DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 82N-0165]

Orally Administered Menstrual 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 proposed rulemaking that would establish conditions under which over-the-counter (OTC) orally administered menstrual drug products (drugs taken internally to treat problems relating to a woman's menstrual period) are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by March 7, 1983, and reply comments by April 6, 1983.

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 (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on October 17, 1981 a report on OTC orally administered menstrual drug products from the Advisory Review Panel on OTC Miscellaneous Internal 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 orally administered menstrual drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

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.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC orally administered menstrual 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 orally administered menstrual 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 monograph 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 tentative final monograph is published. At that time FDA also will consider whether the monograph 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 orally administered menstrual 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 orally administered menstrual drug products should be accompanied by appropriate documentation.

The agency is aware of the Panel's recommendation that pyrilamine maleate be classified in Category I "for the relief of emotional changes related to the premenstrual period, such as anxiety, nervous tension, and irritability." In the **Federal Register** of June 22, 1979 (44 FR 36378), the agency published a final order placing antihistamines, including pyrilamine maleate, in Category II for use as daytime sedatives. FDA concluded that, while antihistamine drugs make the user drowsy or sleepy, there are no data to indicate that the drowsiness effect is related to relieving symptoms of anxiety. The Panel acknowledged the daytime sedative final order but rationalized that the target population for the use of a menstrual product may be different from the population that would commonly use daytime sedatives. In light of the conclusions made in the daytime sedative final order, the agency is concerned that the data relied on by the Panel may not provide substantial evidence of effectiveness for the use of pyrilamine maleate for the symptoms of anxiety, nervous tension, and irritability related to the premenstrual period.

The agency is also aware of the Panel's recommendation that pyrilamine maleate be classified in Category I for water-retention symptoms (weight gain, swelling, etc.) during the premenstrual or menstrual period. The agency recognizes that the study results relied on by the Panel to support this recommendation were conflicting. Although the agency has not fully evaluated the studies, it is concerned that the data may not be sufficient to provide general recognition of effectiveness.

The agency recognizes that pyrilamine maleate has been marketed in combination with analgesics and/or diuretics and indicated for menstrual and premenstrual symptoms. However, the agency is unaware of any product on the OTC market containing pyrilamine maleate as the only ingredient and indicated for menstrual or premenstrual symptoms. Because of the concerns outlined above, the agency believes that products containing pyrilamine maleate as a single ingredient and indicated for any menstrual or premenstrual symptom should not be marketed at this time. The agency invites specific comment on the Panel's conclusions regarding the use of pyrilamine maleate in OTC menstrual drug products.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC orally administered menstrual 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 January 6, 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**. 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 the tentative final monograph for OTC topical antimicrobial drug products (published in the **Federal Register** of July 9, 1982 (47 FR 29986)), 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.

On or after the effective date of the monograph, 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. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31696). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' " In the **Federal Register** of August 27, 1975 (40 FR 38179) a notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of ingredients in miscellaneous internal drug products to be considered in the OTC drug review. This list, which included menstrual and diuretic drug products, was provided to give guidance on the kinds of ingredients for which data should be submitted. The notices of November 16, 1973 and August 27, 1975 informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC drug review to all OTC drug products.

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

James L. Tullis, M.D., Chairman (appointed December 1979)
John W. Norcross, M.D., Chairman (resigned March 1979)
Diana F. Rodriquez-Calvert, Pharm. D. (appointed July 1976, served until September 1981)
Ruth Eleanor Brown, R.Ph. (resigned May 1976)
Elizabeth C. Giblin, M.N., Ed. D.
Richard D. Harshfield, M.D. (deceased June 1, 1981)
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O. (deceased April 13, 1979)
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1976)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D. Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm. D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph. D. All industry liaison members were nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator until July 1979, followed by John R.

Short, R.Ph. Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer until October 1978. Roger Gregorio served as the liaison for the Office of New Drug Evaluation beginning November 1978. Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph., until July 1979.

In order to expand its scientific base the Panel called upon the following consultants

Ralph B. D'Agostino, Ph. D. (statistics)
Lynn R. Brady, Ph. D. (pharmacognosy)
Arthur E. Schwarting, Ph. D. (pharmacognosy)

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for OTC menstrual drug products in this document. The Panel's findings on other categories of OTC miscellaneous internal drug products are being published periodically in the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic in this document were held on December 13 and 14, 1980; January 31 and February 1, June 5, July 10, August 21, 22, and 23, and October 16 and 17, 1981.

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

The following individuals were given an opportunity to appear before the Panel at their own request to express their views on OTC menstrual drug products:

William Bickers, M.D.
Charles N. Jolly, J.D.
J. D. McColl, Ph. D.
Harold I. Silverman, D.Sc.
R. William Soller, Ph. D.
Edward L. Steinberg, M.Sc., O.D.

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

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through October 17, 1981 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel's findings with respect to OTC menstrual drug products are set out in three categories:

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

Category II. Conditions under which OTC menstrual 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.

The Panel reviewed 73 active ingredients for relieving symptoms of the premenstrual and menstrual periods. The Panel placed 10 ingredients in Category I, 58 ingredients in Category II, and 6 ingredients in Category III. (The number of ingredient classifications does not equal the number of ingredients reviewed because some ingredients were reviewed for more than one labeled use.)

I. Submission of Data and Information

Pursuant to the notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) requesting submission of data and information on OTC miscellaneous internal drug products, the following firms made submissions relating to OTC menstrual drug products:

A. SUBMISSION BY FIRMS

Firms	Marketed products
Blair Laboratories, Inc., Norwalk, CT 06856.	Pre-Mens Forte tablets.
Chattem Drug and Chemical Co., Chattanooga, TN 37409.	Pamprin tablets, neo Bromth tablets, Cardui tablets, Zodiex tablets, Predema tablets.
Cooper Laboratories, Inc., Cedar Knolls, NJ 07927.	Lydia E. Pinkham tablets and vegetable compound.
The Emko Company, St. Louis, MO 63143.	Sunrli capsules.
McNeil Laboratories, Inc., Fort Washington, PA 19034.	Tylenol with codeine tablets.
Pfizer Pharmaceuticals, Inc., New York, NY 10017.	Femanol liquid.
Sterling Drug Co., New York, NY 10016.	Midol tablets.
Thompson Medical Company, Inc., New York, NY 10022.	Aqua-Ban tablets.
USV Pharmaceutical Corporation, Tuckahoe, NY 10707.	Femicin tablets.
Whitehall Laboratories, Inc., New York, NY 10017.	Trendar tablets.

B. Ingredients Reviewed by the Panel

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

Acetaminophen
Ammonium chloride
Asclepias tuberosa (pleurisy root)
Aspirin
Caffeine
Cimicifuga racemosa (black cohosh)
Cinnamedrine hydrochloride
Codeine
Ethyl alcohol
Gentiana lutea (gentian)
Gylcyrrhiza (licorice)
Ferrous sulfate
Homatropine methylbromide
Pamabrom (2-amino-2-methyl/-a-/ propanol-8-bromotheophyllinate)
Phenacetin
Phenindamine tartrate
Piscidia erythrina (Jamaica dogwood)
Pyrilamine maleate
Salicylamide
Senecio aureus (life root)
Taraxacum officinale (dandelion rootr)

2. *Other ingredients.* a. In addition to those ingredients included in the products submitted to the Panel, the following ingredients were listed in the **Federal Register** notice of August 27, 1975 (40 FR 38179) as diuretics or as menstrual products:

Alfalfa leaves
Aloes
APAP
Asparagus
Barosma
Calcium lactate
Calcium pantothenate
Chlorprophenpyridamine maleate
Cinnamylephedrine hydrochloride
Cnicus benedictus
Corn silk
Couch grass
Dog grass extract
Ethyl nitrite
Essence pepsin
Extract buchu
Extract hydrangea
Extract stone root
Extract uva ursi
Extracts of bearberry (*Cascara sagrada*)
Extracts of cascara
Ferric chloride
Hydrastis canadensis
Hyoscyamine sulfate
Magnesium sulfate
Methapyrilene hydrochloride
Methenamine
Methylene blue
Natural estrogenic hormone
Niacinamide
Oil of erigeron
Oil of juniper
Oil of nutmeg
Oleoresin capsicum

Parsley
Phenyl salicylate (salol)
Pipsissewa
Potassium acetate
Potassium nitrate
Pyridoxine hydrochloride
Riboflavin
Saw palmetto
Sodium benzoate
Sodium nitrate
Spirit of peppermint
Sucrose
Sulferated oils of turpentine
Theobromine sodium salicylate
Theophylline
Thiamine hydrochloride
Triticum
Urea
Venice turpentine

b. Ingredients reviewed by the Panel in adition to the labeled ingredients submitted and the ingredients listed in the call for data:

Calcium carbaspirin
Choline salicylate
Magnesium salicylate
Sodium salicylate

C. Classification of Ingredients

1. *Active ingredients:*

Acetaminophen (APAP)
Ammonium chloride
Asclepias tuberosa (pleurisy root)
Aspirin
Caffeine
Calcium carbaspirin
Choline salicylate
Cimicifuga racemosa (black cohosh)
Cinnamedrine hydrochloride (cinnamylephedrine hydorchloride)
Codeine
Glycyrrhiza glabra (licorice root)
Homatropine mehtylbromide
Magnesium salicylate
Pamabrom (2-amino-1-methyl-1-propanol-8-bromotheophyllinate)
Phenacetin
Piscidia erythrina (Jamaica dogwood)
Pyridoxine hydrochloride
Pyrilamine maleate
Salicylamide
Senecio aureus (life root)
Sodium salicylate
Taraxacum officinale (dandelion)
Theobromine sodium salicylate
Theophylline

2. *Inactive ingredient: Gentiana lutea* (gentian).

3. *Pharmaceutical necessity.* Ethyl alcohol (The Panel considers that this ingredient may be necessary in a concentration up to 25 percent for solution of ingredients.)

4. *Ingredient reviewed by the Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products whose report was published in the* **Federal Register** *of March 16, 1979 (44 FR 16126).*

Ferrous sulfate (iron) (The Panel has not considered this ingredient because the pertinent claim, the treatment or prevention of iron deficiency anemia, is not within the purview of this Panel.)

5. *Other ingredients.* a. Although some meager data exist for the use of the following ingredients, the Panel concludes that such data (often anecdotal, folkloric, or based on studies without contemporary acceptable controls) are inadequate to establish the safety and effectiveness of any of these ingredients when used as OTC menstrual or diuretic drug products. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be reviewed further in this document:

Barosma
Cnicus benedictus (blessed thistle)
Corn Silk
Couch grass
Dog grass extract
Extract buchu
Extract uva ursi
Hydrastis canadensis (golden seal)
Oil of juniper
Pipsissewa
Triticum

b. The Panel was not able to locate nor is it aware of any body of data demonstrating the safety and effectiveness of the following OTC ingredients when used as menstrual or diuretic drug products. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be reviewed further in this document.

Alfalfa leaves
Aloes
Asparagus
Calcium lactate
Calcium pantothenate
Chlorprophenpyridamine maleate
Ethyl nitrite
Essence pepsi
Extract hydrangea
Extract stone root
Extracts of bearberry (*Cascara sagrada*)
Extracts of cascara
Ferric chloride
Hyoscyamine sulfate
Magnesium sulfate
Methapyrilene hydrochloride
Methenamine
Methylene blue
Natural estrogenic hormone
Niacinamide
Oil of erigeron
Oil of nutmeg
Oleoresin capsicum
Parsley
Phenindamine tartrate
Phenyl salicylate (salol)
Potassium acetate
Potassium nitrate
Riboflavin
Saw palmetto
Sodium benzoate
Sodium nitrate
Spirit of peppermint
Sucrose
Sulferated oils of turpentine
Thiamine hydrochloride
Urea
Venice turpentine

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (39 FR 31696) and August 27, 1975 (40 FR 38179). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on display after January 6, 1983, in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definition of Terms

For the purposes of this document, the Panel has adopted the following definitions:

1. *Diuretic.* A drug that increases the excretion of water.

2. *Dysmenorrhea.* Painful menstruation. This may be accompanied by nausea, vomiting, diarrhea, headache, dizziness, fatigue, and bloating.

3. *Edema.* Water retention in the body tissues.

4. *Menses.* The monthly flow of blood from the genital tract of women.

5. *Menstrual flow.* Menses.

6. *Menstrual period.* The period of time from onset to stoppage of cyclic, physiologic uterine bleeding, which (in the absence of pregnancy) normally recurs, usually at approximately 4-week intervals.

7. *Menstruation.* Menses.

8. *Premenstrual period.* The period of approximately 1 week before onset of menstruation.

9. *Premenstrual syndrome.* A recurrent symptom complex that begins during the week prior to menstruation and usually disappears soon after the onset of the menstrual flow. This symptom complex consists predominantly of edema, lower abdominal pain (including cramps), breast tenderness, headache, abdominal bloating, fatigue, and the feelings of

depression, irritability, tension, and anxiety.

B. General Discussion.

Products bearing labeling claims for the relief of premenstrual tension and/or dysmenorrhea have been submitted to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. The Panel notes that several products bear label indications for both premenstrual tension and dysmenorrhea. It should be recognized that the two syndromes are separate clinical entities and are thought to have different causes although some of the symptoms overlap. Among the active ingredients in products promoted in the past for relief of the discomfort of premenstrual tension and dysmenorrhea have been analgesics, diruetics, smooth muscle relaxants, and antihistamines.

"Premenstrual syndrome" is a term frequently used in current literature and one that the Panel adopted to describe the recurrent symptom complex that begins during the week before menstruation, reaches its peak shortly before menstruation, and usually disappears soon after the onset of the menstrual flow. In some instances, the symptoms may persist to a lesser degree throughout the cycle (Ref. 1). The symptom complex consists predominantly of the following: cramps (Refs. 2 and 3), edema, lower abdominal pain, breast tenderness, headache, abdominal bloating, fatigue, and feelings of depression, irritability, tension, and anxiety (Refs. 1 and 4 through 9).

Dysmenorrhea is distinguished from the premenstrual syndrome in that symptoms generally begin a day or two prior to or at the onset of menstruation, and it is characterized by pelvic pain with complete or marked improvement at the end of menses (Ref. 10). This pain is "of a sharp, cramping, intermittent character," and usually occurs in the lower abdomen, but at times may extend to other parts of the body (Ref. 11). More than 50 percent of dysmenorrheic subjects have been reported to experience associated symptoms of nausea, vomiting, diarrhea, headache, dizziness, fatigue (Refs. 3 and 12) and bloating (Refs. 2 and 13). Dysmenorrhea may be one of the following two types: (1) primary, in which there is no observed organic cause and (2) secondary, in which there is an underlying organic disorder. Because the treatment of secondary dysmenorrhea should be under the supervision of a physician, only primary dysmenorrhea, which can be treated by the use of OTC drugs, will be discussed by the Panel. Not all symptoms and signs attributed to primary dysmenorrhea and the premenstrual syndrome are present in every patient. Marked variability is present among different cultural and ethnic groups and between individual women in each group (Ref. 14). However, the symptom pattern is fairly constant in each patient.

Although the causes of primary dysmenorrhea and the premenstrual syndrome are unclear, the two disorders have long been recognized. "Known to ancient Egyptians, dysmenorrhea was subsequently described in easily recognizable terms by the early Roman physician, Soranus, whose home remedies are still in use today: bed rest in a dark, quiet room, with moist heat applications to the lower abdomen" (Ref. 15).

The Panel notes that various terms have been used to describe the condition that occurs in women just prior to the onset of menstruation. The literature refers to this condition as "premenstrual tension," "premenstrual tension syndrome," and "premenstrual syndrome." Because tension is only one of several component symptoms of this syndrome, the Panel chose to use the term that did not incorporate "tension" in its title. Therefore, throughout this document the text written by the Panel refers to this conditions as the "premenstrual syndrome" but descriptions of work generated by others uses those individuals' terms for this condition.

Various theories as to the cause of "premenstrual tension" have been proposed since the term was applied by Frank (Ref. 16) in 1931 in the first systematic description of this syndrome. Several of these theories are based on the presumed occurrence of some type of hormonal imbalance, which has been considered to take the form of an altered metabolism of estrogen, progesterone, and aldosterone (Refs. 17 and 18). One theory suggests that when edema is associated with premenstrual tension, it is attributable to an abnormal response to target organs to normal circulating hormones of the ovaries and the pituitary gland (Refs. 4 and 6). Another theory is that the effect of elevated levels of prolactin on ovarian hormones and the actions of prolactin in increasing renal retention of water, sodium, and potassium could account for the symptoms associated with premenstrual tension and edema (Refs. 19 and 20). Psychological factors and vitamin deficiency have also been named as causes of "premenstrual tension" (Refs. 7, 18, 19, and 21).

It appears that the symptoms of the premenstrual syndrome cannot be ascribed to a single factor, although evidence indicates that there is a significant relationship of certain premenstrual syndrome symptoms to excessive retention or maldistribution of body water. According to this theory, the number, type, and severity of symptoms vary according to the degree and the anatomic location of the water (Refs. 4, 6, 8, 17, and 18).

The Panel has evaluated Moos' (Ref. 13) "Menstrual Distress Questionnaire," which subjectively grades 47 symptoms during the menstrual, premenstrual, and intermenstrual periods. The symptoms are grouped into eight clusters as follows: pain, water retention, mental concentration, negative affect, behavior change, arousal, autonomic reactions, and control. Each of the groupings represents an "empirically related cluster of symptoms." The Panel considers the pain, water-retention, and negative affect clusters as the ones most appropriate for evaluating the effectiveness of drugs in relieving the symptoms of the premenstrual syndrome. Moos lists symptoms of each of these clusters as follows:

(1) Pain (muscle stiffness, headache, cramps, backache, fatigue, and general aches and pains)

(2) Water retention (weight gain, skin disorders, painful breasts, and swelling)

(3) Negative affect (crying, loneliness, anxiety, restlessness, irritability, mood swings, depression, and tension)

For the purposes of evaluation, the Panel decided that if a manufacturer uses a description of a specific cluster or uses individual symptoms in product labeling, the effectiveness must have been demonstrated for the specific cluster(s) and/or symptom(s).

