

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.

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 cough-cold 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:

Table 1

Cough-Cold Combinations Considered in the Tentative Final Monograph That Contain an Antihistamine or an Antitussive

A. Combinations containing an oral antitussive, but not an antihistamine

1. Analgesic-antipyretic(s) and oral antitussive
2. Analgesic-antipyretic(s) and oral antitussive and oral nasal decongestant
3. Oral antitussive and expectorant (if labeled for nonproductive cough)
4. Oral antitussive and oral nasal decongestant
5. Oral antitussive and expectorant and oral nasal decongestant (if labeled for nonproductive cough)
6. Oral antitussive and anesthetic/analgesic (if available only in a solid dosage form)
7. Oral nasal decongestant and oral antitussive and anesthetic/analgesic (if available only in a solid dosage form)
8. Oral antitussive and oral demulcent (if available in a solid dosage form)
9. Oral nasal decongestant and oral antitussive and oral demulcent (if available only in a solid dosage form)
10. Oral antitussive and anesthetic/analgesic and oral demulcent (if available only in a solid dosage form)
11. Oral nasal decongestant and oral antitussive and anesthetic/analgesic and oral demulcent (if available only in a solid dosage form)
12. Oral antitussive and debriding agent/oral wound cleanser
13. Oral antitussive and astringent
14. Oral bronchodilator and oral antitussive (if labeled for cough associated with asthma)
15. Oral antitussive and bronchodilator used as an antitussive (if labeled for productive cough)
16. Oral antitussive and expectorant (if labeled for productive cough)
17. Oral antitussive and expectorant and oral nasal decongestant (if labeled for productive cough)
18. Analgesic-antipyretic(s) and oral antitussive and expectorant and oral nasal decongestant

B. Combinations containing an antihistamine, but not an oral antitussive.

1. Analgesic-antipyretic(s) and antihistamine
2. Analgesic-antipyretic(s) and antihistamine and oral nasal decongestant
3. Antihistamine and oral nasal decongestant
4. Antihistamine and debriding agent/oral wound cleanser
5. Antihistamine and astringent
6. Antihistamine and expectorant
7. Oral bronchodilator and antihistamine
8. Antihistamine and anticholinergic
9. Anticholinergic and antihistamine and oral nasal decongestant
10. Combinations containing an antihistamine for the relief of symptoms of allergic rhinitis and an additional antihistamine which is added exclusively for sedation, and the product contains labeling which represents the additional antihistamine as a sleep-aid
11. Combinations containing an antihistamine with a sleep-aid claim
12. Antihistamine and oral anesthetic/analgesic
13. Antihistamine and oral demulcent
14. Antihistamine and nasal decongestant (administered topically as spray or drops)

C. Combinations containing both an oral antitussive and an antihistamine.

1. Antihistamine and oral antitussive (if labeled "May cause marked drowsiness")
2. Analgesic-antipyretic(s) and oral antitussive and oral nasal decongestant and antihistamine
3. Antihistamine and oral antitussive and oral nasal decongestant
4. Antihistamine (if antihistamine is also a Category I antitussive) and oral antitussive
5. Oral antitussive (if antitussive is also a Category I antihistamine) and antihistamine

A. OTC cough-cold combinations containing: (1) An oral antitussive, but no antihistamine and (2) an antihistamine, but no antitussive.

1. Comparison of Category I Antitussive Combinations With Category II and III Antihistamine-containing Combinations.

The agency has compared all of the Category I combinations containing an oral antitussive, but not an antihistamine (in Table 1, A.1. through A.11.), with all of the Category II and III combinations containing an antihistamine, but not an oral antitussive (in Table 1, B.4. through B.14.). The agency compared the classes

of ingredients included with an oral antitussive in Category I and the classes included with an antihistamine in Categories II and III to determine which combinations similar to the Category II and III antihistamine combinations were included in the Category I antitussive combinations. The following table lists these combinations:

