

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 21-799**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



United Research Laboratories, Inc.  
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street  
Philadelphia, PA 19124

215-288-6500  
www.urlmutual.com

**"NO RELEVANT PATENTS" STATEMENT**  
**[21 CFR 314.50(i)(1)(ii)]**

As required by 21 CFR 314.50(i)(1)(ii), Mutual Pharmaceutical Company, Inc. hereby states that, in the opinion and to the best knowledge of Mutual Pharmaceutical Company, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

A handwritten signature in cursive script that reads "Robert Dettery".

\_\_\_\_\_  
Robert Dettery  
Vice-President, Regulatory Affairs

A handwritten date in cursive script that reads "September 8, 2004".

\_\_\_\_\_  
Date

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

21-799

NAME OF APPLICANT / NDA HOLDER

Mutual Pharmaceutical Company, Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)

Quinine

STRENGTH(S)

324 mg

DOSAGE FORM

Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

**Date Signed**



September 28, 2004

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

**Name**  
Mutual Pharmaceutical Company, Inc.

**Address**  
1100 Orthodox Street

**City/State**  
Philadelphia, PA

**ZIP Code**  
19124

**Telephone Number**  
215-288-6500

**FAX Number (if available)**  
215-807-1095

**E-Mail Address (if available)**  
rdettrey@urlmutual.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## EXCLUSIVITY SUMMARY

NDA # 21-799

SUPPL # N/A

HFD # 590

Trade Name N/A

Generic Name Quinine Sulfate

Applicant Name Mutual Pharmaceuticals Company

Approval Date, If Known August 12, 2005

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

One study was to compare the rate and extent of absorption under fasted conditions to determine the effect of food, and the second study was to compare the dose proportionality under fasted conditions.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Seven

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 206	Modern Cold Tablets
NDA# 805	La Ken Medicated Vaginal Jelly
NDA# 4425	Rx 2003 Purdum Drug, Guthrie, Okla.

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

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Name of person completing form: Kristen Miller, Pharm.D.

Title: Regulatory Health Project Manager

Date: August 9, 2005

Name of Office/Division Director signing form: Renata Albrecht, M.D.

Title: Director, Division of Special Pathogen and Immunologic Drug Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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Renata Albrecht  
8/10/05 05:22:48 PM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA: 21-799 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: October 14, 2004 Action Date: August 12, 2005

HFD-590 Trade and generic names/dosage form: Quinine Sulfate Capsules

Applicant: Mutual Pharmaceuticals Therapeutic Class: 4050120

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication:

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 0 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 16 Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): 10/22/2009

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

*{See appended electronic signature page}*

Kristen Miller  
Regulatory Project Manager

cc: NDA 21-771 and HFD-960/ Grace Carmouze  
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT,  
HFD-960, 301-594-7337.

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

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Kristen Miller  
10/22/04 03:45:47 PM

**Exclusivity**

Orphan Drug designation for Quinine Sulfate Capsules use in patients with malaria was granted on June 3, 2004 (designation request # 04-1850). Mutual Pharma would expect 7 (seven) year's exclusivity for the use of Quinine in the treatment of patients with malaria from the date of approval of this NDA.

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United Research Laboratories, Inc.  
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street  
Philadelphia, PA 19124

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www.urlmutual.com

### DEBARMENT CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Mutual Pharmaceutical Company, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA. This certification is based upon the list of debarred individuals available on the FDA website ([http://www.fda.gov/ora/compliance\\_ref/debar/default.htm](http://www.fda.gov/ora/compliance_ref/debar/default.htm)), last updated on 31 August 2004.

Mutual Pharmaceutical Company, Inc. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, to the best of Mutual's knowledge, no person affiliated with Mutual Pharmaceutical Company that was responsible for the development or submission of this application has been convicted of an offense described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992.

Debarment certifications for \_\_\_\_\_ are included with the individual study reports.

A handwritten signature in cursive script that reads 'Robert Dettery'.

Robert Dettery  
Vice-President, Regulatory Affairs

A handwritten date in cursive script that reads 'October 12, 2004'.

Date

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-799	Efficacy Supplement Type SE- N/A	Supplement Number : N/A
Drug: Quinine Sulfate, 324 mg capsules		Applicant: Mutual Pharmaceuticals
RPM: Kristen Miller, Pharm.D.		HFD-590 <span style="float: right;">Phone # : 301-827-2127</span>
<p>Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)                      (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p><input checked="" type="checkbox"/> Confirmed and corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>N/A (referenced literature)</p>	
<b>❖ Application Classifications:</b>		
<input checked="" type="checkbox"/> Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<input type="checkbox"/> Chem class (NDAs only)		5
<input type="checkbox"/> Other (e.g., orphan, OTC)		Orphan
<b>❖ User Fee Goal Dates</b>		
		August 14, 2005
<b>❖ Special programs (indicate all that apply)</b>		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
<b>❖ User Fee Information</b>		
<input type="checkbox"/> User Fee		<input type="checkbox"/> Paid UF ID number 4783
<input type="checkbox"/> User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<input type="checkbox"/> User Fee exception		<input checked="" type="checkbox"/> Orphan designation <input checked="" type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
<b>❖ Application Integrity Policy (AIP)</b>		
<input type="checkbox"/> Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<input type="checkbox"/> This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<input type="checkbox"/> Exception for review (Center Director's memo)		N/A

<ul style="list-style-type: none"> <li>• OC clearance for approval</li> </ul>	<p>N/A</p>
<p>Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification &amp; certifications from foreign applicants are cosigned by US agent.</p>	<p><input checked="" type="checkbox"/> Verified</p>
<p>❖ Patent</p>	
<ul style="list-style-type: none"> <li>• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	<p><input checked="" type="checkbox"/> Verified</p>
<ul style="list-style-type: none"> <li>• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	<p>21 CFR 314.50(i)(1)(i)(A)  <input type="checkbox"/> Verified  <p style="text-align: right;">N/A</p> <p>21 CFR 314.50(i)(1)  <input type="checkbox"/> (ii)   <input type="checkbox"/> (iii)</p> </p>
<ul style="list-style-type: none"> <li>• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i></li> <li>• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul>	<p><input checked="" type="checkbox"/> N/A (no paragraph IV certification)  <input type="checkbox"/> Verified</p>
<p>Answer the following questions for each paragraph IV certification:</p>	
<p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p>	<p><input type="checkbox"/> Yes   <input type="checkbox"/> No</p>
<p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p>	<p><input type="checkbox"/> Yes   <input type="checkbox"/> No</p>
<p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of</p>	<p><input type="checkbox"/> Yes   <input type="checkbox"/> No</p>

receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ( ) Yes ( ) No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "No," continue with question (5).*

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>• Exclusivity summary</li> <li>• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<p>X- 8/10/05 (Exclusivity Summary)</p> <p>N/A</p>
<ul style="list-style-type: none"> <li>• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	<p>( ) Yes, Application # _____</p> <p>( X ) No</p>
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	<p>X- 7/27/05</p>

General Information	
Actions	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	(X) AP ( ) TA ( ) AE ( ) NA
<ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>	(X) Materials requested in letter ( ) Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> <li>Press Office notified of action (approval only)</li> </ul>	(X – approval email) Yes ( ) Not applicable
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	( ) None ( ) Press Release ( ) Talk Paper (X- post-marketing commitment) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	X
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	X
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	X
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)</li> </ul>	X- Pregnancy Consult (7/25/05) X- DDMAC for PPI (7/21/05) X- DMETS (7/14/05) X- DDMAC for PI (7/7/05)
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	X- Labeling for other quinine products on the market included
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> <li>Division proposed (only if generated after latest applicant submission)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>Applicant proposed</li> </ul>	X – original and final
<ul style="list-style-type: none"> <li>Reviews</li> </ul>	See labeling reviews
❖ Post-marketing commitments	
<ul style="list-style-type: none"> <li>Agency request for post-marketing commitments</li> </ul>	X
<ul style="list-style-type: none"> <li>Documentation of discussions and/or agreements relating to post-marketing commitments</li> </ul>	X – See telecon minutes
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>EOP2 meeting (indicate date)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>Pre-NDA meeting (indicate date)</li> </ul>	X- 5/24/04 and 7/15/03
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (indicate date; approvals only)</li> </ul>	X – 7/12/05
<ul style="list-style-type: none"> <li>Other</li> </ul>	N/A
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> <li>Date of Meeting</li> </ul>	N/A
<ul style="list-style-type: none"> <li>48-hour alert</li> </ul>	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
X- 1994 and March 20, 1998	

<b>Summary Application Review</b>	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X - 8/12/05
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	X- 8/12/05
❖ Microbiology (efficacy) review(s) (indicate date for each review)	X- 8/2/05
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X- 10/22/05
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	X - 8/11/05
❖ Biopharmaceutical review(s) (indicate date for each review)	X- 8/12/05
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	X- 5/9/05
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	X- 8/9/05
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See Chemistry Review
• Review & FONSI (indicate date of review)	See Chemistry Review
• Review & Environmental Impact Statement (indicate date of each review)	See Chemistry Review (Categorical Exclusion)
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	Not required for approval ( ) Completed ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X- 8/12/05
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A



