DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 350

[Docket No. 78N-0064]

Antiperspirant Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (Proposed Rule)

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed regulation in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) antiperspirant drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Antiperspirant Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by October 19, 1982. New data by August 20, 1983. Comments on the new data by October 20, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Comments on the agency's economic impact determinations by December 20, 1982.

ADDRESS: Written comments, objections, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. New data and comments on new data should also be addressed to the Dockets Management Branch.

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

SUPPLEMENTARY INFORMATION: In the Federal Register of October 10, 1978 (43 FR 46694), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC antiperspirant drug products, together with the recommendations of the Advisory Review Panel on OTC Antiperspirant Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by January 8, 1979. Reply comments in response to comments filed in the initial comment period could be submitted by February 7, 1979.

In a notice published in the Federal Register of March 21, 1980 (45 FR 18403), the agency advised that it had reopened the administrative record for OTC antiperspirant drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final rule.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above) after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the Federal Register on October 10, 1978 (43 FR 46694), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograh (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC antiperspirant drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC antiperspirant drug products.

In response to the proposal, 1 drug manufacturer association, 4 drug manufacturers, 1 research laboratory, 1 medical center, and 17 consumers submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

This proposal to establish Part 350 (21 CFR Part 350) constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC antiperspirant drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

FDA published in the Federal Register of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph (46 FR 47738).

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

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of

an approved new drug application. Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC antiperspirant drug products (published in the Federal Register of October 10, 1978; 43 FR 46694), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the Federal Register and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the Federal Register. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

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) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments.

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the Federal Register of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the Federal Register of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e. g., *National Nutritional Foods Association* v. *Weinberger*, 512 F. 2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 437 F. Supp. 412 (S.D.N.Y. 1980), Affd., 637 F. 2d 877 (2d Cir. 1981).

B. Safety of Antiperspirants.

2. One consumer pointed out that perspiration is a natural body function and questioned the risks of impeding this function by the use of antiperspirants.

The agency points out that the Panel adequately addressed this concern in its report. The Panel recognized that, although cooling of the skin through evaporation of perspiration is often the only effective way of maintaining proper body temperature, even total inhibition of underarm perspiration would not compromise the body's ability to maintain proper thermal regulation. However, the Panel was concerned that use of an antiperspirant over the entire body could affect the thermoregulatory system and for this reason concluded that antiperspirants should not be allowed to be marketed OTC for use over the entire body. The agency concurs with the Panel's conclusions.

3. Four consumers reported side effects they experienced while using OTC aerosol antiperspirant products. These included weeping eyes, sneezing, coughing, gasping for breath, bronchial irritation, and spitting up mucus. One consumer stated that an aerosol powder sprayed under the arms permeated the air in the bathroom and caused her eyes to swell shut.

The Panel concluded that adverse reactions of this type occurring from the use of aerosol antiperspirants constitute an acceptable risk. The Panel also concluded that the acute and subactute toxicity studies adequately document the short-term safety of aluminum chlorhydrate aerosolized products. Because there are equally effective nonaerosol dosage forms available for applying antiperspirants to the axillae, it is a relatively simple matter for consumers to switch to a different dosage form when adverse reactions, such as those reported, occur from the use of aerosols. Based on statements contained in the comments submitted, this is exactly what consumers do. The agency agrees with the Panel that the short-term use of aerosol antiperspirant products poses an acceptable risk to consumers. In addition, recently submitted data indicate that aerosol antiperspirants can generally be recognized as safe and effective for long-term use as well. (See comment 22 below.)

4. Eight consumers reported side effects they experienced while using OTC nonaerosol antiperspirant products. The most common side effects reported were rashes and itching. Two consumers reported having axillary surgical procedures for conditions that they claimed resulted from the use of antiperspirant/deodorant products. One of these individuals included a copy of a medical history that showed the condition to be diagnosed as "hidradenitis suppurativa, chronic state."

The agency points out that, in discussing the safety of antiperspirants, the Panel recognized that some users of these products experience local irritation from applying the product to the underarm area. The major side

effects are rash and irritation, which occur at the site of application and which usually disappear upon discontinuing use of the product. The Panel acknowledged these side effects by recommending a warning to discontinue use if rash occurs.

Hidradenitis suppurativa, a dermatologic condition indigenous to the axillae, is a chronic and indolent disorder of the apocrine sweat glands. The Panel considered this disorder during its review of the safety of antiperspirants (43 FR 46708), but was unable to find any correlation between the disorder and the use of antiperspirants. While treatment of this disorder usually prohibits the use of antiperspirants, current medical thought has not implicated antiperspirants as causative agents.

The Panel concluded that the side effects that occur from the use of Category I antiperspirant active ingredients are an acceptable risk because they are not serious and are readily reversible. The Panel believed that its recommended warnings in § 350.50(c) were adequate to warn consumers to discontinue use of the product should side effects occur. The agency concurs and further believes that expanding the statements in revised § 350.50(c) to include the term "irritation" will adequately warn consumers to discontinue use of the product should rash or irritation occur. This expanded warning will also eliminate the need for the irritation warning recommended in § 350.50(c)(2), and this section can be deleted from the monograph.

C. Effectiveness of Antiperspirants

5. One comment from a research laboratory stated that a "correlation between reduction in axillary odors and reduction in microbial population of the axilla cannot be demonstrated." For this reason, the comment suggested deleting the following statement, which appeared as part of the Panel's discussion of deodorant effectiveness of antiperspirants: "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."

The agency points out that the Panel believed that the probable mechanism for the deodorant effect of antiperspirants is due to the antibacterial action of the antiperspirant ingredients. The Panel did not feel it was necessary for this theory to be proven to justify a deodorant claim for the antiperspirant ingredients reviewed, because "sniff tests" that were conducted using representative products substantiated the claim. However, in the interest of science, the Panel made the statement referenced in the comment hoping that data to prove its theory could be developed. Because data on suppression of bacteria in the axilla as it relates to odor reduction are not required for antiperspirant ingredients subject to this monograph, the agency sees no need to delete the Panel's statement or to address the issue further in this document.

6. One comment protested that the Panel went beyond its legal authority in discussing deodorant effectiveness in its report because a deodorant claim is a cosmetic representation, and the cosmetic aspects of an OTC drug are not subject to the OTC drug review. The comment requested that all references made by the Panel to cosmetic claims and deodorant efficacy not be considered further by the agency.

The agency does not believe that the Panel went beyond its legal authority in discussing deodorant effectiveness in its report. The Panel felt that a discussion of deodorant effectiveness was needed to provide information on the activity and overall effects of antiperspirants. The Panel acknowledged that deodorancy is a cosmetic claim and stated that its concern was limited to the effect of antiperspirants on deodorancy as a means of defining the actions of antiperspirants. This statement is consistent with the procedural regulations governing the OTC drug review (published in the Federal Register of May 11, 1972; 37 FR 9473) which state "Any product for which only cosmetic claims are made and which is therefore not a drug will not be reviewed." In addition, in the calls for data for those panels reviewing drug products with both drug and cosmetic claims, the agency solicited safety data that may be available as a result of testing related to nondrug products, such as cosmetics, but stated that the panels were charged with reviewing the safety and effectiveness of the active ingredients in drug products and not with reviewing the safety and effectiveness of these same ingredients used in products for cosmetic purposes. (See Federal Registers of April 4, 1972 (37 FR 6775); September 7, 1973 (38 FR 24392); and November 16, 1973 (38 FR 31698).) Accordingly, the deodorant effectiveness of antiperspirants is not being considered further in this document.

7. One comment objected to the Panel's determination that a 20-percent reduction in perspiration in at least half the users is the minimum standard of antiperspirant effectiveness, based on the results of user perception tests. The comment argued that the amount of perspiration reduction required or preferred depends upon the individual and that the standard of a 20-percent reduction in half the users tested does not accommodate those individuals who require or prefer less. The comment contended that, for proof of effectiveness, it should be enough to show through well-controlled studies that a product reduces perspiration to a statistically significant degree, rather than by a minimum of 20 percent in half the users tested.

The agency disagrees with the comment. The agency concurs in the Panel's conclusion that, in order for an antiperspirant to be considered effective, the level of perspiration reduction must be such that the majority of users may reasonably expect to perceive it. Merely reducing the level of perspiration to a statistically significant degree will not assure a reduction that will be noticeable to users. The agency concurs with the Panel that data presented from an independent test laboratory (Ref. 1) correlating gravimetric tests with user perception tests establish that 20 percent is the minimum level of reduction required to assure a perceptible effect.

Reference

(1) Majors, P. A., and F. B. Carabello, presentation to the Advisory Review Panel on OTC Antiperspirant Drug Products concerning the Hill Top Research Method of Antiperspirant Evaluations, OTC Volume 140065.

8. Two comments agreed with the Panel's minority opinion that effectiveness testing of final antiperspirant product formulations containing Category I active ingredients is unnecessary. These comments argued that such a requirement is inconsistent with the original intent of the monograph system, namely, to review active ingredients rather than final products. One of the comments stated that no other monograph requires that a finished product containing a Category I active ingredient be tested for effectiveness in humans and that such a test sets an unnecessary requirement, particularly for a product that is not used to treat disease.

The agency agrees with the comments and the Panel's minority opinion that final formulation testing should not be required for antiperspirant drug products. However, as the Panel pointed out in its report, even minor variations in formulation, such as the addition of

emollients or buffers, can alter the effectiveness of an antiperspirant ingredient. Therefore, the agency is making the Panel's recommended testing procedures, with modifications based on the comments, available as guidelines to drug manufacturers. FDA encourages the use of these guidelines to assure the effectiveness of individual products.

D. Combination Policy

9. Two comments objected to the Category II classification of any antiperspirant combinations, i.e., either with other antiperspirant active ingredients or with Category I active ingredients from other pharmacological groups. The comments stated that the combination policy for OTC drugs set forth in § 330.10(a)(4)(iv) (21 CFR 330.10(a)(4)(iv)) allows the combination of two or more safe and effective active ingredients and urged that the Panel's classification of such antiperspirant combinations as Category II be reversed.

The agency points out that the Panel did not receive any data for actual combinations of antiperspirant active ingredients and was not aware of any product that contains more than one identifiable active antiperspirant ingredient. 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 these various antiperspirant ingredients, 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 single identifiable ingredients. One submitted product did contain two ingredients, aluminum sulfate and sodium aluminum lactate. However, the Panel concluded that sodium aluminum lactate is not an active ingredient in the formulation because it is present as a corrective agent to counteract the irritating effects of the aluminum sulfate. In the absence of any information concerning the existence of any such combinations or data to support their safe and effective use, the Panel placed all antiperspirant products containing more than one antiperspirant active ingredient in Category II. The agency concurs with the Panel's conclusion.

The Panel received a submission on a product no longer marketed that contained an antiperspirant and an antibacterial ingredient. The antibacterial ingredient was present in the product to produce a deodorant effect, and the Panel decided early in its review not to review deodorant claims because they have been considered cosmetic claims. The Panel also received data on products containing both antiperspirant and antifungal active ingredients to be used in the treatment of athlete's foot. After evaluating the safety and effectiveness of the antiperspirant ingredients in these products, the Panel deferred the products to the OTC Antimicrobial II Panel for evaluation of the usefulness of such a combination in the treatment of athlete's foot. Hence, the Panel did not classify such a combination.

The Panel, however, recognized that the combination drug policy for OTC drug products set forth in § 330.10(a)(4)(iv) allows an OTC drug product to combine two or more safe and effective active ingredients when each active ingredient makes a contribution to the claimed effect(s) and when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients. The Panel acknowledged the possibility of combining a Category I antiperspirant with Category I ingredients from other OTC drug monographs. In fact, the Antimicrobial II Panel has recommended in its report on OTC antifungal drug products, published in the Federal Register of March 23, 1982 (47 FR 12480), that an antiperspirant-antifungal combination be placed in Category I. The agency will address this recommendation in the tentative final monograph for OTC antifungal drug products.

E. Category I Active Ingredients

10. One comment recommended that a statement in the report that glycine is sometimes added to aluminum zirconium chlorhydrates for formulation purposes should be revised to state that the salts of glycine are also added to antiperspirant active ingredients for formulation purposes. The comment explained that, although the statement is correct, it is somewhat misleading because sometimes a glycine salt is used rather than glycine.

The agency agrees with the comment that both glycine and glycine salts are sometimes added to antiperspirant active ingredients for formulation purposes. Accordingly, the statement under part III. paragraph B.1.b. of the Panel's report is amended to read, "Glycine or its salts are sometimes added to aluminum zirconium chlorhydrates for formulation purposes."

11. Two comments requested that the Panel's recommended § 350.10 be amended to clarify that the maximum allowable concentration of active ingredients in an antiperspirant product does not include buffers. The comments stated that buffers such as glycols and glycine do not contribute to the efficacy of antiperspirant formulas. The comments stated that they interpret § 350.10 to mean that glycine and glycol buffers need not be included in calculating the maximum concentration of active ingredients in a finished formula; however, they believe the Panel should have expressly provided for the exclusion of glycine and glycol buffers in the calculation.

The agency concurs with these comments. The Panel noted that antiperspirant active ingredients form complexes with certain glycols and these complexes have higher alcohol solubility than uncomplexed salts. The Panel found that this property is desirable in antiperspirant products and considered these glycols to be formulation necessities that do not substantially alter the safety or antiperspirant activity of the antiperspirant salt from which they were prepared. In addition, the Panel found that glycine or glycine salts are sometimes added to antiperspirant active ingredients for formulation purposes only. Therefore, the agency concludes that glycine and glycol buffers need not be included in calculating the maximum allowable concentration of active ingredients in an OTC antiperspirant product. To allow expressly for the omission of glycine and glycol buffers in calculating the concentration of antiperspirant active ingredients with which these buffers are used, the agency proposes to revise § 350.10(a) and (b) to include the following directions for calculating the concentration of antiperspirant active ingredients:

(a) Aluminum chlorhydrates * * * 25 percent or less concentration (calculated on an anhydrous basis, omitting from the calculation any buffer component present in the compound) of an aerosol and nonaerosol dosage form.

(b) Aluminum zirconium chlorhydrates * * * 20 percent or less concentration (calculated on an anhydrous basis, omitting from the calculation any buffer component present in the compound) of a nonaerosol dosage form.

12. Two comments contended that the concentration of active ingredients in an antiperspirant container has less meaning than the amount of active ingredient actually deposited on the axilla. The comments maintained that factors such as dosage form and size of the orifice of the product container can affect the amount of active ingredient

applied to the skin. For example, although a given antiperspirant salt may be marketed at a 3-percent level in a pressurized aerosol formula and at a 22-percent level in a lotion base, the quantity of active ingredient deposited on the skin during normal use would be similar for both types of products. The comments contended that because irritation resulting from use of a product is in proportion to the amount of antiperspirant active ingredient deposited on the skin, the monograph should be amended to allow higher concentrations of active ingredient, provided that the amount actually delivered to the skin does not exceed that determined by the Panel to be safe.

