

Questions and Answers about FDA's Enforcement Action Against Unapproved Quinine Products

What action is FDA taking concerning quinine-containing drugs?

FDA has ordered all firms to cease manufacturing unapproved products containing quinine, including quinine sulfate and any other salt of quinine on or after February 13, 2007, and to cease shipping such products interstate on or after June 13, 2007. After these dates only FDA approved quinine products may be manufactured and shipped interstate. This action is described in the Federal Register of December 15, 2006, [71 FR 75557].

Will drug products containing quinine remain on the market?

This action does not affect quinine drug products marketed with FDA approval. FDA has approved one quinine drug product, which is manufactured by Mutual Pharmaceutical Company, Inc. (Mutual), of Philadelphia, PA. It was approved on August 12, 2005, as a prescription drug solely for the treatment of uncomplicated malaria caused by the parasite *Plasmodium falciparum*. It contains quinine sulfate as the active ingredient without any additional active ingredients in 324 mg. capsules and is sold under the trade name Qualaquin™ (quinine sulfate) with the following NDC number: 13310-154.

Under today's action, previously-manufactured unapproved products may still be found on pharmacy shelves for a short period of time. Patients should talk to their health care provider about whether to use any unapproved quinine-containing product. Patients and health care professionals should carefully consider the medical condition being treated, the patient's previous response to the drug, and the availability of approved alternatives as part of discussing the benefits and risks of this treatment.

Why is FDA taking this action?

Numerous drug products containing quinine sulfate are marketed without approved applications for malaria and many are used off-label to treat and/or prevent nocturnal leg muscle cramps and related conditions. Quinine is associated with a variety of serious adverse events, some of them potentially fatal. Additionally, as described in the labeling of Mutual's approved product, quinine interacts with many other drugs its use is contraindicated in many conditions (Quinine interacts with neuromuscular blocking agents, rifampin, class IA and III antiarrhythmic agents, astemizole (Hismanil), cisapride (Propulsid), erythromycin, and other medications known to cause QT prolongation, a change in the heart rhythm that significantly increases the risk of cardiac dysfunction, and is contraindicated in patients with leg cramps, prolonged QT interval, G-6-PD deficiency, optic neuritis, myasthenia gravis, and known hypersensitivity to quinine or related drugs). FDA reviewed the labeling of many unapproved quinine products and found that they did not provide the most up-to-date information physicians need to use quinine drugs as safely and effectively as possible, which could contribute to inappropriate prescribing and unnecessary serious adverse events. Further, quinine

sulfate is known to have a very narrow margin of safety between doses that are therapeutic in the treatment of malaria and doses that are toxic, making proper manufacture and dosing recommendations essential. Only one firm, Mutual, markets a quinine product that has gone through the approval process to ensure that it is accurately labeled and properly manufactured, as well as safe and effective for its labeled uses.

What risks are associated with quinine-containing drugs?

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, a cluster of symptoms that includes tinnitus, dizziness, disorientation, nausea, visual changes, and auditory deficits. There is also evidence that quinine causes 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 (a decrease in blood platelets that can cause hemorrhage or clotting problems) and other serious hematological events, permanent visual and hearing disturbances, hypoglycemia, renal failure 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. Many of the adverse events associated with quinine are dose-related, and because of age-related differences in the rate at which quinine is eliminated from the body, the frequency and severity of adverse effects associated with quinine drug products may be greater in the elderly.

Why does the FDA warn against the use of quinine to treat or prevent leg cramps and related conditions?

Quinine has been used since at least the 1940's for the relief of nocturnal leg cramps. However, over the last decade, there has been significant concern regarding its unfavorable risk/benefit ratio for this and related conditions.

In the 1990s, as part of FDA's review of over-the-counter (OTC) drugs, the Agency evaluated OTC quinine products sold without applications for leg cramps, reviewing extensive information from studies and adverse drug events reported to the agency regarding the safety and efficacy of quinine drugs. Citing numerous safety concerns associated with use of quinine and concluding that the data were not adequate to establish that quinine is effective for prevention and/or treatment of nocturnal leg muscle cramps, the Agency concluded that these products could not continue to be sold OTC for leg cramps without approved applications. *Drug Products for the Treatment and/or Prevention of Nocturnal Leg Muscle Cramps for Over-The-Counter Human Use*, 59 Fed. Reg. 43234, (August 22, 1994)

The labeling for Mutual's approved prescription quinine sulfate includes numerous warnings regarding the use of the product for the treatment or prevention of nocturnal leg cramps. For instance the "Indications and Usage" section notes that "Quinine sulfate oral

capsules are not approved for the treatment or prevention of nocturnal leg cramps.” In a paragraph entitled “Use of Quinine Sulfate for Treatment or Prevention of Nocturnal Leg Cramps” in the “Warnings” section,” the labeling states:

Quinine sulfate may cause unpredictable serious and life-threatening hypersensitivity reactions, QT prolongation, serious cardiac arrhythmias including torsades de pointes, and other serious adverse events requiring medical intervention and hospitalization. Fatalities have also been reported. The risk associated with the use of quinine sulfate in the absence of evidence of its effectiveness for treatment or prevention of nocturnal leg cramps, outweighs any potential benefit in treating and/or preventing this benign, self-limiting condition.

Similar information regarding use of quinine sulfate for leg cramps is included in information designed for patients that is part of the approved labeling.

