DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 328

[Docket No. 93N–0107]

Over-the-Counter Drug Products Intended for Oral Ingestion That Contain Alcohol

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would establish a maximum concentration limit for alcohol (ethyl alcohol) as an inactive ingredient in over-the-counter (OTC) drug products intended for oral ingestion (0.5 percent alcohol for children under 6 years of age, 5 percent alcohol for children 6 to under 12 years of age, and 10 percent alcohol for anyone 12 years of age and over). In addition, the proposal requires that the alcohol content be stated conspicuously or prominently on the principal display panel (front) of product labeling. FDA is issuing this notice of proposed rulemaking after considering recommendations from its OTC Drugs Advisory Committee (the Committee).

DATES: Written comments by January 19, 1994. Written comments on the agency's economic impact determination by January 19, 1994. The agency is proposing that any final rule that may issue based on this proposal become effective 12 months after the date of publication 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, 7520 Standish Place, Rockville, MD 20855, 301–594–5000.

SUPPLEMENTARY INFORMATION: Alcohol is present as an inactive ingredient (e.g., solvent, preservative) in many different types of OTC drug products that are orally ingested: Analgesic, cough-cold, laxative, menstrual, and other drug products. The use of alcohol in those products has been discussed in several rulemakings for OTC drug products, with the majority of the discussion in the rulemaking for OTC cough-cold drug products.

I. Rulemaking for OTC Cough-Cold Drug Products

The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel) took the position that medications administered to children should contain either a minimum amount of alcohol or none at all. (See the **Federal Register** of September 9, 1976, 41 FR 38312 at 38333.) The Panel concluded that alcohol in pediatric formulations should be maintained at the lowest possible concentration, that products should be formulated without alcohol if pharmaceutically possible, and that cough-cold drug products containing alcohol greater than 10 percent weight-to-weight should not be given to children under 6 years of age except under the advice and supervision of a physician.

Subsequently, FDA asked the American Academy of Pediatrics Committee on Drugs (AAP/CD) to evaluate the use of alcohol in OTC drug products for children. The AAP/CD stated that ideally medicinal products intended for use in children should contain no alcohol. However, if alcohol is required to solubilize the active ingredients in a product intended for use in children, the AAP/CD made the following recommendations to FDA: (1) OTC liquid preparations should be limited to a maximum of 5 percent volume-to-volume alcohol, (2) physician supervision is suggested for children less than 6 years of age who use OTC preparations containing alcohol, (3) the amount of alcohol contained in any medicinal preparation should not be capable of producing a blood alcohol concentration greater than 25 milligrams (mg) per 100 milliliters (mL) after a single recommended dose, (4) appropriate intervals between doses should be prescribed to prevent the accumulation of blood alcohol, (5) the packaged volume of alcohol-containing products should be kept to a reasonable minimum to prevent potential lethal ingestions, and (6) safety closures should be used for medications with greater than a 5-percent alcohol content (Ref. 1). The AAP/CD concluded that pediatricians and other health care providers should be aware of the widespread presence of alcohol in liquid medications and its potential toxicity. The AAP/CD recommended that continued efforts be made to remove alcohol from liquid preparations intended for children.

In the tentative final monograph for OTC cough-cold combination drug products, the agency stated that it was considering adopting the AAP/CD recommendations and invited public comment. (See the **Federal Register** of August 12, 1988, 53 FR 30522 at 30528 and 30529.) The agency cited data in support of the proposition that alcohol depresses the central nervous system over a wide range of doses, that threshold effects are observed at blood levels of 20 to 50 mg per 100 mL, and that a detectable impairment of vision occurs at a blood level of about 15 mg per 100 mL (Ref. 2).

In response, the Nonprescription Drug Manufacturers Association (NDMA) objected to many of the AAP/CD recommendations. NDMA contended that alcohol has a number of legitimate uses in formulating OTC drug products, that it: (1) Enhances flavor, (2) provides palatability to distasteful ingredients, especially those extracted from natural sources, (3) acts as an effective preservative against microbial growth and chemical change, (4) enhances the antimicrobial potency of other preservatives that may be needed in a product, (5) maintains stability more effectively with less added volume than water-miscible alternatives, and (6) is less toxic than most alternative solvents. NDMA contended that AAP/CD's recommendation of a 5-percent alcohol limit is unduly restrictive in relation to the dose and package volumes of current OTC drug products. NDMA concluded that the alcohol limit proposed by AAP/CD would not appear to offer greater safety to children when OTC drug products are taken at recommended doses or accidentally ingested.

The agency subsequently received letters from groups concerned about the presence of alcohol in OTC drug products (Refs. 3, 4, and 5). The American Psychiatric Association (Ref. 3) suggested that the agency minimize the alcohol content in medicines. The National Council on Alcoholism and Drug Dependence, Inc. (Ref. 4) stated that drug products should contain only the amount of alcohol that is minimally necessary, as determined solely by the physical and chemical characteristics of the medication. The Consumer Protection Board of the State of New York (Ref. 5) urged the agency to determine whether manufacturers of alcohol-containing OTC drug products could obtain the same results without the use of alcohol.

The subject of alcohol in OTC drug products was also discussed in the final monograph for OTC antihistamine drug products (57 FR 58356, December 9, 1992). This monograph includes warnings in § 341.72(c)(3) (21 CFR 341.72(c)(3)) that advise consumers to avoid alcoholic beverages while taking

products containing any of the following antihistamines: Brompheniramine maleate, chlorcyclizine hydrochloride, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, diphenhydramine citrate, diphenhydramine hydrochloride, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride. Those warnings advise that the product may cause drowsiness and that alcohol may increase the drowsiness effect.

II. The OTC Drugs Advisory Committee Meeting

Because of the concerns discussed above, the agency asked its OTC Drugs Advisory Committee to advise the agency on the appropriate alcohol content of OTC drug products. On December 17, 1992 (Ref. 6), the Committee was presented information on the following topics: Types of OTC drug products that contain alcohol, the pharmaceutical role of alcohol, the pharmacokinetics and pharmacodynamics of alcohol, numerous safety issues concerning alcohol and its use in OTC drug products, possible alcohol content limitations, and nonalcohol formulation alternatives. The Committee considered the benefits and risks of alcohol in OTC drug products and whether limits should be placed on the alcohol concentration in these products. The Committee discussed the bases for alcohol content limitations and sought to determine whether there should be differences in requirements for products intended to be used by consumers of different ages: (1) Under the age of 6 years, (2) age 6 to under 12 years, (3) for adult use (over 12), and (4) for use by the elderly. The Committee considered whether alcohol in OTC drug products contributes significantly to alcohol abuse, what effect it has on alcoholics and children of alcoholics, and what specific actions could be recommended to reduce any risks. The Committee also addressed the pharmaceutical uses of alcohol in OTC drug products and possible alternative solvents or vehicles.

A transcript (Ref. 6) containing the various presentations and the Committee's discussion is on public display in the Dockets Management Branch (address above). A summary of the presentations and discussion follows.

Alcohol has been well recognized as a pharmaceutical excipient and is most commonly used as a solvent in the formulation of oral drug products. Certain drugs are insoluble in water and must be delivered in an alternate vehicle. Alcohol is the preferred solvent because of its high relative ability to dissolve many water-insoluble ingredients, including flavors used in OTC drug products. Alcohol is also used with other solvents, such as glycols and glycerin, to reduce the amount of solvent needed in a product. Alcohol increases the antimicrobial activity of glycol solvents. Alcohol is also used as a preservative to ensure stability, and as a copreservative in conjunction with parabens, benzoates, sorbates, or ethylenediaminetetraacetic acid to broaden and enhance the antimicrobial activity of the preservative system. For example, alcohol shows less pH dependency than the benzoates and parabens and, as a copreservative, makes antimicrobial activities of parabens and benzoates less dependent on the product's pH. Thus, the alcohol-benzoate or alcohol-paraben preservative system can be used in a broader range of products than benzoate or paraben preservatives alone. At a 10-percent concentration, alcohol prevents inactivation of parabens by nonionic surfactants.

