paste was applied directly to the skin and occluded. Under these test conditions, no irritation to human skin was observed after 24 hours of continuous contact.

The skin irritation and sensitization potential of captan was evaluated on guinea pigs by the Draize method (Refs. 4 and 5). Ten daily intracutaneous injections of a 0.1-mL solution of 0.1 percent captan in saline served as the sensitizing dose. Challenging tests were performed 22 and 35 days after the sensitizing dose was given. Observations were made 24 and 48 hours after the challenging dose. Mild primary irritation was observed, and it was concluded that captan is a moderate, but not severe, sensitizer.

Subacute skin toxicity tests on intact and abraded skin of rabbits were also conducted, using an anhydrous soap containing 1 percent captan in a hydrophilic ointment base for application to shaved areas on the backs and rumps of the rabbits (Refs. 1 and 2). Three equal areas of the shaved test site were abraded, and 3 g of each ointment were applied. The captan soap preparation was used on one test site on 10 animals and the control soap preparation was used on one test site on the remaining 10 animals, the remaining site was left untreated. The test area was covered with a gauze bandage and sprayed lightly with water at intervals during the 6-hour exposure to keep the area moist. The ointment was washed off at the end of the 6-hour exposure period. This procedure was repeated for a total of 22 applications over a 30-day period. Irritation was scored daily using the Draize system (Ref. 6). The control soap was found capable of inducing a very mild, transient erythema, but this was not intensified by the presence of captan. No cumulative effect was observed. The reactions were no more severe on the abraded areas of the skin than on the intact areas.

Toxicological studies show captan to be safe for antibacterial use by humans (Refs. 1 and 2). Since 1951, it has been safely used in a large number of commercial preparations involving widespread exposure with no significant complaints of toxic reactions. The data also show that captan is not carcinogenic, mutagenic, or teratogenic (Ref. 7).

(2) *Effectiveness.* A double-blind study using 52 men and women with moderate-to-marked dandruff was performed comparing a cream shampoo containing captan with the cream shampoo base (Ref. 1). A baseline score was established by shampooing with a nonmedicated shampoo on the first evening and again 1 week later. The first examination was made 5 days after the second shampoo. Examinations were made again after 2 weeks and after 4 weeks of using the test medications. Both groups improved markedly, but no significant difference in reduction of dandruff scaling was noted between the captan-containing shampoo and the nonmedicated shampoo. The study failed to demonstrate the effectiveness of the single ingredient. Therefore, the Panel concludes that additional data are needed to show the effectiveness of captan in controlling dandruff.

(3) *Proposed dosage.* For topical use in concentrations of 0.1 to 2 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) OTC Volume 160350.
(2) OTC Volume 160393.
(3) OTC Volume 160308.
(4) OTC Volume 160330.
(5) OTC Volume 160306.
(6) Draize, J. H., G. Woodward, and H. O. Calvery, "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes," *Journal of Pharmacology and Experimental Therapeutics*, 82:377–390, 1944.
(7) "Interim Report on Studies of Pesticides and Other Agricultural and Industrial Chemicals," *Congressional Record*, National Cancer Institute Studies of Pesticides, 10996–11001, May 1, 1969.

f. *Chloroxylenol.* The Panel concludes that the safety and effectiveness data on chloroxylenol (previously known as parachlorometaxylenol (PCMX)) are insufficient to permit its final classification for OTC topical use for controlling dandruff and seborrheic dermatitis in the dosage specified below.

Chloroxylenol is a halogen-substituted phenol compound. Halogen substitution increases the antimicrobial activity of phenol derivatives, the halogen in the para position to the hydroxyl group being considered the most effective substitution. The indications are that this compound would have strong antimicrobial activity, but very little information about its in vivo activity on the skin is available.

(1) *Safety.* The Panel has reviewed the agency's comments on chloroxylenol in the Antimicrobial I tentative final order published in the **Federal Register** of January 6, 1978 (43 FR 1210). The agency's findings were based upon the recommendations of the OTC Antimicrobial I Panel, which received very little information with regard to chloroxylenol (39 FR 33134). Only a few acute oral and inhalation studies were submitted. These studies indicated an oral LD_{50} of greater than 3 g/kg in rats, not a high degree of toxicity.

However, because information was not available with respect to subchronic dosing by various routes of application, determination of target organ, dermal and mucosal absorption, and metablic studies, the Antimicrobial I Panel could not make an evaluation of the safety of this chemical in a topical preparation.

This Panel received two submissions for marketed products containing chloroxylenol in a concentration of 2 percent in combination with other active ingredients (Refs. 1 and 2). The irritation potential of 2 percent chloroxylenol was evaluated in a study using nine rabbits in which 0.1 mL of a 1:3 aqueous dilution of 2 percent chloroxylenol was instilled in one eye of each rabbit (Refs. 1 and 2). The opposite eye served as the control. It was shown that if the product was not rinsed out of the treated eye in 2 to 4 seconds, redness and swelling occurred, the eye became partly closed, and there was a discharge.

The primary skin irritation index of 2 percent chloroxylenol was determined by applying the test material to the intact and abraded skin of rabbits. The irritation index was found to be 1.71 (on a scale of 0 to 4) (Refs. 1 and 2). The 2 percent concentration of chloroxylenol was not shown to be a primary skin irritant, was not a corrosive material, and was not an eye irritant when in a 1:3 dilution.

A 21-day human irritation study was performed to compare the irritancy potential of six test materials: (1) 1 percent selenium sulfide; (2) a shampoo of 1 percent salicylic acid and 1 percent sulfur; (3) 1 percent chloroxylenol; (4) 3 percent selenium sulfide; (5) a shampoo of 3 percent salicylic acid and 3 percent

sulfur, and (6) 3 percent chloroxylenol. The samples were applied to gauze patches that were placed on the backs of the subjects and occluded. The patches were removed daily, the test sites examined, and the test material reapplied. The results of the study show that at the 1- and 3-percent concentrations, chloroxylenol was intermediate in irritancy potential, with selenium sulfide being the most irritating, and the salicylic acid and sulfur combination shampoo being the least irritating (Ref. 1).

In a modified Draize sensitization test on 110 subjects (Ref. 1), chloroxylenol gave no indication of contact sensitization.

The Panel concurs with the Antimicrobial I Panel (39 FR 33134) and with the agency (43 FR 1210) that studies to establish the safety of topically applied chloroxylenol are needed before a final determination can be made about the classification of this ingredient.

(2) *Effectiveness.* To support the effectiveness of the product for controlling dandruff and seborrheic dermatitis, partially controlled and uncontrolled studies were submitted. In addition, pertinent medical and scientific literature was cited.

Chloroxylenol was shown to have an antimicrobial effect on selective bacteria but little or no effect on fungi and yeast. The Panel reviewed reports by two different investigators, but the results were not tablulated and appear to be highly subjective (Ref. 1). No conclusions could be drawn from these reports. Therefore, the Panel concludes that additional data are needed to demonstrate the effectiveness of chloroxylenol for controlling dandruff and seborrheic dermatitis.

(3) *Proposed dosage.* For topical use in a concentration of 2 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) OTC Volume 160311.
(2) OTC Volume 160313.

g. *Coal tar preparations (coal tar USP, coal tar distillate, coal tar extract, coal tar solution).* The Panel classifies coal tar in Category III for any other use than a shampoo that is applied on the scalp. Data are needed to show that coal tar is safe for longer application to the scalp than a shampoo would require or for application to the skin on the body. (See part III. paragraph A.1.a. above—*Coal tar preparations (coal tar USP, coal tar distillate, coal tar extract, coal tar solution).*)

h. *Ethodexadiol.* The Panel concludes that ethohexadiol is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff in the dosage specified below.

Ethohexadiol is also known as 1,3-dihydroxy, 2-ethyl hexane; octylene glycol; and 2-ethyl-3-propyl-1,3-propanediol. The Panel received two submissions, one for a shampoo and one for a hair and scalp conditioner, with the labeled active ingredient 1,3 hexadiol, 2-ethyl hexane, also known as ethohexadiol (Refs. 1 and 2). However, the Panel noted that the effectiveness data contained in the submissions dealt with a compound of ethohexadiol and salicylic acid, not with the ingredient ethohexadiol. The manufacturer confirmed that the active ingredient contained in the marketed products was ethohexadiol (Ref. 3).

(1) *Safety.* Ethohexadiol is a slightly oily liquid that causes central nervous system depression if ingested. It has been used as an insect repellent (Ref. 4).

Oral toxicity studies in which the submitted shampoo and hair and scalp conditioner formulations were force-fed to rats over a 14-day period showed the LD_{50} in rats to be around 24 mg/kg for these formulations. Eye irritation tests done in rabbits showed the shampoo formulation to cause mild irritation to the cornea and to the conjunctiva depending on the length of the exposure. The conditioner formulation caused no irritation to the rabbits' eyes. Application of both formulations to the intact and abraded skin of rabbits showed that they are not primary irritants, and neither formulation caused sensitization reactions in guinea pigs (Refs. 1 and 2).

(2) *Effectiveness.* The clinical data contained in the submissions concerning the effectiveness of ethohexadiol consist of testimony by a dermatologist regarding a formulation containing the salicylic acid monoester of ethohexadiol. As explained above, this is not the active ingredient that is identified on the label of the product. In order to demonstrate that the claimed active ingredient, ethohexadiol, is effective in controlling dandruff, adequate clinical trials should be done testing this ingredient against a control on patients with various degrees of dandruff.

(3) *Proposed dosage.* For topical use in concentrations of 3.4 to 12.4 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) OTC Volume 160343.
(2) OTC Volume 160344.
(3) OTC Volume 160410.
(4) Windholz, M., editor, "Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 492, 1976.

i. *Eucalyptol.* The Panel concludes that eucalyptol is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for contolling dandruff in the dosage specified below.

Eucalyptol (cineole) is a volatile oil obtained from the distillation of the fresh leaves of *Eucalyptus globulus* (Ref. 1). The eucalyptus tree is native to Australia, Tasmania, and Malaysia. Eucalyptol is a colorless or pale yellow volatile liquid with a characteristic aromatic, somewhat camphoraceous odor, and a spicy, cooling taste (Ref. 1). Eucalyptol comprises approximately 70 percent of eucalyptus oil and is one of its more active ingredients (Ref. 2). It is insoluble in water but miscible with alcohol, chloroform, and ether.

Eucalyptol has been used topically for the treatment of certain skin conditions. It is an active germicide, but is not as effective as many other volatile oils (Ref. 3).

(1) *Safety.* Eucalyptol, taken internally in large quantities, can be toxic. Symptoms include a burning sensation in the stomach, nausea, vomiting, rapid beating of the heart, dizziness, muscular weakness, a feeling of suffocation, and in severe cases, delirium and convulsions. Death due to respiratory paralysis has occurred in about one-third of the human subjects who have accidentally ingested between 3.5 and 30 mL of eucalyptol. The sensitivity of some people to small doses of eucalyptol may be manifested by skin eruptions (Refs. 2, 3, and 4), but such sensitization occurs infrequently (Ref. 5).

Samitz and Shmunes (Ref. 6) reported that eucalyptol, as well as menthol, thymol, and methyl salicylate, were among the less frequent sensitizing compounds. Adams and Farber (Ref. 7) pointed out that, while eucalyptus oil and menthol are relatively harmless to intact normal skin, they can, when applied to acute eczematous dermatitis, aggravate the disorder. Eucalyptol was cited by Meyer (Ref. 8) as showing fairly rapid percutaneous absorption. The Panel concludes that eucalyptol is safe when applied topically to intact skin.

(2) *Effectiveness.* The Panel received a submission for a marketed product containing eucalyptol in combination with thymol, methyl salicylate, and menthol (Ref. 9). The manufacturer acknowledged in the submission that

the product is marketed primarily as an antiseptic mouth rinse, but its labeling also contains a claim for treatment of "infectious dandruff." It was pointed out by the manufacturer that the product is a combination of active ingredients in a hydroalcoholic solution, with each ingredient exhibiting some activity, and it is the specific combination of ingredients as formulated that is responsible for the total effectiveness of the product. Although this ingredient has demonstrated antimicrobial activity against a variety of microorganisms, a definitive relationship between reduction of microorganisms and controlling dandruff has not been established. The Panel concludes that additional data are needed to demonstrate the effectiveness of the combination and the contribution of each active ingredient, including eucalyptol, to the combination in controlling dandruff.

(3) *Proposed dosage.* For topical use in a concentration of 0.091 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.)*

References

(1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 517, 1973.

(2) Sollmann, T., "A Manual of Pharmacology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 169, 1957.

(3) Osol, A., and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 458–460, 1950.

(4) Blacow, N. W., and A. Wade, editors, "Martindale. The Extra Pharmacopoeia," 26th Ed., the Pharmaceutical Press, London, pp. 1239-1240, 1972.

(5) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, p. 83, 1973.

(6) Samitz, M. H., and E. Shmunes, "Occupational Dermatoses in Dentists and Allied Personnel," *CUTIS: Cutaneous, Medicine for the Practitioner,* 5:180–184, 1969.

(7) Adams, R.M., and E. M. Farber, "Treatment Dermatitis. 1. Secondary Contact Dermatitis," *Postgraduate Medicine,* 45:95–98, 1969.

(8) Meyer, F., and E. Meyer, "Percutane Resorption von atherischen Olen und ihren Inhaltsstoffen," *Arzneimittelforschung,* 9:516–519, 1959.

(9) OTC Volume 160353.

j. *Hydrocortisone preparations (hydrocortisone acetate and hydrocortisone alcohol).* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of hydrocortisone preparations for OTC topical use for controlling dandruff, seborrheic dermatitis, and psoriasis when used in the dosage specified below.

Hydrocortisone is a naturally occurring steroid found in the adrenal cortex. It is cortisone in which the ketone group on carbon 11 has been converted to a hydroxyl group by the addition of two hydrogen atoms. It is also know as cortisol.

Hydrocortisone preparations have been marketed in the United States as prescription drugs since 1952. This Panel notes that the Topical Analgesic Panel Recommended the OTC use of hydrocortisone and hydrocortisone acetate in concentrations of 0.25 to 0.5 percent. (See **Federal Register** of December 4, 1979; 44 FR 69768.) That Panel stated the clinical use of hydrocortisone and hydrocortisone acetate as prescription drugs has confirmed that they are safe for topical application for adults and children 2 years of age and older when applied in a concentration of 0.25 to 0.5 percent. The Topical Analgesic Panel recommended OTC use "for the temporary relief of minor skin irritations, itching, and rashes due to eczema, dermatitis, insect bites, poison ivy, poison oak, poison sumac, soaps detergents, cosmetics and jewelry, and for itchy genital and anal areas."

This Panel is also aware of the recommendation of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products in its report published on March 23, 1982 (47 FR 12480) for the OTC use of combinations of any antifungal ingredient with hydrocortisone or hydrocortisone acetate in concentrations of 0.5 to 1 percent for the treatment of athlete's foot. That Panel also recommends that such combination products contain the following warning: "Do not use longer than 30 days without consulting your doctor."

The Panel received two submissions for hydrocortisone products which are currently not marketed OTC (Refs. 1 and 2).

One submission (Ref. 1) provided information on a topical antifungal, anti-inflammatory cream containing 3 percent calcium undecylenate and 1 percent hydrocortisone acetate in a water-washable base. This combination of ingredients was claimed to relieve the inflammation and irritation associated with such conditions as "redness and scaling of the scalp, face, forehead, and ears associated with dandruff (seborrheic dermatitis)" and "redness, itching, and scaling associated with psoriasis."

The second submission included information on a drug product containing 5 percent coal tar extract (equivalent to approximately 1 percent crude coal tar) and 0.5 percent hydrocortisone alcohol (Ref. 2). The intended use of the product was for the treatment of psoriasis, eczema, and certain other minor dermatoses.

(1) *Safety.* One submission included skin irritation tests conducted on rabbits (Ref. 1). Four test products were used containing (1) the base with 3 percent calcium undecylenate and 1 percent hydrocortisone acetate, (2) the base alone, (3) the base with 1 percent hydrocortisone acetate, and (4) the base with 3 percent calcium undecylenate. A slight-to-moderate erythema was observed with all test products including the base alone. The erythema produced by the test products containing the single ingredients did not differ significantly from the erythema produced by the base alone. Ointments containing 3 percent calcium undecylenate and 1 percent hydrocortisone acetate were shown to evoke no cumulative or acute local toxicity on the rabbits' skin. A slight redness occurred, but disappeared within 24 to 48 hours after ointment application was discontinued.

The second submission included published clinical studies (Refs. 3 through 7) as supporting data on the safety of the combination product. For supporting safety data on the hydrocortisone preparations, the manufacturer cited references reviewed by the Topical Analgesic Panel (44 FR 69823).

This Panel recognizes the wide clinical use of hydrocortisone preparations as prescription drugs and concurs with the Topical Analgesic Panel that hydrocortisone preparations are safe in concentrations of 0.25 to 0.5 percent for the indications cited above. However, this Panel notes that, while corticosteroids, specifically fluorinated corticosteriods applied topically under occlusion, have been shown to promote blanching and flattening of lesions of psoriasis, suppression may require ever-increasing doses, and, when therapy is gradually discontinued, there is a rebound effect (Ref. 8). It is not known whether this effect may occur with hydrocortisone preparations in concentrations higher than 0.5 percent.

Because of the lack of submitted data on the safety of hydrocortisone ingredients alone for controlling seborrheic dermatitis and psoriasis of the scalp and body and dandruff, the Panel concludes it is not possible to make a final determination of the safety of these ingredients for these indications.

(2) *Effectiveness.* Hydrocortisone preparations have had wide use in the topical treatment of dermatoses.

Numerous controlled and uncontrolled studies provide strong documentation for their efficacy as antipruritic and anti-inflammatory agents. This Panel concurs with the Topical Analgesic Panel that hydrocortisone preparations are effective as anti-inflammatory and antipruritic agents and recognizes the wide clinical use by doctors of 1 percent hydrocortisone in the treatment of seborrheic dermatitis. However, data are lacking to demonstrate the safety of this concentration for OTC use, whereas data are lacking to demonstrate the effectiveness of the lower concentrations.

One manufacturer submitted clinical experience reports on a combination product of 3 percent calcium undecylenate and 1 percent hydrocortisone acetate used for a number of skin disorders (Ref. 1). The reports were limited in terms of information provided and offered no useful information on hydrocortisone preparations for controlling dandruff, seborrheic dermatitis, and psoriasis.

In a second submission for a product containing coal tar extract in combination with hydrocortisone alcohol, the manufacturer submitted published clinical studies (Refs. 3 through 7) as supporting data on the effectiveness of the combination product.

Unfortunately, the submitted studies do not evaluate hydrocortisone ingredients used alone in controlling dandruff, seborrheic dermatitis, and psoriasis. Lacking sufficient data on such use of hydrocortisone, the Panel is unable to make a final determination of the effectiveness of hydrocortisone acetate and hydrocortisone alcohol.

(3) *Proposed dosage.* For topical use in concentrations of 0.25 to 1 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) OTC Volume 160342.

(2) OTC Volume 160365.

(3) Bleiberg, J., "Treatment of Subacute and Chronic Dermatoses with a Tar Extract-Hydrocortisone Cream," *Journal of the Medical Society of New Jersey*, 53:371–374, 1956.

(4) Bleiberg, J., "Pruritus Ani. Treatment with Tar Extract Hydrocortisone Cream," *American Practitioner and Digest of Treatment*, 8:1404–1407, 1957.

(5) Clyman, S. G., "Comparative Effects of Hydrocortisone-Coal Tar Extract Creams in Cases of Atopic Dermatitis," *Postgraduate Medicine*, 12:309–312, 1957.

(6) Strick, S., "Comparison of Two Active Topical Preparations in Psoriasis and Atopic Dermatitis," *CUTIS; Cutaneous Medicine for the Practitioner*, 16:579, 582–583, 1975.

(7) Welsh, A. L., and M. Ede, "Three-Way Therapeutic Effectiveness of Tar-Steroid Cream," *Journal of the American Medical Association*, 166:158–159, 1958.

