DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 351

[Docket No. 82N-0291]

Vaginal Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would establish conditions under which over-the-counter (OTC) vaginal drug products are generally recongized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by January 11, 1984 and reply comments by March 19, 1984.

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, National Center for Drugs and Biologics (HFN-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 December 8, 1978 a report on OTC vaginal drug products from the Advisory Review Panel on OTC Contraceptives and Other Vaginal 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 vaginal drug products 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; (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel 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 report. 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.

In its report, the Panel has recommended the use of various antimicrobials "for relief of minor vaginal irritation and itching," "for temporary relief of minor vaginal irritation and itching," and "for relief of minor vaginal soreness." The Panel is the third OTC advisory review panel to have made recommendations to FDA regarding the use of various OTC drugs in and around the vagina. The Topical Analgesic Panel,s recommendations were published in the **Federal Register** of December 4, 1979 (44 FR 69793), as part of the advance notice of proposed rulemaking for OTC external analgesic drug products; the Antimicrobial II Panel's recommendations were incorporated into the advance notice of proposed rulemaking for OTC antifungal drug products, published in the **Federal Register** of March 23, 1982 (47 FR 12480).

The Topical Analgesic Panel recommended that 0.5 percent hydrocortisone be considered generally recognized as safe and effective for "itchy genital and anal areas." FDA did not dissent from this recommendation. Therefore, as provided in 21 CFR 330.13, this drug was permitted to be marketed OTC. Previously, the drug has been available on a prescription basis only.

The Antimicrobial II Panel recommended that certain antifungals currently available only by prescription be considered generally recognized as safe and effective for "treatment of external feminine itching associated with vaginal yeast (candidal) infection." However, when this recommendation was published in the **Federal Register**, the agency dissented on the Panel's recommendation. The effect of FDA's action was that, in accordance with 21 CFR 330.13, these prescription drugs were prevented from entering the OTC market. The agency stated in its dissent that "self-treating the symptoms of itching around the vagina without knowing or treating the underlying cause of the itching could create a serious health hazard * * *. Furthermore, itching around the vagina can be a symptom of serious systemic disease, such as diabetes, or of a serious gynecological disorder, including trichomoniasis or gonorrhea" (47 FR 12480).

FDA received a number of comments disagreeing with the agency's dissent on the Antimicrobial II Panel's recommendation regarding the treatment of itching around the vagina. These comments asserted that the agency's statements made in response to this recommendation were not consistent with the fact that the agency did not dissent from the recommendation of the Topical Analgesic Panel regarding the use of 0.5 percent hydrocortisone for "itchy genital and anal areas."

The agency notes that the recommendations by the three panels relate to symptoms, such as itching and irritation, that consumers can indentify. The panels recommended that certain antipruritics and antimicrobials/antifungals be generally recognized as safe and effective and available for OTC use to treat these symptoms. The Topical Analgesic Panel recommended hydrocortisone for symptomatic relief of itching in the genital area external to the vagina. The Antimicrobial II Panel and this Panel recommended antimicrobials only for the symptomatic relief of itching, irritation, or soreness. Consumers, however, generally cannot identify the underlying causes of symptoms of this type. And, while the panels were concerned with relieving symptoms only, some of these drugs may actually have an effect on the underlying cause of the symptoms such as candidal infections and other sources of irritation. Yet, the panels were concerned with symptomatic relief only, not treatment, and in fact counseled against self-treatment.

Under the circumstances, the agency believes that the recommendations of the three panels are confusing and possibly contradictory. All three panels have concluded that a woman is unable to self-diagnose and self-treat vaginal infections and that professional consultation is essential for the proper diagnosis and treatment of vaginal infections. Yet, the Antimicrobial II Panel concluded that because vaginal yeast infection is extremely common and recurrent and is the most common cause of intense itching and redness of the vulva, the OTC use of a topical antifungal would be beneficial in

relieving this discomfort until more definitive treament could be obtained. Even though self-diagnosis of candidal infections by a consumer generally is not possible, the Antimicrobial II Panel recommended that an antifungal be available for OTC use with a label warning that if the symptoms did not clear up within 14 days, the woman should consult a physician. The Vaginal Drug Products Panel concluded that proper treatment following professional consultation is essential for vaginal infections, but rationalized that because OTC drug products have been used by women to alleviate symptoms of vaginal irritation, itching, and soreness, they should continue to be available with a label warning that if the symptoms do not resolve in 1 week, the woman should consult a physician.

In light of the different recommendations from the three panels, previous agency actions, and the comments submitted in response to the advance notice of proposed rulemaking for OTC antifungal drug products, there appears to be uncertainty regarding the appropriateness of OTC drug products for treating the symptoms of itching, irritation, or soreness in or around the vagina. The agency is particularly concerned about: (1) the ability of a woman to recognize the nature or cause of the symptom(s) in order to determine which kind of drug product to select to treat them, e.g., an antipruritic or antifungal for the external areas, including the vulva, or an antimicrobial for intravaginal use; and (2) whether 1 to 2 weeks of self-medicating with an OTC drug product may pose an unacceptable delay in seeking professional attention if the symptom(s) are due to gonorrhea, trichomonas, candida, or other organisms that will not be eradicated by topical therapy with OTC drug products. The agency invites specific comment on these issues, and particularly invites comment for gynecolgists, family practitioners, other health professionals, women, and consumer groups dealing with health issues related to women.

As explained in the preambles to the advance notices of proposed rulemaking for antifungal and external analgesic drug products, no final agency decisions were made regarding the panel recommendations. Likewise, the purpose of this advance notice of proposed rulemaking on OTC vaginal drug products is to obtain comment before the agency makes a final decision on the panel recommendations.

In the notice of proposed rulemaking (tentative final monograph) for external analgesic drug products, published in the **Federal Register** of February 8, 1983 (48 FR 5863), the agency tentatively agreed with the Topical Analgesic Panel's recommendation that hydrocortisone can be safely used OTC for external genital itching if accompanied by appropriate warnings. The agency also invited specific comment on this proposal. The agency expects to set forth its position on OTC antifungal drugs for use external to the vagina in its proposed rulemaking (tentative final monograph) on antifungal drug products. The agency's position on the use of OTC drugs to treat conditions within the vagina will be set forth in its proposed rulemaking on vaginal drug products.

The agency is also aware of the Panel's recommendation that the professional labeling of products containing calcium propionate and sodium propionate include the indication "For the treatment of *Candida albicans*." The Panel's recommendation was based on a review of data and information submitted by Wyeth Laboratories on the product Propion Gel(R). This product was also reviewed under the Drug Efficacy Study Implementation (DESI) for a similar indication (for treatment of vulvovaginal candidiasis). In the **Federal Register** of June 4, 1982 (47 FR 24418), FDA published a notice denying a hearing and withdrawing approval of the new application (NDA) for Propion Gel (R) because the drug lacks substantial evidence of effectiveness. In that notice, the agency disagreed with the OTC Panel's recommendation that a professional labeling claim for the treatment of *Candida albicans* be permitted for calcium propionate and sodium propionate. The agency reiterates that conclusion here. Accordingly, FDA considers that professional labeling indication recommended by the Panel for calcium propionate and sodium propionate to be Category II.

In classifying calcium propionate and sodium propionate in Category I for the relief of minor vaginal irritations, the OTC Panel relied on the same studies reviewed and found inadequate by the agency under the DESI program. Because of the inadequacy of those studies and because of the uncertainty about the use of OTC drug products to treat vaginal irritations (discussed above), the agency will not at this time allow into the OTC marketplace products containing calcium propionate or sodium propionate for vaginal use. Sodium propionate and calcium propionate have not previously been marketed in OTC vaginal drug products and, therefore, may not be marketed OTC at this time under the provisions of 21 CFR 330.13. The agency invites comments and data which would support the Panel's recommendation on the safety and effectiveness of sodium propionate and calcium propionate as ingredients in OTC vaginal drug products.

The agency is not aware of the marketing of any drug product containing potassium sorbate as an active ingredient prior to adoption of the Panel's report, although at least one product has entered the marketplace since that time. Because potassium sorbate has not been marketed as a drug to a material extent and for a material time in the United States, the agency considers this ingredient to be a new drug within the meaning of section 201 (p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)). It may not be marketed until FDA has approved a new drug application (NDA) for such use.

FDA is aware that the Panel conducted an extensive review of data and information on the mutagenic and carcinogenic potential of povidone-iodine. The Panel recommended that this ingredient be classified in Category I pending FDA's review of new data that were submitted at the final Panel meeting (Refs. 1, 2, and 3). The agency has reviewed the data and concludes that they do not demonstrate povidone-iodine to be a potential mutagen or carcinogen. However, if any new information shows that the intravaginal use of povidone-iodine poses safety risks requiring immediate action, the agency will provide notice of its determination and take appropriate regulatory action.

FDA is aware that the Panel included in its report a discussion regarding the design of douching equipment. Because douching equipment is considered to be a device and not a drug, the agency is referring that portion of the Panel's report to the Bureau of Medical Devices for consideration. The Panel's discussion on douching equipment will not be further considered by the Office of Drugs.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC vaginal drug products as a 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 vaginal drug products will be stated initially when the tentative final monograph is published in the **Federal Register** as a notice of proposed rulemaking. In that 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 when the notice of proposed rulemaking is published. 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 substantial or significant economic impact that this rulemaking would have on OTC vaginal drug products. Types of impact may include, but are not limited to costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC vaginal drug products should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC vaginal drug products 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 November 14, 1983, 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, National Center for Drugs and Biologics (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 12 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 unless they are the subject of an approved new drug application. 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 unless they are the subject of an approved new drug application. Manufacturers are encouraged to voluntarily comply with the monograph at the earliest possible date.

In some advance notices of proposed rulemaking previously published in the OTC drug review, the agency suggested an earlier effective date. However, as explained in a number of tentative final monographs for OTC drug products, the agency has concluded that, generally, it is more reasonable to have a final monograph be effective 12 months after the date of its publication in the **Federal Register.** This period of time should enable manufacturers to reformulate, relabel, or take other steps to comply with a new monograph with a minimum disruption of the marketplace thereby reducing economic loss and ensuring that consumers have continued access to safe and effective drug products.

References

(1) OTC Volume 110057.

(2) Letter of December 27, 1978 from Robert G. Pinco to Armond M. Welch, included in OTC Volume 17BPAIII.

(3) Letter of February 16, 1979 from Robert G. Pinco to Armond M. Welch, included in OTC Volume 17BPAIII.

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 on all active ingredients used in OTC vaginal contraceptives and other vaginal drug products was issued in the **Federal Register** of May 16, 1973 (38 FR 12840).

The Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report under § 330.10(a) (1) and (5) on the safety, effectiveness, and labeling of those products:

Elizabeth B. Connell, M.D., Chairman
Evelyn M. Benson, R. Ph.
Cynthia W. Cooke, M.D.
Myron Gordon, M.D.
William A. MacColl, M.D.
William H. Pearlman, Ph. D.
Louise B. Tryer, M.D.

The Panel was first convened on August 2, 1973, in an organizational meeting. Meetings at which vaginal drug products were discussed were held on September 28 and 29, October 19 and 20, November 18 and 19, 1973; January 13 and 14, February 8 and 9, March 8 and 9, March 29 and 30, May 9 and 10, June 6 and 7, July 18 and 19, September 20 and 21, November 8 and 9, December 16 and 17, 1974; January 23 and 24, February 7 and 8, March 14 and 15, April 27 and 28, June 23 and 24; July 24 and 25, September 18 and 19, November 7 and 8, December 11 and 12, 1975; February 26 and 27, April 22 and 24, July 22 and 23, August 24 and 25, October 8 and 9, November 19 and 20, December 16 and 17, 1976; January 14 and 15, March 11 and 12, May 20 and 21, June 22 and 23, July 27 and 28, October 1 and 2, November 4 and 5, December 15 and 16, 1977; February 3 and 4, March 13 and 14, April 28 and 29, May 19 and 20, June 8 and 9, July 10, 11, and 31, August 1 and 2, September 28 and 29, and December 7 and 8, 1978.

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

Two nonvoting liaison representatives served on the Panel. Virginia K. Rosenbaum, B.A., served as the consumer liaison. George A. Braun, Ph. D., served as industry liaison, and in his absence, Forrest C. Greenslade, Ph. D. The following FDA employees assisted the Panel: James P. Burns, Jr., Ph. D., served as Executive Secretary until September 1977, followed by A. T. Gregoire, Ph. D., Armond M. Welch, R. Ph., served as Panel Administrator. Lloyd G. Scott, R. Ph., served as Drug Information Analyst until November 1973, followed by Thomas Gingrich, R. Ph., until April 1975, followed by Anne W. Eggers, R. Ph., M.S., until September 1977. Elaine Euchner, R. Ph., served as Drug Information Analyst from April 1978 and William Best, R. Ph., also served from July 1978 until September 1978. George Kerner, M.S., also served as Consumer Safety Officer from February 1975 until July 1977.

The following persons appeared at their own or at the Panel's request to discuss vaginal drug products:

Gary Berger, M.D.
Louis Bleacher
David J. Brusick, Ph. D.
Nancy Chasen
Robert Choate
Richard A. Carchman, Ph. D.
Eugene Conrad, Ph. D.
John C. Cutler, M.D.
Paul A. Fehn, Ph. D.
Matthew Freund, M.D.
Leonard J. Goldwater, M.D.
Forrest C. Greenslade, Ph. D.
Stephen G. Hoag, Ph. D.
Roger Homm, B.S.
Marjorie Horning, Ph. D.
Margaret F. Jones, M.S., M.A.
Maryann Kane
Naomi Kaplan, M.D.
Louis Keith, M.D.
James C. Killeen, Jr., Ph. D.
Ruth Kirschstein, M.D.
S. Robert Kohn, Ph. D.
Eric Kunnas
Bertram Lift
Donald McNellis, Ph. D.
William Masters, M.D.
John Middleton, M.D.
Nathan Millman, Ph. D.
John Mothersell
Robert Pinco, Esq.
Kenneth Rothwell, M.D.
Roger Schnaare, Ph. D.
Daniel Siegel, Ph. D.
Charles Westoff, Ph. D.
Robert J. Weir, Ph. D.
Lillian Yin, Ph. D

No person who so requested was denied an opportunity to appear before the Panel to discuss vaginal drug products.

On January 23 and 24, 1975, the Panel held a symposium concerning scientific aspects of reproduction and fertility control and invited the following participants:

Gerald Bernstein, M.D., Ph. D.
Richard Blandau, M.D., Ph. D.
Forrest C. Greenslade, Ph. D.
Kurt Hirschhorn, M.D.
Sheldon J. Segal, Ph. D.
Thomas Shepard, M.D.
Richard Stambaugh, Ph. D.
Robert Staples, Ph. D.

A symposium on the effectiveness of vaginal contraceptives, which included a segment on consumer concerns about the labeling of vaginal drug products in general, was held on April 28 and 29, 1978, and included the following participants:

William C. Andrews, M.D.
Gary Berger, M.D.
Gerald Bernstein, M.D., Ph. D.
Ron Gray, M.D.
Bernard Greenberg, M.D.
Michelle Harrision, M.D.
Edna Johnson
Philip Kestelman
Jane Menken, Ph. D.
Harold Nash, Ph. D.
Howard Ory, M.D.
Samuel Pasquale, M.D.
Allan Rosenfield, M.D.
Christopher Tietze, M.C.
Ilene Wolcott

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through December 8, 1978 in arriving at its conclusions and recommendations.

In this document the Panel presents its review and proposed monograph for OTC vaginal drug products except contraceptives. That portion of its review which dealt with OTC vaginal contraceptive drug products was published in the **Federal Register** of December 12, 1980 (45 FR 82014).

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel reviewed OTC vaginal drug products with respect to the following three categories:

Category I. Conditions under which OTC vaginal drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC vaginal drug products are 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.

I. Submission of Data and Information

A. Submissions by Firms

Firm	Marketed products
Aloe Vera of America, Garland, TX 75042.	Vagistat Vaginal Douche, Vagistat Vaginal Cream.
Beecham, Inc., Clifton, NJ 07012.	Massengill Liquid Douche Concentrate.
Block Drug Co., Inc., Jersey City, NJ 07302.	Femicare Vaginal Douche Powder.
Boyle & Co., Los Angeles, CA 90022.	Triva Douche Powder.
Bristol-Meyers Co., New York, NY 10022.	Feminique Douche Liquid Concentrate.
G. M. Case Laboratories, San Diego, CA 92103.	PAF Douche Powder.
Chattem Drug & Chemical Co., Chattanooga, TN 37409.	Meta-Cine Douche Powder Concentrate, Pamprin Concentrated Douche Powder.
Julius Schmid, Inc., New York NY 10019.	Vagisec Liquid.
McKesson Laboratories, Fairfield, CT 06430.	V. A. Douche Powder.
Meri Jo, Inc., Tampa, FL 33614.	Fine's Hygienic Powder.
Norcliff Laboratories, Inc., Fairfield, CT 06430.	Zonite Douche, Zonitors Feminine Deodorant Suppositories.
Phenex Laboratory, Inc., Chicago, IL 60641.	Complete Feminine Hygiene Antiseptic Deodorant Douche, Phenex Vaginal Hygiene Suppositories, Phenex Vaginal Therapeutic Suppositories.
The Purdue Frederick Co., Norwalk, CT 06856.	Betadine Douche.
Reed and Carnrick Pharmaceuticals, Kenilworth, NJ 07033.	Cleansing Douche Powders, Trichotine Liquid Douche Concentrate, Trichotine Vaginal Douche.
Rystan Co., Inc., White Plains, NY 10605.	Prophyllin Powder.
R. Schattner Co., Washington, DC 20016.	Gynaseptic Vaginal Solution, Gynaseptic Vaginal Ointment.
Wyeth Laboratories, Inc., Philadelphia, PA 19101.	Propion Gel.

In addition, the following firms, groups, or individuals provided related information:

Carol Angle, M.D., University of Nebraska Medical Center, Omaha, NE 68105.—Camphor.

Beecham Products, Clifton, NJ 07012.—Boric Acid, Lactic Acid.

Center for Science in the Public Interest, Washington, DC 20036.—Talc.

Cosmetic, Toiletry and Fragrance Association, Washington, DC 20005.—Talc.

Foster D. Snell, Inc., General Laboratories, Florham Park, NJ 07932.—Pressure effects of douching.

International Playtex, Inc., Dover, DE 19901.—Polysorbate 20.

F. Nakamura, M. D., California State University, 1250 Bellflower Blvd., Long Beach, CA 90840.—Potassium Sorbate.

Ortho Research Foundation, Raritan, NJ 08869.—Selected bibliography on vaginal contraception and therapeutics.

Proprietary Association, Washington, DC 20006.—Indication language.

U.S. Borax Research Corp., Anaheim, CA 92801.—Boric Acid.

Vicks Chemical Co., Research Division, Mount Vernon, NY 10553.—Vaginal Douche delivery systems.

Young's Drug Products Corp., P.O. Box 385, Piscataway, NJ 08854.—Polysorbate 20.

B. Ingredients Reviewed by the Panel

1. *Labeled ingredients contained in OTC vaginal drug products.*

Alcohol
Alky aryl sulfonate
Allantoin
Alum
Alum (ammonium)
Amerchol L 101
Aromatic oils
Aromatics
Beeswax
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Boric acid
Boro-glycerine
Calcium propionate
Camphor
Cetyl alcohol
Chlorothymol
Citric acid
Cocoa butter
Color
Disodium edetate
Eucalyptol
Fragrance
Glycerin
Glycerine
Hexachlorophene
Isopropyl myristate
Lactic acid
Lactose
Menthol
Methylparaben
Methyl salicylate
Octylphenoxy polyethoxyethanol, octylphenoxy polyethoxy ethanol
Oil of eucalyptus
Oil of peppermint
Oxyquinoline citrate
Oxyquinoline sulfate
Papain
Phenol
Polyoxyethylenenonyl phenol
Polyoxyethylene nonyl phenol
Polysorbate 20
Potassium aluminum sulphate
Potassium hydroxide
Povidone-iodine
Propylene glycol
Propylparaben
Propyl paraben
Purified water
Silica
Sodium bicarbonate
Sodium borate
Sodium carbonate
Sodium chloride
Sodium dioctyl sulfosuccinate
Sodium edetate
Sodium lactate
Sodium lauryl sulfate
Sodium perborate
Sodium phenolate
Sodium propionate
Sodium salicylate
Sodium salicylic acid phenolate
Sodium sulfate
Stabilized aloe vera gel
Steric acid
Talc
Tartaric acid
Thymol
Tragacanth
Vitamins D and A
Water soluble ingredients of chlorophyll
Zinc sulfate
Zinc sulphate

2. *Other ingredients reviewed by the Panel.*

Acetic acid (vinegar)
Potassium sorbate
Talc

C. Classification of Ingredients

The Panel adopted and used for the ingredients reviewed in this document nomenclature based on the currently accepted terminology stated in the 1978 edition of "USAN and the USP Dictionary of Drug Names." Any ingredients which do not have names established in USAN will be referred to by names recommended by FDA.

1. *Active ingredients.*

Acetic acid (vinegar)
Alkyl aryl sulfonate
Allantoin
Alum
Alum (ammonium)
Benzaklonium chloride
Benzethonium chloride
Benzocaine
Boric Acid
Boroglycerin (boro-glycerine)
Calcium propionate
Citric acid
Dioctyl sodium sulfosuccinate (sodium dioctyl sulfosuccinate)
Edetate disodium (disodium edetate)
Edetate sodium (sodium edetate)
Ergocalciferol (Vitamin D)
Hexachlorophene
Lactic acid
Nonoxynol 9 (nonyl phenoxy polyoxyethylene ethanol, nonylphenoxypotyethoxyethanol, polyoxyethylenenonyl phenol, polyexyethylene nonyl phenol)
Octoxynol 9 (octoxynol, octylphenoxy polyetnoxyethanol, octylphenoxy polyethoxy ethanol, *p*-Diisobutylphenoxypdyethoxyethanol, polyethylene glycol of mono-iso-octyl phenyl ether)
Oxyquinoline citrate
Oxyquinoline sulfate
Papain
Phenol
Phenolate sodium (sodium phenolate)
Potassium aluminum sulphate
Potassium sorbate
Povidone-iodine
Sodium bicarbonate
Sodium borate
Sodium carbonate
Sodium lactate
Sodium lauryl sulfate
Sodium perborate
Sodium propionate
Sodium salicylate
Sodium salicylic acid phenolate
Stabilized aloe vera gel
Tartaric acid
Vitamin A
Zinc sulfate (zinc sulphate)

2. *Inactive ingredients.*

Alcohol
Amerchol L 101
Aromatic oils
Aromatics
Beeswax
Camphor
Cetyl alcohol
Chlorothymol
Cocoa butter
Color
Eucalyptol
Fragrance
Glycerin (glycerine)
Isopropyl myristate
Lactose
Menthol
Methylparaben (methyl paraben)
Methyl salicylate
Oil of eucalyptus
Oil of peppermint
Polysorbate 20
Potassium hydroxide
Propylene glycol
Propylparaben (propyl paraben)
Purified water
Silica
Sodium chloride
Stearic acid (steric acid)
Sodium sulfate
Talc
Thymol
Tragacanth
Water soluble ingredients of chlorophyll

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include the submissions made by interested persons in response to the call-for-data notice published in the **Federal Register** of May 16, 1973 (38 FR 12840). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2) November 14, 1983, will be put on public display afterin the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Line Rockville, MD 20857.

