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Guidance for Industry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

GUIDELINE FOR UPGRADING CATEGORY III ANTIPERSPIRANTS TO CATEGORY I

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 produot 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 $H_o p = 0.5$ 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: