DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 343

[Docket No. 77N-0094]

Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Drug Products for the Treatment and/or Prevention of Nocturnal Leg Muscle Cramps

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) drug products for the treatment and/or prevention of nocturnal leg muscle cramps 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 comment 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 January 7, 1986. New data by November 10, 1986. Comments on the new data by January 8, 1987. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by March 10, 1986.

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 Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 1, 1982 (47 FR 43562), FDA published, under § 333.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to reopen the OTC internal analgesic, antipyretic, and antirheumatic drug products rulemaking to consider quinine used OTC for the treatment of nocturnal leg muscle cramps 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 December 30, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by January 31, 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, one drug distributor submitted a comment. A copy of the comment received is 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 Part 343 (21 CFR Part 343), FDA states for the first time its position on the establishment of a monograph for OTC drug products used for the treatment and/or prevention of nocturnal leg muscle cramps. Final agency action on this matter will occur with the publication at a future date of a final rule for OTC internal analgesic, antipyretic, and antirheumatic drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on the OTC use of quinine for nocturnal leg muscle cramps based on the comment received and the agency's independent evaluation of the Panel's report. Vitamin E, which was not reviewed by the Panel, is also included in this proposed rulemaking based on the comment received.

The OTC 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 of 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 products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions 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 they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to this monograph that 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.

In the advance notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products (published in the **Federal Register** of July 8, 1977 (42 FR 35346), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monographs regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the

monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular mononograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

In the advance notice of proposed rulemaking, the Miscellaneous Internal Panel did not recommend any Category I conditions for the OTC use of drug products for the treatment and/or prevention of nocturnal leg muscle cramps, and no monograph was recommended by the Panel in that notice. At this time, no active ingredients have been determined to be generally recognized as safe and effective and not misbranded for OTC use for the treatment and/or prevention of nocturnal leg muscle cramps. However, the agency is proposing Category I labeling in this document in the event that data are submitted that result in the upgrading of any ingredients to monograph status in the final rule.

In the event that new data submitted to the agency during the allotted 12-month period are not sufficient to establish "monograph conditions" for the use of OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps, a final rule will declare these products to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which new drug applications approved under section 505 of the act and 21 CFR Part 314 are required for marketing. Such rule will also declare that in the absence of an approved new drug application, these products would be misbranded under section 502 of the act. A rule will then be incorporated into 21 CFR Part 310, Subpart E—Requirements for Specific New Drugs or Devices, instead of into the OTC drug monograph established under Part 343.

I. The Agency's Tentative Conclusions on the Comment

1. The comment disagreed with the Panel's recommendation that there were insufficient data to establish that quinine is safe and effective for OTC use for the treatment of nocturnal leg muscle cramps. The comment argued that the standard for determination of effectiveness under the OTC drug review is not as stringent as that imposed for approval of a new drug application and, therefore, existing available clinical evidence is sufficient to establish the effectiveness of quinine for the prevention and treatment of nocturnal leg muscle cramps. To support its argument that less stringent requirements for proof of effectiveness should be applied to OTC monograph drugs, the comment referred to 21 CFR 330.10(a)(4)(ii) as authorizing agency waiver of controlled clinical investigations "on the basis of showing that it [the requirement for controlled clinical investigations] is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness."

In addition, the comment maintained that, regardless of what the actual Panel report stated, various individual Panel members actually found quinine to be effective for the treatment and prevention of nocturnal leg muscle cramps. To support its contention, the comment cited various excerpts from the transcripts of Panel meetings. The comment added that the discussion of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel) in the advance notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products at 42 FR 35434 (July 8, 1977) indicates that there are adequate reports of controlled and uncontrolled clinical trials showing that quinine is effective for prevention and treatment of this condition. The comment also submitted additional data, including three market-research studies and a number of supportive testimonials, to support the use of quinine in the treatment of nocturnal leg muscle cramps.

