(Ref. 12) and terbutaline (Ref. 13) produced additive effects when given with theophylline. However, these data concerning additive effects of prescription drugs are irrelevant to OTC use of ephedrine. Reference 14 involved a comparison of a three ingredient combination drug product containing 130 mg theophylline, 24 mg ephedrine, and 8 mg phenobarbital to a single ingredient product containing 300 mg theophylline, given four times a day. The investigators recorded similar pulmonary function responses for the two products. However, it is difficult to assess these results because the two products contained different amounts of theophylline. The appropriate study to establish effectiveness would have been to compare the combination product to a single ingredient product containing the same amount of theophylline.

None of the other reports (Refs. 15 through 48) contains information to demonstrate safety and effectiveness. References 15 through 26 provided general information only. References 27 through 31 do not contain any clinical trials, and references 32 through 48 involved the comment's sustained action formulation. Some of these studies employed either a placebo control (Ref. 33) or a beta-agonist control other than ephedrine (Refs. 35 through 38). Two other studies (Refs. 32 and 34) compare the safety and effectiveness of a theophyllinecontaining sustained action dosage form and a theophylline-containing immediate release dosage form. References 39 through 48 lack study controls and are some of the early 1976 trials in Europe that dealt with a variety of disease entities.

The affidavits contained statements from several health care providers that the combination therapy of 130 mg theophylline and 24 mg ephedrine in fixed doses provides safe and effective therapy for the treatment of mild asthma. However, none of the affidavits included any new scientific data to support the safety and effectiveness of any OTC combination drug product containing theophylline and ephedrine.

The agency concludes that the submitted data do not support any combination bronchodilator drug products containing theophylline as safe and effective for OTC use, particularly with regard to effectiveness at steady state. Substantial evidence has not been provided to demonstrate that each ingredient in the combination of theophylline and ephedrine makes a contribution to the claimed effects as noted in § 330.10(a)(4)(iv) (21 CFR 300.10(a)(4)(iv)). Accordingly, in this final rule, combination bronchodilator

drug products containing theophylline are not generally recognized as safe and effective and are considered misbranded for OTC use.

References

(1) Unpublished Clinical Study No. WM-339, "Clinical-Biostatistical Report, Comment No. C193, Docket No. 76N-052G, Dockets Management Branch.

(2) Sims, J.A. et al., "Bronchodilating Effect of Oral Theophylline-Ephedrine Combination," Journal of Allergy and Clinical Immunology, 62:15–21, 1978. (3) Plummer, A.L., "Choosing a Drug

Regimen for Obstructive Pulmonary Disease," Postgraduate Medicine, 63:36-47, 1978

(4) Piafsky, K.M., and R.I. Ogilvie, "Dosage of Theophylline in Bronchial Asthma," New England Journal of Medicine, 292:1218–1222, 1975.

(5) Tinkelman, D.G., and S. Avner, "Ephedrine Therapy in Asthmatic Children," Journal of the American Medical Association, 237:553-557. 1977.

(6) Plummer, A.L., and B.A. Cassidy, "A Comparison of the Bronchodilator Effects of Terbutaline, Tedral, and the Simultaneous Use of Both Agents," Annals of Allergy, 42:218-223, 1979.

(7) Bierman, C.W. et al., "Exercise-Induced Asthma," Journal of the American Medical Association, 234:295–298, 1975.

(8) Falliers, C.J., and C.P. Katsampes, "Pharmacologic Modification of Induced Asthma," Annals of Allergy, 36:99-103,

(9) Falliers, C.J., and M.A. Redding, "Combined vs. Single-Entity Inhibition of Induced Asthma," Annals of Allergy, 44:335-340. 1980.

(10) Paterson, J.W., and G.M. Shenfield, "Bronchodilators," The British Thoracic and Tuberculosis Association Review, 4:61-74, 1974

(11) Whitcomb, N.J., and E. Rubinstein, Clinical Effectiveness of Commonly Used Oral Bronchodilators in Asthmatic Children," Annals of Allergy, 31:603-606, 1973

(12) Chodosh, S., and W. Baigelman, "Bronchodilator Effects of Metaproterenol and Oxtriphylline in Asthma," Chest, 73:1014-1015, 1978.