Although many factors may contribute to the development and severity of primary dysmenorrhea, it is now generally recognized that the pain itself is produced by uterine contractions (Refs. 11, 12, 17, 22, and 23). From evidence accumulated in the last 20 years, it appears that certain prostaglandins are capable of stimulating contractions of human uterine smooth-muscle strips and that women with primary dysmenorrhea secrete higher levels of prostaglandins in their menstrual fluid than those not experiencing primary dysmenorrhea (Refs. 12, 17, and 24). The similarity between the clinical manifestions of primary dysmenorrhea and symptoms induced by the administration of exogenous prostaglandins is striking; individuals undergoing prostaglandin infusions experience bleeding, cramps, diarrhea, nausea, flushing, fainting, headache, and inability to concentrate (Refs. 12, 17, and 25). On this basis,

prostaglandins appear to have an important role in producing primary dysmenorrhea, but the basic physiologic abnormality responsible for the symptom is still uncertain.

References

(1) Morton, J. H. "Premenstrual Tension," *American Journal of Obstetrics and Gynecology*, 60:343–352, 1950.

(2) OTC Volume 170222.

(3) OTC Volume 170223 (Section E).

(4) Bickers, W., and M. Woods, "Premenstrual Tension: Its Relation to Abnormal Water Storage," *The New England Journal of Medicine*, 245:453–456, 1951.

(5) Morton, J. H., et al., "A Clinical Study of Premenstrual Tension," *American Journal of Obstetrics and Gynecology*, 65:1182–1191, 1953.

(6) Bickers, W., "Premenstrual Tension: A Neglected Phase of Menstrual Disability," *Southern Medical Journal*, 46:873–878, 1953.

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C. Labeling

The Panel has carefully reviewed the submitted labeling claims for products promoted as OTC menstrual drug products and has classified them as Category I, Category II, or Category III. The Panel realizes that other terms may be developed to express the same Category I indications. However, only those indications and warnings listed under Category I are generally recognized to be acceptable at this time.

In order for any labeling to be acceptable, it must include (1) the indication(s) for use, (2) pertinent warnings and contraindications, and (3) clear directions for use that include the recommended dosage.

The Panel believes that all labeling should be clear, concise, easily read, and understood by most consumers. It has followed this concept in the development of all Category I labeling. The Panel also is concerned about the size and color of the print used in the labeling of these and all OTC drug products and recommends that the manufacturers make the necessary effort to design legible labeling.

One of the functions of this Panel is to attempt to eliminate inadequate labeling claims. Some of the labeling on currently marketed OTC menstrual drug products is misleading or unsupported by scientific data. Accordingly, such labeling has been placed in Category II.

The indications for use should be simply and clearly stated; the directions for use should provide enough information for safe and effective use of the product.

The Panel believes that if two ingredients are indistinguishable with regard to effectiveness, it is misleading to claim superiority for one of the ingredients. The Panel understands that its function is not to compare various ingredients in order to determine the OTC drug of choice but only to determine the safety and effectiveness of active ingredients, as well as proper dosage ranges, warnings, and contraindications.

Misleading or undocumented claims and colloquial or provincial expressions that do not have meaning to most people must not be used. In the labeling, effectiveness shall not be related to the physical characteristics of the product, except as those characteristics may relate to the action of the active ingredients.

The Panel is aware of the current OTC labeling regulation dealing with warning statements (21 CFR 330.1(g)). The Panel concurs with the warning "Keep this and all drugs out of the reach of children" and believes that it should be incorporated in the labeling of drug products affected by this document. However, the Panel recommends that the other warning statement required by § 330.1(g), "In case of accidental overdose, seek professional assistance or contact a poison control center immediately," be revised to read as follows: "In case of accidental overdose, contact a poison control center, emergency medical facility, or physician immediately for advice." The Panel believes that this revision will be more useful to the consumer.

In addition, the Panel recommends that the drug product labeling contain instructions for the most effective use of the product. These instructions should be displayed prominently on all package labeling.

The Panel recommends that the label should contain a listing of all ingredients, clearly indicating which are active and which are inactive. Active ingredients should be listed by their established names, and the label should state the quantity of the active ingredient included in a single dose.

III. Categorization of Data

A. Analgesics

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products has reviewed submissions proposing the use of aspirin, acetaminophen, salicylamide, phenacetin, caffeine, and codeine as analgesics for the treatment of dysmenorrhea and premenstrual tension. These analgesic agents plus many others were extensively reviewed by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (hereinafter referred to as the Internal Analgesic Panel), and its conclusions were published in the **Federal Register** of July 8, 1977 (42 FR 35346). The Miscellaneous Internal Panel, in addition to reviewing the ingredients submitted to it, reviewed the remaining Category I analgesics, i.e., calcium carbaspirin, choline salicylate, magnesium salicylate, and sodium salicylate.

The Internal Analgesic Panel concluded that OTC analgesic drugs are intended to alleviate the symptoms of

mild to moderate pain, specifically the type of pain that is self-limiting and requires no special treatment or prior diagnosis by a physician. The Miscellaneous Internal Panel considers the pain associated with primary dysmenorrhea and the premenstrual syndrome to be in that category and has concluded that any analgesic that has been given a Category I designation by the Internal Analgesic Panel for a label claim of "For the temporary relief of occasional minor aches, pain, and headaches" (42 FR 35351) may be used with a label claim relating to the relief of pain associated with the premenstrual syndrome and primary dysmenorrhea. (See part III. paragraph A.1.b. below—Category I labeling.). The Miscellaneous Internal Panel also agrees with the Internal Analgesic Panel's evaluation of phenacetin and salicylamide. The Miscellaneous Internal Panel recommends that the labeling indication for analgesics designated Category I by the Internal Analgesic Panel be amended to include the indications for the relief of pain of the premenstrual syndrome and primary dysmenorrhea. (See part III. paragraph A.1.b. below—Category I labeling.)

1. *Category I conditions.* The following are Category I conditions under which analgesics used for primary dysmenorrhea and the premenstrual syndrome are generally recognized as safe and effective.

a. *Category I active ingredients.* Aspirin, calcium carbaspirin, choline salicylate, magnesium salicylate, and sodium salicylate Acetaminophen

(1) *Aspirin, calcium carbaspirin, choline salicylate, magnesium salicylate, and sodium salicylate.* The Panel concludes that aspirin, calcium carbaspirin, choline salicylate, magnesium salicylate, and sodium salicylate are generally recognized as safe and effective for OTC use in relieving pain of the premenstrual syndrome and primary dysmenorrhea.

(i) *Safety.* Aspirin and the other salicylates were previously reviewed by the Internal Analgesic Panel (42 FR 35382). That Panel concluded that aspirin and the other salicylates noted above are safe OTC analgesics when taken as recommended in its report. However, that Panel noted that although aspirin has a long marketing history and is the most extensively used single drug, the indiscriminate use of aspirin can cause adverse effects. The Internal Analgesic Panel identified and discussed eight areas of concern where aspirin may have some potential for adverse effects, including effects on organ systems, and concluded that, because of the extensive use of and research on aspirin, subsets of the population at risk can be identified so that adequate labeling can be established to provide for safe OTC use of this drug. The Miscellaneous Internal Panel agrees with the above evaluation and concludes that aspirin and the other salicylates are safe for OTC use for the relief of minor pain associated with both primary dysmenorrhea and the premenstrual syndrome in the doses recommended by the Internal Analgesic Panel. Applicable precutionary statements developed by the internal Analgesic Panel for these ingredients should also be included.

(ii) *Effectiveness.* The Internal Analgesic Panel concluded that aspirin is effective for the relief of mild to moderate pain and is only of limited value in the relief of severe pain (42 FR 35382). Since the recognition of the possible etiologic role of prostaglandins in dysmenorrhea, several reviews have indicated that the effect of aspirin, a known inhibitor of prostaglandin synthesis, may be due in part to the depression of the synthesis of prostaglandins (Refs. 1, 2, and 3). These reports indicate that the administration of aspirin leads to significant relief from the symptoms of primary dysmenorrhea, suggesting a possible relationship between decreased prostaglandin concentrations and the relief of primary dysmenorrhea (Refs. 1, 2, and 3). This Panel believes that, while no conclusions can be drawn as to the exact nature of the role of aspirin in inhibiting prostaglandin synthesis, aspirin is effective for the relief of the pain of primary dysmenorrhea.

The Internal Analgesic Panel concluded that aspirin and the other salicylates are effective for OTC use for the relief of minor aches, pain, and headaches. Because the presence of minor pain, such as headache and lower abdominal pain (including cramps), is not uncommon in the premenstrual syndrome, the Miscellaneous Internal Panel concludes that aspirin and the other salicylates are effective for the relief of such pain when it occurs as a component of the premenstrual syndrome.

The other Category I salicylate analgesics have been incorporated in this review of aspirin, even though their mode of action may differ from aspirin in part, because the Panel concludes that they will have a similar type effect to that of aspirin in relieving pain of the premenstrual syndrome and primary dysmenorrhea.

(iii) *Labeling.* The Panel recommmends Category I labeling for analgesics intended to relieve pain of the premenstrual syndrome and primary dysmenorrhea. (See part III. Paragraph A.1.b. below—Category I labeling.) Precautionary statements developed by the Internal Analgesic Panel for aspirin, calcium carbaspirin, choline salicylate, magnesium salicylate, and sodium salicylate should also be included. In addition, the Panel also recommends that the Category I labeling for these ingredients, as recommended by the Internal Analgesic Panel, be amended to include the Category I labeling below.

(iv) *Dosage.* The Panel recommends that the dosage of aspirin, calcium carbaspirin, choline salicylate, magnesium salicylate, and sodium salicylate when used to relieve the pain of the premenstrual syndrome and primary dysmenorrhea be in the dosage ranges recommended by the Internal Analgesic Panel and not be taken for more than 10 days.

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(2) *Acetaminophen.* The Panel concludes that acetaminophen is generally recognized as safe and effective for OTC use in relieving pain of the premenstrual syndrome and primary dysmenorrhea.

(i) *Safety.* The Internal Analgesic Panel reviewed acetaminophen at 42 FR 35412 and concluded that it is safe for OTC use if taken as recommended in its report. That Panel found acetaminophen (when taken in recommended OTC doses) relatively free of adverse effects in most age groups, even in the presence of a variety of disease states. The only known contraindication to the use of acetaminophen at recommended OTC dosage levels and usage periods is hypersensitivity to the drug. This Panel agrees with that evaluation and concludes that acetaminophen is safe for OTC use in the dose recommended by the Internal Analgesic Panel for relief of pain of the premenstrual syndrome and primary dysmenorrhea. Precautionary statements developed by the Internal Analgesic Panel for acetaminophen should also be included.

(ii) *Effectiveness.* Acetaminophen is widely used as an analgesic for relief of mild to moderate pain. The Internal Analgesic Panel reviewed several studies attesting to its analgesic effect (42 FR 35412) and concluded that acetaminophen is equivalent to aspirin

provided that the pain is not associated with local inflammation. Layes Molla and Donald (Ref. 1), in a double-blind crossover study, compared the analgesic effectiveness of ibuprofen and acetaminophen in dysmenorrheic women. The results of that study indicated that both drugs were found to be effective for the relief of dysmenorrhea and there was no statistical difference between the effectiveness of the two drugs. The Miscellaneous Internal Panel concludes that acetaminophen is effective for the relief of pain of primary dysmenorrhea.

The Internal Analgesic Panel concluded that acetaminophen is equivalent to aspirin in its analgesic effects. Therefore, the Miscellaneous Internal Panel concludes that acetaminophen is effective for the relief of pain of the premenstrual syndrome.

(iii) *Labeling.* The Panel recommends Category I labeling for analgesics intended to relieve pain of the premenstrual syndrome and primary dysmenorrhea. (See Part III. paragraph A.1.b. below—Category I labeling.) Precautionary statements developed by the Internal Analgesic Panel for acetaminophen should also be included. In addition, the Panel recommends that Category I labeling for acetaminophen, as recommeded by the Internal Analgesic Panel, be amended and include the Category I labeling referred to above.

(iv) *Dosage.* The Panel recommends that the dosage of acetaminophen when used to relieve pain of the premenstrual syndrome and primary dysmenorrhea be in the dosage ranges recommended by the Internal Analgesic Panel and not be taken for more than 10 days.

Reference

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b. *Category I labeling.* The Panel recommends any of the following Category I labeling for analgesics in relieving pain of the premenstrual syndrome and primary dysmenorrhea. The Panel also recommends that the recommendations of the Internal Analgesic Panel be amended to include any of these claims.

(1) "For the relief of pain of the premenstrual and menstrual periods."

(2) "For the relief of pain of the premenstrual period."

(3) "For the relief of pain of the cramping of the premenstrual period."

(4) "For the relief of pain of the menstrual period."

(5) "For the relief of pain of menstrual cramps."

(6) "For the relief of pain of dysmenorrhea."

The Panel also recommends that the phrase "An aid in relieving" may be used in place of "For the relief of."

2. *Category II conditions.* The following are Category II conditions under which analgesic, when used for primary dysmenorrhea and the premenstrual syndrome, are not generally recognized as safe and effective or are misbranded.

a. *Category II active ingredient—Codeine.* The Panel concludes that codeine is an effective analgesic when taken in the recommended dosage of 30 to 60 milligrams (mg) and is safe for prescription use, but because of its potential for causing dependence and other adverse effects is not safe for OTC use as an analgesic.

(i) *Safety.* The Panel concludes that codeine is not safe for use as an OTC analgesic. Codeine is classified as one of the opium alkaloids and is used primarily for the relief of pain. However, with repeated use there is a potential for physical and psychological dependence. The Panel concurs in the conclusions of the Internal Analgesic Panel (42 FR 35423) that codeine is an effective analgesic and safe for prescription use, but, because of its potential for causing dependence and other adverse effects, is not safe for OTC use as an analgesic.

(ii) *Effectiveness.* The effectiveness of codeine for use as an OTC drug product has been reviewed by two advisory review panels. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (hereinafter referred to as the Cough/Cold Panel), in its report published in the **Federal Register** of September 9, 1976 (41 FR 38312), found codeine effective for OTC use as an antitussive in the dosage range of 10 to 20 mg. The Internal Analgesic Panel (42 FR 35423) concluded that codeine is an effective analgesic when taken in the dosage range of 30 to 60 mg. However, the Internal Analgesic Panel recommended that codeine's availability for OTC analgesic use continue to be limited as set forth under Schedule V of the Federal Controlled Substances Act. That act classifies codeine as an ingredient having dependence liability and restricts its OTC sale to not more than 200 mg per 100 milliliter (mL) container or approximately 10 to 20 mg codeine/dosage and then only when it is combined with nonnarcotic active ingredients. This Panel agrees with the recommendations of the Internal Analgesic Panel that codeine is an effective analgesic in the dosage range of 30 to 60 mg, but at this dosage it should continue to be restricted to prescription use only.

(iii) *Evaluation.* The Panel concludes that codeine is generally recognized as a safe and effective analgesic drug at the dosage restricted to prescription use (30 to 60 mg), but it is not generally recognized as safe for OTC use as an analgesic.

b. *Category II labeling.* The Panel concludes that the following labeling claims are misleading or unsupported by scientific data. Therefore, the claims listed below and other related terms are classified as Category II labeling: "Fast relief," "quick relief," or any other terms which nonspecifically relate to the speed of action.

3. *Category III conditions.* The following are Category III conditions for which the available data are insufficient to permit final classification at this time.

a. *Category III active ingredient—Caffeine (as an analgesic adjuvant).* The Panel concludes that caffeine is safe but ineffective as an analgesic in OTC menstrual drug products, although it may have value as an analgesic adjuvant.

(i) *Safety.* Caffeine was previously reviewed by the Advisory Review Panel on OTC Sedative, Tranquilizer, and Sleep-Aid Drug Products in its report published in the **Federal Register** of December 8, 1975 (40 FR 57292). Caffeine was reviewed for its stimulant properties and found to be safe "* * * when used in the recommended oral dose of 100 to 200 mg not more often than evey 3 to 4 hours." FDA concurred with the panel in the tentative final monograph published in the **Federal Register** of June 13, 1978 (43 FR 25544). The Internal Analgesic Panel also reviewed caffeine and concluded that when used as an adjuvant it is safe at a single adult dosage of 65 mg not to exceed 600 mg in 24 hours (42 FR 35482). This Panel agrees with those Panels and concludes that caffeine is safe as an analgesic adjuvant ingredient in OTC menstrual drug products.

(ii) *Effectiveness.* The Internal Analgesic Panel concluded that caffeine "when used alone in an adult oral dosage of 65 mg not to exceed 600 mg in 24 hours is safe but ineffective as an OTC analgesic, antipyretic and/or antirheumatic ingredient" (42 FR 35482). That Panel further concluded, however, that "there is some inconclusive evidence to suggest that caffeine may exert additional analgesia through an adjuvant action when used in combination with other analgesics." This Panel agrees with the conclusion of the Internal Analgesic Panel and

concludes that caffeine would also have the same action in OTC menstrual drug products.

(iii) *Proposed Dosage.* The Panel recommends that the dose of caffeine as an analgesic adjuvant ingredient for OTC menstrual drug products be limited to 600 mg per 24 hours.

