[4110-03-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 350]

[Docket No. 78N-0064]

ANTIPERSPIRANT DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Establishment of a Monograph; Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) antiperspirant drug products are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Antiperspirant Drug Products, is part of the Food and Drug Administration's ongoing review of OTC drug products.

DATES: Comments by January 8, 1979; reply comments by February 7, 1979.

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

FOR FURTHER INFORMATION CONTACT:

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

SUPPLEMENTARY INFORMATION: Pursuant to Part 330 (21C CFR Part 330), the Commissioner of Food and Drugs received on January 27, 1978, a report of the Advisory Review Panel on OTC Antiperspirant Drug Porducts. In accordance with § 330.10(a)(6) (21 CFR 330.10) (6)), the Commissioner is issuing (1) a proposed regulation containing the mongraph recommended by the Panel, which established conditions under which OTC antiperspirant drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the mongraph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available date are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration (address given above).

An earlier report of this Panel was submitted to the Commissioner and published in the FEDERAL REGISTER of June 5, 1975 (40 FR 24328). At that time, the Commissioner propcsed that any aerosol drug or cosmetic product containing zirconium is a new drug or an adulterated cosmetic. The final regulation was published in the FEDERAL REGISTER of August 16, 1977 (42 FR 41374), and became effective September 15, 1977. It declared that any aerosol drug or cosmetic product containing zirconium is a new drug or an adulterated cosmetic. Any such drug or cosmetic may not be introduced in interstate commerce after September 15, 1977 until safety testing adequate for approval of a new drug application (NDA) has been done.

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report, the Panel's findings are being issued as a formal proposal to obtain full public comment before the agency reaches any decision on the Panel's recommendation. The report has prepare: independently of the Food and Drug Administration (FDA). It represents the best scientific judgment of the members, but does not necessarily reflect the agency position on any particular matter contained in it.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2), all data and information concerning OTC antiperspirant drug products submitted for consideration by the Panel have been handled as confidential by the Panel and FDA. All such data and information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after November 6, 1978, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 33(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510), 5600 Fishers Lane, Rockville, Md. 20857.

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

1. That the conditions included in the mongraph, under which the drug products would be generally recognized as safe and effective and misbranded (Category I), be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

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

3. That the conditions excluded from the monograh because the available date are insufficient (Category III) to classify such conditions either as Category I or Category II be permitted to remain on the market, or may be introduced in to the market after the date of publication of the final monograph in the FEDERAL REGISTER, provided that FDA receives notification of testing in accordance with § 330.10(a)(13) (21 CFR 330.10(a)(13)). The period of time recommended by the Panel within which studies must be completed will be carefully reviewed by the Commissioner after receipt of comments on this document. The Commissioner will determine what time period to permit for Category III testing after that review is completed.

The Commissioner recognizes that changes will result in the current marketing practice of these products if the recommendations are fully implemented. The Panel's recommendations include effectiveness testing of the final product formulations for Category I ingredients. Also, the panel is recommending a statement on the lable explaining the level of effectiveness that can be expected from the use of these products.

At this time, the Commissioner seeks comment on these and all other Pannel recommendations. After careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC antierspirant drug products.

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner announced a proposed review of the safety, effectiveness, and lableling of all OTC drugs by independent advisory review panels. In the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), the Commissioner published the final regulations providing for the OTC drug review under § 330.10 which were made effective immediately. Pursuant to these regulations, the Commissioner issued in the FEDERAL REGISTER of September 7, 1973 (38 FR 24391) a request for data and information on all active ingredients utilized in OTC antiperspirant drug products.

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

E. William Rosenberg, M.D., Chairman.
J. Wesley Clayton, Ph. D., terminated February 1976.
Charles Evans, M.D., Ph. D.
Zenona Mally, M.D.
Jane Rosenzweig, M.D.
Robert Scheuplein, Ph. D.
Eli Shefter, Ph. D.

The panel was first convened on March 15, 1974, in an organizational and informative meeting. Working meetings were held on April 25 and 26, July 9 and 10, August 8 and 9, September 19, 20, and 21, October 31 and November 1 and 2, December 16 and 17, 1974; January 30 and 31, March 24 and 25, April 24 and 25, May 22 and 23, July 9 and 10, August 14 and 15, September 18 and 19, November 20 and 21, December 18 and 19, 1975; January 22 and 23, February 26 and 27, April 29 and 30, June 24 and 25, August 26 and 27, October 28 and 29, December 2 and 3, 1976; February 3 and 4, August 22 and 23, November 17 and 18, 1977; and January 26 and 27, 1978.

Three nonvoting liaison representatives served on the Panel. Marsha W. Gardner served as the consumer liaison until September 1976 and was followed by Emily D. Londos. Both were nominated by the Consumer Federation of America. Robert Giovacchini, Ph. D., nominated by the Cosmetic, Toiletry and Fragrance Association (CTFA), served as the industry liaison.

Dr. Scheuplein, a voting member of the panel from its beginning on March 15, 1974, became employed with FDA in January 1977, as Chief, Dermal and Ocular Toxicology Branch, Division of Toxicology, Bureau of Foods. Although a full-time FDA employee, Dr. Scheuplein remained a voting member of the panel. It was decided that since the panel's basic review had been completed and all major decisions concerning the report already had been made when Dr. Scheuplein's employment with FDA commenced, it would not be necessary to seek a replacement panel member. However, it was also decided that on any formal decision, Dr. Scheuplein's vote should be specifically identified and placed in the public record.

Other employees of FDA served with the Panel as follows: Mary K. Bruch as executive secretary; Lee Geismar as Panel Admisistrator; Lloyd Scott, R. Ph., as Drug Information Analyst served until April 1974, followed by Gary Trosclair, R. Ph., until October 1974, followed by Joe Hussion, R. Ph., until July 1976, followed by Dennis Myers, R. Ph.

In addition to the panel members and liaison representatives, the following individuals were given and opportunity to appear before the panel to express their views either at their own or at the panel's request:

Harold Baer, Ph. D.; Dov Boros, Ph. D.; Edwin V. Buehler, Ph. D.; Frank Carabella, Ph. D.; Robert Choate; Arnold B. Christen, Esq.; George Comstock, M.D.; Ronald Croystal, M.D.; Helen Dickie, M.D.; Robert Drew, Ph. D.; Walter Elvers, D.D.S.; William Epstein, M.D.; D. B. Ericson; Kenneth Ericson; Leon Goldberg, M.D., Ph. D.; Leonard Harber, M.D.; Lester B. Hardy, Ph. D.; G. Hildick-Smith, M.D.; Herman Jass, Ph. D.; Frank Johnson, M.D.; Robert Jones, M.D.; William Jordan, M.D.; Clark Hoffman, Ph. D.; Albert M. Kligman, M.D.; Adalbert Koestner, D.V.M., Ph. D.; Edwin M. Larsen, Ph. D.; Michael Lebowitz, M.D.; Robert Lehnhoff, G. Lord, D.V.M., Ph. D.; Henry C. Maguire, Jr., M.D.; Bertil Magnusson, M.D.; Howard L Maibach, M.D.; Paul Majors; Lollie Marchant; Joseph Page, Esq., F. Polley, Ph. D.; Joseph Robinson, Ph. D.; F. R. Rolle, Ph. D.; W. E. Smith, M.D.; W. G. Spector (Great Britain), M.A., M.B., B. Ch.; H. E. Stokinger, Ph. D.; Irwin Stolloff, M.D.; A. Wehner, D.M.D.; Hans Weill, M.D.; Sidney Wolfe, M.D.; William Wooding; and Ronald J. Wulf, Ph. D.;

No person who so requested was denied and opportunity to appear before the panel.

The panel has thoroughly reviewed the literature and the various data submissions, has listened to additional testimony from interested parties, and has considered all pertinent data and information submitted through January 27, 1978, in arriving at its conclusions and recommendations.

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

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

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

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

I. Submission of Data and Information

Pursuant to the notice published in the Federal Register of September 7, 1973, requesting the submission of data and information on OTC antiperspirant products, the following firms made submissions:

A. Submissions by Firms.

Firm and marketed products

Aerosol Techniques, Inc., Milford, Conn. 06460—Super Dri-Mist Heavy Duty Antiperspirant, Rite-Aid Extra Dry Antiperspirant Spray.

Armour-Dial, Inc., Chicago, Ill. 60608—Dial Antiperspirant (Aerosol, Roll-on), (Scented, Unscented).

Bristol-Myers Products, New York, N.Y. 10022—Ammens Foot Cooler, Ban Roll-on Antiperspirant Deodorant (Scented and Unscented), Ban Antiperspirant Cream Deodorant, Ban Deodorant Spray, Dry Ban Antiperspirant Deodorant Spray, The Dry System Antiperspirant Cream Concentrate, The Dry System Antiperspirant Lotion Concentrate, Mum (Cream, Roll-on, Spray), Deodorant Mum Powder Spray Antiperspirant Deodorant, Softalc Deodorant Spray Powder (Scented and Unscented), Trig Antiperspirant Roll-on Deodorant (Scented and Unscented), Ultra Ban 5000 Antiperspirant (Scented and Unscented), Ultra Ban Powder Spray.

Carter Wallace Products Div., Cranbury, N.J. 08512—Arrid Cream, Arrid Cream with Chlorophyll, Arrid Antiperspirant Roll-on Deodorant, Light Powder Arrid Extra Dry Anti-Perspirant Spray (Scented and Unscented), Arrid Antiperspirant Spray (Scented and Unscented).

Colgate-Palmolive, Piscataway, N.J. 08854—Hour After Hour Antiperspirant.

Gillette Co., Boston, Mass. 02114—Gillette Right Guard (Antiperspirant, Natural Scent Antiperspirant, Powder Dry Antiperspirant), Soft and Dri Lightly Powdered Antiperspirant Deodorant, Soft and Dri Antiperspirant (Scented and Unscented), X-Hydra Antiperspirant Deodorant (Cream, Liquid), Right Guard Extra Strength Antiperspirant, Gillette Right Guard Double Protection Antiperspirant (Scented and Unscented), Super Dry Soft and Dri (Scented and Unscented).

Leon Products, Inc., Jacksonville, Fla. 32216—Certain Dri Antiperspirant Deodorant.

Pennwalt Corp., Rochester, N.Y. 14623—Fresh Stick.

Person and Covey, Inc., Glendale, Calif. 91201—Drysol.

Procter & Gamble Co., Cincinnati, Ohio 45224—Secret Antiperspirant, Sure Antiperspirant.

Redfoot Products Co., Inc., Detroit, Mich. 48228—Redfoot Powder.

Sterling Drug, Inc., New York, N.Y. 10016—Body All Powdery Spray Deodorant and Antiperspirant, Dorothy Gray Antiperspirant Atomist Deodorant, Dorothy Gray Spin Roll-on Deodorant Antiperspirant, Dorothy Gray Antiperspirant Cream, Givenchy Gentleman Antiperspirant Deodorant Spray, Tussy Dry Antiperspirant Spray, Tussy Roll-on Deodorant, Tussy Roll-on Deodorant Extra Strength (Scented and Unscented), Tussy Cream Deodorant, Tussy Extra Strength Cream Deodorant, Tussy Cream Deodorant Unscented.

Texas Pharmacal Co., San Antonio, Tex. 78296—Allercreme Aerosol Antiperspirant Deodorant (Scented and Unscented), Allercreme Antiperspirant Deodorant Creme (Scented and Unscented), Allercreme Liquid Spray Antiperspirant Deodorant (Scented and Unscented), Allercreme Roll-on Antiperspirant Deodorant (Scented and Unscented), Maxi-Dry Hypo-allergenic Antiperspirant Roll-on (Scented and Unscented), Maxi-Dry Hypo-allergenic Antiperspirant Cream (Scented and Unscented).

USV Pharmaceutical Corp., Tuckahoe, N.Y. 10707—Mitchum Antiperspirant Spray (Scented and Unscented), Mitchum Antiperspirant Powder (Scented and Unscent-

ed), Mitchum Cream Antiperspirant, Mitchum Antiperspirant Liquid (Scented and Unscented), Mitchum Antiperspirant Stick.

In addition, the following firms made related submissions:

Firm and submission

Aerosol Techniques, Milford, Conn. 06460—Aluminum chlorhydroxide.

Carter Wallace Products Division, Cranbury, N.J. 08512—Zinc phenol sulfonate.

Proctor & Gamble, Cincinnati, Ohio 45224—Zirconyl hydroxychloride.

Reheis Chemical Co., Berkely Heights, N.J. 07922—Chlorhydrol Powder, Chlorhydrol Solution, Micro-Dry, Micro-Dry Ultrafine, Basic Aluminum Bromide, Rehydrol, Chloracel Solid, Chloracel Solution.

Wickhen Products, Inc., Hugenot, N.Y. 12746—Wickenol 303, 321, 323, 324, 340, 363D.

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

Aluminum chlorhydrate, aluminum chlorhydrate compound, aluminum chlorhydrate zirconium oxychloride aluminum glycinate, aluminum chlorhydroxide, aluminum chlorhydroxide complex, aluminum chlorhydroxide-propylene glycol complex, aluminum chlorhydrol, aluminum chloride, aluminum chlorohydrate, aluminum chlorohydroxide, aluminum glycinate, aluminum hydroxychloride, aluminum potassium sulfate, aluminum sulfate, aluminum-zirconium chlorohydrate complex, aluminum-zirconyl hydroxychloride complex, basic aluminum bromide, benzethonium chloride, boric acid, 8-hydroxyquinoline sulfate, magnesium stearate, potassium aluminum sulfate, salicylic acid, sodium aluminum chlorhydroxylactate, sodium aluminum lactate, water soluble lanolin, zinc phenolsulfonate, zirconium-aluminum-glycine complex, zirconium chlorhydrate-aluminum chlorhydrate-glycine complex, zirconium chlorhydrate, zirconium chlorohydrate, zirconyl hydroxychloride, zirconium oxychloride.

After reviewing the labeled ingredients contained in marketed antiperspirant products submitted to the Panel, there seemed to be no uniform system of nomenclature for describing the antiperspirant materials since many labeled ingredients appeared to have more than one name. For example, the submitted labels contained seven different names for aluminum chlorohydrate. In addition, the Panel was informed that when labels stated that products contained aluminum chlorohydrate and aluminum chloride, in fact it was one of the aluminum chlorhydrates (i.e., dichlorohydrate or sesquichlorohydrate), depending on the aluminum-to-chlorine ratio. The CTFA Antiperspirant Task Force developed a uniform system of nomenclature for the antiperspirant active ingredients which has been accepted by both the CTFA Cosmetic Ingredient Nomenclature Committee and the United States Adopted Names Council.

The Panel has decided to adopt this nomenclature and will use it throughout the report. A more complete definition of the antiperspirant active ingredients is included later in the report. The following table compares the submitted names to the adopted names for the antiperspirant active ingredients.:

COMPARISON OF SUBMITTED NAMES AND ADOPTED NAMES FOR ANTIPERSPIRANT ACTIVE INGREDIENTS

Adopted Nomenclature	Labeled Ingredient Nomenclature	Metal:Halide Ratio Range	Al:Zr Ratio Range
Aluminum chloride	Aluminum chloride	---	---
Aluminum chlorohydrate	Aluminum chlorhydrate Aluminum chlorhydrate compound Aluminum chlorhydroxide Aluminum chlorhydroxide complex Aluminum chlorohydrate Aluminum chlorohydroxide Aluminum hydroxychloride	2.1 down to but not including 1.9:1.	---
Aluminum dichlorohydrate	Aluminum chlorhydroxide, aluminum chloride Aluminum hydroxychloride, aluminum chloride Aluminum chlorhydrol, aluminum chloride	1.25 down to and including 0.9:1.	---
Aluminum sesquichlorohydrate	Aluminum chlorhydroxide, aluminum chloride Aluminum chlorhydrate, aluminum chloride Aluminum chlorhydrol, aluminum chloride	1.9 down to but not including 1.25:1.	---
Aluminum zirconium trichlorohydrate	Aluminum chlorhydrate, zirconium chlorhydrate Aluminum chlorohydrate, zirconium chlorohydrate Aluminum-zirconium chlorohydrate complex	2.1 down to but not including 1.5:1.	2.0 up to but not including 6.0:1.
Aluminum zirconium tetrachlorohydrate	---	1.5 down to and including 0.9:1.	2.0 up to but not including 6.0:1.
Aluminum zirconium pentachlorohydrate	---	2.1 down to but not including 1.5:1.	6.0 up to and including 10.0:1.
Aluminum zirconium octachlorohydrate	---	1.5 down to and including 0.9:1.	6.0 up to and including 10.0:1.
Aluminum chlorohydrex PG	Aluminum chlorhydroxide-propylene glycol complex	2.1 down to but not including 1.9:1.	---
Aluminum dichlorohydrex PG	---	1.25 down to and including 0.9:1.	---
Aluminum sesquichlorohydrex PG	---	1.9 down to but not including 1.25:1.	---
Aluminum chlorohydrex PEG	---	2.1 down to but not including 1.9:1.	---
Aluminum dichlorohydrex PEG	---	1.25 down to and including 0.9:1.	---
Aluminum sesquichlorohydrex PEG	---	1.9 down to but not including 1.25:1.	---
Aluminum zirconium trichlorohydrex Gly	Zirconium chlorhydrate-aluminum chlorhydrate-glycine complex. Zirconium-aluminum-glycine complex	2.1 down to but not including 1.5:1.	2.0 up to but not including 6.0:1.
Aluminum zirconium tetrachlorohydrex Gly	Aluminum chlorhydrate zirconium oxychloride aluminum glycinate. Aluminum-zirconyl hydroxychloride complex	1.5 down to and including 0.9:1.	2.0 up to but not including 6.0:1.
Aluminum zirconium pentachlorohydrex Gly	Zirconium chlorhydrate-aluminum chlorhydrate-glycine complex.	2.1 down to but not including 1.5:1.	6.0 up to and including 10.0:1.
Aluminum zirconium octachlorohydrex Gly	---	1.5 down to and including 0.9:1.	6.0 up to and including 10.0:1.
Aluminum bromohydrate	Basic aluminum bromide	2.1 down to but not including 1.9:1.	---
Aluminum sulfate	Aluminum sulfate	---	---
Buffered aluminum sulfate	Aluminum sulfate and sodium aluminum lactate	---	---
Potassium aluminum sulfate	Potassium aluminum sulfate	---	---
Sodium aluminum lactate	Sodium aluminum lactate	---	---
Sodium aluminum chlorohydroxy lactate	Sodium aluminum chlorhydroxy lactate	---	---

C. CLASSIFICATION OF INGREDIENTS

1. *Active ingredients.* The Panel has classified the following as antiperspirants:

a. Aluminum bromohydrate.
b. Aluminum chlorhydrates.[1]
(1) Aluminum chlorohydrate.
(2) Aluminum dichlorohydrate.
(3) Aluminum sesquichlorohydrate.
(4) Aluminum chlorohydrex PG.[2]
(5) Aluminum sesquichlorohydrex PG.
(6) Aluminum dichlorohydrex PG.
(7) Aluminum chlorohydrex PEG.[3]
(8) Aluminum sesquichlorohydrex PEG.
(9) Aluminum dichlorohydrex PEG.
c. Aluminum chloride.
d. Aluminum sulfate.
e. Aluminum zirconium chlorhydrates.
(1) Aluminum zirconium trichlorohydrate.
(2) Aluminum zirconium trichlorohydrex Gly.[4]
(3) Aluminum zirconium pentachlorohydrate.
(4) Aluminum zirconium pentachlorohydrex Gly.
(5) Aluminum zirconium tetrachlorohydrate.
(6) Aluminum zirconium tetrachlorohydrex Gly.
(7) Aluminum zirconium octachlorohydrate.
(8) Aluminum zirconium octachlorohydrex Gly.
f. Buffered aluminum sulfate.
g. Potassium aluminum sulfate.
h. Sodium aluminum chlorohydroxy lactate.

[1] The Panel has designated this term as the generic term for the various aluminum chlorhydrate compounds listed above. Since the chemical properties of the various aluminum chlorhydrates are similar, and the evidence presented to the Panel on the toxicity of these materials suggest that they have the same risk potential, the Panel will discuss these ingredients as a group in this document. This same reasoning is applicable to the aluminum zirconium chlorhydrate compounds listed above.

[2] Propylene glycol complex.

[3] Polyethylene glycol complex.

[4] Glycine complex.

The Panel has included the following table in which the active ingredients have been categorized:

Categorization of Antiperspirant Ingredients

Active ingredient	Nonaerosol dosage form	Aerosol dosage form
Aluminum bromohydrate[1]	II (S, E)[2]	II (S, E)
Aluminum chlorhydrates	I	III (S)
Aluminum chloride (15 Pct. or less aqueous solutions)	I	III (S)
Aluminum chloride (alcoholic solutions)	II (S)	II (S)
Aluminum sulfate	III (S, E)	III (S, E)
Aluminum zirconium chlorhydrates	I	II (S)
Buffered aluminum sulfate	I	III (S)
Potassium aluminum sulfate	III (S, E)	III (S, E)
Sodium aluminum chlorohydroxy lactate	III (E)	III (S, E)

[1] This ingredient has never been marketed in this country for a material extent or material time and, therefore, cannot receive general recognition of safety and effectiveness.
[2] (S) Refers to safety considerations. (E) Refers to effectiveness considerations.

2. *Other ingredients.* The following are not considered active antiperspirant ingredients:

Benzethonium chloride.[1]
Boric acid.[2]
8-Hydroxyquinoline sulfate.[2]
Magnesium stearate.[3]
Salicylic acid.[2]
Sodium aluminum lactate.[4]
Water soluble lanolin.[3]
Zinc phenolsulfonate.[5]

[1] Reviewed by Antimicrobial I Panel for antibacterial claims.

[2] Under review by Antimicrobial II Panel for antifungal claims.

[3] Considered to be inactive and/or pharmaceutical necessity.

[4] The Panel concludes that the presence of this ingredient in an antiperspirant is to act as a corrective agent rather than as an active antiperspirant ingredient. Therefore, it will not be discussed as an active ingredient in this document.

[5] This ingredient was not submitted as an antiperspirant active ingredient. It is not considered to have antiperspirant activity, and, therefore, will not be discussed further in this document.

[1] The Panel has designated this term as the generic term for the various aluminum chlorhydrate compounds listed above. Since the chemical properties of the various aluminum chlorhydrates are similar, and the evidence presented to the Panel on the toxicity of these materials suggest that they have the same risk potential, the Panel will discuss these ingredients as a group in this document. This same reasoning is applicable to the aluminum zirconium chlorhydrate compounds listed above.

D. REFERENCED OTC VOLUME SUBMISSIONS

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of September 7, 1973 (38 FR 24391). The volumes shall be put on public display after November 9, 1978, in the office of the Hearing Clerk (HFA-305), Food and Drug Administration (address given above).

II. GENERAL STATEMENTS AND RECOMMENDATIONS

A. INTRODUCTION

The charge to this Panel was to evaluate the safety and effectiveness of antiperspirant drug products. These products are widely used. In 1975, sales of antiperspirant and deodorant products in the United States were $619,350,000 (Ref. 1). According to section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)(1)), antiperspirants, because they affect a function of the body, i.e., reduce the amount of perspiration (sweat) production, are classified as drugs. Deodorants are classified as cosmetics because they do not affect a bodily function, and were, therefore, excluded from the Panel's charge in the call for data. Because most of the ingredients considered in this report have both antiperspirant and deodorant properties, it is necessary to keep in mind the distinction between these two interrelated functions. These two functions are discussed in more detail later in this document. (See part II., paragraph H. below—Effectiveness of Antiperspirants.)

REFERENCE

(1) Ryan, J., "What the Public Spent for Drugs, Cosmetics, Tioletries in 1975," Product Management, 5:25-31, 1976.

B. HISTORY OF ANTIPERSPIRANTS

The early Egyptian, Greek, and Roman literature note attempts to control body odor through the practice of various bathing, perfuming, and toilet procedures. During the time of Hippocrates, it was known that vaporous substances were given off through the skin. Galen discussed the insensible perspiration that is discharged from the skin's surface that can, on occasion, be so increased as to take the form of fluid. During the 17th century, the French raised to an art the use of perfumed oils and waters to disguise body odors.

The eccrine sweat glands were first described by Malpighi, who observed watery droplets issuing from the orifices. One hundred years later Purkinje and Wendt in 1833 and Breschet and Roussel de Vouzgeme in 1834 independently described the eccrine sweat gland. They were differentiated from the apocrine gland in 1922 by Schiefferdecker (Ref. 1).

The relationship between body odor and perspiration was undoubtedly little understood during ancient times, and the practices used either washed away or masked unpleasant body odor (Refs. 2 and 3). The first commercial products to alleviate the problem began to appear on the market during the late 1800's, with the first trade named product "Mum" appearing in

1888. The active ingredient in "Mum" was zinc oxide in a cream base. The claims dealt with diminishing axillary odor. "Everdry" appeared in 1902 and "Hush" in 1908. Both of these products were simple solutions of aluminum chloride. Ferric chloride was the active ingredient in "Nonspi," a product introduced in 1910. "Odo-Ro-No," a product introduced commercially in 1914, was the first product to use magazine advertising to nationally intoduce a product; it was claimed to remedy excessive perspiration and keep dresses "clean and dainty." In 1919, the "Odo-Ro-No" advertising theme was changed to introduce, for the first time, the concept that perspiration and body odor are socially shocking and offensive.

These early products were mainly simple solutions of aluminim chloride which were applied with a dampened or cotton pledget. During the 1930's the American Medical Association discussed antiperspirants in its journal in the "Quacks and Nostrums" section. A formula for such products was printed in the journal, and physicians began prescribing solutions of aluminum chloride, as high as 25 percent, to patients. In addition, pharmacists began making their own solutions and an over-the-counter drug business developed. In the 1930's, the first aluminum chloride cream product, "Arrid," appeared. It stressed antiperspirant effectiveness and fabric safety (Ref. 4).

The active antiperspirant ingredients in these early products were invariably salts of aluminum, either aluminum chloride or aluminum sulfate. These highly acid products had among their disadvantages the rotting of clothing and the tendency to irritate the axillary tissue.

The introduction of cream products allowed the chemist to utilize buffers and/or anticorrosive agents which reduced the potential for fabric damage and skin irritancy. Unfortunately, these additives also decreased the product's ability to inhibit perspiration. a variety of buffer systems was utilized during this period, in attempts to decrease irritancy and fabric damage and not inhibit efficiency. However, in the late 1940's a new active ingredient, aluminum chlorihydrate, was introduced. This active ingredient was less acid than the former salts and, therefore, it was suggested, less irritating to the skin and less damaging to fabrics. In addition, this new ingredient gave the formulator a broader range of formulation capabilities (Refs. 5 and 6).

During the late 1950's, sodium zirconium lactate was introduced as an effective antiperspirant active ingredient. This ingredient, however, was later determined to be the cause of granulomatous reactions in the axillary vault of certain users. Its use was discontinued. Later other salts of zirconium were suggested as effective antiperspirant active ingredients (Ref. 7).

During the 1940's these products were used mainly by women, and use was generally seasonal. A survey taken during World War II concluded that women considered these products only slightly less important than soap, rouge, lipstice, and face powder. Since that time, however, these products have become as important to men, which may explain the 4- to 25-percent increase in sales per year since 1945.

Packaging for convenience has also played an important role in the history of these products. The original liquid formulations were "runny" and irritating to skin and fabric. The cream forms were easier to handle, less irritating to skin and fabric, but also less effective. In 1947, the squeeze spray package was introduced and in 1955 the roll-on package. Aerosol packaged products were first unsuccessfully introduced in the early 1950's, and the first successful products were marketed in the 1960's (Refs. 8 through 11).

Since the time that the ancients recognized body odor and Purkinje discovered the sweat glands, a considerable amount of research has been conducted on the anatomy, histology, physiology, biochemistry, and pharmacological aspects of the glands of the axillary vault. Further, studies have been conducted on the microbial flora of the axilla and the relationship of the microbial flora to perspiration and axillary odor. From this work two general categories of products have been developed. They are: (1) The deodorants, whose purpose is either to mask the odor, or by the use of antimicrobial agents, decrease the microbial flora of the axilla; and (2) the antiperspirants, whose purpose is to inhibit perspiration.

REFERENCES

(1) Schieferdecker, P., "Die Haurdrusen des Menschen und des Saugetieres, ihre Bedeutung Sowie die Muscularis Sexualis," Zoologica, 27:1-154, 1922.

(2) Kuno, J., "Human Perspiration," C. C. Thomas, Springfield, 1956.

(3) Stoller, L., "Deodorants Their Place in Modern Cosmetics," The Givaudanian, June 1960.

(4) Anonymous, "External and Internal Personal Deodorants and Antiperspirants," Redbook Magazine, August 1962.

(5) Govett, T., and M. G. deNavarre, "Aluminum Chlorohydrate, New Antiperspirant Ingredient," American Perfumer and Essential Oil Review, 49:365-368, 1947.

(6) Mueller, W., and R. P Quatrale, "Antiperspirants and Deodorants," in "The Chemistry and Manufacture of Cosmetics," vol. 3, edited by deNavarre, M. G., Continental Press, Orlando, pp. 205-226, 1975.

(7) Lewe, I. A., "Granulomas of the Axillae Caused by Deodorant," AMA Archives of Dermatology, 75:765-767, 1957.

(8) Anonymous, "Stopette Spray Deodorant," Modern Packaging, 26:136-141, 292, and 294, 1953.

(9) Anonymous, "The Roll-on Deodorant," Modern Packaging, 28:80-81, and 189-190, 1955.

(10) Anonymous, "Roll-On Applicator," Modern Packaging, 33:98-99, 1960.

(11) Anonymous, "Reheis: Soon Aerosol Antiperspirants Will Dominate Market," Drug Trade News, Mar. 10, 1969, p. 22.

ANATOMY AND PHYSIOLOGY OF THE AXILLA

The human axilla (underarm area) is a concave structure and is marked in adults by conspicuous hair tuft considered to be hallmark of secondary sexual development and by its secretion and perspiration, which is readily visible and often perceptible to the nose.

The specialized structures within the axillary area include the glands—apocrine, eccrine, and sebaceous—the terminal hairs and the various nerves and blood vessels that supply these structures, as well as the remaining nonspecialized epidermis, dermis, and subcutaneous tissues.

1. *Apocrine sweat glands*—a. *Embryology and developement.* At about 5 months of fetal life the fetal precursors of the apocrine glands appear from the side of the hair follicles as solid epithelial buds above the level of the sebaceous gland. At this point the hairs are fully formed. The buds then proceed to form cords which eventually canalize. The duct lies close to and parallel to the hair follicle. Rarely, instead of opening into the hair follicle, the duct opens directly onto the surface of the skin (Ref. 1). The ducts appear over the entire surface of the body. Subsequently, most disappear, so that in the adult the characteristic distribution of the apocrine glands is the axillary, perianal, and areolar areas. In the axilla of humans they are such flourishing organs that they cannot be considered rudiments of a waning organ system (Ref. 2). Modified apocrine glands form the mammary gland, ceruminous gland of the external auditory canal, and the glands of Mol of the eyelid.

The axillary apocrine glands are poorly developed in childhood and enlarge considerably at the approach of puberty. Although these axillary apocrine glands remain relatively undifferentiated up to 7 years of age, some individual glands may develop precociously even in children 5 years of age. There are incipient accumulations of fluid in the lumen, and some of the glands become distended, perhaps due to a blockage of the duct. Beginning in the seventh year and continuing through adolescence, the glands

become progressively larger and gradually attain the structure and histochemical properties of functional glands (Ref. 2).

It is reported (Ref. 3) that in a high proportion of persons of Chinese and Japanese ancestry the apocrine glands are much less well developed than in the majority of blacks and Caucasians. The genetic basis of this difference and its significance in relation to axillary odor is discussed in the section on microbiology of the axilla.

These glands, even in preadolescent children, are larger than the accrine glands, measuring up to 2 millimeters. They are therefore macroscopically visible from the cut surface, lying either deep in the dermis or in the subcutaneous tissue.

In old age the apocrine glands undergo gradual involution, but this is not clearly related to the fading of the sex hormones (Ref. 4).

b. *Innervation.* The innervation of the human apocrine sweat gland is derived from adrenergic fibers of the autonomic nervous system. The apocrine duct, however, does not receive nerve fibers (Ref. 4).

The myoepithelial cells resemble smooth muscle fibers, but arise from the ectoderm. Direct observation of axillary glands through and incision in the axillary skin shows the myoepithelium contracting synchronously in peristaltic waves with the appearance of a droplet of sweat at the orifice (Refs. 4 and 5). Pharmacologic, mechanical, and electrical stimuli which normally initiate contraction of smooth muscle also induce contraction in myoepithelial cells and concurrently bring about discharge of apocrine sweat.

c. *Secretory process.* The apocrine gland secretion is slow and scanty. Total sweat response to be given stimulus is less than 1 milliliter (ml). Glands do not secrete continuously, and there is a long latent period between active cycles (Refs. 4 and 6). There are great individual differences. The free border of tall cells has large microvilli through which the secretions into the lumen probably occur. Since the lumen of normal apocrine tubules only rarely contains visible granules and cell debris, the granules in each cell must dissolve in the terminal cytoplasm before secretion takes place. The secretion could take place by either fragmentation of the terminal part of the microvilli or by oozing out of the secretion through intact microvilli. True apocrine secretion—that is, a pinching off and loss of part of the cell to form the secretion—does not occur. Therefore, apocrine is a misnomer for these glands.

The secretion, sweat or perspiration, is milky, viscid, and pale gray, but may be colored otherwise (Ref. 2). It is odorless when it reaches the surface of the skin and becomes odoriferous only upon bacterial decomposition. When collected, the secretion dries into glistening gluelike granules.

d. *Endocrine factors.* Although the gonadal hormones may play an initial role in development and maintenance of the glands, once the glands mature, they seem relatively self-sufficient. Proof of this has been shown in ovariectomized women without hormonal replacement who have normal apocrine glandular function (Ref. 7). Additionally, topical application or implantation of estrogens or androgens have no effect on the glands. Biopsy specimens from the same woman obtained at weekly intervals in a menstrual cycle showed no changes (Refs. 7, 8, and 9). The same is true with monthly biopsies of pregnant women (Refs. 8 and 9).

e. *Pharmacological responses.* Intradermal injections of adrenalin were effective in producing apocrine sweat in all subjects tested (Ref. 10). The results of testing with acetyl-*beta*-methylcholine are confusing. In one report it was possible to see apocrine sweating responses to intradermal injections (Ref. 2). This conflicts with the data from Shelley and Hurley (Ref. 10) and Hurley and Shelley (Ref. 4), who report that cholinergic agents were completely ineffective in producing apocrine sweating in the axilla. Returning to Montagna's studies (Ref. 2), prior treatment with atropine followed by cholinergic agents inhibited the flow of both apocrine and eccrine sweat.

f. *Function.* The function of the apocrine glands in man is uncertain. The glands may play a role in interpersonal subliminal communications. (See part II. paragraph E.6. below—Pheromones.)

g. *Pathology.* Bromhidrosis or osmidrosis is malodorous sweat. This is often a function of hygiene. Sometimes, however, it may be caused by ingestants such as garlic.

Chromhidrosis is colored sweat. In true chromhidrosis the pigment is a lipofuchsin. Pseudochromhidrosis is a condition in which the sweat colors when it reaches the skin surface. This is usually due to chromogenic bacteria, especially corynebacteria. Ingested drugs and dyes may at times color the sweat.

Hematohidrosis (bloody sweat) is very rare (Ref. 11). It may occur as a part of a bleeding diathesis.

Fox-Fordyce disease is a disorder of the apocrine glands comparable to miliaria of the eccrine glands. The etiology is unknown. The pathophysiologic sequence is the appearance of a small vesicle in the apocrine duct which brings about the inflammatory response. This in turn leads to rupture and plugging of the duct (Ref. 12). It generally occurs in females after puberty and is amenable to therapy with the female hormones in anovulatory doses (Ref. 13).

Hidradenitis suppurativa is a chronic and indolent disorder of the apocrine sweat glands. The sexes are equally susceptible, but axillary lesions are relatively more common in women, and anogenital lesions are more common in men. Most cases occur between the ages of 16 and 40. The onset is more frequent in the hottest months of the year. The cause is unknown. No specific microorganism has been incriminated. The role of local factors is disputed. Maceration leading to keratinous obstruction of the sweat duct is probably an important factor in axillary hidradenitis (Ref. 14). Anogenital hidradenitis is frequently associated with acne conglobata and perifolliculitis capitis, but axillary hidradenitis frequently occurs alone. The earliest inflammatory changes are seen within and around the apocrine glands, the ducts of which may be distended with leucocytes. Groups of cocci may be seen within the glands and in the dermis. Later, the eccrine glands are similarly involved. In simple hidradenitis, cosmetics and especially antiperspirants are usually forbidden. Obesity should be corrected and any metabolic defects such as diabetes should also be corrected. Prolonged administration of an antibiotic is sometimes adequate for control. Superficial radiation therapy and systemic corticosteroid therapy have been advocated, but are less likely to provide lasting control than is surgical attack on the apocrine-bearing areas.

2. *Eccrine sweat glands.*—a. *Embryology and development.* In man there are 2 to 5 million glands spaced at 143 to 339 per square centimeter (Ref. 15). As they are all formed at birth, they are most dense at that time; their density is diluted by growth of the body. Infant skin has 8 to 10 times as many sweat glands per unit area as the skin of an adult. The first fetal precursors are seen in the fourth fetal month in the palms and soles. In the fifth fetal month they appear in the axilla. From the fifth month on, they appear generalized. Their distribution shows characteristic patterns around hair follicles (Ref. 16). They are found on all skin except lips, the glans penis, the inner surface of the prepuce, the clitoris, and the labia minora. The subsequent functioning of sweat glands may in some way reflect these differences in development; thus, sweating of the palms and soles is in response to different stimuli than from the general body surface. Kuno in 1956 suggested that sweat glands that develop earlier in fetal life may have arisen from

a more primitive stem cell than those with later development (Ref. 15).

The myoepithelial cells, which in functional glands resemble smooth muscle fibers insinuated between the epithelium and basement membrane, are not recognizable during fetal life. Nor is the connective tissue stroma around the entire gland differentiated until after birth (Ref. 17).

From the 5th to 10th months of age the glands become gradually active and attain their characteristic histologic features. All the histochemical attributes of the adult glands become discernible by the first postnatal year (Ref. 2).

b. *Anatomy.* The secretory coil lies deep in the lower dermis or in the subcutaneous tissue. It is composed of two cell types—the large clear cells which are secretory and the small dark cells whose function is uncertain. All the cells are attached to the basement membrane. The function of the secretory coil is to produce from plasma a watery secretion to be modified by the duct.

The duct is composed of two layers of uniform cuboidal cells. Its function is to propel the sweat toward the surface and using its active enzyme system to modify the secretion of the coil. The intra-epidermal sweat duct unit is a coil to the surface which travels in a helical manner through the epidermis.

c. *Histochemistry and staining properties.* Clear cells are stippled with delicate lipid granules, while the dark cells have only a few. These granules are not secreted even when the glands are stimulated (Refs. 18, 19, and 20). Most eccrine cells have a diffuse yellow pigment, probably a carotinoid, in their cytroplasm (Ref. 21.) Pigment granules are also noted, increasing in number as a person gets older. Large quantities of glycogen are found in both clear and dark cells (Ref. 22). A substantial amount of cytochrome oxidase is found in both coil and duct, indicating that these areas are rich in mitochondria. Large amounts of carbonic anhydrase are found in both the duct and secretory coil (Ref. 23). Monoamine oxidase is found in moderate amounts. Succinic dehydrogenase is found in large amounts (Refs. 24, 25, and 26). The eccrine gland has more phosphorylase than any other cutaneous appendage. The glands are high in *beta*-glucuronidase activity and aminopeptidase. Alkaline phosphatase is found only in the deeper coils.

The eccrine gland cells contain no cholinesterase. However, the surrounding nerves are rich in specific cholinesterases (Ref. 27 through 31). Delicate, strongly reactive nerve fibers are wound around the coils of the secretory segment. Some of the coils of the duct, but not the straight segments, are also surrounded by nerves that contain specific cholinesterases. The relation of sweat glands with cholinesterase-rich nerves is established as soon as the glands are formed in 4½-month-old fetuses (Ref. 29). The nerves around the sweat glands contain specific cholinesterase (Ref. 2).

d. *Pharmacological responses.* Dale and Feldberg (Ref. 32) in 1934 first demonstrated that eccrine glands are supplied with nerves that, although belonging anatomically to the sympathetic nervous system, are cholinergic. Sweating is readily induced by acetylcholine, pilocarpine, methacholine, carbachol, and even enhanced by physostigmine, a strong inhibitor of cholinesterase. It is inhibited by atropine (Refs 33, 34, and 35). The adrenergic drugs adrenalin, noradrenalin, and isopropyl noradrenalin also cause increased sweating (Refs. 36 through 39). Adrenergic-stimulated sweating is not inhibited by atropine, but is inhibited by dibenamine, tolazoline, and dihydroergotamine (Refs. 37, 38, and 39). Histamine has no sudorific effect.

Severance of the postganglionic sympathetic nerves to the eccrine sweat glands causes a prompt and remarkable decrease in their responsiveness to direct pharmacologic stimulations (Refs. 35 and 40 through 43).

e. *Function of the gland.* Adequate eccrine gland function is vital for maintenance of normal body temperature under usual climatic conditions. Subjects who are deprived of the cooling effect of sweat evaporation are unable to tolerate temperatures much higher than over 80° F. or the excess body heat that arises from exertion at evn lower temperatures. This cooling function of sweat is provided by the mass of sweat glands over the body surface. It has been repeatedly demonstrated, however, that even total inhibition of axillary sweat does not compromise the body's ability to maintain proper thermal regulation. However, since total body inhibition might interfere with the thermal regulatory process, the Panel concludes that antiperspirants should not be permitted for use over the entire body.

While the sweat contains measurable amounts of urea and lactic acid, the popular belief that sweating is necessary to "purify" the blood in an excretory manner analogous to the kidney is not born out by fact. Many people live in air-conditioned or other cool environments and suffer no ill effects from the fact that they sweat little or not at all (Ref. 44).

The techniques for studying the function of the gland are:

(1) Collection of sweat in bags or on pads (Ref. 45).

(2) Direct measurement of water loss (Refs. 44 and 46).

(3) Sampling by means of microcanulae passed into the duct or coil.

(4) Measurement of electrical resistance. Resistance varies with moisture from sweat on the skin and within the duct (Refs. 46 and 47).

(5) Visualization of individual sweat droplets. This can be done in many ways—by direct microscopy, by forming plastic impressions (Ref. 48), or by indicators which color on contact with water. The test most commonly used is the starch-iodine test, in which starch and iodine applied to the skin react to produce a blue color in the presence of sweat (Refs. 49 and 50). The technique is to dry the skin, paint it with 2 percent iodine in alcohol, then press either a paper containing starch against the surface of the skin, or apply starch by painting it on the skin in a castor oil solution of 50 grams (g) of starch per 100 ml. Alternate color indicator tests are bromphenol blue (Refs. 51, 52, and 53) or quinizarin.

For the gland to function, an intact sympathetic nervous system is needed. Deprived of postganglionic nerves, the gland ceases to function, but remains histologically normal. As mentioned before, the sweat gland is unusual by being cholinergic in function, although supplied with sympathetic nerves. It may respond to adrenergic agents, but probably does not have a true adrenergic innervation. The activity of these glands from nervous stimuli is controlled by three factors:

(1) *Thermal.* This is controlled by the heat-regulating center in the hypothalamus, which in turn is activated by changes in the temperature of the blood perfusing it and also, to some extent, by afferent stimuli from the skin. The efferent pathways from the hypothalamus involve nerve fibers relaying in the medulla, lateral horn of the spinal cord, and the sympathetic ganglia (Ref. 54). Thermal regulation of sweating occurs more on the upper trunk and face (Ref. 35).

(2) *Mental.* The centers and pathways are not fully known. Some are in the frontal areas of the brain. Mental stimuli cause increased sweating on the palms and soles (postulated as acting to improve the grip in times of intense activity), in the axilla, and also, to a lesser degree, on the body surface in general.

(3) Gustatory. Sweating around the mouth and on the forehead and nose is stimulated after hot and spicy foods (Ref. 55). Neural reflexes for gustatory sweating have not been fully worked out.

f. *Composition of eccrine sweat.* Under basal conditions there are few impulses passing to the sweat gland. During basal conditions sweat contributes minimally or not at all to water loss. The water loss during nonsweating periods is termed transepidermal

water loss and occurs at a low rate through the intact stratum corneum (Ref. 44). Maximal stimulation can induce 12 liters per 24 hours with an initial maximal rate of 3 liters in an hour (Ref. 56).

The sweat duct is largely responsible for modification and concentration of sweat. For that reason the composition of sweat may vary depending on the rapidity at which sweat passes through the duct. Sweat is usually hypotonic, but with rapid sweating it may approach isotonicity. The constituents of sweat are sodium chloride, potassium, urea, lactate, and glucose in small amounts. Lactate is present at 4 to 40 milliequivalents/liter (meq/liter), greater than the plasma concentration. The pH is 4 to 6.8.

Changes is electrolytes present in sweat may be found in Cushing's disease, Addison's disease, nephrosis, cardiac failure, and after administration of various hormones such as aldosterone.

An increase of sodium chloride in sweat has been reported in miliaria (Ref. 57). There is also a well-known increase of sweat electrolytes in fibrocystic disease, and this is used as a diagnostic test (Ref. 58). Normal children have up to 60 meq sodium chloride per liter of sweat. Fibrocystic children are above this and often above 90 meq. In adults, levels of sodium and chloride are naturally higher, so partial forms and carriers of fibrocystic disease in adulthood cannot be diagonosed with sweat tests.

Sweat glucose levels may be increased in diabetes, but such increases do not correlate with blood levels.

g. *Pathology.* Hyperhidrosis (excessive sweating) may be generalized or asymmetrical. Generalized (symmetrical) hyperhidrosis may be either thermoregulatory in etiology or from mental stimuli. Thermoregulatory causes may result from an instability of the hypothalamic center, induced by febrile illnesses. This may persist, after cessation of the fever, for many months. There may be an infectious cause such as malaria or tuberculosis. Other miscellaneous causes for generalized thermoregulatory hyperhidrosis are as follows: Gout, diabetes, hyperthyroidism, hyperpituitarism, obesity, menopause, malignancy, alcohol intoxication, and postvomiting.

Sweating produced from mental stimuli occurs especially on the palms, soles, and axillae. Most cases presented to the dermatologist are of this type. Only rarely are deep-seated emotional problems found. Usually the enhanced activity is considered a facilitation of already existing nervous pathways. It usually appears in childhood or around puberty, and often spontaneously improves around age 25 (Ref. 59).

Asymmetric hyperhidrosis can occur from lesions at any place along the sympathetic pathways to the nerve endings at the gland (Refs. 54 and 59). It may occur reflexly from visceral disturbances (Ref. 60) or around areas of anhidrosis (absence of sweating) (Ref. 54). Compensatory hyperhidrosis occurs on normal remaining sweat glands when those elsewhere are not functioning from neural disease or skin disease or after sympathectomy (Ref. 61).

In the treatment of hyperhidrosis, reassurance alone is often sufficient. Anticholinergic drugs such as 0.025 percent benzoyl scopolamine hydrobromide are effective, especially in the axilla (Ref. 62). Also effective are propantheline, formalin, and aluminum salts. Systemic treatment includes the atropinelike drugs (Ref. 63). Usually, however, the side effects are more troublesome than the sweating. These side effects are dryness of the mouth, visual disturbances, glaucoma, hyperthermia, and convulsions. Atropine is not used to control sweat because of its pronounced systemic actions. Propantheline is used in doses beginning at 15 mg three times daily. Ganglionic blocking agents can inhibit sweating, but side effects from hypotension are usually to troublesome. Sedatives and tranquilizing drugs have been used in cases with pronounced emotional factors. Surgical management of extreme hyperhidrosis has included sympathectomy and also local excision of the axillary vault (Ref. 64).

In contrast to hyperhidrosis, anhidrosis may occur. The cause may be from the brain with organic lesions at any level, hysteria, or hyperthermia. It may originate in the spinal cord and nerves from such organic lesions as tumor, syringomyelia, or leprosy. It will occur subsequent to sympathectomy or the use of ganglionic blocking agents or anticholinergic drugs.

The anhidrosis may also be caused by malfunction of the sweat gland itself. This occurs in the aplasias, such as congenital ectodermal dysplasia and ichthyosis and in the cutaneous atrophies such as acrodermatitis atrophicans, scleroderma, and Sjogrens disease.

Lack of sweating may occur from localized lesions distal to the gland at the level or the duct of the intraepidermal sweat duct unit with conditions such as miliaria and eczema.

Anhidrosis of uncertain origin include neonatal sweat gland fatigue and idiopathic acquired anhidrosis (Ref. 65).

REFERENCES

(1) Rook, A., D. S. Wilkinson, and F. J. G. Ebling, "Textbook of Dermatology," F. A. Davis Co., p. 1326, 1968.

(2) Montagna, W., "The Structure and Function of Skin," Academic Press, New York, 1962.

(3) Matsunaga, E., "The Dimorphism in Human Normal Cerumen," *Annals of Human Genetics*, 25:273-286, 1962.

(4) Hurley, H. J. and W. B. Shelley, "The Human Apocrine Sweat Gland in Health and Disease," Charles C. Thomas, Springfield, p. 138, 1960.

(5) Hurley, H. J. and W. B. Shelley, "The Human Apocrine Sweat Gland: Two Secretions?" *British Journal of Dermatology*, 66:43-48, 1954.

(6) Shelley, W. B., "Apocrine Sweat," *Journal of Investigative Dermatology*, 17:225, 1951.

(7) Klaar, J., "Zur Kenntnis des weiblichen Axillar-organs bein Menschen," *Wiener Klinische Wochenschrift*, 39:127-131, 1926.

(8) Montagna, W., "Aging of the Axillary Apocrine Sweat Glands in the Human Female," *in* "Ciba Foundation Colloquium on Aging, Vol. II Aging in Transient Tissues," Churchill, London, pp. 188-197, 1956.

(9) Montes, L. F., B. L. Baker, and A. C. Curtis, "The Cytology of the Large Axillary Sweat Glands in Man," *Journal of Investigative Dermatology*, 35:273-291, 1960.

(10) Shelley, W. B. and H. J. Hurley, "The Physiology of the Human Axillary Apocrine Sweat Gland," *Journal of Investigative Dermatology*, 20:285-297, 1953.

(11) Radcliffe-Crocker, H., "Diseases of the Skin," 3d Edition, Lewis, London, p. 1031, 1903.

(12) Shelley, W. B. and E. J. Levy, "Apocrine Sweat Retention in Man II. Fox-Fordyce Disease (Apocrine Miliaria)," *AMA Archives of Dermatology*, 73:38-49, 1956.

(13) Kronthal, H. L., J. R. Pomeranz, and G. Sitomer, "Fox-Fordyce Disease," *Archives of Dermatology*, 91:243-245, 1965.

(14) Shelley, W. B. and M. M. Cahn, "The Pathogenesis of Hidradenitis Suppurativa in Man," *AMA Archives of Dermatology*, 72:562-565, 1955.

(15) Kuno, Y., "Human Perspiration," C. C. Thomas, Springfield, 1956.

(16) Horstmann, E., "Uber Den Papillarkoyser der Menschlichen Haut und Seine Regionalen Unterschiede," *Acta Anatomica*, 14:23-42, 1952.

(17) Tshuchiya, K., "Uber die Ekkrine Schweissdruse des Menschlichen Embryo mit Besonderer Berucksichtigung ihrer Histo-und Cytogenese," *Archives of Histologie*, 6:403-432, 1954.

(18) Shelley, W. B. and H. Mescon, "Histochemical Demonstration of Secretory Activity in Human Eccrine Sweat Glands," *Journal of Investigative Dermatology*, 18:289-301, 1952.

(19) Dobson, R. L. and W. C. Lobitz, Jr., "Some Histochemical Observations of the Human Eccrine Sweat Glands IV. The Recovery From the Effects of Profuse Sweating," *Journal of Investigative Dermatology*, 31:207-213, 1958.

(20) Dobson, R. L., V. Formisano, W. C. Lobitz, and D. Brophy, "Some Histochemical Observations on the Human Eccrine Sweat Glands III. The effect of Profuse Sweating," *Journal of Investigative Dermatology*, 31:147-159, 1958.

(21) Bunting, H., G. B. Wislocki, and E. W. Dempsey, "The Chemical Histology of Human Eccrine and Apocrine Sweat Glands," *Anatomical Record*, 100:61-67, 1948.

(22) Tsukagoshi, M., "Zur Zytologie der Ekkrinen Schweissdrusen der Tiere mit Besonderer Berucksichtigung des Vorkommens der Zwei Arten Drusenzellen und ihrie Apokrinen Sekretion," *Archives of Histologie*, 2:481-497, 1951.

(23) Braun-Falco, O. and B. Rathjens, "Uber die histochemische Darstellung der Kohlensaureanhydratase in Normaler Haut," *Archiv fur Klinische u. experimentelle Dermatologie*, 201:73-82, 1955.

(24) Braun-Falco, O. and B. Rathjens, "Histochemische Darstellung der Bernsteinsaureddhydrogenase in der Menschlichen Haut," *Dermatologische Wochenschrift*, 130:1271-1277, 1954.

(25) Serri, F., "Note de Enzimologica Cutanea II. Recerche Bio ed Istochimiche sull' Activita Succinodeidraseca della Cute Umana Normale," *Bol. Soc. Med-Chir.*, 69:3-19, 1955.

(26) Montagna, W. and V. Formisano, "Histology and Cytochemistry of Human Skin VII. The Distribution of Succinic Dehydrogenase Activity," *Anatomical Record*, 122:65-77, 1955.

(27) Hurley, H. J., W. B. Shelley, and G. B. Koelle, "The Distribution of Cholinesterases in Human Skin, With Special Reference to Eccrine and Apocrine Sweat Glands," *Journal of Investigative Dermatology*, 21:139-147, 1953.

(28) Hellmann, K., "Cholinesterase and Amine Oxidase in the Skin: A Histochemical Investigation," *Journal of Physiology*, 129:454-463, 1955.

(29) Beckett, E. B., G. H. Bourne, and W. Montagna, "Histology and Cytochemistry of Human Skin. The Distribution of Cholinesterase in the Finger of the Embryo and Adult," *Journal of Physiology*, 134:202-206, 1956.

(30) Thies, W. and F. Galente, "Zur Histochemischen Darstellung der Cholinesterasen in Vegetativem Nervensystem der Haut," *Hautazt*, 8:69-75, 1957.

(31) Montagna, W. and R. A. Ellis, "L'Histologie et la Cytolgie de la Peau Humaine XVI. Repartition et concentration des esterases carboxyliques," *Annàles D' Histochimie*, 3:1-17, 1958.

(32) Dale, H. H. and W. Feldberg, "The Chemical Transmission of Secretory Impulses to the Sweat Glands of the Cat," *Journal of Physiology*, 82:121-129, 1934.

(33) Braun, R., F. Favre, and A. Linder, "Experiences sur la Transpiration. Examens semiquantitatifs de la sudation provoquee par certaines substances," *Dermatologica*, 108:257-267, 1954.

(34) Kernen, R. and R. Brun, "Experiences sur la Transpiration. Examens pharmacodynamiques au niveau de la glande sudoripare de l'homme," *Dermatologica*, 106:1-13, 1953.

(35) Randall, W. C. and K. K. Kimura, "The Pharmacology of Sweating," *Pharmacological Reviews*, 7:365-397, 1955.

(36) Barnett, A. J., "Sweating in Man From the Intradermal Injection of norAdrenaline," *Nature*, 167:482-483, 1951.

(37) Chalmers, T. M. and C. A. Keels, "Physiological Significance of the Sweat Response to Adrenaline in Man," *Journal of Physiology*, 114:510-514, 1951.

(38) Haimovici, H., "Evidence for Adrenergic Sweating in Man," *Journal of Applied Physiology*, 2:512-521, 1950.

(39) Sonnenschein, R. R., H. Kobrin, H. D. Janowitz, and M. I. Grossman, "Stimulation and Inhibition of Human Sweat Glands by Intradermal Sympathomimetic Agents," *Journal of Applied Physiology*, 3:573-581, 1951.

(40) Chalmers, T. M. and C. A. Keele, "The Nervous and Chemical Control of Sweating," *British Journal of Dermatology*, 64:43-54, 1952.

(41) Janowitz, H. D. and M. I. Grossman, "The Response of the Sweat Glands to Some Locally Acting Agents in Human Subjects," *Journal of Investigative Dermatology*, 14:453-458, 1950.

(42) Janowitz, H. D. and M. I. Grossman, "An Exception to Cannon's Law," *Experientia*, 7:275, 1951.

(43) Kahn, D. and S. Rothman, "Sweat Response to Acetylcholine," *Journal of Investigative Dermatology*, 5:431-444, 1942.

(44) Rosenberg, E. W. and H. Blank, "Sweating and Water Loss Through the Skin. Studies Using Electrical Humidity Sensor," *Journal of the American Medical Association*, 179:809-811, 1962.

(45) Dobson, R. L. and A. C. Ratner, "A Method for Sweat Stimulation and Collection," *Journal of Applied Physiology*, 18:1038, 1963.

(46) Montagna, W. et al., "Advances in Biology of Skin," Vol. III, Permagon Pess, New York, 1962.

(47) Kennard, D. W., "The Nervous Regulation of the Sweating Apparatus of the Human Skin, and Emotive Sweating in Thermal Sweating Areas," *Journal of Physiology*, 165:457-467, 1963.

(48) Takahashi, Y. and M. Wada, "The Permanent Recording of Sweat by Plastic Impression," *Journal of Investigative Dermatology*, 38:197-198, 1962.

(49) Muller, S. A. and R. R. Kierland, "The Use of a Modified Starch-Iodine Test for Investigating Local Sweating Responses to Intradermal Injection of Methacholine," *Journal of Investigative Dermatology*, 32:126-128, 1959.

(50) Wada, M, "Sudorific Action of Adrenalin on the Human Sweat Glands and Determination of Their Excitability," *Science*, 111:376-377, 1950.

(51) Herrmann, F., P. H. Prose and M. B. Sulzberger, "Studies on Sweating IV. A New Quantitative Methods of Assaying Sweat-Delivery to Circumscribed Areas of the Skin Surface," *Journal of Investigative Dermatology*, 17:241-249, 1951.

(52) Sulzberger, M. B. and F. Herrmann, "The Clinical Significance of Disturbances in the Delivery of Sweat," Thomas, Springfiled, 1954.

(53) Tashiro, G., M. Wada, and M. Sakurai, "A Bromphenol Blue Mehod for Visualizing Sweat at the Openings of the Sweat Ducts," *Journal of Investigative Dermatology*, 36:3-4, 1961.

(54) Rothman, S., "Physiology and Biochemistry of the Skin," University of Chicago Press, Chicago, 1954.

(55) List, C. F. and M. M Peet, "Sweat Secretion in Man IV. Sweat Secretion of the Face and Its Disturbances," *Archives of Neurology and Psychiatry*, 40:443-470, 1938.

(56) Schmidt-Nielsen, K., "Desert Animals. Physiological Problems of Heat and Water," Oxford University Press, Oxford, 1964.

(57) Loewenthal, L. J. A., W. M. Politzer, and C. H. Wyndham, "The Salt Excretion of Miliaria Subjects," *South African Medical Journal*, 38:315-319, 1964.

(58) Anderson, C. M. and M. Freeman, "'Sweat Test' Results in Normal Persons of Different Ages Compared with Families with Fibrocystic Disease of the Pancreas," *Archives of Diseases in Childhood*, 35:581-587, 1960.

(59) Pool, J. L., "Unilateral Thoracic Hyperhidrosis Caused by Osteoma of the Tenth Dorsal Vertebra," *Journal of Neurosurgery*, 13:111-115, 1956.

(60) Korr, I. M., "Skin Resistance Patterns Associated with Visceral Disease," *Federation Proceedings*, 8:87-88, 1949.

(61) Shelley, W. B. and R. Florence, "Compensatory Hyperhidrosis After Sympathectomy," *New England Journal of Medicine*, 263:1056-1058, 1960.

(62) MacMillan, F. S. K, H. H. Reller, and F. H. Snyder, "The Antiperspirant Action of Topically Applied Anticholinergics," *Journal of Investigative Dermatology*, 43:363-377, 1964.