The agency disagrees with these comments and does not at this time propose to allow higher concentrations of antiperspirant active ingredients than those recommended by the Panel. The topical dosages for antiperspirants recommended by the Panel are based on safety data reviewed by the Panel. The comments included no new data to show that a higher concentration of antiperspirant active ingredients marketed in a particular container would deliver no more than the amount of active ingredient judged safe by the Panel.

F. Category I Labeling

13. Three comments objected to the minimum effectiveness statement which the Panel recommended in the monograph, i.e., "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." These comments pointed out that the statement adds no useful information and may even be confusing to consumers.

Two comments stated that, unless the degree of effectiveness of an antiperspirant product is stated in labeling, the consumer has no way to judge the comparative effectiveness of different antiperspirant products.

The agency believes that a minimum effectiveness statement in the labeling does not help consumers compare the effectiveness of different antiperspirants. The minimum effectiveness standard was recommended by the Panel for use in determining the effectiveness of antiperspirant products; but without explanation of the testing method and the reasons for setting this particular standard, the recommended labeling statement is not likely to educate consumers and may become a source of confusion. Accordingly, the minimum effectiveness statement is deleted from the monograph.

14. A comment objected to the limitation of three phrases recommended by the Panel under indications, "Helps reduce wetness," "Helps reduce dampness," and "Helps reduce perspiration," stating that the proposed monograph's reliance on exclusive terminology is unnecessary, arbitrary, and fundamentally unfair. The comment argued that all terminology that indicates that an antiperspirant is effective at reducing perspiration should be permitted in the labeling. Citing "Roget's International Thesaurus" (Ref. 1), the comment offered the following synonyms for the word "reduce" for inclusion in the monograph: "decrease," "diminish," "lessen," "lower," and "mitigate." The comment also argued that there is no evidence that consumers regard "helps reduce underarm wetness" as any different from "decreases underarm wetness." In addition, the comment remarked that the word "helps" is redundant and improper when used together with the word "reduce" in the labeling indications recommended by the Panel because the word "helps" denotes action in concert with other influences; yet, antiperspirants by themselves do reduce perspiration. However, the comment pointed out that the word "helps" is appropriate when used with words such as "stop," "check," "halt," "end," "eliminate," or "protect" because in this instance "help" implies what the comment described as directional benefit, much as "partially stops" would. The comment suggested that this latter group of words should also be allowed in antiperspirant drug labeling.

Since the inception of the OTC drug review, the agency has maintained that a monograph describing the conditions under which an OTC drug will be generally recognized as safe and effective and not misbranded must include both specific active ingredients and specific labeling. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under 21 CFR § 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received.

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA plans to conduct an open public forum on September 29, 1982, where all interested parties can present their views. The forum will be a legislative type administrative hearing under 21 CFR Part 15 that will be held in response to a request for a hearing on the tentative final monograph for nighttime sleep aids (published in the Federal Register of June 13, 1978; 43 FR 25544). Details of the hearing were announced in a notice published in the Federal Register of July 2, 1982 (47 FR 29002). In proposed and tentative final monographs issued in the meantime, the agency will continue to state its longstanding policy.

The agency notes that, in recommending indications for the Category I labeling of antiperspirant drug products, the majority of the Panel rejected words that imply the ability to stop underarm perspiration totally and that could mislead the consumer about enhanced antiperspirant effect. The majority view was that exaggerated claims of effectiveness are sometimes made for antiperspirants in the advertising media, and therefore it is especially important for an antiperspirant drug product's label to provide the consumer with accurate information about the product's effectiveness. The agency believes that the words "decrease," "diminish," and "lessen" adequately achieve the intention of the Panel majority of providing the consumer with accurate information about the antiperspirant drug product's effect on perspiration. Accordingly, the agency proposes that any of these words may be substituted for the word "reduce" under "Indications" in the labeling of antiperspirant drug products, as the agency believes there is little chance that they might create confusion or mislead the consumer.

The word "mitigate," not a commonly used word, has been defined as "to cause to become less harsh or hostile or

to make less severe or painful" (Ref. 2). This is not the sense in which the word "reduce" is used in the Panel's labeling, and therefore "mitigate" will not be proposed in the tentative final monograph. The agency believes that the word "lower" also should not be used in the labeling because this word could create confusion among consumers as to whether it was used in the sense of "reduce" or in the sense of physically "lowering" perspiration from the underarm area. Additionally, the agency believes that words such as "stop," "check," "halt," "end," "eliminate," and "protect" should not be used in the labeling of antiperspirant drug products, even if preceded by the word "helps," because these words imply the ability to stop underarm perspiration totally and would therefore mislead the consumer about the effectiveness of antiperspirant drug products. On this point, the agency rejects the argument of two members of the Panel who filed a minority opinion (43 FR 46724) stating that the Panel did not see data to show that a consumer can differentiate between the intent of words such as "halts," "checks," "stops" versus "diminishes" and "reduces," and that if confusion were to occur between these groups of words no harm is done to the consumer. The agency believes that the first group of words does not have the same meaning as the second, and to permit labeling language that is capable of misleading the consumer with respect to the effectiveness of a product is wrong and in conflict with the OTC drug regulations in § 330.10(a)(4)(iv), which state, "Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular * * *" The agency agrees with the comment that the word "helps" is redundant when used with the word "reduce." Therefore, the agency proposes to delete this word from the labeling language in the tentative final monograph, which is revised as follows:

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

(1) (Any one of the following terms may be used: "Reduces," "Decreases," "Diminishes," or "Lessens") "underarm wetness."

(2) (Any one of the following terms may be used: "Reduces," "Decreases," "Diminishes," or "Lessens") "underarm dampness."

(3) (Any one of the following terms may be used: "Reduces," "Decreases," "Diminishes," or "Lessens") "underarm perspiration."

References

(1) "Roget's International Thesaurus," 3d Ed., Thomas Y. Crowell Company, Inc., New York, 1962, s.v. "reduce."

(2) "Webster's New Collegiate Dictionary," G. & C. Merriam Company, Springfield, MA, 1977, s.v. "mitigate."

15. A comment requested revision of the directions for use recommended by the Panel, i.e., "Apply to skin of underarms. Not to be used generally over the body." The comment objected to the second sentence of the directions ("Not to be used generally over the body."), stating that this sentence appears to be a warning and should not be included under the directions for use of antiperspirant drug products. The comments suggested that the directions for use be revised to read as follows: "Apply to underarms only." The comment stated that this statement would adequately inform consumers of the appropriate use of these products. The comment further contended that there is no evidence that antiperspirant products are being used on any part of the body other than the underarms, or that general body use presents any hazard; that warnings should be used sparingly and only where there is a demonstrated need; and that there is no need for such a warning on the label of antiperspirant drug products.

