DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 341

[Docket No. 90N-0420]

RIN 0905-AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of Final 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 issuing a notice of proposed rulemaking amending the final monograph for over-the-counter (OTC) antitussive drug products to require a drug interaction precaution statement in the labeling of OTC antitussive (relieves cough) drug products containing dextromethorphan or dextromethorphan hydrobromide. These drug products should not be used by individuals who are taking a prescription drug containing a monoamine oxidase inhibitor, without first consulting their doctor. 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 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) placed the ingredients dextromethorphan and dextromethorphan hydrobromide in Category I (generally recognized as safe and effective for OTC use) as an antitussive. The Panel recommended a number of warnings for OTC antitussives, but none included an interaction with monoamine oxidase inhibitor (MAOI) drugs. These drugs, which inhibit monoamine oxidase (MAO), are available by prescription only. They are primarily used to treat depression or high blood pressure.

At the time of the Panel's review, the only known interaction with MAOI drugs that was pertinent to cough-cold drug products involved the sympathomimetic amines, which are used as bronchodilators (41 FR 38312 at 38370 to 38371) and nasal decongestants (41 FR 38312 at 38396 to 38397). The Panel proposed the following labeling for bronchodilator drug products containing sympathomimetic amines: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor." The Panel proposed the same labeling for oral nasal decongestant drug products containing sympathomimetic amines but added the following words at the end of the above statement: "except under the advice and supervision of a physician."

In the tentative final monograph for OTC bronchodilator drug products, published in the Federal Register of October 26, 1982 (47 FR 47520 at 47526), the agency proposed to simplify the precautionary statement as follows: "*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 also is appropriate for oral dosage forms. This statement appears in § 341.76(c)(4) of the final monograph.

In the tentative final monograph for OTC nasal decongestant drug products, published in the Federal Register of January 15, 1985 (50 FR 2220 at 2231), the agency proposed the same precautionary statement as proposed in the tentative final monograph for OTC bronchodilator drug products. (See proposed § 341.80(c)(1)(i)(d).) A final monograph for OTC nasal decongestant drug products has not been published to date.

Although some information on dextromethorphan-MAOI drug interactions was present in the literature (see below), neither the Panel nor the agency was aware of this information, and the subject of such interactions did not arise during the course of the rulemaking for OTC antitussive drug products. Since publication of the final monograph for OTC antitussive drug products on August 12, 1987 (52 FR 30042), the agency has received information that it believes supports the need for a MAOI drug interaction precaution statement in the labeling of OTC drug products containing the ingredient dextromethorphan or dextromethorphan hydrobromide (hereafter referred to generally as dextromethorphan). This information includes reports of adverse reactions, including fatalities, following the ingestion of prescription MAOI drugs and OTC drug products containing dextromethorphan.

Rivers and Horner (Ref. 1) described the death of a 26-year-old female which they believed resulted from a reaction between the drug phenelzine (an MAOI) and dextromethorphan. The woman had been taking phenelzine 15 milligrams (mg) four times daily for 1 month. In the event that led to her death, she had taken 30 mg because she had missed an earlier dose. About 6 hours later she ingested approximately 2 ounces of a cough preparation containing dextromethorphan. Her initial symptoms of the interaction were nausea, dizziness, and collapse. She was brought to the hospital within an hour and was severely hypotensive; her systolic pressure did not rise above 70 millimeters (mm) of mercury. Her temperature varied from 42 °C to 42.2 °C. Four hours and 15 minutes after arriving at the hospital she had a cardiac arrest and died.