The comment also pointed out an apparent inconsistency between the findings of the Miscellaneous Internal Panel and the Internal Analgesic Panel regarding the safety of quinine as an OTC medication. The comment stated that although the Internal Analgesic Panel concluded that quinine was not safe for OTC use, that Panel's evaluation was based on the use of quinine at dosages of 0.3 to 0.6 grams (g), in daily doses up to 2 g. The comment pointed out, however, that the Miscellaneous Internal Panel concluded that quinine was safe for OTC use on the basis of its being reasonably safe over prolonged periods of time in generally recommended doses of 200 to 325 milligrams (mg) daily for use in treating and preventing nocturnal leg muscle cramps.

The comment concluded that the literature, "standard treatises" (Refs. 1, 2, and 3), scientific evidence, physician and patient acceptance, and marketing results provide adequate evidence that quinine is generally recognized as [safe and] effective for prevention and treatment of nocturnal leg muscle cramps. The comment also pointed out a number of difficulties in conducting clinical studies for this condition and felt that FDA had adequate evidence of the effectiveness of the drug to waive the requirement for controlled clinical investigations, as provided in § 330.10(a)(4)(ii).

The question of whether less stringent standards of effectiveness should be applied to drugs under consideration in the OTC drug review was addressed in the preamble of the final regulations establishing the OTC drug review procedures. (See the **Federal Register** of May 11, 1972; 37 FR 9471 to 9472.) In that preamble, the agency stated that the best possible data in establishing a drug's effectiveness would consist of adequate and well-controlled studies. However, the regulations do provide for waiver where there is a showing that such studies are unnecessary or inappropriate and there is an adequate alternative method to substantiate effectiveness. The agency also stated that "objective or subjective clinical studies; bioavailability of ingredients;

documented clinical experience or uncontrolled clinical studies; market research studies; animal studies; general medical and scientific literature, published and unpublished; long use by the professional and the consumer; and common medical knowledge" may be used as corroborative evidence to support effectiveness.

The agency continues to believe that the best data to support effectiveness are obtained from adequate and well-controlled clinical studies and that a waiver of the requirement is appropriate only if evidence from controlled clinical studies is inapplicable or unnecessary and there is an adequate alternative method to substantiate effectiveness. Neither the Internal Analgesic Panel nor the Miscellaneous Internal Panel believed that the information that did not come from controlled studies was an adequate basis for general recognition of quinine as an effective OTC drug for the treatment of nocturnal leg muscle cramps. Also, selected comments from the transcripts of panel meetings do not suffice to establish a panel's recommendation. Members of the OTC advisory review panels commonly expressed differing positions before determining their group's final recommendation. No minority reports were included in the Miscellaneous Internal Panel's statement on quinine.

The agency has reviewed the studies and information discussed by both Panels, and the comments of the Miscellaneous Internal Panel members, and believes that this information is not sufficient to reach a conclusion that quinine is generally recognized as safe and effective for this intended use. Further, because the comment has not provided an adequate alternative method for determining the effectiveness of quinine to treat or prevent nocturnal leg cramps, the agency believes that a waiver is not appropriate in this situation and that evidence from adequate and well-controlled studies is necessary.

The agency has the following comments on the new data submitted:

A study by Kaji et al. (Ref. 4) was a double-blind, controlled study to determine the efficacy of quinine in hemodialysis-induced muscle cramps. Nine patients who were on maintenance hemodialysis three times per week and had frequent muscle cramps were given either 320 mg of quinine sulfate or placebo at the beginning of each dialysis for a period of 12 weeks. Efficacy was measured in terms of reduction in the frequency and severity of muscle cramps. The authors reported 10 episodes of cramps for the 162 dialyses in patients taking quinine, as opposed to 28 episodes of cramps for the 162 dialyses in patients taking placebo. The authors considered these results to be statistically significant.

Although this was a controlled study, the agency considers it unacceptable as evidence of the efficacy of quinine in preventing or treating nocturnal leg muscle cramps because the medical condition in the patients was not nocturnal (or recumbency induced) leg muscle cramps. Furthermore, even if this had been a study of patients with nocturnal leg cramps, the statistical analysis is faulty, because episodes of cramps, and not individual patient experiences, were analyzed.

A study by Morl et al. (Ref. 5) was a single-blind study in 22 adult patients with a minimum of 3 episodes of leg cramps per week to compare the efficacy of a quinine sulfate and aminophylline combination drug to placebo for 4 weeks. Because the drug used in this trial was quinine in combination with aminophylline, the study does not provide any evidence of the effectiveness of quinine alone.

