The additional data submitted by the comments do not change the agency's position. One unpublished study (WM–339) (Ref. 1) addressed the therapeutic benefit of a combination containing 130 mg theophylline and 24 mg ephedrine. This randomized, double-blind, placebo-controlled, four-way crossover study compared the bronchodilator effects of single doses of theophylline, ephedrine, theophylline with ephedrine, and placebo in 30 subjects with reversible bronchospasm. According to the comment, the study demonstrates that ephedrine is an effective single ingredient bronchodilator and that combination drug treatment with theophylline plus ephedrine is significantly more effective than treatment with either single ingredient in providing relief from reversible airway obstruction attributable to bronchial asthma.

The agency finds that study WM–339 (Ref. 1) does not provide substantial evidence that both ingredients in the combination drug product make a contribution to the claimed effects. According to the authors, effectiveness of the two single ingredient products (130 mg theophylline and 24 mg ephedrine), the combination product (both theophylline and ephedrine), and placebo (inert tablet) was compared using the following endpoints: (1) Results of spirometric measurements of forced expiratory volume in 1 second (FEV_1) and the peak expiratory flow rate, (2) subjective evaluations of test subjects, and (3) incidence of therapeutic failure. The authors concluded that the combination therapy was superior to both placebo and to the single ingredients for spirometric measurements at several time points and for subjective patient global responses. Although significantly fewer failure rates were reported for the combination treatment group than for the placebo group, there was no significant difference in treatment failures between either individual ingredient and the combination product.

Flaws in the design and analysis of this study preclude substantiation of the authors' conclusions. First, the agency does not consider a single-dose, crossover study sufficient to establish effectiveness of both components of this fixed combination that would be used for multiple doses in a dynamic illness. Treatment-by-sequence effects, possible carryover effects, and dynamic changes in the subject's baseline disease over time could not be assessed because individual subject information was not provided.

Second, the agency considers inappropriate the method utilized to specify and analyze all effectiveness data recorded for treatment failures. Treatment failures were defined by inability to record at least one FEV_1 measurement with a minimum 15 percent improvement during the first 2 hours, and dropouts after the first 2 hours of observation. The planned analysis specified proper handling of treatment failure dropouts. However, 88 percent (15 of 17) of the subjects with at least a single treatment failure at the 2-hour observation point were allowed to finish the same 6-hour study period and were included in the evaluation of effectiveness. Some of these subjects may have received the allowed 2-hour rescue medication generating ''improved'' data for observation points between 2 and 6 hours, which cannot be attributed to the assigned study drug.

Finally, beta-agonist aerosol rescue medication was allowed by the study protocol at the single 2-hour observation point. This caused effectiveness results to be compromised by inclusion of further data in the analysis of effectiveness whether or not use of the rescue medication was considered a treatment failure.

The agency discussed the Sims et al. study (Ref. 2), submitted by one comment, in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30544). During two phases in that study, several combination products, including one containing 130 mg theophylline and 25 mg ephedrine, were compared to single doses of theophylline and ephedrine in 10 adults with mild but continuously symptomatic asthma and in 10 nonsmoking healthy adults. Reported results were that: (1) A single dose of 130 mg theophylline combined with 25 mg ephedrine produced a bronchodilator effect in subjects with mild to moderate asthma; (2) the theophylline and ephedrine combination caused more side effects (i.e., tremor, nervousness, nausea) than either ingredient alone; and (3) one theopylline and ephedrine combination was more effective than either drug alone, but there was no improvement in bronchodilator effectiveness for another combination despite higher theophylline blood levels achieved after 2 weeks of multiple dosing with a combination product containing theophylline, ephedrine, and phenobarbital. To explain the observed lack of improved lung function after multiple dosing with higher theophylline blood levels, the authors suggested the development of tolerance to theophylline, ephedrine, or both. The agency considers this two-phase study insufficient to support the claim that the combination of theophylline and ephedrine is more effective than either single active ingredient alone for the treatment of mild, continuously symptomatic asthma. The agency concludes that this study does not provide sufficient data to support the use of OTC combination drug products containing theophylline and ephedrine.

The agency has also reviewed the other studies (Refs. 3 through 50) and determined that the data do not substantiate the safe and effective use of OTC combination drug products containing theophylline. References 3 through 6 were previously addressed in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30544). Reference 7 reported superior effects of a combination of two drugs (theophylline and ephedrine) over single ingredient products (theophylline or ephedrine) in ameliorating exercise-induced bronchospasm. However, a three ingredient combination drug product (theophylline, ephedrine, and hydroxyzine hydrochloride) was used in these studies. Further, the side effects (drowsiness, tremors, nausea, insomnia, and palpitations) made the theophylline-ephedrine combination product unacceptable to almost one-half of the subjects in the study.

References 8 and 9 suggested that combinations are more effective than their individual components in controlling induced bronchospasm and modifying both early asthmatic response and late asthmatic response. However, two other reports (Refs. 49 and 50) indicated that oral theophylline has no effect on airway hyperresponsiveness even at dose levels greater than the fixed dose (780 mg per day) currently available OTC.

Reference 10 noted that in some studies additive effects of the combination drug product containing theophylline are recorded and in other studies they are not. Reference 11 was a double-blind, placebo-controlled, randomized cross-over study of a combination of three ingredients (theophylline, ephedrine, and hydroxyzine), another combination of three ingredients (theophylline, ephedrine, and phenobarbital), and a single ingredient product containing ephedrine. The authors reported that both combinations were more effective than ephedrine alone, but the study did not include a single ingredient product containing theophylline. Therefore, the study was unable to evaluate the contribution of ephedrine.

References 12 and 13 indicated that the prescription drugs metaproterenol