Shamsie and Barriga (Ref. 2) reported that a 15-year-old female died of adrenergic crisis after taking capsules containing dextromethorphan hydrobromide 15 mg, phenindamine tartrate 6.25 mg, phenylephrine hydrochloride 5 mg, and acetaminophen 120 mg per capsule while she was being treated for depression with the MAOI drug phenelzine. She had been taking phenelzine 15 mg three times a day for 6 weeks before she took the dextromethorphan. She was also taking thioridazine 25 mg three times a day and 15 mg at bedtime, procyclidine 5 mg twice daily, and metronidazole suppositories for vaginal discharge. She had taken eight capsules of the dextromethorphan compound initially, followed by another five capsules 3 hours after. Prior to her transfer to the hospital, her vital signs were a temperature of 103 °F, blood pressure of

100/60, pulse approximately 160 and strong, with a pulse deficit of 20. Her lungs were clear and her abdomen was soft. A neurological examination revealed bilateral fixed and dilated pupils, absent gag reflex, mild spasticity, and hyperreflexia of the upper limbs. While in the ambulance she became semicomatose and mildly cyanotic and started to show signs of trismus (spasm of the masticatory muscles). She was given oxygen and external cardiac massage. She arrived at the hospital in coma; resuscitation efforts were performed for 55 minutes but to no avail. The autopsy report showed the following: acute cerebral edema with mild tonsillar and uncal notching; marked acute pulmonary edema; petechiae of the epicardium thymus, and gastric mucosa; hemohydrothorax (left 100 milliliters (mL), right 20 mL); and, evidence of fresh thoracotomy (open cardiac massage). Histopathological examination showed acute passive congestion of the kidneys and liver; a granuloma of the right middle lobe of lung; obsolete granulomata of left pulmonary hilar lymph nodes; mild plasmatic vasculosis of splenic arteries; and mild follicular lipidosis of the spleen.

Sovner and Wolfe (Ref. 3) reported an interaction between dextromethorphan and the MAOI drug isocarboxazid. In this case, a 32-year-old woman with a history of chronic atypical depression had been taking isocarboxazid 30 mg daily for 8 weeks, then ingested diazepam 1 mg and 10 mL of a cough syrup containing dextromethorphan hydrobromide 15 mg and guaifenesin 100 mg per 5 mL. Twenty minutes later she was nauseated and dizzy. Within 45 minutes, a fine bilateral leg tremor and muscle spasms of the abdomen and lower back developed. These were followed by bilateral and persistent myoclonic jerks of the legs, occasional choreoathetoid movements of the feet, and marked urinary retention. Nineteen hours after ingesting the cough suppressant, her condition had greatly improved. At followup 2 months later, occasional myoclonic jerks persisted.

Harrison et al. (Ref. 4) reported two cases of interactions between MAOI drugs and OTC drug products containing dextromethorphan. In one case, a 26-year-old depressed woman who was taking phenelzine 60 mg daily ingested 10 mL of a cough syrup containing guaifenesin 300 mg, phenylpropanolamine 37.5 mg, and dextromethorphan hydrobromide 30 mg per 15 mL. She had a hypertensive reaction (systolic blood pressure of 210 mm of mercury and diastolic of 130 mm of mercury) that was treated without sequelae. In the other case, a 35-year-old woman who was taking phenelzine also took two tablets of an OTC drug product containing acetaminophen 325 mg, chlorpheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 15 mg per tablet. She developed a severe hypertensive reaction with intracerebral bleeding. No other information was provided. The authors recommended that manufacturers of OTC drug products provide consumers of those products more complete product information, including specific warnings against concomitant use of certain products containing MAOI drugs.

Laird (Ref. 5) reported an interaction that occurred in a 54-year-old woman who had taken phenelzine for 3 weeks prior to taking an OTC drug product containing dextromethorphan. Exact dosages were not provided. The patient was placed in an intensive care unit in critical condition; she ultimately recovered.

