DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 94N–0355]

Drug Products Containing Quinine for the Treatment and/or Prevention of Malaria for Over-The-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would establish that over-the-counter (OTC) drug products containing quinine for the treatment and/or prevention of malaria are not generally recognized as safe and are misbranded. FDA is issuing this notice of proposed rulemaking after considering data and information on the safety of quinine.

DATES: Written comments by July 3, 1995. Written comments on the agency's economic impact determination by July 3, 1995. The agency is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

ADDRESSES: Written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

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 July 8, 1977 (42 FR 35346), FDA published an advance notice of proposed rulemaking to amend § 330.10(a)(6) (21 CFR 330.10(a)(6)), and to establish a monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products, together with the recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Although the Internal Analgesic Panel did not review the use of quinine as an antimalarial (other than to note its use in lowering the fever of malarial patients), it did review the safety of quinine used OTC as an analgesic, antipyretic, and muscle relaxant. The Internal Analgesic Panel concluded that "Until controlled studies show that a dose of not more than 325 milligrams (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." (See 42 FR 35346 at 35434.)

The agency's proposed regulation, in the form of a tentative final monograph, for OTC internal analgesic, antipyretic, and antirheumatic drug products was published in the **Federal Register** of November 16, 1988 (53 FR 46204). In the proposed rule (53 FR 46204 at 46243), the agency agreed with the Internal Analgesic Panel's conclusions concerning the safety of quinine and proposed that quinine be Category II (not generally recognized as safe and effective, and misbranded) when labeled for any OTC antipyretic or internal analgesic use other than the treatment and/or prevention of nocturnal leg muscle cramps.

In the **Federal Register** of May 10, 1993 (58 FR 27636), the agency issued a final rule for certain Category II and III (more data needed) active ingredients for which no significant comments or new data to upgrade the status of these ingredients had been submitted. In that final rule (58 FR 27636 at 27639), the agency determined that quinine (among other ingredients) is not generally recognized as safe and effective and is misbranded when present in OTC internal analgesic, antipyretic, and antirheumatic drug products.

In the **Federal Register** of October 1, 1982 (47 FR 43562), FDA published an advance notice of proposed rulemaking to amend § 330.10(a)(6) and 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. The document reflected 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. Although the Miscellaneous Internal Panel stated that quinine "* * * appears to be reasonably safe * * * in generally recommended doses of 200 to 325 mg daily" (47 FR 43562 at 43564), the Miscellaneous Internal Panel recommended that quinine be placed in Category III for use in the treatment of nocturnal leg muscle cramps because of the need for more information about both safety and efficacy (47 FR 43564).

The agency's proposed regulation 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). The agency concurred with both the Internal Analgesic and Miscellaneous Internal Panels that no active ingredient (including quinine) in OTC drug products 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. Although the agency acknowledged the OTC availability of quinine for the treatment of malaria (50 FR 46588 at 46592), only its use in the treatment and/or prevention of leg muscle cramps was covered by the proposed rule.

Subsequently, a citizen petition (Ref. 1) requested, among other things, a ban on the OTC sale of all quinine sulfate drug products. Upon review of the citizen petition and other data and information, in the **Federal Register** of August 22, 1994 (59 FR 43234), the agency issued a final rule establishing that any 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. The agency concluded, among other things, that quinine is not safe for OTC use in the treatment and/or prevention of nocturnal leg muscle cramps (59 FR 43234 at 43239). In that final rule, the agency also stated that OTC quinine drug products for antimalarial use would be discussed in future issues of the **Federal Register**.

The agency recognizes that quinine has been marketed for decades, on both an OTC and prescription basis, as an anti-infective agent for the treatment and/or prevention of malaria, a serious and potentially life-threatening disease that at one time was endemic in this country (Ref. 2). However, data and information (discussed elsewhere in this document) reviewed by the agency during the rulemaking for OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps have raised serious safety concerns about the continued OTC availability of quinine for the treatment and/or prevention of malaria.

