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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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing 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 final rule after considering public comment on the agency's notice of proposed rulemaking and all data and information that have come to the agency's attention on the safety of quinine.

EFFECTIVE DATE: April 20, 1998.

FOR FURTHER INFORMATION CONTACT: John D. Lipnicki, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

I. Background

The agency's proposed rule for OTC drug products for the treatment and/or prevention of malaria was published in the **Federal Register** of April 19, 1995 (60 FR 19650). In that proposed rule, the agency summarized the history of quinine in the OTC drug review for use as an analgesic, antipyretic, and muscle relaxant (for the treatment and/or prevention of nocturnal leg muscle cramps). The agency also recognized that quinine has been marketed for decades, on both an OTC and a 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. However, data and information reviewed by the agency during the rulemaking for OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps raised serious safety concerns about the continued OTC availability of quinine for the treatment and/or prevention of malaria. The agency also discussed serious safety and efficacy concerns about the continued OTC availability of quinine for the self-treatment of malaria without the care and supervision of a doctor. Interested persons were invited to file comments by July 3, 1995.

For reasons discussed in this document, FDA is classifying OTC drug products containing quinine or any quinine salt (e.g., quinine sulfate) and labeled for the treatment and/or prevention of malaria as not generally recognized as safe, as misbranded, and as 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, these products are considered misbranded under section 502 of the act (21 U.S.C. 352). The final rule is being incorporated into 21 CFR part 310, Subpart E—Requirements for Specific New Drugs or Devices, by adding new § 310.547.

As discussed in the preamble to the proposed rule for OTC drug products containing quinine for the treatment and/or prevention of malaria, the conditions under which the drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded would be effective 30 days after the date of publication of the final rule in the **Federal Register**. On or after April 20, 1998, no OTC drug product that is subject to the final 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.

In response to the proposed rule, one comment from a drug distributor was submitted. The comment (Ref. 1) is on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

Reference

(1) Comment No. C1, Docket No. 94N–0355, Dockets Management Branch.

II. The Agency's Conclusion on the Comment

The comment contended that the agency had failed to distinguish between the safety of quinine used for malaria and quinine used for leg cramps. The comment contended that the agency appeared to commingle its safety concerns about quinine for these two uses. The comment noted the agency's discussion of adverse reaction reports on file for quinine: 110 reports over 22 years from 1969 through 1990. The comment noted that this was an average of only five cases per year. The comment added that only 26 of the 110 reports were identified as cases where it can be reasonably concluded that quinine was the causative agent and that only 5 of the 26 reports involved quinine products used for the treatment of malaria. The comment concluded that this is an extremely low incidence of adverse reaction reports for quinine used for malaria: On average, 0.25 reports per year from 1969 through 1990. The comment further noted an agency statement in the **Federal Register** of August 22, 1994 (59 FR 43234 at 43252), 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).'' The comment concluded that OTC quinine products are safe and effective for the treatment of malaria due to the very low incidence of reports of adverse reactions for quinine products used for the treatment of malaria and the two-thirds marketing of quinine products for malaria. The comment argued that these facts demonstrate a lack of scientific support for this proposed rule.

The agency does not agree with the comment. The Center for Disease Control and Prevention stated that approximately 1,000 cases of malaria are reported each year in the United States (60 FR 19650 at 19651). It is not known how many of these people might have used quinine as part of their treatment. As discussed in section III of this document, quinine is not the drug of choice for malaria. Although many quinine products are marketed for the treatment of malaria, many of these products may have been used to treat leg muscle cramps. In 1987, a U.S. manufacturer of quinine estimated (based on sales figures) that there are well over 1 million users of quinine for leg muscle cramps in the United States (Ref. 1). Based on the large number of people using quinine for leg muscle cramps, a larger number of adverse drug experiences would be expected to occur

in this population when compared with the much smaller number of people using the drug for malaria. However, the daily dosage of quinine for treating malaria (see below) is greater than the dosage used for leg muscle cramps. Therefore, one would expect a higher rate of adverse reactions in the population using the drug for malaria.

In addition, the agency believes that underreporting of adverse reactions for OTC drug products is substantial. In the **Federal Register** of August 22, 1994 (59 FR 43234 at 43241 and 43242), the agency stated:

> 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 reviewed labeling from eight randomly selected OTC quinine drug products for malaria and found that the dosage recommendations ranged from 200 milligrams (mg) to 975 mg three times a day (for 6 to 12 days) (60 FR 19650 at 19653). The adverse event characteristics of quinine toxicity have been observed in clinical efficacy studies using typical doses for nocturnal leg cramps of 260 mg and 325 mg daily (59 FR 43234 at 43237). Given the much higher dosage recommended for malaria, it is reasonable to assume that these types of dose-related adverse reactions may increase with the malaria dosage. Finally, the agency is greatly concerned that if quinine remains available on an OTC basis labeled for the treatment and/or prevention of malaria, an extensive amount of such products would be sold OTC and used to treat and/or prevent leg muscle cramps, resulting in continued possible serious adverse reactions to OTC users of these products. Quinine was removed from the market for this use because of the lack of substantial evidence of effectiveness of quinine in this condition, along with evidence 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 (59 FR 43234 at 43251).