A submitted article describes a roundtable discussion of peripheral neuropathy by a panel of six experts in the field (Ref. 6). In its discussion of entities causing lower limb distress, the panel stated that it considers quinine to be effective in relieving nocturnal leg muscle cramps. However, such evidence, as well as the testimonials submitted, can at best be classified as anecdotal and is not derived from a controlled clinical trial.

The three market-research studies submitted involved consumer acceptance of a combination product containing quinine, vitamin E, and lecithin (Ref. 7). One survey consisted of telephone interviews of 57 customers who had received a free sample for use in relieving leg muscle cramps. The other two market surveys consisted of responses from consumers who had purchased the same product at retail. Half of the users stated that the product was effective; the other half found it somewhat helpful in the prevention and treatment of nocturnal leg muscle cramps. However, these market research surveys do not provide corroborative evidence of the effectiveness of quinine as a single ingredient because the product tested was a combination of quinine and two other ingredients. The agency finds that the "standard treatises" (Refs. 1, 2, and 3) mentioned by the comment as supporting the effectiveness of quinine in the treatment of nocturnal leg cramps are of historical interest, but do not suffice to support use of quinine for this claim without a clinical study.

The agency notes that the Miscellaneous Internal Panel acknowledged frequent prescribing of quinine by physicians for treatment of nocturnal leg muscle cramps (47 FR 43564). The National Disease and Therapeutic Index (NDTI), a survey based on reports by a panel of office-based physicians, estimates about 175,000 mentions of the drug quinine during 1983, of which 64 percent are related to its use in the relief of leg cramps (Ref. 8). The term "mentions," as used in the NDTI, reflects usage, but should not be interpreted as directly equivalent to prescriptions or patients. The inclusion of quinine sulfate in the 1984 edition of the American Hospital Formulary Service, including reference to its use in the relief or treatment of nocturnal recumbency leg muscle cramps, is a further indication of its prescription use by physicians (Ref. 9).

The agency concludes that these additional data and information do not provide sufficient evidence to establish that quinine is generally recognized as safe and effective for OTC use in the treatment and/or prevention of nocturnal leg muscle cramps.

Although accurately reflecting the Miscellaneous Internal Panel's views on the safety of quinine at the 250-to 325-mg daily dose level, the comment failed to note that the Internal Analgesic Panel stated that "Until controlled studies show that a [quinine] dose of not more than 325 mg daily is safe and useful for relief of nocturnal leg cramps the drug should not be available for OTC use for treatment of nocturnal leg cramps" (42 FR 35434).

Because of the two Panel's conflicting evaluations regarding the safety of a 200- to 325-mg daily dosage of quinine as an OTC drug and the questions raised by both Panels concerning the efficacy of quinine as an OTC drug for the treatment of nocturnal leg muscle cramps, the agency has determined that adequate clinical data are necessary to support the Category I status of quinine for both safety and effectiveness for this OTC use. Based on the above discussion, the agency is also including prevention of nocturnal leg muscle cramps as a potential indication.

The issues to be addressed in any such studies before quinine can be reclassified from Cateory III to Category I are as follows:

(1) Is quinine effective in treating and/or preventing nocturnal leg muscle cramps in low daily doses (e.g., 200 to 325 mg) over short periods of time (e.g., 7 days or less)?

(2) If short-term quinine treatment with low doses is not significantly

effective in reducing recurrent episodes of nocturnal leg muscle cramps, must such medication be taken over extended periods of time to obtain relief? If yes, now long a period of time?

(3) What are the adverse effects experienced by subjects exposed to effective doses of quinine over an effective course of therapy?

References

(1) "AMA Drug Evaluation—1971," 1st Ed., American Medical Association, Chicago, p. 455, 1971.

(2) Osol, A., and J. E. Hoover, editors, "Remington's Pharmaceutical Sciences," 14th Ed., Mack Publishing Co., Easton, PA, p. 1249, 1970.

(3) Rollo, I. M., "Drugs Used in the Chemotherapy of Malaria," *in* "The Pharmacological Basis of Therapeutics," edited by A. G. Gilman, L. S. Goodman, and A. Gilman, 6th Ed., MacMillan Publishing Co., Inc., New York, p. 1057, 1980.

(4) Kaji, D. M., et al., Prevention of Muscle Cramps in Hemodialysis Patients by Quinine Sulfate, *Lancet* 2:66, 1976.

(5) Morl, D., et al., "Nocturnal Leg Cramps—Causes and Treatment," *Medizinische Klinik*, 75:264–267, 1980.

(6) "Helping Patients with Lower Limb Distress," roundtable discussion, *Patient Care*, p. 106, June 1977.

(7) Comment No. C00111, Docket No. 77N-0094, Dockets Management Branch.

(8) "National Disease and Therapeutic Index," (NDTI) Vol. I, IMS America Ltd., Ambler, PA, p. 593, 1983.

(9) "American Hospital Formulary Service, Drug Information," edited by G. K. McEvoy and G. M. McQuairre, American Society of Hospital Pharmacists, Bethesda, MD, pp. 184–186, 1984.

2. The comment also submitted data to support the effectiveness of vitamin E (alphatocopherol) in the treatment and prevention of nocturnal leg muscle cramps. The data included two uncontrolled studies, one letter, one comment regarding leg muscle cramps, and four papers concerned with the treatment of intermittent claudication. The comment pointed out that, although this ingredient was not classified by the Miscellaneous Internal Panel, a brief discussion of vitamin E appears in the report on OTC vitamin and mineral drug products, published in the **Federal Register** of March 16, 1979 (44 FR 16170).

The agency has the following comments on the data and information submitted.

The paper by Ayres and Mihan (Ref. 1) reports a "serendipitous observation" of the value of vitamin E in relieving nocturnal leg cramps in 125 patients who were receiving the vitamin for dermatologic conditions. The patients were taking either 300 or less international units (IU) of vitamin E a day or 400 or more IU a day; the results were drawn from all 125 patients regardless of the dose of vitamin E. The authors concluded that 103 patients (82 percent) had complete relief; 13 (10.4 percent) had 75–90 percent relief; 7 (5.6 percent) had 50 to 75 percent relief; and 2 (1.6 percent) had poor relief. The authors also noted that some of the patients had recurrences of cramps upon the cessation of use of the drug or decrease of the doses, but responded again upon the resumption of vitamin E. The comment stated that the results of this study confirmed the authors' earlier findings. (The earlier study is discussed below.) While the data show potential for a favorable effect on leg muscle cramps, this report is not a scientifically-controlled study to demonstrate the efficacy of vitamin E in the treatment or prevention of nocturnal leg muscle cramps.

The earlier paper by Ayres and Mihan (Ref. 2) reported on 24 patients with leg cramps and 2 patients with "restless leg syndrome" who had prompt relief from their symptons while taking 100 IU of vitamin E three times a day for the treatment of dermatologic conditions. The authors claim that vitamin E is a better choice than quinine for the treatment of leg cramps because vitamin E is relatively free of side effects. The comment also included a letter to the editor of a medical journal (Ref. 3) agreeing with this report by Ayres and Mihan on the effectiveness of vitamin E in relieving nocturnal leg muscle cramps. However, the agency finds that this study does not present scientifically acceptable evidence of the efficacy of vitamin E in the treatment of nocturnal leg muscle cramps because it was uncontrolled and unblinded.

The comment stated that additional evidence supporting vitamin E in the treatment of leg cramps lies in its use in the treatment of intermittent claudication (pain, ache, or cramp due to a deficient blood supply in exercising muscle) (Refs. 5 through 8). The comment contended that because nocturnal leg cramps and intermittent claudication have many of the same causes—reduced blood flow to the legs and a lack of oxygen supplied to muscles in the legs—these findings are relevant and indicative of the effectiveness of vitamin E in the treatment of leg and foot cramps. The agency notes that, although ischemia may be responsible for nocturnal leg muscle cramps in some patients, other etiologies have also been postulated. At the present time, this disorder must be considered one specific subgroup of cramps, and not a model for *all* nocturnal cramps.