(iv) *Labeling.* The Panel recommends Category I labeling for analgesics to be used in OTC menstrual drug products. (See part III. paragraph A.1.b. above—Category I labeling).

(v) *Evaluation.* This Panel recognizes that caffeine has been used in combination with other analgesics in OTC menstrual drug products. It concurs in the finding of the Internal Analgesic Panel that caffeine is safe but not effective as an analgesic, although it may exert some influence as an adjuvant in potentiating the effectiveness of other analgesics.

b. *Category III labeling. None.*

B. Antihistamines

1. *Category I conditions.* The following are Category I conditions under which antihistamines used in OTC menstrual drug products are generally recognized as safe and effective and are not misbranded.

a. *Category I active ingredient—Pyrilamine maleate.* The Panel concludes that pyrilamine maleate is generally recognized as safe and effective for OTC use in the dose noted below in relieving premenstrual symptoms of the negative affect and water-retention clusters, and the pain of cramps and backache of the premenstrual and menstrual periods.

(1) *Safety.* The Panel concurs with the Cough/Cold Panel, which stated in its report published in the **Federal Register** of September 9, 1976 (41 FR 38312) that pyrilamine maleate is safe in an adult dose of 25 to 50 mg every 6 to 8 hours, not to exceed 200 mg in 24 hours, when used as an OTC antihistamine (41 FR 38391). Doses of pyrilamine maleate used in OTC drug products recommended for treatment of premenstrual tension are within the maximum daily dose of 200 mg in 24 hours found safe by the Cough/Cold Panel. Although the frequency of dosing for pyrilamine maleate for premenstrual tension varies from 25 mg every 3 to 4 hours to 60 mg every 12 hours, the Panel does not consider the greater frequency (i.e., every 3 to 4 hours) or the higher single dose (i.e., 60 mg) to be a safety problem.

(2) *Effectiveness.* Pyrilamine maleate is an antihistaminic agent of the ethylenediamine group primarily used for treating allergic disorders caused by histamine release. Its antihistamine properties were described by Bovet (Ref. 1) in 1944, 2 years after Halpern (Ref. 2) described the first clinically useful antihistamine, antergan. Since that time, it has been widely used as an antihistamine. In addition, pyrilamine possesses local anesthetic activity (Refs. 3 and 4) and exerts a mild analgesic action (Ref. 5). The side effects of antihistamines include mild sedation, listlessness, irritability, drying, and loss of appetite (Ref. 6). Pyrilamine maleate has been marketed in combination with other ingredients in OTC drug products for use in the relief of premenstrual tension.

Labeling of products submitted for review by the Panel indicates that pyrilamine maleate is intended to relieve the anxiety, tension, and irritability associated with the premenstrual period. The Panel is aware that pyrilamine maleate had been previously marketed for its mild sedative effect in OTC daytime sedative drug products. The Panel is also aware of the agency's decision, in the final order for OTC Daytime Sedatives, published in the **Federal Register** on June 22, 1979 (44 FR 36378), that while antihistamines make a user drowsy or sleepy, there are no data to indicate the drowsiness is related to symptoms of anxiety. Drowsiness is, in fact, an undesirable side effect for persons using these products during the day, when they need to be alert. For this reason, the agency placed antihistamines in Category II as daytime sedatives, and such products have been eliminated from the marketplace.

The target population for the use of a menstrual drug product may be different from the population that would commonly use daytime sedatives. Moreover, the physiology of pain would minimize any tendency toward sedation that might be induced. Indeed, in one study (Ref. 7) there was less "tiredness and drowsiness" with the pyrilamine maleate than there was with the placebo.

Three submissions promote pyrilamine maleate for the relief of some of the symptoms of premenstrual tension. The mechanism by which relief is accomplished is uncertain, but one submission (Ref. 8) proposed three theories for the mechanism of action. First, it is postulated that the action may be through the effect of pyrilamine's antihistamine action, because Jonassen, Granerus, and Wettergvist (Ref. 9) demonstrated that the amount of histamine in the body increases and decreases with fluctuations in estrogen levels during the menstrual cycle. Second, it is postulated that the mechanism may be through the effect of histamine and antihistamine on the cyclic nucleotide system with secondary effects on smooth muscle and vascular permeability. Indirect support for this theory is provided by Weiss and Hait (Ref. 10), who reported changes in the cyclic nucleotide system which activated various hormones. Lastly, it is postulated that the mechanism may be through reductions of prolactin levels by antihistamines, with secondary reduction in synthesis of prostaglandins, which have an agonistic effect on the uterine musculature. In support of this theory, Chapler, Sherman, and Swanson (Ref. 11) are cited as demonstrating that an antihistamine (promethazine) can block the release of prolactin. It is also possible that pyrilamine maleate may have a more direct effect on uterine musculature through blocking responses to prostaglandins. Ganatra et al. (Ref. 12) showed that cyproheptadine, which, like pyrilamine maleate, is an H_1 antihistamine, in small concentrations completely blocked the responses of isolated muscle of rabbit uterus to prostaglandins E_1 and $F_2\alpha$, and in higher concentrations abolished the rhythmic contractions of the uterus.

An early clinical study by Bickers (Ref. 13) reported an enhanced relief of symptoms of premenstrual tension with concurrent administration of a diuretic and pyrilamine maleate. A double-blind, single crossover study, designated as the Wisconsin study, was reported in which pyrilamine maleate alone, pamabrom alone, and a combination of pyrilamine maleate and pamabrom were each compared with a placebo (Ref. 14). The study was conducted on 194 women with known histories of premenstrual syndrome. Forty-nine of them participated in the pyrilamine maleate alone portion of the crossover study. Subjects rated nine symptoms on a 1 to 4 scale for the days preceding menstruation. Data on 48 subjects for premenstrual days 1 to 3 were available for analysis. The paired t-test was employed for analysis (Ref. 15). For analysis purposes the symptoms investigated in the study were examined separately and as groups of clusters following the Moos cluster grouping of symptoms (Ref. 16). Pyrilamine maleate was significantly superior to the placebo for the negative affect cluster ($p=0.047$), which included the symptoms of irritability ($p=0.020$); premenstrual tension ($p>0.10$, not statistically significant (NS)); and depression ($p>0.10$, NS). There were no significant differences between pyrilamine maleate and placebo for the pain cluster, which included headache and cramps, and for the water-retention cluster, which

included breast tenderness, ankle swelling, finger swelling, and abdominal swelling. Of the individual symptoms in the latter two clusters, pyrilamine maleate was marginally superior to the placebo for the symptoms of finger swelling ($p=0.059$). Finally, pyrilamine maleate was marginally superior to the placebo for the sum of cluster scores ($p=0.060$). The term "negative effects" was used in the submitted data. The Panel was subsequently informed by the firm that "negative affect," as was used in the Moos Questionnaire, was what should have been used. Typographical errors had been made in the firm's writeup of the Wisconsin study and the Boston study discussed below.

Another double-blind, placebo-controlled, crossover study, designated as the Boston study, investigating only pyrilamine maleate was performed on 40 subjects (Refs. 17 and 18). Study subjects rated 13 symptoms on a 1 to 6 scale during the premenstrual period. Data were available for analysis on 27 subjects for premenstrual days 1 to 4. The paired t-test was employed for analysis. For analysis purposes the symptoms, as in the previous study, were examined separately and as clusters following the Moos clustering (Ref. 16). Pyrilamine maleate was significantly superior to the placebo for the negative affect cluster ($p=0.011$), which included the symptoms of anxiety ($p=0.035$), irritability ($p>0.10$, NS), depression ($p=0.059$), and tension ($p=0.058$). It was also significantly superior to the placebo for the water-retention cluster ($p=0.035$), which included the symptoms of weight gain ($p=0.074$), painful breasts ($p>0.10$, NS), and swelling ($p=0.025$). It was marginally superior to the placebo for the pain cluster ($p=0.074$), which included muscle stiffness ($p>0.10$, NS), headache ($p>10$, NS), cramps ($p=0.038$), backache ($p=0.039$), an general aches and pains ($p>0.10$, NS). Finally, pyrilamine maleate was significantly superior to the placebo for the sum of cluster scores ($p=0.015$). The Panel also took note that fewer subjects reported "tiredness and drowsiness" following the administration of the pyrilamine maleate as compared to the placebo.

The Boston study also evaluated the effectiveness of pyrilamine maleate versus placebo for two days into the menstrual period. Pyrilamine maleate proved to be statistically superior to placebo in relieving cramps ($p<0.05$) and backache ($p<0.05$) (Refs. 17 and 18).

Given the results of the above two studies, the Panel concludes that pyrilamine maleate is generally recognized as effective in relieving the premenstrual symptoms of the negative affect cluster and the water-retention cluster. (Note: individual symptoms cannot be used on labeling unless demonstrated to be effective.) It also is generally recognized as effective in relieving the pain of cramps and backache in both the premenstrual and menstrual periods

(3) *Dosage.* The Panel recommends that the dose of pyrilamine maleate in OTC menstrual drug products be 25 to 30 mg every 3 to 4 hours or 60 mg every 12 hours, but not to exceed 200 mg in a 24-hour period.

(4) *Labeling.* The Panel recommends Category I labeling for antihistamines to be used in OTC menstrual drug products. (See part III. paragraph B.1.b. below—Category I labeling). In addition, the Panel recommends that the following warning be included in the labeling: "May cause drowsiness."

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(18) OTC Volume 170224 (Section 4).

b. *Category I labeling.* The Panel recommends any of the following Category I labeling for antihistamines used in OTC menstrual drug products, as well as any specific labeling discussed in the individual ingredient statements.

(1) "For the relief of" ("emotional changes" or "mood changes") "related to the premenstrual period."

(2) "For the relief of" ("emotional changes" or "mood changes") "related to the premenstrual period, such as anxiety, nervous tension, and irritability."

(3) "For the relief of water-retention symptoms related to the premenstrual period."

(4) "For the relief of temporary weight gain or swelling due to water retention during the premenstrual period."

(5) "For the relief of cramps and backache of the premenstrual or menstrual period."

The Panel also recommends that the phrase "An aid in relieving" may replace the phrase "For the relief of."

2. *Category II conditions.* The following are Category II conditions under which antihistamines used in OTC menstrual drug products are not generally recognized as safe and effective or are misbranded.

a. *Category II active ingredients.* None.

b. *Category II labeling.* The Panel concludes that the following labeling claims are either unsupported by scientific data or are misleading. "Fast relief," "quick relief," or any other terms that nonspecifically relate to the speed of action.

3. *Category III conditions.* The following are Category III conditions for which the available data are insufficient to permit final classification at this time.

a. *Category III active ingredients.* None.

b. *Category III labeling.* Antihistamine labeling for those symptoms of the negative affect, pain, and water-retention clusters for which effectiveness in the premenstrual or menstrual period has not been demonstrated are as follows:

(1) "For the relief of" ("emotional changes" or "mood changes") "related to the" ("premenstrual" and/or "menstrual") "period, such as crying, lonelines, restlessness, and mood swings." Note: "Depression" was not included because the Panel does not believe that this term is appropriate for OTC labeling.

(2) "For the relief of water-retention symptoms related to the" ("premenstrual" and/or "menstrual") "period, such as skin disorders and painful breasts."

(3) "For the relief of muscle stiffness, headache, fatigue, and general aches and pains of the" ("premenstrual" and/or "menstrual") "period."

C. Diuretics

The Panel considered the various conditions for which a diuretic could be used (e.g., hypertension, edema, and the premenstrual syndrome) and concludes that the only proper use of OTC diuretics is in eliminating water accumulation during the premenstrual and menstrual periods, thereby relieving the symptoms of water-weight gain, bloating, swelling, and/or full feeling. The safe use of OTC diuretics in the premenstrual syndrome and primary dysmenorrhea is based on the fact that these conditions are self-diagnosable, limited in duration, occur intermittently, and are not symptoms of a potentially serious underlying disorder.

While the cause of the water accumulation during the premenstrual period remains obscure and is not universally present, it is generally accepted that the edema of various organs may be responsible for some of the symptoms associated with this conditions (Refs. 1 and 2). The Panel believes that it is reasonable to assume that water accumulation may also be responsible for symptoms occuring in the menstrual period. Treatment, therefore, is directed at the elimination of excess water that has accumulated in body tissue.

References

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1. *Category I conditions.* The following are Category I conditions under which diuretics used in menstrual drug products are generally recognized as safe and effective and are not misbranded.

a. *Category I active ingredients.*

Ammonium chloride
Caffeine
Pamabrom

(1) *Ammonium chloride.* The Panel concludes that ammonium chloride is generally recognized as a safe and effective diuretic for OTC use in the dose noted below in relieving water-accumulation symptoms of the premenstrual and menstrual periods.

(i) *Safety.* Ammonium chloride is the most commonly used of the so-called "acidifying diuretics." Its long-term clinical use as a diuretic, expectorant, and acidifying agent attests to its safety. This ingredient was previously reviewed by the Cough/Cold Panel in a report published in the Federal Register of September 9, 1976 (41 FR 38312) and was found to be safe in a dosage range of 1 to 3 grams (g) daily when administered in divided oral doses.

When ammonium chloride is used orally in patients with impaired kidney function, progressive hyperchloremic acidosis can result (Ref. 1). When ammonium chloride is ingested by patients with liver disease, a state similar to spontaneous hepatic coma may be produced (Ref. 1). Acidosis was reported by Sleisenger and Freedberg (Ref. 2) to have occurred in six patients receiving 6 to 8 g of ammonium chloride per day. Five of the six patients had congestive heart failure and the other one had subacute glomerulonephritis; each of the five with congestive heart failure had underlying kidney disease. When administered in doses of 8 to 12 g daily (divided doses), ammonium chloride frequently causes gastrointestinal irritation (Ref. 3). However, smaller doses of 1 to 2 g daily in divided doses to correct pre-existing alkalosis appear to be relatively nonirritating when administered for less than 1 week (Refs. 4 and 5) or as an enteric-coated preparation.

The Panel, therefore, concludes that ammonium chloride is safe for use as a diuretic in the treatment of the water-accumulation symptoms of the premenstrual and menstrual periods in an oral dose of up to 3 g per day, administered in divided doses three to four times per day for periods of up to 6 days.

(ii) *Effectiveness.* Orally administered ammonium chloride is absorbed from the intestine. The ammonium ion is then converted to urea as it passes through the liver, thus freeing the chloride ion. This acidifying action results in formation of sodium chloride from sodium bicarbonate in the body and a decrease in the ability of proteins to bind water, thus freeing both water and sodium chloride for elimination. This would result in the depletion of available sodium in the body were it not for a number of defense mechanisms, including the ability of the kidney after 1 or 2 days to produce ammonia which combines with available hydrogen ion to form an ammonium ion that in turn is excreted with chloride ion. Thus, within a 3 or 4-day period, the amount of ammonium chloride excreted begins to equal the amount ingested and diuretic action decreases (Refs. 3, 6, and 7).

Because of this self-limiting action, ammonium chloride has very limited value for long-term use. It is effective only in promoting an initial net loss of extractable fluids and becomes less effective after 4 or 5 days of administration. As a result, this drug is usually administered for 4 days and then discontinued for at least 4 days (Refs. 3, 8, and 9). There is no justification for the prolonged administration of ammonium chloride as the sole diuretic agent (Ref. 4).

Ammonium chloride is usually administered as enteric-coated tablets at a dosage of 3 to 12 g daily, given in divided doses at mealtimes (Refs. 4, 6, and 7). Its main diuretic use has been to augment the action of the mercurial diuretics and occasionally to treat premenstrual tension (Refs. 4, 6, and 10). In the treatment of premenstrual tension, ammonium chloride is used in the lower dose range of 1 g three times daily (Ref. 6).

A study evaluating a combination of 100 mg caffeine and 325 mg ammonium chloride against placebo in 22 adult females showed a statistically significant relief of symptoms attributed to premenstrual weight gain when this combination product was administered for 6 days immediately prior to the onset of the menstrual flow (Ref. 5). The Panel concludes that ammonium chloride is an effective diuretic and may be used to relieve the water-accumulation symptoms of water-weight gain, bloating, swelling, and/or full feeling associated with the premenstrual and menstrual periods.

(iii) *Dosage.* The Panel recommends that the dose of ammonium chloride as a diuretic in OTC menstrual drug products

be 1 g three times a day for no longer than 6 days.

(iv) *Labeling.* The Panel recommends Category I labeling for diuretics to be used in OTC menstrual drug products. (See part III. paragraph C.1.b. below—Category I labeling). In addition, the labeling should contain the following warning: "Do not use if you have kidney or liver disease." The labeling should also contain the following precaution; "This drug may cause nausea, vomiting, or gastrointestinal distress."

References

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(5) Hoffman, J. J., 'A Double Blind Crossover Clinical Trial of an OTC Diuretic in the Treatment of Premenstrual Tension and Weight Gain," *Current Therapeutic Research,* 26:575–580, 1979.

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(10) Krantz, J. C., and C. J. Carr, editors, "The Pharmacological Principles of Medicinal Practice," 6th Ed., the Williams and Wilkins Co., Baltimore, pp. 811–812, 1965.

(2) *Caffeine.* The Panel concludes that caffeine is generally recognized as a safe and effective diuretic for OTC use in the doses noted below in relieving water accumulation symptoms of the premenstrual and menstrual periods.

(i) *Safety.* The toxicity of caffeine has been reviewed extensively by the Advisory Review Panel on OTC Sedative, Tranquilizer, and Sleep-Aid Drug Products in its report published in the **Federal Register** of December 8, 1975 (40 FR 57292). That Panel also discussed the mutagenic effects of caffeine in detail. It found caffeine to be safe "* * * when used in the recommended oral dose of 100 to 200 milligrams (mg) not more often than every 3 to 4 hours."