(63) Herxheimer, A., "Trans. a. Rep. St. Johns Hosp.," *Derm. Soc.*, 40:20, 1958.

(64) Hurley, H. J. and W. B. Shelley, "Axillary Hyperhidrosis. Clinical Features and Local Surgical Management," *British Journal of Dermatology*, 78:127-140, 1966.

(65) Gordon, B., H. Maibach, and W. Epstein, "Generalized Acquired Anhidrosis," *Archives of Dermatology*, 90:347-348, 1964.

D. MICROBIOLOGY OF THE AXILLA

A knowledge of the microbial flora of the normal axilla and of the effect of antiperspirants on these organisms is pertinent to two aspects of the evaluation of safety and effectiveness of antiperspirants: (1) Is the use of antiperspirants associated with an increased risk of bacterial infection due to disturbance of the normal flora? This question is discussed in the section on safety (see part II. paragraph G.3. below—Microbiological safety considerations.); and (2) are the claims of deodorancy of antiperspirants in the nature of drug claims that are based on a change of body function, or are they cosmetic claims that are not based on a change of body function?

Knowledge of the microbial populations of the normal axilla has developed with remarkable slowness despite the fact that, as will be shown, bacteria are the immediate cause of the underarm odor which the American public spends hundreds of millions of dollars annually to combat. Among the more significant contributions to this subject are the papers by Shehadeh and Kligman in 1963 (Ref. 1), Somerville in 1969 (Ref. 2), Marples and Williamson in 1969 (Ref. 3), Prince and Rodgers in 1974 (Ref. 4), and Voss in 1975 (Ref. 5). A review of the subject will be found in the book by Noble and Somerville (Ref. 6).

The variation in total numbers of aerobic bacteria in the normal axilla was studied by Prince and Rodgers (Ref. 4). Among 10 subjects cultured repeatedly over a 2-week period, variations up to more than 100-fold were found. Only two subjects varied less than 10-fold. These data are important in showing that a "decline" in numbers of bacteria in a test subject in an evaluation of a soap, an antiperspirant, or some other product could be

merely a chance fluctuation in numbers, even if the decline is as much as a 90 percent or even a 99 percent decrease in aerobic popuations.

Although anaerobic propionibacteria, both *P. acnes* and *P. granulosum*, are frequently present, often in substantial numbers, the predominant organisms in the axilla grow best in the presence of air. Most studies have been limited to aerobic culture methods.

In most axillae well over 90 percent of the organisms present are either aerobic diphtheroids, coagulase negative staphylococci, or a combination of these two groups. Both of these groups are heterogeneous.

Among the bacteria of the genus *Staphylococcus* that occur on the human body, the most important distinction is between *S. aureus* and all other staphylococci. *S. aureus* is a coagulase positive organism that has the capability of causing a wide variety of infections, some minor, some severe. The coagulase test is the most widely used method for making a distinction among them. Further classification of coagulase negative staphylococci is a matter of containing research and disagreement among specialists. Marples and Williamson, in their studies of axillary flora (Ref. 3), found that most of these organisms fell into Baird-Parker Group SII.

The aerobic diphtheroids of the axilla do not include any organisms with major disease-producing capability. A major differentiation in this group is based on their response to the addition to the growth medium of certain lipids such as Polysorbate 80 (which contains oleic acid). Most of the axillary aerobic diphtheroids are lipophilic, that is, they grow better and form larger colonies if a lipid supplement such as Polysorbate 80 is provided.

The relative numbers of coagulase negative cocci and aerobic diphtheroids in the axilla vary widely in different individuals. Marples and Williamson found that on the average, persons with a predominance of diphtheroids harbored total populations of several million per square centimeter, whereas those with more than 50 percent cocci averaged several hundred thousand total bacteria per square centimeter. They also showed that if the diphtheroids were selectively suppressed by antibiotic treatment, the cocci resistant to the antibiotic increased proportionately. Thus, the diphtheroids appear to limit the growth of cocci in the normal axilla (Ref. 3).

With respect to organisms other than propionibacteria, aerobic diphtheroids, and coagulase negative cocci, the data are fragmentary and sometimes conflicting. Noble and Somerville (Ref. 6) state that 5 to 10 percent of adults are carriers of *S. aureus* in the axilla, based on extensive studies by Somerville and a review of data by others. Prince and Rodgers found a much higher carrier rate of *S. aureus* and documented an interesting seasonal change with a substantial increase in the summer. Unfortunately, they based their identification on mannitol fermentation and pigment formation and did not confirm it with the coagulase test (Ref. 4).

Pseudomonas aeruginosa is a potential pathogen of considerable significance. Prince and Rodgers (Ref. 4) did not find this organism in any of their approximately 1,400 axillary cultures from 235 subjects over a 2-year period. Noble and Somerville (Ref. 6) agree that this organism does not appear to colonize the axilla in normal adults, but add that it may do so in persons with a reservoir of this organisms elsewhere, as in a burn.

Gram negative rods, other than *Pseudomonas*, have been a subject of interest in several studies. Prince and Rodgers (Ref. 4) found a substantial change in number of gram negative rods with the season. *Acinetobacter* was the most common gram negative rod by a wide margin, with coliforms the only other group present except for a single person who carried *Proteus* and *Achromobacter* as well as *Acinetobacter*. In winter, 21 percent of 33 subjects tested 6 times over 13 days were carriers of gram negative rods on at least one occasion. In summer, 80 percent of 20 subjects were similarly positive. However, the tests in summer were more numerous and extended over a longer time period (11 tests in 25 days). Some subjects were positive for these organisms in all tests, others in only one or two tests. Those with 60 percent or more of their cultures positive were called persistent carriers, the others transient carriers. Thirty-five percent of all subjects were persistent carriers in summer and 9 percent were persistent carriers in winter.

Somerville (Ref. 2) found that the axillary flora in children was more varied than in adults. Aerobic spore-forming bacilli and *Sarcina* were more common, and aerobic diphtheroids were less frequently present. Mimae (*Acinetobacter*) have been reported in children by a number of observers.

Two relatively mild diseases in which members of the normal flora are causally involved are trichomycosis axillaris and erythrasma. In both, certain of the aerobic diphtheroids are regularly present and contribute to the development of the condition.

REFERENCES

(1) Shehadeh, N. H. and A. M. Kligman, "The Effect of Topical Antibacterial Agents on the Bacterial Flora of the Axilla," *Journal of Investigative Dermatology*, 40:61-71, 1963.

(2) Somerville, D., "The Normal Flora of the Skin in Different Age Groups," *British Journal of Dermatology*, 81:248-258, 1969.

(3) Marples, R. R. and P. Williamson, "Effects of Systemic Demethyl- chlortetracycline on Human Cutaneous Microflora," *Applied Microbiology*, 18:228-234, 1969.

(4) Prince, H. N. and J. A. Rodgers, "Studies on the Aerobic Axillary Microflora Employing a Standardized Swabbing Technique: Total Counts, Speciation, and Ecological Drift." Draft of Unpublished paper is included in OTC Volume 140065.

(5) Voss, J. G., "Effects of an Antibacterial Soap on the Ecology of Aerobic Bacterial Flora of Human Skin," *Applied Microbiology*, 30:551-556, 1975.

(6) Noble, W. C. and D. A. Somerville, "Microbiology of Human Skin," W. B. Saunders, Co., London, 1974.

E. AXILLARY ODOR.

In deciding whether claims of deodorancy of antiperspirants are drug claims or cosmetic claims it is necessary to consider the mechanisms involved in producing the odor and the probable mechanism of the claimed deodorancy. The term "axillary odor" in this report denotes the strong smell characteristic of the axilla, which many persons seek to prevent by washing, shaving, and applying antiperspirants and other deodorants.

There is convincing evidence that axillary odor arises from the growth of bacteria in the secretion of apocrine sweat glands. Shelley, Hurley, and Nichols (Ref. 1) collected drops of secretion from the orifices of single apocrine glands of the axilla and showed that this fluid was odorless at the time of discharge but acquired the characteristic axillary odor if held under conditions permitting bacterial growth. Since apocrine glands are a part of the normal anatomy of the axilla, and bacteria are universally present in this region, one must inquire further for the reasons why odor may be present or absent.

A description of the mechanisms controling secretion by apocrine and eccrine sweat glands is presented in the section on the anatomy and physiology of the axilla. (See part II. paragraph C. above—Anatomy and Physiology of the Axilla.)

1. *Genetics of axillary odor and of cerumen.* In Japan, where axillary odor has long been viewed as a medical problem, laymen as well as physicians have observed an association between that condition and a particular type of cerumen (ear wax). Matsunaga of the National Institute of Genetics, Mishima, Japan (Ref. 2), reviewed previous studies and reported additional data on the dimorphism in human normal cerumen.

The cerumen of most Japanese is of the "dry" type. It is gray, brittle, and not sticky. Smaller numbers of Japanese have cerumen of the wet type; it is brownish and sticky. From surveys

of 23,000 Japanese reported by various authors from 1934 through 1958, Matsunaga found the mean frequency of wet cerumen to be 16.3 percent. Family studies from as early as 1932 supported the hypothesis that "the ear-wax types are controlled by a pair of autosomal alleles with complete dominancy, W and w, the genotype of wet cerumen being WW or Ww and the genotype of dry cerumen ww."

The frequency of wet cerumen in American Caucasians and Blacks was estimated by Matsunaga to be 97.5 percent and 99.5 percent, respectively, on the basis of studies of children of Japanese mothers married to American Caucasians or American Blacks. Other surveys of representative groups have reported low frequencies of the wet type of cerumen in peoples of East Asia, such as the Chinese and Koreans, and high frequencies in Caucasians, such as residents of Germany, as well as those native to African countries, such as Ghana and Nigeria. (Ref. 3).

The morphogenetic basis of the association between cerumen type and susceptibility to axillary odor is attributed to the morphologic and functional similarity between the cerumen glands of the external auditory canal and the apocrine glands of the axilla. The apocrine glands are reported to be much less well developed in those with dry cerumen than in persons with wet cerumen.

2. *Evidence concerning the kinds and numbers of bacteria that cause axillary odor.* The evidence presented by Shelley and his colleagues (Ref. 1) to prove that axillary odor resulted from multiplication of bacteria in the secretions of apocrine sweat glands included the following: (1) No odor was detected from freshly collected secretion; (2) a strong smell characteristic of axillary odor was produced in 6 hours if apocrine sweat collected from an uncleansed axilla was held at room temperature; (3) refrigeration at 0° C prevented the appearance of odor; (4) no odor developed in apocrine sweat from axillae that were shaved and disinfected with alcohol; (5) hexachlorophene prevented the development of odor in vitro for 14 days; (6) in vivo, the axillae cleansed with hexachlorophene remained odor free as much as 18 hours after control axillae had developed odor.

a. *Attempts to determine which kinds of bacteria cause axillary odor.* Although the evidence cited above supported the essentiality of microbial action, it did not identify the organisms involved. Strauss and Kligman (Ref. 4), in an attempt to resolve this problem, inoculated various organisms into apocrine sweat. They reported that some strains of *Aerobacter aerogenes, Escherichia coli, Poroteus,* coagulase negative micrococci, coagulase positive micrococci, and diphtheroids produced the characteristic odor. However, in a later study, Shehadeh and Kligman (Ref. 5) found that suppression of gram-positive organisms in the axilla by treatment with topical neomycin prevented the development of axillary odor despite a high population of gram-negative rods (*Alkaligenes, Proteus,* and *Aerobacter*). They commented that the earlier report was in error, that gram-negative bacteria growing in apocrine sweat do not produce typical axillary odor but that "* * * gram-negatives have a putrid odor of their own in vitro * * *. This clinically inapparent odor is that of the organisms themselves and not a consequence of the decomposition of apocrine sweat."

Meyer-Rohn (Ref. 6) reported that *S. epidermidis* and corynebacteria isolated from the axilla can produce typical axillary odor when grown in "sterile sweat."

From the published evidence it is not possible to state which of the organisms of the axilla produce axillary odor nor what numbers must be present to generate the odor. The causative organism is probably one or more of the gram-positive species. *S. ediderm idis,* propionibacteria, or aerobic diphtheroids of various kinds are obvious possibilities.

b. *Amount of reduction in bacterial populations required to produce a deodorant effect.* The Advisory Review Panel on OTC Topical Antimicrobial I Drug Products considered the issue of deodorancy of products under their purview. They reported in the FEDERAL REGISTER of September 13, 1974 (39 FR 33108) as follows:

> It was the estimate of a group of experts from industry and academia (who appeared before the Panel to discuss the effectiveness of antimicrobials in the classes of products currently being reviewed by the Panel) that approximately a "70 percent reduction" in the microbial flora (as measured by handwashing tests) would produce a deodorant effect. The exact percent reduction required to achieve a deodorant effect either on the entire body or in the axillae was not established by the data submitted. The view of the Panel is that perhaps some bar soaps which achieve a 90 percent or more reduction of gram-positive organisms may be so active as to be harmful.

In the absence of any other evidence, the present Panel cannot accept a 70 percent or a 90 percent reduction in bacterial populations of the axilla as having any significance with respect to the deodorant effect or the possible harmful effect. This position is based on the knowledge that total numbers of bacteria in the healthy axillae of different people or of the same person at different times vary more than 100-fold (Refs. 7 and 8), and such differences have been observed without any noticeable axillary odor (Ref. 9). since the organisms that cause axillary odor are unknown, it is possible that they constitute less than 1 percent of the total population in axillae with or without odor. If that were the case, data with respect to changes in the total population of bacteria might not be a valid indicator of changes in the numbers of those odor-producing organisms.

3. *The role of eccrine sweat and of hair in the genesis of axillary odor.* From the preceding evidence it is clear that axillary odor depends upon an adequate supply of apocrine secretion and conditions favorable to the multiplication and metabolic activity of some as yet unidentified bacteria. Conditions that favor retention of the necessary substrate, and those favorable to rapid multiplication of bacteria, should be conducive to the development of odor. The following appear to be reasonable assumptions about variables that influence the axillary ecosystem and odor production:

Shaving the axilla is helpful in preventing axillary odor. Hair of the axilla tends to favor odor development by several mechanisms. The apocrine secretion is somewhat sticky and is presumably retained to an appreciable extent on hair. When the axilla is washed there may be a greater retention of bacteria as well as of apocrine secretions in the presence of hair than when the bare skin is fully exposed to the mechanical and detergent action of washing. Multiplication of the bacteria of the axilla is probably favored by the increased surface provided by hair, as this expands the environment in which there is a favorable combination of nutrients, wetness, and temperature. Relative wetness of the axilla is probably one important factor in determining whether odor develops. The principal source of wetness in the axilla is eccrine sweat. In this way eccrine sweat exerts some influence on odor production.

4. *Mechanisms of the deodorant effects of antiperspirants.* Advertising claims often assert that antiperspirants will prevent axillary odor, and it appears that consumers commonly use antiperspirants with the intention of suppressing axillary odor. Submitted data show that standardized use of a number of products was followed by an odor-free state or a diminished odor for time periods that would be meaningful to a user. Disregarding the masking effects of perfumes, which are clearly cosmetic in nature, there are two mechanisms that are at least theoretically possible in this deodorancy process: (1) Suppression of relative wetness and (2) direct antibacterial action.

Even though antiperspirants reduce the level of perspiration in the axilla,

most antiperspirants do not make the axilla dry enough to interfere totally with bacterial growth. The deodorant effect of antiperspirants, therfore, is not merely secondary to their reducing the moisture necessary for bacteria to grow in.

In view of the probable inadequacy of the antiprespirant action as an explanation of the deodorant effect of antiperspirants, one might expect to find good evidence for an antibacterial mechanism. Unfortunately, the available evidence is fragmentary and inadequate to support a definitive conclusion as to this effect.

There is surprisingly little information on the question of a direct antibacterial action of antiperspirants on bacteria in the axilla. The only bacteriologically adequate data that we have found in the literature was that of Shehadeh and Kligman (Ref. 5) concerning neomycin, an ingredient not now used in antiperspirants. Other tests have been made using antisperspirant ingredients on the forearm or on callus or agar in vitro.

Leyden and Kilgman (Ref. 10) found that a drop of 1 percent solution of aluminum chlorohydrate inhibited the growth of *S. aureus, Pseudomonas aeruginosa, Escherichia coli, Pityrosporum ovale,* and *Candida albicans* on agar. When applied to skin of a forearm, occluded by a sheet of polythylene, 0.1 ml of a 20 percent solution supressed growth of all bacteria over an area of 25 square centimeters. If the skin was occluded 48 hours before the test, an initial population of millions of bacteria per square centimeter was reduced to zero. In each case, the lowest concentration was reduced to zero. In each case, the lowest concentration of aluminum chlorohydrate tested gave the results cited. Similar results were obtained with various concentrations of aluminum chloride hexahydrate and aluminum acetate in vitro and in vivo.

Blank, Moreland, and Dawes (Ref. 11) reported that daily application of 20 percent solutions of aluminum chloride, aluminum chlorhydroxide, and aluminum sulfate to the axilla resulted in a reduction of numbers of gram-positive cocci. Their methods were only crudely quantitative and were not suitable for the detection of the diphtheroids which are reported to constitute the most abundant organisms in the axillae of most adults. In laboratory tests of the growth of bacteria on hydrated callus from the sole of the foot, they found that micrococci grew in the presence of 1 percent concentrations of the aluminum salts and were inhibited by 2 percent concentrations. Results were erratic in tests with diphtheroids and with coliform organisms at the concentration levels tested, 0.25 to 4 percent. All three salts in aqueous solution were bactericidal for micrococci and diphtheroids, but the killing concentrations ranged from 1:100,000 to below 1:100.

It is distressing to find no published data on the effects of active ingredients of currently used antiperspirants on odor-producing bacteria of the axilla in spite of the fact that this kind of evidence might be the most reliable way of determining the extent and duration of the deorant effect of antiperspirants.

Although the evidence is grossly deficient, the Panel concludes that it is highly probable that the principal deodorancy effect of antiperspirants in current use is a result of antibacterial actions of the products. Persumably these different products have variable levels of antibacterial activity, and in the axialla, this effect is modified by local conditions as well as by the elapsed time from application of the product. These and other factors were not investigated by the Panel when it became apparent that the deodorant effect was primarily one that did not depend upon alteration of body function.

5. *Conclusion.* The panel finds that axillary odor is produced by bacterial action on apocrine secretion, and this action is aided by the wetness of the axilla which is largely attributable to eccrine sweat glands. The deorant action of antiperspirants cannot be accounted for primarily as suppression of eccrine gland action. The evidence for direct antibacterial action is fragmentary, but this appears to be the probable mechanism insofar as antiperspirants are indeed deodorants.

REFERENCES

(1) Shelley, W. B., H. J. Hurley, and A. C. Nichols, "Axillary Odor. Experimental Study of the Role of Bacteria, Apocrine Sweat, and Deodorants," *AMA Archives of Dermatology and Syphilology,* 68:430-446, 1953.

(2) Matsunaga, E., "The Dimorphism in Human Normal Cerumen," *Annals of Human Genetics,* 25:273-286, 1962.

(3) Petrakis, N. L., "Cerumen Genetics and Human Breast Cancer," *Science,* 173:347-349, 1971.

(4) Strauss, J. S. and A. M. Kligman, "The Bacteria Responsible for Apocrine Odor," *Journal of Investigative Dermatology,* 27:67-71, 1956.

(5) Shehadeh, N. H. and A. M. Kligman, "The Effect of Topical Antibacterial Agents on the Bacterial Flora of the Axilla," *Journal of Investigative Dermatology,* 40:61-71, 1963.

(6) Meyer-Rohn, J., "Uber die ursachen lastigen korpergeruches," *Fette, Seifen, Anstrichm.,* 67:353-354, 1965.

(7) Prince, H. N. and J. A. Rodgers, "Studies on the Aerobic Axillary Microflora Employing a Standardized Swabbing Technique: Total Counts, Speciation, and Ecological Drift," Draft of paper submitted for publication is included in OTC Volume 140065.

(8) Marples, R. R. and P. Williamson, "Effects of Systemic Demethylchlortetracycline on Human Cutaneous Microflora," *Applied Microbiology,* 18:228-234, 1969.

(9) Evans, C. W., Draft of unpublished data is included in OTC Volume 140065.

(10) Leyden, J. J. and A. M. Kligman, "Aluminum Chloride in the Treatment of Symptomatic Athlete's Foot," *Archives of Dermatology,* 111:1004-1010, 1975.

(11) Blank, I. H., M. Moreland, and R. K. Dawes, "The Antibacterial Activity of Aluminium Salts," *Proceedings of the Scientific Section of the Toilet Goods Association,* 27:32-36, 1957.

6. *Pheromones.* A discussion of axillary odor is incomplete without some discussion of pheromones. Since odoriferous secretions are widespread throughout the animal kingdom and recognized up and down the phylogentic scale as important elements of social communication, it is reasonable to consider the possibility of a human chemical communication. These chemical communicators are called pheromones and are defined as substances or mixtures of substances which are produced by an individual and received by a second individual of the same species in which they produce one or several specific actions.

The pheromones are classified in two ways. First, they can be discussed with reference to their mode of recognition, i.e., olfaction, ingestion, or absorption.

Second, they can be classified according to the action on the recipient. There are three kinds of pheromones that can be discussed according to their action on the recipient. There can be an immediate and reversible process rapidly acting through neurohumoral (chemical nerve transmitter) channels. These usually show fairly immediate responses and are known as "releaser" pheromones.

The second kind are known as "primer" pheromones. This action is slow to develop, demands prolonged stimulation, and initiates a chain of physiologic effects in the recipient.

The third kind of action on the recipient can be "imprinting." This is stimulation at a critical period in development, resulting in a permanent modification of behavior in the adult.

The presence and effects of pheromones have been studied both in the laboratory and under natural free conditions (Refs. 1 through 4).

In lower primates, Evans and Goy (Ref. 5) found while studying the ring tailed lemur that their social integration is dependent on a whole series of olfactory responses, and they felt that these animals possessed an olfactory repertoire whose complexity rivals the more sophisticated visual and acoustic systems of larger-brained primates.

Curtis, et al. (Ref. 6) in their studies of the rhesus monkey noted certain

volatile fatty acids of vaginal origin were trigger factors in the mating process and that similar chemicals are present in high concentration in ovulating or pregnant human females.

What is the likelihood that there is such a thing as a human pheromone? Pheromonal primer effects are nearly universal in mammals, including primates, while humans have a complete set of organs which are traditionally described as nonfunctional, but which if seen on some other mammal would be recognized as a part of a pheromonal system.

Consider the evidence that might suggest that the adult human axilla is a useful, functioning source of sexual attractant. Axillary sweating functions apart from the usual thermoregulatory sweating system. It is stimulated by emotional signals, not just heat. It becomes active only after puberty. The combination of a potentially odorous substrate; a hospitable, warm, moist environment for the requisite bacterial growth; a large volume of evaporate vehicle for odor dissemination; and a wicklike tuft of hair all point to an efficient system for broadcasting chemical signals.

That pheromonal stimulation from axillary odors is not consciously perceived does not militate against such a possibility; pheromones in the animal kingdom typically appear to act at an unconscious level. Nor is the requirement that bacteria are necessary for odor production evidence that the human axilla should, by nature, be odor free. Well-known vaginal sex attractants in monkeys are produced by the action of the vaginal flora on odorless precursors.

Obviously, discussions of putative human pheromones are now no more than speculative, but this Panel feels that it would be erroneous to dismiss out of hand the presence of useful olfactory exchange between humans, or that axillary odor might serve that purpose.

REFERENCES

(1) Michael, R. P., J. Herbert, and J. Welegalla, "Ovarian Hormones and the Sexual Behavior of the Male Rhesus Monkey (Macaca Mulatta) Under Laboratory Conditions," *Journal of Endocrinology*, 39:81-89, 1967.

(2) Michael, R. P. and E. B. Keverne, "Pheromones in the Communication of Sexual Status in Primates," *Nature*, 218:746-749, 1968.

(3) Bruce, H. M., "Pheromones," *British Medical Bulletin*, 26:10-13, 1970.

(4) Smith, R. D., "Chemical Communications in Mammals," *Sciences*, 16:21-24, 1976.

(5) Evans, C. S. and R. W. Goy, "Social Behavior and Reproductive Cycles in Captive Ring-Tailed Lemurs," *Journal of Zoology*, 156:181-197, 1968.

(6) Curtis, R. F., et al., "Identification of Primate Sexual Pheromones and the Properties of Synthetic Attractants," *Nature*, 232:396-398, 1971

F. PHARMACOLOGY OF ANTIPERSPIRANTS

There is no agreement on the mechanism of action of the commonly used antiperspirant ingredients despite their widespread use for many years. Three possible mechanisms have been suggested in the recent scientific literature.

Shelley and Hurley (Ref. 1) believe that aluminum or zirconium ions bind to the COOH groups of keratin. They go on to state that metallic ions penetrate some distance into the sweat duct. A functional closure results from reaction of the metal ion with the intraductal keratin fibrils. They postulate further that the intraluminal pressure rises to the point where it acts by a feedback mechanism, stopping glandular secretion. The obstruction continues until the affected keratin is shed in the normal process of desquammation. The effects on the sweat duct reach deeper than the superficial regions located in the stratum corneum (the most superficial portion of the epidermis).

Experiments reported by Papa and Kligman in 1967 (Ref. 2) contradict in part the hypothesis that poral closure is responsible for anhidrosis. They suggested that the aluminum salts alter the permeability to water of the sweat duct and that the sweat then diffuses out into the skin instead of being deposited on the surface in droplets. In support of their view they cite evidence that show (1) the lack of restoration of function with cellophane tape stripping, (2) identification of patent sweat pores with methylene blue iontophoresis, (3) lack of distention of the ducts during thermal sweating, and (4) lack of formation of PAS positive, diastase resistant casts in the treated ducts. Shelley and Hurley (Ref. 1) term this "leaky hose" analogy a "strange theory."

Patocha (Ref. 3) reported that aluminum chloride is capable of markedly influencing the activity of cholinesterase and acetylcholinesterase. This suggests the possibility that aluminum ion might diminish sweating by interrupting the neurologic input to the gland.

Sato and Dobson (Ref. 4) demonstrated that the anhidrotic effect of glutaraldehyde, a well-known protein precipitant, could be removed by cellophane tape stripping. Gordon and Maibach (Ref. 5), however, showed that the effect of aluminum salts could not. This suggests a simple, superficial occlusive effect of glutaraldehyde which is different from the still disputed effects of the metallic salt antiperspirants.

At one of the Panel's meetings it was suggested by an industry representative that a complex of zirconium chlorhydrate, aluminum chlorhydrate, and glycine formed a totally inert gel which worked by superficially occluding the sweat pore (Ref. 6). The Panel received no data in support of this hypothesis.

REFERENCES

(1) Shelley, W. B. and H. J. Hurley, "Studies on Topical Antiperspirant Control of Axillary Hyperhidrosis," *Acta Dermatovener*, 55:241-260, 1975.

(2) Papa, C. M. and A. M. Kligman, "Mechanisms of Eccrine Anidrosis. II. The Antiperspirant Effect of Aluminum Salts," *Journal of Investigative Dermatology*, 49:139-145, 1967.

(3) Patocha, J., "The Influence of Al+++ On Cholinesterase and Acetylcholinesterase Acitivity," *Acta Biologica et Medica Germanica*, 26:845-846, 1971.

(4) Sato, K. and R. L. Dobson, "Mechanism of the Antiperspirant Effect of Topical Glutaraldehyde," *Archives of dermatolgy*, 100:564-569, 1969.

(5) Gordon, B. I. and H. I. Maibach, "Studies on the mechanism of Aluminum Anhidrosis," *Journal of Investigative Dermatology*, 50:411-413, 1968.

(6) Transcript of Open Session, December 16 and 17, 1974.

G. SAFETY OF ANTIPERSPIRANTS

The Panel addressed the question of safety of antiperspirants in its discussion of aerosol drug and cosmetic products containing zirconium in the FEDERAL REGISTER of June 5, 1975 (40 FR 24328). In that discussion it was pointed out that since the benefits derived from the use of OTC antiperspirant products are not large, there must be little or no risk associated with their use to be acceptable for OTC use. As was also pointed out in that discussion, there is a substantial potential difference in the kinds of adverse reactions that might result from the same ingredient, depending upon its route of application.

Antiperspirants are applied in two chief ways: one, directly to the skin in the form of a lotion, cream, stick, or roll-on; two, in the form of a spray, delivered either via a pressurized propellant system or by way of a mechanically actuated spray system.

1. *Systemic safety of antiperspirants applied directly to the skin.* Because of the relatively impermeable properties of the skin to metallic salts and complexes, there is no evidence to suggest that the direct application of antiperspirant products to intact skin has been associated with systemic toxic effects (Ref. 1).

Percutaneous dermal toxicity test have been performed on animals for a great number of antiperspirants. The reported results indicated no ill effects on the animals (Refs. 2 through 12).

2. *Skin safety of anitperspirants applied directly to the skin.* There is little doubt, however, that some users of antiperspirant products have experienced local cutaneous irritation as a result of using those products. In its discussion of aerosol drug and cosmet-

ic products containing zirconium, published in the FEDERAL REGISTER of June 5, 1975 (40 FR 24330), the Panel concluded that such reactions constitute an acceptable risk. The statement made at that time about locally applied zirconium salts applies similarly to the whole range of antiperspirant ingredients:

1. *Adverse reactions.* These adverse reactions are ordinarily not serious and are reversible.
2. *Site of reaction.* These reactions occur locally at the site of application where they are to be expected, where they are visible, and where, once detected, they can be treated and the product discontinued.
3. *Incidence.* The reported prevalance of such adverse reactions is extremely low, of the order of 6 per million units sold.
4. *Body burden.* Because these are applied topically, the entrance of zirconium-containing particles into the body is reduced virtually to zero when the skin's barrier is intact.
5. *Effectiveness.* This topically applied antiperspirant is reasonably effective.
6. *Misuse.* The Panel recommends that adequate labeling be provided to warn against applying the product to open, broken or abraded skin where the skin's barrier is breached. But even if this warning is ignored by the consumer, and the product is misused, the Panel believes the consequences will not be unreasonably severe.

