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

FDA received 89,990 new foreign facility registration applications 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 requirements 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 in 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.

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. E6–21375 Filed 12–14–06; 8:45 am]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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 20903–0002.

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.

For further information contact: John Loh, Center for Drug Evaluation and Research (HFD–310), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

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. Q
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
(GRAE), 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 several types of leg cramps.

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 more favorable
risk/benefit ratios for other medications
known to cause QT prolongation.

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). 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, HSILAMIT (azamiflozole),
PROPULS (caspasprine), erythromycin,
and other medications known to cause
QT prolongation.

Serious safety concerns, including
fatally 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
cinchaonism, a cluster of symptoms of
varying severity that include tinnitus,
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(i) of the act (21 U.S.C. 360(i)). 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.

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. Any firm distributing such an unapproved product may not ship the product 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.

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 (9th 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”].)

3The agency’s general approach in dealing with these products in an orderly manner is spelled out in the Marketed Unapproved Drugs CPG. The 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.

4If 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 (9th 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.


Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 06–9731 Filed 12–12–06; 11:00 am]

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.

SUPPLEMENTAL INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (the 1971 Convention). 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.