5,557 theophylline-related toxicity reports from two hospitals over a 2-year period. Ten percent of the reported cases had serum theophylline concentrations above the therapeutic range, while 2 percent of these cases reported serum theophylline concentrations greater than 30 micrograms per milliliter (µg/mL). Of the 116 cases having serum theophylline concentrations greater than 30 µg/mL, 12 percent were due to acute overdose and 88 percent due to chronic overmedication. Sessler stated that cases of theophylline-induced toxicity are relatively common in hospital emergency departments, result primarily from patient and physician dosing errors, and cause a broad range of toxic manifestations of varying severity. Sessler indicated that the most common single cause of toxicity is inappropriate drug administration by the patient, i.e., additional doses administered for the relief of bronchospasm and/or dyspnea (difficulty in breathing).

In a recent prospective study (Ref. 10), Shannon evaluated major theophylline toxicity of 249 subjects with acute theophylline intoxication: 119 subjects with acute intoxication who were not receiving theophylline therapy, 92 subjects with chronic intoxication due to overmedication, and 38 subjects who ere acutely intoxicated while on theophylline therapy. The study pointed out that chronic overmedication is responsible for the high rate of morbidity and mortality in elderly subjects with theophylline intoxication. Shannon concluded that the data support the admonition that theophylline should be used cautiously, if at all, in elderly patients, and that close patient monitoring is necessary.

The data discussed above demonstrate an incidence of theophylline-related, life-threatening events and deaths, and a narrow therapeutic window for the safe use of theophylline. Accordingly, the agency concludes that theophylline should be administered under professional supervision and not be available OTC. Therefore, all OTC cough-cold combination drug products containing theophylline are considered nonmonograph.

References

(1) Comment No. C211, Docket No. 76N–052G, Dockets Management Branch.

(2) Letter from M. Maher, Association of Trial Lawyers of America, to J. S. Benson, FDA, dated October 25, 1990, in OTC Vol. 04THFM, Docket No. 76N–052G, Dockets Management Branch.

(3) Department of Health and Human Services, Food and Drug Administration, ''Spontaneous Reporting System, Line Listing of Adverse Reports: Theophylline Adverse Drug Event Profile,'' January 1969 to March 1994, in OTC Vol. 04THFM, Docket No. 76N–052G, Dockets Management Branch.

(4) Litovitz, T.L. et al., ''1990 Annual Report of the American Association of Poison Control Centers National Data Collection System,'' The American Journal of Emergency Medicine, 9:488, 1991.

(5) Litovitz, T.L. et al., ''1991 Annual Report of the American Association of Poison Control Centers National Data Collection System,'' The American Journal of Emergency Medicine, 10:480, 1992.

(6) Litovitz, T.L. et al., ''1992 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System,'' The American Journal of Emergency Medicine, 11:530, 1993.

(7) Litovitz, T.L. et al., ''1993 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System,'' The American Journal of Emergency Medicine, 12:580, 1994.

(8) Tsiu, S.J. et al., ''Theophylline Toxicity: Update,'' Annals of Allergy, 64:241–257, 1990.

(9) Sessler, C.N., ''Theophylline Toxicity: Clinical Features of 116 Consecutive Cases,'' The American Journal of Medicine, 88:567–576, 1990.

(10) Shannon, M., ''Predictors of Major Toxicity after Theophylline Overdose,'' Annals of Internal Medicine, 119:1161–1167, 1993.

2. Two comments disagreed with the agency's Category II classification of any OTC cough-cold combination drug product containing theophylline (53 FR 30544 at 30546). One comment stated that OTC combination bronchodilator drug products containing theophylline and ephedrine provide the same benefit to asthmatics as either single active ingredient when used for temporary relief of symptoms associated with episodic asthma. The comment asserted that low dose theophylline and ephedrine combinations have an extensive marketing history and a record of safe and effective use. The comment submitted two clinical studies (Refs. 1 and 2) in support of the therapeutic benefit of both theophylline and ephedrine and the additive effect(s) when both ingredients are taken in combination in fixed dosage. The comment contended that the two clinical studies confirm the following: (1) Low dose theophylline in combination products is therapeutically effective; (2) addition of low dose theophylline enhances the effectiveness of ephedrine; and (3) significant clinical benefit is achieved from using the combination product. The comment concluded that these studies provide substantial evidence to adequately support a final determination by the agency that low dose theophylline in combination with ephedrine is generally recognized as safe and effective as an OTC combination bronchodilator drug product.

The second comment stated that adequate and well-controlled clinical studies and 50 years of successful OTC use in the management of reversible bronchospastic disorder have demonstrated the safety and effectiveness of its OTC combination bronchodilator drug product containing 130 mg theophylline, 24 mg ephedrine, and 8 mg phenobarbital. In support of the additive effects and benefits from combining theophylline with ephedrine, the comment submitted data, literature reviews, and affidavits from several health care providers (Refs. 3 through 50). The comment stated that the data presented show that the combination drug product containing theophylline and ephedrine is a rational drug combination by virtue of the synergistic effects of the two bronchodilators, and that the reduction in the dosage of each component reduces the risk of toxicity from either ingredient. The comment added that such combination drug products provide mild to moderate chronic and stable asthmatic individuals with safe and effective medication that is convenient and cost-effective.

The agency has reviewed the submitted data and information, considered other pertinent information, and determined that the existing data do not support the safety and effectiveness of OTC combination drug products containing theophylline and ephedrine. The agency notes that on July 20 and 21, 1981, the FDA Pulmonary-Allergy Drugs Advisory Committee (the Committee) met and concluded that there was insufficient evidence to demonstrate the additive effect for combination drug products containing theophylline and ephedrine (Ref. 51). The Committee met again on November 4, 1982, and stated that it did not favor the continued OTC or prescription marketing of theophylline and ephedrine fixed combination drug products (Ref. 52). In the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30545 to 30546), the agency agreed with the Committee that: (1) Insufficient evidence exists to support the use of theophylline and ephedrine in combination; (2) ephedrine adds little benefit to the theophylline and ephedrine combination when theophylline is given in a dosage titrated for the individual patient; (3) individual dosage titration for theophylline is needed; and (4) an increase in adverse effects has been associated with the use of theophylline and ephedrine combination drug products.