The Panel believes that the risks of the nonaerosolized product are inherent in the effective use of the drug and are therefore unavoidable; other topically applied, nonaerosolized antiperspirants give comparable adverse reactions. Overall, the impact of these adverse reactions on the health of the target population is not large; these reactions are ordinarily not serious; they are reversible; and their prevalance is low.

Further on in this report it will be noted that certain antiperspirant ingredients for direct skin application are classified as category III on the basis of safety. This designation is based partly on published reports characterizing some ingredients as more irritating than others and on the inadequacy of safety information about some others (See part III., paragraph B.3. below—Category III conditions under which the available data are insufficient to permit final classification at this time.)

None of the metallic antiperspirant ingredients have been reported to cause allergic contact dermatitis to any significant extent (Ref. 13), and, as noted above, antiperspirant-induced irritation appears to be readily reversible.

Antiperspirant ingredients have been blamed by some users for inducing papular or follicular eruptions in the axillae, and it seems clear that certain individuals find themselves unable to use these products (Ref. 14). These eruptions are not treated as agent-specific conditions in standard dermatologic texts. In the judgment of the Panel, such eruptions may be secondary to a nonspecific irritation of follicular openings induced by these products. Individuals who have this difficulty appear able to associate the eruption with antiperspirant use clearly enough to discontinue use of the products. Long-term effects of such reactions do not appear to be a problem.

The dermatologic conditions that are indigenous to the axillae include hidradenitis suppurativa, Fox-Fordyce disease, and seborrheic dermatitis. While the use of antiperspirant products is frequently interdicted in those diseases, current medical thought does not implicate antiperspirants as significant initial etiologic agents.

3. *Microbiological safety considerations*—a. *Contaminants.* Since antiperspirants are often applied to the skin of the axilla after shaving, it is important that they should not contain pathogenic organisms that might cause infection of abraded skin. The limited microbiological information available currently is not adequate to establish that the antibacterial activity of aluminum chlorhydrates and other active antiperspirant ingredients is sufficient to suppress growth of all contaminants. The Panel is aware that there is a very low incidence of axillary infections attributed to the use of antiperspirants by the user. The Panel's judgment is that the antiperspirant ingredients placed in Category I and Category III have been so widely used with so little evidence of infection that they can be accepted as generally recognized as safe with respect to the question of infection.

If antiperspirants with new active ingredients are introduced in the future, they should be tested to determine whether such organisms as *Candida, Pseudomonas spp, Staphylococcus aureus* or *Streptococcus pyogenes* can survive or multiply in them on repeated challenge in use. It is possible that these organisms can in fact penetrate through sites of abrasion or cuts caused by shaving and set up foci of infection.

b. *Suppression of normal flora and possible compensatory multiplication of resistant organisms.* The deodorant action of antiperspirants now widely used appears to result from inhibition of bacteria normally present in the axilla. (See part II., paragraph E.4. above—Mechanisms of the deodorant effects of antiperspirants.) This suppressive action is far from complete and is commonly overridden by the organisms so that underarm odor develops after some hours. Probably, it is because this bacterial suppression of normal flora is only limited and partial and that other, more resistant, transient organisms are kept from multiplying and possibly causing infections. We are not aware of any evidence that infections have occurred on this basis.

If antiperspirants with new active ingredients are introduced in the future, they should be evaluated with respect to disturbances of the normal flora that might lead to infection due to secondary growth of organisms capable of causing infection.

4. *Safety of aerosol products.* The majority of safety concerns over antiperspirants involve those that are applied as sprays. In brief these concerns can be categorized as relating to (a) the added body burden which might be incurred by inhaling the antiperspirant product over many years, (b) problems with various propellant systems, and (c) other agents, such as talc, which are added to spray preparations to impart cosmetic properties to the products.

a. *Safety of long-term use of aerosolized antiperspirants.* The most popular method of applying antiperspirants to the axillae and other parts of the body is by aerosol-generating systems. The aerosol particles generated by these systems should have sufficient velocity to be directed at, and impact on, the target site. The particles must have adhesive properties so that they will stick to the skin on impact.

In the early 1960's pressurized aerosol delivery systems for antiperspirants were introduced into the market (Ref. 15). This method of applying the antiperspirant rapidly became the most popular dosage form. The consumer preferred the convenience in application of the antiperspirant and the feel of the material which impacted on the axillae.

The pressurized systems that are presently being marketed make use of liquified compressed gases (propellants) to discharge the antiperspirant formulation. The propellants by virtue of their high vapor pressure expel the formulation from its container as a fine particulate spray. The particle size distribution of the aersol produced by the escaping propellant depends on a number of formulation factors, including the pressure inside the container and the dimensions of the actuator chamber (Refs. 16 and 17). The actuator is the button which the consumer presses to activate the valve system, which in turn permits the contents of the container to be released. This button and the valve system influence not only the spray pattern of the generated aerosol but also the particle size distribution.

There are two general classes of antiperspirant pressurized aerosol formulations now marketed. In one case the antiperspirant is discharged from the container as fine solid particulates (suspension formulations) and in the other it is dissolved in fine droplets of

the spray. The former of these aerosol sprays has a cosmetic appeal to the public because it does not leave a moist feeling on the skin.

Although the majority of the aerosolized antiperspirant produced by these devices impacts on the area of skin toward which the spray is directed, there will always be some material which will reach the breathing zone of the user. The divergent nature of the spray will place some of the aerosol directly in the air. A substantial amount of turbulence is produced at the target site by the escaping propellant gases which hinders the impaction of some of the finer particles. These particles are carried away by the gases to the immediate envionment of the area sprayed. Some particles will also reach the environment by rebounding after hitting the skin (Ref. 18). The aerosol particles reaching the air about the user can remain suspended for relatively long periods of time.

The public is not able to purchase self-pressurized spray packagess of antiperspirants. There are two types available; the squeeze bottle and the spray pump (Ref. 19). The former of these consists of a soft squeezable plastic container which when compressed forces the antiperspirant formulation through a small orifice where it is broken up into coarse droplets. In general, the applied force is not sufficient to obtain as finely a dispersed aerosol as is derived from propellant pressurized systems. Spray pumps on the other hand do produce a fine spray of the formulation which can closely duplicate that obtained with pressurized systems (Ref. 19). These pumps are primed by depressing a spray actuator which forces the formulation through the nozzle.

The sprays produced by these systems will not experience the same degree of turbulence when they impact on the skin as the propellant devices. This means that a somewhat greater fraction of the aerosol spray will impact on the target site and less will escape to the environment than is the case with the propellant systems. The Panel was not provided with data that would conclusively rule out any potential inhalation risk for these products. For this reason, their safety is judged by the same standards as those for the pressurized aerosol systems.

Aerosol particles can invade the body through inhalation. Whether they will be deposited in or be exhaled from the respiratory tract depends on their physical characteristics and certain physiological parameters. Numerous depositon studies have been carried out to delineate the parameters which influence the degree and sites of deposition. These investigations have been summarized in a number of publications (Refs. 19, 20, and 21).

The most important fact in governing the deposition of aerosols in the respiratory tract is the size, shape, and density of the particles. It is customary to characterize aerosol particles in terms of their effective aerodynamic size (Ref. 20). The proposed deposition models suggest that particles with an aerodynamic diameter greater than 10 micrometers (um) will be deposited almost exclusively in the nose and mouth. The ability of aerosols to penetrate further into the respiratory system increases as the particle decreases below 10 um. Particles below 5 um can be deposited in the alveoli of the air-exchanging portions of the lung. Particle size data submitted to the Panel on commercial aerosol antiperspirants shows that most products produce a significant amount of particles which could deposit in all regions of the respiratory tract.

Particle characteristics alone do not determine the deposition site of aerosols. Individual variations that arise with aging, pathological processes, and nature of breathing (nose versus mouth) will influence the depositon (Ref. 20).

The fate of particles deposited in the respiratory system depend on the location of their impaction and the solubility of the particles (Refs. 21 and 22). Highly soluble particles will dissolve rapidly in the mucus where they deposit. Once dissolved the material will diffuse in the liquid milieu of the body. Many materials can be absorbed from all portions of the respiratory tract.

Insolube material impacting in the oral and nasal cavities will eventually be swallowed and pass through the gastrointestinal tract. When relatively insoluble particles deposit in the upper regions of the lung, they are usually removed by the mucocilliary escalator. The cilia move mucus and particles to the pharynx where they are swallowed or coughed up. In the deeper portions of the lung (alveolar region) where cilia do not exist, insoluble particles may be engulfed by motile alveolar macrophages. These particles may be carried to the ciliated region of the lung for removal or they may remain in the alveolar regions. Phagocytized particles may be absorbed into the interstitium where they can be lodged for long periods or removed to the lymphatic system.

A most important factor in the consideration of the safety of relatively insoluble aerosol particles is the time it takes for the particles to be removed from the lung. This is known as the retention or clearance time. The retention times for relatively insoluble particles deposited in the ciliated portions of the lung are generally on the order of minutes or hours. In contrast, alveolar clearance of these insoluble materials requires a much greater time, with half lives on the order of weeks and months. Where the particles have penetrated the tissue of the pulmonary space, it may take years to clear them (Ref. 23).

Though aluminum salts are soluble in acidic solutions, they will form insoluble aluminum hydroxides as the pH of the solutions is raised, usually above a pH of 5. Since the lung surfactant system is maintained at physiological pH (approximately 7.4), the majority of aluminum antiperspirant material which reaches the lung probably will be converted to water insoluble salts. Aside from the hydroxides, aluminum salts most likely will form insoluble compounds with phosphates and carboxylic acids present in the lung. It is reasonable to believe that aerosol particles of aluminum antiperspirants that impact on the walls of the respiratory tract will behave in the same manner as other insoluble materials.

Recent inhalation studies with aluminum chlorhydrate aerosols provide some indication of the retention times that could be expected. It was shown that the overall clearance time (time it takes for the lung concentration of aluminum to return to normal background burden) of aluminum from the lungs of hamsters was in excess of 2 months after a single exposure to an aerosol of an aluminum chlorhydrate (Ref. 18). As a result of the long retention time, repeated daily exposures bring about accumulation of aluminum compounds in the lung (Ref. 24). The buildup of aluminum in the lungs of animals which are chronically exposed to aerosolized aluminum chlorhydrates was demonstrated in a series of inhalation studies with rats and guinea pigs (Refs. 25 and 26).

The average user of aerosol antiperspirant products would be expected to apply them at least once daily for a significant portion of his/her life. This type of use could very well lead to an accumulation of the insoluble forms of aluminum in the deeper portions of the lung. The actual burden on the lung would depend on the individual's clearance rate of the respirable material and the amount of respirable particles that reach the breathing zone. If the retention time is on the order of months, as was found in animal studies, it might take years of continual use before the steady state concentration in the lung is achieved (Ref. 27).

There are two types of inhalation testing procedures that have been routinely carried out to assess the safety of aerosol antiperspirant products. One is the standard acute Draize Test (Ref. 28), and the other, the Federal Hazardous Substances Act inhalation

tests (16 CFR Part 1500). These acute tests can provide the LC_{50} (the aerosol concentration that is lethal for 50 percent of the test animals) for a particular material, but they do not foretell the safety of a product which is to be used daily on a long-term basis.

In two acute inhalation studies (Refs. 29 and 30) an assessment was made of the no effect/effect toxic level for an aerosolized aluminum chlorhydrate. Hamsters and rabbits were exposed to varying concentrations of particles with aerodynamic sizes of less than 10 um. This assured maximum accessibility of the particles to the lung. Granulomatous lesions of the lung were found at extremely high aerosol concentrations. The no effect level (concentration of aerosol where no adverse pathology could be detected) was found to be at a much greater concentration than would be experienced under normal human use. The most that can be concluded from these studies is that there is essentially little toxicological risk associated with short-term use of aerosol aluminum chlorhydrate products.

The other test procedure is a subchronic 90-day inhalation study. In the subchronic studies submitted (Refs. 2, 6, 8, 31, 32, and 33), the animals were exposed to a variety of aerosol concentrations, usually on a daily basis for the duration of the study. The aerosol concentrations to which the animals were exposed were always significantly greater than a human would be exposed to under normal use. A variety of animals has been used in these studies, including the cynomologus monkey, rat, mouse, hamster, and rabbit. During the course of the study the animals were watched for any abnormal behavior. At the conclusion of the study the animals were sacrificed and a thorough pathological examination, both gross and microscopic, was carried out.

The results of these subchronic studies suggest that the amount of material inhaled under normal use should not be harmful. However, no product data were submitted to demonstrate the safety of long-term use (years).

The Panel spent considerable time deliberating whether the subchronic 90-day inhalation test is an accurate predictor of what might be expected for long-term human use. In a previous report issued by the Panel on aerosolized zirconium-containing antiperspirants, published in the FEDERAL REGISTER of June 5, 1975 (40 FR 24328), the adequacy of the 90-day test period was questioned.

If one is to assess the potential of a material to produce granulomatous or fibrotic lung disease, it is necessary to carry out lifetime animal studies. These diseases, in humans, can take years to develop. The Panel has concluded that long-term safety should be measured for all aerosol antiperspirant materials to ensure their lack of pulmonary disease potential. The disease potential for aerosolized aluminum chlorhydrate compounds has been very well assessed for acute exposures. It has not been measured to the satisfaction of the Panel for long-term repeated exposure. Since there are other dosage forms for applying aluminum chlorhydrates to the axillae which are at least as effective as aerosol systems and have a zero potential pulmonary toxicological risk, the Panel is requiring that a long-term repeated inhalation study be carried out on aerosol formulae of these compounds. (See part III, paragraph D.2. below—Guidelines for tests to be done for aerosolized antiperspirant sprays to be classified as Category I.) All aerosol antiperspirant products have been classified in Category III until such time that the proposed studies are complete. The studies should be completed within 5 years after publication of the final monograph. Interim reports of these safety studies should be filed with FDA.

Further support of the Panel's decision to require long-term inhalation toxicity studies of 2 years' duration is found in two investigations on an aluminum chlorhydrate that are now in progress. In one of these, the animals are being exposed to three concentration levels of the material for 6 hours a day, 5 days a week (Refs. 25 and 26). The aerosolized material in the exposure chambers has an average particle size diameter between 2 and 3 um which assures access of the material to the deeper portions of the lung. After 1 year of exposure, granulomatous conditions were observed in the lungs of all animals sacrificed, even those exposed to the lowest concentration level (0.25 milligram (mg) of aluminum chlorhydrate per cubic meter). The other investigation is assessing the toxicological effects when the lung burden of aluminum is maintained at a steady-state concentration over an extended period of time (Ref. 24). The investigators suggest that the lung aluminum concentration used is approximately 100-fold greater than would be expected for a heavy user of antiperspirant aerosol products containing aluminum chlorhydrates. The lungs of the test animals sacrificed after 9 months exhibited distinct histopathology. Focally prominent accumulations of alveolar macrophages and mild alveolar wall thickening were observed. In both studies the most distinct pathological changes appeared after 6 months of exposure, which is significantly longer than the test period of the subchronic inhalation test.

Although these investigations suggest that aluminum chlorhydrates have a potential for producing pathological alterations of the lung, their designs are such that it is difficult to extrapolate the finding to normal human use of commercial aerosol products. The studies proposed by the Panel should delineate the toxicological risk of antiperspirant aerosol products. There are two approaches which the Panel could use to evaluate this risk. The first approach would maintain a constant lung burden in the animal throughout the duration of the test. The other approach would not maintain a constant lung burden, but would seek to exaggerate expected lung burden which would be obtained under normal human use. This exaggeration would be obtained by a graded series of high-exposure concentrations. The Panel has selected the latter approach for several reasons: (1) It does not require the prior delineation of pharmacokinetic parameters which would be required in the first approach; (2) the method adopted would provide for the toxicological assessment of the varying conditions of exposure that are likely to be experienced; and (3) the dose exaggeration included in this test procedure would ensure that the animal lung burden will exceed that experienced during long-term human use of aerosol antiperspirant ingredients. Among the parameters taken into account in designing the protocol, the Panel considered the normal time of exposure, the presence of formulation excipients, and the particle size distributions produced by the aerosol devices. The long-term repeated inhalation study will include preparations whose inhalation characteristics are comparable to those of the marketed formulations which have the greatest potential for pulmonary deposition. Once these reference formulations have been identified, the respirable aluminum concentrations generated in the breathing zone of human users will be considered the temporary upper limit for marketed aerosolized aluminum salt antiperspirants. At the conclusion of the long-range inhalation study, this upper limit will be adjusted, if necessary, to relate to the highest test level which will have been judged to be a no-effect level (defined as that level which produces no toxicologically significant product-associated pathology in the judgment of pathologists). For all aerosolized aluminum salt antiperspirants, the conformance to these respirable aluminum "upper limit" standards will be measured under the use conditions specified below in the testing guidelines.

The technology now exists for the formulation of suspension-type aerosol antiperspirant systems which have a

small fraction of solid particulates below 10 um (Refs. 34 and 35). Particle size analysis of some antiperspirant aerosols generated with this type of active ingredient indicates that they would have a greatly diminished potential for pulmonary deposition over the typical aerosol materials generally marketed. It now appears feasible to manufacture solid particulate aerosol sprays with 10 percent or less of the particles below 10 um. The Panel recommends that all marketed suspension-type aerosol systems be formulated to emit at least 90 percent of their particles over 10 um in size as obtained from impaction measuring devices.

b. *Problems with safety of propellants.* Pressurized antiperspirant systems make almost exclusive use of chlorofluorocarbon (F.C.) propellants. They are saturated organic compounds which contain both fluorine and chlorine. The ones which are most commonly employed in antiperspirant formulations (Ref. 36) are trichloromonofluoromethane (F.C. 11), dichlorodifluoromethane (F.C. 12), and dichlorotetrafluoroethane (F.C. 114). In the past decade a large number of toxicological studies have been carried out on these compounds. The results of these studies have been summarized in a number of recent publications (Refs. 36, 37, and 38). These compounds have been found to be cardio-toxic, but only when the concentration level of the propellant gas is many times greater than that which would be achieved under normal use of commercial household products. The concentration required to produce serious toxic effects is reached when aerosol product uses are perverted. In the Panel's opinion the scientific data indicate that when aerosol antiperspirants are properly used, the propellants will not pose any undue risk to the user.

However, the Panel recognizes that because of the environmental effects of chlorofluorocarbons, FDA published proposed regulations in the FEDERAL REGISTER of May 13, 1977 (42 FR 24535), which were made final on March 17, 1978 (43 FR 11301) concerning the use of these agents as propellants. These regulations prohibit the use of these agents as propellants in aerosolized products except for specified essential uses.

c. *Problems with the safety of talc in aerosol antiperspirants.* Talc is incorporated into a number of propellant aerosol antiperspirant formulations because of its cosmetic appeal. It serves as a dusting powder in this capacity. The Panel's concern about the presence of talc in these products stems from reports that certain talc constituents will produce toxicological responses when inhaled over extended periods (Refs. 39 and 40).

An open session of the Panel was held on July 9, 1975 to discuss this subject (Ref. 41). Presentations were made by a number of experts on talc chemistry and toxicology. In addition, the Panel received a submission from the Cosmetic, Toiletry and Fragrance Association, Inc., on this matter (Ref. 42).

Talc is a magnesium silicate which is sometimes found to contain two groups of asbestos minerals: the serpentine and amphibole groups. It is these asbestiform minerals which are associated with the toxic effects of talc (Refs. 39 and 40). The analytical procedures now used to detect asbestiform fibers in talc are sensitive to 0.5 percent (Ref. 42). The talc used in antiperspirant products is devoid of any asbestiform fibers when determined by this procedure.

After studying the scientific literature and the data presented at the open session, the Panel concluded that there is virtually no risk from asbestos in aerosolized talc in the amounts found in antiperspirant products if the material is determined to be free of asbestiform fibers by the Cosmetic, Toiletry and Fragrance Association, Inc., procedure (Ref. 42). This analytical procedure should be used until more sensitive techniques are available. It is important that further work be undertaken to set limits for asbestiform fibers and to reduce the limit of detection to as low as possible from the now accepted 0.5 percent.

The Panel did not consider the safety of talc in products other than antiperspirants.

REFERENCES

(1) Blank, I. H., M. Moreland, and R. K. Dawes, "The Antibacterial Activity of Aluminum Salts," *Proceedings of the Scientific Section of the Toilet Goods Association*, 27:32-36, 1957.

(2) OTC Volume 140001.

(3) OTC Volume 140006.

(4) OTC Volume 140009.

(5) OTC Volume 140010.

(6) OTC Volume 140011.

(7) OTC Volume 140015.

(8) OTC Volume 140020.

(9) OTC Volume 140021.

(10) OTC Volume 140022.

(11) OTC Volume 140023.

(12) OTC Volume 140024.

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

(14) List of consumer complaint files. Copies are included in the Administrative Record.

(15) Rubino, A. M., "The Development of Antiperspirants," *Manufacturing Chemist and Aerosol News*, pp. 50-64, November 1971.

(16) Sanders, P. A., "Principles of Aerosol Technology," Van Nostrand Rheinhold Co., New York, 1970.

(17) Sciarra, J. J. and L. Stoller, "The Sciences and Technology of Aerosol Packaging," John Wiley and Sons, New York, 1974.

(18) Aerosolized Consumer Products Project Staff, "Inhaled Biology of Propelled Cosmetic Substances," Annual Report, Inhalation Toxicology Research Institute, Lovelace Foundation, pp. 1-45, 1976.

(19) Iannacone, A., "'Non-self-pressurized' Spray Systems," *Cosmetics and Perfumery*, 90:43-44, 1975.

(20) Hatch, F. F. and P. Gross, "Pulmonary Deposition and Retention of Inhaled Aerosols," Academic Press, New York, 1964.

(21) Brain, J. D. and P. A. Valberg, "Models of Lung Retention Based on ICRP Task Group Report," *Archives of Environmental Health*, 28:1-11, 1974.

(22) Morrow, P. E., "Alveolar Clearance of Aerosols," *Archives of Internal Medicine*, 131:101-108, 1973.

(23) Transcript of Open Session, December 17, 1974.

(24) Damon, E. G. et al., "Effects of Repeated Inhalation Exposure of Hamsters to Aerosolized Aluminum Chlorhydrate," Inhalation Toxicology Research Institute, Lovelace Foundation, pp. 325-330, 1976.

(25) Cavender, F. L., "Chronic Inhalation Toxicity of Aluminum Chlorhydrate," Draft of paper submitted for publication is included in OTC Volume 140065.

(26) Steinhagen, W. H., F. L. Cavender, and B. Y. Cockrell, "Six Month Inhalation Exposure of Rats and Guinea Pigs to Aluminum Chlorhydrate," Draft of unpublished paper is included in OTC Volume 140065.

(27) Jones, R. K., Letter to G. E. Thompson, FDA, October 3, 1975, copy is included in OTC Volume 140065.

(28) Draize, J. H., A. A. Nelson, S. H. Newburger, and E. A. Kelley, "Inhalation Toxicity Studies of Six Types of Aerosol Hair Sprays," *Proceedings of the Scientific Section of the Toilet Goods Association*, 31:28-32, 1959.

(29) Hardy, L. B., "Dose-Response Profile for Aluminum Chlorhydrate," Presentation to Open Session, December 17, 1974, Draft of presentation is included in OTC Volume 140065.

(30) Drew, R. I. et al., "Inhalation Studies With A Glycol Complex of Aluminum-Chloride-Hydroxide," *Archives of Environmental Health*, 28:321-326, 1974.

(31) OTC Volume 140005.

(32) OTC Volume 140007.

(33) Giovacchini, R. P. and L. B. Hardy, "Pulmonary Granulomatosis and Aerosolized Axillary Products," *CTFA Cosmetic Journal*, 5:11-15, 1973.

(34) Rubino, A. M., "'Microspherical Powder' Aerosol Antiperspirant Systems," *Aerosol Age*, 19:21-25, 1974.

(35) Siciliano, A. A., Letter to Dr. Eli Shefter, June 10, 1977, Copy is included in OTC Volume 140065.

(36) Aviado, D. M., "Toxicity of Propellants," *Progress in Drug Research*, 18:365-397, 1974.

(37) Giovacchini, R. P., "Aerosols: The Safety Issues Reviewed," *CTFA Cosmetic Journal*, 7:4-16, 1975.

(38) "FDA Reports on Pressurized Consumer Spray Products," February, 1975, Copy is included in OTC Volume 140065.

(39) National Research Council Committee on Biologic Effects of Atmospheric Pollutants, "Asbestos—The Need for and Feasibility of Air Pollution Controls," National Academy of Sciences, Division of Medical Sciences, Washington, DC, 1971.

(40) DHEW, "Occupational Exposure to Asbestos," National Institute of Occupational Safety and Health, 1972.

(41) Transcript of Open Session, July 9, 1975.

(42) OTC Volume 140062.

H. EFFECTIVENESS OF ANTIPERSPIRANTS

1. *General discussion.* The need to assure the effectiveness of OTC drugs has been underscored by recent Congressional decisions and is a major reason for the present OTC review. The average person expects the OTC drugs he/she buys to be safe. He/she purchases them for the drug manufacturers' promises of effectiveness and usually takes their safety for granted. The manufacturers' responsibility clearly does not end once its product is safe; its product also should do what the manufacturer claims it will do. This dual performance of OTC drugs is emphasized in the FDA charge to the Panel that the benefit to risk ratio of antiperspirant drug products be considered.

Americans spend more than ½ billion dollars annually on products claiming to reduce axillary odor and perspiration. These include a wide variety of antiperspirants, deodorants, and deodorant soaps. It is probable that relatively few consumers give much thought to how these products accomplish their purpose or what their limitations may be. It appears that many people are unaware of the distinction between antiperspirants and deodorants and often use antiperspirants expecting deodorant action or vice versa (Ref. 1).

The Panel has been made aware of the confusion about the use of these products and their limitations (Ref. 2). It feels that it is in the public interest to discuss these issues fully so that the individual's decision to use them may be an informed one.

Axillary odor and perspiration are closely interrelated phenomena. (See Part II, paragraph E. above—Axillary Odor.) Because of the confusion about the use and purpose of anitiperspirant-deodorant products, it is helpful to distinguish between the purposes they are intended to serve.

OTC antiperspirants are designed primarily to reduce underarm (axillary) wetness. They are classified legally as drugs because their mode of action affects a body function, namely, eccrine sweating. Deodorants are designed to reduce axillary odor. Since this is considered a nontherapeutic purpose and a function of the body is not considered to be altered, they are classified as cosmetics. Many OTC antiperspirant drug products claim to perform both functions and indeed may do so. Some deodorant cosmetics may also reduce wetness, but may not carry a label claim to this effect.

The consumer who desires to know whether a given product acts as an antiperspirant, as a deodorant, or as both is not helped by these legal classifications or by current labeling practices. He/she really should know what specific active ingredients are present and be knowledgeable about their probable effects.

2. *Deodorant effectiveness of antiperspirants.* Laboratory studies indicate that both eccrine and apocrine sweat are sterile and odorless at the time of secretions (Ref. 2). The odor is produced later through the action of bacteria on primarily the apocrine sweat, which is rich in organic material and is an ideal substrate for bacterial growth. The far more abundant eccrine sweat, the source of axillary wetness, is a highly dilute water solution and has been shown to be much less important as a source of axillary odor (Ref. 3). However, the moisture from eccrine glands probably promotes odor production indirectly in two important ways. The small amount of sticky, oily material from the axillary apocrine glands is dispersed over a wider surface. Secondly, the moisture in the warm axillary vault completes an ideal environment for the rapid growth and proliferation of the resident bacteria feeding on this organic material. Axillary hair also has been found to promote the development of odor (Ref. 3). It is thought that axillary hair acts as a collecting site for apocrine sweat and increases the surface area available for bacterial proliferation.

These findings several obvious ways to reduce or control axillary odor: (a) Reduce apocrine sweating in the axillae; (b) remove the secretions from both types of sweat gland as quickly as practicable; (c) impede bacterial growth.

Of these, there can be little doubt that adequate personal hygiene including regular, effective bathing is the primary means of controlling both bacterial growth on skin and body odor. The effect of shaving the axillae is also quite helpful. In women who shave regularly there is a markedly reduced axillary odor (Ref. 3). Unlike eccrine glands, the apocrine glands are indifferent to ordinary thermal stimuli, but respond to emotional stress such as fear, anger, and strong pain and also to mechanical stimulation such as a mild stroking of the skin. Although the quantity of apocrine sweat produced is very small, there is no known OTC product that can eliminate it or indeed that has any apocrine antiperspirant effect.

Antiperspirant which are designed for the reduction of eccrine sweating might conceivably be capable of reducing odor by drying the axilla and creating arid and less favorable conditions for bacterial growth. However, commercially available OTC antiperspirants do not provide substantially more than a 20 to 40 percent reduction in axillary wetness. It is very doubtful that this limited reduction in wetness could in most individuals result in appreciable odor inhibition. However, some of the active ingredients in current OTC antiperspirants (in particular aluminum chlorhydrates and aluminum chloride) possess a degree of anitbacterial activity and may work as deodorants (Ref. 4). (See part II, paragraph E.4. above—Mechanisms of the deodorant effects of antiperspirants.)

The application of a deodorant is not substitute for cleansing, and deodorant use should follow adequate bathing. Some deodorants do not contain ingredients which affect bacterial growth. They depend entirely on odor substitution; that is, their perfume temporarily masks a disagreeable odor with a more pleasant one. Other deodorant products contain antimicrobial chemicals which are intended to reduce the microbial flora of the skin surface (e.g., deodorant soaps).

Deodorancy is considered a cosmetic claim and is a concern of the Panel only so far as labeling claims of deodorancy appear on antiperspirant products. Since these types of data were not requested in the call for data, full submissions to substantiate deodorant claims were not made.

From the data submitted on deodorancy, the Panel is satisfied that the submitted compounds of aluminum and zirconium that are effective as antiperspirants also appear to be effective as deodorants. This conclusion is based on data submitted by industry on "sniff tests" carried out with a representative range of products tested in the axilla (Refs. 5 through 17). Since the deodorancy is largely dependent on suppression of bacterial growth, washing the axilla to remove apocrine and eccrine secretion and desquamated epithelial debris is essential to achieving optimal deodorancy effectiveness. The Panel chooses not to be concerned with comparative deodorancy claims.

If new antiperspirant products or ingredients are reviewed for deodorancy, data on suppression of bacteria in the axilla should be a part of the data considered and should be correlated with assessments of odor reduction.