The article by Roberts (Ref. 4) mentioned that both the public and many "nutritionists" regard the use of vitamin E as therapeutic or prophylactic for a wide variety of disorders, including leg cramps. Roberts mentioned that some of his patients resumed the use of vitamin E because of its apparent benefit on their leg cramps or other symptoms, even though they risked a recurrence of hypertension or thrombophlebitis (which did occur). Roberts noted that the purported safety of vitamin E is repeatedly underscored by physicians in popular health-oriented publications, but Roberts pointed out that he continues to encounter patients with problems that "seem to have been caused or aggravated by" self-medication with vitamin E (used here to designate the various tocopherols) in high dosage.

None of the papers contained controlled studies to show the efficacy of vitamin E in the treatment of nocturnal leg cramps. In addition, the paper by Roberts raises some questions about the safe dose of vitamin E. Roberts mentions that there is bound to be considerable controversy as to what constitutes excessive vitamin E therapy. He regards a daily intake of a fully active tocopherol in excess of 100 to 300 units as a "megadose." Roberts mentions that another study (Ref. 9) demonstrated that 300 mg of DL-x-tocopheryl acetate, given daily for three weeks to men and young boys, produced a significiant depression in the bactericidal activity of the leukocyte and mitogen-induced lymphocyte transformation. A safe and effective OTC dosage of vitamin E used for the treatment and/or prevention of nocturnal leg muscle cramps has not been established. Therefore, the agency classifies this ingredient in Category III for this indication.

References

(1) Ayres, S., Jr., and R. Mihan, "Nocturnal Leg Cramps (Systremma): A Progress Report on Vitamin E" *Southern Medical Journal*, 67: 1308–1312, 1974.

(2) Ayres, S., Jr., and R. Mihan, "Leg Cramps (Systremma) and Restless Leg Syndrome-Response to Vitamin E (Tocopherol)," *California Medicine*, 3:87–91, 1969.

(3) Cathcart, R. F., "Leg Cramps and Vitamin E," Letter to the editor, *Journal of the American Medical Association*, 219:216–217, 1972.

(4) Roberts, H. J., "Perspective on Vitamin E as Therapy," *Journal of the American Medical Association*, 246:129–131, 1981.

(5) Williams, H. T. G., D. Fenna, and R. A. MacBeth, "Alpha-Tocopherol in the Treatment of Intermittent Claudication," *Surgery, Gynecology and Obstetrics*, 132:662–666, 1971.

(6) Williams, H. T. G., L. J. Clein, and R. A. MacBeth, "Alpha-Tocopherol in the Treatment of Intermittent Claudication. A Preliminary Report," *Canadian Medical Association Journal*, 87:538–541, 1962.

(7) Hamilton, M., et al., "The Treatment of Intermittent Claudication with Vitamin E," *Lancet*, 1:367–370, 1953.

(8) New York Academy of Science, Conference on Vitamin E: Biochemical, Hematological and Clinical Aspects, Abstracts, New York, pp. 1–21, November 11–13, 1981.

(9) Prasad, J. S., "Effect of Vitamin E Supplementation on Leukocyte Function," *American Journal of Clinical Nutrition*, 33:606–608, 1980.

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

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

1. Summary of Ingredient Categories

The agency has reviewed the Miscellaneous Internal Panel's recommendation, as well as other data and information available at this time, and concurs with the Panel's classification of quinine sulfate. The agency has also reviewed the Internal Analgesic Panel's discussion of quinine and concurs with that Panel that until controlled studies show that a quinine dose of not more than 325 mg daily is safe and useful for relief [or prevention] of nocturnal leg cramps, the drug should not be generally recognized as safe and effective for this use.

The agency acknowledges that, in another rulemaking pertaining to combinations containing aminophylline, one firm previously marketing a prescription aminophylline-quinine sulfate combination product for nocturnal leg muscle cramps has been allowed to remove the aminophylline for lack of effectiveness as an antiasthmatic drug and to continue marketing the 260-mg quinine sulfate component as a prescription drug, pending final action of this rulemaking for OTC nocturnal leg muscle cramps drug products. (See the **Federal Register** of April 9, 1976; 41 FR 15053.) The agency is also aware of other products containing 260 mg of quinine sulfate labeled for prescription use only.

