DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 89P–0040]

RIN 0905–AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter Human Use; Proposed Amendment to Monograph for OTC Antitussive 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 monograph for over-the-counter (OTC) antitussive drug products to include the ingredients diphenhydramine citrate and diphenhydramine hydrochloride. OTC antitussive drug products are used to relieve cough. This proposal addresses only single-ingredient antitussive drug products containing one of these ingredients. In a future issue of the **Federal Register**, the agency will propose to amend the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products to address combination cough-cold drug products containing diphenhydramine citrate or diphenhydramine hydrochloride. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments or objections by February 8, 1993; written comments on the agency's economic impact determination by February 8, 1993.

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, 301–295–8000.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of August 12, 1987 (52 FR 30042), FDA issued a final monograph for OTC antitussive drug products in Part 341 (21 CFR Part 341) that lists in § 341.14 (21 CFR 341.14) the active ingredients that are generally recognized as safe and effective for use in these products. Diphenhydramine citrate and diphenhydramine hydrochloride were not included in § 341.14 at that time. Subsequently, two manufacturers petitioned the agency to amend the final monograph for OTC antitussive drug products to include diphenhydramine citrate and diphenhydramine hydrochloride as monograph active ingredients (Refs. 1 and 2).

In the advance notice of proposed rulemaking published in the **Federal Register** of September 9, 1976 (41 FR 38312 at 38340 to 38342), the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel) classified diphenhydramine hydrochloride in Category I (generally recognized as safe and effective and not misbranded) for OTC antitussive use. However, FDA deferred a decision on the Panel's recommendation to place this ingredient in Category I for antitussive use (41 FR 38313). Subsequently, the agency announced in the **Federal Register** of November 30, 1976 (41 FR 52536), that the Commissioner did not accept the Panel's recommendation that diphenhydramine hydrochloride be classified in Category I for OTC use. The Commissioner concluded that the recommended antitussive dose of diphenhydramine hydrochloride (25 milligrams (mg)) causes an unacceptable level of drowsiness for OTC use, even with a warning statement in the labeling as recommended by the Panel. Furthermore, although agreeing with the Panel that some data indicated that this ingredient has an antitussive effect, the Commissioner found a lack of substantial evidence consisting of adequate and well-controlled studies, as required by § 314.126 (21 FR 314.126), formerly § 314.111(a)(5)(ii) (21 CFR 314.111(a)(5)(ii)), on which to base a determination of the effectiveness of diphenhydramine hydrochloride as an antitussive.

In the **Federal Register** of August 31, 1979 (44 FR 51512), FDA published a final decision on the issues that had been presented in a formal evidentiary public hearing concerning a supplemental new drug application (NDA) for diphenhydramine hydrochloride as an antitussive. In this final decision, the Commissioner extensively reviewed the safety and effectiveness data submitted by the manufacturer and considered diphenhydramine hydrochloride's safety and effectiveness as an OTC antitussive. The Commissioner stated that studies to demonstrate the effectiveness of an antitussive either must be done in the target population, i.e., subjects with acute upper respiratory infections, or, if studies are done in a population other than the target population, such as with subjects with chronic cough, the mechanism of action must be shown to act specifically on the cough center of the brain. The Commissioner also stated that induced cough studies are not a substitute for adequate and well-controlled studies in the target population and determined that the available data did not show that diphenhydramine hydrochloride was effective as an antitussive by the above criteria. With regard to the safety of diphenhydramine hydrochloride, the Commissioner stated:

> I believe that, if [diphenhydramine hydrochloride] were shown to be an effective antitussive drug, it might be possible to devise labeling that would provide adequate warnings of the risk of drowsiness and other ill effects and that, coupled with child resistant packaging, would enable the product to be safely used as an OTC drug. In devising any such labeling [it would be necessary] to consider inclusion of approved labeling for prescription [drug products containing diphenhydramine hydrochloride] as well as that recommended by the * * * Panel [footnote omitted]. The risk to patients from a drug that causes drowsiness is indirect. The drowsiness itself does not cause harm. It is only when the patient tries to undertake a task that requires alertness such as driving a car, that the drug's sedative qualities pose a risk to the patient and to other members of the public. Suitable labeling of an OTC drug may provide sufficient safeguards for a drug that presents such indirect risks. When a drug presents serious direct risks (e.g., of cancer or other serious disease), adequate labeling for any lay use without medical supervision generally cannot be written (44 FR 51512 at 51524 and 51525).

In response to the agency's final decision concerning diphenhydramine hydrochloride as an antitussive, new data on the mechanism of action of diphenhydramine hydrochloride were submitted to the agency under a NDA. These data consisted of unpublished studies that were considered to be confidential information under 21 CFR 20.61 and, thus, were not publicly available. Based on the agency's review of the unpublished studies, it approved a supplemental NDA for diphenhydramine hydrochloride for OTC antitussive use. However, in the tentative final monograph for OTC antitussive drug products published in the **Federal Register** of October 19, 1983 (48 FR 48576 at 48581 to 48583), the agency classified diphenhydramine hydrochloride in Category III because there was not adequate information publicly available at that time to

demonstrate that the drug is generally recognized as effective.

References

(1) Comment No. CP2, Docket No. 89P–0040, Dockets Management Branch.
(2) Comment No. CP3, Docket No. 89P–0040, Dockets Management Branch.

II. The Agency's Conclusions on the Petitions

1. One company stated in its petition (Ref. 1) that it currently markets diphenhydramine hydrochloride as an OTC antitussive drug product under an approved supplemental NDA and requested that diphenhydramine be included in the monograph for OTC antitussive drug products. The company stated that diphenhydramine hydrochloride was not included in the final monograph because the data upon which the agency's approval of the supplemental NDA was based were not then publicly available. The company's petition now included these data, consisting of unpublished studies that demonstrate a central mechanism of action for diphenhydramine hydrochloride as an antitussive. In its petition, the company formally requested that the previously confidential efficacy studies referenced by FDA in the tentative final monograph for OTC antitussive drug products (48 FR 48576 at 48582) be made part of the rulemaking procedure and waived any further claim of privilege and confidentiality with respect to these studies (Ref. 1).

Another company (Ref. 2) requested that FDA amend the final monograph for OTC antitussive drug products to include diphenhydramine citrate based on the safety and effectiveness studies submitted for diphenhydramine hydrochloride. The comment noted that, in the final rule for OTC nighttime sleep-aid drug products (February 14, 1989, 54 FR 6814 at 6824), the agency stated that the citrate salt of diphenhydramine could be considered identical to the hydrochloride salt.

The agency agrees with the petitions and is proposing to amend the antitussive final monograph to include diphenhydramine citrate and diphenhydramine hydrochloride as active ingredients. The agency has evaluated the data submitted by one company (Ref. 1) and agrees that they are the same data that were included in the supplemental NDA approved by the agency. The agency previously determined that diphenhydramine citrate is bioequivalent to and therapeutically equivalent to diphenhydramine hydrochloride. In the final rule for OTC nighttime sleep-aid drug products (54 FR 6814 at 6823 and 6824), the agency concluded that the citrate salt could be considered identical to the hydrochloride salt because the citrate salt is rapidly converted in the stomach to the hydrochloride salt. The agency determined that a dose of 76 mg diphenhydramine citrate is necessary to supply a diphenhydramine content equivalent to 50 mg diphenhydramine hydrochloride. Accordingly, the agency is proposing to amend the final monograph on OTC antitussive drug products to include diphenhydramine citrate and diphenhydramine hydrochloride in § 341.14(d)(5) and (d)(6).

References

(1) Comment No. CP2, Docket No. 89P–0040, Dockets Management Branch.
(2) Comment No. CP3, Docket No. 89P–0040, Dockets Management Branch.

2. Both petitions requested that the following warnings for antitussive products containing diphenhydramine be added to § 341.74(c) (21 CFR 341.74) of the antitussive monograph: (1) "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the sedative effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting a doctor. Use caution when driving a motor vehicle or operating machinery," (2) "May cause excitability especially in children," and (3) "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." The petitioners mentioned that these warning were proposed for diphenhydramine in the antihistamine tentative final monograph (January 15, 1985, 50 FR 2200 at 2216).