FDA concurred with the Panel in the tentative final monograph published in the **Federal Register** of June 13, 1978 (43 FR 25544).

The Internal Analgesic Panel also reviewed caffeine for its analgesic properties (42 FR 35482) and expressed its agreement with the conclusions reached by the Advisory Review Panel on OTC Sedative, Tranquilizer, and Sleep-Aid Drug Products regarding the safety of caffeine. The Miscellaneous Internal Panel agrees with the above reports and concludes that caffeine is safe as an OTC diuretic for relieving water-accumulation symptoms of the premenstrual and menstrual periods in doses of 100 to 200 mg every 3 to 4 hours.

(ii) *Effectiveness.* The ingestion of coffee, tea, and other beverages containing caffeine has long been known to result in a diuretic effect (Refs. 1 and 2). This diuretic effect was acknowledged by the Advisory Review Panel on Sedative, Tranquilizer, and Sleep-Aid Drug Products with an extensive discussion of caffeine (40 FR 57292).

The diuretic effect on caffeine was also demonstrated by Dorfman and Jarvik (Ref. 3) in a double-blind clinical trial comparing it with theobromine and with no drug at all. The authors reported an increase in overnight urine volume and an increase in sodium excretion.

As with all xanthine diuretics, caffeine acts by increasing the glomerular filtration rate in the kidney. The use of xanthine diuretics has become less popular in recent times with the advent of newer and more effective diuretics such as the chlorothiazides (Ref. 4). The diuretic action of caffeine chiefly involves water output, although sodium, calcium, potassium, and chloride ion output is also increased, and urea output is increased somewhat. The usual adult oral dose is 200 mg within a dose range of 100 to 500 mg (Ref. 5). The Panel concludes that caffeine is an effective diuretic and may be used to relieve the water-accumulation symptoms of water-weight gain, bloating, swelling, and/or full feeling associated with the premenstrual and menstrual periods.

Separate from its diuretic effect, caffeine was reviewed for its stimulant action in the report on Nighttime Sleep-Aid, Daytime Sedative, and Stimulant Products at 40 FR 57292, with the conclusion that caffeine is a Category I stimulant at a dose of 100 to 200 mg every three to four hours. The agency concurred in this finding in the tentative final monograph (43 FR 25597). One submission to the Miscellaneous Internal Panel for an OTC menstrual drug product made a claim for "fatigue" associated with the premenstrual period. Because the Panel has included "fatigue" as a symptom of the premenstrual syndrome and because caffeine so far has been given a Category I classification as a stimulant, this Panel concludes that caffeine is effective for fatigue associated with the premenstrual syndrome.

(iii) *Dosage.* The Panel recommends that a dose of caffeine as a diuretic for OTC menstrual drug products be 100 to 200 mg every 3 to 4 hours while symptoms persist.

(iv) *Labeling.* The Panel recommends Category I labeling for diuretics used in OTC menstrual drug products. (See part III. paragraph C.1.b. below—Category I labeling.) The following claim specific to caffeine is also recommended: "For the relief of fatigue associated with the premenstrual period." In addition, the labeling should contain those warnings listed in § 340.50(c) (1) and (2) at 43 FR 35602 of the agency's tentative final monograph for OTC Nighttime Sleep-Aid and Stimulant Products. The statement "This product contains caffeine. It may cause sleeplessness if taken within 4 hours of bedtime" should also be included.

References

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(3) *Pamabrom.* The Panel concludes that pamabrom is generally recognized as a safe and effective diuretic for OTC use in the dose noted below in relieving water-accumulation symptoms of the premenstrual and menstrual periods.

(i) *Safety.* Pamabrom, a xanthine derivative, was approved for OTC marketing as a single entity diuretic in 1952 under an NDA and also under other NDA's in combination with pyrilamine maleate and in combination with pyrilamine maleate, phenacetin, and salicylamide. Because these NDA's were approved prior to October 10, 1962, they were approved for safety only. FDA issued a regulation (21 CFR

310.201(a)(21)) that allows the OTC marketing of pamabrom and a suitable analgesic (with or without other OTC ingredients) for "temporary relief of the minor pains and discomforts that may occur a few days before and during the menstrual period" in a dosage of not more than 50 mg per dose not to exceed 200 mg in 24 hours. During this marketing period, no evidence of significant toxicity or adverse reactions has been encountered (Ref. 1).

Studies by Patterson and Baer (Ref. 2) showed no evidence of toxicity when 800 to 1,600 mg pamabrom was administered daily for 5 to 7 days to 38 pregnant women with edema.

Doherty and Beard (Ref. 3) investigated the diuretic effect of pamabrom (in conjunction with mercurial diuretics) on 18 patients with congestive heart failure and found it to have little value in this treatment. Fourteen patients were treated over a period of 14 to 137 days and received 300 to 900 mg of pamabrom daily in divided doses. Four of the patients had to discontinue treatment due to nausea and vomiting, which the manufacturer attributed to injections of mercurial diuretics (Ref. 4). After 120 days, one patient developed diarrhea, which the authors attributed to the pamabrom. There also was one case of rash, which cleared when the drug was discontinued, and one case of pyelonephritis, which the authors considered unrelated to the drug.

McGavack (Ref. 5) conducted a human toxicological study in which nine subjects were given 200 mg of pamabrom (combined with pyrilamine maleate) four times daily for periods of 4 consecutive weeks and found no side effects. "No changes were observed in the urinary formed elements nor in the excretion of albumin. The blood counts were not adversely influenced by the drug and several measures designed to test the function of the liver showed no alterations in this organ." Albumin, under normal circumstances, is not excreted, but this conclusion was meant to infer no harmful effect of the drug, such as inducing albuminuria.

The Panel, therefore, concludes that pamabrom in a dose of 50 mg up to four times daily (200 mg maximum daily dose), as already established by FDA (§ 310.201(a)(21)), is safe for OTC administration.

(ii) *Effectiveness.* A study designated only as the Wisconsin Study (Ref. 6), was designed to assess the effects of pamabrom (2-amino-2-methyl-1-propanol-8-bromotheophyllinate) alone, pyrilamine maleate alone, and both in combination in relieving symptoms of the premenstrual syndrome. This study, involving 194 women, was a randomized, double-blind, placebo-controlled, single-crossover design. Only that portion of the study in which pamabrom was administered alone will be discussed here. The portions of the study dealing with the use of pyrilamine alone and the use of combination are discussed elsewhere in this document. (See part III. paragraph B.1.a. above—Pyrilamine maleate and part III. paragraph G.2.b. below—Pamabrom and pyrilamine maleate.)

Study subjects had an established history of the premenstrual syndrome and were recruited from the technical staff of a research institute (Ref. 6). The subjects were given active drug and placebo on a double-blind, single-crossover basis for one menstrual period each. Pamabrom was given at a dose of 50 mg four times daily, and no other drugs were permitted. Each subject was provided a 10-day supply with instructions to initiate treatment 5 to 7 days prior to the anticipated onset of menstruation and to stop treatment at onset. The women filled out a questionnaire daily to assess subjectively, on a 4-point scale, the premenstrual syndrome signs and symptoms of the pain cluster (consisting of headache and premenstrual cramps), the water-retention cluster (consisting of ankle, finger, and abdominal swelling and breast tenderness), and the negative affect cluster (consisting of irritability, depression, and premenstrual tension). They also were requested to record their weight to the nearest 0.5 pound upon arising each morning.

Forty-eight subjects participated in the pamabrom-alone portion of the crossover study. Data on all 48 subjects for premenstrual days 3 to 5 were available for analysis. The paired t-test was employed for analysis (Ref. 7). For analysis purposes the symptoms were examined separately and as clusters of symptoms following the Moos cluster grouping of symptoms (Ref. 8). There was statistically significant superiority of pamabrom over the placebo for the pain cluster ($p=0.014$), which included headache ($p=0.009$), and premenstrual cramps ($p>0.10$, NS). Pamabrom did not attain statistically significant superiority over the placebo for the water-retention cluster with symptoms of ankle, finger, and abdominal swelling and breast tenderness, and the negative affect cluster with symptoms of irritability, depression, and premenstrual tension. It did, however, attain statistically significant superiority over the placebo for the individual symptoms of finger swelling ($p=0.056$) and depression ($p=0.007$). No significant weight gain was recorded while on placebo or pamabrom.

Hutcheon (Ref. 9) investigated the diuretic properties of pamabrom unrelated to the premenstrual syndrome. The objective of the study was to determine whether or not a 50-mg dose of pamabrom would produce a mild, short-acting diuresis along with increased excretion of sodium, potassium, and chloride. Nine healthy women in the 5th to the 14th day of their menstrual cycle were evaluated during one day in which no treatment in the morning was used as a control and the afternoon was used for the pamabrom treatment. Urine was collected at 8 a.m., 9 a.m., 10 a.m. and 12 noon. A standard meal was given at 9 a.m., and 120 mL of water was given at 10 a.m. In the afternoon, the effectiveness of pamabrom was tested; at 12 noon 50 mg of pamabrom was administered. The same standard meal was given at 1 p.m.; 120 mL of water was given at 2 p.m. Urine was collected at 1 p.m., 2 p.m., and 4 p.m. The author reported that pamabrom produced a significant increase in urine volume. Peak urine flow rates during the first hour after drug administration increased from an average of 1.69 mL per minute during the control period to 3.54 mL per minute following the administration of pamabrom ($p<0.001$). This was accompanied by an increase in sodium excretion ($p<0.02$), chloride excretion ($p<0.05$), and potassium excretion ($p>0.1$, NS). No placebo was used. Even though the drug was administered in the afternoon with no crossover (the morning served as the control time), the Panel is aware that this is a xanthine diuretic and that these results are what would be expected of any diuretic of this class.

In a different study, Hutcheon (Ref. 10) made an attempt to demonstrate the effectiveness of pamabrom on the relief of symptoms associated with the premenstrual syndrome. This involved a double-blind, crossover study, using a latin square design. Subjects were selected and drug effects were assessed by using the menstrual distress questionnaire developed by Moos (Ref. 8). Healthy women took 50 mg pamabrom four times daily for approximately 7 days prior to the anticipated onset of menstruation and continued through the day following its onset. Each subject completed the questionnaire each day while on treatment. The investigator considered the use of a global baseline score to establish the effect of a drug administered over a 3-month interval to be an appropriate evaluation method

instead of using a placebo. The Panel does not agree with using this as a baseline; a placebo control should have been used. The relief of the negative affect cluster, which included anxiety, irritability, depression, and tension, was reported to have attained a statistical significance ($p<0.01$).

The Panel considers the one Hutcheon study (Ref. 10) and the Wisconsin study (Refs. 6 and 7) to be only suggestive of the effectiveness of pamabrom as a diuretic. However, based upon the results of the other Hutcheon study (Ref. 9), the Panel concludes that pamabrom is generally recognized as a safe and effective diuretic in relieving the water-accumulation symptoms of water-weight gain, bloating, swelling, and/or full feeling associated with the premenstrual and menstrual periods.

(iii) *Dosage.* The Panel concludes that the appropriate dosage of pamabrom for OTC use is 50 mg in a single dose, not to exceed 200 mg per day. This is consistent with the current FDA regulations, i.e., 21 CFR 310.201(a)(21).

(iv) *Labeling.* The Panel recommends the Category I labeling for diuretics to be used in OTC menstrual drug products. (See part III. paragraph C.1.b. below—Category I labeling.)

References

(1) Letter from Chattem, Inc. dated June 1, 1981, OTC Volume 17MPAII.

(2) Patterson, R. E., and H. Baer, "Evaluation of a Diuretic Substance in the Management of Mild Pre-Eclampsia," *American Journal of Obstetrics and Gynecology,"* 76:1264–1267, 1958.

(3) Doherty, J. E., nd O. W. Beard, "A Study of Diuretic action of Pamabrom (2-mino-2-Methyl-Propanol-1-8-Bromotheophylline) in Cardiac Failure," *American Heart Journal,* 46:288–290, 1953.

(4) OTC Volume 170209 (p. 56).

(5) McGavack, T. H., et al., "The Treatment of Premenstrual Tension with a Combination of an Antihistaminic and a Theophylline Derivative," *American Journal of Obstetrics and Gynecology,* 72:416–422, 1956.

(6) "Wisconsin Study (1978)," unpublished study, OTC Volume 170209 (pp. 163–186).

(7) OTC Volume 170221.

(8) Moos, R. H., "Menstrual Distress Questionnaire," 1977, OTC Volume 170209 (pp. 133–160).

(9) Hutcheon, D. E., "A Study of the Diuretic Activity of Pamabrom (2-Amino-2-Methyl-1-Propanol-8-Bromotheophylliate)," unpublished study, OTC Volume 170209 (pp. 95–118).

(10) Hutcheon, D. E., "The Effect of Pamabrom on Menstrual Symptomatology," unpublished study, OTC Volume 170209 (pp. 119–132). The name for this study was provided by Chattem, Inc. in a letter dated October 20, 1981, Panel Administrator's File (OTC Volume 17MPAII).

b. *Category I labeling.* The Panel recommends any of the following Category I labeling for diuretics used in OTC menstrual drug products, as well as any specific labeling discussed in the individual ingredient statements:

(1) "For the relief of temporary water-weight gain, bloating, swelling, and/or full feeling associated with the premenstrual and menstrual periods."

(2) "For the relief of temporary water-weight gain, bloating, swelling, and/or full feeling associated with the premenstrual period."

(3) "For the relief of temporary water-weight gain, bloating, swelling, and/or full feeling associated with the menstrual period."

(4) "A diuretic for the relief of temporary premenstrual water-weight gain."

(5) "A diuretic which helps to control temporary water-weight gain during the menstrual period."

The Panel also recommends that the phrase "An aid in relieving" may replace the phrase "For the relief of."

2. *Category II conditions.* The following are Category II conditions under which diuretics used in menstrual drug products are not generally recognized as safe and effective or are misbranded.

a. *Category II active ingredients.* None.

b. *Category II labeling.* The Panel concludes that the following labeling claims are either unsupported by scientific data or are misleading: "Fast relief," "quick relief," or any other terms that nonspecifically relate to the speed of action.

3. *Category III conditions.* The following are Category III conditions for which the available data are insufficient to permit final classification at this time.

a. *Category III ingredients.*

Theobromine sodium salicylate
Theophylline

(1) *Theobromine sodium salicylate.* Theobromine (3,7-dimethylxanthine) sodium salicylate shares several pharmacological actions with other xanthines, caffeine and theophylline. They all stimulate the central nervous system, act on the kidney to produce diuresis, stimulate cardiac muscle, and relax smooth muscle, notably bronchial muscle (Ref. 1). Theobromine has been used as a diuretic because its action on the kidneys is more lasting than the other xanthines (Ref. 2). It is less potent as a diuretic than theophylline, but more potent than caffeine (Ref. 1).

(i) *Safety.* According to Laurence (Ref. 3), "theobromine is weak and of no clinical importance." However, Swinyard (Ref. 2) categorizes it as being practically devoid of toxicity and thus can be used on occasions when the more toxic diuretics are contraindicated, for example, when renal function is poor. Swinyard continues, however, by stating that the wide choice of more effective diuretics has markedly limited the use of theobromine even for this purpose.

(ii) *Effectiveness.* In clinical practice, xanthines have received relatively limited application because, in general, they do not have the effectiveness of other diuretics. Continued use often leads to the loss of their effectiveness for reasons that have not been adequately explained. In addition, gastric irritation becomes a limiting factor with some xanthines (Ref. 4).

Dorfman and Jarvik (Ref. 5) performed a double-blind clinical study to determine the effect of theobromine (as compared with caffeine and no drug) on sleep and on overnight urine volume. Although it appears that the use of theobromine alone only occurred in a small percentage of the total subjects, the authors observed that theobromine had no detectable effect on the time it took to fall asleep (sleep latency), on the quality of sleep, and on the overnight urine volume. Caffeine, on the other hand, showed a lengthening of sleep latency, a decline in sleep quality, and an increase in overnight urine volume (also an increase in sodium excretion).

Because there is conflicting information regarding the effectivness of theobromine sodium salicylate as a diuretic, the Panel recommends that it be placed in Category III.

(iii) *Proposed dosage.* The Panel recommends the dosage of theobromine sodium salicylate to be 300 to 500 mg taken three to four times daily.

(iv) *Labeling.* The Panel recommends Category I labeling for diuretics used in OTC menstrual drug products. (See part III. paragraph C.1.b. above—Category I labeling.)

(v) *Evaluation.* The Panel concludes that theobromine sodium salicylate is safe for OTC use, but that data are insufficient to demonstrate its effectiveness in relieving water-retention symptoms of the premenstrual and menstrual periods.

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(4) Mudge, G. H., "Diuretics and Other Agents Employed in the Mobilization of Edema Fluid," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, MacMillan Publishing Company, Inc., New York, p. 840, 1975.

(5) Dorfman, L. J., and M. E. Jarvik, "Comparative Stimulant and Diuretic Actions of Caffeine and Theobromine in Man," *Clinical Pharmacology and Therapeutics*, 11:869–872, 1970.

(2) *Theophylline.* Theophylline (1,3-dimethylxanthine) shares several pharmacological actions with other xanthines, caffeine and theobromine. They all stimulate the central nervous system, act on the kidney to produce diuresis, stimulate cardiac muscle, and relax smooth muscle, notably bronchial muscle (Ref. 1). Theophylline is the most potent diuretic of the xanthines (Ref. 1).

(i) *Safety.* Theophylline can be quite toxic in high doses and has occasionally proved fatal (Ref. 2) in toxic doses due to central nervous system stimulation.

