

estimated to be 34,125 hours (13,650 x 2.5 hours).

FDA received 89,990 new foreign facility registrations during 2003; 49,574 during 2004; and 29,193 during 2005. Based on this experience, FDA estimates the annual number of new foreign facility registrations will be 29,200. FDA estimates that listing the information required by the Bioterrorism Act and presenting it in a format that will meet the agency's registration regulations will require a burden of approximately 8.5 hours per average foreign facility registration. The average foreign facility burden hour estimate of 8.5 hours includes an estimate of the additional burden on a foreign facility to obtain a U.S. agent, and takes into account that for some foreign facilities the respondent completing the registration may not be fluent in English and/or not have readily available Internet access. Thus, the total annual burden for new foreign facility registrations is estimated to be 248,200 hours (29,200 x 8.5 hours).

FDA received 131,354 updates to facility registrations during 2003; 137,384 during 2004; and 92,835 during 2005. Based on this experience, FDA estimates that it will receive 92,850 updates annually. FDA also estimates that updating a registration will, on average, require a burden of approximately 1 hour, taking into account fluency in English and Internet access. Thus, the total annual burden for updating all registrations is estimated to be 92,850 hours.

FDA received 12,556 cancellations of facility registrations during 2003; 7,467 during 2004; and 1,280 during 2005. Based on this experience, FDA estimates the annual number of cancellations will be 1,300. FDA also estimates that cancelling a registration will, on average, require a burden of approximately 1 hour, taking into account fluency in English and Internet access. Thus, the total annual burden for cancelling registrations is estimated to be 1,300 hours.

In cases where a regulation implements a statutory information collection requirement, only the additional burden attributable to the regulation, if any, has been included in FDA's burden estimate.

Dated: December 11, 2006.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

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**BILLING CODE 4160-01-S**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. 2006N-0476]

#### Drug Products Containing Quinine; Enforcement Action Dates

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing its intention to take enforcement action against unapproved drug products containing quinine (including quinine sulfate and any other salt of quinine) and persons who cause the manufacture of such products or their shipment in interstate commerce. Drug products containing quinine, quinine sulfate, and any other salt of quinine are new drugs that require approved applications. One firm has an approved application to market a drug product containing quinine sulfate to treat malaria; this product has been designated an orphan drug product. Other manufacturers who wish to market a drug product containing quinine, quinine sulfate, or any other salt of quinine must obtain FDA approval of a new drug application (NDA) or an abbreviated new drug application (ANDA); consideration of any such applications will be subject to the rights of the current NDA holder under the Orphan Drug Act.

**DATES:** This notice is effective December 15, 2006.

For marketed, unapproved drug products containing quinine, quinine sulfate, or any salt of quinine that have a National Drug Code (NDC) number that is listed with FDA on the effective date of this notice (i.e., "currently marketed products"), however, the agency intends to exercise its enforcement discretion to permit products marketed with those NDC numbers a brief period of continued marketing after December 15, 2006 as follows. Any firm manufacturing such an unapproved product may not manufacture that product on or after February 13, 2007. Any firm distributing such an unapproved product may not ship the product in interstate commerce on or after June 13, 2007. Unapproved drug products containing quinine, quinine sulfate, or any salt of quinine that are not currently marketed products on the effective date of this notice must, as of the effective date of this notice, have approved applications prior to their shipment in interstate commerce. Submission of an application does not

excuse timely compliance with this notice.

**ADDRESSES:** All communications in response to this notice should be identified with Docket No. 2006N-0476 and directed to the appropriate office listed as follows:

*Regarding applications under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(b)):* Division of Special Pathogen and Transplant Products, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993-0002.

*Regarding applications under section 505(j) of the act:* Office of Generic Drugs, Center for Drug Evaluation and Research (HFD-600), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855.

*All other communications:* John Loh, Center for Drug Evaluation and Research (HFD-310), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** John Loh, Center for Drug Evaluation and Research (HFD-310), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-8965, e-mail: [john.loh@fda.hhs.gov](mailto:john.loh@fda.hhs.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. Background

Quinine is the chief alkaloid of cinchona, the bark of the cinchona tree indigenous to parts of South America. Recorded medical use of cinchona dates back to the 17th century. Quinine was first isolated from cinchona in 1820. Quinine (the term "quinine" as used in this notice refers to quinine, quinine sulfate, and other quinine salts) has been used to treat malaria since the 19th century. It was used extensively for mass prophylaxis in malaria control programs in the early 20th century. As more predictable and effective synthetic antimalarial drugs began to be developed in the 1930s, the use of quinine to treat and/or prevent malaria declined. However, with the increasing resistance of the malaria parasite to some of these synthetic malarial treatments, quinine is again emerging as an important treatment for malaria.

Quinine also has been used for the treatment and/or prevention of nocturnal leg muscle cramps, similar conditions such as a restless leg syndrome, and, very rarely, a number of other conditions, including Babesiosis (another parasitic infection) and certain myotonic disorders. The predominant

use of quinine in the United States is for leg cramps and similar conditions.

Quinine has a history of being marketed over-the-counter (OTC) and by prescription, as a single-ingredient product or sometimes in combination with other ingredients, such as vitamin E. Its use as a treatment for leg cramps and as an antimalarial agent was considered in the OTC drug monograph review. In the **Federal Register** of August 22, 1994 (59 FR 43234), the agency announced its conclusion that OTC drug products for the treatment and/or prevention of nocturnal leg muscle cramps are not generally recognized as safe and effective (GRASE), and are therefore new drugs under section 201(p) of the act (21 U.S.C. 321(p)). In reaching this conclusion, the agency reviewed extensive information from studies and adverse drug events reported to the agency regarding the safety and efficacy of products containing quinine sulfate. The agency identified numerous safety concerns associated with use of quinine sulfate (59 FR 43234 at 43235 through 43244). Further, the agency's review assessed the effectiveness of quinine sulfate for prevention and/or treatment of leg cramps, and concluded that the data were not adequate to establish that quinine sulfate, alone or in combination with vitamin E, is effective for these uses (59 FR 43234 at 43245 through 43249). The agency's conclusions regarding OTC drug products containing quinine indicated for treatment or prevention of nocturnal leg cramps are provided in 21 CFR 310.546.

Subsequently, in the **Federal Register** of March 20, 1998 (63 FR 13526), the agency announced its conclusions regarding OTC drug products containing quinine or any quinine salt (e.g., quinine sulfate) labeled for the treatment and/or prevention of malaria. Because of the safety issues associated with these products, the agency concluded that these OTC products are not generally recognized as safe (GRAS) and are therefore new drugs as well. The agency's conclusions regarding OTC drug products containing quinine indicated for treatment or prevention of malaria are provided in 21 CFR 310.547.

## II. Safety Issues in Use of Quinine Drug Products

Serious safety concerns, including fatalities, associated with drug products containing quinine are well-documented in the literature and in adverse drug events reported to the agency. One of these adverse events is quinine toxicity, which is known as cinchonism, a cluster of symptoms of varying severity that include tinnitus,

dizziness, disorientation, nausea, visual changes, and auditory deficits. There also is evidence that quinine causes QT prolongation and serious cardiac arrhythmias including torsades de pointes. People taking quinine are at risk of developing hypersensitivity to the drug and experiencing a serious, life-threatening, or fatal reaction as a consequence. Serious adverse reactions associated with quinine use also include severe skin reactions, thrombocytopenia and other serious hematological events, permanent visual and hearing disturbances, hypoglycemia, and generalized anaphylaxis. Overall, from 1969 through September 11, 2006, FDA received 665 reports of adverse events with serious outcomes associated with quinine use, including 93 deaths. Among the more common types of events with serious outcomes reported to the agency are cardiac events, thrombocytopenia, renal failure, hypersensitivity/skin reactions, ophthalmologic events, hearing disorders, and thrombotic thrombocytopenic purpura (TTP).<sup>1</sup>

Further, quinine sulfate is known to have a narrow therapeutic index, with a very narrow margin of safety between doses that are therapeutic in the treatment of malaria and doses that are toxic. Many of the adverse events associated with quinine are dose-related (63 FR 15526 at 13527). Overdosing of quinine sulfate can result in cardiac arrhythmia, ototoxicity, blindness, or death. The rate of clearance of quinine sulfate tends to decline with age, meaning the blood level of quinine tends to be higher for a longer period of time in the elderly for a given dose compared to younger persons and the frequency and severity of adverse effects may also be greater in the elderly (63 FR 13526 at 13527).

## III. Current Status of Quinine Drug Products

Mutual Pharmaceutical Company, Inc., (Mutual), of Philadelphia, PA, submitted an NDA for single-ingredient quinine sulfate in 324-milligram capsules (NDA 21-799), which was approved by FDA on August 12, 2005. The product is approved to treat uncomplicated *Plasmodium falciparum* malaria only and is a prescription drug product.

<sup>1</sup>Serious adverse reactions include the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or an important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other mentioned serious outcomes (§ 314.80 (21 CFR 314.80)).

NDA 21-799 is the only approved application for a product containing quinine. Because the incidence of malaria in the United States is rare, Mutual sought and was granted orphan drug status for its product under section 526 of the act (21 U.S.C. 360bb).<sup>2</sup>

The approved labeling for Mutual's quinine sulfate product provides extensive warnings regarding the use of the product. It states that the product is not approved for the prevention or treatment of nocturnal leg cramps and explicitly warns against the use of the product for these indications. It describes findings related to use of quinine sulfate and QT interval prolongation, along with the association of the drug with potentially fatal cardiac arrhythmias. The labeling contraindicates use of the product in patients with prolonged QT interval, G-6-PD deficiency, optic neuritis, myasthenia gravis, and known hypersensitivity to quinine or related drugs. The labeling also identifies numerous drugs that should not be used concomitantly with quinine, including neuromuscular blocking agents, rifampin, class IA and III antiarrhythmic agents, HISMANIL (astemizole), PROPULSID (cisapride), erythromycin, and other medications known to cause QT prolongation.

Because of the risks associated with use of quinine sulfate, Mutual agreed, as part of the approval of its product, to implement an educational program for physicians and other health care providers regarding the safe and effective use of quinine sulfate for treatment of uncomplicated *P. falciparum* malaria. The firm also agreed to provide written information to physicians regarding the unfavorable risk/benefit ratio of oral quinine sulfate for treatment of nocturnal leg cramps, as compared with the favorable risk/benefit ratio for treatment of uncomplicated *P. falciparum* malaria. For 3 years following approval, Mutual will also provide the agency with twice-yearly analyses of postmarketing adverse event data, in addition to 15-day and quarterly reports required under § 314.80(c)(1) and (c)(2).

<sup>2</sup>The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans. Enacted in 1983, the intent of the Orphan Drug Act is to stimulate the research, development, and approval of products that treat rare diseases. Under this law, which amended the act and is provided in 21 U.S.C. 360aa to 360ee, a firm that receives approval for a product designated as an orphan drug receives for the product a special period of exclusivity of 7 years after the date of approval, during which the agency will not approve another application for the same drug, as defined in 21 CFR 316.3, for the same condition submitted by another applicant.

Unapproved quinine sulfate products are also available on the market. The agency reviewed the labeling of unapproved quinine products listed with FDA under the requirement of section 510(j) of the act (21 U.S.C. 360(j)). In general, labeling for the unapproved products does not contain many of the warnings found in the approved product labeling and therefore does not reflect the most current data regarding quinine sulfate. For instance, unapproved products typically do not provide information about prolongation of the QT interval, warn against use of the product to treat leg cramps, or identify many of the contraindications and drug interactions for quinine sulfate products. The agency also reviewed dosing regimens recommended in the labeling of unapproved quinine sulfate products and found that many of the recommend dosing regimens, for which supporting evidence has not been evaluated by the agency, are inconsistent with the dosing recommendations for the approved product, which are based on clinical evidence. These regimens, at one end of the spectrum of recommended doses, could lead to substantial underdosing, risking treatment failure, and promoting the development of malarial resistance to quinine, and, at the other end of the spectrum, could lead to overdosing, increasing the risk of serious adverse events, and death.

#### IV. Legal Status

##### A. Quinine Products Are New Drugs Requiring Approved Applications

Based on the safety and effectiveness considerations described previously, drugs containing quinine, quinine sulfate, or any other salt of quinine are not GRASE for the treatment or prevention of malaria, leg cramps, or any other condition under section 201(p) of the act. Therefore, a drug product containing any of these ingredients, alone or in combination with other drugs, is regarded as a new drug as defined in section 201(p) of the act and is subject to the requirements of section 505 of the act. An approved application is required to market the product. As set forth in this notice, approval of an NDA under section 505(b) of the act (including section 505(b)(2)) and 21 CFR 314.50 or an ANDA under section 505(j) of the act and 21 CFR 314.94 is required as a condition for manufacturing or marketing all quinine products. After the dates identified in this notice (see **DATES**), FDA intends to take enforcement action, as described in this notice, against unapproved drug

products containing quinine and persons who cause the manufacture or interstate shipment of such products. Submission of an application does not excuse timely compliance with this notice.