For reasons discussed in this document, FDA is proposing to classify OTC drug products containing quinine or any quinine salt (e.g., quinine sulfate) labeled for the treatment and/or prevention of malaria as not generally recognized as safe, as misbranded, and a new drug within the meaning of 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, the proposed rule would also declare these products misbranded under section 502 of the act (21 U.S.C. 352). The rule will be incorporated into 21 CFR part 310, subpart E—Requirements for Specific New Drugs or Devices, by adding new § 310.547.

If this proposal is adopted as a final rule, the agency advises that the conditions under which the drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded will be effective 30 days after the date of publication of the final rule in the **Federal Register**. On or after that date, no OTC drug product that is subject to the rule may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to the final rule that is repackaged or relabeled after the effective date of the final rule must be in compliance with the final rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce.

References

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

(2) Russell, P. F., "The United States and Malaria: Debits and Credits," *Bulletin of the New York Academy of Medicine*, 44(6):623–653, 1968.

I. Quinine Use In The Treatment and/or Prevention of Malaria

Malaria is an infectious and potentially fatal disease caused by microscopic parasites (known as protozoa) of the genus *Plasmodium* (Refs. 1 and 2). Of the four species of *Plasmodium* typically associated with malaria in humans (*P. falciparum, P. vivax, P. ovale,* and *P. malariae*), malaria caused by *P. falciparum* (i.e., falciparum malaria) is the form of the disease usually associated with severe symptoms and death (if not promptly and properly treated). Malaria is most commonly transmitted to humans through the bite of an infected *Anopheles* mosquito (Refs. 1 and 2).

Malaria is initially characterized by nonspecific symptoms similar to those in viral illnesses. Symptoms include fever, lack of well-being, headache, fatigue, and muscle aches (Refs. 1 and 2). Laboratory analysis of blood samples from persons suspected of having malaria in conjunction with medical assessment and monitoring are necessary to: (1) Confirm a diagnosis of malaria; (2) determine the species of parasite(s) involved; (3) determine the density of parasites in the blood; (4) monitor therapeutic efficacy of treatment; (5) determine the potential for possible exposure to drug-resistant *P. falciparum* and (6) assess coexistent medical complications (all of which influence treatment decisions) (Refs. 1, 2, and 3).

Malaria was a major infectious disease in the United States in the 19th century and through the first third of the 20th century (Ref. 4). Through a combination of control programs, drug development, and education, malaria has since been virtually eradicated from North America (Refs. 1 through 4). Although, approximately 1,000 cases of malaria are reported to the Centers for Disease Control and Prevention (CDC) each year, all but a few cases are associated with travel to or from malaria-endemic areas in other parts of the world (Ref. 3). In those areas, however, malaria remains a major infectious disease and cause of death (Ref. 3).

Preparations made from the bark of one or more species of tree of the genus *Cinchona* have been used for centuries in the treatment and prevention of malaria (Ref. 5). Although *Cinchona* bark contains varying amounts of several drugs with antimalarial action, collectively known as quinoline alkaloids, quinine is the chief member of this group. Use of the term "quinine" in this document includes both the purified alkaloid and its derivatives. Oral quinine for the treatment of malaria is most commonly available as the salt quinine sulfate (Refs. 5 and 6).

In discussing the period in which malaria was endemic in the United States, Russell (Ref. 4) states that quinine "* * * in large bottles stood on the clock shelf in thousands of homes" in the 19th century and was extensively used as a mass prophylactic in malaria control programs in the first quarter of the 20th century. Russell notes that the use of less toxic and more effective synthetic antimalarial drugs (especially chloroquine) replaced quinine as the drug of choice by the 1930's. However, quinine has again become therapeutically important in the management of malaria due to the increasing resistance of *P. falciparum* (and more recently *P. vivax*) to chloroquine (Refs. 3 and 7).

Current treatment of malaria includes the use of oral quinine (in combination with other prescription antimalarial drugs) in medically uncomplicated cases when the disease is diagnosed or suspected of having been caused by *P. falciparum* contracted in areas where the parasite has become resistant to treatment with chloroquine, and the person is able to tolerate oral medications (Refs. 1, 2, and 3). Quinine is also used for the treatment of malaria following therapies involving exchange blood transfusions and/or intravenous drug therapy during hospitalization for complicated or high density falciparum malaria (a medical emergency), or when the species/drug sensitivity of the parasite is unknown (Refs. 2 and 3).

