DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 82N-0165]

Orally Administered Menstrual Drug Products for Over-the Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) orally administered menstrual drug products (drugs taken internally to relieve symptoms relating to a woman's menstrual period) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by March 16, 1989. Because this document is being published concurrently with the notice of proposed rulemaking on OTC internal analgesic, antipyretic, and antirheumatic drug products elsewhere in this issue of the **Federal Register**, the agency is allowing a period of 120 days for comments and objections instead of the normal 60 days. New data by November 16, 1989. Comments on the new data by January 16, 1990. Written comments on the agency's economic impact determination by March 16, 1989.

ADDRESS: Written comments, objections, new data, or requests for oral hearing 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, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-6000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 7, 1982 (47 FR 55076), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC orally administered menstrual drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by March 7, 1983. Reply comments in response to comments filed in the initial comment period could be submitted by April 6, 1983.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information.

In response to the advance notice of proposed rulemaking, five drug manufacturers, two consulting firms, and the Panel chairman submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

In order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10), the present document is designated as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Subpart K of Part 357 (21 CFR Part 357), FDA states for the first time its position on the establishment of a monograph for OTC orally administered menstrual drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC orally administered menstrual drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC orally administered menstrual drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

After reviewing and evaluating the Panel's recommendations regarding the use of OTC internal analgesic ingredients during the premenstrual and menstrual periods, the agency has decided to include premenstrual and menstrual claims for these ingredients as part of the rulemaking for OTC internal analgesic drug products rather than to retain them as part of the rulemaking for OTC menstrual drug products. In this way, the various conditions for which an OTC internal analgesic drug product is effective will be listed in one monograph. Elsewhere in this issue of the **Federal Register**, the agency is proposing in the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products to include premenstrual and menstrual claims. Final agency action on OTC internal analgesic ingredients for premenstrual and menstrual use will occur with publication of the final rule establishing a monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products. Comments relevant to OTC internal analgesics are discussed in that document.

Although this tentative final monograph contains indications for antihistamine and smooth-muscle relaxant active ingredients, no ingredients from either of these pharmacologic groups are included in Category I at this time. In the event that no new data are submitted to the agency during the allotted 12-month new data period or if submitted data are not sufficient to establish "monograph conditions" for these classes of ingredients, those classes will not be included in the final monograph. Should new data be sufficient to establish "monograph conditions" for these classes of ingredients, appropriate warnings and directions will be included in the final monograph.

The OTC drug procedural regulations (21 CFR 330.10) 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. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead 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 at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that 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 it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is 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.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Tentative Conclusions on the Comments

A. Comments on Orally Administered Menstrual Active Ingredients

1. One comment stated that, although the pharmacologic literature contains anecdotal evidence of the diuretic activity of ammonium chloride, the Panel did not consider or have available any quantitative data on ammonium chloride at the dosage of 1 gram (g) three times a day that it recommended as Category I.

The agency has reviewed the available data and information and believes that there is sufficient support for general recognition of ammonium chloride's effectiveness at the Panel's recommended dosage. The scientific literature contains several published clinical studies demonstrating ammonium chloride's mechanism of action as a diuretic (Refs. 1 through 5). Greenhill and Freed (Ref. 6) also reported that ammonium chloride is effective in relieving premenstrual and menstrual symptoms. In this study, ammonium chloride administered in doses of 1 g three times a day produced relief in 34 of 40 patients. Those patients who usually showed visible edema did not do so after therapy. Similar results have also been reported by Tecoz (Ref. 7) and Provenzano (Ref. 8). In addition, several pharmacology textbooks state that a dosage of 1 g of ammonium chloride three times a day is useful in treating premenstrual and menstrual symptoms (Refs. 9 through 12). Based on the above, the agency believes that ammonium chloride can be generally recognized as safe and effective for use as a diuretic in OTC menstrual drug products.

References

(1) Lyons, R.H., S.D. Jacobson, and N.L. Avery, "The Effect on the Plasma Volume of Dehydration Produced by a Low-Salt Diet and Ammonium Chloride," *American Heart Journal*, 27:353–359, 1944.

(2) Gamble, J.L., K.D. Blackfan, and B. Hamilton, "A Study of the Diuretic Action of Acid Producing Salts," *Journal of Clinical Investigation*, 1:359–388, 1925.

