to under 12 years of age: oral dosage is 19 milligrams every 4 hours, not to exceed 114 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

The dosage for diphenhydramine hydrochloride in § 341.72(d)(7) of the antihistamine monograph (21 CFR 341.72(d)(7)) reads:

Adults and children 12 years of age and over: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 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 § 341.72(d)(6) of the antihistamine monograph (21 CFR 341.72(d)(6)) reads:

Adults and children 12 years of age and over: oral dosage is 38 to 76 milligrams every 4 to 6 hours, not to exceed 456 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 19 to 38 milligrams every 4 to 6 hours, not to exceed 228 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

The agency believes that an OTC drug product containing diphenhydramine citrate or diphenhydramine hydrochloride that is labeled both as an antitussive and an antihistamine should conform to the same labeling restrictions that apply to combination drug products containing a different antitussive and antihistamine ingredient. In the tentative final monograph for OTC cough-cold combination drug products, the agency proposed that when there is a difference in the directions established for the individual ingredients in a combination drug product, e.g., when the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph (53 FR 30522 at 30554). Therefore, when diphenhydramine citrate or diphenhydramine hydrochloride is labeled for both antitussive and antihistamine use, the limiting factor for directions for use for both the dosage amount and dosing interval for OTC labeling is the antitussive dosage in § 341.74(d)(1)(iv) and (d)(1)(v). However, the limiting factor for directions for use for professional labeling is the antihistamine dosage in § 341.90(j) and (k) (21 CFR 341.90(j) and (k)), respectively. As noted above, 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).

The comment also questioned how the statements of identity, indications, and warnings required for both OTC antitussive and antihistamine drug products could be combined when the product contains diphenhydramine for concurrent antitussive and antihistamine use. The agency has determined that the labeling of such products should conform to the labeling requirements for combination drug products containing an antitussive and an antihistamine. The proposed labeling section for OTC cough-cold combinations (§ 341.85) states that the statements of identity, indications, and warnings may be combined to eliminate duplicative wording or phrases so that the resulting information is clear and understandable (53 FR 30522 at 30562).

When applied to diphenhydramine for concurrent use, the statement of identity would be "antihistamine/cough suppressant" or "antihistamine/ antitussive (cough suppressant)." The indications would be combined from §§ 341.72(b) and 341.74(b). The warnings would be combined from § 341.7Ž(c)(1), (c)(2), (c)(4), and (c)(6) and § 341.74(c)(1), (c)(2), (c)(3), and (c)(4). The warnings for diphenhydramine for antitussive use in § 341.74(c)(4) encompass all of the same warnings for diphenhydramine for antihistamine use in $\S 341.72(c)(1)$, (c)(2), (c)(4), and (c)(6). In addition, the product would need to have the required warnings for antitussive use in § 341.74(c)(1), $(c\bar{)}(2)$, and (c)(3), as applicable (depending on the ages for which the product is labeled). Thus, an easy rule to follow when using diphenhydramine citrate or diphenhydramine hydrochloride as a single ingredient for both antihistamine and antitussive use is to follow all of the warnings in § 341.74(c) of the antitussive monograph. This example illustrates how a single uniform warning results when the duplicative words or phrases from the respective warnings are eliminated.

Accordingly, the agency is proposing the following labeling for drug products that contain diphenhydramine citrate or diphenhydramine hydrochloride for concurrent antitussive and antihistamine use: Labeling of drug products containing diphenhydramine citrate or diphenhydramine hydrochloride for concurrent antitussive and antihistamine use either as a single ingredient product or as a single ingredient in combination with other

active ingredients. The statements of identity, indications, and warnings required for antitussive and antihistamine use may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. The directions for OTC labeling shall follow § 341.74(d)(1)(iv) or (d)(1)(v), as applicable. The directions for professional labeling shall follow § 341.90(j) or (k), as applicable.

The agency notes that allowing the use of diphenhydramine in the same product as both an antitussive and antihistamine for treating concurrent symptoms is a new concept. Therefore, the agency would like to receive public comment on the proposed new concept and on the proposed labeling approach before marketing begins. Although the agency is proposing in this amendment to the cough-cold combination tentative final monograph to allow the use of diphenhydramine in the same product as both an antitussive and an antihistamine, OTC marketing may not begin at this time. The agency is providing a short comment period of 75 days and plans to issue a notice of enforcement policy at a later date to state whether marketing may begin prior to the issuance of the final monograph for OTC cough-cold combination drug products.

Reference

(1) Comment No. C0001, Docket No. 89P-0040, Dockets Management Branch.

IV. Summary of the Agency's Proposals for OTC Cough-Cold Combinations Containing Diphenhydramine as an Antitussive

The agency has reviewed all combinations containing an oral antitussive and/or an antihistamine that were classified as Category I, II, or III in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30556 and 30557), to clarify the use of diphenhydramine citrate and diphenhydramine hydrochloride as antitussive active ingredients in these combinations. For the convenience of the reader, the following table is included as a summary of the proposed classification changes by the agency of combinations containing an antitussive in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30556 and 30557) and the proposed classification by the agency of these combinations when the antitussive or the antihistamine active ingredient is either diphenhydramine citrate or diphenhydramine hydrochloride. Table 3 includes only