DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR part 310

[Docket No. 77N–0094]

RIN 0905–AA06

Drug Products for the Treatment and/or Prevention of Nocturnal Leg Muscle Cramps for Over-The-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any over-the-counter (OTC) drug product for the treatment and/or prevention of nocturnal leg muscle cramps is not generally recognized as safe and effective and is misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on drug products for the treatment and/or prevention of nocturnal leg muscle cramps that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: February 22, 1995.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 1, 1982 (47 FR 43562), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to reopen the rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products to consider the OTC use of quinine 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 display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps was published in the **Federal Register** of November 8, 1985 (50 FR 46588). Interested persons were invited to file by January 7, 1986, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by March 10, 1986. New data could have been submitted until November 10, 1986, and comments on the new data could have been submitted until January 8, 1987. Final agency action occurs with the publication of this final rule on OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps.

In the preamble to the agency's proposed rule on OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps (50 FR 46588), the agency stated that no active ingredient in drug products used OTC for the treatment and/or prevention of nocturnal leg muscle cramps had been found to be generally recognized as safe and effective and not misbranded, but that Category I labeling was being proposed in that document in the event that data were submitted that resulted in the upgrading of any ingredients to monograph status in the final rule. In this final rule, no ingredient in OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps has been determined to be generally recognized as safe and effective. Therefore, proposed part 343 (21 CFR 343), subpart E for OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps is not being issued as a final regulation.

This final rule declares OTC drug products containing active ingredients for the treatment and/or prevention of nocturnal leg muscle cramps to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)), for which an application or abbreviated application (hereinafter called application) approved under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 is required for marketing. In the absence of an approved application, products containing drugs for this use also would be misbranded under section 502 of the act (21 U.S.C. 352). In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application.

This final rule amends 21 CFR part 310 to include drug products containing active ingredients for the treatment and/or prevention of nocturnal leg muscle cramps by adding new § 310.546 (21 CFR 310.546) to subpart E. The inclusion of OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps in part 310 is consistent with FDA's established policy for regulations in which there are no monograph conditions. (See, e.g., §§ 310.510, 310.519, 310.525, 310.526, 310.532, 310.533, and 310.534.) If, in the future, any ingredient is determined to be generally recognized as safe and effective for use in an OTC drug product for the treatment and/or prevention of nocturnal leg muscle cramps, the agency will promulgate an appropriate regulation at that time.

The OTC drug procedural regulations (21 CFR 330.10) 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 does not 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. In place of Category I, the term "monograph conditions" is used; in place of Categories II or III, the term "nonmonograph conditions" is used.

In the proposed rule for OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps (50 FR 46588), the agency advised that it would provide a period of 12 months after the date of publication of the final monograph in the **Federal Register** for relabeling and reformulation of drug products for the treatment and/or prevention of nocturnal leg muscle cramps to be in compliance with the monograph. Although several manufacturers submitted data and information in response to the proposed rule, the data and information were not sufficient to

support monograph conditions, and no monograph is being established at this time. Therefore, drug products for the treatment and/or prevention of nocturnal leg muscle cramps that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). The agency also stated that 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. As stated below, a safety problem has been identified for OTC drug products containing quinine sulfate for the treatment and/or prevention of nocturnal leg muscle cramps. Therefore, the agency has determined that initial introduction or initial delivery for introduction into interstate commerce of quinine sulfate for the treatment and/or prevention of nocturnal leg muscle cramps must cease effective February 22, 1995. After that date, no OTC drug products that are subject to this final rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application. The agency is unaware of any quinine sulfate drug product for this indication that is the subject of an approved application. Any such drug product in interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action.

In response to the proposed rule on OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps, three drug manufacturers and a nutrition information service submitted comments. One comment included a request for an oral hearing before the Commissioner of Food and Drugs.

After the administrative record closed, a citizen petition was submitted on December 1, 1988. In response to this petition, nine additional comments were submitted. The Commissioner found that the petition and subsequent comments raised safety and effectiveness issues that warranted consideration before the final rule issued. Accordingly, under § 330.10(a)(7)(v), the Commissioner determined that good cause was shown to warrant consideration of the petition and the additional comments before the final rule issued. Copies of the comments received and the petition are on public display in the Dockets Management Branch (address above). Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments

1. One comment disagreed with the agency's determination that adequate clinical data did not exist to support the Category I status of quinine for both safety and effectiveness for OTC use in the treatment and/or prevention of nocturnal leg muscle cramps (50 FR 46588 at 46590). The comment expressed the belief that sufficient evidence already exists for this use of quinine. In support of its position, the comment referred to information it had submitted on December 27, 1982, in response to the advance notice of proposed rulemaking for this class of drug products.

The agency discussed this information in the tentative final monograph (50 FR 46588 at 46589) and concluded that it did not provide sufficient evidence to establish that quinine is generally recognized as safe and effective for OTC use for the treatment and/or prevention of nocturnal leg muscle cramps. The agency identified the issues to be addressed in studies before quinine could be reclassified from Category III to Category I (50 FR 46590 and 46591). The comment did not provide any new information to address these issues. New data and information submitted by other interested persons are discussed in section I.B., comments 4 through 9 of this document.

B. Comments on the Safety of Nocturnal Leg Muscle Cramp Ingredients

2. Two comments contended that FDA accepted the safe OTC use of quinine sulfate for nocturnal leg cramps when it published, and did not dissent from, the Miscellaneous Internal Panel's conclusions and recommendations that "* * * quinine appears to be reasonably safe over prolonged periods of time in generally recommended doses of 200 to 325 mg daily" (47 FR 43562 at 43564).

Contrary to the comments' contention, the record makes it clear that neither the agency nor the advisory panels accepted the safety of OTC use of quinine for nocturnal leg muscle cramps. The July 8, 1977 report of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (42 FR 35346 at 35434) summarized the safety of quinine and stated "Although quinine has demonstrated analgesic, antipyretic and muscle relaxant actions, its numerous toxic effects give it an unfavorable benefit to risk ratio for these purposes." The Panel concluded that "Until controlled studies show that a 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." While the Miscellaneous Internal Panel's report stated that quinine "* * * appears to be reasonably safe * * *" (47 FR 43564), the Panel did not conclude that quinine was safe in doses used for the treatment of nocturnal leg muscle cramps. The Panel's recommendation that quinine should be placed in Category III for use in the treatment of nocturnal leg muscle cramps cited the need for more information about both safety and efficacy in its concluding statement (47 FR 43564).

In the tentative final monograph for OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps, the agency concurred with: (1) The Miscellaneous Internal Panel's classification of quinine sulfate as Category III, and (2) the Internal Analgesic Panel's conclusion that the drug should not be generally recognized as safe and effective (Category II) for this use until its safety and efficacy are demonstrated in controlled clinical trials (50 FR 46588 at 46592). It is clear, therefore, that neither the agency nor its advisory panels have determined that quinine may be safely used for this indication.

3. Three comments stated that quinine has been safely used by millions of consumers for a variety of conditions, including leg cramps, for more than 50 years, and that this long history of usage demonstrates the safety of quinine.

General reference to the history of use of quinine cannot be accepted as evidence of its safety. Historically, there has been no clear location for the organized collection and analysis of adverse drug experience reports on OTC drug products. Adverse events associated with OTC drug products are still vastly underreported for a number of reasons. First, for most OTC drugs there is no requirement that manufacturers and distributors report adverse events to the FDA, even those that are serious or life threatening. Second, physicians, who are the principal reporters to the United States spontaneous reporting system, may not become aware of reactions to OTC drugs. Patients often do not mention OTC drugs in giving medication histories. If they do, it is often not clear to physicians to which manufacturer the adverse event should be reported.

4. Two comments in support of keeping quinine available OTC discussed the adverse event reports on

file for quinine in FDA's spontaneous reporting system. Lavy (Ref. 1) stated that there were 52 reports suggestive of hypersensitivity reactions, including 8 deaths, among the reports on file from 1969 to 1988. Lavy concentrated on reports of thrombocytopenia (a decrease in the number of blood platelets) and stated that bleeding secondary to thrombocytopenia may have been related to four of the eight deaths reported in this 20-year period. The comment stated that only one case provided sufficient information to fulfill all diagnostic criteria for drug-induced immunologic thrombocytopenia (consistent clinical history, exclusion of other causes, positive in vitro test and, theoretically, the demonstration of recurrent thrombocytopenia after rechallenge). Lavy pointed out that adverse event reports should reflect a significant prevalence of severe quinine-associated purpura (if occurring) because this reaction is readily identifiable by the patient, physician, and hospital. Using industry quinine sales figures and data from the FDA spontaneous reporting system, Lavy concluded that the number of reported quinine-related hypersensitivity reactions is quite low, even if greatly underreported.

Aster (Ref. 2) reviewed adverse drug reactions reported to FDA from 1969 through December 1989 and estimated that approximately 1,000 reactions in 313 individuals were reported for quinine. Aster's estimate was not limited to hypersensitivity reactions, but included all reported reactions (including multiple reactions per individual). Aster did not report the specific search criteria used to obtain the adverse drug reaction reports other than to state that the "FDA materials provide a cumulative listing of all adverse drug reactions (ADR) reported in connection with quinine since 1969." After eliminating reactions considered highly unlikely to bear a cause-and-effect relationship to quinine, Aster identified 254 reactions that he considered "significant." There were 83 hematologic reactions and 46 additional reactions possibly associated with hypersensitivity. Of 63 possible cases of thrombocytopenia, 36 included information verifying low platelet levels. Aster identified 50 fatalities (15 from hematologic complications, 3 from hypersensitivity, and 32 from other causes). Overall, Aster classified 51 percent of the adverse reactions as idiosyncratic and eight percent as the result of overdose. The remaining 41 percent were of indeterminate etiology and consisted of liver and kidney dysfunction, neurologic disorders, and various hemorrhagic manifestations. Of the reports in which inadequate information was provided for full evaluation, Aster noted the possibility that some of the six cerebrovascular accidents reported may have been associated with thrombocytopenia induced by quinine. Aster concluded that: (1) No information is available that would enable the identification of people at risk to sensitivity reactions to quinine; (2) the rarity of sensitivity reactions and the rapidity with which they occur make early detection of such reactions impossible and, (3) the dramatic symptomatology of such reactions, when they occur, leads people to seek prompt medical attention. Aster concluded, therefore, that serious adverse reactions would neither be prevented nor reduced in incidence by restricting quinine availability to prescription status.

The agency has reviewed the comments and the reports of adverse reactions to quinine products (listed in the agency's spontaneous reporting system under quinine, quinine sulfate, and three brand name products used for the treatment and/or prevention of nocturnal leg muscle cramps). From 1969 through June 1992, FDA received 157 adverse reaction reports in which quinine was listed as a suspect drug. There were 84 serious reactions: 23 deaths, 5 cases in which the person was disabled, and 56 hospitalizations not involving death or disablement. Of the 157 adverse reaction reports, 52 (approximately 33 percent) did not contain dosage and/or product name information, or reported daily dosages in excess of those typically recommended for the treatment and/or prevention of nocturnal leg muscle cramps. The remaining 105 reports listed the names of quinine products labeled for use in the treatment and/or prevention of nocturnal leg muscle cramps and/or daily dosages recommended by these products, and included 60 serious reactions involving 16 deaths, 4 cases of disablement, and 40 hospitalizations not involving death or disablement. More importantly, 56 of the 105 reports (approximately 53 percent) have been received since 1988, and there is an alarming trend of increasing numbers of reports per year since 1986 as the market for OTC drug products containing quinine for the treatment and/or prevention of nocturnal leg muscle cramps has expanded during that period. Approximately 70 percent (42 of 60) of all reports of serious reactions, 44 percent (7 of 16) of all reported deaths, and 78 percent (31 of 40) of all reported hospitalizations on file since 1969 were reported in the 4 1/2-year period between January 1988 and July 1992. There were 20 cases (19 percent of reports on file) reported in 1991 alone: 3 were disabling, 11 required hospitalization, and 1 resulted in death.

Nocturnal leg muscle cramps are a common condition in the elderly (Ref. 3). Presumably, with an increasing average age in the American population, the market for OTC drug products containing quinine for the treatment and/or prevention of nocturnal leg muscle cramps also increased during this period. The number of adverse reaction reports for people 60 years of age or older, involving quinine products and/or quinine dosages used in the treatment and/or prevention of nocturnal leg muscle cramps, has increased by a factor of five (from 2 to 10) during the period between January 1988 and December 1991.

The agency conducted a detailed review of 110 reports on file from 1969 through 1990; 69 (approximately 63 percent) of these reports involved hypersensitivity reactions ranging from rash and fever to angioneurotic edema, thrombocytopenia, or generalized anaphylaxis. Of these 69 reports, 57 (approximately 83 percent) involved quinine products and/or quinine dosages used in the treatment and/or prevention of nocturnal leg muscle cramps. An attempt was made to identify only those reports in which the relationship between quinine and the reported event was strong and reasonably unrelated to other factors. Factors considered included the temporal relationship between quinine administration and the event, absence of concomitant medications (or abatement of the adverse event after quinine was discontinued), absence of confounding medical conditions, a positive test for quinine mediated antibodies, or history of a similar reaction associated with previous quinine exposure. Using these factors, of the 110 reports 26 were identified in which it can be reasonably concluded that quinine was the causative agent. These included 6 moderately severe to severe skin reactions, 2 of which were erythema multiforme-like reactions; 13 hematologic events, with 2 resulting in death; 2 cases of hepatitis or elevated liver enzymes; 2 renal reactions, one leading to renal failure requiring dialysis, the other leading to death; 2 cases of a hypersensitivity syndrome with symptoms that included chills, nausea, vomiting, and diarrhea; and 1 report of anaphylaxis complicated by seizures and hypoxia following a single

dose of quinine. None of these cases reported an overdose of the drug, and 21 of the 26 reports (approximately 81 percent) involved quinine products and/or quinine dosages used in the treatment and/or prevention of nocturnal leg muscle cramps.

