

MEETING OF THE PANEL ON REVIEW OF
MISCELLANEOUS EXTERNAL OTC DRUG PRODUCTS

Twentieth Meeting
August 5 and 6, 1977

Parklawn Building
Rockville, Maryland
and
Holiday Inn
Bethesda, Maryland

Panel Members

William E. Lotterhos, M.D., Chairman
Chester L. Rossi, D.P.M.
Rose Dagirmanjian, Ph.D.
Harry E. Morton, Sc.D.
George C. Cypress, Jr., M.D.
Marianne N. O'Donoghue, M.D.

Liaison Representatives

Consumer Liaison (C.U.)
Marvin M. Lipman, M.D.
Industry Liaison
Bruce Semple, M.D.
Saul A. Bell, Pharm.D. (CTFA)

Consultants

A. Belmonte, Ph.D.
Jon Tanja

FDA Members

John M. Davitt, M.Sc. - Executive Secretary
Michael D. Kennedy, B.Sc. - Panel Administrator
Victor Lindmark, Pharm.D. - Drug Information Analyst

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Whenever there is a lack of unanimity on any given point, the vote will be given. Regulations do not permit voting by the Liaison Members, Consultants, or FDA Staff Members.

Adopted 30th Sept., 1977
William E. Lotterhos, M.D.
Chairman

Also Present:

Billy C. Coats	Aloe Vera of American, Inc. (8/5/77 only)
Clinton Howard	AVA Cosmetics, Inc. (8/5/77 only)
Michele Deschenes	"The Pink Sheet"
Jim Wright	Marion Laboratories
Bill Guinty	Marion Laboratories
J. K. Gwinner	Procter and Gamble
Pat Dsida	Westwood Pharmaceuticals
Arthur Auer	FDA/Bureau of Drugs (8/5/77 only)

Minutes:

Minutes of the (18th) meeting were reviewed, amended and approved.

General Panel Business:

1. The agenda had indicated that Commissioner Kennedy and Dr. Gilbertson would meet with the Panel, but they were unable to attend this meeting.

2. The Panel has now nearly completed 3 categories of the 41 therapeutic categories in the FEDERAL REGISTER's "Call for Data". The Panel will pick up the deficiencies so as to complete these 3 categories.

Industry Presentation

Mr. Billy C. Coats, President of Aloe Vera of America, Inc., Garland, Texas, spoke to the Panel on the aloe vera used in his product and submitted a compilation of background information to

each of the Panel members. He stated that the laxative principles in this plant are present only in the outer rind, and that the material his company uses is the clear gel occurring within the leaf. He said there is a stability problem with this material; it is subject to oxidation, with consequent color change and loss of activity. His firm (AVA) now has a patent on stabilized aloe vera gel and markets pharmaceuticals containing it, in Texas only. One such product is "Vagistat Vaginal Cream". Other of AVA's products are considered cosmetics, rather than drugs and are sold in interstate commerce.

Mr. Coats discussed several of the published and unpublished studies which have been done on his products including: (1) an uncontrolled efficacy study in animals by R. B. Northway (Vet. Med./ Small Animal Clinician Jan. 1975, p. 89), in which "Aloe 99" Gel, Cream and Lotion were used; In vitro studies on "Aloe 99" Gel (Oral Surgery, Oral Medicine and Oral Pathol. 27 (1): 122, 1969); and (3) toxicity studies done by Mr. Coats in collaboration with Dr. Mervin Grossman. All of these reports were included in the handout.

Another of AVA's products is an aloe vera-containing mouthwash which one Texas dentist (Dr. Paul Carrington) reports he has used "on 80,000 patients".

Mr. Coats said he had filed an IND several years ago for a fever blister medication containing aloe vera gel. Apparently there is some evidence that the product is virucidal vs H. simplex. He said, however that the FDA had recommended extensive toxicity tests which the firm could not afford at the time.

Mr. Coats mentioned obtaining aloe vera leaves grown on a plantation in Mexico. In response to a Panel question, he said that aloe vera gel obtained from these leaves is used only in cosmetic products and that only domestic (Texas) leaves are used in the manufacture of any AVA product classified as a drug.

Among the efficacy studies presented were experiments with a H. simplex/rat tail model (International Chemical and Nuclear) and in vitro efficacy studies of Aloe 99 Gel vs Trichomonas (Drs. Zimmerman and Simms). With regard to the antitrichomonal studies, Dr. Morton asked whether Mr. Coats thought a vehicle control would have been advisable. Mr. Coats said that, in retrospect, he would agree - the vehicle contained potassium sorbate as a stabilizer.

Other clinical experience with AVA's aloe products, according to Mr. Coats, includes use by athletes. He said these products have been used by the Texas Rangers and the Dallas Cowboys. Moreover, Mr. Frank Medina, the Olympic trainer used them in the Canada Olympics last year.

Mr. Coats said that the active components of aloe vera gel that have been identified thus far are:

1. Proteolytic enzymes
2. Long chain muco polysaccharides
3. Allantoin

The Panel received the presented material as submission number 160252.

Ingredients Discussed:

Coal Tar

A report was presented on the safety of coal tar, which took into consideration the recent OTC coal tar symposium. The Panel concluded that coal tar should be tentatively placed in Category III for safety until the results of a retrospective study, now underway at the Mayo Clinic, on the incidence of skin cancer in patients treated with coal tar preparations has been completed.

A discussion of the problem of a lack of identity ensued concerning the constituents of crude coal tar. The Panel would like more information on:

- a. Uniformity of batch-to-batch and company-to-company preparations.
- b. The Panel is aware of known carcinogens in coal tar (e.g., benz(a)pyrene). What fractions cause malignancy?

Zirconium Compounds

On the basis of subsequent review, the Panel has revised its position on efficacy in Rhus dermatitis treatment. (Refer to minutes of the May 16-17, 1976 meeting). These drugs are now in Category II with regard to both safety and efficacy.

The matter of identity of active ingredient in the Rhus dermatitis remedies was also discussed. It is unclear to the Panel whether the material is always charged as zirconium carbonate and assayed as zirconium oxide, or is sometimes present as the oxide per se.

An extensively revised Panel report has been prepared and has been accepted for information.

Salicylic Acid

An additional report has been accepted for information. One Panel member feels that 6 % salicylic acid should be considered generally effective and safe as a keratolytic, and that higher concentrations should not be distributed OTC. There was a lack of agreement with this position on the part of the other Panel members.

The Panel's consultants have been asked to furnish a overall write-up on topical use of salicylic acid, including existing experimental data, influence of concentration and vehicle, and conditions and indications for use.

Talc

A Panel report has been prepared. Talc is placed in Category I (both safety and efficacy) for use on intact skin as a lubricant and adsorbent.

Camphor

At our 15th meeting camphor was declared Category II for all indications assigned to this Panel for review. This stand was taken in view of the safety issue.

The Panel recognizes that other Panels have rated camphor in various categories (I, II and III) for other indications. This matter was discussed, and the Panel concluded that they can see no reason to change their previous opinion.

Future Meetings

The next Panel meeting is scheduled for September 30 - October 1, 1977. Two additional meetings are planned for this year: October 30-31 and December 11-12.