(3) Wiley, F.H., L.L. Wiley, and D.S. Waller, "The Effect of the Ingestion of Sodium, Potassium, and Ammonium Chlorides and Sodium Bicarbonate on the Metabolism of Inorganic Salts and Water," *Journal of Biological Chemistry*, 101:73–82, 1933.

(4) Folling, A., "On the Mechanism of the Ammonium Chloride Acidosis," *Acta Medica Scandinavica*, 71:221–257, 1929.

(5) Keith, N.M., C. W. Barrier, and M. Whelan, "The Diuretic Action of Ammonium Chlorid and Novasurol in Cases of Nephritis with Edema," *Journal of the American Medical Association*, 85:799–806, 1925.

(6) Greenhill, J.P., and S.C. Freed, "The Electrolyte Therapy of Premenstrual Distress," *Journal of the American Medical Association*, 117:504–507, 1941.

(7) Tecoz, R.M., "Traitement des Troubles Pre-Menstruels par Le Chlorure d' Ammonium," *Praxis*, 34:617–619, 1945.

(8) Provenzano, M.I., "Tensao Pre-Menstrual Seu Tratamento," *Revista de Ginecologia e D'Obstetricia*, 38:268–274, 1944.

(9) Beckman, H., "Pharmacology (The Nature, Action and Use of Drugs)," 2d Ed., W.B. Saunders Co., Philadelphia, pp. 466–467, 1961.

(10) Krantz, J.C., and C.J. Carr, editors, "The Pharmacological Principles of Medicinal Practice," 7th Ed., the Williams and Wilkins Co., Baltimore, pp. 639–640, 1969.

(11) "The Merck Manual," 11th Ed., Merck, Sharp, and Dohme Research Laboratories, Rahway, NJ, p. 659, 1966.

(12) Israel, S.L., "Diagnosis and Treatment of Menstrual Disorders and Sterility," 5th Ed., Harper and Row, New York, p. 158, 1967.

2. One comment stated that although the pharmacologic literature includes anecdotal evidence of the diuretic activity of caffeine, the Panel did not consider or have available any quantitative data for caffeine at the dose of 100 to 200 milligrams (mg) that it recommended as Category I. The comment noted that the results of the one study cited by the Panel to support its conclusions (Ref. 1) did show a significant increase in sodium output, but did not show a significant increase in urine volume following a 300-mg dose of caffeine. Another comment also noted an absence of data demonstrating caffeine's effectiveness in relieving subjective symptoms of the menstrual period.

The agency has reviewed the data and information cited by the Panel (Refs. 1 through 5), as well as other data and information in the scientific literature (Refs. 6, 7, and 8) and tentatively concludes that the data are adequate to support the effectiveness of the Panel's recommended dose of caffeine (100 to 200 mg) for use in OTC menstrual drug products.

The rationale for the use of diuretics during the premenstrual and menstrual periods was discussed by the Panel at 47 FR 55086. Although the Panel did not specifically discuss clinical studies that would support the recommended diuretic dose, the agency finds that caffeine's diuretic activity is well known and generally recognized (Refs. 2 through 5). Studies reported in the literature also support the Panel's conclusion regarding caffeine's diuretic action (Refs. 6, 7, and 8). In a double-blind, placebo-controlled, randomized, crossover study conducted by Robertson et al. (Ref. 6), 250 mg caffeine was found to produce a greater volume of urine in all patients as compared with placebo, with a mean increase of 29 percent. Eddy and Downs (Ref. 7) reported the minimum effective diuretic dose of caffeine to be 0.48 milligram per kilogram (mg/kg) in persons who were not coffee drinkers and 1.12 mg/kg in persons who were coffee drinkers (equivalent to 33 mg and 76 mg, respectively, in a 150-pound person). Victor, Lubetsky, and Greden (Ref. 8) reported that of 124 patients studied, 60 percent reported diuresis when

consuming less than 249 mg of caffeine per day.

As discussed in comment 3 below, in addition to caffeine's diuretic activity, its stimulant effect can provide additional benefit to persons suffering from fatigue during the premenstrual and menstrual periods.

Based on the above, the agency concurs with the Panel's recommendations and is including caffeine as an active ingredient in the tentative final monograph for OTC menstrual drug products.

References

(1) 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) Grollman, A., "Pharmacology and Therapeutics," 6th Ed., Lea and Febiger, Philadelphia, p. 555, 1965.

(3) de Stevens, G., "Diuretics, (Chemistry and Pharmacology)," Academic Press, New York, p. 12, 1963.

(4) Modell, W., editor, "Drugs of Choice, 1968–1969," C.V. Mosby Co., St. Louis, p. 88, 1967.

(5) Osol, A., R. Pratt, and M.D. Altschule, editors, "The United States Dispensatory," 27th Ed., Lippincott, Philadelphia, pp. 206–208, 1973.

(6) Robertson, D., et al., "Effects of Caffeine on Plasma Renin Activity, Catecholamines and Blood Pressure," *New England Journal of Medicine*, 298:181–186, 1978.

(7) Eddy, N.B., and A.W. Downs, "Tolerance and Cross-Tolerance in the Human Subject to the Diuretic Effect of Caffeine, Theobromine and Theophylline," *Journal of Pharmacology and Experimental Therapeutics*, 33:167–174, 1928.

(8) Victor, B.S., M. Lubetsky, and J.F. Greden, "Somatic Manifestations of Caffeinism," *Journal of Clinical Psychiatry*, 42:185–188, 1981.

3. One comment requested that the agency resolve certain inconsistencies relating to caffeine between the proposed rulemaking for OTC stimulant drug products and the advance notice of proposed rulemaking for OTC menstrual drug products. The comment noted that the stimulant tentative final monograph stated that caffeine could be expected to increase nervousness associated with premenstrual tension (43 FR 25561) and that the proposed labeling for caffeine included a warning advising that the use of caffeine may be associated with increased nervousness, anxiety, irritability, and other side effects (43 FR 25602). The comment pointed out that these same symptoms occur in the menstrual syndrome, a condition for which caffeine is being indicated for use as a diuretic. The comment implied that it is inappropriate to use a drug for a condition that includes symptoms that the drug itself caused as side effects.

The agency does not believe that the proposed rulemaking for OTC stimulant drug products and the advance notice of proposed rulemaking for OTC menstrual drug products are inconsistent with respect to caffeine. The agency notes that the proposed warning for caffeine in the tentative final monograph on OTC stimulant drug products (43 FR 25544) advises against excessive intake of caffeine, informs consumers to use caution when taking caffeine-containing drug products with other caffeine-containing products such as coffee or cola, and states that certain side effects such as anxiety, nervousness, and irritability may occur if the recommended dose is exceeded. The amount of caffeine that causes the side effects varies greatly among individuals, and the side effects are not expected to occur in most people from the usual stimulant or diuretic therapeutic dose of caffeine (100 to 200 mg).

As the Miscellaneous Internal Panel acknowledged in its report, caffeine can serve two purposes in OTC menstrual drug products (47 FR 55087). First, through its mild diuretic action, caffeine can relieve the symptoms of bloating, swelling, and water-weight gain during the premenstrual and menstrual periods. Second, the Panel acknowledged that fatigue is also a symptom of the premenstrual period, and caffeine's stimulant effect could relieve the fatigue. Although the premenstrual and menstrual syndrome may include the symptoms of nervousness, anxiety, and irritability, these symptoms do not necessarily occur in every individual (47 FR 55080). Even in those who are experiencing these symptoms, caffeine's diuretic effect may still provide a therapeuric benefit for the water-retention symptoms. Therefore, the agency does not believe it is inappropriate to use caffeine during the premenstrual and menstrual periods. However, to provide fully informative labeling to the consumer, the agency is proposing the following warning for OTC menstrual drug products containing caffeine: "The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart rate." The agency believes this warning is more appropriate for OTC menstrual drug products than the warnings recommended by the Panel in § 357.1054(c)(2) and is consistent with the warning in the final monograph for OTC stimulant drug products published in the **Federal Register** of February 29, 1988 (53 FR 6100).

4. Although phenyltoloxamine citrate was not reviewed by the Miscellaneous Internal Panel, one comment requested that products containing this ingredient in combination with acetaminophen or with acetaminophen and caffeine, which have been marketed for many years, be placed in Category III for relief of menstrual pain. The comment stated that the recommendations of the Miscellaneous Internal Panel concerning pyrilamine are equally applicable to other antihistamines and specifically to phenyltoloxamine because of their similarity in action. The comment pointed out that these products were reviewed by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel) and that clinical studies submitted to that Panel support this use of phenyltoloxamine. A reply comment stated that, whether or not other antihistamines share the effectiveness demonstrated by pyrilamine in relieving menstrual symptoms, all antihistamines should be subject to clinical investigations on an individual basis.

