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; Amendment of Final Monograph for OTC Antitussive Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule amending the final 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 final rule 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 final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: June 5, 1995.

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 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). The petitions are on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

In the Federal Register of December 9, 1992 (57 FR 58378), the agency discussed these petitions and proposed that diphenhydramine citrate and diphenhydramine hydrochloride be generally recognized as safe and effective for OTC antitussive use. The agency previously determined that diphenhydramine citrate is bioequivalent and therapeutically equivalent to diphenhydramine hydrochloride (54 FR 6814 at 6824, February 14, 1989). The agency proposed specific warnings and directions for these ingredients for OTC antitussive use. The agency advised in its proposed rule (57 FR 58378 at 58380) that any final rule resulting from this proposed rule would be effective 12 months after the final rule's date of publication in the Federal Register.

The agency invited written comments by February 8, 1993, on the proposed rule and the agency's economic impact determination for the proposal. In response to the proposed rule, the agency received two comments from manufacturers. Copies of the comments are on public display in the Dockets Management Branch (address above).

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 Comments

1. Two comments requested that the agency's proposed OTC antitussive dosage for diphenhydramine hydrochloride (25 milligrams (mg) every 4 hours (h), not to exceed 150 mg in 24 h) be expanded to a range of 25 to 50 mg every 4 to 6 h, not to exceed 300 mg in 24 h. One of the comments also requested a corresponding expansion of the OTC antitussive dosage for diphenhydramine citrate, i.e., a dosage of 38 to 76 mg every 4 to 6 h, not to exceed 456 mg in 24 h.

To support an expanded dosage range for antitussive use, one of the comments provided pharmacokinetic data for diphenhydramine hydrochloride dosed at 25 mg every 4 h and 50 mg every 6 h. The data included the following steady state concentrations (C_{ss}), minimum concentrations at steady state ($C_{ss\ min}$), and maximum concentrations at steady state ($C_{ss\ max}$) in nanograms/milliliter (ng/mL) for both dosages; and the areas under the curve (AUC) for both dosages in ng x h/mL:

Diphenhydramine Hydrochloride Pharmacokinetic Data

	($C_{ss\ max}$)	($C_{ss\ min}$)	(C_{ss})	(AUC)
25 mg every 4 h	55 ng/mL	27.5 ng/mL	40 ng/mL	160 ng x h/mL
50 mg every 6 h	85 ng/mL	30 ng/mL	52 ng/mL	312 ng x h/mL

The comment pointed out that the two $C_{ss\ min}$ concentrations are comparable. The comment stated that the 50 mg every 6 h dosing regimen is as efficacious as the 25 mg every 4 h regimen because the 50 mg dose does not fall below the minimum effective concentration. The comment added that further substantiation is provided by the C_{ss} and AUC data, which fall within the minimum effective concentration levels.

The other comment stated that the potential for conflict between the different dosages for antitussive and antihistamine use of diphenhydramine would be eliminated by accepting the broader antihistamine dosage (e.g., for diphenhydramine hydrochloride, 25 to 50 mg every 4 to 6 h, not to exceed 300 mg in 24 h) for products intended for both uses. The comment added that this approach would reduce the potential for consumer confusion. The comment argued that it would not be in the consumer's interest to establish a lower dose for diphenhydramine in products that will not meet consumer expectations of the antihistamine effect. The comment contended that, based on the established safety of diphenhydramine citrate and diphenhydramine hydrochloride for both antitussive and antihistamine use, monograph status for four uses, and potential use for more than one

indication in a cough-cold product, the broader dosage range (e.g., for diphenhydramine hydrochloride, 25 to 50 mg every 4 to 6 h) should be permitted to provide maximum effectiveness. Both comments concluded that diphenhydramine hydrochloride has been found safe for a variety of OTC uses at dosages of 25 to 50 mg every 4 to 6 h and, thus, safety is not an issue at this dosage range.

In the **Federal Register** of September 9, 1976 (41 FR 38312 at 38341), the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products based its 25 mg every 4 h recommendation for diphenhydramine hydrochloride for antitussive use on data demonstrating effectiveness and acceptable tolerability at this dosage. All approved applications for diphenhydramine hydrochloride as an OTC antitussive are for a dosage of 25 mg every 4 h, based on supporting clinical data. No clinical data have been received by the agency to support the safety or increased effectiveness of higher dosages of diphenhydramine hydrochloride or diphenhydramine citrate for OTC antitussive use either under the OTC drug review or an approved application. One comment submitted pharmacokinetic data concerning diphenhydramine at both the 25 mg every 4 h dose and the 50 mg every 6 h dose showing that C_{ss} min for both regimens were similar. It is therefore likely that dosing at 50 mg every 6 h is effective. That regimen, however, produces higher $C_{ss\ max}$ and almost twice the drug exposure, with increased potential adverse effects such as sedation, but with no evidence of greater effectiveness than the every 4 h regimen. In conclusion, the agency cannot consider to be generally recognized as safe and effective an antitussive dosage (25 to 50 mg every 4 to 6 h for diphenhydramine hydrochloride) that is not supported by clinical data. Therefore, based on the Panel's recommended dosage and the approved application labeling for OTC antitussive drug products containing diphenhydramine hydrochloride, the agency is establishing the monograph antitussive dosage of diphenhydramine hydrochloride as follows:

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 monograph antitussive dosage of diphenhydramine citrate is as follows:

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.

With respect to the comment's discussion of a single ingredient drug product containing diphenhydramine for concurrent use as both an antihistamine and an antitussive, this issue will be addressed in an amendment to the OTC cough-cold combinations tentative final monograph in a future issue of the **Federal Register**.

2. One comment discussed "multiuse" labeling of OTC drug products that contain diphenhydramine. The comment described this as labeling a product with some or all of the proven pharmacologic activities of the drug whether or not the conditions to be treated are related. As an example, the comment stated that a product containing diphenhydramine could be labeled for both antitussive and antihistamine use. If this occurred, the statement of identity could be expressed as "cough suppressant/antihistamine." The comment stated that the product's labeling could describe each use separately under the product's "Indications," with accompanying warnings and directions for both uses. The comment contended that there is no legal restriction that prevents "multiuse" labeling whether or not the conditions to be treated are related. The comment discussed several aspects of "multiuse" labeling.

This final rule addresses only single-ingredient diphenhydramine citrate and diphenhydramine hydrochloride drug products for antitussive use. The agency acknowledges that "multiuse" labeling is possible for products containing diphenhydramine but is not aware of any such products having been or currently being in the marketplace. The agency intends to address "multiuse" labeling in a future issue of the **Federal Register** in an amendment to the tentative final monograph for OTC cough-cold combination drug products. The agency will discuss: (1) Concurrent use of diphenhydramine as an antitussive and as an antihistamine for concurrent symptoms, and (2) different uses of diphenhydramine with separate full labeling for different, nonconcurrent symptoms. Manufacturers may not introduce diphenhydramine products having "multiuse" labeling into the OTC marketplace until the agency's proposal on how this should be done appears in a future issue of the **Federal Register**.

3. One comment contended that an agency statement in the proposed rule appeared to be inconsistent with the agency's general provisions and administrative procedures for marketing OTC combination drug products under 21 CFR 330.13(b)(2) and Compliance Policy Guide 7132b.16. The agency statement said: "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" (57 FR 58378 at 58380). The comment stated that, because FDA recognizes diphenhydramine as both an OTC antihistamine and an OTC antitussive, marketing of diphenhydramine for both claims in combination drug products should be allowed under the provisions of the tentative final monograph for OTC cough-cold combination drug products. The comment listed a number of examples where an antitussive can be combined with an antihistamine and stated that diphenhydramine should be able to perform both functions in the product. The comment contended that this approach should be acceptable provided that all of the labeled uses are for Category I combinations.

This final rule does not address combination drug products containing diphenhydramine citrate or diphenhydramine hydrochloride as an antitussive active ingredient. There are a number of issues that need to be resolved before diphenhydramine can be used to perform both functions (antitussive and antihistamine) in a single product. These include, among others, a difference in the monograph directions for use (amount of drug to be taken and time interval for taking the drug) and different warnings related to the individual uses. The agency intends to discuss these matters in a future issue of the **Federal Register**, as noted above. At this time, the agency reaffirms its position stated above that any OTC cough-cold combination drug product containing diphenhydramine citrate or diphenhydramine hydrochloride labeled for antitussive use can only be marketed if it is the subject of an approved application.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking. FDA has examined the impacts of this final 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 final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and, thus, 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. Currently marketed OTC single ingredient diphenhydramine drug products already meet the conditions of the final monograph. Other manufacturers will be able to enter the OTC marketplace without having to obtain an approved application. Accordingly, the agency certifies that the final 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 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.

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, 21 CFR part 341 is 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.

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

§ 341.74 Labeling of antitussive drug products.

* * * * *

(c) * * *

(4) * * *

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

(viii) *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."

(ix) *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 the 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."

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

§ 341.90 Professional labeling.

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(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: May 16, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 94–13586 Filed 6–2–94; 8:45 am]

BILLING CODE 4160–01–F