The agency agrees with the comment that the statement "Not to be used generally over the body" is a warning rather than a direction for use. The Panel recommended this statement because of its concern that the use of an antiperspirant over the entire body could possibly interfere with the body's thermal regulatory process. Because of this concern, the Panel concluded that claims for use of antiperspirants over the entire body should not be allowed. The agency agrees with this conclusion. The agency further believes that the specific direction for use recommended by the comment, i.e., "Apply to underarms only," renders the directions, "Apply to skin of underarms. Not to be used generally over the body," unnecessary. Accordingly, the agency has proposed the directions in the tentative final monograph as follows: "Apply to underarms only." The agency notes that the Panel placed claims for the use of antiperspirant products on the hands and feet in Category III and that these claims have the potential to become Category I, at which time the monograph would be revised accordingly.

16. A comment from a consumer, who claimed to be allergic to metal, requested that the label of antiperspirant drug products containing metal compounds, such as aluminum chlorhydrate, include the statement "Contains metal."

Under section 502(e)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(e)(1)) (hereafter referred to as the act), all drug products are required to state the name(s) of the active ingredient(s) on the label. All Category I antiperspirant ingredients contain a metallic substance, aluminum, as part of the chemical entity. The agency believes that the name of the specific metal contained in the product, which will be listed on the label in accordance with the requirements of the act, is more beneficial to the consumer than the statement "Contains metal."

G. Category II Labeling

17. One comment objected to the Panel's placement of the term "extra-strength" in Category II, contending that this term is equivalent to the term "extra-effective," which the Panel placed in Category III. The comment stated that the Panel's assumption that the term "extra-strength" implies improved performance through increased concentration of active ingredient is unfounded. The comment added that the relative concentration of active ingredients in antiperspirants is not of interest to consumers, who judge antiperspirants in terms of the benefits received. Therefore, the comment concluded, the term "extra-strength" should be considered synonymous with the term "extra-effective" and requested that both terms be permitted for eligible antiperspirant products.

The agency agrees with the Panel that the term "extra-strength" on an OTC drug product usually refers to an increased amount of drug per dosage unit, and this increased amount normally correlates to increased effectiveness of the product. However, the Panel concluded that in an antiperspirant drug product an increased amount of active ingredient does not necessarily result in an added effect because minor variations in formulation can alter the product's antiperspirant activity. The comment did not provide any information that would alter the Panel's conclusions, and the agency concurs with the Panel that the term "extra-strength" is Category II. As mentioned below, the claim "extra-effective" is tentatively placed in Category II by the agency. (See comment 19 below.)

H. Category III Active Ingredients

18. One comment suggested that the nomenclature for potassium aluminum sulfate be changed to "potassium alum."

The agency concurs with this comment. The United States Pharmacopeia (Ref. 1) states that aluminium potassium sulfate "should be identified on the label as potassium alum." Section 502(e)(3) of the act (21 U.S.C. 352(e)(3)) provides that the use of a drug name other than the official established name would cause the drug to be misbranded. Therefore, the name "potassium aluminum sulfate" is changed to "potassium alum" in this document. (See part II. paragraph A.1. below—Summary of Ingredient Categories.)

Reference

(1) "The United States Pharmacopeia, 20th Revision," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 22, 1980.

I. Category III Labeling

19. Two comments objected to the Panel's classification of "extra-effective" claims in Category III. One contended that the Panel's definition of "extra-effective" is arbitrary and reduces the incentive to improve product efficacy. The comment pointed out that manufacturers should be allowed to use appropriate descriptive language to inform consumers about the differing effectiveness of antiperspirants and concluded that the extra-effectiveness criterion should be eliminated. The other comment argued that establishing an additional category of labeling for "extra-effective" claims serves no useful function. The comment stated that a product that is "extra-effective" for one person may be only marginally effective for another, adding that consumers will choose those products which best suit them. The comment insisted that it should be the prerogative of the manufacturer to determine the means of conveying product superiority to consumers, as long as comparative claims are honest and scientifically valid.

The agency agrees that there is no useful function in establishing an additional category of "extra-effective," because, as pointed out by one of the comments, a product that is "extra-effective" for one person may be only marginally effective for another person. The claim is an ambiguous one and difficult to quantify for scientific validation. Accordingly, the agency is proposing that the claims "extra effectiveness" or any comparative effectiveness claim be Category II.

20. One comment objected to the Panel's placement of "emotional sweating" claims in Category III. The comment contended that there is no reason to believe that an antiperspirant will not be effective when the perspiration stimulation is emotional rather than thermal. For this reason, the comment argued that the Panel's requirement that a user perception test be performed with sweating induced by emotional rather than thermal stimuli is wasteful and unnecessary.

The agency agrees with the Panel's Category III classification of the claim "for the control of emotional sweating" because there are insufficient data to show that an antiperspirant that is effective in reducing thermally induced sweat is also effective in reducing emotionally induced sweat. The Panel noted that under emotional stress the amount of axillary sweat produced was found to be twice as great as that produced under hotroom conditions. Although data available to the Panel suggest that emotionally induced sweat can be reduced, data were not available to show that such a reduction would be perceptible to the user. The user perception test, as recommended by the Panel for this claim, would determine the point at which reduction of emotionally induced sweat is perceptible to the user. These data are needed before a decision can be made on whether the claim "for the control of emotional sweating" can become Category I.

J. Data Required To Upgrade Category III Conditions to Category I

21. Two comments took issue with specific aspects of the protocol for testing the long-term safety of aerosolized antiperspirants. They disagreed with the Panel's guidelines for the preliminary respirable aluminum assay, the selection of dose levels for the chronic inhalation study, and the number of organs to be prepared for histopathology. The comments recommended that the preliminary assay should be conducted on prototypes representing the vast majority of the marketed products. The comments also objected to the exposure levels of 1, 10, and 100 times the anticipated human exposure levels, stating that this recommendation by the Panel is arbitrary and scientifically unsound. Finally, the comments contended that only the respiratory system organs need to be examined histopathologically. Other organs, they stated, should be retained for examination at some later time if necessary, because these organs have been examined and found free of pathologic lesions in chronic studies involving small animal species (Refs. 1 and 2).

Data and information submitted subsequent to the publication of the Panel's report appear to be adequate to establish general recognition for the safe and effective use of aerosol antiperspirants by consumers (See comment 22 below). Therefore, the long-term inhalation studies recommended by the Panel will not be required, and there is no need for further discussion of the protocal for such studies in this document.

References

(1) Steinhagen, W. H., and F. L. Cavender, "Six Month Inhalation Exposures of Rats and Guinea Pigs to Aluminum Chlorhydrate," *Journal of Environmental Pathology and Toxicology*, 1:267–277, 1978.

(2) Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, "Inhalation Toxicology Studies of Aerosolized Products," Final Report, Albuquerque, NM, pp. 1–288, 1979, filed as SUP Docket No. 79N–0084, Dockets Management Branch.

22. One comment submitted the final reports (Refs. 1 and 2) of long-term inhalation studies of aerosolized aluminum chlorhydrate in animals (rodents) plus data from other studies (Ref. 3) and concluded that these data justify Category I status for aerosol antiperspirant drug products. In addition, a citizen petition to reopen the administrative record of the OTC antiperspirant drug products rulemaking was submitted to include in the record new data and correspondence with the agency in further support of a Category I status for aluminum chlorhydrate aerosol antiperspirants. The petition was granted on May 7, 1982. (Refs. 16, 17, and 18.)