Quinine is currently available as an OTC drug for use in treating and preventing noctural leg muscle cramps, as well as for other uses, such as for treatment of chills and fever of malaria (in 200 and 325 mg dosages). The only use of quinine covered by this document is its use in the treatment and/or prevention of leg muscle cramps.

Vitamin E, which was not reviewed by the Panel, is proposed as Category III for the treatment and/or prevention of nocturnal leg muscle cramps.

As a convenience to the reader the following list is included as a summary of the categorization of these two orally administered active ingredients for the treatment and/or prevention of nocturnal leg muscle cramps.

Active ingredients	Panel	Agency
Quinine sulfate	[1] III	III
Vitamin E	NA	III

[1] Classified for use in treatment of nocturnal leg muscle cramps only.

In proposing labeling for quinine in this document, the agency is including the existing caution for quinine in 21 CFR 369.20 in the warning section of the proposed monograph under § 343.150. The agency is expanding this caution to inform consumers to discontinue using the product if diarrhea or nausea occur because, as the Panel noted, quinine sometimes leads to gastrointestinal symptoms (47 FR 43564). These types of warnings were included in draft labeling submitted to the Miscellaneous Internal Panel to review (Ref. 1), and the Panel acknowledged this labeling in its report (47 FR 43564). The Panel also noted that among quinine's more serious side effects are the induction of abortion and occasional cases of autoimmune thrombocytopenic purpura and hemolytic anemia (47 FR 43564). Therefore, the agency is proposing that quinine products bear a warning that the drug not be taken by anyone who is pregnant or sensitive to quinine. The agency notes that some currently marketed OTC quinine-containing drug products bear labeling that states not to take the drug product if pregnant. Finally, the Panel noted that nocturnal leg cramps occur in middle life and beyond (47 FR 43564). Thus, the agency is proposing that quinine products bear a warning that children under 12 years of age not take the drug. Based on the above, the agency is proposing the following warning in this tentative final monograph for products containing quinine: "Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. Do not take if pregnant, sensitive to quinine, or under 12 years of age."

The agency is also proposing a definition for nocturnal leg muscle cramps in the tentative final monograph, based on the Miscellaneous Internal Panel's recommendations (47 FR 43564). This definition reads: "A condition of localized pain in the lower extremeties occurring in middle life and beyond with no regular pattern concerning time or severity and variously attributed to:

(1) Arterial insufficiency with resulting anoxic muscle spasm;

(2) Excessive venous dilation secondary to sudden emptying of small venules into larger vessels during recumbency; and

(3) Acccumulation of products of muscle metabolism with local pH changes due to lactic acid accumulation."

The agency is not aware of any data demonstrating the safety and effectiveness of any other ingredients used OTC as orally administered drug products for the treatment and/or prevention of nocturnal leg muscle cramps. Therefore, the agency classified all other ingredients as Category II for this use.

Reference

(1) OTC Volume 170050

2. Testing of Category III Conditions

The Panel did not recommend any testing guidelines for OTC orally administered drug products for the treatment of nocturnal leg muscle cramps. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any orally administered ingredient for the treatment and/or prevention of nocturnal leg muscle cramps or about any 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.

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 drug products for the treatment and/or prevention of nocturnal leg muscle cramps, is a major rule.

For purposes of the Regulatory Flexibility Act, Public Law 96–354, the

economic assessment concluded that, while the average economic impact of the overall OTC drug review on small entities will not be significant, the possibility of larger-than-average impacts on some small firms in some years might exist. Therefore, the assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose a significant impact on a substantial number of small entities. The analysis identified the possibilities of reducing burdens on small firms through the use of (a) relaxed safety and efficacy standards or (b) labels acknowledging unproven safety and efficacy. However, the analysis concluded that there is no legal basis for any preferential waiver, exemption, or tiering strategy for small firms compatible with the public health requirements of the Federal Food, Drug, and Cosmetic Act. Nevertheless, to avoid overlooking any problems or feasible possibilities of relief peculiar to this group of products, the agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC orally administered drug products for the treatment and/or prevention of nocturnal leg muscle cramps. Comments regarding the economic impact of this rulemaking should be accompanied by appropriate documentation.