Table 2

Category I Oral Antitussive Combination	Corresponding Category II or III Antihistamine Combination
Oral antitussive and an expectorant	Antihistamine and expectorant
Oral antitussive and an expectorant and a nasal decongestant (if labeled for nonproductive cough)	None
Oral antitussive and an anesthetic/analgesic in a solid dosage form	Antihistamine and an anesthetic/analgesic in a solid dosage form
Oral antitussive and a demulcent in a solid dosage form	Antihistamine and a demulcent
Oral nasal decongestant and an oral antitussive and an anesthetic/analgesic in a solid dosage form	None
Oral nasal decongestant and an oral antitussive and a demulcent in solid dosage	None

(a) *Combination drug products containing an expectorant and an oral antitussive that is also an antihistamine.* The Panel recommended a Category I classification for combinations containing an oral antitussive and an expectorant that is labeled for nonproductive cough (41 FR 38312 at 38328). The agency concurred in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30556). However, the Panel recommended a Category II classification for combinations containing an antihistamine and an expectorant. In this combination, the anticholinergic effect (drying action) of the antihistamine would produce the opposite effect of the secretory action of the expectorant ingredient. Thus, the combination would be medically irrational (41 FR 38312 at 38326). The agency concurred with the Panel in the OTC cough-cold combinations tentative final monograph (53 FR 30522 at 30556). Because diphenhydramine is an antihistamine as well as an antitussive, it would have anticholinergic effects whether it is included in a combination as an oral antitussive or as an antihistamine. Accordingly, the agency is proposing a Category II classification for all combinations containing an expectorant and an oral antitussive if the antitussive is also an antihistamine. The agency is revising proposed § 341.40(g) and (i) 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.

(b) *Combination drug products containing an anesthetic/analgesic and/or a demulcent (in a solid dosage form) and an oral antitussive that is also an antihistamine.* The Cough-Cold Panel reviewed data relating to combination drug products containing cough-cold and oral health care active ingredients with claims for relief of sore throat (41 FR 38312 at 38325). The Panel established specific criteria for the treatment of symptoms with combination products and based its Category I recommendations on whether the combination is rational concurrent therapy for a significant and existing population. The Panel determined that products containing an antitussive or a nasal decongestant combined with an oral anesthetic/analgesic in a lozenge dosage form are rational and

recommended a Category I classification for these combinations. The agency concurred with the Panel in the tentative final monograph for OTC cough-cold combination drug products. However, the agency determined that such a combination could be rational only if the combination drug product were in a solid dosage form so that the anesthetic/analgesic ingredient or the demulcent ingredient may exert its topical effect and the antitussive can be ingested (53 FR 30522 at 30536 and 30537).

The Panel did not discuss combinations containing an antihistamine with an anesthetic/analgesic or a demulcent. However, the agency considered such combinations in the OTC cough-cold combinations tentative final monograph (53 FR 30522 at 30537). The agency stated that the combination of an antihistamine and an oral anesthetic/analgesic or an oral demulcent could be rational if the combination drug product is in a solid dosage form. In addition, the symptoms of allergic rhinitis and minor throat irritation that may result from the nasal congestion that often occurs with allergic rhinitis and subsequent breathing through the mouth could be treated concurrently with such combinations. However, the agency also stated that it was unaware of any currently marketed drug product that contains such a combination and that no data were submitted to demonstrate a significant target population with concurrent symptoms that would benefit from such a combination. Therefore, the agency proposed a Category III classification for the combination of an antihistamine with an oral anesthetic/analgesic or an oral demulcent. The agency has since determined that data do exist to support a target population for such combinations based on epidemiological data accepted by the Panel (41 FR 38312 at 38325). The agency believes that a Category I classification is appropriate for combinations containing an oral antitussive (which is also an antihistamine, although antihistamine claims cannot be made for these combinations) with an oral anesthetic/analgesic or an oral demulcent if in a solid dosage form. Thus, the agency is proposing to include diphenhydramine citrate and diphenhydramine hydrochloride in combinations specified in § 341.40(j), (q), (u), (w), (x), and (z). At this time, sufficient data have not been provided to support a suitable target population with concurrent symptoms of sufficient duration to justify an antihistamine

claim for any of these combination drug products. Therefore, any of these combinations that contain diphenhydramine citrate or diphenhydramine hydrochloride as the antitussive cannot also make antihistamine claims.

