DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 333

[Docket No. 75N-0183]

Alcohol Drug Products for Topical Antimicrobial Over-the-Counter Human Use; Establishment of a Monograph; and Reopening of Administrative Record

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking and reopening of administrative record.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would establish conditions under which over-the-counter (OTC) alcohol drug products for topical antimicrobial use are generally recognized as safe and effective and not misbranded. This notice relates to the development of monograph for topical antimicrobial drug products in general, which is part of the ongoing review of OTC drug products conducted by FDA. This notice also reopens the administrative record for OTC topical antimicrobial drug products to allow for consideration of recommendations on alcohol drug products that have been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

DATES: Written comments by August 19, 1982 and reply comments by September 20, 1982.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on October 6, 1980 a report on OTC alcohol drug products for topical antimicrobial use from the Advisory Review Panel on OTC Miscellaneous External Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed rule containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC alcohol drug products for topical antimicrobial use are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

Because alcohol ingredients are marketed in OTC drug products for topical antimicrobial use, FDA has determined that the Miscellaneous External Panel's recommendations on OTC alcohol drug products should be included as part of the proposed rulemaking for OTC topical antimicrobial drug products. Development of this rulemaking has been ongoing for some time.

In the **Federal Register** of September 13, 1974 (39 FR 33103), FDA issued an advance notice of proposed rulemaking to establish the monograph for OTC topical antimicrobial drug products. In the **Federal Register** of January 6, 1978 (43 FR 1210), FDA issued a tentative final monograph (notice of proposed rulemaking) for OTC topical antimicrobial drug products. In the **Federal Register** of March 9, 1979 (44 FR 13041) FDA reopened the administrative record and announced its intent to publish an updated (amended) tenative final monograph (amended notice of proposed rulemaking) for OTC topical antimicrobial drug products. FDA advises that it is again reopening the administrative record for OTC topical antimicrobial drug products only as it pertains to alcohol drug products in order to allow for the consideration of the Miscellaneous External Panel's recommendations on alcohol drug products. An amended tentative final monograph (amended notice of proposed rulemaking) will be published in a future issue of the **Federal Register.** At that time, comments received on this advance notice of proposed rulemaking concerning alcohol drug products will be addressed. Also, the proceeding to develop a monograph for alcohol drug products will be merged with the general proceeding to establish a monograph for OTC topical antimicrobial drug products. Because the Panel recommended Category I conditions for alcohol drug products, three new sections which would amend Part 333 are being included in this advance notice of proposed rulemaking (§§ 333.3(k), 333.55, and 333.98).

The unaltered conclusions and recommendations of the Panel relating to OTC alcohol drug products for topical antimicrobial use are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the Panel's recommendations. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** an amended tentative final monograph for OTC topical antimicrobial drug products, including alcohol drug products, as an amended notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC topical antimicrobial drug products will be restated when the amended tentative final monograph is published in the **Federal Register.** In that amended notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered in the amended notice of proposed rulemaking. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC alcohol drug products for topical antimicrobial use. Types of impact may include, but are not limited to, the following: increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any.

Comments regarding the impact of this rulemaking on OTC alcohol drug products for topical antimicrobial use should be accompanied by appropriate documentation. Comments will not be accepted at this time on any portion of the OTC topical antimicrobial rulemaking other than that relating to alcohol drug products.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC alcohol drug products for topical antimicrobial use submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after June 21, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy,* 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph.

Although it was not required to do so under *Cutler,* FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous external drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31697). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.'" In the **Federal Register** of August 27, 1975 (40 FR 38179) a notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of ingredients in miscellaneous external drug products to be considered in the OTC drug review. The list, which included "alcohol" active ingredients, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the the OTC review to all OTC drug products.

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous external drug products:

William E. Lotterhos, M.D., Chairman
Rose Dagirmanjian, Ph. D.
Vincent J. Derbes, M.D. (resigned July 1976)
George C. Cypress, M.D. (resigned November 1978)
Yelva L. Lynfield, M.D. (appointed October 1977)
Harry E. Morton, Sc. D.
Marianne N. O'Donoghue, M.D.
Chester L. Rossi, D.P.M.
J. Robert Hewson, M.D. (appointed September 1978)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Marvin M. Lipman, M.D., of Consumers Union served as the consumer liaison. Gavin Hildick-Smith, M.D., served as industry liaison from January until August 1975, followed by Bruce Semple, M.D., until February 1978. Both were nominated by the Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, also served as an industry liaison since June 1975.

Two nonvoting consultants, Albert A. Belmonte, Ph. D., and Jon J. Tanja, R.Ph., M.S., have provided assistance to the Panel since February 1977.

The following FDA employees assisted the Panel: John M. Davitt served as Executive Secretary until August 1977, followed by Arthur Auer until September 1978, followed by John T. McElroy, J.D., Thomas D. DeCillis, R.Ph., Served as Panel Administrator until April 1976, followed by Michael D. Kennedy until January 1978, followed by John T. McElroy, J.D., Joseph Hussion, R.Ph., served as Drug Information Analyst until April 1976, followed by Victor H. Lindmark, Pharm. D., until March 1978, followed by Thomas J. McGinnis, R.Ph.

