

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 350, and 369

[Docket No. 78N-0064]

RIN 0910-AA01

AUR

Display Date

JUN - 6 2003

Publication Date

JUN - 9 2003

Certifier

Skese

**Antiperspirant Drug Products For Over-the-Counter Human Use; Final Monograph**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

---

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antiperspirant drug products are generally recognized as safe and effective and not misbranded as part of FDA's ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on its proposed regulation, issued as a tentative final monograph (TFM), and all new data and information on antiperspirant drug products that have come to the agency's attention.

**DATES:** *Effective Date:* This rule is effective [insert date 18 months after date of publication in the **Federal Register**].

*Compliance Dates:* The compliance date for products with annual sales less than \$25,000 is [insert date 24 months after date of publication in the **Federal Register**]. The compliance date for all other products is [insert date 18 months after date of publication in the **Federal Register**].

**FOR FURTHER INFORMATION CONTACT:** Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2307.

**SUPPLEMENTARY INFORMATION:**

**Table of Contents**

- I. Background
  - II. The Agency's Conclusions on the Comments
    - A. General Comments on OTC Antiperspirant Drug Products
    - B. General Comments on Labeling of OTC Antiperspirant Drug Products
    - C. Comments on Category III Effectiveness Testing
    - D. Comments on Testing Guidelines
    - E. Comments on Antiperspirant Active Ingredients
    - F. Comments on the Safety of Aluminum Ingredients
  - III. Agency Changes
  - IV. Summary of Changes From the Proposed Rule
  - V. The Agency's Final Conclusions
  - VI. Analysis of Impacts
  - VII. Paperwork Reduction Act of 1995
  - VIII. Environmental Impact
  - IX. Federalism
  - X. Section 369.20 Revision
  - XI. References
- Monograph (Part 350)

**I. Background**

In the **Federal Register** of October 10, 1978 (43 FR 46694), FDA published 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 (the Panel), which evaluated the data on these products. The agency's proposed regulation (TFM) for OTC antiperspirant drug products was published in the **Federal Register** of August 20, 1982 (47 FR 36492).

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency issued a final rule establishing that certain active ingredients in OTC drug products are not generally recognized as safe and effective and are misbranded. These ingredients included seven antiperspirant ingredients, which are included in § 310.545(a)(4) (21 CFR 310.545(a)(4)). In this rulemaking, the agency is adding one additional ingredient to this section. (See section III.1 of this document.)

In the **Federal Register** of March 23, 1993 (58 FR 15452), the agency requested public comment on two citizen petitions, and a response to one of the petitions, related to the safety of aluminum compounds in OTC antiperspirant drug products. This final monograph completes the TFM and provides the substantive response to the citizen petitions.

Twenty-four months after the date of publication in the **Federal Register**, for products with annual sales less than \$25,000, and 18 months after the date of publication in the **Federal Register**, for all other products, no OTC drug product that is subject to this final rule and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application (NDA) or abbreviated new drug application. Further, any OTC drug product subject to this final monograph that is repackaged or relabeled after the compliance dates of the final rule 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 as soon as possible.

In response to the TFM on OTC antiperspirant drug products and the request for comment on the citizen petitions, the agency received 20 comments. One manufacturer requested an oral hearing before the Commissioner of Food and Drugs on six different issues. Copies of the information considered by the Panel, the comments, and the hearing request are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. "OTC Volumes" cited in this document refer to information on public display.

The agency received some "feedback" communications under the OTC drug review procedures (see the **Federal Registers** of September 29, 1981 (46 FR 47740) and April 1, 1983 (48 FR 14050)). The agency has included these communications in the administrative record and addressed them in this document.

The safety issues raised by the citizen petitions are discussed in section II.F of this document. The agency believes it has adequately responded to the six issues related to the hearing request; therefore, a hearing is not necessary.

## **II. The Agency's Conclusions on the Comments**

### *A. General Comments on OTC Antiperspirant Drug Products*

(Comment 1) One comment requested that FDA reconsider its position that OTC drug monographs are substantive, as opposed to interpretive, regulations.

The agency addressed this issue and reaffirms its conclusions as stated in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products (May 11, 1972, 37 FR 9464 at 9471 to 9472) and in

paragraph 1 of the preamble to the TFM in the present proceeding (47 FR 36492 at 36493).

(Comment 2) Three comments disagreed with the agency's proposed definition of an antiperspirant: "A drug product that, when applied topically to the underarm, will reduce the production of perspiration (sweat) at that site," (47 FR 36492 at 36503). One comment contended it was unduly restrictive and unnecessary to limit use only in the underarm area because it is not the only area of the body upon which these products could potentially be applied. The comment asked the agency to modify the definition to parallel the pharmacologic activity of the active ingredients and suggested: "A drug product that, when applied topically, will reduce the production of perspiration (sweat) at that site."

A second comment stated that the definition limiting use to the underarm only would adversely affect its products labeled for use on the hands and for use with orthotic and prosthetic appliances (to keep appliance-skin contact areas dry). Noting that the agency and the Panel recognized the similarities and differences between axillary and foot perspiration, a third comment stated that ingredients effective in the underarm area are probably effective to control foot perspiration.

The agency agrees with the first comment that it is not necessary to specify the area of use on the body in the definition of an antiperspirant because that information is included in the product's labeling. Accordingly, the agency is deleting the phrase "to the underarm" from the definition of an antiperspirant in § 350.3 (21 CFR 350.3) of this final monograph to read: "*Antiperspirant*. A drug product applied topically that reduces the production of perspiration (sweat) at that site." The use of an antiperspirant on other areas of the body,

as mentioned by the second and third comments, is discussed in section II.A, comment no. 4 and section II.C, comment 14 of this document.

(Comment 3) One comment stated that the TFM for OTC antiperspirant drug products was substantively and procedurally defective because it failed to address adequately the Panel's Category III recommendations concerning "enhanced duration of effect" and "problem perspiration" and failed to state what testing was required to substantiate these claims. The comment requested that FDA issue a new or amended TFM to address these issues.

The agency has determined that there is no need to withdraw, amend, or initiate a new TFM. Since the Panel's report was published in 1978, the procedural regulations for the OTC drug review were revised to comply with the Court ruling in *Cutler v. Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The revised regulations (46 FR 47730, September 29, 1981) provide that TFMs and final monographs will no longer contain recommended testing guidelines. The agency is not required by statute or regulation to include testing guidelines as part of OTC panel reports or TFMs. The agency stated in proposed § 350.60 of the TFM (47 FR 36492 at 36504) and states in § 350.60 of this final monograph (21 CFR 350.60) that "To assure the effectiveness of an antiperspirant, the Food and Drug Administration is providing guidelines that manufacturers may (emphasis added) use in testing for effectiveness."

The "enhanced duration of effect" and the "problem perspiration" issues are discussed in section II.C, comments 10 and 12 of this document. Extended duration of effect claims have been placed in Category I based on data submitted by other comments (see also comment 12). The agency has determined that claims for problem perspiration are outside the scope of this

monograph because no data were submitted to support such claims (see also comment 10).

(Comment 4) One comment contended that the proposed monograph would have a disastrous economic effect on its company, which markets an antiperspirant product first formulated in 1902 and labeled for excessive perspiration, including keeping the hands free of perspiration (labeled for use on the hands for tennis, racquetball, bowling, football, and other sporting uses), and marketed for prosthesis and orthotic use (for amputees to keep their appliance contact areas dry).

To qualify for exemption from the "new drug" definition under the 1938 grandfather clause of the act, the drug product must have been subject to the Food and Drug Act of 1906, prior to June 25, 1938, and at such time its labeling must have contained the same representations concerning the conditions of its use (21 U.S.C. 321(p)(1)). Under the 1962 grandfather clause of the act, a drug product which on October 9, 1962 was: (1) Commercially used or sold in the United States; (2) not a "new drug" as defined in the 1938 act; and (3) not covered by an effective NDA under the 1938 act, would not be subject to the added requirement of effectiveness "when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day." (Public Law 87-781, section 107(c)(4), 76 Stat. 788, note following 21 U.S.C. 321).

The person seeking to show that a drug comes within a grandfather exemption must prove every essential fact necessary for invocation of the exemption. See *United States v. An Article of Drug \* \* \* "Bentex Ulcerine,"* 469 F.2d 875, 878 (5th Cir. 1972), *cert. denied*, 412 U.S. 938 (1973). Furthermore, the grandfather clause will be strictly construed against one who

invokes it. See *id.*; *United States v. Allan Drug Corp.*, 357 F.2d 713, 718 (10th Cir.), *cert. denied*, 385 U.S. 899 (1966). A change in composition or labeling precludes the applicability of the grandfather exemption. See *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 663 (1973).

Although the comment stated that its drug products have been marketed since 1902 with hand perspiration labeling claims, no evidence was submitted to show that the labeling and composition of the products have remained unchanged since either 1938 or 1962, so that they qualify as grandfathered products. The agency requested product labeling from these years on several occasions (Refs. 1, 2, and 3), but none was ever provided. Without such evidence, the products do not qualify for either grandfather exemption. The burden of proof with respect to the grandfather exemption is not on FDA, but on the person seeking the exemption. See *An Article of Drug \* \* \* "Bentex Ulcerine," supra*.

The 1938 and 1962 grandfather clauses apply only to the new drug provisions of the act (see 21 CFR 314.200(e)) and not to the adulteration and misbranding provisions. The OTC drug review was designed to implement both the misbranding and the new drug provisions of the act. (See § 330.10 (21 CFR 330.10), 37 FR 9464 at 9466.) The grandfather clauses do not preclude the agency from reviewing any currently marketed OTC drug product, regardless of whether it has grandfather protection from the new drug provisions, in order to ensure that it is not misbranded.

Although the comment claimed this final rule would have a disastrous economic effect on its company if antiperspirants can be labeled only for underarm use, it provided no documentation about this impact. The agency notes that while the company's products would need to be relabeled to bear

different indications, as long as the monograph conditions are met, the products could remain in the marketplace after relabeling occurred. The economic impact of this final rule is discussed in section VI of this document.

*B. General Comments on Labeling of OTC Antiperspirant Drug Products*

(Comment 5) Several comments contended that FDA should not incorporate the “exclusivity policy” in the final monograph by prescribing specific labeling terminology to the exclusion of other truthful nonmisleading language.

After these comments were submitted, in the **Federal Registers** of May 1, 1986 (51 FR 16258) and March 17, 1999 (64 FR 13254), the agency published final rules changing its labeling policy for stating the indications for use of OTC drug products. Under § 330.1(c)(2) (21 CFR 330.1(c)(2)), the agency provides options for labeling OTC drug products. The final monograph in this document is subject to the labeling provisions in § 330.1(c)(2). In addition, the monograph labeling follows the format and content requirements of § 201.66 (21 CFR 201.66).

(Comment 6) One comment objected to limiting the terms proposed in § 350.50(b)(1), (b)(2), and (b)(3) to “reduces,” “decreases,” “diminishes,” and “lessens.” The comment stated that “lower” and “mitigate” are synonyms for “reduce” and other words and phrases state, truthfully and accurately, the effect of antiperspirants.

Several comments disagreed with the agency 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. The comments mentioned the minority Panel position that “The Panel did not see scientific data to indicate that a consumer can differentiate between such words as ‘halts,’ ‘checks,’ ‘stops,’ and ‘ends,’ as disallowable words versus ‘diminishes’ and ‘reduces’ as allowable words,” (43 FR 46694 at 46725). One comment agreed with the minority because a review of the entire record of this proceeding found no studies or data to support a decision to disallow “protects,” “halts,” “checks,” and “stops.” Another comment requested a hearing on this issue.

One comment disagreed with the Panel’s Category II status for the following labeling claims (43 FR 46694 at 46724): “Dry,” “dry formula,” “super dry,” “helps stop wetness,” “completely guards your family,” “helps stop embarrassing perspiration wetness,” “complete protection,” “really helps keep you dry,” and “gentle enough for sensitive areas of the body.” The comment asked the agency to allow these claims in the final monograph.

The agency has re-evaluated these claims in light of the comments’ arguments and its current policy to provide consumer friendly OTC drug product labeling. The agency is deleting one previously proposed word (“diminishes”) and adding some more consumer-friendly words (“sweat” and “sweating”) to antiperspirant product labeling.

The agency proposed the word “diminishes” in § 350.50(b) as one of the optional terms that could be used as the first word of the indications statement. While the word “diminish” means to “reduce,” the agency does not consider it as consumer-friendly as the other optional words “reduces,” “decreases,” or “lessens.” Therefore, the agency is not including “diminishes” in § 350.50(b) of this final monograph as an FDA-approved term. The agency rejected the words “mitigate” and “lower” in the TFM (comment 14, 47 FR

36492 at 36496 to 36497). The agency's position has not changed. While the terms "mitigate," "lower," and "diminishes" are not in the monograph and the agency does not favor their use, manufacturers may use these terms, or other words or phrases that truthfully and accurately express a similar meaning, under the flexible labeling policy in § 330.1(c)(2).

The agency is not changing its position on the use of the word "helps" in conjunction with the words "stop," "halt," "check," "end," and "eliminate." In the TFM (comment 14), the agency stated that these words imply the ability to stop underarm perspiration totally and would therefore mislead consumers about antiperspirant effectiveness. Although neither the Panel nor the agency had any consumer comprehension studies to support a decision to disallow this information, the comments also did not provide any data to support these terms. The agency would consider these terms if data are provided to show that consumers would not be misled about the effect of antiperspirant drug products. The agency is not including "helps protect" before "underarm dampness," "underarm perspiration," or "underarm wetness," because the language is not clear and could confuse consumers.

The agency is not including any "dry" or similar claims ("dry," "dry formula," "super dry," "really helps keep you dry") in this final monograph because no criteria have been established to define "dry." Thus, what may be "dry" for one manufacturer's product may not be "dry" for another manufacturer's product. The agency would consider including "dry" claims in the monograph if appropriate criteria for such claims are developed.

The agency is not including claims such as "complete protection" or "completely guards your family" in the monograph because there is no evidence that antiperspirant drug products provide "complete" protection. The

agency is not including the claim “gentle enough for sensitive areas of the body” because the words “sensitive areas” may imply that the product can be used on other body areas in addition to the underarm. The agency is not including the claim “helps stop embarrassing perspiration wetness” because what is “embarrassing” or “problem” perspiration for one individual may not be “embarrassing” or a “problem” for others. (See section II.C, comment 10 of this document.)