(8) Johnson, M. L, "Certain Cutaneous Diseases with Significant Systematic Manifestations," *in* "Cecil Textbook of Medicine," 15th Ed., edited by P. B. Beeson, W. McDermott, and J. B. Wyngaarden, W. B. Saunders Co., Philadelphia, pp. 2280–2281, 1979.

k. *Juniper tar.* The Panel concludes that juniper tar is safe but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff, seborrheic dermatitis, and psoriasis when used in the dosage specified below.

This ingredient is more commonly referred to as oil of cade or cade oil (Ref. 1). It is obtained by distillation of the woody portion of *Juniperus oxycedrus*. It is a dark brown, clear, thick liquid having a tarry odor and a faintly aromatic bitter taste. Its solubility in water is slight, but it is soluble in alcohol and ether.

Juniper tar is classified as a mild irritant oil and is employed as a topical antipruritic to treat several dermatolgical disorders such as psoriasis, atopic dermatitis, pruritis, eczema, and seborrheic dermatitis (Ref. 2).

Because it is an irritant to the conjunctiva and may also cause swelling of the cornea, care must be taken to keep juniper tar out of the eyes. Labeling of juniper tar products should therefore include a warning to avoid contact of the products with the eyes and to rinse the eyes immediately should this occur.

(1) *Safety.* Conclusive data on oral toxicity are not available; however, if juniper tar is swallowed, it may be damaging to the kidneys (Refs. 2 an 3). The Topical Analgesic Panel concluded that juniper tar is safe for topical use (44 FR 69768), and this Panel concurs that it is safe for topical application in concentrations up to 5 percent up to four times daily.

(2) *Effectiveness.* Juniper tar is markedly keratolytic and has widespread use in the treatment of cutaneous lesions.

Four products containing juniper tar were submitted for review (Refs. 4 through 7); however, none of the submissions contained data on the effectiveness of juniper tar as a single ingredient, and the Panel is unaware of any data to show that this ingredient is effective by itself for controlling dandruff, seborrheic dermatitis, and psoriasis. This ingredient is therefore placed in Category III in order that well-controlled, double-blind studies may be done to demonstrate its effectiveness.

(3) *Proposed dosage.* For topical use in concentrations up to 5 percent to be applied up to four times a day.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) "The National Formulary," 14th Ed., American Pharmaceutical Association, Washington, pp. 803–804, 1975.

(2) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, Mack Publishing Co., Easton, PA, p. 725, 1980.

(3) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 647, 1973.

(4) OTC Volume 160364.

(5) OTC Volume 160407.

(6) OTC Volume 160040.

(7) OTC Volume 160379.

1. *Lauryl isoquinolium bromide.* The Panel concludes that lauryl isoqinolinium bromide is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff when used in the dosage specified below.

Lauryl isoquinolinium bromide (2-dodecylisoquinolinium bromide) is a quaternary ammonium compound; quaternary ammonium compounds are a group of salts that have been used as surface-active and antimicrobial agents since 1935.

(1) *Safety.* Available toxicological testing data indicate that lauryl isoquinolinium bromide has little or no dermal toxicity, but has potential toxicity if ingested orally (Ref. 1).

In a study utilizing nine rabbits, 0.1 mL of a combination product containing 0.05 percent lauryl isoquinolinium bromide and 0.05 percent benzalkonium chloride was instilled in the right eye of each rabbit (Ref. 2). The left eye served as the control. The product was found to be essentially nonirritating.

A repeated insult patch test using the same combination product on 61 subjects showed mild irritation characteristic of skin fatigue; however, there was no evidence of sensitization to the samples in any test subjects (Ref. 2).

Based on clinical experience and the amount of data available in the literature, the Panel concludes that lauryl isoquinolinium bromide is safe for use on the scalp in a concentration of 0.05 percent.

(2) *Effectiveness.* No data were submitted on the effectiveness of lauryl

isoquinolinium bromide as a single ingredient for controlling dandruff.

One submission furnished data on a combination of 0.05 percent lauryl isoquinolinium bromide with 0.05 percent benzalkonium chloride, a similar quaternary ammonium salt (Ref. 2). A crossover home use test of this combination product claimed for use as an after shampoo rinse, showed a significant decrease in dandruff in subjects using this product twice a week for 5 weeks. When the same subjects shampooed twice a week for 5 weeks and did not use the rinse, a small, but not significant, decrease in dandruff was also observed. In another study the product was used after shampooing by 2 groups of 10 adult males who had moderately severe dandruff (a clinical grade of 5 on a 10-point scale). The product was judged to have a moderating effect on dandruff. These results were supported by several other studies, and the product was also shown to be effective against *Pityrosporum ovale* and *Staphylococcus aureus* (Ref. 2). No submitted studies assessed the contribution of the lauryl isoquinolinium bromide to the combination, and the Panel knows of no data to show that this ingredient is effective when used alone for controlling dandruff. Although this ingredient has demonstrated antimicrobial activity against a variety of microorganisms, a definitive relationship between reduction of microorganisms and controlling dandruff has not been established. The Panel concludes that additional data are needed to demonstrate the effectiveness of lauryl isoquinolinium bromide for controlling dandruff.

(3) *Proposed dosage.* For topical use in a concentration of 0.05 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) OTC Volume 160297.
(2) OTC Volume 160352.

m. *Menthol.* The Panel concludes that menthol is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff, seborrheic dermatitis, and psoriasis when used in the dosage specified below.

Menthol is a secondary alcohol obtained from peppermint oil and other mint oils, or prepared synthetically by hydrogenation of thymol (Refs. 1 and 2). It is known chemically as hexahydrothymol or 3-paramenthanol. Menthol exists as colorless hexagonal crystals, as needlelike crystals in fused masses, or as a crystalline powder with a peppermint-like odor. Menthol is only slightly soluble in water, but soluble in alcohol, ether, chloroform, mineral oil, and fixed and volatile oils (Refs. 2 and 3).

Menthol is lipophilic and germicidal, being more powerful than phenol (Ref. 2). Gershenfeld and Miller (Ref. 4) reported that a saturated aqueous solution of menthol has some antimicrobial properties.

Menthol also has antipruritic activity and is thought to provide relief by substituting a cool sensation for that of itching. It has been used topically in a 1- to 10-percent solution (Ref. 2).

(1) *Safety.* Menthol can cause sensitization in certain individuals (Refs. 5 and 6); however, the index for potential sensitization is low. Symptoms include urticaria, erythema, and other cutaneous lesions.

Menthol may be dangerously toxic if ingested in large quantities. Toxic effects include nausea, abdominal pain, vomiting, and symptoms of central nervous system depression, such as dizziness, staggering gait, flushed face, sleepiness, slow respiration, and coma. Menthol is excreted in the bile and urine as a glucuronide; the fatal oral does in humans is estimated to be about 2 g (Ref. 5).

When a 20-percent solution of menthol is vigorously applied to the skin, an intense and lasting cooling sensation results. This is followed by numbness with a slight smarting sensation and hyperemia. Irritation beyond the rubefacient stage does not occur.

This Panel finds menthol safe for topical use, but concurs with the Topical Analgesic Panel that care should be taken to ensure that safety of this ingredient is maintained through adequate packaging, labeling, and application. (See **Federal Register** of December 4, 1979; 44 FR 69828.)

(2) *Effectiveness.* The Panel received a submission for a marketed product containing menthol in combination with thymol, eucalyptol, and methyl salicylate (Ref. 7). The manufacturer acknowledged that the product is marketed primarily as an antiseptic mouth rinse, but its labeling also contains an indication for the treatment of "infectious dandruff." It was pointed out by the manufacturer that the product is a combination of active ingredients in a hydroalcoholic solution, with each ingredient exhibiting some activity, and that it is the specific combination of ingredients as formulated that is responsible for the total effectiveness of the product.

The Panel also received a submission for a hair and scalp conditioner containing a combination of 1 percent menthol and 2 percent sulfur (Ref. 8). This product is used as a grooming aid to treat dandruff and itchy scalp. The manufacturer states that menthol is added as an antipruritic, referring for support of effectiveness to the finding of the Topical Analgesic Panel (44 FR 69828) that menthol is an effective antipruritic agent at concentrations of 0.1 to 1 percent.

A third submission reviewed was for a shampoo containing a combination of 1.5 percent menthol and 7.5 percent coal tar solution intended for use in dandruff, seborrheic dermatitis, and psoriasis (Ref. 9).

The Panel concludes that the data submitted are insufficient to demonstrate the effectiveness of menthol as a single ingredient for controlling dandruff, seborrheic dermatitis, and psoriasis. Although menthol has demonstrated activity against a variety of microorganisms, a definitive relationship between reduction of microorganisms and control of these conditions has not been established. The submitted data are also insufficient to demonstrate that the addition of menthol to the other ingredients contributes to the effectiveness of the combinations.

(3) *Proposed dosage.* For topical use in concentrations of 0.04 to 1.5 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 757, 1976.

(2) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 697–698, 1973.

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(4) Gershenfeld, L., and R. E. Miller, "The Bactericidal Efficiency of Menthol and Camphor," *American Journal of Pharmacy*, 105:490–500, 1933.

(5) Blacow, N. W., and A. Wade, editors, "Martindale. The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, pp. 374–375, 1972.

(6) Rudzki, E., and D. Kleniewska, "Kontaktallergie auf einige Lokaltherapeutika und Konservierungsmittel," *Dermatologica*, 143:36–42, 1971.

(7) OTC Volume 160353.

(8) OTC Volume 160404.

(9) OTC Volume 160315.

n. *Methylbenzethonium chloride.* The Panel concludes that methylbenzethonium chloride is safe, but there are insufficient data available to permit its final classification for OTC topical use for controlling cradle cap when used in the dosage specified below.

Methylbenzethonium chloride is a quaternary ammonium compound, the quaternary ammonium compounds being a group of salts that have been used widely as antimicrobial agents since 1935. These compounds have been used for cold instrument sterilization in hospitals (Ref. 1).

Methylbenzethonium chloride has cationic surface activity. Surface-acting antimicrobials have been shown to affect cell membrane permeability causing the loss or leakage of cell contents.

(1) *Safety.* The Panel is aware of the agency's conclusions on the use of quaternary ammonium compounds as described in the tentative final order on OTC topical antimicrobial drug products. (See **Federal Register** of January 6, 1978; 43 FR 1218.) In that document the Commissioner expressed no serious concern with the safety of quaternary ammonium compounds including methylbenzethonium chloride for topical use.

The Panel concurs with the agency and concludes that methylbenzethonium chloride is safe for OTC topical use at the dosage specified below.

(2) *Effectiveness.* The Panel received one submission and supplemental data for a marketed product containing 0.07 percent methylbenzethonium chloride in an emulsified petrolatum base (Refs. 2 and 3). The product is labeled for infant scalp care. In addition, the product is claimed to soften and separate crusts and scales from the scalp and help prevent and treat local infection. The manufacturer indicated that methylbenzethonium chloride is included for its bacteriostatic activity in prevention of infection of a cradle cap lesion by susceptible microorganisms. The directions for treatment are to massage the product into the affected scalp area three times daily for 3 days followed by a cleansing shampoo and fine combing or brushing to remove residual scales. Two references from the literature were provided to support the effectiveness of the product (Refs. 4 and 5). In one study by Pasachoff and Maffia (Ref. 4), 150 infants were followed for development of cradle cap. A product containing methylbenzethonium chloride was used on 50 infants, soap and water was used on 50 infants, and petroleum jelly was used on the remaining 50 infants. In the study, 15 infants developed cradle cap. Of these, eight infants had been treated with soap and water, six had been treated with petroleum jelly, and one had been treated with the product containing methylbenzethonium chloride. In a second study, 60 of 120 infants with cradle cap were treated with the methylbenzethonium product, 30 were treated with soap and water, and 30 were treated with a 1-percent salicylic acid ointment. It is reported that, of the 60 infants treated with the methylbenzethonium product, 97 percent experienced cure or improvement. Of the 30 infants treated with soap and water, 60 percent experienced improvement; and 92 percent of the 30 who were treated with salicylic acid experienced improvement.

In a study by Agerty and Fischer (Ref. 5) two groups of infants and children with cradle cap were treated with either a salicylic acid lotion or the methylbenzethonium chloride product. Sixty children ranging in age from 3 weeks to 15 months were examined. Thirty children were treated with the product containing methylbenzethonium chloride, and 30 were treated with the salicylic acid lotion. The concentrations of both ingredients were not given; however, the article refers to the marketed product submitted to the Panel which contains 0.07 percent methylbenzethonium chloride. Twenty-two of the 30 children treated with the product containing methylbenzethonium chloride were described as cured as compared with 12 of the 30 that were treated with the salicylic acid lotion. Eight children who did not respond at all to the salicylic acid treatment were subsequently treated with the methylbenzethonium chloride product, and six of these eight children were described as cured. Two showed no improvement.

While these studies suggest that methylbenzethonium chloride may be effective in controlling or preventing cradle cap, they are not adequate to permit final classification of this ingredient. Details necessary for a complete evaluation of the studies are lacking.

(3) *Proposed dosage.* For topical use in a concentration of 0.07 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed. edited by A. Osol, Mack Publishing Co., Easton, PA, p. 1100, 1980.

(2) OTC Volume 160319.

(3) OTC Volume 160322.

(4) Pasachoff, H. D., and A. J. Maffia, "A New Treatment for Cradle Cap," *New York Journal of Medicine,* 57:265–267, 1957.

(5) Agerty, H. A., and C. C. Fischer, "The Prevention and Treatment of Seborrhea Capitis with an Antibacterial Emulsion Containing Methylbenzethonium Chloride," *Archives of Pediatrics,* 74:219–222, 1957.

o. *Methyl salicylate.* The Panel concludes that methyl salicylate is safe, but there are insufficient effectiveness data available to permit its final classification for OTC topical use for controlling dandruff when used in the dosage specified below.

Methyl salicylate, also known as 2-hydroxybenzoic acid methyl ester, wintergreen oil, betula oil, sweet birch oil, and teaberry oil, occurs as a colorless, yellowish, or reddish oily liquid with a fragrant odor and a taste of wintergreen. One g is soluble in 1,500 mL water. It is soluble in chloroform and ether and miscible with alcohol and glacial acetic acid. Its pharmacologic activities are similar to those of salicylic acid and 1 mL methyl salicylate has a salicylate content equivalent to 1.4 g aspirin. Its primary topical use is as a counterirritant. It is also employed for flavoring candies, etc., and in perfumery (Refs. 1 and 2).

(1) *Safety.* Except for severe local irritation of the mucous membranes, ingestion of methyl salicylate is not notably different in its toxic actions from other salicylates (Ref. 3). The average lethal dose of methyl salicylate is estimated to be approximately 10 mL for children and 30 mL for adults (Refs. 4 and 5), but the ingestion of as little as 4 mL methyl salicylate has been reported to cause fatalities in children (Ref. 6). The Topical Analgesic Panel reviewed and evaluated methyl salicylate for OTC topical use as a counterirritant and found it safe in concentrations ranging from 10 to 60 percent. (See **Federal Register** of December 4, 1979; 44 FR 69830.) This Panel concurs.

(2) *Effectiveness.* The Panel received a submission for a marketed product containing methly salicyalte in combination with thymol, eucalyptol, and menthol (Ref. 7). The product is marketed primarily as an antiseptic mouth rinse, but its labeling also contains an indication for the treatment of "infectious dandruff." It was pointed out by the manufacturer that the product is a combination of active ingredients in a hydroalcoholic solution, each exhibiting some activity, and that the specific combination of ingredients as formulated is responsible for the total effectiveness of the product. The Panel is unaware of any data which

demonstrate the effectiveness of methyl salicylate as a single ingredient in the control of dandruff.

(3) *Proposed dosage.* For topical use in a concentration of 0.06 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) Culbreth, D. M. R., "A Manual of Materia Medica and Pharmacology," 7th Ed., Lea and Febiger, Philadelphia, pp. 460–462, 1927.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 798, 1976.

(3) Davison, C., E. F. Zimmerman, and P. K. Smith, "On the Metabolism and Toxicity of Methyl Salicylate," *Journal of Pharmacology and Experimental Therapeutics*, 132:207–211, 1961.

(4) Deichmann, W. B., and H. W. Gerarde, "Toxicology of Drugs and Chemicals," Academic Press, New York, p. 662, 1969.

(5) Soine, T. O., and R. E. Willette, "The Antipyretic Analgesics," *in* "Textbook of Organic Medicinal and Pharmaceutical Chemistry," 5th Ed., edited by C. O. Wilson, O. Gisvold, and R. F. Doerge, J. B. Lippincott Co., Philadelphia, p. 675, 1965.

(6) Beckman, H., "The Year Book of Drug Therapy—1969," Year Book Medical Publishers, Chicago, p. 268, 1969.

(7) OTC Volume 160353.

p. *Phenol and phenolate sodium.* The Panel concludes that phenol and phenolate sodium are safe, but there are insufficient effectiveness data available to permit final classification for OTC topical use for controlling seborrheic dermatitis and psoriasis when used in the dosage specified below.

Phenol, also referred to as carbolic acid, has been used as an antimicrobial since 1867; however, its use topically has declined in recent years with the availability of new and more effective antimicrobials. It also has demonstrated activity as an external analgesic.

Although phenol is no longer a significantly used antimicrobial, it is still formulated in topical products, and there is a large body of literature concerning its effectiveness. Phenol can be bacteriostatic or bactericidal, depending on the concentration; it is not sporicidal. Its antimicrobial activity may be decreased in the presence of excess oil or fats.

(1) *Safety.* Phenol is absorbed by all routes of administration and can reach the circulation even when applied to intact skin. One portion is oxidized to hydroquinoline and pyrocatechol, and another portion is oxidized more completely. Approximately 80 percent is excreted by the kidney, either unchanged or conjugated with glucuronic and sulfuric acids (Ref. 1). Because of this metabolism, phenol can be quite toxic to the kidneys. The Panel does not recommend its use in body folds or on large areas of the body.

One case was reported in which an adult male ingested a 2-ounce bottle of a phenol and saline combination, containing 600 mg of phenol. There were no untoward effects. Leider and Moser (Ref. 2) suggest that the fatal dose of phenol for adults may be between 1.5 and 8.5 g.

The Panel is aware of the findings of the Topical Analgesic Panel published in the **Federal Register** of December 4, 1979 (44 FR 69832) in which it concluded that phenol was safe for OTC use in concentrations from 0.5 to 2 percent. The Panel also has reviewed the agency's findings on phenol as stated by the Commissioner in the Antimicrobial I tentative final order in the **Federal Register** of January 6, 1978 (43 FR 1222 and 1237). The Commissioner noted a published report that indicated that doses of phenol above 5 percent act to promote tumors in mice when applied topically (Ref. 3) and that the Antimicrobial I Panel concluded that carcinogenicity studies should be done. The Commissioner recognized that the accepted protocol for determining the potential for carcinogenicity of a drug is the standard bioassay of the National Cancer Institute (NCI). Phenol has been included in the NCI National Toxicology Program, but the results are not yet available. This Panel is aware that the agency will carefully review the results of the NCI study when they are available and will determine at that time whether any regulatory action is appropriate.

The Commissioner concluded that the total concentration of phenol in powders and in aqueous, alcoholic or oil formulations should be restricted to less than 1.5 percent, and phenolate sodium should be considered as phenol in the calculation of the total phenol in any formulation. The Commissioner further concluded that phenol may be used as an inactive ingredient for its aromatic characteristics, but at a concentration of less than 0.5 percent.

Concentrations of phenol of 1.5 percent of more are not generally recognized as safe. The Panel finds phenol safe for use on the scalp in the control of seborrheic dermatitis and psoriasis in the dosage specified below.

(2) *Effectiveness.* Phenol presumably exerts its germicidal action by denaturing protein (Ref. 1). The protein-phenol complex is a loose one. Therefore, phenol is diffusible and penetrates the tissues. The compound has a markedly toxic action, and because of its penetrability, affects even intact skin. This toxic action to cells is the probable action in psoriasis; in a disease in which the cells are duplicating as frequently as in seborrheic dermatitis and psoriasis, such an action may be helpful.