Even using strict criteria to identify cases in which a causal relationship of quinine to adverse event is likely, FDA finds that quinine is associated with serious adverse events. There is no compelling reason to restrict evaluation of the safety of quinine to reported cases of thrombocytopenia, as Lavy did. The other adverse effects are also serious and must be considered in weighing the benefits and risks of products containing quinine. The agency agrees with Aster that there is currently no way in advance to identify people at risk of hypersensitivity reactions and, therefore, no effective way to warn against use by such individuals (see section I.B., comment 10). It does not agree, however, that physician monitoring might not minimize serious reactions. Thrombocytopenia, for example, can lead to bruising and other evidence of cutaneous bleeding. A physician could warn patients to report such signs and stop the drug, perhaps preventing a significant hemorrhagic event.

eferences

(1) Lavy, N. W., "Overview: Efficacy and Safety of Quinine Sulfate in the Treatment and/or Prevention of Nocturnal Leg Cramps", unpublished report in SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(2) Aster, R. H., "Q-Vel: Could Serious Adverse Reactions be Prevented by Having the Drug Available Only on Prescription," unpublished report in Comment No. C176, Docket No. 77N–0094, Dockets Management Branch.

(3) Jones, K., and C. M. Castleden, "A Double-Blind Comparison of Quinine Sulphate and Placebo in Muscle Cramps," *Age and Ageing*, 12(2):155–158, 1983.

5. Several comments contended that the true incidence of quinine-induced thrombocytopenia is many times smaller than that suggested by estimates based on events reported from exposure to quinine-containing drug products alone. The comments contended that such estimates fail to account for the much larger exposure to quinine through beverages. Lavy estimated exposure to quinine in beverages to be about 10 times greater than exposure to quinine in drug products (Ref. 1). An agency search of the medical literature identified only 10 cases of persensitivity reactions attributed to inine in beverages (Refs. 2 through 9). One of these reactions occurred following ingestion of a drug product containing quinine by a person presumed to have been previously sensitized by exposure to beverages (Ref. 5). None of these events was fatal.

The agency finds that the available information supports the safe use of quinine in beverages such as tonic water and bitter lemon. Given the level of consumption of quinine beverages, there is a scarcity of reported hypersensitivity reactions, even assuming that reactions to food products are vastly underreported.

Despite these safety data from beverage use, the agency does not consider pooling total consumption and adverse reaction data on quinine from food and drug products to be a legitimate basis to judge the safety of drug products containing quinine. First, there are differences in the quinine exposure levels because quinine is present in much greater amounts in drug products. Second, there is a great disparity in the incidence of reports of hypersensitivity reactions to beverage and drug products.

The agency considers the appropriate basis on which to estimate the incidence of hypersensitivity to quinine-containing drug products in leg cramp sufferers is to evaluate reports of reactions in the people who take such products at the dose, frequency, and for the duration recommended in product labeling. Adjusting the reported incidence of reactions to drug products by pooling data on beverages erroneously exaggerates the risk of reaction to quinine in beverages, vastly underestimates the risk of reaction to quinine-containing drug products, and contradicts the raw data on these products. Both the number and the severity of reported hypersensitivity reactions to drug products containing quinine raise safety concerns about these products (see section I.B., comment 4).

The agency considers the virtual absence of reports of reactions to beverages containing small amounts of quinine (i.e., not more than 83 parts per million) as support for the safety of such use. Thus, the use of quinine salts in food in accord with conditions described in 21 CFR 172.575 is not affected by this final rule on drug products for the treatment and/or prevention of nocturnal leg muscle cramps.

References

(1) Lavy, N. W., "Overview: Efficacy and Safety of Quinine Sulfate in the Treatment and/or Prevention of Nocturnal leg Cramps", unpublished report in SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(2) Belkin, G. A., "Cocktail Purpura. An Unusual Case of Quinine Sensitivity," *Annals of Internal Medicine*, 66(3):583–586, 1967.

(3) Korbitz, B. C., and E. Eisner, "Cocktail Purpura. Quinine-dependent Thrombocytopenia," *Rocky Mountain Medical Journal*, 70(10):38–41, 1973.

(4) Siroty, R. R., "Purpura on the Rocks - With a Twist," *Journal of the American Medical Association*, 235(23):2521–2522, 1976.

(5) Elliott, H. L., and D. B. Trash, "Intravenous Coagulation Induced by Quinine," *Scottish Medical Journal*, 24(3):244–245, 1979.

(6) Murray, J. A. et al., "Bitter Lemon Purpura," *British Medical Journal*, 2(6204):1551–1552, 1979.

(7) Calnan, C. D., and G. A. Caron, "Quinine Sensitivity," *British Medical Journal*, 2:1750–1752, 1961.

(8) Cundall, R. D., "Idiosyncrasy to Quinine in Bitter Lemon," *British Medical Journal*, 1:1638, 1964.

(9) Callaway, J. L., and W. E. Tate, "Toxic Epidermal Necrolysis Caused by 'Gin and Tonic'," *Archives of Dermatology*, 109:909, 1974.

6. Four comments submitted five reports (Refs. 1 through 5) of controlled clinical studies of quinine alone or in combination with vitamin E. The agency has reviewed these studies for evidence pertaining to the safety of quinine used to treat and/or prevent nocturnal leg muscle cramps.

The first study (Ref. 1) was a 10-week, crossover study of 69 subjects randomized to either 260 milligrams (mg) quinine sulfate or placebo. Subjects were 26 to 77 years of age, with a mean age of 51. Five adverse reactions to quinine (a 7 percent incidence) were reported. One subject was unable to tolerate the quinine because tinnitus (ringing in the ears) in both ears occurred while taking the study drug. Two additional subjects experienced tinnitus while taking quinine, but continued the medication and completed the study (although the protocol called for discontinuation of the study drug if ringing in the ears occurred). One additional subject experienced disorientation and another reported dizziness while taking quinine. No adverse events to placebo were reported.

The second study (Ref. 2) was a 10-week, double-blind, randomized, crossover study of 62 subjects receiving daily doses of either 325 mg quinine sulfate or placebo. Subjects were 21 to 76 years of age, with a mean age of 47. Three subjects on quinine and three subjects on placebo reported adverse events. The quinine reactions included tinnitus (which quickly resolved when the drug was discontinued), blurred vision, and headache, which occurred on 3 days during drug administration.

One of the subjects dropped out of the study because of dizziness and drowsiness. Another subject discontinued quinine for the last two days of the treatment period because of tinnitus. In the placebo group, one subject reported chest pains and heartburn; another subject experienced fever and nausea; and one subject reported constipation and dropped out of the study. An additional eight subjects dropped out of the study for reasons described in the report as not related to the drug products, but no details were provided.

The third study (Ref. 3) was a 5-week randomized, crossover study involving 205 subjects randomly assigned to quinine sulfate 260 mg/day, vitamin E 1,600 international units (I.U.)/day, a combination of quinine and vitamin E in the above doses, or placebo. Subjects were 18 to 80 years of age, with a mean age of 44. Twenty-seven adverse reactions were reported: 9 (4.4 percent) in subjects receiving the combination of quinine and vitamin E, 8 (3.9 percent) in subjects on quinine alone, 6 (2.9 percent) in subjects on vitamin E alone, and 4 (2 percent) in subjects receiving placebo. There was an almost twofold difference in overall adverse experiences when subjects were taking either of the test drugs containing quinine. Adverse events in subjects receiving quinine alone included stomach cramps, headache, nausea, diarrhea, swollen hands, and slight muscle twitching. Adverse events in subjects receiving the quinine and vitamin E combination included upset stomach, headache, diarrhea, tiredness, constipation, and pain in the legs. Adverse effects in subjects receiving vitamin E included abdominal cramps, vomiting, loose bowels, headache, and intensified menstrual cramps. Adverse events in the placebo group included nausea, stomach cramps, and tingly fingers. Gastrointestinal disturbances were reported by twice as many subjects when they were taking quinine alone or in combination than when assigned to vitamin E alone or placebo. Most of the adverse experiences in this study, irrespective of treatment group, were described by investigators as not related or probably not related to the study medication. Reported events, however, were consistent with those classically associated with quinine toxicity, which includes gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), vasodilation, sweating, headache, tinnitus, vertigo, and visual disturbances (Ref. 6).

The fourth study (Ref. 4) was a 5-week, crossover study involving 24 subjects 51 to 64 years of age (with a mean age of 57). All subjects received placebo in weeks 1, 3, and 5; half of the subjects were assigned to quinine sulfate (260 mg per (/) day) and half to the combination of quinine sulfate and vitamin E during week 2. In week 4, those subjects on the combination in week 2 were assigned to quinine alone and vice versa. Nausea was reported by 3 subjects (12.5 percent) who received quinine sulfate during week 2. No details of the reported reactions were provided. No other adverse events were reported.

The fifth and largest study was a multicenter, block-randomized, parallel design involving 559 subjects 18 to 84 years of age (Ref. 5). A 1-week, single-blind, placebo phase was followed by a 2-week, double-blind, randomized, treatment phase. Subjects who had at least one leg cramp per night for a minimum of 3 nights during the single-blind placebo week and met other selection criteria were randomized to one of four double-blind treatment groups: Quinine sulfate 259.2 mg (subject ages ranged from 19 to 79 years with a mean age of 46), vitamin E, 1,600 I.U. (subject ages ranged from 18 to 76 years with a mean age of 42), a combination of quinine and vitamin E in the above doses (subject ages ranged from 18 to 83 years with a mean age of 46), and placebo (subject ages ranged from 21 to 84 years with a mean age of 45). Besides meeting the criteria for frequency of nocturnal leg cramps, subjects admitted to the study were generally in good health, were predominantly female, and had a mean age of less than 50 years. The study report stated that no unexpected or idiosyncratic adverse events were seen "* * * among patients taking an effective course of therapy * * * nor was there a higher than usual incidence of recognized adverse drug reactions associated with ingestion of quinine."

One subject randomized to the combination product was reported to have experienced a reaction consisting of fever, headache, nausea, vomiting, and diffuse muscle pain after 5 days. The episode was sufficiently severe to warrant medical intervention in which the test drug (quinine/vitamin E) was stopped and the subject was treated with analgesic/antipyretic therapy and a prescription antiemetic. Symptoms subsided over 3 days. When the study medication was resumed, the subject again experienced nausea, vomiting, abdominal pain, severe headache, diffuse myalgia with severe pain in the legs, and fever. The subject required hospitalization. Therefore, the study drug was stopped. When the subject was discharged 5 days later, the physician advised her to consider herself sensitive to quinine. Given the temporal relationship between the onset of symptoms and administration of the study drug as well as the positive rechallenge, this case appears to be a well-documented hypersensitivity reaction.

In addition, another subject on quinine experienced itching, nausea, and vomiting and discontinued the drug. Two other subjects experienced moderately severe wheezing on the 8th and 12th days of quinine treatment, but neither subject discontinued the medication.

The overall incidence of adverse events reported in the fifth study (Ref. 5) was high and approximately equal in all groups (quinine sulfate, 43.3 percent; vitamin E, 37.2 percent; the combination of quinine sulfate and vitamin E, 39.3 percent; and placebo, 41.3 percent). Headache accounted for the greatest number of reported events in each group (quinine sulfate, 19.1 percent; vitamin E, 16.8 percent; combination of quinine sulfate and vitamin E, 19.1 percent; and placebo, 21 percent), but did not appear to be treatment related. Differences in the side- effect profile of the treatments emerge when only events with an incidence of 1 percent or more are considered, and both headache and events considered by the investigators as not related to the study drug are excluded. This analysis shows an adverse event rate of 12.8 percent with quinine sulfate (nausea, vomiting, diarrhea, dizziness, tinnitus, pruritus, and urticaria); 3.6 percent with vitamin E (nausea and myalgia); and 12 percent with the combination product (nausea, vomiting, diarrhea, tinnitus, and fever). None of the events reported by subjects on placebo, which the investigators considered potentially related to the study drug, had an incidence of 1 percent or more. Similarly, events reported to be severe or moderately severe (excluding headache and events with an incidence less than 1 percent) were more frequent in subjects taking quinine sulfate (6.4 percent) or the combination product (7.1 percent) than vitamin E alone (3.6 percent) or placebo (2.2 percent).

The potential for symptoms of quinine toxicity from the low doses generally recommended for the OTC treatment and/or prevention of nocturnal leg muscle cramps has been confirmed in several other studies (Refs. 7, 8, and 9). A recent study of the relationship between plasma quinine levels and hearing impairment (Ref. 7) found that quinine, even at low doses, produced auditory changes. In this

study, single oral doses of quinine of 5 milligrams/kilogram (mg/kg), 10 mg/kg, and 15 mg/kg were administered to six healthy females 24 to 39 years of age. The study did not specify subject weights. If subject weights of 50 to 60 kg were assumed, these doses would correspond to single quinine doses of 250 to 300 mg, 500 to 600 mg, and 750 to 900 mg, respectively. Even at the lowest dose (which is equivalent to the dose used in OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps), a drug effect on hearing impairment was detected in half of the subjects. When plasma concentrations exceeded 15 micromoles/liter (mmol/L), subjective hearing loss or tinnitus was observed in all subjects. No symptoms were detectable at levels below 5 mmol/L. The shift in hearing threshold was equal over the frequency range studied. The effect over time was consistent with the level of the dose given. The investigators concluded that a consistent effect-concentration relationship for hearing impairment caused by quinine can be defined by audiometry.

Zajtchuk (Ref. 8) compared the effect on vestibular and auditory function of 0, 52.5 mg, and 105 mg quinine administered in the form of commercial tonic water (containing 52.5 mg of quinine per 822 milliliter (mL) bottle) in 17 active duty military personnel. The study was initiated following findings of low levels of quinine in post-mortem tissues from military pilot fatalities. Tonic water was administered over a 3-hour period daily for 14 days. While control subjects and subjects given the low dose had normal function throughout the test, three of the four subjects given 105 mg/day developed transient vestibular abnormalities (manifested by rapid, involuntary, rhythmic movements of the eyeball associated with certain positions of the head or body) on positional testing.