II. General Discussion

A. Introduction

When it first convened, the Panel considered its specific mandate and general objectives. It recognized that its primary concern must be the evaluation and categorization of the ingredients under its review as defined by the enabling regulation; however, it was also deeply concerned about the health of women and their offspring, the latter both during intrauterine life and after birth. The Panel, therefore, concluded that, as a part of its mandate, it would give special attention to the issues involved in labeling and patient instruction, effectiveness rates, delivery

systems, vaginal absorption, fetal and infant damage, mutagenicity, and carcinogenicity.

The Panel believes that it is particularly important for OTC vaginal drug product labeling to explain what benefits consumers can expect from the use of such products. For example, the labeling of contraceptive agents should clearly state that the use of such products is intended for the prevention of pregnancy. Conversely, the labeling of vaginal douches should clearly reveal the probable failure of such products when used for the prevention of pregnancy.

The Panel considers it essential, because proper use is important both in relation to safety and effectiveness, that each vaginal product be accompanied by instructions which are written in a manner easily understood by the average consumer.

Regarding vaginal douches, the Panel considers appropriate douching methods and the design of douching equipment to be as important for the safe and effective use of vaginal douches as the ingredients. Therefore, the Panel has devoted a section of this document to the methodology of douching and the design of the equipment. (See part IV. paragraph G. below—Vaginal Douche Equipment.)

The Panel also recognizes that OTC vaginal drug products might be used by the consumer inadvertently during early pregnancy. Moreover, these products might be used during lactation. The Panel has, therefore, included considerations of fetal and infant safety in this document.

The Panel also considered mutagenic and carcinogenic potential, a relatively new aspect of ingredient and product safety. Several ingredients under review have been subjected to in vitro or in vivo (animal) screening, or both, for mutagenic-carcinogenic potential.

The Panel is also concerned about the lack of information on the possible absorption of these ingredients from the vagina into the systemic circulation. It has been well established that many ingredients can be absorbed in this manner. The Panel recognizes that the potential for the development of toxicity and sensitivity reactions is theoretically greater with the use of vaginal suppositories than with vaginal douches. Nonliquid vehicles, which are designed to keep the medication in the vagina for a longer period, allow greater opportunity for systemic absorption. The significance of this factor is unknown, because there are no relevant data available at the present. However, since the technology required to generate information in this area is now becoming available, the Panel recommends that appropriate vaginal absorption studies be conducted on all of these ingredients wherever feasible.

B. Data Search

Prior to the information of the Panel, the FDA Medical Library conducted a literature search covering relevant American publications between 1950 and 1973. Additionally, interested people and firms submitted data on the ingredients and products which were to be reviewed. After a thorough review of these data, the Panel noted that the majority of the references cited were 10 years old or older. Virtually no studies could be found which had been carried out in accordance with today's standards for the evaluation of possible teratogenic, mutagenic, carcinogenic, or toxic effects of the ingredients in these products.

Because there was very little information in both the submissions and the FDA literature search, the Panel conducted its own independent review of the pertinent world literature and asked medical and scientific journals to run advertisements requesting additional data. However, only a limited amount of new material was obtained as a result of these efforts.

At the Panel's request, the industry liaison submitted, in April 1974, a listing of articles entitled "Selective Biblography on Vaginal Contraception and Therapeutics" compiled by the Science Information Division of the Ortho Pharmaceutical Corporation. In addition, the Panel listened to testimony from interested parties and a number of invited consultants.

In summary, using every means at its disposal, the Panel attempted to gather and review all of the information available on the subjects under consideration before arriving at its conclusions and recommendations. However, the combined efforts described above served to substantiate the original observation that very little work had been done in this field in recent years.

C. Vaginal Anatomy and Physiology

The Panel reviewed both OTC vaginal contraceptives and other vaginal drug products. The background section on anatomy and physiology of the vagina was published in the **Federal Register** of December 12, 1980 (45 FR 82014) and will not be repeated in this document.

D. Drug Evaluation for Safety and Effectivensss

1. *Safety.* As all of the ingredients under its review are applied to the vagina, the Panel believes that the guidelines for safety testing are identical no matter what the ingredient, the vehicle, or the drug's intended pharmacological purpose. Although the Panel's discussion on safety testing as published in the **Federal Register** of December 12, 1980 (45 FR 82014) will not be repeated in this document, the Panel has included a comment on the safety of inactive ingredients contained in vaginal drug products (See part IV. paragraph D. below—Inactive Ingredients—Comments on Safety).

2. *Effectiveness.* Testing guidelines for vaginal drug products are outlined elsewhere in this document. (See part IV. paragraph F. Below—Testing Guidelines for Effectiveness of Vaginal Drug Products.) That portion of the Panel's review which deals with the effectiveness testing of vaginal contraceptive drug products was published in the **Federal Register** of December 12, 1980 (45 FR 82014).

E. Advertising

The Panel is aware that FDA has jurisdiction over the labeling but not the advertising of OTC drugs. Having completed its review of labeling provided in the submitted data and information, the Panel is concerned that control of labeling alone may be insufficient to assure the safe and effective use of vaginal drug products.

The Panel, therefore, concludes that the advertising of these products must be carefully monitored by those having the appropriate jurisdiction. Such advertising should carry over, reflect, or incorporate the approved terms and statements found in product labeling in the monograph which specify the indications for use, contraindications, and appropriate warnings to the consumer.

F. Labeling

The Panel reviewed the general and specific labeling requirements previously adopted by FDA for OTC drug products in Part 201 (21 CFR 201) and Part 369 (21 CFR 369). These regulations relate to labeling information concerning the identity of ingredients, directions for use, and general and specific warnings. The Panel considered these regulations and concludes that, in general, these requirements are appropriate for OTC vaginal drug products. The term "labeling," as understood by the Panel, refers to any language developed for the consumer and placed upon the carton, the container, and package inserts. Any special labeling which the Panel believes is indicated for a particular

ingredient will be included in the ingredient evaluations below.

According to its mandate, the Panel reviewed and classified all of the labeling terms on the products submitted. Those terms classified in Category I are appropriate and may continue to be used. Terms in Category II are vague, poorly defined, or apt to promote impressions of unproven effectiveness. The Panel believes that the claims in Category III are potentially provable by scientific methods, but adequate data were not submitted to allow their approval as Category I claims. Any manufacturer who wishes to perform the necessary research to substantiate such claims should do so and submit the results to FDA for approval.

After careful consideration of all labeling submitted, the Panel recommends the following general labeling guidelines:

1. *Indications for use.* The indications for use should be simply and concisely stated. They should enable the consumer to have a clear understanding of the results which can be anticipated from the use of the product. Any statement regarding the indications for use should be specific and should be confined to the conditions for which the product is being recommended. A vaginal drug product may not contain additional indications for use on other areas of the body unless there are sufficient valid data to support such claims.

Claims of therapeutic benefit for treatment of specific vaginal infections must be restricted to professional labeling, e.g., for the treatment of trichomoniasis or moniliasis. Furthermore, any claim of such therapeutic benefit shall be based upon valid studies of effectiveness, by documenting cures proven by repeated cultures following the treatment regimen outlined for each specific infection for which a professional labeling claim is to be made.

2. *Ingredients.* The Panel concludes that it is important for the consumer to know all of the ingredients in a product because of the possibility of allergic states and idiosyncracies. For example, although aromatic compounds such as perfumes have no pharmacologic activity in vaginal drug products, these agents should be listed on the label because of their potential to sensitize. Although the Panel recognizes that current statutes require that only the active ingredients be listed, it strongly recommends that all inactive ingredients (including those which are necessary for formulation and product identification) also be listed, preferably with a statement of their quantity in metric units. The Panel further concludes that no product should be promoted on the basis of its inactive ingredients, nor should the label create a false impression of value beyond that which is scientifically valid.

3. *Principal display panel.* The Panel is aware of the current regulations regarding the principal display panel, statement of identity , and the declaration of net quantity of contents for OTC drugs and concurs with those requirements (21 CFR 201.60, 201.61, and 201.62).

4. *Effectiveness and claimed advantages.* After reviewing the claims made by manuffcturers of vaginal drug products, the Panel concludes that certain claims for effectiveness have been made in the past without valid supporting data. Any language which promises specific health benefits which are unsubstantiated by the scientific information submitted is unacceptable. Futhermore, claims may not be used to promote the sale of these products unless these claims are specifically approved by the panel as set forth in this document. For example, manufacturers may not make use-effectiveness or comparative-effectiveness claims such as "better than" or "the most" unless valid scientific data have been provided upon which to base these claims. Further details on specific claims will be included in the appropriate sections of this document.

5. *Directions for use and warnings.* The label should consist of a clear statement of the usual effective dose. The phrase "except under the advice and supervision of a physician" should appear where appropriate. When an ingredient is known to induce a somewhat higher than average incidence of hypersensitivity reactions, an additional warning stating this fact should be included on the label.

G. Combination Policy

The Panel notes the regulation in 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 observed that a number of the vaginal preparations under its review contain multiple ingredients. However, the Panel concludes that, in general, the fewer ingredients in a combination product, the safer and more rational the therapy. It further concludes that consumers should be exposed to the fewest possible ingredients and at the lowest possible dosage consistent with a satisfactory level of effectiveness. Thus, in gereral, OTC products containing a single, safe, and effective active ingredient are to be preferred over those having multiple active ingredients. Such an approach is totally in accord with established medical principles and will reduce the risks of toxic, allergic, or idiosyncratic reactions, as well as the possibility of unrecognized or undesirable drug interactions. The Panel concludes that OTC combination drugs should contain only those inactive ingredients which are absolutely essential for pharmaceutical necessity of product indentification. As previoulsy stated, the Panel believes that a listing of these inactive ingredients and the quantities present should be included in the product labeling. (See part II. paragraph F. above-Labeling.)

The Panel concludes that combination vaginal drug products should contain more than one active ingredient only if each of the ingredients is not only safe, but also makes a clear and specific contribution to the claimed effectiveness of the product.

1. *Combinations of Category I ingredients.* With regard to the vaginal products under its review, the Panel concludes that there are insufficient data to support combining any two or more Category I ingredients. Therefore, if a manufacturer combines two or more Category I ingredients, the specific ingredients as well as the combination product must be subjected to laboratory and clinical testing using the recommended testing guidelines for effectiveness outlined elsewhere in this document. (See part IV. paragraph F. below—Testing Guidelines for Effectiveness of Vaginal Drug Products.)

2. *Category II combinations.* The Panel concludes that any combination vaginal drug product which contains a Category II ingredient is to be placed in Category II. The Panel fully realizes that its recommendation pertains to the drug use of these combination products and not to the cosmetic use. However, the Panel recommends to FDA that any Category II ingredient which causes a combination product to be placed in Category II by virtue of its lack of safety be removed from the product regardless of whether its intended vaginal use is as a drug or as a cosmetic. This recommendation is made to ensure that

the consumer is not exposed to ingredients which this Panel has judged to be unsafe.

The following combinations reviewed by the Panel contain at least one Category II ingredient. The Panel therfore concludes that these combinations are unsafe or ineffective for any OTC vaginal use.

a. Hexachlorophene, boric acid, zinc sulfate, potassium aluminum sulphate, tartaric acid, camphor, phenol, and octoxynol 9.

b. Phenol (greater than 1.5 percent), sodium borate, and sodium salicylate.

c. Sodium salicylic acid phenolate (greater than 1.5 percent phenol), boroglycerin (greater than 1 percent boron), and benzocazine.

d. Sodium salicylic acid phenolate (greater than 1.5 percent phenol), boroglycerin (greater than 1 percent boron), benzocaine, and povidone-iodine.

3. *Category III combinations.* The Panel concludes that available data are insufficient to permit final categorization of the following combination products.

The Panel recommends that these combinations be subjected to the appropriate testing guidelines for effectiveness for the specific indication which is claimed. (See part IV. paragraph F. below—Testing Guidelines for Effectiveness of Vaginal Drug Products.) If any of the ingredients in these combinations require evaluation for safety, this evaluation should be done in accordance with the safety guidelines contained in part II. paragraph D—Drug Evaluation for Safety—of the Panel's review of OTC vaginal contraceptive drug products published in the **Federal Register** of December 12, 1980 (45 FR 82020).

a. Citric acid and papain.

b. Oxyquinoline sulfate, alkyl aryl sulfonate, and disodium edetate.

c. Nonoxynol 9 and sodium edetate.

d. Alum (ammonium) and zinc sulfate.

e. Benzalkonium chloride and disodium edetate.

f. Sodium lactate, lactic acid, and octoxynol 9.

g. Phenol and sodium phenolate.

h. Sodium lauryl sulfate, sodium bicarbonate, and sodium carbonate.

i. Stabilized aloe vera gel, allantoin, vitamin A, and vitamin D.

j. Sodium perborate, sodium borate, and sodium lauryl sulfate.

k. Oxyquinoline citrate, boric acid alum, and zinc sulfate.

l. Sodium lauryl sulfate, sodium perborate, and sodium borate.

m. Calcium propionate, sodium propionate, and boric acid.

n. Sodium borate and sodium lauryl sulfate

III. Vaginal Drug Products

A. Introduction

The Panel was unable to find standard acceptable definitions of a "vaginal douche" and of a "vaginal suppository." It also had difficulty in attempting to define the actions of specific ingredients present in vaginal drug products. Therefore, in order to aid in the categorization of the ingredients under its review, the Panel developed the following definitions which are stated in terms of the actions of the ingredients.

B. Definitions of Terms

1. *Vaginal douche.* A vaginal douche is a liquid preparation used to irrigate the vagina over an indeterminate period for one or more of the following purposes; (1) cleansing, (2) producing soothing and refreshing effects, (3) deodorizing, (4) relieving minor irritations, (5) reducing the number of pathogenic microorganisms, (6) altering the pH so as to encourage the growth of normal vaginal flora, (7) producing an astringent effect, (8) lowering surface tension, (9) producing a mucolytic effect, or (10) producing a proteolytic effect.

2. *Vaginal suppository.* A vaginal suppository is a small globular mass, designed for easy introduction into the vagina. It is usually made of two major components—a vehicle and one or more chemical agents. It is solid at room temperature and either liquifies at body temperature or dissolves in vaginal fluids. Vaginal suppositories are designed to be used for one or more of the following purposes: (1) Producing soothing and refreshing effects, (2) deodorizing, (3) relieving minor irritations, (4) reducing the number of pathogenic microorganisms, (5) altering the pH so as to encourage the growth of normal vaginal flora, or (6) producing an astringent effect.

C. General Discussion

1. *Drug vs. cosmetic status.* The Panel reviewed the definitions of "drugs" and "cosmetics" as set forth in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)(1)(B) and (i)(1)). With regard to the labeling of vaginal douches, it also reviewed the historical position of FDA in § 369.20 (21 CFR 369.20) which recommends that the label bear a statement, "Warning: Do not use more often than twice weekly unless directed by physician."

The Panel decided that certain labeling claims for vaginal products more properly fall within the cosmetic category, while other claims fit more accurately into the drug category. In this regard, the Panel recognizes that vaginal douches and suppositories may be viewed by a consumer as either cosmetics or drugs.

If the use of a vaginal douche produces only transitory changes in an essentially normal vagina by the removal of secretions and bacteria for example, it is then considered as having only a cleansing effect and thus may be classified as a cosmetic. However, the Panel observed that in the Federal Food, Drug, and Cosmetic Act the term "drug" means "articles intended for the use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" (21 U.S.C. 321(g)(1)(B)). Therefore, the Panel concludes that certain ingredients in vaginal douches and suppositories under its review fall into this category as they prevent, mitigate, or treat disease. For example, ingredients may produce a beneficial effect by removing secretions and changing the vaginal flora either by suppressing or actually eliminating specific pathogens. In this instance, the Panel concludes that these agents are exerting a therapeutic effect and, therefore, are classified as drugs.

This classification as drug or cosmetic is determined by both the type of claim made for the product and the type and strength of ingredients present in the product. If an active ingredient is present in a therapeutic concentration, the product is a drug, even if that prouduct does not claim to produce the effect which will result from the action of the therapeutically effective ingredient.

As the result of its extensive deliberations on this matter, the Panel concludes that the first three parts of its definition of a vaginal douche are cosmetic claims, since the washing of any surface will result in: (1) Cleansing, and may also produce (2) soothing and refreshing, and (3) deodorizing effects. Similarly, the Panel concludes that the first two parts of its definition of a vaginal suppository: (1) Producing soothing and refreshing effects, and (2) deodorizing, are cosmetic claims. Vaginal products which make these claims only are not under the purview of this Panel and do not require testing for effectiveness.

The Panel deliberated at length as to whether the term "deodorant" should be regarded as a drug or cosmetic claim for a vaginal preparation. Taking into consideration the cosmetic product warnings in 21 CFR 740.12 with regard to feminine deodorant sprays, the Panel concludes that a deodorant claim for a vaginal preparation constitutes a cosmetic claim.

In the Panel's opinion, the consumer generally believes that an offensive odor is diminished by a deodorant rather than simply being masked by a pleasant odor. Therefore, the Panel recommends that until a uniform definition of the term "deodorant" is rendered by FDA, and explicit statement describing the mode of action of a deodorant should be included in vaginal product labeling because the consumer is entitled to this information and should be told.

A deodorant may be effective because it: (1) Cleanses the vagina by removing secretions, seminal fluid, and contraceptive products; (2) reduces the number of microorganisms that cause vaginal and vulvar odors; or (3) masks the odors with a pleasant odor. Because currently marketed deodorants do not actually destroy disagreeable body odors but only diminish the perception of these odors, the Panel recommends that the term "destroys odor" not be incorporated into the labeling of deodorant vaginal products because it is not accurate. (See part IV. paragraph B.4. below—Category II labeling.)

The other actions of vaginal drug products ((4) through (10) for vaginal douches and (3) through (6) for vaginal suppositories) must be substantiated by testing if a claim is to be made, as discussed later in this document. (See part IV. paragraph G. below—Testing Guidelines for Effectiveness of Ingredients in Vaginal Drug Products.) Testing guidelines for vaginal suppositories marketed with a contraceptive claim were outlined in the Panel's review of vaginal contraceptive drug products, published in the **Federal Register** of December 12, 1980 (45 FR 82014).

2. *The use of precoital douching to influence the sex of offspring.* A method of influencing the sex of offspring by using acid or basic douches precoitally has been proposed and promoted by Shettles (Refs. 1 and 2), who claims an 80-percent success rate for his method. His basic assumption is that the X-bearing sperm (the female determinant) is larger, stronger (longer-lived), and more resistent to destruction by an acid environment than the smaller, Y-bearing sperm (the male determinant). According to his theory, just before or at the time of ovulation, the cervical mucous is most alkaline and, therefore, prone to favor male offspring; at other times of the cycle, fertilization is more likely to result in female offspring. In order to conceive a child of the desired sex, Shettles suggests that intercourse should be scheduled for those times when cervical mucous is more favorable to either X- or Y-bearing sperm. Shettles also proposes that alkaline or acid douches (soda acid or vinegar) can be used precoitally to alter the pH and facilitate the desired results.

Shettles' claim of 80 percent effectiveness when utilizing the entire method (douching, timing, etc.) has been supported by the work of one investigator who worked with artificial insemination (Ref. 3); others, however, have not been able to duplicate this work (Refs. 4 and 5). In vitro, it does not appear that the rate of X or Y sperm migration is influenced by the pH of the environment (Ref. 6). Much of the work in sex preselection using various methods, including douches, was reviewed by Glass (Ref. 7), and his conclusion was that it "would not be accurate to tell prospective parents that they can choose the sex of their child" using these methods. On the other hand, there are no reports of detrimental effects from using these methods other than the disappointment in failing to achieve the desired results; thus it does not appear necessary to warn against their use.

3. *Labeling guidelines for vaginal douches.* The Panel reviewed the history of douching as both a therapeutic and an elective procedure. There are no data to demonstrate clearly that routine douching is necessary for the normal, healthy woman. On the other hand, there would appear to be no medical contraindication to douching for the normal, healthy, nonpregnant woman who believes that she derives some benefit from this practice.

a. *Method of douching.* In order to develop guidelines and recommendations for the proper labeling of ingredients, the Panel believes that it is necessary to consider simultaneously the safety and the effectiveness of the method by which ingredients are delivered. Vaginal douching requires such consideration because:

(1) Its primary purpose is the irrigation of a body cavity (the vagina) lined by an absorptive mucosa which is, in itself, susceptible to chemical, mechanical, and thermal injury.

(2) The vagina is in direct continuity with the internal organs of reproduction (i.e., the uterus and fallopian tubes) and the abdominal cavity. In addition, it has a commonly derived and interrelated blood supply and lymphatic drainage with these organs.

(3) Improper douching practices and improper care of equipment may lead to pathogenic microorganisms being introduced into the vagina and upper reproductive tract.

As previously stated, the Panel concludes that there is no proven therapeutic usefulness for routine douching by the normal, healthy woman; however, the Panel is concerned with the methods of nontherapeutic douching insofar as safety to the consumer is concerned. The Panel disagrees with the practice, as recommended in several package inserts which it reviewed, of occluding the vaginal opening until the woman notes a sensation of fullness in the vagina or the lower abdomen, supposedly indicating distentation of the vagina with the fluid. Several reports in the literature suggest the possibility that douche fluid may be carried through the uterus and fallopian tubes and cause chemical pelvic peritonitis (Refs. 8 through 11). In one of these reports, the apparent relationship of peritonitis to occlusive or pressure douching is detailed in five cases (Ref. 10).

Although a causal relationship between the practice of vaginal occlusion during douching and peritonitis is not completely established by these reports, the Panel believes that common sense dictates that the use of high intravaginal hydrostatic pressure is potentially dangerous and that the warning based upon a "feeling of fullness" is too vague and variable to be of significant value in preventing injury. The Panel recommends that any reference to occlusion of the vaginal opening during douching be removed from all labeling, and that this practice be discouraged except at the direction of a physician.

b. *Contraindications.* There are no data available relative to the safety of douching during pregnancy. From a study of 1,600 women, of whom 510 were pregnant, approximately 12 percent of the pregnant women douched; Stock, Stock, and Hutto (Ref. 12) concluded that, in the absence of complications of pregnancy, such a practice would seem to be harmless. On the other hand, several reports detail case studies of fatal air embolism in pregnancy following vaginal insufflation with chemical powder (Refs. 13 through 16) and with air blown into the vagina during oral-genital sex play (Ref. 17).

In one article reviewed by the Panel, the author noted: "Pregnant women should never douche. Especially dangerous is the use of a syringe. Air may be forced into the uterine blood vessels with consequent fatal air embolism. Embolism with soap or disinfectant solutions may lead to intravascular hemolysis, also with fatal consequences" (Ref. 18). Several of the Panel members reported clinical experiences with the latter type of case in self-induced abortions, as well as the transtubal passage of douche solutions

used for the same purpose. The increased vascularity of the uterus in pregnancy, the volume of the uteroplacental blood flow, and the large surface area of the vascular placental site all combine to place the pregnant woman at increased risk for these vascular accidents.

In addition, potential complications include the initiation of bleeding due to the detachment of placental implantation, rupture of the chorioamniotic membrance, introduction of intrauterine infection, and adverse effects of chemicals, either direct or absorbed, on the developing fetus.

The Panel concludes that the real and potential dangers associated with routine douching during pregnancy outweigh any possible benefits. The Panel, therefore, recommends that labeled instructions include an admonition against douching during pregnancy except on the advice and instruction of a physician.