Panel members were reminded to have reports distributed prior to the meeting for Panel member review.

SUMMARY MINUTES
MISCELLANEOUS EXTERNAL OTC DRUG PRODUCTS

Twenty-First Meeting

September 30, 1977
Parklawn Buidling - Rockville, Maryland

and

October 1, 1977
Holiday Inn - Chevy Chase, Maryland

PANEL MEMBERS

William E. Lotterhos, M.D., Chairman
Chester L. Rossi, D.P.M.
Rose Dagirmanjian, Ph.D.
Harry E. Morton, Sc.D.
George C. Cypress, Jr., M.D. (absent)
Marianne N. O'Donoghue, M.D.

Consultants

Albert Belmonte, Ph.D.
Jon Tanja, R.Ph.

LIAISONS MEMBERS

Consumer Union
Marvin M. Lipman, M.D. (absent)

CTFA

Saul A. Bell, Pharm.D.

Proprietary Association

Bruce Semple, M.D.

FDA STAFF MEMBERS

Arthur E. Auer, B.Sc. - Executive Secretary
Consumer Safety Officer
Division of Cardio-renal Drug Products

Michael Kennedy, B.Sc. - Panel Administrator
Division of OTC Drug Evaluation

Victor Lindmark, Pharm.D. - Drug Information Analyst
Division of OTC Drug Evaluation

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The summary minutes for this meeting are contained in 11 pages.

Adopted Harry E. Morton
for Wm. E. Lotterhos
12-11-77

Chairman
William E. Lotterhos, M.D.

Open Public Meeting - Presentations

A. Aloe Vera Gel - Aloe Creme Laboratories

Chester DeZeh, Director of Research and Development, read a presentation for Aloe Creme Laboratories with exhibits, testimonials, and references to show the value of products containing their "Aloe Vera Gel as an aid to healing of all types of minor burns, cuts, chafing, skin irritations and abrasions". The submission characterizes the botanically derived "gel" and reports the animal and clinical experiences and literature related to their product. (Submission number 106196). The gel is derived from the leaves of "Aloe Vera Barbadosis Linne" and consists of about 99% water and 1% solids. Although a number of components of the solid have been chemically defined; neither the active principle(s) nor the mechanism of action have been established.

Five animal studies were referenced. Four suggested improvement in about half the time of control animals whereas the fifth (Ashley) reported no benefit.

The value of Aloe Vera Gel in human topical use is acknowledged to be one of utility and experience in treating severe traumatic lesions such as third degree thermal burns and accidental irradiation. The submission states that no well-controlled clinical evaluation of the effect of Aloe Vera Gel and wound healing aid has appeared in the literature. Eight references to clinical experiences and evaluations in published

literature were listed suggesting some beneficial aid in the treatment of skin lesions.

Mr. DeZeh suggested that there were some old studies which compared the product (base) with the active (gel). He was asked to submit this data. Mr. Herman Jass, Consultant to Aloe Creme Laboratories, was asked to submit a copy of a study published by Rowe and co-workers in the American Pharmaceutical Association Journal reporting on treatment of white rats with Aloe ointment.

B. Salicylic Acid - Phillip R. Brachman, D.P.M.

Dr. Brachman appeared on behalf of the Illinois College of Podiatric Medicine at the request of the Scholl Company.

The College made a retrospective evaluation of the records of 3165 patients treated in 1974 and surveyed 953 patients treated up through September, 1977 to determine if any "admissions" were made because of treatment of corns with salicylic acid products. None were identified.

Dr. Brachman did not evaluate or address the question of the effectiveness of salicylic acid in corn and/or callus treatment and had no data on this subject. He also indicated salicylic acid was not used routinely or clinically to any significant extent by the Illinois College of Podiatric Medicine (ICPM) in the treatment of corns and/or calluses.

The Panel members pointed out that the percentage of salicylic acid in corn treatment preparations was not an appropriate basis for comparison. A better basis for comparison would be the total amount of salicylic acid available per square centimeter of skin surface.

Minutes

The Panel approved the summary minutes for the joint meeting with OTC Antimicrobial II Panel on June 25, 1977. This constituted the official nineteenth meeting of this panel.

The Panel also approved the summary minutes of the twentieth meeting of August 5th and 6th, 1977 with editorial corrections.

Introduction to Dr. Gilbertson, Director, Division of OTC Drug Evaluations

Dr. Gilbertson outlined the large task before this panel and the importance the Commissioner placed on its completion in a timely and responsible manner. He explained that the approach of this panel will be somewhat different, in that, in place of one large report each therapeutic class will be the subject of a separate (monograph) report, e.g., thumb-sucking agents, skin bleaching products, etc. He also explained the three major development stages - i.e., proposal, tentative final, and final. The panel's work is targeted for completion in 1979.

The relationship between FTC's responsibility for monitoring OTC drug advertising and the FDA's final monograph was also explained. The idea

is to define the labeling terms in the monograph precisely so that FTC's enforcement of advertising will be simplified to restricting use of terms and concepts to those clearly stated in the monograph.

The monographs will contain four segments: (A) General conditions, (B) Active Ingredients, (C) Testing and (D) Labeling.

The Panel was also asked to explain how a manufacturer or sponsor of a Category III ingredient could get it into Category I, i.e., the kinds of animal or clinical tests which should be done to develop the necessary safety or effectiveness data.

Dr. Gilbertson emphasized the importance of documenting panel judgements so they are not easily overturned in subsequent administrative (hearing) or legal challenges. He pointed out that the final monograph would be a "substantive" regulation rather than an "interpretive" type of rule.

Finally, Dr. Gilbertson explained that after the final report is published and the clock is running for two years on Category III products, we propose to publish the names of those companies which are going to do tests in the FEDERAL REGISTER. The purpose is to make it unnecessary for every manufacturer of a product affected to do the same tests. They can get together and share responsibility for the test data or do it on their own.

Reports - General

A. The Panel was provided with three working papers:

1. General principles in testing topical preparations
2. Criteria for evaluating safety and effectiveness of topically administered medications.
3. Outline of monograph dealing with foot preparations

Volume 4 of Advances in Toxicology entitled "Dermato-Toxicology and Pharmacology" by Frances Marzulli and Howard Maibach, Holsted Press, 1977 was brought to the Panel's attention as a useful reference.

B. The initial draft FEDERAL REGISTER proposal on Skin Bleaching Agents was provided to each Panel member for their review and comment before further processing.

Reports - Ingredients

The Panel reports submitted and categorized after discussion were:

<u>Ingredient</u>	<u>Safety</u>	<u>Effectiveness</u>	<u>For</u>
Thymol	I	III	as antipruritic only
Zinc Chloride	I in conc. less than 2%	III	corn and callus removal
Coal Tar	III	I	psoriasis; with warnings (3)
Benzethonium Chloride (in karaya/tragacanth as vehicle)	Tabled	Tabled	anti-infective
Denatonium Benzoate	Tabled	Tabled	thumb-sucking deterrent
Ferric Chloride	II	III	prevention of rhus dermatitis

The Panel was informed that alkaloids of belladonna, amyl salicylate, beeswax, benzalkonium chloride, camphor gum, ether, methylbenzethonium chloride, methyl salicylate, and sodium carbonate are not being used as active ingredients in corn pads, plasters and remedies, foot balm, baths and creams, and ingrown toenail preparations.