Worden, Shephard, and Frape (Ref. 9) conducted two similar studies. In one study, 6 men and 14 women (18 to 39 years of age) were given 100 mg quinine hydrochloride daily in the form of tonic water for 14 days. In the second study, 4 men and 6 women (18 to 53 years of age) were divided into 2 groups. One group received 120 mg in a fortified tonic water, while the other drank a carbonated drink without quinine. No audiometric changes were found in any of the subjects in either study. However, 12 subjects (60 percent) in the first study complained of visual disturbances, 14 (70 percent) reported dizziness, and 14 (70 percent) experienced headache.

The potential for adverse effects from quinine may be greater in the elderly. A survey at one hospital (Ref. 10) of 201 inpatients 70 years of age or older found that 23 (11 percent) were taking quinine for cramps. Sixty percent were taking 300 mg nightly; 40 percent were taking twice that amount (600 mg nightly). Approximately one-third of these subjects had been taking the drug continuously and chronically for 2 years or more. The authors noted that the mean elimination half-life of quinine in elderly patients has been reported to be 19 hours compared with 8.5 hours in younger adults. The authors also stated that "Chronic therapy is likely to result in accumulation of quinine, putting elderly patients at greater risk of adverse effects. Possible adverse effects include symptoms of cinchonism (tinnitus, headache, nausea, rash, visual disturbance and temporary blindness), allergic reactions, and thrombocytopenia and haemolytic anaemia."

Wanwimolruk et al. (Ref. 11) found the elimination half-life of quinine to be 18.4 ± 5.7 hours in 8 healthy elderly subjects 65 to 78 years old compared with 10.5 ± 1.6 hours in 12 subjects 20 to 35 years old. Furthermore, a significantly greater amount of quinine was excreted unchanged in the elderly subjects, suggesting that quinine metabolism is reduced in elderly people. Overall, there was a 26-percent reduction in clearance of quinine in the older group. The authors concluded that accumulation of quinine may occur in elderly people, thus placing them at a greater risk of adverse events.

These studies indicate that serious safety concerns exist with regard to the OTC availability of quinine sulfate for the treatment and/or prevention of nocturnal leg muscle cramps. Subjects in all studies submitted were generally in good health, with a mean age of 44 to 57 years in the various groups. However, the adverse reactions reported in these studies suggest that quinine doses of 260 to 325 mg/day in healthy, middle-aged adults can produce symptoms of quinine toxicity, including auditory, visual, and gastrointestinal effects. Some studies (Refs. 7, 8, and 9) suggest that the vestibular, auditory, visual, and vascular effects of quinine can occur in healthy young adults at doses in and below the range commonly employed for the treatment and/or prevention of nocturnal leg muscle cramps. Altered pharmacokinetics with age also result in a longer half-life of quinine in older people. This longer half-life increases the frequency and severity of adverse effects in the elderly (Ref. 11), a group in which leg cramps are a common condition (Refs. 12 and 13). Therefore, the agency concludes that quinine is not safe for OTC use in the treatment and/or prevention of nocturnal leg muscle cramps.

References

(1) Bottner, M., "Clinical Trial of the Efficacy of Quinine Sulfate in the Treatment of Nocturnal Leg Muscle Cramps, Protocol 84–46," draft of an unpublished paper in Comment No. C123, Docket No. 77N–0094, Dockets Management Branch.

(2) Hays, R., and J. J. Goodman, "Clinical Trial of the Efficacy of Quinine Sulfate in the Treatment of Nocturnal Leg Muscle Cramps, Protocol 86–48," draft of an unpublished paper in Comment No. C126, Docket No. 77N–0094, Dockets Management Branch.

(3) Leo Winter Associates, Inc., "FinalMedical Report and Data Summary Analysis and Final Statistical Report on Double Blind Randomized Crossover Study of Q-VELR Versus Quinine Sulfate Versus Vitamin E Versus Placebo in the Treatment of Nocturnal Leg Muscle Cramps (No. 1285–5082)," draft of an unpublished paper in Comment No. SUP00031, Docket No. 77N–0094, Dockets Management Branch.

(4)Biodesign GmbH, "Clinical Evaluationof Q-VELR in Patients with Nocturnal Leg Muscle Cramps," draft of an unpublished paper in Comment No. SUP00031, Docket No. 77N–0094, Dockets Management Branch.

(5) Draft of an unpublished study entitled: "A Short-Term, Randomized, Double-Blind, Parallel Study of Q-Vel vs. Quinine Sulfate vs. Vitamin E vs. Placebo in the Prevention and Treatment of Nocturnal Leg Cramps," Comment No. SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(6) Bateman, D. N., and E. H. Dyson, "Quinine Toxicity," *Adverse Drug Reactions and Acute Poisoning Reviews*, 4:215–233, 1986

(7) Alvan, G. et al., "Hearing Impairment related to Plasma Quinine Concentration in Healthy Volunteers," *British Journal of Clinical Pharmacology*, 31:409–412, 1991.

(8) Zajtchuk, J. T. et al., "Electronystagmographic findings in Long-term Low-Dose Quinine Ingestion," Archives of Otolaryngology, 110:788–791, 1984.

(9) Worden, A. N., N. W. Shephard, and D. L. Frape, "Report on the Daily Consumption for 14 Days by Normal Subjects of Tonic Water Containing Quinine Hydrochloride," unpublished report, copy in OTC Vol. 03AFM, Docket No. 77N–0094, Dockets Management Branch.

(10) Blackbourn, J., and D. Bajrovic, "Quinine—Forever and Ever?," *Hospital Pharmacy*, 23:732, 735, 1988.

(11) Wanwimolruk, S. et al., "Pharmacokinetics of Quinine in Young and Elderly Subjects," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 85(6):714–717, 1991.

(12) Griggs, R. C., "Pain, Spasm, and Cramps of Muscle," in "Harrison's Principles of Internal Medicine," 12th ed., edited by J. D. Wilson et al., McGraw-Hill, Inc., New York, pp. 173–176, 1991.

(13) Jones, K., and C. M. Castleden, "A Double-Blind Comparison of Quinine

Sulphate and Placebo in Muscle Cramps," *Age and Ageing*, 12(2):155–158, 1983.

7. One comment (Ref. 1) requested a ban on the OTC marketing of any quinine sulfate products used in the treatment of nocturnal recumbency leg cramps. The comment based this request, in part, on adverse reactions reported to the FDA, including eight deaths it described as closely linked to quinine products. The comment contended that serious and fatal adverse reactions to quinine sulfate purchased OTC for this use continue to be reported. The comment mentioned that these reactions can occur in several ways: (1) In persons hypersensitive to quinine, (2) from the innate toxicity of quinine, or (3) as a result of interactions with other drugs, including digoxin, anticoagulants, and antiarrhythmics. The comment concluded that the risks associated with quinine used for leg cramps are unacceptable in light of its lack of efficacy for this use.

The agency agrees that quinine has the potential to elicit serious hypersensitivity reactions at doses employed in OTC drug products used for the treatment and/or prevention of nocturnal leg muscle cramps. The agency's spontaneous adverse reaction reporting system includes reasonably unconfounded reports of thrombocytopenia, hemolytic anemia, leukopenia, granulocytopenia, anaphylaxis, hypersensitivity syndrome, severe skin reactions (including urticaria, angioedema, and erythema multiforme), liver abnormalities, renal failure, and death (see section I.B., comment 4). Reports in the literature have identified quinine sulfate (in doses typically recommended for the treatment and/or prevention of nocturnal leg muscle cramps) as the causative agent in cases of photosensitive dermatitis (Refs. 2, 3, and 4), psychosis (Ref. 5), disseminated intravascular coagulation (Ref. 6), and hemolytic uremic syndrome (Ref. 7).

The agency agrees that quinine may interact with several other drugs (Refs. 8, 9, and 10), including those mentioned by the comment. This information could be included in the labeling of OTC quinine drug products. However, the agency does not need to make a decision on such drug interaction precautions because no ingredients for treating and/or preventing nocturnal leg muscle cramps are currently generally recognized as safe and effective for inclusion in an OTC drug monograph.

Cinchonism is a cluster of symptoms of varying severity that includes: Tinnitus, dizziness, disorientation, nausea, visual changes, auditory deficits, and (at higher doses) cardiac arrhythmias. Cinchonism is dose related. The clinical studies discussed in section I.B., comment 6 demonstrate that adverse events typical of quinine toxicity (in some cases, sufficiently severe to lead to discontinuation of the drug) occur in some people at doses generally recommended for the treatment and/or prevention of nocturnal leg muscle cramps. These studies indicate that some people who self-medicate with quinine to treat and/or prevent nocturnal leg muscle cramps at doses recommended in product labeling will experience these quinine-related adverse events. In addition, people taking quinine remain at risk of developing hypersensitivity to the drug and experiencing a serious, life threatening, or fatal reaction as a consequence. Even if quinine were effective for the treatment and/or prevention of nocturnal leg muscle cramps, this risk would require that a prescribing physician participate in the decision to use the drug, by assuring the diagnosis, considering alternative treatment options, evaluating concurrent medical problems and medications, and monitoring patient safety throughout treatment.

References

(1) Comment No. CP0006, Docket No. 77N–0094, Dockets Management Branch.

(2) Diffey, B. L. et al., "The Action Spectrum in Quinine Photosensitivity," *British Journal of Dermatology*, 118:679–685, 1988.

(3) Ferguson, J. et al., "Quinine Induced Photosensitivity: Clinical and Experimental Studies," *British Journal of Dermatology*, 117:631–40, 1987.

(4) Ljunggren, B., and P. Sjovall, "Systemic Quinine Photosensitivity," *Archives of Dermatology*, 122:909–911, 1986.

(5) Verghese, C., "Quinine Psychosis," *British Journal of Psychiatry*, 153:575–576, 1988.

(6) Spearing, R. L. et al., "Quinine-induced Disseminated Intravascular Coagulation," *Lancet*, 336:1535–1537, 1990.

(7) Gottschall, J. L. et al., "Quinine-Induced Immune Thrombocytopenia Associated with Hemolytic Uremic Syndrome: A New Clinical Entity," *Blood*, 77(2):306–310, 1991.

(8) Lavy, N. W., "Overview: Efficacy and Safety of Quinine Sulfate in the Treatment and/or Prevention of Nocturnal Leg Cramps", unpublished report in SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(9) USPDI, "Drug Information for the Health Care Professional," The U. S. Pharmacopeial Convention, Inc., Rockville, MD, vol. I, 14th ed., pp. 2379–2382, 1994.

(10) "Drug Evaluations Subscription," American Medical Association, Chicago, 1 (4):10–11, 1993.

8. Several comments downplayed the potential for hypersensitivity reactions to quinine, particularly quinine-induced immunologic thrombocytopenia, arguing that the continued OTC marketing of quinine for the treatment and/or prevention of nocturnal leg muscle cramps should not be stopped because of this potential consequence of its use. One comment (Ref. 1) submitted an expert review of drug-induced immunologic thrombocytopenia (DIITP), which stated that DIITP has been reported with over 100 drugs. Gold salts, heparin, and the cinchona alkaloids are the drugs most commonly associated with this condition. According to the expert review supplied by the comment, there is no known information about the dose of quinine required to induce DIITP sensitivity. DIITP occurs more frequently in people over 50 years old, possibly because of their greater exposure to drugs. It typically is characterized by a warm sensation, followed by a chill. Bleeding episodes, manifested by petechiae (pinpoint red spots, caused by intradermal or submucosal hemorrhage), purpura (purplish or brownish red discolorations visible through the skin, caused by hemorrhage into the tissues), hemorrhagic lesions of the oral mucosa, and occasionally hemorrhage of the gastrointestinal and urinary tracts may occur 6 to 12 hours after drug exposure in individuals who develop severe thrombocytopenia. Intracerebral hemorrhage and lethal intrapulmonary hemorrhage have been reported. Primary treatment is to discontinue the offending drug; bleeding usually subsides in 3 to 4 days. Other interventions (including glucocorticoid therapy and platelet transfusions) have not been shown to be beneficial.

Another comment argued that many drugs and additives to foods have the propensity to induce a variety of adverse reactions (Ref. 2). The comment stated that the prevalence of hypersensitivity to tartrazine (FD&C Yellow No. 5), a widely used dye, has been estimated to be about 1 in 10,000 in the general population. The comment pointed out that when tartrazine is used in OTC drug products, a labeling statement is required to inform consumers that the product contains tartrazine and that it may cause allergic-type reactions. The comment stated that this was "a clear precedent for the OTC drug use of products that have potential for rare hypersensitivity." The comment also described aspirin sensitivity as widespread and emphasized that a brief warning statement in labeling regarding use by people with asthma or aspirin sensitivity is deemed adequate to ensure safe OTC use.

The agency finds that the information in the first comment indicates that

quinine is one of the drugs most frequently associated with DIITP. While other drugs (e.g., gold salts and heparin) cause DIITP, quinine is the only drug highly associated with DIITP that is available OTC.

In March 1985, the Department of Health and Human Services established an Ad Hoc Advisory Committee on Hypersensitivity to Food Constituents (the Committee) to evaluate data relevant to allergic-type reactions in humans that were associated with food constituents. The Committee concluded that tartrazine may cause mild cases of urticaria (hives) in a small subset of the population (usually not requiring medical intervention). The Committee found no evidence that the color additive constitutes a hazard to the general public when used in food at its current levels. Prior to the Committee's findings, the agency had decided that labeling provides an adequate safeguard for those sensitive to tartrazine. (See the **Federal Register** of February 4, 1977 (42 FR 6835) and June 26, 1979 (44 FR 37212).) The agency requires the label of OTC and prescription drug products containing tartrazine intended for oral, nasal, rectal, or vaginal use to specifically declare the presence of tartrazine by listing the color additive using the names "FD&C Yellow No. 5" and "tartrazine." (See 21 CFR 74.1705(c)(2).) In addition to this label statement, prescription drug products for these uses must also include in their labeling the warning statement "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

There are a number of differences between hypersensitivity reactions to tartrazine and aspirin and hypersensitivity reactions to quinine. In a review of allergic reactions to drug additives (Ref. 3), Simon stated that reactions to tartrazine "if they occur at all, are indeed quite rare for the asthmatic population, even for the aspirin-sensitive subpopulation." Simon further reported that no positive responses were found after 125 double-blind, placebo-controlled tartrazine challenges (with at least 25 mg) in an aspirin-sensitive asthmatic population. Simon also reviewed adverse reactions to food additives (Ref. 4) and stated that, although tartrazine is the food additive most frequently associated with hypersensitivity reactions, "tartrazine has been confirmed to be at best only occasionally associated with flares of urticaria or asthma." Reports of these relatively mild tartrazine reactions, however, are in contrast to the serious reports for quinine, which involve life threatening and fatal hypersensitivity reactions.