2. Category II and III Combinations Containing an Antitussive.

The agency has considered all OTC cough-cold combinations containing an oral antitussive, but no antihistamine, that were placed in Category II or III in the OTC cough-cold combinations tentative final monograph (combinations in Table 1 under A.1. through A.18.). The agency has determined that these combinations would be categorized in the same manner if diphenhydramine were used as the antitussive. The agency is not aware of any data or information that would support reclassification of any of these combinations because they contain diphenhydramine rather than any other monograph oral antitussive ingredient.

3. Combinations Containing an Antihistamine With no Corresponding Category I Antitussive Combination.

The agency considered all antihistamine combinations (not including an oral antitussive) that did not have a corresponding Category I antitussive combination (not including an antihistamine), e.g., an antihistamine and an anticholinergic. The agency is not changing the classification of any of these combinations because they do not contain an antitussive component. Thus, these combinations are not pertinent to combinations that include an antitussive that is also an antihistamine.

B. OTC cough-cold combinations containing: (1) An oral antitussive and an antihistamine if the antitussive is also a antihistamine or (2) an antihistamine and an oral antitussive if the antihistamine is also an antitussive.

The Panel recommended a Category II classification for combinations containing: (1) An oral antitussive and an antihistamine if the antitussive is also a Category I antihistamine, and (2) an antihistamine and an oral antitussive if the antihistamine is also a Category I antitussive (41 FR 38312 at 38326). Such combinations include diphenhydramine and dextromethorphan or diphenhydramine and chlorpheniramine. The Panel stated that the combinations are not safe because the side effects of two drugs having the same action may combine. For example, the drowsiness effect of each ingredient may be additive and result in an unacceptable level of

drowsiness for the combination drug product.

In the proposed rule for OTC cough-cold 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 § 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

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 § 341.72(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 § 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)(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

the proposed changes in classification made in § 341.40 of the cough-cold combination drug products tentative

final monograph. All other combination classifications remain the same:

Table 3

Cold-Cough Combinations	Tentative Final Monograph Proposed Classification	New Proposed Classification for Diphenhydramine-Containing Combinations
Oral antitussive and expectorant (if labeled for nonproductive cough)	I	II
Oral antitussive and expectorant and oral nasal decongestant (if labeled for nonproductive cough)	I	II
Oral antitussive and bronchodilator used as an antitussive (if labeled for productive cough)	III	II
Oral antitussive and expectorant (if labeled for productive cough)	III	II
Oral antitussive and expectorant and oral nasal decongestant (if labeled for productive cough)	III	II
Analgesic-antipyretic(s) and oral antitussive and expectorant and oral nasal decongestant	III	II
Antihistamine and oral antitussive (if labeled "May cause marked drowsiness")	I	III
Analgesic-antipyretic(s) and oral antitussive and oral nasal decongestant and antihistamine	I	III
Antihistamine and oral antitussive and oral nasal decongestant	I	III

1. 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) * * *" to exclude the ingredients diphenhydramine citrate and diphenhydramine hydrochloride. (See section II.B.)

2. The agency is revising § 341.40(d) through (g) and (i) 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) * * *" to exclude the ingredients diphenhydramine citrate and diphenhydramine hydrochloride. (See sections II.A.(i) and II.B.)

3. The agency is proposing to include diphenhydramine citrate and diphenhydramine hydrochloride in combinations specified in § 341.40(h), (j), (k), (q), (u), (w), (x), and (z). (See section II.A.(ii).)

4. The agency is proposing in § 341.40(d), (e), and (f) the use of diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) as both the antihistamine and the antitussive active ingredient

provided that the product is labeled according to § 341.70.

5. The agency is revising § 341.40(f) and (k) to include the specific section numbers for allowed internal analgesic ingredients.

6. In the oral health care tentative final monograph published on September 24, 1991 (56 FR 48302), the agency redesignated the active anesthetic/analgesic ingredients previously proposed in § 356.10 as § 356.12. Accordingly, the agency is revising § 341.40(j), (q), (x), and (z) to replace the phrase "any single oral anesthetic/analgesic active ingredient identified in § 356.10 * * *" with the phrase "any single oral anesthetic/analgesic active ingredient identified in § 356.12 * * *".