When applied locally, phenol exerts a depolarizing anesthetic action. A 5-percent solution, even on the unabraded epithelial surface, produces a feeling of warmth and tingling and eventually a rather complete local anesthesia. This concentration can cause necrosis. In one submission reviewed by the Panel, the concentration of phenol is less than 1 percent by volume in a paraffin base (Ref. 4). This would enable the phenol to exert a mild anesthetic-antipruritic effect without causing necrosis. The clinical studies included in this submission were not recent and were not controlled (Refs. 5, 6, and 7). The only control was withdrawing treatment, at which time the psoriatic scaling or seborrheic dermatitis returned.

The Panel also reviewed a combination of phenol, salicylic acid, and allantoin in an emulsion base for psoriasis; a mixture of phenol and sulfur in an ointment base for softening scaly, dry patches of skin in psoriasis; and a mixture of phenol and phenolate sodium to control itching in seborrheic dermatitis (Refs. 8 through 11). These submissions did not include adequate studies to demonstrate the effectiveness of phenol or phenolate sodium in controlling psoriasis and seborrheic dermatitis.

Although these ingredients have demonstrated antimicrobial activity against a variety of microorganisms, a definitive relationship between reduction of microorganisms and controlling seborrheic dermatitis and psoriasis has not been established. The Panel concludes that effectiveness data are insufficient for final classification of phenol and phenolate sodium at this time.

(3) *Proposed dosage.* For topical use in a total phenol concentration up to 1.2 percent.

(4) *Labeling.* The Panel recommends the category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) Harvey, S.C., "Antiseptic and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmaceutical Basis of Therapeutics," 5th Ed., edited by A. G. Gilman, L. S. Goodman, and A. Gilman, MacMillan Publishing Co., Inc., New York, p. 967, 1980.

(2) Leider, M., and H. S. Moser, "Toxicology of Topical Dermatologic

Preparations. Report of a Case in which 2 Ounces of a Phenol-Saline Preparation Were Swallowed," *Archives of Dermatology*, 83:928–929, 1961.

(3) Boutwell, R. K., and D. K. Bosch, "The Tumor-Promoting Action of Phenol and Related Compounds for Mouse Skin," *Cancer Research*, 19:413–424, 1959.

(4) OTC Volume 160201.

(5) Vickers, M. A., "The Clinical evaluation of a Liquid Suggested for Psoriasiform Problems of the Scalp," *Journal of the Main Medical Association*, 45:332, 1954.

(6) Sulzberger, M. D., and J. Obadia, "A Modified Liquid Petrolatum Preparation," *Archives of Dermatology*, 73:373–375, 1956.

(7) Goldberg, L. C., and S. B. Barnett, "Treatment of Cutaneous Problems with a Carbolated Medication, "*Antibiotic Medicine and Clinical Therapy*, 4:594–597, 1957.

(8) OTC Volume 160060.

(9) OTC Volume 160326.

(10) OTC Volume 160408.

(11) OTC Volume 160255.

q. *Pine tar preparations (pine tar and rectified pine oil).* The Panel concludes that pine tar preparations are safe, but there are insufficient effectiveness data available to permit their final classification for OTC topical use for controlling dandruff, seborrheic dermatitis, and psoriasis in the dosage specified below.

Pine tar is commonly referred to in the compendia as "tar" and is classified as a topical antieczematic and rubefacient (Refs. 1 and 2). Its principal use, when suitably diluted, is as a mildly stimulating and antiseptic application to treat chronic skin diseases such as eczema, seborrheic dermatitis, and psoriasis (Refs. 3. and 4).

Pine tar is usually obtained as a byproduct in the manufacture of charcoal or acetic acid from the destructive distillation of the wood of the *Pinus palustris* (Refs. 4 and 5). It is a complete mixture of phenolic bodies, for the most part insoluble in water. It is a very viscid, blackish-brown liquid. It is translucent in thin layers but becomes granular and opaque with age. It has a characteristic odor and bitter taste (Ref. 4).

Rectified tar oil is defined as the volatile oil from pine tar rectified by steam distillation (Ref. 6). It consists largely of phenolic substances and occurs as a thin liquid having a dark reddish-brown color. It is insoluble in water, but miscible with alcohol. It is prefered to pine tar for most medicinal uses, because the insoluble and inert substances have been removed.

(1) *Safety.* The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products stated in their report of September 9, 1976 (41 FR 38367) that pine tar was safe for oral ingestion in the dosage range used as an expectorant, pointing out that it had been used for decades as an expectorant without any recorded reports of adverse effects. Current reference texts (Refs. 2 and 4 through 8) list pine tar as moderately toxic.

Pine tar is used for the same conditions as coal tar and can also cause allergic sensitization and folliculitis. Caution should be observed regarding its photosensitizing effects. Systemic toxic effects may occur if used over widespread areas, especially in children (Ref. 9).

The Miscellaneous External Panel finds pine tar safe for application to the scalp for controlling dandruff, seborrheic dermatitis, and psoriasis.

(2) *Effectiveness.* Pine tar, like coal tar, is not uniform in composition, and there is no accurately standardized pine tar product. The Panel is aware of no data to show that pine tar alone is effective for use in controlling dandruff, seborrheic dermatitis, and psoriasis, and none were submitted (Refs. 10 through 15). This ingredient is therefore placed in Category III so that well-controlled, double-blind studies may be done to demonstrate its effectiveness in controlling dandruff, seborrheic dermatitis, and psoriasis.

(3) *Proposed dosage.* For topical use in concentrations of 0.33 to 8 percent.

(4) *Labeling.* the Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.)*

References

(1) "National Dispensatory," J. B. Lippincott Co., Philadelphia, pp. 1254–1256, 1894.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Mack Publishing Co., Rahway, NJ, p. 969, 1975.

(3) Osol, A., and R. Pratt, editors, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1141, 1973.

(4) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharamaceutical Sciences," 16th Ed., edited by A. Osol, Mack Publishing Co., Easton, PA, p. 725, 1980.

(5) "The National Formulary," 14th Ed., American Pharmaceutical Association, Washington, p. 578, 1975.

(6) "The National Formulary," 10th Ed., American Pharmaceutical Association, Washington, pp. 588–590, 1955.

(7) "AMA Drug Evaluations," 1st Ed., American Medical Association, Chicago, p. 498, 1971.

(8) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, pp. 128–129, 1976.

(9) Modell, W., editor, "Drugs of Choice. 1968–1969," C. V. Mosby Co., St. Louis, p. 690, 1967.

(10) OTC Volume 160069.

(11) OTC Volume 160070.

(12) OTC Volume 160364.

(13) OTC Volume 160407.

(14) OTC Volume 160310.

(15) OTC Volume 160328.

r. *Povidone-iodine.* The Panel concludes that povidone-iodine is safe, but data are lacking to demonstrate its effectiveness for OTC topical use for controlling dandruff and seborrheic dermatitis of the scalp when used in the dosage specified below.

Povidone-iodine is a complex of iodine and the nonsurfactant polymer, polyvinylpyrrolidone from which free iodine is released slowly, providing a broad spectrum of antimicrobial activity (Ref. 1).

(1) *Safety.* The Panel received two submissions for a shampoo containing 7.5 percent povidone-iodine (Refs. 2 and 3). Its formulation is similar to that of a povidone-iodine surgical scrub and skin cleanser.

Povidone-iodine has been found to be nonirritating to the skin and mucous membranes. Only one alleged sensitivity reaction resulted from controlled skin patch testing according to data obtained from published literature. Microscopic examination of tissue cultures and minor skin wounds showed less intense tissue injury following the application of povidone-iodine compared with other antimicrobial agents (Ref. 2).

No adverse skin or mucosal reactions were reported in 16 controlled studies involving over 3,400 patients (Ref. 2). This, coupled with the patch-testing results cited above, provides substantial evidence to support the safety of povidone-iodine for topical use.

(2) *Effectiveness.* Three controlled studies were performed to show the effectiveness of povidone-iodine used in a shampoo for controlling dandruff (Refs. 2, 3, and 4). In one submission, 106 subjects with severe or moderately severe dandruff were studied in a double-blind study using the shampoo detergent base as the control (Ref. 3). The subjects shampooed twice weekly for the first 2 weeks of the study, after which the improvement of the patients using the shampoo with povidone-iodine was found to be significantly greater (95 percent confidence level) than those patients using the control. Fifty-nine percent of the patients using the povidone-iodine shampoo and 32 percent of the patients using the control experienced improvement, but none were completely cleared of dandruff. Both groups then shampooed once weekly with no significant difference seen between the active and control groups at 4, 6, and 8 weeks. This study suggests that the povidone-iodine shampoo is effective in controlling dandruff when used twice weekly, but not once weekly.

Frank (Ref. 4) treated 114 patients with seborrheic dermatitis of the scalp with the povidone-iodine shampoo for 6 weeks. Complete control of symptoms and scaling resulted in 102 patients; the other 12 patients showed improvement but still had some scaling. Ten additional seborrheic dermatitis patients using only the detergent shampoo base as a control improved, but complete control of the condition was achieved in only three. In the Panel's opinion, the control group was too small for adequate comparison.

A double-blind study using 101 subjects with seborrheic dermatitis of the scalp compared the povidone-iodine shampoo with a 2.5-percent selenium sulfide suspension (Ref. 3). The subjects shampooed twice weekly for 2 weeks and once weekly thereafter.

On a single return visit, 1 to 12 weeks later (average 3 weeks for povidone-iodine, 3.6 weeks for selenium sulfide), itching, redness, and scaling were evaluated. Eighty percent of the subject using the povidone-iodine shampoo and 85 percent of the subjects using the selenium sulfide shampoo improved.

While this study indicates that povidone-iodine may be effective in the control of seborrheic dermatitis of the scalp, it lacks a control group, and return visits were not precisely timed.

The Panel concludes that additional data are needed to demonstrate the effectiveness of povidone-iodine in controlling dandruff and seborrheic dermatitis of the scalp.

(3) *Proposed dosage.* For topical use as a shampoo in a concentration of 7.5 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) "AMA Drug Evaluations," 4th Ed., John Wiley and Sons, Inc., New York, pp. 1021–1022, 1980.

(2) OTC Volume 160331.

(3) OTC Volume 160395.

(4) Frank, L., "Povidone-Iodine Shampoo for Seborrheic Dermatitis and Pyodermas," *New York State Journal of Medicine*, 59:2892–2894, 1959.

s. *Sodium salicylate.* The Panel concludes that sodium salicylate is safe, but data are lacking to show its effectiveness in controlling dandruff and seborrheic dermatitis when used in the dosage specified below.

Sodium salicylate is obtained by mixing salicylic acid with distilled water and sodium carbonate (Ref. 1) and occurs as an amorphous or microcrystalline powder or scales. It may either be colorless or have a faint pink tinge, and has a slightly saline taste. It has a long history of use for relieving pain and reducing fever when taken orally and was introduced into therapy about 25 years before aspirin (Ref. 2).

(1) *Safety.* Sodium salicylate has similar side effects to aspirin and the other salicylic acid derivatives. Systemic absorption occurs whether these compounds are administered orally, rectally, intravenously, or cutaneously. The possible side effects of toxic dose, collectively know as salicylism, are nausea, decreased ability to hear, ringing in the ears, confusion, metabolic disturbances, hallucinations, and, in some extreme cases, death. However, the Panel is unaware of any instances of salicylism resulting from topical application of sodium salicylate in a 0.5-percent concentration.

Salicylic acid softens and destroys the outer layer of the skin by increasing its water concentration. This causes the epithelium, or horny layer of skin, to swell, soften, and shed. The Panel believes that the amount of salicylic acid released by the 0.5-percent concentration of sodium salicylate is not sufficient to damage the skin. The Panel concludes that sodium salicylate in this concentration is safe for use on the scalp.

(2) *Effectiveness.* In the preparation in which it was submitted, sodium salicylate is combined with sulfur in a synthetic detergent base. The rationale for the inclusion of the sodium salicylate is that in the process of shampooing a small amount of salicylic acid is released to exert a mild keratolytic effect on the scalp (Ref. 3).

The original formulation also included an antiseptic, which has since been removed because of safety concerns. In one study, this original formulation was tested in a group of 150 women who had seborrheic dermatitis, seborrhea oleosa, or excessive dandruff (Ref. 4). Subjects were instructed to apply about a tablespoonful of the preparation to the wet hair, rub it in thoroughly, and rinse. A second application was worked into a lather and allowed to remain on the hair 3 to 5 minutes, after which the scalp was rinsed thoroughly. The procedure was repeated twice weekly for 2 or 3 weeks, and once weekly thereafter. After a period of time ranging from 3 weeks to a year, the subjects were evaluated, with 100 showing excellent results, 30 showing good results, and 6 showing poor results. There were 2 instances of adverse reactions to the preparation amounting to burning and increased itching, and 14 subjects were not adequately followed.

The Panel finds this study deficient in that it was not double-blinded or placebo-controlled, and the contribution of the sodium salicylate to the combination was not assessed. In fact, the Panel is not aware of any data showing the effectiveness of sodium salicylate in controlling dandruff and seborrheic dermatitis, and none were submitted. The Panel recommends double-blind, placebo-controlled clinical trials testing sodium salicylate alone for effectiveness in controlling dandruff and seborrheic dermatitis.

(3) *Proposed dosage.* For topical use in a concentration of 0.5 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) Swinyard, E. A., "Analgesics and Antipyretics," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, Mack Publishing Co., Easton, PA, p. 1062, 1980.

(2) Martin, B. K., "Significant Factors in the History of Aspirin," *in* "Salicylates: An International Symposium," edited by A. St. J. Dixon et al., Little, Brown and Co., Boston, pp. 6–8, 1963.

(3) OTC Volume 160320.

(4) Robinson, R. C. V., and D. Roberts, "A New Medicated Shampoo for Seborrheic Scalp Conditions," *Maryland State Medical Journal*, 12:223–225, 1963.

t. *Thymol.* The Panel concludes that thymol is safe, but data are lacking to show its effectiveness in controlling dandruff when used in the dosage specified below.

Thymol (5-methyl-2-isopropyl-1-phenol) is also known as thyme camphor. It may be prepared synthetically or obtained from volatile oils distilled from *Thymus vulgaris* and other related plant sources. Thymol occurs as large colorless crystals or as a white crystalline powder; it melts at 48°to 51° C. One g dissolves in 1000 mL of water. It is highly soluble in alcohol, chloroform, in mineral, and in volatile oils (Ref. 1). Thymol has a characteristic aromatic odor of thyme and a pungent taste. Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal, and anthelmintic properties (Ref. 2).

(1) *Safety.* Thymol has long been used for a variety of medicinal purposes, but has been supplanted by newer, more effective drugs. It has been used in mouthwashes for its antiseptic action and as a flavoring agent. It also has been used internally as an intestinal antiseptic and anthelmintic, especially against hookworm (Refs. 3 and 4).

The intravenous LD_{50} of thymol in mice is 74 mg/kg (Ref. 5). Jenner (Ref. 6) studied the acute oral toxicity of thymol instilled by intubation into the stomachs of rats and guinea pigs. The oral LD_{50} for the rat was 980 mg/kg and for the guinea pig was 880 mg/kg. The oral toxicity of thymol is about one-fourth that of phenol, and, if it is absorbed, only one-half is metabolized. The remainder is conjugated with sulfuric acid and glucuronic acid and excreted in the urine (Ref. 4).

Five male and four female rats were given an oral dose of 10,000 ppm of thymol for 19 weeks. No untoward effects were noted after this period of time (Ref. 7).

According to Sollmann (Ref. 4), doses larger than 1 g produce dizziness, severe epigastric pain, and excitement, followed by nausea, vomiting, weakness, drowsiness, and even deafness and cyanosis. Samitz and Shmunes (Ref. 8) noted that dentists found thymol one of the less frequent sensitizers in occupational dermatoses. Thymol irritates the mucous membranes, but when topically applied to the skin it has little effect and is virtually unabsorbed (Ref. 4).

(2) *Effectiveness.* The Panel received a submission for a marketed product containing thymol in combination with eucalyptol, methyl salicylate, and methol (Ref. 9). The manufacturer acknowledged that the product is marketed primarily as an antiseptic mouth rinse, but it is also labeled for the treatment of "infectious dandruff." It was pointed out by the manufacturer that the product is a combination of active ingredients in a hydroalcoholic solution, each exhibiting some activity, and that the specific combination of ingredients as formulated is responsible for the total effectiveness of the product. The Panel is not aware of any data which demonstrate the effectiveness of thymol as a single ingredient for controlling dandruff.

(3) *Proposed dosage.* For topical use in a concentration of 0.06 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*).

References

(1) Osol, A., and R. Pratt, editors "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1189–1190, 1973.

(2) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasidicides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, the Macmillan Publishing Co., Inc., New York, p. 992, 1975.

(3) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol, et al., Mack Publishing Co., Easton, PA, p. 1101, 1975.

(4) Sollmann, T., "A Manual of Pharmacology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 227–228, 1975.

(5) Edwards, E. H., and B. Hall, "Thymol as a Bacteriostatic Agent," *The Pharmaceutical Journal*, 166:54, 1951.

(6) Jenner, P. M., et al., "Food Flavourings and Compounds of Related Structure: I. Acute Oral Toxicity," *Food and Cosmetic Toxicology*, 2:327–343, 1964.

(7) Hagan, E. C., et al., "Food Flavourings and Compounds of Related Structure: II. Subacute and Chronic Toxicity," *Food and Cosmetics Toxicology, 5:141–157, 1967.*

(8) Samitz, M. H., and E. Shmunes, "Occupational Dermatoses in Dentists and Allied Personnel," *CUTIS; Cutaneous Medicine for the Practitioner*, 5:180–185, 1969.

(9) OTC Volume 160353.

u. *Undecylenate preparations (calcium undecylenate and undecylenic acid monoethanolamide sulfosuccinate, sodium salt).* The Panel concludes that data are lacking to show safety and effectiveness of undecylenate preparations in contolling dandruff, seborrheic dermatitis, and psoriasis when used in the dosage specified below.

The submissions received included an ointment containing calcium undecylenate for topical use in the control of psoriasis (Ref. 1) and three shampoos containing undecylenic acid monoethanolamide sulfosuccinate, sodium salt for the control of dandruff and seborrheic dermatitis (Refs. 2, 3, and 4). Undecylenate preparations are not presently marketed OTC in this country for controlling dandruff, seborrheic dermatitis, and psoriasis.

Undecylenic acid is obtained by pyrolysis of the principal fatty acid of castor oil, ricinoleic acid. It is a liquid ranging from clear to pale yellow in color and is practically insoluble in water but miscible with alcohol, chloroform, and ether (Ref. 5). Undecylenate preparations are primarily used for their antifungal activity, but are also considered to have weak antibacterial activity.

(1) *Safety.* The oral LD_{50} of undecylenic acid in rats is estimated by one source to be 2.5 g/kg of body weight (Ref. 6); however, one submission included tests purporting to show that the LD_{50} in rats of another undecylenate preparation, undecylenic acid monoethanolamide sulfosuccinate, sodium salt, was greater than 10 g/kg of body weight (Ref. 3).

Local irritation tests using four test materials on rabbit skin were performed according to the Draize method. Two-hundred mg of each test material (base plus 3 percent calcium undecylenate and 1 percent hydrocortisone acetate; base as the control; base plus 1 percent hydrocortisone acetate; base plus 3 percent calcium undecylenate) was applied three times a day for 2 weeks (Ref. 1). Results showed no cumulative or acute toxicity on the skin. When 25 mg of the same test materials were instilled in the conjunctival sacs of six rabbits three times a day for 2 weeks, no cumulative or acute toxicity was observed. The slight changes that were observed disappeared 24 to 48 hours after the medication was discontinued.

Tests conducted using the calcium undecylenate and hydrocortisone acetate ointment on patients with various forms of dermatoses resulted in no signs of irritation or adverse effects over the study period of 1 month (Ref. 1). No human safety data on calcium undecylenate as a single ingredient were presented.

The Panel concludes that the submitted data are insufficient to determine the safety of undecylenate preparations used for controlling dandruff, seborrheic dermatitis, and psoriasis.