It was suggested and agreed that where a submission lists the ingredients, the Panel should determine as part of its deliberations whether it is considered active or inactive.

Thymol

The Panel moved and seconded a motion to put Thymol in Category III for its antipruritic effect only in foot preparations. The motion was adopted.

The effective concentration was suggested as 0.25 percent.

Zinc chloride

The Panel adopted a recommendation to consider Zinc chloride safe (Category I) in concentrations of less than 2 percent when used on corns or calluses. They further voted to place Zinc chloride in Category III - for effectiveness as corn and callus remover.

After discussion, the panel suggested that a firm could move a product for corn or callus removal from Category II or III to Category I by conducting a controlled double-blind study with zinc chloride alone or by providing additional information or data for evaluation.

Coal Tar

The Panel adopted a motion to classify crude coal tar, two to ten percent as Category I for efficacy for psoriasis. The Panel has

previously placed coal tar in Category III for safety pending the report of the Mayo Clinic retrieving information regarding systemic and skin cancer.

There was an extensive discussion of warning statements for coal tar products with the agreed conclusion of the panel that three warning statements were appropriate for this type of product:

- (1) If rash gets worse, discontinue use.
- (2) If skin does not clear in ninety (90) days, consult your physician.
- (3) Do not use in groin.

Camphor

Camphor is used in a lip balm (inactive ingredient). However, the Poison Control Center statistics for 1975 listed 47 reactions for camphor in a lip balm, mostly in children under 5 years of age. This information was deferred for consideration at another meeting.

Denatonium Benzoate

The first report contained acute and chronic toxicity data. The second contained LD₅₀ type information. A final installment from the Department of Housing and Urban Development should be received this fall.

The Panel recognized that denatonium is a bitter substance, but did not reach any conclusion, in its discussion, about its effectiveness as "thumb-sucking deterrent".

The Panel voted to table until further information was received.

Benzethonium Chloride (in Karaya/Tragacanth as a Vehicle)

This ingredient was in a spray-on type of product for prompt control of superficial bleeding and prevent infection of minor cuts, burns, and abrasions. The product contained gums to stop the bleeding. The mechanical spray-on feature as a bandage suggest it could be considered a device whereas the benzethonium chloride could be considered a preservative (inhibit bacterial growth) or to prevent infection (an antiseptic). The Panel administrator agreed to get more information about the product standing as a medicated "device". The Panel thereupon voted to table the matter until more information was received.

Ferric Chloride

The Panel adopted a motion (recommendation) classifying Ferric Chloride as Category II from the standpoint of safety due to side effects (pigmentation when used on damaged skin).

The Panel voted to classify Ferric Chloride in Category III for effectiveness as a preventive in the treatment of rhus dermatitis with a request that controlled studies be performed "in vivo".

Alcohols

The report on seven alcohols discussed at the twelfth meeting, was brought up to get the Panel's judgements on safety and efficacy as antiseptics to enable the OTC Staff to draft a monograph.

Only denatured alcohol and isopropyl alcohol were submitted to the Panel as single ingredient products. The Panel made the following judgements on safety and efficacy for antiseptic use:

Alcohol	Safety	Efficacy
Methyl Alcohol	II	Deferred
Ethyl Alcohol	I	I
Isopropyl Alcohol	I	I
Cetyl Alcohol	I	Deferred-not used
Stearyl Alcohol	I	Deferred
Benzyl Alcohol	I	II

The Panel placed isopropyl alcohol in Category I for safety and efficacy as an antiseptic in concentrations of fifty (50) to ninety-one (91) percent because some moisture is needed for it to be an effective germicide.

The Panel deferred action on methanol until more information was obtained.

The question of whether "acetone" is considered an active ingredient when combined with alcohol in products was raised. The reason for its presence was that it reduced surface tension and increased evaporation. The statement was made that it functions as a pharmaceutical aid. Although there was no objection, the Panel did not formally vote on the question.

Ethylene oxide as an ingredient with alcohol was also considered a pharmaceutical aid because isopropyl alcohol is a poor sporocide.

Assignments

Twenty-four (24) ingredients of foot corn pads, balms, and ingrown toenail remedies were assigned to panel members in blocks of four each.

Meeting

The next meeting is scheduled for October 30th and 31st at Bethesda Holiday Inn (30th) and Parklawn Building (31st).

Attendance

All Panel members were present except for: George C. Cypress, M.D.
and Marvin M. Lipman, M.D.

Guests in attendance included:

<u>Name</u>	<u>Representing</u>
Chester J. Dezeih, Director Research and Development	Alo Creme Laboratories
Herman E. Jass, Consultant	Alo Creme Laboratories
Carlisle H. Snell	" " "
Phillip R. Brachman, D.P.M.	Illinois College of Podiatric Medicine
Barry Brooks	Scholl, Inc.
D. E. Harting	" "
John K. Gwinner	Procter and Gamble
Thomas DiNicola	Westwood Pharmaceuticals
E. A. Trevson	Bio-Evaluation, Inc.
John Foder	Texas Pharmacol
Billy C. Coats	Aloe Vera of America, Inc.
Rosanne Justi,	"The Pink Sheet"

MEETING OF THE PANEL ON REVIEW OF
MISCELLANEOUS EXTERNAL OTC DRUG PRODUCTS
Twenty-Eighth Meeting
October 29 and 30, 1978

Parklawn Building
Rockville, Maryland
and
Holiday Inn
Bethesda, Maryland

Panel Members

William E. Lotterhos, M.D.
Chairman
Rose Dagirmanjian, Ph.D. (absent)
Harry E. Morton, Sc.D.
George C. Cypress, Jr., M.D. (absent)
Marianne N. O'Donoghue, M.D.
Yelva L. Lynfield, M.D.
Chester L. Rossi, D.P.M.
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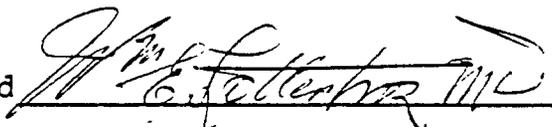
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FDA Members

John McElroy, J.D. - Panel Administrator
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1/14/79 Adopted 

William E. Lotterhos, M.D.
Chairman

SUMMARY MINUTES

1. The 28th meeting of the Panel was called to order on October 29, 1978 at 9:00 a.m. and a quorum was present.
2. Commerce Drug Company (Dell Labs.), represented by Harry Gordon, Ph.D., William Jordan, M.D., Adalbert Vajay, Ph.D., presented safety and effectiveness data on 7.5 percent benzocaine gel for premature ejaculation.
3. Benzocaine. The Panel voted to place benzocaine 5 to 10 percent in Category I for safety and effectiveness as a premature ejaculation remedy. Benzocaine was placed in Category II for safety for use on abraded or broken skin, for stasis dermatitis, leg ulcers, chronic dermatosis, foot balms, contact diaper rash, or for use on children under the age of 2.
4. Camphor. The subject of the accidental ingestion of camphorated oil due to its being mistaken for castor oil has recently been editorialized in the trade press. Also, the Panel received a recent submission from the American Pharmaceutical Association requesting that Camphorated Oil be placed in Category II as not safe.

