

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 chlorohydrates or aluminum zirconium chlorohydrates 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 chlorohydrates or aluminum zirconium chlorohydrates 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 chlorohydrates 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 chlorohydrates 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