The agency is not including both “perspiration” and “wetness” in the same claim because it considers the duplicative wording unnecessary. The currently allowed claims are “\* \* \* underarm wetness” or “\* \* \* underarm perspiration.” The agency would have no objection to “\* \* \* underarm perspiration wetness,” but such would have to be done under the flexible labeling provisions of § 330.1(c)(2). The agency is adding the words “sweat” and “sweating” in § 350.50(b) as other ways to describe “wetness” and “perspiration,” because consumers regularly use these terms to describe perspiration. Based on the previous discussion, the agency concludes that a hearing is not warranted on these issues.

(Comment 7) Three comments requested that OTC antiperspirant drug products be exempted from the keep out of reach of children and accidental ingestion warnings in § 330.1(g) because these products are not toxic by oral ingestion. One comment noted only one reported ingestion in 30 years of marketing antiperspirant products. Another comment stated that aerosols, in particular, should be exempt from the ingestion warning due to the characteristics of the delivery system and the warnings already required for aerosols pressurized by gaseous propellants under § 369.21 (21 CFR 369.21).

Although the comments did not submit any data to show that antiperspirant drug products are safe if ingested, the agency believes these products should not be toxic by oral ingestion for most individuals. However, individuals with renal dysfunction or immature renal function (i.e., infants) are at a higher risk from any exposure to aluminum. Further, ingestion of the various inactive ingredients present in these products may make young children ill or cause other undesirable consequences. Without adequate proof of safety if accidental ingestion were to occur, the agency has no basis to exempt OTC antiperspirant drug products from the accidental ingestion warning.

Although aerosol antiperspirant drug products are unlikely to be accidentally ingested by most consumers, the agency notes that the product containers are similar to those used for some food products. Spraying an aerosol into the mouth and ingesting it could be more hazardous than ingesting other dosage forms of the product because of the aerosol propellants. The warnings required under § 369.21, for those drugs in dispensers pressurized by gaseous propellants, are not related to ingestion, but state the following: "Avoid spraying in the eyes. Do not puncture or incinerate. Do not store at temperatures above 120 °F. Keep out of reach of children." The agency does not consider these warnings a basis to exempt aerosol antiperspirants from the accidental ingestion warning required by § 330.1(g) for topical drug products. The last statement of the warning required by § 369.21 and the first warning required by § 330.1(g) (i.e., "Keep out of reach of children.") are identical as of March 17, 1999 (64 FR 13254 at 13294). Section 350.50(c)(4)(ii) of the final monograph requires aerosol antiperspirant drug products to bear the language in § 369.21. These products do not have to repeat the first general warning

required by § 330.1(g) but need to have the accidental ingestion warning required by § 330.1(g).

(Comment 8) Two comments objected to the proposed warning in § 350.50(c) for aerosol antiperspirants, which states: “Avoid excessive inhalation.” The comments argued that the warning duplicates and gives less information than the current warning required for aerosol drug products under § 369.21.

Section 369.21 requires the following warning statement for a drug packaged in a self-pressurized container in which the propellant consists in whole or in part of a halocarbon or hydrocarbon: “Use only as directed. Intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.” The agency does not consider this warning (which addresses deliberate misuse) as being the same as a general statement warning people to avoid excessive inhalation. There are many people who would not deliberately misuse the product who should be alerted to keep away from their face and mouth and to avoid excessive inhalation. The warning appears in the final monograph in more consumer friendly language and in the new labeling format as follows: “When using this product [bullet] keep away from face and mouth to avoid breathing it.” (See § 201.66(b)(4) for description of a “bullet.”)

### *C. Comments on Category III Effectiveness Testing*

(Comment 9) Several comments objected to user perception testing to substantiate Category III effectiveness claims. (See comment 24, 47 FR 36492 at 36499.) The comments contended that the user perception test is not reliably indicative of product effectiveness and offers at best a crude index of activity that is difficult to employ for precise qualitative and quantitative evaluations. The comments considered objective gravimetric sweat collection procedures

more reliable than user perception testing to assess antiperspirant activity levels and requested that user perception testing be deleted. Three comments submitted data on user perception testing of Category III claims, including extra effective, 24-hour duration, emotional sweating, and foot perspiration (see section II.C, comments 11 through 14 of this document).

The agency has determined that user-perception test data support emotional sweating, 24-hour protection, and extra effective claims. Accordingly, the agency concludes that there are sufficient data on user perception tests (including both user and independent observer perception tests) for use of antiperspirants for the underarm. No further user perception tests are necessary if an underarm antiperspirant shows at least 20 percent sweat reduction by gravimetric tests for emotional sweating and 24-hour protection claims or 30 percent sweat reduction for extra effective claims. Adequate user perception tests have not been conducted for parts of the body other than the underarms, such as the hands or feet. The agency will still require user perception and other effectiveness data to support use of antiperspirants on the hands and feet (see section II.A, comment 4 and section II.C, comment 14 of this document).

(Comment 10) Several comments objected to the Category III status of the claims “problem perspiration” and “especially troublesome perspiration.” One comment contended these claims are not inherently misleading or untruthful and many people who do not perspire heavily may, at times, consider themselves to have “problem” or “troublesome” perspiration.

Other comments objected to the agency’s definition of problem perspiration as affecting the upper 5 percent of perspirers, contending that a more realistic approach would be to let consumers define the meaning of

these words by running efficacy studies on people who identify themselves as having problem or especially troublesome perspiration. One comment objected to the economic consequences of testing the top 5 percent of the population to establish a “problem perspiration” claim, because this could raise the price for one efficacy evaluation from the current \$5,000 to \$10,000 up to \$200,000. The comment requested a hearing on this issue if FDA did not revise its approach.

No data were submitted to the agency to show that any OTC antiperspirant drug product is effective in reducing “problem” or “especially troublesome” perspiration. The agency is not aware of any products that currently qualify as effective for those conditions. If products are found to be effective in the future, the agency will include a definition and labeling for “problem” or “especially troublesome” perspiration in the monograph. The agency proposed in the tentative final monograph that a 30 percent reduction in sweat production in the upper 5 percent of perspirers is necessary for a “problem perspiration claim” (47 FR 36492 at 36500). As discussed in section II.C, comment 9 of this document, gravimetric testing is sufficient to prove these claims. The agency would find acceptable an antiperspirant effectiveness study on a population of individuals who perceive themselves to have “problem perspiration,” as one comment suggested. Based on changes in the testing to support these claims, the agency concludes that a hearing is not needed.

(Comment 11) Several comments objected to the agency’s proposed Category II classification of the claims “extra strength,” “extra effective,” or any other comparative effectiveness claims (see comment 19, 47 FR 36492 at 36498). The comments argued that if manufacturers can demonstrate by appropriate testing and methods of statistical analysis that one product is more

effective than another, they should be permitted to so inform consumers. The comments noted that the agency had approved an NDA for an acetaminophen “extra strength” product and allowed sunscreen products to label their degree of effectiveness. One comment requested a hearing on this subject.

To prove the validity of comparative claims, two comments submitted both gravimetric and perceptual data (Refs. 4 and 5). Another comment submitted gravimetric data only (Refs. 6 and 7) and stated that one study showed that a 10 percent difference in antiperspirant effectiveness can be measured with currently marketed antiperspirant products. This comment stated that adequate data (Ref. 8) had been submitted to the Panel (43 FR 46694 at 46715) to show that as differences in antiperspirant performance levels increase, larger numbers of consumers perceive the difference. These data included a chart plotting differences in sweat reduction against the percentage of subjects who noted variations in axillary wetness. The chart shows that at 20 percent sweat reduction, approximately 45 to 50 percent of the subjects noticed a difference; at 35 percent sweat reduction, approximately 60 percent noticed a difference; and at 50 percent sweat reduction, approximately 75 percent noticed a difference. The comment contended that this study confirmed the Panel’s determination that the user can perceive a shift of at least 10 percent in antiperspirant effectiveness and that a product providing a 30 percent or greater sweat reduction is perceived as more effective than a standard antiperspirant. The comments requested monograph status for “extra strength” and “extra effective” claims, as qualified by gravimetric studies.

The agency has determined that some of the studies (Ref. 4) meet the Panel’s “guidelines for user perception test to be done for claims of ‘extra-effective’ to be classified as Category I” (43 FR 46694 at 46730). In these

studies, two solid stick antiperspirant products (containing either 10 percent or 25 percent aluminum chlorohydrate) were compared by both a gravimetric and a user perception test. In the gravimetric test, 91 female subjects used the 10-percent product, and 88 used the 25-percent product. A 17-day conditioning period with no antiperspirant use was followed by four daily applications of one of the products to a randomly selected axilla (armpit or underarm). The opposite axilla received no treatment and served as the control. Baseline sweat production was determined the first day of the test. On days two and three, the antiperspirant was applied and 1 hour later a sweat production sample was collected. On day five, 24 hours after the fourth application, a sweat production sample was collected. Both the 10- and 25-percent products were more effective than the no treatment control for all time periods according to the statistical methods (Wilcoxon signed rank test) in the agency's guidelines for effectiveness testing of OTC antiperspirant drug products (Ref. 9).

Evaluation of the Z values for the two 1-hour test days and the 24-hour test day showed that both products were statistically (Wilcoxon test) at least 20 percent better than the control axilla for all time periods ( $p < 0.001$  for all three cases). Thus, both products met the requirements for standard effectiveness, i.e., a minimum of 20-percent reduction in underarm perspiration. Applying the same statistical methods to a 30-percent reduction in underarm perspiration on the last 24-hour data showed that the 25-percent product was more effective than no treatment ( $p < 0.001$ ) and, thus, met one of the extra effective criteria.

The same study design was used in the user perception test except that the subjects applied the 10-percent product under one axilla and the 25-percent product under the other axilla. On day five, 24 hours after the fourth

application, the 100 female subjects were asked “Under which arm do you feel drier?” All subjects had a preference: 33 favored the 10-percent product and 67 favored the 25-percent product. A statistically significant number of the subjects were able to perceive that the 25-percent product was more effective than the 10-percent product ( $p = 0.0005$  one-sided). This result exceeded the Panel’s requirement that 58 out of 100 subjects have a preference for the test antiperspirant (43 FR 46694 at 46731). Thus, these studies showed that the 25-percent aluminum chlorohydrate met the Panel’s criteria (gravimetric measurements and user perception) for an extra effective claim.

The agency has determined that the studies indicate that gravimetric testing shows an adequate difference between a standard antiperspirant (with a 20-percent reduction in sweat) and an antiperspirant with at least a 30-percent reduction in sweat, as required by the Panel, to support an “extra effective” claim. The agency stated in the tentative final monograph (47 FR 36492 at 36499) that once the level of activity that is perceivable by users has been established using the Panel’s recommended guidelines, it will not be necessary to perform user perception testing on individual products. Accordingly, the agency concludes that no further user perception testing is necessary for an “extra effective” claim, which is being included in the monograph for those antiperspirant products that reduce underarm perspiration by 30 percent or more using the guidelines for effectiveness testing of antiperspirant drug products referred to in § 350.60.

The Panel placed “extra-strength” claims in Category II because it concluded that “the presence of more active ingredient in an antiperspirant product cannot be used as a basis for a claim of added effectiveness because additional amounts of antiperspirant active ingredient do not necessarily result

in improved product effectiveness” (43 FR 46694 at 46724). The Panel also stated that “the term ‘extra-strength’ normally refers to increased concentration of the active ingredient which would normally mean added effectiveness.” Several comments agreed that more active ingredient may not yield more effectiveness. Thus, a product containing 20 percent of an active ingredient (compared to 15 percent) that did not provide 30 percent or more sweat reduction could not claim “extra strength” or “extra effective.”

The agency does not believe that for antiperspirants the claim “extra strength” is as informative to consumers as the claim “extra effective.” The agency considers “extra effective” to be the key information that consumers want to know to select an appropriate antiperspirant product. The agency is including this new labeling claim in § 350.50(b)(4) of this final monograph. Based on this discussion, the agency concludes that a hearing is not needed on this subject.

(Comment 12) Several comments objected to the Panel’s Category III classification of claims for enhanced duration of effect, such as “24-hour protection,” “one spray keeps you comfortably dry all day,” “prolonged protection,” etc. (43 FR 46694 at 46728). One comment stated that if an antiperspirant product can be shown to provide the required 20-percent reduction in perspiration under hotroom conditions for 24, 48, etc. hours after application, then duration claims have been substantiated.

Three manufacturers submitted gravimetric studies (Refs. 4, 7, 10, and 11) that used a hotroom to induce sweating and measured sweat collected in cotton pads twice over a 24-hour period. The tested ingredients showed a 20-percent or more reduction in sweat production for both collection times, which the comments contended satisfied enhanced duration claims such as “24 hour

protection” and “all day protection.” One comment added that its data (Ref. 11) support a variety of product forms (cream, roll-on, solid stick) and, thus, the enhanced duration effect is not limited to product form.

The agency has determined that the data support a claim of enhanced duration for 24 hours according to the Panel’s criteria. The protocols in seven of the studies (Refs. 7 and 10) varied only slightly from the Panel’s recommended protocol. Subjects in one study abstained from antiperspirant use for 2 weeks prior to the study. Subjects in the other six studies stopped using antiperspirants 4 weeks prior to the studies. The subjects were pretreated with an antiperspirant for the 5 days prior to beginning sweat collection procedures. Sweat was collected 4 and 24 hours following the last antiperspirant application. Five studies included untreated axilla controls, and two studies included placebo controls. One product was tested in two different studies (one with a placebo and one without), and the results were virtually identical. The tests supported enhanced duration efficacy of 20 percent sweat reduction over the 24-hour period for aluminum zirconium tetrachloride (15.5 percent roll-on and 18.2 percent stick), zirconium tetrachloride (20 percent roll-on), aluminum chlorohydrate (6.8 percent aerosol), and aluminum chloride (20 percent solution).

Other data (Ref. 4) also supported enhanced duration of effectiveness for antiperspirant solid sticks containing 10 and 25 percent aluminum chlorohydrate. Subjects, who abstained from antiperspirant use for 17 days prior to the study, were pretreated with an antiperspirant for the 3 days prior to sweat collection, 1 and 24 hours after the last antiperspirant application. Standard hotroom and sweat collection procedures were used. Over the 24-hour period, both 10 percent and 25 percent aluminum chlorohydrate sticks

reduced sweat production in the treated axilla by 20 percent compared to the untreated axilla. The 25-percent aluminum chlorohydrate product also showed a 30-percent reduction in sweat production.

Six other studies (Ref. 11) support enhanced duration claims. Most products showed a 20-percent reduction in sweat production compared to an untreated axilla for both the 4- and 24-hour evaluation periods, with several products showing a 30-percent sweat reduction. However, the studies did not identify the antiperspirant active ingredients.

The agency is including the following enhanced duration claims in § 350.50(b)(3) of this final monograph: “all day protection,” “lasts all day,” “lasts 24 hours,” or “24 hour protection.” In order to make such a claim, an antiperspirant product must reduce sweat production by at least 20 percent over a 24-hour period after application using the guidelines for effectiveness testing referred to in § 350.60. Antiperspirant products that meet the extra effective criteria (see section II.C, comment 11 of this document) over a 24-hour period can be labeled with both extra effective and enhanced duration claims (e.g., “24 hour extra effective protection,” “all day extra effective protection,” “extra effective protection lasts all day,” etc.). Claims of enhanced duration for more than 24 hours are nonmonograph because the agency has not received any data to demonstrate antiperspirant effectiveness for more than 24 hours according to the Panel’s criteria.

(Comment 13) Several comments objected to the Panel’s Category III classification of claims for control of emotional sweating, e.g., induced by tension or stress (43 FR 46694 at 46728). The comments contended that a product’s antiperspirant activity is the same whether the sweat is due to thermal conditions or emotional factors. Some comments disagreed with the

need for additional testing, especially consumer perception testing, to establish these claims. One comment requested a hearing.

One comment submitted clinical data (Refs. 7 and 12) which it contended showed: (1) There is a valid scientific protocol that combines a gravimetric sweat test with a word-quiz stress test to measure reduction in emotionally-induced sweat; (2) an antiperspirant is not washed from the axillae during controlled emotional stressing, and excessive sweat does not diminish antiperspirant effectiveness; (3) an antiperspirant effective in reducing thermally-induced sweat is effective in reducing emotionally-induced sweat also; and (4) an antiperspirant that reduces emotionally-induced sweat by 20 percent or more meets the standard for antiperspirant effectiveness for which user perception and benefit has already been accepted and, thus, there is no need for additional user perception testing. The studies included aerosol, roll-on, and stick products containing aluminum chlorohydrate or aluminum zirconium tetrachlorohydrate, the major antiperspirant active ingredients.

The agency has determined that gravimetric sweat tests combined with mental stress tests support an emotionally-induced sweating claim. The data included 12 studies with the same design of 5 days each on panels of approximately 25 female subjects: Pretest-abstention from all antiperspirants for at least 4 weeks prior to the study; day one—pretreatment control sweat collection under no stress; day two—pretreatment control sweat collection under emotional stressing; days two through five—apply test product; and days four and five—posttreatment sweat collection under emotional stressing. Subjects applied the antiperspirant test formulation to one axilla and used either a comparative formulation, a control placebo formulation, or no treatment on the opposite axilla. A control emotional challenge test, which

lasted for about 60 minutes, was done on day two and an emotional challenge test was done on days four and five of the study.

Emotional sweating was induced by having subjects do a word definition test conducted by a moderator experienced at insuring optimum stress. The subjects received monetary rewards for a correct definition, but forfeited some of their rewards for incorrect or untimely definitions. Subjects had a 5-second time limit to begin a response and a 15-second maximum time to give the actual word definition. After 60 minutes, sweat was measured gravimetrically from the preweighed absorbent pads. Standard sweat collection and statistical evaluation procedures were used. The median sweat output for the 12 studies was 1,257 milligrams (mg) for the pretreatment control under emotional stressing compared to 415 mg for the pretreatment control under no stress. This word definition test effectively elicited a sweat response.

In the 12 studies using the word definition test, there was at least a 20-percent reduction of sweat production. The top 10 percent of heavy sweaters from each study (25 subjects) having the highest sweating rates on the untreated axilla had a 36.8 percent average sweat reduction compared to 38.2 percent reduction in the remaining 90 percent of each population (196 subjects), showing no significant difference in effectiveness in the two groups. Majors and Wild (Ref. 13) obtained similar results when comparing individual percent reduction in thermal sweating in the antiperspirant-treated axilla to rate of sweating from the untreated axilla in 89 subjects. They found that heavy sweating did not affect the rate of reduction.

The products tested under the emotional sweat protocol were also evaluated under a standard thermal sweat protocol at 100 °F with 30 percent relative humidity. The average percent sweat reduction for aerosols was 37.0

percent for emotional sweating and 34.0 percent for thermal sweating, for sticks it was 46.0 percent for emotional sweating and 41.4 percent for thermal sweating, and for roll-ons it was 51.3 percent for emotional sweating and 53.3 percent for thermal sweating. These data show that the same products have similar average percent sweat reduction for both emotional and thermal sweating.

The agency concludes that gravimetric sweat tests combined with mental stress tests are sufficient to show effectiveness for control of emotionally-induced sweating; the data show antiperspirant drug products that are effective for thermal sweating are also effective for emotional sweating. The agency has determined that no additional testing (e.g., user perception tests) is required for an emotionally-induced sweating claim for products containing monograph ingredients that meet the guidelines for effectiveness testing of antiperspirant drug products referred to in § 350.60.

The agency is including the following emotionally-induced sweating claim in § 350.50(b)(2) of this final monograph: “also [select one of the following: ‘decreases,’ ‘lessens,’ or ‘reduces’] underarm [select one of the following: ‘dampness,’ ‘perspiration,’ ‘sweat,’ ‘sweating,’ or ‘wetness’] due to stress”. Based on the previous discussion, the agency concludes that a hearing is not needed on this subject.

(Comment 14) One comment requested monograph status for 25 percent aluminum chlorohydrate to control foot perspiration based on gravimetric and perceptual data from four randomized, double-blind, bilateral, paired-comparison trials, each having 12 female subjects (Ref. 14). Treatment was randomly assigned; aluminum chlorohydrate was used on one foot and placebo on the other foot. A 25 percent aluminum chlorohydrate solution in 50 percent

ethanol:50 percent water and a placebo control consisting of 50 percent ethanol:50 percent water were used in the first study. The same solutions in aerosol form were used in the other three studies. The procedure in the agency's "Guidelines for Effectiveness Testing of OTC Antiperspirant Drug Products" (Ref. 9) was modified for foot testing: (1) A 3-day pre-treatment period during which subjects were not to use any foot care products, with each subject receiving four daily product applications prior to final hotroom posttreatment testing collection; (2) sweat collection media were cotton socks rather than absorbent pads; (3) a required 5-minute period of mild exercise (walking around the hotroom at the beginning of each collection period); and (4) a modified method to calculate effectiveness due to the erratic rate of sweat collections for both treated and control feet.

The comment stated that the calculation technique included in the agency's guidelines could not be used for the following several reasons: (1) The increased number and higher concentration of sweat glands in the foot area, (2) the occlusive nature of the foot area, and (3) the erratic rate of sweat collections for both treated and control feet. The comment contended that by considering the baseline, the posttreatment sweat collections, and the preferential subject perception data, statistically significant differences could be shown between sweat collection values for the treated foot compared to baseline values.

The comment stated that based on at least a 5-percent difference between the measured sweat output of each foot, sweat reduction was achieved for the treated foot in 25 of 48 subjects (52 percent) compared to only 10 of 48 subjects (21 percent) for the control foot. The comment added that, based on the user perception questionnaire, 75 percent of the subjects (29 out of 39 subjects who

were able to discriminate) were able to perceive after the hotroom exposure that the treated foot was drier compared to only 21 percent of the subjects (10 out of 48) who perceived the control foot to be drier.

A second comment submitted a proposed clinical protocol (Ref. 15), but never submitted any clinical data.

The agency has found the data are insufficient to support a foot antiperspirant claim. In axillary sweating tests submitted to the Panel, the range of effectiveness (average percent sweat reduction) of antiperspirants was 20 to 40 percent in most tests, with aerosols having a reduction range of 20 to 33 percent (43 FR 46694 at 46713). In the comment's studies on aluminum chlorohydrate for foot antiperspirancy (Ref. 14), the average percent sweat reduction was below 10 percent, which is considerably below the 20 percent minimum level of sweat reduction recommended by the Panel for efficacy testing of OTC antiperspirant drug products on the foot (43 FR 46728). In addition, the agency has a number of concerns about the comment's data treatment methods: (1) The particular sweat collections selected for analysis were not chosen consistently across studies but were based on arbitrarily chosen final sweat measurements that varied with the different studies, (2) the choice of a 5-percent difference between the measured sweat output of each foot as "clinically significant" seems arbitrary and was not prespecified in the protocol, (3) the efficacy criterion used (greater than 15 percent reduction from baseline) was apparently defined after the data were collected and the results are therefore potentially biased, and (4) comparison with baseline is not an adequate basis upon which to conclude product efficacy because it ignores placebo and time effects that are accounted for in between product comparisons. The agency's analysis of "across study" data (using the average

of the two sweat collections on day four, or average of the four collections on day four and five as the baseline, and the average of the two final collections as a measure of the final sweat product) did not show a statistically significant mean (or mean percent) sweat reduction from baseline in treated or control feet.

The agency does not agree with the comment's evaluation of its user perception data, but considers the product as ineffective both in subjects who preferred placebo and in subjects with no preference. It appears that the comment chose to ignore tied preferences. However, when subjects with no preference were included in the analysis, 22 out of 48 subjects (45.8 percent) and 29 out of 48 subjects (60.4 percent) preferred the treated foot, before entering and after leaving the hotroom, respectively. Both proportions are not significantly different from 1/2 (two-tailed,  $p = 0.28$  and  $0.15$ , respectively). Furthermore, the subjects apparently could not perceive which foot, treated or untreated, was drier. More subjects failed to choose the drier foot, than chose it correctly, both at baseline and posttreatment. Thus, the wetness perception study failed to show that subjects are able to tell marginal differences in sweating of the feet.

The agency has concluded that no statistically significant treatment effect was found in sweat reduction or in subject's perception of sweat (Ref. 16). Thus, 25 percent aluminum chlorohydrate has not been shown to be an effective foot antiperspirant. The agency provided the second comment suggestions on its protocol; a revised protocol was acceptable (Ref. 17), but no test data were ever submitted. The agency is not including foot antiperspirancy claims in the final monograph.

#### *D. Comments on Testing Guidelines*

(Comment 15) Several comments requested that the background section of the effectiveness testing guidelines include the following: "FDA recognizes that alternative methodologies may be appropriate to qualify an antiperspirant drug product as effective. These guidelines do not preclude the use of alternative methodologies that provide scientifically valid results."

The agency is adding this statement (but changing the words "alternative methodologies" to "alternate methods") and adding "subject to FDA approval" to provide for alternate methods and statistical evaluations of effectiveness test data.

(Comment 16) Several comments requested that the relative humidity of 35 to 40 percent in the effectiveness testing guidelines be lowered to 30 percent, the hotroom condition widely used by industry. One comment submitted the results of effectiveness studies (Refs. 7, 10, and 18) that used a hotroom operated at 30 + 3 percent relative humidity. The comment stated that 30 percent relative humidity accurately measures antiperspirant effectiveness without causing excessive discomfort to test subjects. Two other comments submitted effectiveness test data where the relative humidity in the hotroom was "about 35 percent" (Refs. 19 and 20) or "35 percent  $\pm$  5 percent" (Ref. 21).

Based on these data, the agency is revising the relative humidity range for hotroom conditions in the antiperspirant effectiveness testing guidelines from 35 to 40 percent to a range of 30 to 40 percent. Seven studies (Ref. 10) that showed an enhanced duration of effectiveness of 20 percent sweat reduction over a 24-hour period for several antiperspirant products (see also section II.C, comment 12 of this document) used a protocol (Ref. 18) in which

the subjects were placed in a controlled environment with the temperature held at  $100 \pm 2$  °F and the relative humidity held at  $30 \pm 3$  percent. Because the subjects were able to generate at least 150 mg of sweat per axilla per 20 minute period, the agency considers the results of the gravimetric tests valid. In other studies (Refs. 20 and 21), sweating was induced by having the subjects sit in a hotroom maintained at a temperature of  $100 \pm 2$  °F and at a relative humidity of about 35 percent or  $35 \pm 5$  percent. These studies support claims of extra effectiveness and enhanced duration (24-hour claims). See section II.C, comments 11 and 12 of this document. To assure that test subjects sweat adequately during the hotroom test, the agency is adding the following baseline perspiration rate condition: "*Baseline perspiration rate.* Test subjects must produce at least 100 milligrams of sweat from the untreated or placebo control axilla in a 20-minute collection in the controlled environment."

(Comment 17) Two comments requested revision of the part of the antiperspirant effectiveness testing guidelines that involves application of a control formulation to the alternate axilla during testing. Noting that the guidelines state that the control formulation is to be "devoid of any antiperspirant activity \* \* \* determined in a test compared to no treatment," a comment contended that it should be appropriate to compare antiperspirant activity directly against an untreated axilla and, thereby, reduce the time, complexity, and cost of the testing, especially the cost of developing a control formulation "devoid" of antiperspirant activity. The comment requested that the testing guidelines be revised to provide for the application of a control formulation or no treatment to the other axilla of each test subject. The other comment submitted data from two studies (Refs. 22 and 23) where one antiperspirant formulation was tested against both a placebo control and an

untreated axilla control with virtually identical results; therefore, a placebo control was unnecessary to evaluate product effectiveness.

The data (Refs. 22 and 23) involved an aerosol spray containing 6.8 percent aluminum chlorohydrate tested by two gravimetric sweat tests under hotroom conditions to substantiate the claim that the product provides “all day wetness protection.” Both studies had the same design: Day one—pretreatment control collection; days two, three, and four—application of antiperspirant; and days four and five—posttreatment sweat collection 4 and 24 hours after application. The data were evaluated using one of the statistical methods recommended in the antiperspirant testing guidelines. In one study (Ref. 22), the product was tested against a placebo aerosol in 44 subjects. The placebo was identical to the test formulation and supposedly devoid of antiperspirant activity; the formula difference was adjusted with aerosol propellant. The results were statistically significant and showed that the aluminum chlorohydrate aerosol effectively reduced sweat production by at least 20 percent more than the placebo aerosol at 4 and 24 hours after application. However, the placebo showed some antiperspirant activity. In the second study (Ref. 23), the same product was tested against an untreated axilla control in 49 subjects with statistically significant results. The aluminum chlorohydrate aerosol effectively reduced sweat production by at least 20 percent more on the treated axilla than the untreated control axilla at 4 and 24 hours after application.

