

§ 201.304

the Federal Food, Drug, and Cosmetic Act any drug containing more than 5 percent methyl salicylate (wintergreen oil), the labeling of which fails to warn that use otherwise than as directed therein may be dangerous and that the article should be kept out of reach of children to prevent accidental poisoning.

(c) This statement of interpretation in no way exempts methyl salicylate (wintergreen oil) or its preparations from complying in all other respects with the requirements of the Federal Food, Drug, and Cosmetic Act.

§ 201.304 Tannic acid and barium enema preparations.

(a) It has become a widespread practice for tannic acid to be added to barium enemas to improve X-ray pictures. Tannic acid is capable of causing diminished liver function and severe liver necrosis when absorbed in sufficient amounts. The medical literature reports a number of deaths associated with the addition of tannic acid to barium enemas. There is a lack of scientific evidence to establish the conditions, if any, under which tannic acid is safe and effective for use in enemas. Tannic acid for rectal use to enhance X-ray visualization is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act.

(b) In view of the hazards involved when tannic acid is used in barium enemas, any shipments of tannic acid labeled to come within the exemptions under 502(f) of the Act containing such phrases as: "Caution: For manufacturing, processing, or repackaging," "For prescription compounding," or "Diagnostic reagent—For professional use only" will be regarded by the Commissioner of Food and Drugs as misbranded within the meaning of section 502(f) of the Federal Food, Drug, and Cosmetic Act unless the label and the labeling bear conspicuously a warning to the effect: "Warning—Not for use in enemas."

(c) Any tannic acid intended for use by man and found within the jurisdiction of the Federal Food, Drug, and Cosmetic Act labeled contrary to this section after 60 days from the date of its publication in the FEDERAL REG-

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ISTER may be made the subject of regulatory proceedings.

§ 201.305 Isoproterenol inhalation preparations (pressurized aerosols, nebulizers, powders) for human use; warnings.

(a) Accumulating reports have been received by the Food and Drug Administration and have appeared in the medical literature of severe paradoxical bronchoconstriction associated with repeated, excessive use of isoproterenol inhalation preparations in the treatment of bronchial asthma and other chronic bronchopulmonary disorders. The cause of this paradoxical reaction is unknown; it has been observed, however, that patients have not responded completely to other forms of therapy until use of the isoproterenol inhalation preparation was discontinued. In addition, sudden unexpected deaths have been associated with the excessive use of isoproterenol inhalation preparations. The mechanism of these deaths and their relationship, if any, to the cases of severe paradoxical bronchospasm are not clear. Cardiac arrest was noted in several of these cases of sudden death.

(b) On the basis of the above information and after discussion with and concurrence of the Respiratory and Anesthetic Drugs Advisory Committee for Food and Drug Administration, the Commissioner of Food and Drugs concludes that in order for the labeling of such drugs to bear adequate information for their safe use, as required by § 201.100, such labeling must include the following:

Warning: Occasional patients have been reported to develop severe paradoxical airway resistance with repeated, excessive use of isoproterenol inhalation preparations. The cause of this refractory state is unknown. It is advisable that in such instances the use of this preparation be discontinued immediately and alternative therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn.

Deaths have been reported following excessive use of isoproterenol inhalation preparations and the exact cause is unknown. Cardiac arrest was noted in several instances.

(c)(1) The Commissioner also concludes that in view of the manner in

which these preparations are self-administered for relief of attacks of bronchial asthma and other chronic bronchopulmonary disorders, it is necessary for the protection of users that warning information to patients be included as a part of the label and as part of any instructions to patients included in the package dispensed to the patient as follows:

Warning: Do not exceed the dose prescribed by your physician. If difficulty in breathing persists, contact your physician immediately.

(2) The warning on the label may be accomplished (i) by including it on the immediate container label with a statement directed to pharmacists not to remove the label or (ii) by including in the package a printed warning with instructions to pharmacists to place the warning on the container prior to dispensing.

(d) The marketing of isoproterenol inhalation preparations may be continued if all the following conditions are met:

(1) Within 30 days following the date of publication of this section in the FEDERAL REGISTER:

(i) The label and labeling of such preparations shipped within the jurisdiction of the act are in accordance with paragraphs (b) and (c) of this section.

(ii) The holder of an approved new-drug application for such preparation submits a supplement to his new-drug application to provide for appropriate labeling changes as described in paragraphs (b) and (c) of this section.

(2) Within 90 days following the date of publication of this section in the FEDERAL REGISTER, the manufacturer, packer, or distributor of any drug containing isoproterenol intended for inhalation for which a new-drug approval is not in effect submits a new-drug application containing satisfactory information of the kinds required by § 314.50 of this chapter, including appropriate labeling as described in paragraphs (b) and (c) of this section.

(3) The applicant submits additional information required for the approval of the application as may be specified in a written communication from the Food and Drug Administration.

(e) After 270 days following expiration of said 90 days, regulatory proceedings based on section 505(a) of the Federal Food, Drug, and Cosmetic Act may be initiated with regard to any such drug shipped within the jurisdiction of the act for which an approved new-drug application is not in effect.

[40 FR 13998, Mar. 27, 1975, as amended at 55 FR 11576, Mar. 29, 1990]

§ 201.306 Potassium salt preparations intended for oral ingestion by man.

(a) The Food and Drug Administration will initiate no regulatory action with respect to the continued marketing of coated tablets containing potassium chloride or other potassium salts which supply 100 milligrams or more of potassium per tablet provided all the following conditions are met:

(1) Within 30 days from the date of publication of this statement of policy in the FEDERAL REGISTER:

(i) The labeling of the drug bears the prescription caution statement quoted in section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act;

(ii) The labeling on or within the package from which the drug is to be dispensed bears adequate information for its use by practitioners in accord with the "full disclosure" labeling requirements of § 201.100 of this chapter, including the following warning statement:

Warning—There have been several reports, published and unpublished, concerning non-specific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics. These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required and deaths have occurred. Based on a large survey of physicians and hospitals, both United States and foreign, the incidence of these lesions is low, and a causal relationship in man has not been definitely established. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered