DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 343

[Docket No. 77N-0094]

Quinine for the Treatment of Nocturnal Leg Muscle Cramps for Over-the-Counter Human Use; Establishment of a Monograph; and Reopening of Administrative Record

AGENCY: Food and Drug Administration.

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

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would establish conditions under which quinine used over-the-counter (OTC) for the treatment of nocturnal leg muscle cramps is generally recognized as safe and effective and not misbranded. This notice relates to the development of a monograph for internal analgesic drug products in general, which is part of the ongoing review of OTC drug products conducted by FDA. This notice also reopens the administrative record for OTC internal analgesic, antipyretic, and antirheumatic drug products to allow for consideration of a statement on quinine used OTC for the treatment of nocturnal leg muscle cramps that has been received from the Advisory Review Panel on OTC Miscellaneous Internal Drug Products.

DATES: Written comments by December 30, 1982 and reply comments by January 31, 1983.

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

FOR FURTHER INFORMATION CONTACT: Willian E. Gilbertson, National Center for Drugs and Biologics (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on August 23, 1981, a statement on quinine used OTC for the treatment of nocturnal leg muscle cramps from the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed rule containing (1) the monograph recommended by the Panel, which establishes conditions under which this OTC drug product is generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drug not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

Because a review of quinine was previously included in the advance notice of proposed rulemaking for internal analgesic, antipyretic, and antirheumatic drug products at 42 FR 35434, FDA has determined that the Miscellaneous Internal Panel's recommendations regarding the OTC use of quinine for the treatment of nocturnal leg muscle cramps should be included as part of the proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products, which has been ongoing for some time.

In the **Federal Register** of July 8, 1977 (42 FR 35346), FDA issued an advance notice of proposed rulemaking to establish a monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products. FDA advises that it is reopening the administrative record for OTC internal analgesic, antipyretic, and antirheumatic drug products in order to allow for the consideration of the Miscellaneous Internal Panel's statement on quinine used OTC for the treatment of nocturnal leg muscle cramps. Comments received on this advance notice of proposed rulemaking will be addressed in a future issue of the **Federal Register**. Because the Panel did not recommend any Category I conditions for quinine used OTC for the treatment of nocturnal leg muscle cramps, no new sections to amend Part 343 are being included in this advance notice of Proposed rulemaking.

The unaltered statement of the Panel is issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The statement has been prepared independently of FDA, and the agency has not yet fully evaluated the Panel's recommendations. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's statement. this statement represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will amend the rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products to include quinine used OTC for the treatment of nocturnal leg muscle cramps. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

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

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC quinine products used for the treatment of nocturnal leg muscle cramps. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC quinine products used for the treatment of nocturnal leg muscle cramps should be accompanied by appropriate documentation. Comments will not be accepted at this time on any portion of the OTC internal analgesic, antipyretic, and antirheumatic rulemaking other than that relating to OTC quinine products used for the treatment of nocturnal leg muscle cramps.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information considered by the Panel concerning OTC quinine products used for the treatment of nocturnal leg muscle cramps. All this information will be put on public display in the Dockets Management Branch,

Food and Drug Administration, after November 1, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureaus of Drugs and Biologics (HFD–510) (address above).

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

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

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

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

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

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

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

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

The Panel was first convened on January 13, 1975 in an organizational meeting. The only meeting at which quinine used OTC for the treatment of nocturnal leg muscle cramps was discussed was held on August 23, 1981.

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

No individuals requested to appear before the Panel to discuss quinine used OTC for the treatment of nocturnal leg muscle cramps, nor was any individual requested to appear by the Panel.

The Panel has thoroughly reviewed the one submission received and the material prepared by FDA in arriving at its conclusions and recommendations for quinine used OTC for the treatment of nocturnal leg muscle cramps.

In accorance with the OTC drug review regulations in § 330.10, the Panel reviewed quinine for the OTC treatment of nocturnal leg muscle cramps with respect to the following three categories:

Category I. Conditions under which quinine used OTC for the treatment of nocturnal leg muscle cramps is generally recognized as safe and effective and is not misbranded.

Category II. Conditions under which quinine used OTC for the treatment of nocturnal leg muscle cramps is not generally recognized as safe and effective or is misbranded.