Virchow et al. (Ref. 5) evaluated sensitivity to tartrazine in 156 Europeans with confirmed aspirin-induced asthma. Oral challenges were performed with increasing doses. All positive challenges were repeated under double-blind conditions. Only four subjects had positive reactions; none were serious. The incidence of tartrazine cross sensitivity to aspirin in this European population was 2.6 percent. In a similar study, Morales et al. (Ref. 6) conducted 141 challenge tests on 47 subjects with asthma associated with intolerance to analgesics, using tartrazine doses of 5, 25, 50, 100, and 200 mg and a placebo. Only five tests were positive in four of the subjects; repeat tests were negative in three of the four subjects. The authors stated that clinical instability in these subjects may be the cause of some respiratory symptoms attributed to tartrazine and that the practice of recommending color free diets should be reserved for cases in which a positive challenge test has been obtained on at least two occasions. This experience suggests that: (1) The incidence of tartrazine sensitivity may be overestimated, and (2) the nature of reactions to tartrazine is sufficiently benign to permit multiple rechallenges to confirm intolerance. Rechallenge of quinine-sensitive individuals, in contrast, is contraindicated because the reactions are serious, life threatening, or fatal, even under controlled conditions.

Safford (Ref. 7) was unable to detect antibody formation with tartrazine and its metabolites in animal studies, suggesting that an immunologic response is not involved in tartrazine sensitivity. Hypersensitivity to quinine, in contrast, is mediated by an immunologic mechanism.

Aspirin sensitivity is relatively common compared to quinine sensitivity, but is more manageable and usually predictable. In a review of aspirin sensitivity, Settipane (Ref. 8) described a number of factors that are predictive of subjects in whom intolerance is most likely to occur. Sensitivity is seen in 23 to 28 percent of people with chronic urticaria, 14 to 23 percent of people with nasal polyps, and up to 19 percent of people with asthma. These people are likely to be under a doctor's care and to have been told to avoid aspirin products. Genton et al. (Ref. 9) studied the usefulness of oral provocation tests to aspirin and food additives in 34 subjects with asthma or chronic urticaria, concluding that such investigations are safe and useful in managing such subjects by identifying intolerance to various compounds. As with tartrazine, hypersensitivity to aspirin does not appear to be mediated by an immunologic response (Ref. 8). In contrast to aspirin, there are no predictive factors for quinine hypersensitivity and, as noted above, in vivo rechallenge is contraindicated.

Sensitivity to aspirin (Ref. 8) and tartrazine (Ref. 10) is a problem that is manageable. The sensitivity generally results in urticarial or bronchospastic symptoms that are responsive to medical treatment. Anaphylaxis has been reported with aspirin, but is extremely rare given the extensive use of products containing aspirin. In a retrospective study of anaphylaxis occurring outside of hospitals in a hospital catchment area in Denmark over a 13-year period, the rate of anaphylaxis caused by aspirin was 0.48 cases per 100,000 inhabitants (Ref. 11). Sensitivity to quinine, in contrast to aspirin or tartrazine, affects a number of body systems and may be serious, manifested as urticaria/angioedema, hepatic injury, renal failure, serious dermatologic conditions, serious hematologic events, and death (Ref. 12) (also see section I.B., comment 6). Three sources estimate the incidence of quinine-induced immunologic thrombocytopenia to be in the range of about 1:1,000 to 1:3,000 (see section I.B., comment 9).

FDA's spontaneous reporting system contains 110 case reports involving quinine for the period from 1969 through 1990. Sixty-nine (approximately 63 percent) of these reports represent possible hypersensitivity reactions, including 22 reports of thrombocytopenia (57 of these cases [approximately 83 percent] involved quinine products and/or quinine dosages typically used in the treatment and/or prevention of nocturnal leg muscle cramps). Of the eight deaths that occurred among the reported hypersensitivity reactions, medical records and autopsy findings were sufficiently complete in two of these cases (both involving OTC quinine products indicated for the treatment of leg muscle cramps) to implicate quinine-induced thrombocytopenia as precipitating fatal hemorrhages in each case. Underreporting of such reactions into the agency's spontaneous reporting system is believed to be very substantial for OTC drug products. This may be due to physicians (the principal reporters to the spontaneous reporting system) not

becoming aware of reactions to OTC drugs, and because manufacturers and distributors are not generally required to transmit reports of serious adverse reactions involving OTC drugs to FDA.

The agency concludes that the severity of quinine hypersensitivity reactions, even in their first occurrence, and the inability to identify predisposing factors to this occurrence create a risk clearly different from that presented by tartrazine or aspirin. The agency does not consider it likely that a warning statement in quinine product labeling would be of significant value because it is impossible to prospectively identify the groups at risk (see section I.B., comment 10).

References

(1) Aster, R. H., "Thrombocytopenia Induced by Quinine and Other Drugs", unpublished report in Comment No. C143, Docket No. 77N–0094, Dockets Management Branch.

(2) Lavy, N. W., "Overview: Efficacy and Safety of Quinine Sulfate in the Treatment and/or Prevention of Nocturnal Leg Cramps", unpublished report in SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(3) Simon, R. A., "Adverse Reactions to Drug Additives," *Journal of Allergy* and Clinical Immunology, 74(4 Pt 2):623–630, 1984.

(4) Simon, R. A., "Adverse Reactions to Food Additives," *New England and Regional Allergy Proceedings*, 7(6):533–542, 1986.

(5) Virchow, C. et al., "Intolerance to Tartrazine in Aspirin-Induced Asthma: Results of a Multicenter Study," *Respiration*, 53(1):20–23, 1988.

(6) Morales, M. C. et al., "Challenge Tests with Tartrazine in Patients with Asthma Associated with Intolerance to Analgesics (ASA-Triad): A Comparative Study with Placebo," *Clinical Allergy*, 15(1):55–59, 1985.

(7) Safford, R. J., and B. F. Goodwin, "Immunological Studies on Tartrazine and its Metabolites. I. Animal Studies." *International Archives of Allergy and Applied Immunology*, 77(3):331–336, 1985.

(8) Settipane, G. A., "Aspirin and Allergic Diseases: A Review," *American Journal of Medicine*, 74(6A):102–109, 1983.

(9) Genton, C., P. C. Frei, and A. Pecoud, "Value of Oral Provocation Tests to Aspirin and Food Additives in the Routine Investigation of Asthma and Chronic Urticaria," *Journal of Allergy and Clinical Immunology*, 76(1):40–45, 1985.

(10) Dipalma, J. R., "Tartrazine Sensitivity," *American Family Physician*, 42(5):1347–1350, 1990.

(11) Sorensen, H. T., B. Nielsen, and J.Ostergaard-Nielsen, "Anaphylactic Shock Occurring Outside Hospitals," *Allergy*, 44(4):288–290, 1989.

(12) Bateman, D. N., and E. H. Dyson, "Quinine Toxicity," *Adverse Drug Reactions and Acute Poisoning Reviews*, 4:215–233, 1986.

9. Two comments provided estimates of the incidence of quinine-induced immunologic thrombocytopenia (QIITP). Lavy (Ref. 1) presented several estimates, each based on different assumptions and information. For one estimate, Lavy noted that four of six hypersensitivity reactions reported to FDA in 1987 were cases of thrombocytopenia. Lavy converted the total sales of quinine drug products for 1987 by dosage unit to "total number of days of therapy sold" by dividing the number of tablets and capsules sold by the dose per day described in product labeling. Lavy assumed that quinine was taken for leg cramps approximately one quarter of the year by each subject. By dividing the "total days of therapy purchased" by the "total days used per person," Lavy estimated the size of the population exposed to drug products containing quinine in 1987 to be 1.66 x 106, and calculated the incidence of QIITP to be 1 case per 415,000 people, based upon 4 cases reported to FDA that year. Lavy did not try to correct for underreporting.

Using another approach, Lavy reported that quinine has been estimated to be the causative agent in approximately 10 percent of all drug-induced immunologic thrombocytopenia reports. He noted that secondary thrombocytopenia was the principal diagnosis in approximately 4,000 discharges in the 1987 National Hospital Discharge Survey. Assuming that 10 percent of these thrombocytopenia cases were drug-induced and 10 percent of drug-induced immunologic thrombocytopenia cases are related to quinine, 40 cases could be attributed to quinine. Assuming the population exposed to drug products containing quinine in 1987 was 1.66 x 106 (as calculated above), Lavy calculated the incidence of QIITP to be 1:41,500. Lavy cited a third estimate of the incidence of QIITP based on information from Danielsen's report on drug-induced blood disorders among admissions at the Group Health Cooperative of Puget Sound (Ref. 2). In this retrospective study, 6 cases of thrombocytopenia related to quinine or quinidine among 5,089 subjects were reported for an apparent incidence of 1 case per 848 subjects taking 1 or the other of the 2 drugs.

Another comment (Ref. 3) estimated the incidence of QIITP from ingestion of drug products to be 1:3,300 per year. The comment based its calculations on the number of cases of documented quinine-induced thrombocytopenia at the Blood Center of Southeastern Wisconsin over a 10-year period. In making this estimate, it was assumed that at least half of all cases occurring in this population would have been referred to the laboratory for confirmation of diagnosis.

The agency notes that the estimates of the incidence of thrombocytopenic reactions to drug products containing quinine range from more than 1 in 1,000 (for quinine and quinidine considered together) to less than 1 in 400,000. This wide range suggests that a precise estimate will be hard to obtain. It is difficult to conclude, however, that the first estimate proposed by Lavy is correct. The number of events used by Lavy is the number reported to FDA in 1987. While no one knows the extent of underreporting, it is believed to be very substantial. For example, if even a 1 percent rate is assumed, this would translate, using Lavy's other figures, to about 1 in 4,000 people. The exposure estimate could also be considerably in error. Lavy assumed the drug was used for one-quarter of the year by each person. If, in fact, it was used for one half of the year, the number of exposed people would be half that proposed and the rate of drug-induced immunologic thrombocytopenia would be double that calculated.

The incidence calculated based on the National Hospital Discharge Survey (Ref. 1) employed the estimate of population discussed above and assumed 1 percent of the diagnoses of secondary thrombocytopenia were attributable to quinine. There is no way to know the accuracy of this estimate; if it were higher, even by a factor of 5, the estimated rate would be above 1 in 10,000, a substantial rate.

Probably the most credible of Lavy's estimates is the Puget Sound-based estimate (Ref. 2), because it is based on hospital diagnoses and well-documented exposure. The estimate of the incidence of QIITP based on the number of documented cases occurring in the population served by the Blood Center of Southeastern Wisconsin over a 10-year period (Ref. 3) also is based on relatively few assumptions and appears reliable. The only assumption in this calculation was that twice as many events occurred as were reported to the laboratory. The estimates from these two sources, 1:848 (Puget Sound) and 1:3,300 (Southeastern Wisconsin) are similar to the estimate of 1:1,000 cited by Mitchell (Ref. 4). These three sources provide a reasonably small range for the incidence of QIITP that can be expected, about 1:1,000 to 1:3,000.

Therefore, while the agency believes that a precise estimate of the incidence of QIITP will be difficult to obtain, credible estimates from three sources (Refs. 2, 3, and 4) do not support the assertion that QIITP is a rare event.

References

(1) Lavy, N. W., "Overview: Efficacy and Safety of Quinine Sulfate in the Treat ment and/or Prevention of Nocturnal Leg Cramps", unpublished report in SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(2) Danielson, D. A. et al., "Drug-induced blood disorders," *Journal of the American Medical Association*, 252(23):3257–3260, 1984.

(3) Aster, R. H., "Thrombocytopenia Induced by Quinine and Other Drugs," unpub-lished report in Comment No. C143, Docket No. 77N–0094, Dockets Management Branch.

(4) Mitchell, T. R., and J. D. Morrow, "Quinine Purpura," *Journal of the Tennessee Medical Association*, 81(9):578, 1988.

10. Three comments contended that warnings in product labeling could adequately inform and protect consumers from the well-known side effects of quinine, including idiosyncratic reactions. One comment stated that warnings recommended by the Miscellaneous Internal Panel (47 FR 43562 at 43564), including those concerning idiosyncratic reactions, have been incorporated into the labeling of currently marketed products. Another comment stated that careful warning language in its product labeling helps to further protect consumers by informing them of the possibility of untoward, idiosyncratic reactions. This labeling states: "Discontinue use and consult your doctor immediately if swelling, bruising, skin rash, skin discoloration or bleeding occurs. These symptoms may indicate a serious condition. Discontinue use if ringing in the ears, deafness, diarrhea, nausea or visual disturbances occur * * * Do not take if * * * allergic or sensitive to quinine or under 12 years of age." A third comment, citing a report by Lavy (Ref. 1), stated that serious adverse effects occur at a frequency probably less than 1 in 40,000 people (see section I.A., comment 9), the clinical course is only rarely complicated, and that labeling can clearly and concisely warn "* * * regarding the more common yet low frequency side effects, which are generally treated simply by discontinuing use."

In the tentative final monograph (50 FR 46588 at 46592) the agency proposed the following warning in § 343.150(c) for OTC drug 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 proposed this labeling in the event that data were submitted that resulted in the inclusion of quinine in a monograph in the final rule. While proposed, this labeling was not required at that time.

The agency has reviewed the warning information currently appearing on OTC quinine products marketed for the treatment and/or prevention of leg muscle cramps. The language varies slightly between products, but the information provided is similar. In general, labeling warns patients to discontinue taking the drug should any of a number of listed events occur. However, the labeling differs in the events listed and in recommending when a physician should be contacted.

There are several factors that argue against the sufficiency of label warnings to protect consumers from serious adverse events related to quinine. The frequency of these reactions is probably greater than assumed by the comments (see section I.B., comment 9). Many of the adverse advents are unpredictable. For example, thrombocytopenia may occur after 1 week of exposure or after months or years of quinine administration. Further, there may be no characteristic that would predict an adverse event in the person using the product. The agency believes that a physician could help people using this drug appreciate the nature and frequency of the risk and help in the consideration whether that risk is acceptable. The physician could also advise about the signs of thrombocytopenia, such as petechiae (pinpoint, nonraised, round, purplish red spots) and purpura (small hemorrhage), perhaps allowing identification of this condition before a significant hemorrhage occurred. A number of the adverse reaction reports note the occurrence of a similar prior event related to previous ingestion of quinine in which neither the user nor the physician recognized the relationship of the illness to quinine ingestion. Use of quinine under a physician's prescription, with appropriate emphasis on warning signs, may make timely recognition easier.

Although drug-induced immunologic thrombocytopenia may be the best studied idiosyncratic reaction caused by quinine (Ref. 2), quinine has also been reported to have been associated with a number of other hypersensitivity reactions and pharmacologic effects. Lavy (Ref. 1) notes that these include "the possibility of decreased digoxin clearance, increased half-life of quinine when given concurrently with cimetidine, pseudo-allergic reactions in aspirin-sensitive patients, drug fever, nonspecific granulomatous hepatitis, asthma, hemolytic anemia, inhibition of tolbutamide metabolism, hypoprothrombinemia, hemolytic anemia in glucose-6-phosphate dehydrogenase (G–6–PD) deficient patients, etc." Cooper and Bunn (Ref. 3) reported that G-6-PD-deficient individuals (i.e., those variants susceptible to hemolytic anemia from quinine) are relatively common among eastern Mediterranean and Chinese people. Quinine may also interact with several other drugs (see section I.B., comment 7). Furthermore, the possible pharmacologic effects may have particular significance for the elderly who may be taking concomitant medications that either provoke muscle cramps or adversely interact with quinine. Altered pharmacokinetics with age also result in a longer half-life of quinine in older people, which suggests that the frequency and severity of adverse effects may be greater in the elderly (Ref. 4) (also see section I.B., comment 6). The foregoing possible additional adverse reactions, including those related to ethnicity, age, and concurrent drug therapy, are not addressed by the labeling of the comment's product and would generally be difficult to address in OTC drug product labeling.

It should also be noted that the number of reports of serious adverse reactions submitted to FDA's spontaneous reporting system, including those resulting in hospitalization and death, has been increasing over the past several years in spite of the industry's revision of labeling to incorporate the warnings suggested by the Miscellaneous Internal Panel in 1982. There has been an increasing number of reports per year since 1986, and 56 of 105 reports (approximately 53 percent) have been received by FDA since 1988. (See section I.B., comment 4.)

The agency concludes there is insufficient evidence that warnings in product labeling could adequately inform and protect consumers from the well-known side effects of quinine, including idiosyncratic reactions. This conclusion is based primarily on the severity of hypersensitivity reactions to drug products that contain quinine and the inability to identify predisposing factors to these reactions, the frequency of such reactions, and the relationship of quinine-related adverse events to factors such as ethnicity, age, and concurrent drug therapy.

References

(1) Lavy, N. W., "Overview: Efficacy and Safety of Quinine Sulfate in the Treat-ment and/or Prevention of Nocturnal Leg Cramps", unpublished report in SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(2) Aster, R. H., "Q-Vel: Could Serious Adverse Reactions be Prevented by Having the Drug Available Only on Prescription,"

unpublished report in Comment No. C176, Docket No. 77N–0094, Dockets Management Branch.

(3) Cooper, R. A., and H. F. Bunn, "Hemolytic Anemias," in "Harrison's Principles of Internal Medicine," 12th ed., edited by J. D. Wilson et al., McGraw-Hill, New York, pp. 1531–1543, 1991.

(4) Blackbourn, J., and D. Bajrovic, "Quinine—Forever and Ever?," *Hospital Pharmacy*, 23:732, 735, 1988.

11. Two comments objected to the agency's discussion on the safety of vitamin E (50 FR 46588 at 46591), contending that a considerable body of data demonstrating safety in humans had been excluded from the agency's evaluation. The comments primarily objected to the agency's emphasis on the observations of one physician as an expert on vitamin E because they considered the data referred to by this individual to be anecdotal, uncontrolled, and largely subjective. The comments provided a literature review and other data (Refs. 1, 2, and 3) to support the safe use of vitamin E in humans.

Another comment disagreed with the agency's Category III classification of vitamin E both individually and in combination with quinine sulfate for the treatment and prevention of nocturnal leg muscle cramps, contending that adequate information already existed to support the safety of these ingredients (alone or in combination). The comment included the results of two new clinical studies (Refs. 4 and 5) comparing vitamin E, quinine sulfate, a combination product containing vitamin E and quinine sulfate, and placebo to support the safe use of the individual ingredients as well as the combination of these ingredients for this indication. In both studies, subjects received a daily dose of 1,600 I.U. of vitamin E, either alone or in combination with quinine sulfate.

One additional comment included the results of a third new clinical study comparing vitamin E, quinine sulfate, a combination product containing vitamin E and quinine sulfate, and placebo (Ref. 6). Some safety information on vitamin E can be derived from this study.

In the tentative final monograph, the agency classified vitamin E in Category III for the treatment and prevention of nocturnal leg muscle cramps, stating that a safe and effective OTC dosage had not been established for this use (50 FR 46588 at 46591). The agency evaluated all of the data that had been submitted to this rulemaking proceeding but acknowledges that these data were not the total body of information that has been published on vitamin E. The agency did point out that the paper by Roberts (Ref. 7) raised some questions about a safe dose of OTC vitamin E.

The agency has reviewed the additional data and information that have been submitted and determined that sufficient evidence has been presented to support the safety of vitamin E for the treatment and/or prevention of nocturnal leg muscle cramps. However, the evidence is inadequate to support the effectiveness of vitamin E for this use (see section I.C., comment 13).

Farrell and Bieri (Ref. 2) evaluated potential toxic and/or beneficial effects of vitamin E intake. Twenty-eight adults who had been self-administering 100 to 800 I.U. of vitamin E daily for an average of 3 years were studied. A review of the subjects' past medical histories did not reveal any apparent gross evidence of toxicity from vitamin E intake. The highest plasma alpha-tocopherol concentrations in the vitamin E subjects were two times the upper limit of normal, as determined in control subjects. A broad range of laboratory tests were performed to assess toxic effects on various organ systems. No disturbance in liver, kidney, muscle, thyroid gland, erythrocytes, leukocytes, coagulation parameters, or blood glucose was found.

Salkeld (Ref. 1) reviewed over 9,000 cases in which daily doses of up to 3,000 I.U. of vitamin E were taken for up to 11 years (and 55,000 I.U. daily for 5 months in a few subjects). In 1,014 cases with vitamin E intake from 200 I.U. up to 3,000 I.U. daily for up to 11 years, it was stated that no side effects were observed. In another 8,241 cases with similar intake and duration, there was no mention of side effects. In other trials, 82 of 813 subjects complained of one or more side effects. The reported effects included dermatitis, pruritus ani, acne, cheilosis, fatigue and weakness, gastrointestinal symptoms, prostatic obstruction, tachycardia, and vasodilation. Thus, in a total of 10,068 cases, Salkeld found a 0.8 percent overall incidence of side effects. The Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products relied in part on this same literature review by Salkeld in stating its conclusion "that vitamin E is safe" (March 16, 1979, 44 FR 16126 at 16172). The Advisory Review Panel on OTC Antimicrobial (II) Drug Products, in the advance notice of proposed rulemaking for OTC topical acne drug products (March 23, 1982, 47 FR 12430), mentioned that there are no notable pharmacological or toxicological effects of oral vitamin E and that numerous experiments indicate that high dietary intakes of vitamin E (up to 800 I.U. daily for up to 3 years) are apparently without toxic side effects (47 FR 12462).

One of the new clinical studies submitted includes the results of laboratory tests performed in 24 patients to evaluate the effect of the product on various organ systems (Ref. 4). Tests were performed at baseline and at the end of each 1-week treatment period. No abnormal results in liver, kidney, leukocytes, erythrocytes, platelets, electrolytes, or blood glucose were found in any of the patients at any time. In this study vitamin E was used only in a combination product, and each subject had a daily intake of 1,600 I.U. of vitamin E. However, the combination product was only taken during 1 week of the study. Therefore, the laboratory data do not provide any useful information on the long-term effects of vitamin E.

The second new clinical study (Ref. 5) was a four-period crossover study in which each subject received 1,600 I.U. of vitamin E daily (either singly or in a combination product) for 5 days during two of the four treatment periods of the study. Although no laboratory tests were performed, the subjects were asked to report any adverse reactions at the end of each treatment period. Twenty-seven adverse reactions were reported by 19 subjects out of 205 individuals completing all phases of the study. Six of these adverse reactions were from subjects who received vitamin E singly. Complaints included: Abdominal cramps, nausea, loose bowels, and headache. The most commonly occurring complaint was gastrointestinal disturbance (nausea, flatulence, or diarrhea) of a transient nature. These reactions are consistent with those previously reported in other studies; however, the investigators considered the reactions as not related or probably not related to the study drug.

In the third new clinical study (Ref. 6), vitamin E (1,600 I.U. daily for 2 weeks) was compared with placebo, quinine sulfate, and a combination of quinine sulfate and vitamin E for the treatment and/or prevention of nocturnal leg muscle cramps. Details of this multicenter, parallel-design study are described in section I.C., comment 12. Vitamin E alone was administered to 137 subjects. Headache was the most frequently reported adverse event, occurring in 23 subjects (16.8 percent). However, a similar rate of headache (21 percent) was reported in subjects taking placebo. The investigators described only six of these events as possibly related to the study medication. Other adverse events described by the investigators as possibly related to

vitamin E included three of four reports of nausea, two of three reports of myalgia, and one of three reports of local edema. Thus, daily doses of 1,600 I.U. of vitamin E were well tolerated in this study.

Bendich and Machlin (Ref. 8) reviewed six double-blind studies involving vitamin E at doses as high as 3,200 I.U. daily for up to 6 months. Very few adverse effects were noted, and no specific side effect was consistently observed in all the studies. In one study, 202 college students received 600 I.U. of vitamin E or placebo daily for 28 days in a randomized, double-blind trial (Ref. 9). No effects on prothrombin time, total blood leukocyte count, or serum creatine phosphokinase activity were evident. In a randomized, double-blind, placebo-controlled study, 30 healthy adults were given 800 I.U. of vitamin E or placebo daily for 16 weeks. There were no significant differences in effects on plasma lipids between the vitamin E and placebo groups (Ref. 10). No side effects were observed in a double-blind, crossover study of 48 subjects who received 1,600 I.U. of vitamin E or placebo daily for a period of 6 months (Ref. 11). There were no reports of significant side effects, weakness, fatigue, or thrombophlebitis in a double-blind, crossover study in which 2,000 I.U. of vitamin E or placebo was given daily to 25 adult onset-diabetic subjects for a period of 6 weeks (Ref. 12). Thyroid hormone levels were found to be identical for both the treatment and placebo periods. Hale et al. (Ref. 13) examined the incidence of various clinical disorders and measured a number of laboratory variables in 369 subjects who used vitamin E supplements and 1,861 subjects who did not. All subjects were over age 65. Use of vitamin E appeared to have little influence on clinical disorders or hematologic or biochemical parameters. Only the serum glutamic oxaloacetic transaminase was higher in vitamin E users. However, the values were still within the accepted normal range. There were no significant differences between users and nonusers in the prevalence of hypertension, vaginal bleeding, frequent headache, dizziness, recurrent diarrhea, diabetus mellitus, lightheaded-ness, or thyroid disorders.

Roberts (Ref. 7) raised concerns about an increased incidence of thrombophlebitis associated with excessive vitamin E intake. In over 10 years of practice, Roberts encountered more than 80 patients with problems that he attributed to self-medication with high doses of vitamin E (greater than 800 I.U. daily). He suggested that vitamin E may encourage thrombosis in patients with a predisposing condition. Symptoms of thrombophlebitis were said to have abated upon cessation of vitamin E therapy. Conventional treatment for thrombophlebitis (e.g., bed rest, local heat) was administered along with the discontinuation of vitamin E therapy. Thus, it is difficult to assess which action was responsible for the improvement. In addition, no controlled studies or concurrent references were included in support of his conclusions.

Fitzgerald and Brash (Ref. 14) stated that vitamin E at 1,600 I.U. a day in humans decreases platelet thromboxane production which could consequently reduce the potential for thrombosis formation. In addition, they noted that associations between thrombophlebitis and vitamin E use have not been reported by other authors.

Several authors (Refs. 2, 9, and 15) have reported that oral intake of high doses of vitamin E has not produced blood coagulation abnormalities in normal humans. However, in individuals deficient in vitamin K (caused by malabsorption, diet, or anticoagulant therapy), large doses of vitamin E can exacerbate coagulation defects. Therefore, high levels of supplemental vitamin E may be contraindicated in such conditions (Ref. 8).

Based on the discussion above, the agency concludes that sufficient evidence exists to support the safety of vitamin E at the daily doses that have been commonly used for the treatment and/or prevention of nocturnal leg muscle cramps.

References

(1) Salkeld, R. M., "Safety and Tolerance of High-Dose Vitamin E Administration in Man: A Review of the Literature," draft of unpublished data in Comment No. C124, Docket No. 77N–0094, Dockets Management Branch.

(2) Farrell, P. M., and J. G. Bieri, "Megavitamin E Supplementation in Man," *The American Journal of Clinical Nutrition*, 28:1381–1386, 1975.

(3) Hathcock, J., "Vitamin Safety: A Current Appraisal," in "Vitamin Issues," Vol. V, No. 1, published by Vitamin Nutrition Information Service, in Comment No. C122, Docket No. 77N–0094, Dockets Management Branch.

(4) Biodesign GmbH, "Clinical Evaluation of Q-VELR in Patients with Nocturnal Leg Muscle Cramps," draft of an unpublished paper in Comment No. SUP00031, Docket No. 77N–0094, Dockets Management Branch.

(5) Leo Winter Associates, Inc., "Final Medical Report and Data Summary Analysis and Final Statistical Report on Double-Blind Randomized Crossover Study of Q-VELR Versus Quinine Sulfate Versus Vitamin E Versus Placebo in the Treatment of Nocturnal Leg Muscle Cramps (No. 1285–5082)," draft of an unpublished paper in Comment No. SUP00031, Docket No. 77N–0094, Dockets Management Branch.

(6) Draft of an unpublished study entitled "A Short-Term, Randomized, Double-Blind, Parallel Study of Q-Vel vs. Quinine Sulfate vs. Vitamin E vs. Placebo in the Prevention and Treatment of Nocturnal Leg Cramps," Comment No. SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(7) Roberts, H. J., "Perspective On Vitamin E as Therapy," *Journal of the American Medical Association*, 246(2):129–131, 1981.

(8) Bendich, A., and L. J. Machlin, "Safety of Oral Intake of Vitamin E," *The American Journal of Clinical Nutrition*, 48:612–619, 1988.

(9) Tsai, A. C. et al., "Study on the Effect of Megavitamin E Supplementation in Man," *The American Journal of Clinical Nutrition*, 31(5):831–837, 1978.

(10) Stampfer, M. J. et al., "Effect of Vitamin E on Lipids," *American Journal of Clinical Pathology*, 79(6):714–716, 1983.

(11) Gillilan, R. E., B. Mondell, and J. R. Warbasse, "Quantitative Evaluation of Vitamin E in the Treatment of Angina Pectoris," *American Heart Journal*, 93(4):444–449, 1977.

(12) Bierenbaum, M. L. et al., "The Effect of Supplemental Vitamin E on Serum Parameters in Diabetics, Post Coronary and Normal Subjects," *Nutrition Report International*, 31(6):1171–1180, 1985.

(13) Hale, W. E. et al., "Vitamin E Effect on Symptoms and Laboratory Values in the Elderly," *Journal of the American Dietetic Association*, 86(5):625–629, 1986.

(14) Fitzgerald, G. A., and A. R. Brash, "Endogenous Prostacyclin and Thromboxane Biosynthesis During Chronic Vitamin E Therapy in Men," *Annals of the New York Academy of the Sciences*, 393:209–211, 1982.

(15) Corrigan, J. J., "The Effect of Vitamin E on Warfarin-Induced Vitamin K Deficiency," *Annals of the New York Academy of Sciences*, 393:361–368, 1982.

C. Comments on the Effectiveness of Nocturnal Leg Muscle Cramp Ingredients

12. One comment disagreed with the agency's Category III classification of quinine sulfate for the treatment and/or prevention of nocturnal leg muscle cramps on the basis of a lack of adequate clinical data demonstrating the effectiveness of quinine sulfate for this indication (50 FR 46588 at 46590). The comment contended that there is sufficient evidence of quinine's effectiveness for this indication at present to warrant classifying it in Category I. The comment subsequently submitted the results of two clinical studies (Refs. 1 and 2) comparing quinine sulfate, vitamin E, a combination product containing quinine sulfate and vitamin E, and placebo for the treatment and prevention of nocturnal leg muscle cramps to support the effectiveness of the individual ingredients (quinine sulfate and vitamin

E) as well as the combination of these ingredients for this indication. Another comment provided the results of three clinical studies (Refs. 3, 4, and 5) that it felt addressed the effectiveness issues raised by the agency in the tentative final monograph (50 FR 46590). This comment requested an oral hearing if the submitted data were not found adequate to upgrade quinine sulfate to Category I. In addition, in response to a citizen petition, one comment included the results of a clinical study intended to demonstrate the efficacy of a combination product containing quinine sulfate and vitamin E (Ref. 6).

In the tentative final monograph, the agency concluded, on the basis of its review of the new data submitted and the studies and information discussed by the Internal Analgesic and Miscellaneous Internal Panels, that quinine sulfate for use in OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps should be classified in Category III. The agency stated that adequate clinical data are necessary to support the reclassification of quinine from Category III to Category I and that any such studies should address the following safety and effectiveness issues (50 FR 46588 at 46590):

(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, how long a period of time?

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

The agency has reviewed the additional clinical data that have been submitted and determined that they are not adequate to support the reclassification of quinine sulfate to Category I for this use. Three studies (Refs. 3, 4, and 5) compared quinine to placebo. In one study (Ref. 3), 75 subjects were enrolled in a double-blind, randomized, placebo-controlled, crossover study that was conducted over a 10-week period in five 2-week intervals. Subjects with a history of at least two cramps per week for at least 3 months were included in this study and randomized to one of two treatment groups (group I or II). The initial 2-week period was a baseline period and patients who failed to have at least two cramps per week were dropped from the study. Subjects who had a sufficient number of cramps during the baseline period were either given the placebo (group I) or 325 mg of quinine sulfate per night (group II) for a period of 2 weeks. No treatment was given for the next 2-week period and in the fourth 2-week period subjects crossed over to the alternate treatment. A final 2-week period of no treatment followed. Subjects were issued weekly case report forms upon which they were instructed to record the number of cramps experienced per night, the time of the cramp, and the severity of the cramp. Subjects were also asked to rate the effectiveness of the medication just completed at weeks 4 and 8 of the study. According to the protocol, subjects were assigned to the treatment sequence, on the basis of a predetermined randomization schedule, prior to entering the baseline period. Therefore, the removal of subjects from the study in the first 2 weeks for not having enough events may have biased the study.

In the statistical analysis of the study data, three efficacy variables were evaluated: The mean frequency of leg cramps (per night), the mean severity of leg cramps per night, and the total number of nights per week that leg cramps occurred. The last variable (total number of nights per week that leg cramps occurred) appears to be constructed from the primary data because no such variable is listed on the weekly case report forms from which these variables are derived. The subjects' overall assessment of the effectiveness of the drug was collected but not analyzed.

Sixty-two of the 75 subjects enrolled in the study were included in the data analysis. Of the 13 subjects found to be unevaluable, 8 withdrew from the study on their own accord. No specific reasons for these withdrawals were given, but it is stated in the study report that they were unrelated to the treatment. The remaining five subjects were dropped for various medical reasons and noncompliance with the protocol. No "intent-to-treat" analysis was performed.

A number of analyses were carried out. Two of the analyses treated the unblinded baseline and washout periods as if they were treatment periods. This type of analysis is incorrect for a crossover trial. The relevant comparisons that should be made are between the treatments in the double-blind periods, possibly with adjustments for baseline, provided there are no major changes in baseline values for each period.

When Patel's joint test for equal carryover and equal pretreatment severity (Ref. 7) is applied to the data, however, significant differences are seen in pretreatment severity before the second period. Analysis of the second period is thus compromised; therefore, analysis should be limited to the first treatment period (weeks 3 and 4). This comparison does not show a significant advantage for quinine sulfate over placebo for any of the effectiveness variables.

Another clinical study (Ref. 4) used the same study design as the study discussed above except that the dose of quinine sulfate was 260 mg/night, not the 325 mg/night used in the first study. In addition, five efficacy variables were analyzed: Frequency, severity, and duration of leg cramps, and induction and quality of sleep.

Although the predetermined randomization chart submitted for this study provided for enrollment of 74 subjects, 84 subjects entered the study. No explanation for entry of the additional 10 subjects was provided. As in the first study, randomization to treatment sequence occurred at the time of entry into the baseline period; thus, subsequent removal of subjects prior to the first double-blind treatment period may also have introduced bias into this study. Of the 84 subjects entered at baseline, 69 (34 assigned to group I and 35 to group II) entered the double- blind treatment phase.

The study concluded that significant differences at the 5-percent level exist between quinine sulfate and placebo for three of the five variables: Frequency of cramps, induction of sleep, and quality of sleep. However, no documentation of any statistical analysis supporting these claims was provided.

The statistical report that accompanied the study addressed the question of comparing the effectiveness of quinine sulfate and placebo with a multivariate analysis of covariance which compared the vector of efficacy variables over four observation periods (two treatment periods plus two washout periods with the initial baseline value as a covariate). The conclusion of the analysis was that the treatment effect was not significant ($p = 0.106$). Univariate analyses of covariance comparing these four observation periods were referred to in the statistical report, but no p-values for treatment effect were provided (although a significant order by treatment interaction was reported). Also included in the statistical analyses of the study were comparisons of the four observation periods separately by sequence (quinine sulfate-placebo and

placebo-quinine sulfate), which included baseline-adjusted means and comparisons between periods using Duncan's Multiple Range Test. These comparisons showed that significant differences were demonstrated between quinine and placebo only for the placebo-quinine sulfate sequence (group II), and only for three variables: Frequency of cramps, quality of sleep, and induction of sleep. However, the adjusted means for the quinine sulfate-placebo sequence (group I) favored placebo over quinine sulfate for all five efficacy variables. In addition, as for the first study, the appropriate statistical analysis for this type of study was not done. The hypothesis of equal carryover effect was not tested and not rejected before any of the other statistical tests for treatment effect were performed. The results of this study are not adequate to support the effectiveness of quinine sulfate for the treatment and/or prevention of nocturnal leg muscle cramps.

The study by Jones and Castleden (Ref. 5) also does not provide adequate evidence of quinine sulfate's effectiveness for this indication. The study was a double-blind crossover study of nine patients with four 2-week periods of observation (a run-in period and a washout period in addition to two treatment periods of placebo or quinine sulfate 300 mg/day). The same five efficacy values as in the second study above were evaluated: Frequency, severity, and duration of leg cramps, and induction and quality of sleep. No raw data were included to substantiate any of the statistical claims made by the authors; nor was a protocol included in the article.

Of the five primary efficacy variables, only severity of cramps was claimed to show a significant difference between quinine sulfate and placebo ($p < 0.025$), although an analysis of frequency of cramps after 2 a.m. was also claimed to be significant ($p < 0.025$). There was no indication that the time period after 2 a.m. was identified in the protocol as defining a primary endpoint; thus, this is assumed to be a post-hoc analysis done after reviewing the data. In general, the isolated severity finding is not convincing on its face. In addition, the published article did not provide sufficient information to permit an independent analysis of the data. For these reasons, the study does not provide evidence that quinine sulfate is an effective treatment for nocturnal leg muscle cramps.

Three studies (Refs. 1, 2, and 6) were submitted to support the effectiveness of quinine sulfate and vitamin E individually and in combination for the treatment and/or prevention of nocturnal leg muscle cramps. The Freiburg study (Ref. 1) was a 5-week, double-blind, randomized, crossover study in 24 subjects. All subjects received placebo during week 1 (baseline), week 3, and week 5. Subjects in group I received quinine in week 2 and the combination of quinine and vitamin E in week 4, while subjects in group II were given the combination product in week 2 and quinine in week 4. A statistically significant difference in frequency of attacks between the combination product and quinine sulfate was reported, but no difference in duration or severity of attack was found between these two active treatments. The report described an "obvious" improvement in frequency, duration, and severity of attacks between the placebo periods and both active treatments, but no statistical evidence or analysis to support this conclusion was provided. Moreover, the comparison of treatments and placebo did not involve randomized patient groups, nor was it blinded. Only the portion of the study comparing the combination product versus quinine was a randomized, double-blind trial. The study report did not include the study protocol, details of the statistical analysis conducted, or individual subject data. The model described in the summary of the data analysis did not properly separate carryover effect from treatment effect. The study provides no evidence from a controlled trial that quinine is effective for nocturnal leg muscle cramps.

The other study (Ref. 2) also employed a complicated randomized, four-period, crossover design. There were 205 subjects randomly assigned to one of four treatment groups: Quinine sulfate 260 mg/day, vitamin E 1,600 I.U./day, a combination of quinine and vitamin E, or placebo. The combination of quinine and vitamin E was reported as being statistically superior to both its components and placebo for six variables: Effect of cramps on falling asleep, nighttime awakening due to cramps, number of cramps, severity of cramps, subject global evaluation, and difficulty falling asleep due to cramps. The study also reported statistically significant positive findings on quinine sulfate versus placebo for the first five of these six variables. As in the Freiburg study, the model used in the statistical analysis does not properly separate the carryover effect from the treatment effect. Neither the data listings nor the results by period were provided. Therefore, the agency was unable to independently analyze the results of this study or to rely on the analysis provided as evidence that the reported results were attributable to drug treatment.

The third clinical study compared quinine sulfate, vitamin E, and a combination of quinine sulfate and vitamin E to placebo, for the treatment and/or prevention of nocturnal leg muscle cramps (Ref. 6). This study was a multicenter, randomized, block parallel-design with a single-blind, placebo, run-in period, followed by a 2-week, double-blind, randomized, treatment phase. Subjects who had at least one leg cramp per night for a minimum of 3 nights during the single-blind placebo week, and met all other selection criteria, were randomly assigned to one of the four double-blind treatment groups. Capsules, identical in appearance, contained either placebo, quinine sulfate 64.8 mg, vitamin E 400 I.U., or a combination of quinine sulfate 64.8 mg and vitamin E 400 I.U. Subjects were instructed to take two capsules following their evening meal, and two capsules before bedtime, which provided daily doses of 259.2 mg of quinine sulfate, 1,600 I.U. of vitamin E, or the combination thereof.

Efficacy endpoints identified in the protocol were: (1) Number of episodes of nocturnal leg cramps per week, (2) sleep disturbance due to nocturnal leg cramps, (3) severity of nocturnal leg cramps, and (4) duration of nocturnal leg cramps. However, none of the parameters was designated as a primary efficacy variable in the protocol. The protocol specified that efficacy would be analyzed by analysis of variance with repeated measures test, as well as other methods deemed appropriate. On the basis of an estimated 30 percent difference between the combination product and its components, assuming an alpha of 0.05 and statistical power of 70 percent, a sample size of 972 evaluable subjects was planned (243 subjects/group). Enrollment was suspended, however, and the data were analyzed after 498 evaluable subjects (51 percent) completed the study. Subjects were approximately evenly distributed among treatment groups.

