DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-799/S-013 **SUPPLEMENT APPROVAL**

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 June 29, 2009, received June 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for QUALAQUIN® (quinine sulfate USP) Capsules, 324 mg.

We acknowledge receipt of your submissions dated, July 16, 2009, and December 9, 17, and 21, 2009.

This Prior Approval supplemental new drug application provides for revisions to the product labeling in response to our March 2, 2009 letter requesting that you submit labeling in accordance with the January 24, 2006, Final Rule titled, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products* (Federal Register Vol. 71, No. 15, 3921-3997).

The labeling submitted in this supplement in accordance with the January 24, 2006 Final Rule was based mostly on the labeling approved in S-008 on November 14, 2008 but also includes additional language based on three *in vivo* clinical pharmacology studies, MCP-001-07-1001, MPC-001-07-1002, MPC-001-06-0001 submitted and reviewed in S-013, and furthermore incorporates the revisions approved in S-014 on November 20, 2009.

The specific new language that has been added based on the review of the above-mentioned three clinical pharmacology studies is now included in Sections 7.1 and 7.2 as follows:

1. Under **7.1 Effects of Drugs and Other Substances on Quinine Pharmacokinetics**

   Theophylline or aminophylline:
   In 20 healthy subjects who received multiple doses of QUALAQUIN (648 mg every 8 hours × 7 days) with a single 300 mg oral dose of theophylline, the quinine mean C_{max} and AUC were increased by 13% and 14% respectively. Although no change in the QUALAQUIN dosage regimen is necessary with concomitant theophylline or

aminophylline, patients should be monitored closely for adverse reactions associated with quinine.

2. Under **7.2 Effects of Quinine on the Pharmacokinetics of Other Drugs**

   Midazolam (CYP3A4 substrate): In 23 healthy subjects who received multiple doses of QUALAQUIN (324 mg three times daily x 7 days with a single oral 2-mg dose of midazolam, the mean AUC and C_{max} of midazolam and 1-hydroxymidazolam were not significantly affected. This finding indicates that 7-day dosing with QUALAQUIN 324 mg every 8 hours did not induce the metabolism of midazolam.

   Theophylline or aminophylline (CYP1A2 substrate): In 19 healthy subjects who received multiple doses of QUALAQUIN 648 mg every 8 hours x 7 days) with a single 300 mg oral dose of theophylline, the mean theophylline AUC was 10% lower than when theophylline was given alone. There was no significant effect on mean theophylline C_{max}. Therefore, if QUALAQUIN is co-administered to patients receiving theophylline or aminophylline, plasma theophylline concentrations should be monitored frequently to ensure therapeutic concentrations.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and text for the Medication Guide). For administrative purposes, please designate this submission, "**SPL for approved NDA 21-799/S-013.**"

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
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}

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

Enclosure: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21799	SUPPL-13	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/

RENATA ALBRECHT
12/23/2009