Falciparum malaria contracted in some areas has demonstrated a reduced susceptibility to standard quinine therapy (Refs. 3 and 7). Increasing resistance to quinine in such endemic areas may in part be due to its extensive use in unsupervised therapy (Ref. 7). Unsupervised therapy (with a drug known to commonly cause unpleasant adverse effects (see section II)) allows for incomplete treatments due to poor compliance with dosing instructions, a practice that may promote proliferation of malarial parasites less sensitive to quinine (Ref. 7). During the treatment of falciparum malaria with quinine, it is recommended that therapeutic efficacy be monitored by the daily examination of blood samples for the presence of malarial parasites until the samples are negative (Ref. 2). Failure to show parasite reduction may indicate drug resistance and necessitate a change in therapy. It is believed that the use of combinations of drugs (e.g., quinine plus either sulfadoxine/pyrimethamine or tetracycline) in the treatment of malaria may help prevent the development of drug-resistant strains of malarial parasites (Refs. 7, 8, and 9). Furthermore, it is believed that such interrupted or irregular quinine therapy during the treatment of falciparum malaria may predispose persons to the serious complications of blackwater fever, including anemia, red blood cell destruction, and renal failure (Refs. 10 and 11).

The continued spread of chloroquine-resistant *P. falciparum* has reduced the number of effective drugs for malaria prevention. CDC recommendations for the prevention of malaria in travelers take into account "* * * the risk of exposure to malaria, the effectiveness and safety of antimalarial drugs, and the use of personal protective measures." Quinine is not included in the list of drugs currently recommended by CDC for the prevention of malaria (Ref. 12).

In summary, malaria is an infectious disease that has been virtually eradicated from North America. Quinine, once the major therapeutic

agent for the treatment of malaria, was replaced in the 1930's with less toxic and more effective drugs. Current public health recommendations do not include the use of quinine in the prevention of malaria and limit its use in the treatment of the disease. Current recommendations for the treatment of malaria only include the use of quinine in combination therapies with other prescription drugs or as part of an intensive therapy involving blood transfusions and parenteral drugs during hospitalization. Clinical and laboratory assessments are necessary for prompt and proper diagnosis and treatment, including clinical monitoring during drug therapy to determine therapeutic efficacy and confirm the successful treatment of this serious and potentially fatal disease.

References

(1) Wyler, D. J., "Plasmodium Species (Malaria)," in *Principles and Practice of Infectious Diseases*, 3d ed., edited by G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett, Churchill Livingstone, New York, pp. 2056–2066, 1990.

(2) White, N. J., and J. G. Breman, "Malaria," in *Harrison's Principles of Internal Medicine*, 13th ed., edited by K. J. Isselbacher et al., McGraw–Hill, New York, pp. 887–895, 1994.

(3) McCarthy, A. E., and J. S. Keystone, "Malaria," in *Conn's Current Therapy, 1994*, edited by R. E. Rakel, W. B. Saunders Co., Philadelphia, pp. 94–100, 1993.

(4) Russell, P. F., "The United States and Malaria: Debits and Credits," *Bulletin of the New York Academy of Medicine*, 44(6): 623–653, 1968.

(5) Webster, Jr., L. T., "Drugs Used in the Chemotherapy of Protozoal Infections," in *The Pharmacological Basis of Therapeutics*, 8th ed., edited by A. G. Gilman et al., Pergamon Press, New York, pp. 978–998, 1990.

(6) McEvoy, G. K., editor, *AHFS Drug Information*, American Society of Hospital Pharmacists, Bethesda, MD, pp. 437–440, 1993.

(7) Weinke, T. et al., "Malaria Therapy in 452 Patients with Special Reference to the Use of Quinine," *Journal of Infection*, 25(2): 173–180, 1992.

(8) Smit, E. H. D., "Quinine Is Not What It Used To Be," *Acta Leidensia*, 55:21–27, 1987.

(9) Gramiccia, G., "Quinine: Should the Past Be Taken as a Guidance for the Future," *Acta Leidensia*, 55:15–20, 1987.

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

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

(12) "Recommendations for the Prevention of Malaria Among Travelers," *Morbidity and Mortality Weekly Report*, Public Health Service, Centers for Disease Control, 39(RR–3):1–10, 1990.

II. Safety Considerations

Quinine taken orally is currently used as part of a combination drug treatment of uncomplicated, low-density, chloroquine-resistant falciparum malaria. The adult dosage of quinine sulfate used for treatment of this condition is 600 to 650 mg three times daily for 3 to 7 days (Refs. 1 through 5).

In the final rule for OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps (59 FR 43234), the agency discussed a number of safety concerns related to the OTC availability of quinine for this use. The agency noted that adverse reaction reports (59 FR 43234 at 43239) suggested that quinine doses of 260 to 325 mg/day (which are much lower than the dosage used for the treatment of malaria) in healthy, middle-aged adults can produce symptoms of quinine toxicity, including auditory, visual, and gastrointestinal effects. The agency also noted that 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 (59 FR 43234 at 43239).

Symptoms of side effects associated with quinine (collectively referred to as "cinchonism") include tinnitus (a ringing or buzzing in the ear), nausea, vomiting, visual changes, auditory deficits, and cardiovascular abnormalities (Ref. 1). These symptoms are of varying severity depending upon the amount of quinine used. Some people will experience these side effects even at quinine doses of 260 to 325 mg/day (59 FR at 43239). These side effects occur more frequently at the higher dosages generally used in the treatment of malaria (Ref. 1).

A more severe problem is that people taking quinine remain at risk of developing hypersensitivity to the drug and experiencing a serious, life-threatening, or fatal reaction as a consequence. Reports of adverse reactions to quinine products listed in the agency's spontaneous reporting system show that, from 1969 through June 1992, FDA received 157 reports in which quinine was listed as a suspect drug. (See 59 FR 43234 at 43236.) There were 84 serious reactions: 23 deaths, 5 cases in which the person was disabled, and 56 hospitalizations not involving death or disablement. A trend of increasing numbers of reports per year since 1986 was also observed as the marketing of OTC drug products containing quinine for the treatment and/or prevention of nocturnal leg muscle cramps expanded after 1986.

A detailed review of 110 reports on file from 1969 through 1990 (59 FR 43236 to 43237) showed 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, 26 of the 110 reports were identified as cases where 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.

Quinine-induced thrombocytopenia may occur after 1 week of exposure or after months or years of quinine administration, and there may be no characteristic that would predict an adverse event in the person using the product (59 FR 43234 at 43243). The agency believes that a physician could help people using this drug appreciate the nature and frequency of the risk and 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, quinine has also been reported to have been associated with a number of other hypersensitivity reactions and pharmacologic effects (59 FR 43234 at 43243). 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, and hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD) deficient patients (59 FR 43234 at 43243). Furthermore, the possible pharmacologic effects may have particular significance for the elderly, who may be taking concomitant medications that adversely interact with quinine. Blackbourn and Bajrovic (Ref. 6) mention that altered pharmacokinetics with age 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.

The agency is aware of reports asserting that the labeling of OTC quinine products for malaria may not be consistent with current medical recommendations and/or may be associated with excessive or inadequate dosages (Refs. 7 and 8). Houlihan (Ref. 7) reported a case involving a 63-year-old man with a history of malaria who thought he was having a recurrence and began self-treatment with 975 mg of quinine sulfate three times a day in accordance with the product's labeling. After 2 days of self-treatment, the man was hospitalized for blindness (that resolved after 10 days) and exhibited electrocardiographic abnormalities (that resolved after 2 days). However, blood tests after hospitalization showed no indication of the existence of malarial parasites. The agency randomly reviewed labels from eight OTC quinine products labeled for use in malaria (Ref. 9) and noted dosage recommendations as low as 200 mg three times a day (for 6 to 12 days) and as high as 975 mg three times a day (for 6 to 12 days). A fatal dose of quinine for an adult is approximately 2,000 to 8,000 mg (Refs. 3, 10, and 11).

