CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-799

CHEMISTRY REVIEW(S)

NDA 21-799

Quinine Sulfate Capsules USP, 324 mg

Mutual Pharmaceutical Company, Inc.

Gene W. Holbert, Ph.D.

Division of Special Pathogen and
Immunologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-799

2. REVIEW #: 1

3. REVIEW DATE: 21-JUL-2005

4. REVIEWER: Gene W. Holbert, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	13-OCT-2004
Amendment (BC)	30-MAR-2005
Amendment (BC)	06-JUL-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Mutual Pharmaceutical Company, Inc.
Address:	1100 Orthodox Street Philadelphia, PA 19124
Representative:	Robert Dettery, Vice President, Regulatory Affairs
Telephone:	(215) 288-6500 / (800) 523-3684

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Quinine Sulfate Capsules USP, 324 mg
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Antimalarial

11. DOSAGE FORM: Capsule CODE: 600

12. STRENGTH/POTENCY: 324 mg (equivalent to ——— free base)

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

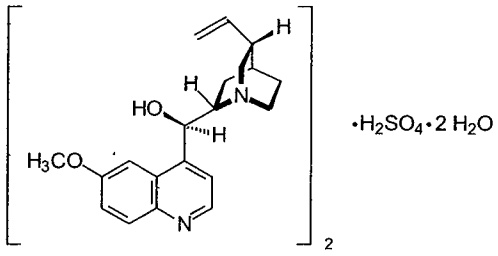
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(8α,9*R*)-6'-Methoxy-cinchonan-9-ol sulfate (2:1) salt, dihydrate

bis[(*R*)-(6-methoxyquinolin-4-yl)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl]methanol] sulfate dihydrate



Molecular Formula: $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2\ H_2O$
Molecular Weight: 782.96
CAS: 6119-70-6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[illegible]	II			1	Adequate	05-MAY-2005	LOA 23-FEB-2004
	IV			3	Adequate	30-DEC-2003 (G.Lunn)	LOA 20-JAN-2004
	IV			4, 7	Adequate	See Lunn review of DMF —	LOA 20-JAN-2004
	III			3	Adequate	15-SEP-2000 D.N. Klein	LOA 23-JAN-2004
	III			7	Adequate	See Klein review of DMF —	LOA 31-AUG-2004
	III			3	Adequate	22-MAR-2001 P. Maturu	LOA 26-JAN-2004
	III			3	Adequate for —	27-JUL-2004 S.C. Pope	LOA 08-JAN-2003
	III			3	Adequate	06-DEC-2004 R. D. Madurawe	LOA 03-NOV-2000
[illegible]	III			3	Adequate	01-AUG-2002 R. Sood	LOA 05-MAY-2004

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,012	Quinine Sulfate

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	18-MAR-2005	S. Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not requested. No unusual methods.		
DMETS	Revise primary display panel of container labels to make use of "TALL MAN" differentiation.	14-JUL-2005	Charlie Hoppes, R.Ph., M.P.H.
EA	N/A		
Microbiology	N/A		

The Chemistry Review for NDA 21-799

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval of this application is recommended from the CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Quinine Sulfate Capsules USP, 324 mg (equivalent to — mg of the free base) are supplied for oral administration as clear cap/clear body size — hard gelatin capsules, imprinted with "Mutual 102". Inactive ingredients include Corn Starch, NF; Talc, USP; and Magnesium Stearate, NF. The product will be packaged in ——— ——— bottles containing 30, 100, 500 or 1000 capsules per bottle. The 30-count bottles will utilize child-resistant closures. Quinine Sulfate Capsules are labeled for storage at 25-30°C (77-86°F).

Mutual Pharma has been marketing quinine sulfate capsules for over 15 years using the same manufacturing procedures as described in this application. For the purposes of this NDA, the sponsor has revised the control procedures and methods the comply with the most recent FDA and ICH regulatory standards.

Quinine Sulfate is an odorless, white crystalline. It has a persistent very bitter taste. Aqueous solutions are neutral to litmus and the pH of a saturated solution is 6.2. Quinine is the primary alkaloid of various species of *Cinchona*, family *Rubiaceae*. The alkaloid content of the bark varies according to the source. Bark from cultivated plants contains 7-10% total alkaloids, and about 70% of the total is quinine. Quinine is isolated from the cinchona bark by [redacted]. Quinine may be used as a flavoring in carbonated beverages at levels up to 83 ppm (21 CFR 172.575). See also *The Merck Index*, 13th Edition, Merck, Whitehouse Station, NJ, 2001, abstracts 2305 and 8151.

B. Description of How the Drug Product is Intended to be Used

Quinine Sulfate is indicated for treatment of uncomplicated *Plasmodium falciparum* malaria. It is not indicated for malaria prophylaxis or for the treatment of nocturnal leg cramps. Quinine has been shown to be effective in geographical regions where other antimalarials, such as chloroquine, may have an unacceptable failure rate, possibly due to drug resistance.

The dosage for adult patients is 648 mg (two capsules) three times a day for [redacted] 7 days,

[redacted]

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and the Drug Master File ultimately provided adequate information on the chemistry and manufacturing controls for the production of Quinine Sulfate Capsules USP, 324 mg. At the Pre-NDA meeting, the agency requested that the sponsor develop modern analytical methods for the drug substance and drug product to supplement the current USP methods, some of which are outmoded. During the review, a number of issues, including the following were resolved:

- Limits of detection and quantitation for the impurities [redacted] could not be located in the drug substance HPLC method.
- A clarification concerning the system suitability requirements for the HPLC method for Related Substances and Degradation Products in the drug substance was requested. The method stated that the [redacted]

- It was not clear from the application which in-process controls are applied to each commercial batch of the drug product.
- One of the container labels listed the contents as tablets instead of capsules.

As amended, all acceptance criteria and analytical method were found adequate to ensure the identity, strength, quality, purity and potency of the drug product.

The Division of Medication Errors and Technical Support Office (DMETS) has reviewed the application with respect to the established name confusion between Quinine and Quinidine. From a search of FDA databases, DMETS found 22 medication errors involving these two products which are commonly stored in close proximity on the pharmacy shelves.

In a attempt to reduce the frequency of these errors, DMETS has recommended that the concept of "Tall Man Lettering", developed by the Office of Generic Drugs be used for [redacted] In this system, the names Quinine [redacted] would appear as QuiniNE [redacted] in the primary display panel of the immediate container to alert the pharmacist to the conflicting names.

III. Administrative

A. Reviewer's Signature

{See appended electronic signature page.}

B. Endorsement Block

Chemist Name/Date: Gene W. Holbert, Ph.D./21-JUL-2005
Chemistry Team Leader Name (Acting)/Date: Mark R. Seggel, Ph.D.
Project Manager Name/Date: Kristen E. Miller, Pharm.D.

C. CC Block

45 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Gene Holbert
8/9/05 01:28:10 PM
CHEMIST

Mark Seggel
8/9/05 01:44:19 PM
CHEMIST