The agency has evaluated the two reports (Refs. 1 and 2) submitted by the comment, in addition to other information and data that were sent to the agency after the above-mentioned reports (Refs. 4 through 16). Based on the review of this material, the agency has determined that aluminum chlorhydrate aerosol antiperspirants can be generally recognized as safe and effective for use by consumers. The existing safety data provide a broad toxicological profile that can be used to establish general recognition of the safety of aerosolized aluminum chlorhydrate antiperspirants, and are adequate to support including aerosol aluminum chlorhydrate antiperspirants in the tentative final monograph. Therefore, aluminum chlorhydrates in aerosol dosage forms will be placed in Category I rather then Category III as recommended by the Panel. However, in order to prevent misuse of such dosage forms the agency is proposing the following additional label warning for aerosol antiperspirants in § 350.50(c) of the tentative final monograph: "Avoid

excessive inhalation." The agency's evaluation of the data and recommendations for a Category I status for aerosol antiperspirants are on file in the Dockets Management Branch (Refs. 17 and 18).

References

(1) "Inhalation Toxicology Studies of Aerosolized Products, Final Report," Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM, 1979, Coded "SUP," Docket No. 78N–0064, Dockets Management Branch.

(2) "Final Report on Aluminum Chlorhydrate Study," Becton, Dickinson Research Center, Research Triangle Park, NC, 1978, Coded "SUP," Docket No. 78N–0064, Dockets Management Branch.

(3) Comment No. C00027, Docket No. 78N–0064, Dockets Management Branch.

(4) Hazelton Laboratories America, Inc., "90-Day Inhalation Toxicity Study of Aerosol #769 in Cynomolgus Monkeys, Final Report," Comment No. C00026, Docket No. 78N–0064, Dockets Management Branch.

(5) Hazelton Laboratories America, Inc., "Subacute Toxicity Potential in Monkeys, Project No. 260–120, Final Report," Comment No. C00026, Docket No. 78N–0054, Dockets Management Branch.

(6) Klosterkotter, W., "Effects of Ultramicroscopic Gamma-Aluminum Oxide on Rats and Mice," *Archives of Industrial Health*, 21:458–472, 1960.

(7) Stenback, F. G., et al., "Synergistic Effects of Diethylnitrosamine and Different Dusts on Respiratory Carcinogenesis in Hamsters," *Cancer Research*, 33:2209–2214, 1973.

(8) King, E. J., et al., "The Effect of Aluminum and of Aluminum Containing 5 Percent of Quartz in the Lungs of Rats," *Journal of Pathology and Bacteriology*, 75:429–434, 1958.

(9) Englebrecht, F. M., et al., "Tissue Reactions to Injected Aluminum and Alumina in the Lungs and Livers of Mice, Rats, Guinea-Pigs and Rabbits," *Journal of Pathology and Bacteriology*, 77:407–416, 1959.

(10) Stacy, B. D., et al., "Tissue Changes in Rat's Lungs Caused By Hydroxides, Oxides, and Phosphates of Aluminum and Iron," *Journal of Pathology and Bacteriology* 77:417–426, 1959.

(11) Weller, W., "On the Increased Incidence of Tumors Following Inhalation of Poly-2-Vinylpyridin-N-Oxid," *Zeitschrift fur die Gesamte Experimentelle Medizin*, 154:235–246, 1971.

(12) Kobayashi, N., et al., "Inhibitory Effect of Aluminum on the Development of Experimental Lung Tumor in Mice Induced By 4-Nitroquinoline-1-Oxide," GANN, 61:239–244, 1970.

(13) Kano, R., "Experimental Studies of Occupational Lung Cancer," *Bulletin of the Tokyo Medical and Dental University*, 9:440–441, 1962.

(14) "Toxicology of Metals—Volume II," Report of the Office of Research and Development, Environmental Protection Agency, Publication No. EPA–600/1–77–022, 1977.

(15) Sorenson, John, R. J., et al., "Aluminum in the Environment and Human Health," *Environmental Health Persepctives*, 8:3–95, 1974.

(16) Citizen Petition, CP, Docket No. 78N–0064, Dockets Management Branch.

(17) Letter from William F. Randolph, FDA, to James H. Merritt, CTFA, dated May 7, 1982 Docket No. 78N–0064.

(18) Letter from William E. Gilbertson, FDA, to James H. Merritt, CTFA, dated May 12, 1982, Docket No. 78N–0064.

23. A comment suggested that the Panel's guidelines for skin irritation tests be revised to permit all equivalent tests that use comparative controls in evaluating the tendency of antiperspirant active ingredients to irritate the skin. The comment stated that tests equivalent to the Lanman technique that use comparative controls and that have a demonstrated ability to distinguish among antiperspirant active ingredients as well as dose levels should be allowed. The comment included five references to support its position (Refs. 1 through 5).

The agency wishes to clarify that the Panel's discussion of the Lanman techique was intended only to provide guidance to manufacturers on the type of data the Panel considered necessary before an ingredient placed in Category III because of questions of skin irritancy could be reclassified into Category I. The agency will not limit manufacturers to the Lanman technique of comparative testing. It is the responsibility of the manufacturers to use whatever technique they believe is appropriate. The agency will evaluate the data on their own merit, including the methodology used.

References

(1) Draize, J. H., G. Woodard, and H. O. Calvery, "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to Skin and Mucous Membrances," *Journal of Pharmacology and Experimental Therapeutics*, 82:377–390, 1944.

(2) Draize, J. H., "Dermal Toxicity," *in* "Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics," Association of Food and Drugs Officials of the United States, Austin, TX. pp. 46–59, 1959.

(3) Kligman, A. M., and W. M. Wooding, "A Method for the Measurement and Evaluation of Irritants on Human Skin," *Journal of Investigative Dermatology*, 40:78–94, 1967.

(4) Schwartz, L., and S. M. Peck, "The Patch Test in Contact Dermatitis," *Public Health Reports*, 59:546–557, 1944.

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

24. Three comments suggested deletion of the user perception test required to substantiate certain Category III claims, such as "extra-effective", "problem" or "especially troublesome" perspiration, and "emotional sweating." One comment stated that user perception tests of differences between a reference formulation and a proposed "extra-effective" formulation are impractical for individual product evaluations. The comment submitted an approach for a one-time perception test for the "extra-effective" class. It suggested comparing a standard antiperspirant to a series of potentially "extra-effective" products. The individual responses to a wetness perception questionnaire would be compared to individual sweating differences obtained between axillae treated with the 20-percent formula and the "extra-effective" formulations. From the responses and sweating values, a graph would be used to determine what level of difference in hotroom tests would be required for subjective perception of difference. Another comment stated that the cosmetic attributes of a product can appear to enhance or reduce its antiperspirant effects, depending upon the cosmetic effect desired. The comment added that a product that demonstrates its effects by objective methods might be disqualified because it is so formulated that consumers may not readily perceive its true effects.

The third comment objected to the user perception test because it is unreliable, has not been tried, and is not generally recognized or accepted. The comment stated that there is no perception test that manufacturers can routinely follow. This comment also complained that perception testing would be influenced by product attributes.

As noted in comment 19 above, the claim of "extra-effective," has been proposed as Category II by the agency. The agency agrees with the Panel's decision to include user perception testing for the Category III claims of "problem or especially troublesome" perspiration, and "emotional sweating." Although the Panel postulated that a 30-percent reduction in perspiration would be necessary to support these claims, the agency believes that the user perception tests will determine the actual level of perspiration reduction necessary to support each of these claims. In this regard, user perception testing was not intended to be required for each individual product, but rather for each class of "problem perspiration," or "emotional sweating" products. Once the level of activity that is perceivable by users has been established for each of these claims, using the Panel's recommended guidelines, it will not be necessary to perform user perception

testing on individual products. The agency points out that the Panel considered the problem of cosmetic attributes on user perception testing and suggested a method for minimizing this problem as part of its guidelines at 43 FR 46730.