The Advisory Review Panel on OTC Miscellaneous External Drug Products was charged with the review of many categories of drugs. Due to the large

number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents in this document its conclusions and recommendations on OTC alcohol drug products for topical antimicrobial use. The Panel's findings on other categories of miscellaneous external drug products are being published periodically in the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic in this document were held on June 27 and 28, August 15 and 16, November 9 and 10, 1975; February 20 and 21, April 2 and 3, May 16 and 17, June 11 and 12, October 8 and 9, 1976; September 30 and October 1, 1977; January 14 and 15, May 18 and 19, 1979; April 20 and 21, June 22 and 23, August 3 and 4, and October 5 and 6, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

No individuals requested to appear before the Panel to discuss alcohol drug products for topical antimicrobial use, nor was any individual requested to appear by the Panel.

The Panel has thoroughly reviewed the literature and data submissions, and has considered all pertinent information submitted through October 5, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations set forth in § 330.10, the Panel reviewed OTC alcohol drug products for topical antimicrobial use with respect to the following three categories:

Category I. Conditions under which OTC alcohol drug products for topical antimicrobial use are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC alcohol drug products for topical antimicrobial use not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed four alcohol active ingredients for topical antimicrobial use. Two ingredients were placed in Category I and two ingredients were placed in Category II.

I. Submission of Data and Information

In an attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, the agency compiled a list of ingredients recognized, either through historical use or use in marketed products, as alcohol active ingredients. Seven ingredients were identified as follows: absolute alcohol 70 percent, denatured alcohol, ethyl alcohol 92 percent, isopropyl alcohol 70 percent, isopropyl alcohol 90 percent, isopropyl alcohol 91 percent, and isopropyl alcohol with ethylene oxide. Notices were published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC alcohol drug products.

A. Submissions

Pursuant to the above notices, the following submissions were received:

Firms	Marketed products
Bowman Pharmaceuticals, Inc., Canton, OH 44702.	Isopropyl Alcohol, 91 percent; Isopropyl Alcohol, 70 percent.
Eli Lilly and Co., Indianapolis, IN 46206.	Isopropyl Alcohol-Lilly 91 Percent.
Holland Rantos Co., Inc., Piscataway, NJ 08854.	Steri-Wipe/Alcohol Swab.
Cramer Products, Inc., Gardner, KS 66030.	Fung-O Spray, Iso-Quin, Nitrotan.
Marion Health and Safety, Inc., Rockford, IL 61101.	70/10 Isopropanol Sepps, 70 percent Isopropanol.
Parke Davis & Co., Detroit, MI 48232.	Lavacol.
Sea Breeze Laboratories, Inc., Pittsburgh, PA 15244.	Sea Breeze.
Vestal Laboratories, Saint Louis, MO 63100.	Alcare.
Whitehall Laboratories, Inc., New York, NY 10017.	Anbesol.

In addition, Holland Rantos Co., Inc. made a related submission on ethylene oxide.

B. Ingredients Reviewed by the Panel

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Alcohol 30 percent
Alcohol 43 percent
Alcohol 50 percent
Alcohol 70 percent
Benzyl alcohol 3 percent
Ethyl alcohol 54 percent
Ethyl alcohol 70 percent
Isopropanol 91 percent
Isopropyl alcohol 7.5 percent
Isopropyl alcohol 12.5 percent
Isopropyl alcohol 20 percent
Isopropyl alcohol 24 percent
Isopropyl alcohol 31 percent
Isopropyl alcohol 35 percent
Isopropyl alcohol 50 percent
Isopropyl alcohol 70 percent

2. *Other ingredients reviewed by the Panel.*

Absolute alcohol 70 percent
Cetyl alcohol
Chlorobutanol
Denatured alcohol
Ethyl alcohol 92 percent
Ethylene oxide
Isopropyl alcohol 90 percent
Isopropyl alcohol 91 percent
isopropyl alcohol with ethylene oxide
Stearyl alcohol

C. Classification of Ingredients

The Panel is aware that the "United States Pharmacopeia" (USP) contains standards of quality and purity for several specific concentrations of the alcohols discussed in this document (Ref. 1); however, the Panel has concluded, based on the available data, that concentrations other than those specified in the USP can be generally recognized as safe and effective for the OTC market.

1. *Active ingredients.*

Benzyl alcohol (benzyl alcohol 3 percent)
Chlorobutanol
Ethyl alcohol (absolute alcohol 70 percent, alcohol 30 percent, alcohol 43 percent, alcohol 50 percent, alcohol 70 percent, denatured alcohol, ethyl alcohol 54 percent, ethyl alcohol 70 percent, and ethyl alcohol 92 percent)
Isopropyl alcohol (isopropanol 91 percent, isopropyl alcohol 7.5 percent, isopropyl alcohol 12.5 percent, isopropyl alcohol 20 percent, isopropyl alcohol 24 percent, isopropyl alcohol 31 percent, isopropyl alcohol 35 percent, isopropyl alcohol 50 percent, isopropyl alcohol 70 percent, isopropyl alcohol 90 percent, and isopropyl alcohol 91 percent)

2. *Inactive ingredients.*

Cetyl alcohol
Ethylene oxide
Stearyl alcohol

Reference

(1) "United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 16 and 428, 1980.