Reference

(1) Levy, 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.

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

Malaria is rare in the United States, but is a serious and potentially deadly disease. Diagnosis and treatment of malaria depend on such factors as the specie(s) of parasite involved, the density of parasites in the blood, the potential for possible exposure to drug-resistant parasites that are associated with malaria in humans, e.g., *Plasmodium falciparum* or *P. vivax*, and concomitant medical conditions. 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 the therapeutic efficacy of the treatment used 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 if the malarial parasites have been eradicated. Section 503(b)(1)(B) of the act (21 U.S.C. 353(b)(1)(B)) requires that a drug intended for use by man which, ''* * * because of its toxicity or other potentiality for harmful effect, * * * or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug * * *,'' be limited to prescription use only. Quinine used for malaria has considerable potential for toxic or harmful effects, and its use requires substantial collateral measures to ensure safe and effective treatment.

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 these and lower doses (59 FR 43234 at 43239). 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 could be greater in the elderly.

Adverse events associated with quinine toxicity are possible 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.

In addition to toxic effects, serious and unpredictable hypersensitivity reactions to quinine drug products 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 adverse event. 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 idiosyncratic hypersensitivity reactions to quinine drug products.

In addition, 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.

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 for malaria should be under the care and supervision of a doctor.

Based upon quinine's demonstrated toxic effects and potential for harm and the extensive collateral measures necessary to ensure a successful outcome for quinine therapy, the agency has determined that consumers cannot safely and effectively self-treat malaria. Accordingly, the agency concludes that quinine is not safe and effective for OTC use in the treatment of malaria.

This final rule requires that any OTC quinine drug product for the treatment and/or prevention of malaria have an approved application for continued marketing.

IV. Analysis of Impacts

An analysis of the costs and benefits of this regulation, conducted under Executive Order 12866, was discussed in the proposed rule for OTC quinine drug products for the treatment and/or prevention of malaria (60 FR 19650 at 19654). No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking.

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). 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). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities.

Title II of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation). The proposed rule that has led to the development of this final rule was already well into the publication cycle at the time the Unfunded Mandates Reform Act was enacted, publishing approximately 1 month later on April 19, 1995. The agency explains in this final rule that the final rule will not result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million.

The agency believes that this final rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this final rule is to establish that OTC quinine drug products for the treatment and/or prevention of malaria are not generally recognized as safe and are misbranded. Quinine formulations for the treatment of malaria are currently marketed as both OTC and prescription drug products. There are a limited number of quinine products marketed at this time. The agency's Drug Listing System identifies approximately 22 products containing quinine sulfate in dosage unit strengths of 200 mg to 325 mg. These products are marketed by 14 different manufacturers, most of which are considered to be small entities, using the U.S. Small Business Administration designations for this industry (750 employees). The agency believes that any other unidentified manufacturer of these products is also likely to be a small entity.

Manufacturers will no longer be able to market OTC quinine drug products for the treatment and/or prevention of malaria after the effective date of this final rule. While the manufacturers will incur a loss of revenue from the sale of these products, the agency believes the economic impact will be minimal for several reasons. First, it appears that current use in the United States of oral OTC quinine for the treatment of malaria is minimal. Approximately 1,000 cases of malaria are reported each year in the United States (60 FR 19650 at 19651). However, 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. The agency does not believe that any of the affected manufacturers have any considerable amount of sales of OTC quinine drug products that are used for the treatment of malaria. Second, when quinine is needed for treatment of malaria, this final rule does not affect the availability of quinine products by a doctor's prescription.

Manufacturers have known since April 1995 that if adequate data were not submitted to establish general recognition of the safety of quinine drug products for OTC use in the treatment and/or prevention of malaria, cessation of marketing of the current OTC drug products would be required when the final rule published. No data have been received. Further, the agency is concerned that if quinine remains available on an OTC basis labeled for the treatment and/or prevention of malaria, an extensive amount of such products would be sold and used to treat and/or prevent leg muscle cramps, resulting in continued possible adverse reactions to users of these products. Due to the safety concerns discussed in this document, manufacturers are required to comply with the provisions of this final rule 30 days after its date of publication in the **Federal Register**.

The agency considered but rejected several alternatives: (1) To allow continued marketing of OTC quinine drug products for the treatment of malaria, and (2) to allow a longer implementation period. FDA does not consider either of these approaches acceptable because the agency does not consider quinine to be safe for OTC drug use and because no new data concerning the safety of OTC quinine are forthcoming.

The analysis shows that this final rule is not economically significant under Executive Order 12866 and that the agency has considered the burden to small entities. The agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities. Finally, this analysis shows that the Unfunded Mandates Act does not apply to the final rule because it would not result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 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 April 20, 1998, 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: March 9, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[CA–169–0065; FRL–5974–6]

Approval and Promulgation of Implementation Plans; California State Implementation Plan Revision, South Coast Air Quality Management District

AGENCY: Environmental Protection Agency (EPA).