In the final report, results were separately analyzed for weeks 1 and 2 of the double-blind treatment. The change from baseline scores obtained during the single-blind, placebo week was analyzed on seven variables for each of the treatment groups at days 7 and 14 using a two-way analysis of variance test with terms for treatment, center, and treatment by center interaction. The data were not analyzed using the analysis of variance with repeated measures test, as prospectively

stated in the protocol. The variables were: (1) Number of nights per week with leg cramps, (2) average number of leg cramps per night, (3) average severity of leg cramps per night, (4) average duration of leg cramps per night, (5) average number of leg cramps per night with sleeping difficulty, (6) average degree of difficulty getting to sleep per night, and (7) average number of nights per week awakened by leg cramps. The placebo group was compared with the remaining treatment groups with the least-significant-difference test using error mean square from the analysis of variance table. Within each treatment group, the amount of change from baseline for each efficacy parameter was compared for each double-blind treatment week using the Wilcoxon sign rank test. P-values of 0.05 or less were considered statistically significant.

Twelve centers initially participated in the study. Three centers were terminated because of low enrollment (less than four evaluable subjects in at least one treatment group). These low enrollment centers were combined in the analysis.

In the final report, the number of nights per week with leg cramps was declared the primary efficacy variable. During the baseline period, a mean of approximately 5 nights per week with leg cramps was recorded in all groups (placebo 4.72, combination 4.95, quinine sulfate 5.04, vitamin E 4.98). All groups improved during week 1 with a reduction in frequency to approximately 4 nights per week with cramps (placebo 4.04, combination 3.73, quinine sulfate 3.53, vitamin E 3.97). The greatest reductions were in subjects given quinine sulfate and the combination product and the difference in week 1 was found to be statistically significant compared to placebo for these treatment groups (p less than or equal to 0.04).

Statistically significant differences between quinine sulfate and placebo were reported in the first week of the study for four of the six remaining efficacy variables declared to be secondary parameters in the final report. Quinine was reported to be significantly better than placebo in reducing the average number of leg cramps per night, average severity of leg cramps per night, average duration of leg cramps per night, and average number of nights per week with sleeping difficulty. No statistically significant differences between any of the treatment groups for any variable were reported for the second week of the study. The comment concluded that quinine sulfate, alone and in combination with vitamin E, at a daily dose of approximately 260 mg was safe and effective in the short term (1-week) treatment of nocturnal leg muscle cramps.

The agency finds that there were a number of flaws in the analysis of this study. First, the primary endpoint (number of nights per week with leg cramps) appears to have been arbitrarily chosen after the study was completed. None of the efficacy variables was declared the primary endpoint in the protocol. Second, the study was of 2 week's duration, and there was no provision in the protocol for separate evaluation of the data from week 1 and week 2. Thus, there is no basis for the decision to analyze week 1 and week 2 separately in the absence of such an analysis declared prospectively in the protocol. In fact, an analysis of both weeks together (see below) does not show a significant benefit of quinine. Third, an adjustment for multiple comparisons should have been included in the data analysis. Given seven variables, two active treatments, and at least three time points at which data could be analyzed (first week, second week, both weeks), the nominally significant differences between treatments at the end of week one would not be expected to retain statistical significance if an adjustment for multiple comparisons were included in the analysis. Even considering the retrospectively identified primary endpoint, a correction for three "looks" (week 1, week 2, and together) would at least double the nominal p-value.

Even without correction for multiplicity, the results do not support the conclusion that quinine sulfate and vitamin E, alone or in combination, are effective for the treatment and/or prevention of nocturnal leg muscle cramps. First, week 2 results fail to replicate the results of week 1. No differences between any of the treatment groups for any parameter were found at the end of week 2, nor was the investigators' global assessment, conducted at the end of the 2-week double-blind period, able to differentiate between treatments. Second, a significant treatment by center interaction was found for the reported superiority of quinine sulfate over placebo in week 1 in reducing the number of nights per week with leg cramps. The result was driven by two of nine centers. In one of these centers, the combination product was indistinguishable from placebo, and in the other, the superiority of placebo over the combination neared statistical significance (p = 0.10). Thus, in the two clinics responsible for the favorable week 1 results of treatment with quinine, there was a failure to replicate the result reported with quinine sulfate alone. Vitamin E was ineffective in all parameters measured throughout the study.

The four retrospectively-declared secondary endpoints for which statistically significant reductions were reported in week 1 in the quinine sulfate group compared to placebo were: (1) The number of cramps per night, (2) the number of nights with sleeping difficulty, (3) the severity of the cramps, and (4) the duration of the cramps. Although a consistent benefit on these endpoints would render a finding on the primary endpoint more persuasive, as with the primary efficacy endpoint, none of the differences between active treatment and placebo persisted through to the end of week 2. For the reasons discussed above, the post hoc, week-1 analysis of these endpoints fails to provide convincing evidence to support the efficacy of quinine sulfate for the treatment and/or prevention of nocturnal leg muscle cramps.

Two additional analyses of the results of the study were submitted (Refs. 8 and 9). The first (Ref. 8) was an analysis of the number of leg cramps per day for each day of the study. This analysis showed occasional days in which quinine was superior to placebo, but is on the whole not helpful. Given an entry cramp rate of one cramp episode per night for at least 3 nights per week, significant differences in any endpoint would not be expected on a day-by-day (i.e., noncumulative) evaluation.

The second analysis (Ref. 9) was of the total cramp rate (mean number of cramps per day over the course of the entire study period) for both the evaluable subset of subjects and the intent-to-treat population. Two analyses were performed on each group. In one analysis, only those subjects who completed the study with at least 14 days of treatment (the completer analysis) were analyzed, while the other analysis involved the results from all subjects with efficacy observations (the endpoint analysis) for the quinine sulfate and placebo treatment groups. In the endpoint analyses, where less than 14 days of treatment was completed, leg cramps for the observed number of days were calculated, and the mean was carried forward to 14 days. None of the four analyses revealed statistically significant reductions in the mean number of leg cramps experienced during 14 days of treatment in the quinine-treated subjects compared with placebo subjects. The endpoint analysis for evaluable patients approached statistical significance for quinine sulfate (p = 0.06), but the results of the completer analysis for evaluable

subjects and both intent-to-treat analyses were clearly negative. The total cramp rate over the entire study is the most straightforward effectiveness measure; it did not show a drug effect on cramps. While the favorable trend on one analysis could suggest activity, the study was already of very substantial size and should have been able to detect a clinically meaningful response. This study, therefore, does not provide evidence of efficacy of quinine sulfate, vitamin E, or the combination thereof in the treatment and/or prevention of nocturnal leg muscle cramps.

Based on the above discussion, the agency concludes that the submitted data are inadequate to establish the effectiveness of quinine sulfate for the treatment and/or prevention of nocturnal leg muscle cramps. Further, the agency concludes that the submitted data do not adequately address the safety and effectiveness issues raised by the agency in the tentative final monograph (see discussion above).

Additional agency comments and evaluations of the data are on file in the Dockets Management Branch (Refs. 10, 11, and 12).

The Commissioner has determined that there are not reasonable grounds in support of a hearing and that a hearing on this issue is not warranted. Six clinical trials have been submitted and have failed to establish the safety and efficacy of quinine sulfate in treating and/or preventing nocturnal leg muscle cramps. Occasional significant differences favoring quinine were not replicated within or between studies. In two crossover design studies (Refs. 3 and 4), appropriate analyses revealed no significant differences between quinine sulfate and placebo. The results of a very large parallel-design, 2-week study showed no significant effect in an analysis of the 2-week data.

In addition, deficiencies in the studies themselves render the reported results unreliable. Each of these studies involved multiple endpoints, none of which was prospectively declared as the primary efficacy variable(s) in any of the studies. There was no attempt to correct significance levels for multiple endpoints. The design of one study did not permit the independent evaluation of the efficacy of quinine sulfate alone (Ref. 1). In three crossover studies (Refs. 2, 3, and 4), the treatment effect was confounded by potential carryover effect and baseline differences. The 2-week, parallel-design study (Ref. 6) showed no effect overall for the entire treatment period, including the investigator's global assessment. Only by considering the results of week 1 separately, an unplanned analysis, was any significant difference between quinine and placebo found in this study, and this finding was confounded by a significant treatment-by-center interaction. For these reasons, the studies cannot be considered adequate and well-controlled clinical investigations as required under § 330.10(a)(4)(ii). The Commissioner concludes that a hearing on this issue is not justified for the reasons stated above.

References

(1) Biodesign GmbH, "Clinical Evaluation of Q-VELR in Patients with Nocturnal Leg Muscle Cramps," draft of an unpublished paper in Comment No. SUP00031, Docket No. 77N–0094, Dockets Management Branch.

(2) Leo Winter Associates, Inc., "Final Medical Report and Data Summary Analysis and Final Statistical Report on Double Blind Randomized Crossover Study of Q-VELR Versus Quinine Sulfate Versus Vitamin E Versus Placebo in the Treatment of Nocturnal Leg Muscle Cramps (No. 1285–5082)," draft of an unpublished paper in Comment No. SUP00031, Docket No. 77N–0094, Dockets Management Branch.

(3) Hays, R., and J. J. Goodman, "Clinical Trial of the Efficacy of Quinine Sulfate in the Treatment of Nocturnal Leg Muscle Cramps, Protocol 86–48," draft of an unpublished paper in Comment No. C126, Docket No. 77N–0094, Dockets Management Branch.

(4) Bottner, M., "Clinical Trial of the Efficacy of Quinine Sulfate in the Treatment of Nocturnal Leg Muscle Cramps, Protocol 84–46," draft of an unpublished paper in Comment No. C123, Docket No. 77N–0094, Dockets Management Branch.

(5) Jones, K., and C. M. Castleden, "A Double-Blind Comparison of Quinine Sulphate and Placebo in Muscle Cramps," Age and Ageing, 12(2):155–158, 1983.

(6) Draft of an unpublished study entitled "A Short-Term, Randomized, Double-Blind, Parallel Study of Q-Vel vs. Quinine Sulfate vs. Vitamin E vs. Placebo in the Prevention and Treatment of Nocturnal Leg Cramps," Comment No. SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(7) Patel, H., "Use of Baseline Measurements in the Two-Period Cross-Over Design," *Communications in Statistics-Theory and Methods*, 12(23):2693–2712, 1983.

(8) Comment No. C159, Docket No. 77N–0094, Dockets Management Branch.

(9) Comment No. SUP00041, Docket No. 77N–0094, Dockets Management Branch.

(10) Letter from W. E. Gilbertson, FDA, to K. M. O'Brien, Scholl, Inc., coded LET00059, Docket No. 77N–0094, Dockets Management Branch.

(11) Letter from W. E. Gilbertson, FDA, to L. D. Fantasia, Ciba Consumer Pharmaceuticals, coded LET00060, Docket No. 77N–0094, Dockets Management Branch.

(12) Memorandum of telephone conversation between L. Fantasia, Ciba Consumer Pharmaceuticals, and L. Geismar, FDA, January 4, 1989, coded MT0009, Docket No. 77N–0094, Dockets Management Branch.

13. One comment disagreed with the agency's Category III classification of vitamin E for the treatment and/or prevention of nocturnal leg muscle cramps on the basis of a lack of adequate clinical data demonstrating the effectiveness of vitamin E for this indication (50 FR 46588 at 46591). The comment contended that there is sufficient evidence of vitamin E's effectiveness for this indication at present to warrant classifying it in Category I. The comment subsequently submitted the results of two clinical studies (Refs. 1 and 2) comparing vitamin E, quinine sulfate, a combination product containing vitamin E and quinine sulfate, and placebo for the treatment and/or prevention of nocturnal leg muscle cramps to support the effectiveness of the individual ingredients (vitamin E and quinine sulfate) as well as the combination of these ingredients for this indication. In addition, in responding to a citizen petition, one comment included a clinical study comparing vitamin E, quinine sulfate, a combination product containing both ingredients, and placebo (Ref. 3).

In the tentative final monograph, the agency concluded that there was a lack of controlled studies demonstrating the effectiveness of vitamin E in the treatment and/or prevention of nocturnal leg muscle cramps. The agency also determined that a safe and effective OTC dosage of vitamin E had not been established (50 FR 46588 at 46591). Therefore, the agency classified vitamin E in Category III for this use.

The agency has reviewed the additional clinical data that have been submitted and determined that they are not adequate to support the reclassification of vitamin E to Category I for this use. In one double-blind, randomized, crossover study (Ref. 1), a combination product containing 64.8 mg quinine sulfate and 400 I.U. of vitamin E in a lecithin base was compared to 64.8 mg of quinine sulfate for the treatment and/or prevention of nocturnal leg muscle cramps in subjects with a history of nocturnal leg muscle cramps. Subjects were randomized into two groups. All subjects took placebo during week 1 and at the end of week 1 only those subjects reporting at least three cramps per week were allowed to continue in the study. One group received the combination product during week 2 and quinine sulfate during week 4, while for the other group this order was reversed. Both groups also received placebo during weeks 3 and 5.

Both quinine sulfate and the combination of quinine sulfate and vitamin E were reported to reduce the frequency of nocturnal leg muscle

cramps in this study. A greater reduction in the frequency of these leg cramps was observed in subjects taking the combination product compared to subjects taking quinine alone. The difference was reported to be statistically significant using Wilcoxon's signed-rank test. No significant differences were found between treatments for either duration or severity of attacks. However, as previously discussed (see section I.C., comment 12), the study report did not include the study protocol, details of the statistical analysis, or individual subject data, and the analysis described does not properly separate carryover effect from treatment effect. Therefore, it is not possible to conclude that either treatment used in this study was effective for this indication.

The second clinical study (Ref. 2) was a double-blind, randomized, crossover study conducted at two sites and involved subjects with at least a 3-month history of at least two significant nocturnal leg muscle cramps per week. The subjects did not receive any drug for the first 1-week run-in period, then received four treatment periods (5 days each) that were separated by a 2-day washout period that included a 2-day drug-free period after the last treatment period. Thus, each subject received each of the four treatments (quinine sulfate 64.8 mg in combination with 400 I.U. vitamin E, 64.8 mg quinine sulfate, 400 I.U. vitamin E, and placebo). A total of 205 subjects (out of 209 subjects originally enrolled) completed the study at the two locations.