(2) *Effectiveness.* One study using a shampoo containing 2 percent undecylenic acid monoethanolamide sulfosuccinate, sodium salt on 25 patients with seborrheic dermatitis of the scalp showed that 80 percent had good results, 12 percent had fair results, and 8 percent had poor results (Ref. 7). In another study, a similar preparation was used by 131 subjects with dandruff and itching of the scalp (Ref. 8). This study tested the vehicle, the vehicle with tar, and the vehicle with tar and undecylenic acid monoethanolamide sulfosuccinate, sodium salt. All three shampoos were shown to reduce dandruff for a few days. The vehicle with tar and the vehicle with tar and undecylenic acid monoethanolamide sulfosuccinate, sodium salt were superior to the vehicle alone in this respect. The vehicle with tar and undecylenic acid monoethanolamide sulfosuccinate, sodium salt showed a greater mean reduction in dandruff than the other two.

The Panel believes that undecylenic acid and its salts show promise in controlling dandruff, seborrheic dermatitis, and psoriasis, but additional data are needed to demonstrate effectiveness conclusively for this use. Well-controlled, double-blind clinical trials should be done testing undecylenate preparations against their vehicles alone as controls to show that these ingredients are effective in controlling dandruff, seborrheic dermatitis, and psoriasis.

(3) *Proposed dosage.* For topical use in the following concentrations: (a) Calcium undecylenate—3 percent and (b) Undecylenic acid monoethanolamide sulfosuccinate, sodium salt—2 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described above. (See part III. paragraph A.2. above—*Category I labeling.*)

References

(1) OTC Volume 160342.
(2) OTC Volume 160345.
(3) OTC Volume 160394.
(4) OTC Volume 160402.
(5) Harvey, S. C., "Antimicrobial Drugs," *in* Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, Mack Publishing Co., Easton, PA, p. 1177, 1980.
(6) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 135, 1976.
(7) Lubowe, I. L., "The Treatment of Seborrhea Capitis with Undecylenic Alkanolamides," *Soap, Perfumery, and Cosmetics*, 35:908, 1962.
(8) Alexander, S., "Do Shampoos Affect Dandruff?" *The British Journal of Dermatology*, 79:92–95, 1967.

2. *Category III labeling.* None.

D. Combination Products

1. *Combination policy.* The Panel concurs with the combination drug policy for OTC products as set forth in 21 CFR 330.10(a)(4)(iv):

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

In general, the Panel believes that the interests of the consumer are best served by exposure to the fewest ingredients possible at the lowest possible dose that will still be effective. Single ingredient products are preferred to multiple ingredient products to reduce the likelihood of toxic or other undesirable effects. However, the Panel recognizes that combinations of active ingredients may be desirable in some circumstances. For example, the FDA "General Guidelines for OTC Drug Combination Products," placed on file in the Dockets Management Branch on November 28, 1978, Docket No. 78D–0322, provide for the combination of active ingredients from different therapeutic categories to treat different concurrent symptoms. While the Panel generally agrees with this guideline, it is difficult to apply in the case of dandruff, seborrheic dermatitis, and psoriasis drug products. Even though ingredients from various therapeutic categories are often included in these products, with the exception of antipruritics, which are intended to relieve the symptom of itching, they are included to control dandruff, seborrheic dermatitis, and psoriasis. Itching can be a symptom of these conditions, but temporary relief of itching does not amount to control of the condition. It should be noted that several of the ingredients reviewed by the Panel which are claimed to control these conditions have inherent antipruritic activity in addition to other activity (e.g., tars, hydrocortisone, resorcinol, menthol, and phenol).

The Panel strongly believes that, for a combination to be generally recognized as safe and effective, it must be demonstrated by adequate data that each active ingredient contributes to the claimed effects of the product. The Panel concludes that data are lacking to demonstrate that the addition of an antipruritic ingredient to other ingredients used in the control of dandruff, seborrheic dermatitis, and psoriasis contributes to the effectiveness of the product.

Most of the combination products submitted for review have been used empirically with little attempt to demonstrate the contribution of each active ingredient to the combination. In fact, of all the submitted combination products, the Panel is aware of only a few studies which attempted to demonstrate that the combination of ingredients was more effective than the single ingredients when used alone, and these studies were concerned only with the treatment of psoriasis.

One study was conducted to evaluate the effectiveness of three different psoriasis lotions: 2 percent allantoin, 5, percent coal tar extract, and 5 percent coal tar extract with 2 percent allantoin (Ref. 1). While the study was claimed to demonstrate that the combination product is "radically more effective than the coal tar or allantoin used alone," the Panel points out that the details of the study are insufficient to allow for a conclusive evaluation.

2. *Category I combination.* A study compared shampoo formulations of 2 percent salicylic acid, 2 percent sulfur, and a combination of sulfur and salicylic acid (2 percent each) against the vehicle alone in controlling dandruff (Ref. 2). The products were used under supervision twice a week. Clinical grading of dandruff, on a scale of 0 to 10, and corneocyte counts were made at weekly intervals. The results of this study showed that salicylic acid was significantly more effective in reducing both the clinical grade of dandruff and the corneocyte counts than either the sulfur alone or the vehicle. The combination of salicylic acid and sulfur proved to be significantly more effective than salicylic acid alone in reducing the clinical grade of dandruff and the corneocyte counts. Based on these data the Panel concludes that combinations of sulfur (2 to 5 percent) with salicylic acid (1.8 to 3 percent) are safe and effective for use in controlling dandruff.

The Panel is unaware of any other data on products containing combinations of ingredients used for controlling dandruff, seborrheic dermatitis, or psoriasis which demonstrate a contribution of each active ingredient to the claimed effects of the combination product.

3. *Category II combinations.* The Panel concludes that any combination product containing a Category II ingredient is Category II.

4. *Category III combinations.* All other combinations submitted to the Panel are Category III. (See list below.)

Before any of these combinations may move to Category I, appropriately designed studies must demonstrate that each of the active ingrediants contributes to the claimed effect.

Allantoin and phenol
Benzalkonium chloride and alkyl isoquinolinium bromide
Benzalkonium chloride and lauryl isoquinolinium bromide
Benzalkonium chloride and salicylic acid
Benzalkonium chloride and captan
Calcium undecylenate and hydrocortisone acetate
Coal tar, benzalkonium chloride, and salicylic acid
Coal tar extract and allantoin
Coal tar extract and hydrocortisone alcohol
Coal tar extract and menthol
Coal tar solution and menthol
Coal tar, pine tar, and juniper tar
Coal tar and salicylic acid
Phenol, allantoin, salicylic acid, and sodium lauryl sulfate
Sulfur, coal tar, and salicylic acid
Sulfur, coal tar distillate, and salicylic acid
Sulfur and menthol
Sulfur and pine tar
Sulfur, recitified tar oil, and captan
Sulfur and sodium salicylate
Thymol, methyl salicylate, eucalyptol, and menthol

References

(1) OTC Volume 16047.
(2) OTC Volume 16014.

List of Subjects in 21 CFR Part 358

OTC drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding to Part 358 (proposed in the Federal Register of November 3, 1978 (43 FR 51546) and September 3, 1982 (47 FR 39108), a new Subpart H, to read as follows:

PART 358—MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart H—Drug Products for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis

Sec.

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

Subpart H—Drug Products for Control of Dandruff, Seborrheic Dermatitis, and Psoriasis

§ 358.701 Scope.

(a) An over-the-counter dandruff, seborrheic dermatitis, or psoriasis drug product in a form suitable for topical application is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter 1 of Title 21 unless otherwise noted.

§ 358.703 Definitions.

As used in this subpart:

(a) *Dandruff control drug product.* A drug product applied to the scalp to control the itching and excess shedding of dead epidermal cells.

(b) *Seborrheic dermatitis control drug product.* A drug product applied to the scalp and/or body to control the irritation, itching, and excess shedding of dead epidermal cells.

(c) *Psoriasis control drug product.* A drug product applied to the scalp and/or body to control the itching, redness, and excess shedding of dead epidermal cells.

(d) *Cradle cap control drug product.* A drug product applied to the scalp to control the inflammation, irritation, itching, crusting, and excess shedding of dead epidermal cells in infants, i.e., a drug product to control infantile seborrheic dermatitis.

§ 358.710 Active ingredients for the control of dandruff, for the control of seborrheic dermatitis, or for the control of psoriasis.

The active ingredient of the product consists of any of the following within the specified concentration established for each ingriedient:

(a) Coal tar distillate 4 percent.
(b) Coal tar extract 2 to 8.75 percent.
(c) Coal tar solution 2.5 to 5 percent.
(d) Coal tar, USP, 0.5 to 5 percent.
(e) Pyrithione zinc 1 to 2 percent.
(f) Pyrithione zinc 0.1 to 0.25 percent.
(g) Salicylic acid 1.8 to 3 percent.
(h) Selenium sulfide 1 percent.
(i) Sulfur 2 to 5 percent.

§ 358.712 Active ingredients for the control of cradle cap. [Reserved]

§ 358.720 Permitted combinations of active ingredients.

Salicylic acid identified in § 358.710(g) may be combined with sulfur identified in § 358.710(i) provided the product is labeled according to § 358.750(b)(1).

§ 358.750 Labeling of drug products for the control of dandruff, for the control of seborrheic dermatitis, or for the control of psoriasis.

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

(1) Any product labeled according to paragraph (b)(1) of this section is identified as "Controls dandruff."

(2) Any product labeled according to paragraph (b)(2) of this section is identified as "Controls seborrheic dermatitis of the scalp."

(3) Any product labeled according to paragraph (b)(3)(i) of this section is identified as "Controls seborrheic dermatitis of the body."

(4) Any product labeled according to paragraph (b)(3)(ii) of this section is identified as "Controls psoriasis of the body."

(5) Any product labeled according to paragraph (b)(4) of this section is identified as "Controls psoriasis of the scalp."

(6) The statements of identity for any product with more than one indication identified in paragraph (b) of this section may be combined to eliminate duplicate words.

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

(1) *For products containing any ingredient identified in § 358.710.* "Relieves the itching and scalp flaking associated with dandruff."

(2) *For products containing any ingredient identified in § 358.710(a), (b), (c), (d), (e), (f), or (g).* "Relieves the itching, irritation, and skin flaking associated with seborrheic dermatitis of the scalp."

(3) *For products containing salicylic acid identified in § 358.710(g).* (i) "Relieves the itching, irritation, and skin flaking associated with seborrheic dermatitis of the body."

(ii) "Relieves the itching, redness, and scaling associated with psoriasis of the body."

(4) *For products containing any ingredient identified in § 358.710(a), (b), (c), (d), or (g).* "Relieves the itching, redness, and scaling associated with psoriasis of the scalp."

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

(1) *For products containing any ingredient identified in § 358.710.* (i) "For external use only."

(ii) "Avoid contact with the eyes—if this happens, rinse thoroughly with water."

(iii) "If condition worsens or does not improve after regular use of this product as directed, consult a doctor."

(iv) "Do not use on children under 2 years of age except as directed by a doctor."

(2) *For products containing coal tar identified in § 358.710(a), (b), (c), or (d).* (i) "Use caution in exposing skin to sunlight after applying this product. It may increase your tendency to sunburn for up to 24 hours after application."

(ii) "Do not use this product in or around the rectum or in the genital area or groin except on the advice of a doctor."

(3) *For products containing selenium sulfide identified in § 358.710(h).* "Do not use if you have open sores on your scalp."

(4) *For products labeled according to paragarph (a) (3) or (4) of this section.* "If the condition covers a large area of the body, consult your doctor before using this product."

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

(1) *For products formulated for use as a shampoo.* "For best results use twice a week. Wet hair, apply to scalp and massage vigorously. Rinse and repeat."

(2) *For products formulated for use as a hairgroom.* "Apply a small amount to scalp daily. For best results, also shampoo twice a week."

(3) *For products formulated for use on the body.* "Apply a thin layer to the affected area one to two times daily."

§ 358.752 Labeling of drug products for the control of cradle cap.

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

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrase: "Relieves scaly inflammation of the scalp associated with cradle cap."

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

(1) "For external use only."

(2) "Avoid contact with the eyes—if this happens, rinse thoroughly with water."

(3) "If condition worsens or does not improve after regular use of this product as directed, consult a doctor."

(d) *Directions.* [Reserved]

Interested persons may, on or before March 3, 1983, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before April 4, 1983. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

Dated: November 22, 1982.

[FR Doc. 82–32846 Filed 12–2–82; 8:45 am]

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federal register

Friday
December 3, 1982

Part V

Department of Labor

Employment and Training Administration

Unemployment Compensation for Federal Civilian Employees; Final Rule

DEPARTMENT OF LABOR

Employment and Training Administration

20 CFR Part 609

Unemployment Compensation for Federal Civilian Employees

AGENCY: Employment and Training Administration, Labor.

ACTION: Final rule.

SUMMARY: These are the Department of Labor's revised regulations for implementing the program of Unemployment Compensation for Federal Civilian Employees (UCFE Program). Changes to the regulations incorporate statutory amendments, which principally concern the finality of Federal findings as to the reasons for termination of Federal employment; the treatment of the Virgin Islands as a participating State in the Federal-State Unemployment Compensation Program; and which prescribe a new rule for determining the Federal share of the costs of benefits on joint claims under the UCFE Program and State unemployment compensation laws. One other statutory change affecting the UCFE Program that was overlooked in the proposed rule is added to this final rule. It pertains to the exclusion of commissioned officers of the National Oceanic and Atmospheric Administration (NOAA) from coverage under the UCFE Program and their coverage under the Unemployment Compensation Program for Ex-servicemembers effective March 25, 1980.

The regulations are also reorganized and revised to state the rights and obligations of claimants for the benefits and to clarify the respective duties and responsibilities of the Federal Government and the State agencies. The setting forth of this information in each part dealing with a separate unemployment compensation program conforms to the more recent practice in writing regulations for unemployment compensation and related benefit programs. The final regulations incorporate the substantive changes and improvements as set forth in the published proposal.

EFFECTIVE DATE: January 3, 1983.

FOR FURTHER INFORMATION CONTACT: Bert Lewis, Administrator, Unemployment Insurance Service, Employment and Training Administration, U.S. Department of Labor, 601 "D" Street, N.W., Washington, D.C. 20213; telephone: (202) 376-7032 (this is not a toll-free number).

SUPPLEMENTARY INFORMATION: The UCFE Program is a program financed by Federal funds to furnish unemployment benefits to eligible individuals who are separated from Federal employment and are unable to obtain work. The UCFE Program was created by Pub. L. 83-767, approved on September 1, 1954. It has been codified in 5 U.S.C. 8501-8508.

Part 609, Chapter V, Title 20 of the Code of Federal Regulations (20 CFR Part 609) implements the statute creating the UCFE Program, as most recently amended by Public Law 94-566 and Public Law 96-215. The proposal to revise the regulations was published in the **Federal Register** on January 23, 1981 (46 FR 7786), and this document contains the final revised regulations for Part 609.

Comments on the proposal published on January 23, 1981, were solicited through March 24, 1981, and the proposal was further reviewed in the Department. As a result of comments and review, a few changes have been made in the proposal. Also, changes have been made as a result of the statutory amendment relating to commissioned officers of the National Oceanic and Atmospheric Administration.

1. Commissioned officers of the National Oceanic and Atmospheric Administration were covered under the UCFE Program until March 25, 1980. First claims for unemployment compensation filed after that date are covered under the program of Unemployment Compensation for Ex-servicemembers (UCX Program; 20 CFR Part 614 and 5 U.S.C. Chapter 85), pursuant to an amendment to 5 U.S.C. 8521(a)(1) in Public Law 96-215 (94 Stat. 123). This coverage change is reflected in § 609.2(f)(2) and in the regulations for the UCX Program at 20 CFR 614.2(g).

2. The Nevada Employment Security Department commented that the revision of § 609.8 in assigning all Federal wages at the time of first claim filing would require a revision to Form ES-931 to allow inclusion of service and wages not previously reported.

While that is true, we foresee no problems with State agencies adopting this modification or the Federal agencies being able to furnish the requested information. No change is made in § 609.8 as proposed.

3. Section 609.1(d)(1) requires each State agency to forward a copy of each judicial or "administrative decision" ruling on an individual's entitlement to payment of UCFE or to credit for a waiting period. The Oregon Department of Human Resources requested a definition of the term "administrative decision" because their interpretation of the term includes nonmonetary determinations. They also commented that the procedures outlined in § 609.1(d)(2), relating to procedures to assure nationwide uniformity in the application of the Act and the regulations, seem unnecessary.

"Administrative decision" as contemplated by the Department are first and second appeal level decisions concerning claims for UCFE. The phrase does not include or apply to monetary or nonmonetary determinations, which are identified in § 609.1(d) as determinations and redeterminations. No change is made in § 609.1(d).

The Department believes that it should notify the State agency of its view if a State agency's determination, redetermination, or decision (regarding an appeal) is inconsistent with the Department's interpretation of the Act or Part 609.

This will assure nationwide uniformity in the application of the Act and the regulations. No change is made in § 609.1(d)(2) as proposed.

4. The Oregon Department of Human Resources also commented that § 609.6(e)(2) appears to say that the State agency will wait 12 days before determining a UCFE claim on the basis of a claimant affidavit even though procedurally they are required to complete an affidavit as part of the initial claim process. Section 609.6(e)(2) does not differ from the current regulation as to when a determination of entitlement will be made absent timely Federal findings. However, we have suggested in a directive that State agencies consider taking the claimant affidavit (Form ES-935) at the time the "new claim" is filed, provided credible evidence of Federal civilian employment is available. If State agencies adopt this suggestion, it would assist in ensuring that first payments are being made promptly. However, this suggestion is not a procedural requirement nor is it required by § 609.6(e)(2). No change is made in this regulation.

5. In addition, a few minor proofing and technical errors were made in the proposed document as published in the **Federal Register** on January 23, 1981 (46 FR 7786). Those errors have been corrected.

Drafting Information

This document was prepared under the direction and control of the Administrator of the Unemployment Insurance Service, Employment and Training Administration, U.S. Department of Labor, 601 "D" Street, N.W., Washington, D.C. 20213; telephone (202) 376-7032 (this is not a toll-free number).

Classification—Executive Order 12291

This rule is not classified as a "major rule" under Executive Order 12291 on Federal Regulations, because it is not likely to result in: 1. an annual effect on the economy of $100 million or more; 2. a major increase in cost or prices for consumers, individual industries, Federal, State or local government agencies, or geographic regions; or 3. significant adverse effects on competition, employment, investment, productivity, innovation, or the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. Accordingly, no regulatory impact analysis is required.

Paperwork Reduction

Information collection requirements contained in this regulation (§§ 609.1(d)(1), 609.5(a) and 609.6(e)(2)) have been approved by the Office of Management and Budget under the provisions of 44 U.S.C. Chapter 35 and have been assigned OMB control numbers 1205–0163 (pertaining to § 609.1(d)(1)) and 1205–0179 (pertaining to §§ 609.5(a) and 609.6(e)(2)).

Regulatory Flexibility Act

The Department believes that the rule will have no "significant economic impact on a substantial number of small entities" within the meaning of section 3(a) of the Regulatory Flexibility Act, Pub. L. No. 96–354, 91 Stat. 1164 (5 U.S.C. 605(b)). The Secretary has certified to the Chief Counsel for Advocacy of the Small Business Administration to this effect. This conclusion is reached because this rule only implements amendments to an individual entitlement program, and thus no economic impact is expected with respect to any small entities. Accordingly, no regulatory flexibility analysis is required.

Regulatory Flexibility Act Certification

I, Raymond J. Donovan, Secretary of Labor, hereby certify, pursuant to 5 U.S.C. 605(b), that the final regulations published hereinafter (20 CFR Part 609, Final Amendments to the Unemployment Compensation Program for Federal Employees Regulations) will not, if promulgated, have a significant economic impact on a substantial number of small entities because this is an individual entitlement program and affects only individuals applying for benefits under the Unemployment Compensation Program for Federal Employees.

Dated: November 29, 1982.

Raymond J. Donovan.

List of Subjects in 20 CFR Part 609

Unemployment Compensation for Federal Employees (UCFE), Unemployment compensation.

Words of Issuance

Accordingly, Part 609 of Title 20 of the Code of Federal Regulations is revised as set forth below.

Signed at Washington, D.C., on November 29, 1982.

Albert Angrisani,

Assistant Secretary of Labor.

PART 609—UNEMPLOYMENT COMPENSATION FOR FEDERAL CIVILIAN EMPLOYEES

Subpart A—General Provisions

Subpart B—Administration of UCFE Program

Subpart C—Responsibilities of Federal Agencies

Authority: 5 U.S.C. 8508; Secretary's Order No. 4–75, 40 FR 18515; (5 U.S.C. 301). Interpret and apply secs. 8501–8508 of title 5, United States Code.

Subpart A—General Provisions

§ 609.1 Purpose and application.

(a) *Purpose.* Subchapter I of chapter 85, title 5 of the United States Code, as amended by Pub. L. 94–566, 90 Stat. 2667, 5 U.S.C. 8501–8508, provides for a permanent program of unemployment compensation for unemployed Federal civilian employees. The unemployment compensation provided for in Subchapter I is hereinafter referred to as unemployment compensation for Federal employees, or UCFE. The regulations in this part are issued to implement the UCFE Program.

(b) *First rule of construction.* The Act and the implementing regulations in this part shall be construed liberally so as to carry out the purposes of the Act.

(c) *Second rule of construction.* The Act and the implementing regulations in this part shall be construed so as to assure insofar as possible the uniform interpretation and application of the Act throughout the United States.

(d) *Effectuating purpose and rules of construction.* (1) In order to effectuate the provisions of this section, each State agency shall forward to the United States Department of Labor (hereafter Department), not later than 10 days after issuance, a copy of each judicial or administrative decision ruling on an individual's entitlement to payment of UCFE or to credit for a waiting period. On request of the Department, a State agency shall forward to the Department a copy of any determination or redetermination ruling on an individual's entitlement to UCFE or waiting period credit.

(2) If the Department believes that a determination, redetermination, or decision is inconsistent with the Department's interpretation of the Act or this part, the Department may at any time notify the State agency of the Department's view. Thereafter the State agency shall issue a redetermination or appeal if possible, and shall not follow such determination, redetermination, or decision as a precedent; and, in any subsequent proceedings which involve such determination, redetermination, or decision, or wherein such determination, redetermination, or decision is cited as precedent or otherwise relied upon, the State agency shall inform the claims deputy or hearing officer or court of the Department's view and shall make all reasonable efforts, including appeal or other proceedings in an appropriate forum, to obtain modification, limitation, or overruling of the determination, redetermination, or decision.

(3) If the Department believes that a determination, redetermination, or decision is patently and flagrantly violative of the Act or this part, the Department may at any time notify the State agency of the Department's view. If the determination, redetermination, or decision in question denies UCFE to a claimant, the steps outlined in paragraph (d)(2) of this section shall be followed by the State agency. If the

determination, redetermination, or decision in question awards UCFE to a claimant, the benefits are "due" within the meaning of section 303(a)(1) of the Social Security Act, 42 U.S.C. 503(a)(1), and therefore must be paid promptly to the claimant. However, the State agency shall take the steps outlined in paragraph (d)(2) of this section, and payments to the claimant may be temporarily delayed if redetermination or appeal action is taken not more than one business day following the day on which the first payment otherwise would be issued to the claimant; and the redetermination action is taken or appeal is filed to obtain a reversal of the award of UCFE and a ruling consistent with the Department's view; and the redetermination action or appeal seeks an expedited redetermination or appeal within not more than two weeks after the redetermination action is taken or the appeal is filed. If redetermination action is not taken or appeal is not filed within the above time limit, or a redetermination or decision is not obtained within the two-week limit, or any redetermination or decision or order is issued which affirms the determination, redetermination, or decision awarding UCFE or allows it to stand in whole or in part, the benefits awarded must be paid promptly to the claimant.

(4)(i) If any determination, redetermination, or decision, referred to in paragraph (d)(2) or paragraph (d)(3) of this section, is treated as a precedent for any future UCFE claim or claim under the UCX Program (Part 614 of this chapter), the Secretary will decide whether the Agreement with the State entered into under the Act shall be terminated.

(ii) In the case of any determination, redetermination, or decision that is not legally warranted under the Act or this Part, including any determination, redetermination, or decision referred to in paragraph (d)(3) of this section, the Secretary will decide whether the State shall be required to restore the funds of the United States for any sums paid under such a determination, redetermination, or decision, and whether, in the absence of such restoration, the Agreement with the State shall be terminated and whether other action shall be taken to recover such sums for the United States.

(5) A State agency may request reconsideration of a notice issued pursuant to paragraph (d)(2) of paragraph (d)(3) of this section, and shall be given an opportunity to present views and arguments if desired.

(6) Concurrence of the Department in a determination, redetermination, or decision shall not be presumed from the absence of a notice issued pursuant to this section.

§ 609.2 Definitions of terms.

For the purposes of the Act and this part:

(a) "Act" means subchapter I of chapter 85, title 5, United States Code, 5 U.S.C. 8501–8508.

(b) "Agreement" means the agreement entered into pursuant to the Act between a State and the Secretary under which the State agency of the State agrees to make payments of unemployment compensation in accordance with the Act and the regulations and procedures thereunder prescribed by the Department.

(c) "Based period" means the base period as defined by the applicable State law for the benefit year.

(d) "Benefit year" means the benefit year as defined by the applicable State law, and if not so defined the term means the period prescribed in the agreement with the State or, in the absence of an Agreement, the period prescribed by the Department.

(e) "Federal agency" means any department, agency, or governmental body of the United States, including any instrumentality wholly or partially owned by the United States, in any branch of the Government of the United States, which employs any individual in Federal civilian service.

(f) "Federal civilian service" means service performed in the employ of any Federal agency, except service performed—

(1) By an elective official in the executive or legislative branches of the Government of the United States; (2) As a member of the Armed Forces or the Commissioned Corps of the National Oceanic and Atmospheric Administration;

(3) By Foreign Service personnel for whom special separation allowances are provided under chapter 14 of title 22 of the United States Code;

(4) Outside the 50 States, the Commonwealth of Puerto Rico, the Virgin Islands, and the District of Columbia, by an individual who is not a citizen of the United States;

(5) By an individual excluded by regulations of the Office of Personnel Management from civil service retirement coverage provided by Subchapter III of chapter 83 of title 5 of the United States Code because the individual is paid on a contract or fee basis;

(6) By an individual receiving nominal pay and allowances of $12 or less a year;

(7) In a hospital, home, or other institution of the United States by a patient or inmate thereof;

(8) By a student-employee as defined by 5 U.S.C. 5351; that is: (i) A student nurse, medical or dental intern, resident-in-training, student dietitian, student physical therapist, or student occupational therapist, assigned or attached to a hospital, clinic, or medical or dental laboratory operated by an agency as defined in section 5351; or (ii) any other student-employee, assigned or attached primarily for training purposes to such a hospital, clinic, or medical or dental laboratory operated by such an agency, who is designated by the head of the agency with the approval of the Office of Personnel Management;

(9) By an individual serving on a temporary basis in case of fire, storm, earthquake, flood, or other similar emergency;

(10) By an individual employed under a Federal relief program to relieve the individual from unemployment;

(11) As a member of a State, county, or community committee under the Agricultural Stabilization and Conservation Service or of any other board, council, committee, or other similar body, unless such body is composed exclusively of individuals otherwise in the full-time employ of the United States;

(12) By an officer or member of the crew on or in connection with an American vessel which is: (i) Owned by or bareboat chartered to the United States, and (ii) the business of which is conducted by a general agent of the Secretary of Commerce, and (iii) if contributions on account of such service are required under section 3305(g) of the Internal Revenue Code of 1954 (26 U.S.C. 3305(g)) to be made to an unemployment fund under a State law;

(13) By an individual excluded by any other Federal law from coverage under the UCFE Program; or

(14) By an individual whose service is covered by the UCX Program to which Part 614 of this chapter applies.

(g) "Federal employee" means an individual who has performed Federal civilian service.

(h) "Federal findings" means the facts reported by a Federal agency pertaining to an individual as to: (1) Whether or not the individual has performed Federal civilian service for such an agency; (2) the period or periods of such Federal civilian service; (3) the individual's Federal wages; and (4) the reasons for termination of the individual's Federal civilian service.

(i) "Federal wages" means all pay and allowances, in cash and in kind, for Federal civilian service.

(j) "First claim" means an initial claim for unemployment compensation under the UCFE Program, the UCX Program (Part 614 of this chapter), a State law, or some combination thereof, whereby a benefit year is established under an applicable State law.

(k) "Official station" means the State (or country, if outside the United States) designated on a Federal employee's notification of personnel action terminating the individual's Federal civilian service (Standard Form 50 or its equivalent) as the individual's "duty station." If the form of notification does not specify the Federal employee's "duty station", the individual's official station shall be the State or country designated under "name and location of employing office" on such form or designated as the individual's place of employment on an equivalent form.

(l) "Secretary" means the Secretary of Labor of the United States.

(m) "State" means the 50 States, the District of Columbia, the Commonwealth of Puerto Rico, and the Virgin Islands.

(n) "State agency" means the agency of the State which administers the applicable State law and is administering the UCFE Program in the State pursuant to an Agreement with the Secretary.

(o)(1) "State law" means the unemployment compensation law of a State approved by the Secretary under section 3304 of the Internal Revenue Code of 1954, 26 U.S.C. 3304, if the State is certified under section 3304(c) of the Internal Revenue Code of 1954, 26 U.S.C. 3304(c).

(2) "Applicable State law" means the State law made applicable to a UCFE claimant by § 609.8.

(p)(1) "Unemployment compensation" means cash benefits (including dependents' allowances) payable to individuals with respect to their unemployment, and includes regular, additional, emergency, and extended compensation.

(2) "Regular compensation" means unemployment compensation payable to an individual under any State law, but not including additional compensation or extended compensation.

(3) "Additional compensation" means unemployment compensation totally financed by a State and payable under a State law by reason of conditions of high unemployment or by reason of other special factors.

(4) "Emergency compensation" means supplementary unemployment compensation payable under a temporary Federal law after exhaustion of regular and extended compensation.

(5) "Extended compensation" means unemployment compensation payable to an individual for weeks of unemployment in an extended benefit period, under those provisions of a State law which satisfy the requirements of the Federal-State Extended Unemployment Compensation Act of 1970, as amended, 26 U.S.C. 3304 note, and Part 615 of this chapter, with respect to the payment of extended compensation.

(q) "Week" means, for purposes of eligibility for and payment of UCFE, a week as defined in the applicable State law.

(r) "Week of unemployment" means a week of total, part-total, or partial unemployment as defined in the applicable State law, which shall be applied in the same manner and to the same extent to all employment and earnings, and in the same manner and to the same extent for the purposes of the UCFE Program, as if the individual filing for UCFE were filing a claim for State unemployment compensation.

Subpart B—Administration of UCFE Program

§ 609.3 Eligibility requirements for UCFE.

An individual shall be eligible to receive a payment of UCFE or to waiting period credit with respect to a week of unemployment if:

(a) The individual has Federal civilian service and Federal wages in the base period under the applicable State law;

(b) The individual meets the qualifying employment and wage requirements of the applicable State law, either on the basis of Federal civilian service and Federal wages alone or in combination with service and wages covered under a State law or under the UCX Program (Part 614 of this chapter);

(c) The individual has filed an initial claim for UCFE and, as appropriate, has filed a timely claim for waiting period credit or a payment of UCFE with respect to that week of unemployment; and

(d) The individual is totally, part-totally, or partially unemployed, and is able to work, available for work, and seeking work within the meaning of or as required by the applicable State law, and is not subject to disqualification under this Part or the applicable State law, with respect to that week of unemployment.

§ 609.4 Weekly and maximum benefit amounts.

(a) *Total unemployment.* The weekly amount of UCFE payable to an eligible individual for a week of total unemployment shall be the amount that would be payable to the individual as unemployment compensation for a week of total unemployment as determined under the applicable State law.

(b) *Partial and part-total unemployment.* The weekly amount of UCFE payable for a week of partial or part-total unemployment shall be the amount that would be payable to the individual as unemployment compensation for a week of partial or part-total unemployment as determined under the applicable State law.

(c) *Maximum amount.* The maximum amount of UCFE which shall be payable to an eligible individual during and subsequent to the individual's benefit year shall be the maximum amount of all unemployment compensation that would be payable to the individual as determined under the applicable State law.

(d) *Computation rules.* (1) The weekly and maximum amounts of UCFE payable to an individual under the UCFE Program shall be determined under the applicable State law to be in the same amount, on the same terms, and subject to the same conditions as the State unemployment compensation which would be payable to the individual under the applicable State law if the individual's Federal civilian service and Federal wages assigned or transferred under this Part to the State had been included as employment and wages covered by that State law.

(2) All Federal civilian service and Federal wages for all Federal agencies shall be considered employment with a single employer for purposes of the UCFE Program.

§ 609.5 Claims for UCFE.

(a) *First claims.* A first claim for UCFE shall be filed by an individual in any State agency of any State (or Canada) according to the applicable State law, and on a form prescribed by the Department which shall be furnished to the individual by the State agency where the claim is filed.

(b) *Weekly claims.* Claims for waiting week credit and payments of UCFE for weeks of unemployment shall be filed in any State agency (or Canada) at the times and in the manner as claims for State unemployment compensation are filed under the applicable State law, and on forms prescribed by the Department which shall be furnished to the

individual by the State agency where the claim is filed.

(c) *Secretary's standard.* The procedure for reporting and filing claims for UCFE and waiting period credit shall be consistent with this Part 609 and the Secretary's "Standard for Claim Filing, Claimant Reporting, Job Finding and Employment Services" (*Employment Security Manual,* Part V, sections 5000 *et seq.*).

§ 609.6 Determinations of entitlement; notices to individual.

(a) *Determination of first claim.* The State agency whose State law applies to an individual under § 609.8 shall, promptly upon the filing of a first claim for UCFE, determine whether the individual is eligible and whether a disqualification applies, and, if the individual is found to be eligible, the individual's benefit year and the weekly and maximum amounts of UCFE payable to the individual.

(b) *Determinations of weekly claims.* The State agency promptly shall, upon the filing of a claim for payment of UCFE or waiting period credit with respect to a week, determine whether the individual is entitled to a payment of UCFE or waiting period credit with respect to such week, and, if entitled, the amount of UCFE or waiting period credit to which the individual is entitled.

(c) *Redetermination.* The provisions of the applicable State law concerning the right to request, or authority to undertake, reconsideration of a determination pertaining to State unemployment compensation under the applicable State law shall apply to determinations pertaining to UCFE.

(d) *Notices to individual.* The State agency promptly shall give notice in writing to the individual of any determination or redetermination of a first claim, and, except as may be authorized under paragraph (g) of this section, of any determination or redetermination of any weekly claim which denies UCFE or waiting period credit or reduces the weekly amount or maximum amount initially determined to be payable. Each notice of determination or redetermination shall include such information regarding the determination or redetermination and notice of right to reconsideration or appeal, or both, as is furnished with written notices of determinations and redeterminations with respect to claims for State unemployment compensation; and where information furnished by a Federal agency was considered in making the determination, or redetermination, the notice thereof shall include an explanation of the right of the individual to seek additional information pursuant to § 609.23 and/or a reconsideration of Federal findings pursuant to § 609.24.

(e) *Obtaining information for claim determinations.* (1) Information required for the determination of claims for UCFE shall be obtained by the State agency from claimants, employers, and others, in the same manner as information is obtained for claim purposes under the applicable State law, but information (including additional and reconsidered Federal findings) shall be obtained from the Federal agency that employed the UCFE claimant as prescribed in §§ 609.21 through 609.25. On request by a UCFE claimant, the State agency shall seek additional information pursuant to § 609.23 and reconsideration of Federal findings pursuant to § 609.24.

(2) If Federal findings have not been received from a Federal agency within 12 days after the request for information was submitted to the Federal agency, the State agency shall determine the individual's entitlement to UCFE on the basis of an affidavit completed by the individual on a form prescribed by the Department. In addition, the individual shall submit for examination by the State agency any documents issued by the Fedeal agency (for example, Standard Form 50 or W–2) verifying that the individual performed services for and received wages from such Federal agency.

(3) If Federal findings received by a State agency after a determination has been made under this section contain information which would result in a change in the individual's eligibility for or entitlement to UCFE, the State agency promptly shall make a redetermination and notify the individual, as provided in this section. All payments of UCFE made prior to or after such redetermination shall be adjusted in accordance therewith.

(f) *Promptness.* Full payment of UCFE when due shall be consistent with this Part 609 and shall be made with the greatest promptness that is administratively feasible, but the provisions of Part 640 of this chapter (relating to promptness of benefit payments) shall not be applicable to the UCFE Program.

(g) *Secretary's standard.* The procedures for making determinations and redeterminations, and furnishing written notices of determinations, redeterminations, and rights of appeal to individuals applying for UCFE, shall be consistent with this Part 609 and with the Secretary's "Standard for Claim Determinations—Separation Information" *(Employment Security Manual,* Part V, sections 6010 *et seq.).*

§ 609.7 Appeal and review.

(a) *Applicable State law.* The provisions of the applicable State law concerning the right of appeal and fair hearing from a determination or redetermination of entitlement to State unemployment compensation shall apply to determinations and redeterminations of eligibility for or entitlement to UCFE and waiting period credit. Any such determination or redetermination shall be subject to appeal and review only in the manner and to the extent provided in the applicable State law with respect to determinations and redeterminations of entitlement to State unemployment compensation.

(b) *Rights of appeal and fair hearing.* The provisions on right to appeal and opportunity for a fair hearing with respect to claims for UCFE shall be consistent with this Part and with sections 303(a)(1) and 303(a)(3) of the Social Security Act, 42 U.S.C. 503(a)(1) and 503(a)(3).

(c) *Promptness on appeals.* (1) Decisions on appeals under the UCFE Program shall accord with the Secretary's "Standard for Appeals Promptness—Unemployment Compensation" in Part 650 of this chapter, and with § 609.1(d).

(2) Any provision of an applicable State law for advancement or priority of unemployment compensation cases on judicial calenders, or otherwise intended to provide for the prompt payment of unemployent compensation when due, shall apply to proceedings involving claims for UCFE.

(d) *Appeal and review by Federal agency.* If a Federal agency believes that a State agency's determination or redetermination of an individual's eligibility for or entitlement to UCFE is incorrect, the Federal agency may seek appeal and review of such determination or redetermination in the same manner as an interested employer may seek appeal and review under the applicable State law.

§ 609.8 The applicable State for an individual.

(a) *The applicable State.* The applicable State for an individual shall be the State to which the individual's Federal civilian service and Federal wages are assigned or transferred under this section. The applicable State law for the individual shall be the State law of such State.

(b) *Assignment of service and wages.* (1) An individual's Federal civilian service and Federal wages shall be assigned to the State in which the

individual had his or her last official station prior to filing a first claim unless:

(i) At the time a first claim is filed the individual resides in another State in which, after separation from Federal civilian service, the individual performed service covered under the State law, in which case all of the individual's Federal civilian service and wages shall be assigned to the latter State; or

(ii) Prior to filing a first claim an individual's last official station was outside the States, in which case all of the individual's Federal civilian service and Federal wages shall be assigned to the State in which the individual resides at the time the individual files a first claim, provided the individual is personally present in a State when the individual files the first claim.

(2) Federal civilian service and wages assigned to a State in error shall be reassigned for use by the proper State agency. An appropriate record of a reassignment shall be made by the State agency which makes the reassignment.

(3) Federal civilian service and Federal wages assigned to a State shall be transferred to another State where such transfer is necessary for the purposes of a combined-wage claim filed by an individual.

(c) *Assignment deemed complete.* All of an individual's Federal civilian service and Federal wages shall be deemed to have been assigned to a State upon the filing of a first claim. Federal civilian service and Federal wages shall be assigned to a State only in accordance with paragraph (b) of this section.

