DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 341

[Docket No. 91N-0323]

RIN 0905-AA06

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking amending the final monograph for over-the-counter (OTC) bronchodilator drug products to modify the drug interaction precaution statement required in the labeling of OTC bronchodilator drug products. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments on the proposed regulation by August 18, 1992; written comments on the agency's economic impact determination by August 18, 1992. FDA is proposing that the final rule based on this proposal be effective 12 months after the date of publication of the final rule in the **Federal Register**.

ADDRESSES: Written comments on the proposed regulation 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: In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published an advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel) recommended the following warning statement for the labeling of OTC bronchodilator drug products: "*Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor" because of marked and potentially dangerous increases in blood pressure that were known to occur in patients taking monoamine oxidase inhibitor (MAOI) drugs and sympathomimetic amine bronchodilator drugs (41 FR 38312 at 38370 through 38373).

The agency discussed this statement in the tentative final monograph for OTC bronchodilator drug products (47 FR 47520 at 47523, October 26, 1982). In response to the Panel's recommendation, one comment contended that terms such as "antihypertensive," "antidepressant," and "monoamine oxidase inhibitor" are highly technical; that only a small percentage of the population is likely to understand this warning; and that including such a warning in the labeling of an OTC drug is contrary to the well-established principle that unnecessary or confusing precautions tend to dilute the significance of all instructions in the labeling and, hence, should be avoided (47 FR 47520 at 47523).

The agency acknowledged that the Panel's proposed drug interaction precaution might not be readily understood by all consumers. However, the agency considered a statement of this type to be necessary to alert consumers because antihypertensive and antidepressant drugs are widely prescribed. The agency proposed to simplify the precaution statement by substituting the term "high blood pressure" for "antihypertensive," and the term "depression" for "antidepressant." The agency also believed that the words "monoamine oxidase inhibitor" would be confusing to consumers and need not be included in the precautionary statement to convey the intended message. Accordingly, the agency proposed the following: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." (See proposed § 341.76(c)(3).) In the final monograph for OTC bronchodilator drug products, published in the **Federal Register** of October 2, 1986 (51 FR 35326 at 35338), the agency substituted the word "use" for the word "take" in this statement because the word "use" is more appropriate for inhalation drug products and is also appropriate for oral dosage forms. This statement appears in § 341.76(c)(4) of the final monograph.

Elsewhere in this issue of the **Federal Register**, the agency is proposing to amend the final monograph for OTC antitussive drug products to include a drug interaction precaution statement about MAOI drugs in the labeling of OTC drug products containing dextromethorphan or dextromethorphan hydrobromide and proposing to amend the tentative final monograph for OTC nasal decongestant drug products to revise the proposed drug interaction precaution involving MAOI drugs. The agency is aware of a resurgence in the use of MAOI drugs after a period of decline in the 1970's (Refs. 1, 2, and 3). While tricyclic and other antidepressants are the most widely used drugs for patients with major depression, MAOI drugs may be used in selected patients with dysthymic and atypical depression (Refs. 3, 4, and 5). There is evidence that MAOI drugs are also being used to treat bulimia and panic disorders (Refs. 3 and 5 through 8), phobic disorders (Refs. 3, 4, 5, and 7), anxiety (Refs. 3, 4, and 5), and obsessive compulsive disorder (Refs. 3 and 8). On the other hand, use of these drugs in hypertension has essentially ceased. Therefore, the agency has reconsidered the wording of the drug interaction precaution statement currently required for OTC bronchodilator drug products. The agency now believes that the reference to "high blood pressure" is not needed and that "depression" is too narrow a description to convey the intended warning to most people being treated with MAOI drugs for other conditions. In addition, while some patients may not understand the term "monoamine oxidase inhibitor," many will; and if in doubt, patients being given psychotropic drugs can ask their doctor or other health professional.