Although adverse events associated with quinine drugs also can occur when it is used to treat the approved indication, because untreated malaria, unlike leg cramps, is life-threatening, these risks may be justified. Because of the risks associated with use of quinine drugs, Mutual will be providing written information to physicians regarding the drug’s unfavorable risk/benefit for treatment of nocturnal leg cramps, as compared with its favorable risk/benefit ratio for treatment of uncomplicated *P. falciparum* malaria. As a matter of policy, FDA does not ordinarily interfere in the practice of medicine. In the exercise of their professional judgment, physicians may generally prescribe approved drugs for unapproved uses. These warnings regarding quinine drugs do not change that policy.

What is FDA’s approach to addressing unapproved, marketed drugs?

In June, 2006, FDA issued a final guidance entitled “Marketed Unapproved Drugs-- Compliance Policy Guide” designed to make sure that all drugs marketed in the United States, prescription and over-the-counter, have been shown to be safe and effective. For a variety of historical reasons, some drugs, mostly older products, continue to be marketed illegally in the United States without required FDA approval. This guidance clearly articulates FDA’s expectation that manufacturers of products requiring FDA approval submit applications to FDA to show that their products are safe and effective. The guidance also outlines the agency’s enforcement policies aimed at efficiently and rationally bringing all such drugs into the approval process.

Why did FDA issue a final guidance on its approach to unapproved, marketed prescription drugs?

FDA issued the guidance for reasons directly related to its mission of protecting and advancing the public health. The drug approval process is essential to providing patients and prescribers with the assurance that prescription drugs are marketed based on reliable, scientific data showing that they are safe, effective, well-made, and accurately labeled. The final guidance emphasizes that illegally marketed prescription drugs must obtain

FDA approval and explains how the agency will prioritize enforcement actions against illegally marketed drugs to maximize protection of the public health. This final guidance is based on careful review and consideration of comments received on a previously published draft guidance.

Why is FDA acting now on unapproved drugs?

FDA is committed to ensuring the safety and quality of the nation's drug supply. FDA's current actions against unapproved drugs are part of our important role in protecting and advancing the public's health. FDA approval means FDA scientists, physicians, inspectors, and experts have reviewed critical information about a drug and have concluded that the benefits of the drug exceed its risks. Drugs that are not FDA approved may be unsafe, ineffective, of poor quality, or have inadequate labeling. FDA's unapproved drugs actions reflect FDA's broader initiative to provide consumers and the health care community with established and emerging drug safety information so they can make the best possible medical decisions. Although these unapproved drugs have not demonstrated their safety and effectiveness through the drug approval process, health care providers are often unaware of their status and have continued to prescribe them. Their labels do not disclose that they lack approval, and often they are advertised in reputable medical journals or are included in widely used pharmaceutical references such as the Physician's Desk Reference (PDR). The general lack of awareness about the approval status of these drugs, the absence of FDA review of their effectiveness, and the uncertainty about their safety, product quality, and adequacy of labeling, all combine to make it important that unapproved drugs undergo the FDA approval process.

Has the FDA taken previous actions against unapproved drugs that illustrate the importance of the approval process?

Yes. Levothyroxine is a widely prescribed and beneficial drug for thyroid hormone replacement that for years was marketed without FDA approval. FDA received reports of problems with the quality of unapproved levothyroxine products that made it difficult for patients and doctors to predict if a patient was getting a consistent amount of the active ingredient of the drug. In 1997, FDA notified levothyroxine manufacturers that they had three years (later extended to four) to upgrade their manufacturing and submit new drug applications for marketing. This approach avoided shortages for patients and allowed manufacturers time to make the needed improvements, perform testing on the drug, and submit that information in a drug application for FDA approval. Today, all levothyroxine that is marketed must be approved by FDA and meet quality standards.

Because FDA considered levothyroxine to be medically necessary, FDA allowed companies to stay on the market while they were seeking approval and provided ample time for companies to obtain approval.

In other circumstances, FDA may simply issue warning letters ordering the immediate cessation of illegal drug manufacturing. As explained in the guidance, the decision about how to proceed will be made on a case-by-case basis.

What drugs will FDA take off the market?

FDA's June, 2006, Compliance Policy Guide outlines a prioritized enforcement approach encouraging companies currently manufacturing drugs without required FDA approval to comply with the drug approval process and ensure the safety and efficacy of their marketed products. If companies do not do so, FDA may take enforcement action. The highest priorities for enforcement action continue to be drugs with potential safety risks, drugs that lack evidence of effectiveness, and health fraud drugs. FDA intends to proceed on a case-by-case basis with these priorities in mind, with every effort made to avoid adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the drug supply.

How does FDA intend to handle situations where there is an approved and unapproved version of the same drug?

In deciding whether, and in what manner, to take enforcement action against an unapproved drug, FDA intends to consider, among other factors, whether there is also an approved drug available to serve consumers who need the drug. Allowing continued marketing of unapproved drugs that compete against approved counterparts challenges the integrity of the drug approval system that is designed to avoid the risks associated with potentially unsafe and ineffective drugs, and puts companies that comply with the law at a disadvantage. Allowing continued marketing of these unapproved drugs also undermines the incentives needed to conduct the scientific studies to determine the safety and effectiveness of drugs, which benefits the public health.

Is FDA required to publish a Federal Register notice before taking any action against any unapproved drug?

No. FDA may take action against unapproved new drugs without first publishing its intentions in the Federal Register. However, FDA will continue to be mindful of the effects of its action on consumers and health professionals and set its priorities according to their public health impact.

For further information, please see FDA's Unapproved Drugs Web Page, located at http://www.fda.gov/cder/drug/unapproved_drugs/default.htm