

§ 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