The agency is unable to conclude from these data that an untreated comparator is equivalent to use of a placebo. The observed effect of a treatment (e.g., antiperspirant) may represent the sum of the pharmacological effects of the test drug and other effects associated with the intervention effort, which may include psychological effects and the effects of the excipients used in a

product formulation. Although studies have been conducted in the past using no treatment for one axilla, the use of a placebo control for that axilla allows for assessment of the net treatment effects of the test article. Therefore, the agency is retaining the requirement for a placebo/vehicle control in the antiperspirant effectiveness testing guidelines.

The proposed guidelines stated that the control formulation is as similar as possible to the test formulation and devoid of any antiperspirant activity. As the placebo used in one study (Ref. 22) was not completely devoid of antiperspirant activity, the agency is revising the guidelines to state:

*Hotroom procedure.* (1) For gravimetric and user perception testing, treatments consist of the application of the test formulation to one axilla and the application of a placebo control formulation to the other axilla of each test subject. Except for the active ingredient, the placebo control formulation should be as similar as possible to the test formulation.

The agency concludes that this revised testing procedure will reduce the time, complexity, and cost of testing because it eliminates the cost of developing a control formulation “devoid” of antiperspirant activity.

#### *E. Comments on Antiperspirant Active Ingredients*

(Comment 18) Several comments noted a discrepancy in a heading in an active ingredient table in the Panel’s report (43 FR 46694 at 46697), where “Metal:Halide” is used, and in proposed § 350.10 (47 FR 36492 at 36504), where “Al:Cl” is used. Two comments suggested that “Al:Cl” in the table heading and in § 350.10 should be changed to “Metal:Cl,” because the ratio range in the table is for the ratio of the “Cl” to either aluminum (“Al”) or aluminum plus zirconium (“Al+Zr”).

The agency notes that the ratio range designated as “A1:Cl” in the TFM should have been “Metal:Halide,” as it was in the Panel’s report. The agency is not including the ratio range table in § 350.10 of this final monograph because this information is now included in the U.S. Pharmacopeia-National Formulary (USP–NF) monographs for each active ingredient included in § 350.10, where applicable. The agency is changing the introductory text of § 350.10 to state: “Where applicable, the ingredient must meet the aluminum to chloride, aluminum to zirconium, and aluminum plus zirconium to chloride atomic ratios described in the United States Pharmacopeia-National Formulary.”

(Comment 19) Two comments agreed with the agency that buffer components present in the compound, such as glycine or glycol, should be omitted when calculating the maximum allowable concentration of active ingredients in an antiperspirant product (47 FR 36492 at 36495). One comment noted a potential source of confusion because the active ingredients table in proposed § 350.10 included the buffer names along with the active ingredient names. To minimize confusion and to be consistent with the agency’s policy regarding buffers, the comment requested the agency to remove the buffer names from the “active ingredient” column in § 350.10. The comment proposed a number of changes in the active ingredient section.

When the Panel first discussed terminology for aluminum chloride and aluminum chlorohydrate antiperspirant active ingredients, the buffer additives were not included (Ref. 24). Subsequently, the Cosmetic, Toiletry, and Fragrance Association (CTFA) Antiperspirant Task Force developed definitions for aluminum chlorohydrate complexes with propylene glycol or polyethylene glycol, and for aluminum zirconium chlorohydrate complexes with glycine

(Ref. 25). The Panel adopted these definitions, including those for ingredients with buffered additives, in its report (43 FR 46694 at 46696 and 46697), and the agency proposed this nomenclature in the TFM (47 FR 36492). Since the comment was submitted, the USP–NF developed names for these antiperspirant active ingredients that include the names of the buffers, where applicable, and active ingredient names in this final monograph include the buffer, where applicable.

The agency considers calculation of the concentration of an antiperspirant ingredient present in a product based on the amount of anhydrous ingredient to be appropriate. Buffered antiperspirant ingredients contain the same active chemical moiety as the corresponding nonbuffered ingredients, and the antiperspirant activity of both ingredients is similar.

(Comment 20) One comment requested the agency allow concentrations of antiperspirant active ingredients above those proposed in the monograph as long as the amount of ingredient applied to the skin is not greater than the amount judged safe by the Panel. The comment noted that, in the TFM (comment no. 12, 47 FR 36492 at 36495 to 36496), the agency had disagreed with earlier comments on this issue and stated that “the comments included no new data to show that a higher concentration of antiperspirant active ingredient marketed in a particular container would deliver no more than the amount of active ingredient judged safe by the Panel.”

The comment submitted new data from eight usage studies (Ref. 26) to support a higher (up to 35 percent) active ingredient concentration for powder roll-on antiperspirant drug products. Fifty male and female subjects, between the ages of 18 and 55, participated in each study. Subjects were given a preweighed product and instructed to use only that product, to keep a record

of how many times they used it, and not to allow anyone else in the household to use the product. An average of 43 subjects completed the 1-week studies and returned their product to the laboratory where it was reweighed.

The amount of product applied with each use was calculated. The four powder roll-ons, which contained 33 percent aluminum zirconium tetrachlorohydrate, were found to deliver between 23 and 44 mg of antiperspirant ingredient per axilla per use. The other product forms (solid stick, cream, or liquid roll-on), containing 18 to 19 percent of either aluminum chlorohydrate or aluminum zirconium tetrachlorohydrate, were found to deliver between 54 and 98 mg of antiperspirant ingredient per axilla per use. The comment contended these data show that higher concentrations of active antiperspirant ingredients, as used in powder roll-on systems, deposit no more and, in fact, deposit less active ingredient than is deposited in a liquid roll-on, solid stick, or cream product containing proposed monograph concentrations of active ingredients. Thus, the comment argued that concentrations up to 35 percent of Category I active ingredients should be allowed in powder roll-on antiperspirants.

This issue was specifically brought before the Panel, which did not agree to change the maximum concentration (Ref. 27). The Panel noted that aluminum antiperspirants can be irritating, expressed concern that a small amount of a concentrated formulation may be more irritating than a large amount of a more dilute formulation, and concluded that antiperspirant products with a higher concentration would need an NDA with additional safety studies. The agency notes that increasing the concentration of aluminum antiperspirant ingredients increases the acidity of the material and irritation of the skin (Refs. 28, 29, and 30). The agency concludes that safety data are

needed to show that powder roll-on dosage forms containing up to 35 percent aluminum chlorhydrates or aluminum zirconium chlorhydrates are not irritating.

Since the TFM was published, several citizen petitions have raised concerns about the amount of aluminum absorbed from topical antiperspirant drug products. (See section II.F, comment 23 of this document.) The agency has no data showing that products containing up to 35 percent aluminum chlorhydrates or aluminum zirconium chlorhydrates increase aluminum absorption and is not revising the monograph to provide for powder roll-on dosage forms containing up to 35 percent antiperspirant active ingredient, without additional safety data being provided.

(Comment 21) One comment requested monograph status for aluminum sesquichlorohydrate prepared by neutralizing aluminum chloride with magnesium hydroxide even though the aluminum to chloride (Al:Cl) ratio of the ingredient prepared in this manner does not fall within the range specified for aluminum sesquichlorohydrate in the TFM. The comment stated that during the course of the rulemaking all aluminum chlorhydrates placed in Category I were prepared by conventional techniques: Either by neutralization of aluminum chloride with aluminum monochlorohydrate or by a controlled reaction of aluminum metal with hydrochloric acid. Thus, the comment argued that it was both appropriate and convenient to characterize the various aluminum chlorhydrates in terms of their Al:Cl ratios.

The comment stated that its data showed that the reaction of aluminum chloride with magnesium hydroxide yields aluminum sesquichlorohydrate equivalent to that listed in the TFM and the neutralizer magnesium hydroxide does not contribute either aluminum or chloride ions to the neutralization

process; thus, the Al:Cl ratio of aluminum sesquichlorohydrate prepared this way will always remain 0.33, the same as aluminum chloride alone. The comment was concerned because this Al:Cl ratio of 0.33 does not fall within the ratio range of 1.9 down to but not including 1.25:1 proposed for aluminum sesquichlorohydrate in the tentative final monograph (47 FR 36492 at 36504). The comment contended that if the final product is regarded as a mixture of aluminum sesquichlorohydrate and magnesium chloride, and if the amount of chloride that serves as counter ions for the magnesium ions were subtracted from the total chloride, then the Al:Cl ratio of the aluminum sesquichlorohydrate component of the mixture would have the Al:Cl ratio specified in the TFM. The comment submitted data (Ref. 31) using gel permeation chromatography and elemental analysis of the eluates (the substance separated out by washing) to show that aluminum sesquichlorohydrate prepared by this neutralization method is chromatographically indistinguishable from that prepared by conventional methods. The comment suggested designating the ingredient prepared by the neutralization method as "aluminum sesquichlorohydrate MAG."

The agency does not find these analytical data sufficient to support the comment's claim that the ingredient prepared by this neutralization method is chemically equivalent in composition to aluminum sesquichlorohydrate. The chromatographic indistinguishability from aluminum sesquichlorohydrate prepared by conventional methods only demonstrates that the chromatographic method in this study is insufficient to support the claim. This result perhaps is to be expected because the gel permeation chromatographic method used in this study is based primarily on a size exclusion principle; however, the agency doubts that any chromatographic method will provide such support.

USP 23–NF 18 Fifth Supplement (Ref. 32) added a monograph for aluminum sesquichlorohydrate and described it as consisting of complex basic aluminum chloride that is polymeric and loosely hydrated and encompasses a range of aluminum-to-chloride atomic ratios between 1.26:1 and 1.90:1. Its chemical formula is stated as:  $\text{Al}_y(\text{OH})_{3y-z}\text{Cl}_z \cdot n\text{H}_2\text{O}$ .

According to the method described in the comment, when aluminum sesquichlorohydrate is prepared by the reaction of aluminum chloride with magnesium hydroxide, the product must be a mixture of aluminum sesquichlorohydrate and magnesium chloride. The agency does not consider it suitable from a technical point of view to simply designate this material as aluminum sesquichlorohydrate. Information provided by the comment shows that the alternate process material is not “equivalent in composition” because the aluminum to chloride ratio of 0.33 is outside the specified range for aluminum sesquichlorohydrate and because the material contains measurable amounts of magnesium. Also, as discussed in section II.E, comment 18 of this document, because the atomic ratio range should be metal to halide, magnesium should be counted as a metal in the atomic ratio range of the comment’s material. Using the name aluminum sesquichlorohydrate for an ingredient prepared by neutralization of aluminum chloride with magnesium hydroxide would be misleading because this would imply that the drug is the same identifiable ingredient as aluminum sesquichlorohydrate prepared by neutralization of aluminum chloride with aluminum chlorohydrate. The agency believes the material described in the comment should be classified as a new ingredient, perhaps an aluminum magnesium chlorohydrate, rather than aluminum sesquichlorohydrate.

The agency concludes that additional information on the chemical characterization of the proposed material, particularly its ionic structure, is needed to permit a more scientific review. The submitted information does not provide a technical basis for allowing the substitution of aluminum sesquichlorohydrate manufactured by neutralization with magnesium chloride for that neutralized with aluminum monochlorohydrate. The USP–NF monograph (Ref. 32) does not contain information to characterize or identify an aluminum sesquichlorohydrate containing magnesium (e.g., no identification or content test, and no assay involving magnesium calculations).

Further, the agency notes that no clinical efficacy data were provided to show that the material proposed in the comment would be equally effective as aluminum sesquichlorohydrate prepared in the conventional manner. Even minor variations in formulation, such as the addition of emollients or buffers, can alter the effectiveness of an antiperspirant ingredient. (See comment no. 8 in the TFM (47 FR 36492 at 36494).) The new mixture may be just as effective. However, whether such a finding would apply to equal amounts, or whether an equivalent effect could be achieved with a greater or lesser amount of aluminum sesquichlorohydrate prepared with magnesium hydroxide, should be determined by effectiveness testing that follows the guidelines referred to in § 350.60 of the final monograph. The agency needs appropriate effectiveness data and an appropriate USP–NF monograph amendment (see 21 CFR 330.14(i)) before the ingredient prepared by the new method can be generally recognized as safe and effective and included in the final monograph.

(Comment 22) One comment objected to the agency's rejection of its earlier request (discussed in comment no. 9 of the TFM, 47 FR 36492 at 36495) that combinations of two or more Category I antiperspirant ingredients should be

Category I. The comment stated that the combination policy in § 330.10(a)(4)(iv) allows combinations of two or more safe and effective active ingredients; thus, the Panel should be reversed.

In the TFM (47 FR 36495), the agency concurred with the Panel (43 FR 46694 at 46718) that both combinations of antiperspirant active ingredients and combinations of antiperspirant active ingredients with other types of active ingredients (except for a deferred antiperspirant/antifungal combination) are Category II because of no information on the existence of any such combinations or any data to support their safe and effective use.

The agency classified antiperspirant/antifungal combination drug products in Category III in the TFM for OTC antifungal drug products (December 12, 1989, 54 FR 51136 at 51148 and 51149). No additional data were submitted to support this combination, and in the final monograph for OTC antifungal drug products (September 23, 1993, 58 FR 49890 at 49891), the agency classified all antifungal combination drug products as nonmonograph.

The comment did not provide any supporting data or specific examples of Category I antiperspirant ingredients that would be suitable for use in combination with other antiperspirant or nonantiperspirant Category I ingredients. Thus, the combination policy does not apply. These combinations remain nonmonograph. However, new clinical data may be submitted to support safety and effectiveness.

#### *F. Comments on the Safety of Aluminum Ingredients*

(Comment 23) The information and arguments presented by the citizen petitions that questioned the safety of aluminum-containing ingredients in OTC antiperspirant drug products and the comment that disagreed with one of the citizen petitions were discussed in detail in the **Federal Register** of

March 23, 1993 (58 FR 15452 at 15453 and 15454). One petition was concerned that aluminum can be absorbed and get into the blood and that some of the aluminum in the blood enters the brain, where it remains and accumulates. The petition cited a study by Perl and Good (Ref. 33) that suggested that inhaled aluminum compounds could have a direct nasal-olfactory pathway to the brain. The other petition contended that two inhalation studies (Refs. 34 and 35) provided by industry showed aluminum absorption in the peribronchial lymph nodes, brain, and adrenal glands of the animals after 12 and 24 months. Both petitions expressed concern about the potential neurotoxicity of aluminum upon chronic use, especially a possible link to Alzheimer's disease.