ACTION: Direct final rule.

SUMMARY: EPA is taking direct final action on revisions to the California State Implementation Plan. This action is an administrative change which revises the definitions in South Coast Air Quality Management District (SCAQMD or District) Rule 102, Definition of Terms. The intended effect of approving this action is to incorporate changes to the definitions for clarity and consistency with revised Federal and state definitions.

DATES: This action is effective on May 19, 1998 unless adverse or critical comments are received by April 20, 1998. If the effective date is delayed, timely notice will be published in the **Federal Register**.

ADDRESSES: Comments must be submitted to Andrew Steckel, Rulemaking Office (AIR–4), Air Division, U.S. Environmental Protection Agency, Region 9, 75 Hawthorne Street, San Francisco, CA 94105–3901.

Copies of the rule revisions and EPA's evaluation report are available for public inspection at EPA's Region IX office during normal business hours. Copies of the submitted rule revisions are available for inspection at the following locations:Rulemaking Office (AIR–4), Air Division, U.S. Environmental Protection Agency, Region IX, 75 Hawthorne Street, San Francisco, CA 94105.

Environmental Protection Agency, Air Docket (6102), 401 M Street, SW., Washington, DC 20460.

California Air Resources Board, Stationary Source Division, Rule Evaluation Section, 2020 L Street, Sacramento, CA 95814

South Coast Air Quality Management District, 21865 E. Copley Drive, Diamond Bar, CA 91765.

FOR FURTHER INFORMATION CONTACT: Cynthia G. Allen, Rulemaking Office (AIR–4), Air Division, U.S. Environmental Protection Agency, Region IX, 75 Hawthorne Street, San Francisco, CA 94105, Telephone (415–744–1189).

SUPPLEMENTARY INFORMATION:

I. Applicability

The rule being approved into the California SIP is: SCAQMD Rule 102, Definition of Terms, submitted on March 26, 1996, by the California Air Resources Board.

II. Background

On March 3, 1978, EPA promulgated a list of ozone nonattainment areas under the provisions of the Clean Air Act, as amended in 1977 (1977 Act or pre-amended Act), that included South Coast, see 43 FR 8964, 40 CFR 81.305. On May 26, 1988, EPA notified the Governor of California, pursuant to section 110(a)(2)(H) of the 1977 Act, that the South Coast AQMD portion of the California SIP was inadequate to attain and maintain the ozone standard and requested that deficiencies in the existing SIP be corrected (EPA's SIP-Call). In response to the SIP call and other requirements, the SCAQMD submitted many rules which EPA approved into the SIP.

This document addresses EPA's direct-final action for the following SCAQMD rule: Rule 102, Definition of Terms. This rule was adopted by SCAQMD on November 17, 1995, and submitted by the State of California for incorporation into its SIP on March 26, 1996. This rule was found to be complete on August 6, 1997, pursuant to EPA's completeness criteria that are set forth in 40 CFR part 51, appendix V [1] and is being finalized for approval into the SIP. This rule was originally adopted as part of SCAQMD's efforts to achieve the National Ambient Air Quality Standards (NAAQS) for ozone and in response to EPA's SIP-Call and the section 182(a)(2)(A) CAA requirement.

The following is EPA's evaluation and final action for this rule.

III. EPA Evaluation and Action

In determining the approvability of a rule, EPA must evaluate the rule for consistency with the requirements of the CAA and EPA regulations, as found in section 110 and part D of the CAA and 40 CFR part 51 (Requirements for Preparation, Adoption, and Submittal of Implementation Plans). The EPA interpretation of these requirements appears in various EPA policy guidance documents. [2]

EPA previously reviewed many rules from the SCAQMD and its predecessor agencies and incorporated them into the federally approved SIP pursuant to section 110(k)(3) of the CAA. Those rules that are being superseded by today's action are as follows:

- Los Angeles County Rule 2, Definitions (submitted 6/30/72)
- Orange County Rule 2, Definitions (submitted 6/30/72)
- Riverside County Rule 2, Definitions (submitted 2/21/72 and 6/30/72)
- San Bernardino County Rule 2, Definitions (submitted 2/21/72)
- South Coast Air Quality Management District Rule 102, Definition of Terms (submitted 2/10/77, 10/13/77, and 6/22/78)

[1] EPA adopted the completeness criteria on February 16, 1990 (55 FR 5830) and, pursuant to section (110)(k)(1)(A) of the CAA, revised the criteria on August 26, 1991 (56 FR 42216).

[2] Among other things, the pre-amendment guidance consists of those portions of the proposed post-1987 ozone and carbon monoxide policy that concern RACT, 52 FR 45044 (November 24, 1987); ''Issues Relating to VOC Regulation Cutpoints, Deficiencies, and Deviation, Clarification to Appendix D of November 24, 1987 Federal Register Notice'' (Blue Book)(notice of availability was published in the Federal Register on May 25, 1988); and the existing control technique guidelines (CTGs).