period of time for relabeling and reformulation of products covered by the monograph (53 FR 30522 at 30523).

In the case of OTC combination bronchodilator drug products containing theophylline, the agency has determined that no combination is generally recognized as safe and effective for this use. Accordingly, the agency is not establishing any monograph conditions for these combination drug products. Thus, there is no need for a 12-month period for relabeling and reformulation of these products. As stated in the advance notice of proposed rulemaking, these conditions should be eliminated from OTC drug products effective 6 months after the date of publication of this final rule. Therefore, on or after January 29, 1996, no OTC cough-cold combination drug products containing theophylline may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application. Any such OTC drug product in interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action. Manufacturers are urged to comply voluntarily with this final rule at the earliest possible date.

In the final rule for OTC bronchodilator drug products (51 FR 35326 at 35338), the agency listed a number of nonmonograph bronchodilator ingredients. At that time, § 310.545 had not been established. Thus, none of these nonmonograph bronchodilator ingredients are listed in that regulation.

Accordingly, at this time, the agency is also listing in § 310.545(a)(6)(iv) all of the nonmonograph bronchodilator active ingredients discussed in that final rule. The effective date of nonmonograph status for these ingredients, which did not apply to combinations containing theophylline, was October 2, 1987. The date of nonmonograph status of combinations containing theophylline will be January 29, 1996.

II. The Agency's Conclusions on the Comments

1. One comment requested that the agency ban theophylline in OTC drug products. The comment mentioned the growing body of medical literature highly critical of theophylline's safety record. The comment contended that theophylline can be a dangerous drug and its use should be tailored (by a physician) to the individual patient. The comment mentioned 26 incidents of theophylline-caused injuries, most of which involved young asthma patients who sustained brain damage from seizures or died as a result of using theophylline. The comment emphasized the need for greater understanding of the use of theophylline, especially when used by children or anyone suffering from fever or a viral infection, such as the flu.

Another comment reported a case involving a 6-year-old child who had been admitted to the hospital with a diagnosis of complex febrile seizures (Ref. 1). Because such febrile seizures often do not reoccur, the child was not placed on anticonvulsant medication, but was observed over time. Several months later, when the child was readmitted with gastroenteritis presumably of viral etiology, the physician discovered that the child had been taking an OTC drug product containing 130 milligrams (mg) theophylline, 24 mg ephedrine, and 8 mg phenobarbital twice daily for asthma prophylaxis. The comment indicated that the presence of phenobarbital in this product could have affected the patient's clinical course and/or recognition of reoccurring seizures. The comment urged the agency to remove this type of combination product from the OTC marketplace.

The agency agrees with the comments that theophylline-containing combination drug products should no longer be available OTC. In the OTC cough-cold combination tentative final monograph (53 FR 30522 at 30544 to 30546), the agency stated its awareness of the increase in adverse effects associated with the use of theophylline and ephedrine combination drug products. Moreover, the agency concluded that whether theophylline is administered as a single ingredient or in combination with other drugs, it is essential that a physician titrate theophylline dosage based on individual patient measurements of theophylline serum levels. Thus, the agency classified any OTC combination drug product containing theophylline as Category II (not generally recognized as safe and/or effective) and reaffirmed its position that theophylline should be administered under professional supervision.

More recent data also support the conclusion that theophylline is not safe for OTC use. These include:

(1) Twenty-six incidents of theophylline-caused injury between 1980 and 1991 (involving mostly young asthma patients), including 6 deaths (likely causally related), 15 cases of brain damage (not otherwise defined), 4 seizures and/or coma, and 1 rapid heartbeat (Ref. 2); (2) FDA adverse reaction reports for the years 1969 to March, 1994 (Ref. 3); and (3) the American Association of Poison Control Centers National Data Collection System (Refs. 4 through 7).

The agency's adverse reaction reporting system (Ref. 3) includes 116 adverse reactions associated with theophylline-containing combination drug products. Twenty-two of these reactions were serious: 4 resulted in death; 15 resulted in hospitalization; and 3 were disabling. These reports include both prescription and OTC use of theophylline combination drug products. Adverse reaction reports involving single ingredient theophylline drug products include 2,175 cases. Of these, 782 were serious, 111 resulted in death, 5 others were considered life-threatening, 4 required medical intervention to prevent impairment, 698 resulted in hospitalization, and 27 were disabling (Ref. 3).

The annual reports of the American Association of Poison Control Centers for the years 1990 to 1993 (Refs. 4 through 7) concerning theophylline exposures state the following: (1) In 1990, there were 6,527 theophylline exposures resulting in 36 deaths, 93 major (severe) outcomes, 622 moderate outcomes, and 2,039 minor outcomes; (2) in 1991, there were 6,744 theophylline exposures resulting in 38 deaths, 138 major outcomes, 619 moderate outcomes, and 2,101 minor outcomes; (3) in 1992, there were 5,735 theophylline exposures resulting in 35 deaths, 113 major outcomes, 596 moderate outcomes, and 1,343 minor outcomes; and (4) in 1993, there were 4,473 theophylline exposures resulting in 27 deaths, 120 major outcomes, 782 moderate outcomes, and 1,026 minor outcomes. The agency notes that these reports do not differentiate theophylline exposure as resulting from prescription or OTC drug products; nor do the reports differentiate exposure as resulting from drug products containing theophylline as a single ingredient or in combination with another active ingredient.

Tsiu et al. (Ref. 8) reported 1,570 published cases of theophylline-induced toxicities from 1973 through 1988, which included 198 seizures, 525 cardiovascular complications, and 63 deaths. The study indicates that many patients suffered serious and frequently fatal side effects, despite receiving ''standard'' prescription doses of theophylline. This type of reporting emphasizes the narrow therapeutic index of theophylline and the need to determine individual dose titration levels.

Sessler (Ref. 9) examined the clinical and pharmacokinetic characteristics of