25. One comment suggested that "the Panel's requirement that a 'problem perspiration' claim may only be used if a product passes a consumer perception test using the upper five percent of 'sweaters' and a gravimetric test showing 30% reduction in perspiration should be changed to allow the 'problem perspiration' claim to be used if a consumer panel made up of people who consider themselves to be problem sweaters experience a 20% reduction in perspiration." The comment added that the Panel's requirements are apparently based on the premise that problem perspiration is defined as a large volume of sweat and that only the very heaviest of perspirers suffer from it, and to arbitrarily define problem perspiration as only heavy perspiration is unrealistic and improper. The comment stated that its suggestion would require smaller test panels and would accomplish the result of claim substantiation (i.e., effectiveness) for problem perspiration using a more meaningful standard.

The agency points out that the Panel received no data that would support claims of "problem" or "especially troublesome" perspiration, nor were any data submitted with the comment. The Panel defined problem perspiration as that afflicting the upper 5 percent of perspirers. The comment has not presented any convincing argument to change this definition. The agency concurs with the Panel that in order for a product to contain a "problem" or "especially troublesome" perspiration claim it should be shown to reduce perspiration by a greater amount than a standard antiperspirant in those persons who perspire heavily. The user perception test is necessary to determine at what level reduction in perspiration will be perceptible to the upper 5 percent of perspirers. The comment's suggestion is not being adopted because it could potentially allow a minimally standard antiperspirant to make a claim for "problem" or "especially troublesome" perspiration.

K. Final Formulation Testing Procedures

26. One comment suggested that testing procedures recommended in the monograph should be clarified to state that suitable temperature and humidity conditions for the hotroom test procedure are tempertures around 100° F and between 30 and 35 percent relative humidity. The comment contended that it is difficult, if not impossible, to maintain an exact temperature of 100° F and a relative humidity of 35 percent or greater.

As noted in comment 8 above, the Panel's recommended formulation testing procedures are no longer included in the monograph, but will be available as guidelines to drug manufacturers. As for the content of these guidelines, the agency is in partial agreement with the comment. The Panel stated in its report that temperatures around 100° F and humidities in excess of 35 percent will elicit sufficient axillary sweat from test subjects in reasonable lengths of time so that gravimetric measurements can be made of the axillary perspiration rate. The Panel stated in its report that a temperature of 100° F, plus or minus 2°, was acceptable; apparently an error was made in transposing this information to the monograph. Because it is difficult to maintain an exact temperature of 100° F and a relative humidity of 35 percent with currently used equipment, the agency believes that the controlled environment described in the testing guidelines should be changed to read: "* * * (temperatures at 100° F, plus or minus 2°, and relative humidity of 35 to 40 percent) * * *." This would provide a degree of latitude that is practical for a test procedure of this nature.

27. Three comments were made regarding the control formulation in the Panel's recommended testing procedures. One comment suggested that the control formulation should be "as identical as possible" rather than "identical to" the test formulation without the active ingredient. The comment added that the production of the control formulation is difficult because the active ingredient in some products is an integral part of the vehicle and removal of the active ingredient often results in an unstable formula. Another comment stated that the control formulation should be a careful selection because it should have no effect on sweating. The comment further suggested that evaluation for antiperspirants should be based on the activity of the complete formulations when compared to no treatment or to treatment with a true placebo. This comment suggested water or water plus "Cab-o-sil" as a thickening agent for the inactive control. The comment further suggested that if a vehicle control is used it should be determined in a test compared to no treatment that the control is inactive. The third comment stated that the requirement for using a control product for product evaluation and pretreatment evaluations is unnecessary. The comment stated "by using an untreated control, rather than a control product, a more realistic estimate of benefit derived from formulated products as opposed to the active ingredient per se will be obtained."

The agency disagrees with the comment that stated that using a control product for product evaluations and pretreatment evaluations is unnecessary. Because the effect of antiperspirants is pharmacological, the agency believes that a control should be used in testing antiperspirant products to achieve unbiased results. The purpose of the test must be to establish whether an antiperspirant has a useful effect in the reduction of sweat and to conclude that the product is effective and the adverse effects are minimal. A control is desirable in a test of this kind and is important for differentiating between a true antiperspirant effect or adverse effect and psychological effects, or effects that might be attributed to fragrance, feel, color, etc. The Panel, in its report, listed many factors affecting antiperspirant evaluation and realized the difficulties occurring from variations in formulation. Therefore, the agency agrees with the comments that suggested that the control formulation should be inactive and as similar as possible to the test formulation without the active antiperspirant ingredient. In view of this, the agency proposes to amend the testing guidelines to state that "* * * [The control formulation is as similar as possible to the test formulation and devoid of any antiperspirant activity. Its inactivity is determined in a test compared to no treatment.]"

28. One comment requested that the proposed test procedures be changed to allow for a preconditioning period requiring test subjects to be placed in the controlled environment for a 10- to 40-minute warmup period. The comment stated that this warmup period is necessary for a practical and efficient hotroom test and is consistent with standard test protocols and procedures that have been used to test antiperspirants in the past. The comment suggested the test procedures be changed to read: "Test subjects are placed in the controlled environment for a 10 to 40 minute warmup period."

The agency agrees with the comment that a warmup period should be required for test subjects in a hotroom test. The Panel also stated, in its report, that "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." The warmup period eliminates extreme variations in individual sweating patterns and provides more reproducible data for a more precise evaluation of antiperspirant activity. The warmup period also provides time for the subject's emotional adjustment to the conditions of testing.

Therefore, the agency proposes to revise the testing guidelines to allow for the test subjects to be placed in the controlled environment for a 40-minute warmup period.

29. One comment recommended changing the following statement in the proposed testing procedures: "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." The comment stated that "most of the efficacy data reviewed by the Advisory Panel was based upon an informal industry standard of 0.50 g of solid and roll-on forms and a 2-second spray, or approximately 120 mg of an aerosol." The comment therefore recommended that these amounts or similar standard amounts of an antiperspirant product for application to the test subjects should be specified in this section to allow comparison and correlation of test results among antiperspirant manufacturers. The comment contended that such standards would also lessen the possibility that minimally effective products could, by being liberally applied in unlimited amounts, achieve the established standard of effectiveness and qualify as antiperspirants.

The agency disagrees with the comment and concurs with the Panel's recommendation that the quantity of formulation applied to each test subject during gravimetric testing should reflect the amount that a typical person would apply under normal use conditions. The agency also concurs with the Panel's conclusion that "additional amounts of antiperspirant active ingredient do not necessarily result in improved product effectiveness."

For these reasons; the agency is not persuaded that it would be useful to standardize the amount of different antiperspirant formulations applied during gravimetric testing. Accordingly, the agency proposes not to change the statement in the testing guidelines regarding the quantity of formulation to be applied to test subjects.