The Mutual quinine sulfate product (NDA 21-799) described in section III of this notice has been designated as the reference listed drug product. Firms should be aware that review and approval of any applications for quinine products will be subject to the rights of the current NDA holder under the Orphan Drug Act, including section 527 of the act (21 U.S.C. 360cc) and FDA's regulations in 21 CFR part 316.

##### B. Notice of Enforcement Action

Although not required to do so by the Administrative Procedure Act, the act, or any rules issued under its authority, or for any other legal reason, FDA is providing this notice to firms that are marketing drug products containing quinine without an approved application that the agency intends to take enforcement action against such products and those who cause them to be manufactured or shipped in interstate commerce. Consistent with the priorities identified in the agency's guidance entitled "Marketed Unapproved Drugs—Compliance Policy Guide" (the Marketed Unapproved Drugs CPG), the agency is taking action at this time against unapproved quinine products because: (1) As described in section II of this notice, quinine is a drug with significant safety risks; and (2) the agency has approved an application to market a drug product containing quinine sulfate, and thus the continued marketing of unapproved quinine products is a direct challenge to the drug approval process. Manufacturing or shipping unapproved quinine products can result in seizure, injunction, or other judicial proceeding. Consistent with policies described in the Marketed Unapproved Drugs CPG, the agency does not expect to issue a warning letter or any other further warning to firms marketing unapproved drug products containing quinine prior to taking enforcement action. The agency also reminds firms that, as stated in the Marketed Unapproved Drugs CPG, any unapproved drug marketed without a required approved drug application is subject to agency enforcement action at any time. The issuance of this notice does not in any way obligate the agency to issue similar notices or any notice in the future regarding marketed unapproved drugs.<sup>3</sup>

<sup>3</sup>The agency's general approach in dealing with these products in an orderly manner is spelled out

As described in the Marketed Unapproved Drugs CPG, the agency may, at its discretion, exercise its enforcement discretion and identify a period of time during which the agency does not intend to initiate an enforcement action against a currently marketed unapproved drug on the grounds that it lacks an approved application under section 505 of the act, to preserve access to medically necessary drugs, or ease disruption to affected parties, for instance. The agency notes the following: (1) Quinine is a drug with significant safety risks that are comprehensively described only in the labeling of the approved product; (2) the most common use of quinine is an off-label use for which the drug has an unfavorable risk-benefit profile, which is described in the labeling of the approved product, but not the unapproved products; (3) Mutual can provide the market with enough approved quinine sulfate to meet patients' needs for the approved indications; and (4) Mutual has now obtained approval of its quinine sulfate product. Therefore, the agency intends to proceed as follows.

This notice is effective December 15, 2006. Unapproved drug products containing quinine, quinine sulfate, or any salt of quinine that are not currently marketed products on the effective date of this notice must, as of this date, have approved applications prior to their shipment in interstate commerce. For marketed, unapproved quinine-containing products that have an NDC number that is listed with the agency on the effective date of this notice, however, the agency intends to exercise its enforcement discretion to permit products marketed with those NDC numbers a period of continued marketing after December 15, 2006 as follows. Any firm manufacturing such an unapproved drug product containing quinine may not manufacture that product on or after February 13, 2007.<sup>4</sup> Any firm distributing such an unapproved product may not ship the

in the Marketed Unapproved Drugs CPG. However, this CPG provides notice that any product that is being marketed illegally, and the persons responsible for causing the illegal marketing of the product, are subject to FDA enforcement action at any time.

<sup>4</sup>If a firm continues to manufacture or market a product covered by this notice after the applicable enforcement date has passed, to preserve limited agency resources, FDA may take enforcement action relating to all of the firm's unapproved drugs that require applications at the same time. (See, e.g., *United States v. Sage Pharmaceuticals*, 210 F.3d 475, 479-480 (5th Cir. 2000) (permitting the agency to combine all violations of the act in one proceeding, rather than taking action against a firm with multiple violations of the act in "piecemeal fashion").)

product in interstate commerce on or after June 13, 2007. The agency, however, does not intend to exercise its enforcement discretion as outlined in this paragraph if: (1) A manufacturer or distributor of an unapproved product covered by this notice is violating other provisions of the act; or (2) it appears that a firm, in response to this notice, increases its manufacture or interstate shipment of quinine drug products above its usual volume during these periods.

Drug manufacturers and distributors should be aware that the agency is exercising its enforcement discretion as described previously only in regard to drug products containing quinine that are marketed under an NDC number listed with the agency on the effective date of this notice. Unapproved drug products containing quinine that are not currently marketed and listed with the agency on the effective date of this notice must, as of the effective date of this notice, have approved applications prior to their shipment in interstate commerce. Moreover, submission of an application does not excuse timely compliance with this notice.

### C. Discontinued Products

Some firms may have previously discontinued the manufacturing or distribution of products covered by this notice without removing them from the listing of their products under section 510(j) of the act. Other firms may discontinue manufacturing or marketing listed products in response to this notice. Firms that wish to notify the agency of product discontinuation should send a letter, signed by the firm's chief executive officer, fully identifying the discontinued product(s), including its NDC number(s), and stating that the product(s) has (have) been discontinued and will not be marketed again without FDA approval, to John Loh (see **ADDRESSES**). Firms should also update the listing of their products under section 510(j) of the act to reflect discontinuation of unapproved quinine products. FDA plans to rely on its existing records, the results of a subsequent inspection, or other available information when it initiates enforcement action.

This notice is issued under sections 502 and 505 of the act (21 U.S.C. 352) and under authority delegated to the Deputy Commissioner for Policy under section 1410.10 of the FDA Staff Manual Guide.

Dated: December 11, 2006.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

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**BILLING CODE 4160-01-S**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. 2006N-0493]

#### **International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization Scheduling Recommendations for Dronabinol and its Stereoisomers, and Oripavine**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is providing interested persons with the opportunity to submit written comments concerning recommendations by the World Health Organization (WHO) to impose international manufacturing and distributing restrictions, under international treaties, on certain drug substances. The comments received in response to this notice will be considered in preparing the U.S. position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs (CND) in Vienna, Austria, March 12 to 16, 2007. This notice is issued under the Controlled Substances Act.

**DATES:** Submit written or electronic comments by January 16, 2007.

**ADDRESSES:** Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

**FOR FURTHER INFORMATION CONTACT:** James R. Hunter, Center for Drug Evaluation and Research (HFD-9), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5563, e-mail: [james.hunter@fda.hhs.gov](mailto:james.hunter@fda.hhs.gov).

#### **SUPPLEMENTARY INFORMATION:**

##### **I. Background**

The United States is a party to the 1971 Convention on Psychotropic Substances (the 1971 Convention). Section 201(d)(2)(B) of the Controlled Substances Act (the CSA) (21 U.S.C. 811(d)(2)(B)) provides that when the United States is notified under Article 2

of the 1971 Convention that CND proposes to decide whether to add a drug or other substance to one of the schedules of the 1971 Convention, transfer a drug or substance from one schedule to another, or delete it from the schedules, the Secretary of State must transmit notice of such information to the Secretary of Health and Human Services (the Secretary of HHS). Section 201(d)(2)(B) requires the Secretary of HHS, after receiving notification proposing scheduling, to publish a summary of such information in the **Federal Register** to provide opportunity for interested persons to submit comments on the proposed scheduling action. The Secretary of HHS must then evaluate the proposal and furnish a recommendation to the Secretary of State that shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

As detailed in the following paragraphs, the Secretary of State has received notification from the Secretary-General of the United Nations (the Secretary-General) regarding the drug substance dronabinol (INN), including its stereoisomers, to be considered for control under the 1971 Convention. The notification reflects the recommendations from the 34th WHO Expert Committee for Drug Dependence (ECDD), which met in March 2006. In the **Federal Register** of December 13, 2005 (70 FR 73775), FDA announced the WHO ECDD review and invited interested persons to submit information for WHO's consideration.

The United States is also a party to the 1961 Single Convention on Narcotic Drugs (the 1961 Convention). The Secretary of State has received notification from the Secretary-General regarding the drug substance oripavine to be considered for control under the 1961 Convention. The CSA does not require the Secretary of HHS to publish a summary of such information in the **Federal Register**. Nevertheless, in an effort to provide interested and affected persons an opportunity to submit comments on the WHO ECDD recommendations for narcotic drugs, notification on this substance is also included in this **Federal Register** notice. The comments will be shared with other relevant agencies to assist the Secretary of State in formulating the U.S. position on the control of these substances. The HHS recommendations are not binding on the representative of the United States in discussions and negotiations relating to the proposal on control of substances under the 1961 Convention.