(a) Effectiveness. The Panel extensively discussed camphor and the following motions were voted upon: Camphor in any concentration, Category II, as an antipruritic was defeated (2 for, 3 opposed);

Camphor in any concentration, Category II, as an antiinfective was approved unanimously.

Camphor in any concentration, Category II, for analgesia, was defeated (1 for, 3 opposed, 1 abstention);

Camphor in any concentration, Category II, as a counterirritant, was defeated (2 for, 3 opposed);

Camphor in any concentration, Category II, as a rubefacient, was defeated (2 for, 3 opposed).

In summary Camphor was placed in Category III for effectiveness testing for antipruritic, analgesic, counterirritant, or rubefacient indications - approved unanimously.

(b) Safety. Camphor, Category I for safety, in any container, up to and including 5 percent.

Camphor, Category I for safety, in a concentration above 5 percent up to and including 20 percent, when packaged in a distinctive container to prevent oral ingestion, and in a container not to exceed 30 ml for a liquid. Motion approved (3 for, 2 abstentions, none opposed).

Camphor, Category I for safety, in a concentration above 5 percent up to and including 20 percent in an ointment or cream, when packaged in a container of any size. Motion approved (3 for, 2 abstentions, none opposed).

The Panel recommended to FDA (and any other Agency having an interest) that regulations be promulgated to require that camphorated oil be placed in a distinctive container to prevent oral ingestion, and in a container not to exceed 30 ml. This motion was approved unanimously.

5. Cresol, aqueous saponated cresol, cresol with camphor.

The Panel voted to place all concentrations of cresol alone, aqueous saponated cresol solutions, or cresol in combination with camphor, in Category II as an antiseptic or astringent.

6. Lard. Lard, for use in foot products as a skin protectant, or as a lubricant, was placed in Category II for effectiveness because of no submissions and the lack of acceptable data available to the Panel.

7. Cottonseed oil. Cottonseed oil, for use in foot products as a skin protectant, or as a lubricant, was placed in Category II for effectiveness because of no submissions and the lack of acceptable data available to the Panel.

8. Hair growing remedies. The Panel questioned the use of antimicrobials on the scalp as beneficial for hair growing. The Panel requested that an outside expert, Dr. Norman Orentreich be invited to address the Panel on the subject of hair products, their antiseptic qualities, and the rationale for use of ingredients on the scalp as related to hair growing.

9. Benzethonium chloride. The Panel defeated a motion that benzethonium chloride, in an aqueous concentration of 1:500, be Category I for effectiveness as an antiseptic for use on the hair and scalp.

The Panel motion to place all concentrations of benzethonium chloride in Category III for effectiveness, as an antiseptic-antimicrobial for use on the hair and scalp, was approved with one dissenting vote.

10. Tar oils (crude coal tar oil). The Panel voted to place tar oils (crude coal tar oil) in Category III for safety and effectiveness for use on the scalp for psoriasis, and made a preliminary determination of Category III for use as a hair grower.

11. Amino acids, ascorbic acid, essential oils, fatty acids.
Amino acids, ascorbic acid, essential oils, and fatty acids for external use as hair growers, were placed in Category II for effectiveness because of no submissions and the lack of acceptable data available to the Panel.
12. Foot balms and foot lotions. Nomenclature: The Panel regards "foot baths" and "foot soaks" as synonymous.
13. Calcium acetate - aluminum sulfate in combination to form aluminum acetate, in Category I for effectiveness when the combination is dissolved in an appropriate amount of water, as directed in product labeling, for use as a wet dressing or soak, as an astringent, and/or for relief of inflammatory skin conditions.
14. Aluminum acetate. The Panel voted unanimously to place aluminum acetate in Category III as an antimicrobial agent.
15. Skin antiseptic. The Panel adopted the definition of "skin antiseptic" as set forth in the OTC Topical Antimicrobial Products and Drug and Cosmetic Products Report (39 FR 33114). Claims stating or implying an effect against microorganisms must be supported by controlled human studies which demonstrate prevention of infection."

The Panel approved the following motion on the labeling of wet dressings: "Labeling should include the following information: directions for applying the wet dressing; a statement that if the condition worsens, discontinue use and consult physician; for external use only; keep away from eyes; keep out of reach of children; after reconstitution, label the container as to contents; as a dressing, do not use plastic or other impervious material to prevent evaporation; discard solution after use; if stock solution is made, label statement as to duration of stability of the stock solution."

16. Combinations of foot balm and foot lotion formulations were considered by the Panel. Formulations containing specified amounts of aluminum sulfate, sodium bicarbonate, carbowax, calcium acetate, and white potato dextrin were classed as Category I, for safety and effectiveness.

Foot powder combinations containing specified amounts of calcium acetate, aluminum acetate, and potato dextrin were classed as Category I for safety and effectiveness.

17. Sucrose octoacetate in concentrations up to and including 6 percent was placed in Category I for safety as a nail biting and thumb-sucking deterrent and Category III for effectiveness.

18. Zinc sulfate for use in foot products was placed in Category II, for effectiveness because of no submissions and the lack of acceptable data available to the Panel.

19. A copy of the report on "warts" was distributed to all panelists for their review and comment.

20. It was announced that the Panel's "Skin Bleaching" report, together with the FDA proposed monograph will be published in the FEDERAL REGISTER of November 3, 1978.

21. The Panel's next meeting was scheduled for January 14 and 15, 1979.

The Panel adjourned on October 30th at 3:30 p.m.

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MISCELLANEOUS EXTERNAL OTC DRUG PRODUCTS
Thirty-First Meeting
May 18 and 19, 1979

Parklawn Building
Rockville, Maryland
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Bethesda, Maryland

Panel Members

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Adopted Aug. 4, 1979

Harry E. Morton for Wm. E. Lotterhos
William E. Lotterhos, M.D.
Chairman

SUMMARY MINUTES

1. The 31st meeting of the Panel was called to order on May 18, 1979 at 9:00 a.m. A quorum was present.

2. George W. Rogers, M.D., Consumer Products Division, Winthrop Laboratories, presented information on the marketing experience of Campho-Phenique as proof of the safety. Over the years, millions of ounces of Campho-Phenique have been sold. In those instances of accidental ingestion, which have been reported to the firm, there were no fatalities or serious adverse reactions. In 1978, two reports of accidental ingestion by young children were reported to the company. After stomach emptying, both children recovered uneventfully. Campho-Phenique is presently marketed in distinctive bottles with a choice of a conventional screw-cap closure or a child-proof closure for use in households having young children.

3. Panel discussion of Wart Remover Draft Report--The Panel reviewed and completed its draft report on OTC wart remover products.