7. The agency is proposing to add to § 341.70 labeling for diphenhydramine-containing drug products for concurrent antitussive and antihistamine use under the heading: *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.* (See section III.)

V. Effective Date

The agency advises that any final rule resulting from this proposed rule will be effective 12 months after its date of

publication in the **Federal Register**. On or after that date, any OTC drug product that is not in compliance may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to the rule that is repackaged or relabeled after the effective date of the rule must be in compliance with the rule regardless of the date that the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

VI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the

proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This proposed rule clarifies the use of diphenhydramine citrate or diphenhydramine hydrochloride as an antitussive active ingredient in OTC cough-cold combination drug products and proposes marketing of either a single-ingredient or a combination drug product containing one of these ingredients for concurrent antitussive and antihistamine use. Manufacturers may market such products at their option when marketing is allowed to begin. (See marketing discussion in section III.) Accordingly, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC cough-cold combination drug products. Comments regarding the impact of this rulemaking on these drug products should be accompanied by appropriate documentation.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Request for Comments

Interested persons may, on or before May 9, 1995, submit to the Dockets Management Branch (address above) written comments or objections. Three copies of all comments or objections are to be submitted, except that individuals may submit one copy. Comments and objections are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments and objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 341

Labeling, Over-the-counter drugs. Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that

21 CFR part 341 (as proposed in the Federal Register of August 12, 1988 (53 FR 30522)) be amended as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. Section 341.40 is amended by revising paragraphs (d) through (k), (q), (u), (w), (x), and (z) to read as follows:

§ 341.40 Permitted combinations of active ingredients.

* * * * *

(d) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) provided that the product is labeled according to § 341.85(c)(5). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70.

(e) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70.

(f) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single analgesic-antipyretic active ingredients identified in § 343.10 of this chapter, or any combination of acetaminophen with other analgesic-antipyretic active ingredients identified in § 343.20(a) of this chapter, or any aspirin and antacid combination identified in § 343.20(b)(3). Diphenhydramine citrate in §§ 341.12(f)

and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70.

(g) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) may be combined with any single expectorant active ingredient identified in § 341.18.

(h) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(6) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) provided the product contains only the labeling claims identified in this paragraph.

(i) Any single oral antitussive drug ingredient identified in § 341.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single expectorant active ingredient identified in § 341.18.

(j) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(6) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.12 of this chapter provided that the product is available in a solid dosage form to be dissolved in the mouth and swallowed and provided the product contains only the labeling claims identified in this paragraph.

(k) Any single oral antitussive drug ingredient identified in § 341.14(a)(1) through (a)(6) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single analgesic-antipyretic active ingredients identified in § 343.10 of this chapter, or any combination of acetaminophen with other analgesic-antipyretic active ingredients identified in § 343.20(a) of this chapter, or any aspirin and antacid combination identified in § 343.20(b)(3) provided the product contains only the labeling claims identified in this paragraph and provided the product contains only the labeling claims identified in this paragraph.

* * * * *

(q) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(6) and any single oral anesthetic/analgesic active ingredient identified in § 356.12 of this chapter provided that the product is available in a solid dosage form to be dissolved in the mouth and swallowed and provided the

product contains only the labeling claims identified in this paragraph.

* * * * *

(u) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(6) may be combined with any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the product is available in a solid dosage form to be dissolved in the mouth and swallowed and provided the product contains only the labeling claims identified in this paragraph.

* * * * *

(w) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(6) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the product is available in a solid dosage form to be dissolved in the mouth and swallowed and provided the product contains only the labeling claims identified in this paragraph.

(x) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(6) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.12 of this chapter and any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the product is available in a solid dosage form to be dissolved in the mouth and swallowed and provided the product contains only the labeling claims identified in this paragraph.

* * * * *

(z) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(6) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single oral anesthetic/analgesic active ingredient identified in § 356.12 of this chapter and any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the product is available in a solid dosage form to be dissolved in the mouth and swallowed and provided the

product contains only the labeling claims identified in this paragraph.

3. New § 341.70 is added to subpart C to read as follows:

§ 341.70 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.

Dated: January 31, 1995.

William K. Hubbard,

Interim Deputy Commissioner for Policy.

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