Nine other adverse interactions between MAOI drugs and dextromethorphan have been reported to the agency. In one case (Ref. 6), a woman being treated for major depression with tranylcypromine sulfate took 10 mL of an OTC drug product containing dextromethorphan 15 mg and guaifenesin 100 mg per 5 mL and experienced psychotic episodes. The dextromethorphan cough mixture was discontinued while tranylcypromine was continued. Symptoms abated and the condition resolved. In another case (Ref. 7), a 65-year-old female being treated with phenelzine took one OTC cough lozenge containing 5 mg dextromethorphan. Shortly afterward, she became drowsy and exhibited bizarre behavior. She was admitted to a hospital emergency room where behavior, physical examination, and vital signs were within normal limits. She recovered and was released the next morning. In another case (Ref. 8), a 61-year-old man had been taking 10 mg isocarboxazid four times a day for an undetermined number of years. Concomitant medications were chlorpropamide for diabetes and prednisone and naproxen for arthritis. Dosages were not stated. Approximately 1 day after consuming a dextromethorphan-containing cough mixture, the man was taken to a hospital emergency room in an unresponsive state. Two days later, the man was alert, but exhibited severe myoclonic movements of both legs and was severely diaphoretic. Isocarboxazid was discontinued. On the following day, the man was almost completely recovered, with residual slight tremor of the hands. Approximately 16 days after the onset of the reaction, the man was discharged from the hospital and his problem was completely resolved. Another case (Ref. 9) described a phenelzine sulfate-dextromethorphan polistirex interaction in an adult woman that was characterized by accelerated heart rate, increased blood pressure, and loss of strength in the legs. No additional information was provided. Dosages, duration of therapy, duration of reaction, and final outcome are unknown. In another case (Ref. 10), a 32-year-old woman on phenelzine therapy for depression became lethargic and unresponsive approximately 45 minutes after taking an unstated amount of a guaifenesin-dextromethorphan hydrobromide cough mixture. The woman was taken to an emergency room and found to be unarousable and in a coma. This state continued for approximately 12 hours. With supportive medical care (unspecified), the woman subsequently recovered and was discharged. In another case (Ref. 11), a 42-year-old man had taken 52.5 to 60 mg phenelzine daily for approximately 1 month. Other drugs used concomitantly were 100 mg trazodone at bedtime, 0.25 mg levothyroxine, and 10 mg prednisone per day. Within 15 minutes of taking 10 to 15 mL of a guaifenesin-dextromethorphan cough mixture, the man developed shaking, diaphoresis, and elevated temperature and respiration rate. The man was admitted to an intensive care unit where treatment consisted of intravenous fluids, cooling blanket, and four doses of dantrolene at 0.6 mg per kilogram (kg) per dose. The ultimate outcome of this case was not reported. In another case (Ref. 12), a 28-year-old woman who had been taking phenelzine for depression and bulimia (and propoxyphene napsylate with acetaminophen) took 5 to 10 mL of a cough mixture containing 30 mg iodinated glycerol and 10 mg dextromethorphan hydrobromide per 5 mL. Approximately 30 minutes later, the woman experienced abdominal cramps, wheezing, tightness in the chest, and appeared panicky and stimulated. Symptoms persisted for 30 to 60 minutes. In another case (Ref. 13), a 20-year-old woman had taken phenelzine for several months when she took one dose of a cough mixture containing dextromethorphan. Shortly thereafter, the woman was admitted to an emergency room with tachycardia, diaphoresis, muscular rigidity, temperature of 101 °F, and blood

pressure of 130/90. Treatment involved unspecified doses of valium and labetalol; the hospital course was uneventful, and the woman recovered and was discharged. In another case (Ref. 14), a 28-year-old woman being treated for depression had taken tranylcypromine sulfate, 20 mg every morning and 10 mg every evening, for 3 years without adverse reaction. Minutes after ingesting 20 mL of a cough suppressant containing 7.5 mg dextromethorphan hydrobromide per 5 mL, the woman experienced shakiness and diaphoresis. The woman was admitted to an emergency room with dilated pupils, shaking, hallucinations, temperature of 99.3 °F, pulse 84, blood pressure 132/88, and respiration rate 20. Treatment involved the use of diazepam and diphenhydramine intravenously. The woman remained in the intensive care unit for 12 hours (vital signs were stable throughout this time) and then was released. Based upon these reports, the agency has revised the labeling of the prescription antidepressant MAOI drugs isocarboxazid, phenelzine, and tranylcypromine to include the following statement: "The combination of MAOI inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior" (Ref. 15).