A. The following single active ingredients were discussed:

- (1) Acetic Acid--The decision was made to have acetic acid declared on the labeling in terms of percentage of glacial acetic acid. Glacial acetic is defined in the U.S.P. as being 99.5 to 100.5 percent, by weight, of acetic acid. Since the specific gravity of glacial acetic acid is approximately 1, the percentage of glacial acetic acid will be the same whether expressed in terms of weight to weight or volume to volume (1% glacial acetic acid being equal to 1 gm or 1 cc glacial acetic acid per 100 gms or 100 cc of product). This method of declaration will suitably define the amount of acetic acid when present as an active ingredient in any given wart remover product.
- (2) Ascorbic Acid--The Panel placed this ingredient in Category III for both safety and effectiveness for topical use in wart remover products.

- (3) Calcium pantothenate--This ingredient was placed in Category III for both safety and effectiveness for topical use in wart remover products.

B. The following combinations of active ingredients were discussed:

- (1) Anesthetic ingredients--The Panel decided that any OTC wart remover combination product that contains any anesthetic is Category II because the presence of any anesthetic would seriously compromise the safe use of the product by the layman.
- (2) Ascorbic acid--all combinations that contain this ingredient are Category III for both safety and effectiveness.
- (3) Calcium pantothenate--all combinations that contain this ingredient are Category III for both safety and effectiveness.
- (4) Lactic acid--(2 to 17%) in combination with salicylic acid (2 to 17%) in collodion--this combination was placed in Category I for both safety and effectiveness. The Panel also concluded that the combination of lactic acid and salicylic acid is more effective than either ingredient when used alone as a wart remover.
- (5) Salicylic acid and acetic acid--in a collodion base was placed in Category III for effectiveness for use as a wart remover.

4. Camphor--the Panel reviewed the safety and effectiveness of OTC camphor containing products intended for external use.

- a. Safety--Because of an adverse risk (accidental ingestion) to benefit ratio, the Panel concluded that a camphor concentration of 2.5% or greater is Category II for safety in any OTC product for external use.
- b. Effectiveness--the Panel concluded that camphor is Category II for effectiveness for any topical use in any concentration.

5. Foot products including ingrown toenail remedies

A. Single ingredients

- (1) Aluminum acetate--this ingredient is Category III for both safety and effectiveness as a wet dressing or solution for use on the foot.
- (2) Sulfur--when present in a suitable base, is Category III for both safety and effectiveness as a keratolytic and as a topical antifungal agent.

B. Combination(s)--the combination of tannic acid (25%), chlorobutanol (1 to 5%), and isopropyl alcohol (50 to 91%) was placed in Category I for safety and effectiveness for the "temporary relief of ingrown toenails."

6. Lead Acetate. Lead Acetate in a concentration of 0.005 percent was placed in Category I for safety and Category II for effectiveness for the treatment of dandruff or seborrhea.

7. Foot powders. Urea, in concentrations of 10 to 20%, was placed in Category I for safety and effectiveness for use as a keratolytic on rough dry skin of feet.

8. Dandruff and seborrhea--the Panel considered definitions for these terms. A panelist objected to the consideration of dandruff as a drug claim. FDA staff suggested that the scaling and itching of dandruff is a condition affecting the scalp. Accordingly, the term dandruff may be considered as a drug claim.

9. Physiology of the skin--the Panel accepted a report by one of the Panel members and directed that this report be appended to the Panel's summary minutes of this meeting.

10. The Panel approved the summary minutes of its previous meeting March 18 and 19, 1979.

11. The Panel's next meeting was scheduled for August 3 and 4, 1979.

The Panel adjourned on May 19 at 3:00 p.m.

PHYSIOLOGY OF THE HUMAN SKIN

The skin consists of several functional units. It can be divided into (1) the epidermis, which contains the keratinocyte, melanocyte, and Langerhans' cells, hair follicles, sebaceous glands, apocrine glands, and eccrine glands; (2) the dermis, which contains fibroblasts, histiocytes, mast cells, lymphocytes, and plasma cells (in ground substance and fibrin), and (3) the systems with which the skin most clearly connects--the vascular, neural, myeloid, and reticuloendothelial (lymphocyte).

It will be our primary concern to study the physiology of healthy skin with reference to its main function--that of a barrier to the outside environment.

The cellular structure of the epidermis consists of the (a) basal cell layer (new cells are proliferating laterally and vertically at a high rate of duplication); (b) malpighian cell layer (cells here differentiate and mature); (c) the granular layer (this population is losing its nuclei and undergoing cell death--it is marked by intracellular granules of unknown structure and

function), and (d) the stratum corneum (this layer consists of flattened squames which become strongly packed together. This layer on the palms and soles also includes a clear layer called the stratum lucidum which adds to the important stress that the skin on the palms and soles has.)

The melanocyte synthesizes pigment to protect the skin from sunlight. The Langerhans' cell function has not been clearly defined as yet. According to Rudolf Baer, it may have something to do with allergic reactions.

The epidermis has several interruptions in the otherwise firm keratin barrier, such as pilosebaceous units, eccrine glands, and apocrine glands. This interruption allows for the egress of sebum and sweat. Sebum is the skin surface film made by the sebaceous gland and the lipid of keratinization. It consists of triglycerides, mono and diglycerides, fatty acids, wax esters, squalene, sterols, sterol esters, and diol esters. Sebum has been thought to offer barrier protection, regulate percutaneous absorption, emulsify the skin, and contain a Vitamin D precursor. There is no absolute proof of function for sebum at this time. The eccrine sweat gland functions primarily in heat

regulation. The apocrine glands are only found in certain areas of the body. They are not usually found on the foot.

The cornified layer functions as:

1. The body's major barrier. It's vital properties consists of the following:
 - a. Relative impermeability to water and electrolytes that prevent dehydration by loss of internal fluids and limits penetration by external fluids and gases.
 - b. Resistance against damaging corrosives.
 - c. Physical toughness that mutes the injurious effect of external trauma such as mechanical injury (this is especially important on the foot).
 - d. High electrical impedance that restricts passage of electrical current.
 - e. Relatively dry surface that retards proliferation of microorganisms.

2. A rate-limiting membrane for passage of water and other molecules between the "wet" internal environment of the body and the "dry" external environment.

3. A reservoir for topical medications (Ref. 1).

There are three pathways by which external substances can be transported through the skin. The first is by direct diffusion through the cells, the second is by going through the intercellular pathway, and the third is through the pilosebaceous units.

"During the first stages of transepidermal transport, before diffusion reaches a steady state, the adnexal orifices are the principal pathways for penetration. The adnexal shortcut to percutaneous absorption is taken by molecules with very low permeability coefficients and large molecules" (Ref. 2). Only during the first five minutes immediately after the application of the test substances is absorption through the appendages greater than that through the stratum corneum (Ref. 3). Transappendageal absorption occurs by diffusion and

involves water and water-soluble substances primarily. After this initial phase, however, most of the percutaneous absorption takes place across the stratum corneum, which has a much greater surface area than do the hair follicles and sweat ducts through the intercellular route. Only water and low molecular weight molecules such as polar alcohols pass.

