DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 76N-052G]

RIN 0905-AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Amendment of the Tentative Final Monograph for Combination Drug Products

AGENCY: Food and Drug Administration, HHS.

11115.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the tentative final monograph for over-the-counter (OTC) cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products to classify combination drug products containing the ingredients diphenhydramine citrate or diphenhydramine hydrochloride. The agency recently amended the final monograph for OTC antitussive drug products (products used to relieve cough) to include the ingredients diphenhydramine citrate and diphenhydramine hydrochloride. The agency also previously included diphenhydramine citrate and diphenhydramine hydrochloride in the final monograph for OTC antihistamine drug products. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments or objections by May 9, 1995; written comments on the agency's economic impact determination by May 9, 1995.

ADDRESSES: Written comments or objections to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR

330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. In that notice, the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel) discussed OTC cough-cold combination drug products, including combinations containing an oral antitussive and/or an antihistamine (41 FR 38312 at 38327). The Panel considered combinations containing the ingredient diphenhydramine hydrochloride. (Diphenhydramine citrate was not submitted for the Panel's consideration.) The Panel recommended that diphenhydramine hydrochloride be Category I (generally recognized as safe and effective) as both an oral antitussive and an antihistamine. However, the Panel recommended a Category II classification (not generally recognized as safe and effective or misbranded) for any combination containing an oral antitussive ingredient and an antihistamine if the antitussive ingredient is also a Category I antihistamine or if the antihistamine is also a Category I antitussive. Diphenhydramine hydrochloride was the only ingredient that the Panel classified in Category I for both antitussive and antihistamine use.

In the Federal Register of August 12, 1988 (53 FR 30522), FDA published the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products. FDA did not include specific combinations for OTC cough-cold drug products containing diphenhydramine citrate or diphenhydramine hydrochloride for OTC oral antitussive use in that tentative final monograph. At that time, these ingredients were not included in the final monograph for OTC antitussive drug products because adequate data to support monograph status were not publicly available. Subsequently, data were submitted to the rulemaking for OTC antitussive drug products (see discussion below).

In the tentative final monograph, the agency discussed combinations containing a drug recognized as both an antitussive and an antihistamine combined with another oral antitussive and/or antihistamine (53 FR 30522 at 30539). The agency proposed that such combinations be Category III (available data are insufficient to classify as safe and effective, and further testing is required).

In the **Federal Register** of December 9, 1992 (57 FR 58378), the agency proposed that diphenhydramine citrate and diphenhydramine hydrochloride be included in the final monograph for OTC antitussive drug products as single ingredients. This action was taken because the data needed to support monograph status had been made publicly available. The proposal was recently finalized in the Federal **Register** of June 3, 1994 (59 FR 29172). In that final rule, the agency stated that it would address the following matters in a future issue of the Federal Register: (1) OTC cough-cold combination drug products containing diphenhydramine citrate or diphenhydramine hydrochloride for antitussive use, (2) concurrent antitussive and antihistamine use of diphenhydramine ingredients (either in an OTC coughcold single-ingredient or combination drug product) for concurrent symptoms, and (3) "multiuse" labeling for OTC drug products containing an ingredient that may be used separately for more than one indication for nonconcurrent symptoms--with full, separate labeling for each indication. The first two subjects are addressed in this proposed rule. The third will be addressed in a future issue of the Federal Register. Labeling issues relating to that topic are broader than diphenhydramine, applying to other OTC drug ingredients that have more than one pharmacologic activity and that are included or proposed for inclusion in more than one OTC drug monograph. For example, sodium bicarbonate has a number of drug uses.

II. The Agency's Proposals for OTC Cough-Cold Combination Drug Products Containing Diphenhydramine Citrate or Diphenhydramine Hydrochloride for Antitussive Use

In this proposed rule, the agency has considered all OTC cough-cold combination products classified in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522) that could include diphenhydramine as an oral antitussive or as an antihistamine. The agency is proposing only a few changes in the classification of these combinations when diphenhydramine is included in the combination as an antitussive or an antihistamine (see section III). The following table lists the combinations that were considered: