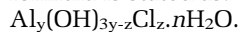


to but not including 1.25:1 proposed for aluminum sesquichlorohydrate in the tentative final monograph (47 FR 36492 at 36504). The comment contended that if the final product is regarded as a mixture of aluminum sesquichlorohydrate and magnesium chloride, and if the amount of chloride that serves as 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:



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,