GUIDELINES FOR EFFECTIVENESS TESTING OF OTC ANTIPERSPIRANT DRUG PRODUCTS

1. BACKGROUND.

The Food and Drug Administration (FDA) is offering suggested guidelines for testing the effectiveness of an OTC antiperspirant drug product in finished product form in accordance with § 350.60 (21 CFR 350.60) of the final monograph (final rule) for OTC antiperspirant drug products, published in the FEDERAL REGISTER on June 9, 2003 (68 FR 34273). These guidelines set forth criteria for the test subjects, test conditions, test procedures, and treatment of the data obtained. 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. To qualify as effective, an antiperspirant drug product in finished product form should meet the criteria established in these guidelines. These guidelines apply to all antiperspirant formulations. Because minor variations in formulation, such as adding emollients or buffers, can alter the effectiveness of an antiperspirant ingredient, FDA encourages the use of these guidelines to test the product whenever a change is made, except for the addition or change in color or perfume ingredients. In testing OTC

antiperspirant drug products, the agency believes it is important to assure that the perspiration reduction that is achieved can be readily perceived by the majority of users. Merely reducing the level of perspiration by a statistically significant amount will not assure a reduction that will be noticeable to the user. The agency considers this factor in the data treatment in these guidelines.

2. TEST SUBJECTS.

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

(b) Test subjects are required to abstain from using all antiperspirant and deodorant materials (except those deodorants, furnished by the investigator, that have been tested and found to have no antiperspirant effect on axillary sweating) for at least 17 days prior to pretreatment or treatment sweat collections.

3. TESTING CONDITIONS.

Either hotroom or ambient conditions may be used to

obtain gravimetric measurements of axillary perspiration rate.

(a) Hotroom conditions. (1) Test subjects are placed in a controlled environment (temperatures at 100?F, plus or minus 2?, and relative humidity of 30 to 40 percent) to thermally induce perspiration.

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

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

(c) 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.

4. TEST PROCEDURES.

(a) Hotroom procedure. (1) For gravimetric 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.

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

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

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

(5) Test subjects are placed in the controlled environment as defined in paragraph (a)(1) under "TESTING CONDITIONS" for a 40-minute warmup period.

(6) Preweighed absorbent pads are placed in both axillae of each test subject at the end of the warmup period.

(7) Test subjects remain in the controlled environment

for a period of 20 minutes, perspiration is collected on the absorbent pads, and the pads are again weighed at the end of the collection period. Perspiration is collected during one of two successive 20-minute periods for evaluation.

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

(b) Ambient procedure. The ambient procedure is performed in the same manner as the hotroom procedure except that test

subjects are allowed to go about their normal daily routines, and the collection period lasts 3 to 5 hours.

5. DATA TREATMENT TO DEMONSTRATE STANDARD ANTIPERSPIRANT EFFICACY.

(a) When there is no pretreatment observation, the unadjusted ratio of right axilla to left axilla is determined by the formula:

Unadjusted right-to-left ratio = R/L.

Where R is the raw milligram weight measure of moisture from the right axilla and L is the corresponding quantity from the left axilla.

To adjust for 20 percent reduction due to treatment, the measure of moisture for the control axilla is multiplied by 0.80. For subjects treated on the right axilla, the adjusted right-to-left ratio is determined by the formula:

Adjusted right-to-left ratio = X = R/(0.8L)

Where X is the adjusted value for a subject treated on the right axilla. For subjects treated on the left axilla, the corresponding adjustment is defined by the formula:

Adjusted right-to-left ratio = Y = (0.8R)/L

Where Y is the adjusted value for a subject treated on the left axilla. Thus, if the product is effective, X should be a relatively small number (less than one), and Y should be a relatively large number (greater than one). The hypothesis that reduction in perspiration exceeds 20 percent is tested statistically by comparing X to Y using the Wilcoxon Signed Rank Test. In statistical terminology, the test is of the null hypothesis: Median X $\geq$ Median Y versus the alternative hypothesis: Median X < Median Y. This is a test of the null against a one-sided alternative at a predetermined level of significance, usually taken to be 0.05. Rejection of the null hypothesis at significance level 0.05 will justify the conclusion that at least 50 percent of the target population will obtain a sweat reduction of at least 20 percent. An

error will be committed in no more than 5 percent of the cases in which the sweat reduction does not exceed 20 percent.

(b) When pretreatment observations are recorded, the ratio of treated axilla to control axilla adjusted for the ratio of right-to-left axillary sweating rate is defined for each subject by the formula:

$$Z = (PC \times T) / (PT \times C).$$

Where Z is the adjusted ratio, PC is the pretreatment measure of moisture for the control axilla, PT is the pretreatment measure for the test axilla, T is the treated measure for the test axilla, and C is the corresponding quantity for the control axilla.

The hypothesis that reduction in perspiration exceeds 20 percent is tested statistically by subtracting 0.80 from Z for all subjects. The Wilcoxon Signed Rank Test is applied to compare the adjusted ratio to 0.80, the value which corresponds to a 20-percent reduction in moisture due to treatment. In statistical terminology, this is a test of the null hypothesis: Median $Z \geq 0.80$, versus the alternative hypothesis: Median $Z < 0.80$.

Again, the null is being tested against a one-sided alternative at a predetermined level of significance. Rejection of the null hypothesis will justify the conclusion

that at least 50 percent of the target population will obtain a sweat reduction of at least 20 percent.

(c) For both testing situations the rank tests are 95 percent as efficient as the appropriate t-test when the data are normal. When the data are nearly normally distributed, the rank tests and the t-test are nearly identical in efficiency. Estimates of sample size can therefore be based on calculations or tables for the t-test.

(d) The test will demonstrate that, with high probability, at least 50 percent of the target population will obtain a sweat reduction of at least 20 percent.

6. DATA TREATMENT TO DEMONSTRATE EXTRA-EFFECTIVE ANTIPERSPIRANT EFFICACY.

(a) When there is no pretreatment observation, the hypothesis that reduction in perspiration exceeds 30 percent is tested statistically by the Wilcoxon Signed Rank Test (see 5.(a) above). To adjust for 30 percent reduction in perspiration due to treatment, the measure of moisture for the control axilla is multiplied by 0.70, and X and Y values calculated accordingly.

(b) When pretreatment observations are recorded, the hypothesis that reduction in perspiration exceeds 30 percent is tested statistically by subtracting 0.70 from Z for all

subjects and applying the Wilcoxon Signed Rank Test (see 5.(b) above).

(c) The test will demonstrate that, with high probability, at least 50 percent of the target population will obtain a sweat reduction of at least 30 percent.

7. DATA TREATMENT TO DEMONSTRATE ENHANCED DURATION ANTIPERSPIRANT EFFICACY.

(a) As noted in section 4.(a)(4), 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.

(b) Products having an enhanced duration of effect may be either standard efficacy of extra-effective antiperspirant products. For standard efficacy products, the data treatment methods in section 5. of the guidelines shall be used. For extra-effective products, the data treatment methods in section 6. of the guidelines shall be used.