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All of the information included in these volumes, except for those deletions which are made in accordance with confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after June 21, 1982, in the Dockets Management Branch (HFA–305), Food and Drug

Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Discussion

The skin, as the protective covering of the body, is frequently subjected to injuries. Microorganisms, both resident and transient, dwell on the surface of the skin, and when the skin is broken, there is always the possibility that harmful microorganisms might spread from the site of injury to the deeper tissues or into the bloodsteam, producing a serious infection.

The Panel believes that decreasing the number of microorganisms on the surface of the skin is rational OTC therapy when the skin surface has been broken by a minor cut or scrape, prior to breaking the skin for removal of a splinter, or prior to injection. Ethyl and isopropyl alcohol possess many desirable features as antimicrobial agents in such therapy. The antimicrobial effectiveness of ethyl and isopropyl alcohol is not impressive against fungi and viruses. However, these alcohols are bactericidal; that is, they kill bacteria instead of preventing their growth and immobilizing them, which would be a bacteriostatic action. In addition, these alcohols evaporate readily and remove dirt and grime. Because ethyl and isopropyl alcohols are colorless, they do not stain the skin and thus would not mask inflammation, a warning sign of infection.

The Panel does not recommend that a consumer attempt to use an alcohol to self-treat a deep, extensive wound, or a puncture wound, or attempt to remove a large or deeply embedded splinter. Professional treatment should be sought immediately for such injuries. Alcohols are not recommended in these instances, as they have an irritant effect on damaged, deeply cut tissue (Ref. 1). The irritant action of alcohols is particularly marked on mucosa. The more concentrated the alcohol, the more pronounced are its irritant effects (Ref. 2). The Panel recommends caution in the use of topical alcohols on the mucous membranes in concentrations recommended for antimicrobial use in this document.

References

(1) Zanowiak, P., "Topical Anti-Infective Products," *in* "Handbook of Nonprescription Drugs," 16th Ed., American Pharmaceutical Association, Washington, p. 371, 1979.

(2) Ritchie, J. M., "The Aliphatic Alcohols," *in* "The Pharmacological basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 137–146, 1975.

III. Categorization of Data

A. Category I Conditions

These are conditions under which alcohol active ingredients for topical antimicrobial use are generally recognized as safe and effective and are not misbranded.

1. *Category I ingredients.*

Ethyl alcohol
Isopropyl alcohol

a. *Ethyl alcohol.* Ethyl alcohol (ethanol) has been used in beverages for centuries, and its medicinal, pharmacological, and nutritional properties have been studied extensively. Alcohol is an established name for ethyl alcohol (Ref. 1); however, the Panel will refer to the ingredient as ethyl alcohol in this document in order to distinguish clearly between it and isopropyl alcohol. Ethyl alcohol has an astringent action, precipitating protein; it cools the skin surface by rapid evaporation and, therefore, has been used topically to lower the body temperature; it produces mild redness and a burning sensation when rubbed on the skin and can be used as a counterirritant and rubefacient; and it cleans the skin by its solvent action on oils and greases.

Because of its solvent action, ethyl alcohol is also frequently used in a diluted form as a vehicle for other topical medications. It is capable of altering the stratum corneum (skin surface) and enhancing its permeability, thus facilitating the penetration through the skin of any ingredient that is dissolved in it (Ref. 2). This has been demonstrated with corticosteroids (Ref. 3), salicylic acid (Ref. 4), and iodine (Ref. 5).

Ethyl alcohol rubs have been used in hospitals for many years, and ethyl alcohol is also used frequently on bedridden patients as an adjunct to prevent decubitus ulcers (bedsores) (Ref. 6). However, washing the skin with a 74-percent concentration of ethyl alcohol has been reported to result in the recovery of increased numbers of surface inoculated *Staphylococcus aureus* 5 hours later. The assumption was that an increase in bacteria occurred as a result of removing antibacterial organic matter through the defatting action of the alcohol (Ref. 7).

Ethyl alcohol that is marketed for topical OTC use contains denaturants which are added to make it unsuitable for drinking purposes.

(1) *Safety.* The long use of ethyl alcohol in beverages attests to its relative nontoxicity when ingested in small quantities. It is readily absorbed from the stomach, small intestine, and colon, and vapors may be absorbed from the lungs. After absorption, ethyl alcohol is fairly uniformly distributed through the tissues and fluids of the body, and 90 to 98 percent is slowly and completely oxidized (Ref. 6).

Regardless of how ethyl alcohol enters the body, its greatest effect is on the central nervous system, and it acts as a primary and continuous depressant (Ref. 6). A concentration of 50 milligrams (mg) ethyl alcohol per 100 milliliters (mL) blood may impair muscular coordination and judgment, and a concentration of 200 mg per 100 mL of blood may produce a state of mild-to-moderate intoxication. A concentration of 300 mg per 100 mL blood will cause severe alcoholic intoxication, and a fatal concentration is estimated to be about 400 mg per 100 mL blood (Ref. 6).

Contact allergy to the lower primary aliphatic alcohols (methyl, ethyl, and propyl) has been reported, but is rare (Refs. 8 and 9). Because ethyl alcohol has been reported to be 7.5 times more toxic to white blood cells in vitro than to staphylococci (Ref. 10), its use is not recommended for open, extensive wounds. The application of antimicrobial concentrations of ethyl alcohol to such wounds might possibly do more harm than good by interfering with the body's basic defense mechanisms. The Panel therefore limits its recommendation for OTC use of this ingredient to application to minor cuts and scraps, application to the skin prior to breaking it for the removal of small splinters that are not deeply embedded, and for preparation of the skim prior to an injection.

(2) *Effectiveness.* Ethyl alcohol has been shown by in vitro and in vivo tests in kill bacteria. Some interesting early work on the antibacterial effectiveness of ethyl alcohol was conducted by Prombo and Tilden (Ref. 11) and Nungester and Kempf (Ref. 12). The most plausible explanation for this action is the denaturing of proteins by this ingredient. The most concentrated form of ethyl alcohol (100 percent), however, is less bactericidal than mixtures of ethyl alcohol and water. (See tables below.) This is probably because proteins are not denatured so readily in the absence of water as when water is present (Ref. 13).

THE EFFECT OF VARIOUS CONCENTRATIONS OF ETHYL ALCOHOL TEST ORGANISM: PSEUDOMONAS AERUGINOSA (REF. 14)

Ethyl alcohol		Exposure of test organism to germicide													
Percent by volume	Percent by weight	Seconds					Minutes								
		10	20	30	40	50	1	2	3	4	5	10	15	25	30
100	100	−	−	−	−	−	−								
95	92	−	−	−	−	−	−								
90	85	−	−	−	−	−	−								
80	73	−	−	−	−	−	−								
70	62	−	−	−	−	−	−								
60	52	−	−	−	−	−	−								
50	42	−	−	−	−	−	−								
40	33	−	−	−	−	−	−								
30	24	−	−	−	−		−	−	−	−	−	−	−		
25	20						−	−	−	−	−	−	−	−	−
20	16						+	+	+	−	−	−	−	−	−
(1)	(1)						+	+	+	+	+	+	+	+	−
							+	+	+	+	+	+	+	+	+

[1] Dist. water (control).
[2] + = growth. − = no growth.

THE EFFECT OF VARIOUS CONCENTRATIONS OF ETHYL ALCOHOL TEST ORGANISM: STAPHYLOCOCCUS AUREUS (REF. 14)

Ethyl alcohol		Exposure of test organism to germicide																
Percent by volume	Percent by weight	Second					Minutes								Hours			
		10	20	30	40	50	1	2	3	4	5	10	15	45	1	1½	2	3
100	100	+	±	+	±	−	−	−	−	−	−	−	−					
95	92	−	−	−	−	−	−	−	−	−	−	−	−					
90	85	−	−	−	−	−	−	−	−	−	−	−	−					
80	73	−	−	−	−	−	−	−	−	−	−	−	−					
70	62	−	−	−	−	−	−	−	−	−	−	−	−					
60	52	−	−	−	−	−	−	−	−	−	−	−	−					
50	42	+	−	−	−	−	−	−	−	−	−	−	−					
40	33	+	+	+	+	+	+	+	+	±	−	−	−					
30	24										+	+	+	+	−	−	−	−
25	20										+	+	+	±	+	−	−	−
20	16										+	+	+	+	+	+	+	−
(1)	(1)										+	+	+	+	+			

[1] Dist. water (control).
+ =growth. − = no growth.

When exposed to the air, ethyl alcohol (100 percent) takes up water vapor and establishes an equilibrium of 95 percent ethyl alcohol, by volume, and 5 percent water.

Bacteria in a dry environment are more resistant to a bactericidal action than in a moist environment (Refs. 15 and 16). *Mycobacterium tuberculosis,* when suspended in water and in sputum, was killed more rapidly by 95 percent than by 70 percent ethyl alcohol; but in dried sputum smears, 70 percent and 50 percent ethyl alcohol killed the tubercle bacilli more rapidly than the 95-percent solution (Ref. 17).

In general, fungi are more resistant than bacteria to the antimicrobial action of ethyl alcohol. Many fungi are dimorphic, exhibiting tissue (yeast) and culture (spore) phases, with the spore phase being particularly resistant to the action of ethyl alcohol. *Blastomyces dermatitidis, Coccidioides immitis,* and *Histoplasma capsulatum* in aerosol containers were sprayed and allowed to dry on the surfaces of such materials as asphalt tile, painted wood, glass, and stainless steel. The sprayed surfaces were then treated with various concentrations of ethyl alcohol, and it was noted that the most rapid killing of both phases of the three fungi was obtained with concentrations of approximately 70 percent ethyl alcohol; (Ref. 18) with the spore phase requiring the longer exposure period (Ref. 19). The age of the fungal spores was found to be a significant factor in determining the length of time required for different concentrations of ethyl alcohol to effect a killing action. Ten-day-old conidia (spores) of *Penicillium expansum* were killed in 8 minutes of exposure to a 90-percent concentration, whereas 438-day-old conidia of *P. expansum* required 60 minutes of exposure to this concentration. For a 70-percent concentration of ethyl alcohol the time required to kill the 10-day-old conidia of *P. expansum* was 15 minutes, whereas 14 hours were required to kill the 438-day-old conidia of *P. expansum* (Ref. 20).

That ethyl alcohol is less effective against spores than against vegetative forms of bacteria was also demonstrated by immersing pieces of sterile wire in a culture of gas-producing, sporulating anaerobic bacilli and exposing the pieces of wire to 70 percent ethyl alcohol for time periods ranging from 5 to 60 minutes. Each wire then produced, after 24 hours of incubation, an abundant growth of the test microorganism, indicating that the spores adhering to the wire at the time of culturing had been undisturbed by the ethyl alcohol. Because of the resistance of spores to ethyl alcohol; it is no longer used in hospitals for sterilizing surgical instruments (Ref. 18).

Concentrations ranging from 30 to 70 percent ethyl alcohol inactivated each of seven representative viruses in an exposure period of 10 minutes (Ref. 21). Those viruses with a lipid envelope (herpes simplex, Asian influenza, and vaccinia) were inactivated by 30 to 40 percent concentrations of ethyl alcohol. The other viruses (adenovirus; Coxsackie B, type 1; echo, type 6; and poliovirus, type 1) required concentrations of 50 to 70 percent (Ref. 21). Influenza virus, type A, was completely inactivated by 70 percent ethyl alcohol, whereas a 35-percent concentration had only a weakly inactivating activity (Ref. 21). Seventy percent ethyl alcohol produced a strong but not complete inactivation of vaccinia virus (Ref. 22).

Ethyl alcohol acts relatively quickly to decrease the number of microorganisms on the skin surface. Each minute that scrubbed hands and arms were

immersed in approximately 77 percent ethyl alcohol by volume was found to be equivalent to 6.5 minutes of scrubbing in water; if the skin was scrubbed with the alcohol, the rate was further increased (Ref. 23)

The Panel finds ethyl alcohol safe and effective for use as a topical antimicrobial preparation in concentrations of 60 to 95 percent by volume in an aqueous solution. It is denatured for topical use according to formulas approved by the Treasury Department's Bureau of Alcohol, Tobacco, and Firearms and specified in 27 CFR 212.

(3) *Labeling.* The Panel recommends Category I labeling for alcohol drug products for topical antimicrobial use. (See part III. paragraph A.2 below—Category I labeling.)

(4) *Directions.* "Apply to skin directly or with clean gauze, cotton, or swab."

References

(1) "United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 18, 1980.

(2) Scheuplein, R. J., and I. H. Blank, "Mechanism of Percutaneous Absorption. IV. Penetration of Nonelectrolytes (Alcohols) from Aqueous Solutions and from Pure Liquids," *Journal of Investigative Dermatology,* 60:286–296, 1973.

(3) Polano, M. K., et al., "Factors Influencing the Penetration of Corticosteriods Through the Epidermis," *Advances in Biology of the Skin,* 12:325–338, 1972.

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b. *Isopropyl alcohol.* Isopropyl alcohol is an isomer of propyl alcohol. It is prepared from propylene, which is obtained in the refining of petroleum or by reduction of acetone (Ref. 1). Isopropyl alcohol forms an azeotrope with water that contains 91.3 percent isopropyl alcohol by volume with a boiling point of 80.4° C (Ref. 2). It has no beverage use, because it is roughly twice as toxic as ethyl alcohol (Ref. 3).

(1) *Safety.* After ingestion, isopropyl alcohol is rapidly absorbed from all portions of the intestinal tract. It is metabolized more slowly than ethyl alcohol, and extracorporeal hemodialysis proved effective in treating two patients who had consumed an amount that would otherwise probably have proved fatal (Refs. 4 and 5). As little as 10 mg isopropyl alcohol per 100 mL blood have produced a noticeable effect in an adult (Ref. 6), and a comatose condition in children has been observed when the level of isopropyl alcohol in the blood was 128 to 130 mg per 100 mL (Refs. 7 and 8). Symptoms of toxic ingestion of isopropyl alcohol are flushing, headache, dizziness, mental depression, nausea, vomiting, narcosis, anesthesia, and coma. One hundred mL taken orally can be fatal (Ref. 1).

Isopropyl alcohol is sometimes used for bathing to reduce body temperatures, as it evaporates rapidly and cools the skin. The vapors, however, may be absorbed through the lungs, and cases of acute poisoning by this means have occurred when excessive amounts of alcohol have been used for bathing in poorly ventilated areas (Refs. 6 through 9). Garrison (Ref. 7) notes that sponging with cool or cold water can accomplish the same effect without risk of inhaling toxic vapors.

There is a report of one individual who had an allergic reaction to isopropyl alcohol and no reaction to the primary alcohols, methyl, ethyl, butyl, and amyl (Ref. 10). Other individuals have been observed to be allergic to isopropyl alcohol and to ethyl and methyl alcohols as well (Refs. 11, 12, and 13), while an eczematous type of allergic reaction has been reported in still another individual to methyl, ethyl, and propyl alcohols, but not to isopropyl or benzyl alcohols (Ref. 14).

The application of an antimicrobial concentration of isopropyl alcohol to open, extensive wounds could be very irritating and more harmful than beneficial. The Panel, therefore, limits its recommendation for OTC use of this ingredient to application to minor cuts and scraps, application to the skin prior to breaking it for the removal of small splinters that are not deeply imbedded, and for preparation of skin prior to an injection.

(2) *Effectiveness.* As with ethyl alcohol, water must be present in order for isopropyl alcohol to exert its antibacterial action. In one study, sterile metal strips were partially immersed in bacterial cultures, removed, allowed to dry, and then completely immersed in isopropyl alcohol solutions of different strengths for varying periods of time. When the metal strips were dried in a current of sterile air and transferred to tubes of culture medium, it was shown that 100 percent isopropyl alcohol did not kill *Staphylococcus aureaus,* whereas a 50-percent concentration killed *S. aureus* in less than 10 seconds (Ref. 15).

