

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  $30 \pm 3$  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 “Al: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-