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

The Panel considered quinine only for OTC use for the treatment of nocturnal leg muscle cramps and classified it in Category III.

Pursuant to the notices published in the Federal Register of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) requesting submission of data and information on OTC miscellaneous internal drug products, the Purex Corporation, Carson, CA 90745, was the only firm to make a submission for quinine (quinine sulfate) for OTC use for the treatment of nocturnal leg muscle cramps.

The "OTC Volumes" cited in this document include the one submission made by the Purex Corporation in response to the call-for-data notices published in the Federal Register of November 16, 1973 (39 FR 31696) and August 27, 1975 (40 FR 38179) and the material prepared by the agency. All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on display after November 1, 1982, in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

Statement by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products on Quinine Used OTC for the Treatment of Nocturnal Leg Muscle Cramps

The Panel reviewed quinine used OTC for the treatment of nocturnal leg muscle cramps and offers the following general information:

Nocturnal leg muscle cramps occur in middle life and beyond. They are of unknown etiology but have been 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 change due to lactic acid accumulation. The attacks do not have a regular pattern with respect to time or severity. They appear to be more common after a day of exercise or heavy physical activity. However, they sometimes occur during sedentary periods. The attacks tend to occur regularly for a few nights or weeks and then may clear spontaneously. Analgesics (including quinine), antihistamines, and mechanical means of obtaining relief, such as elevating the foot of the bed, have been used for this condition for many years with variable results.

Extracts of the bark of the cinchona tree have been used successfully for the treatment of malaria since the early 1700's. The principal extract component, quinine, also has been found to be an effective antipyretic and analgesic, and it has been used for arthralgia and neuralgia in oral doses of 300 to 600 milligrams (mg). Its side effects include severe tinnitus and partial damage to the eighth cranial nerve if prolonged toxic doses are employed. It sometimes leads to gastrointestinal symptoms. Among its more serious side effects are the induction of abortion and occasional cases of autoimmune thrombocytopenic purpura and hemolytic anemia. In the latter instances the drug appears to act as a hapten, linking a specific blood cell to an autoantibody.

Quinine was reviewed as an analgesic by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products and the Panel concluded that it has demonstrable analgesic, antipyretic, and muscle relaxant actions, but its numerous toxic side effects represent an unfavorable benefit-to-risk ratio (42 FR 35434). This Panel received a single industry submission containing 10 literature references regarding the use of quinine for the relief of nocturnal leg cramps and other muscular disorders (Ref. 1). The Panel also reviewed additional material prepared by FDA on this subject (Ref. 2).

The industry submission proposed a 3-grain (200 mg) OTC tablet of quinine sulfate with directions for use as an antispasmodic for the prevention and symptomatic relief of nocturnal leg muscle cramps. The proposed directions specify one or two tablets at bedtime and advise the consumer to consult a physician if the symptoms persist more than 1 week. The proposed labeling also includes a warning to discontinue use if tinnitus, deafness, diarrhea, skin rash, nausea, or visual disturbance occur, and warnings against use during pregnancy, by individuals sensitive to quinine, or by children under 12 years of age. No clinical trials were included in the submission.

Despite these occasional side effects, quinine appears to be reasonably safe over prolonged periods of time in generally recommended doses of 200 to 325 mg daily. However, no controlled trials have demonstrated whether this dose range will effectively control nocturnal leg muscle cramps.

Despite frequent prescribing of quinine by physicians for treatment of nocturnal leg muscle cramps, no controlled trials are available to establish its effectiveness beyond a reasonable doubt. The Panel, therefore, concludes that quinine should be placed in category III because of insufficient data to show that it is safe and effective for treatment of nocturnal leg muscle cramps.

References

(1) OTC Volume 170050.

(2) OTC Volume 170234.

List of Subjects in 21 CFR Part 343

Internal antipyretic and antirheumatic drug products.

Interested persons may, on or before December 30, 1982, submit to the dockets Management branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before January 31, 1983. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Arthur Hull Hayes, Jr.,

Commissioner of food and Drugs.

Dated: September 22, 1982.

Richard S. Schweiker,

Secretary of Health and Human services.

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