(d) *Use of assigned service and wages.* All assigned Federal civilian service and Federal wages shall be used only by the State to which assigned or transferred in accordance with paragraph (b) of this section.

§ 609.9 Provisions of State law applicable to UCFE claims.

(a) *Particular provisions applicable.* Except where the result would be inconsistent with the provisions of the Act or this Part or the procedures thereunder prescribed by the Department, the terms and conditions of the applicable State law which apply to claims for, and the payment of, State unemployment compensation shall apply to claims for, and the payment of, UCFE and claims for waiting period credit. The provisions of the applicable State law which shall apply include, but are not limited to:

(1) Claim filing and reporting;

(2) Information to individuals, as appropriate;

(3) Notices to individuals and Federal agencies, as appropriate, including notice to each individual of each determination and redetermination of eligibility for or entitlement to UCFE;

(4) Determinations and redeterminations;

(5) Ability to work, availability for work, and search for work; and

(6) Disqualifications.

(b) *IBPP.* The *Interstate Benefit Payment Plan* shall apply, where appropriate, to individuals filing claims for UCFE.

(c) *Wage combining.* The State's provisions complying with the *Interstate Arrangement for Combining Employment and Wages* (Part 616 of this chapter) shall apply, where appropriate, to individuals filing claims for UCFE.

(d) *Procedural requirements.* The provisions of the applicable State law which apply hereunder to claims for and the payment of UCFE shall be applied consistently with the requirements of Title III of the Social Security Act and the Federal Unemployment Tax Act which are pertinent in the case of State unemployment compensation, including but not limited to those standards and requirements specifically referred to in the provisions of this part, except as provided in paragraph (f) of § 609.6.

§ 609.10 Restrictions on entitlement.

(a) *Disqualification.* If the week of unemployment for which an individual claims UCFE is a week to which a disqualification for State unemployment compensation applies under the applicable State law, or would apply but for the fact that the individual has no right to such compensation, the individual shall not be entitled to a payment of UCFE for that week.

(b) *Allocation of terminal annual leave payments.* Lump-sum terminal annual leave payments shall not be allocated by a Federal agency and shall be allocated by a State agency in the same manner as similar payments to individuals employed by private employers are allocated under the applicable State law. In a State in which a private employer has an option as to the period to which such payments shall be allocated, such payments shall be allocated to the date of separation from employment.

§ 609.11 Overpayments; penalties for fraud.

(a) *False statements and representations.* Section 8507(a) of the Act provides that if a State agency, the Department, or a court of competent jurisdiction finds that an individual—

(1) Knowingly has made, or caused to be made by another, a false statement or representation of a material fact, or knowingly has failed, or caused another to fail, to disclose a material fact; and

(2) As a result of that action has received an amount as UCFE to which the individual was not entitled; the individual shall repay the amount to the State agency or the Department. Instead of requiring repayments, the State agency or the Department may recover the amount by deductions from UCFE payable to the individual during the 2-year period after the date of the finding. A finding by a State agency or the Department may be made only after an opportunity for a fair hearing, subject to such further review as may be appropriate under § 609.7.

(b) *Prosecution for fraud.* Section 1919 of title 18, United States Code, provides that whoever makes a false statement or representation of a material fact knowing it to be false, or knowingly fails to disclose a material fact, to obtain or increase for himself or for any other individual any payment authorized to be paid under chapter 85 of title 5, United States Code, or under an agreement thereunder, shall be fined not more than $1,000 or imprisoned not more than one year, or both.

(c) *Absence of fraud.* If a State agency or court of competent jurisdiction finds that an individual has received a payment of UCFE to which the individual was not entitled under the Act and this part, which was not due to a false statement or representation as provided in paragraph (a) or (b) of this section, the individual shall be liable to repay to the applicable State the total sum of the payment to which the individual was not entitled, and the State agency shall take all reasonable measures authorized under any State law or Federal law to recover for the account of the United States the total sum of the payment to which the individual was not entitled.

(d) *Recovery by offset.* (1) The State agency shall recover, insofar as is possible, the amount of any overpayment which is not repaid by the individual, by deductions from any UCFE payable to the individual under the Act and this Part, or from any unemployment compensation payable to the individual under any Federal unemployment compensation law administered by the State agency, or from any assistance or allowance payable to the individual with respect to unemployment under any other Federal law administered by the State agency.

(2) A State agency shall also recover, insofar as is possible, the amount of any overpayment of UCFE made to the individual by another State, by

deductions from any UCFE payable by the State agency to the individual under the Act and this part, or from any unemployment compensation payable to the individual under any Federal unemployment compensation law administered by the State agency, or from any assistance or allowance payable to the individual with respect to unemployment under any other Federal law administered by the State agency.

(3) Recoupment of fraudulent overpayments referred to in paragraph (a) of this section shall be limited to the 2-year period stated in that paragraph. Recoupment of fraudulent overpayments referred to in paragraph (b) of this section, and nonfraudulent overpayments referred to in paragraph (c) of this section shall be subject to any time limitation on recoupment provided for in the State law that applies to the case.

(e) *Debts due the United States.* UCFE payable to an individual shall be applied by the State agency for the recovery by offset of any debt due to the United States from the individual, but shall not be applied or used by the State agency in any manner for the payment of any debt of the individual to any State or any other entity or person except pursuant to a court order for child support or alimony in accordance with the law of the State and Section 459 of the Social Security Act, 42 U.S.C. 659.

(f) *Application of State law.* (1) Except as indicated in paragraph (a) of this section, any provision of State law that may be applied for the recovery of overpayments or prosecution for fraud, and any provision of State law authorizing waiver of recovery of overpayments of unemployment compensation, shall be applicable to UCFE.

(2) In the case of any finding of false statement or representation under the Act and paragraph (a) of this section, or prosecution for fraud under 18 U.S.C. 1919 or pursuant to paragraph (f)(1) of this section, the individual shall be disqualified or penalized in accordance with the provisions of the applicable State law relating to fraud in connection with a claim for State unemployment compensation.

(g) *Final decision.* Recovery of any overpayment of UCFE shall not be enforced by the State agency until the determination or redetermination establishing the overpayment has become final, or if appeal is taken from the determination or redetermination, until the decision after opportunity for a fair hearing has become final.

(h) *Procedural requirements.* (1) The provisions of paragraphs (c), (d), and (g) of § 609.6 shall apply to determinations and redeterminations made pursuant to this section.

(2) The provisions of § 609.7 shall apply to determinations and redeterminations made pursuant to this section.

(i) *Fraud detection and prevention.* Provisions in the procedures of each State with respect to detection and prevention of fraudulent overpayments of UCFE shall be, as a minimum, commensurate with the procedures adopted by the State with respect to State unemployment compensation and consistent with the Secretary's "Standard for Fraud and Overpayment Detection" *(Employment Security Manual,* Part V, section 7510 *et seq.*).

(j) *Recovered overpayments.* An amount repaid or recouped under this section shall be—

(1) Deposited in the fund from which payment was made, if the repayment was to a State agency; or

(2) Returned to the Treasury of the United States and credited to the current applicable appropriation, fund, or account from which payment was made, if the repayment was to the Department.

§ 609.12 Inviolate rights to UCFE.

Except as specifically provided in this part, the rights of individuals to UCFE shall be protected in the same manner and to the same extent as the rights of persons to State unemployment compensation are protected under the applicable State law. Such measures shall include protection of applicants for UCFE from waiver, release, assignment, pledge, encumbrance, levy, execution, attachment, and garnishment of their rights to UCFE, except as provided in § 609.11. In the same manner and to the same extent, individuals shall be protected from discrimination and obstruction in regard to seeking, applying for, and receiving any right to UCFE.

§ 609.13 Recordkeeping; disclosure of information.

(a) *Recordkeeping.* Each State agency will make and maintain records pertaining to the administration of the UCFE Program as the Department requires, and will make all such records available for inspection, examination, and audit by such Federal officials or employees as the Department may designate or as may be required by law.

(b) *Disclosure of Information.* Information in records maintained by a State agency in administering the UCFE Program shall be kept confidential, and information in such records may be disclosed only in the same manner and to the same extent as information with respect to State unemployment compensation and the entitlement of individuals thereto may be disclosed under the applicable State law. This provision on the confidentiality of information maintained in the administration of the UCFE Program shall not apply, however, to the Department or for the purposes of §§ 609.11 or 609.13, or in the case of information, reports and studies required pursuant to §§ 609.17 or 609.25, or where the result would be inconsistent with the Freedom of Information Act (5 U.S.C. 552), the Privacy Act of 1974 (5 U.S.C. 552a), or regulations of the Department promulgated thereunder.

§ 609.14 Payments to States.

(a) *State entitlement.* Each State is entitled to be paid by the United States with respect to each individual whose base period wages included Federal wages, an amount bearing the same ratio to the total amount of compensation paid to such individual as the amount of the individual's Federal wages in the individual's base period bears to the total amount of the individual's base period wages.

(b) *Payment.* Each State shall be paid, either in advance or by way of reimbursement, as may be determined by the Department, the sum that the Department estimates the State is entitled to receive under the Act and this Part for each calendar month. The sum shall be reduced or increased by the amount which the Department finds that its estimate for an earlier calendar month was greater or less than the sum which should have been paid to the State. An estimate may be made on the basis of a statistical, sampling, or other method agreed on by the Department and the State agency.

(c) *Certification by the Department.* The Department, from time to time, shall certify to the Secretary of the Treasury the sum payable to each State under this section. The Secretary of the Treasury, before audit or settlement by the General Accounting Office, shall pay the State in accordance with the certification from the funds for carrying out the purposes of the Act and this part.

(d) *Use of money.* Money paid a State under the Act and this Part may be used solely for the purposes for which it is paid. Money so paid which is not used solely for these purposes shall be returned, at the time specified by the Agreement, to the Treasury of the United States and credited to the current applicable appropriation, fund, or account from which payments to states

under the Act and this part may be made.

§ 609.15 Public access to Agreements.

The State agency of a State will make available to any individual or organization a true copy of the Agreement with the State for inspection and copying. Copies of an Agreement may be furnished on request to any individual or organization upon payment of the same charges, if any, as apply to the furnishing of copies of other records of the State agency.

§ 609.16 Administration in absence of an Agreement.

(a) *Administering Program.* The Department shall administer the UCFE Program through personnel of the Department or through other arrangements under procedures prescribed by the Department, in the case of any State which does not have an Agreement with the Secretary as provided for in 5 U.S.C. 8502. The procedures prescribed by the Department under this section shall be consistent with the Act and this part.

(b) *Applicable State law.* On the filing by an individual of a claim for UCFE in accordance with arrangements under this section, UCFE shall be paid to the individual, if eligible, in the same amount, on the same terms, and subject to the same conditions as would be paid to the individual under the applicable State law if the individual's Federal civilian service and Federal wages had been included as employment and wages under the State law. Any such claim shall include the individual's Federal civilian service and Federal wages, combined with any service and wages covered by State law. However, if the individual, without regard to his or her Federal civilian service and Federal wages, has employment or wages sufficient to qualify for compensation during the benefit year under that State law, then payments of UCFE under this section may be made only on the basis of the individual's Federal civilian service and Federal wages.

(c) *Fair hearing.* An individual whose claim for UCFE is denied under this section is entitled to a fair hearing under rules of procedure prescribed by the Department. A final determination by the Department with respect to entitlement to UCFE under this section is subject to review by the courts in the same manner and to the same extent as is provided by section 205(g) of the Social Security Act, 42 U.S.C. 405(g).

§ 609.17 Information, reports, and studies.

State agencies shall furnish to the Department such information and reports and conduct such studies as the Department determines are necessary or appropriate for carrying out the purposes of the UCFE Program.

Subpart C—Responsibilities of Federal Agencies

§ 609.20 Information to Federal civilian employees.

Each Federal agency shall:

(a) Furnish information to its employees as to their rights and responsibilities under the UCFE Program and 18 U.S.C. 1919; and

(b) Furnish a completed copy of a form approved by the Department, "Notice to Federal Employee About Unemployment Compensation," in accordance with instructions thereon, to each employee at the time of separation from Federal civilian service, when transferred from one payroll office to another, or when the office responsible for distribution of the form is advised that an individual is in nonpay status for seven consecutive days or more.

§ 609.21 Findings of Federal agency.

(a) *Answering request.* Within four workdays after receipt from a State agency of a request for Federal findings on a form furnished by the State agency, and prescribed by the Department, a Federal agency shall make such Federal findings, complete all copies of the form, and transmit the completed copies to the State agency. If documents necessary for completion of the form have been assigned to an agency records center or the Federal Records Center in St. Louis, the Federal agency shall obtain the necessary information from the records center. Any records center shall give priority to such a request.

(b) *Failure to meet time limit.* If a completed form containing the Federal agency's findings cannot be returned within four workdays of receipt, the Federal agency immediately shall inform the State agency, and shall include an estimated date by which the completed form will be returned.

(c) *Administrative control.* Each Federal agency shall maintain a control of all requests for Federal findings received by it, and the Federal agency's response to each request. The records shall be maintained so as to enable the Federal agency to ascertain at any time the number of such forms that have not been returned to State agencies, and the dates of the Federal agency's receipt of such unreturned forms.

§ 609.22 Correcting Federal findings.

If a Federal agency ascertains at any time within one year after it has returned a completed form reporting its findings, that any of its findings were erroneous, it shall promptly correct its error and forward its corrected findings to the State agency.

§ 609.23 Furnishing additional information.

On receipt of a request for additional information from a State agency, a Federal agency shall consider the information it supplied initially in connection with such request and shall review its findings. The Federal agency promptly shall forward to the State agency such additional findings as will respond to the request. The Federal agency shall, if possible, respond within four workdays after the receipt of a request under this section.

§ 609.24 Reconsideration of Federal findings.

On receipt of a request for reconsideration of Federal findings from a State agency, the Federal agency shall consider the initial information supplied in connection with such request and shall review its findings. The Federal agency shall correct any errors or omissions in its findings and shall affirm, modify, or reverse any or all of its findings in writing. The Federal agency promptly shall forward its reconsidered findings to the requesting authority. The Federal agency shall, if possible, respond within four workdays after the receipt of a request under this section.

§ 609.25 Furnishing other information.

(a) *Additional Information.* In addition to the information required by §§ 609.21, 609.22, 609.23, and 609.24, a Federal agency shall furnish to a State agency or the Department, within the time requested, any information which it is not otherwise prohibited from releasing by law, which the Department determines is necessary for the administration of the UCFE Program.

(b) *Reports.* Federal agencies shall furnish to the Department or State agencies such reports containing such information as the Department determines are necessary or appropriate for carrying out the purposes of the UCFE Program.

§ 609.26 Liaison with Department.

To facilitate the Department's administration of the UCFE Program, each Federal agency shall designate one or more of its officials to be the liaison with the Department. Each Federal agency will inform the Department of its designation(s) and of any change in a designation.

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Friday
December 3, 1982

Part VI

Department of Labor

Employment and Training Administration

Unemployment Compensation for Ex-Servicemembers; Final Rule

DEPARTMENT OF LABOR

20 CFR Part 614

Unemployment Compensation for Ex-Servicemembers

AGENCY: Employment and Training Administration, Labor.

ACTION: Final rule.

SUMMARY: These are the Department of Labor's revised regulations for implementing the program of Unemployment Compensation for Ex-Servicemembers (UCX Program). Changes to the regulations incorporate statutory amendments, which require treatment of the Virgin Islands as a participating State in the Federal-State Unemployment Compensation Program, which prescribe a new rule for determining the Federal share of the cost of benefits in connection with joint claims under the UCX Program and State unemployment compensation laws, and which revise the eligibility requirements for entitlement to the program benefits. The final regulations also incorporate the amendment in Public Law 96–215, which provides that Commissioned Corps Officers of the National Oceanic and Atmospheric Administration (NOAA) shall be covered under the UCX Program. The regulations are also reorganized and revised to state the rights and obligations of claimants for the benefits and to clarify the respective duties and responsibilities of the Federal Government and the State agencies. The setting forth of this information in each Part dealing with a separate unemployment compensation program conforms to the more recent practice in writing regulations for unemployment compensation and related benefit programs. The final regulations incorporate the substantive changes and improvements as set forth in the published proposal.

EFFECTIVE DATE: January 3, 1983.

FOR FURTHER INFORMATION CONTACT: Bert Lewis, Administrator, Unemployment Insurance Service, Employment and Training Administration, U.S. Department of Labor, 601 "D" Street, N.W., Washington, D.C. 20213, telephone: (202) 376–7032 (this is not a toll-free number).

SUPPLEMENTARY INFORMATION: The UCX Program is financed by Federal funds to furnish unemployment benefits to eligible individuals who are separated from military service and are unable to obtain work. The program was created by Pub. L. 85–848, approved on August 28, 1958. It has been codified in 5 U.S.C. 8521–8525.

Part 614, Chapter V, Title 20 of the Code of Federal Regulations (20 CFR Part 614), implements the Unemployment Compensation for Ex-Servicemembers Programs as most recently amended by Pub. L. 94–566, Pub. L. 96–215, and Pub. L. 96–364. The proposal to revise the regulations was published in the **Federal Register** on January 23, 1981 (46 FR 7796), and this document contains the final revised regulations for Part 614. Comments on the proposal published on January 23, 1981, were solicited through March 24, 1981, and the proposal was further reviewed in the Department. As a result of comments and review, a few changes have been made in the proposal. Also, a new statutory amendment has been added.

1. Public Law 96–215 amended 5 U.S.C. 8521(a)(1) to read: "Federal service means active service, including active duty for training purposes, in the armed forces *or the Commissioned Corps of the National Oceanic and Atmospheric Administration* * * *". This amendment provides that ex-officers of NOAA are entitled to file for benefits under the UCX Program after March 25, 1980.

2. The New York Department of Labor and Washington Employment Security Department suggested in a comment that we amend § 614.2(f) to take in consideration the passage of Pub. L. 96–215 regarding the coverage of members of the Commissioned Corps of NOAA. Although this change was overlooked in the proposal, we recognize the need for the change and therefore have changed §§ 614.2(f) and 614.2(g).

3. The New York Department of Labor (and the Colorado Division of Employment and Training orally) suggested that we eliminate the requirement in § 614.11(d)(3) that limits recovery of UCX fraud overpayments by offsets during the 2-year period after the date of the finding establishing the overpayments. They contend that this is different from the time limit in applicable State laws and is harder to administer.

The current requirement as reflected in §§ 614.11(a)(2) and 614.11(d)(3) of the proposed regulations is not a new requirement. It specifically follows Section 8507 of the law. Time limits on recovery of nonfraudulent overpayments are governed by the applicable State law. Although this may result in different time limits on recovery of fraudulent and nonfraudulent overpayments, the 2-year period is specifically required by the law. Therefore, no change is made in § 614.11 (a) or (b).

4. The Illinois Division of Unemployment Insurance found an error in the text of § 614.23(a) of the proposed rule. The minimum service requirement was changed by amendment instead in Pub. L. 96–364 from "90" days to "365" days. In the proposal, this change was made in § 614.2(g), but was overlooked in § 614.23(a). The error is corrected in the final regulations.

5. A review of proposed Part 614, § 614.2(h), revealed an error in the definition of Federal wages. That error has been corrected in the text.

6. In addition, a few minor proofing and technical errors were made in the proposed document as published in the **Federal Register** on January 23, 1981. Those errors have been corrected.

Drafting Information

This document was prepared under the direction and control of the Administrator of the Unemployment Insurance Service, Employment and Training Administration, U.S. Department of Labor, 601 "D" Street, N.W., Washington, D.C. 20213; telephone: (202) 376–7032 (this is not a toll-free number).

Classification—Executive Order 12291

This rule is not classified as a "major rule" under Executive Order 12291 on Federal Regulations, because it is not likely to result in (1) an annual effect on the economy of $100 million or more; (2) a major increase in cost or prices for consumers, individual industries, Federal, State or local government agencies, or geographic regions; or (3) significant adverse effects on competition, employment, investment, productivity, innovation, or the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. Accordingly, no regulatory impact analysis is required.