Additionally, the Panel believes that there is a misconception among the public that douching is effective as a means of preventing pregnancy. All available data, however, suggest that douching is ineffective for this use (Ref. 19); and the Panel, therefore, believes that this should be prominently stated in all labeling.

c. *Limitations*—(1) *Frequency.* The Panel examined at length the issue of the frequency of nontherapeutic douching as stated in the labeling instructions given to the consumer. Instructions on all current labels caution against douching more than twice weekly except on the advice of a physician. Review of the scientific literature has failed to reveal data to support this labeling restriction. In fact, several studies report only transient effects, if any, of douching on the vaginal pH, and no adverse effects of daily douching on the vaginal mucosa (Refs. 20, 21, and 22).

There is no proof that the frequency of douching plays a role in adversely modifying the vagina flora, encouraging the development of chemical vaginitis, or producing injury due to resultant excessive dryness in most women. However, it must be noted that these effects have been observed, indicating that adverse effects will vary from one woman to another and from one solution to another. Therefore, the Panel recommends that no restriction be placed on the frequency of using OTC vaginal douches.

(2) *Adverse reactions.* Some individuals may experience adverse reactions to one or more of the ingredients present in a douche. Sensitivity may be signaled by the development of vaginal itching, redness, swelling, or pain in the vagina after douching. The onset of abdominal or vaginal pain while douching may be indicative of improper use of the douche, excessively high temperature of the fluid, or the presence of a serious disorder within the pelvic region.

The consumer should be warned of the potential for these adverse reactions and cautioned to discontinue douching and consult a physician if symptoms persist.

(3) *Minor vaginal irritation.* Although the Panel is unaware of any serious consequences which may result from prolonged douching, it believes that a specific time limitation of 1 week should be placed on the self-treatment of minor vaginal irritation or itching. If significant improvement has not occurred by that time the patient should consult a physician.

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IV. Categorization of Vaginal Drug Products

The following chart is included to assist the reader in quickly identifying each active ingredient claim and the category to which the Panel assigned the ingredient for that claim.

CATEGORIZATION OF ACTIVE INGREDIENTS

Active ingredients	Relief of minor irritation	Alters pH	Astringent	Lower surface tension and mucolytic
Acetic acid		III		III.
Alkyl aryl sulfonate				
Allantoin	III.			
Aloe vera, stabilized	III.			
Alum			III.	
Benzalkonium chloride	III.			
Benzethonium chloride	III.			
Benzocaine	III.			
Boric acid	III.	III.	III.	III.
Boroglycerin	III.	III.	III.	III.
Calcium and sodium propionate	I.			
Citric acid		III.		
Dioctyl sodium sulfosuccinate				I.
Edetate disodium	III.			
Edetate sodium	III.			
Hexachlorophene	II.			

CATEGORIZATION OF ACTIVE INGREDIENTS—Continued

Active ingredients	Relief of minor irritation	Alters pH	Astringent	Lower surface tension and mucolytic
Latic acid		III		
Nonoxynol 9	III			
Octoxynol 9	III			I.
Oxyquinoline citrate	III			I.
Oxyquinoline sulfate	III			
Papain				
Phenol	II			III.
Phenolate sodium	II			
Potassium sorbate	I			
Povidone-iodine	I			
Sodium bicarbonate		III		
Sodium borate	III	III		III.
Sodium carbonate		III	III	III.
Sodium lactate		III		
Sodium lauryk sulfate				
Sodium perborate	III	III	III	I.
Sodium salicylate	II			III.
Sodium salicylic acid phenolate	II			
Tartaric acid		III		
Zinc sulfate			III	

A. Category I Conditions

The following are Category I conditions under which vaginal drug products are generally recognized as safe and effective and not misbranded:

1. *Category I active ingredients*—a. *Ingredients for the relief of minor irritations of the vagina.*

Propionate (calcium or sodium salts)
Potassium sorbate
Providone-iodine

(1) *Propionate (calcium or sodium salts).* The Panel concludes that the propionates in concentrations up to 20 percent are safe and effective for OTC use in vaginal drug products which claim to relieve minor irritations of the vagina.

(i) *Safety.* Propionates are used extensively in the baking and dairy industry for mold retardation. Veterinarians use them for treating wound infection, otitis, conjunctivitis, and vaginitis; and they are used topically in humans to control otomycosis and epidermophytosis in a 0.5- to 10-percent concentration range (Ref. 1). The safety of these compounds is well established in the literature. Their acute toxicity is so low that it does not seem necessary or practical to determine the LD_{50} (Ref. 2). One investigator reported that 20 percent solutions caused no harmful effect in rabbit eyes (Ref. 3). A 10-percent solution, with a pH of 7.2, applied to the conjuntiva and nasal mucosa of human subjects caused only slight, temporary stinging; when applied to the intact skin of human subjects, 20 percent solutions, with pH values ranging from 7 to 8.5, produced no appreciable irritation (Ref. 3). The Panel, therefore, concludes that the propionates are safe for OTC use at concentrations up to 20 percent.

(ii) *Effectiveness.* The propionates are fungiostatic and bacteriostatic against a number of gram-positive cocci. Substantial clinical data have been submitted on a product containing the propionates that has been marketed for 30 years as a prescription item. These data show an 80-percent remission of itching and ultimate cure in nonpregnant women with mycotic vaginitis (Ref. 2). Even though these studies are 30 years old, enough data were presented to prove to the Panel that these ingredients would be of benefit to women with minor irritations of the vagina and that they are appropriate for OTC use within the labeling guidelines established below. (See Part IV. paragraph A.2.c.(1) below—Ingredients for the relief of minor irritations of the vagina.) Therefore, the Panel concludes that the propionates are effective ingredients for OTC use in the relief of minor irritations of the vagina. The only formulation reviewed by the Panel was a vaginal gel (Ref. 2).

(iii) *Dosage and directions.* The Panel recommends that propionates be used in vagina doses of up to 2.3 grams (g) in concentrations of up to 20 percent in a vaginal gel twice daily.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) below—Ingredients for the relief of minor irritations of the vagina.)

(v) *Professional labeling.* The Panel is aware that the propionates are safe and effective for the physician-supervised treatment of *Candida albicans.* Therefore, the following professional labeling claim may be made for its use. "For the treatment of *Candida albicans.*" The Panel emphasizes that this is not an OTC labeling claim and should not appear on any consumer labeling which accompanies a vaginal drug product containing the propionates. Professional labeling for vaginal drug products in general is discussed elsewhere in this document. (See part IV. paragraph A.2.d. below—Professional labeling.)

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(2) *Potassium sorbate.* The panel conculdes that potassium sorbate in a concentration of 1 to 3 percent is safe and effective for OTC use as a vaginal douche for the relief of minor irritations of the vagina.

(i) *Safety.* The sorbates have been safely used as mold inhibitors in food for 20 years (Ref. 1) The Panel reviewed many animal and human toxicity tests using potassium sorbate (Refs. 2 and 3) and determined that the vaginal use of this ingredient does not pose any safety problem. The oral LD_{50} for potassium sorbate in rats has been found to be 7,360 milligrams per kilogram (mg/kg) of body weight.

In addition to the fact that this compound is nontoxic when ingested orally and applied vaginally, the Panel noted that in two studies of 132 and 122 women who used potassium sorbate for yeast vaginitis (*Candida albicans*), no incidence of allergic reaction or mucosal irritation was reported with the use of 1 and 5 percent solutions (Refs. 2 and 3). Burning sensations did result from the use of a 10-percent solution of potassium sorbate. The Panel concludes that potassium sorbate is safe for OTC use.

(ii) *Effectiveness.* The Panel reviewed clinical data which support the use of potassium sorbate in vaginal douches for the treatment of minor vaginal irritations. In one study of 132 women with longstanding yeast infections, the vagina was wiped clean and painted with a 1-percent solution of potassium sorbate in water or a 1-percent douche solution was used. in many of these cases, symptoms of irritation subsided after an initial treatment, and symptoms of irritation were still absent several months afterward. Objectively, cytologic smears (agar cultures) demonstrated diminished yeast growth after treatment with potassium sorbate (Ref. 2).

In a second study of 122 women (61 having yeast vaginitis alone, 51 having a mixture of yeast vaginitis plus *Trichomonas vaginalis,* and 10 having

Trichomonas vaginalis alone), the use of both 1-percent and 3-percent solutions (saturated cotton tampons) of potassium sorbate resulted in the gradual disappearance of symptoms in an average of 10 days for the 1-percent solution and an average of 7 days for the 3-percent solution. Objective signs of yeast infection gradually disappeared in an average of 14 days for the 1-percent solution and average of 7 days for the 3-percent solution. The investigators indicated that the use of a 3-percent solution resulted in fewer recurrences after therapy was discontinued (Ref. 3). The Panel concludes that potassium sorbate is effective for OTC use in the relief of minor irritations of the vagina.

(iii) *Dosage and directions.* The Panel recommends that potassium sorbate be used as a vaginal douche in a concentration of 1 to 3 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) below—Ingredients for the relief or minor irritations of the vagina.) The Panel also recommends Categhory I labeling for vaginal douches. (See part IV. Paragraph A.2.a. below—Package inserts for vaginal douches, and part IV. Paragraph A.2.b. below—Principal display panel.)

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(3) McKinnon, D. A., and E. B. Rodgerson, "Use of Potassium Sorbate for Treatment of Fungal Infections," *Obstetrics and Gynecology,* 45:108-110, 1975.

(3) *Providone-iodine.* The Panel concludes that providone-iodine in a concentration of 0.15 to 0.3 percent is safe and effective for OTC use as a vaginal douche for the relief of minor irritations of the Vagina.

(i) *Safety.* Acute and chronic toxicity studies of providone-iodine in animals and humans have shown little local or general toxicity and few sensitizations. In experimental animals, dilute solutions cause little or no irritation or sensitivity reaction when applied to open wounds, oral mucosa, vaginal mucosa, and the eye (Refs. 1 through 5). In its review, the Panel found ample evidence from clinical studies in humans attesting to the absence of significant local or general toxicity when providone-iodine, both in undiluted form and as a dilute douche, was used to cleanse and disinfect skin and mucous membranes (Refs. 2 and 6 through 16).

Providone-iodine is absorbed from mucous membranes and causes a transient rise in the serum protein-bound iodine level, athough proof of this is not constant in all studies. This elevation returns to normal in 7 to 30 days, and there is no evidence that this has clinical significance with respect to thyroid function (Refs. 9 through 12 and 16).

Two reports were reviewed which demonstrate that providone-iodine is capable of modifying the deoxyribonucleic acid of both bacterial and human diploid cells in vitro (Refs. 17 and 18). In certain cases, chemical modification of deoxyribonucleic acid has been shown to result in mutagenic alteration which, in turn, has been related to carcinogenic potential in animals (Ref. 19). Criticism of these studies (Refs. 20 and 21) emphasized that the altered environment conditions required for expression of the mutagenic potential in the bacterial system study, and the deoxyribonucleic stand-breakage in cultured human diploid cells treated with povidone-iodine may not be evidence of mutation, but rather a cytotoxic effect.

The Panel also reviewed the results of additional cytogenic toxicity and mutagenic studies (Refs. 20, 21, and 22). These studies included: micronucleus test, chromosome examination using bone marrow cells from Chinese hamsters, dominant lethal test, a mouse lymphoma assay, and a mammalian cell transformation assay. The test results were all negative for the mutational or clastogenic effect of providone-iodine.

In addition, the Panel reviewed a providone-iodine migration and absorption study in three experimental animal species using radioactively tagged providone-iodine (Ref. 20). Although there was evidence of absorption of iodine from the vagina into the systemic circulation, these experiments showed little or no flow of radioactively tagged providone-iodine into the uterus from the vagina. The Panel believes that the weight of the evidence is sufficient to conclude that povidone-iodine does not have a significant mutagenic or carcinogenic effect.

The Panel concludes that providone-iodine is safe when used as an OTC vaginal douche for the relief of minor vaginal irritations.

(ii) *Effectiveness.* Microbiocidal effectiveness of providone-iodine has been clearly demonstrated by in vitro studies against a variety of pathogenic bacteria, fungi, and protozoan organisms. Spermicidal and antiviral activity has also been demonstrated (Refs. 23, 24, and 25). In clinical studies, povidone-iodine has been shown to disinfect skin and mucous membrane, and to be effective as a cleansing douche (Refs. 13 and 26 through 30). The Panel concludes that povidone-iodine is effective when used as an OTC vaginal douche for the relief of minor vaginal irritations.

(iii) *Dosage and directions.* The Panel recommends that providone-iodine be used as a vaginal douche in a concentration of 0.15 to 0.3 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) below—Ingredients for the relief of minor irritations of the vagina.)

(v) *Professional labeling.* The following claims are supported by the submitted evidence and may be used only in professional labeling.

(*a*) The claim of "microbiocidal douche" is well supported by both in vitro and in vivo studies (Refs. 1, 2, 23, 24, 25, and 30).

(*b*) The claim of "clinically effective in vaginal moniliasis, T-vaginales vaginitis, and nonspecific vaginitis" is adequately supported by the data presented. However, because the treatment regimen includes the use of the dilute douche combined with application of the full-strength solutions to the vaginal mucosa, it is recommended that the labeling be changed to include the words "clinically effective in a program of treatment for . . . ."

(*c*) The professional labeling should also detail the therapeutic regimen used in the studies which resulted in clinical effectiveness so that the physician may appropriately advise the patient.

(*d*) While not affecting its safety, the possible effect of providone-iodine on serum protein-bound iodine should be made a part of labeling as a matter of information to the physician. The following wording is recommended: "The use of providone-iodine as a douche may cause a transient rise of serum protein-bound iodine."

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b. *Ingredients which lower surface tension and which produce a mucolytic or proteolytic effect.*

Anionic surface active agents (dioctyl sodium sulfosuccinate or sodium lauryl sulfate)

Nonionic surface active agents (nonoxynol 9 or octoxynol 9)

(1) *Anionic surface active agents (dioctyl sodium sulfosuccinate or sodium lauryl sulfate).* The Panel concludes that the anionic surface active agents dioctyl sodium sulfosuccinate and sodium lauryl sulfate in a concentration of 0.002 and 0.02 percent are safe and effective for OTC use as a vaginal douche to produce a mucolytic effect.

(i) *Safety.* Long-term toxicity studies in which animals (principally rats) were given these ingredients orally and intraperitoneally revealed that the toxic and lethal concentrations are extremely high when compared to the concentrations normally used in vaginal douche products (Refs. 1, 2, and 3). Human safety data show high oral tolerance (Ref. 4). Tests of local application of solutions of 1 percent or greater to mucous membranes have demonstrated irritation (Refs. 5 and 6), but this is a significantly greater concentration than the final concentration (0.00235 percent) generally used in vaginal douche products.

In a 25-percent concentration, sodium lauryl sulfate serves as a tumor "promoter" on mouse skin. However, this activity rapidly diminishes with reduced concentrations, and the ingredient has been shown to have no such activity at a 2-percent or lower concentration (Ref. 7). The Panel concludes that the testing proved that the ingredients are safe at concentrations of 0.2 percent or less.

(ii) *Effectiveness.* The anionic surface active agents are generally recognized as wetting, solubilizing, and mucolytic agents and are widely used as such by the pharmaceutical industry (Ref. 8).

The Panel is aware of an in vitro test which showed that sodium lauryl sulfate was active in lysing trichomonads and bacteria (Ref. 9). (This can be extrapolated to pertain also to dioctyl sodium sulfosuccinate.) This same study gave evidence of the in vivo mucolytic effect of the ingredient in a douche. The Panel, therefore, concludes that these two ingredients are recognized as mucolytic agents.

(iii) *Dosage and directions—(a) For products containing dioctyl sodium sulfosuccinate.* The Panel recommends that dioctyl sodium sulfosuccinate be used as a vaginal douche in a concentration of 0.002 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(b) For products containing sodium lauryl sulfate. The Panel recommends that sodium lauryl sulfate be used as a vaginal douche in a concentration of 0.01 to 0.02 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which lower surface tension and produce a mucolytic effect. (See part IV. paragraph A.2.c.(4) below—Ingredients which lower surface tension and produce a mucolytic effect.) The Panel also recommends Category I labeling for vaginal douche products. (See part IV. paragraph A.2.a. below—Package inserts for vaginal douches, and part IV. paragraph A.2.b. below—Principal display panel.) In addition, the Panel recommends that the following warning be required for these two ingredients when they are in concentrated forms which require mixing: "Avoid prolonged contact with the skin and avoid contact with the eyes."

(v) *Professional labeling.* The Panel concludes that sodium lauryl sulfate and

dioctyl sodium sulfosuccinate are safe and effective for the physician-supervised treatment of *Trichomonas vaginalis* (Ref. 9). Therefore, the following professional labeling claim may be made for their use. "For the treatment of *Trichomonas vaginalis*." The Panel emphasizes that this is not an OTC labeling claim and should not appear on any consumer labeling which accompanies a vaginal douche product containing sodium lauryl sulfate or dioctyl sodium sulfosuccinate. Professional labeling for vaginal drug products in general is discussed elsewhere in this document. (See part IV. paragraph A.2.d. below—Professional labeling.)

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(2) *Nonionic surface active agents (nonoxynol 9 or octoxynol 9).* The Panel concludes that the nonionic surface active agents nonoxynol 9 and octoxynol 9 in concentrations of 0.0176 and 0.088 percent, respectively, are safe and effective for OTC use as a vaginal douche to produce a mucolytic effect.

(i) *Safety.* Nonoxynol 9 and octoxynol 9 are widely used in pharmaceutical preparations as nonionic surfactants. They have significant advantages over ionic surfactants with respect to stability and compatibility (Ref. 1). The Panel reviewed numerous animal eye and skin irritation studies which used concentrations of up to 25 percent and which showed slight to moderate irritation (Refs. 2 through 10). However, even at 100 percent concentration, these ingredients rarely sensitize or irritate human skin or mucous membranes. Manifestation of symptoms in animals dosed orally is related to gastrointestinal irritation, i.e., diarrhea and bloating, with little, if any, intestinal absorption or decomposition (Ref. 11).

The safety of these two ingredients was discussed in more detail in that portion of the Panel's review which dealt with OTC vaginal contraceptives, published in the **Federal Register** of December 12, 1980 (45 FR 82028–82030).

(ii) *Effectiveness.* The nonionic surface active agents are generally recognized as wetting, solubilizing, and mucolytic agents, widely used as such by the pharmaceutical industry. Since they act as detergents, the Panel has determinded that these two ingredients are to be considered effective mucolytic agents. The only dosage form containing these ingredients that the Panel reviewed was a vaginal douche (Refs. 8 and 10).

(iii) *Dosage and directions—(a) For products containing nonoxynol 9.* The Panel recommends that nonoxynol 9 be used as a vaginal douche in a concentration of 0.0176 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(b) For products containing octoxynol 9. The Panel recommends that octoxynol 9 be used as a vaginal douche in a concentration of 0.088 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which lower surface tension and produce a mucolytic effect. (See part IV. paragraph A.2.c.(4) below—ingredients which lower surface tension and produce a mucolytic effect.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. below—Package inserts for vaginal douches, and part IV. paragraph A.2.b. below—Principal display panel.)

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2. *Category I labeling.* The following specific labeling requirements are furnished to elaborate on the general labeling guidelines discussed elsewhere in this document. (See part II. paragraph F. above—Labeling.)

a. *Package inserts for vaginal douches.* The Panel has reviewed all of the currently used package inserts which provide the consumer general instructions for douching. The Panel concludes that the required information should be included in a package insert or other appropriate labeling. This information should be presented in language which can be easily read, easily understood, and readily retained by the consumer. At a minimum, this information should incorporate warnings and directions for douching.

Package inserts for use in professional labeling, e.g., in the treatment of vaginitis, should be separately prepared since the instructions for recommended method, frequency, and duration of treatment will differ significantly from those included with products intended solely for OTC use.

(1) *Recommended methods for douching.* The Panel reviewed the methods of douching as submitted by manufacturers of the various products. It observed that the instructions given to the consumer as to the use of these products and the required equipment ranged from none to explicit diagramed instruction sheets.

The Panel recommends that the following directions be included with douche products:

(i) All solutions requiring preparation should be thoroughly mixed according to the manufacturer's directions immediately prior to use. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(ii) Three body positions are presented in the instruction materials given to the consumer: Sitting, standing, and reclining. The reclining position is recommended as the most effective; however, either of the other two positions is usually adequate.

(iii) Suspend the bag no more than 3 feet above the vagina. After the bag is filled and suspended, release the clamp so that the solution will expel any air out of the tubing before placing the nozzle into the vagina.

(iv) Insert the nozzle into the vagina, then release the clamp to permit the solution to flow gently into the vagina.

(v) Do not press the lips of the vagina around the nozzle. Allow free outflow of the solution.

(vi) All equipment, especially the tubing, should be thoroughly rinsed and allowed to brain before storage.

(vii) To use the bulb syringe, fill the bulb completely with solution, being careful to expel any air. Insert the nozzle gently into the vagina and exert only enough pressure to cause the solution to flow gently into the vagina.

(viii) To use prepackaged disposable units, insert the nozzle gently into the vagina and exert only enough pressure to cause the solution to flow gently into the vagina.

(2) *Warnings*—(i) "Do not use during pregnancy except upon the advice and under the supervison of a physician,"

(ii) "Do not press the lips of the vagina around the nozzle. Overfilling the vagina may force fluid into the uterus (womb) and cause inflammation."

(iii) "Douching does not prevent pregnancy."

(iv) "If douching results in pain, soreness, itching, excessive dryness, or irritation, stop douching. If symptoms dersist, consult a physician."

(v) "Keep this and all drugs out of the reach of children."

(vi) When a douche contains an ingredient which is Category I for the treatment of minor vaginal irritation, the following warning must be included: "If minor irritation has not improved after 1 week of use, consult your physician."

b. *Principal display panel.* In addition to the promotional material for a product, the principal display panel of all vaginal douche products should contain certain information which the Panel believes to be important for the correct use of the product by the consumer.

(1) The Panel reviewed the principal display panels of submitted products and has found that vaginal douches are frequently not identified as such. It, therefore, recommends that the term "vaginal douche," "vaginal douche concentrate," "vaginal gel," or "vaginal suppository," appear on the principal display panel.

(2) In view of the commonly held misconception about the effectiveness of vaginal douches for the prevention of pregnancy, the Panel recommends that the principal display panel contain the following wording in a prominent position: "Does Not Prevent Pregnancy." This wording should appear on the label of the immediate outer container and all associated labeling. This statement is necessary in order to inform the consumer at the time of purchase, during conditions of ordinary use, and to correct misconceptions.

(3) The attractiveness and colorful appearance of many products may encourage children to open and consume the contents. Therefore, bottle containers should have a child-resistant cap, and the principal display panel and associated labeling should contain the phrase "Keep this and all drugs out of the reach of children", and display a poison control symbol as dictated by specific ingredients contained in the product.

c. *Indications and warnings.* The Panel recommends the following Category I labeling (indications and warnings) for vaginal drug products (ingredients) to be generally recognized as safe and effective and not misbranded, as well as specific labeling set forth under specific ingredient evaluations.

(1) *Ingredients for the relief of minor irritations of the vagina.*

(i) *Indications*—(*a*) "For relief of minor vaginal irritation and itching."

(*b*) "For temporary relief of minor vaginal irritation and itching."