In addition, the agency is aware of a study by Sinclair (Ref. 16) in which he examined the effects of dextromethorphan in MAOI-pretreated rabbits. New Zealand white rabbits of both sexes were treated with phenelzine sulfate 30 mg per kg intraperitoneally, pargyline hydrochloride 40 mg per kg intraperitoneally, and nialamide hydrochloride 50 mg per kg intraperitoneally, on 2 successive days. On the following day, the animals were monitored for temperature, and when the temperature was stable for 30 minutes, dextromethorphan 5 mg per kg was slowly administered via a marginal ear vein. Dextromethorphan produced motor restlessness, shivering-like tremors, hyperexcitability, dilated pupils, tachypnea, and hyperpyrexia in phenelzine-pretreated rabbits. Five of seven rabbits died within 1 hour of being given dextromethorphan. The same dose of dextromethorphan in rabbits that were not pretreated with phenelzine produced none of the signs exhibited in the pretreated rabbits. A lower dose of 3 mg per kg dextromethorphan produced similar but generally less intense symptoms of the interaction that occurred in phenelzine-pretreated rabbits. One of four rabbits receiving this dose exhibited a 3 °C rise in temperature and death. Animals pretreated with pargyline succumbed to the interaction when challenged with dextromethorphan less consistently than did phenelzine-pretreated animals. One hour after the dextromethorphan injection, the mean temperature increase in pargyline-pretreated animals was 0.38 °C + 0.48 °C. However, two of the seven animals tested died. Nialamide-pretreated rabbits developed intense symptoms of the interaction when dextromethorphan was administered. The mean temperature increase in these animals at one hour was 3.78 °C + 0.03 °C, and all four animals died.

A number of other authors and general references warn of MAOI-dextromethorphan interactions (Refs. 17 through 22). Reactions described in these sources include central nervous system stimulation, hyperpyrexia (a highly elevated body temperature), hypertension (abnormally high blood pressure), hypotension (abnormally low blood pressure), peripheral vascular collapse, and possible death.

Magurno and Board (Ref. 23) report that one manufacturer has, of its own volition, included an MAOI warning in the "Drug Interaction Precautions" section of its physician labeling (information provided to health care professionals but not to the general public) for its antitussive products that contain dextromethorphan. That warning states: "Serious toxicity may result if dextromethorphan is used with MAOIs." (See Ref. 24.) The authors report that while most patients do not see this specific contraindication, the manufacturer has also added a "Drug Interaction Precaution" to the immediate (consumer-purchased) containers of these products. This precaution states: "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 Ref. 24.) This is the same drug interaction precaution statement proposed in the tentative final monographs for OTC bronchodilator and OTC oral nasal decongestant drug products. (See discussion above.)

The agency is aware of a resurgence in the use of MAOI drugs after a period of decline in the 1970's (Refs. 21, 22, and 25). 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 or atypical depression (Refs. 19, 25, and 26). There is evidence that MAOI drugs are also being used to treat bulimia and panic disorders (Refs. 4, 19, 25, 27, and 28), phobic disorders (Refs. 19, 25, 26, and 27), anxiety (Refs. 19, 25, and 26), and obsessive compulsive disorder (Refs. 25 and 28). 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 and proposed for OTC oral nasal decongestant 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. 4 and 19). 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.

The agency tentatively concludes that there is sufficient evidence of serious MAOI-dextromethorphan drug interactions that a drug interaction precaution statement is needed in the labeling of OTC drug products

containing dextromethorphan. Accordingly, the agency is proposing to amend the final monograph for OTC antitussive drug products to require an MAOI drug interaction precaution statement in the labeling of OTC drug products containing dextromethorphan by adding new § 341.74(c)(4)(v) for oral antitussives to read: "*For products containing dextromethorphan or dextromethorphan hydrobromide as identified in § 341.14(a)(3) and (a)(4) when labeled for adults or for adults and children under 12 years of age. 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." The agency is also proposing to require the MAOI drug interaction precaution statement in the labeling of OTC drug products containing dextromethorphan or dextromethorphan hydrobromide when labeled for children by adding new § 341.74(c)(4)(vi) for oral antitussives to read: "*For products containing dextromethorphan or dextromethorphan hydrobromide as identified in § 341.14(a)(3) and (a)(4) when labeled only for use by children under 12 years of age. Drug Interaction Precaution.* Do not give this product to a child who is taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression or psychiatric or emotional conditions), without first consulting the child's doctor. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product." The agency is inviting comment on the specific wording of these warnings, 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) Rivers, N., and B. Horner, "Possible Lethal Reaction Between Nardil and Dextromethorphan," *Canadian Medical Association Journal*, 103:85, 1970.