The comment that disagreed with one petition contended that the majority of the petitioner's references described findings from in vitro studies that did not consider the blood-brain barrier, which is the brain's main defense against potentially toxic substances such as aluminum. The comment contended that extraordinarily high concentrations of aluminum were used in these studies, and that aluminum from antiperspirants would never reach a biologically significant level to be of concern. The comment stated that the majority of researchers investigating the etiology of Alzheimer's disease would consider current evidence insufficient to link aluminum to Alzheimer's disease. The comment concluded that current scientific information does not support the need to reclassify the safety of aluminum-containing antiperspirants.

The agency does not find the current evidence sufficient to conclude that aluminum from antiperspirant use results in Alzheimer's disease. Both petitions mention the widely quoted study by Perl and Good (Ref. 33) as showing that inhaled aluminum compounds may get directly into the brain

by a nasal-olfactory pathway. The agency does not consider this animal study (published as a one-page Letter to the Editor in *Lancet*) as adequate to establish a direct nasal-olfactory pathway for aluminum. This study was only a small pilot animal study, about which the agency has a number of concerns.

First, the method of introducing the aluminum to these animals was not physiologically relevant. Two strips of Gelfoam (absorbable gelatin sponge, USP) saturated with high concentrations of aluminum salts (15 percent aluminum lactate or 5 percent aluminum chloride) were inserted into rabbits' left nasal recess through a hole drilled into the frontal bone. While the authors attempted to demonstrate the accessibility of aluminum from the nasal recess to the brain, the agency questions whether the normal use of antiperspirant aerosols would ever produce a high aluminum concentration in this relatively distant anatomic site. Second, the size of this study was very small (only three rabbits in each group). The agency is concerned that any error in this complicated surgical procedure to introduce the aluminum salts or in preparing the specimens for analysis could have caused a major difference in the final results. Third, the results were not consistent. Of the three animals exposed to aluminum lactate, besides the involvement of the left olfactory bulb and the cerebral cortex, only one rabbit had a lesion in the hippocampus while the other two rabbits had granulomas found in the pyriform cortex. In the group exposed to aluminum chloride, only one rabbit had a granuloma in the olfactory bulb while the other two rabbits were free of lesions. The distribution of lesions in this study was fairly random. If a nasal-olfactory pathway exists for neuronal aluminum transport, the agency believes that the distribution of these lesions should follow a more persistent anatomical pattern. In addition, the authors were unable to explain why two of the six rabbits were free of

lesions. Finally, although some of the rabbits had granulomas, these lesions did not resemble the plaques or neurofibrillary tangles found in Alzheimer's disease, and none of the rabbits had any symptomatic neurologic deficit. While this study implied that access to the brain via the nasal recess may be possible under nonphysiological conditions, a direct nasal-olfactory pathway and any relationship to Alzheimer's disease cannot be established. Several other studies, which were not done with aluminum, are of no value in establishing a direct nasal-central nervous system pathway for aluminum antiperspirants.

Aluminum lactate, one aluminum salt used in this study (Ref. 33), is not included in this final monograph. Sodium aluminum lactate has been used as a buffer for aluminum sulfate in a nonaerosol dosage form, but that product is nonmonograph.

In one of the inhalation studies (Ref. 34), the life-span of the male hamsters exposed to the aluminum chlorhydrate aerosol was shorter (583 days) than that of the controls (661 days). The female hamsters exposed to aluminum chlorhydrate had a slightly longer life-span (489 days) than the controls (481 days). Male hamsters exposed to aluminum chlorhydrate coated with a high concentration of isopropyl myristate, an emollient frequently used to increase the retention on the skin of the aluminum salts used in antiperspirant products, had a life-span (646 days) comparable to the controls (661 days). Overall, these numbers do not follow a consistent pattern and could be affected by other experimental conditions.

The same petition criticized the other inhalation study (Ref. 35), contending that the results showed that the animals had suffered significant weight loss and increased terminal brain-to-body weight ratios, results it considered consistent with clinical aluminum toxicity, and that the increase

in brain weight was possibly due to cerebral edema. The petition claimed that because aluminum was found to be deposited in the animals' brains, peribronchial lymph nodes, and adrenal glands, this proved that systemic absorption of aluminum had occurred and that aluminum had been transported to the brain. Other comments disagreed with the petition's argument that the rats in this study were found to have detectable aluminum levels in their brains after 12 months, contending that this finding may only be artificial considering the analytical methods used. The comments added that if aluminum did accumulate in the rats' brains, those rats should have had symptoms of neurotoxicity, which they did not have. The comments concluded that the artificial finding should be ignored.

The agency does not concur with the petition's extrapolations. The weight loss occurred only in rats and not in guinea pigs that were similarly treated. The increase in terminal brain-to-body weight ratio occurred only in the female rats at 12 months in the low- and high-dose groups. The female rats in the middle-dose group and all the males were not affected. At 24 months, this same ratio was found to increase only in the high-dose groups of both sexes; however, the increase in the female high-dose group was not statistically significant. The agency notes that all of these findings did not follow any predictable pattern or a pattern that would be expected from a dose-related or cumulative toxin exposure.

The pattern of deposition was not consistent. In the guinea pigs, aluminum was found in the peribronchial lymph nodes, but not in the adrenal glands and brains (as occurred in the rats). The agency finds it possible that aluminum absorption and deposition may be animal dependent. If this were the case, then even if the rat data were evidence of a problem, the same situation may not

apply to humans. The agency is not aware of other investigators having similar results.

The petitions and the comment had different views on a study by Rollin, Theodorou, and Kilroe-Smith (Ref. 36) in which rabbits were exposed to aluminum oxide dust for 8 hours a day, 5 days a week, for 5 months. The authors of the study found that the brains of these rabbits had a significant increase in aluminum at the end of the study. The first petition contended that this study showed that the inhalation of aluminum antiperspirants poses a special risk because this route of delivery bypasses the blood-brain barrier. The comment calculated that this study would be equivalent to a person using spray antiperspirants for approximately 10 seconds daily for 789 years to experience the same toxicity. The second petition contended that this 10-seconds-exposure assumption was incorrect because the aluminum particles in an antiperspirant aerosol remain suspended in the air for a long period of time, and the exposure will be more than the comment calculated.

The agency finds this study has a number of limitations: (1) The extraordinary high concentrations of aluminum oxide exposure in the animals, (2) the small sample size (eight animals in each group), and (3) an overlap in the standard deviations of the results obtained decreases the power and generalizability of the study. While the study shows an accumulation of aluminum in the rabbits' body tissues under certain exposure conditions, the agency does not consider the study as providing evidence of a direct nasal-olfactory pathway or that normal use of aluminum-containing antiperspirants would provide comparable results. Further, the second petition's position includes a number of assumptions, which might not occur: (1) That the place where the product is used is a confined, poor-ventilated airspace, and (2) that

the user remains in the vicinity of the dispersed aerosol for a period of time during which significant inhalation would occur.

One petition claimed that an epidemiology study by Graves et al. (Ref. 37) has shown that Alzheimer's disease was associated with the use of aluminum antiperspirants and that a high incidence of amyotrophic lateral sclerosis (ALS) and Parkinson's disease in Chamorro natives of Guam, as reported by Garruto (Ref. 38), may be related to high environmental aluminum. The agency has looked closely at the Graves et al. study (Ref. 37) because it explored the association between exposure to aluminum through the lifetime use of antiperspirants and antacids and Alzheimer's disease. This was a case-control study of 130 matched pairs, where the controls were friends or nonblood relatives of the case. Subjects (cases and controls) were matched by age, sex, and the relationship between the case/control and his or her surrogate (spouse or child).

The authors mentioned that, in general, antiperspirants contain aluminum and deodorants do not, except for some deodorants marketed for women. The authors reported that there was no association between the use of "any" antiperspirant/deodorant and Alzheimer's disease. However, when the data were stratified by aluminum-containing antiperspirants the overall odds ratio showed a modest increase in risk and a statistically significant trend emerged between increasing lifetime use of aluminum-containing antiperspirants and the estimated relative risk of Alzheimer's disease.

The authors commented that, to their knowledge, this was the first epidemiological study of this association between antiperspirants and Alzheimer's disease, and there were several methodologic limitations that made interpretation of their results difficult. First, there were missing data

because the case surrogate and the control surrogate could only recall all variables (frequency and duration of use, and product brand name) in about one-half of the matched pairs. Second, there might have been some misclassification because the analyses were based on the most common brand provided, while some subjects may have used multiple brands. Third, the authors considered the validity of the data, resulting from difficulty in learning the subjects' exposure using telephone interview methods, to be a critical limitation. Despite these limitations, the authors considered an association between aluminum-containing antiperspirants and Alzheimer's disease as biologically plausible, but concluded that their findings are provocative and, due to methodologic problems, should be considered preliminary.

Garruto (Ref. 38) described efforts to establish models of chronic motor neuron degeneration in a long-term effort to understand the cellular and molecular mechanisms of aluminum neurotoxicity. He studied foci of dementia (ALS and Parkinson's disease) in western Pacific populations. He mentioned experimental models in rabbits and cell culture as demonstrating that chronic, rather than acute, toxicity is the cause of human neurodegenerative disorders with a long latency and slow progression. However, Garruto stated that he and his colleagues had been most deficient in the design and implementation of good epidemiological studies, particularly of Alzheimer's disease and the epidemiology of aluminum intoxication per se, and described what he felt was needed for future well-designed studies.

The petitions/comment also discussed environmental exposure to aluminum, percutaneous absorption after topical use, inhaled absorption after aerosol use, aluminum neurotoxicity (and a possible relationship to Alzheimer's disease), and possible mechanisms of action. Numerous references

were provided. The agency has reviewed these references and other literature published on aluminum since the petitions were submitted. Many early references were simply hypotheses and different theories that have not been adequately substantiated in humans or any animal models. A number of studies were pilot projects in a few animals, and the agency is unable to draw any definite conclusions based on the small sample sizes.

The agency notes Priest's (Ref. 39) statement that most investigators now agree that aluminum is unlikely to be implicated in causing Alzheimer's disease, whereas Rowan (Ref. 40) contended it would be considerably more correct to state that the issue is controversial. More recently, Savory et al. (Ref. 41) stated that the question whether aluminum presents a health hazard to humans as a contributing factor to Alzheimer's disease is still subject to debate.

The agency finds the literature shows the issue of aluminum toxicity and Alzheimer's disease remains controversial and is not resolved. Scott et al. (Ref. 42) reported that aluminum has been detected in Alzheimer neurofibrillary tangles, but the significance of its presence is unknown. Kasa, Szerdahelyi, and Wisniewski (Ref. 43) reported that histochemical staining showed that aluminum was present in brain samples from Alzheimer's disease victims, but the structural localization indicated that it is not primarily involved in the etiology of the disease. Candy et al. (Ref. 44) reported that data from post mortem brain examinations of patients with chronic renal failure who did not have dialysis encephalopathy suggest that it is unlikely that aluminum plays any major role in neurofibrillary tangle formation and that its role in senile plaque formation is likely to be only part of a complex cascade of changes. Savory et al. (Ref. 41) stated that the lack of agreement on the question whether

the brain content of aluminum is increased in Alzheimer's disease attests to the complexity of the issue.

Savory et al. (Ref. 41) indicated that most of the data linking aluminum exposure to Alzheimer's disease have been derived from several epidemiological studies of aluminum in drinking water, which represents only a small percentage of the total exposure. They concluded that quantification of the risk of Alzheimer's disease from other sources of aluminum (such as food additives, cosmetics, deodorants, antiperspirants, pharmaceuticals, and respiratory dusts) is needed before the total risk from all environmental sources of aluminum can be fully evaluated.

Despite Graves et al.'s acknowledgment of the limitations of their study (Ref. 37), other authors, e.g., Anane et al. (Ref. 45), report that Graves et al. found an increased risk of Alzheimer's disease with lifetime use of aluminum-containing antiperspirants after an epidemiological study. Anane et al. applied low aqueous concentrations (0.025 to 0.1 micrograms ( $\mu\text{g}$ )/square centimeter) of aluminum chloride ( $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ ) to healthy shaved Swiss mouse skin for 130 days. They reported that this led to a significant increase in urine, serum, and whole brain aluminum, especially in the hippocampus area, compared to control animals. They mentioned that this percutaneous uptake and accumulation of aluminum in the brain was greater than that caused by dietary exposure to 2.3  $\mu\text{g}$  per day in feed and water.

Anane et al. conducted in vitro and in vivo mouse skin studies and showed for the first time that aluminum is absorbed through mouse skin and this contributes to a greater body burden than does oral uptake. They also mentioned that several antiperspirant preparations containing  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$  are applied to sensitive regions of the skin, which may increase penetration and

could be an important source of body aluminum burden. Anane et al. recommended that an epidemiological study be conducted to ascertain whether use of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ -containing antiperspirants correlates with neurodegenerative disease, because such cannot be excluded based on the results of their study.

Forbes and Agwani (Ref. 46) stated that there is uncertainty about how aluminum-containing substances enter the body, but current information suggests that the skin and/or the lung are important. They mentioned that Priest (Ref. 39) noted that at least some antiperspirant sprays contain aluminum compounds of a particle size of about 1 micrometer (micron) ( $\mu$ ), which is ideally sized for deposition in the deep lung, and that such deposition may also be relevant for skin.

Salib and Hillier (Ref. 47) examined clinically diagnosed Alzheimer's disease patients and controls (other dementias and nondementias) and collected information to examine the association between Alzheimer's disease and aluminum occupation. They reported that manual work, such as welding, expected to be in direct contact with aluminum dust and fumes does not appear to be significantly associated with the risk of Alzheimer's disease. The authors concluded that no significant association was shown between developing Alzheimer's disease later in life and previous occupational history for all of the occupations in the study. This included both manual workers, who would be expected to have had a higher exposure opportunity to aluminum dust and fumes, and other workers at an aluminum factory. The authors concluded that neither Alzheimer's disease nor dementia in general were shown to be associated with previous aluminum occupation.