(*c*) "For relief of minor vaginal soreness."

(ii) *Warnings*—(*a*) "Keep this and all drugs out of the reach of children."

(*b*) "Does Not Prevent Pregnancy."

(*c*) "Do not use during pregnancy except upon the advice and under the supervison of your physician."

(*d*) "If symptoms continue or redness, swelling, or pain develop, stop douching. Consult your physician if these symptoms persist."

(*e*) "If minor irritation has not improved after 1 week of use, consult your physician."

(2) *Ingredients which alter vaginal pH so as to encourage the growth of normal vaginal flora*—(i) *Indications.* "Helps keep vagina in its normal acid state."

(ii) *Warnings*—(*a*) "Keep this and all drugs out of the reach of children."

(*b*) "Does Not Prevent Pregnancy."

(*c*) "Do not use during pregnancy except upon the advice and under the supervison of your physician."

(*d*) "If vaginal itching, redness, swelling, or pain develop, stop douching. Consult your physician if these symptoms persist."

(3) *Ingredients which produce an astringent effect*—(i) *Indications.* "Astringent."

(ii) *Warnings*—(*a*) "Keep this and all drugs out of the reach of children."

(*b*) "Does Not Prevent Pregnancy."

(*c*) "Do not use during pregnancy except upon the advice and under the supervison of your physician."

(*d*) "If vaginal itching, redness, swelling, or pain develop, stop douching. Consult your physician if these symptoms persist."

(4) *Ingredients which lower surface tension and which produce a mucolytic effect*—(i) *Indications.*

(*a*) "Removes vaginal discharge."

(*b*) "Removes vaginal secretions."

(*c*) "Mild detergent action."

(*d*) "Thins out vaginal mucus, discharge."

(ii) *Warnings*—(*a*) "Keep this and all drugs out of the reach of children."

(*b*) "Does Not Prevent Pregnancy."

(*c*) "Do not use during pregnancy except upon the advice and under the supervison of your physician."

(*d*) "If vaginal itching, redness, swelling, or pain develop, stop douching. Consult your physician if these symptoms persist."

d. *Professional labeling.* Some of the submissions provided to the Panel contain information indicating that the ingredients are intended for the treatment of specific disease conditions such as trichomoniasis or moniliasis. Separate professional labeling should be supplied to the physician for ingredients which have been proven to be safe and effective in the treatment of specific disease conditions.

Professional labeling should include, as a minimum, the following information:

(1) *Indication for use.* The specific disease states for which the ingredient has been proven to be effective.

(2) *Usual dosage, frequency, and duration of treatment.* The specific treatment regimen which has been shown to be effective in the treatment of the particular disease state.

(3) *Method of douching.* The specific directions for therapeutic douching as detailed in the above treatment regimen. (See part IV. paragraph A.2.a.(1) above—Recommended methods for douching).

(4) *Warnings.* Information to alert the physician to the contraindications and the possible adverse reactions to the use of the ingredient or product. Contraindications should include a history of sensitivity or adverse reaction to any of the ingredients or the product. Potential adverse reactions include the onset of pain, swelling, irritation, bleeding, or aggravation of symptoms.

B. Category II Conditions

The following are Category II conditions under which vaginal drug products are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredients.*

Hexachlorophene
Phenol (in concentrations greater than 1.5 percent)
Phenolate sodium (in concentrations greater than 1.5 percent phenol)
Sodium salicylic acid phenolate (in concentrations greater than 1.5 percent phenol)
Sodium salicylate

a. *Hexachlorophene.* Although there are insufficient data available concerning the antimicrobial effectiveness of hexachlorophene in vaginal douches, the Panel concludes that concentrations high enough to be effective for the relief of symptoms of minor vaginal irritation (greater than 0.75 percent) would not be safe for OTC use based on the reported toxicity of hexachlorophene. Therefore, the Panel classifies hexachlorophene as a Category II ingredient.

(1) *Safety.* Hexachlorophene has been widely used in the past as an antibacterial agent, particularly in nurseries for the newborn (Ref. 1). The central nervous system toxicity of hexachlorophene is well documented and has been reviewed by Lockhart (Ref. 2). The LD_{50} of hexachlorophene in the dog is 140 mg/kg, 150 to 200 mg/kg in the mouse, and 250 mg/kg in the guinea pig (Ref. 1). In experimental animals and in man, it has been shown that blood levels of approximately 1 microgram per milliliter (ug/mL) result in neuropathology, and higher levels result in fatality (Ref. 2).

Hexachlorophene has been shown to be absorbed through the skin (Ref. 3) and after oral administration (Ref. 2). Therefore, it is reasonable to assume that it can be absorbed through the vaginal mucosa. More recently, there has been evidence which links the use of hexachlorophene (0.5 percent) with fetal damage in nurses who were pregnant at the time they used it as a surgical scrub (Ref. 4 and 5). Based on safety concerns similar to those set forth here, FDA proposed in the **Federal Register** of January 7, 1972 (37 FR 219) to restrict the use of hexachlorophene in OTC drug formulations to "a level no higher than necessary to achieve the intended preservative function and in no event higher than 0.1 percent." In response to comments generated by the proposal, FDA concluded: ". . . based upon current benefit to risk ratio, that hexachlorophene is not necessary as a preservative in any drug and/or cosmetic products, which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes" (37 FR 23537). This prohibition for OTC use has been codified in 21 CFR 250.250(d). Because all vaginal products are intended to be used on mucous membranes they are covered by this regulation.

(2) *Effectiveness.* The Panel found no evidence to indicate that hexachlorophene in the concentration present in submitted products is effective against vaginal bacteria. In addition, no evidence was submitted to prove that this ingredient is effective in relieving the symptoms of minor irritations of the vagina.

(3) *Evaluation.* The Panel concludes that hexachlorophene should be excluded from all vaginal products based on the compound's potential to produce central nervous system toxicity in the conceptus or fetus. The Panel is unaware of new evidence that would establish the safety of the use of hexachlorophene in vaginal products and, therefore, sees no reason to recommend a change to existing FDA regulations.

References

(1) Gluck, L., "A Perspective on Hexachlorophene," *Pediatrics*, 51:400–406 1973.

(2) Lockhart, J. D., "How Toxic is Hexachlorophene?," *Pediatrics*, 50:229–235, 1972.

(3) Kopelman, A. E., "Cutaneous Absorption of Hexachlorophene in Low-Birth-Weight Infants," *Journal of Pediatrics*, 82:972–975, 1973.

(4) Check, W., "New Study Shows Hexachlorophene is Teratogenic in Humans," *Journal of the American Medical Association*, 240:513–514, 1978.

(5) "Hexachlorophene—Interim Caution Regarding Use in Pregnancy," *FDA Drug Bulletin*, August-September, 1978.

b. *Phenol, phenolate sodium, or sodium salicylic acid phenolate.* On the basis of the available data, the Panel concludes that preparations containing phenol in concentrations greater than 1.5 percent are unsafe for use in OTC vaginal products. In its review, the Panel considered phenol and phenolate sodium to exist in an equilibrium once they are in solution together. The Panel concludes that in this equilibrium, the total available phenol is more accurately represented by the sum of the concentrations of the phenol and phenolate ion, and is not dependent on the original proportions of the two substances.

(1) *Safety.* Phenol is a toxic chemical which is rapidly absorbed through normal skin and even more rapidly through abraded skin. There is little doubt that rapid absorption into the blood stream would occur after application to the vaginal mucosa (Refs. 1, 2, and 3). As little as 1.5 g ingested orally can cause nausea, vomiting, circulatory collapse, central nervous system disturbances, coma, necrosis of the mouth and gastrointestinal tract, and cardiac failure (Ref. 1). Phenol has also been shown to be absorbed and cause toxic reactions when incorporated into ointments at concentrations as low as 2 percent (Ref. 3).

Because of the well-known toxic effects of phenol in humans, the highly absorptive characteristics of the vaginal mucosa, and the large blood supply to the vagina which affords rapid uptake and distribution of absorbed substances, the Panel concludes that phenol is unsafe for vaginal use in concentrations greater than 1.5 percent.

(2) *Effectiveness.* Phenol is a mildly effective topical antibacterial agent, and a concentration of at least 1 percent is needed to exhibit bactericidal activity (Ref. 1). It is widely used as an ingredient in mouthwashes and anesthetic lozenges for the oral cavity and is also found in some rectal preparations. Many papers have been submitted to the Panel on the safety of the lower doses of phenol (1.4 percent) in the human oral cavity and in animal studies (Ref. 3), but the one study available in the literature on the effectiveness of phenol as an ingredient of vaginal products was poorly controlled (Ref. 4). Therefore, the Panel concludes that insufficient data are available to determine the effectiveness of phenol in concentrations greater than 1.5 percent.

(3) *Evaluation.* The Panel concludes that, due to its toxic character, phenol in concentrations greater than 1.5 percent should be removed from all vaginal drug products. This includes any compound, complex, or other formulation, e.g., phenolate, sodium and sodium salicylic acid phenolate which contains or delivers to the pharmacological site of action any phenol in concentrations greater than 1.5 percent.

This ingredient has also been reviewed by the Advisory Review Panel on OTC Topical Antimicrobial Drug Products in the **Federal Register** of September 13, 1974 (39 FR 33103), and the conclusions of that Panel were the same.

References

(1) Harvey, S. C., "Antiseptics and Disinfectants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 990–991, 1975.

(2) Deichmann, W. B., "Local and Systemic Effects Following Skin Contact with Phenol. A Review of the Literature," *Journal of Industrial Hygiene and Toxicology*, 31:146–154, 1949.

(3) OTC Volume 110031.

(4) Smith, C. E., and J. F. J. Clark, "Gynaseptic in the Treatment of Vaginitis," *Journal of the National Medical Association*, 55:317–319, 1963.

c. *Sodium salicylate.* The Panel concludes that sodium salicylate, which is generally recognized as an antipyretic, analgesic, and keratolytic agent (Regs. 1 and 2), is ineffective as an ingredient in vaginal products.

(1) *Safety.* No data were submitted to the Panel, nor is the Panel aware of any data which prove that sodium salicylate is safe when used intravaginally. The Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products found this ingredient to be safe as an internal analgesic in doses of 325 to 650 mg every 4 hours. The Panel's review was published in the **Federal Register** of July 8, 1977 (42 Fr 35420). However, its findings can by no means be extrapolated to topical application to the vaginal mucosa.

(2) *Effectiveness.* This substance is included in a product with phenol and sodium hydroxide. The manufacturer calls this complex sodium salicylic acid phenolate, but the Panel doubts the existence of this complex. No data were submitted to the Panel which prove that sodium salicylate has any beneficial effect which would make it appropriate for inclusion in an OTC vaginal drug product.

(3) *Evaluation.* The Panel concludes that there are no data to support the use of sodium salicylate in vaginal drug products and, therefore, recommends that it be removed from all such products.

References

(1) "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 1120, 1976.

(2) Woodbury, D. M., and e. fingl, "Analgesic-Antipyretics, Anti-Inflammatory Agents, and Drugs Employed in the Therapy of Gout," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 326–339, 1975.

2. *Category II combination vaginal drug products.* The following combinations reviewed by the Panel contain at least one Category II ingredient. This factor has led the Panel to conclude that these combinations are unsafe or ineffective for any OTC vaginal use. Therefore, the Panel has placed the following combinations in Category II.

(1) Hexachlorophene, boric acid, zinc sulfate, potassium aluminum sulphate, tartaric acid, camphor, phenol, and octoxynol 9.

(2) Phenol (greater than 1.5 percent), sodium borate, and sodium salicylate.

(3) Sodium salicylic acid phenolate (greater than 1.5 percent phenol), boroglycerin (greater than 1 percent boron), benzocaine.

(4) Sodium salicylic acid phenolate (greater than 1.5 percent phenol), boroglycerin (greater than 1 percent boron), benzocaine, and providone-iodine.

The Panel realizes that its recommendation pertains to the drug use of these combination products and not to the cosmetic use. However, the Panel recommends to FDA that any Category II ingredient which causes a combination product to be placed in Category II by virtue of its lack of safety be removed from the product regardless of whether its intended use is as a drug or as a cosmetic, in order to ensure that the consumer is not exposed to ingredients which this Panel has judged to be unsafe.

3. *Category II Labeling.* The Panel recognizes that labels containing inaccuracies and inconsistencies may mislead the consumer about the anticipated benefits of a product. The Panel concludes that such labeling is unacceptable and classifies such claims as Category II for vaginal drug products. In reviewing the various terms, the Panel rejected them for a number of reasons. While these reasons may not be mutually exclusive, they do serve to define unacceptable labeling practices. Terms were placed in Category II when they were found to promote impressions of unproven effectiveness, to be vaguely stated, or not amenable to proof by scientific methods. While some of these terms may at times be found on labeling for cosmetic products, it is the Panel's conclusion that they are no less false and misleading in cosmetic product labeling than when they are used in labeling for OTC vaginal drug products.

a. *Unproven claims that promote impressions of effectiveness.*

"Effectively cleanses."
"Effectively deodorizes."
"Cleans thoroughly."
"Destroys odor."
"Continued vaginal cleanliness."
"Alters vaginal pH."
"Virtually non-irritating."
"Hospital tested effectiveness."
"Prevents itch."
"Will not sting or irritate."
"Cleanses more thoroughly than other douches."
"Removes contraceptive jellies and creams."

b. *Claims that are vaguely stated.*

"Fortified triple strength."
"Scientifically balanced formula."
"Intimately understood."
"Changes water into a cleansing solution."
"Completely refreshed."
"Naturally safe ingredients."
"Formula like the natural environment in your body."
"pH of 3.5."
"Complete feminine hygiene."
"Routine feminine hygiene."
"Personal hygiene."
"Reduces the number of pathogenic organisms."
"Efective liquid."
"Nonacid."
"Hypoallergenic."
"Intended for all women who want to enjoy extra confidence in meeting people."
"As with all vaginal douches, its function is not to cover up odor."
"Unlike spray deodorants which offer less protection."
"Feminine hygiene."
"Complete feminine daintiness."
"Clinically tested."
"Intimate cleanliness."
"Dainty and feminine."
"Gentle."
"Safe for delicate membranes."

c. *Claims that are not amenable to proof by scientific methods.*

"Contains only the mildest ingredients."
"Completely compatible with normal vaginal environment."
"Buffered to control a normal vaginal pH."
"Prevents disagreeable odors."

d. *Claims that imply a therapeutic value for a specific disease condition or require professional supervision and, therefore, represent misbranding for OTC use.*

"Antiseptic."
"Antibacterial."
"Vaginal antiseptic."
"Effective germ-killer."
"Therapeutic."
"For medicinal purposes."
"Use as directed by a doctor."
"Important, during menstruation, continue douching as instructed."

e. *Claims that imply unwarranted approval, e.g., the use of the following logos or symbols.*

Red cross logo.
Rx prescription logo.

f. *Instructions that may be potentially hazardous.* Any reference to occlusion of the vaginal opening during douching.

C. Category III Conditions

The following are Category III conditions for which available data are

insufficient to permit final classification at this time.

1. *Category III active ingredients*—a. *Ingredients for the relief of minor irritations of the vagina.*

Allantoin
Aloe vera, stabilized
Benzocaine
Boron compounds (boric acid, boroglycerine, sodium borate, or sodium perborate)
Edetate salts (edetate disodium or edetate sodium)
Nonionic surface active agents (nonoxynol 9 or octoxynol 9)
Oxyquinoline compounds (oxyquinoline citrate or oxyquinoline sulfate)
Phenol (in concentrations less than 1.5 percent)
Quaternary ammonium compounds (benzalkonium chloride or benzethonium chloride)
Vitamin A and ergocalciferol (Vitamin D)

(1) *Allantoin.* The Panel concludes that allantoin is safe in the concentration below, but data are insufficient to prove its effectiveness for the relief of minor vaginal irritations.

(i) *Safety.* Allantoin has had a long history of use in topical preparations without specific reports of toxicity appearing in the literature. In addition, the Panel is aware that this ingredient was thoroughly reviewed by the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn and Sunburn Treatment and Prevention Products and was found to be safe by that Panel in its report published in the **Federal Register** of August 25, 1978 (43 FR 38256–38257). It was also found to be safe for application to the oral mucosa by the Advisory Review Panel on OTC Dentifrices and Dental Care Agents in its report published in the **Federal Register** of November 2, 1979 (44 FR 63284–63285). Consequently, the Panel believes that allantoin is safe for vaginal use.

(ii) *Effectiveness.* Allantoin, also known as 5-ureidohydantoin, is an end product of purine metabolism (Ref. 1). Its medicinal properties were discovered during World War I when it was noticed that maggot-infested wounds healed better than uninfested wounds. The maggots were the source for the production of allantoin, the substance to which the healing was attributed (Ref. 2). Since that time, allantoin has been used in topical preparations for the stimulation of tissue repair in pus forming wounds, resistant dermatologic ulcers, acne, seborrhea, and other dermatologic conditions. Allantoin is also included in oral dental preparations and has frequently been combined with antifungals and antiseptics in the treatment of minor skin or mucous membrane irritations.

The only dosage form containing allantoin that the Panel reviewed was a vaginal cream (Refs. 3 and 4). No data were presented which proved that this ingredient is effective in the treatment of minor vaginal irritations.

(iii) *Dosage and directions.* The Panel recommends that allantoin be used in vaginal creams in a concentrations of 0.33 percent.

(iv) *Labeling.* The Panel recommends the Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) above—Ingredients for the relief of minor irritations of the vagina.)

(v) *Evaluation.* The Panel recommends that allantoin be subjected to the studies outlined in the testing guidelines for vaginal drug products in order to prove its effectiveness. (See part IV. paragraph F.1.a. below—Relieving minor irritations of the vagina.)

References

(1) "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 35, 1976.
(2) Harvey, S. C., "Topical Drugs," *in "Remington's Pharmaceutical Sciences," 15th Ed., edited by Osol, A., and J. E. Hoover, Mack Publishing Co., Easton, Pa, p. 729, 1975.*
(3) OTC Volume 110042.
(4) OTC Volume 110043.

(2) *Aloe vera, stabilized.* The Panel concludes that stabilized aloe vera is safe in the concentrations cited below, but that data are insufficient to prove its effectiveness for the relief of minor irritations of the vagina.

Aloe vera is a plant. For medicinal purposes, the leaves are cut and squeezed to produce an exudate. This exudate is not stable and deteriorates within several hours. A manufacturer submitted information on a vaginal cream and douche containing a stabilized form of aloe vera called "Stabilized Aloe Vera Gel" (Refs. 1 and 2).

(i) *Safety.* Aloe vera has been widely used in many areas of the world where the plant grows. The exudate from a freshly cut leaf is applied directly to the area that is to be treated. There are many reports of its use throughout history, even in the Papyrus Ebers 3,500 years ago. Treatment of minor burns, insect bites, and other conditions in which a wet dressing of aloe vera is used has been widely reported and handed down from generation to generation.

In the 1930's, several reports appeared in the scientific literature pertinent to the use of this substance for radium burns and ulcers, and no adverse effects were noted (Refs. 3 through 8). These reports, however, were not controlled studies and are presented only to support the safety of the ingredient.

In more than 100 reports of vaginal application of the stabilized aloe vera that were submitted to the Panel, no adverse side effects were reported (Ref. 1). In addition, the Panel notes that this same type of aloe vera product has been used as an oral solution for several years, and topically as a lotion and gel.

Standard animal testing procedures reviewed by the Panel have adequately demonstrated the safety of this substance in rats, dogs, and rabbits. The oral LD_{50} for rats is 21.5 grams per kilogram (g/kg). The oral LD_{50} for dogs was determined to be greater than 31.5 g/kg, with no deaths reported after 14 days of dosing. Acute dermal application for rabbits resulted in an LD_{50} determination of greater than 10 g/kg. No histopathic alterations were found in these animals, and no deaths or other signs of toxicity resulted from skin absorption of this substance (Ref. 1).

(ii) *Effectiveness.* Data submitted to the Panel indicate that stabilized aloe vera gel may be useful in the treatment of minor irritations of the vagina (Ref. 2).

Adequate in vitro testing shows the substance to be fungicidal and bacteriocidal for microorganisms such as *Candida albicans, Staphylococcus aureus, Streptococcus viridans, Trichomonas vaginalis,* and various tinea-causing microorganisms.

The clinical reports reviewed by the Panel were of an anecdotal nature with no indication of how the diseased states were diagnosed. There were no controls used; and, if culturing was used to identify the microorganisms, it was not reported. No reports of patient follow-ups were given (Ref. 1).

(iii) *Dosage and directions.* The Panel recommends that stabilized aloe vera be used in a cream base in a concentration of 75 percent and as a vaginal douch in a concentration of 90 percent. If applicable, the Panel further recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) above—Ingredients for the relief of minor irritations of the vagina.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal; douches, and part IV.

paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that stabilized aloe vera be subjected to the studies outlined in the testing guidelines for vaginal drug products in order to prove its effectiveness. (See part IV. paragraph F.1.a. below—Relieving minor irritations of the vagina.)

References

(1) OTC Volume 110043.

(2) OTC Volume 110042.

(3) Collins, C. E., "Alvagel as a Therapeutic Agent in the Treatment of Roentgen and Radium Burns," *The Radiological Review*, 57:137–138, 1935.

(4) Collins, C. E., and C. Collins, "Roentgen Dermatitis Treated with Fresh Whole Leaf of Aloe Vera," *American Journal of Roentgenology and Radium Therapy*, 33:396–397, 1935.

(5) Wright, C. S., "Aloe Vera in the Treatment of Roentgen Ulcers and Telangiectasis," *Journal of the American Medical Association*, 106:1363–1364, 1936.

(6) Waldron, C. H., and G. L. Jenkins, "Medicinal Agents in the Treatment of Burns," *American Professional Pharmacist*, 367:15–18, 1937.

(7) Rowe, T. D., B. K. Lovell, and L. M. Parks, "Further Observations on the Use of Aloe Vera Leaf in the Treatment of Third Degree X-Ray Reactions," *Journal of the American Pharmacuetical Association (Scientific Edition)*, 30:266–269, 1941.

(8) El Zawahry, M., M. R. Hegazy, and M. Helal, "Use of Aloe in Treating Leg Ulcers and Dermatoses," *Dermatology*, 12:68–73, 1973.

(3) *Benzocaine.* The Panel concludes that benzocaine is safe at the doses cited below, but that data are insufficient to prove its effectiveness for the relief of minor vaginal irritations.

(i) *Safety.* No human safety data on the use of benzocaine in vaginal drug products were presented to the Panel. However, benzocaine has been widely used as a topical anesthetic agent for many years. Topical use of benzocaine has been found to be very safe with only occasional allergic reactions being reported (Ref. 1). On rare occasions, methemoglobinemia has been reported (Ref. 2).

(ii) *Effectiveness.* As a component of rectal suppositories, benzocaine has activity in relieving pain and itching, and the Panel believes that this activity offers rationale for its inclusion in a vaginal drug product. The ingredient is generally recognized as an anesthetic agent in concentrations between 5 and 20 percent (Ref. 3); however, its presence in vaginal drug products is in such a low concentration (The only dosage form which contained benzocaine reviewed by the Panel was a combination vaginal suppository which claimed to have anesthetic properties (Ref. 4).) that the Panel recommends that testing be performed to substantiate its effective use.

(iii) *Dosage and directions.* The Panel recommends that benzocaine be used in vaginal suppositories in a concentration range of 0.2 to 0.65 percent.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) above—Ingredients for the relief of minor irritations of the vagina.) The Panel further recommends that the following additional indication and warning be present on all benzocaine-containing vaginal drug products.

(*a*) *Indication.* "Local anesthetic."

(*b*) *Warning.* "Do not use this product if you are allergic to local anesthetics."

(v) *Evaluation.* The Panel recommends that benzocaine be subjected to the studies outlined in the testing guidelines for vaginal drug products in order to prove its effectiveness. (See part IV. paragraph F.1.a. below—Relieving minor irritations of the vagina.)

References

(1) "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p.495, 1976.

(2) Jacobziner, H., "Briefs on Accidental Chemical Poisonings in New York City," *New York State Journal of Medicine*, 61:2322–2325. 1961.

(3) Adriani, J., et al., "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics*, 5:49–62, 1964.

(4) OTC Volume 110022.

(4) *Boron compounds (boric acid, boroglycerine, sodium borate, and sodium perborate—all at concentrations greater than preservative levels (1 percent boron)).* The Panel concludes that the data submitted on the boron compounds are insufficient to prove that they are effective for any of the following uses for vaginal drug products: relieving minor irritations of the vagina, decreasing pathogenic microorganisms, altering vaginal pH so as to encourage the growth of normal vaginal flora, or producing an astringent, mucolytic, or proteolytic effect. Additionally, there is a question as to the safety of these ingredients when used by the pregnant woman because of possible adverse effects upon the fetus. The Panel, therefore, classifies these ingredients in Category III with respect to both safety and effectiveness.

Boron compounds have been used for many years, following the popularization of the use of boric acid by Lord Lister in England in 1875. Boron and its salts are readily soluble in water, glycerin, and alcohol, and have been widely used as antiseptics in the form of solutions, ointments, and powders in ear, nose, throat, and eye preparations, as irrigant solutions in many body cavities, and as dressings for burns. Because of a mild astringent action, talc with boric acid has been employed as a dusting powder for its drying, anti-inflammatory, and antipruritic effects. Boron compounds have also been widely used in industry as food preservatives, although in recent years their use has sharply declined.

As experience with the toxic aspects of the borates accumulated and as more effective therapeutic agents were developed, borates fell into disfavor except for a few relatively minor uses. This may be due in part to the findings of Novak and Taylor (Ref. 1) which suggest that, in concentrations greater than 2 percent, normal phagocytosis is inhibited by the borates, thus counteracting their antibacterial action. However, boron concentrations between 0.5 and 2 percent were found by these same investigators (Ref. 2) to be bacteriostatic against three types of pyogenic bacteria commonly found in the eye.

(i) *Safety.* Gleason (Ref. 3) has placed boric acid and sodium perborate in toxicity class three to four (moderate to highly toxic), indicating that their probable lethal dose in humans could range from 50 mg to 5 g/kg of body weight. In an adult, the mean lethal dose of boric acid probably exceeds 30 g. Sodium borate and boroglycerine are class three toxins (moderately toxic) with a probable lethal dose in humans ranging from 500 mg 5 g/kg of body weight (Ref. 3).

As the antiseptic use of boric acid became widespread, reports of poisonings resulting from ingestion, application of ointments, and irrigation of closed body cavities began to appear in the literature. The current literature is replete with survey reports of poisonings and toxicity (Refs. 4 through 10). Many of the clinical cases of boric acid poisonings have resulted from accidents or misuse of the pure material, and not from the use of ointments or preparations containing less than 10 percent boric acid. Nevertheless, a review of 113 cases of boric acid poisoning by Goldbloom and Goldbloom (Ref. 8) emphasized that boric acid is readily absorbed from abraded skin surfaces and mucous membranes, and that young infants are particularly sensitive to the toxic effects of boric acid. The highest organ concentration of boron was found in the brain and changes in the central nevous system consisted of edema and congestion of

the brain and meninges. The review further indicated that of a group of 80 cases of boric acid poisonings in which adequate descriptions of signs and symptoms were recorded, nervous system symptoms were present in 67 percent. In younger patients, the common findings were those of meningeal irritation with convulsions, delirium, and coma appearing frequently. In adults, headache, marked weakness, and excitement or depression have been reported.

There are reports in the literature, which taken together, at least raise a question as to the potential teratogenicity or embryotoxicity of boron compounds. Ploquin (Ref. 11), reporting the work of Nguyen Phy Lich, indicated that boric acid (at 350 parts per million (ppm) as boron equivalent) in the diet of rats produced stillbirth or death 3 or 4 weeks after birth. Ploquin also related this finding to the earlier work of Caujolle et al. (Ref. 12) and the teratogenic effect observed by Ridgway and Karnofsky (Ref. 13). Landaur (Ref. 14), using the chick embryo technique to evaluate boric acid, found numerous skeletal anomalies unless riboflavin was given. The Panel recognizes that the latter test is of debatable value, relevant to humans, but still believes that such information is significant.

Weir and Fisher (Ref. 6) reported no adverse effects on the reproduction of rats receiving a diet containing either borax or boric acid at 117 and 350 ppm as boron equivalent. Litter size, weights of progency, and appearance were normal compared with those of the controls. However, rats fed borax or boric acid at 1,170 ppm as boron equivalent were found to be sterile. Microscopic examination revealed no viable sperm and atrophied testes in all males at the 1,170 ppm boron level. A similar result was obtained in male dogs treated at the same level. An attempt to obtain litters by mating females that were fed 1,170 ppm boron with males fed only the basal diet was unsuccessful. Examination of the ovaries of these females showed evidence of decreased ovulation. Although Weir and Fisher (Ref. 6) offered no suggestion as to the exact mechanism by which boron exposure resulted in sterility, it appears to be possible that the pituitary secretion of follicle stimulating hormone was inhibited.

In this same context, it is significant that in cases of boric acid poisoning the highest concentrations of boron have been found in the brain (Refs. 5 and 15). In a study by Dousset (Ref. 16) on the penetration of boron into the cerebrospinal fluid of the pregnant rat, an aqueous solution of boric acid was injected intraperitoneally into pregnant and nonpregnant rats in a dosage of 0.2 g of boron per kg of body weight. Boron could not be detected in the cerebrospinal fluid of the nonpregnant rats. It appeared, however, in substantial concentrations (4.7 ug/mL) in the cerebrospinal fluid of pregnant rats beginning on days 7 to 20 of gestation. These levels dropped abruptly after birth. The author concluded that the blood-brain, i.e., hemo-meningeal, barrier to the passage of boron is lowered during pregnancy.

The study by Dousset (Ref. 16) also suggests the possibility that boric acid may be absorbed from the vagina in early pregnancy when a woman does not know that she is pregnant, and that placental transfer of boron from the maternal compartment to the fetal compartment may lead to the localization and even concentration of boron in critical tissues, such as the neural tubes or brain of the developing embryo or fetus. Additionally, previously cited reports have shown that the fetus is particularly susceptible to the toxic action of chemical pollutants in general and that the placenta is not an effective barrier.

Because of its concerns about the safety of boron compounds, the Panel attempted to determine if there was any evidence that boric acid is absorbed to a significant extent from the vagina. In the review by Goldbloom and Goldbloom (Ref. 8), three cases of boric acid intoxication following the application of vaginal packs of boric acid were cited. Swate and Weed (Ref. 17) successfully treated vulvovaginal candidiasis with boric acid. Capsules containing 600 mg of boric acid were inserted in the vaginas of nonpregnat women twice daily for 14 days, and boric acid could not be detected in the serum. However, the Panel points out that a relatively insensitive turmeric paper test was used. Swate and Weed were of the opinion that traumatized vaginal mucosa could possibly absorb appreciable quantities of boric acid.

In studies described in a submission to the Panel (Ref. 18), plasma borate levels were determined in normal women (Group I), women with pre-existing vaginitis (Group II), and normal women who had been regular users of a boric acid douche for at least 5 years (Group III), Measured before and after douching with 0.8 percent acid, the borate levels remained at normal physiological levels in all three groups. The investigators concluded that the borate ion was not absorbed to any measurable extent from the vaginal tract. In the opinion of the Panel, this conclusion would have been on firmer ground if the borate concentration in the urine had also been measured because this is the major route for the excretion of boric acid (Ref. 5).

In laboratory experiments carried out on rabbits the half-time (t ½) for the disappearance of boric acid from the blood was found to be 6.5 to 11 hours (Ref. 19). When the rabbits' kidneys were damaged by sulfonamide treatment, boric acid disappeared much more slowly from the blood, i.e., t ½=12.5 to 73 hours. Absorption of boric acid in humans with impaired kidney function thus may lead to high blood levels of boric acid. Farr and Konikowski (Ref. 20) found the renal clearance rate for sodium perborate to be 40 and 39 mL per minute per 1.73 square meters (m^2) surface area in mice and humans, respectively. These rates are much lower than those for the glomerular filtration rate (125 mL per minute) or the urea clearance rate (70 mL per minute) calculated per 1.73 m^2 surface area in humans. The rate of disappearance of borate from blood has not been established.

In studies on dogs by Pfeiffer et al. (Ref. 5) boric acid ointment was applied to burned areas or to wounds. Large amounts of borate were subsequently excreted in the urine but appreciable amounts also accumulated in the brain, liver, kidneys, and body fat. However, borate levels in the plasma were not reported.

Toxic symptoms of boron poisoning include gastrointestinal upsets, vomiting and diarrhea, gastrointestinal bleeding, central nervous system depression, acute erythematous rashes with exfoliation, systemic shock with vascular collapse, and many other symptoms referable to other body systems. Fatal doses by mouth range from 2 to 3 g for small children up to 30 g for adults. As much as 50 percent of the ingested or absorbed dose is excreted through sweat and the kidneys within 24 hours, although excretion continues for several weeks.

Following its review of the literature, the Panel concluded that boric acid in vaginal preparations might be hazardous to the fetus, breast-fed infant, and possibly to the woman herself. If boric acid preparations are to be used in the vagina, it would be important to determine the rate of vaginal absorption of boric acid particularly during early pregnancy, the rate of uptake and biological half-life of boric acid in critical fetal and maternal tissues, and the extent of excretion of boron in milk.

Studies on the biochemical mechanisms by which boric acid exerts its toxic action are also needed. The affinity of boric acid for certain tissues and their molecular components may reside in its well-known property for forming complexes with polyhydroxy compounds, particularly those containing a 1:2-cis-diol group, e.g., certain carbohydrates and polyhydroxylated fatty acids, and with glycerol (Ref. 21).

(ii) *Effectiveness.* No data have been presented to the Panel which prove that the boron compounds are effective in treating conditions of the vagina which are amenable to self-diagnosis and self-treatment, i.e., relieving minor irritations of the vagina, decreasing pathogenic microorganisms, altering vaginal pH so as to encourage the growth of normal flora, or producing an astringent, mucolytic, or proteolytic effect. The only dosage forms containing these ingredients reviewed by the Panel were a vaginal powder, a vaginal gel, a vaginal suppository, and a hygienic powder.

(iii) *Dosage and directions.* The Panel is unable to recommend any concentrations greater than preservative levels (1 percent boron) at which boron compounds are safe and effective for use in vaginal drug products. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) above—Ingredients for the relief of minor irritations of the vagina. The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel concludes that the presence of the boron compounds in a vaginal preparation which could be used in early pregnancy presents a question of safety for the fetus. However, because the Panel cannot conclude that the ingredients are safe or not, it recommends that the boron compounds be subjected to the safety testing guidelines discussed in the first portion of the Panel's review of OTC vaginal contraceptive drug products, published in the **Federal Register** of December 12, 1980. (See part II. paragraph D.—Drug Evaluation for Safety (45 FR 82020).)

Because of the lack of effectiveness data, the Panel recommends that the boron compounds be subjected to the studies outlined in the testing guidelines for vaginal drug products in order to prove its effectiveness. (See part IV. paragraph F. below—Testing Guidelines for Effectiveness of Vaginal Drug Products.)

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(5) *Edetate salts (edetate disodium or edetate sodium).* The Panel concludes that data are insufficient to prove that the edetate salts edetate disodium or edetate sodium are safe and effective for the relief of minor vaginal irritations.

(i) *Safety.* Until very recently, it was believed that the edetate salts in vaginal drug products took part only in the metabolic process of binding calcium ions on flagellate surfaces. However, more recent studies have noted that the capacity of edetate salts to tie up certain metal ions may cause toxic effects (Regs. 1 and 2). Studies on female rats that were fed ethylenediaminetetraacetic acid (EDTA) during the early period of fertilization suggest that a subsquent loss of zinc ions led to numerous anomalies in the developing fetus (Refs. 1 and 2). These anomalies can be prevented by feeding the mother additional supplies of zinc, which then provide enough zinc so that the edetates become nonfunctional so far as the conceptus is concerned. Prior to 1970, the literature contained no references documenting these adverse effects from the use of the edetate salts.

The fact that supplemental ions can be used as such does not justify the use of the edetate salts in vaginal drug products if appotential hazard exists. The Panel is uncertain as to whether or not the edetate salts pose such a hazard when used in the low concentrations present in vaginal drug products. However, due to the serious nature of the adverse effects of these ingredients, as reported in the literature, the Panel recommends that they be further tested to prove their safety.

(ii) *Effectiveness.* The edetates have been used for many years in food processing, in the treatment of heavy metal poisoning, and as carriers for

certain ions in industrial processes. Their use in vaginal douches is primarily in the treatment of flagellate microorganisms (Refs. 3, 4, and 5). Effectiveness depends upon the capacity of the edetates to tie up calcium ions on surface areas of the flagella, thereby interfering with the essential metabolism of the microorganism and eventually leading to the death of the flagellate. The Panel believes that through this activity there is a potential for the edetates to make the OTC claim of relieving minor irritations of the vagina, as well as the professional antibacterial claim of reducing the number of pathogenic microorganisms. The only dosage forms containing these ingredients reviewed by the Panel were a vaginal suppository and a vaginal douche.

(iii) *Dosage and directions.—(a) For products containing edetate disodium.* The Panel recommends that edetate disodium be used as a vaginal suppository at a concentration of 0.01 percent or as a vaginal douche at a concentration of 0.33 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(*b*) *For products containing edetate sodium.* The Panel recommends that edetate sodium be used as a vaginal douche at a concentration of 4.4 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part III. paragraph A.2.c.(1) above—Ingredients for the relief of minor irritations of the vagina.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.) In addition, the Panel recommends that the following information be contained in the labeling of products provided to health professionals.

(a) Indication for professional labeling. "For the treatment of *Trichomonas vaginalis.*"

(b) Warning. "Products containing edetate salts should not be used when pregnancy is either contemplated or suspected because of possible interference with organ development of the fetus."

(v) *Evaluation.* The Panel concludes that the presence of edetate disodium or edetate sodium in a vaginal preparation which could be used in early pregnancy presents a question of safety for the fetus. However, because the Panel cannot conclude that these ingredients are safe or not, it recommends that the edetate salts be subjected to the teratology testing descussed in the first portion of the Panel's review of OTC vaginal contraceptives, published in the **Federal Register** of December 12, 1980 (see part II. paragraph D.—Drug Evaluation for Safety (45 FR 82024)).

Data submitted to the Panel support the effectiveness of edetate salts in the treatment of trichomonas infections, which is a condition not amenable to self-diagnosis and self-treatment. The Panel recommends that additional studies be conducted to establish the safety and effectiveness of edetate sodium when used at a final concentration of 4.4 percent.

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(6) *Nonionic surface active agents (nonoxynol 9 or octoxynol 9).* The Panel concludes that the nonionic surface active agents nonoxynol 9 and octoxynol 9 are safe at the doses cited below, but that data are insufficient to prove that these ingredients are effective in relieving minor irritations of the vagina.

(i) *Safety.* The nonionic surface active agents have been found to be safe in the doses used in vaginal douche products. The safety of these ingredients is discussed above (see part IV. paragraph A.1.b.(2) above—Nonionic surface active agents (nonoxynol 9 or octoxynol 9)) and in that portion of the Panel's review which dealt with OTC vaginal contraceptives, published in the **Federal Register** of December 12, 1980 (45 FR 82028–92030).

(ii) *Effectiveness.* During its extensive evaluation of these ingredients, the Panel reviewed clinical data which indicated that a reduction of pathogenic vaginal microorganisms occurred after douching with a vaginal preparation containing nonoxynol 9 (Ref. 1). In vitro studies also reported the inhibition of *Trichomonas vaginalis* with this product and the ingredient alone (Ref. 1). The Panel, however, concludes that these clinical and in vitro data are inadequate to substantiate either the OTC claim of relieving minor irritations of the vagina or the professional antibacterial claim of reducing the number of pathogenic microoganisms. Therefore, the Panel recommends that further testing be conducted to substantiate these claims. (See part IV. paragraph F.1.a. below—Relieving minor irritations of the vagina.)

(iii) *Dosage and directions.—(a) For products containing nonoxynol 9.* The Panel recommends that nonoxynol 9 be used as a vaginal douche in a concentration of 0.02 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(*b*) *For products containing octoxynol 9.* The Panel recommends that octoxynol 9 be used as a vaginal douche in a concentration of 0.088 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) above—Ingredients for the relief of minor irritations of the vagina.) The Panel also recommends the Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that the nonionic surface active agents nonoxynol 9 and octoxynol 9 be subjected to the studies outlined in the testing guidelines for vaginal drug products in order to prove their effectiveness. (See part IV. paragraph F.1.a. below—Relieving minor irritations of the vagina.)

Reference

(1) OTC Volume 110019.

(7) *Oxyquinoline compounds (oxyquinoline citrate or oxyquinoline sulfate).* The Panel concludes that data are insufficient to prove that the oxyquinoline compounds oxyquinoline citrate or oxyquinoline sulfate are safe

and effective for the relief of minor irritations of the vagina.

(i) *Safety.* Oxyquinoline compounds were used extensively in the 1930's and 1940's for the treatment of gonorrhea and other infections. The oxyquinoline complexes with metal ions such as zinc and copper in solution, and the complex thus formed is believed to be an active antibacterial agent (Refs. 1, 2, and 3). In the treatment of gonorrhea, the agents were applied to the urethra and vagina in repeated, concentrated doses (Refs. 4, 5, and 6). In these studies there were no reports of adverse reactions.

Over the past few years, there has been increasing concern over the potential carcinogenicity of these substances. In a presentation to the Panel, Dr. Marjorie Horning postulated that, based on their chemical structure, these compounds would probably give positive results in the in vitro Ames and Huberman tests for mutagenicity, which may be predictive of carcinogenicity (Ref. 7). However, to the Panel's knowledge these tests have not been performed.

There have been numerous studies in animals on the carcinogenicity of 8-hydroxyquinoline. Many of these were reviewed and summarized by a working group of the World Health Organization's International Agency for Research on Cancer (Ref. 8). This working group, however, left the question of the carcinogenic potential of these substances unresolved. Some studies indicated significant carcinogenic effect while others did not. These studies included vaginal application in mice and rats but the results were inconclusive.

(ii) *Effectiveness.* The oxyquinolines are historically recognized to be antibacterial agents and, therefore, may be of value in relieving minor vaginal irritations. However, the Panel received no data which would substantiate an antibacterial claim. The only dosage form containing these ingredients reviewed by the Panel was a vaginal douche.

(iii) *Dosage and directions.* The Panel recommends that oxyquinoline citrate or oxyquinoline sulfate be used as a vaginal douche at a concentration of 2 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c. (1) above—Ingredients for the relief of minor irritations of the vagina.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that oxyquinoline citrate or oxyquinoline sulfate be subjected to the carcinogenicity testing presented in the first portion of the Panel's review on OTC vaginal contraceptives in order to prove their safety for use in OTC vaginal products. (See part II. paragraph D.5.—Mutagenicity and carcinogenicity studies, 45 FR 82022.)

The Panel further recommends that oxyquinoline citrate and oxyquinoline sulfate be subjected to the studies outlined in the testing guidelines for OTC vaginal drug products in order to prove their effectiveness. (See part IV. paragraph F.1.a. below—Relieving minor irritations of the vagina.)

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(8) *Phenol.* The Panel concludes that data are insufficient to prove that phenol in concentrations of 1.5 percent and less is safe and effective for the treatment of minor irritations of the vagina.

(i) *Safety.* The safety of phenol has been extensively reviewed by the Advisory Review Panel on OTC Topical Antimicrobial Drug Products in the **Federal Register** of September 13, 1974 (39 FR 33133). Although not specifically concluding that phenol in a concentration of 1.5 percent and less is unsafe, that Panel stated that there are inadequate data on the elimination and the toxicity of this ingredient in young animals and thus recommended that further research in young animals be undertaken in order to define the toxicity potential of phenol in human infants.

The Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products agrees with the OTC Topical Antimicrobial Drug Products Panel in that it believes that the use of phenol in concentrations of 1.5 percent or less does not present a known health hazard to the consumer. This Panel concludes, however, that since there are no safety data pertinent to the vaginal use of phenol, this ingredient should be further tested to prove its lack of systemic and local toxicity when applied to the vaginal mucosa.

(ii) *Effectiveness.* The Panel believes that phenol, by virtue of its antibactierial activity, could be effective in relieving minor vaginal irritations. Dosage forms containing this ingredient reviewed by the Panel were a vaginal douche, vaginal suppository, and vaginal ointment. However, no data to prove antibacterial effectiveness were submitted to this Panel.

The effectiveness of topically applied phenol was also reviewed by the Advisory Review Panel on OTC Topical Antimicrobial Drug Products (39 FR 33133). That Panel concluded that a demonstration of antibacterial effectiveness at 1.5 percent and less concentration was needed.

(iii) *Dosage and directions.* The Panel recommends that phenol be used at a concentration range of 0.31 to 1.5 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) above—Ingredients for the relief of minor irritations of the vagina.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that phenol in concentrations of 1.5 and less be

subjected to the safety testing discussed in the first protion of the Panel's review of OTC vaginal contraceptives (see part II. paragraph D.2.c.(1)—Local toxicity studies, and part II paragraph D.4—Vaginal absorption studies (45 FR 82021 and 45 FR 82022)). The Panel also recommends that phenol in concentrations of 1.5 percent and less be subjected to the studies outlined in the testing guidelines for vaginal drug products in order to prove its effectiveness. (See part IV. paragraph F.1.a. below—Relieving minor irritations of the vagina.)

(9) *Quaternary ammonium compounds (benzalkonium chloride or benzethonium chloride).* The Panel concludes that data are insufficient to prove that the quaternary ammonium compounds benzalkonium chloride and benzethonium chloride are safe and effective for the relief of minor vaginal irritations.

The quaternary ammonium compounds which are classified as cationic surfactants or detergents, and commonly known as "quaternaries," are organic substituted ammonium compounds, a class of amines. The biochemical and pharmacological properties of the quaternaries under consideration in this document, i.e., benzalkonium chloride and benzethonium chloride, are sufficiently similar to permit joint evaluation prior to their consideration as individual ingredients. When only one ingredient is discussed below, that is because data exist for only that specific ingredient.

The quaternaries consist of an organically (lipophilic)-substituted ammonium group in which the nitrogen atom is in a +5 oxidation state and is associated with a negative ion such as chloride or sulfate. They are wetting agents with detergent, keratolytic, and emulsifying properties. In the past, quaternaties have been considered to be germicidal for many microorganisms in vitro, although some strains of *Pseudomonas* species, *Mycobacterium tuberculosis,* and other gram-negative microorganisms have been considered to be resistant to this action. Gram-positive microorganisms generally are more susceptible to the germicidal action of the quaternaries than gram-negative microorganisms. Reports of antiviral, antifungal, and sporicidal activity are conflicting, probably due to variable conditions of study (Ref. 1).

Quaternaries readily dissolve in water and ionize. The nitrogen-substituted part of the molecule is positively charged and lipophilic; therefore, it imparts high surface activity to the compounds. The surface active ability is associated with the bactericidal activity of the quaternaries. The latter action is variously attributed to the inactivation of cellular enzymes, the denaturing of proteins, and the disruption of the cell membrane.

Anionic and cationic surfactants interfere with each other's germicidal activity and cannot be combined. On the other hand, nonionic surfactants (with the exception of polysorbate 80) can be combined with quaternaries and have been widely used as germicidal detergents. In the dilute solutions generally used, these compounds have been considered to be practically nontoxic and nonirritating to human tissue.

The Panel has noted that initially the quaternaries were received with enthusiam and have, in the past, been considered to be very safe and effective germicides. They have been widely used in clinical practice for wound and skin cleansing and instrument sterilization. However, after consideration of the material summarized below, the Panel has concluded that there is significant doubt concerning both the safety and effectiveness of these compounds (Refs. 1, 2, and 3).

Early estimations of the bactericidal activity of quaternaries were exaggerated. This occurred for various reasons. For example, the carryover of the quaternary comound resulting from its adsorbtion on the surface of the bacteria was enough to produce bacteriostasis in subculture. (Addition of a neutralizing chemical results in removal of the bacteriostatic effect.) Furthermore, the high surface activity of the quaternaries may cause "clumping" of bacteria, thus isolating a significant population of a false estimation of the actual reduction in the bacterial population (Ref. 1).

The quaternaries are inactivated by interaction with a variety of substances such as soaps, anionic surfactants, tissue, protein matter, cellulose, plastic, and cork. In addition, their antibacterial effect may be decreased or eliminated by contact with their container, gauze, or the tissue in the body to which the compound is being applied. Quaternary compounds also form a film on the skin surfaces that may be sterile on its outer surface (antibacterial), but remain contaminated on its inner surface.

Gram-negative microorganisms are relatively resistant to the antibacterial effect of quaternaries and, in fact, bacterial growth may actually be enhanced by the presence of a quaternary substance in the culture medium.

Outbreaks of *Pseudomonas* bacteremia in several hospitals have been shown to be due to the use of contaminated solutions of quaternary ammonium compounds (Refs. 2 through 6). Consequently, warnings and admonitions against the continued use of quaternaries as sterilizing agents have appeared in the editorial pages of several medical journals (Refs. 7, 8, and 9).

Thus, there is a large body of evidence demonstrating the relative ineffectiveness of quaternaries as bactericidal agents and raising significant concern as to their safety. Nevertheless, in the long marketing history of douches and vaginal compounds containing these ingredients, no vaginal or pelvic infections attributable to these compounds have been reported. Because specific investigations of these problems have not been carried out, however, this lack of reported adverse effects cannot be accepted as proof of safety.

Toxicologically, the quaternaries appear to be relatively safe when used in dilute solution and without occlusive dressings. Data from studies of local irritation and sensitization in humans support the conclusion of a low level of toxicity. There are no direct data on human systemic absorption in the data submitted to the Panel, although a warning of skeletal muscle weakness is noted, and caution is urged when quaternaries are used for irrigating body cavities (Ref. 10).

Finally, since the combination of quaternary compound with anionic surfactants and with Tween 80 would result in the inactivation of the quaternary's surface active ability, such combinations would be considered to be ineffective.

(i) *Safety.* In dilute solution or concentrations of 0.13 percent or less, benzalkonium chloride has low local and systemic toxicity and a wide margin of safety. Like other quaternary ammonium compounds, it is inactivated by soaps, protein, plastic, and cellulose. It may produce a film on skin surfaces which is sterile on its superficial surface, but contaminated with bacteria on its inner surface. Contamination of solutions containing benzalkonium chloride has been specifically implicated in outbreaks of bacteremia in hospital populations, as cited above. However, there is no evidence that vaginal drug products containing benzalkonium chloride as an ingredient have been associated with the introduction of pathogenic microorganisms into the vagina or resulted in gram-negative bacteremia.

Benzethonium chloride is generally recognized to be safe in dilute solutions when applied to the skin. In additions to

acute and chronic toxicity studies of this ingredient in animals, the Panel reviewed animal and human safety data for other quarternary ammonium compounds. Based on these reviews, the Panel concludes that benzethonium chloride, as a single ingredient, is safe in the concentrations used intravaginally. However, the Panel also believes that the addition of quaternaries to any vaginal product represents enough of a concern regarding sterility and the possible overgrowth of pathogenic microorganisms to warrant further microbiological testing in order to prove that these products are safe for OTC use.

(ii) *Efectiveness.* The only dosage form containing these ingredients reviewed by the Panel were a vaginal douche, a vaginal suppository, and a vaginal foam, However, the Panel did not receive any data which prove that the quaternaries are effective in the treatment of minor irritations of the vagina.

The bactericidal effectiveness of quaternary ammonium compounds is questioned today, not only when they are used under circumstances which deactivation of the quaternary solution occurs, but also because of laboratory techniques which may lead to mistaken conclusions of effectiveness.

In the past, and in many of the studies in the submitted data, benzalkonium chloride and benzethonium chloride have been considered to be superior bactericidal agents. However, in view of the significant doubts concerning the bactericidal effectiveness of this class of compounds, the Panel concludes that the quaternary ammonium compounds should be considered to be of unproven effectiveness for the OTC claim of relieving minor irritations of the vagina and the potential claim in professional labeling for reducing pathogenic microorganisms.

(iii) *Dosage and directions.*—(*a*) *For products containing benzalkonium chloride.* The Panel recommends that benzalkonium chloride be used in a concentration of 0.1 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(b) For products containing benzethonium chloride. The Panel recommends that benzethonium chloride be used in a concentration range of 0.2 to 0.5 percent. If applicable, the Panel recommends that the manufacture provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) above—Ingredients for the relief of minor irritations of the vagina.) The Panel also recommends Category I labeling for vaginal douches (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that the quaternary ammonium compounds benzalkonium chloride and benzethonium chloride be subjected to microbiological testing in order to prove that their use in vaginal products presents no threat of overgrowth of pathogenic microorganisms. (See part IV. paragraph F.1.b. below—Decreasing the number of pathogenic microorganisms). The Panel also recommends that the quaternaries be subjected to the studies outlined in the testing guidelines for vaginal drug products in order to prove its effectiveness. (See part IV. paragraph F.1.a. below—Relieving minor irritations of the vagina.)

The Panel further recommends that the quaternaries be subjected to safety testing according to the guidelines discussed in the first portion of the Panel's review of OTC vaginal contraceptives. (See part II. paragraph D.—Drug Evaluation for Safety (45 FR 82020).)

References

(1) Sykes, G., "Disinfection and Sterilization," 2d Ed., J. B. Lippincott, Philadelphia, pp. 362–380, 1965.

(2) Malizia, W. F., et al., "Benzalkonium Chloride as a Source of Infection," *The New England Journal of Medicine,* 263:800–802, 1960.

(3) Frank, M. J., and W. Schaffner, "Contaminated Aqueous Benzalkonium Chloride: An Unnecessary Hospital Infection Hazard," *Journal of the American Medical Association,* 236:2418–2419, 1976.

(4) Kaslow, R. A., D. C. Mackel, and G. F. Mallison, "Nosocomial Pseudobactermia: Positive Blood Cultures Due to Contaminated Benzalkonium Antiseptic," *Journal of the American Medical Association,* 236:2407–2409, 1976.

(5) Dixon, R. E., et al., "Aqueous Quaternary Ammoninum Antiseptics and Disinfectants: Use and Misuse," *Journal of the American Medical Association,* 236:2415–2417, 1976.

(6) Plotkin, S. A., and R. Austrian, "Bacteremia Caused by Pseudomonas Sp. Following the Use of Materials Stored in Solutions of a Cationic Surface-Active Agent," *American Journal of Medical Science,* 235:621–627, 1958.

(7) Hussey, H. H., "Benzalkonium Chloride: Failures as an Antiseptic," *Journal of the American Medical Association,* 236:2433, 1976.

(8) Fox, R. F., and I. Douglas-Wilson, Eds., "Failure of Detergent to Disinfect," *Lancet,* 2:306, 1958.

(9) Anonymous Editorial, "Bacteria in Antiseptic Solutions," *British Medical Journal,* 2:436, 1958.

(10) "AMA Drug Evaluations—1977," 3d Ed., American Medical Association, Chicago, pp. 890–891, 1977.

(10) *Vitamin A and ergocalciferol (Vitamin D).* The Panel concludes that vitamins A and D are safe in the concentrations cited below, but that data are insufficient to prove their effectiveness for the relief of minor irritations of the vagina.

(i) *Safety.* The Panel is unware of any safety problem associated with the topical use of vitamins A and D. These vitamins have been found to be safe for application to the rectal mucosa by the Advisory Review Panel on OTC Hemorrhoidal Drug Products.

(ii) *Effectiveness.* Vitamins A and D have been historically known as soothing, healing substances when used topically. The Advisory Review Panel on OTC Hemorrhoidal Drug Products, however, has thoroughly reviewed the claim of "wound-healing" and has found no basis for this claim. The only dosage form, containing these ingredients reviewed by the Panel was vaginal cream which claims to relieve minor irritations (Refs. 1 and 2). The Panel concludes that although these ingredients are known to have been used for the treatment of infections, burns, and wounds (Ref. 3), there are no data which substantiate their inclusion as active ingredients in a vaginal drug product.

(iii) *Dosage and directions.*—(*a*) *For products containing vitamin A.* The Panel recommends that vitamin A be used in vaginal creams in a concentration of 0.035 percent.

(*b*) *For products containing ergocalciferol.* The Panel recommends that ergocalciferol be used in vaginal creams in a concentration of 0.07 percent.

(iv) *Labeling.* The Panel recommends the Category I labeling for ingredients used for the relief of minor irritations of the vagina. (See part IV. paragraph A.2.c.(1) above—Ingredients for the relief of minor irritations of the vagina.)

(v) *Evaluation.* The Panel recommends that vitamins A and D be subjected to the studies outlined in the testing guidelines for vaginal drug products in order to prove their effectiveness. (See par' IV. paragraph

F.1.a. below—Relieving minor irritations of the vagina.)

References

(1) OTC Volume 110042.
(2) OTC Volume 110043.
(3) Mandel, H. G., "Fat Soluble Vitamins-Vitamin A," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S., and A. Gilman, The MacMillan Co., New York, p. 1577, 1975.

b. *Ingredients which alter vaginal pH so as to encourage the growth of normal vaginal flora.*

Acetic acid
Boron compounds (boric acid, boroglycerine, sodium borate, and sodium perborate—all at concentration greater than preservative levels (1 percent boron))
Citric acid
Lactate (as either lactic acid or sodium lactate)
Sodium bicarbonate
Sodium carbonate
Tartaric acid

(1) *Acetic acid.* Although vinegar was not submitted for review, the Panel has evaluated this ingredient (also known as acetic acid solution) because it has a long history of use as a vaginal douche. Vinegar is approximately 4 to 6 percent acetic acid; the Panel concludes that this concentration is safe when properly diluted in vaginal douches. However, data are insufficient to prove that vinegar is effective in altering the vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora.

(i) *Safety.* When vinegar is used in the usual dose of 1½ teaspoonsful (7.5 mL) per liter (or per quart) of water as vaginal douche, the Panel concludes that it is safe for vaginal use.

(ii) *Effectiveness.* The only dosage form containing vinegar reviewed by the Panel was a vaginal douche. The Panel concludes that data are insufficient to determine the extent to which vaginal pH is altered by vinegar or if such action is of sufficient duration to encourage the growth of normal vaginal flora.

(iii) *Dosage and directions.* The Panel recommends that vinegar be used as a douche in a concentration of 1½ teaspoonsful (7.5 mL) per liter of water. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which alter vaginal pH. (See part IV. paragraph A.2.c.(2) above—Ingredients which alter vaginal pH so as to encourage the growth of normal vaginal flora.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* If vinegar is to be included as an active ingredient in any OTC vaginal drug product which claims to alter vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora, the Panel recommends that it be subjected to the studies outlined in the testing guidelines in order to prove its effectiveness. (See part IV. paragraph F.1.c. below—Altering vaginal pH so as to encourage the growth or normal vaginal flora.) The Panel recognizes the difficulty of regulating the use of household materials such as vinegar for self-prescribed uses such as vaginal douching. The use of a dilute vinegar solution as a cleansing, refreshing, and soothing douche is considered cosmetic and, therefore, not under the purview of this Panel. (See part III. paragraph C.1. above—Drug vs. cosmetic status.)

(2) *Boron compounds (boric acid, boroglycerine, sodium boarate, and sodium perborate—all at concentrations greater than preservative levels (1 percent boron)).* The Panel concludes that data are insufficient to prove that boron compounds are safe and effective for use in altering vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora. The Panel's review of the safety and effectiveness of boron compounds above includes reference to their use to alter vaginal pH (see part IV. paragraph C.1.a.(4) above).

(3) *Citric acid.* The Panel concludes that citric acid is safe in the concentrations generally used in vaginal douches, but that data are insufficient to prove that it is effective in altering vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora.

(i) *Safety.* Long medical use of weak acid douches for vaginal cleansing, and the notable lack of any report of irritation or toxicity, indicate that citric acid is safe for vaginal use. The Panel is aware of one animal toxicity study which determined the LD_{50} of citric acid in rats to be 975 mg/kg (Ref. 1).

(ii) *Effectiveness.* In vaginal douches, citric acid is used as a buffer to assist in maintenance of the slightly acidic pH of the normal vagina (3.0 to 5.5) (Ref. 2). The potential usefulness of this ingredient as a vaginal acidifier is supported by the fact that normal vaginal secretions are acidic (except at the time of ovulation) (Ref. 3). The only dosage form containing this ingredient reviewed by the Panel was a vaginal douche. However, no data have been presented to the Panel which demonstrate to what extent vaginal pH is altered by citric acid or prove that this action is of sufficient duration to result in a beneficial effect on the growth of normal vaginal flora.

(iii) *Dosage and directions.* The Panel recommends that citric acid be used as a douche in a concentration range of 0.1 to 0.5 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which alter vaginal pH. (See part IV. paragraph A.2.c.(2) above—Ingredients which alter vaginal pH so as to encourage the growth of normal vaginal flora.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that citric acid be subjected to the studies outlined in the testing guidelines in order to prove its effectiveness. (See part IV. paragraph F.1.c. below—Altering vaginal pH so as to encourage the growth of normal vaginal flora.)

References

(1) United States Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health, "Toxic Substances List," p. 262, 1973.
(2) OTC Volume 110008.
(3) Long, J. H., et al., "The Vaginal Douche: Observations on Some of Its Effects," *Western Journal of Surgery, Obstetrics and Gynecology*, 71:122–127, 1963.

(4) *Lactate (as either lactic acid or sodium lactate).* The Panel concludes that lactic acid alone, and in combination with sodium lactate, is safe in the concentrations generally used as vaginal douches. However, the data are insufficient to prove that these ingredients are effective in altering vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora.

(i) *Safety.* The Panel has reviewed both animal and human toxicity data on lactic acid and its sodium salt. The LD_{50} of lactic acid has been determined to be 3.73 g/kg in rats and 1.81 g/kg in guinea pigs (Ref. 1). It has been given a toxicity rating of three (Ref. 2), meaning that pure lactic acid itself is moderately toxic, the probable oral human lethal dose being from 500 mg/kg to 5 g/kg.

Although tests reported are not pertinent to the vaginal use of highly dilute solutions of lactic acid, dilute preparations of this substance do have a corrosive action on the esophagus and stomach (Ref. 2).

The safety of lactic acid as an ingredient in vaginal douches is supported not only by a long history of use without reported adverse effects, but also by general recognition in the medical literature (Refs. 3 through 7).

Sodium lactate is a neutral salt and is nontoxic. A long history of low toxicity in the use of sodium lactate in vaginal douche preparations indicates its safety for human use.

(ii) *Effectiveness.* The potential effectiveness of lactic acid and the lactic acid-sodium lactate combination in altering vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora is supported by the fact that lactic acid is present in the normal vagina and aids in maintaining the normal vaginal pH in an acid state. The only dosage form containing these ingredients reviewed by the Panel was a vaginal douche. The Panel received no data, however, to substantiate the above claim and, therefore, recommends that further testing be conducted.

(iii) *Dosage and directions.* The Panel recommends that lactic acid alone and in combination with sodium lactate be used as a douche in a concentration range of 0.4 to 1.3 percent. If applicable, the Panel further recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which alter vaginal pH. (See part IV. paragraph A.2.c. (2) above—Ingredients which alter vaginal pH so as to encourage the growth of normal vaginal flora.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that lactic acid and the combination of lactic acid and sodium lactate be subjected to the studies outlined in the testing guidelines in order to prove their effectiveness. (See part IV. paragaph F.l.c. below—Altering vaginal pH so as to encourage the growth of normal vaginal flora.)

References

(1) Smyth, H. F., Jr., J. Seaton, and L. Fischer, "The Single Dose Toxicity of Some Glycols and Derivatives," *Journal of Industrial Hygiene and Toxicology*, 23:259–268, 1941.

(2) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 4th Ed., The Williams and Wilkins Co., Baltimore, MD, p. 71, 1976.

(3) "AMA Drug Evaluations—1973," 2d Ed., American Medical Association, Acton, MA, p. 627, 1973.

(4) Brewer, J. I., "Textbook of Gynecology," 3d Ed., The Williams and Wilkins Co., Baltimore, p. 219, 1961.

(5) Curtis, A. H., and J. W. Huffman, "A Textbook of Gynecology," 6th Ed., p. 624, 1950.

(6) Greenhill, J. P., "Office Gynecology," 9th Ed., Year Book Medical Publishers, Chicago, pp. 84 and 181, 1971.

(7) Kistner, R. W., "Gynecology: Principles and Practice," 2d Ed., Year Book Medical Publishers, Chicago, p. 81, 1971.

(5) *Sodium bicarbonate.* The Panel concludes that sodium bicarbonate is safe in the concentrations generally used in vaginal douches, but that data are insufficient to prove that it is effective in altering vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora.

(i) *Safety.* Sodium bicarbonate is a widely used ingredient in many OTC drugs. Its oral use was found to be safe by the Advisory Review Panel on OTC Antacid Drug Products in the **Federal Register** of June 4, 1974 (39 FR 19875) and by FDA (21 CFR 331). The use of sodium bicarbonate as an ingredient in vaginal douches is recognized in the general literature (Refs. 1 and 2); however, no indication for use or substantiation of safety for vaginal use is specifically mentioned.

(ii) *Effectiveness.* Sodium bicarbonate has been used as an antacid for stomach distress and as an antipruritic paste for bee stings. Alone of mixed with table salt it has also been used in eyewash, nose drops, gargle, otic preparation, and toothpaste. Sodium bicarbonate is available in powder form without restriction and can be found in most kitchens or medicine chests.

The rationale for including sodium bicarbonate in a douche presumably is because it will neutralize the acidity of vaginal secretions. However, observations have indicated that such an action is only temporary (Refs. 3 and 4).

The only dosage form containing this ingredient reviewed by the Panel was a vaginal douche. No data were presented to the Panel which indicate that sodium bicarbonate is effective in altering vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora.

(iii) *Dosage and directions.* The Panel recommends that sodium bicarbonate be used as a douche in a concentration range of 1 and 2 teaspoonsful per liter of water.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which alter vaginal pH. (See part IV. paragraph A.2.c.(2) above—Ingredients which alter vaginal pH so as to encourage the growth of normal vaginal flora.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* If sodium bicarbonate is to be included as an active ingredient in any OTC vaginal drug product which claims to alter vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora, the Panel recommends that it be subjected to the studies outlined in the testing guidelines in order to prove its effectiveness. (See part IV. paragraph F.1.c. below—Altering vaginal pH so as to encourage the growth of normal vaginal flora.) The Panel recognizes the difficulty of regulating the use of household materials such as sodium bicarbonate for self-prescribed uses such as vaginal douching. The use of dilute solutions of this ingredient as a cleansing, refreshing, and soothing douche is considered to be cosmetic and, therefore, not under the purview of this Panel. (See part III. paragraph C.1. above—Drug vs. cosmetic status.)

References

(1) Harvey, S. C., "Gastric Antacids and Digestants," in "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, p. 966, 1975.

(2) Swinyard, E. A., "Gastrointestinal Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 736, 1975.

(3) Glynn, R., "Daily Douching: Effect on Vaginal Mucosa" *Obstetrics and Gynecology*, 22:640–642, 1963.

(4) Glynn, R., "Vaginal pH and the Effect of Douching," *Obstetrics and Gynecology*, 20:369–372, 1962.

(6) *Sodium carbonate.* The Panel concludes that data are insufficient to prove that sodium carbonate is safe and effective for use in altering vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora.

(i) *Safety.* The Panel is unaware of any data which prove that sodium carbonate is safe for vaginal use. Concentrated sodium carbonate is highly corrosive; its LD_{50} in rats is 4000 mg/kg (Ref. 1). Sodium carbonate is used in some antacid preparations.

(ii) *Effectiveness.* Sodium carbonate is a potent alkalinizing agent. (Ref. 2). The only dosage form containing this ingredient reviewed by the Panel was a vaginal douche. However, the panel is unaware of any data which demonstrate that sodium carbonate is effective in altering the vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora.

(iii) *Dosage and directions.* The Panel recommends that sodium carbonate be used as a douche at a concentration of 1 tablespoonful per liter of water.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which alter vaginal pH. (See part IV. paragraph A.2.c. above—Ingredients which alter vaginal pH so as to encourage the growth of normal vaginal flora.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that sodium carbonate be subjected to the studies outlined in the testing guidelines in order to prove its effectiveness. (See part IV. paragraph F.1.c. below—Altering vaginal pH so as to encourage the growth of normal vaginal flora.)

The Panel also recommends that sodium carbonate be subjected to the studies outlined in the testing guidelines discussed in the first portion of the Panel's review of OTC vaginal contraceptives. (See part II. paragraph D.—Drug Evaluation for Safety (45 FR 82020).)

References

(1) "Registry of Toxic Effects of Chemical Substances," Department of Health, Education, and Welfare, Washington, D.C., p. 1062, 1975.

(2) Swinyard, E. A., "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 1265–1266, 1975.

(7) *Tartaric acid.* The Panel concludes that tartaric acid is safe when used in vaginal douches, but that data are insufficient to prove that it is effective in altering vaginal pH for a sufficient length of time to encourage the growth of normal vaginal flora.

(i) *Safety.* Tartaric acid is a fruit acid which is a byproduct of the fermentation process used in the wine industry. It has been used extensively in the soft drink industry, and the sodium salt has been used as a laxative. Strong solutions of tartaric acid are only mildly irritating (Ref. 1), but 30 g ingested orally can cause adverse gastrointestinal symptoms and circulatory disturbances (Ref. 2). The Panel considers tartaric acid to be safe at the low concentrations (0.047 percent) used in vaginal drug products.

(ii) *Effectiveness.* Tartaric acid is a weak acid, and as such is used as a buffer to maintain the acid pH of a douche solution. The only dosage form containing this ingredient reviewed by the Panel was a vaginal douche. However, no data were presented to the Panel which demonstrate the extent to which vaginal pH is altered by tartaric acid or prove that such an action lasts long enough to encourage the growth of normal vaginal flora.

(iii) *Dosage and directions.* The Panel recommends that tartaric acid be used as a douche in a concentration of 0.047 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which alter vaginal pH. (See part IV. paragraph A.2.c.(2) above—Ingredients which alter vaginal pH so as to encourage the growth of normal vaginal flora.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that tartaric acid be subjected to the studies outlined in testing guidelines in order to prove its effectiveness. (See part IV. paragraph F.1.c. below—Altering vaginal pH so as to encourage the growth of normal vaginal flora.)

References

(1) "The Merck Index," 9th Ed., Merck and Company, Inc., Rahway, NJ, p. 1174, 1976.

(2) Arena, J. M., "Toxicology—Symptoms—Treatment," *in* "Poisoning" 2d Ed., C. C. Thomas Publishers, Springfield, IL, p. 496, 1970.

c. *Ingredients which produce an astringent effect.*

Alum compounds (alum ammonium or potassium aluminum sulfate)
Boron compounds (boric acid, boroglycerine, sodium borate, sodium perborate—all at concentration greater than preservative levels (1 percent boron))
Zinc Sulfate

(1) *Alum compounds (alum ammonium or potassium aluminum sulfate).* The Panel concludes that alum compounds are safe in the concentrations present in the products submitted for review (0.037 to 0.06 percent), but that data are insufficient to prove that they are effective as astringents in the vagina at this concentration range. In concentrations known to produce an astringent action (0.5 to 5 percent), these ingredients are of unproven safety.

(i) *Safety.* Alum compounds have had a long history of medical use as douche ingredients and also enjoy widespread use in veterinary medicine as an astringent, antiseptic, and antimycotic (Ref. 1). Alum has a toxicity rating of two, which means that the probable lethal human dosage is from 5 to 15 g/kg of body weight. Large doses ingested orally may burn the mouth and pharynx (Ref. 2).

The Panel believes that alum compounds are safe for use in the vagina in a concentration of 0.037 and 0.06 percent; however, at generally recognized astringent concentrations of 0.5 to 5 percent, there are insufficient data to determine their safety when used in the vagina. Therefore, the Panel recommends that safety testing be done if these higher levels are to be used for producing an astringent effect in the vagina.

(ii) *Effectiveness.* The alum compounds are powerful astringents in acidic solution (pH of 6) and have very low antiseptic properties. The only dosage form containing these ingredients reviewed by the Panel was a vaginal douche. However, there are insufficient data to demonstrate the effectiveness of alum compounds as astringents when used in the vagina at the concentration levels in the vaginal drug products submitted for review. Therefore, the Panel recommends that testing be done on the currently marketed concentrations in order to substantiate the claim of astringency.

(iii) *Dosage and directions.* The Panel recommends that the alum compounds be used as a douche in a concentration range of 0.037 to 0.06 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which produce an astringent effect. (See part IV. paragraph A.2.c.(3) above—Ingredients which produce an astringent effect.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel's recommendation for the testing of alum compounds is in two parts:

(*a*) If the alum compounds are to be used in the dosage concentration range (0.037 to 0.06 percent) currently marketed, the Panel recommends that they be subjected to the studies outlined in the testing guidelines in order to prove their effectiveness. (See part IV. paragraph F.1.d. below—Producing an astringent effect.)

(*b*) If the alum compounds are to be used in the dosage range (0.5 to 5 percent) generally recognized as having an astringent action, the Panel recommends that they be subjected to the studies outlined in the safety testing guidelines discussed in the first portion of the Panel's review of OTC vaginal conrtraceptives. (See part II. paragraph D.—Drug Evaluation for Safety (45 FR 82020).)

References

(1) Rossoff, I.S., "Handbook of Veterinary Drugs," Springer Publishing Co., New York, pp. 10–11, 1974.

(2) Gosselin, R. E. et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 4th Ed., The Williams and Wilkins Co., Baltimore, MD, P. 89, 1976.

(2) *Boron compounds (boric acid, boroglycerine, sodium borate, and sodium perborate—all at concentrations greater than preservative levels (1 percent boron)).* The Panel concludes that there are insufficient data to prove that boron compounds are safe and effective for use as astringents in the vagina. The Panel's review of the safety and effectiveness of boron compounds above includes reference to their use as an astringent in the vagina. (See part IV. paragraph C.1.a.(4) above.)

(3) *Zinc sulfate.* The Panel concludes that zinc sulfate is safe in the concentration (0.02 percent) present in the products submitted for review, but that data are insufficient to prove that it is effective as an astringent in the vagina at this concentration. In concentrations (0.2 to 1.0 percent) known to produce an astringent action, this ingredient is of unproven safety.

(i) *Safety.* Zinc sulfate is an astringent and weak antiseptic which dissolves in water to form an acidic solution (pH 4.5) (Ref. 1). Because of these properties, it has been used in ophthalmic preparations for many years. Zinc sulfate is also a recognized ingredient of astringent lotions (at 0.2 to 1.0 percent concentrations) used in the treatment of acne, impetigo, and poison ivy (Ref. 1). Veterinarians administer doses of 300 to 2000 mg of zinc sulfate to dogs as an emetic. Doses of 660 mg have been administered orally to humans in order to heal wounds (Ref. 2 and 3).

The Panel concludes that zinc sulfate is safe for use in the vagina in a concentration of 0.02 percent; however, there are insufficient data to determine the safety of this ingredient when used in the vagina in generally recognized astringent concentrations of 0.2 to 1.0 percent (Ref. 1). The Panel recommends that safety testing be done if these higher levels are to be used for producing an astringent effect in the vagina.

(ii) *Effectiveness.* The only dosage form containing zinc sulfate reviewed by the Panel was a vaginal douche. Although zinc sulfate is generally recognized as an astringent (Ref. 4), there are insufficient data to prove its effectiveness as an astringent for use in the vagina in the concentration in the product submitted for review. Therefore, the Panel recommends that testing be done on the currently marketed concentration in order to substantiate the claim of astringency.

(iii) *Dosage and directions.* The Panel recommends that zinc sulfate be used as a vaginal douche in a concentration of 0.02 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for ingredients which produce an astringent effect. (See part IV. paragraph A.2.c.(3) above—Ingredients which produce an astringent effect.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.3.a. above—Package inserts for vaginal douches, and part IV. paragraph A.3.b. above—Principal display panel.)

(v) *Evaluation.* The Panel's recommendation for the testing of zinc sulfate is in two parts:

(*a*) If zinc sulfate is to be used in the 0.02 percent concentration currently marketed, the Panel recommends that it be subjected to the studies outlined in the testing guidelines in order to prove its effectiveness. (See part IV. paragraph F.1.d. below—Producing an astringent effect.)

(*b*) If zinc sulfate is to be used in the 0.2 to 1.0 percent concentration range, the Panel recommends that it be subjected to the studies outlined in the safety testing guidelines reported in the first portion of the Panel's review of OTC vaginal contraceptives. (See part II. paragraph D.—Drug Evaluation for Safety (45 FR 82020).)

References

(1) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 1101–1102, 1975.

(2) O'Riain, S., H. J. Copenhagen, and J. S. Calnan, "The Effect of Zinc Sulphate on the Healing of Incised Wounds in Rats," *British Journal of Plastic Surgery,* 21:240–243, 1967.

(3) Husain, S. L., "Oral Zinc Sulphate in Leg Ulcers," *Lancet,* 1:1069–1071, 1969.

(4) OTC Volume 110022.

d. *Ingredients which lower surface tension or which produce a mucolytic or proteolytic effect.*

Alkyl aryl sulfonate
Boron compounds (boric acid, boroglycerine, sodium borate, and sodium perborate—all at concentrations greater than preservative levels (1 percent boron)).
Lactic acid
Papain

(1) *Alkyl aryl sulfonate.* The Panel concludes that alkyl aryl sulfonate is safe at the dosage concentration presently used in vaginal drug products, but that data are insufficient to prove that it is effective as a mucolytic agent under conditions of actual vaginal use.

(i) *Safety.* Alkyl arly sulfonate has been widely used as a dispersing agent in insecticides and dust sprays; it is also used commercially to remove insecticide residues from fruit (Ref. 1). There have been no reports of human toxicity attributed to the use of this ingredient even though there has probably been significant human ingestion. Several long-term animal experiments using alkyl aryl sulfonate (including reproduction studies) have revealed no evidence of toxicity (Refs. 2 and 3).

(ii) *Effectiveness.* Alkyl aryl sulfonate is generally recognized as an anionic surfactant, a wetting agent (Ref. 4). The only dosage form containing this ingredient reviewed by the panel was a vaginal douche. No studies were submitted to establish its effectiveness; therefore, the Panel recommends that this ingredient be subjected to testing in order to prove its effectiveness as a mucolytic ingredient in vaginal douches.

(iii) *Dosage and directions.* The Panel recommends that alkyl aryl sulfonate be used as a douche in a concentration of 0.1 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for mucolytic ingredients. (See part IV. paragraph A.2.c.(4) above—Ingredients which lower surface tension and produce a

mucolytic effect.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.) In addition, the Panel recommends that the following warning be included in the labeling of vaginal products containing alkyl aryl sulfonate: "Avoid contact with the eyes."

(v) *Evaluation.* The Panel recommends that alky aryl sulfonate be subjected to the studies outlined in the testing guidelines to prove its effectiveness. (See part IV. paragraph F.1.f. below—Producing mucolytic or proteolytic effects.)

References

(1) Gosselin, R. E. et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 4th Ed., The Williams and Wilkins Co., Baltimore, MD, p. 177, 1976.

(2) Paynter, O. E., and R. J. Weir, Jr., "Chronic Toxicity of Santomerase Number 3 from Olefin (Dodecyl Benzene Sodium Sulfonate)," *Toxicology and Applied Pharmacology,* 2:641–648, 1960.

(3) Tusing, T. W., O. E. Paynter, and D. L. Opdyke, "The Chronic Toxicity of Sodium Alkylbenzenesulfonate by Food and Water Administration to Rats," *Toxicology and Applied Pharmacology,* 2:464–473, 1960.

(4) Gleason, M. N. et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 3d Ed., The Williams and Wilkins Co., Baltimore, MD, p. 10, 1969.

(2) *Boron compounds (boric acid, boroglycerine, sodium borate, and sodium perborate—all at concentrations greater than preservative levels (1 percent boron)).* The Panel concludes that data are insufficient to prove that boron compounds are safe and effective for use as a mucolytic or proteolytic agent under conditions of actual vaginal use. The Panel's review of the safety and effectiveness of boron compounds above includes reference to their use as agents to lower surface tension or to produce a mucolytic or proteolytic effect. (See part IV. paragraph C.1.a.(4) above.)

(3) *Lactic acid.* The Panel concludes that lactic acid is safe in the amounts used in vaginal douches, but that data are insufficient to prove that it is effective as a mucolytic agent under conditions of actual vaginal use.

(i) *Safety.* The Panel concludes that lactic acid is safe for use as a mucolytic agent in vaginal drug products when used within the dosage limit set forth below.

The Panel has discussed the safety of lactic acid above. (See part IV. paragraph C.1.b.(4)(i) above—Safety.)

(ii) *Effectiveness.* The only dosage form containing this ingredient reviewed by the Panel was a vaginal douche (Ref. 1). The Panel believes that lactic acid may have mucolytic properties that would substantiate its usefulness in a vaginal douche; however, no data proving such an action have been presented.

(iii) *Dosage and directions.* The Panel recommends that lactic acid be used as a douche in a concentration range of 0.04 to 1.3 percent. If applicable, the Panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The Panel recommends Category I labeling for mucoltic ingredients. (See part IV. paragraph A.2.c.(4) above—Ingredients which lower surface tension and produce a mucolytic effect.) The Panel also recommends Category I labeling for vaginal douches. (See part IV. paragraph A.2.a. above—Package inserts for vaginal douches, and part IV. paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that lactic acid be subjected to the studies outlined in the testing guidelines to prove its effectiveness. (See part IV. paragraph F.1.f. below—Producing mucolytic or proteolytic effects.)

Reference

(1) OTC Volume 110025.

(4) *Papain.* The Panel concludes that papain is safe in the doses generally used in vaginal douches, but that data are insufficient to prove that it is effective as a mucolytic or proteolytic agent under conditions of actual vaginal use.

(i) *Safety.* Papain has been used for many years in dermatologic preparations. The Panel is unaware of any adverse effects or evidence of sensitization resulting from the topical use of papain or of any problems arising from its use on open wounds. No specific animal or human toxicity studies were submitted to the Panel.

(ii) *Effectiveness.* Papain is a proteolytic agent that has been used for many years as a debriding agent in the treatment of wounds (Refs. 1, 2, and 3). Most of the documentation regarding the effectiveness of this ingredient comes from experience in dermatology and surgery, where its use has been widely accepted in the removal of scabs, pus, and decayed tissue. The only vaginal dosage form containing this ingredient reviewed by the Panel was a douche. No data were submitted to the Panel concerning the effectiveness of this enzyme in a vaginal douche.

(iii) *Dosage and directions.* The Panel recommends that papain be used as a douche in a concentration of 0.005 percent. If applicable, the panel recommends that the manufacturer provide the consumer with adequate directions stating how the product should be mixed to attain the proper concentration of the active ingredient.

(iv) *Labeling.* The panel recommends Category I labeling for mucolytic ingredients. (See part IV, paragraph A.2.c.(4) above—Ingredients which lower surface tension and produce a mucolytic effect. The Panel also recommends Category I labeling for vaginal douches. (See part IV, paragraph A.2.a. above—Package inserts for vaginal drug products, and part IV, paragraph A.2.b. above—Principal display panel.)

(v) *Evaluation.* The Panel recommends that papain be subjected to the studies outlined in the testing guidelines in order to prove its effectiveness. (See part IV, paragraph F.1.f. below—Producing mucolytic or proteolytic effects.)

References

(1) Sherry. S., and A. P. Fletcher, "Proteolytic Enzymes: A Therapeutic Evaluation," *Clinical Pharmacology and Therapeutics,* 1:202–226, 1960.

(2) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, p. 958, 1975.

(3) "AMA Drug Evaluations—1977," 3d Ed., American Medical Association, Chicago, p. 1201, 1977.

2. *Category III labeling.* The Panel concludes that, while these terms may be amenable to proof by scientific methods, insufficient data were submitted to permit the Panel to reach a final conclusion as to their validity. Any manufacturer who wishes to make these claims must perform the necessary research to substantiate their validity and submit the results to FDA. The panel classifies the following terms in Category III.

a. Mucolytic
b. Proteolytic

D. *Inactive Ingredients—Comments on Safety.*

Even though the OTC drug review is primarily an evaluation of the safety, effectiveness, and labeling of "active" therapeutic ingredients, the Panel decided to comment on the safety of certain "inactive" ingredients which are contained in vaginal drug products. Accordingly, the Panel recommends that particulate materials, such as silica and talc, which ordinarily are regarded as inactive ingredients, be excluded from

vaginal products. The Panel makes this recommendation because it believes that particulate material is potentially hazardous, especially if it is not readily biodegradable, and is also dense, abrasive, or irritating to tissues.

1. *Silica (fine).* Silica (fine) is silicon dioxide, an insoluble, dense, hard, and abrasive material (Ref. 1). It is incorporated into certain douche powders for use as a flow promoter in the manufacturing process to facilitate product packaging.

Because silica (fine) does not contribute to the effects of a vaginal douche, the Panel has concluded that it can be considered an inactive ingredient. The Panel, however, is very concerned about the presence of particulate material in a vaginal douche, especially material having and abrasive nature. The introduction of silica (fine) into a soft tissue area such as the vagina is potentially hazardous. The Panel believes that it would be in the best interest of the consumer for manufacturers to remove such an inactive ingredient from any manufacturing process, thereby eliminating it from the final product formulation.

2. *Talc* Although talc is not an ingredient contained in any of the vaginal drug products reviewed by this Panel, a submission was made which suggested that there would be concern about the safety of talc if it were applied intravaginally (Ref. 2). This ingredient has been the subject of intense review by the Advisory Review Panel on OTC Antiperspirant Drug Products (43 FR 46694). In the course of that Panel's review, data were presented to show that there is considerable variation in the purity of various commercial talcs. For example, some contain contaminants of asbestos, a known lung carcinogen (Ref. 3 and 4). Other evidence showed that certain ovarian and cervical tumors were found to contain particles of talc. This suggests that talc itself may be a carcinogen (Ref. 3). Therefore, this Panel concludes that FDA should closely regulate any drugs or devices intended for use in the vagina to insure that only pure, cosmetic talc is used in any of these products.

3. *Camphor.* The Panel concludes that camphor is ineffective as an antibacterial ingredient at the low concentration present in vaginal douches and that at antimicrobial levels it would be unsafe for OTC or any use.

Camphor is an aromatic and soothing agent that has been used for many years in many forms. It is well recognized as a class five toxin (Ref. 5) when ingested (probable lethal human dose is 50 to 500 mg/kg of body weight), but few studies have focused on its effects when absorbed through skin or mucous membranes. Camphor has been used in mothballs, chest rubs for colds, and liniment. It is present in one vaginal douche product in a unit dose of 0.03 mg and at a level of 0.05 percent in the package; but there is very little information on its use or effectiveness in a vaginal douche. Presumably, it is present because of its aromatic and soothing effects.

a. *Safety.* When ingested or absorbed by humans, camphor has been known to cause vertigo, mental confusion, delirium, convulsions, coma, vomiting, respiratory failure, and even death (Ref. 6). A review of the current literature indicates that camphor is highly toxic when swallowed in the form of camphorated oil. In one case reviewed by the Panel, camphorated oil was mistakenly taken in place of castor oil to induce labor (Ref. 6). The patient collapsed almost immediately after ingesting 12 g of camphor and was lavaged 30 minutes later with apparent recovery. No camphor was present in the mother's blood sample 8 hours later; at 36 hours after ingestion the child was delivered. The infant has a pulse of 80 beats per minute, no respiration, poor muscle tone, and cyanotic extremities. Attempts at resusciation failed to establish breathing and the child was pronounced dead 30 minutes after delivery. At the autopsy, camphor in significant amounts was found in all organs, and there was evidence of diffuse neuronal necrosis throughout the brain. Camphor was also found in the amniotic fluid and the cord blood. The apparent explanation is that camphor is conjugated in the mature liver to a metabolically incactive form and excreted through the urine, presumably protecting the mother but allowing a buildup in the amniotic fluid from which it may be reabsorbed and concentrated in fetal tissue.

b. *Effectiveness.* The Panel concludes that camphor is not effective for treating any vaginal conditions which are amenable to self-diagnosis and self-treatment, e.g., relieving minor irritations of the vagina, decreasing pathogenic microorganisms, altering vaginal pH so as to encourage the growth of normal vaginal flora, or producing an astringent or mucolytic effect. As stated above, it is probably present in vaginal drug products because of its aromatic, sooting action.

Although there are limited data available concerning the antimicrobial effectiveness of camphor in vaginal douches, the Panel believes, on the basis of the reported toxicity of camphor, that doses high enough to be antimicrobial in OTC vaginal douche preparations would not be safe.

c. *Evaluation.* Because nothing is known concerning the capacity of the fetal tissues to handle this very toxic substance, and because it appears to have no effective function in vaginal drug products, the Panel recommends that camphor be removed from all such drug products.

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(1) Merck Index, 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 1099, 1976.

(2) OTC Volume 110001.

(3) Blejer, H. P., and R. Arlon, "Talc: A Possible Occupational and Environmental Carcinogen," *Journal of Occupational Medicine*, 15:92–97, 1973.

(4) Henderson, W. J. et al., "Talc and Carcinoma of the Ovary and Cervix," *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 78:266–272, 1971.

(5) Gleason, M. N. et al., "Clinical Toxicology of Commercial Products. Acute Poisoning." 3d Ed., Williams and Wilkins Co., Baltimore, MD, p. 30, 1969.

(6) Riggs, J. et al., "Camphorated Oil Intoxication in Pregnancy: Report of a Case, *"Obstetrics and Gynecology*, 25:255–258, 1965.

E. Testing Guidelines for Safety of Vaginal Drug Products.

Saftey testing guidelines for all vaginally applied ingredients are discussed in the first portion of the Panel's review of OTC vaginal contraceptives. (See part II. paragraph D.—Drug Evaluation for Safety (45 FR 82020).) The Panel believes that because all of the ingredients under its review are applied to the vagina, the guidelines for safety testing are identical no matter what the ingreidents or the drug's intended pharmacological purpose.

F. Testing Guidelines for Effectiveness of Vaginal Drug Products.

1. *Vaginal douches.* The ultimate test of the effectiveness of a vaginal douche preparation is a clinical trial simulating condition of actual use. Effectiveness testing is required for those ingredients in vaginal douches that make the following drug claims: Relieving minor irritations of the vagina, decreasing the number of pathogenic microorganisms (professional labeling claim only), altering vaginal pH so as to encourage the growth of normal vaginal flora, producing an astringent effect, lowering surface tension, and producing a mucolytic or proteolytic effect. As mentioned earlier in this document, the Panel does not require effectiveness testing for douches which only make cosmetic cliams, e.g., "cleansing," because cosmetic claims are not within the purview of the Panel. The Panel

recommends that the following general testing guidelines be used to substantiate the corresponding claims.

a. *Relieving minor irritations of the vagina.* The Panel recognizes that douche products have been and will continue to be used by consumers to alleviate symptoms of vaginal irritations such as itching and burning. Therefore, in order to claim effectiveness for relief of these symptoms for any ingredient contained in a douche product, it will be necessary to carry out clinical studies to prove the validity of such a claim. Proof of effectiveness will consist of evidence (both subjective and objective) that the product relieves vaginal irritation; such evidence should be statistically significant when compared with appropriate controls. While allowing that such a claim is appropriate for an OTC drug product, the Panel concludes that the labeling should clearly state that if symptoms are not relieved after 1 week of use, professional consultation should be obtained. (See part IV. paragraph A.2. above—Category I labeling.)

b. *Decreasing the number of pathogenic microorganisms (restricted to professional labeling claims).* The Panel recognizes that douching may temporarily reduce the number of bacterial, parasitic, fungal, and viral microorganisms which may be present in the vagina. However, it is the Panel's opinion that women in general are unable to self-diagnose and self-treat vaginal infections and that professional consultation is essential for the proper treatment of these conditions. Therefore, the Panel is recommending that such claims be restricted to professional labeling.

The Panel is aware that certain ingredients under review have been shown to be anti-infective agents and, therefore, are being prescribed by physicians for the treatment of vaginal infections. In the event that such claims are made for these agents in professional labeling, the appropriate testing for safety and effectiveness (as described above under the evaluations of specific ingredients) should be required. In order to make therapeutic claims in professional labeling, a vaginal douche must be evaluated by in vitro and human testing. For example, an antimicrobial effect could be assessed by demonstrated clinical remission of the disease process.

c. *Altering vaginal pH so as to encourage the growth of normal vaginal flora.* The Panel recognizes that numerous claims have been made for the action of douches in lowering the vaginal pH so as to encourage the growth of normal vaginal flora. However, the evidence to date suggests that the pH changes induced by douching are transitory and, therefore, must be considered to be of little clinical significance. Nevertheless, if such a claim is to be made, appropriate testing for safety and effectiveness must be carried out. (See evaluations of specific ingredients above.)