Most molecules go through the cell membrane and the cells of the cornified layer. Once through the cornified layer there is little resistance to transport to blood vessels and lymphatics in the papillary dermis. Because of this, the importance of the barrier function of the stratum corneum must be stressed. Only in the last decade has it been realized that this barrier function is not limited to the lowest layer of cells in the stratum corneum, but rather can be attributed to its entire thickness (Ref. 2). The passage of water across the intact stratum corneum can be directly correlated with known mathematical principles of water diffusion without invoking the concept of active transport mechanism. A concentration gradient is probably the sole driving force behind the percutaneous absorption across the stratum

corneum. Hydration of the stratum corneum increases its permeability.

The factors affecting the absorption of substances through the skin are several. For example, the anatomical site of the skin on the palms and soles is 600 microns in depth and is less permeable than skin in other regions with a thickness of 10-15 microns. The intertriginous areas (creases and folds) have greater absorption. Eyelid and scrotal skin is the thinnest.

The local cutaneous circulation affects absorption. A person could absorb more of a chemical on cheek skin with its increased vasculature than from the skin on the tips of the fingers or toes with decreased vascular bed. Another factor that affects skin absorption is the temperature of the skin. An increase in skin temperature causes an increased absorption through the skin and vice versa.

In addition to the above absorption factors, neonatal skin is more permeable, while aged skin is a special problem.

"The water content of the stratum corneum is probably lower in the older person. This may well be related to

changes in the surface lipids and to a resultant decrease in its water holding capacity" (Ref. 2). All of this can result in chapping and dryness. Older patients may have decreased tolerance to some compounds because the barrier is not intact. However, because of the decreased lipid content of the skin, there is less absorption of a topical substance. Aged skin has atrophic pilosebaceous apparatuses. This can cause less permeability. It is a known fact that older patients have a lower incidence of contact dermatitis. This may be because of less percutaneous absorption, or because the immunological system is not as responsive in old age. Older skin has less subcutaneous fat which should allow for quicker passage to the blood vessels, but because the barrier lacks lipids, this has not been a problem.

The nature and absorption characteristics of the vehicle affects the rate and quality of absorption.

The greater the drug concentration in the vehicles, the greater the amount available to the skin (providing the drug doesn't want to stay in solution (Ref. 4)). The partition coefficient of the drug between membrane and vehicle will help to determine the amount of absorption, i.e.:

$$\frac{K_m = \text{Drug concentration (barrier)}}{\text{Drug concentration (vehicle)}}$$

A K_m of 2 signifies that a drug is 2 x more soluble in the barrier than it is in the vehicle. Whereas, a K_m of 0.5 signifies the reverse. This is the driving force of the product through the membrane. Increasing the lipid solubility favors the penetration of drugs through the skin. E. G. Scheuplein studied homologous alcohols methanol--octonal. The higher the number, the better absorbed was the alcohol. K_m is dependent upon the nature of the vehicle.

The diffusion coefficient factor of the drug in the membrane is a measure of the extent to which the matrix of the barrier interacts and restricts the mobility of the drug, and is, therefore, dependent upon both the nature of the drug and the nature of the barrier. The stratum corneum is thick and this alone decreases absorption. The size of the molecule or its polar group can affect a decreased absorption.

Affecting the absorption is the barrier thickness, as well as, location, hydration, and blood flow; furthermore, if the vehicle injures the stratum corneum, there can be increased absorption.

Ionic and nonionic surface active agents are widely used as emulsifiers and detergents (Ref. 5). These surfactants damage the barrier layer of the skin even in concentrations as low as 1 percent. Certain nonaqueous bases promote penetration by producing structural or chemical damage in the barrier layer. Many of these vehicles are aprotic material, accepting rather than donating protons. Dimethyl sulfoxide (DMSO), dimethylacetamide, and dimethylformamide are examples of these vehicles. Low molecular weight volatile solvents such as ether, methanol, ethanol, and acetone may also damage the skin's barrier layer. This occurs because of lipid extraction.

The properties of the penetrating molecule will effect the absorption capability.

A change in the pH of the 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, but small molecules, that are both water and lipid soluble, are more easily absorbed.

In conclusion, if the epidermis is intact, the barrier is intact. Vehicles which destroy the barrier, such as detergents and solvents, can have increased absorption. Vehicles which duplicate the physiology of the skin can have increased absorption. All of the variables mentioned above must be taken into consideration when applying any agent topically to the skin.

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APP-16.1

MEETING OF THE PANEL ON REVIEW OF
MISCELLANEOUS EXTERNAL OTC DRUG PRODUCTS
Thirty-Second Meeting
August 3 and 4, 1979

Parklawn Building
Rockville, Maryland
and
Holiday Inn
Bethesda, Maryland

Panel Members

William E. Lotterhos, M.D. (absent)
Chairman
Rose Dagirmanjian, Ph. D.
Harry E. Morton, Sc. D.
Marianne N. O'Donoghue, M.D.
Yelva L. Lynfield, M.D.
Chester L. Rossi, D.P.M.
J. Robert Hewson, M.D.

Liaison Representatives

Consumer Liaison (C.U.)
Marvin M. Lipman, M.D.

Industry Liaison
Saul A. Bell, Pharm. D.

Consultants
A. Belmonte, Ph. D.
Jon Tanja, M.S., R. Ph.

FDA Members

John McElroy, J.D. - Panel Administrator
Tom McGinnis, R. Ph. - Drug Information Specialist
Conrad J. Ledet - Consumer Safety Officer

Statements made herein are provisional in nature and may be modified or revised in subsequent meetings of the Panel or in its final complete report to the Commissioner.

Whenever there is a lack of unanimity on any given point, the vote will be given. Regulations do not permit voting by the Liaison Members, Consultants, or FDA Staff Members.

Adopted 28 Sept. 1979
Wm E. Lotterhos M.D.
William E. Lotterhos, M.D.
Chairman

SUMMARY MINUTES

1. The 32nd meeting of the Panel was called to order on August 3, 1979 at 9:00 a.m. A quorum was present.
2. Dr. George F. Hoffnagle, V.P. for Scientific and Regulatory Affairs, VICK RESEARCH, RICHARDSON MERRELL, recommended that camphor be placed in Category III for effectiveness for all combination dosage ranges that are before the Panel and that camphor be placed in Category I for safety in concentrations up to 5 percent, weight to volume. (In the submissions to the Panel camphor, as a single ingredient or in combination with other ingredients, is present in a concentration range of 0.1 to 65.8 percent.)

Further action on camphor was deferred until the next meeting.

3. Panel discussion of Wart Remover Draft Report--The following single active ingredients were discussed:

Ascorbic acid and calcium pantothenate, either alone or in combination with other ingredients, were changed from Category III to Category II because of no data to show effectiveness as a wart remover.

4. Sulfur in foot care products--Sulfur will most likely be considered as a keratolytic agent. The Panel has not fully characterized the role of sulfur in foot care products but will develop an appropriate definition for its use in such products.
5. Menthol--The decision was made that menthol be considered as an analgesic or as an antipruritic.
6. Ethyl alcohol--was placed in Category I for safety and effectiveness for antimicrobial action in concentrations of 60 to 95 percent either by weight or by volume.
7. Isopropyl alcohol--was placed in Category I for effectiveness for antimicrobial action in concentrations of 50 to 91 percent.
8. Cetyl alcohol--as an active ingredient was placed in

Category I for safety in concentrations of 8 percent or less and Category II for effectiveness for antimicrobial action.