3. *Antiperspirant effectiveness of antiperspirants.* Eccrine sweating is a perfectly normal and often an essential part of the body's thermoregulatory system. Eccrine sweat glands are distributed in great numbers over the entire body surface (over 3 million on the average adult). Normally, these glands become active under conditions of thermal stress, i.e., (a) when the environmental temperature becomes high, (b) when internal heat is produced which must be eliminated (as in muscular exercise), and (c) when other mechanisms of heat loss such as air convection or thermal radiation are prevented. The cooling of the skin by

the evaporation of this moisture (and thereby cooling the circulating blood in the skin's blood vessels) is often the only effective way of maintaining a proper constant body temperature.

The axillary sweat glands and also those of the palms and soles do not appear to be essential to the proper functioning of this thermoregulatory system. The palms and soles in most individuals react only weakly or not at all to thermal stimulation (Refs. 18 and 19), and the sweat from the axillae usually cannot readily evaporate. Perceptible underarm wetness is the result of two processes—the amount of sweat produced and the rate of evaporation.

In certain specific regions of the body (palms, soles, axillae, and forehead) eccrine glands respond to emotional or sensory stimulation such as the pain produced by touching a hot object, and in some individuals the gustatory stimulation provided by eating spicy food. In contrast to thermal sweating, which begins only after a latent period, emotional or sensory sweating commences immediately and ceases immediately on withdrawal of the stimulus.

Available OTC antiperspirants are capable of reducing underarm wetness to some degree. The range of effectiveness (average percent sweat reduction) of OTC antiperspirants in laboratory hotroom tests submitted to the Panel is given below:

RANGE OF AVERAGE PERCENT SWEAT REDUCTION OF OTC ANTIPERSPIRANTS

Dosage form	Average percent reduction
Aerosols	20-33
Creams	35-47
Roll-ons	14-70
Lotions	38-62
Liquids	15-54
Sticks	35-40

No OTC antiperspirant product can eliminate wetness completely, but the partial reduction that can be achieved has been shown to be 20 to 40 percent in most tests.

The mechanism of antiperspirant action has not yet been established. It is possible that different active ingredients act in different ways. (See part II. paragraph F. above—Pharmacology of Antiperspirants.) The Panel has found no evidence that these products are harmful to the sweat glands. Completely normal axillary eccrine sweating is resumed usually within a week after antiperspirant use is discontinued.

In summary, the eccrine sweat glands of the axillae (and the forehead) are unique in that they can be stimulated both by thermal and emotional stimuli. Sweating in the axillae is not essential to the thermoregulatory function, and the onset, amount, and duration of sweating are highly variable factors dependent on the type of stimulus, its intensity, and the pattern of individual response. Axillary eccrine sweat can be reduced but not eliminated by the use of OTC antiperspirants. The Panel did not receive sufficient data to support a claim of activity for these OTC products and ingredients on body parts other than the axillae. Therefore, effectiveness in the axillae should not be extrapolated to signify effectiveness elsewhere on the body.

The effectiveness (percent reduction values) of most aerosolized OTC antiperspirant products containing an aluminum chlorhydrate, the most widely used active ingredient, falls between 20 and 33 percent. Variability in individual response, test protocols, data evaluation, test subject selection, method of administration, and dosage form and differences in formulation are some of the factors which contribute to this broad range of effectiveness. A summary of pooled percentage reduction data from submissions to the Panel is given in the table above. These include a variety of OTC antiperspirants containing different active ingredients. These data attest in particular to the very large role that variations in individual response play in antiperspirant effectiveness. One general conclusion which appears valid is that aerosolized versions of antiperspirants are generally not as effective as the other dosage forms. It is important to recognize that these numbers are averages from tests and that individual responses are far more variable.

The effectiveness range for aerosolized aluminum chlorhydrates can be restated by saying that an individual test subject using such an antiperspirant product may be expected to sweat with 67 to 80 percent efficiency rather than his normal 100 percent. Drawing upon the analogy of a "leaky raincoat," critics of currently available antiperspirants challenge the effectiveness of a formula that permits up to 80 percent of the perspiration to go unchecked.

The CTFA has argued against this view in its submission to the Panel (Ref. 20). This group states that the purpose of an antiperspirant is to reduce sweating below a critical level where "* * * frank wetness perceivable to the consumer begins to develop" and not necessarily totally to inhibit sweating. They contend that an antiperspirant effective even at the 20 percent level may well achieve this result and thereby prove beneficial to the consumer.

The Panel agrees in principle that total inhibition of axillary sweating is probably neither necessary nor desirable for an effective antiperspirant. The perception of a beneficial effect by an individual using an antiperspirant under normal everyday conditions is the desirable goal.

Antiperspirant manufacturers have universally adopted objective gravimetric tests for antiperspirant effectiveness evaluations. These tests show that currently marketed antiperspirants are generally limited in the pharmacologic ability to reduce axillary sweating.

4. *Effectiveness testing of antiperspirants*—a. *General discussions.* Several different approaches have been used to estimate the extent of perspiration on human skin. The simplest of these have been visual, such as Minor's or Wada's method and its modifications (Refs. 21 through 24). All these techniques enhance the visibility of sweat droplets on the skin by their colorimetric reaction with various dyes. In general, the visual methods are only semiquantitative, but are simple and suitable for screening purposes or for studies aimed at determining individual sweat pore patterns. Another type of method permits accurate measurements of sweat output from small and precisely defined areas of skin (Refs. 25, 26, and 27). These methods usually involve a cup glued to the skin through which dry air or gas is passed, carrying any moisture to a suitable sensing device. The methods are quantitative and often permit measurement truly reflective of the pulstile nature of moderate sweating. But since these methods require complex equipment and considerable technical monitoring, they are not readily adaptable to a large number of subjects (Ref. 28). Other techniques using tiny micropipettes permit the entire sweat production from individual glands to be measured and analyzed (Refs. 29, 30, and 31). These measurements have provided the evidence for the presence of reabsorption phenomena in the sweat gland (Ref. 31) and are used routinely as diagnostic aids for the detection of fibrocystic disease.

b. *Gravimetric test.* The method used by most testing laboratories is based on gravimetric (weight) determinations of a constant fraction of the total sweat production from the axilla over a moderately long time interval (Refs. 32, 33, and 34). The test antiperspirant is used in one axilla of each subject, and the other is left as a control. Absorbent pads of known weight are placed in each axilla and kept in position during the test period. After this period the pads are removed, reweighted, and the reduction in sweat output of the treated axilla computed. This general procedure, with a few variants, is universally used by industry to test the effectiveness of marketed antiperspirants. The method is

adaptable to large numbers of human subjects, is fairly rapid, and requires a minimum of special equipment. It is claimed that this method adequately represents the real-life situation, produces a minimum of interference with the normal physiological response of the subjects, and produces quantitative results suitable for conversion into a meaningful percent sweat reduction figure (Refs. 26 and 33).

(1) *"Hotroom" vs. ambient conditions.* One of the major variants in the way this test has commonly been conducted is the nature, duration, and intensity of the sweat-provoking stimulus given. In the more widely used hotroom procedure, test subjects are placed in controlled temperature rooms maintained at 100±2° F and at approximately 35 percent relative humidity (Refs. 28, 35, and 36). The use of controlled hotroom conditions rather than ambient conditions is predicated on the belief that a controlled environment with the test subjects under constant supervision offers the best opportunity for accurate and reproducible estimates of percent sweat reduction. Since thermal stimulation of sweating requires a latent period before a constant sweat rate is established, the usual procedure is to allow a 40-minute warmup period after hotroom entry before beginning the actual sweat collection. Sweat rate data obtained during one or two successive 20-minute collection periods are usually used for evaluation. It is claimed that testing after the warmup period eliminates extreme variations in individual sweating patterns and provides more reproducible data for a more precise evaluation of antiperspirant activity (Ref. 28). The warmup period also provides time for an individual's emotional adjustment to the conditions of testing. Because of this and because the test subjects used have often been through the procedure previously, it is likely that the sweat stimulus is largely, if not entirely, thermal. The Panel cannot find any evidence to support the hypothesis that 100° F hotroom conditions provoke nonthermal sweating (Ref. 36), although it is clear that the thermal stimulus provided by hotroom conditions is more intense than that likely to be experienced by most individuals in normal activity.

The normal activity or ambient method does not utilize controlled temperature conditions or constant supervision of the subjects. Test subjects are fitted with absorbent pads designed to retain absorbed moisture for a period of several hours. They are then free to pursue normal activities during the test period, usually 3 to 5 hours (Ref. 36). At the end of this period the pads are removed and weighed again and the determination of effectiveness made in the standard way. The results are claimed to give reproducible percent reductions, comparable to the hotroom methods, and in some cases at least, capable of better discrimination between similar antiperspirant formulations (Ref. 36). In this procedure the sweat stimuli are likely to be of lower intensity overall and could be of both emotional and thermal origin. These conditions are closer to those expected in the normal use of antiperspirants than are hotroom conditions, and this is the principal advantage claimed for the method.

(2) *Data evaluation methods.* Different computational procedures are used to convert antiperspirant data to a percent reduction figure and these methods can give different estimates of antiperspirant effectiveness from the same set of data (Ref. 37). These different procedures appear to arise largely from two areas of disagreement: The nature of the statistical distribution of the responses of subjects to antiperspirants, and the proper method of controlling the "handedness" or asymmetry of the antiperspirant response.

There is evidence that axillary sweating is asymmetric (Refs. 28, 32, and 38) and correlated with locomotor dominance. Crossed locomotor and sudomotor innervation has been found in the forearm (Ref. 39) and asymmetric sweating on other body areas has also been reported (Ref. 40). Similar hemihidrotic effects due to posture or applied pressure were noted by Kuno (Ref. 18) and are factors that have to be considered in designing and conducting a test protocal (Ref. 38).

Majors and Wild (Ref. 35) and others attempt to control for the asymmetry in axillary sweating by adjusting the test data with the use of predetermined ratios. In effect, the test and pretest ratios of the amount of sweat from opposite axillae are compared instead of the absolute milligram amounts. Their basic formula for the calculation of percent sweat reduction is:

$$\text{Percent sweat reduction} = 1 - \frac{\left(\frac{T}{C}\right)_{\text{Test}}}{\left(\frac{T}{C}\right)_{\text{Pretest}}} \times 100$$

where T is the milligrams of sweat collected from the test axilla (treated or to be treated) and C is that collected from the control or untreated axilla. This calculation assumes that the radio of sweat output from opposite axillae is constant and independent of sweat rate or the time of collection. Majors and Wild also report that the response of test subjects to antiperspirants follows an essentially normal distribution, thus justifying the use of arithmetic means of estimating the most probable value of the parent distribution.

Wooding and Finklestein (Ref. 37) contend that the responses of test subjects to antiperspirants are positively skewed and therefore require log-transformation before parametric statistical techniques can be applied. This procedure results in using geometric rather than arithmetic means and usually increases the apparent percent sweat reduction values. These authors also contend that the use of pretest ratios is, at best, unnecessary and, at worst, can introduce a serious bias into estimates of percent sweat reduction. They suggest that such ratios are not found to be strictly constant and that asymmetry effects are best controlled by the use of a suitable experimental design (Ref. 37).

Comparison of results of analysis of antiperspirant data using these two approaches show differences of from 1 to 6 percent in estimates of percent sweat reduction (Ref. 37).

c. *Minimum requirements for antiperspirant effectiveness.* The definition of drug effectiveness provided by FDA regulations states in part that OTC drugs "* * * will provide clinically significant relief of the type claimed" (21 CFR 330.10(a)(4)(ii)). Furthermore, to establish effectiveness within a reasonable expectation, acceptable evidence which can withstand scientific scrutiny must be provided. The Panel is specifically instructed by its charge and by FDA regulations to exclude from consideration random experience and reports lacking the details which permit scientific evaluation.

The commonly used gravimetric tests of antiperspirant effectiveness reveal a wide range and a relatively low order of absolute effectiveness. Can tests of this kind provide a basis of evidence to establish a reasonable expectation for clinically significant relief of the type claimed? The Panel believes that they can if they are properly conducted and if appropriate standards governing the significance of the test data are established.

Gravimetric tests of antiperspirant effectiveness are not evaluations of clinical effectiveness. These tests simply measure the amount of sweat reduction under controlled conditions. In such a test, a product could achieve a statistically significant reduction in perspiration of only a few percent,

Such a low level of gravimetrically detected antiperspirant effect, though real, could be of trivial significance and would not ordinarily be perceived by the average user. To base a test for antiperspirant effectiveness entirely on the mere detection of a pharmacological effect of possibly trivial significance could not be said to provide the user with a reasonable expectation of "* * * clinically significant relief of the type claimed."

The basic drug claim made for antiperspirants is a reduction in underarm wetness. The Panel maintains that this claim contains the implied representation that the reduction in wetness is not trivial and will be perceptible to the user. That a perceptible antiperspirant benefit will accrue to the user of these products is often made explicit on the label in the form of statements of cosmetic puffery and in the advertising media. On this basis the Panel has determined that antiperspirant products, in order to be considered effective, attain or exceed a specific minimum level of effectiveness in gravimetric tests and that this level be such as to provide a reasonable expectation that an antiperspirant effect will be perceptible to the user under ordinary conditions of use.

In an effort to establish this minimum level of gravimetric effectiveness, the Panel requested information from a major independent test laboratory with 22 years' experience in the evaluation of OTC antiperspirant effectiveness (Ref. 41). The results on the correlation between hotroom gravimetric tests and user perception tests of antiperspirant effectiveness were presented at the Antiperspirant Panel meeting of August 1975.

The results indicated that the hotroom effectiveness of an antiperspirant required for a perceptible subjective effect is approximately a sweat reduction equal to 20 percent. Or stated in another way: A hotroom sweat reduction of at least 20 percent is required before an individual, who notices his own underarm perspiration, is able to locate correctly at least half the time, the underarm treated with antiperspirant. The data also suggested that individuals who exhibit higher measured effectiveness in hotroom tests experience a greater subjective antiperspirant effect.

The Panel considers that these data validate the use of a properly conducted hotroom test for antiperspirant effectiveness and that a 20 percent reduction in sweating achieved under hotroom conditions is sufficient to justify the use of the label claim "antiperspirant" as long as it is accompanied by a statement explaining the level of effectiveness that can be expected. (See Part III. paragraph B.1. below—Category I Labeling.)

Since a product with a sweat reduction of 20 percent promises only a barely perceptible antiperspirant effect, antiperspirants that achieve less than 20 percent effectiveness in hotroom tests are probably worthless in terms of consumer benefit. Therefore, the Panel has proposed a statistical criterion that provides a reasonable assurance that only antiperspirant products that are likely to give a 20 percent sweat reduction in at least half of the subjects will be marketed. The Panel recognizes that the statistical criterion is more stringent than those conventionally used, but it believes this is necessary to insure that truly ineffective products, with no perceptible user benefit, are not marketed.

The Panel believes that both the ambient method and the hotroom method are generally acceptable and can provide the necessary objective test data. The minimum standard of antiperspirant effectiveness developed above in connection with hotroom data applies equally well to gravimetric data using the ambient method.

d. *Factors affecting antiperspirant effectiveness evaluation.* In its review of the scientific literature and industrial submissions, the Panel has become aware of the many factors which can alter the effectiveness of OTC antiperspirants. Additional considerations determine the accuracy, dependability, and predictive value of tests used to assay antiperspirant effectiveness. The following factors were specifically considered by the Panel in its determination of the methods and data evaluation to be followed in the proposed effectiveness test:

(1) Currently marketed OTC antiperspirants appear incapable of totally inhibiting axillary sweating except, possibly, in rare, isolated cases. Any benefit to the average user therefore must be measured in terms of reduction in sweating rather than in terms of total sweat inhibition.

(2) On the basis of the best evidence currently available, antiperspirants which in hotroom tests give percent sweat reductions of approximately 20 percent or less exert no perceptible antiperspirant effect on the average user (Ref. 41).

(3) Minor variations in formulation can critically affect a product's antiperspirant activity (Ref. 35). The fact that a known active ingredient is present in proper concentration cannot, per se, be taken as a guarantee of effectiveness of the finished product. Higher concentrations of known active ingredients in poorly formulated products are often less effective than lower concentrations of active ingredients in well formulated products.

(4) Individuals are extremely varied in their response to antiperspirant materials. Some individuals do not respond at all to certain active antiperspirant formulations, but do respond to others. Even properspirant (increase in sweating) effects are observed when antiperspirants are used in some individuals (Refs. 35, 41, and 42). There are sizable variations in determinations in average percent sweat reduction values with small numbers of test subjects. To some extent this can be overcome by using larger numbers of test subjects, 30 or more (Refs. 35 and 41).

(5) Axillary sweating is affected by unilateral pressure applied to the body (Ref. 38). Leaning against a chair, crossing the legs, or using a bulky collection device in one axilla can all produce unilateral effects on axillary sweating. This effect can be controlled by proper management of the subjects and design of the test.

(6) Axillary sweating during an individual's normal activity is intermittent and is responsive to emotional stress, as well as thermal stimuli. Emotional responses are potentiated in a warm environment, and a greater amount of sweat is secreted (Ref. 38).

(7) No clear correlation between sweating rate and the effectiveness of antiperspirant materials has been established (Ref. 35). But it remains possible that effectiveness is modified by sweat rate (Ref. 38). Emotional stimuli are known to generate more rapid sweating than thermal stimuli (Ref. 43).

(8) Conventional gravimetric effectiveness tests do not control for race, sex, conditioning, acclimatization or season. All these factors are known to affect the responsiveness of eccrine glands (Ref. 44). Only the influence of sex difference seems to have been determined, and even though men are known to sweat more than women in response to a standard stimulus, no significant differences in their response to antiperspirants were reported (Ref. 34).

(9) Axillary sweating does not appear to be as readily inhibited by at least some topical antiperspirant materials as sweating on other body sites (Ref. 4). Test results that are to be used in substantiation of the effectiveness of axillary antiperspirants must originate from procedures using axillary test sites.

(10) Currently marketed antiperspirants are normally not effective immediately after application to the skin. Some appear to become effective after a few hours (Ref. 38); others require more time and repeated applications to achieve maximum effectiveness (Refs. 34 and 35).

(11) The mechanism of action of topical antiperspirants is not known. It cannot be assumed that the mechanisms of action of different active in-

gredients are identical. Data on the effect of sex difference, sweat rate, and other factors that have been obtained with unidentified antiperspirant materials or specific active ingredients cannot be generalized to apply to all antiperspirant materials.

(12) Differences between the two principal statistical methods for evaluating effectiveness do not appear to lead to serious differences in percent sweat reduction values (Refs. 28 and 35). The Panel is more concerned with the undisputed low overall level of measured effectiveness revealed by current tests and the predictive value of such tests for the population-at-large.

e. *Panel statements concerning effectiveness testing.* During its inquiries into the effectiveness of antiperspirant products, the Panel discussed two things that subsequently resulted in a pronounced difference of opinion among the Panel members:

(1) Although formulated with the same active ingredients, different antiperspirant products, especially those prepared for aerosol application, may vary widely in the percentage reduction in perspiration they produce (Ref. 35 and 41).

(2) Marketed antiperspirant products have been shown under test conditions to produce a reduction in perspiration that varies roughly from 20 percent to nearly 50 percent. At the same time, the Panel ascertained that the lower figure of 20 percent reduction in sweating is the lowest level at which most users would be subjectively aware that there was any antiperspirant effect at all from the product they were using. (Remember, however, that users apparently buy these products for both antiperspirant and deodorant effects, and there is not necessarily a correlation between the degree of effectiveness of these two actions).

Faced with this information, the Panel disagreed on what it should recommend to insure that marketed OTC antiperspirant products are effective.

The majority of the Panel (four voting members) felt that the facts warranted a requirement that even though an antiperspirant product was formulated with Category I (safe and effective) ingredients it should, in addition, be required to be tested as a product, to demonstrate proof of adequate effectiveness.

A minority of the Panel (two voting members) felt that even though antiperspirant products might vary in effectiveness, and might, in fact, be less effective than the recommended minimum levels, they should be allowed to remain on sale provided they were made with Category I ingredients.

f. *Antiperspirant effectiveness qualification test*—(1) *General discussion.* Because minor variations in formulation can alter the actual effectiveness of the product, the Panel has recommended that the effectiveness test be performed on the final product formulation regardless of the tests that may be carried out on the active ingredient in other forms or vehicles. The Panel recommends that a standard protocol be adopted.

It is a fact well known to the antiperspirant industry and testing laboratories that excipient ingredients added in the formulation of an antiperspirant product may seriously impede or even totally destroy the effectiveness of an otherwise active antiperspirant ingredient. This is not a rare circumstance, but occurs frequently with all forms of antiperspirant products. It occurs when special substances are added to aerosol formulations to prevent clogging of the spray nozzle. It occurs when emollients are added to enhance the cosmetic acceptability of powders, sticks, and roll-ons. And it occurs with aluminum chloride salt ingredients which are often buffered in formulations to reduce irritancy.

The effectiveness testing of antiperspirants in final product form has been the means by which manufacturers of these products monitor, assure, and improve the effectiveness of their products. Many of these products have been marketed in several versions which differ only with respect to the color and perfume ingredients which are present in very low concentrations and which do not materially alter the physical and chemical properties of the formula. They are not considered to have any material effect on antiperspirant activity. This can be contrasted to the interferences which have been reported to arise from the influence of other vehicle components. While such interferences are occasionally traceable to the presence of a particular excipient, they are generally not understood or predictable.

Product testing is the only way generally recognized by makers of antiperspirants to assure that the active ingredients remain active in the final product form available to the consumer.

Therefore, since antiperspirant active ingredients can and often do become ineffective when formulated, and since the mechanism of topically induced antiperspirancy is now unknown, and the effect of formulation on the final effectivensss of the purported active ingredients cannot be predicted, the Panel recommends that the final formulation of OTC antiperspirants be tested for effectiveness in the manner described herein and that the product must exceed the minimal standards set by the proposed effectiveness test or an acceptable equivalent test.

To qualify as effective in finished product form, an antiperspirant must meet or exceed the criteria established by the following test procedures and definitions.

This qualification requirement applies to all formulae except those variants which differ from a qualified formula only with respect to color and/or perfume ingredients.

A gravimetric test measuring the amount of axillary perspiration under either controlled hotroom or ambient conditions will be used. Multiple, independent testing is permitted provided that the evaluation of effectiveness is based on preset proper statistical analysis for a combined set of such experiments.

(2) *Protocol.* The test subjects will be required to abstain from the use of all antiperspirant materials for at least 1 week prior to pretreatment or treatment collections. Antiperspirants can have residual activity; a week or longer has been deemed sufficient for a washout period. The test subjects must be sufficiently representative in that the differences between the highest and lowest rates of sweating amongst the test subjects must exceed 600 milligrams/20 minutes/axilla.

When a large number of subjects were subjected to the hotroom conditions described below, differences in perspiration rate in excess of 600 milligrams/20 minutes/axilla were found. Information on the sweating rate will be obtained during pretreatment collections or by collections taken from the control axilla during treatment.

There are two generally accepted procedures for conducting antiperspirant tests. These are referred to as the hotroom and ambient condition tests. In the hotroom test the subjects are placed in a controlled environment which thermally stresses them to perspire. It has been found that temperatures around 100° F and humidities in excess of 35 percent will elicit sufficient axillary sweat from the subjects in reasonable lengths of time so that gravimetric measurements can be made of the axillary perspiration rate. The perspiration is usually collected on an absorbent material for a period of 10 to 30 minutes and weighed (Ref. 45). Care must be taken to insure that all factors which are known to influence axillary sweating and in particular those known to have a unilateral effect on sweating rate are properly controlled (Refs. 20, 33, 38, and 41). Aside from temperature and humidity, air movement and mental or emotional stimulation can influence sweating rate. There are some less well defined variables, such as the position of the trunk and extremities, which will produce unilateral effects (Refs. 18 and 38).

Ambient tests permit an assessment of antiperspirant activity of a formulation under normal use conditions. In these tests the subjects, after having the materials applied to the axillae, are allowed to go about their normal daily routines. Absorbent pads are placed in their axillae to collect perspiration. The pads usually collect sufficient perspiration for a gravimetric determination in 3 to 5 hours (Ref. 36).

A treatment will consist of the application of the product under evaluation to one axilla of a subject and the control formulation to the other axilla. The quantity of each formulation applied to all the test subjects must reflect the amount that a typical person would apply under normal use conditions. Half of the subjects will be randomly assigned to receive the test product under the left (L) axilla, leaving the other group of subjects to be assigned oppositely. If a pretreatment is desired to establish a control ratio of the left to right axillary sweating rate, it will consist of the application of the control product to both axillae. The control product will consist of a formulation devoid of the active ingredient and will be applied in the same manner as the product being evaluated. All treatment applications will be made once daily.

It is important that the number of treatments preceding the collections of axillary perspiration for evaluation be recorded. At least one daily treatment should be carried out before the test.

(3) *Data treatment.* Sweat reduction is defined for each subject by the formula:

$$\text{Percent sweat reduction} = \frac{C - T}{C} \times 100$$

where C is the raw milligram weight measure of moisture from the control axilla and T is the corresponding quantity for the test axilla. When pretreatment ratios are used appropriate modifications of this formula are acceptable.

A statistical analysis of the percent sweat reduction values will be conducted by a binomial test. This test will demonstrate that with high probability at least 50 percent of the target population will obtain a sweat reduction of at least 20 percent. In statistical terminology:

$H_o = P00.5$

$H_A = P00.5$ ($= 0.05$, one sided),

where H_o is the null hypothesis, P is the probability, H_A is the alternative hypotheses and is the predetermined arbitrary level of significance.

This test reduces to the simple procedure of counting the number of subjects with a sweat reduction equal or greater than 20 percent and comparing it with tabulated values. If this number equals or exceeds the tabulated value for a given sample size, the product qualifies for effectiveness. For example, binomial statistics requires the following:

Total number of test subjects	Minimum number of subjects required to have at least a 20 percent sweat reduction
20	15
25	18
30	20
100	58

g. *Minority opinion.* Two members of the Panel disagreed with the majority of the Panel's recommendation that all antiperspirant formulated products, as well as ingredients, be subjected to specified testing for effectiveness. It was the feeling of these two members that product-by-product effectiveness testing would not be necessary for the following reasons:

(1) Although the Panel was told that variations in the formulation of antiperspirant products, all made with comparable concentrations of the same agents (mostly aluminum chlorhydrates), would produce differing amounts of antiperspirant effectiveness, the fact that so many different formulations of aluminum chlorhydrates seemed adequately effective suggested that Category I ingredients in proper amount could ordinarily be put into an effective product without any special compounding art.

(2) Despite the charge to the Panel to determine that all OTC drug products be safe and effective for their labeled indications, we feel that it is permissible, and even wise, to allow the possibility that some formulated antiperspirant products will, in fact, turn out not to be adequately effective, as defined. Even if a product were compounded in such a way as to make it less than adequately effective, no real harm would be done. The user should be able to perceive the difference, the ineffective product would be discarded, or not repurchased, and the purchaser of such a product would have suffered only a modest inconvenience and the loss of a very small purchase price.

(3) Eliminating the need for product-by-product effectiveness testing would reduce the complexity of testing new formulations. The resulting cost savings would be expected to be reflected in the market price of the products.

(4) Even more importantly, the requirement for product-by-product effectiveness evaluation would substantially increase the regulatory task of FDA. The OTC review process was designed as an ingredient rather than a product review in order to allow a relatively manageable review of the vast number of OTC products. While the review process as implemented is flexible enough to permit product-by-product review in certain compelling situations, if utilized throughout the review process it would vastly complicate this long-needed review of the OTC arena. Such a complication should be avoided whenever possible.

REFERENCES

(1) deNavarre, M. G., "Desiderata," *Cosmetics and Toiletries*, 91:8, 1976.

(2) Shelley, W. B., H. J. Hurley, and A. C. Nichols, "Axillary Odor. Experimental Study of the Role of Bacteria, Apocrine Sweat, and Deodorants," *AMA Archives of Dermatology and Syphilology*, 68:430-446, 1953.

(3) Hurley, H. J. and W. B. Shelley, "The Human Apocrine Sweat Gland in Health and Disease," Charles C. Thomas, Springfield, 1960.

(4) Shelley, W. B. and H. J. Hurley, "Studies on Topical Antiperspirant Control of Axillary Hyperhidrosis," *Acta Dermatovener*, 55:241-260, 1975.

(5) OTC Volume 140003.

(6) OTC Volume 140004.

(7) OTC Volume 140005.

(8) OTC Volume 140006.

(9) OTC Volume 140007.

(10) OTC Volume 140008.

(11) OTC Volume 140009.

(12) OTC Volume 140010.

(13) OTC Volume 140011.

(14) OTC Volume 140013.

(15) OTC Volume 140027.

(16) OTC Volume 140033.

(17) OTC Volume 140058.

(18) Kuno, Y., "Human Perspiration," C. C. Thomas, Springfield, 1956.

(19) Montagna, W. et al., "Advances in Biology of Skin," Vol. III, Permagon Press, New York, 1962.

(20) OTC Volume 140054.

(21) Wada, M., "Sudorific Action of Adrenalin on the Human Sweat Glands and Determination of Their Excitability," *Science*, 111:376-377, 1950.

(22) Minor, H. V., "Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung," *Deut. Z. Nervenh.*, 101:302-308, 1927.

(23) Brun, R., "Studies on Perspiration," *Journal of the Society of Cosmetic Chemists*, 10:70-77, 1959.

(24) Malmo, R. B., "Finger-Sweat Prints in the Differentiation of Low and High Incentive," *Psychophisiology*, 1:231-240, 1965.

(25) James, R. J., "A New and Realistic Electronic Approach to the Evaluation of Antiperspirant Activity," *Journal of the Society of Cosmetic Chemists*, 17:749-767, 1966.

(26) Jenkins, J. W. et al., "A Techinique for Perspiration Measurement," *Proceedings of the Scientific Section of the Toilet Goods Association*, 42:12-15, 1964.

(27) O'Malley, W. J. and J. E. Christian, "The Design of a Continuous Recording *In Vivo*-Method of Measuring Sensible Perspiration Over a Limited Area," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 49:398-401, 1960.

(28) Wooding, W. M., "Interpretation of Gravimetric Axillar Antiperspirant Data," *in* "Proceedings of the Joint Conference on Cosmetic Sciences," Washington, D.C., pp. 91-103, 1968.