30. One comment, made by a research laboratory that has conducted extensive research with antiperspirant products, disagreed with the statement in the Panel's report under part II. Paragraph H.3., "Completely normal axillary eccrine sweating is resumed usually within a week after antiperspirant use is discontinued." The comment submitted data demonstrating that complete washout of antiperspirants occurred in 17 days. The laboratory conducted many crossover studies in which the panelists participated in a series of test periods separated by 2-week recovery periods. In attempts to shorten the time required to complete these studies, some studies were attempted using a 1-week recovery period. In these instances, most individuals who showed high levels of reduction in sweating continued to show a significant reduction in sweating 10 days following the final application of the antiperspirant. The laboratory also found that collections made 17 days following applications of antiperspirant showed sweating ratios essentially equal to the initial baseline values, indicating that complete washout of antiperspirant effects is usually accomplished within this period. The data also indicated that deodorant products that were tested and claimed to have no antiperspirant effect did, indeed, have some antiperspirant effect. Based on these data and experience in testing antiperspirant products, the comment recommended that the subject selection criteria in the recommended testing procedures be changed to require that test subjects not use any antiperspirant or deodorant materials (except deodorants, furnished by the investigator, which have been tested and found to have no antiperspirant effect on axillary sweating) for a minimum of 17 days, rather than 1 week, prior to entering an antiperspirant test.

The agency concurs with the comment. Based on the data submitted, the agency believes that 17 days would be a more accurate length of time than 1 week to allow for antiperspirant washout to occur. These data also show that deodorants may have some effect on axillary sweating; therefore, an abstinence from deodorants (except those furnished by the investigator and which have been tested and found to have no antiperspirant effect), as well as antiperspirants, should be required as a criterion for a subject entering an antiperspirant test. The agency believes that these requirements will produce more accurate results in the effectiveness qualification test. The agency proposes to revise the testing guidelines accordingly.

L. Data Treatment

31. For comments objected to the methods of data treatment recommended by the Panel for the final formulation testing of antiperspirant products. One comment objected to the method of handling the percent of sweat reduction and also the power of the binomial test conditioned by the method of handling the ratio between the values obtained from the control axilla and the test axilla. The comment stated that this ratio is lognormal, and standard techniques exist for testing hypotheses. It suggested that the test of the median and confidence bands for the median should be used which would be valid and more efficient. The comment stated that it calculated the power of the proposed binomial procedure and appended power curves showing its lack of power. The comment further contended that the proposed test procedure is based on the assumption that the median is equal to one and this is incorrect, and the bias is such that it would require a percent reduction greater than 20 percent in order to give the appearance of a 20-percent reduction. Three comments stated that a parametric statistical analysis should be recognized in the monograph as an equivalent and acceptable alternative to the binomial test. One of these comments submitted a protocol for a parametric statistical analysis and stated that the binomial test fails to make use of much of the information provided by the quantitative measurements, whereas the parametric approach relies upon the original quantitative measurements. The binomial test, it stated, has a lower statistical efficiency and requires much larger sample sizes than the parametric analysis. All of these comments remarked that the parametric approach can test the same hypotheses as the binomial test, and with the same degree of confidence, but that it is more sensitive, precise, and statistically efficient. They believe that all valid statistical techniques should be permitted by the monograph and the monograph should be modified to accept the parametric method as an alternative to the binomial test for the statistical testing of antiperspirants.

The agency has carefully reviewed the binomial test recommended by the Panel and the parametric test suggested by the comments. The binomial test recommended by the Panel is very conservative, making no distributional assumptions and making no correction for the asymmetry of individual perspiration rates. The binomial test fails to make use of the information provided by the actual percent of reduction in perspiration, reducing everything to greater than 20 percent or

less than 20 percent. The parametric tests rely on an assumption of lognormality that does not appear to be always valid. The parametric tests also lead to inference about population means only indirectly addressing the question posed by the definition of an antiperspirant product, which is a question about the population median. In addition, the error rates for the parametric tests cannot be interpreted in terms of the probability of allowing an ineffective product, as defined by the agency, to be marketed.

In view of the above-mentioned weaknesses of both the binomial and the parametric tests, the agency recommends a statistical test based on ranks that will have none of the deficiencies noted above. The goal is a statistical test which will provide assurance that the product produces a median reduction in perspiration of at least 20 percent. The agency believes that the statistical test based on ranks will provide a better method for the treatment of data than the binomial or the parametric method.

Therefore, the agency proposes to revise the testing guidelines by describing two different test procedures: one for the case of a single observation of each axilla, with one axilla receiving the test formulation while the other is receiving the control formulation, and one for the case of a pretreatment observation to determine the ratio of right-to-left axillary sweating rate before applying test and control formulations. These guidelines are on file in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and are available on request to that office.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's categorization of ingredients. For the convenience of the reader the following table is included as a summary of the categorization of OTC antiperspirant active ingredients.

Active ingredient	Category	
	Nonaerosol dosage form	Aerosol dosage form
Aluminum bromohydrate[1]	II (S, E)[2]	II (S, E).
Aluminum chlorhydrates[3]	I	I.
Aluminum chlorohydrate		
Aluminum dichlorohydrate		
Aluminum sesquichlorohydrate.		
Aluminum chlorohydrex PG[4]		
Aluminum dichlorohydrex PG		
Aluminum sesquichlorohydrex PG.		
Aluminum Chlorohydrex PEG[5].		
Aluminum dichlorohydrex PEG.		
Aluminum sesquichlorohydrex PEG.		
Aluminum chloride (15 percent 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).
Aluminum zirconium trichlorohydrate.		
Aluminum zirconium tetrachlorohydrate.		
Aluminum zirconium pentachlorohydrate.		
Aluminum zirconium octachlorohydrate.		
Aluminum zirconium trichlorohydrex Gly[6].		
Aluminum zirconium tetrachlorohydrex Gly.		
Aluminum zirconium pentachlorohydrex Gly.		
Aluminum zirconium octachlorohydrex Gly.		
Buffered aluminum sulfate	I	III (S).
Potassium alum	III (S, E)	III (S, E).
Sodium aluminum chlorohydroxy lactate.	III (E)	III (S, E).

[1] This ingredient has not 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.
[3] The Panel designated this term as the generic term for the various aluminum chlorhydrate compounds. Because the chemical properties of the various aluminum chlorhydrates are similar, and the available data on the toxicity of these materials suggest that they have the same risk potential, the agency will treat these ingredients as a group in this document. This same reasoning is applicable to the aluminum zirconium chlorhydrate compounds.
[4] Propylene glycol complex.
[5] Polyethylene glycol complex.
[6] Glycine complex.

2. *Testing of Category II and Category III conditions.* The Panel recommended data required to upgrade Category III antiperspirant conditions to Category I. (See the Federal Register of October 10, 1978—"Data Required for Evaluation" at 43 FR 46728). The agency is offering these guidelines as the Panel's recommendations, with some revisions based on the comments, but without adopting them or making any formal comment on them except as otherwise noted in this document. (See comments 23 through 25 above.)

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any antiperspirant drug product ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations.

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's response to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's conclusions and recommendations follows.

1. The Panel included in its recommended monograph procedures for testing effectiveness of final antiperspirant formulations. The Panel believed such testing should be required because it is possible for even minor variations in formulation to alter the effectiveness of an antiperspirant ingredient. The agency proposes to delete these testing procedures from the monograph and to make them available, with modifications based on the comments, as guidelines to manufacturers. (See comments 8 and 26 through 30 above.)

2. The agency is redesignating proposed Subpart D of the monograph as Subpart C, placing the labeling sections under Subpart C and information relating to the testing guidelines under Subpart D.

3. The agency proposes to revise the sections of the monograph which specify the maximum allowable concentration of active ingredients in antiperspirant products to allow for the omission of buffers such as glycine or glycine salts in calculating the concentration of antiperspirant active ingredients. (See comment 11 above.)

