

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