The agency has reviewed the administrative record of the rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products and determined that products containing phenyltoloxamine in combination with acetaminophen or acetaminophen and caffeine have been marketed OTC for relief of menstrual pain. Therefore, the agency agrees with the comment that it is reasonable to include phenyltoloxamine citrate in Category III in the review of OTC menstrual drug products. However, the data are insufficient to demonstrate that phenyltoloxamine citrate in combination with acetaminophen or acetaminophen and caffeine provides any contribution to the product's effectiveness. The agency is placing phenyltoloxamine in Category III, and additional data will be necessary to establish the effectiveness of this ingredient for use in OTC menstrual drug products. (For a discussion of pyrilamine in OTC menstrual drug products, see comment 5 below.)

5. Two comments responded to the agency's concern that the Panel's conclusions on the use of pyrilamine maleate in OTC menstrual drug products may be inconsistent with the final order for OTC daytime sedative drug products. The comments contended that the agency's conclusions with respect to antihistamines in the daytime sedative final order (44 FR 36378) were not

relevant to the use of pyrilamine maleate in products for premenstrual syndrome because the pharmacological basis for pyrilamine's use in the premenstrual and menstrual syndrome relates to its effects as an H_1 histamine antagonist and possibly to its ability to reduce prolactin levels, with consequent reduction in prostaglandin synthesis, but not to its drowsiness side effect. The comments also argued that although a target population that could benefit from the drowsiness effect for use as a daytime sedative had not been demonstrated, the target population that can benefit from an effective menstrual drug product is well defined. The comments added that the results of two studies submitted to the Panel provide the necessary evidence demonstrating the effectiveness of pyrilamine maleate alone or in combination with pamabrom in relieving symptoms of the premenstrual and menstrual periods (Refs. 1 and 2).

The agency has reviewed all of the available data and acknowledges that the conclusions regarding antihistamines in the daytime sedative final rule may not be relevant to the use of pyrilamine maleate in products used for the premenstrual and menstrual syndrome. However, the agency does not believe the data are sufficient to establish the effectiveness of pyrilamine maleate alone or in combination for use in relieving symptoms of the premenstrual and menstrual syndromes. Therefore, the agency is classifying pyrilamine maleate (and its combinations) in Category III in this document.

Two studies were cited by the Panel in support of the effectiveness of pyrilamine maleate. The Boston study, a randomized, double-blind, crossover study, was conducted to compare the effectiveness of pyrilamine maleate vs placebo in the treatment of the premenstrual syndrome (Ref. 1). Although several parameters were analyzed, the sponsor indicated that water retention, negative affects (anxiety, irritability, depression, and tension), and pain were of primary concern. However, because the sponsor's statistical analysis of the study results (Ref. 3) did not take into consideration the crossover design of the study, the results cannot be relied upon as proof of effectiveness. In addition, patients should not have been excluded from the efficacy population for failing to receive each treatment for the same length of time.

The Wisconsin study, also a placebo-controlled, double-blind, randomized crossover study, was conducted to assess the effects of pamabrom and pyrilamine maleate alone and in a fixed combination in the treatment of the premenstrual syndrome (Ref. 2). As in the Boston study, the statistical analysis did not take into consideration the crossover design of the study (Ref. 4). Consequently, the results cannot be relied upon.

Although both of these studies appeared to be well-controlled clinical trials, the lack of sufficient data precluded a proper analysis of the studies. For example, in the Wisconsin study, although the raw data were submitted, the protocol was not included. In addition, the fact that the treatment order was based on whether the patient's study number was odd or even indicated that a proper randomization procedure was not employed. In the Boston study, individual patient data were not provided. The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (address above) (Refs. 5 and 6). For the reasons above, the agency concludes that the studies are inadequate to establish effectiveness for pyrilamine maleate alone or in combination with pamabrom. Therefore, the agency is reclassifying pyrilamine maleate alone or in combination with pamabrom in Category III at this time.

In the preamble to the advance notice of proposed rulemaking for OTC menstrual drug products (47 FR 55076), the agency stated that it was not aware of any product on the OTC market containing pyrilamine maleate as the only ingredient and indicated for menstrual or premenstrual symptoms. The agency concluded that, because of its concerns regarding pyrilamine maleate, products containing pyrilamine maleate as a single ingredient and indicated for any menstrual or premenstrual symptoms should not be marketed at that time. The agency reaffirms in this document that products containing pyrilamine maleate as the sole ingredient and indicated for any menstrual or premenstrual symptoms should not be marketed as OTC menstrual drug products until the agency considers the ingredient to be generally recognized as safe and effective (Category I) for such use.

References

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

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

(3) OTC Volume 170224 (Section 4).

(4) OTC Volume 170221.

(5) Letter from W.E. Gilbertson, FDA, to C.N. Jolly, Chattem, Inc., dated February 22, 1985, coded LET009, Docket No. 82N–0165, Dockets Management Branch.

(6) Letter from W.E. Gilbertson, FDA, to C.N. Jolly, Chattem, Inc., dated July 29, 1988, coded LET011, Docket No. 82N–0165, Dockets Management Branch.

B. Comments on Labeling of Orally Administered Menstrual Drug Products

6. One comment noted that the Panel's recommended labeling for OTC menstrual drug products would provide for a distinction between products for use in the premenstrual and menstrual periods. The comment stated that because the Panel itself recognized that there was not a clear distinction between the symptoms occurring during these two periods, it would be simpler and less confusing to label all products in this category for relief of symptoms associated with "menstruation" or "the menstrual period," without attempting to distinguish between "premenstrual" and "menstrual" products.

The agency does not agree that the products should be indicated for "menstruation" only. Although the premenstrual and menstrual periods are two distinct syndromes, the symptoms that occur during these periods overlap significantly, and the ingredients used to relieve these symptoms would be the same whether the symptoms occurred during the menstrual or the premenstrual periods. Therefore, the agency does not believe it would be beneficial to the consumer to distinguish between these two periods in the indications. In this tentative final monograph, the agency is proposing that the products be indicated for the particular symptoms of the "premenstrual and menstrual periods" rather than distinguishing between the two periods. However, this would not preclude the selective use of these terms as part of the product name or as part of other promotional labeling statements, e.g., "premenstrual pain relief formula," "menstrual pain relief," etc. Such terms would be considered descriptive terms advising consumers of the product's benefits. While not included in the monograph, these terms are subject to the provisions of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading and will be evaluated by the agency in conjunction with normal enforcement activities relating to that section of the act.

In reviewing the labeling claims recommended by the Panel, the agency also notes that the Panel placed the term "dysmenorrhea" in Category I. The agency does not believe that "dysmenorrhea", when used alone, is a

word that is commonly understood by consumers, nor was this word used in any of the OTC drug product labeling submitted to the Panel. Therefore, the agency has not provided for its use as a sole indication but has provided for its optional use parenthetically with other terms, e.g., "For the relief of painful premenstrual and menstrual cramps" [which may be followed by: "(dysmenorrhea)."]

7. The Miscellaneous Internal Panel Chairman commented that the Panel's Category III classification of "skin-disorder" claims for antihistamine-containing ingredients (47 FR 55086) was an apparent oversight. He explained that although the classification accurately reflected the Panel's deliberations during the October 16–17, 1981 meeting, it was his personal opinion that such claims should be Category II. He was concerned that such claims would invite teenage girls to use these menstrual products to treat acne.

The agency has reviewed the administrative record for this rulemaking and has found no data to substantiate "skin disorder" claims for OTC menstrual drug products. Therefore, the agency concurs with the Panel Chairman. Skin disorder claims for OTC menstrual drug products are considered Category II.

C. Comments on Combinations

8. Two comments stated that the advance notice of proposed rulemaking for OTC menstrual drug products did not properly reflect all of the Panel's conclusions. The comments pointed out that at its October 16–17, 1981 meeting, the Panel classified the combination of a Category I analgesic and pyrilamine maleate in Category I, but the published document did not reflect this determination.

The agency has reviewed the transcripts of the meeting and concludes that the comments are correct in stating that the Panel classified the combination of a Category I analgesic and pyrilamine maleate as a Category I menstrual drug product. However, due to an editorial omission, the advance notice of proposed rulemaking did not reflect this conclusion. Nonetheless, as discussed in comment 5 above, the agency disagrees with the Panel's recommendation to include such a combination in Category I and has placed this combination in Category III. Therefore, the combination is not included in this tentative final monograph.

Criteria for establishing combinations as Category I are provided in the General Guidelines for OTC Drug Combination Products (Ref. 1). Paragraph 6 of these guidelines states, "In those cases where the data are sufficient to support a finding by the agency that several ingredients in a therapeutic category can be considered interchangeable for purposes of formulating combinations, the monograph will so state and list those ingredients. This is the preferred approach and will be done whenever supported by data and the opinion of experts." Therefore, the agency agrees with the Panel's concept of listing combination drug products by pharmacological class, but does not agree that sufficient data have been provided to allow for all of the ingredients in the various pharmacologic classes to be interchanged for the purpose of forming combinations. Therefore, only those combinations for which the agency has determined that adequate data exist have been included in the tentative final monograph. Data are necessary to establish the safety and effectiveness of other specific combinations or to demonstrate that the specific ingredients in a pharmacological class are chemically and pharmacologically interchangeable.

References

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 76D–0322, Dockets Management Branch.

9. One comment requested that the combination of acetaminophen, pyrilamine maleate, ammonium chloride, caffeine, and iron be classified as a Category I combination for the relief of menstrual discomfort. The comment contended that this would be a reasonable combination because it is a merger of two Category I combinations recommended by the Panel, with the addition of iron. The comment added that the iron is included in the combination because of the "known menstrual iron losses" that were identified in the advance notice of proposed rulemaking for OTC vitamin and mineral drug products. (See the **Federal Register** of March 16, 1979; 44 FR 16183.)

One reply comment questioned whether this product would be intended for use even in the absence of symptoms, in order to provide iron supplementation, or whether the inclusion of iron in the formula has a symptom-specific role.

The comment did not provide any data, and the agency is unaware of any evidence, demonstrating that a suitable target population exists that could benefit from the short-term use of OTC menstrual drug products containing the four proposed ingredients plus iron. The Advisory Review Panel on OTC Vitamin and Mineral Drug Products stated in its report (44 FR 16183) that a daily extradietary iron supplement to supplement the dietary stores and to preserve iron stores seems reasonable because of the prevalance of iron deficiency in menstruating females. Menstrual drug products, however, are not taken daily for long-term dietary supplementation, but are intended for occasional short-term use to alleviate symptoms associated with the premenstrual and menstrual periods. Therefore, the addition of iron as a concurrent therapy in OTC menstrual drug products does not appear warranted.

In addition, pyrilamine maleate and the combinations containing pyrilamine maleate have been reclassified as Category III because of the lack of evidence of effectiveness. (See comment 5 above.) Therefore, the combination requested by the comment would also be considered a nonmonograph combination.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and is proposing one change in the categorization of orally administered menstrual active ingredients recommended by the Panel. The agency has also reviewed the ingredient phenyltoloxamine citrate, which was not submitted to the Panel, and is proposing Category III status for this ingredient. (See comment 4 above.) As a convenience to the reader, the following list is included as a summary of the categorization of orally administered menstrual active ingredients recommended by the Panel and the proposed categorization by the agency.

Menstrual active ingredients	Panel	Agency
Analgesics: [2]		
Acetaminophen	I	
Aspirin	I	
Caffeine	III	
Carbaspirin calcium	I	
Choline salicylate	I	
Codeine	II	
Magnesium salicylate	I	
Sodium salicylate	I	
Antihistamines:		
Phenyltoloxamine citrate.	Not Reviewed	III

Menstrual active ingredients	Panel	Agency
Pyrilamine maleate	I	III
Diuretics:		
Ammonium chloride	I	I
Caffeine	I	I
Pamabrom	I	I
Theobromine sodium salicylate.	III	III
Theophylline	III	III
Smooth muscle-relaxants:		
Cinnamedrine hydrochloride.	III	III
Homatropine methylbromide.	II	II
botanical or vegetable herbs:		
Asclepias tuberosa (pleurisy root).	II	II
Cimicifuga racemosa (black cohosh).	II	II
Piscidia erythrina (Jamaica dogwood).	II	II
Senecio aureus (life root).	II	II
Taraxacum officinale (dandelion root).	II	II
Vitamins:		
Pyridoxine hydrochloride.	III	III
Other ingredients:		
Cnicus benedictus (blessed thistle).	II	II
Corn silk	II	II
Couch grass	II	II
Dog grass extract	II	II
Extract buchu	II	II
Extract uva ursi	II	II
Hydrastis canadensis (golden seal).	II	II
Oil of juniper	II	II
Pipsissewa	II	II
Triticum	II	II

[1] The agency's conclusions regarding the use of internal analgesic active ingredients for menstrual and premenstrual symptoms are presented elsewhere in this issue of the FEDERAL REGISTER.

2. *Testing of Category II and Category III conditions.* Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any orally administered menstrual active ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. Because of the changes summarized below, many of the section and paragraph numbers have been redesignated in this tentative final monograph.