(29) Berenson, B. S. and G. E. Burch, "A Study of the Sodium, Potassium, and Chloride Contents of Thermal Sweat of Man Collected From Small Isolated Areas of Skin," *Journal of Laboratory and Clinical Medicine*, 42:58-77, 1953.

(30) Barbero, G. J., I. C. Kim, and J. McGavran, "A Simplified Technique for the Sweat Test in the Diagnosis of Fibrocystic Disease of the Pancreas," *Pediatrics*, 18:189-192, 1956.

(31) Slegers, J. F., "The Secretion and Reabsorption of Salt and Water in the Sweat Gland," Doctorate Thesis, University of Michigan, 1966.

(32) Fredell, W. G., and R. R. Read, "Antiperspirant—Axillary Method of Determining Effectiveness," *Proceedings of the Scientific Section of the Toilet Goods Association*, 15:23-27, 1951.

(33) Fredell, G. W. and J. Longfellow, "Report on Evaluating Antiperspirant and Deodorant Products," *Journal of the Society of Cosmetic Chemists*, 9:108-111, 1958.

(34) Daley, E. W., "Antiperspirant Testing: A Comparison of Two Methods," *Proceeding of the Scientific Section of the Toilet Goods Association*, 30:1-6, 1958.

(35) Majors, P. A. and J. E. Wild, "The Evaluation of Antiperspirant Efficacy—Influence of Certain Variables," *Journal of the Society of Cosmetic Chemists*, 25:139-152, 1974.

(36) Jungerman, E., "Antiperspirants: New trends in Formulation and Testing Technology," *Journal of the Society of Cosmetic Chemists*, 25:621-638, 1974.

(37) Wooding, W. M. and P. Finkelstein, "A Critical Comparsion of Two Procedures for Antiperspirant Evaluation," *Journal of the Society of Cosmetic Chemists*, 26:255-275, 1975.

(38) Reller, H. H., "Factors Affecting Axillary Sweating," *Journal of the Society of Cosmetic Chemists*, 15:99-110, 1964.

(39) Karl, J. A., A. Zenisek, and J. Kopecka, "Crossed Locomotor and Sudomotor Innervation. Asymmetry and Sex Differences in Sweat Gland Irritability," *Int. Z. angew. Phsiol.*, 27:165-170, 1969.

40) Herrmann, F., P. H. Prose, and M. B. Sulzberger, "Studies on Sweating V. Studies of Quantity and Distribution of Thermogenic Sweat Delivery to the Skin," *Journal of Investigative Dermatology*, 18:71-86, 1952.

(41) Majors, P. A. and F. B. Carabello, "Presentation to the OTC Panel for Antiperspirants of the Hill Top Research Method of Antiperspirant Evaluations and General Discussion of Results Obtained," Presented at the Open Session, August 14, 1975, Draft of Presentation is included in OTC Volume 140065.

(42) Bakiewicz, J. A., "A Critical Evaluation of the Methods Available for Measurement of Antiperspirancy," *Journal of the Society of Cosmetic Chemists*, 24:245-258, 1973.

(43) Quatrale, R. P. et al., "A Method for the Study of Emotional Sweating," *Journal of the Society of Cosmetic Chemists*, 28:91-101, 1977.

(44) Dobson, R. L. and K. Sato, "The Stimulation of Eccrine Sweating By Pharmacologic Agents," *in* "Advances in Biology of Skin Vol. XII Pharmacology and the Skin," Edited by Montagna, W., et al., Appleton-Century-Crofts, New York, pp. 447-475, 1972.

(45) Uttley, M., "Measurement and Control of Perspiration," *Journal of the Society of Cosmetic Chemists*, 23:23-43, 1972.

I. COMBINATION POLICY.

The combination drug policy for OTC products is 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 recoginzed 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.

After reviewing the labels of the submitted antiperspirant products, it appeared to the Panel that many products contained combinations of two or more antiperspirant active ingredients. However, in an attempt to clarify the naming of the various antiperspirant ingredients (Ref. 1), the Panel was informed that these products were not combinations in the true meaning of the word. Rather, the chemistry involved in the combining of the labeled ingredients in the final product resulted in one of the identifiable ingredients listed by the Panel in the nomenclature section of the document. (See part I. paragraph B., in the table above—Comparison of Submitted Names and Adopted Names for Antiperspirant Active Ingredients.) The Panel is not aware of any product which contains more than one identifiable active antiperspirant ingredient.

One submitted product contained aluminum sulfate and sodium aluminum lactate. The Panel has concluded elsewhere in this document that the presence of sodium aluminum lactate is to act as a corrective agent to counteract the irritating nature of the aluminum sulfate, rather than to act as an active ingredient. (See part III. paragraph B.1.d. below—Buffered aluminum sulfate.)

The Panel recognizes the possibility of combining a Category I antiperspirant with Category I ingredients from other OTC monographs. For example, one submission to the Panel contained information on a product no longer marketed containing an antiperspirant ingredient and an antibacterial ingredient. The presence of the antibacterial in this product was for a deodorant effect rather than an antiperspirant effect. However, the Panel has concluded elsewhere in this document not to review deodorant claims since they are deemed cosmetic claims. (See part II. paragraph E. above—Auxillary Odor.)

The Panel was made aware of other products containing both antiperspirant and antifungal ingredients to be used in the treatment of athlete's foot. While the Panel has evaluated the antiperspirant ingredients in these combinations for their antiperspirant safety and effectiveness, it defers to the OTC Antimicrobial II Panel any evaluation of the usefulness of such a combination in the treatment of athlete's foot.

In summary, since the Panel has no data for actual combinations of antiperspirant active ingredients, these combinations are Category II. In addition, except for the antiperspirant/antifungal combinations which have been deferred to another OTC Panel for evaluation, combinations of antiperspirant active ingredients with active ingredients from other OTC monographs are also Category II since the Panel has no data on such combinations.

REFERENCES

(1) OTC Volume 140061.

III. ANTIPERSPIRANT AGENTS

A. GENERAL DISCUSSION

Most submissions to the Panel described formulations made with only a few common ingredients. Included with these submissions were descriptions of safety testing, hotroom effectiveness testing, and marketing experience.

Because most manufacturers use essentially the same ingredients, this meant that the Panel was presented with a truly massive amount of documentation about the leading antiperspirant ingredients, most notably the aluminum, chlorhydrates.

Despite the very large amount of information reviewed by the Panel about the safety and effectiveness of the aluminum chlorhydrates it was decided to categorize as Category I only products made for direct application to the skin. The decision to require added testing for aerosol products reflects the fact that damage to the lung, by occurring more insidiously, carries a greater potential for serious illness than damage to the skin.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which antiperspirants are generally recognized as safe and effective and not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

CATEGORY I ACTIVE INGREDIENTS

The Panel has classified the following antiperspirant active ingredients in topical nonaerosol dosage formulations as generally recognized as safe and effective and not misbranded:

Aluminum chlorhydrates:
- Aluminum chlorohydrate
- Aluminum dichlorohydrate

Aluminum sesquichlorohydrate
Aluminum chlorohydrex PG
Aluminum sesquichlorohydrex PG
Aluminum dichlorohydrex PG
Aluminum chlorohydrex PEG
Aluminum sesquichlorohydrex PEG
Aluminum dichlorohydrex PEG
Aluminum zirconium chlorhydrates:
Aluminum zirconium trichlorohydrate
Aluminum zirconium trichlorohydrex Gly
Aluminum zirconium pentachlorohydrate
Aluminum zirconium pentachlorohydrex Gly
Aluminum zirconium tetrachlorohydrate
Aluminum zirconium tetrachlorohydrex Gly
Aluminum zirconium octachlorhydrate
Aluminum zirconium octachlorohydrex Gly
Aluminum chloride
Buffered aluminum sulfate

a. *Aluminum chlorhydrates (aluminum chlorohydrate, aluminum dichlorohydrate, aluminum sesquichlorohydrate, aluminum chlorohydrex PG, aluminum sesquichlorohydrex PG, aluminum dichlorohydrex PG, aluminum chlorohydrex PEG, aluminum sesquichlorohydrex PEG, aluminum dichlorohydrex PEG).* The Panel concludes that those materials, known as aluminum, chlorhydrates, in 25 percent or less concentrations calculated on an anhydrous basis are safe and effective for use as OTC antiperspirants as specified in the dosage and labeling sections discussed below.

Aluminum chlorohydrate has also been referred to as aluminum oxychloride, aluminum hydroxychloride, aluminum chloride hydroxide, aluminum chlorhydrate, and chlorhydrol. The aluminum chlorhydrates are commercially available in a number of forms which differ in the ratio of aluminum to chlorine. The empirical formulae of the salts most widely used as antiperspirants are $Al_2(OH)_4Cl_2$ and $Al_2(OH)_5Cl$, which are known as ⅔ basic and ⅚ basic aluminum chloride, respectively.

The aluminum chlorhydrate compounds are also available as polyethylene glycol or propylene glycol complexes. These comlexes have higher alcohol solubility than the uncomplexed salts. This property is desirable in certain topical formulations. The Panel considers these glycols to be formulation necessities which do not substantially alter the skin safety or antiperspirant activity of the salt from which they were prepared.

In water these materials will undergo hydrolysis, forming cationic polymeric species. The molecular weights determined for extremely dilute solutions of the ⅔ basic and ⅚ basic compounds are 975 and 1571, respectively (Ref. 1). A number of chemicals, e.g., sodium lactate (Ref. 2), will have a pronounced effect on the size and nature of the complex polymeric species formed. Increasing the pH of these solutions will tend to increase the size of the polymers.

Solutions of the aluminum chlorhydrates are acidic. The greater the aluminum to chlorine ratio in the material, the less acidic are its solutions. The pH of a 10 percent solution of the ⅔ basic compound is 3.5, while the pH of a 10 percent solution of the ⅚ basic material is 4.4 (Ref. 1).

Although physico-chemical measurements on these materials show significant differences, they do not appear to behave differently when applied to the skin.

(1) *Safety.* The Panel concludes, based on laboratory tests and market experience, that those materials known as aluminum chlorhydrates when applied topically to the underarms in nonaerosol formulations in concentrations of 25 percent or less calculated on any anhydrous basis are safe for use as antiperspirants.

Prior and Cronk in 1959 (Ref. 5) performed an experimental study to determine changes in skin pathology in albino rabbits following application of aluminum chlorhydroxide, aluminum sulfate, sodium aluminum lactate, or zirconium tetraisopropoxide. Acute inflammatory reactions with tissue necrosis and ulceration were noted when the aluminum compounds were injected subcutaneously or intravenously, with a more marked reaction at sites which had been previously deliberately injured. Percutaneous application of aluminum chlorhydroxide did not produce any significant lesions.

Primary skin irritation studies in rabbits using 2 to 24 percent concentrations of aluminum chlorhydrates produced a range of primary irritation indexes on the Draize scale from 0 to 3.7 (Refs. 6 through 18). The aluminum chlorhydrates would be considered mild to moderate irritants in animals based on this scale.

Subchronic dermal toxicity studies have been performed in rabbits using 3.4 to 30 percent concentrations of aluminum chlorhydrates. Except for skin irritation, no other significant adverse findings that could be attributed to the test compounds were found in any of the parameters investigated, which included hematologic studies, clinical blood chemistry studies, urine analyses, pathologic studies, and effects on body and organ weights (Refs. 6, 9, 12, 13, 15, 17, and 19 through 22).

Primary irritation patch tests using 3.5 to 30 percent concentrations of aluminim chlorhydrates in humans resulted in little or no irritation (Refs. 14, 20, and 23). Most of the results of repeated insult patch tests with 3.5 to 20 percent concentrations of aluminum chlorhydrates did not produce visible skin changes consistent with the criteria deemed characteristic of a primary irritant, a "skin fatiguing" agent, or a sensitizer (Refs. 6, 7, 9, 11, 12, 13, and 15). Only two manufacturers' submissions noted mild to moderate irritation with the repeated insult patch tests (Refs. 20 and 22). Results of various other patch testing techniques were consistent in producing little or no irritation with the aluminum chlorhydrates (Refs. 14, 18, 20, 21, 22, 24, and 25).

Market experience with aluminum chlorhydrates is also favorable. The number of cutaneous adverse reactions reported on products containing aluminum chlorhydrates is on the order of 6-per-million units according to industry (from combined complaint files). This is a relatively low number for topical products.

Recent data have shown skin changes in rabbits from injection of an aluminum chlorhydrate (Ref. 26). The Panel concludes, however, that those data support the findings of the Panel, that these reactions are not serious enough to disallow their OTC use.

(2) *Effectiveness.* The Panel was presented with a large amount of effectiveness data for the various aluminum chlorhydrates. Various methods have been used to determine the effectiveness of antiperspirants. The controlled hotroom gravimetric procedure to determine the percent reduction of axillary sweat is most often used. The procedure for this test is discussed elsewhere in this document. (See part II. paragraph H.4. above—Effectiveness testing of antiperspirants.)

Hotroom tests with 20 percent aqueous aluminum chlorhydrates produced sweat reductions in a range of 26 to 46 percent. Concentrations of aluminum chlorhydrates used in aerosol formulations (3 to 3.5 percent) produced sweat reduction values from 20 to 32 percent. Control tests using the vehicle without any active ingredient in the formulation produced sweat reduction values from 0.7 to 3.6 percent (Refs. 6 through 17, 19, 22, 23, 24, and 27 through 34).

A hotroom test using a 9 percent aluminum chlorhydrex PG, a propylene glycol complex of an aluminum chlorhydrate, produced a sweat reduction value of 43 percent (Ref. 23).

A gravimetric test performed with a 20 percent concentration of an aluminum chlorhydrate under ambient conditions produced a mean sweat reduction value of 30 percent (Ref. 15).

Emotionally induced sweat tests have also been used to determine the effectiveness of aluminum chlorhydrates as antiperspirants. Quatrale (Ref. 35) states that the volume of persipiration produced under emotional stress far exceeds that produced by subjects under thermal stress. The emotional sweat test involves gravimetric determinations of axillary sweat secreted under conditions of emotional

stress in an environment of 80° to 85° F and 35 to 50 percent relative humidity for a 15-minute timed interval. The amounts of sweat secreted from each axilla are compared by means of a ratio. Control ratios and rations obtained after treating one axilla with the antiperspirant are compared to obtain the percent sweat reduction. To induce emotional sweating, challenges are designed to produced tension, apprehension, frustration, or embarrassment. The word association list has been used most successfully, but alternative methods such as mental arithmetic and electric shock have also been used. Aerosel formulations containing 3 percent of an aluminum chlorhydrate were demonstrated to provide sweat reductions in the range of 25 to 33 percent, with an average of 30 percent. Two tests using 1.5 percent of an aluminum chlorhydrate aerosol produced sweat reductions of 11 and 13 percent, respectively (Ref. 18).

An exercise-induced sweat test in which sweating was generated by walking for 10 minutes at 3.5 miles per hour on a treadmill was also used to determine the effectiveness of an aluminum chlorhydrate. The results produced an average sweat reduction of 32 percent (Ref. 18).

A modified Wada's starch-iodine method using double-blind conditions was used to determine the effectiveness of 13 different products of varying concentrations of aluminum chlorhydrates (Ref. 21). The degree of inhibition of sweating was estimated to the nearest 25 percent. The scoring system was as follows: 0—treated side not different from control, 1—25 percent inhibition on treated side, 2—50 percent inhibition on treated side, 3—75 percent inhibition on treated side, 4— complete anhidrosis on treated side. Different groups of five men were utilized for each of the products tested. Total scores were determined for each product by adding the individual scores of each group of five men. The results were as follows:

RESULTS OF EFFECTIVENESS TESTING OF ALUMINUM CHLORYDRATES USING A MODIFIED WADA'S STARCH-IODINE METHOD

dosage form	Percent aluminum chlorhydrate	Total score of 5 subjects
Liquid	18	8
Cream	25	5
Cream	25	5
Roll-on	25	4
Cream	20	3
Cream	18	3
Liquid	22	2
Roll-on	24	2
Aerosol	3	2
Roll-on	21	1
Aerosol	5	1
Cream	11	1
Aerosol	4	0

It must be noted that this test is purely relative and estimates the effect of the treated axilla only in comparison to the untreated axilla. Results from this type of study do not permit conclusive judgments. However, it is interesting to note that the method of application can markedly influence the effectiveness of aluminum chlorhydrates, with the aerosols scoring the lowest.

The Panel concludes that those materials known as aluminum chlorhydrates in topical nonaerosol formulations in concentrations of 25 percent or below calculated on an anhydrous basis are effective as antiperspirants according to the criteria established above by the Panel. (See part II paragraph H.4.f. above—Antiperspirant effectiveness qualification test.) The ability of certain organic and inorganic compounds to form complexes with aluminum salts is well established (Ref. 36). The presence of certain excipients which would alter the chemical activity of the aluminum chlorhydrate species could conceivably alter its biological activity. The ability of the aluminum chlorhydrates to reduce perspiration is known to be influenced by the presence of a variety of excipients (Ref. 37). In certain instances the formulation excipients have been known to reduce the level of antiperspirant activity below the level required by the Panel for effectiveness. Therefore, the Panel recommends that final product formulations be tested according to the procedures outlined in the effectiveness testing section of this document. (See part II. paragraph H.4.f. above—Antiperspirant effectiveness qualification test.)

(3) *Dosage.* Dosage is 25 percent or less concentration calculated on an anhydrous basis of a nonaerosol dosage form applied topically to the underarms.

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

REFERENCES

(1) Bretschneider, E. S., A. M. Rubino, and J. L. Jones, Jr., "Physical Properties of Antiperspirants as Related to Their Efficacy," *Cosmetics and Perfumery*, 90:27-31, 1975.
(2) OTC Volume 140043.
(3) Cotton, F. A. and G. Wilkinson, "Advanced Inorganic Chemistry. A comprehensive Text," Interscience Publishers, New York 1972.
(4) Hem, S. L. et al., "Effect of pH Precipitation on Antiacid Properties of Hydrous Aluminum Oxide," *Journal of Pharmaceutical Sciences*, 59:317-321, 1970.
(5) Prior, J. T. and G. A. Cronk, "Pathological Changes Associated With Aluminum and Zirconium Compounds," *Archieves of Dermatology*, 80:447-454, 1959.
(6) OTC Volume 14001.
(7) OTC Volume 140004.
(8) OTC Volume 140005.
(9) OTC Volume 140006.
(10) OTC Volume 140007.
(11) OTC Volume 140008.
(12) OTC Volume 140009.
(13) OTC Volume 140010.
(14) OTC Volume 140013.
(15) OTC Volume 140015.
(16) OTC Volume 140016.
(17) OTC Volume 140024.
(18) OTC Volume 140033.
(19) OTC Volume 140011.
(20) OTC Volume 140020.
(21) OTC Volume 140021.
(22) OTC Volume 140023.
(23) OTC Volume 140014.
(24) OTC Volume 140018.
(25) OTC Volume 140030.
(26) Kang, K. Y. et al, "Experimental Studies of Sensitization to Beryllium, Zirconium, and Aluminum Compounds in the Rabbit," *Journal of Allergy and Clinical Immunology*, 59:425-436, 1977.
(27) OTC Volume 140002.
(28) OTC Volume 140003.
(29) OTC Volume 140012.
(30) OTC Volume 140025.
(31) OTC Volume 140026.
(32) OTC Volume 140027.
(33) OTC Volume 140028.
(34) OTC Volume 140029.
(35) Quatrale, R. P., K. L. Stoner, and C. B. Felger, "A Method for the Study of Emotional Sweating," *Journal of the Society of Cosmetic Chemists*, 28:91-101, 1977.
(36) Lind, C. J. and J. D. Hem, "Effects of Organic Solutes on Chemical Reactions of Aluminum," U.S. Geological Survey Water-Supply Paper 1827-G, U.S. Government Printing Office, Washington, D.C., 1975.
(37) Majors, P. A. and J. E. Wild, "The Evaluation of Antiperspirant Efficacy—Influence of Certain Variables," *Journal of the Society of Cosmetic Chemists*, 25:139-152, 1974.

b. *Aluminum zirconium chlorhydrates (aluminum zirconium trichlorohydrate, aluminum zirconium trichlorohydrex Gly, aluminum zirconium pentachlorohydrate, aluminum zirconium pentachlorohydrex Gly, aluminum zirconium tetrachlorohydrate, aluminum zirconium tetrachlorohydrex Gly, aluminum zirconium octachlorohydrate, aluminum zirconium octachlorohydrex Gly).* The Panel concludes that those materials, known as aluminum zirconium chlorhydrates, in 20 percent or less concentrations calculated on an anhydrous basis are safe and effective for use as OTC antiperspirants as specified in the dosage and labeling sections discussed below. There are now three types of aluminum zirconium chlorhydrate complexes which are commercially available for antiperspirant use. They differ in their atomic ratios of aluminum to zirconium to chlorine.

Glycine is sometimes added to these complexes for formulation purposes. It will coordinate with these polymeric species by displacing some of the waters of hydration. When glycine is present, the name given to the aluminum-zirconium complex should be suffixed with the letters "Gly."

These materials are cationic polymeric species which are loosely hydrated. Solutions of them are acidic, having a pH around 4. They will precipitate from solutions as gels when the pH is above 5. An evaluation of these compounds was discussed in a previous report of the Panel published in the FEDERAL REGISTER of June 5, 1975 (40 FR 24328).

While the Panel expressed serious concern over the advisability of permitting aerosolized forms of those salts to be sold, it found no reason not to permit their use for direct application to the skin.

(1) *Safety.* Safety testing and marketing experience with the aluminum zirconium chlorhydrates suggest that such products should be categorized as safe provided they are not in a respirable aerosol form. The safety of the zirconium-containing compounds was discussed in an earlier report of this Panel and published in the FEDERAL REGISTER of June 5, 1975 (40 FR 24328).

Subsequently, experimental data showed skin changes in rabbits that had undergone injections of zirconium aluminum glycine complex compound (Refs. 1 and 2). The Panel concludes, however, that those data support the earlier finding of the Panel—that these reactions are not serious enough to disallow their OTC use when applied topically by a nonaerosol method.

(2) *Effectiveness.* Effectiveness testing and marketing experience with the aluminum zirconium chlorhydrates in concentrations of not more than 20 percent calculated on an anhydrous basis suggest that such products should be Category I for effectiveness as antiperspirants. However, since the presence of certain excipients has been known to reduce the level of antiperspirant activity below the level required by the Panel for effectiveness, the Panel recommends that final product formulations of the aluminum zirconium chlorhydrates be tested for effectiveness according to the procedures outlined in the effectiveness testing section of this document. (See part II. paragraph H.4.f. above—Antiperspirant effectiveness qualification test.)

(3) *Dosage.* Dosage is 20 percent or less concentration calculated on an anhydrous basis of a nonaerosol dosage form applied topically to the underarms.

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

REFERENCES

(1) Kang, K. Y. et al., "Experimental Studies of Sensitization to Beryllium, Zirconium, and Aluminum Compounds in the Rabbit," *Journal of Allergy and Clinical Immunology*, 59:425-436, 1977.

(2) Kang, K. Y., D. Bice, and J. Salvaggio, "Delayed Hypersensitivity Study on Zirconium Compounds and Beryllium Sulfate," *Medical Journal of Osaka University*, 26:131-145, 1976.

c. *Aluminum chloride.* The Panel concludes that aluminum chloride in 15 percent or less concentration calculated on the hexahydrate form in aqueous solution is safe and effective for use as an OTC antiperspirant as specified in the dosage and labeling sections discussed below. Although the structure of this compound has been established in the solid state (Ref. 1), its structure in aqueous solutions has not been fully elucidated (Ref. 2). The compound hydrolyzes in water, resulting in the formation of oxychlorides and a high concentration of hydrogen ion. The pH of a 10 percent solution is approximately 2.5. Various experiments indicate that the oxychlorides formed are polymeric species (Ref. 2).

The hydrolysis of aluminum chloride can be influenced by the presence of other compounds in solution. For example, potassium chloride suppresses hydrolysis (ref. 3). Altering the pH of aluminum chloride solutions will have a profound effect on the polymeric species formed on hydroloysis.

(1) *Safety.* Results of primary skin irritation studies in rabbits using aluminum chloride in concentrations from 10 to 20 percent in aqueous solutions show that aluminum choride is a mild to moderate irritant producing primary irritation indexes in a range from 0.5 to 2.8 (Ref. 4).

An acute eye irritation study in rabbits using a 13.3 percent aqueous solution of aluminum chloride hexahydrate produced mild conjunctivitis at the 24 hour reading only. No irritation of the eye was noted after the 48 or 72 hour readings (Ref. 5).

The responses of mouse, rabbit, and pig skin to topically applied solutions of six aluminum salts (aluminum chloride, aluminum nitrate, aluminum sulfate, aluminum hydroxide, aluminum acetate, and an aluminum chlorhydrate) were also studied (Ref. 6). Test solutions wer applied daily for 5 consecutive days. The test sites remained uncovered throughout the test period. Epidermal changes consisted of hyperplasia, microabscess formation, dermal inflammatory cell infiltration and occasionally ulceration in all three species treated with aluminum chloride in a 10 percent concentration, but not with 10 and 25 percent concentrations of aluminum chlorhydrate.

A 21-day repeat insult patch test was used to evaluate in irritancy of a 20 percent aqueous solution of aluminum chloride hexahydrate in humans (Ref. 7). Test substance was applied to 1-inch squares of a nonwoven cloth and placed on the back of the subject with an occlusive tape. The patch remained in place for 24 hours and was reapplied daily at the same site. The end point was determined as the first day that redness appeared at the site. Twenty-five subjects were used in this study. Irritation was produced on day 2 in one subject, between days 3 and 5 in 23 of 25 subjects, and on day 7 in the final subject.

Ten and 15 percent aqueous solutions of aluminum chloride hexahydrate were tested for irritancy with 6 other formulations using the repeat insult patch method (Ref. 7). Both of these solutions proved relatively irritating to the skin compared to the other compounds with an average day of reaction at 7 days.

During a gravimetric hotroom effectiveness test with a 13.3 percent aqueous solution of aluminum cloride, all 6 test subjects tested during the first test period developed irritation. Four of these six test subject also complained of tenderness and burning of the axillae. Becasue of the irritation observed during the first test period, one of the applications of aluminum chloride was omitted during the second test period. Four of the six test subjects treated with aluminum chloride during this second test period showed slight erythema. The irritation during this period was much less severe than that observed during the first test period. There were no complaints of discomfort (Ref. 5).

Other effectiveness tests have also reported irritation (Ref. 8). Because of the high incidence of irritation in one test, only 4 of 12 test subjects received all 7 scheduled applications of a 15 percent aqueous solution of aluminum chloride hexahydrate. Six of the other eight test subjects received six applications, and two test subjects received only three applications of the antiperspirant material. No irritation was noted, however, in two subsequent effectiveness tests performed with the same concentration of aluminum chloride hexahydrate.

Market experience with aluminum chloride also suggests that it is more irritating than other compounds placed in Category I as antiperspirants.

The Panel concludes, based on the irritation studies and market experience presented, that aluminum chloride, in aqueous solutions of 15 percent or less calculated on the hexahydrate form, is safe for use as an antiperspirant. However, the Panel concludes that the consumer should be warned about the irritation potential of this material. (See part III. paragraph B.1.c.(4) below—Labeling.)

(2) *Effectiveness.* Herrmann, in 1961, noted that experimentally, a decline in

axillary sweating may be achieved with an aqueous solution of 12 to 20 percent aluminum chloride (Ref. 9).

Several tests using the starch-iodine technique on the forearms of subjects show that aluminum chloride hexahydrate is an effective antiperspirant as compared to untreated sites (Ref. 8).

Zahejsky and Rovensky, in 1972 (Ref. 10), compared the effectiveness of several antiperspirants, including a 15 percent aqueous solution of aluminum chloride hexahydrate, on the forearms of human subjects. Changes in the sweat pattern were recorded with a resistance hygrometer and simultaneously with a contact indicator test when sweating was induced by exposing the subjects to heat (55° C) in a polypropylene tent. The authors noted a significant reduction in sweating after a 3-hour exposure to the aluminum chloride solution, and even greater reduction after a 10-hour exposure.

Three different gravimetric hotroom tests were performed to compare the effectiveness of a 15 percent aqueous solution of aluminum chloride hexahydrate and a 22 percent solution of an aluminum chlorhydrate (Ref. 8). In each of the three tests, both of the antiperspirants were found to be equally effective. It must be noted, however, that the procedures used in each of the three tests had weaknesses, since both axillae were treated during the test period, and the reduction in the amount of perspiration could be determined only in reference to the control period. Also, in one of the tests, the irritation produced with aluminum chloride hexahydrate caused a majority of the test subjects to discontinue applications of that test material prior to the final test day.

A study was performed to determine and compare the effectiveness of a 13.3 percent aqueous solution of aluminum chloride hexahydrate and a 22 percent solution of an aluminum chlorhydrate (Ref. 5). Evaluations of antiperspirant activity were made at 1 hour following the second sample application and 12 and 84 hours following the third and fourth applications, for each of the 2 test periods. The percent sweat reductions within 95 percent confidence limits were as follows:

EFFECTIVENES COMPARISON OF TWO ANTIPERSPIRANT MATERIALS

Sample	Percent sweat reduction		
	Hours after application		
	1	12	84
13.3 percent aluminum chloride hexahydrate	17.8	48.5	48.8
22 percent aluminum chlorhydrate	26.3	34.7	21.7

Significantly greater reductions in sweating were noted from the applications of aluminum chloride than from the aluminum chlorhydrate at 12 and 84 hours following application.

The Panel concludes that a 15 percent or less aqueous solution of aluminum chloride is an effective antiperspirant, but also has a greater potential for producing irritation compared with other Category I ingredients. However, since 15 percent or less aqueous solutions of aluminum chloride show significantly greater reductions in perspiration compared with other antiperspirant materials which produce little or no irritation, the Panel recommends that 15 percent or less aqueous solutions of aluminum chloride calculated on the hexahydrate form applied topically by a nonaerosol technique be placed in Category I. However, since the presence of certain excipients has been known to reduce the level of antiperspirant activity below the level required by the Panel for effectiveness, the Panel recommends that final product formulations of aluminum chloride preparations be tested for effectiveness according to the procedures outlined in the effectiveness testing section of this document. (See part II. paragraph H.4.f. above—Antiperspirant effectiveness qualification test.)