Thus, in the treatment of malaria, a narrow margin of safety exists between a therapeutic dose and a toxic dose of quinine. The agency believes this risk requires that a prescribing physician participate in the decision to use the drug, by assuring the diagnosis, considering the species and possible drug resistance of the infecting parasite, evaluating concurrent medical problems and medications, counseling patients concerning common and potentially severe adverse reactions, and monitoring patient safety and treatment effectiveness.

References

(1) White, N. J., and J. G. Breman, "Malaria," in *Harrison's Principles of Internal Medicine*, 13th ed., edited by K. J. Isselbacher et al., McGraw-Hill, New York, pp. 887–895, 1994.

(2) McCarthy, A. E., and J. S. Keystone, "Malaria," in *Conn's Current Therapy, 1994*, edited by R. E. Rakel, W. B. Saunders Co., Philadelphia, pp. 94–100, 1993.

(3) Webster, Jr., L. T., "Drugs Used in the Chemotherapy of Protozoal Infections," in *The Pharmacological Basis of Therapeutics*, 8th ed., edited by A. G. Gilman et al., Pergamon Press, New York, pp. 978–998, 1990.

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

(7) Houlihan, G. M., "Labeling of Nonprescription Quinine Needs Revision," *American Journal of Hospital Pharmacy*, 48(9):1892, 1991.

(8) Letter from H. Most, New York University Medical Center, to E. J. Martin, FDA, copy in OTC Vol. 260001, Docket No. 94N–0355, Dockets Management Branch.

(9) Copies of labeling for Genetco Quinine Sulfate 5 grain Capsules, Major Quinine Sulfate 325 mg Capsules, Royce Quinine Sulfate 325 mg Capsules, Rugby Quinine Sulfate 325 mg Captabs and Capsules, Westward Quinine Sulfate 200 mg and 325 mg Capsules, and Zenith Quinine Sulfate 200 mg Capsules, copy in OTC Vol. 260001, Docket No. 94N–0355, Dockets Management Branch.

(10) *Drug Facts and Comparisons*, Facts and Comparisons, Inc., St. Louis, pp. 366–368, January 1993.

(11) McEvoy, G. K., editor, *AHFS Drug Information*, American Society of Hospital Pharmacists, Bethesda, MD, pp. 437–440, 1993.

III. The Agency's Tentative Conclusions on OTC Quinine Drug Products for the Treatment and/or Prevention of Malaria

Malaria is a rare (in the United States) but serious and potentially deadly disease that exhibits several biologic patterns. Diagnosis and treatment of the disease depend on such factors as the species of parasite(s) involved, the density of parasites in the blood, the potential for possible exposure to drug-resistant *P. falciparum* or *P. vivax*, and the existence of coexistent medical complications. Malaria requires a medical diagnosis both to confirm the disease and to determine the treatment of choice. Prompt and proper diagnosis, treatment, and monitoring of therapeutic efficacy require laboratory analyses of blood samples and clinical assessments. Continuous physician monitoring is then necessary to determine if the selected drug therapy is effective and to determine if the malarial parasites have been eradicated. Accordingly, the agency concludes that consumers cannot safely and effectively self-treat malaria. Except for quinine products, no other antimalarial drug is available OTC.

Current public health recommendations do not include the use of oral quinine in the prevention of malaria and limit its use in the treatment of the disease (primarily to uncomplicated, low-density, chloroquine-resistant falciparum malaria). Current treatments for malaria include the use of quinine only in combination therapies with prescription drugs or as part of an intensive therapy involving blood transfusions and parenteral drugs during hospitalization. Thus, any patient properly using quinine should be under the care and supervision of a doctor.

Unsupervised quinine therapy (allowing for incomplete or interrupted treatments due to poor compliance with dosing instructions) is a practice believed to promote proliferation of malarial parasites less sensitive to quinine. Furthermore, interrupted quinine therapy in persons with falciparum malaria may also predispose them to the serious complications of blackwater fever, including anemia, red blood cell destruction, and renal failure.