2. The agency's conclusions regarding the use of internal analgesic active ingredients for menstrual and premenstrual symptoms are presented elsewhere in this issue of the **Federal Register.**

3. The word "precaution" has been deleted from the recommended warning for ammonium chloride in § 357.1052(c)(1)(ii). The agency considers the word "warning" alone to be the simplest, clearest signal to alert consumers and has routinely used the word "warning" in the labeling sections of other OTC drug tentative final and final monographs.

4. The recommended warnings relevant to the use of caffeine as an OTC menstrual drug have been revised. (See comment 3 above.)

5. Phenyltoloxamine citrate has been added to the menstrual rulemaking as a Category III ingredient. (See comment 4 above.)

6. Pyrilamine maleate as an individual ingredient and in combination has been reclassified from Category I to Category III. (See comments 5 and 8 above.)

7. The agency has modified the indications for OTC menstrual drug products to eliminate the distinction between the premenstrual and menstrual periods. (See comment 6 above.)

8. Skin disorder claims for OTC menstrual drug products have been reclassified from Category III to Category II. (See comment 7 above.)

9. The Panel recommended that the combination of ammonium chloride (650 mg) and caffeine (200 mg) given three times a day be classified in Category I. The Panel concluded this to be a rational combination because the diuretic mechanisms of action are different and adjunctive (47 FR 55095). The agency agrees that the combining of ingredients from the same therapeutic category with different mechanisms of action is rational and is provided for in the agency's general guidelines for OTC drug combination products (Ref. 1) which state that "* * * ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the OTC combination policy in all respects and the combination is on a benefit-risk basis equal to or better than each of the active ingredients used alone at its therapeutic dose." However, the study cited by the Panel to support the combination of ammonium chloride (650 mg) and caffeine (200 &g) (Ref. 2) was not designed to assess the individual contribution of each ingredient to the combination. Such data are necessary to satisfy the requirements of 21 CFR 330.10(a)(4)(iv), i.e., that each active ingredient must make a contribution to the claimed effect of the product, particularly in light of the fact that the product contains 200 mg caffeine, which has been shown to be effective alone at this dose. The contribution of ammonium chloride in a subtherapeutic dose to a product already containing an effective ingredient at an effective dose level needs to be demonstrated. This is particularly important in this case because, as discussed in comment 1 above, the agency is unaware of any evidence of the effectiveness of ammonium chloride at doses less than the recommended dose of 1 g. Likewise, the agency is unaware of any evidence to establish that the addition of subtherapeutic amounts of ammonium chloride to caffeine would provide any effect above the caffeine alone. Therefore, the agency is classifying the combination of ammonium chloride (650 mg) and caffeine (200 mg) in Category III. However, because the agency considers ammonium chloride in combination with caffeine to be rational for use as an OTC menstrual drug product, the agency has no objections to a drug product that would contain each of these ingredients at their therapeutic dose. Therefore, provisions for ammonium chloride and caffeine in combination at their therapeutic dose have been included in the monograph.

References

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D–0322, Dockets Management Branch.

(2) 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.

10. The agency has expanded the combination section of the monograph to provide for allowable combinations of analgesics (as identified in § 343.20(a)) to be combined with a diuretic.

11. The agency has not included several of the Panel's recommended indications statements for OTC menstrual diuretic drug products (§ 357.1054(b)(2) through (5)) in this

tentative final monograph because they duplicate information already contained in the statement of identity and the primary indications statement.

12. The Panel's recommended directions for OTC menstrual diuretic drug products containing pamabrom have been clarified to include a time interval as follows: Adult oral dosage is 50 milligrams four times a day, not to exceed 200 milligrams per day.

13. The Panel provided indications and directions for two specific combination products in § 357.1058 (a)(1) and (2) and (b)(1) of its proposed monograph. However, it did not provide labeling information for all of the combinations it recommended as Category I. Therefore, the agency is replacing the Panel's recommended § 357.1058 with a new general section (renumbered § 357.1060 in this tentative final monograph) for labeling of permitted combinations of active ingredients that conforms with the format of other recently published tentative final monographs. This combination labeling section contains provisions for combining duplicative words or phrases in the indications, warnings, and directions for each active ingredient in the combination, and contains a paragraph covering "Statement of identity," "Indications," "Warnings," and "Directions."

The information recommended by the Panel in § 357.1058(a) is not being included in this tentative final monograph because pyrilamine has been reclassified from Category I to Category III. (See comments 5 and 8 above.)

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph where exact language has been established and identified by quotation marks in an applicable monograph or other regulation, e.g., 21 CFR 201.63 or 330.1(g). The proposed rule in this document is subject to the labeling provisions in § 330.1(c)(2).

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC orally administered menstrual drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC orally administered menstrual drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC orally administered menstrual drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by March 16, 1989. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before November 16, 1989, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before March 16, 1989. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before March 16, 1989, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before January 16, 1990. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on January 16, 1990. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 357

Labeling, Orally administered menstrual drug products, Over-the-counter drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 357 as follows:

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

1. The authority citation for 21 CFR Part 357 continues to read as follows:

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); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

2. A new Subpart K consisting of §§ 357.1001 through 357.1060 is added to read as follows:

Subpart K—Orally Administered Menstrual Drug Products

Sec.

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 condition 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.

§ 357.1003 Definitions.

As used in this subpart:

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

(b) *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.

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

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

(e) *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 Antihistamine active ingredients. [Reserved]

§ 357.1012 Diuretic active ingredients.

The active ingredients of the product consist of the following within the dosage limits established for each ingredient in § 357.1052(d):

(a) *Acidifying diuretic.* Ammonium chloride.

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

(2) Pamabrom.

§ 357.1014 Smooth muscle-relaxant active ingredients. [Reserved]

§ 357.1020 Permitted combinations of active ingredients.

The following combinations are permitted provided each active ingredient is present within the established dosage limits and the product is labeled in accordance with § 357.1060.

(a) Any analgesic identified in § 343.10 of this chapter or any combination of analgesics identified in § 343.20(a) of this chapter and any diuretic identified in § 357.1012.

(b) Ammonium chloride identified in § 357.1012(a) with any one ingredient identified in § 357.1012(b).

§ 357.1050 Labeling of orally administered menstrual drug products containing antihistamine 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 a "premenstrual/menstrual symptom reliever."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph (b). Other truthful and nonmisleading statements describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

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

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

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

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

(c) *Warnings.* [Reserved]

(d) *Directions.* [Reserved]

§ 357.1052 Labeling of orally administered menstrual drug products containing diuretic ingredients identified 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 "diuretic."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

(2) In addition to the indication in paragraph (b)(1) of this section, products

containing caffeine identified in § 357.1012(b)(1) may also contain the following indication: "For the relief of fatigue associated with the premenstrual and menstrual periods."

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

(1) *For products containing ammonium chloride identified in § 357.1012(a).* (i) "Do not use if you have kidney or liver disease."

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

(2) *For products containing caffeine identified in § 357.1012(b)(1).* "The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and occasionally rapid heart rate."

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

(1) *For products containing ammonium chloride identified in § 357.1012(a).* Adult oral dosage is 1 gram three times a day for no longer than 6 days.

(2) *For products containing caffeine identified in § 357.1012(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 § 357.1012(b)(2).* Adult oral dosage is 50 milligrams four times a day, not to exceed 200 milligrams per day.

§ 357.1054 Labeling of orally administered menstrual drug products containing smooth muscle-relaxant 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 "muscle relaxant."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph (b). Other truthful and nonmisleading statements describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) "For the relief of painful premenstrual and menstrual cramps" [which may be followed by: "(dysmenorrhea)."]

(2) "For the relief of premenstrual and menstrual cramps."

(3) "For the relief of backache associated with premenstrual and menstrual cramps."

(4) "For the relief of cramps associated with the premenstrual and menstrual periods."

(c) *Warnings.* [Reserved]

(d) *Directions.* [Reserved]

§ 357.1060 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For the permitted combinations identified in § 357.1020(a).* "For the temporary relief of minor aches and pains and temporary water-weight gain, bloating, swelling, and full feeling associated with the premenstrual and menstrual periods."

(2) *For the permitted combinations identified in § 357.1020(a) that contain caffeine identified in § 357.1012(b)(1) the following indication may be used as an alternative to the one identified in § 357.1060(b)(1) above.* "For the temporary relief of minor aches and pains and temporary water-weight gain, bloating, swelling, full feeling, and fatigue associated with the premenstrual and menstrual periods."

(c) *Warnings.* The labeling of the product states, under the heading "Warning," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs. When the time intervals or age limitations of administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph. For example, an appropriate direction for a tablet containing 25 milligrams pamabrom and 325 mg aspirin would be "Two tablets every 4 to 6 hours not to exceed 8 tablets per day."

Dated: August 5, 1988.

Frank E. Young,

Commissioner of Food and Drugs.

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