In a study employing a more conventional in vitro technique, 0.5 mL of bacteria cultures were added to 5 mL of isopropyl alcohol in varying concentrations and subcultured after varying periods of time (Ref. 16). It was shown that 50 to 91 percent

concentrations of isopropyl alcohol killed *S. aureus* in an exposure of 1 minute, whereas 10, 20, and 30 percent concentrations did not kill in 5 minutes. *Escherichia coli* was killed by concentrations of 30 to 91 percent isopropyl alcohol in a 5-minute exposure but not by 10 and 20 percent concentrations. Concentrations of 30 to 91 percent killed four non-spore-forming microorganisms, *S. aureus*, hemolytic streptococcus, *E. coli*, and *Salmonella typhosa* in a 30-minute exposure, but 10 and 20 percent concentrations did not.

Against tubercle bacilli in dried sputum smears, 100 percent isopropyl alcohol did not kill in a 60-minute exposure, while 91 percent killed in 10 minutes, 70 percent killed in 1 minute, and 50 and 30 percent killed in 2 minutes (Ref. 17).

Influenza, type A, and vaccinia viruses were inactivated by 48.5 and 99 percent isopropyl alcohol during an exposure period of 10 minutes (Ref. 18). Against the lipophilic viruses, Asian influenza; adenovirus, type 2; vaccinia; and herpes simplex, 20 to 50 percent concentrations of isopropyl alcohol had an inactivating effect in a contact period of 10 minutes. Against the hydrophilic viruses, poliovirus, type 1; Coxsackie B, type 1; and echo virus, type 6, results were mixed. Echo virus, type 6, was inactivated by a 10-minute exposure to 90 percent isopropyl alcohol, but poliovirus, type 1, and Coxsackie B, type 1, were not inactivated by 95 percent isopropyl alcohol (Ref. 19).

Isopropyl alcohol, like ethyl alcohol, is poor in sporicidal activity and therefore not appropriate for use in sterilizing surgical instruments. Concentrations of isopropyl alcohol ranging from 20 to 91 percent failed to kill spores of *Bacillus subtilis* and *Clostridium novyi* in an exposure of 60 minutes, and commercial isopropyl alcohol has been reported to have been contaminated with a saprophytic spore former (Ref. 16).

Based on the available data, the Panel concludes that isopropyl alcohol is safe and effective for use as an OTC topical antimicrobial agent in aqueous solutions ranging from 50 to 91.3 percent by volume.

(3) *Labeling.* The Panel recommends Category I labeling for alcohol drug products for topical antimicrobial use. (See part III. paragraph A.2. below—Category I labeling.)

(4) *Directions.* "Apply to skin directly or with clean gauze, cotton, or swab."

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2. *Category I labeling.* The Panel recommends the following labeling for Category I alcohol drug products for topical antimicrobial use:

a. *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases:

(1) "For first aid use to decrease germs in minor cuts and scrapes."

(2) "To decrease germs on the skin prior to removing a splinter or other foreign object."

(3) "For preparation of the skin prior to an injection."

b. *Directions.* "Apply to skin directly or with clean gauze, cotton, or swab."

c. *Warnings.* (1) *For all alcohol-containing drug products for topical antimicrobial use.* (i) "For external use only. Do not use in or near the eyes. In case of deep or puncture wounds, consult your doctor."

(ii) "Flammable, keep away from fire or flame."

(2) *For products containing isopropyl alcohol.* "Use only in a well-ventilated area; fumes may be toxic."

The Panel notes that in accordance with § 201.10(d)(2) (21 CFR 201.10(d)(2)) the concentration of ethyl alcohol in alcohol drug products must be expressed as the percentage by volume of absolute alcohol. The Panel recommends that the concentration of isopropyl alcohol also be expressed in terms of percentage by volume.

B. *Category II Conditions.* These are conditions under which alcohol active ingredients for topical antimicrobial use are not generally recognized as safe and effective or are misbranded.

1. *Category II ingredients.*

Benzyl alcohol.

Chlorobutanol.

a. *Benzyl alcohol.* Benzyl alcohol is a primary alcohol with a very faint odor. It is a clear liquid with a boiling point of 206° C at a pressure of 760 mm mercury, and it is only slightly soluble in water (1 part in 25 parts). It possesses local anethetic properties; a 1-percent solution applied to the tongue or lips produces an anesthetic effect that may persist for half an hour or longer. Its anesthetic effect on a rabbit's cornea is noticeable 1 or 2 minutes after instillation. Injected intravenously into dogs or rabbits, benzyl alcohol produces a drop in blood pressure due to dilation of the periperal blood vessels.

(1) *Safety.* The minimum lethal dose of benzyl alcohol per kilogram (kg) of body weight for mice was found to be 1.6 to 2.5 mL, for rats it was 1 to 3 mL, and for guinea pigs it was 1 to 2.5 mL. The subcutaneous injection of 2 mL benzyl alcohol per kilogram body weight (mL/kg) of rabbits usually was not fatal, and 2 mL/kg body weight of dogs was never fatal (Ref. 1).