(13) Shapiro, G.G. et al., "Effectiveness of Terbutaline and Theophylline Alone and in Combination in Exercise-Induced Bronchospasm," Pediatrics, 67:508-513, 1981

(14) Steen, S.N. et al., "Clinical Efficacy of Theophylline Combination Therapy for Chronic Obstructive Airways Disease, Current Therapeutic Research, 27:608-619, 1980

(15) Knott, R.P., "Drug Therapy of Bronchial Asthma," Pharmindex, 24:7-18, 1982

(16) Baigelman, W., "Here Come the Anticholinergics," Chest, 85:297, 1975. (17) Tong, T.G., "Aminophylline—Review

of Clinical Use," Drug Intelligence and Clinical Pharmacy, 7:156-167, 1973.

(18) Klein, J.J. et al., "Relationship Between Serum Theophylline Levels and Pulmonary Function Before and After Inhaled Beta

Agonist in 'Stable' Asthmatics," American Review of Respiratory Disease, 127:413-416, 1983

(19) Caplin, I., and J.T. Haynes, "A Reevaluation of Ephedrine/Theophylline Combinations in the Treatment of Asthma," Journal of the Indiana State Medical Association, 71:492-495, 1978.

(20) Mountain, R.D., and T.A. Neff, "Oral Theophylline Intoxication," Archives of Internal Medicine, 144:724–727, 1984.

(21) Culpit, G.C., "Pharmacologic Management of Asthma in Children,"

Hospital Pharmacy, 9:490-499, 1974.

(23) Wolfe, J.D. et al., "Bronchodilator Effects of Terbutaline and Aminophylline Alone and in Combination in Asthmatic Patients," New England Journal of Medicine, 298:363-367, 1978.

(24) Brooks, S.M. et al., "The Effects of Ephedrine and Theophylline on Dexamethasone Metabolism in Bronchial Asthma," Journal of Clinical Pharmacology, 17:308-318, 1977.

(25) Cohen, B.M., "Sympathomimetic/ Xanthine Broncholysis in Obstructive Ventilatory Disorder," International Journal

of Clinical Pharmacology, 9:6–15, 1974. (26) Jenne, J.W., "Beta Adrenergic Drugs-How Much Is Enough?" Journal of Allergy and Clinical Immunology, 63:74-78, 1979.

(27) Wray, B.F., "Pharmacologic

Management of Asthma in Childhood," Southern Medical Journal, 71:1387-1392 and 1396, 1978.

(28) Richards, W., "Differential Diagnosis of Childhood Asthma," Current Problems in Pediatrics, 4:1–36, 1974.

(29) Freedman, S.O., "Drug Treatment of the Out-Patient Asthmatic (Chronic Asthmatic),'' Applied Therapy, 11:81–84, 1969

(30) AMA Drug Evaluations, 3rd ed., American Medical Association, Publishing Sciences Group, Inc., Littleton, MA, pp. 627-643, 1977.

(31) Berman, B.A., "Bronchial Asthma," in Current Pediatric Therapy, 7th ed., edited by S.S. Gellis, and B.M. Kagan, W.B. Saunders Co., Philadelphia, pp. 650-658, 1976.

(32) Heimlich, E.M. et al., "Clinical and Laboratory Evaluation of an Antiasthmatic Preparation with Prolonged Action," Journal of Allergy, 35:27-37, 1964.

(33) Cohen, B., "Double-Blind Crossover Comparative Study of the Effect of Tedral SA vs. Placebo on Airway Resistance," Clinical-Biostatistical Report No. 932-0387, Comment No. C193, Docket No. 76N-052G, Dockets Management Branch.

(34) Bellis, T.G.L. et al., "General Practitioner Clinical Trial: A Long- and Short-Acting Antiasthmatic Drug, Practitioner, 191:218-220, 1963.

(35) Cohen, B.M., "The Cardiorespiratory Effects of Oral Terbutaline and an Ephedrine-Theophylline-Phenobarbital Combination; Comparison in Patients with Chronic Obstruction Ventilatory Disorders," Annals of Allergy, 40:233-239, 1978.

(36) Bush, R.K. et al., "A Comparison of a Theophylline-Ephedrine Combination with Terbutaline," Annals of Allergy, 41:13-17, 1978