drowsiness for the combination drug product.

In the proposed rule for OTC coughcold combination drug products (53 FR 30522 at 30539), FDA did not include any specific OTC cough-cold combination drug products containing diphenhydramine citrate or diphenhydramine hydrochloride as oral antitussive active ingredients. These ingredients were not included in the final monograph for OTC antitussive drug products because of a lack of publicly available data that would support the antitussive effectiveness of diphenhydramine. (See the Federal Register of October 19, 1983, 48 FR 48576.) However, the agency did discuss combinations containing a drug that is both an antitussive and an antihistamine (such as diphenhydramine) combined with another oral antitussive or antihistamine (53 FR 30522 at 30539). The agency considered such products to be combinations containing two ingredients from the same pharmacologic group and proposed a Category III classification based on the agency's "General Guidelines for OTC Drug Combination Products" (Ref. 1). Under the guidelines, Category I active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredient in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. However, the guidelines also state that such ingredients may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC drug combination policy in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose.

Accordingly, the agency is proposing to place combinations containing a drug recognized as both an antitussive and an antihistamine with another oral antitussive and antihistamine in Category III. At the present time, this proposal only involves combinations containing diphenhydramine citrate or diphenhydramine hydrochloride with any monograph antihistamine in § 341.12 or any monograph antitussive in § 341.14. The agency is revising proposed § 341.40(d), (e), and (f) to replace the phrase "Any single antihistamine active ingredient identified in § 341.12 \*\*\* \*" with the phrase "Any single antihistamine active ingredient identified in § 341.12(a)

through (e) and (h) through (m) \* \* \*." This revision specifically excludes combinations containing diphenhydramine citrate or diphenhydramine hydrochloride as an antihistamine with an antitussive.

The agency is also revising proposed § 341.40(d), (e), and (f) to replace the phrase "any single oral antitussive active ingredient identified in § 341.14(a) \* \* \*" with the phrase "any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) \* \* \*." This revision specifically excludes combinations containing diphenhydramine citrate or diphenhydramine hydrochloride as an antitussive with an antihistamine.

The agency has also considered combinations containing a dose of diphenhydramine as the oral antitussive component and an additional dose of diphenhydramine as the antihistamine. The agency concludes that such a combination would contain too large a dose of diphenhydramine to be safe. Thus, the agency is proposing that such a combination be Category II.

The use of a single dose of diphenhydramine as an antitussive and antihistamine for treating concurrent symptoms in either a single-ingredient or combination drug product is discussed in section III.

## Reference

(1) Food and Drug Administration "General Guidelines for OTC Drug Combination Products, September 1976," Docket No. 78D–0322, Dockets Management Branch.

III. Use of a Single Dose of Diphenhydramine Citrate or Diphenhydramine Hydrochloride as an Antitussive and Antihistamine for Treating Concurrent Symptoms (in Either a Single-Ingredient or Combination Drug Product)

In the **Federal Register** of December 9, 1992 (57 FR 58378), the agency proposed to amend the final monograph for OTC antitussive drug products to add diphenhydramine citrate and diphenhydramine hydrochloride. In response, one comment stated that a single-ingredient drug product containing diphenhydramine hydrochloride for concurrent use as both an antihistamine and an antitussive should be labeled with a broader dosing range (e.g. diphenhydramine hydrochloride, 25 to 50 milligrams (mg) every 4 to 6 hours, not to exceed 300 mg in 24 hours) to eliminate confusion to consumers (Ref. 1). The comment also contended that the broader dosage range should be permitted to provide the maximum

antihistamine effectiveness for consumers. In addition, the comment stated that the labeling of products for concurrent antihistamine/antitussive use should include the appropriate warnings for both indications.

The Panel believed that the interests of consumers are best served by exposing the user of OTC drug products to the smallest number of ingredients possible at the lowest possible dosage consistent with a satisfactory level of effectiveness (41 FR 38312 at 38322). Thus, an OTC drug product in which diphenhydramine citrate or diphenhydramine hydrochloride serves both as the antitussive and antihistamine component for treating concurrent symptoms would reduce the number of ingredients in the product. For example, a Category I combination drug product containing diphenhydramine as an antihistamine and antitussive combined with a nasal decongestant would contain only two ingredients. Such a combination would contain one less ingredient than a similar combination product containing three different ingredients for the same therapeutic uses. Similarly, an antihistamine-antitussive combination could contain only diphenhydramine to serve both functions.

In a final rule that amended the OTC antitussive monograph to include diphenhydramine citrate and diphenhydramine hydrochloride (59 FR 29172), the agency determined that the available clinical data and marketing history of products containing these ingredients for antitussive use do not support a broader dosage range. The agency concluded that it could not generally recognize as safe and effective an antitussive dosage (25 to 50 mg every 4 to 6 hours for diphenhydramine hydrochloride) that is not supported by clinical data. The dosage for diphenhydramine hydrochloride in  $\S 341.74(d)(1)(v)$  of the antitussive monograph (21 CFR 341.74(d)(1)(v)) reads:

Adults and children 12 years of age and over: oral dosage is 25 milligrams every 4 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

The dosage for diphenhydramine citrate in § 341.74(d)(1)(iv) of the antitussive monograph (21 CFR 341.74(d)(1)(iv)) reads:

Adults and children 12 years of age and over: oral dosage is 38 milligrams every 4 hours, not to exceed 228 milligrams in 24 hours, or as directed by a doctor. Children 6