Each morning upon arising, subjects recorded on a daily evaluation form their response to questions regarding their difficulty or failure to get to sleep due to night leg cramps and whether or not the cramps had awakened them the previous night. Subjects were also asked to rate on a scale from 0 (no cramps) to 3 (very difficult) the effect of leg cramps on their ability to fall asleep and to record the number, time of occurrence, duration, and severity of leg cramps on the evaluation form. At the end of each weekly treatment period, subjects were asked to complete a global evaluation form and to record any change in their condition during that period, as follows: Greatly improved, slightly improved, no improvement, or worse. Subjects who selected "worse" were asked to explain why.

The comment's statistical analysis of the study evaluated the following variables based on portions of the subjects' daily evaluation forms and their global evaluation of treatment effect: (1) Number of nights per week subjects had difficulty getting to sleep due to night leg cramps, (2) effect of leg cramps on subject's ability to get to sleep, (3) number of nights per week that leg cramps prevented subjects from going to sleep, (4) number of nights per week that leg cramps woke subjects up, (5) number of leg cramps per week, (6) severity of the leg cramps, and (7) subjects' global evaluations of how their condition changed over the previous week. In addition, the following parameters were derived from these variables and evaluated: (1) Number of nights per week with leg cramps, (2) mean number of leg cramps per night, (3) total severity score during each week, (4) mean effect of leg cramps on sleep per week, and (5) mean severity per cramp. Separate analyses of the results from each site and analysis of pooled results from both study cites were reported. Vitamin E was found to be statistically significantly superior to placebo in 7 of the 12 efficacy variables evaluated on the basis of the combined data and in 6 of the 12 variables on the basis of data from at least one of the locations. The combination was found to be statistically superior to the individual ingredients and placebo on 11 out of the 12 variables evaluated on the basis of both the combined data and data from at least one of the locations. On that same basis, quinine sulfate was found to be statistically superior to placebo in 9 of the 12 variables evaluated and to vitamin E in 1 of the 12 variables. The comment concluded that quinine and vitamin E were significantly additive in their effects, and that it was this additive effect that resulted in the highly significant superiority of the combination over its individual components.

The agency has determined that the statistical analysis presented with this study is inadequate for review because the model used does not properly separate the carryover effect from the treatment effect. The model consisted of a sequence or code effect, a subject within code effect, a visit effect, and a treatment effect. For a given subject, this model says that code effect is constant over all visits; thus, carryover effect must be partially confounded with treatment effect. Therefore, the analysis presented cannot be relied upon to demonstrate the efficacy of any of the treatments.

The third clinical study was a multicenter, randomized, block, parallel-design with a single-blind, placebo, run-in period, followed by a 2-week double-blind, randomized, treatment phase (see section I.C., comment 12). No statistically significant treatment effect of vitamin E was detected at the end of the double-blind phase for any variable in this study.

The agency concludes that the submitted data are inadequate to establish the effectiveness of vitamin E or the combination of vitamin E and quinine sulfate for the treatment and/or prevention of nocturnal leg muscle cramps. Therefore, both vitamin E individually and in combination with quinine sulfate are nonmonograph conditions.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Refs. 4 and 5).

References

(1) Biodesign GmbH, "Clinical Evaluation of Q-VELR in Patients with Nocturnal Leg Muscle Cramps," draft of an unpublished paper in Comment No. SUP00031, Docket No. 77N–0094, Dockets Management Branch.

(2) Leo Winter Associates, Inc., "Final Medical Report and Data Summary Analysis and Final Statistical Report on Double Blind Randomized Crossover Study of Q-VELR Versus Quinine Sulfate Versus Vitamine E Versus Placebo in the Treatment of Nocturnal Leg Muscle Cramps (No. 1285–5082)," draft of an unpublished paper in Comment No. SUP00031, Docket No. 77N–0094, Dockets Management Branch.

(3) Draft of an unpublished study entitled "A Short-Term, Randomized, Double-Blind, Parallel Study of Q-Vel vs. Quinine Sulfate vs. Vitamin E vs. Placebo in the Prevention and Treatment of Nocturnal Leg Cramps," Comment No. SUP00033, Docket No. 77N–0094, Dockets Management Branch.

(4) Letter from W. E. Gilbertson, FDA, to L. D. Fantasia, Ciba Consumer Pharmaceuticals, coded LET00060, Docket No. 77N–0094, Dockets Management Branch.

(5) Memorandum of telephone conversation between L. Fantasia, Ciba Consumer Pharmaceuticals, and L. Geismar, FDA, January 4, 1989, coded MT00009, Docket No. 77N–0094, Dockets Management Branch.

D. Comments on Labeling

14. Several comments requested revisions in parts of the labeling proposed in the tentative final monograph. Two comments disagreed with the agency's statement of identity. One comment argued that it was a restatement of the indication proposed in § 343.150(b). In place of the agency's proposed statement of identity ("nocturnal leg muscle cramps treatment and/or prevention"), one comment requested that "muscle relaxant pain reliever" or "analgesic" be used. The comment contended that its suggestions were more descriptive of general pharmacological categories as described in 21 CFR 201.61. Another comment suggested changing the statement to "night leg cramp relief," arguing that this statement would be

more "meaningful to the layman" in accord with 21 CFR 201.61. The comment added that its suggested term is currently used in the labeling of a major OTC quinine product and reflects a more contemporary description of the condition being treated.

Referring to the warning proposed in § 343.150(c) that reads "Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur," one comment requested that the words "and consult a physician" be added following "discontinue use." The comment believed that such a warning would facilitate further medical treatment, if deemed necessary. The comment added that the agency had proposed similar warnings in other OTC drug monographs, for example, proposed § 333.50(c)(2) and (c)(3) for topical acne drug products (January 15, 1985, 50 FR 2172 at 2181). The comment explained that this addition to the warning would better serve the elderly, the population most likely to use the product.

One comment recommended that the agency distinguish between treatment and prevention directions for the drug, and proposed the following: "When night leg cramps occur, take 200–325 mg at once. To help prevent further night leg cramps, take 200–325 mg two hours before bedtime for 14 days. Do not exceed more than 325 mg daily." The comment concluded that, in providing adequate directions for use, it is appropriate to discuss dosages for initial onset of leg muscle cramps and for prevention of future cramps.

No ingredients for treating and/or preventing nocturnal leg muscle cramps are currently generally recognized as safe and effective for inclusion in an OTC drug monograph; thus, no OTC labeling is being finalized at this time. Accordingly, the comments' requests are not being addressed in this document. However, in the event that any ingredient for treating and/or preventing nocturnal leg muscle cramps reaches OTC drug monograph status, the agency will determine appropriate labeling at that time and publish it in a future issue of the **Federal Register**.

II. The Agency's Final Conclusions on OTC Drug Products For The Treatment and/or Prevention of Nocturnal Leg Muscle Cramps

The agency concludes that the data and information submitted are inadequate to establish the safety and effectiveness of quinine sulfate, vitamin E, or the combination of quinine sulfate and vitamin E for the treatment and/or prevention of nocturnal leg muscle cramps.

Three clinical studies of vitamin E, alone or in combination with quinine sulfate, were submitted. The report of one of the studies provided no details of the statistical analysis conducted; the model described in the summary of the analysis failed to separate carryover effect from treatment effect; and neither the protocol nor the individual subject data were provided. Independent verification of the conclusions presented, therefore, was not possible. On the basis of the information provided in the report, no conclusions about the efficacy of vitamin E are possible from this study. In another study, a statistically significant effect of vitamin E was reported in 7 of 12 endpoints, and statistically significant differences from placebo were reported in 11 of 12 endpoints for the combination product. In this study, however, treatment effect was confounded by carryover effect making it impossible to ascribe observed differences to vitamin E. Further, the third study, a large, multicenter, 2-week, parallel-design study comparing vitamin E, quinine sulfate, a combination of vitamin E and quinine sulfate, and placebo showed no significant difference for vitamin E compared to placebo on any parameter at the end of the double-blind treatment period.

Six clinical trials were submitted to establish the safety and efficacy of quinine sulfate in treating and/or preventing nocturnal leg muscle cramps. Effectiveness results reported as significant were not replicated within or between studies. In two crossover studies, significant differences between quinine sulfate and placebo were seen only in the second leg of the crossover, and there were significant pretreatment differences. Analysis of the first leg of these crossover studies showed no effect of quinine. In a large, 2-week, parallel study of quinine sulfate, vitamin E, and the combination of these ingredients versus placebo, no statistically significant differences were found between active treatments and placebo for the full 2 weeks of the study. Furthermore, each study involved multiple endpoints, none of which was prospectively declared as the primary efficacy variable(s) in any study. Statistical analysis was conducted without regard to adjustment for multiple comparisons, casting doubt on the validity of claimed statistical significance in many cases. In three crossover studies, the treatment effect was confounded by potential carryover effect making it impossible to attribute the results to the study drugs. The agency concludes that the data and information submitted do not provide substantial evidence of effectiveness of quinine sulfate, vitamin E, or a combination of quinine sulfate and vitamin E, in the treatment and/or prevention of nocturnal leg muscle cramps.

Finally, new information has raised serious safety concerns over the OTC availability of quinine sulfate for this use. Adverse events characteristic of quinine toxicity were observed in the healthy populations enrolled in the clinical efficacy studies at doses of 260 mg and 325 mg daily. These events included: Visual, auditory, and gastrointestinal symptoms, and fever. Studies of auditory, vestibular, and visual function in subjects given quinine confirm sensory disturbances at even lower doses. Altered pharmacokinetics with age results in a longer half-life of quinine in older people that suggests the frequency and severity of adverse effects may be greater in the elderly.

In addition to these adverse effects, serious and unpredictable hypersensitivity reactions to quinine occur. Symptoms are often dramatic, leading people to seek medical treatment. Hospitalization may be required, and fatalities have been reported. While quinine-induced thrombocytopenia is the hypersensitivity reaction most frequently reported to the agency's spontaneous reporting system, estimates of the incidence of quinine-induced thrombocytopenia are unreliable. Estimates based on the most direct evidence, however, suggest occurrence rates between 1:1,000 and 1:3,500. Quinine is the only drug available OTC that has such a high association with this serious hematologic sensitivity. Because there are no known factors that predispose people to the development of hypersensitivity to quinine, which may occur after 1 week of exposure or after months or years of use, label warnings cannot be expected to protect consumers from hypersensitivity reactions to quinine products.

Given the benign nature of nocturnal leg muscle cramps, the failure of the clinical studies to demonstrate efficacy of quinine sulfate in this condition, the evidence of symptoms of quinine toxicity at the OTC doses employed for leg cramps in a proportion of the target population, and the potential for serious, life threatening, and fatal hypersensitivity reactions to quinine, the agency concludes that quinine is not safe for OTC use in the treatment and/or prevention of nocturnal leg muscle cramps.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (47 FR 43562 and 50 FR 46588 at 46593).

An analysis of the cost and benefits of this regulatuion, conducted under Executive Order 12291, was discussed in the tentative final rule of November 8, 1985, (50 FR 46588). No comments were received in response to the agencies tentative final rule, and the substances of that analysis has not changed. Executive Order 12291 has been superseded by Executive Order 12866. FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Although the final rule will result in the removal of some products from the OTC marketplace, only a limited number of products are affected. These include: (1) All combination products containing quinine sulfate and vitamin E, (2) products containing quinine sulfate alone labeled for the treatment and/or prevention of nocturnal leg muscle cramps, (3) products containing vitamin E alone labeled with the same claim, and (4) any other products marketed OTC for this claim. No further initial introduction or delivery for introduction into interstate commerce of any OTC drug product labeled for the treatment and/or prevention of nocturnal leg muscle cramps will be allowed after the effective date of this final rule. Quinine is currently available as an OTC drug for treating chills and fever of malaria. Based on an agency review of currently marketed products, it appears that approximately two-thirds of these quinine-containing products are marketed for antimalarial use (with approximately one-third for the treatment and/or prevention of nocturnal leg muscle cramps). (OTC quinine drug products for antimalarial use will be discussed in future issues of the **Federal Register**.) Vitamin E is currently available OTC for use as a vitamin. This final rule does not affect the continued marketing and availability of products containing this vitamin provided the products are not labeled for the treatment and/or prevention of nocturnal leg muscle cramps. Products containing quinine sulfate and/or vitamin E may be relabeled and reformulated where necessary (e.g., combination products) and remain in the marketplace with other allowed claims, as described above. Accordingly, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

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.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512-516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. New § 310.546 is added to subpart E to read as follows:

§ 310.546 Drug products containing active ingredients offered over-the-counter (OTC) for the treatment and/or prevention of nocturnal leg muscle cramps.

(a) Quinine sulfate alone or in combination with vitamin E has been present in over-the-counter (OTC) drug products for the treatment and/or prevention of nocturnal leg muscle cramps, i.e., a condition of localized pain in the lower extremities usually occurring in middle life and beyond with no regular pattern concerning time or severity. There is a lack of adequate data to establish general recognition of the safety and effectiveness of quinine sulfate, vitamin E, or any other ingredients for OTC use in the treatment and/or prevention of nocturnal leg muscle cramps. In the doses used to treat or prevent this condition, quinine sulfate has caused adverse events such as transient visual and auditory disturbances, dizziness, fever, nausea, vomiting, and diarrhea. Quinine sulfate may cause unpredictable serious and life-threatening hypersensitivity reactions requiring medical intervention and hospitalization; fatalities have been reported. The risk associated with use of quinine sulfate, in the absence of evidence of its effectiveness, outweighs any potential benefit in treating and/or preventing this benign, self-limiting condition. Based upon the adverse benefit-to-risk ratio, any drug product containing quinine or quinine sulfate cannot be considered generally recognized as safe for the treatment and/or prevention of nocturnal leg muscle cramps.

(b) Any OTC drug product that is labeled, represented, or promoted for the treatment and/or prevention of nocturnal leg muscle cramps is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use for the treatment and/or prevention of nocturnal leg muscle cramps is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After February 22, 1995, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Dated: August 4, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

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