There are serious safety concerns about the continued availability of quinine sulfate for OTC use, even at dosages much lower than those used for the treatment of malaria. Adverse events characteristic of quinine toxicity have been observed in healthy individuals at doses of 260 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 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.

Adverse events associated with quinine toxicity are common at the therapeutic doses of quinine used in the treatment of malaria (i.e., 600 to 650 mg three times daily for 3 to 7 days). A fatal dose of quinine for an adult is approximately 2,000 to 8,000 mg. Thus, in the treatment of malaria, a narrow margin of safety exists between a therapeutic dose and a toxic dose of quinine. Based upon quinine's demonstrated toxic effects and potential for harm if used in an unsupervised manner, the agency has determined that quinine should be available for the treatment of malaria only under the supervision of a doctor.

In addition to toxic effects, serious and unpredictable hypersensitivity reactions to quinine can occur. Symptoms are often dramatic, leading people to seek medical treatment. Hospitalization may be required, and fatalities have been reported. Quinine is the only drug available OTC that has such a high association with thrombocytopenia, a 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.

Quinine is an important drug in the treatment of drug-resistant forms of malaria. However, it is no longer the primary drug of choice for initial treatment of most types of malaria. In addition, there are serious and complicating aspects of the disease itself and some potentially serious and life threatening risks associated with the use of quinine at doses employed for the treatment of malaria. For these reasons, the agency tentatively concludes that quinine is not safe for OTC use in the treatment of malaria.

The agency is aware that quinine for the treatment of malaria has been marketed both OTC and by prescription, in all cases without approved new drug applications. This proposal would require that any OTC quinine drug products for the treatment and/or prevention of malaria be required to have an approved application for continued marketing. Prescription quinine drug products will be addressed in a future issue of the **Federal Register**.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed 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 proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and, so, 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. Quinine formulations for the treatment of malaria are currently marketed as both OTC and prescription products. None have an approved application. The final rule would stop the initial introduction or initial delivery for introduction into interstate commerce of all OTC quinine products that are labeled for the treatment and/or prevention of malaria, until such time as an approved application is obtained. The final rule would not affect the continued marketing and availability of quinine products by a doctor's prescription. The agency will address this form of marketing in a future issue of the **Federal Register**. The final rule may impose a direct one-time cost associated with changing product labels to conform with prescription labeling requirements. Due to the safety concerns discussed elsewhere in this document, manufacturers would be required to comply with the provisions of the final rule, if implemented, 30 days after its date of publication. Manufacturers are therefore urged to comply voluntarily with this proposed rule and to cease OTC marketing at the earliest possible date. Accordingly, the agency certifies that the proposed 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 invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC quinine drug products for the treatment and/or prevention of malaria. Types of impact may include, but are not limited to, costs associated with relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC quinine drug products for the treatment and/or prevention of malaria should be accompanied by appropriate documentation. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

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

Interested persons may, on or before July 3, 1995, submit written comments to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before July 3, 1995. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

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, it is proposed that 21 CFR part 310 be 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 § 310.547 is added to subpart E to read as follows:

§ 310.547 Drug products containing quinine offered over-the-counter (OTC) for the treatment and/or prevention of malaria.

(a) Quinine and quinine salts have been used OTC for the treatment and/or prevention of malaria, a serious and potentially life-threatening disease. Quinine is no longer the drug of choice for the treatment and/or prevention of most types of malaria. In addition, there are serious and complicating aspects of the disease itself and some potentially serious and life- threatening risks associated with the use of quinine at doses employed for the treatment of malaria. There is a lack of adequate data to establish general recognition of the safety of quinine drug products for OTC use in the treatment and/or prevention of malaria. Therefore, quinine or quinine salts cannot be safely and effectively used for the treatment and/or prevention of malaria except under the care and supervision of a doctor.

(b) Any OTC drug product containing quinine or quinine salts that is labeled, represented, or promoted for the treatment and/or prevention of malaria is regarded as a new drug within the meaning of section 201(p) of 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 malaria 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 May 19, 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: April 12, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

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