DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-799/S-014

AR Holding Company, Inc.
Attention: Robert Dettery
Vice-President, Regulatory Affairs
1100 Orthodox Street
Philadelphia, PA 19124

Dear Mr. Dettery:

Please refer to your supplemental new drug application, dated and received October 22, 2009 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Qualaquin® (quinine sulfate) Capsules, 324 mg.

We acknowledge receipt of your submission dated November 13, 2009.

Reference is made to our letter dated September 23, 2009, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Qualaquin® (quinine sulfate). This information pertains to the risk of serious hematologic adverse events associated with the use of Qualaquin® (quinine sulfate) to treat or prevent nocturnal leg cramps. These adverse events include serious and life-threatening hematologic reactions, including thrombocytopenia and hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP). Chronic renal impairment associated with the development of TTP has been reported. This new safety information should be included in the labeling of Qualaquin® (quinine sulfate).

This supplemental new drug application provides for revisions to the labeling for Qualaquin® (quinine sulfate) consistent with our September 23, 2009, letter (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. Boxed Warning has been added as follows:

WARNING:
Qualaquin use for the treatment or prevention of nocturnal leg cramps may result in serious and life-threatening hematologic reactions, including thrombocytopenia and hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP). Chronic renal impairment associated with the development of TTP has been reported. The risk associated with Qualaquin use in the absence of evidence of its effectiveness in the treatment or prevention of nocturnal leg cramps outweighs any potential benefit (see **WARNINGS).**

2. The **WARNINGS** section has been revised as follows:

Use of Qualaquin for Treatment or Prevention of Nocturnal Leg Cramps

Qualaquin may cause unpredictable serious and life-threatening hematologic reactions including thrombocytopenia and hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) in addition to hypersensitivity reactions, QT prolongation, serious cardiac arrhythmias including torsades de pointes, and other serious adverse events requiring medical intervention and hospitalization. Chronic renal impairment associated with the development of TTP, and fatalities have also been reported. The risk associated with the use of Qualaquin 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 (See **BOXED WARNING**, **CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS**).

Thrombocytopenia
Quinine-induced thrombocytopenia is an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life threatening have been reported, including cases of HUS/TTP. Chronic renal impairment associated with the development of TTP has also been reported. Thrombocytopenia usually resolves within a week upon discontinuation of quinine. If quinine is not stopped, a patient is at risk for fatal hemorrhage. Upon re-exposure to quinine from any source, a patient with quinine-dependent antibodies could develop thrombocytopenia that is more rapid in onset and more severe than the original episode.

3. The Patient Package Insert has been converted into a Medication Guide to incorporate additional safety information included in labeling and is located at the end of the Package Insert.

This supplemental new drug application provides for additional agreed upon labeling changes as follows:

4. The **PRECAUTIONS/Information for Patients** subsection has been revised as follows:

Information for Patients
Patients should be instructed to:
- Take all of the medication as directed.
- Take no more of the medication than the amount prescribed.
- Take with food to minimize possible gastrointestinal irritation.

If a dose is missed, patients should also be instructed not to double the next dose. If more than 4 hours has elapsed since the missed dose, the patient should wait and take the next dose as previously scheduled. (See Medication Guide.) ~~Patient Package Insert~~.)

We have completed our review of this supplemental application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than one month from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical in content to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "**SPL for approved supplement NDA 21-799/S-014**."

In addition, within 21 days of the date of this letter, amend any pending applications for this NDA with content of labeling in structured product labeling (SPL) format to include the changes approved in this application.

Marketing the product with labeling that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

Please note that you must comply with the Medication Guide Regulations as specified in 21 CFR 208.24. In particular, the carton and container labels must comply with 21 CFR 208.24 (d). Please submit proposed labels for review within 30 days of receipt of this letter.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D., MPH
Deputy Director for Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: Package Insert, Medication Guide

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21799	SUPPL-14	AR HOLDING CO INC	QUALAQUIN SULFATE CAPSULES 324MG

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OZLEM A BELEN
11/20/2009