The agency previously invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on quinine used OTC for the treatment of nocturnal leg muscle cramps. 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 10, 1986. 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) (April 26, 1985; 50 FR 16636) 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.

In the **Federal Register** of April 22, 1985 (50 FR 15810) the agency proposed to change its "exclusivity" policy for the labeling of OTC drug products that has existed during the course of the OTC drug review. Under this policy, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph.

The proposed rule would establish three alternatives for stating the indications for use in OTC drug labeling while all other aspects of OTC drug labeling (i.e., statement of identity, warnings, and directions for use) would continue to be subject to the existing exclusivity policy. The proposed rule for OTC drug products for the treatment/prevention of nocturnal leg muscle cramps included in this document incorporates the exclusivity proposal by providing for the use of other truthful or nonmisleading statements in the product's labeling to describe the indications for use. After considering all comments submitted on the proposed revision to the exclusivity rule, the agency will announce its final decision on this matter in a future issue of the **Federal Register**. This final rule for OTC drug products for the treatment/prevention of nocturnal leg muscle cramps will incorporate the final decision on exclusivity for labeling.

Interested persons may, on or before January 7, 1986 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 10, 1986. 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 above office 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 November 10, 1986; 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 8, 1987. 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 8, 1987. 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 343

OTC drugs: Internal analgesics, antipyretics, and antirheumatics.

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 by adding new Part 343 consisting of new Subpart E as follows:

PART 343—INTERNAL ANALGESIC, ANTIPYRETIC AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—[Reserved]

Subpart B—[Reserved]

Subpart C—[Reserved]

Subpart D—[Reserved]

Subpart E—Drug Products for the Treatment and/or Prevention of Nocturnal Leg Muscle Cramps

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

Subpart E—Drug Products for the Treatment and/or Prevention of Nocturnal Leg Muscle Cramps

§ 343.100 Scope.

(a) An over-the-counter drug product for the treatment and/or prevention of nocturnal leg muscle cramps 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.

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

§ 343.103 Definitions.

As used in this part:

Nocturnal leg muscle cramps. A condition of localized pain in the lower extremeties occurring in middle life and beyond with no regular pattern concerning time or severity and variously attributed to:

(1) Arterial insufficiency with resulting anoxic muscle spasm;

(2) Excessive venous dilation secondary to sudden emptying of small venules into larger vessels during recumbency; and

(3) Accumulation of products of muscle metabolism with local pH changes due to lactic acid accumulation.

§ 343.110 Active ingredients for the treatment and/or prevention of nocturnal leg muscle cramps. [Reserved]

§ 343.150 Labeling of products for the treatment and/or prevention of nocturnal leg muscle cramps.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "nocturnal leg muscle cramps treatment," or "nocturnal leg muscle cramps treatment and prevention."

(b) *Indications.* The labeling of the product states, under the heading "Indications", the following: "For the treatment and/or prevention of nocturnal leg muscle cramps." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed above, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the prohibitions in section 502(a) of the act against misbranding by the use of false or misleading labeling and the prohibition in section 301(d) of the act against the introduction into interstate commerce of unapproved new drugs.

(c) *Warnings.* For products containing quinine: "Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. Do not take if pregnant, sensitive to quinine, or under 12 years of age."

(d) *Directions.* [Reserved]

Frank E. Young,

Commissioner of Food and Drugs.

Dated: September 10, 1985.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 85-24747 Filed 11-7-85; 8:45 am]

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21 CFR Part 357

[Docket No. 79N-0379]

Exocrine Pancreatic Insufficiency 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) exocrine pancreatic insufficiency drug products (drug products used to treat pancreatic enzyme deficiency) 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 January 7, 1986. New data by November 10, 1986. Comments on the new data by January 8, 1987. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination March 10, 1986.

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 Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 21, 1979 (44 FR 75666) 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 exocrine pancreatic insufficiency drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, 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 April 21, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by May 21, 1980.

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, two manufacturers, one foundation, and two physicians submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on December 21, 1979 (44 FR 75666), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations 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 E of Part 357, FDA states for the first time its position on the establishment of a monograph for OTC exocrine pancreatic insufficiency 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 exocrine pancreatic insufficiency drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC exocrine pancreatic insufficiency 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