Benzyl alcohol for the most part is excreted in urine in the form of hippuric acid, which may account for its low toxicity for mammals. The subcutaneous or intramuscular injection of benzyl alcohol is irritating and produces necrosis of the tissue. Aqueous or saline

solutions of benzyl alcohol in 1 to 4 percent concentration were reported never to proudce irritation or destruction of the tissues into which they were injected (Ref. 1). However, when 4 mL pure benzyl alcohol was accidentally injected in connection with a circumcision operation, complete anethesia was produced, followed by local necrosis of the tissues and complete recovery. Aqueous solutions of benzyl alcohol are not very efficient for surface anesthesia because of their poor power of penetration into the tissues. The main use of benzyl alcohol in anethesia is for infiltration anesthesia. If surface anethesia is desired, the pure chemical should be used (Ref. 2).

It is not uncommon for benzyl alcohol to be present as a preservative or bacteriostatic agent in solutions intended for parenteral administration, and, as such, it is absorbed into the bloodstream (Ref. 3). However, it appears to be well-tolerated at low concentrations (Ref. 4).

Although it was not possible to demonstrate any lethal toxicity for dogs when benzyl alcohol was administered by stomach tube (Ref. 5), the single oral LD_{50} for rats has been stated to be 3.10 g/kg (Ref. 6).

No instances of hypersensitivity to benzyl alcohol have been found in the literature.

(2) *Effectiveness.* Benzyl alcohol has a definite but weak antimicrobial action. Against *S. typhosa* it has been reported to have a phenol coefficient (measurement of the killing power of a substance compared to that of phenol) of 0.76 (Ref. 7).

In an infection-prevention test using mice (36 to 50 mice for each disinfectant) and *S. pneumoniae* (Type 1) there was a mortality rate of 42 percent among the mice when the *S. pneumoniae* were treated with 4 percent benzyl alcohol. The technique employed was to swab the last 1 to 2 centimeters (cm) of the tail of an anesthetized mouse with a virulent culture of *S. pneumoniae,* type 1, using 5 firm strokes. The tail was then immersed in different disinfectant solutions for 2 minutes. A 1-cm portion was snipped from the end of the tail and placed in a small, sterile Petri dish, the small portion of the tail was then placed in the peritoneal cavity of the same mouse, and the incision was closed. The entire procedure took about 4 minutes per mouse (Ref. 8).

The mortality rate was 13 percent after treatment with 70 percent ethyl alcohol (by weight), 14 percent after treatment with 99 percent isopropanol, 17 percent after treatment with 70 percent ethyl alcohol (by volume), and 18 percent after treatment with a mixture of 70 percent ethyl alcohol and 4 percent benzyl alcohol (both by weight). There was a 24-percent mortality rate among the mice exposed to a mixture of 0.04 percent nitromersol and 4 percent benzyl alcohol, compared to 96 percent mortality when nitromersol was used alone, and 42 percent mortality when benzyl alcohol was used alone. When *S. pyogenes* was used as the challenging microorganism, there was a mortality rate of 97 percent among the mice after the microorganisms had been exposed to 0.04 percent nitromersol, a 17-percent mortality rate after exposure to 4 percent benzyl alcohol, and a 12-percent mortality rate after the microorganisms had been exposed to a mixture of 0.04 percent nitromersol and 4 percent benzyl alcohol.

Benzyl alcohol was tested for its bacteriostatic activity using a sodium chloride solution (0.9 percent) as a control, and sodium chloride solution (0.9 percent) containing 0.9 percent benzyl alcohol. To verify the bacteriostatic action, 1 mL of a 1-to-100 dilution of an overnight broth culture of *P. aeruginosa* was added to 150 mL of a 0.9-percent sodium chloride solution (control). This immediately produced a concentration of 62,000 *P. aeruginosa* per mL. After 24 hours at room temperature, the bacterial count had increased to 18,000,000 *P. aeruginosa* per mL. However, when some of the same diluted culture was added to 150 mL of a 0.9-percent sodium chloride solution containing 0.9 percent benzyl alcohol, the immediate concentration was 75,000 *P. aeruginosa* per mL. After 24 hours at room temperature, the concentration of microorganisms had decreased to 5,000 *P. aeruginosa* per mL, a 92.5 percent kill. After 48 hours at room temperature, the concentration was 52 microorganisms per mL, a 99.9 percent kill. After 72 hours at room temperature, the saline-benzyl alcohol solution was sterile. The action of 0.9 percent benzyl alcohol in the saline was shown to be bactericidal rather than bacteriostatic, but the killing action was slow as would be expected at that low concentration (Ref. 9).

The antimicrobial action of benzyl alcohol was also shown to be bactericidal rather than bacteriostatic when it was added to a drug preparation intended for parenteral administration (injection). *E. coli, P. aeruginosa, S. aureus,* and *Candida albicans* were not killed after an exposure of 1 week, but were killed after an exposure of 2 weeks at room temperature. *Aspergillus niger* was not killed after an exposure of 3 weeks, but was killed after 4 weeks (Ref. 4).

The Panel concludes that although benzyl alcohol at a concentration of 0.9 percent maybe useful in pharmaceutical preparations as a preservative, its bactericidal action is so slow that it cannot be recommended for use as a topical antimicrobial agent.

(3) *Evaluation.* The Panel concludes that benzyl alcohol is safe but not effective for OTC topical antimicrobial use.