Although alcohol offers certain advantages in formulation, as discussed above, one Committee member noted that it is not an absolute pharmaceutical necessity. Glycerin, polyethylene glycol, and propylene glycol can be used as substitutes. However, these other ingredients lack the solvent power of alcohol. Polyethylene glycol and propylene glycol are on FDA's Generally Recognized As Safe (GRAS) list of food additive ingredients. However, ingestion of large amounts of propylene glycol has resulted in lactic acidosis (increased blood lactic acid concentrations). Also, when propylene glycol is eliminated from the body, isopropyl alcohol is a metabolic byproduct. When excess amounts of glycerin are ingested, hyperosmolar nonketotic coma, diabetic acidosis, pulmonary edema, and minor symptoms of headache, nausea, vomiting, and dizziness can occur.

The pharmacokinetics and pharmacodynamic effects of alcohol were discussed by the Committee. Alcohol at significant blood concentration levels exhibits zero order (or saturable) pharmacokinetics, i.e., the quantity of alcohol elimination per unit of time is constant and is not proportional to the concentration of alcohol in the body. Alcohol does not have a defined half-life because the half-life changes according to the quantity of alcohol remaining in the body. The amount of alcohol does not decrease by a constant fraction per unit time, but decreases by a constant amount per unit time. Zero order pharmacokinetics can create a blood alcohol concentration that is no longer proportional to the dose, i.e., a small increase in dose may have a large increase in the blood alcohol concentration. One Committee member stated that several studies have shown that there is little difference in alcohol pharmacokinetics for the geriatric population. Also, there is insufficient scientific data in the literature to demonstrate the pharmacokinetics of alcohol in the pediatric population.

In acute alcohol intoxication, lactic acidosis develops, with hypoglycemia occurring in some people. These effects pose a serious toxicologic problem, especially in children who consume alcohol-containing products. The principal action of alcohol is central nervous system depression. As increasing levels of depression occur, changes in perception and motor incoordination occur and, finally, coma and loss of dependent reflexes can occur. Different effects occur as the blood alcohol concentration increases: At 50 mg per deciliter (dL), some motor function impairment occurs; at about 80 mg per dL, the motor impairment becomes very evident; at about 200 mg per dL, significant central nervous system depression occurs; at 400 mg per dL, respiratory failure can occur. Death can occur due to respiratory failure or as a result of pulmonary aspiration of gastric contents.

Individuals can vary greatly in their sensitivity to alcohol, i.e., in the concentration that produces a particular intensity of effect. Individuals who have developed a tolerance to alcohol will experience a less intense effect at a particular concentration than normal, nontolerant individuals.

Other effects of alcohol are cutaneous vasodilation (a relatively small effect on the cardiovascular system), withdrawal syndrome, stimulation of gastric acid secretion, and stomach irritation. Alcohol is a teratogen. Fetal alcohol syndrome has been well described in babies of women who consume large amounts of alcohol during certain stages of pregnancy.

A number of studies have correlated alcoholism with age, sex, race, drinking pattern, socioeconomic status, family history, genetic factors, environmental factors, consumption, and cirrhosis mortality and morbidity. A large number of case reports on hepatic and renal injury have involved simultaneous use of alcohol and OTC drugs, particularly acetaminophen. Large doses of acetaminophen (greater than recommended in labeling) taken with

alcohol can produce potentially fatal hepatic and renal necrosis. Data from studies in monkeys suggest that alcohol increases the reinforcing effects of other drugs in terms of implications for human behavior and increased liability for abuse. Alcoholics are known to drink mouthwashes that contain alcohol, and it is not unusual for individuals in addiction treatment programs to use OTC medications that are formulated with alcohol as a source of alcohol.

Children's exposure to medicines having a high alcohol content raises special concerns. However, one Committee member noted that there are little data on the use of alcohol in children, probably because alcohol intake is not legal in children or in young adults under 18 to 21 years of age. In March 1984, the AAP/CD (Ref. 1) established that a child's blood alcohol concentration should not exceed 25 mg per dL following a single dose of alcohol-containing medication. The AAP/CD estimated the volumes (mL) of alcohol preparations predicted to produce a blood alcohol concentration of 25 mg/dL in different aged children, as stated in the following chart:

ESTIMATED VOLUMES (mL) OF ALCOHOL PREPARATION REQUIRED TO PRODUCE A BLOOD ALCOHOL CONCENTRATION OF 25 MG PER DL

Percent absolute ethanol (v/v) in product	Age (weight)					
	2 yr (12 kg)	4 yr (16 kg)	6 yr (21 kg)	8 yr (27 kg)	10 yr (32 kg)	12 yr (38 kg)
2.5	91	122	160	205	243	289
5.0	46	61	80	103	122	144
7.5	30	41	53	68	81	96
10.0	23	30	40	51	61	72
12.5	18	24	32	41	49	58
20.0	11	15	20	26	30	36
25.0	9	12	16	21	24	29

These figures are based on data taken from adults and, therefore, are strictly hypothetical with respect to children. Nonetheless, after this paper was published, many manufacturers voluntarily reduced the amount of alcohol in their products. The AAP/CD report did not endorse the use of alcohol in orally ingested OTC drug products intended for use in children. The report stated that it was desirable to have no alcohol in medicinal products intended for use in children and recommended that a continued effort be made to remove alcohol from these products.

It was noted by one Committee member that the concentration of alcohol in OTC drug products was not as much a concern as the palatability of the product and the willingness of a child to take the product. Once ingested, alcohol's effects are the same regardless of the source or vehicle. Between 1987 and 1991, 17,000 cases of ingestion of alcohol-containing mouthwashes were reported to poison control centers, with 39 cases experiencing major (life-threatening) effects. Several of these cases involved children, and there were four deaths, including one child. Out of 145,000 reported incidents involving alcohol in perfume, cologne, and aftershave, only 14 cases were classified as major, with no deaths reported.

According to NDMA, reports from the American Association of Poison Control Centers National Data Collection System showed no deaths in children less than 6 years of age due to accidental ingestion of alcohol-containing OTC drug products intended for oral ingestion. Data from poison control centers do not indicate a widespread acute intoxication problem from the accidental ingestion of alcohol in OTC drug products. For example, in a study monitored by the Maryland Poison Control Center, covering the period from June 1989 to June 1992, there was no major difference in adverse effects between products containing alcohol (10 to 25 percent) and alcohol-free products. No deaths, major effects, or moderate effects were reported. Most ingestions involving products containing alcohol were in the 2 ounce (oz) range, with the maximum ingestion reported being 4 oz in a slightly older child.

A representative from Canada stated that manufacturers of pediatric medications marketed in Canada are encouraged to use other suitable solvents, and they are required to justify the use of alcohol. When use can be justified, the concentration of alcohol should not exceed 5 percent volume-to-volume, with the amount of alcohol contained in the product not capable of producing a blood concentration greater than 25 mg per dL per dose, when taken as directed.

NDMA proposed to the Committee the following alcohol concentration limits for OTC monographed drug products intended for oral ingestion: 10 percent alcohol volume-to-volume for adults and children ages 12 and over, except in cases where higher concentrations of alcohol must be used (e.g., plant extracts); up to 5 percent volume-to-volume for children 6 to under 12 years of age, and alcohol-free products (defined as less than 0.5 percent alcohol) for children under 6 years of age (Ref. 7). These limits would be implemented by the OTC drug industry on a voluntary basis. The NDMA program also includes current agency required warnings (such as for antihistamines, as discussed above) and additional direction statements for OTC alcohol-containing drug products. According to NDMA, directions for use of products containing between 5 and 10 percent alcohol should convey that physician supervision is recommended for children under 12 years of age. For pediatric products with an alcohol concentration above 0.5 percent, directions for use should state that supervision of a physician is recommended for children under 6 years of age. NDMA member companies with affected OTC drug products intend to make these changes "as soon as practicable," with the goal of voluntary compliance for reformulating and labeling to the new 5- and 10-percent alcohol limitations targeted for November 1993. The goal for the reformulation and labeling of alcohol-free OTC drug products is December 1994.

Reference was made to the Cough-Cold Panel's recommendation that products containing alcohol 10 percent weight-to-weight, equivalent to about 12 to 13 percent volume-to-volume, not be given to children under 6 years of age, except under the advice and supervision of a physician. NDMA concluded that its proposed maximum alcohol concentration of 10 percent volume-to-volume is more conservative than that recommended by the Cough-Cold Panel.

The Committee members concluded that OTC drug products for oral ingestion should not contain more than the minimum amount of alcohol needed as a solvent for the active ingredient, for preservative purposes, or for taste enhancement.

The Committee agreed with NDMA's recommendations as follows:

1. For persons 12 years of age and above, a maximum alcohol concentration up to and including 10 percent volume-to-volume. (While the Committee members could not identify any specific data that showed a difference in safety between 5 and 10 percent concentrations of alcohol in products, they generally preferred that a lower concentration, closer to 5 percent, be used whenever possible.)

2. For children age 6 to under 12, a maximum alcohol concentration up to and including 5 percent volume-to-volume. (However, the Committee stated that a lower concentration, closer to 0.5 percent, should be used whenever possible.)

3. For children under 6 years of age, a maximum alcohol concentration up to and including 0.5 percent volume-to-volume.

The Committee recognized that metabolism and toxicity data in children under 12 years of age were lacking, but decided that these recommendations were reasonable and the best guidelines to follow at this time. For products intended for use in children under 6 years of age, the Committee recommended that only products containing no alcohol be labeled "alcohol free." Some Committee members felt that all products for use in children under 12 years of age should be alcohol free because a number of these products have been reformulated to remove the alcohol, which suggests that no alcohol is needed for the formulation of these products.

The Committee concluded that the only exception to the 10 percent maximum alcohol concentration should be those products that cannot be formulated with a 10 percent or lower alcohol concentration (e.g., plant extracts). The Committee recommended that such products obtain a special exemption from FDA based upon suitable justification.

The Committee also discussed where the alcohol content should be disclosed in the product's labeling, e.g., the principal display panel (front) or the product information panel (not usually the front). Several Committee members, who felt that the information should be conspicuous, favored placement of this information on the principal display panel. However, no formal vote was taken on this issue.

III. The Agency's Tentative Conclusions on the Committee's Recommendations

The agency agrees with the Committee's recommendations to limit the use of alcohol in OTC drug products. The agency has considered whether such limits should be voluntary, as suggested by NDMA. The agency is aware that a voluntary program may not involve all OTC drug manufacturers and their products. Further, a voluntary program would not be enforceable by the agency. Therefore, the agency is proposing that alcohol limitations and related labeling requirements for all OTC drug products intended for oral ingestion be implemented by regulation. These regulations would apply to OTC drug products regulated under the monograph system (21 CFR parts 330 to 358), and those approved under new drug applications.

The agency concurs with the Committee that OTC drug products for oral ingestion should not contain more than the minimum amount of alcohol needed as a solvent for the active ingredient, for preservative purposes, or for taste enhancement. In keeping with public health goals, the agency strongly encourages the lowest amount of alcohol necessary for pharmaceutical purposes to be used. Lower concentrations would help limit potential misuse of products for their alcohol content and reduce undesirable alcohol ingestions by adolescents. Therefore, a 5-percent alcohol concentration limit is preferred, even though no specific data have been presented to demonstrate a difference in safety between 5 and 10 percent alcohol in OTC drug products intended for oral ingestion.

However, in this document, based on the Committee's concurrence with NDMA's proposal for OTC drug products intended for oral ingestion that contain alcohol, the agency is proposing: (1) A 10-percent alcohol limit for OTC drug products intended for adults and children 12 years of age and over, (2) a 5-percent alcohol limit for OTC drug products intended for children 6 to under 12 years of age, and (3) a 0.5-percent alcohol limit for OTC drug products intended for children under 6 years of age. The agency invites specific comment on the proposed 10-percent maximum alcohol concentration, including specific data and reasons that might support lowering this concentration to a 5-percent limit.

The agency notes that NDMA suggested that products containing up to 0.5 percent alcohol be called "alcohol free." However, this designation would be misleading because it infers that the product contains no alcohol whatsoever. Individuals taking an alcohol-deterrent medication, such as disulfiram, could suffer untoward reactions by ingesting an alcohol-containing drug product labeled as "alcohol free" that actually contained a small amount of alcohol. Therefore, the agency is proposing that the term "alcohol free" mean that the product contains no alcohol at all. The agency also invites specific comment on this labeling term.

The agency agrees with the NDMA suggestion (see Section II of this document) that products containing alcohol include additional directions regarding supervised use by a physician when the product is used in children below a certain age. However, it is possible that these age limitations based on alcohol content may differ from age limitations based on other ingredients contained in the product that are included in an OTC drug monograph. Therefore, the agency is including a provision in the proposed regulation that if age limitation statements differ, the direction referring to the higher age limitation should be used. For example, for an OTC drug product containing the antihistamine ingredient diphenhydramine hydrochloride and 10 percent alcohol, the antihistamine monograph requires labeling for diphenhydramine products to advise users to consult a physician for use in children under 6 years of age. The proposed alcohol regulation would require the labeling direction to consult a physician for use in children under 12 years of age for products containing between 5 and 10 percent alcohol. In this case, the direction for the higher age limitation (i.e., to consult a physician for use in children under 12 years of age) would be required in the product's labeling, and the labeling could not include directions for children age 6 to under 12. A provision to use this higher age-limitation labeling is being included in the proposed regulation.

The agency has considered where the alcohol content of a product should be stated in labeling. The agency believes that consumers need to know this information when they purchase the product. The agency is concerned that consumers do not necessarily read all of a product's labeling at the time of purchase. The agency believes that the product's alcohol content should be prominently and conspicuously displayed in the product's labeling, and that this information should be readily available and visible to consumers at the time of purchase. Therefore, the agency

is proposing that this information appear on the front (principal) display panel of the product's labeling and that the information be in a size reasonably related to the most prominent printed matter on that panel. In addition, some manufacturers are presently placing the term "alcohol free" on their products' principal display panel and will likely do so for new or revised products containing no alcohol. Therefore, to facilitate comparison, the agency believes that the alcohol content of products containing alcohol should also appear on the principal display panel. Further, because section 502(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(e)) requires that the quantity, kind, and proportion of alcohol be stated on a drug product's label, the alcohol content will also need to appear on the immediate container label when the immediate container (e.g., a glass bottle) is marketed in another retail package, e.g., an outer box. This dual labeling of alcohol content will be beneficial should a consumer discard the outer package. The agency invites specific comment on the location of this information in OTC drug product labeling, particularly from consumers who have an interest in this type of information.

The agency is proposing that any final rule that may issue based on this proposal become effective 12 months after the date of publication in the **Federal Register**. Based on the time that this is likely to occur, the effective date would be consistent with NDMA's goals for its voluntary program, which are November 1993 for the reformulation and labeling of affected OTC drug products to the new 5- and 10-percent alcohol limitations, and December 1994 for the reformulation and labeling of alcohol-free OTC drug products.

If the agency determines that any condition included in the final regulation should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular condition not in conformance with the final regulation, a shorter deadline may be set for removal of that condition from OTC drug products. The agency encourages manufacturers to implement voluntarily the provisions of this proposed rule at their earliest convenience.

Within the OTC drug product marketplace, the agency is not aware of a significant number of products that would be affected due to their alcohol content as an inactive ingredient. Products that would be affected consist of a limited number of OTC liquid cough-cold, internal analgesic, and laxative drug products. Therefore, the agency concludes that the economic impact of this proposed rule, if implemented, would be minimal and that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC drug products intended for oral ingestion that contain alcohol as an inactive ingredient. Types of impact may include, but are not limited to, costs associated with reformulating, product (stability) testing, repackaging, and relabeling. Comments regarding the impact of this rulemaking on OTC drug products intended for oral ingestion that contain alcohol as an inactive ingredient should be accompanied by appropriate documentation. A period of 90 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 January 19, 1994, submit to the Dockets Management Branch (address above) written comments on the proposed amendment and on the agency's economic impact determination. 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

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) American Academy of Pediatrics, Committee on Drugs, "Ethanol in Liquid Preparations Intended for Children," Pediatrics, 73:405–407, 1984.

(2) Maling, H.M., "Toxicology of Single Doses of Ethyl Alcohol," in International Encyclopedia of Pharmacology and Therapeutics, Pergamom Press, Elmsford, NY, 2:227–299, 1970.

(3) Letter from M. Sabshin, Medical Director, American Psychiatric Association to FDA, July 28, 1992.

(4) Letter from P. Wood, National Council on Alcoholism and Drug Independence, Inc., to FDA, July 30, 1992.

(5) Letter from R.M. Kessel, State of New York Consumer Protection Board to FDA, July 12, 1991.

(6) Transcript of Open Proceedings of OTC Drugs Advisory Committee, December 17, 1992.

(7) Alcohol Content Limitation for Monograph'd OTC's Intended for Oral Ingestion, Nonprescription Drug Manufacturers Association, presented at OTC Drugs Advisory Committee meeting, December 17, 1992.

List of Subjects in 21 CFR Part 328

Alcohol, Drugs, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that chapter I of title 21 of the Code of Federal Regulations be amended to add part 328 as follows:

PART 328—OVER-THE-COUNTER DRUG PRODUCTS INTENDED FOR ORAL INGESTION THAT CONTAIN ALCOHOL

Subpart A—General Provisions

Sec.
328.1 Scope.
328.3 Definitions.

Subpart B—Ingredients

328.10 Alcohol.

Subpart C—Labeling

328.50 Principal display panel of all OTC drug products intended for oral ingestion that contain alcohol.

Authority: Secs. 201, 301, 501, 502, 503, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 371).

Subpart A—General Provisions

§ 328.1 Scope.

Reference in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21 unless otherwise noted.

§ 328.3 Definitions.

As used in this part:

(a) *Alcohol* means the substance known as ethanol, ethyl alcohol, or Alcohol USP.

(b) *Inactive ingredient* means any component of a product other than an active ingredient as defined in § 210.3(b)(7) of this chapter.

Subpart B—Ingredients

§ 328.10 Alcohol.

(a) Any over-the-counter (OTC) drug product intended for oral ingestion shall not contain alcohol as an inactive ingredient in concentrations that exceed those established in this part, unless a specific exemption, as provided in paragraph (e) of this section, has been approved.

(b) For any OTC drug products intended for oral ingestion and labeled for use by adults and children 12 years of age and over, the amount of alcohol in the product shall not exceed 10 percent.

(c) For any OTC drug product intended for oral ingestion and labeled for use by children 6 to under 12 years of age, the amount of alcohol in the product shall not exceed 5 percent.

(d) For any OTC drug product intended for oral ingestion and labeled for use by children under 6 years of age, the amount of alcohol in the product shall not exceed 0.5 percent.

(e) The Food and Drug Administration will grant an exemption from paragraphs (b), (c), and (d) of this section where appropriate, upon petition under the provisions of § 10.30 of this chapter. Appropriate cause, such as a specific solubility or manufacturing problem, must be adequately documented in the petition. Decisions with respect to requests for exemption shall be maintained in a permanent file for public review by the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

Subpart C—Labeling

§ 328.50 Principal display panel of all OTC drug products intended for oral ingestion that contain alcohol.

(a) The amount (percentage) of alcohol present in a product shall be stated in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) in accordance with § 201.10(d)(2) of this chapter.

(b) A statement expressing the amount (percentage) of alcohol present in a product shall appear prominently or conspicuously on the "principal display panel," as defined in § 201.60 of this chapter. For products whose principal display panel is on the immediate container label and that are not marketed in another retail package (e.g., an outer box), the statement of the percentage of alcohol present in the product shall appear prominently or conspicuously on the "principal display panel" of the immediate container label.

(c) For products whose principal display panel is on the retail package and the retail package is not the immediate container, the statement of the percentage of alcohol present in the product shall also appear on the immediate container label; it may appear anywhere on that label in accord with section 502(e) of the Federal Food, Drug, and Cosmetic Act.

(d) The statement expressing the amount (percentage) of alcohol present in the product shall be in a size reasonably related to the most prominent printed matter on the panel or label on which it appears, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed.

(e) For a product to state in its labeling that it is "alcohol free," it must contain no alcohol (0 percent).

(f) For any OTC drug product intended for oral ingestion containing over 5 percent alcohol and labeled for use by adults and children 12 years of age and over, the labeling shall contain the following statement in the directions section: "Consult a physician for use in children under 12 years of age."

(g) For any OTC drug products intended for oral ingestion containing over 0.5 percent alcohol and labeled for use by children ages 6 to under 12 years of age, the labeling shall contain the following statement in the directions section: "Consult a physician for use in children under 6 years of age."

(h) When the direction regarding age in paragraph (f) or (g) of this section differs from an age-limiting direction contained in any OTC drug monograph in this chapter, the direction containing the higher age limitation shall be used.

Dated: July 30, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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