The agency is aware that "monoamine oxidase inhibitor" and "MAOI" are highly technical terms that the average consumer may not recognize or understand. On the other hand, the agency believes that use of these terms in the precaution statement is justified because the more general term "depression" may not alert everyone who is taking an MAOI drug, for bulimia or phobic disorders, for example (Refs. 3 through 8). OTC drug product labeling cannot accommodate a listing of every condition that an MAOI could be used for. Thus, the agency is adding a sentence to the drug interaction precaution advising consumers to seek help if they are uncertain whether or not their prescription drug is an MAOI. The new sentence is similar to the one used to warn pregnant or nursing women about using an OTC drug. (See 21 CFR 201.63.) During the development of a warning to pregnant or nursing women who are considering using an OTC drug (47 FR 54750, December 3, 1982), the agency considered the preference of wording to designate persons who could provide information concerning OTC

drugs to consumers. The agency concluded at that time that "health professional" is the preferred term, because the woman who is considering using an OTC drug is in the best position to choose the specific health professional to help her, and the warning should not limit her sources of information. The agency believes that other health professionals, such as pharmacists or nurses, can help consumers determine whether the drug they are taking contains an MAOI.

Accordingly, the agency is proposing to amend § 341.65(c)(4) of the final monograph for OTC bronchodilator drug products to read: "*Drug interaction precaution.* Do not take this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression or psychiatric or emotional conditions), without first consulting your doctor. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product." The agency is inviting comment on the specific wording of this warning, and the best way to convey this information to persons who are taking MAOI drugs.

References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Linden, C. H., B. H. Rumack, and C. Strehlke, "Monoamine Oxidase Inhibitor Overdose," Annals of Emergency Medicine, 13:1137–1144, 1984.

(2) Guzé, B. H., and L. R. Baxter, Jr., "Current Concepts: Neuroleptic Malignant Syndrome," The New England Journal of Medicine, 313:163–166, 1985.

(3) Pitts, F. N., editor, "Monoamine Inhibitor Drugs in Contemporary Psychiatry," The Journal of Clinical Psychiatry, 45:2–84, 1984.

(4) "AMA Drug Evaluations," 5th ed., American Medical Association, Chicago, pp. 253–255, 1983.

(5) "AMA Drug Evaluations," 6th ed., American Medical Association, Philadelphia, pp. 139–141, 1986.

(6) Harrison, W. M., et al., "MAOIs and Hypertensive Crises: The Role of OTC Drugs," The Journal of Clinical Psychiatry, 50:64–65, 1989.

(7) Golwyn, D. H., and R. C. Weinstock, "MAOIs, OTC Drugs and Hypertensive Crisis," The Journal of Clinical Psychiatry, 51:213, 1990.

(8) Harrison, W., "MAOIs, OTC Drugs and Hypertensive Crisis," The Journal of Clinical Psychiatry, 51:213, 1990.

The agency is proposing that this revised drug interaction precaution become effective 12 months after the date of publication of the final rule in the **Federal Register**. Manufacturers of OTC bronchodilator drug products are encouraged to voluntarily implement this labeling as of the date of publication of this proposal, subject to the possibility that FDA may change the wording of the drug interaction precaution as a result of comments filed in response to this proposal. Because FDA is encouraging the proposed drug interaction precaution to be used on a voluntary basis at this time, the agency advises that manufacturers will be given ample time after publication of a final rule to use up any labeling implemented in conformance with this proposal.

The agency has examined the economic consequences of this proposed rulemaking 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 bronchodilator 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 for OTC bronchodilator drug products is not expected to pose such an impact on small businesses. The only action needed will be minor labeling revisions at the time that the final monograph amendment becomes effective. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant 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 bronchodilator drug products. Comments regarding the impact of this rulemaking on OTC bronchodilator drug products should be accompanied by appropriate documentation. A period of 60 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively having 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 August 18, 1992, submit written comments on the proposed regulation to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before August 18, 1992. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments 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 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 341.76 is amended by revising paragraph (c)(4) to read as follows:

§ 341.76 Labeling of bronchodilator drug products.

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(c) * * *

(4) "*Drug interaction precaution.* Do not use this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression or psychiatric or emotional conditions), without first consulting your doctor. If you are uncertain whether your

prescription drug contains an MAOI, consult a health professional before taking this product."

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Dated: March 18, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

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