Paperwork Reduction

Information collection requirements contained in this regulation (§§ 614.1(d)(1), 614.5(a) and 614.22(a)) have been approved by the Office of Management and Budget under the provisions of 44 U.S.C. Chapter 35 and have been assigned OMB control numbers 1205–0163 (pertaining to § 614.1(d)(1)) and 1205–0176 (pertaining to §§ 614.5(a) and 614.22(a)).

Regulatory Flexibility Act

The Department believes that the rule will have no "significant economic impact on a substantial number of small

entities" within the meaning of section 3(a) of the Regulatory Flexibility Act, Pub. L. No. 96–354, 91 Stat. 1164 (5 U.S.C. 605(b)). The Secretary has certified to the Chief Counsel for Advocacy of the Small Business Administration to this effect. This conclusion is reached because this rule only implements amendments to an individual entitlement program, and thus no economic impact is expected with respect to any small entities. Accordingly, no regulatory flexibility analysis is required.

Regulatory Flexibility Act Certification

I, Raymond J. Donovan, Secretary of Labor, hereby certify, pursuant to 5 U.S.C. 605(b) that the final regulations published hereinafter (20 CFR Part 614, Final Amendments to the Unemployment Compensation Program for Ex-Servicemembers Regulation) will not, if promulgated, have a significant economic impact on a substantial number of small entities because this is an individual entitlement program and affects only individuals applying for benefits under the Unemployment Compensation Program for Ex-Servicemembers.

Dated: November 29, 1982.

Raymond J. Donovan.

List of Subjects in 20 CFR Part 614

Unemployment Compensation for Ex-Servicemembers (UCX), Unemployment compensation.

Words of Issuance

Accordingly, Part 614 of Title 20 of the Code of Federal Regulations is revised as set forth below.

Signed at Washington, D.C. on November 29, 1982.

Albert Angrisani,

Assistant Secretary of Labor.

PART 614—UNEMPLOYMENT COMPENSATION FOR EX-SERVICEMEMBERS

Subpart A—General Provisions

Sec.

Subpart B—Administration of UCX Program

Subpart C—Responsibilities of Federal Military Agencies and State Agencies

Authority: 5 U.S.C. 8508; Secretary's Order No. 4–75, 40 FR 18515 (5 U.S.C. 301). Interpret and apply secs. 8521–8525 of title 5, United States Code.

Subpart A—General Provisions

§ 614.1 Purpose and application.

(a) *Purpose.* Subchapter II of chapter 85, title 5 of the United States Code, as amended by Pub. L. 94–566, 90 Stat. 2667 (5 U.S.C. 8521–8525), provides for a permanent program of unemployment compensation for unemployed individuals separated from the Armed Forces. The unemployment compensation provided for in Subchapter II is hereinafter referred to as Unemployment Compensation for Ex-Servicemembers, or UCX. The regulations in this part are issued to implement the UCX Program.

(b) *First rule of construction.* The Act and the implementing regulations in this part shall be construed liberally so as to carry out the purposes of the Act.

(c) *Second rule of construction.* The Act and the implementing regulations in this part shall be construed so as to assure insofar as possible the uniform interpretation and application of the Act throughout the United States.

(d) *Effectuating purpose and rules of construction.* (1) In order to effectuate the provisions of this section, each State agency shall forward to the United States Department of Labor (hereafter Department), not later than 10 days after issuance, a copy of each judicial or administrative decision ruling on an individual's entitlement to payment of UCX or to credit for a waiting period. On request of the Department, a State agency shall forward to the Department a copy of any determination or redetermination ruling on an individual's entitlement to UCX or waiting period credit.

(2) If the Department believes that a determination, redetermination, or decision is inconsistent with the Department's interpretation of the Act or this part, the Department may at any time notify the State agency of the Department's view. Thereafter, the State agency shall issue a redetermination or appeal if possible, and shall not follow such determination, redetermination, or decision as a precedent; and, in any subsequent proceedings which involve such determination, redetermination, or decision, or wherein such determination, redetermination, or decision is cited as precedent or otherwise relied upon, the State agency shall inform the claims deputy or hearing officer or court of the Department's view and shall make all reasonable efforts, including appeal or other proceedings in an appropriate forum, to obtain modification, limitation, or overruling of the determination, redetermination, or decision.

(3) If the Department believes that a determination, redetermination, or decision is patently and flagrantly violative of the Act or this part, the Department may at any time notify the State agency of the Department's view. If the determination, redetermination, or decision in question denies UCX to a claimant, the steps outlined in paragraph (2) above shall be followed by the State agency. If the determination, redetermination, or decision in question awards UCX to a claimant, the benefits are "due" within the meaning of section 303(a)(1) of the Social Security Act, 42 U.S.C. 503(a)(1), and therefore must be paid promptly to the claimant. However, the State agency shall take the steps outlined in paragraph (d)(2) of this section, and payments to the claimant may be temporarily delayed if redetermination or appeal action is taken not more than one business day following the day on which the first payment otherwise would be issued to the claimant; and the redetermination action is taken or appeal is filed to obtain a reversal of the award of UCX and a ruling consistent with the Department's view; and the redetermination action or appeal seeks an expedited redetermination or appeal within not more than two weeks after the redetermination action is taken or the appeal is filed. If redetermination action is not taken or appeal is not filed within the above time limit, or a redetermination or decision is not obtained within the two-week limit, or any redetermination or decision or order is issued which affirms the determination, redetermination, or decision awarding UCX or allows it to stand in whole or in part, the benefits awarded must be paid promptly to the claimant.

(4)(i) If any determination, redetermination, or decision, referred to

in paragraph (d)(2) or paragraph (d)(3) of this section, is treated as a precedent for any future UCX claim or claim under the UCFE Program (Part 609 of this chapter), the Secretary will decide whether the Agreement with the State entered into under the Act shall be terminated.

(ii) In the case of any determination, redetermination, or decision that is not legally warranted under the Act or this Part, including any determination, redetermination, or decision referred to in paragraph (d)(3) of this section, the Secretary will decide whether the State shall be required to restore the funds of the United States for any sums paid under such a determination, redetermination, or decision, and whether, in the absence of such restoration, the Agreement with the State shall be terminated and whether other action shall be taken to recover such sums for the United States.

(5) A State agency may request reconsideration of a notice issued pursuant to paragraph (d)(2) or paragraph (d)(3) of this section, and shall be given an opportunity to present views and arguments if desired.

(6) Concurrence of the Department in a determination, redetermination, or decision shall not be presumed from the absence of a notice issued pursuant to this section.

§ 614.2 Definitions of terms.

For purposes of the Act and this Part:

(a) "Act" means subchapter II of chapter 85 of title 5 of the United States Code, 5 U.S.C. 8521–8525.

(b) "Agreement" means the Agreement entered into pursuant to 5 U.S.C. 8502 between a State and the Secretary under which the State agency of the State agrees to make payments of unemployment compensation in accordance with the Act and the regulations and procedures thereunder prescribed by the Department.

(c) "Base period" means the base period as defined by the applicable State law for the benefit year.

(d) "Benefit year" means the benefit year as defined by the applicable State law, and if not so defined the term means the period prescribed in the Agreement with the State or, in the absence of an Agreement, the period prescribed by the Department.

(e) "Ex-servicemember" means an individual who has performed Federal military service.

(f) "Federal military agency" means any of the Armed Forces of the United States, including the Army, Air Force, Navy, Marine Corps, and Coast Guard, and the National Oceanic and Atmospheric Administration (Department of Commerce).

(g) "Federal military service" means a period of active service, including active duty for training purposes, in the Armed Forces or (with respect to first claims filed after March 25, 1980) the Commissioned Corps of the National Oceanic and Atmospheric Administration if—

(1) Such service was continuous for 365 days or more or was terminated in less than 365 days because of an actual service-incurred injury or disability; and

(2) With respect to such service the individual (i) was discharged or released under conditions other than dishonorable, (ii) was not given a bad conduct discharge, or (iii) if an officer, did not resign for the good of the service.

(h) "Federal military wages" means all pay and allowances in cash and in kind for Federal military service, computed on the basis of the pay and allowances for the pay grade of the individual at the time of his or her latest discharge or release from Federal/military service, as determined in accordance with the Schedule of Remuneration applicable at the time the individual files his or her first claim for compensation for a benefit year.

(i) "First claim" means an initial claim for unemployment compensation under the UCX Program, the UCFE Program (Part 609 of this chapter), or a State law, or some combination thereof, first filed by an individual after the individual's latest discharge or release from Federal military service, whereby a benefit year is established under an applicable State law.

(j) "Military document" means an official document or documents issued to an individual by a Federal military agency relating to the individual's Federal military service and discharge or release from such service.

(k) "Period of active service" means a period of continuous active duty (including active duty for training purposes) in a Federal military agency or agencies, beginning with the date of entry upon active duty and ending on the effective date of the first discharge or release thereafter which is not qualified or conditional.

(l) "Schedule of Remuneration" means the schedule issued by the Department from time to time under 5 U.S.C. 8521(a)(2) and this part, which specifies for purposes of the UCX Program, the pay and allowances for each pay grade of servicemember.

(m) "Secretary" means the Secretary of Labor of the United States.

(n) "State" means the 50 States, the District of Columbia, the Commonwealth of Puerto Rico, and the Virgin Islands.

(o) "State agency" means the agency of the State which administers the applicable State unemployment compensation law and is administering the UCX Program in the State pursuant to an Agreement with the Secretary.

(p)(1) "State law" means the unemployment compensation law of a State approved by the Secretary under section 3304 of the Internal Revenue Code of 1954, 26 U.S.C. 3304, if the State is certified under section 3304(c) of the Internal Revenue Code of 1954, 26 U.S.C. 3304(c).

(2) "Applicable State law" means the State law made applicable to a UCX claimant by § 614.8.

(q)(1) "Unemployment compensation" means cash benefits (including dependents' allowances) payable to individuals with respect to their unemployment, and includes regular, additional, emergency, and extended compensation.

(2) "Regular compensation" means unemployment compensation payable to an individual under any State law, but not including additional compensation or extended compensation.

(3) "Additional compensation" means unemployment compensation totally financed by a State and payable under a State law by reason of conditions of high unemployment or by reason of other special factors.

(4) "Emergency compensation" means supplementary unemployment compensation payable under a temporary Federal law after exhaustion of regular and extended compensation.

(5) "Extended compensation" means unemployment compensation payable to an individual for weeks of unemployment in an extended benefit period, under those provisions of a State law which satisfy the requirements of the Federal-State Extended Unemployment Compensation Act of 1970, as amended, 26 U.S.C. 3304 note, and Part 615 of this chapter, with respect to the payment of extended compensation.

(r) "Unemployment Compensation for Ex-Servicemember" means the unemployment compensation payable under the Act to claimants eligible for the payments, and is referred to as UCX.

(s) "Week" means, for purposes of eligibility for and payment of UCX, a week as defined in the applicable State law.

(t) "Week of unemployment" means a week of total, part-total, or partial unemployment as defined in the applicable State law, which shall be applied in the same manner and to the same extent to all employment and earnings, and in the same manner and to

the same extent for the purposes of the UCX Program, as if the individual filing for UCX were filing a claim for State unemployment compensation.

Subpart B—Administration of UCX Program

§ 614.3 Eligibility requirements for UCX.

An individual shall be eligible to receive a payment of UCX or waiting period credit with respect to a week of unemployment if:

(a) The individual has Federal military service and Federal military wages in the base period under the applicable State law;

(b) The individual meets the qualifying employment and wage requirements of the applicable State law, either on the basis of Federal military service and Federal military wages alone or in combination with service and wages covered under a State law or under the UCFE Program (Part 609 of this chapter);

(c) The individual has filed an initial claim for UCX and, as appropriate, has filed a timely claim for waiting period credit or payment of UCX with respect to that week of unemployment; and

(d) The individual is totally, part-totally, or partially unemployed, and is able to work, available for work, and seeking work within the meaning of or as required by the applicable State law, and is not subject to disqualification under this Part or the applicable State law, with respect to that week of unemployment.

§ 614.4 Weekly and maximum benefit amounts.

(a) *Total unemployment.* The weekly amount of UCX payable to an eligible individual for a week of total unemployment shall be the amount that would be payable to the individual as unemployment compensation for a week of total unemployment as determined under the applicable State law.

(b) *Partial and part-total unemployment.* The weekly amount of UCX payable for a week of partial or part-total unemployment shall be the amount that would be payable to the individual as unemployment compensation for a week of partial or part-total unemployment as determined under the applicable State law.

(c) *Maximum amount.* The maximum amount of UCX which shall be payable to an eligible individual during and subsequent to the individual's benefit year shall be the maximum amount of all unemployment compensation that would be payable to the individual as determined under the applicable State law.

(d) *Computation rule.* The weekly and maximum amounts of UCX payable to an individual under the UCX Program shall be determined under the applicable State law to be in the same amount, on the same terms, and subject to the same conditions as the State unemployment compensation which would be payable to the individual under the applicable State law if the individual's Federal military service and Federal military wages assigned or transferred under this part to the State had been included as employment and wages covered by that State law, subject to the use of the applicable Schedule of Remuneration.

§ 614.5 Claims for UCX.

(a) *First claims.* A first claim for UCX shall be filed by an individual in any State agency of any State according to the applicable State law, and on a form prescribed by the Department which shall be furnished to the individual by the State agency where the claim is filed.

(b) *Weekly claims.* Claims for waiting week credit and payments of UCX for weeks of unemployment shall be filed in any State agency (or Canada) at the times and in the manner as claims for State unemployment compensation are filed under the applicable State law, and on forms prescribed by the Department which shall be furnished to the individual by the State agency where the claim is filed.

(c) *Secretary's standard.* The procedures for reporting and filing claims for UCX and waiting period credit shall be consistent with this Part 614 and the Secretary's "Standard for Claim Filing, Claimant Reporting, Job Finding and Employment Services" (*Employment Security Manual*, Part V, sections 5000 *et seq.*).

§ 614.6 Determinations of entitlement; notices to individual.

(a) *Determination of first claim.* Except for findings of a Federal military agency or the Veterans Administration and the applicable Schedule of Remuneration which are final and conclusive under § 614.25, the State agency whose State law applies to an individual under § 614.8 shall, promptly upon the filing of a first claim for UCX, determine whether the individual is otherwise eligible, and, if the individual is found to be eligible, the individual's benefit year and the weekly and maximum amounts of UCX payable to the individual.

(b) *Determinations of weekly claims.* The State agency promptly shall, upon the filing of a claim for a payment of UCX or waiting period credit with respect to a week, determine whether the individual is entitled to a payment of UCX or waiting period credit respect to such week, and, if entitled, the amount of UCX or waiting period credit to which the individual is entitled.

(c) *Redetermination.* The provisions of the applicable State law concerning the right to request, or authority to undertake, reconsideration of a determination pertaining to State unemployment compensation under the applicable State law shall apply to determinations pertaining to UCX.

(d) *Notices to individual.* The State agency promptly shall give notice in writing to the individual of any determination or redetermination of a first claim, and, except as may be authorized under paragraph (g) of this section, of any determination or redetermination of any weekly claim which denies UCX or waiting period credit or reduces the weekly amount or maximum amount initially determined to be payable. Each notice of determination or redetermination shall include such information regarding the determination or redetermination and notice of right to reconsideration or appeal, or both, as is furnished with written notices of determinations and redeterminations with respect to claims for State unemployment compensation. Such notice shall include the findings of any Federal military agency or the Veterans Administration, and shall inform the individual of the finality of such findings and of the individual's right to request correction of such findings as is provided in §§ 614.22 and 614.24.

(e) *Obtaining information for claim determinations.* (1) Information required for the determination of claims for UCX shall be obtained by the State agency from claimants, employers, and others, in the same manner as information is obtained for claim purposes under the applicable State law, but Federal military findings shall be obtained from military documents, the applicable Schedule of Remuneration, and from Federal military agencies and the Veterans Administration as prescribed in §§ 614.21 through 614.26.

(2) Procedures for requesting correction of Federal findings and Veterans Administration findings, and State agency procedures when requests are made and responses are received, are prescribed in §§ 614.22 through 614.24.

(f) *Promptness.* Full payment of UCX when due shall be consistent with this part and shall be made with the greatest promptness that is administratively feasible, but the provisions of Part 640 of

this chapter (relating to promptness of benefit payments) shall not be applicable to the UCX Program.

(g) *Secretary's standard.* The procedures for making determinations and redeterminations, and furnishing written notices of determinations, redeterminations, and rights of appeal to individuals applying for UCX, shall be consistent with this part and with the Secretary's "Standard for Claim Determinations—Separation Information" (*Employment Security Manual,* Part V, sections 6010 *et seq.*).

§ 614.7 Appeal and review.

(a) *Applicable State Law.* The provisions of the applicable State law concerning the right of appeal and fair hearing from a determination or redetermination of entitlement to State unemployment compensation (exclusive of findings which are final and conclusive under § 614.25) shall apply to determinations and redeterminations of eligibility for or entitlement to UCX and waiting period credit. Any such determination or redetermination shall be subject to appeal and review only in the manner and to the extent provided in the applicable State law with respect to determinations and redeterminations of entitlement to State unemployment compensation.

(Section 614.24 governs appeals of findings of the Veterans Administration)

(b) *Rights of appeal and fair hearing.* The provisions on right of appeal and opportunity for a fair hearing with respect to claims for UCX shall be consistent with this part and with sections 303(a)(1) and 303(a)(3) of the Social Security Act, 42 U.S.C. 503(a)(1) and 503(a)(3).

(c) *Promptness on appeals.* (1) Decisions on appeals under the UCX Program shall accord with the Secretary's "Standard for Appeals Promptness—Unemployment Compensation" in Part 650 of this chapter, and with § 614.1(d).

(2) Any provision of an applicable State law for advancement or priority of unemployment compensation cases on judicial calendars, or otherwise intended to provide for the prompt payment of unemployment compensation when due, shall apply to proceedings involving claims for UCX.

(d) *Appeal and review by Federal military agency.* If a Federal military agency believes that a State agency's determination or redetermination of an individual's eligibility for or entitlement to UCX is incorrect, the Federal military agency may seek appeal and review of such determination or redetermination in the same manner as an interested employer may seek appeal and review under the applicable State law.

§ 614.8 The applicable State for an individual.

(a) *The applicable State.* The applicable State for an individual shall be the State to which the individual's Federal military service and Federal military wages are assigned or transferred under this section. The applicable State law for the individual shall be the State law of such State.

(b) *Assignment of service and wages.* (1) When an individual files a first claim, all of the individual's Federal military service and Federal military wages shall be deemed to be assigned to the State in which such claim is filed, which shall be the "Paying State" in the case of a combined-wage claim. (§ 616.6(e) of this chapter.)

(2) Federal military service and Federal military wages assigned to a State in error shall be reassigned for use by the proper State agency. An appropriate record of the reassignment shall be made by the State agency which makes the reassignment.

(c) *Assignment deemed complete.* All of an individual's Federal military service and Federal military wages shall be deemed to have been assigned to a State upon the filing of a first claim. Federal military service and Federal military wages shall be assigned to a State only in accordance with paragraph (b) of this section.

(d) *Use of assigned service and wages.* All assigned Federal military service and Federal military wages shall be used only by the State to which assigned in accordance with paragraph (b) of this section, except that any Federal military service and Federal military wages which are not within the base period of the State to which they were assigned shall be subject to transfer in accordance with Part 616 of this chapter for the purposes of any subsequent Combined-Wage Claim filed by the individual.

§ 614.9 Provisions of State law applicable to UCX claims.

(a) *Particular provisions applicable.* Except where the result would be inconsistent with the provisions of the Act or this Part or the procedures thereunder prescribed by the Department, the terms and conditions of the applicable State law which apply to claims for, and the payment of, State unemployment compensation shall apply to claims for, and the payment of, UCX and claims for waiting period credit. The provisions of the applicable State law which shall apply include, but are not limited to:

(1) Claim filing and reporting;

(2) Information to individuals, as appropriate;

(3) Notices to individuals, as appropriate, including notice to each individual of each determination and redetermination of eligibility for or entitlement to UCX;

(4) Determinations and redeterminations;

(5) Ability to work, availability for work, and search for work; and

(6) Disqualifications, except in regard to separation from any Federal military agency.