Salib and Hillier (Ref. 47), in 1996, repeated Doll's (Ref. 48) conclusions from 1993 that it is generally accepted that the delayed effects of chronic aluminum exposure have not been adequately assessed in man. Factors that govern the bioavailability, neurotoxicity, and the effect of chronic low dose exposure to aluminum compounds remain unclear. Flaten et al. (Ref. 49) stated that the lack of a readily available radioactive isotope of aluminum has been a major obstacle toward elucidating the mechanisms of absorption, distribution, and excretion of the metal.

Both Doll (Ref. 48) and Salib and Hillier (Ref. 47) stated that the possibility of a causal link between aluminum and Alzheimer's disease must be kept open until uncertainty about neuropathological evidence is resolved and the prognosis of humans exposed to aluminum by inhalation is known. Flaten et al. (Ref. 49) stated that multidisciplinary collaborative research efforts, involving scientists from many different specialties, are needed, with emphasis placed on: (1) Increasing knowledge of the chemistry of aluminum in biologic systems and determining the cellular and molecular mechanisms of aluminum toxicity, and (2) variations in neuropathology from long-term, low-level exposure to aluminum.

In summary, the literature shows that at high doses and long-term industrial exposures, aluminum can be associated with recognizable, specific neurologic effects. However, to date, the agency considers the evidence insufficient to link aluminum to Alzheimer's disease, Parkinson's disease, or ALS. Although aluminum uptake and transport by a "nasal-olfactory pathway" has been suggested in a nonphysiologic study in an animal model (Ref. 36), the agency is not aware of any evidence in humans that supports an olfactory-neuronal transport of aluminum to the brain.

One petition suggested that the agency require that 90 percent of the particles of an aerosol aluminum antiperspirant be greater than 50  $\mu$  (currently the requirement is between 10 and 50  $\mu$ ) to reduce exposure to the upper respiratory tract. The agency notes that both Priest (Ref. 39) and Forbes and Agwani (Ref. 46) discussed a particle size of 1  $\mu$  for deposition in the deep lung. Based on current knowledge (no proof in humans of an olfactory neuronal transport of aluminum to the brain) and the lack of information on a minimum particle size to affect the respiratory tract, the agency finds no basis to impose a greater than 50 $\mu$  requirement at this time. Flaten et al. (Ref. 49) stated that the possible human toxicity of aluminum has been a matter of controversy for well over 100 years. Despite many investigators looking at this issue, the agency does not find data from topical and inhalation chronic exposure animal and human studies submitted to date sufficient to change the monograph status of aluminum containing antiperspirants. The agency will continue to monitor the scientific literature on aluminum and, if new information appears, will reassess the status of aluminum-containing antiperspirants at such time.

The agency acknowledges that small amounts of aluminum can be absorbed from the gastrointestinal tract and through the skin. Assuming a person has normal renal function, accumulation of aluminum resulting from usual exposures to antiperspirant drug products (application to the underarms once or twice daily) and subsequent absorption is considered minimal. However, people with renal dysfunction have an impairment in normal renal excretion of aluminum.

Flaten et al. (Ref. 49) noted that the first human conditions generally accepted to be causally related to aluminum exposure did not occur until the

1970's, shortly after the introduction of routine dialysis therapy in persons with chronic renal failure. Dialysis encephalopathy was perhaps the first disease recognized in this population (1972, 1976). Later, fracturing osteomalacia (1977, 1978) and a microcytic hypochromic anemia (1980) were related to aluminum exposure in dialysis patients. Flaten et al. indicated that aluminum can cause encephalopathy, bone disease, and anemia in dialysis patients resulting from the introduction of aluminum directly into the blood stream via high-aluminum dialysate or the consumption of large oral doses of aluminum-containing phosphate binders. Reduced urine production (the major route for aluminum excretion) contributes to this problem. The authors noted that, in the early 1980's, reports began to appear describing aluminum neurotoxicity and osteotoxicity in children with renal failure who were not on dialysis treatment.

The agency is concerned that people with renal dysfunction may not be aware that the daily use of antiperspirant drug products containing aluminum may put them at a higher risk because of exposure to aluminum in the product. The agency considers it prudent to alert these people to consult a doctor before using or continuing to use these products on a regular basis and is including a warning in the final monograph: "Ask a doctor before use if you have kidney disease."

Flaten et al. (Ref. 49) mentioned several reports of aluminum accumulation and toxicity in individuals without chronic renal failure, especially preterm infants (primarily fed intravenously), and stated that preterm infants are at risk for aluminum loading because of their immature kidney function. Term infants with normal renal function may also be at risk because of their rapidly growing and immature brain and skeleton, and an immature blood-brain barrier. Until

they are 1 to 2 years old, infants have lower glomerular filtration rates than adults, which affects their kidney function. The agency is concerned that young children and children with immature renal function are at a higher risk resulting from any exposure to aluminum. Accordingly, the agency is requiring both general warnings in § 330.1(g) on all aluminum-containing antiperspirant drug products to inform parents and others to keep these products away from children, and to seek professional assistance if accidental ingestion occurs.

(See also section II.B, comment 7 of this document.)

(Comment 24) One comment submitted a research paper (Ref. 50) containing the author's theories concerning how antiperspirants and aluminum in these products may be associated with breast cancer: The secretions of the apocrine sweat glands contain androgens, which are blocked by the antiperspirant and thus caused to spread internally. These androgens may be converted in the surrounding adipose tissues to estrogens, and excess estrogens have been associated with an increase in breast cancer. Alternatively, these excess androgens may interfere with the normal functioning of the hypothalamic-pituitary axis, thereby causing an imbalance of estrogen in the body. About 50 percent of breast cancers occur in the upper outer quadrant of the breast, and axillary sweat glands are anatomically very close to this site. A protein marker called GCDFP-15 (Gross Cystic Disease Fluid Protein), which is normally found only in the sweat glands, was found in the fluids of many breast cysts. The author postulated that the blocked axillary sweat glands would cause GCDFP-15 and other markers to migrate to the breast due to its proximity and gravity, and because the fetal precursors for apocrine sweat glands and mammary glands are the same, these migrated protein markers may stimulate the breast and play a role in the carcinogenic process.

The author also postulated that aluminum may play a role in the development of breast cancer because calcification of breast tissues (commonly seen in breast cancer) may be caused by a local electrolyte imbalance induced by the absorbed aluminum. The author noted that breast cancer in Japan was more than five times lower than in the United States and postulated this has occurred because Japanese women, especially the older population, do not use antiperspirants. The author noted that the breast cancer rate is currently on the rise in Japan, especially among young premenopausal women, and postulated that this is occurring because the young Japanese generation has adopted the western habit of using antiperspirants.

The agency finds these theories lack sufficient evidence. The agency notes that the amount of androgens produced by the sweat glands is relatively insignificant compared to normal physiologic amounts produced by the adrenals and the gonads. The agency is not aware of any studies that have shown an "internal spread" of androgens or that establish that GCDFP-15 or other protein markers are carcinogenic in humans.

The agency considers the author's views about a local electrolyte imbalance by absorbed aluminum causing breast tissue calcification inconsistent with knowledge about the calcification process. In addition, there are many benign calcifications. Finally, many proposals (e.g., diet, lifestyle changes) have been made as to why there is an increased incidence of breast cancer among Japanese women. However, there is no evidence to associate this increase with an increased use of antiperspirants. Thus, the agency concludes that there is insufficient evidence to support these theories.

(Comment 25) The agency previously assessed the carcinogenic potential of aerosolized aluminum chlorhydrate antiperspirants in comment 22 of the

TFM (47 FR 36492 at 36498 and 36499). Primary lung tumors, granulomatous lesions, and macrophagic activity were evaluated in animal studies. No increase in lung tumors was seen in the low- and mid-dose rats given doses at least 100 times greater than the expected human exposure via aerosolized antiperspirants. Normal macrophage response and pulmonary fibrosis were observed at higher doses with chronic exposure. No increase in tumors was noted in guinea pigs or hamsters at any dose levels in the studies. While the agency removed aerosol antiperspirant products containing zirconium from the market because of granuloma formation (August 16, 1977, 42 FR 41374), the agency is not aware of data that indicate aluminum antiperspirants cause foreign body granulomas or pulmonary tumors.

### III. Agency Changes

1. It has been agency policy since April 3, 1989 (54 FR 13480 at 13486), that before any ingredient is included in a final OTC drug monograph, it must have a compendial (USP-NF) monograph. Compendial monographs include an ingredient's official name, chemical formula, and analytical chemical tests to confirm the quality and purity of the ingredient. These monographs establish public standards for the strength, quality, purity, and packaging of ingredients and drug products available in the United States. Eighteen of the 19 antiperspirant active ingredients that the agency proposed in § 350.10 of the antiperspirant TFM (47 FR 36492 at 36504) currently have compendial monographs. Nine of the official compendial names are the same as those proposed in § 350.10, while 10 of the names have changed slightly. (See Table 1 of this document for the previous and current ingredient names.)

TABLE 1.—ANTIPERSPIRANT ACTIVE INGREDIENTS

Name in Tentative Final Monograph	Current Name
Aluminum chloride	Same
Aluminum chlorohydrate	Same
Aluminum chlorohydrate polyethylene glycol complex	Aluminum chlorohydrate polyethylene glycol
Aluminum chlorohydrate propylene glycol complex	Aluminum chlorohydrate propylene glycol
Aluminum dichlorohydrate	Same
Aluminum dichlorohydrate polyethylene glycol complex	Aluminum dichlorohydrate polyethylene glycol
Aluminum dichlorohydrate propylene glycol complex	Aluminum dichlorohydrate propylene glycol
Aluminum sesquichlorohydrate	Same
Aluminum sesquichlorohydrate polyethylene glycol complex	Aluminum sesquichloro-hydrate polyethylene glycol
Aluminum sesquichlorohydrate propylene glycol complex	Aluminum sesquichloro-hydrate propylene glycol
Aluminum sulfate buffered <sup>1</sup>	Same
Aluminum zirconium octachlorohydrate	Same
Aluminum zirconium octachlorohydrate glycine complex	Aluminum zirconium octachlorohydrate gly
Aluminum zirconium pentachlorohydrate	Same
Aluminum zirconium pentachlorohydrate glycine complex	Aluminum zirconium pentachlorohydrate gly
Aluminum zirconium tetrachlorohydrate	Same
Aluminum zirconium tetrachlorohydrate glycine complex	Aluminum zirconium tetrachlorohydrate gly
Aluminum zirconium trichlorohydrate	Same
Aluminum zirconium trichlorohydrate glycine complex	Aluminum zirconium trichlorohydrate gly

<sup>1</sup> Aluminum sulfate buffered with sodium aluminum lactate.

The agency is including in § 350.10 of this final monograph those antiperspirant active ingredients that currently have a compendial monograph. Only one active ingredient, aluminum sulfate buffered, does not have a current or proposed compendial monograph. While aluminum sulfate does have a compendial monograph, the buffer component, sodium aluminum lactate, does not. This buffer ingredient must also have a compendial monograph or there must be a compendial monograph for aluminum sulfate buffered in order for aluminum sulfate buffered to be included in the antiperspirant final monograph. At the present time, this ingredient is being included in § 310.545(a)(4)(ii) as a nonmonograph ingredient because the agency is not aware of any pending compendial monograph being developed. Should a compendial monograph eventually be developed, the agency will move this ingredient from § 310.545(a)(4)(ii) to § 350.10.

2. The agency is revising the format for active ingredients in § 350.10 for consistency with recent monographs: The proposed chart format is now a paragraph format listing ingredients in alphabetical order. The amount of active ingredient is stated as “up to \_\_\_\_\_ percent” instead of as \_\_\_\_\_ percent or less concentration.” The information about calculating the concentration on an anhydrous basis is moved to the preamble of § 350.10. The preamble statement about aluminum to chloride and/or aluminum to zirconium ratios is revised to state: “Where applicable, the ingredient must meet the aluminum to chloride, aluminum to zirconium, and aluminum plus zirconium to chloride atomic ratios described in the United States Pharmacopeia-National Formulary.” The proposed ratio range table is not included in the final monograph because this information is now included in the USP–NF monographs for each active ingredient in § 350.10, where applicable.

3. The agency is expanding the indications proposed in § 350.50(b) of the TFM to provide additional uses based on new effectiveness data. The agency is also revising the uses format to make it more concise.

Because the indications proposed in § 350.50(b)(1), (b)(2), and (b)(3) of the TFM are very similar, the agency is combining them as a single indication with choices under § 350.50(b)(1): [Select one of the following: “decreases,” “lessens,” or “reduces”] “underarm” [select one of the following: “dampness,” “perspiration,” “sweat,” “sweating,” or “wetness”]. (See section II.B, comment 6 of this document.) The agency is adding a new additional indication in § 350.50(b)(2): “also [select one of the following: ‘decreases,’ ‘lessens,’ or ‘reduces’] underarm [select one of the following: ‘dampness,’ ‘perspiration,’ ‘sweat,’ ‘sweating,’ or ‘wetness’] due to stress”. (See section II.B, comment 6 and section II.C, comment 13 of this document.) The agency is adding a new

additional indication in § 350.50(b)(3): Select one of the following: [“all day protection,” “lasts all day,” “lasts 24 hours,” or “24 hour protection”]. (See section II.C, comment 12 of this document.) The agency is adding a new additional indication in § 350.50(b)(4) that states “extra effective”. This claim applies to products that demonstrate 30 percent or more sweat reduction using the guidelines for effectiveness testing of antiperspirant drug products referred to in § 350.60. (See section II.C, comment 11 of this document.) The agency is adding a new additional indication in § 350.50(b)(5) for products that demonstrate extra effectiveness sustained over a 24-hour period: These products may state the claims in §§ 350.50(b)(3) and (b)(4) either individually or combined, e.g., “24 hour extra effective protection,” “all day extra effective protection,” “extra effective protection lasts 24 hours,” or “extra effective protection lasts all day”. (See section II.C, comment 12 of this document.)

4. The agency is revising the “Do not apply \* \* \*” warning in proposed § 350.50(c)(1) to the new labeling format. The warning now reads: “Do not use on broken skin” and “Stop use if rash or irritation occurs”.

5. The agency is including a warning to alert people with renal dysfunction to consult a doctor before using antiperspirants containing aluminum. The warning appears in the new labeling format and states: “Ask a doctor before use if you have kidney disease”. (See section II.F, comment 23 of this document.)