(ii) *Effectivness.* The Cough/Cold Panel in its report (41 FR 38312) found theophylline preparations safe and effective for OTC use as bronchodilators in an adult dosage based on the anhydrous theophylline equivalent of 100 to 200 mg every 6 hours not to exceed 800 mg in 24 hours (41 FR 38373). FDA, however, dissented from this recommendation by pointing out a belief that there is a scientific issue whether the recommended dosage levels are therapeutically effective for a significant identifiable population of asthmatics (41 FR 38313).

In clinical practice, xanthines have received relatively limited application because, in general, they do not have the effectiveness of other diuretics. Continued use often leads to the loss of their effectiveness for reasons that have not been adequately explained. In addition, gastric irritation becomes a limiting factor with some xanthines (Ref. 3).

Because there is conflicting information regarding the effectiveness of theophylline as a diuretic, the Panel recommends that it be placed in Category III.

(iii) *Proposed dosage.* The Panel recommends the dosage of theophylline to be 200 mg taken three to four times daily.

(iv) *Labeling.* The Panel recommends Category I labeling for diuretics used in OTC menstrual drug products. (See part III. paragraph C.1.b. above—Category I labeling.)

(v) *Evaluation.* The Panel concludes that theophylline is safe at the above recommended dose for OTC use, but that data are insufficient to demonstrate its effectiveness in relieving water-retention symptoms of the premenstrual and menstrual periods.

References

(1) Ritchie, J. M., "Central Nervous System Stimulants: The Xanthines," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, MacMillan Publishing Company, Inc., New York, p. 368, 1975.

(2) Ritchie, J. M., "Central Nervous System Stimulants: The Xanthines," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, MacMillan Publishing Company, Inc., New York, p. 373, 1975.

(3) Mudge, G. H., "Diuretics and Other Agents Employed in the Mobilization of Edema Fluid," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, MacMillan Publishing Company, Inc., New York, p. 840, 1975.

b. *Category III labeling.* None.

D. Smooth-Muscle Relaxants

Considering the symtoms of the premenstrual syndrome and those associated with primary dysmenorrhea, the Panel concludes that a smooth-muscle relaxant may be of value in relieving cramps associated with primary dysmenorrhea and/or the premenstrual syndrome.

1. *Category I conditions.* The following are Category I conditions under which smooth-muscle relaxants used to treat primary dysmenorrhea and premenstrual cramps are generally recognized as safe and effective and are not misbranded.

a. *Category I active ingredients.* None.

b. *Category I labeling.* Although the Panel has not classified any ingredients in Category I, it recommends any of the following Category I labeling for smooth-muscle relaxants used in OTC menstrual drug products if found to be generally recognized as safe and effective and not misbranded.

(1) "For the relief of painful menstrual cramps."

(2) "For the relief of dysmenorrhea."

(3) "For the relief of menstrual cramps."

(4) "For the relief of backache associated with menstrual cramps."

(5) "For the relief of cramps associated with the premenstrual or menstrual period."

(6) "For the relief of cramps associated with menstruation."

The Panel also recommends that the phrase "An aid in relieving" may replace the phrase "For the relief of."

2. *Category II conditions.* The following are Category II conditions under which smooth-muscle relaxants used to treat primary dysmenorrhea and premenstrual cramps are not generally recognized as safe and effective or are misbranded.

a. *Category II active ingredient—Homatropine methylbromide.* The Panel concludes that homatropine methylbromide is safe for OTC use in the dose noted below, but is not generally recognized as effective in relieving cramps of the premenstrual syndrome or primary dysmenorrhea.

(1) *Safety.* The Panel previously reviewed the safety of homatropine methylbromide in its report on Digestive Aid Drug Products (47 FR 454) and concluded that it is safe for OTC use in a recommended dosage of 2.5 to 5.0 mg four times daily (20 mg in 24 hours). Because the dosage of homatropine methylbromide of 1 mg every 3 to 4 hours with a maximum of 6 mg per day proposed for use in treating dysmenorrhea (Ref. 1) is far below the recommended dosage for its use as a digestive aid, the Panel concludes that homatropine methylbromide is generally recognized as safe in a dose of 1 mg every 3 to 4 hours.

(2) *Effectiveness.* Homatropine methylbromide, a quaternary ammonium derivative of belladonna alkaloids, is much less active than the related belladonna alkaloid atropine in its antimuscarinic activity, but is four times more potent as a ganglionic blocking agent (Ref. 2). The 1972 edition of Current Therapy (Ref. 3) recommended the use of a phenobarbital-belladonna combination in treating symptoms of dysmenorrhea based on the smooth muscle relaxant and antispasmodic action of these agents, but a look at a later edition of this text (Ref. 4) did not mention this combination. Innes and Nickerson (Ref. 2) point out that because atropine has negligible effects on the human uterus, the ingredient is useless in treating dysmenorrhea. The Panel also notes that the proposed dosage of homatropine methylbromide for treating dysmenorrhea (1 mg every 3 to 4 hours) is far below the usual therapeutic dose of 2.5 to 5.0 mg four times daily (Ref. 5). The Panel is not aware of any data demonstrating the effectiveness of homatropine methylbromide in relieving cramps of the premenstrual syndrome or primary dysmenorrhea and, therefore, it is not generally recognized as an effective treatment for these conditions.

(3) *Evaluation.* The Panel concludes that homatropine methylbromide is generally recognized as safe for OTC use but is not generally recognized as effective in relieving cramps of the premenstrual syndrome or primary dysmenorrhea.

References

(1) OTC Volume 170025.

(2) Innes, I. R., and M. Nickerson, "Atropine, Scopolamine, and Related Antimuscarinic Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co.,Inc., New York, pp. 514–532, 1975.

(3) Weingold, A. B., "Dysmenorrhea," *in* "Current Therapy 1972," edited by H. F. Conn, W. B. Saunders Co., Philadelphia, pp. 769–770, 1972.

(4) Barnes, A. B., "Dysmenorrhea," *in* "Current Therapy 1979," edited by H. F. Conn, W. B. Saunders Co., Philadelphia, pp. 813–815, 1979.

(5) Harvey, S. C., "Antimuscarinic and Antispasmodic Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, Mack Publishing Co., Easton, PA, p. 855, 1980.

b. *Category II labeling.* The Panel concludes that the following labeling claims are either unsupported by scientific data or are misleading: "Fast relief," "quick relief," or any other terms which nonspecifically relate to speed of action.

3. *Category III conditions.* The following are Category III conditions for which the available data are insufficient to permit final classification at this time.

a. *Category III active ingredient—Cinnamedrine hydrochloride.* The Panel concludes that cinnamedrine hydrochloride is safe at the dose recommended below, but that data are insufficient to demonstrate its effectiveness in relieving cramps of the premenstrual syndrome or primary dysmenorrhea.

(1) *Safety.* The Panel is not aware of any safety studies conducted with cinnamedrine hydrochloride as a single ingredient. Two acute oral toxicity studies in mice were reported in a submission to the Panel (Ref. 1). One study used a formulation containing aspirin, caffeine, cinnamedrine, and phenacetin and resulted in oral LD_{50}'s of 3,250±394 mg per kilogram (mg/kg) at 24 hours and 3,100±374 mg/kg at 7 days. The other study used a formulation containing aspirin, caffeine, cinnamedrine, and acetaminophen and resulted in oral LD_{50}'s of 2,75±488 mg/kg at 24 hours and 2,700±478 mg/kg at 7 days. In another toxicity study, Schultz and Barbour (Ref. 2) determined that the approximate LD_{50}'s of the levo and dextro isomers of cinnamylephedrine in mice were 150 mg/kg and 75 mg/kg, respectively (Ref. 2).

The Panel regards these LD_{50}'s and the long, safe marketing history (35 years with few reported side effects) as evidence indicative of the safety of cinnamedrine hydrochloride. The Panel concludes that cinnamedrine hydrochloride is generally recognized as safe for OTC use in the dose recommended by the manufacturer (from a combination preparation) of 14.9 to 29.8 mg every 4 hours (maximum 120 mg per day).

(2) *Effectiveness.* Cinnamedrine hydrochloride is an unsaturated tertiary amine. The Panel is aware of one uncompleted clinical trial comparing a combination preparation containing cinnamylephedrine (cinnamedrine) (7.5 mg), caffeine (15 mg), aspirin (128 mg), and phenacetin (96 mg) with various combination preparations containing chlormezanone (antianxiety agent), aspirin, nicotinic acid, phenacetin, caffeine, and/or acetaminophen, in relieving symptoms of the premenstrual syndrome and the menstrual syndrome (Ref. 3.). The combination containing cinnamedrine is reported to be second only to a combination containing chlormezanone and acetaminophen in overall effectiveness in relieving the symptons of the premenstrual and menstrual syndrome (same symptoms used in both). The combination containing cinnamedrine is reported to be the one which is most effective in relieving pain. Because none of the individual ingredients in the cinnamedrine combination was tested alone, it is not possible to determine the effectiveness of the cinnamedrine over that of aspirin, phenacetin, or caffeine. There also was no placebo used.

The Panel notes that Csaky (Ref. 4) states that although certain members of the isoproterenol group of drugs, which includes cinnamedrine, have been used to relax the uterus in dysmenorrhea, final assessment of the clinical value of these agents has not been made. The Panel has been unable to locate any other current pharmacological or pharmaceutical texts in which cinnamedrine is discussed.

Although the Panel is not aware of any clinical data demonstrating the effectiveness of cinnamedrine hydrochloride alone in treating the minor pain of primary dysmenorrhea, the above study (Ref. 1) indicates potential effectiveness. Therefore, the Panel recommends further testing to determine the efectiveness of cinnamedrine hydrochloride in relieving cramps of the premenstrual and menstrual periods.

(3) *Proposed dosage.* The Panel recommends cinnamedrine hydrochloride as a smooth-muscle relaxant in OTC menstrual drug products in a dosage range of 14.9 to 29.8 mg to be given every 4 hours, not to exceed a maximum daily dose of 120 mg.

(4) *Labeling.* The Panel recommends Category I labeling for smooth-muscle relaxants used in OTC menstrual drug products. (See part III. paragraph D.1.b. above—Category I labeling.)

(5) *Evaluation.* The Panel concludes that cinnamedrine hydrochloride is safe for OTC use, but that data are insufficient to demonstrate its effectiveness in relieving cramps of the premenstrual and menstrual periods.

References

(1) OTC Volume 170022 (pp. 5–10).

(2) Schultz, F. H., and P. H. Barbour, "The Local Anesthetic Properties of Cinnamylephedrine," *Journal of Pharmacology and Experimental Therapeutics,* 76:295–300, 1942.

(3) OTC Volume 170022 (pp. 76–944).

(4) Csaky, T. Z., "Sympathetic Stimulants and Adrenergic Agents," *in* "Cutting's Handbook of Pharmacology: The Action and Uses of Drugs," 6th Ed., Appleton-Century-Crofts, New York, pp. 447–455, 1979.

b. *Category III labeling.* None.

E. Botanical or Vegetable Herbs

An array of preparations, usually alcoholic in nature and containing extracts of a variety of botanical or vegetable herbs, originated in the 19th century. The number of these preparations, the variety of their ingredients, and the level of alcohol content has decreased greatly over the last century. The most flagrant claims for these compounds have also been eliminated. Although these remedies may have been or are also used for menopause symtoms, claims for the treatment of menopause, wherein there are tremendous endocrine changes and which bears no relationship to primary dysmenorrhea, will not be evaluated in this document.

In light of the history and established usefulness of many potent drugs derived from plant sources (e.g., digitalis, opium, quinine, and cascara), the Panel regrets that detailed studies have not been carried out to search for potential effectiveness of the botanicals discussed in this portion of the report.

Only one of these preparations, in both elixir and tablet form, has been submitted to this Panel for review. However, numerous formula changes over the last century, including both the addition and deletion of ingredients, make evaluation difficult or impossible. Moreover, the elixir and the tablet preparations do not contain the same ingredients. The present elixir formula contains the following herb extracts as potential active ingredients: *Piscidia erythrina* (Jamaica dogwood), *Asclepias tuberosa* (pleurisy root), *Cimicifuga racemosa* (black cohosh), *Senecio aureus* (life root), and *Taraxacum Officinale* (dandelion root) (Ref. 1). Only

these five extracts will be reviewed in this report. The elixir also contains *Gentiana lutea* (a bitter), which is regarded as a flavoring agent and will not be reviewed. *Glycyrrhiza glabra* (licorice root), which has been demonstrated to have a potential estrogenic effect, will also not be reviewed in this document because this document does not deal with menopause, as stated above.

The formula for the tablet lacks *Gentiana lutea, Cimicifuga racemosa, Senecio aureus,* and *Taraxascum officinale,* but does contain 65 mg of ferrous sulfate, which is approximately equivalent to the daily adult requirement of 15 mg of elemental iron. The Panel has not considered ferrous sulfate (iron) because the claim of treating or preventing iron deficiency anemia is not within the purview of this Panel.

Reference

(1) OTC Volume 170076.

1. *Category I conditions.* None.

2. *Category II conditions.* The following are Category II conditions under which botanical or vegetable herbs used in menstrual drug products are not generally recognized as safe and effective or are misbranded.

a. *Category II active ingredients. Asclepias tuberosa* (pleurisy root); *Cimicifuga racemosa* (black cohosh); *Piscidia erythrina* (Jamaica dogwood); *Senecio aureus* (life root); and *Taraxacum officinale* (dandelion root).

(1) *Asclepias tuberosa.* The Panel concludes that *Asclepias tuberosa* is safe for OTC use, but is not generally recognized as effective in the treatment of primary dysmenorrhea.

Asclepias tuberosa, also known as pleurisy root and as butterfly weed, was recognized in the "United States Pharmacopeia" of 1840 and in the "National Formulary" until 1936 (Ref. 1). This root drug has been used in treating bronchitis and rheumatism, and in large doses, for its emetic and cathartic activity (Refs. 1 and 2). There are no records of its use by itself in dysmenorrhea.

(i) *Safety.* The fluidextract of *Asclepias tuberosa* at a concentration of 500 mg/fluid ounce (oz) has been used for more than 100 years in the elixir preparation at a dosage of ½ oz four times a day for a total daily dose of 1 g. The tablet formulation contains the fluidextract of *Asclepias tuberosa* at a concentration of 300 mg/tablet taken four times daily for a total daily dose of 1.2 g. Animal studies have been performed to determine toxicity and pharmacological effects (Ref. 3). No human safety studies have been submitted for this ingredient.

(ii) *Efectiveness.* No data supporting the effectiveness of this individual ingredient were presented to the Panel, nor has the Panel been able to locate such information. Effectiveness testing of multiple-ingredient final formulations containing this ingredient is discussed elsewhere in this document. (See part III. paragraph G.3. below—Combination of herb extracts.)

(iii) *Evaluation.* While the safety of this fluidextract at levels of up to 1 g a day appears assured because of its long history of use at these levels, there are no data supporting the individual effectiveness of this ingredient and no history of its use alone in the treatment of primary dysmenorrhea.

References

(1) Osol, A., and G. E. Farrar, Jr., editors, "The Dispensatory of the United States of American," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 1591, 1955.

(2) King, J., "American Dispensatory," Moore, Wistich and Keep, Cincinnati, pp. 288–291, 1897.

(3) OTC Volume 170076.

(2) *Cimicifuga racemosa.* The Panel concludes that *Cimicifuga racemosa* is not generally recognized as safe and effective in the treatment of primary dysmenorrhea.

Cimicifuga racemosa, also known as black cohosh, black snakeroot, and squaw root, was last listed as the fluidextract in the "National Formulary" in 1946 (Ref. 1).

(i) *Safety.* The fluidextract of *Cimicifuga racemosa* at a concentration of 445 mg/fluid oz has been used for more than 100 years in the previously described elixir preparation at a dosage of ½ oz four times a day for a total daily dose of 890 mg. It was introduced to the medical profession in 1831 for the treatment of chorea, tinnitus aurium, chronic rheumatism, and as a bitter tonic (Ref. 1). In 1962, Genazzani and Sorrentino (Ref. 2) isolated a resinous portion of cimicifuga and found the oral minimum lethal dose in rats to be 1 g/kg of body weight for this more concentrated preparation. Another animal study, in 1943, by Costello and Butler (Ref. 3) showed intravenous injection of 5 mL of the buffered fluidextract well tolerated by rabbits. A study by Macht and Cook (Ref. 4), in 1932, however, showed cimicifuga to be toxic to the circulatory and respiratory systems in animals. No long-term human or animal studies of the safety of this ingredient have been submitted.

(ii) *Effectiveness.* While *Cimicifuga racemosa* has a history of use in folk medicines in the treatment of chronic rheumatism, chorea, tinnitus aurium, and as an emmenagogue (an agent that promotes menstrual discharge), some authors state that the use of this plant as an emmenagogue was sometimes confused with *Caulophyllum thalictroides,* a plant also known as squaw root and widely used in the treatment of uterine disorders such as amenorrhea, dysmenorrhea, and menorrhagia. A pharmacological study by Macht and Cook (Ref. 4) was carried out in 1932 on cimicifuga to establish the effects of this drug on convulsions, neuromuscular coordination, intestinal and uterine movements, and circulation and respiration. The drug has no effect on camphor-induced convulsions and was without effect on neuromuscular coordination in laboratory animals. It exhibited a depressive and paralyzing effect on isolated intestinal and uterine muscles. The study concluded that there was no pharmacologic evidence of any therapeutic value for cimicifuga.

No human studies are available on the individual effectiveness of *Cimicifuga racemosa* in the treatment of primary dysmenorrhea. Effectiveness testing of multiple ingredient final formulations containing this ingredient is discussed elsewhere in this document. (See part III. paragraph G.3. below—Combination of herb extracts.)