The agency agrees with the petitions that the same warnings that are required for the diphenhydramine salts in the antihistamine monograph should be required for these ingredients in the antitussive monograph. For clarity, the agency revised some of the above warnings for OTC antihistamine drug products in final monograph for these drug products, published elsewhere in this issue of the **Federal Register**. In addition, the agency notes that both the antitussive and antihistamine monographs include warnings for drug products labeled for use only by children under 12 years of age. Because antitussive drug products can be marketed with labeling for use only by children under 12 years of age and the antitussive monograph already provides specific labeling for such products, specific warnings for antitussive products containing diphenhydramine labeled for use only in this age group are being proposed in this monograph amendment. Therefore, the agency is proposing warnings in § 341.74(c)(4)(v) through (c)(4)(vii)(*b*) for OTC antitussive drug products containing diphenhydramine citrate or diphenhydramine hydrochloride.

In a future issue of the **Federal Register**, the agency will be proposing to revise the warnings that appear in § 338.50(c)(3) (21 CFR 338.50(c)(3)) that are required for products containing diphenhydramine citrate or diphenhydramine hydrochloride used as an OTC nighttime sleep-aid. The warnings will be made consistent with those proposed in § 341.74(c)(4)(vii)(a) of this document and § 341.72(c)(2) of the final monograph for OTC antihistamine drug products (21 CFR 341.72(c)(2)). Also, in a future issue of the **Federal Register**, the agency will be proposing to revise the warnings that appear in § 336.50(c)(1) that are required for products containing diphenhydramine and other ingredients listed in § 336.10 for OTC antiemetic use. The warnings also will be made consistent with those proposed in § 341.74(c)(4)(vii)(a) of this document and § 341.72(c)(2).

3. One petition requested the following directions for diphenhydramine hydrochloride as an antitussive: "Adults: 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." Another comment requested the following directions for diphenhydramine citrate as an antitussive: "Adults: oral dosage is 38 milligrams every 4 hours, not to exceed 228 milligrams in 24 hours except 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 except as directed by a doctor. Children under 6 years of age: consult a doctor."

In its advance notice of proposed rulemaking for OTC cough-cold drug products (41 FR 38312 at 38341), the Panel recommended the same dosages as requested by the petition. The currently approved NDA labeling for diphenhydramine hydrochloride-containing antitussive drug products (Ref. 3) includes the following directions: "Adults (12 years and older): Take 25 mg every 4 hours. Do not

exceed 150 mg in 24 hours. Children (6–12 years): Take 12.5 mg every 4 hours. Do not exceed 75 mg in 24 hours."

Based on the Panel's recommended dosages and the approved NDA labeling, the agency is proposing the following directions for OTC antitussive drug products containing diphenhydramine hydrochloride: "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." This format is consistent with the wording for the directions of other ingredients in the antitussive monograph.

The agency is also proposing the following directions for OTC antitussive drug products containing diphenhydramine citrate: "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." These dosages are equivalent to the above dosages for diphenhydramine hydrochloride.

In the advance notice of proposed rulemaking for OTC cough-cold drug products (41 FR 38312 at 38341), the Panel provided professional labeling for diphenhydramine hydrochloride for OTC antitussive use. The Panel recommended that such labeling (but not that provided to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 milligrams every 4 hours, not to exceed 37.5 milligrams in 24 hours. This type of information is included in § 341.90 (21 CFR 341.90) of the professional labeling of the cough-cold monograph. Accordingly, the agency is proposing the dosage information for children 2 to under 6 years of age in § 341.90(r) and (s), respectively, of the professional labeling.

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.

The agency has approved a number of NDA's and abbreviated NDA's (ANDA's) that currently allow for the OTC marketing of single-entity drug products containing diphenhydramine hydrochloride for antitussive use. Thus, FDA does not believe it is necessary to prohibit OTC marketing of new single-entity drug products containing diphenhydramine hydrochloride or diphenhydramine citrate for antitussive use while public comment to the proposed monograph status of these ingredients are being evaluated. OTC marketing may be initiated subject to the terms and conditions of the final monograph for OTC antitussive drug products (21 CFR Part 341) and the terms and conditions of this proposed monograph amendment. Such products marketed at this time are subject to the enforcement policy in § 330.13 (21 CFR 330.13). That policy provides that FDA may, by notice in the **Federal Register**, permit interim marketing before the issuance of a final monograph, subject to the risk that the agency may, in the final monograph, adopt a different position that could require relabeling, recall, or other regulatory action. At this time, FDA is allowing single-entity products containing diphenhydramine hydrochloride or diphenhydramine citrate for antitussive use to be marketed pursuant to this proposal provided the product is labeled in accord with § 341.74 and the labeling proposed in this notice. Marketing of such products with labeling not in accord with § 341.74 and the labeling proposed in this notice also may result in regulatory action against the product, the marketer, or both.

This proposal does not address combination drug products containing diphenhydramine citrate or diphenhydramine hydrochloride. These matters will be addressed in a future issue of the **Federal Register**. In the tentative final monograph for OTC cough-cold combination drug products (August 12, 1988, 53 FR 30522 at 30556 and 30557), the agency classified the following combination drug products in Category III and said that such products can not be marketed at this time: (1) Combinations containing an antihistamine (such as diphenhydramine citrate or diphenhydramine hydrochloride that is also a Category I antitussive) with an antitussive, (2) combinations containing an antitussive (such as diphenhydramine citrate or diphenhydramine hydrochloride that is also an antihistamine) with an antihistamine, (3) combinations containing an antitussive (such as diphenhydramine citrate or diphenhydramine hydrochloride) with an expectorant (if labeled for productive cough), and (4) combinations containing an antitussive (such as diphenhydramine citrate or diphenhydramine hydrochloride) with an expectorant and an oral nasal decongestant (if labeled for productive cough). Until the agency amends the tentative final monograph for OTC cough-cold combination drug products, no cough-cold combination drug product containing diphenhydramine citrate or diphenhydramine hydrochloride labeled for antitussive use can be marketed OTC unless it is the subject of an approved NDA or ANDA.

The agency has examined the economic consequences of this proposed rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC antitussive drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking amending the final monograph for OTC antitussive drug products is not expected to pose such an impact on small businesses. This proposed rule would allow OTC antitussive drug products containing diphenhydramine citrate or diphenhydramine hydrochloride as a single active ingredient to be marketed without having to obtain an approved NDA, as is currently required. This will be beneficial to small manufacturers. Therefore, the agency certifies that this

proposed rule will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC antitussive drug products. Comments regarding the impact of this rulemaking on OTC antitussive 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.

Interested persons may, on or before February 8, 1993, submit written comments or objections to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before February 8, 1993. 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 be amended as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC 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 341.14 is amended by adding new paragraphs (a)(5) and (a)(6) to read as follows:

§ 341.14 Antitussive active ingredients.

* * * * *

(a) * * *

(5) Diphenhydramine citrate.

(6) Diphenhydramine hydrochloride.

* * * * *

3. Section 341.74 is amended by adding new paragraphs (c)(4)(v), (c)(4)(vi), (c)(4)(vii) ,(d)(1)(iv) and (d)(1)(v), to read as follows:

§ 341.74 Labeling of antitussive drug products.

* * * * *

(c) * * *

(4) * * *

(v) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.14(a)(5) and (a)(6).* "May cause excitability especially in children."

(vi) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.14(a)(5) and (a)(6) when labeled only for children under 12 years of age*—(*a*) "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

(*b*) "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor."

(vii) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.14(a)(5) and (a)(6) when labeled for use in adults and children under 12 years of age*—(*a*) "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of prostate gland."

(*b*) "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery."

* * * * *

(d) * * *

(1) * * *

(iv) *For products containing diphenhydramine citrate identified in § 341.14(a)(5).* 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.

(v) *For products containing diphenhydramine hydrochloride identified in § 341.14(a)(6).* 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.

* * * * *

4. Section 341.90 is amended by adding new paragraphs (r) and (s) to read as follows:

§ 341.90 Professional labeling.

* * * * *

(r) *For products containing diphenhydramine citrate identified in § 341.14(a)(5).* Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 hours, not to exceed 57 milligrams in 24 hours.

(s) *For products containing diphenhydramine hydrochloride identified in § 341.14(a)(6).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 hours, not to exceed 37.5 milligrams in 24 hours.

Dated: September 9, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 92–29719 Filed 12–8–92; 8:45 am]

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