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b. *Chlorobutanol.* Chlorobutanol is a substituted tertiary butyl alcohol. It is a colorless-to-white crystalline substance having a camphor-like odor and taste. One gram dissolves in about 125 mL water, 10 mL glycerin, and 1 mL alcohol. It is readily soluble in chloroform, ether, acetone, and oils (Refs. 1 and 2).

The stability of aqueous solutions of chlorobutanol is influenced by pH of the solution, temperature, and chemical nature of the container. It is more stable in an acid than in an alkaline medium. At a pH of 3 and a temperature of 25° C, the half-life of chlorobutanol has been calculated to be 90 years, but at a pH of 7.5 and a temperature of 25° C, the half-life was estimated to be 0.23 year. The main degradation products of

chlorobutanol in aqueous solution are acetone and carbon monoxide (Ref. 3).

(1) *Safety.* Chlorobutanol is a central nervous system depressant and has been used clinically as a hypnotic drug. The oral lethal dose for humans is estimated to be 50 to 500 mg/kg (Ref. 4). It is claimed to have a local anesthetic action and has been shown in vitro to decrease the ability of uterine muscle strips to contract (Ref. 5).

One drop of a 2-percent solution of chlorobutanol applied to both eyes of nine rabbits twice each day for 7 days produced no conjunctival or corneal reaction (Ref. 6).

(2) *Effectiveness.* Chlorobutanol has been found to be a slow-acting bactericidal agent. A contact time of 12 hours was required for a 0.5-percent solution to kill *P. aeruginosa,* and a concentration of 0.7 percent killed this species of bacteria in 9 hours (Ref. 7). In testing 26 strains of *P. aeruginosa,* the time required for 0.5 percent chlorobutanol to kill the microorganisms when they were supsended in a phosphate buffer varied from 1 to 48 hours, and the killing times of chlorobutanol in this concentration for 5 strains of *Proteus* species varied from less than 30 minutes to 3 hours (Ref. 8). Concentrations of 0.25 to 0.26 percent were found to kill 50 percent of *E. coli* cells in an exposure period of about 3½ hours (Ref. 9).

Because chlorobutanol has some bactericidal properties and is not irritating to the eye, it has been used extensively in topical ophthalmic drugs as a preservative (Ref. 10).

(3) *Evaluation.* The Panel concludes that chlorobutanol in concentrations up to 5 percent is safe, but its bactericidal action is too slow for it to be considered effective as a topical antimicrobial agent.

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2. *Category II labeling.* The Panel recommends that the following label claims be placed in Category II:

a. "For application to mucous membranes."

(b) "As a local antiseptic in such conditions as simple sunburn, hand iron burns, mouth burns caused by hot food, kitchen burns caused by hot pots, etc."

c. "Useful for preparation for surgical procedures."

d. "For use in sterilizing (preparing) needles and syringes for hypodermic injection."

C. *Category III Conditions.* None.

D. *Combination Policy.* The Panel recommends that any combination of ethyl alcohol or isopropyl alcohol with other antimicrobial ingredients should be in accordance with § 330.10(a)(4)(iv) (21 CFR 330.10(a)(4)(iv)) which states:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel does not believe that the combination of isopropyl and ethyl alcohol is rational

List of Subjects in 21 CFR Part 333

Over-the-counter drugs.

PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended in Part 333 (as set forth in the notice of proposed rulemaking for topical antimicrobial drug products that was published in the **Federal Register** of January 6, 1978 (43 FR 1210)) as follows:

1. In Subpart A, § 333.3 is amended by adding a new paragraph (k), to read as follows:

§ 333.3 Definitions.

* * * * *

(k) *Alcohol drug product.* A drug product containing an alcohol ingredient that is applied topically for antimicrobial use.

2. In Subpart B, § 333.55 is added to read as follows:

§ 333.55 Alcohol active ingredients.

(a) Alcohol (ethyl alcohol) 60 to 95 percent by volume in an aqueous solution denatured according to the Treasury Department's Bureau of Alcohol, Tobacco, and Firearms regulations at 27 CFR 212.

(b) Isopropyl alcohol 50 to 91.3 percent by volume in an aqueous solution.

3. In Subpart D, § 333.98 is added to read as follows:

§ 333.98 Labeling of alcohol drug products.

(a) *Statement of indentity.* The labeling of any product containing an ingredient identified in § 333.55 contains the established name of the drug, if any, and identifies the product as an "alcohol for topical antimicrobial use."

(b) *Indications.* The labeling of any product containing an ingredient identified in § 333.55 contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases:

(1) "For first aid use to decrease germs in minor cuts and scrapes."

(2) "To decrease germs on the skin prior to removing a splinter or other foreign object."

(3) "For preparation of the skin prior to an injection."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading, "Warnings":

(1) *For products containing any ingredient identified in § 333.55.* (i) "For external use only. Do not use in or near the eyes. In case of deep or puncture wounds, consult your doctor."

(ii) "Flammable, keep away from fire or flame."

(2) *For products containing isopropyl alcohol identified in § 333.55(b).* "Use only in a well-ventilated area; fumes may be toxic."

(d) *Directions.* The labeling of any product containing an ingredient identified in § 333.55 contains a statement of the directions for use under the heading "Directions" that is limited to the phrase, "Apply to skin directly or with clean gauze, cotton, or swab."

Interested persons may, on or before August 19, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any 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. Comments replying to comments may also be submitted on or before September 20, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 25, 1982.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: May 6, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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