(iii) *Evaluation.* While a 150-year history of use of this fluidextract at levels of up to 890 mg a day gives some reassurance of the safety of this compound, additional safety testing, particularly chronic animal studies, is necessary in light of its reported effect upon respiratory and circulatory systems of animals. The history of its use as a folk remedy appears confused with that of another drug, also known as squaw root, *Caulophyllum thalictroides,* which has a long history of use in the treatment of various uterine disorders. The primary animal study available declares cimicifuga to be without potential therapeutic value. No human studies are available on its individual effectiveness in the treatment of primary dysmenorrhea.

References

(1) Osol, A., and G. E. Farrar, Jr., editors, "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 1634, 1955.

(2) Genazzani, E., and L. Sorrentino, "Vascular Action of Acteina: Active Constituent of *Actaea racimosa* L.," *Nature, 194:544–545, 1962.*

(3) Costello, C. H., and C. L. Butler, "Uterine Depressants II: A Preliminary Report on *Aletris farinosa, Chamaelirium luteum* and *Cimicifuga racemosa,*" from the minutes of the 61st Annual Meeting of the

Proprietary Association of America, May 18 and 19, 1943, OTC Volume 17MPAII.

(4) Macht, D. I., and H. M. Cook, "A Pharmacological Note on Cimicifuga," *Journal of the American Pharmaceutical Association*, 21:324–330, 1932.

(3) *Piscidia erythrina*. The Panel concludes that *Piscidia erythrina* is safe for OTC use, but it is not generally recognized as effective in the treatment of primary dysmenorrhea.

Piscidia erythrina is a tropical and semitropical legume, also known as Jamaica dogwood or fish-poison tree.

(i) *Safety*. The fluidextract of *Piscidia erythrina* at a concentration of 500 mg/fluid oz has been used for approximately 30 years in the elixir preparation at a dosage of ½ oz four times a day for a total daily dose of 1 g. The tablet formulation contains the fluidextract of *Piscidia erythrina* at a concentration of 780 mg/tablet and given four times daily for a total daily dose of 3.12 g. In 1948, a study on rats, using a 60-percent isopropyl alcohol dried extract of *Piscidia erythrina* dispersed in water, established that two of seven rats died within 1 hour when 10 g per kilogram (g/kg) of the extract, equivalent to 106 g/kg of the dried bark, was administered orally (Ref. 1). An additional study, using mice, in 1965, established an intravenous LD_{50} of 1.5 g/kg of body weight and an intraperitoneal LD_{50} of 3.75 g/kg of body weight for the fluidextract (Ref. 2). Although no human safety studies have been submitted for this ingredient individually, the Panel has relied on the animal data presented and its long marketing history in combination and concludes that it is safe for OTC use at the dose noted above.

(ii) *Effectiveness*. Historically, the bark and other parts of the Jamaica dogwood or fish-poison tree have been used for catching fish. Usually, the leaves, twigs, and bark are macerated together with the residue from the distillation of rum or sometimes with lime. This material is then placed in baskets and dragged through the water until the fish are stupified. The bark of the tree has also been used in medicine. Extracts of the bark have been promoted as an anodyne, which was used to relieve neuralgia and to treat dysmenorrhea.

Pharmacological studies on the bark have offered conflicting evidence. The most convincing study shows quite clearly a uterine depressant activity, both in vitro and in vivo in various laboratory animals (Ref. 1). This activity is of the same order as papaverine. This report confirmed an earlier study that indicated that an extract was remarkedly depressant to tone and excursion amplitude of isolated uterus muscle. However, in other studies the extract was inactive when tested on both isolated (Ref. 3) and intact animal uteri (Ref. 4).

The Panel is not aware of any human studies with this individual ingredient in treating primary dysmenorrhea. Effectiveness testing of multiple-ingredient final formulations containing this ingredient is discussed elsewhere in this document. (See part III. paragraph G.3. below—Combination of herb extracts.)

(iii) *Evaluation*. The 30-year history of use of this fluidextract, at levels of up to 1 g per day, and animal data showing an LD_{50} at well over 100 times this dosage level, would appear to allay any safety concerns about this ingredient.

Animal studies of the ingredient's effect on uterine contraction are contradictory. While there is some history of this use of the fluidextract in the treatment of primary dysmenorrhea, there are no human studies available on its effectiveness (individually) in the treatment of primary dysmenorrhea.

References

(1) Costello, C. H., and C. L. Butler, "An Investigation of *Piscidia Erythrina* (Jamaica dogwood)," *Journal of American Pharmaceutical Association*, 37:89–97, 1948.

(2) Aurousseau, M., C. Berny, and O. Albert, "Recherches sur Quelques Proprietes Pharmacodynamiques du *Piscidia Erythrina* L. (Legumineuses)," *Annales Pharmaceutiques Francaises*, 23:251–257, 1965.

(3) Pilcher, J. D., G. E. Burman, and W. R. Delzell, "The Action of the So-called Female Remedies on the Excised Uterus of the Guinea-Pig," *Archives of Internal Medicine*, 18:557–583, 1916.

(4) Pilcher, J. D., and R. T. Mauer, "The Action of 'Female Remedies' on Intact Uteri of Animals," *Surgery, Gynecology and Obstetrics*, 27:97–99, 1918.

(4) *Senecio aureus*. The Panel concludes that *Senecio aureus* may not be safe for OTC use and is not generally recognized as effective in the treatment of primary dysmenorrhea.

Extracts of *Senecio aureus*, known as golden ragwort, have been used to promote the menstrual discharge, but their use is of doubtful value.

(i) *Safety*. The fluidextract of *Senecio aureus* at a concentration of 445 mg/fluid oz has been used for more than 100 years in the elixir preparation at a dosage of ½ oz four times a day for a total daily dose of 890 mg. The Panel is not aware of any reports of adverse reactions related to the use of *Senecio aureus* in this preparation. However, the only communication dealing with this ingredient states the manufacturer's intention to omit *Senecio aureus* from the formulation after 1975 because "during the past decade, the *Senecio* alkaloids have been shown to cause pulmonary and hepatic lesions in animals." The manufacturer goes on to state, ". . . because of the toxicity attached to *Senecio* plants in general, it has been decided to reformulate . . . by omitting it beginning in 1976" (Ref. 1). The submitted data document the toxicity of some *Senecio* species (about 10 percent of the approximately 1,200 species of *Senecio* contain toxic alkaloids) in both humans and animals with a list of 44 references, all of which have been published since 1952, with more than half being published since 1968 (Ref. 1). The Panel is also aware that *Senecio aureus* contains about 0.006 percent senecionine (Ref. 2), an alkaloid of known toxicity in animals (Refs. 3 and 4). Senecionine was observed to cause death (within 1 to 7 days) in rats when administered in an intraperitoneal dose of 0.1 millimoles/kilogram (mmoles/kg) body weight and to cause both liver and lung lesions at the lowest dose tested (0.025 mmoles/kg body weight) (Ref. 3).

The continued inclusion of *Senecio aureus* in the formulation in 1981 was verified in a telephone conversation with the firm (Ref. 5).

The Panel concludes, in the absence of definitive studies, that *Senecio aureus* may not be safe for OTC use because of the presence of low concentrations of senecionine, a toxic pyrrolizidine alkaloid.

(ii) *Effectiveness*. No data supporting the effectiveness of this individual ingredient were presented to the Panel. A study conducted in 1934 established that the fluidextract produced no effect on the tone or on the amplitude of contraction of the isolated uterine muscle of laboratory animals (Ref. 6). Effectiveness testing of multiple-ingredient final formulations containing this ingredient is discussed elsewhere in this document. (See part III. paragraph G.3. below—Combination of herb extracts.) The Panel concludes that *Senecio aureus* is not effective nor is it generally recognized as effective for treating any menstrual disorders.

(iii) *Evaluation*. The Panel concludes that *Senecio aureus* may not be safe for OTC use. The Panel also concludes that this ingredient is not generally recognized as effective for use in OTC menstrual drug products to treat primary dysmenorrhea, because of the total lack of any proof of effectiveness or even medical rationale for the use of this ingredient in menstrual drug products.

References

(1) OTC Volume 170076.

(2) Manske, R. H. F., and H. L. Homes, editors, "The Alkaloids," vol. I, Academic Press Inc., New York, p. 159, 1950.

(3) Culvenor, C. C. J., et al., "Hepato- and Pneumotoxicity of Pyrrolizidine Alkaloids and Derivatives in Relation to Molecular Structure," *Chemoco-Biological Interactions,* 12:299–324, 1976.

(4) Smith, L. W., and C. C. J. Culvenor, "Plant Sources of Hepatotoxic Pyrrolizidine Alkaloids," *Journal of Natural Products,* 44:129–152, 1981.

(5) Memorandum of telephone conversation between John R. Short, Panel Administrator, OTC Miscellaneous Internal Panel, and Mary Ann Mulford, Regulatory Affairs, Cooper Laboratories, subject: "Product Formulation," dated April 22, 1981, OTC Volume 17MPAII.

(6) Kelley, E. A., and E. V. Lynn, "The Value of Senecio in Medicine," *Journal of the American Pharmaceutical Association,* 23:113–118, 1934.

(5) *Taraxacum officinale.* The Panel concludes that *Taraxacum officinale* is safe for OTC use, but is not generally recognized as effective in the treatment of primary dysmenorrhea.

Taraxacum Officinale, also known as dandelion root, has long been used as a bitter in "atonic dyspepsia" and as a mild laxative.

(i) *Safety.* The fluidextract of *Taraxacum officinale* at a concentration of 345 mL/fluid oz has been used for more than 65 years in the previously described elixir preparation at a dosage of ½ oz four times a day for a total daily dose of 690 mL. It was listed in the "National Formulary" as long ago as 1926 as a gastrointestinal stimulant. A Romanian study in 1974 established an intraperitoneal LD_{50} in mice of the fluidextract at 28.8 g/kg body weight (Ref. 1). This same study showed that the fluidextract given in a dose of 8 mL/kg of body weight for 30 days produced a weight loss as high as 30 percent in mice and rats. This loss may have been due in part to a diuretic activity. Although no human safety studies have been submitted for this ingredient individually, the Panel has relied on the animal data presented and its long marketing history in combination with other botanicals, and concludes that it is safe for OTC use at the dose noted above.

(ii) *Effectiveness.* The fluidextract of *Taraxacum officinale,* or dandelion root, has a long history of use as a bitter in "atonic dyspepsia" and as a mild laxative. In 1974, a Romanian study showed it to have diuretic properties and the ability to induce up to 30 percent weight loss in 1 month in animal tests (Ref. 1). No data were submitted suggesting the exact role or rationale for this ingredient in the treatment of dysmenorrhea. No data supporting its individual effectiveness for these conditions were presented to the Panel and none could be located. Effectiveness testing of final formulations containing this ingredient are discussed elsewhere in this document. (See part III. paragraph G.3. below—Combination of herb extracts.)

(iii) *Evaluation.* Because of the long history of use of *Taraxacum officinale* and the high LD_{50} in animals (Ref. 1), the safety of this fluid extract, at levels of 690 mg a day, appears sufficient to allay any safety concerns about this ingredient.

There are no data supporting the effectiveness of this individual ingredient and no history of its use alone in the treatment of primary dysmenorrhea, although some animal data showing a diuretic action do exist.

References

(1) Racz-Kotilla, E., G. Racz, and A. Solomon, "The Action of *Taraxacum officinale* Extracts on the Body Weight and Diuresis of Laboratory Animals," *Planta Medica,* 26:212–217, 1974.

b. *Category II labeling.* The Panel concludes that the following labeling claims and any related terms are either unsupported by scientific data or are misleading and, therefore, are classified as Category II:

(1) "For relieving cramps and other distress of monthly periods (Menstruation)."

(2) "Acts as a uterine sedative."

3. *Category III conditions.* None.

F. Vitamins

Pyridoxine hydrochloride (vitamin B–6) was listed in the call-for-data notice of August 27, 1975 (40 FR 38183) and has received support in some scientific literature in conjunction with the treatment of primary dysmenorrhea and the symptoms of the premenstrual syndrome. The Panel's conclusions on this ingredient are presented below. Other vitamins were not reviewed by the Panel because it is not aware of any data demonstrating their safety or effectiveness when used in OTC menstrual drug products. (See part I. paragraph C.5. above—Other ingredients.)

1. *Category I conditions.* None.

2. *Category II conditions.* The following are Category II conditions under which vitamins used in OTC menstrual drug products are not generally recognized as safe and effective or are misbranded.

a. *Category II active ingredients.* See part I. paragraph C.5. above—Other ingredients.

b. *Category II labeling.* None.

3. *Category III conditions.* The following are Category III conditions for which the available data are insufficient to permit final classification at this time.

a. *Category III active ingredient—Pyridoxine hydrochloride.* The Panel concludes that pyridoxine hydrochloride is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness in relieving symptoms of the premenstrual syndrome or primary dysmenorrhea.

(1) *Safety.* Pyridoxine hydrochloride (vitamin B–6) is a water-soluble vitamin of the vitamin-B complex and is present in many foodstuffs. It has been reviewed by an FDA Advisory Review Panel in its report on OTC Vitamin and Mineral Drug Products published in the **Federal Register** of March 16, 1979 (44 FR 16126) and found to be safe in the doses up to 25 mg daily (treatment of a deficiency) (44 FR 16157). Much larger doses, up to 200 mg/day or more, have been widely used in the treatment of various disorders (e.g., sideroblastic anemias) with no significant toxicity. The Panel concludes that pyridoxine hydrochloride is safe in doses up to 200 mg/day.

(2) *Effectiveness.* Pyridoxine hydrochloride has been tried as a therapeutic agent to treat depression caused by the use of oral contraceptives. Later, its use was extended to treatment of the symptoms of the premenstrual syndrome and primary dysmenorrhea. One author postulates that the pyridoxine hydrochloride in doses of 200 to 800 mg per day plays a synergistic role in the utilization of magnesium ions across myometrial cell membranes, resulting in an antispasmodic effect and relief of dysmenorrhea (Ref. 1). However, several reports (Refs. 1, 2, and 3) that claim effectiveness of pyridoxine hydrochloride for relief of the symptoms of premenstrual tension or dysmenorrhea are not convincing because of lack of controls, small sample size, or other defects (Refs. 4, 5, and 6). One double-blind study (Ref. 7) failed to show effectiveness of pyridoxine hydrochloride over placebo.

(3) *Proposed dosage.* The Panel recommends that a dose of pyridoxine hydrochloride used in OTC menstrual drug products not exceed 200 mg per day in divided doses.

(4) *Labeling.* The Panel recommends that labeling of pyridoxine hydrochloride for relieving the symptoms of the premenstrual syndrome and primary dysmenorrhea consist of those symptoms or clusters of symptoms (from the Moos Questionnaire) that are demonstrated to be relieved by this ingredient.

(5) *Evaluation.* The Panel concludes that pyridoxine hydrochloride is safe in the recommended dose, but that data are insufficient to demonstrate that it is effective for relieving symptoms of the premenstrual syndrome or primary dysmenorrhea. The Panel recommends further testing using adequate and well-controlled clinical investigations.

References

(1) Abraham, G. E., "Primary Dysmenorrhea," *Clinical Obstetrics and Gynecology,* 21:139–145, 1978.

(2) Baumblatt, M. J., and F. Winston, "Pyridoxine and the Pill," *Lancet,* 1:832–833, 1970.

(3) Kerr, G. D., "The Management of the Premenstrual Syndrome," *Current Medical Research and Opinion,* 4 (Supplement 4):29–34, 1977.

(4) Clare, A. W., "The Treatment of Premenstrual Systems," *British Journal of Psychiatry,* 135:576–579, 1979.

(5) Anonymous, "The Premenstrual Syndrome," *Drug and Therapeutics Bulletin,* 17:101–103, 1979.

(6) Steiner, M., and B. J. Carroll, "The Psychobiology of Premenstrual Dysphoria: Review of Theories and Treatments," *Psychoneuroendocrinology,* 2:321–335, 1977.

(7) Stokes, J., and J. Mendels, "Pyridoxine and Premenstrual Tension," *Lancet.* 1:1177–1178, 1972.

b. *Category III labeling. None.*

G. Combination Policy

The Panel has reviewed and concurs with the FDA regulations regarding combinations of ingredients in OTC drug products (21 CFR 330.10(a)(4)(iv)). In addition, the Panel is aware of the agency's combination guidelines for OTC drug products, the availability of which was announced in the **Federal Register** of November 26, 1978 (43 FR 55466). The Panel has applied these regulations and guidelines in reaching its conclusions on combination drug products for use in treating symptoms of premenstrual syndrome and primary dysmenorrhea.

1. *Rationale for combining ingredients in menstrual drug products (for relieving symptoms of the premenstrual syndrome and primary dysmenorrhea).* As discussed previously, the premenstrual syndrome and primary dysmenorrhea are distinct clinical entities. Each entity has multiple symptoms that may overlap in time. It seems rational in either clinical entity to combine different ingredients to treat the multiple symptoms concurrently. While some symptoms are common to both the premenstrual syndrome and primary dysmenorrhea, other symptoms occur predominantly in one or the other condition. For example, symptoms attributable to water retention occur in the premenstrual syndrome, but are less frequently a component of primary dysmenorrhea. Because pain and cramping are common to both the premenstrual syndrome and primary dysmenorrhea, the Panel concludes it is rational to combine Category I analgesics with a Category I smooth-muscle relaxant to treat premenstrual and menstrual pain and cramps. However, because the one smooth-muscle relaxant, cinnamedrine hydrochloride, has been placed in Category III (none in Category I), a combination of this ingredient and Category I analgesics would also be placed in Category III. Because pain and water retention may occur concurrently in the premenstrual syndrome or primary dysmenorrhea, the Panel concludes it would be rational to combine a Category I analgesic and a Category I diuretic to relieve pain and water-accumulation symptoms (water-weight gain, bloating, swelling, or full feeling) of the premenstrual and menstrual periods.