The vaginal pH should be measured before and after douching. Direct measurement with a pH meter can be made by placing a pH glass electrode in the vagina without speculum separation of the vaginal walls (Ref. 1). Electrodes for this special purpose are commercially available. In addition, the pH of the douche solution itself must, of course, be measured.

The extent to which altering vaginal pH encourages the growth of normal flora can be ascertained by using various microbiological analyses (smears and cultures) to identify the exact microorganisms present in the vagina during times of varying pH.

d. *Producing an astringent effect.* Astringents are locally acting drugs that precipitate proteins but have so little penetration that they only affect the surface of cells. Consequently, the permeability of the cell membrane is reduced but the cell itself remains viable (Ref. 2). Astringents cause actual constrictions of the mucous membranes. The end result of astringent action is a reduction in local edema, inflammation, and exudation (Ref. 3). The irritation provoked by astringents shows that they may produce tissue damage; however, the injury is usually brief and easily repaired (Ref. 4).

Because astringent action depends on precipitation of proteins, this effect may be tested directly or by measuring certain biological effects such as diminished flexibility of tissues (Ref. 4). Appropriate histological tests for determining transient and possibly permanent effects of astringent douche ingredients on animal and human vaginal and cervical mucosa need to be performed. (See the first portion of the Panel's review of OTC vaginal contraceptives, part II. paragraph D.—Drug Evaluation for Safety (45 FR 82020).)

e. *Lowering surface tension.* The term "surfactant" is a convenient contraction of the term "surface active agent." The best known and oldest of the surface active agents is soap. The newer synthetic surfactants are most often referred to as detergents or wetting agents. Surfactants cause a lowering in surface tension. Although low surface tension does not guarantee good detergency, most good detergents do show low surface tension values (Ref. 5).

The surface activity of an ingredient may be easily evaluated by determining its surface tension and comparing this value with that of a standard solution of a reference detergent such as sodium oleate or sodium lauryl sulfate. Of the various devices which may be used to determine surface tensions, the most frequently used are the capillary tube, the stalagmometer, and the tensionmeter. For making such determinations, the tensionmeter, using the ring method, is the most widely used in industrial laboratories, with the Du Nouy form of this tensionmeter being favored (Ref. 5). This device measures the force necessary to pull a ring of known diameter, usually made of platinum, away from the surface of a liquid. It uses a torsion wire to measure the force of detachment and is calibrated by using a liquid of known surface tension and adjusting the indicator to show the correct reading at the point of detachment.

f. *Producing mucolytic or proteolytic effects.* One reason for using a douche with mucolytic or proteolytic properties is to remove cervical and vaginal mucus. Mucolytic properties of a douche may be readily ascertained by in vitro tests on bovine cervical mucus or human cervical mucus obtained at various phases of the menstrual cycle. Alterations in the rheological properties of cervical mucus such as viscosity, flow elasticity, spinnbarkeit, thixotropy, and lack of stickiness may serve as an index of mucolytic action. Alterations in the biological properties of cervical mucus following in vitro exposure to a douche, particularly sperm receptivity and penetrability, may also be observed. Procedures for studying the rheological and biological properties of cervical mucus may be found in the original literature (Ref. 6 and 7).

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(1) Masters, W. H., "The Sexual Response Cycle of the Human Female: Vaginal Lubrication," *Annals of the New York Academy of Sciences*, 83:301–317, 1959.

(2) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Company, New York, p. 951, 1975.

(3) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA., pp. 716–717, 1975.

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(6) Hafez, E. S. E., "Gamete Transport," *in* "Human Reproductioin," edited by E. S. E.

Hafez and T. N. Evans, Harper and Row, New York, pp. 85–118, 1973.

(7) Moghissi, K. S., "The Effect of Steroidal Contraceptives on the Reproductive System," *in* "Human Reproduction," edited by E. S. E. Hafez and T. N. Evans, Harper and Row, New York, pp. 559–587, 1973.

2. *Vaginal suppositories.* Vaginal suppositories are used for one or more of the following purposes: (a) Producing soothing and refreshing effects, (b) deodorizing, (c) relieving minor irritations of the vagina, (d) reducing the number of pathogenic microorganisms, (e) altering the pH of the vagina so as to encourage the growth of normal vaginal flora, and (f) producing an astringent effect.

The Panel does not require effectiveness testing for suppositories which only make the cosmetic claims noted in (a) and (b) above because such claims as not within the purview of the Panel. The Panel, however, does require substantiation of claims (c) through (f) and has discussed testing guidelines for these types of claims earlier in this document. (See part IV. paragraph F.1. above—Vaginal douches.) These guidelines may be applied to vaginal suppositories as well as to vaginal douches.

G. Vaginal Douche Equipment.

1. *Geneal discussion.* The procedures for the review of OTC drugs published in the **Federal Register** of May 11, 1972, provide for the Panel's review of "any conditions relating to active ingredients, labeling indications, warnings and adequate directions for use, prescription or OTC status, and any other conditions necessary and appropriate for the safety and effectiveness of drugs covered by the monograph" (37 FR 9479). Because the effectivess and safety of douching depend on the ingredients, the method, and the equipment used, the Panel also evaluated douche equipment. The FDA Advisory Review Panel on Obstetrical and Gynecological Devices has not yet reviewed the equipment used for douching and has stated that it is most appropriate for this Panel to make its recommendations concerning this equipment at this time.

The Panel has serious concerns about any device which uses a nozzle with a single unshielded central opening. Direct application of such a nozzle into a patulous (expanded) cervix could allow the introduction of douche fluid or air into the uterus, fallopian tubes, and abdominal cavity. Introduction of douche fluid in this manner could subsequently result in chemical peritonitis and introduction of air could result in an air embolus. Accordingly, in the absence of more definitive data and because of the potential for producing problems, the Panel recommends that only nozzles with multiple openings be permitted. However, if a nozzle with a single opening is to be used, it must be shielded to deflect the douche-liquid stream. Furthermore, in order to minimize the danger of direct injury to the vaginal mucosa, the Panel believes that only blunt-ended nozzles should be permitted.

Some of the bulb-type syringes available to consumers are equipped with an occulsive shield that is designed to prevent the outflow of the douche liquid from the vagina. The Panel questions the safety of vaginal occlusion during douching because it believes that this practice potentially hazardous. Therefore, it recommends that occlusive shields not be allowed on douche devices.

2. *Evaluation of equipment currently available—a. Douche bag.* The currently available douche bags are of 1- and 2-quart volume. They are supplied with tubing and a clamp with a shutoff valve. Intravaginal pressure is exerted by gravity flow.

The douche bag apparatus contains a vaginal pipe or nozzle to be used for douching and, frequently, a rectal pipe or nozzle to be used for administering rectal enemas. The rectal pipe is shorter in length than the vaginal pipe and should not be used for douching because it has a single nonoccluded opening at the tip. For this reason, the Panel recommends that both nozzles be labeled as to their intended use ("For Rectal Enema" or "For Vaginal Douche") in order to avoid confusion and prevent possible adverse effects.

The Panel's specific recommendations regarding labeling for the safe use of douche bag equipment are presented earlier in this document. (See part IV. paragraph A.2.a.(1) above—Recommended methods for douching.)

b. *Bulb syringe.* The currently marketed bulb syringes have a volume range of 8 to 16 ounces. The vaginal pipe is attached directly to the bulb, and pressure is exerted by hand. The Panel's specific recommendations regarding labeling for the safe use of the bulb syringe are presented earlier in this document. (See part IV. paragraph A.2.a.(1) above—Recommended methods for douching.)

c. *Prepackaged disposable units.* The currently marketed prepackaged disposable units have a volume range of 3 to 9 ounces. The vaginal pipe is attached directly to the disposable container, and pressure is exerted by hand. The Panel's specific recommendations regarding labeling for the safe use of prepackaged disposable units are presented earlier in this document. (See part IV. paragraph A.2.a.(1) above—Recommended methods for douching.)

3. *Intravaginal pressure.* During its review of submitted material and subsequent literature search, the Panel became concerned about the lack of precise data concerning the intravaginal pressures which are produced during douching. There appeared to be no reliable information available regarding the amount of pressure which can be generated by the various disposable and reusable douche products currently on the market. The Panel was unable to determine whether or not douching might be hazardous for women, as has been suggested, and also whether one type of douching apparatus might be more dangerous than another. The Panel was also interested in knowing whether or not the method of douching (occluded vs. unoccluded) and the position during douching (erect or supine) made any significant difference in the intravaginal and intracervical pressures which could be generated by the various types of douching apparatus.

The Panel urged that industry undertake a study which might help in answering certain of the questions posed above. Such a study was subsequently conducted by a contract research consultant firm (Ref. 1). There were two major variables in the study design: The douching equipment itself and the women who used it. A douche bag (gravity flow), a bulb syringe (manual pressure), and five different disposable products (manual pressure) containing between 3 and 14 ounces of fluid were used. Eighteen women were evaluated, ranging in age from 21 to 44 years and having 0 to 3 children. The mean age of the total group was 30.3 years, the mean age of those with children was 35.6 years, and those without children 23.7 years. Seven of the women douched regularly and 11 did not. Each of the women used each of the douching techniques as assigned randomly on each day of testing.

The stated objective of the study was "to compare the intravaginal pressure produced by a douche bag used in a standard manner to that produced by the bulb syringe and by disposable douche products during both occlusive and nonocclusive douching." Prior to douching, a sterile tube was placed, always by the same gynecologist, along the posterior wall of the vagina with the open end opposite the cervical opening. All subjects douched in the sitting position, and the instructions provided with the products and apparatus were followed in all instances. Pressures were

measured using a transducer, and permanent records were made with a strip-chart recorder.

Following completion of the study, a number of generalization could be made regarding pressure induced by douching: (a) Vaginal pressures were lower in women who had borne children. The differences in peak pressure values ranged from 1.8 millimeters (mm) of mercury to 6.5 mm of mercury with nonocclusive douching and from 3.5 mm of mercury to 11.7 mm of mercury with occlusive douching. This variation was believed to be due either to increased age or to greater vaginal elasticity following childbirth. (b) Higher pressures were observed in those who did not douche than in those who regularly douched. The reasons for this were unclear. The differences in mean peak pressures varied from 0.4 mm of mercury to 4.8 mm of mercury. (c) Peak intravaginal pressures were essentially the same for the douche bag and disposal products, using both occlusive and nonocclusive techniques. During nonocclusive douching with the douche bag, the mean pressure was 15.0 mm of mercury; and, disposable douches ranged from 6.7 mm of mercury to 20.1 mm of mercury with a mean peak of 14.2 mm of mercury. The median peak pressures were essentially the same. During occlusive douching, these values ranged 12.6 mm of mercury to 21.3 mm of mercury. (d) The total time taken and the pressures generated by douching varied directly with the volume of the solution employed. Douching time was 5.2 minutes with the douche bag and 1.5 minutes with the 3-ounce disposable product. Peak pressure with high volume douches (6 ounces or less) averaged 10.7 mm of mercury. (e) Occlusive techniques appeared to produce higher pressures than nonocclusive ones; but, with one single and minor exception, the variations were quite small, averaging 4.0 mm of mercury.

These data were of great help to the Panel as it formulated its guidelines for labeling. However, two issues are still unresolved: First, a quantification of the pressures which are generated by douching in the reclining position; and second, a determination of the amount of pressure which is transmitted into the endocervical canal and possibly the uterine cavity and fallopian tubes. In the latter issue, while such information would be of interest and importance, the Panel recognized the difficult technical and ethical considerations which would be involved in carrying out a study designed to answer this question.

4. *Volume of douche fluid.* The Panel recognizes that vaginal douching has been performed with volumes of fluid ranging from approximately 250 to 2,000 mL, with the usual amount being about 1,000 mL. The recent advent of disposable douches, which deliver a volume of 90 to 180 mL of solution, has raised the question of the effectiveness of these smaller volumes of fluid in carrying out the intended functions of a vaginal douche.

In a review of the literature, the Panel was able to find only one unpublished study on the comparative effectiveness of high and low volume douches in removing cellular material from the vagina. The results of this study were open to various interpretations. In the absence of further scientific information relative to douche volume, the Panel has decided that, for cosmetic uses, volume of the douche is not a consideration. However, if there are any therapeutic claims made for the douche, the manufacturer must prove that the volume of the douche product is adequate to achieve the claimed effect.

5. *Labeling of douche equipment.* The Panel recommends that instructions for douching and accompanying warnings be included with all douche equipment. (See part III. paragraph A.3. above—Category I labeling.)

Reference

(1) OTC Volume 110038.

List of Subjects in 21 CFR Part 351

Over-the-counter drugs.

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, 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 by adding in Part 351, new Subpart B, to read as follows:

PART 351—VAGINAL CONTRACEPTIVE AND OTHER VAGINAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

* * * * *

Subpart B—Vaginal Drug Products

Sec.

Subpart B—Vaginal Drug Products

Authority: Sec. 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); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

§ 351.101 Scope.

(a) An over-the-counter vaginal drug product in a form suitable for vaginal administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 351.103 Definitions.

As used in this subpart:

(a) *Vaginal douche.* A vaginal douche is a liquid preparation used to irrigate the vagina over an indeterminant period for one or more of the following purposes: cleansing, producing soothing and refreshing effects, deodorizing, relieving minor irritations, reducing the number of pathogenic microorganisms, altering the pH so as to encourage the growth of normal vaginal flora, producing an astringent effect, lowering surface tension, producing a mucolytic effect, or producing a proteolytic effect.

(b) *Vaginal suppository.* A vaginal suppository is a small globular mass, designed for easy introduction into the vagina. It is usually made of two major components—a vehicle and one or more chemical agents. It is solid at room temperature and either liquifies at body temperature or dissolves in vaginal fluids. Vaginal suppositories are

designed to be used for one or more of the following purposes: producing soothing and refreshing effects, deodorizing, relieving minor irritation, reducing the number of pathogenic microorganisms, altering the pH so as to encourage the growth of normal vaginal flora, or producing an astringent effect.

§ 351.110 Active ingredients for the relief of minor irritations of the vagina.

The active ingredients of the product consist of any of the following when used within the concentrations and dosage forms established for each ingredient.

(a) Propionates:

(1) Calcium propionate, 20 percent gel.

(2) Sodium propionate, 20 percent gel.

(b) Potassium sorbate, 1 to 3 percent douche.

(c) Povidone-iodine, .15 to .30 percent douche.

§ 351.111 Active ingredients which lower surface tension and which produce a mucolytic or proteolytic effect.

The active ingredients of the product consist of any of the following when used within the concentrations and dosage forms established for each ingredient.

(a) Dioctyl sodium sulfosuccinate, .002 percent douche.

(b) Nonoxynol 9, .0176 percent douche.

(c) Octoxynol 9, .088 percent douche.

(d) Sodium lauryl sulfate, .01 to .02 percent douche.

§ 351.112 Active ingredients which alter vaginal pH. [Reserved]

§ 351.113 Active ingredients which produce an astringent effect. [Reserved]

§ 351.120 Permitted combinations of active ingredients. [Reserved]

§ 351.150 Labeling definitions applicable to vaginal drug products.

(a) The following definitions draw distinctions between various parts of the labeling:

(1) According to the definition in section 201(m) of the Federal Food, Drug, and Costmetic Act (21 U.S.C. 321(m)) (the act), the term "labeling" means all labels and other written, printed, or graphic matter (e.g., package inserts) on or accompanying any article or any of its containers or wrappers.

(2) According to the definition in section 201(k) of the act, the term "label" specifically means that part of the labeling which appears on the immediate container of any article.

(3) According to the definition in § 201.60, the term "principal display panel" means that part of the label that is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale.

(b) The distinctions in paragraph (a) of this section are pointed out because certain information is to be contained in specific locations within the labeling of vaginal drug products. Accordingly, the labeling of the product contains all the information required by §§ 351.152, 351.154, 351.156, and all applicable information required by §§ 351.158, 351.160, 351.162, and 351.164. The label of the product contains all the information required by §§ 351.152, 351.154, and all applicable information required by §§ 351.158, 351.160, 351.162, and 351.164. And the principal display panel of the product contains all the information required by § 351.152, and all applicable information required by §§ 351.158, 351.160, 351.162, and 351.164.

§ 351.152 Principal display panel.

(a) *Statetment of identity.* The principal display panel of the product identifies the product as a "vaginal douche," "vaginal douche concentrate," "vaginal gel," or "vaginal suppository," as appropriate.

(b) *Other information.* The principal display panel of the product contains the following additional information:

(1) "DOES NOT PREVENT PREGNANCY."

(2) "Keep this and all drugs out of the reach of children."

§ 351.154 Label.

(a) *Warnings.* The label of the product contains the following warning under the heading "Warnings." "Do not use during pregnancy except upon the advice and under the supervision of your physician."

(b) *Other required information.* The label of the product contains the following additional information: *For products identified as a vaginal douche or vaginal douche concentrate.* Adequate directions stating how the product should be mixed to obtain the proper concentration of active ingredient.

§ 351.156 Labeling.

(a) *Methods for douching.* The package insert or other labeling of a product which is identified as a vaginal douche or vaginal douche concentrate contains the following information, as applicable, under the heading "Methods for douching."

(1) Adequate directions stating how product should be mixed to attain the proper concentration of active ingredient and a statement indicating that such a product should be mixed immediately prior to use.

(2) Appropriate instructions relevant to the use of a douche in a sitting, standing, and reclining position.

(3) A statement indicating that a douche bag should not be suspended more than 3 feet (91 centimeters) above the vagina.

(4) A statement explaining that after a douche bag is filled and suspended, the clamp should be released prior to placing the nozzle into the vagina so that the solution will expel any air from the tubing.

(5) A statement pointing out that the lips of the vagina should not be pressed around the nozzle, and free outflow of the solution should be permitted.

(6) A statement noting that all douche equipment, especially the tubing, should be thoroughly rinsed and allowed to drain prior to storage.

(7) Instructions for the use of a bulk syringe which state that the bulb should be completely filled with solution (with the user being careful to expel any air) and only enough pressure should be exerted to cause the solution to flow gently into the vagina.

(8) Instructions for the use of a prepackaged disposable unit which state that the nozzle should be inserted gently into the vagina and only enough pressure should be exerted to cause the solution to flow gently into the vagina.

(b) *Warnings.* The package insert or other labeling of a product which is identified as a vaginal douche or vaginal douche concentrate contains the following information under the heading "Warnings":

(1) "Do not press the lips of the vagina around the nozzle. Overfilling the vagina may force fluid into the uterus (womb) and cause inflammation."

(2) "Douching does not prevent pregnancy."

(3) "If douching results in pain, soreness, itching, excessive dryness, or irritation, stop douching. If symptoms persist, consult a physician."

§ 351.158 Label of vaginal drug products containing active ingredients for the relief of minor irritations of the vagina.

(a) *Statement of identity.* The principal display panel contains the established name of the drug, if any, and identifies the product as a "Vaginal drug product—For minor irritations."

(b) *Indications.* The label 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 relief of minor vaginal irritation and itching."

(2) "For temporary relief of minor vaginal irritation and itching."

(3 "For relief of minor vaginal soreness."

(c) *Warnings.* The label of the product contains the following warning under the heading "Warnings":

(1) "If minor irritation has not improved after 1 week of use, consult your physician."

(2) *For products identified as a vaginal douche or vaginal douche concentrate:* "If symptoms continue or redness, swelling, or pain develop, stop douching. Consult your physician if these symptoms persist."

(d) *Directions.* The label of the product contains the following information under the heading "Directions", followed by "except under the advice and supervision of a physician."

(1) *For products containing calcium propionate or sodium propionate identified in § 351.110(a) (1) and (2).* "Apply to the vagina twice a day not to exceed 2.3 grams daily."

(2) *For products containing potassium sorbate identified in § 351.110(b).* "Use as a douche as needed."

(3) *For products containing providone-iodine identified in § 351.110(c).* "Use as a douche as needed."

§ 351.160 Label of vaginal drug products containing active ingredients which lower surface tension and which produce a mucolytic or proteolytic effect.

(a) *Statement of identity.* The principal display panel contains the established name of the drug, if any, and identifies the product as a "Vaginal drug product—For removing secretions."

(b) *Indications.* The label 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) "Removes vaginal discharge."

(2) "Removes vaginal secretions."

(3) "Mild detergent action."

(4) "Thins out vaginal mucus discharge."

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

(1) *For products identified as a vaginal douche or vaginal douche concentrate.* "If vaginal itching, redness, swelling, or pain develop, stop douching. Consult your physician if these symptoms persist."

(2) *For products identified as a vainal douche concentrate and containing dioctyl sodium sulfosuccinate identified in § 351.111(a) or sodium lauryl sulfate identified in § 351.111(d).* "Avoid prolonged contact with the skin and avoid contact with the eyes."

(d) *Directions.* The label of the product contains the following information under the heading "Directions," followed by "except under the advice and supervision of a physician."

(1) *For products containing dioctyl sodium sulfosuccinate identified in § 351.111(a).* "Use as a douche as needed."

(2) *For products containing nonoxynol 9 identified in § 351.111(b).* "Use as a douche as needed."

(3) *For products containing octoxynol 9 identified in § 351.111(c).* "Use as a douche as needed."

(4) *For products containing sodium lauryl sulfate identified in § 351.111(d).* "Use as a douche as needed."

§ 351.162 Label of vaginal drug products containing active ingredients which alter vaginal pH.

(a) *Statement of identity.* The principal display panel contains the established name of the drug, if any, and identifies the product as a "Vaginal drug product—For modifying vaginal pH."

(b) *Indications.* The label of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrase. "Helps keep vagina in its normal acid state."

(c) *Warnings.* The label of the product contains the following warning under the heading "Warnings": *For products identified as a vaginal douche or vaginal douche concentrate.* "If vaginal itching, redness, swelling, or pain develop, stop douching. Consult your physician if these symptoms persist."

(d) *Directions.* [Reserved]

§ 351.164 Label of vaginal drug products containing active ingredients which produce an astringent effect.

(a) *Statement of identity.* The principal display panel of the product contains the established name of the drug, if any, and identifies the product as a "vaginal drug product-Astringent."

(b) *Indications.* The label of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrase: "Astringent."

(c) *Warnings.* The label of the product contains the following warning under the heading "Warnings": *For products identified as a vaginal douche or vaginal douche concentrate.* "If vaginal itching, redness, swelling, or pain develop, stop douching. Consult your physician if these symptoms persist."

(d) *Directions.* [Reserved]

§ 351.180 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public) may contain the following additional indications:

(a) *For products containing calcium propionate or sodium propionate identified in § 351.110(a) (1) and (2).* "For the treatment of *Candida albicans.*"

(b) *For products containing providone-iodine identified in § 351.110(c).*

(1) "Microbiocidal douche."

(2) "Clinically effective in a program of treatment for vaginal moniliasis, T-vaginales vaginitis, and nonspecific vaginitis."

(3) "The use of providone-iodine as a douche may cause a transient rise of serum protein-bound iodine."

(4) The professional labeling should detail the therapeutic regimen used in the studies which resulted in clinical effectiveness.

(c) *For products containing dioctyl sodium sulfosuccinate identified in § 351.111(a) of sodium lauryl sulfate identified in § 351.111(d).* "For the treatment of *Trichomonas vaginalis.*"

Interested persons may, on or before January 11, 1984, 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. These 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 March 19, 1984. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Mark Novitch,

Deputy Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

Dated: September 21, 1983.

[FR Doc. 83–27596 Filed 10–7–83; 8:45 am]

BILLING CODE 4160–01–M