(2) Shamsie, S. J., and C. Barriga, "The Hazards of Use of Monoamine Oxidase Inhibitors in Disturbed Adolescents," *Canadian Medical Association Journal*, 104:715, 1971.

(3) Sovner, R., and J. Wolfe, "Interaction Between Dextromethorphan and Monoamine Oxidase Inhibitor Therapy With Isocarboxazid," *The New England Journal of Medicine*, 319:1671, 1988.

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

(5) Letter from R. D. Laird, M.D., to A. J. Mustafa, FDA, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(6) Case Report No. 458131, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(7) Case Report No. 414881, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(8) Case Report No. 338049, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(9) Case Report No. 489170, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(10) Case Report No. 468738, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(11) Case Report No. 491372, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(12) Case Report No. 507638, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(13) Case Report No. 548005, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(14) Case Report No. 637761, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(15) Approved labeling for isocaboxazid (Hoffman-La Roche Laboratories), phenelzine sulfate (Parke-Davis), and tranylcypromine sulfate (SmithKline & French Laboratories), and letters from P. Leber, FDA, to above firms, in OTC Vol. 04TFMA2, Docket No. 90N–0420, Dockets Management Branch.

(16) Sinclair, J. G., "Dextromethorphan-Monoamine Oxidase Inhibitor Interaction in Rabbits," *Journal of Pharmacy and Pharmacology*, 25:803–808, 1973.

(17) Clayman, C. B., editor, "The American Medical Association Guide to Prescription and Over-the-Counter Drugs," Random House, Inc., New York, p. 307, 1988.

(18) Cardinale, V. A., editor, "Drug Topics Red Book," 92d ed., Medical Economics Co., Inc., Oradell, NJ, p. 35, 1988.

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

(20) "USP Dispensing Information—1989," 9th ed., the United States Pharmacopeial Convention, Inc., Rockville, MD, Vol. 1A, pp. 309–314.

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

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

(23) Magurno, J. A. J., and A. W. Board, "MAOIs, OTC Drugs, and Hypertensive Crisis," *The Journal of Clinical Psychiatry*, 51:212–213, 1990.

(24) "Physicians' Desk Reference For Nonprescription Drugs," 11th ed., Medical Economics Co., Inc., Oradell, NJ, pp. 656 and 660–661, 1990.

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

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

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

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

The agency is proposing that these revised drug interaction precautions become effective 12 months after the date of publication of the final rule in the **Federal Register**. Manufacturers of OTC antitussive 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 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 for OTC antitussive drug products is not expected to pose such an impact on small businesses. The only

action needed will be a labeling revision 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 antitussive drug products. Comments regarding the impact of this rulemaking on OTC antitussive 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 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 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 received 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 341.74 is amended by adding new paragraphs (c)(4)(v) and (c)(4)(vi) to read as follows:

§ 341.74 Labeling of antitussive drug products.

* * * * *

(c) * * *

(4) * * *

(v) *For products containing dextromethorphan or dextromethorphan hydrobromide identified in § 341.14(a)(3) and (a)(4) when labeled for adults or for adults and children under 12 years of age.* "*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."

(vi) *For products containing dextromethorphan or dextromethorphan hydrobromide identified in § 341.14(a)(3) and (a)(4) when labeled only for children under 12 years of age.* "*Drug Interaction Precaution.* Do not give this product to a child who is taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression or psychiatric or emotional conditions), without first consulting the child's doctor. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product."

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Dated: March 18, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

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BILLING CODE 4160-01-F