The Panel reviewed data on OTC menstrual drug products containing a diuretic (pamabrom) and antihistamine (pyrilamine maleate) combination and classified the combination as Category I for relieving symptoms of the premenstrual syndrome and primary dysmenorrhea. A product was also submitted using the same ingredients plus acetaminophen. The Panel concludes that the addition of any Category I analgesic to this preparation would also result in a Category I combination because analgesics already (earlier in the report) have been given a Category I designation for the premenstrual and menstrual periods. The Panel recommends allowing any Category I diuretic or Category I analgesic in these preparations, but is specific as to which antihistamine to use, i.e., pyrilamine maleate. Based upon the data reviewed by the Panel, pyrilamine maleate seems to be unique among other antihistamines in that it possesses certain pain relief and diuretic properties (Refs. 1 and 2).

The Panel also reviewed a combination of two diuretics (ammonium chloride and caffeine) and concludes this to be a rational combination because the diuretic mechanisms of action are different and adjunctive. The Panel recommends the use of any two diuretics as long as their mechanisms of action are different and adjunctive.

The Panel was presented with some data regarding combinations of various herb extracts. However, the studies attempting to demonstrate effectiveness are not adequate and well-controlled clinical investigations; nor is it clear which formulations were employed. In addition, each of the ingredients included in the various formulations have been classified as Category II in this document. Therefore, combinations of these ingredients have been placed in Category II.

2. *Category I combinations.* The following are Category I combinations:

a. A Category I analgesic and a Category I diuretic (e.g., acetaminophen and pamabrom);

b. A Category I analgesic, a Category I antihistamine, and a Category I diuretic (i.e., acetaminophen or any other Category I analgesic, pyrilamine maleate, and pamabrom or any other Category I diuretic);

c. A Category I antihistamine and a Category I diuretic (i.e., pyrilamine maleate and pamabrom or any other Category I diuretic);

d. Any two Category I diuretics with different and adjunctive mechanisms of action, (e.g., ammonium chloride and caffeine).

References

(1) "The Effect of Pyrilamine Maleate on the Relief of Symptoms Associated with the Menstrual Syndrome (Boston Study 1981)," unpublished study, OTC Volume 170218.

(2) OTC Volume 170224 (Section 4).

For those Category I combinations for which appropriate data have been submitted for review of safety and effectiveness, the Panel offers the following discussion:

a. *Ammonium chloride and caffeine.* The Panel concludes that a combination of ammonium chloride and caffeine in the dose recommended below is generally recognized as safe and effective in relieving water-accumulation symptoms of the premenstrual and menstrual periods.

(1) *Safety.* For safety of ammonium chloride, see part III. paragraph C.1.a.(1) above—Ammonium chloride. For safety of caffeine, see part III. paragraph C.1.a.(2) above—Caffeine.

Hoffman (Ref. 1) conducted a study in which he used a combination of 325 mg ammonium chloride and 100 mg caffeine per tablet against placebo (lactose) in treating edema in 22 patients. The study was conducted for two menstrual cycles. One side effect was reported by one subject who complained of feeling "headachy." Gastrointestinal discomfort, while not unexpected for subjects taking ammonium chloride, was not reported (Ref. 1).

In a study involving 90 patients, Levine, et al. (Ref. 2) used a preparation containing 330 mg ammonium chloride, 33 mg caffeine, 0.5 mg homatropine methylbromide, and vitamin-B complex

against placebo for a 6-month period. The investigators reported the medication was "well tolerated by the patients." Only four patients (6 percent) reported any side effects. Three of these side effects were in the form of nausea and one was a papular rash.

Another study, conducted by Morton, et al. (Ref. 3), with 249 subjects, used the same preparation as the Levine study against placebo. This study covered a 3-month period and no adverse effects were reported.

The Panel, therefore, concludes that the combination of ammonium chloride at a dose of 325 mg and caffeine at a dose of 100 mg is generally recognized as safe for OTC use.

(2) *Effectiveness.* The effectiveness of either ingredient alone is reviewed separately in this document as per references cited under Safety above. There also have been clinical studies performed with this combination of ingredients.

In a double-blind, placebo-controlled crossover study, Hoffman (Ref. 1) evaluated the effectiveness of the combination for controlling premenstrual weight gain in 22 patients. Of these 22 patients, 14 were taking oral contraceptives and "characteristically" retained fluids during the last several days of the menstrual cycle. The remaining eight were not taking oral contraceptives, but also had a history of premenstrual weight gain.

The drug (325 mg ammonium chloride and 100 mg caffeine) and the placebo (lactose) were identical appearing enteric-coated tablets. Dosage for both products consisted of two tablets three times a day starting on day 18 of the menstrual cycle and continuing for 6 days.

During the first cycle, using the weight on day 18 as a baseline, Group I on active medication showed a weight loss of 1.50 pounds at the end of day 23. Group II on placebo gained 1.39 pounds at the end of day 23 compared with the baseline. During the second cycle, Group I on placebo gained 2.88 pounds by the end of day 23, and Group II on active medication lost 0.98 pound. The active medication was significantly superior ($p<0.005$) to placebo in controlling premenstrual weight gain (Ref. 1). Hoffman states the weight gain/loss was due to the elimination/retention of excessive body fluids.

Levine et al. (Ref. 2) evaluated a group of 90 women over a period of 6 months. The test medication consisted of 330 mg ammonium chloride, 33 mg caffeine, 0.5 mg homatropine methylbromide, and vitamin-B complex.

All patients displayed fairly regular menstrual cycles and symptoms of premenstrual tension. During each cycle of the test, 70 of the patients received the medication in a dosage of two tablets three times daily, starting 10 days before the menses, and continued daily until the onset of menstruation. Twenty patients received the placebo on the same schedule. Throughout the study each patient was examined periodically and each was asked to maintain a daily diary for recording the presence and degree of severity of symptoms as well as body weight gain under standardized conditions.

The investigators reported that of the 70 patients receiving the test medication, 49 (70 percent) obtained excellent relief from their symptoms; 11 (15 percent) obtained good results, and the remaining experienced little or no relief. Patients receiving the placebo were reported to have failed to exhibit significant improvement in premenstrual tension. No details were given on how it was determined whether a patient obtained relief and no statistical analyses were performed comparing the treatment group with the placebo group.

Average weight gain for the patients during the months before taking the medication was reported to be 3.9 pounds, while during administration of the medication, the average weight gain was reported to be 1.2 pounds. No figures on weight gain for the placebo group were provided, and no statistical analysis was performed comparing the treatment and placebo groups.

Morton et al. (Ref. 3) conducted a 3-month study using 249 inmates (131 from a prison and 118 from a reformatory). The test medication, consisting of 330 mg ammonium chloride, 33 mg caffeine, 0.5 mg homatropine methylbromide, and vitamin-B complex was administered to 129 patients. The other 120 were given a placebo.

Volunteers for the study were given a self-rating scale of 21 items, which reflected nervous and emotional tension, symptoms due to hypoglycemic reactions, water retention, and disturbances in menstruation. They were requested to circle the appropriate word beside each symptom that might be present during the days preceding the menstrual period. Symptoms were rated as none, mild, or severe.

The subjects were divided into four experimental groups, two groups in the prison and two groups in the reformatory. In both settings, one group was given medication and the other was given a placebo. The medication and placebo were identical appearing enteric-coated tablets taken on the same schedule, i.e., two tablets taken three times daily for 10 days preceding the expected onset of the menstrual flow and discontinued with the onset of menstruation. All subjects in the prison were also given a supplementary high protein diet.

Six weeks after first using the self-rating scale of premenstrual symptoms, a second form was distributed. The second form duplicated the first, with additional questions that asked the subject to indicate (1) whether she thought her symptoms had changed since the treatment, and (2) whether or not she benefited from the treatment.

At the end of one cycle, of the 68 women in the prison who started the medication, 5 dropped out of the study; 79 percent of the remaining subjects reported improvement from the medication; and 21 percent reported no change or worse symptoms. In the control group who received the placebo, 2 subjects out of 64 dropped out of the experiment; 39 percent of the subjects reported symptom improvement; and 61 percent reported no change or worse symptoms. The difference between the treatment and placebo group is statistically significant at the 0.001 level.

In the group that received the medication in the reformatory, of those who continued the survey, 61 percent improved, and 39 percent reported no change or worse symptoms. Those who received the placebo reported a 15-percent improvement with 85 percent of the subjects indicating no change or worse symptoms. The sample sizes on which the above percentages were computed are not given in the article, but the dropout rate is said to have been high.

The article gives no details as to how subjects were assigned to the treatment and control groups, such as whether subjects were assigned in a double-blind fashion. Further, the factors or symptoms that constituted an improvement are not explicitly stated.

The Panel concludes that a combination of ammonium chloride and caffeine in the dose noted below is generally recognized as effective for OTC use in relieving weight gain, bloating, swelling, and/or full feeling associated with the premenstrual and menstrual periods. In addition, a "fatigue" claim could also be used based upon the caffeine portion of the combination, as discussed earlier. (See part III. paragraph C.1.a. (2) above—Caffeine.)

(3) *Dosage.* The Panel recommends that the dosage for a combination of ammonium chloride and caffeine consists of 650 mg ammonium chloride and 200 mg caffeine to the taken three times daily for a daily dose of 1,950 mg ammonium chloride and 600 mg caffeine.

(4) *Labeling.* The Panel recommends Category I labeling for diuretics. (See part III. paragraph C.1.b. above—Category I labeling.) The combination may also include a "fatigue" claim for the caffeine component. (See part III. paragraph C.1.a. (2)(iv) above—Labeling.) In addition, the labeling should contain those warnings for ammonium chloride and caffeine listed earlier in this document. (See part III. paragaraph C.1.a. (1)(iv) and (2)(iv) above—Labeling.)

References

(1) Hoffman, J. J., "A Double-Blind Crossover Clinical Trial of an OTC Diuretic in the Treatment of Premenstrual Tension and Weight Gain," *Current Therapeutic Research,* 26:575–580, 1979.

(2) Levine, A. J., et al., "An Effective Medication in the Treatment of Premenstrual Tension," *Clinical Medicine,* 5:907–909, 1958.

(3) Morton, J. H., et al., "A Clinical Study of Premenstrual Tension," *American Journal of Obstetrics and Gynecology,* 65:1182–1191, 1953.

b. *Pamabrom and pyrilamine maleate.* The Panel concludes that a combination of pamabrom and pyrilamine maleate in the dose recommended below is generally recognized as safe and effective in relieving premenstrual symptoms of the negative affect and water retention clusters, and the pain of cramps and backache of the premenstrual and menstrual periods.

(For the reviews of pamabrom and pyrilamine maleate as single ingredients, see part III. paragraph C.1.a.(3) above—Pamabrom, and part III. paragraph B.1.a. above—Pyrilamine maleate.)

(1) *Safety.* James and Johnson (Ref. 1) studied a combination of 50 mg pamabrom and 30 mg pyrilamine maleate per tablet in treating edema associated with pregnancy (180 patients). They found it necessary to administer 8 to 10 tablets per day to treat this condition. This treatment was given over a 2-year period (no indication of the time period in any one patient), and the authors concluded that the medication itself appeared to be nontoxic.

This combination of ingredients has been marketed under an NDA since 1952.

The Panel, therefore, concludes that the combination of pamabrom, at a dose of 50 mg, and pyrilamine maleate, at a dose of 30 mg, is generally recognized as safe for OTC use.

(2) *Effectiveness.* Bickers (Ref. 2) conducted a study involving a formulation containing 50 mg of pamabrom and 30 mg pyrilmaine maleate (referred to in this study as "bromaleate"). This study was not blinded nor did it contain a placebo or any other control drug. Fifty-six patients who suffered from moderate to severe premenstrual tension and menorrhalgia were given the drug and instructed to take two tablets in the morning and at night beginning 4 to 12 days before the expected onset of menstruation and to discontinue medication at onset of flow. In cycles recorded prior to treatment, patients had recorded an average weight gain of 4.2 pounds, but an average weight gain of only 1.6 pounds was recorded during treatment. Bickers claimed relief of the premenstrual symptoms, but gave no supportive data other than weight gain and made no comment as to what degree of relief was obtained or what symptoms were relieved. He also claimed that the premenstrual symptoms are directly related to the degree of tissue edema that occurs premenstrually and is reflected in the weight gain.

McGavack et al. (Ref. 3) conducted a study to determine the effect of a combination of 50 mg pamabrom and 30 mg of pyrilamine maleate in the treatment of premenstrual tension in 43 women with varying degrees of water retention. The study was not blinded, nor was it placebo-controlled, except to the extent that "placebo cycles" were used in 26 patients between cycles on active drug where questions of reliability arose. The patients were taken from an outpatient clinic or private practice and had severe symptoms of premenstrual tension that had not improved with previous therapy. They were divided into three groups according to the severity of water accumulation: (1) those with frank edema (17 patients), (2) those with water retention as shown by marked changes in weight, tightness of shoes, rings, etc., but with no obvious edema (12 patients), and (3) those without clinically recognizable water retention (14 patients). In general, the drug was started in each cycle when the patient was aware of the first premenstrual symptoms. The patient was then instructed to take one to two tablets two to four times daily. Results indicated that 37 percent of the patients were unimproved and 63 percent showed improvement. Of the 26 patients who also received the placebo, only 5 showed any relief at all while taking the placebo. When the data were analyzed for the three groups mentioned above, the authors found that the patients with recognizable water retention responded better than those without. They also observed that water retention was probably the one most consistently improved symptom, with nervous and mental symptoms of tension next. Breast engorgement, gastrointestinal symptoms, and pelvic manifestations were controlled in most patients, while marked improvement was observed in headaches in slightly over half the subjects.

McGavack et al. (Ref. 4) conducted another study in a manner similar to the one described above and used in same pamabrom/pyrilamine maleate combination. This was a crossover study and also used a placebo control and another active drug consisting of ammonium chloride, homatropine methylbromide, caffeine, and vitamins. Only 19 patients were involved in this study. Overall relief was obtained in 68 percent of the patients on the pamabrom combination, whereas only 32 percent improved on the other formulation. Pelvic distress, breast engorgement, and headache were about equally controlled by each preparation. Water and salt retention, nervous and mental symptoms, and acne responded more favorably and with greater frequency to the pamabrom combination than to the vitamin formulation.

In the Wisconsin study, the effects of pamabrom alone, pyrilamine maleate alone, and both in combination were tested on the symptoms of the premenstrual syndrome in 194 women (Ref. 5). The study was double-blind, placebo-controlled, and single-crossover in design. Only the results of the combination product (50 mg pamabrom and 30 mg pyrilamine maleate) used in this study will be discussed in this portion of the document. Ninety-nine subjects participated in this combination portion of the crossover study. Each subject was instructed to take one tablet four times daily starting 5 to 7 days prior to menstruation and to cease at onset. Each rated nine symptoms on a 1 to 4 scale for the premenstrual days. Data on all 99 subjects for premenstrual days 1 to 5 were available for analysis. The paired t-test was employed for analysis (Ref. 6). For analysis purposes the symptoms were examined separately and as clusters following the Moos cluster of symptoms (Ref. 7). There was statistically significant superiority of the combination over the placebo for the pain cluster ($p=0.017$), which included the symptoms of headache ($p=0.080$), and premenstrual cramps ($p=0.042$), and for the cluster of water retention ($p=0.003$), which included the symptom of ankle swelling ($p=0.022$), finger swelling ($p=0.012$), abdominal swelling ($p=0.002$), and breast tenderness ($p>0.010$, NS). It was also significantly superior to the placebo for the negative affect cluster ($p=0.005$), which included

the symptoms of irritability ($p=0.004$), depression ($p=0.032$), and premenstrual tension ($p=0.006$). The combination was also highly significant as compared with the placebo for the sum of cluster scores ($p=0.0007$).

An additional study, designated as the Boston study, evaluated the effectiveness of pyrilamine maleate alone versus placebo for 2 days into the menstrual period. Pyrilamine maleate proved to be statistically superior to placebo in relieving cramps ($p<0.05$) and backache ($p<0.05$) (Refs. 8 and 9).

Because of a lack of placebo controls in the Bickers (Ref. 2) and McGavack (Ref. 3) studies, the Panel considers that the results of these studies are only suggestive of the possible effectiveness of the combination of pamabrom and pyrilamine maleate in relieving symptoms of the premenstrual syndrome. However, because each individual ingredient was found effective in this document and the results of the Wisconsin study (Refs. 5 and 6) and Boston study (Refs. 8 and 9) were very positive, the Panel concludes that a combination of pamabrom (in a dose of 50 mg) and pyrilamine maleate (in a dose of 30 mg) is generally recognized as effective in relieving the premenstrual symptoms of the negative affect cluster and water-retention cluster.

Note.—individual symptoms cannot be used in labeling unless demonstrated to be effective.

It also is generally recognized as effective in relieving the pain of cramps and backache in both the premenstrual and menstrual periods.

(3) *Dosage.* The Panel recommends that the dosage for a combination of pamabrom and pyrilamine maleate consist of 50 mg pamabrom and 25 to 30 mg pyrilamine maleate to be taken four times daily for a daily dose of 200 mg pamabrom and 100 to 120 mg pyrilamine maleate.

(4) *Labeling.* The Panel recommends the following labeling claims for a combination of pamabrom and pyrilamine maleate:

(i) "For the relief of" ("emotional changes" or "mood changes") "related to the premenstrual period."

(ii) "For the relief of" ("emotional changes" or "mood changes") "related to the premenstrual period, such as anxiety, nervous tension, and irritability."

(iii) "For the relief of water-retention symptoms related to the premenstrual period."