(3) *Dosage.* Dosage is 15 percent or less concentration calculated on the hexahydrate form of an aqueous solution nonaerosol dosage form applied topically to the underarms.

(4) *Labeling.* The Panel recommends the Category I labeling for antiperspirant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition to the standard warning required for antiperspirants, the following warning should prominently appear on the container to warn the user of the greater irritancy potential of aluminum chloride over other marketed antiperspirants: *"Warning:* Some users of this product will experience skin irritation."

REFERENCES

(1) Andress, K. R. and C. Carpenter, "Kristallhydrate. II. Die Sturktur von Chromchlorid and Aluminum- chloridhexahydrat," *Zeitschift fur Kristallographie,* 87:446–463, 1934.

(2) Cotton, F. A. and G. Wilkinson, "Advanced Inorganic Chemistry, A Comprehensive Text," Interscience Publishers, New York, 1972.

(3) Tikhonov, V. N., "Analytical Chemistry of Aluminum," John Wiley and Sons, New York, 1973.

(4) OTC Volume 140025.

(5) OTC Volume 140044.

(6) Lansdown, A. B. G., "Production of Epidermal Damage in Mammalian Skin by Some Simple Aluminum Compounds," *British Journal of Dermatology,* 89:67–76, 1973.

(7) OTC Volume 140026.

(8) OTC Volume 140028.

(9) Herrmann, F., "Axillary Deodorants," *Journal of the American Medical Association,* 176:1063, 1961.

(10) Zahejsky, J. and J. Rovensky, "A Comparison of the Effectiveness of Several External Antiperspirants," *Journal of the Society of the Cosmetic Chemists,* 23:775–789, 1972.

d. *Buffered aluminum sulfate.* A product containing 8 percent aluminum sulfate buffered with 8 percent sodium aluminum lactate has had wide use over many years. The discussion of unbuffered aluminum sulfate appears elsewhere in this document. (See part III. paragraph B.3.d. below—Aluminum sulfate.)

(1) *Safety.* The safety of aluminum sulfate as an antiperspirant ingredient is discussed elsewhere in this document. (See part III. paragraph B.3.d.(1) below—Safety.) Aluminum sulfate when used alone as an antiperspirant produces a high degree of irritation. The presence of sodium aluminum lactate alters the pH in such a way so as to decease the irritating nature of the aluminum sulfate.

A primary irritation study was performed using three different formulations of buffered aluminum sulfate (Ref. 1). The test material was applied to the shaved backs of three groups of six albino rabbits and held in place for 24 hours. Dermal irritation readings were taken at the end of the 24-hour period and again at 72 hours. Dermal irritation scores using the Draize scale (Ref. 2) were zero in all of the rabbits tested.

Numerous-use tests in humans, each test of 2 weeks' duration, have been performed to evaluate the safety of buffered aluminum sulfate (Ref. 1). Irritation or sensitization was not reported in any of the tests.

A standard Draize-Shelanski repeated insult patch test was also performed in 204 human subjects (Ref. 1). The scoring system was as follows: (0)—no reaction; (1+)—slight reaction; (2+)—marked erythema; (3+)—marked erythema, edema, with or without vesicles; (4+)—marked erythema, edema, with vesicles and oozing. Forty-six of the 204 subjects had a score of 1+, 20 had a score of 2+, and 4 subjects had a score of 3+. None of the subjects had a score of higher than 3+. The reactions produced with the test material (8 percent aluminum sulfate buffered with 8 percent sodium aluminum lactate) were milder and less numerous than those produced with the control, which was Ivory™ soap.

The incidence of complaints of adverse reactions with buffered aluminum sulfate is also low, on the order of 0.9 complaint per million units shipped (Ref. 1).

(2) *Effectiveness.* The effectiveness of unbuffered aluminum sulfate is discussed elsewhere in this document.

(See part III. paragraph B.3.d.(2) below—Effectiveness.)

A gravimetric test performed under ambient conditions was conducted on 36 subjects to determine the effectiveness of buffered aluminum sulfate (Ref. 1). Mean percent sweat reductions were produced in the range of 25.43 to 28.94 percent.

Another gravimetric test was conducted under both ambient and hotroom conditions on 36 subjects (Ref. 3). Buffered aluminum sulfate proved effective as an antiperspirant producing mean percent sweat reductions of 29.1 percent under ambient conditions and 31.3 percent under hotroom conditions.

The Panel concludes that 8 percent aluminum sulfate when buffered with 8 percent sodium aluminum lactate is safe and effective when applied topically in nonaerosol form, and therefore places it in Category I. However, since the presence of certain excipients has been known to reduce the level of antiperspirant activity below the level required by the Panel for effectiveness, the Panel recommends that final product formulation of buffered aluminum sulfate be tested for effectiveness according to the procedures outlined in the effectiveness testing section of this document. (See part II. paragraph H.4.f. above—Antiperspirant effectiveness qualification test.)

(3) *Dosage.* Dosage is 8 percent concentration of aluminum sulfate buffered with 8 percent concentration of sodium aluminum lactate in a nonaerosol dosage form applied topically to the underarms.

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

REFERENCES

(1) OTC Volume 140019.

(2) Draize, J. H., "Dermal Toxicity," *in* "Appraisal of Safety of Chemicals in Foods, Drugs, and Cosmetics," Association of Food and Drug Officials of the U.S., Texas State Dept. of Health, Austin, Tex., pp. 46-59, 1959.

(3) OTC Volume 140052.

CATEGORY I LABELING

The Panel recommends the following Category I labeling for antiperspirant active ingredients to be generally recognized as safe and effective and not misbranded.

a. *Indications.* (1) "Helps reduce underarm wetness," or "Helps reduce underarm dampness," or "Helps reduce underarm perspiration."

(2) In addition, the Panel concludes that the following statement should appear on the label to explain to the consumer the level of effectiveness that can be expected: "Products described as antiperspirants can be expected to produce at least a 20 percent reduction in underarm perspiration in at least half the users when applied once daily."

The Panel concludes that a minimum effectiveness statement is necessary on the label to disclose material facts of significant benefit to the consumer. The facts are as follows: (1) The antiperspirant the consumer is buying has been tested for effectiveness; (2) the probable percent sweat reduction is as little as 20 percent; and (3) since individuals vary in their response to antiperspirants, the product may or may not acheive a 20 percent sweat reduction for the user.

Claims are made for antiperspirants in the advertising media which exaggerate their effectiveness. Strong marketing efforts of a highly competitive nature create an apparent necessity for these products. The Panel believes that there should be one place where the consumer can find accurate information about the product's effectiveness. This information should be accessible to all potential users; there seems to be no better place for it than on the label. The Panel believes that this information is of significant value to the consumer in that it counters the misleading statements of antiperspirant advertisers that antiperspirants are extremely effective.

b. *Warnings*—(1) *For products containing any antiperspirant ingredient.* The Panel concurs with the warning now required under 21 CFR 369.20 for antiperspirants: "Do not apply to broken skin. If a rash develops, discontinue use."

(2) *For products containing aluminum chloride*—"*Warning:* Some users of this product will experience skin irritation."

c. *Directions for use.* "Apply to skin of underarms. Not to be used generally over the body."

2. *Category II conditions under which antiperspirants are not generally recognized as safe as effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC antiperspirant drug products effective 6 months after the date of publication of the final mongraph in the FEDERAL REGISTER.

CATEGORY II ACTIVE INGREDIENTS

The Panel has classified the following antiperspirant active ingredients as not generally recognized as safe and effective or are misbranded.

Zirconium-containing salts (aerosolized).
Aluminum chloride (alcoholic solution).
Aluminum bromohydrate.

a. *Zirconium-containing salts (aerosolized).* In the FEDERAL REGISTER of August 16, 1977 (42 FR 41374), the Commissioner issued a final rule that any aerosol drug or cosmetic product containing zirconium is a new drug or adulterated cosmetic. This action had the effect of removing these agents from the market until safety testing adequate for approval of a new drug application has been conducted.

The Commissioner's action had previously been urged by the Panel in a report published in the FEDERAL REGISTER of June 5, 1975 (40 FR 24328). The Commissioner's decision was based on the Panel's judgment of unresolved questions concerning the likelihood that zirconium-containing aerosol products might produce granulomas when inhaled by users over a period of many months or years. The Panel report cited published and submitted evidence that under certain conditions, zirconium-containing chemicals have produced granulomas in man and in experimental animals. The report concluded that in the light of such evidence, and in the absence of satisfactory chronic inhalation toxicity studies, benefit to risk considerations did not warrant the continued sale of aerosolized zirconium-containing salts.

b. *Aluminum chloride (alcoholic solutions).* Shelley and Hurley (Ref. 1) have reported that an alcoholic aluminum chloride solution is both safe and effective when applied to a fully dried axilla at bedtime or at the start of some other prolonged nonsweating period, and when covered with an impermeable polyethylene-type plastic wrap for a period of 6 to 8 hours. The Panel concludes, however, that alcoholic solutions of aluminum chloride are Category II for use as OTC antiperspirants. While one manufacturer submitted data to consider a 20 pecent alcoholic solution of aluminum chloride for OTC use, the Panel recognizes that the marketing history of the product has, heretofore, been limited to prescription use.

(1) *Safety.* An irritancy evaluation comparing a 15 percent aqueous aluminum chloride solution and a 20 percent alcoholic solution of aluminum chloride showed that the alcoholic solution was no more irritating than the aqueous solution (Ref. 2). The Panel concludes that this single test is not adequate to establish the safety of alcoholic solutions of aluminum chloride for OTC use since the product has been limited to carefully contolled conditions of use (applied to a fully dried axilla and covered with plastic wrap for 6 to 8 hours). Data are lacking to show that the product would be safe if proper attention was not given to these special conditions of use.

(2) *Effectiveness.* Shelley and Hurley (Ref. 1) claim not only the usual level of antiperspirant effectiveness for the 20 percent alcoholic aluminum chloride products, but they also state that

when used as directed the product can provide total control of axillary wetness in patients who have sweating excessive enough to be classified as hyperhidrosis. While the submissions for the alcoholic solution of aluminum chloride did not include the vast quantity of hotroom data which accompanied most other product submissions, the Panel concluded that this ingredient would produce enough reduction in underarm perspiration to be classified as an effective antiperspirant (Refs. 2, 3, and 4).

(3) *Evaluation.* The Panel concludes that alcoholic solutions of aluminum chloride are Category II because of the paucity of skin irritancy data and the fact that this product has been limited to prescription use. Whether or not this product, if available OTC, would be used correctly, with proper attention to a dry axilla and plastic film occlusion, cannot be determined from the data submitted. It cannot be determined from the submitted data to what degree this product could be used without special attention to a dry axilla and/or plastic film occlusion without altering its safety and/or effectiveness.

Until each of these questions can be answered, the Panel concludes that alcoholic solutions of aluminum chloride should remain limited to prescription use as antiperspirants.

REFERENCES

(1) Shelley, W. B. and H. J. Hurley, "Studies on Topical Antiperspirant Control of Axillary Hyperhidrosis," *Acta Dermatovener*, 55:241-260, 1975.
(2) OTC Volume 140063.
(3) OTC Volume 140057.
(4) OTC Volume 140060.

c. *Aluminum Bromohydrate.* The Panel concludes that aluminum bromohydrate is Category II for use as an OTC antiperspirant. While aluminum bromohydrate could be proven both safe and effective with further testing, this material is a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) since it has never been marketed in this country as an antiperspirant. This material has a similar chemical formula to the 5/6 basic aluminum chlorohydrate. The aluminum to bromine ratio is 2 to 1 and the pH of a 10 percent aqueous solution is approximately 4.2.

(1) *Safety.* The oral LD_{50} of aluminum bromohydrate appears to be greater than 8,000 mg/kg in rats, which would be considered nontoxic (Ref. 1). Aluminum bromohydrate has been tested on animals for irritancy, sensitization, and acute inhalation toxicity. Aerosol applications of 3.5 percent and 10 percent concentrations of aluminum bromohydrate to the corneal surface of the eye of albino rabbits did not cause irritation when tested in accordance with procedures outlined in the Federal Hazardous Substances Act. However, when a 10 percent concentration of an aluminum bromohydrate aerosol was expelled and the liquid placed directly in the eye, the material was found to be a severe irritant (Ref. 1).

Aluminum bromohydrate has also been tested for primary skin irritancy (Ref. 1). When 3.5 or 10 percent concentrations of aluminum bromohydrate were applied to albino rabbits according to the Draize procedure (Ref. 2), neither concentration was deemed a primary skin irritant.

A 3-week dermal toxicity study was performed with 3.5 and 10 percent concentrations of aluminum bromohydrate (Ref. 1). Except for varying degrees of irritation, no other adverse findings were reported in any of the other parameters investigated which included hematology, biochemistry, and urinalysis studies.

Based on the Results of a dermal sensitization study performed in guinea pigs, a 10 percent concentration of aluminum bromohydrate would appear to be a sensitizer in man, whereas a 3.5 percent concentration would not (Ref. 1).

No adverse effects which could be attributed to the test material were noted in two separate 5-day acute inhalation studies using 10 percent aerosol formulations of aluminum bromohydrate in rats and guinea pigs (Ref. 1).

The Panel did not receive any human safety data on this material, nor was it able to find any such information in the scientific literature.

(2) *Effectiveness.* A gravimetric hotroom test was performed in humans with a 3.5 percent aerosol formulation and four other liquid formulations of aluminum bromohydrate varying in concentration from 20 to 32 percent. Reductions in sweating were reported in the range of 35 to 51 percent (Ref. 1).

(3) *Evaluation.* The Panel concludes that while aluminum bromohydrate could possibly be proven a safe and effective OTC antiperspirant with further testing, it is placed in Category II since it has never been marketed in this country as an antiperspirant. Before this material can be marketed as an OTC antiperspirant, an approved new drug application is required, or a determination must be made that this ingredient is generally recognized as safe and effective in a monograph.

REFERENCES

(1) OTC Volume 140014.
(2) Draize, J. H., "Dermal Toxcity," *in* "Appraisal of Safety of Chemicals in Foods, Drugs, and Cosmetics," Association of Food and Drug Officials of the U.S., Texas State Dept. of Health, Austin, Tex., pp. 46-59, 1959.

CATEGORY II LABELING

The Panel has examined the submitted labeling claims for antiperspirants and has placed certain claims into Category II:

a. Those implying the ability to totally stop underarm perspiration: "stops," "halts," or "ends," since antiperspirants are not capable of totally inhibiting perspiration production.

b. Those which may misled about enhanced antiperspirant effect by using descriptions of their formulation with terms like "dry" and "dry formula." The use of such terms to describe physical attributes of the product such as "goes on dry," or other descriptive terms such as "mild," "gentle," "pleasant," "comfortable," however, are considered cosmetic claims and will not be disallowed.

c. Those which suggest use for other areas of the skin beyond the axillae, except for hand and foot claims which are discussed in Category III. (See part III. paragraph B.3. below—Category III Labeling.)

The Panel discussed the rationale for this limitation earlier in this document. (See part II. paragraph C.2.e. above—Function of the gland.)

d. *Extra-strength claims:* The term "extra-strength" normally refers to increased concentration of the active ingredient which would normally mean added effectiveness. However, the Panel concludes that the presence of more active ingredient in an antiperspirant cannot be used as a basis for a claim of added effectiveness since additional amounts of antiperspirant active ingredient do not necessarily result in improved product effectiveness. (See part II. paragraph H. above—Effectiveness of Antiperspirants.) Therefore, the Panel concludes that the term "extra-strength" is Category II. However, the Panel will allow claims of "extra-effective" if properly substantiated. (See part III. paragraph B.3. below—Category III Labeling.)

e. *Unacceptable labeling claims:* The following is a list of unacceptable labeling claims that were submitted for the antiperspirant products: "Helps stop wetness," "Completely guards your family," "Helps stop embarrassing perspiration wetness," "Complete protection," "Super dry," "Really helps keep you dry," "Gentle enough for sensitive areas of the body."

MINORITY STATEMENT REGARDING LABELING

A minority opinion exists with regard to permissible labeling claims. Two Panel members believe that to enumerate allowable words and phrases and to disallow all others is

unduly restrictive and subject to inherent difficulty in enforcement.

The Panel did not see scientific data to indicate that a consumer can differentiate between such words as "halts," "checks," "stops," and "ends" as disallowable words versus "diminishes" and "reduces" as allowable words. Further, to disallow such aptly descriptive words as "dry formula" for fear that they might imply complete cessation of perspiration is hardly likely and even if this confusion were to occur, no real harm is done to the consumer.

These phrases are historically and correctly part of American competitive marketing.

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

CATEGORY III ACTIVE INGREDIENTS

The Panel has concluded that the available data are insufficient to permit final classification of the following antiperspirant active ingredients listed below. The Panel believes it reasonable to provide 5 years for the development and review of the necessary data to prove the safety of long term use of aersolized anitperspirants and 2 years for the development and review of the necessary data for all other Category III conditions. The active ingredients are as follows:

Aluminum chlorohydrates (aerosol formulations):

Aluminum chlorohydrate, aluminum dichlorohydrate, aluminum sesquichlorohydrate, aluminum chlorohydrex PG, aluminum sesquichlorohydrex PG, aluminum dichlorohydrex PG, aluminum chlorohydrex PEG, aluminum sesquichlorohydrex PEG, aluminum dichlorohydrex PEG, sodium aluminum chlorohydroxy lactate, aluminum chloride (aerosol formulations), aluminum sulfate, and potassium aluminum sulfate.

a. *Aluminum chlorohydrates (aluminum chlorohydrate, aluminum dichlorohydrate, aluminum sesquichlorohydrate, aluminum chlorohydrex PG, aluminum dichlorohydrex PG, aluminum sesquichlorohydrex PG, aluminum chlorohydrex PEG, aluminum dichlorohydrex PEG, aluminum sesquichlorohydrex PEG).* The Panel concludes that there are insufficient data to determine the safety and effectiveness of those materials known as aluminum chlorohydrates for use as OTC antiperspirants when used in aerosol formulations in concentrations of 25 percent or less calculated on an anhydrous basis.

(1) *Safety.* The Panel has concluded above that the aluminum chlorohydrates when applied topically in nonaerosol fomulations are safe for use as antiperspirants. (See part III. paragraph B.1.a.(1) above—Safety.) However, the Panel questions the safety of the long term use of these ingredients when applied in an aerosol form. (See part II. paragraph G.4.a. above—Safety of long time use of aerosolized antiperspirants.) The Panel concludes that the available data on the long term use of aerosolized aluminum chlorohydrates as antiperspirants are insufficient to permit final classification at this time.

The commerical aerosol aluminum chlorohydrate products will either spray the antiperspirant as solid particulates or fine liquid droplets. From the inhalation data provided to the Panel it is not possible to gauge which of these systems has a greater inhalation risk associated with its use. Therefore, the Panel expects that a series of preliminary studies on the different aluminum chlorohydrate active ingredients in a variety of vehicles will determine the inhalation risk of these aerosol sprays. This will require data on their aerodynamic particle size distributions, acute inhalation toxicologies, and rebound characteristics from the target site.

Acute inhalation studies have been performed in animals using the various aluminum chlorohydrates. In several tests albino rabbits were exposed to 20-second sprays of aluminum chlorohydrate every 30 minutes for at least 4 hours (Refs. 1 through 4). An equal number of animals were used as controls and were handled in the same manner as the test animals, but were not exposed to any test material. Each animal was observed for gross signs of systemic toxicity during the exposure period and daily thereafter for 14 days. At the conclusion of the 14 days each animal was sacrificed and necropsied. This same type of inhalation study has been performed in rats (Refs. 5 and 6). All of the tests produced consistent results. Observations for gross toxic signs, gross necropsy findings, and histopathology showed no difference between the test and the control animals.

In another type of acute inhalation test, 20 rats were exposed to a 200 mg/liter concentration of aluminum chlorohydrate for a single 1-hour period (Ref. 1). Twelve rats not exposed to the test material served as the control group. Twenty-four hours after exposure, half of the animals were necropsied. The remaining animals were observed daily for physical and behavioral changes and necropsied 14 days after the initial exposure. Fourteen of the 20 test animals developed wheezing within 24 hours after exposure to the aluminum chlorohydrate. Two of the 12 control animals also developed wheezing. Other gross signs, gross necropsy findings, and histopathology showed no difference between the test and untreated control animals.

The Panel has also reviewed a number of subchronic inhalation studies using aerosol formulations of the various aluminum chlorohydrates (Refs. 1 through 5). In one study (Ref. 1) cynomolgus monkeys were exposed to a 10-second aerosol burst of a 3.4 percent aluminum chlorohydrate every 5 minutes for 20 minutes in the morning and again in the afternoon for 90 consecutive days. The untreated control animals were also placed in an inhalation chamber for two 20-minute periods daily without any aerosol exposure.

Observations were made with respect to incidence of mortality and behavioral and body weight effects. Hematological and clinical blood chemistry studies, urine analyses, and pulmonary function tests were conducted on all animals. At the conclusion of the study, all animals were sacrificed and subjected to gross pathological examinations. This same procedure was used in another test (Ref. 2), except the cynomolgus monkeys were exposed to a 13-second burst aersolized 3.4 percent aluminum chlorohydrate every 5 minutes for 20 minutes in the morning and afternoon for 90 consecutive days.

In another inhalation study, rhesus monkeys were exposed to 5-second sprays every 5 minutes for a total of 3 sprays in the morning and again in 5 hours, 5 days a week for 13 weeks. The control animals were exposed to distilled water.

Albino rabbits have also been used in subchronic inhalation studies (Ref. 4). The test rabbits were exposed to a 30-second burst of 3.5 percent aluminum chlorohydrate followed by a 15-minute exposure to the resulting atmosphere. The procedure was repeated twice daily, 5 days a week for 13 weeks. Control animals were exposed to the aerosol minus the active ingredient using an identical exposure regimen. This same procedure has been used in rats (Ref. 5).

In all of the subchronic inhalation tests outlined above, there were no adverse effects produced in the animals which could be attributed to the inhalation of the test materials. Results of the test groups of animals were essentially the same as those for the controls.

The Panel concludes that the acute and subchronic toxicity studies adequately document the short-term safety of aluminum chlorhydrate aerosolized products. However, the Panel recognizes that consumers may use these products for a significant portion of their lives. Since the Panel has not been presented with any data to demonstrate the safety of long term use, it is requiring an inhalation toxicity study which would reflect this long term use. (See part III. paragraph C.2. below—Guidelines for tests to be done for aerosolized antiperspirant sprays to be classified as Category I.)

(2) *Effectiveness.* The Panel concludes that the various aluminum chlorhydrates have been found to be effective antiperspirants. (See part III. paragraph B.1.a.(2) above—Effectiveness.) However, the aerosol method of application requires a number of excipients which are unique to these systems. Some of the excipients required can be expected to retard the activity of the antiperspirant to a level below that required under the Panel's definitin of an antiperspirant (Ref. 7).

Therefore, as with all other antiperspirant formulations, aerosol formulations of aluminum chlorhydrates will be required to be tested for effectiveness. (See part II. paragraph H.4.f. above—Antiperspirant effectiveness qualification test).

(3) *Proposed dosage.* Dosage is 25 percent or less concentration calculated on an anhydrous basis applied topically to the underarms.

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

(5) *Evaluation.* The Panel concludes that while the aluminum chlorhydrates may be effective as antiperspirants, the safety data on the long term use of these products in an aerosolized form are insufficient to permit final classification at this time. Therefore, aerosol formulations of the aluminum chlorhydrates are Category III until such data are made available. To become Category I, an inhalation test as outlined below is required by the Panel (See part III. paragraph C.2. below—Guidelines for tests to be done for aerosolized antiperspirant sprays to be classified as Category I.) In addition, since various excipients used in the formulation may retard the effectiveness of the aluminum chlorhydrates, aerosol formulations will be required to be tested for effectiveness as outlined above. (See part II. paragraph H.4.f. above—Antiperspirant effectiveness qualification test.)

(1) OTC Volume 140001.
(2) OTC Volume 140005.
(3) OTC Volume 140007.
(4) OTC Volume 140011.
(5) OTC Volume 140020.
(6) OTC Volume 140033.
(7) Majors, P. A. and J. E. Wild, "The Evaluation of Antiperspirant Efficacy—Influence of Certain Variables," *Journal of the Society of Cosmetic Chemists,* 25:139-152, 1974.

b. *Sodium aluminum chlorhydroxy lactate.* This material is produced by the reaction of aluminum chlorhydrate (⅚ basic) with lactic acid and subsequent neutralization with alkali up to a pH of 8.5. The compound is used in stick formulations where a compound which is compatible with soaps is needed (Ref. 1). The acidic aluminum salts react with soaps. This complex will produce anionic aluminum species in solution.

(1) *Safety.* Although no specific human safety studies were reported in the scientific literature, a few authors note that the material is not a human skin irritant (Refs. 1 and 2). Studies using rabbits (Ref. 3) suggest that the material is not a primary irritant on the skin, but do show that the compound can produce severe irritation of the eye when placed in the conjunctival sack. A human primary irritancy and sensitization study as a stick formulation containing approximately 18 percent of the active ingredient was submitted (Ref. 3). The repeated patch test was performed on the upper back of the subjects by standard procedures. There was no indication of any primary irritation and no indication of a sensitization potential on the challenge performed after the patch testing.

(2) *Effectiveness.* Hotroom tests performed on a stick formulation of the compound showed a mean perspiration reduction of 12 percent (Ref. 3). This is far below the level required for antiperspirant effectiveness by the Panel. Formulation changes could possibly alter the activity of the ingredient sufficiently to meet the effectiveness requirement.

(3) *Proposed dosage.* Dosage is 18 percent or less concentration calculated on the anhydrous form of a nonaerosol dosage form applied topically to the underarms.

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

(5) *Evaluation.* The Panel concludes that sodium aluminum chlorohydroxy lactate is safe, but has placed this compound in Category III because the available effectiveness data are insufficient to permit final classification at this time. To become Category I, evidence of effectiveness as described earlier in this document is required. (See part II. paragraph H.4.f. above—Antiperspirant effectiveness qualification test.)

REFERENCES

(1) Kalish, J., "Aluminum Chlorhydroxylactate Complex," *Drug and Cosmetic Industry,* 79:318-319, 1956.
(2) Alexander, P. and V. Kinglake, "Antiperspirants and Deodorants: Formulations and Techniques and a Tabular Guide to UK Products," *Manufacturing Chemist Aerosol News,* 40:25-40, 1969.
(3) OTC Volume 140041.

c. *Aluminum chloride.* The Panel concludes that aluminum chloride may be effective, but there are insufficient data to determine safety for use as an OTC antiperspirant when used in aerosolized aqueous solutions of 15 percent or less calculated on the hexahydrate form.

(1) *Safety.* In addition to topical nonaerosol formulations, as discussed under the Category I conditions above, aluminum chloride is also available to the public as an aerosol spray which is generated by a pump delivery system (Ref. 1). The concentration of the material in these spray systems is between 10 and 15 percent. To date the Panel has not received any data on the inhalation safety characteristics of this material. Without such information it is impossible to assess the safety of these products.

These products are being classified in Category III until such time that chronic aerosol inhalation tests are complete. The inhalation test for aluminum chloride should be of the same design as the one required for the aerosolized aluminum chlorhydrates except that aluminum chloride will be the test material. (See part III. paragraph C.2. below—Guidelines for tests to be done for aerosolized antiperspirant sprays to be classified as Category I.) The dose selected for these inhalation studies will be derived from experimentation designed to measure the concentration and particle size distribution of the active ingredient that reaches the breathing zone (area in front of nose and mouth) under heavy use conditions.

(2) *Effectiveness.* The effectiveness of this ingredient has been discussed earlier in this document. (See part III. paragraph B.1.c.(2) above—Effectiveness.) While aluminum chloride may be effective as an OTC antiperspirant, aerosol formulations must conform to the standards of effectiveness set by the Panel. (See part II. paragraph H.4.f. above—Antiperspirant effectiveness qualification test.)

(3) *Proposed dosage.* Dosage is 15 percent or less concentration of an aerosol dosage form applied topically to the underarms.

(4) *Labeling.* The Panel recommends the Category I labeling for antiperspirant active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the following warning should prominently appear on the label to warn the user of the greater irritancy potential of aluminum chloride over other marketed antiperspirants: "*Warning:* Some users of this product will experience skin irritation."

(5) *Evaluation.* The Panel concludes that aluminum chloride in concentrations of 15 percent or less may be effective as an antiperspirant, but the safety data on the long term use of aerosolized formulations are insufficient to permit final classification at this time. Therefore, aerosolized formulations of 15 percent or less concentrations of aluminum chloride are Cat-

egory III until such data become available. (See part III. paragraph C.2 below—Guidelines for tests to be done for aerosolized antiperspirant sprays to be classified as Category I.) In addition, aluminm chloride in aerosol form must conform to the standards set by the Panel concerning effectiveness. (See part II. paragraph H.4.f. above—Antiperspirant effectiveness qualification test.)

REFERENCES

(1) OTC Volume 140044.

d. *Aluminum sulfate.* The Panel concludes that there are insufficient data to determine the safety and effectiveness of aluminum sulfate for use as an OTC antiperspirant when used in topical nonaerosol formulations in concentrations of 11 percent or less. This compound, also known as cake alum and patent alum, exists in a number of hydrated states; the most common commercial product is the octadecahydrate (18 water of hydration). Aqueous solutions of this material are acidic, having pH values around 3. The compound hydrolyzes in water to form a series of complex species similar to aluminum chloride.

This compound is either formulated as a single ingredient or in combination with sodium aluminum lactate. The sodium aluminum lactate reduces the acidity of the sulfate. The buffered combination will have chemical properties uniquely different from each ingredient alone.

(1) *Safety.* A number of products containing this compound in concentrations less than 11 percent are available to the consumer. Animal tests and consumer complaints (Ref. 1) indicate that this compound is capable of producing skin irritation. The Panel is unaware of any controlled human studies on the material to assess its irritation potential and dermal safety. Such studies are necessary before the Panel can recognize the material as being generally safe for use as an antiperspirant.

(2) *Effectiveness.* Although aluminum sulfate has been shown to exhibit antiperspirant activity (Ref. 2), the Panel has not received any data on controlled human effectiveness studies.

(3) *Proposed dosage.* Dosage is 11 percent or less concentration of a nonaerosol dosage form applied topically to the underarms.