(b) *IBPP.* The *Interstate Benefit Payment Plan* shall apply, where appropriate, to individuals filing claims for UCX.

(c) *Wage combining.* The State's provisions complying with the *Interstate Arrangement for Combining Employment and Wages* (Part 616 of this chapter) shall apply, where appropriate, to individuals filing claims for UCX.

(d) *Procedural requirements.* The provisions of the applicable State law which apply hereunder to claims for and the payment of UCX shall be applied consistently with the requirements of Title III of the Social Security Act and the Federal Unemployment Tax Act which are pertinent in the case of State unemployment compensation, including but not limited to those standards and requirements specifically referred to in the provisions of this part, except as provided in paragraph (f) of § 614.6.

§ 614.10 Restrictions on entitlement.

(a) *Disqualification.* If the week of unemployment for which an individual claims UCX is a week to which a disqualification for State unemployment compensation applies under the applicable State law, the individual shall not be entitled to a payment of UCX for that week. As provided in § 614.9(a), no disqualification shall apply in regard to separation from any Federal military agency.

(b) *Effect of "days lost".* The continuity of a period of an individual's Federal military service shall not be deemed to be interrupted by reason of any "days lost" in such period, but "days lost" shall not be counted for purposes of determining:

(1) Whether an individual has performed Federal military service;

(2) Whether an individual meets the wage and employment requirements of a State law; or

(3) The amount of an individual's Federal military wages.

(c) *Allocation of military accrued leave.* A State agency shall allocate the number of days of unused military leave

specified in an ex-servicemember's military document, for which a lump-sum payment has been made, in the same manner as similar payments by private employers to their employees are allocated under the applicable State law, except that the applicable Schedule of Remuneration instead of the lump-sum payment shall be used to determine the amount of the claimant's Federal military wages. In a State in which a private employer has an option as to the period to which such payments shall be allocated, such payments shall be allocated to the date of the individual's latest discharge or release from Federal military service. An allocation under this paragraph shall be disregarded in determining whether an individual has had a period of active service constituting Federal military service.

(d) *Education and training allowances.* An individual is not entitled to UCX under the Act or this Part for a period with respect to which the individual receives:

(1) A subsistence allowance for vocational rehabilitation training under chapter 31 of title 38 of the United States Code, 38 U.S.C. 1501 *et seq.*, or under Part VIII of Veterans Regulation Numbered 1(a); or

(2) An educational assistance allowance or special training allowance under chapter 35 of title 38 of the United States Code, 38 U.S.C. 1700 *et seq.*

§ 614.11 Overpayments; penalties for fraud.

(a) *False statements and representations.* Section 8507(a) of the Act provides that if a State agency, the Department, or a court of competent jurisdiction finds that an individual—

(1) Knowingly has made, or caused to be made by another, a false statement or representation of a material fact, or knowingly has failed, or caused another to fail, to disclose a material fact; and

(2) As a result of that action has received an amount as UCX to which the individual was not entitled; the individual shall repay the amount to the State agency or the Department. Instead of requiring repayment, the State agency or the Department may recover the amount by deductions from UCX payable to the individual during the 2-year period after the date of the finding. A finding by a State agency or the Department may be made only after an opportunity for a fair hearing, subject to such further review as may be appropriate under § 614.7.

(b) *Prosecution for fraud.* Section 1919 of title 18, United States Code, provides that whoever makes a false statement or representation of a material fact knowing it to be false, or knowingly fails to disclose a material fact, to obtain or increase for himself or for any other individual any payment authorized to be paid under chapter 85 of title 5, United States Code, or under an agreement thereunder, shall be fined not more than $1,000 or imprisoned not more than one year, or both.

(c) *Absence of fraud.* If a State agency or court of competent jurisdiction finds that an individual has received a payment of UCX to which the individual was not entitled under the Act and this part, which was not due to a false statement or representation as provided in paragraph (a) or (b) of this section, the individual shall be liable to repay to the applicable State the total sum of the payment to which the individual was not entitled, and the State agency shall take all reasonable measures authorized under any State law or Federal law to recover for the account of the United States the total sum of the payment to which the individual was not entitled.

(d) *Recovery by offset.* (1) The State agency shall recover, insofar as is possible, the amount of any overpayment which is not repaid by the individual, by deductions from any UCX payable to the individual under the Act and this part, or from any unemployment compensation payable to the individual under any Federal unemployment compensation law administered by the State agency, or from any assistance or allowance payable to the individual with respect to unemployment under any other Federal law administered by the State agency.

(2) A State agency shall also recover, insofar as is possible, the amount of any overpayment of UCX made to the individual by another State by deductions from any UCX payable by the State agency to the individual under the Act and this part, or from any unemployment compensation payable to the individual under any Federal unemployment compensation law administered by the State agency, or from any assistance or allowance payable to the individual with respect to unemployment under any other Federal law administered by the State agency.

(3) Recoupment of fraudulent overpayments referred to in paragraph (a) of this section shall be limited to the 2-year period stated in that paragraph. Recoupment of fraudulent overpayments referred to in paragraph (b) of this section, and nonfraudulent overpayments referred to in paragraph (c) of this section shall be subject to any time limitation on recoupment provided for in the State law that applies to the case.

(e) *Debts due the United States.* UCX payable to an individual shall be applied by the State agency for the recovery by offset of any debt due to the United States from the individual, but shall not be applied or used by the State agency in any manner for the payment of any debt of the individual to any State or any other entity or person except pursuant to a court order for child support or alimony in accordance with the law of the State and Section 459 of the Social Security Act, 42 U.S.C. 659.

(f) *Application of State law.* (1) Except as indicated in paragraph (a) of this section, any provision of State law that may be applied for the recovery of overpayments or prosecution for fraud, and any provision of State law authorizing waiver of recovery of overpayments of unemployment compensation, shall be applicable to UCX.

(2) In the case of any finding of false statement of representation under the Act and paragraph (a) of this section, or prosecution for fraud under 18 U.S.C. 1919 or pursuant to paragraph (f)(1) of this section, the individual shall be disqualified or penalized in accordance with the provision of the applicable State law relating to fraud in connection with a claim for State unemployment compensation.

(g) *Final decision.* Recovery of any overpayment of UCX shall not be enforced by the State agency until the determination or redetermination establishing the overpayment has become final, or if appeal is taken from the determination or redetermination, until the decision after opportunity for a fair hearing has become final.

(h) *Procedural requirements.* (1) The provisions of paragraphs (c), (d), and (g) of § 614.6 shall apply to determinations and redeterminations made pursuant to this section.

(2) The provisions of § 614.7 shall apply to determinations and redeterminations made pursuant to this section.

(i) *Fraud detection and prevention.* Provisions in the procedures of each State with respect to detection and prevention of fraudulent overpayments of UCX shall be, as a minimum, commensurate with the procedures adopted by the State with respect to State unemployment compensation and consistent with the Secretary's "Standard for Fraud and Overpayment Detection" (*Employment Security Manual,* Part V, sections 7510 *et seq.*).

(j) *Recovered overpayments.* An amount repaid or recouped under this section shall be—

(1) Deposited in the fund from which payment was made, if the repayment was to a State agency; or

(2) Returned to the Treasury of the United States and credited to the current applicable appropriation, fund, or account from which payment was made, if the repayment was to the Department.

§ 614.12 Schedules of remuneration.

(a) *Authority.* Section 8521(a)(2) of chapter 85, title 5 of the United States Code, 5 U.S.C. 8521(a)(2), requires the Secretary of Labor to issue from time to time, after consultation with the Secretary of Defense, a Schedule of Remuneration specifying the pay and allowances for each pay grade of members of the Armed Forces.

(b) *Elements of schedule.* A schedule reflects representative amounts for appropriate elements of the pay and allowances, whether in cash or kind, for each pay grade of members of the Armed Forces, with a statement of the effective date of the schedule. Benefit amounts for the UCX Program are computed on the basis of the Federal military wages for the pay grade of the individual at the time of the individual's latest discharge or release from Federal military service, as specified in the schedule applicable at the time the individual files his or her first claim for compensation for the benefit year.

(c) *Effective date.* Any new Schedule of Remuneration shall take effect beginning with the first week of the calendar quarter following the calendar quarter in which such schedule is issued, and shall remain applicable until a subsequent schedule becomes effective. Prior schedules shall continue to remain applicable for the periods they were in effect.

(d) *Publication.* Any new Schedule of Remuneration shall be issued by the Secretary of Labor to the State agencies and the Federal military agencies. Promptly after the issuance of a new Schedule of Remuneration it shall be published as a notice in the **Federal Register.**

§ 614.13 Inviolate rights to UCX.

Except as specifically provided in this Part, the rights of individuals to UCX shall be protected in the same manner and to the same extent as the rights of persons to State unemployment compensation are protected under the applicable State law. Such measures shall include protection of applicants for UCX from waiver, release, assignment, pledge, encumbrance, levy, execution, attachment, and garnishment of their rights to UCX, except as provided in § 614.11. In the same manner and to the same extent, individuals shall be protected from discrimination and obstruction in regard to seeking, applying for, and receiving any right to UCX.

§ 614.14 Recordkeeping; disclosure of information.

(a) *Recordkeeping.* Each State agency will make and maintain records pertaining to the administration of the UCX Program as the Department requires, and will make all such records available for inspection, examination, and audit by such Federal officials or employees as the Department may designate or as may be required by law.

(b) *Disclosure of information.* Information in records maintained by a State agency in administering the UCX Program shall be kept confidential, and information in such records may be disclosed only in the same manner and to the same extent as information with respect to State unemployment compensation and the entitlement of individuals thereto may be disclosed under the applicable State law. This provision on the confidentiality of information maintained in the administration of the UCX Program shall not apply, however, to the Department or for the purposes of §§ 614.11 or 614.14, or in the case of information, reports and studies required pursuant to §§ 614.18 or 614.26, or where the result would be inconsistent with the Freedom of Information Act, 5 U.S.C. 552, the Privacy Act of 1974, 5 U.S.C. 552a, or regulations of the Department promulgated thereunder.

§ 614.15 Payments to States.

(a) *State entitlement.* Each State is entitled to be paid by the United States with respect to each individual whose base period wages included Federal military wages, an amount bearing the same ratio to the total amount of compensation paid to such individual as the amount of the individual's Federal military wages in the individual's base period bears to the total amount of the individual's base period wages.

(b) *Payment.* Each State shall be paid, either in advance or by way of reimbursement, as may be determined by the Department, the sum that the Department estimates the State is entitled to receive under the Act and this part for each calendar month. The sum shall be reduced or increased by the amount which the Department finds that its estimate for an earlier calendar month was greater or less than the sum which should have been paid to the State. An estimate may be made on the basis of a statistical, sampling, or other method agreed on by the Department and the State agency.

(c) *Certification by the Department.* The Department, from time to time, shall certify to the Secretary of the Treasury the sum payable to each State under this section. The Secretary of the Treasury, before audit or settlement by the General Accounting Office, shall pay the State in accordance with the certification from the funds for carrying out the purposes of the Act and this part.

(d) *Use of money.* Money paid a State under the Act and this Part may be used solely for the purposes for which it is paid. Money so paid which is not used solely for these purposes shall be returned, at the time specified by the Agreement, to the Treasury of the United States and credited to the current applicable appropriation, fund, or account from which payments to States under the Act and this Part may be made.

§ 614.16 Public access to Agreements.

The State agency of a State will make available to any individual or organization a true copy of the Agreement with the State for inspection and copying. Copies of an Agreement may be furnished on request to any individual or organization upon payment of the same charges, if any, as apply to the furnishing of copies of other records of the State agency.

§ 614.17 Administration in absence of an Agreement.

(a) *Administering program.* The Department shall administer the UCX Program through personnel of the Department or through other arrangements under procedures prescribed by the Department, in the case of any State which does not have an Agreement with the Secretary as provided for in 5 U.S.C. 8502. The procedures prescribed by the Department under this section shall be consistent with the Act and this part.

(b) *Applicable State law.* On the filing by an individual of a claim for UCX in accordance with arrangements under this section, UCX shall be paid to the individual, if eligible, in the same amount, on the same terms, and subject to the same conditions as would be paid to the individual under the applicable State law if the individual's Federal military service and Federal military wages had been included as employment and wages under the State law. Any such claims shall include the individual's Federal military service and Federal military wages, combined with any service and wages covered by State law. However, if the individual, without regard to his or her Federal military

service and Federal military wages, has employment or wages sufficient to qualify for compensation during the benefit year under that State law, then payments of UCX under this section may be made only on the basis of the individual's Federal military service and Federal military wages.

(c) *Fair hearing.* An individual whose claim for UCX is denied under this section is entitled to a fair hearing under rules of procedures prescribed by the Department. A final determination by the Department with respect to entitlement to UCX under this section is subject to review by the courts in the same manner and to the same extent as is provided by section 205(g) of the Social Security Act, 42 U.S.C. 405(g).

§ 614.18 Information, reports, and studies.

State agencies shall furnish to the Department such information and reports and conduct such studies as the Department determines are necessary or appropriate for carrying out the purposes of the UCX Program.

Subpart C—Responsibilities of Federal Military Agencies and State Agencies

§ 614.20 Information to ex-servicemembers.

At the time of discharge or release from Federal military service, each Federal military agency shall furnish to each ex-servicemember information explaining rights and responsibilities under the UCX Program and 18 U.S.C. 1919, and military documents necessary for filing claims for UCX.

§ 614.21 Findings of Federal military agency.

(a) *Findings in military documents.* Information contained in a military document furnished to an ex-servicemember shall constitute findings to which § 614.25 applies as to:

(1) Whether an individual has performed Federal military service, or whether paragraph (b) of this section or §§ 614.23 and 614.24 are applicable;

(2) The beginning and ending dates of the period of military service and "days lost" during such period;

(3) The type of discharge or release terminating the period of military service; and

(4) The individual's pay grade at the time of discharge or release from military service.

(b) *Bad Conduct and Dishonorable discharges.* A military document which shows that an individual received a bad conduct or dishonorable discharge shall be a finding to which § 614.25 applies, that the individual did not perform Federal military service.

§ 614.22 Correcting Federal findings.

(a) *Request for correction.* (1) If an individual believes that a finding specified in § 614.21 is incorrect or that information as to any finding has been omitted from a military document, the individual may request the issuing Federal military agency to correct the military document. A request for correction may be made through the State agency, which shall forward such request and any supporting information submitted by the individual to the Federal military agency.

(2) The Federal military agency shall promptly forward to the individual or State agency making the request the corrected military document. Information contained in a corrected military document issued pursuant to such a request shall constitute the findings of the Federal military agency under § 614.21.

(3) If a determination or redetermination based on a finding as to which correction is sought has been issued by a State agency before a request for correction under this paragraph is made, the individual who requested such correction shall file a request for redetermination or appeal from such determination or redetermination with the State agency, and shall inform the State agency of the request for correction.

(4) An individual who files a request for correction of findings under this paragraph shall promptly notify the State agency of the action of the Federal military agency on such request.

(b) *State agency procedure when request made.* (1) If a determination of entitlement has not been made when an individual notifies a State agency of a request for correction under paragraph (a) of this section, the State agency may postpone such determination until the individual has notified the State agency of the action of the Federal military agency on the request.

(2) If a determination of entitlement has been made when an individual notifies a State agency that a request for correction of Federal findings has been made, or if an individual notifies a State agency prior to a determination of entitlement that a request has been made but such determination is not postponed by the State agency, the individual may file a request for redetermination or appeal in accordance with the applicable State law.

(3) Except as provided in paragraph (c) of this section, no redetermination shall be made or hearing scheduled on an appeal until the individual has notified the State agency of the action of the Federal military agency on a request for correction under paragraph (a) of this section.

(c) *State agency procedure when request answered.* On receipt of notice of the action of a Federal military agency on a request for correction of its findings, a State agency shall:

(1) Make a timely determination or redetermination of the individual's entitlement, or

(2) Promptly schedule a hearing on the individual's appeal.

If such notice is not received by a State agency within one year of the date on which an individual first filed a claim, or such notice is not given promptly by an individual, a State agency without further postponement may make such determination or redetermination or schedule such hearing.

(d) *Findings corrected without request.* Information as to any finding specified in § 614.21 contained in a corrected military document issued by a Federal military agency on its own motion shall constitute the findings of such agency under § 614.21, if notice thereof is received by a State agency before the period for redetermination or appeal has expired under the State law. On timely receipt of such notice a State agency shall take appropriate action under the applicable State law to give effect to the corrected findings.

§ 614.23 Findings of Veterans Administration.

(a) *Request for findings.* If a military document shows that an individual's discharge or release from Federal military service was under conditions other than honorable, or that the period of such service was less than 365 days the Veterans Administration on request of a State agency shall decide whether the individual was discharged or released—

(1) Under conditions other than dishonorable, or

(2) In the case of an officer, by reason of resignation for the good of the service, or

(3) By reason of an actual service-incurred disability.

(b) *Qualified or conditional separations.* On request of a State agency, the Veterans Administration also shall decide whether an individual's discharge or release from Federal military service was qualified or conditional.

(c) *Finality of findings.* Any decision by the Veterans Administration under this section shall constitute a finding to which § 614.25 applies.

(d) *Promptness of decision.* The Veterans Administration shall promptly

act on and reply to any request received under this section.

§ 614.24 Correcting Veterans Administration findings.

(a) *Request for correction.* (1) If an individual believes that a finding under § 614.23 is incorrect, the individual may request reconsideration of or appeal such finding under the procedures of the Veterans Administration. The decision of the Veterans Administration on any such request shall constitute the findings of the Veterans Administration under § 614.23.

(2) Any request for correction must be filed before the period for redetermination or appeal of the UCX claim has expired under the applicable State law.

(3) A request for correction may be made through the State agency, which shall forward such request and any supporting information submitted by the individual to the Veterans Administration. If a request for correction is not made through the State agency, the individual shall notify the State agency promptly that a request for correction has been filed with the Veterans Administration.

(4) The individual making a request for correction under this section shall notify the State agency promptly of the action of the Veterans Administration on the request, unless the State agency is notified directly by the Veterans Administration.

(b) *State agency procedure when request made.* (1) If a State agency has not made a determination of entitlement when an individual requests correction of a Veterans Administration finding under paragraph (a) of this section, the State agency shall postpone such determination until it is notified of the action of the Veterans Administration on the request.

(2) If a determination of entitlement has been made when an individual requests correction of a Veterans Administration finding under paragraph (a) of this section, the individual may file with the State agency a request for redetermination or an appeal in accordance with the applicable State law. No redetermination shall be made, or hearing scheduled on an appeal, until the State agency receives notice of the action of the Veterans Administration on such request.

(c) *State agency procedure when request answered.* On receipt of the action of the Veterans Administration, a State agency shall:

(1) Make a timely determination or redetermination of the individual's entitlement; or

(2) Promptly schedule a hearing on the individual's appeal.

(d) *Promptness of correction.* The Veterans Administration shall promptly act on and reply to any request received under this section.

§ 614.25 Finality of findings.

The findings of a Federal military agency referred to in §§ 614.21 and 614.22, the findings of the Veterans Administration referred to in §§ 614.23 and 614.24, and the Schedules of Remuneration issued by the Department pursuant to the Act and § 614.12, shall be final and conclusive for all purposes of the UCX Program, including appeal and review pursuant to § 614.7 or § 614.17.

§ 614.26 Furnishing other information.

(a) *Additional information.* In addition to the information required by §§ 614.21, 614.22, 614,23, and 614.24, a Federal military agency or the Veterans Administration shall furnish to a State agency or the Department, within the time requested, any information which it is not otherwise prohibited from releasing by law, which the Department determines is necessary for the administration of the UCX Program.

(b) *Reports.* Federal military agencies shall furnish to the Department or State agencies such reports containing such information as the Department determines are necessary or appropriate for carrying out the purposes of the UCX Program.

§ 614.27 Liaison with Department.

To facilitate the Department's administration of the UCX Program, each Federal military agency and the Veterans Administration shall designate one or more of its officials to be the liaison with the Department. Each Federal military agency will inform the Department of its designation(s) and of any change in a designation.

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