4. The labeling requirements in the Panel's recommended monograph stipulated that a minimum effectiveness statement must appear on the label. The agency, believing that such a statement would not serve its intended purpose, proposes to delete it from the monograph. (See comment 13 above.) Furthermore, the agency proposes to expand the labeling to provide for other allowable statements in addition to the phrase: "Reduces underarm perspiration." (See comment 14 above.) Also, the agency is deleting the statement: "Not to be used generally over the body," and is amending the

directions for use to read: "Apply to underarms only." (See comment 15 above.) In addition, one of the label statements in the recommended monograph warns consumers to discontinue use of the antiperspirant if a rash develops. The agency proposes to expand this statement to include "irritation" in addition to "rash." (See comment 4 above.) For aerosol antiperspirant drug products the agency is adding the following warning: "Avoid excessive inhalation." (See comment 22 above.)

5. The agency proposes to move the claim "extra effective" from Category III to Category II. (See comment 19 above.)

6. In view of the fact that the directions statement has been amended to read "Apply to underarms only," the agency is also amending the definition in § 350.3 to read, "Antiperspirant. A drug product that, when applied topically to the underarm, will reduce the production of perspiration (sweat) at that site." (See comment 15 above.)

7. Although no comments were received on the Panel's recommended nomenclature for antiperspirant ingredients, the agency realizes that many of these ingredient names are not recognized in the official compendia. For this reason the agency proposes to incorporate pertinent portions of the Panel's nomenclature table (43 FR 46697) into the proposed monograph.

8. The agency is proposing a Category I status for aluminum chlorhydrate aerosol antiperspirants rather than the Category III status recommended by the panel. This resulted from the submission of additional data including a citizen petition to reopen the administrative record for the consideration of additional data.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354). Specifically, it would move aerosol antiperspirants from Category III to Category I, making the Panel's recommended long-term inhalation studies unnecessary, and would delete final formulation testing procedures from the monograph. Instead of being required, these procedures would be made available to manufacturers as optional guidelines. Minor relabeling would be necessary, but could be done in the normal course of reordering, keeping costs to a minimum. Additionally, the costs associated with reformulations are expected to be minimal because so few products will be affected. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC antiperspirant drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC antiperspirant drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on antiperspirant drug products, a period of 120 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the Federal Register of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 350

OTC drugs: Antiperspirants.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), it is proposed 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 DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
350.1 Scope.
350.3 Definitions.

Subpart B—Active Ingredients

350.10 Antiperspirant active ingredients.

Subpart C—Labeling

350.50 Labeling of antiperspirant drug products.

Subpart D—Guidelines for Effectiveness Testing

350.60 Guidelines for effectiveness testing of antiperspirants.

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

Subpart A—General Provisions

§ 350.1 Scope.

(a) An over-the-counter antiperspirant drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part in addition to each of the general conditions established in § 330.1.

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

§ 350.3 Definition.

As used in this part:

Antiperspirant. A drug product that, when applied topically to the underarm, will reduce the production of perspiration (sweat) at that site.

Subpart B—Active Ingredients

§ 350.10 Antiperspirant active ingredients.

The active ingredients of the product consist of any of the following within the established concentration and dosage formulation. Where applicable, the ingredient must meet the described aluminum to chloride and/or aluminum to zirconium ratio.

Active ingredient	Concentration	Ratio range	
		Al:Cl	Al:Zr
(a) Aluminum chlorohydrate	25 percent or less concentration (calculated on an anhydrous basis, omitting from the calculation any buffer component present in the compound) of an aerosol and nonaerosol dosage form.	2.1 down to, but not including 1.9:1	
(b) Aluminum dichlorohydrate	do	1.25 down to and including 0.9:1	
(c) Aluminum sesquichlorohydrate	do	1.9 down to, but not including 1.25:1	
(d) Aluminum chlorohydrex propylene glycol complex.	do	2.1 down to, but not including 1.9:1	
(e) Aluminum dichlorohydrex propylene glycol complex.	do	1.25 down to and including 0.9:1	
(f) Aluminum sesquichlorohydrex propylene glycol complex.	do	1.9 down to, but not including 1.25:1	
(g) Aluminum chlorohydrex polyethylene glycol complex.	do	2.1 down to, but not including 1.9:1	
(h) Aluminum dichlorohydrex polyethylene glycol complex.	do	1.25 down to and including 0.9:1	
(i) Aluminum sesquichlorohydrex polyethylene glycol complex.	do	1.9 down to, but not including 1.25:1	
(j) Aluminum zirconium trichlorohydrate	20 percent or less concentration (calculated on an anhydrous basis, omitting from the calculation any buffer component present in the compound) of a nonaerosol dosage form.	2.1 down to, but not including 1.5:1	2.0 up to, but not including 6.0:1
(k) Aluminum zirconium tetrachlorohydrate.	do	1.5 down to and including 0.9:1	2.0 up to, but not including 6.0:1
(l) Aluminum zirconium pentachlorohydrate.	do	2.1 down to, but not including 1.5:1	6.0 up to and including 10.0:1
(m) Aluminum zirconium octachlorohydrate.	do	1.5 down to and including 0.9:1	6.0 up to and including 10.0:1
(n) Aluminum zirconium trichlorohydrex glycine complex.	do	2.1 down to, but not including 1.5:1	2.0 up to, but not including 6.0:1
(o) Aluminum zirconium tetrachlorohydrex glycine complex.	do	1.5 down to and including 0.9:1	2.0 up to, but not including 6.0:1
(p) Aluminum zirconium pentachlorohydrex glycine complex.	do	2.1 down to, but not including 1.5:1	6.0 up to and including 10.0:1
(q) Aluminum zirconium octachlorohydrex glycine complex.	do	1.5 down to and including 0.9:1	6.0 up to and including 10.0:1
(r) Aluminum chloride	15 percent or less concentration (calculated on the hexahydrate form) of an aqueous solution nonaerosol dosage form.		
(s) Aluminum sulfate buffered	8 percent concentration of aluminum sulfate buffered with 8 percent concentration of sodium aluminum lactate in a nonaerosol dosage form.		

Subpart C—Labeling

§ 350.50 Labeling of antiperspirant drug products.

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

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

(1) (Any one of the following terms may be used: "Reduces," "Decreases," "Diminishes," or "Lessens") "underarm wetness."

(2) (Any one of the following terms may be used: "Reduces," "Decreases," "Diminishes," or "Lessens") "underarm dampness."

(3) (Any one of the following terms may be used: "Reduces," "Decreases," "Diminishes," or "Lessens") "underarm perspiration."

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

(1) "Do not apply to broken skin. If rash or irritation develops, discontinue use."

(2) For products in an aerosolized dosage form. "Avoid excessive inhalation."

(d) *Directions.* The labeling of the product contains the following statement under the heading "Directions": "Apply to underarms only."

Subpart D—Guidelines for Effectiveness Testing

§ 350.60 Guidelines for effectiveness testing of antiperspirants.

An antiperspirant in finished dosage form may vary in degree of effectiveness because of minor variations in formulation. To assure the effectiveness of an antiperspirant, the Food and Drug Administration is providing guidelines that manufacturers may use in testing for effectiveness. These guidelines are on file in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and are available on request to that office.

Interested persons may, on or before October 19, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 19, 1982. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

Interested persons, on or before August 20, 1983 may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before October 20, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305)

(address above). Received data and comments may also be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on October 20, 1983. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: June 25, 1982.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: July 29, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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