DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-799/S-006

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

Dear Mr. Dettery:

Please refer to your supplemental new drug application dated July 21, 2006, received July 21, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qualaquin™ (quinine sulfate) Capsules, 324 mg.

We acknowledge receipt of your submission dated August 15, 2007, in response to our approvable letter dated August 2, 2007.

This "Changes Being Effected" supplemental new drug application provides for revisions to the **PRECAUTIONS** section of the package insert (PI) to include information from the *in vitro* study of the effect of quinine on the induction of P450 isoenzymes in human hepatocytes. Revisions were also made in the **Patient Information** subsection of the PI to reflect the revisions made in the **PRECAUTIONS** section of the PI. The **HOW SUPPLIED** section and the **Patient Information** subsection of the package insert (PI) were revised to update storage information. Revisions are as follows (deletions = ~~strikethrough~~ and additions = <u>underline</u>):

1. ~~QUININE SULFATE~~ **<u>Rx only</u>**

2. The **PRECAUTIONS/Drug Interactions:/Effect of Quinine on the Pharmacokinetics of Other Drugs** subsection was modified as follows:

   Results of *in vivo* and *in vitro* drug interaction studies suggest that quinine has the potential to inhibit the metabolism of drugs that are substrates of CYP3A4 and CYP2D6, as well as inhibit the biliary excretion of drugs like digoxin.

   <u>In an *in vitro* induction study using human hepatocytes, quinine (5 to 30 µM) increased the metabolic activities of CYP1A2 and CYP3A4. Quinine did not significantly induce the activities of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.</u>

3. The **PRECAUTIONS/Drug Interactions:/Effect of Quinine on the Pharmacokinetics of Other Drugs/ Neuromuscular blocking agents (pancuronium, succinylcholine, tubocurarine)** subsection was modified as follows:

In one report, quinine potentiated neuromuscular blockade in a patient who received pancuronium during an operative procedure, and subsequently (3 hours after receiving pancuronium) received quinine 1800 mg daily. Quinine may also enhance the neuromuscular blocking effects of succinylcholine and tubocurarine (See **WARNINGS**).

Theophylline or aminophylline (CYP1A2 substrate): Although not studied clinically, quinine has been shown to induce the activity of CYP1A2 *in vitro* using human hepatocytes. Therefore, concomitant administration of Qualaquin and theophylline or aminophylline is likely to decrease the plasma theophylline concentrations, possibly reducing the effect of theophylline or aminophylline. Plasma theophylline concentrations should be monitored frequently during concurrent therapy with theophylline or aminophylline and Qualaquin.

4. The **HOW SUPPLIED** subsection was modified as follows:

~~How Supplied:~~ HOW SUPPLIED:
~~Quinine Sulfate Capsules~~ Qualaquin capsules
USP, 324 mg are available as clear/clear capsules imprinted ~~MUTUAL~~ AR 102:

Bottles of 30	NDC ~~53489-221~~13310-153-07
Bottles of 100	NDC ~~53489-221~~13310-153-01
Bottles of 500	NDC ~~53489-221~~13310-153-05
Bottles of 1000	NDC ~~53489-221~~13310-153-10

Store at ~~controlled room temperature,~~ 25-30ºC (77-86ºF).

5. The **Patient Information** subsection was modified as follows:

Patient Information:
~~Quinine Sulfate~~QUALAQUIN®
quinine sulfate
CAPSULES USP 324 mg ~~Capsules~~

How do I store ~~Quinine Sulfate~~Qualaquin?
Keep ~~Quinine Sulfate~~Qualaquin out of reach of children. Keep the capsules in a tightly closed container. Do not refrigerate or freeze. Store at ~~room temperature;~~ 25-30ºC (77-86ºF).

In addition, in multiple places through out the label, clarification was made between the trade name "Qualaquin," and the generic names "quinine sulfate" or "quinine."

This "Changes Being Effected" supplemental new drug application also provides for revisions to the Qualaquin container label in response to the August 2, 2007 approvable letter. The following changes were made in the label:

1. Size of the Tradename: Increased the prominence of the established name so that it is at least ½ the size of the proprietary name.
2. Position of the strength: Relocated the strength closer to the proprietary name.
3. Position of tablet count: Relocated the bottle count away from the strength.
4. Decreased prominence of logo: Decreased the prominence of the AR Scientific logo.
5. Location of the *Rx* symbol: Moved to lower front panel.
6. Removal of the "controlled room temperature" from the storage statement.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the submitted labeling dated August 15, 2007.

Within 21 days of the date of this letter, submit 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 submitted labeling dated August 15, 2007. 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 NDA 21-799/S-006."

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
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Ms. Tina M. Ennis, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures

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

/s/

Renata Albrecht

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