6. The agency has revised the August 1982 Guidelines for Effectiveness Testing. The revised guidelines (dated as of the date of publication of this document) state that “FDA recognizes that alternate methods may be appropriate to qualify an antiperspirant drug product as effective. These guidelines do not preclude the use of alternate methods that provide

scientifically valid results, subject to FDA approval.” (See section II.D, comment 15 of this document.)

The agency has revised parts of the test procedures section of the guidelines to delete the requirement that the control formulation be devoid of “any” antiperspirant activity. Therefore, the control formulation no longer needs to be compared to no treatment. (See section II.D, comment 17 of this document.) The agency has changed the permitted relative humidity of the hotroom conditions from 35 to 40 percent to a range of 30 to 40 percent. (See section II.D, comment 16 of this document.) The agency has added a requirement for “baseline perspiration rate” to assure that test subjects sweat adequately during a hotroom test: “Test subjects must produce at least 100 milligrams of sweat from the placebo control axilla in a 20-minute collection in the controlled environment.” (See comment 16 also.)

Because the final monograph contains 24-hour duration effectiveness claims, the agency has revised section 4(a)(4) of the guidelines to state: “For claims of enhanced duration of effect, the test should be conducted at least two times during the period of the claim, such as 1 hour and 24 hours after the last daily treatment for 24 hour claims.” (See section II.C, comment 12 of this document.) Because the final monograph contains “extra-effective” claims shown by standard gravimetric testing to have a 30-percent or more reduction in sweat, the agency has revised the guidelines to include a section on data treatment to demonstrate, with high probability, at least 50 percent of the target population will obtain a sweat reduction of at least 30 percent. (See section II.C, comment 11 of this document.)

The revised “Guidelines for Effectiveness Testing of OTC Antiperspirant Drug Products” are now dated as of the date of publication of this final rule

and are on file in the Dockets Management Branch (address above) and on FDA's Web site at <http://www.fda.gov/cder/otc/index.htm>. Persons wishing to obtain a copy of the guidelines should submit a Freedom of Information (FOI) request in writing to FDA's FOI Staff (HFI-35), 5600 Fishers Lane, Rockville, MD 20857. The agency has revised § 350.60 to include this information about the guidelines.

#### **IV. Summary of Changes from the Proposed Rule**

1. The agency is modifying the definition of an antiperspirant that was proposed in § 350.3 of the TFM to delete the phrase "to the underarm." (See section II.B, comment 2 of this document.)

2. The agency is revising the format for listing active ingredients in § 350.10. (See section III.2. of this document.)

3. The agency is expanding the indications for OTC antiperspirant drug products based on new data that support these additional uses (see section III.3. of this document) and is expanding the "Guidelines for Effectiveness Testing of OTC Antiperspirant Drug Products" to address some of these additional uses (see section III.6. of this document).

#### **V. The Agency's Final Conclusions**

The agency is issuing a final monograph establishing conditions under which OTC antiperspirant drug products are generally recognized as safe and effective and not misbranded; 18 ingredients listed in § 350.10 are a monograph condition. In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule in part 310 establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective.

That final rule included the antiperspirant ingredients aluminum bromohydrate, aluminum chloride (alcoholic solutions), aluminum chloride (aqueous solution) (aerosol only), aluminum sulfate, aluminum sulfate buffered (aerosol only), potassium alum, and sodium aluminum chlorohydroxy lactate in § 310.545(a)(4), and was effective on May 7, 1991. In this final rule, the agency is redesignating the text of paragraph (a)(4) as paragraph (a)(4)(i), adding new paragraph (a)(4)(i) heading, and adding new paragraph (a)(4)(ii) to contain aluminum sulfate buffered with sodium aluminum lactate. Any drug product labeled, represented, or promoted for use as an OTC antiperspirant drug that contains any of the ingredients listed in § 310.545(a)(4)(i) or (a)(4)(ii) or that is not in conformance with the monograph (21 CFR part 350) may be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352). Such a drug product can not be marketed for OTC antiperspirant use unless it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314. An appropriate citizen petition to amend the monograph may also be submitted in accord with 21 CFR 10.30 and § 330.10(a)(12)(i). Any OTC antiperspirant drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of the final rule for § 310.545(a)(4)(i) or after the compliance dates of this final rule that is not in compliance with the regulations is subject to regulatory action.

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and

monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the act. This judgment balances the benefits of these drug products against their potential risks (see § 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see "Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, Final Rule" (67 FR 72555, December 6, 2002).

## **VI. Analysis of Impacts**

An analysis of the costs and benefits of this regulation, conducted under Executive Order 12291, was discussed in the TFM for OTC antiperspirant drug products (47 FR 36492 at 36503). The one comment received is addressed in section II.A, comment 4 of this final rule and further addressed later in this section.

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 et seq.). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental,

public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation). The proposed rule that has led to the development of this final rule was published on August 20, 1982, before the Unfunded Mandates Reform Act of 1995 was enacted. This final rule will not result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million.

The agency concludes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. Additionally, the final rule is not a significant regulatory action as defined by the Executive order. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this final rule, because the final rule will not result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

FDA has determined that this final rule will not have a significant economic impact on a substantial number of small entities. While the exact number of affected small entities is difficult to determine at any given time, the agency received only one comment from a small entity, which is discussed

later in this section. This discussion explains the agency's determination that this final rule will not have a significant economic impact on a substantial number of small entities.

The purpose of this final rule is to establish conditions under which OTC antiperspirant drug products are generally recognized as safe and effective and not misbranded. This includes establishing the allowable monograph ingredients and labeling. Eighteen of the 19 active ingredients under review are included in the final monograph. The remaining ingredient could have been included had a USP–NF monograph been developed for this ingredient. If a USP–NF monograph is developed before the effective date of this final monograph, products containing this ingredient could continue to be marketed without reformulation. Without a USP–NF monograph for the ingredient, product reformulations to include a monograph antiperspirant active ingredient or discontinuation of the products will need to occur. The agency believes that this one antiperspirant active ingredient is currently in only a few products. Based on the large number of antiperspirant drug products in the OTC marketplace and the vast array of products that one known affected company currently markets, the agency considers the required reformulation or discontinuation of a few products not to be overly burdensome or substantial. The one known affected company markets at least 30 products not affected by this final rule. Only one of its products includes the active ingredient excluded under the final rule. Any company using this active ingredient has the option to: (1) Reformulate using any of the 18 active ingredients included in this final rule, (2) reformulate without this active ingredient and market the product as a deodorant, or (3) discontinue the product.

This final rule establishes the monograph labeling for OTC antiperspirant drug products and will require relabeling of all products covered by the monograph. The agency's Drug Listing System identifies approximately 200 manufacturers and 700 marketers of 1,300 OTC antiperspirant drug products containing the 19 ingredients covered by this final rule. It is likely that there are additional products that are not currently included in the agency's system. While it is difficult to determine an exact number, the agency estimates that about 1,500 OTC antiperspirant drug products will need to be relabeled based on this final rule.

The agency has been informed that relabeling costs of the type required by a final monograph generally average about \$3,000 to \$5,000 per stock keeping unit (SKU) (individual products, packages, and sizes). However, some of the relabeling that occurs as a result of this specific final monograph will be due to additional indications that the agency has included in the final monograph and that manufacturers will wish to add to their labeling. Assuming that there are about 1,300 to 1,500 affected OTC SKUs in the marketplace, total one-time costs of relabeling would be \$3.9 million (\$3,000 per SKU x 1,300 SKUs) to \$7.5 million (\$5,000 per SKU x 1,500 SKUs). The agency believes that actual costs will be lower for several reasons. First, many of the label changes will be made by private label manufacturers that tend to use relatively simple and less expensive labeling. Second, the agency has finalized a revised labeling format for OTC drug products in § 201.66. The agency is allowing manufacturers to incorporate the labeling changes required by this final rule along with the new general OTC drug labeling format. Thus, the relabeling costs resulting from two different but related final rules will be individually reduced by implementing both required changes at the same time.

Some relabeling costs will be further reduced because the agency is allowing up to 18 months (24 months for products with annual sales less than \$25,000) for these revisions so they may be done in the normal course of business. Thus, manufacturers who wish to add additional indications included in this final monograph can do so at their next regular printing of product labeling. Among the steps the agency is taking to minimize the impact on small entities are: (1) To provide enough time to enable entities to use up existing labeling stock, and (2) to allow the labeling changes required by this final monograph to be done concurrently with the changes required by the new OTC drug labeling format. The agency believes that these actions provide small entities substantial flexibility and reductions in cost.

The agency considered but rejected several labeling alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. While the agency believes that consumers would benefit from having this new labeling in place as soon as possible, a longer time period would unnecessarily delay the benefit of new labeling and a few revised formulations. Conversely, a shorter time period was also considered but rejected because it would be inflexible and more costly for the affected companies. The agency rejected an exemption for small entities because the new labeling and revised formulations, where applicable, are also needed by consumers who purchase products marketed by those entities. However, a longer (24-month) compliance date is being provided for products with annual sales less than \$25,000.

One small manufacturer has indicated that it will suffer economic consequences because it will no longer be able to make claims for use of its antiperspirant products on the hands, and for prosthesis and orthotic use.

However, the manufacturer did not provide sufficient data to show that its products were safe and effective for these uses and did not provide documentation to show the economic impact of this final rule on its sales. The agency notes that the company could: (1) Relabel its products to contain only the monograph indications and then remain in the marketplace, or (2) discontinue its products. While revising the product labeling may have an economic impact on a company, it will be able to continue to market its products and can use the expanded indications provided by the final monograph to try to enhance product sales.

The final rule would not require any new reporting and recordkeeping activities, and no additional professional skills are needed. There are no other Federal rules that duplicate, overlap, or conflict with the final rule.

For the reasons in this section and under the Regulatory Flexibility Act (5 U.S.C. 605(b)), the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

## **VII. Paperwork Reduction Act of 1995**

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 et seq.). Rather, the labeling statements are a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

## VIII. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## IX. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

## X. Section 369.20 Revision

Section 369.20 (21 CFR 369.20) contains a recommended warning and caution statement for OTC antiperspirant drug products under the heading "ANTIPERSPIRANTS:" "Do not apply to broken skin. If a rash develops, discontinue use." This statement is very similar to, but not quite as extensive as, the warnings required by the final monograph: "Do not use on broken skin" and "Stop use if rash or irritation occurs". The agency is removing the entry for "ANTIPERSPIRANTS" under § 369.20 because it is superseded by §§ 350.50(c)(1) and (c)(2).

## XI. References

The following references are on display in the Dockets Management Branch (see section I of this document) under Docket No. 78N-0064 unless otherwise stated and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Memorandum of telephone conversation between R. Bolger, C. Holland, and K. Holland, Perspi-Cura Co., and V. Miguele, FDA, in OTC vol. 1400FR, dated November 20, 1995.
2. Memorandum of fax from V. Miguele, FDA, to R. Bolger and C. Holland, Perspi-Cura Co., in OTC Vol. 1400FR, dated February 8, 1996.
3. Memorandum of telephone message from R. Bolger, Perspi-Cura Co., to V. Miguele, FDA, in OTC Vol. 1400FR, dated March 25, 1996.
4. Studies 83-0768-70 and 83-0769-70 in Comment RPT.
5. Studies S-1367, S-1617, and ST-2280/2376) in Comment No. C00039.
6. "Antiperspirant Efficacy Study of AP10016 (Currently Marketed Roll-on Antiperspirant With Aluminum Zirconium Tetrachlorohydrate) Against AP10021 (Currently Marketed Roll-on Antiperspirant With Aluminum Chlorohydrate)," Exhibit 24 in Comment No. C00040.
7. Comment No. LET006.
8. Majors, P. A., and F. B. Carabello, "Presentation to the OTC Panel for Antiperspirants of the Hill Top Research Method of Antiperspirant Evaluations and General Discussion of Results Obtained," in OTC Vol. 140065, August 1975.
9. FDA, "Guidelines for Effectiveness Testing of OTC Antiperspirant Drug Products," in OTC Vol. 140065, August 1982.
10. Exhibits 1 through 7 in Comment No. C00040.
11. "Claim for 'Twenty Four Hour Protection' etc., Antiperspirant Tests," studies S-825, S-1434, S-1473, S-1518, S-1546, and S-1604, in Comment No. C00039.

12. Exhibits 9 through 20 and 22, in Comment No. C00040.
13. Majors, P. A., and J. E. Wild, "The Evaluation of Antiperspirant Efficacy—Influence of Certain Variables," *Journal of the Society of Cosmetic Chemists*, 25:139–152, 1974.
14. "New Data on Pedal Antiperspirant Activity," studies in Comment C00041.
15. *Pedal Antiperspirant Efficacy Evaluation*, protocol in Comments PR1 and PR2.
16. Letter from W. E. Gilbertson, FDA, to K. R. Johannes, Scholl, Inc., coded LET11.
17. Letters from W. E. Gilbertson, FDA, to R. C. Stites, Numark Laboratories, Inc., coded LET12 and LET13.
18. "Protocol for the Clinical Evaluation of Antiperspirant Efficacy Against Thermally Induced Sweating," exhibit 21, in Comment No. C00040.
19. Study 83–0769–70 in Comment No. RPT.
20. "Claim for 'Twenty Four Hour Protection' etc., Antiperspirant Tests," studies No. S–825, S–1367, S–1434, S–1473, S–1518, and S–1546, in Comment No. C00039.
21. Studies ST–2280/2376 in Comment No. C00039.
22. "Twenty-Four Hour Enhanced Duration AP Efficacy Evaluation Under Thermal Stress of: A = AP10001 (Currently Marketed Aerosol Antiperspirant With aluminum chlorohydrate) Against B = AP10008, Placebo Aerosol Antiperspirant," Exhibit 6, in Comment No. C00040.
23. "AP Efficacy 24 Hour Absolute Sweat Reduction Study of: AP10001 (Marketed Aerosol Antiperspirant With Aluminum Chlorohydrate)," Exhibit 5, in Comment No. C00040.
24. Summary Minutes of the 18th Meeting of the Advisory Review Panel on OTC Antiperspirant Drug Products, in OTC Vol. 1400FR, February 26 and 27, 1976.
25. OTC Vol. 140059.

26. Comment No. C00039.

27. Transcript of the 27th Meeting of the Advisory Review Panel on OTC Antiperspirant Drug Products, pp. 75–85, included in OTC Vol. 1400FM, January 26, 1978.