9. Stearyl alcohol--as an active ingredient was placed in Category I for safety in concentrations of 8 percent or less. (No judgment has been made on effectiveness since the Panel regards this ingredient as a pharmaceutical aid.)

10. Benzyl alcohol--as an active ingredient was placed in Category II for effectiveness for antimicrobial action in concentrations of 4 percent or less in aqueous solution. (Panel previously characterized this ingredient as Category I for safety in concentrations of 10 percent or less.)

11. Phenoxyacetic acid--was placed in Category III for safety and effectiveness as a corn and callous remover.

12. The following ingredients were placed in Category II for effectiveness as a hair grower because of no effectiveness data:

- Wheat germ oil
- Coconut oil
- Isopropyl alcohol
- Methyl ethyl ketone
- Sulfonated vegetable and mineral oils
- Ammonium lauryl sulfate
- Di-isobutyl ethoxy ethyl dimethyl benzyl ammonium chloride monohydrate
- Crude coal tar
- Tetracaine hydrochloride
- Benzoic acid
- Ascorbic acid
- Oil of eucalyptus
- Olive oil
- Proteins
- Vegetable oil
- Topically applied vitamins

13. The following ingredients were placed in Category II for effectiveness as antidandruff, antiseborrheic agents because of no scientific evidence or data:

Benzocaine
Cholesterol
Cresol
1, 3-dihydroxy-2-ethyl hexane
Entsufon
Hydroxypropyl methylcellulose
Liquid parafin oil
Sodium chloride
Stearic acid
Sulfosuccinate sodium salt
Triethanolamine lauryl sulfate
Undecylenic acid monoethanolamide

14. The following ingredients were placed in Category II for lack of effectiveness of use in corn pads, corn plasters, and foot remedies:

Iodine
Panthenol
Thymol
Vitamin A

15. Sodium borate--was placed in Category II for effectiveness as an antidandruff, antiseborrheic dermatitis, or antiseborrheic agent.

16. Boric acid--was placed in Category II for effectiveness as an antidandruff, antiseborrheic dermatitis, or antiseborrheic agent.

17. The Panel adopted the following definition for a powder:

A homogeneous dispersion of finely divided relatively dry particulate material consisting of one or more substances.

18. The Panel approved the summary minutes of its previous meeting held on May 18 and 19, 1979.

19. The Panel's next meeting was scheduled for September 28 and 19, 1979.

The Panel adjourned on August 4, 1979 at 1:00 p.m.

MEETING OF THE PANEL ON REVIEW OF
MISCELLANEOUS EXTERNAL OTC DRUG PRODUCTS
Thirty-Seventh Meeting
March 7 and 8, 1980

Parklawn Building
Rockville, Maryland
and
Marriott Hotel
Bethesda, Maryland

Panel Members

William E. Lotterhos, M.D.
Chairman
Rose Dagirmanjian, Ph. D.
Harry E. Morton, Sc. D.
Marianne N. O'Donoghue, M.D.
Yelva L. Lynfield, M.D.
Chester L. Rossi, D.P.M.
J. Robert Hewson, M.D. (absent)

Liaison Representatives

Consumer Liaison (C.U.)
Marvin M. Lipman, M.D.

Industry Liaison
Saul A. Bell, Pharm. D.

Consultants
A. Belmonte, Ph. D.
Jon Tanja, M.S., R.Ph.

FDA Members

John McElroy, J.D. - Panel Administrator
Tom McGinnis, R.Ph. - Drug Information Specialist
Conrad J. Ledet - Consumer Safety Officer (absent)

Statements made herein are provisional in nature and may be modified or revised in subsequent meetings of the Panel or in its final complete report to the Commissioner.

Whenever there is a lack of unanimity on any given point, the vote will be given. Regulations do not permit voting by the Liaison Members, Consultants, or FDA Staff Members.

20 April 1980

Adopted

William E. Lotterhos, M.D.

William E. Lotterhos, M.D.
Chairman

SUMMARY MINUTES

1. The meeting was called to order on March 7, 1980.
2. Scholl, Inc. represented by Barry Brooks, J.D., submitted data and information on an audit of an IBT study on the safety and effectiveness of Onixol - a product containing sodium sulfide for the temporary relief of the pain and discomfort of "ingrown toenail."

Whitehall Laboratories, represented by Joel Hertz, Ph. D., presented information relating to the combination of tannic acid and chlorobutanol to substantiate epidermal hardening in the treatment of "ingrown toenail."

Abbott Laboratories, represented by Arnold Winfield, R. Janicki, Ph. D., J. Kesterson, Ph. D., B. Bopp, Ph. D., D. Anderson, Ph. D., presented information on the safety of selenium sulfide. Reported were two chronic toxicity studies, run by NCI, on Swiss mice utilizing the dermal application of selenium sulfide. These studies did not show a carcinogenic effect.

Vick Inc., represented by George F. Hoffnagle, Sc. D., commented on the Panel's report on Camphorated Oil. Vick was concerned that the Panel's report, placing 20 percent camphor in cottonseed oil in Category II for safety and effectiveness, did not reflect on other dosage forms using lower concentrations of camphor. Attention was called to previous Vick submissions relating to, among other things, the external use of 4.7 percent concentration of camphor in petrolatum for antitussive effect. Preliminary studies indicate the effectiveness of camphor in raising local skin temperature by external applications for counterirritant effect. The company will conduct a further well-controlled comparative study to scientifically confirm the effect of camphor on skin temperature.

3. Camphorated Oil Report - The Panel, after making minor changes in its report, voted unanimously to adopt the Camphorated Oil Report as amended.

4. Male Genital Desensitizing Drug Products Report - The Panel deferred action on its report until its next meeting in order to hear urologist opinions on the claimed effectiveness of benzocaine or lidocaine for the treatment of premature ejaculation. It approved the use of water soluble bases only for benzocaine and lidocaine formulations and stated that a metered pump or aerosol container for lidocaine would be safe for OTC use provided the dose is limited to not more than 120 mg. The Panel is concerned that not more than 120 mg lidocaine be applied per dose. Manufacturers may have metered or un-metered dosage forms. If un-metered, the pressurized can may contain no more than 120 mg lidocaine. If metered, directions must indicate that not more than 120 mg lidocaine may be applied per dose.

5. Corn/Callus Report - The Panel deleted from its report the concentration of 2-6 percent salicylic acid. This action was taken because the data before the Panel related to keratolytic action on normal skin and not on corn and callus lesions. The Panel did not receive any drug product submissions for corn or callus treatment with less than 12 percent salicylic acid. The topical dosage for hard corn and callus is a 12-40 percent salicylic acid preparation in plasters, pads, and discs, or 12-17.8 percent salicylic acid in a collodion vehicle.