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

(5) *Evaluation.* The Panel concludes that the available data on both the safety and effectiveness of topical nonaerosol Formulations of aluminum sulfate in 11 percent or less concentrations are insufficient to permit final classification at this time, and, therefore, classifies this ingredient as Category III. The Panel is requiring that a test be performed to determine the safety of this ingredient when applied to the skin. (See part III., paragraph C.1. below—Guidelines for products categorized as Category III because of inadequate data concerning their safety for the skin.) In addition, aluminum sulfate must conform to the standards set by the Panel concerning effectiveness. (See part II., paragraph H.4.f. above—Antiperspirant effectiveness qualification test.)

REFERENCES

(1) OTC Volume 140017.

(2) O'Malley, W. J., and J. E. Christian, "An Evaluation of the Ability of Antiperspirant Compounds to Reduce Perspiration Flow," *Journal of the American Pharmaceutical Association* (Scientific Edition), 49:402–404, 1960.

e. *Potassium aluminum sulfate.* This compound in its hydrated form is commonly referred to as alum. Aqueous solutions of it are acidic, having a pH of between 3 and 4. The compound is able to precipitate proteins from solution (Ref. 1). The styptic and astringent properties of the compound derive to a great extent from this property.

(1) *Safety.* Although the compound has been used as a topical astringent for an extensive period of time (Ref. 1) without any reports of adverse effects, the Panel is unaware of any controlled human safety data on the compound. Such tests must be carried out before the material can be recognized as being safe for topical use.

(2) *Effectiveness.* The Panel is unaware of any controlled human antiperspirant studies on this compound.

(3) *Proposed dosage.* Dosage is 1.5 percent or less concentration of a nonaerosol dosage form applied topically to the underarms.

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

(5) *Evaluation.* The Panel concludes that both the safety and effectiveness data on potassium aluminum sulfate as an antiperspirant are insufficient and, therefore, classifies this ingredient as Category III. In order become Category I, the Panel is requiring an effectiveness test as outlined above and safety tests as outlined below. (See part II., paragraph H.f.4. Above—Antiperspirant effectiveness qualification test and part III., paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) Stone, T. O., and C. O. Wilson, "Roger's Inorganic Pharmaceutical Chemistry," Lea and Febiger, Philadelphia, 1967.

CATEGORY III LABELING

The Panel has examined the submitted labeling claims for antiperspirants and has placed certain claims into Category III, for lack of adequate efficacy data.

a. *Claims of "extra-effective."* The presence of more active ingredient in an antiperspirant product cannot be used as a basis for a claim of "extra-effective" because additional amounts of active ingredient do not necessarily result in improved product effectiveness. (See part II., paragraph H. above—Effectiveness of Antiperspirants.) The Panel has placed the "extra-strength" claim in Category II because it implies improved performance through increases concentration. (See part III., paragraph B.2. above—Category II Labeling.)

The Panel concludes that antiperspirant products that can be proven to possess superior effectiveness ought to be allowed to claim this added benefit on their labels. However, the Panel believes it prudent and fair to both industry and the public to require satisfactory proof of additional effectiveness at a level meaningful to the user before such claims are allowed.

The Panel recommends the following to substantiate claim of "extra-effective": The product must produce at least a 30-percent reduction in perspiration as measured gravimetrically in adequately controlled, laboratory clinical tests using the procedures outlined by the Panel in the effectiveness testing section of this document. (See part II., paragraph H.4.f. above—Antiperspirant effectiveness qualification test.) In addition, a user perception test must be conducted to assure that the objectively validated increase in effectiveness is large enough to be perceptible by the user under normal conditions of use. The user perception test must be so designed as to measure the benefit attributable to the antiperspirant effect and not to the perfume or any other cosmetic feature. The statistical criteria and protocol for the user perception test are discussed later in this document. (See part III., paragraph C.3. below—Guideline for user perception test to be done for claims of "extra-effective" to be classified as Category I.)

b. *Claims for foot and hand antiperspirancy.* The materials placed in Category I have been shown through numerous clinical tests to be safe and effective antiperspirants when used in the axillae. Although these materials would very likely reduce perspiration from other surfaces of the body, notably the hands and feet, there is a dearth of clinical evaluations of this effect.

The Panel is aware of only two controlled studies (Ref. 1) which tested an aluminum chlorhydrate formulation

as a foot antiperspirant. Although these investigations demonstrated a reduction of perspiration from the treated foot, the level of effectiveness was not correlated with user perception. To establish a standard for antiperspirant activity for the foot or hand, it is necessary to have information from the test subjects with regards to their perception of effectiveness. A user perception test similar in design to that required for Category III claims of extra-effective should be performed except that the test antiperspirant will be compared on the hands and/or feet to a placebo rather tha a standard antiperspirant. (See part III., paragraph C.3. below—Guidelines for user perception test to be done for claims of "extra-effective" to be classified as Category I.) Also, the test antiperspirant should produce at least a 20-percent reduction in the objectively measured test rather than the 30-percent reduction required for "extra-effective" antiperspirants. Until such information is provided, the claim of antiperspirancy on the hands and feet is to be considered a Category III claim.

c. *Claims for enhanced duration of effect.* The Panel has not received any scientific data which would support a claim of enhanced duration of antiperspirancy. The duration of the pharmacological effect of Category I and III ingredients has never been established. Without such information it is not possible for a product to claim prolonged or enhanced duration of effect. If a claim for a specific or prolonged duration of activity is to be made for an antiperspirant formulation it must be substantiated by a modification of the protocol described for the measurement of effectiveness. (See part II., paragraph H.4.f. above—Antiperspirant effectiveness qualification test.) The perspiration rate of the test subjects must be measured at various times after application. At least two times must be selected which span the period of the claim. The percent sweat reduction values determined at the various times must pass the statistical test outlined for data treatment.

d. *Claims suggesting use for "problem" or "especially troublesome" perspiration.* The Panel has not received any data which would support a claim for use in problem or especially troublesome perspiration. The Panel concludes that in order for claims of this type to become Category I, a user perception test, similar in design to that required for claims of "extra-effective," must be performed except that only the upper 5 percent of sweaters (heavy sweaters) should be included in the test. (See part III., paragraph C.3. below—Guidelines for user perception test to be done or claims of "extra-effective" to be classified as Category I.) The user perception test should be performed only if the test antiperspirant produces at least a 30-percent reduction using the objective gravimetric test.

e. *Claims for control of emotional sweating.* Axillary perspiration can also be elicited by emotional stimuli. Under certain psychologically stressful situations the amount of axillary sweat produced was found to be twice as great as that derived under typical hotroom procedures (Ref. 2). Although there is a sufficient amount of scientific evidence to make an assessment of the effectiveness of many materials in controlling thermally induced perspiration, such is not the case regarding emotional sweating.

Some general procedures have been described for the measurement of the effectiveness of a formulation in retarding emotionally stimulated axillary sweat (Refs. 2 and 3). The procedures are similar in many respects to those used in the hotroom test. The major exceptions are with regard to the environmental conditions, usually between 70° F and 80° F, and the challenge used to initiate emotional sweat. The test subjects can be challenged individually or as a group. The stimuli can take the form of mental arithmetic, memory games, word associations, lists, electric shock, singing, storytelling, and verbal quizzes. The degree of reduction of emotionally induced perspiration can be assessed by comparing a test formulation against a control. It is important that the control and test formulations be studied under similar stress conditions. For treatment of data see the antiperspirant effectiveness testing section of this report. (See part II., paragraph H.4. above—Effectiveness testing of antiperspirants.)

The copious amounts of perspiration stemming from psychological stress are exceedingly difficult to control. Shelley and Hurley (Ref. 4) suggested that many antiperspirants are washed away from their site of action by the large amounts of sweat produced by emotional stimuli. This could result in a greatly diminished activity.

The data available to the panel on aluminum chlorhydrate (Ref. 3) suggest that this material can be formulated in a manner which can reduce emotional sweating. Whether the degree of reduction measured is perceptible to the subjects was not determined. Since the sweat output is high under such stress, it is important to have information regarding the perceived degree of axillary wetness to establish standards for antiperspirancy.

A user perception test similar in design to the one required for "extra-effective" claims will be required for claims for control of emotional sweating to move from Category III to Category I. However, the test antiperspirant will be compared to a placebo rather than a standard antiperspirant, and sweating will be induced by emotional stimuli rather than the hotroom or ambient methods. (See part III., paragraph C.3. below—Guidelines for user perception test to be done for claims of "extra-effective" to be classified as Category I.)

Until such a time (within 2 years after the final monograph) that these data are made available and evaluated, all claims regarding control of emotional sweating are deemed Category III.

f. *Category III labeling claims.* The following is a list of submitted labeling claims which have been placed into Category III: "One spray keeps you comfortably dry all day," "Prolonged protection," "24-hour Protection," "Round the clock protection," "Long-lasting Protection," "Protects as you need it," "Reacts when you do," "Time-release," "Heat-Tension-Exercise. Fights all three kinds of wetness and odor."

REFERENCES

(1) OTC Volume 140027.
(2) Quatrale, R. P., K. L. Stoner, and C. B. Felger, "A Method for the Study of Emotional Sweating," Journal of the Society of Cosmetic Chemists, 28:91-101, 1977.
(3) OTC Volume 140033.
(4) Shelley, W. B., and H. J. Hurley, "Studies on Topical Antiperspirant Control of Axillary Hyperhidrosis," Acta Dermatovener, 55:241-260, 1975.

C. DATA REQUIRED FOR EVALUATION

The guidelines recommended in this document for the studies required to bring a Category III antiperspirant drug product into Category I are in accord with the present state of the art and do not preclude the use of any advances or improved technology in the future.

1. *Guidelines for products categorized as Category III because of inadequate data concerning their safety for the skin.* Skin reactions to topically applied agents are customarily thought to occur by one of two different mechanisms, either due to allergens or irritants.

It may be difficult to test for allergens prior to marketing because allergens depend for their effect on individual differences in susceptibility to sensitization (Refs. 1 through 4). Of the antiperspirant materials that have been reviewed, those in Category I are not sensitizers and the Panel feels that nothing more than the standard older tests (Refs. 1 and 2) should be required for other antiperspirants.

Primarily because of their low pH, however, all of the antiperspirant materials are capable of producing some skin irritation. Considering the irritating nature of these chemicals, it is fortunate that they are designed to be

applied to the axillary vault. Dermatologists have long recognized that hairy areas are relatively resistant to the development of contact dermatitis from either allergens or irritants.

Lanman, Elvers, and Howard (Ref. 3) and Elvers and Lanman (Ref. 4) have suggested the use of comparative controls in evaluating the tendency of agents to irritate the skin. This concept of comparing the irritancy of the test agent with the irritancy of other widely used agents makes special sense in evaluating antiperspirant products. For one thing, a single ingredient, aluminum chlorohydrate, so dominates the present antiperspirant market that comparative testing against aluminum chlorohydrate affords a sensible, practical technique of evaluation. For another, the use of known marketed products for comparison permits the rational introduction of risk/benefit considerations into the question of "how much?" risk.

At this point it might be noted that the Panel applied such considerations to the topical application of aqueous solutions of aluminum chloride, deeming them more irritating than the aluminum chlorhydrates but at the same time more effective and, therefore, placed them in Category I with an additional warning, *"Warning:* Some users of this product will experience skin irritation."

The following is, therefore, suggested as a technique for deciding whether ingredients now in Category III because of questions of skin irritancy could be reclassified into Category I, or into Category I with special irritancy warnings, or into Category II.

a. If the ingredient in final product form is no more irritating than aluminum chlorohydrate in the same vehicle using the Lanman technique, it is acceptable as Category I.

b. Ingredients in final product form which are more irritating in the comparative irritancy test than aluminum chlorohydrate in the same vehicle, must demonstate a significantly greater reduction in perspiration than the effectiveness standard.

c. If the ingredient in final product form although more irritating than aluminum chlorohydrate in the same vehicle, is more effective, it must bear an additional label warning of irritation, *"Warning:* Some users of this product will experience skin irritation," but may be classifed as Category I.

Summary of Guidelines for Converting Category III Ingredients to Category I

Category	Skin irritation (compared with aluminum chlorohydrate)	Effectiveness
I	No more irritating	20 pct.
I plus warning label	More irritating	Statistically significantly better than 20 pct.
II	do	Not statistically significantly better than 20 pct.

2. *Guidelines for tests to be done for aerosolized antiperspirant sprays to be classified as Category I.* Since the aluminum chlorohydrates are the predominant active ingredients in the antiperspirant market, the following guidelines are written specifically for them. Other aerosolized antiperspirant ingredients which are Category III should follow the same guidelines except that the test material will be the active ingredient used in the marketed formulation rather than the aluminum chlorohydrates as discussed below.

a. *Preliminary studies.* Prior to conducting the chronic animal inhalation study the following steps will be taken:

(1) *Determination of 1 times human exposure level.* The concentration, which shall be the 1 times level for the chronic animal inhalation study, of respirable aluminum to which persons are exposed during heavy usage of aerosolized antiperspirants in finished product form will be determined. Heavy usage is defined as the upper 95 percent tolerance limit (i.e., that concentration exceeded by only 5 percent of the population) of the distribution of individual respirable aluminum concentration values as determined by the following procedure.

A minimum of 20 subjects should participate in the test. They are given finished product samples of the aerosol antiperspirant to be used for a 1-week period prior to the exposure assay in order to permit them to become accustomed to the product. Subjects may not be selected for their pattern of use of antiperspirant products. Each subject should participate in a series of supervised normal use collections. The number of such collections (5 to 15) should be determined by the efficiency of the sampling instrument used; the objective being to collect a sufficient quantity of material to permit an accurate aluminum assay. For each of these collections the subject should be given a sample of the product and asked to spray both axillae according to his/her normal practice, and to remain in the test room (simulated home bathroom) for 15 minutes. During the application and 15-minute postapplication period the collection of respirable aluminum in the breathing zone should be continuous. Room air should be changed between subject runs, but not during the collection period.

Upon entering the test room the subject should be positioned near a respirable mass sampling device, with the collection port located in close proximity to the nose. The subject should be given an aerosol package and asked to apply the product to both axillae in his/her usual manner. Having had the opportunity in the pretest period to consult the label directions, the subject should receive no specific instructions on the test days with respect to distance, duration, or direction of product application. Air sampling of the breathing zone should be initiated at the start of product application and continued for 15 minutes. During the entire collection period a constant sampling flow rate should be maintained at the level appropriate for the specific instrument used.

At the end of each subject's scheduled series of 15-minute test exposures, the cumulative amount of aluminum in the collected respirable particles should be analyzed by a suitable analytical method. The quantity of aluminum so determined, divided by the product of exposure time and flow rate, represents that individual's respirable aluminum concentration value.

(2) *Determination of animal chamber conditions equivalent to human exposure.* Conditions of chamber flow rate and duration and frequency of actuation necessary to produce a chamber concentration equivalent to the human 1 times exposure levels and multiples thereof, should be determined.

(3) *Preparation of prototype product forms.* For the animal studies, prototype aerosolized antiperspirants should be formulated which are representative of marketed product forms and which, for each of these marketed forms, deliver the highest concentration of respirable aluminum in the breathing zone.

(4) *Pulmonary deposition of aluminum in animals.* Preliminary studies to relate exposure conditions to pulmonary deposition of aluminum from prototye product formulation and to provide the basis for the selection of dose levels and product formulation type to be used in the chronic animal inhalation studies should be conducted.

b. *Chronic animal inhalation study.*—(1) *Test material.* The Panel believes that to test every chemical known as aluminum chlorhydrate would be an enormous undertaking that is not necessary to assess the chronic pulmonary toxicity of aerosol products of these materials. The chemical properties of the aluminum chlorhydrates are very similar and all evidence presented to the Panel on the toxicity of these materials suggests that they have the same risk potential. The Panel concludes that it would be sufficient to carry out the proposed test on the aluminum chlorhydrate formulation which in the preliminary studies has been demonstrated to show the greatest potential for pulmonary deposition.

(2) *Animals.* The respiratory systems of lower animals are sufficiently different from humans that it is difficult to assign the burden of proof of safety to one animal species (Refs. 5 and 6). By selecting two animal species, a large and a small one, a check on species variation would be provided. The two groups of animals to be selected for this long-term study are the cynomolgus monkey for the larger test animal, and the syrian hamster, rabbit, or rat for the smaller one. There is a substantial body of knowledge on the respiratory characteristics of these animals which should facilitate the extrapolation of the experimental results to humans (Ref. 5).

(3) *Exposure conditions.* The animals should be whole-body exposed to the test material from aerosol packages for 15 minutes twice daily in the morning and evening for 7 days a week for the duration of the study. Air control animals should be exposed to filtered room air in a similar chamber with flow characteristics identical to those of the treatment groups.

(4) *Duration of test.* The duration of the inhalation test should be 2 years. The Panel took into its consideration a number of factors in deciding on this duration. The primary factors considered were the period necessary to induce in animals or humans lung disorders of the type that might develop from the chronic use of aerosol antiperspirants, the length of time these products are used by the public, and the practicality of carrying out a long-term inhalation study on laboratory animals. In the case of the smaller animal, 2 years represents its life expectancy, while for the larger animal it is a significant fraction of their lives.

(5) *Group design.* The following group design should be followed:

Group Design for Inhalation Study

Group [1]	Number of large animals	Number of small animals
Air control	8 (4 males, 4 females)	200 (100 males, 100 females).
1 times [2]	8 (4 males, 4 females)	100 (50 males, 50 females).
10 times	8 (4 males, 4 females)	100 (50 males, 50 females).
100 times	8 (4 males, 4 females)	100 (50 males, 50 females).
Recovery group [3]	8 (4 males, 4 females)	None.

[1] The five groups listed are the minimum suggested for this test, although additional levels may be added to provide a more precise estimate of the maximum no-effect level.

[2] The 1 times will be determined by the preliminary studies.

[3] The recovery group will be exposed at the 100 times level for 24 months and sacrificed at 27 months. No recovery group is included for the small animal due to animal longevity.

(6) *Chamber monitoring.* Total particulate, particulate size distribution, and active ingredient analysis should be monitored in the chambers during exposure.

(7) *Biological measurements.*—(i) *Body weights.* The small animals should be weighed weekly for the first 13 weeks and every 2 weeks thereafter. The large animals should be weighed weekly throughout the study.

(ii) *Daily observations.* All animals should be observed twice daily during exposure for pharmacologic activity and/or toxic effects.

(iii) *Serum chemistry.* Serum chemistry should be performed on the large animals prior to exposure and every 3 months thereafter.

(iv) *Hematology.* Hematology studies should be performed on the large animals prior to exposure and every 3 months thereafter.

(v) *Urinalysis.* Urinalysis studies should be performed on the large animals prior to exposure and every 3 months thereafter.

(vi) *Ophthalmoscopic examination.* The large animals should have an ophthalmoscopic examination prior to exposure and prior to sacrifice.

(8) *Post-mortem examination.*—(i) *Gross pathology.* (*a*) The following tissues from each animal should be removed at necropsy and weighed: Brain, thyroids, lungs, adrenals, liver, kidneys, spleen, gonads, and heart. Organ/body-weight and organ/brain-weight ratios should be calculated and analyzed statistically.

(*b*) The following tissues should be removed at necropsy and fixed: Brain (cerebellum, midbrain, cerebrum); stomach; esophagus; thyroid, parathyroid; pituitary; eyes; thymus; heart; spleen; bone marrow (sternum); skeletal muscle; pancreas; small intestine; large intestine; adrenals; cervical lymph node; mesenteric lymph node; liver; skin; gonads; peripheral nerve; kidneys; aorta (thoracic); respiratory system (external nares, larynx, lungs, nasopharynx, trachea, tonsils, cervical lymph nodes, nasal turbinates, peribronchial lymph nodes).

(ii) *Histopathology.* The following organs from the 100-times and the air control group should be prepared for histopathologic examination. If effects at the 100-times level are noted, lower concentration groups should be examined, in order, until a no-effect level is established: Brain, stomach, pituitary, eyes, thymus, heart, peripheral nerve, kidneys, esophagus, thyroids, small intestine, cervical lymph node, skeletal muscle, spleen, bone marrow (sternum), adrenals, pancreas, large intestine, mesenteric lymph node, gonads, liver, skin, respiratory system (external nares, lungs, larynx, nasopharynx, trachea, cervical lymph nodes, nasal turbinates, peribronchial lymph node, tonsils). All animals that die during the study should be autopsied and the tissues saved for histopathology. Animals that appear moribund during the study should be sacrificed and the tissues saved for histopathology.

(9) *Deposition of aluminum.* Aluminum deposition in the tracheal-bronchial-aveolar systems of the large and the small animals will be determined. The measured level of aluminum in the lungs of the test animals exposed to the highest concentration of aluminum salt must be significantly above background.

(10) *Good laboratory practice.* The study should be conducted in accordance with good laboratory practices.

3. *Guidelines for user perception test to be done for claims of "extra-effective" to be classified as Category I.* The test antiperspirant should be compared with a standard antiperspirant (20 percent sweat reduction in at least half of the subjects using the binomial test). The perception trial should be properly blinded and randomized such that half the subjects will receive the test antiperspirant under the left arm and the standard antiperspirant under the right arm, and the other half of the subjects will have treatment assignments in the reverse order. Sweating may be induced by either the hotroom or ambient method. At the end of the trial, subjects will be asked whether they felt that their right axilla or their left axilla was kept drier. Questions such as: "Which product did you prefer?" should not be allowed as the only question, because greater preference for one product

cannot be directly attributed to extra antiperspirant performance, but may be due to less stinging, perfume, etc.

After deleting the "no difference" response (i.e., those subjects who could not decide for either product) the binomial test with $H_0p=0.5$ may be applied. That is, if the null hypothesis of no difference between the two products may be rejected at the 0.05 level in the reduced sample (ties removed), then the manufacturer may make an extra effective claim.

This statistical test reduces to the simple procedure of counting the number of subjects who expressed a preference for the test antiperspirant as follows:

Total number of test subjects expressing a preference	Number of subjects required to express preference for the test antiperspirant
20	15
25	18
30	20
100	58

This test will demonstrate that with high probability at least 50 percent of the target population will experience the added benefit.

REFERENCES

(1) Shelanski, H. A., and M. V. Shelanski, "A New Technique of Human Patch Tests," Proceedings of the Scientific Section of the Toilet Goods Association, 19:46-49, 1953.

(2) Draize, J. H., "Dermal Toxicity," in "Appraisal of Safety of Chemicals in Foods, Drugs, and Cosmetics," Association of Food and Drug Officials of the United States, Texas State Department of Health, Austin, Tex., pp. 46-59, 1959.

(3) Lanman, B. M., W. B. Elvers, and C. S. Howard, "The Role of Human Patch Testing in a Product Development Program," in "Proceedings of the Joint Conference on Cosmetic Sciences," Washington, D.C., pp. 135-145, 1968.

(4) Elvers, W. B., and B. M. Lanman, "The Role of Human Patch Testing in a Product Development Program: An Update," in "Proceedings of the Joint Conference on Cosmetic Sciences," Washington, D.C., 1972, copy is included in OTC volume 140065.

(5) Jones, R. K., letter to G. E. Thompson, FDA, October 3, 1975, copy is included in OTC volume 140065.

(6) Transcript of open session, December 18, 1975.

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

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended by adding new part 350, to read as follows:

PART 350—ANTIPERSPIRANT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
350.1 Scope.
350.3 Definitions.

Subpart B—Active Ingredients

350.10 Antiperspirants.

Subpart C—Testing Procedures

350.40 Effectiveness qualification test.
350.41 Test subjects.
350.42 Test conditions.
350.43 Test procedures.
350.44 Data treatment.

Subpart D—Labeling

350.50 Labeling of antiperspirant products.

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

Subpart A—General Provisions

§ 350.1 Scope.

An over-the-counter antiperspirant is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part 350 and each of the general conditions established in § 330.1 of this chapter.

§ 350.3 Definition.

Antiperspirant. A product which when applied topically will help reduce the production of perspiration (sweat).

Subpart B—Active Ingredients

§ 350.10 Antiperspirants.

The active ingredients of the product consist of the following within the dosage limit estiblished for each ingredient:

(a) *Aluminum chlorhydrates (aluminum chlorohydrate, aluminum dichlorohydrate, aluminum sesquichlorohydrate, aluminum chlorohydrex PG, aluminum sesquichlorohydrex PG, aluminum dichlorohydrex PG, aluminum chlorohydrex PEG, aluminum sesquichlorohydrex PEG, aluminum dichlorohydrex PEG).* Dosage is 25 percent or less concentration (calculated on an anhydrous basis) of a nonaerosol dosage form.

(b) *Aluminum zirconium chlorhydrates (aluminum zirconium trichlorohydrate, aluminum zirconium trichlorohydrex Gly, aluminum zirconium pentachlorohydrate, aluminum zirconium pentachlorohydrex Gly, aluminum zirconium tetrachlorohydrate, aluminum zirconium tetrachlorohydrex Gly, aluminum zirconium octachlorohydrate, aluminum zirconium octachlorohydrex Gly).* Dosage is 20 percent or less concentration (calculated on an anhydrous basis) of a nonaerosol dosage form.

(c) *Aluminum chloride.* Dosage is 15 percent or less concentration (calculated on the hexahydrate form) of an aqueous solution nonaerosol dosage form.

(d) *Buffered aluminum sulfate.* Dosage is 8 percent concentration of aluminum sulfate buffered with 8 percent concentration of sodium aluminum lactate in a nonaerosol dosage form.

Subpart C—Testing Procedures

§ 350.40 Effectiveness qualification test.

To qualify as effective, and antiperspirant in finished product form must meet or exceed the criteria established in this subpart. This qualification requirement applies to all formulae except those variants which differ from a qualified formula only with respect to color and/or perfume ingredients.

§ 350.41 Test subjects.

(a) Test subjects must be sufficiently representative in that the differences between the highest and lowest rates of sweating among the test subjects must exceed 600 mg/20 minutes/axilla. Information on the sweating rate will be obtained during pretreatment sweat collections or by sweat collections taken from the control axilla during treatment.

(b) Test subjects are required to abstain from the use of all antiperspirant materials for at least 1 week prior to pretreatment or treatment sweat collections.

§ 350.42 Test conditions.

Either hotroom or ambient conditions may be used to obtain gravimetric measurements of axillary perspiration rate.

(a) *Hotroom conditions.* (1) Test subjects are placed in a controlled environment (100° F and 35 percent relative humidity) to thermally induce perspiration.

(2) Care must be taken to insure that factors which are known to influence axillary sweating (i.e., air movement,—mental, or emotional stimuli, position of the trunk and extremities) are properly controlled.

(b) *Ambient conditions.* Test subjects are allowed to go about their normal daily routines during the collection period.

§ 350.43 Test procedures.

(a) *Hotroom procedure.* (1) Treatments consists of the application of the test formulation to one axilla and the control formulation to the other axilla of each of the test subjects. (The control formulation is identical to the test formulation except that it is devoid of the active antiperspirant ingredient.)

(2) Half of the subjects will be randomly assigned to receive the test formulation under the left axilla and the control formulation under the right axilla, leaving the remaining subjects to be assigned oppositely.

(3) The quantity of each formulation applied to all the test subjects must reflect the amount that a typical person would apply under normal use conditions.

(4) Treatment applications are made once daily. It is important that the number of treatments preceding the collections of axillary perspiration for evaluation be recorded. At least one daily treatment should be carried out before the test.

(5) Preweighed absorbent pads are placed in both axillae of each of the test subjects.

(6) Test subjects are placed in the controlled environment for a period of from 10 to 30 minutes.

(7) Perspiration is collected on the absorbent pads, and the absorbent pads are again weighed at the end of the collection period.

(8) If a pretreatment evaluation is made to determine the ratio of right to left axillary sweating rate of each subject, the control formulation will be applied to both axillae of each test subject.

(b) *Ambient procedure.* The ambient procedure is performed in the same manner as the hotroom procedure except that the test subjects are allowed to go about their normal daily routines, and the collection period is for a period from 3 to 5 hours.

§ 350.44 Data treatment.

(a) Sweat reduction is defined for each subject by the formula:

$$\text{Percent sweat reduction} = \frac{C - T}{C} \times 100$$

where C is the raw milligram weight measure of moisture from the control axilla and T is the corresponding quantity from the test axilla.

Appropriate modifications of this formula are acceptable if pretreatment ratios of the right to left axillary sweating rate are determined.

(b) A statistical analysis of the percent sweat reduction values will be conducted by a binomial test. In statistical terminology:

$H_0 = P < 0.5$.
$H_A = P > 0.5$ ($\alpha = 0.05$, one sided).

where H_0 is the null hypothesis, P is the probability, H_A is the alternative hypothesis, and α is the predetermined arbitrary level of significance.

(c) A product qualifies as effective if the number of subjects having a percent sweat equal to or greater than 20 percent is equal to or exceeds the number of a given sample size as follows:

Total number of test subjects:	*Sweat reduction* [1]
20	15
35	18
30	20
100	58

[1] Minimum number of subjects required to have at least a 20-pct. sweat reduction.

(d) The test will demonstrate that with high probability at least 50 percent of the target population will obtain a sweat reduction of at least 20 percent.

Subpart D—Labeling

§ 350.50 Labeling of antiperspirant drug products.

(a) *Statement of identity.* The labeling of the product shall contain the established name of the drug, if any, and shall identify the product as an "antiperspirant."

(b) *Indications.* The labeling shall contain a statement under the heading "Indication(s)" that shall be limited to one or more of the following phrases: "Helps reduce wetness," "Helps reduce dampness," "Helps reduce perspiration." The labeling shall also include the following statement: "Products described as antiperspirants can be expected to produce at least a 20-percent reduction in underarm perspiration in at least half the users when applied once daily."

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

(1) For products containing any antiperspirant ingredient identified in § 350.10: "Do not apply to broken skin. If a rash develops, discontinue use."

(2) For products containing aluminum chloride identified in § 350.10(c): "*Warning:* Some users of this product will experience skin irritation."

(d) *Directions.* The labeling of the product shall contain the following statement under the heading "Directions": "Apply to skin of underarms. Not to be used generally over the body."

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the hearing clerk docket number found in brackets in the heading of this document) regarding this proposal on or before January 8, 1979. Such comments should be addressed to the Office of the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before February 7, 1979. Received comments may be seen in the above office from 9 a.m. to 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the hearing clerk, Food and Drug Administration.

Dated: September 22, 1978.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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