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

29. Govett, T., and M. G. DeNavarre, "Aluminum Chlorohydrate, New Antiperspirant Ingredient," *The American Perfumer and Essential Oil Review*, 49:365–368, 1947.

30. "Zirconyl Hy+droxy Chloride Antiperspirant Combinations," Patent No. 2,854,382, U.S. Patent Office, included in Appendix B in OTC Vol. 140037, September 30, 1958.

31. "Characterization of Category I Aluminum Chlorohydrates and Comparison to an Aluminum Chlorohydrate Prepared With an Alternate Neutralization Agent," report in Comment No. C00038.

32. Fifth Supplement, USP 23–NF 18, U.S. Pharmacopeial Convention, Inc., Rockville, MD, p. 3363, 1996.

33. Perl, D. P., and P. F. Good, "Uptake of Aluminum into Central Nervous System Along Nasal-Olfactory Pathways," *Lancet*, 1:1028, May 2, 1987.

34. Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, "Inhalation Toxicology Studies of Aerosolized Products, Final Report," in Comment SUP.

35. Becton, Dickinson Research Center, "Final Report on Aluminum Chlorohydrate Study," in Comment SUP.

36. Rollin, H. B., P. Theodorou, and T. A. Kilroe-Smith, "Deposition of Aluminum in Tissues of Rabbits Exposed to Inhalation of Low Concentrations of A1203 Dust," *British Journal of Industrial Medicine*, 48:389–391, 1991.

37. Graves, A. B. et al., "The Association Between Aluminum-Containing Products and Alzheimer's Disease," *Journal of Clinical Epidemiology*, 43:35–44, 1990.
38. Garruto, R. M., "Pacific Paradigms of Environmentally Induce Neurological Disorders: Clinical, Epidemiological and Molecular Perspectives," *Neurotoxicology*, 12:347–377, 1991.
39. Priest, N. D., Satellite Symposium on 'Alzheimer's Disease and Dietary Aluminum', "The Bioavailability and Metabolism of Aluminum Compounds in Man," *Proceedings of the Nutrition Society*, 52:231–240, 1993.
40. Rowan, M. J., "Recent Research on the Causes of Alzheimer's Disease," *Proceedings of the Nutrition Society*, 52:255–262, 1993.
41. Savory, J. et al., "Can the Controversy of the Role of Aluminum in Alzheimer's Disease be Resolved? What are the Suggested Approaches to This Controversy and Methodological Issues to be Considered?," *Journal of Toxicology and Environmental Health*, 48:615–635, 1996.
42. Scott, C. W. et al., "Aggregation of Tau Protein by Aluminum," *Brain Research*, 628:77–84, 1993.
43. Kasa, P., P. Szerdahelyi, and H. M. Wisniewski, "Lack of Topographical Relationship Between Sites of Aluminum Deposition and Senile Plaques in the Alzheimer's Disease Brain," *Acta Neuropathologica*, 90:526–531, 1995.
44. Candy, J. M. et al., "Aluminum Accumulation in Relation to Senile Plaque and Neurofibrillary Tangle Formation in the Brains of Patients With Renal Failure," *Journal of the Neurological Sciences*, 107:210–218, 1992.
45. Anane, R. et al., "Bioaccumulation of Water Soluble Aluminum Chloride in the Hippocampus After Transdermal Uptake in Mice," *Archives of Toxicology*, 69:568–571, 1995.
46. Forbes, W. F., and N. Agwani, "A Suggested Mechanism for Aluminum Biototoxicity," *Journal of Theoretical Biology*, 171:207–214, 1994.

47. Salib, E., and V. Hillier, "A Case-Control Study of Alzheimer's Disease and Aluminum Occupation," *British Journal of Psychiatry*, 168:244–249, 1996.

48. Doll, R., "Review: Alzheimer's Disease and Environmental Aluminum," *Age and Ageing*, 22:138–153, 1993.

49. Flaten, T. P. et al., "Status and Future Concerns of Clinical and Environmental Aluminum Toxicology," *Journal of Toxicology and Environmental Health*, 48:527–541, 1996.

50. Comments No. C46, RPT2, and RPT3.

## List of Subjects

### 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

### 21 CFR Part 350

Labeling, Over-the-counter drugs.

### 21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR Chapter I is amended as follows:

## PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.545 is amended by redesignating the text of paragraph (a)(4) as paragraph (a)(4)(i), by adding new paragraph (a)(4)(i) heading and paragraphs (a)(4)(ii) and (d)(34), and by revising paragraph (d)(1) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) \* \* \*

(4) \* \* \*

(i) *Ingredients—Approved as of May 7, 1991.* \* \* \*

(ii) *Approved as of [insert date 18 months after date of publication in the Federal Register]; [insert date 24 months after date of publication in the Federal Register], for products with annual sales less than \$25,000.*

6-303  
bbodo/OPR  
King  
Banks

6-3-03  
bbodo/OPR  
King  
Banks

← Aluminum sulfate buffered with sodium aluminum lactate

\* \* \* \* \*

(d) \* \* \*

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3)(i), (a)(4)(i), (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(10)(i) through (a)(10)(iii), (a)(12)(i) through (a)(12)(iv)(A), (a)(14) through (a)(15)(i), (a)(16) through (a)(18)(i)(A), (a)(18)(ii) (except as covered by paragraph (d)(22) of this section), (a)(18)(iii), (a)(18)(iv), (a)(18)(v)(A), and (a)(18)(vi)(A) of this section.

\* \* \* \* \*

(34) *[Insert date 18 months after date of publication in the Federal Register], for products subject to paragraph (a)(4)(ii) of this section. [Insert date 24 months after date of publication in the Federal Register], for products with annual sales less than \$25,000.*

\* \* \* \* \*

3. Part 350 is added 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 Definition.

### **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 antiperspirant drug products.

**Authority:** 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

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

### **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 condition in this part and each general condition established in § 330.1 of this chapter.

(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 applied topically that reduces the production of perspiration (sweat) at that site.

### Subpart B—Active Ingredients

#### § 350.10 Antiperspirant active ingredients.

The active ingredient of the product consists of any of the following within the established concentration and dosage formulation. Where applicable, the ingredient must meet the aluminum to chloride, aluminum to zirconium, and aluminum plus zirconium to chloride atomic ratios described in the U.S. Pharmacopeia-National Formulary. The concentration of ingredients in paragraphs (b) through (j) of this section is calculated on an anhydrous basis, omitting from the calculation any buffer component present in the compound, in an aerosol or nonaerosol dosage form. The concentration of ingredients in paragraphs (k) through (r) of this section is calculated on an anhydrous basis, omitting from the calculation any buffer component present in the compound, in a nonaerosol dosage form. The labeled declaration of the percentage of the active ingredient should exclude any water, buffer components, or propellant.

- (a) Aluminum chloride up to 15 percent, calculated on the hexahydrate form, in an aqueous solution nonaerosol dosage form.
- (b) Aluminum chlorohydrate up to 25 percent.
- (c) Aluminum chlorohydrax polyethylene glycol up to 25 percent.
- (d) Aluminum chlorohydrax propylene glycol up to 25 percent.
- (e) Aluminum dichlorohydrate up to 25 percent.
- (f) Aluminum dichlorohydrax polyethylene glycol up to 25 percent.
- (g) Aluminum dichlorohydrax propylene glycol up to 25 percent.
- (h) Aluminum sesquichlorohydrate up to 25 percent.
- (i) Aluminum sesquichlorohydrax polyethylene glycol up to 25 percent.
- (j) Aluminum sesquichlorohydrax propylene glycol up to 25 percent.

- (k) Aluminum zirconium octachlorohydrate up to 20 percent.
- (l) Aluminum zirconium octachlorohydrate gly up to 20 percent.
- (m) Aluminum zirconium pentachlorohydrate up to 20 percent.
- (n) Aluminum zirconium pentachlorohydrate gly up to 20 percent.
- (o) Aluminum zirconium tetrachlorohydrate up to 20 percent.
- (p) Aluminum zirconium tetrachlorohydrate gly up to 20 percent.
- (q) Aluminum zirconium trichlorohydrate up to 20 percent.
- (r) Aluminum zirconium trichlorohydrate gly up to 20 percent.

### 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 states, under the heading “Uses,” the phrase listed in paragraph (b)(1) of this section and may contain any additional phrases listed in paragraphs (b)(2) through (b)(5) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the uses that have been established and listed in paragraphs (b)(1) through (b)(5) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) For any product, the labeling states [select one of the following: “decreases,” “lessens,” or “reduces”] “underarm” [select one of the following: “dampness,” “perspiration,” “sweat,” “sweating,” or “wetness”].

(2) The labeling may state “also [select one of the following: ‘decreases,’ ‘lessens,’ or ‘reduces’] underarm [select one of the following: ‘dampness,’ ‘perspiration,’ ‘sweat,’ ‘sweating,’ or ‘wetness’] due to stress”.

(3) For products that demonstrate standard effectiveness (20 percent sweat reduction) over a 24-hour period, the labeling may state [select one of the following: “all day protection,” “lasts all day,” “lasts 24 hours,” or “24 hour protection”].

(4) For products that demonstrate extra effectiveness (30 percent sweat reduction), the labeling may state “extra effective”.

(5) Products that demonstrate extra effectiveness (30 percent sweat reduction) sustained over a 24-hour period may state the claims in paragraphs (b)(3) and (b)(4) of this section either individually or combined, e.g., “24 hour extra effective protection”, “all day extra effective protection,” “extra effective protection lasts 24 hours,” or “extra effective protection lasts all day”.

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

(1) “Do not use on broken skin”.

(2) “Stop use if rash or irritation occurs”.

(3) “Ask a doctor before use if you have kidney disease”.

(4) *For products in an aerosolized dosage form.* (i) “When using this product [bullet]<sup>1</sup> keep away from face and mouth to avoid breathing it”.

(ii) The warning required by § 369.21 of this chapter for drugs in dispensers pressurized by gaseous propellants.

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

<sup>1</sup> See § 201.66(b)(4) of this chapter for definition of bullet.

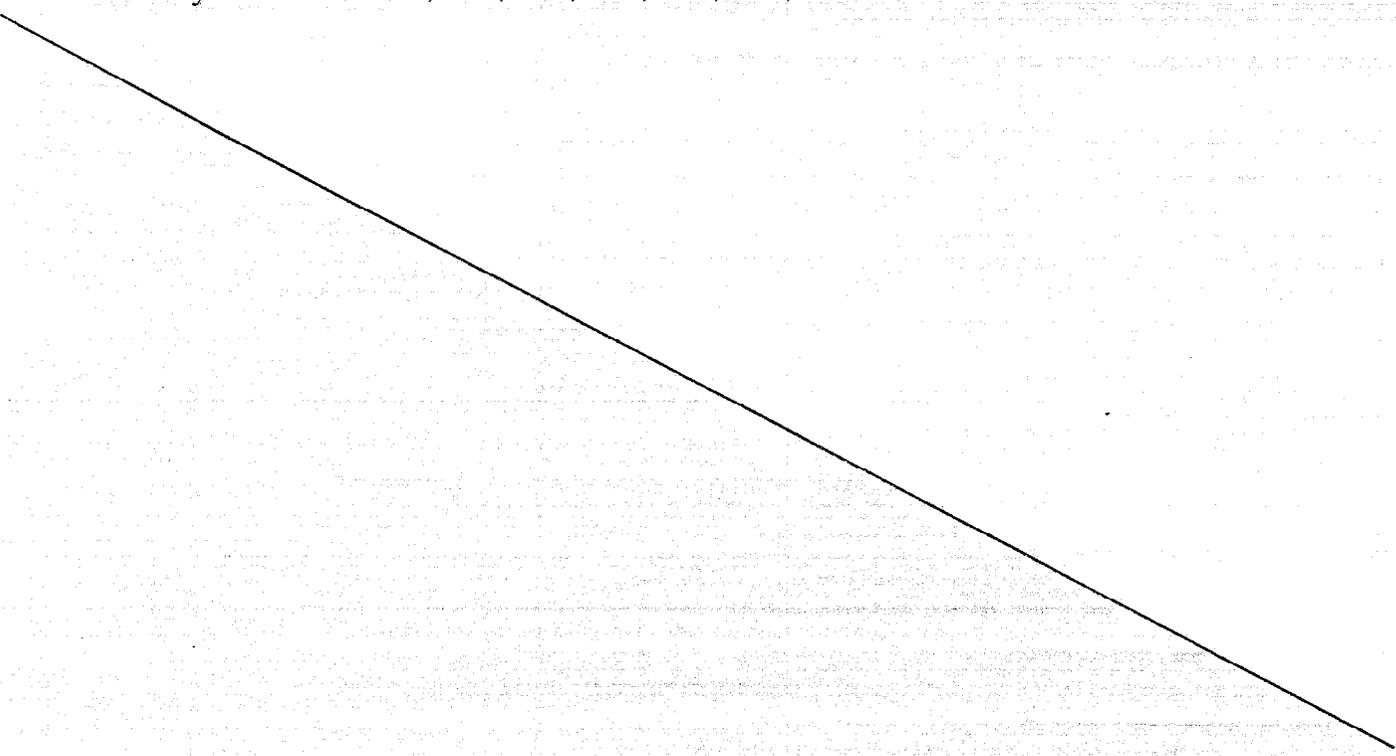
**Subpart D—Guidelines for Effectiveness Testing****§ 350.60 Guidelines for effectiveness testing of antiperspirant drug products.**

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, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. These guidelines are available on the FDA's Web site at <http://www.fda.gov/cder/otc/index.htm> or on request for a nominal charge by submitting a Freedom of Information (FOI) request in writing to FDA's FOI Staff (HFI-35), 5600 Fishers Lane, rm. 12A-16, Rockville, MD 20857.

**PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE**

4. The authority citation for 21 CFR part 369 continues to read as follows:

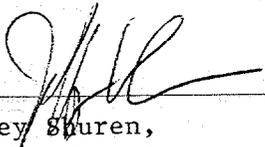
**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 371.



§ 369.20 [Amended]

5. Section 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entry for "ANTIPERSPIRANTS."

Dated: 5/16/03  
May 16, 2003.



Jeffrey Spuren,  
Assistant Commissioner for Policy.

[FR Doc. 03-????? Filed ??-??-03; 8:45 am]

BILLING CODE 4160-01-S

CERTIFIED TO BE A TRUE  
COPY OF THE ORIGINAL