6. Dandruff and Seborrhea Drug Products Report

Tar Shampoos

Tar in shampoos (Coal tar, pine tar, or juniper tar) was placed in Category I for both safety and effectiveness in the treatment of dandruff.

Selenium sulfide

Selenium sulfide 1 percent was accepted as safe and effective for the indication "helps control dandruff, itching, and flaking with regular use."

7. Ingrown Toenail Report - The Panel accepted the audit of an IBT study by Scholl and moved sodium sulfide to Category I for effectiveness as a nail softener for use in the treatment of "ingrown toenail."

Tannic acid remains in Category III alone or in combination with chorobutanol. An additional in vivo study using tannic acid alone is needed to show effectiveness.

8. Mercury Drug Products Report

Thiomerosal (merthiolate)

Thiomerosal was placed in Category II for safety as a preservative in any preparation that is likely to come in contact with the skin, and in Category II for effectiveness as a skin antiseptic in any concentration. (Vote 5 for, 1 against.)

Orthohydroxyphenylmercuric chloride

Orthohydroxyphenylmercuric chloride was placed in Category I for safety in a concentration of 0.056 percent, and in Category II for effectiveness as an antiseptic and for "healing."

Phenylmercuric nitrate

Phenylmercuric nitrate was placed in Category I for safety in a concentration of 1:10,000, and in Category II for effectiveness as an antiinfective (1:10,000) and as a "healing" agent.

9. Minutes - The Panel approved the minutes of its previous meeting, January 27 and 28, 1980.

10. The Panel scheduled its next meeting for April 20 and 21, 1980.

MEETING OF THE PANEL ON REVIEW OF
MISCELLANEOUS EXTERNAL OTC DRUG PRODUCTS
Thirty-Ninth Meeting
June 22 and 23, 1980

Parklawn Building
Rockville, Maryland
and
Holiday Inn
Bethesda, Maryland

Panel Members

William E. Lotterhos, M.D.
Chairman
Rose Dagirmanjian, Ph. D.
Harry E. Morton, Sc. D.
Marianne N. O'Donoghue, M.D.
Yelva L. Lynfield, M.D.
Chester L. Rossi, D.P.M.
J. Robert Hewson, M.D.

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FDA Members

John McElroy, J.D. - Panel Administrator
Tom McGinnis, R.Ph. - Drug Information Specialist
Conrad J. Ledet - Consumer Safety Officer

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3 August 1980
Adopted
W E Lotterhos MD
William E. Lotterhos, M.D.
Chairman

SUMMARY MINUTES

The meeting was called to order on June 22, 1980 at 9:00 a.m.

1. Herbert Lapidus, Ph. D., of Combe Inc., introduced Mr. Mark Taylor who submitted a protocol for the comparison of phenoxyacetic acid as a corn and callus remover against the known action of salicylic acid. The firm requested that the Panel delay adopting its report pending completion of the firm's study, projected for October 1980. The Panel decided to proceed with its report and noted that the firm would have ample opportunity to submit data following publication of the Panel report and proposed monograph.

2. George Hoffnagle, D.Sc., Vick Research, presented results from a study demonstrating a rise in skin temperature following the topical application of camphor in concentrations of 5, 2.5, and 1 percent. The Panel did not regard this study as demonstrating a counterirritant or rubefacient effect but rather a local pharmacological effect. No clinical data were presented to demonstrate the safe and effective use of the camphor-containing product.

3. Corn and Callus Report--The Panel reviewed comments received from the display of the information copy of its report in the Hearing Clerk's office. Following discussion of these comments the Panel made the following changes in its report: benzocaine, eucalyptus oil, menthol, and thymol were moved from the list of inactive ingredients and placed in Category II as active ingredients.

The Panel unanimously approved a motion that labeling information should include a warning statement that care should be used to avoid contact of the product with the skin surrounding the corn or callus.

The Panel unanimously adopted its Corn and Callus Report.

4. Mercury Report--The Panel developed the following name for its report: "OTC Topical Mercurial Drug Products for Antimicrobial Use." All ingredients are in Category II.

Mercuric Oleate--The Panel found that this agent is not effective as a topical antimicrobial.

5. Camphor Statement--The Panel adopted its statement on camphor-containing drugs. The Panel concluded that OTC products containing greater than 2.5 percent camphor have a low benefit-to-risk ratio. The Panel recommended that camphor be limited in OTC drug products for external use to less than 2.5 percent and that the quantity of camphor in a package be limited to a total of 360 mg per package, preferably in a child-proof container.

6. Dandruff and Seborrhea Drug Products

Alkyl isoquinolinium bromide--was placed in Category I for safety in a concentration up to 0.15 percent and Category III for effectiveness as a treatment for dandruff.

Allantoin--was placed in Category I for safety in concentrations up to 2 percent and Category III for effectiveness in the treatment of dandruff.

Benzalkonium chloride--was placed in Category I for safety in concentrations up to 0.2 percent and Category III for effectiveness in the treatment of dandruff.

Benzocaine--was placed in Category II for effectiveness as a treatment for dandruff due to lack of data on this use.

Chloroxylenol (parachlorometaxylenol)--was placed in Category I for safety and Category III for effectiveness in concentrations of 2 percent in the treatment of dandruff.

Entsufon sodium--was placed in Category III for safety and effectiveness in concentrations up to 50 percent in the treatment of dandruff.

Ethyl alcohol--was placed in Category III for effectiveness as a treatment for dandruff.

Menthol--was placed in Category I for safety in concentrations up to 2 percent and Category II for effectiveness in treating dandruff.

Methyl benzethonium chloride--was placed in Category III for safety in concentrations of 1 to 1500 and Category III for effectiveness in the treatment of cradle cap.

Mineral oil and Glycerin--were placed in Category II for effectiveness in the treatment of dandruff.

Povidone iodine--was placed in Category I for safety in concentrations up to 7.5 percent and Category III for effectiveness for dandruff.

Salicylic acid--was placed in Category I for safety in concentrations up to 5 percent and Category III for effectiveness in treating dandruff.

Salicylic acid--sulfur--combinations reviewed contained salicylic acid in concentrations up to 3 percent and sulfur in concentrations up to 5 percent. All salicylic acid-sulfur combinations were placed in Category I for safety and Category III for effectiveness for dandruff.

Thymol--was placed in Category I for safety in a concentration of 0.063 percent and Category II for effectiveness in treating dandruff.

7. Psoriasis--a general discussion on the etiology of psoriasis was presented by a dermatologist on the Panel. Ingredients used to treat psoriasis will be presented at the next Panel meeting.

8. Parasiticide Report

Copper oleate, kerosene, mercury compounds, petroleum distillates, and sabadilla were placed in Category II due to lack of data.

Pyrethrins--were placed in Category I for safety and effectiveness in a concentration of 0.1 - 0.3 percent when combined with the synergist piperonyl butoxide in the treatment of head, body, and pubic lice.

9. Minutes--The Panel approved the minutes of its previous meeting, April 20 and 21, 1980.

10. The Panel scheduled its next meeting for August 3 and 4, 1980.

11. The meeting was adjourned at 3:15 p.m. on June 23, 1980.