(iv) "For the relief of water-retention symptoms related to the premenstrual period, such as ankle, finger, and abdominal swelling."

(v) "For the relief of cramps and backache of the premenstrual or menstrual period."

In addition, any warnings included earlier in the discussion of pyrilamine maleate should be included. (See part III. paragraph B.1.a.(4) above—Labeling.)

The Panel also recommends the following labeling claims (other symptoms of the negative affect, water-retention, and pain clusters) for which insufficient data (Category III) were available to demonstrate the effectiveness of the pyrilamine maleate and pamabrom combination:

1. "For the relief of" ("emotional changes" or "mood changes") "related to the" ("premenstrual" and/or "menstrual") "period, such as crying, loneliness, restlessness, and mood swings."

2. "For the relief of water-retention symptoms related to the" ("premenstrual" and/or "menstrual") "period, such as weight gain, skin disorders, and painful breasts."

3. "For the relief of muscle stiffness, headache, fatigue, and general aches and pains of the" ("premenstrual" and/or "menstrual") "period."

If a Category I analgesic were to be added to this combination, the incorporation of Category I analgesic labeling would be appropriate.

References

(1) James, W. F. B., and A. P. Johnson, "Toxemia in Pregnancy: A New Treatment for Controlling Edema," *American Journal of Obstetrics and Gynecology,* 74:1054–1056, 1957.

(2) Bickers, W., "Premenstrual Tension: A Neglected Phase of Menstrual Disability," *Southern Medical Journal,* 46:873–878, 1953.

(3) McGavack, T. H., et al., "The Treatment of Premenstrual Tension with a Combination of an Antihistaminic and a Theophylline Derivative," *American Journal of Obstetrics and Gynecology,* 72:416–422, 1956.

(4) McGavack, T. H., et al., "Therapy of Premenstrual Tension—The Influence of Theophyllinate-Antihistamine and Ammonium Chloride-Vitamin-Vagotropic Preparations," *New York State Journal of Medicine,* 56:2846–2849, 1956.

(5) "Wisconsin Study (1978)," unpublished study, OTC Volume 1720209 (pp. 163–186).

(6) OTC Volume 170221.

(7) Moos, R. H., "Menstrual Distress Questionnaire," 1977, OTC Volume 170209 (pp. 133–160).

(8) "The Effect of Pyrilamine Maleate on the Relief of Symptoms Associated with the Menstrual Syndrome (Boston Study 1981)," unpublished study, OTC Volume 170218.

(9) OTC Volume 170224 (Section 4).

3. *Category II combinations.* The Panel considers the following combinations not generally recognized as safe and effective or are misbranded in relieving the symptoms of primary dysmenorrhea.

Combination of herb extracts. The Panel reviewed a submission on two formulations of herb extract ingredients. One formulation (elixir) contains extracts of the following herbs, which the Panel considers to be the potential active ingredients: *Piscidia erythrina, Asclepias tuberosa, Cimicifuga racemosa, Taraxacum officinale, Glycyrrhiza glabra,* and *Senecio aureus.* The other formulation (tablet) is similar except that it lacks *Cimicifuga racemosa, Senecio aureus,* and *Taraxacum officinale* and contains in addition 65 mg ferrous sulfate. As stated earlier, the Glycyrrhiza will not be reviewed because the Panel considers that its only potential use would be for relieving menopausal symptoms, which this document does not address.

(a) *Studies of multiple-ingredient final formulations*—(1) *Animal safety testing.* In 2- to 4-month chronic toxicity studies conducted from 1943 to 1945, 13 rabbits were administered twice the proportional daily dose of what is described as Formula R and showed no pathological changes and, in some cases, gained weight beyond the control animals (Ref. 1). The exact formula tested is not given, although it appears that one ingredient currently contained in the marketed product submitted for review was absent and four ingredients not now contained in that same product were present.

(2) *Human safety testing.* In 1953, Karnaky (Ref. 2) studied 20 patients who were given 2 or 3 times the recommended dose for an average of 58 days. No toxicity was noted. The formula tested was similar, but does not appear to be the same as the formula currently marketed by the firm.

(3) *Uncontrolled and partially controlled clinical effectiveness studies.* An intrauterine balloon study (Ref. 3) on 48 dysmenorrheic patients given an elixir showed a depression of the abnormal uterine contraction pattern.

A similar study on dysmenorrheic patients with an elixir without *Asclepias tuberosa* was effective to a lesser degree (Ref. 4).

In a 4-month study of 27 women using the elixir for dysmenorrhea, 20 received relief of pain (16 complete and 4 partial) (Ref. 5). Of the seven who were not relieved, four submitted to laparotomy and endometriosis was found in each (as an explanation of the persistent pain).

In a 3-month study of 26 patients with dysmenorrhea, all felt better when treated with formula "139–056" elixir,

but 6 patients thought they had felt better on analgesics they had taken previously (Ref. 6).

Tests with a tablet version of the above compound elixir gave variable benefits in 25 dysmenorrheic women (Ref. 7).

One table formulation relieved 19 of 25 dysmenorrheic patients (Ref. 8).

Many unpublished clinical effectiveness studies were submitted, attempting to demonstrate the effectiveness of herbal formulations in treating dysmenorrhea. They present uniformly favorable results and used some ingenious intrauterine balloon experiments. However, all of the studies discussed above were uncontrolled by any modern standards. The exact nature and composition of the formula or formulas being tested are seldom clear. Most of the studies appear to have been performed using formulas significantly different from the currently marketed compound elixir.

(4) *Controlled clinical effectiveness studies.* A study of the compound elixir versus placebo on 82 dysmenorrheic patients was made by Fisher and Teabrock (Ref. 9) in 1953. The details of this study are not well presented. Apparently, treated patients were sequentially compared with previous treatment, no treatment, placebo, analgesics, and narcotics. Undocumented statements of improvement were made. All patients were given elixir formula "139–056," but the ingredients of this formula are not given. The authors concluded that formula "139–056" contains one or more drugs active in relieving the symptoms of dysmenorrhea.

(5) *Evaluation of clinical studies on multiple-ingredient formulations.* Most of the submitted data were unpublished and were generated using employees (as subjects) of the submitting company, a fact not always too plain in the material presented. Many of the studies were confusing, incomplete, and vague. The firm altered its formulation frequently, and the formulas tested are not clearly stated. The exact composition of the formula tested was seldom discribed, although the inference would appear to be that it was identical to or was some modification of the formula marketed by the submitting company at the time of the test. Therefore, no real conclusion can be reached as to the effectiveness of either the currently marketed products of the submitting firm or the individual active ingredients contained in this product.

The Panel concludes that while most of the individual ingredients have been found safe for OTC use, neither the elixir nor the tablet formulation is generally recognized as effective for OTC use in relieving the symptoms of primary dysmenorrhea for the following reasons: (1) no studies have been conducted on the individual ingredients attempting to identify their contribution to the total formulation; and (2) the composition has varied over the years.

References

(1) Boos, W. F., "Post-Mortem Studies of Experimental Animals Administered Formula R," unpublished study, OTC Volume 170077 (pp. 110–126).

(2) Karnaky, K. J., "Toxicity Study in 20 Patients," unpublished study, OTC Volume 170078 (pp. 275–299).

(3) Bickers, W., "Clinical studies with compound Elixir in 48 Patients with Dysmenorrhea," unpublished study, OTC Volume 170078 (pp. 300–333).

(4) Bickers, W., "Clinical Studies with Compound Elixir in 57 Patients with Dysmenorrhea," unpublished study, OTC Volume 170078 (pp. 334–345).

(5) Phillips, J. H., "Clinical Studies with Compound Elixir in 27 Patients with Dysmenorrhea," unpublished study, OTC Volume 170078 (pp. 380–415).

(6) Reed, H. E., "Clinical studies with Compound Elixir in 26 Patients with Dysmenorrhea," unpublished study, OTC Volume 170078 (pp. 451–511).

(7) Bickers, W., "Clinical Studies with Tablet Extract in 25 Patients with Dysmenorrhea," unpublished study, OTC Volume 170078 (pp. 512–534).

(8) Phillips, J. H., "Clinical Studies with Tablet Extract in 25 Patients with Dysmenorrhea," unpublished study, OTC Volume 170078 (pp. 590–621).

(9) Fisher, M. M., and Teabrock, H. E., "Clinical Studies with Compound Elixir and Pacebo in 82 Patients with Dysmenorrhea," unpublished study, OTC Volume 170079 (pp. 654–750).

4. *Category III combination.* The Panel has identified only one combination which it considers to meet the Category III condition of having insufficient data available to determine its effectiveness. A preparation containing cinnamedrine hydrochloride, aspirin, and caffeine was submitted. The cinnamedrine hydrochloride (as a smcoth-muscle relaxant) and caffeine (as analgesic adjuvant) have been classified by the Panel as Category III and aspirin (as an analgesic) as Category I. If each ingredient were elevated to a Category I status, the Panel would consider the combination as Category I for relieving pain and cramps of the premenstrual and menstrual periods.

List of Subjects in 21 CFR Part 357

OTC 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 proposed Part 357, which was published at 47 FR 444; January 5, 1982, a new Subpart K, to read as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart K—Orally Administered Menstrual Drug Products

Sec.

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

Subpart K—Orally Administered Menstrual Drug Products

§ 357.1001 Scope.

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

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

(c) References to Part 343 are to the internal analgesic proposed monograph published in the **Federal Register** of July 8, 1977 (42 FR 35346).

(d) References to Part 340 are to the stimulant tentative final monograph published in the **Federal Register** of June 13, 1978 (43 FR 25544).

§ 357.1003 Definitions.

As used in this subpart:

(a) *Diuretic.* A drug that increases the excretion of water.

(b) *Dysmenorrhea.* Painful menstruation. This may be accompanied by nausea, vomiting, diarrhea, headache, dizziness, fatigue, and bloating.

(c) *Menstrual period.* The period of time from onset to stoppage of cyclic, physiologic uterine bleeding which (in the absence of pregnancy) normally recurs, usually at approximately 4-week intervals.

(d) *Menstruation.* The monthly flow of blood from the genital tract of women.

(e) *Premenstrual period.* The period of time approximately 1 week before onset of menstruation.

(f) *Premenstrual syndrome.* A recurrent symptom complex which begins during the week prior to menstruation and usually disappears soon after the onset of the menstrual flow. This symptom complex consists predominately of edema, lower abdominal pain (including cramps), breast tenderness, headache, abdominal bloating, fatigue, and the feelings of depression, irritability, tension, and anxiety.

§ 357.1010 Analgesic active ingredients.

The active ingredients of the product consist of any analgesic active ingredient identified in Part 343 when used within the dosage limits established for each ingredient in Part 343.

§ 357.1012 Antihistamine active ingredients.

The active ingredient of the product consists of pyrilamine maletate within the dosage limit established in § 357.1052(d).

§ 357.1014 Diuretic active ingredients.

The active ingredients of the product consist of the following within the dosage limits established for each ingredient in § 357.1054(d):

(a) *Acidifying diuretic.* Ammonium chloride.

(b) *Xanthine diuretics.* (1) Caffeine.

(2) Pamabrom.

§ 357.1016 Smooth-muscle relaxant active ingredients. [Reserved]

§ 357.1020 Permitted combinations of active ingredients.

(a) Any analgesic identified in Part 343 and any diuretic identified in § 357.1014.

(b) Any analgesic identified in Part 343, pyrilamine maleate identified in § 357.1012, and any diuretic identified in § 357.1014.

(c) Any diuretic identified in § 357.1014 and pyrilamine maleate identified in § 357.1012.

(d) Two diuretics identified in § 357.1014 with different mechanisms of action.

(e) *Specific combinations:* (1) Ammonium chloride identified in § 357.1014(a) and caffeine identified in § 357.1014(b)(1) when used in the dose specified in § 357.1058(b)(1).

(2) Pamabrom identified in § 357.1014(b)(2) and pyrilamine maleate identified in § 357.1012 when used in the dose specified in § 357.1058(a)(2).

§ 357.1050 Labeling of orally administered menstrual drug products containing analgesic ingredients identified in § 357.1010.

(a) *Statement of Identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "analgestic."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrases, except that "For the relief of" may be replaced by "An aid in relieving":

(1) "For the relief of pain of the premenstrual and menstrual periods."

(2) "For the relief of pain of the premenstrual period."

(3) "For the relief of pain of the cramping of the premenstrual period."

(4) "For the relief of pain of the menstrual period."

(5) "For the relief of pain of the menstrual cramps."

(6) "For the relief of pain of dysmenorrhea."

(c) *Warnings.* The labeling of the product contains the warnings as identified in Part 343 under the heading "Warnings."

(d) *Directions.* The labeling of the product contains the dosage and any applicable directions identified in Part 343 under the heading "Directions."

§ 357.1052 Labeling of orally administered menstrual drug products containing antihistamine ingredients indentified in § 357.1012.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "menstrual/premenstrual symptom reliever."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrases, except that "For the relief of" may be replaced by "An aid in relieving":

(1) "For the relief of" ("emotional changes" or "mood changed") "related to the premenstrual period."

(2) "For the relief of" ("emotional changes" or "mood changed") "related to the premenstrual period, such as anxiety, nervous tension, and irritability."

(3) "For the relief of water-retention symptoms related to the premenstrual period."

(4) "For the relief of temporary weight gain or swelling due to water retention during the premenstrual period."

(5) "For the relief of of cramps and backache of the premenstrual or menstrual period."

(c) *Warning.* The labeling of the product contains the following warning under the heading "Warning": "May cause drowsiness."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing pyrilamine maleate identified in § 357.1012.* Adult oral dosage is 25 to 30 mg every 3 to 4 hours or 60 mg in 12 hours, but does not exceed 200 mg in a 24-hour period.

(2) [Reserved]

§ 357.1054 Labeling of orally administered menstrual drug products containing diuretic ingredients identified in § 357.1014.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "diuretic menstrual product."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrases, except that "For the relief of" may be replaced by "An aid in relieving":

(1) "For the relief of temporary water-weight gain, bloating, swelling, and/or full feeling associated with the premenstrual and menstrual periods."

(2) "For the relief of temporary water-weight gain, bloating, swelling, and/or full feeling associated with the premenstrual period."

(3) "For the relief of temporary water-weight gain, bloating, swelling, and/or

full, feeling associated with the menstrual period."

(4) "A diuretic for the relief of temporary premenstrual water-weight gain."

(5) "A diuretic which helps to control temporary water-weight gain during the menstrual period."

(6) In addition to the indications in paragraph (b) (1) through (5) of this section, products containing caffeine identified in § 357.1014(b)(1) may also contain the following indication: "For the relief of fatigue associated with the premenstrual period."

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

(1) *For products containing ammonium chloride identified in § 357.1014(a).* (i) "Do not use if you have kidney or liver disease."

(ii) *"Precaution.* This drug may cause nausea, vomiting, and gastrointestinal distress."

(2) *For products containing caffeine identified in § 357.1014(b)(1).* (i) All warnings identified in § 340.50(c) (1) and (2).

(ii) "This product contains caffeine. It may cause sleeplessness if taken within 4 hours of bedtime."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing ammonium chloride identified in § 357.1014(a).* Adult oral dosage is 1 gram three times daily for no longer than 6 days.

(2) *For products containing caffeine identified in § 357.1014(b)(1).* Adult oral dosage is 100 to 200 milligrams every 3 to 4 hours while symptoms persist.

(3) *For products containing pamabrom identified in § 357.1014(b)(2).* Adult oral dosage is 50 milligrams and not to exceed 200 milligrams per day.

§ 357.1056 Labeling of orally administered menstrual drug products containing smooth muscle relaxant ingredients identified in § 357.1016.

(a) *Statement of identity.* The labeling of the product contains the established name, if any, and identifies the product as a "muscle relaxant menstrual product."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrases, except that "For the relief of " may be replaced by "An aid in relieving"

(1) "For the relief of painful menstrual cramps."

(2) "For the relief of dysmenorrhea."

(3) "For the relief of menstrual cramps."

(4) "For relief of backache associated with menstrual cramps."

(5) "For the relief of cramps associated with the premenstrual or menstrual period."

(6) "For the relief of cramps associated with menstruation."

(c) *Warnings.* [Reserved]

(d) *Directions.* [Reserved]

§ 357.1058 Labeling of combinations.

(a) *For products containing pamabrom and pyrilamine maleate identified in § 357.1020(e)(2)*—(1) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrases, except that "For the relief of" may be replaced by "An aid in relieving":

(i) "For the relief of" ("emotional changes" or "mood changes") "related to the premenstrual period."

(ii) "For the relief of" ("emotional changes"or "mood changes") "related to the premenstrual period such as anxiety, nervous tension, and irritability."

(iii) "For the relief of water-retention symptoms related to the premenstrual period."

(iv) "For the relief of water-retention symptoms related to the premenstrual period, such as ankle, finger, and abdominal swelling."

(v) "For the relief of cramps and backache of the premenstrual or menstrual period."

(2) *Directions.* The labeling of the product contains the following information under the heading "Directions": Adult oral dosage is 50 milligrams pamabrom and 25 to 30 milligrams pyrilamine maleate taken four times daily for a daily dose of 200 milligrams pamabrom and 100 to 120 milligrams pyrilamine maleate.

(b) *For products containing ammonium chloride and caffeine identified in § 357.1020(e)(1)*—(1) *Directions.*—The labeling of the product contains the following information under the heading "Directions": Adult oral dosage is 650 milligrams ammonium chloride and 200 milligrams caffeine taken three times daily for a daily dose of 1,950 milligrams ammonium chloride and 600 milligrams caffeine.

(2) [Reserved]

Interested persons may, on or before March 7, 1983, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before April 6, 1983. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 4, 1982.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

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