## Teleconference Minutes

**Teleconference Date:** August 8, 2005  
**Application Numbers:** NDA 21-799 (Quinine Sulfate)  
**Sponsor:** Mutual Pharmaceuticals  
**Attendees:**

### Mutual Pharmaceuticals Participants

Robert Dettery, Ph.D. Regulatory Affairs

/ / /

### Division of Special Pathogen and Immunologic Drug Products

Eileen Navarro, M.D.	Medical Officer Team Leader
Mary Singer, M.D.	Medical Officer Reviewer
Leonard Sacks, M.D.	Medical Officer Team Leader
LaRee Tracy, M.A.	Statistics Reviewer
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology/Biopharmaceutics Team Leader
Gerlie Gieser, Ph.D.	Clinical Pharmacology/Biopharmaceutics Reviewer
Kristen Miller, Pharm.D.	Regulatory Project Manager

**BACKGROUND:** On October 14, 2004, Mutual submitted a new drug application (NDA) 21-799 for quinine sulfate. On July 22, 2005, the Review Team sent Mutual revisions to the proposed labeling. A telecon was held on July 27, 2005 to further discuss the proposed changes. On August 3, 2005, the Review Team sent revised changes to the package insert (PI) and Patient Package Insert (PPI) and proposed a teleconference for August 8, 2005 to discuss the changes. On August 5, 2005, the Review Team sent proposed post-marketing commitments (PMCs) to Mutual to be discussed during the August 8, 2005 teleconference.

**DISCUSSION POINTS:** Following introductions, the Review Team stated that additional feedback had been received from other Divisions and Offices regarding the patient package insert.

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NDA 21-799

Page 3

3. The Review Team agreed to sent Mutual the amended PMCs by close of business on August 9, 2005.

Minutes Preparer: Kristen Miller, Pharm.D., Project Manager

Chair Concurrence: Eileen Navarro, M.D., Medical Officer Team Leader

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

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Kristen Miller  
8/12/05 08:28:57 AM  
CSO

Eileen Navarro  
8/12/05 12:15:15 PM  
MEDICAL OFFICER



## Teleconference Minutes

**Teleconference Date:** June 13, 2005  
**Application Numbers:** NDA 21-799 (Quinine Sulfate)  
**Sponsor:** Mutual Pharmaceuticals, Co.  
**Attendees:**

### Mutual Pharmaceuticals

Robert Dettery, Ph.D.  
Brendan Magrab

Regulatory Affairs  
V.P., Intellectual Property

### Division of New Drugs and Labeling Compliance, Office of Compliance (DNDLC) & Division of Special Pathogen and Immunologic Drug Products (DSPIDP)

John Loh, M.D.  
Fred Richman, M.D.  
Eileen Navarro, M.D.  
Mary Singer, M.D.  
Kristen Miller, Pharm.D.

Team Leader, DNDLC  
Acting Director, DNDLC  
Medical Officer Team Leader, DSPIDP  
Medical Officer Reviewer, DSPIDP  
Regulatory Project Manager, DSPIDP

**BACKGROUND:** On October 14, 2004, Mutual submitted a new drug application (NDA) 21-799 for quinine sulfate, 324 mg, for the proposed indication of treatment of uncomplicated *Plasmodium falciparum* malaria. Mutual has been granted an Orphan Drug Designation for this product which, upon approval of its NDA, will provide Mutual with the sole legal right to market quinine sulfate for uncomplicated *Plasmodium falciparum* malaria for seven years. However, there are currently multiple other manufacturers distributing unapproved quinine sulfate products for malaria. On June 7, 2005, Mutual submitted a meeting package for the June 13, 2005 teleconference, which contained a rationale for why the FDA should take enforcement action to remove unapproved quinine drug products from the market immediately upon approval of Mutual's NDA.

**DISCUSSION POINTS:** Following introductions, Mutual provided a brief overview of their June 7, 2005 letter and asked for the Agency's position regarding this situation. The Agency understands Mutual's position and supports having an approved quinine product on the market, but referred Mutual to the Office of Compliance's (OC) draft Compliance Policy Guide (CPG). The CPG states that because of limited resources, enforcement is limited to focusing on issues related to safety, efficacy or fraud. All products, issues and resources are assessed prior to making a decision of what enforcement actions will be taken. The Agency cautioned that enforcement action may not be as immediate as Mutual would like.

NDA 21-799

Page 2

Mutual suggested that the OC contact OODP to discuss the situation since Quinine Sulfate was granted orphan drug status and Mutual will receive seven years of exclusivity upon approval. The Agency noted that this was a good recommendation. Mutual asked for a timeline for enforcement action and asked if the OC takes into account previous actions taken regarding quinine (one action to remove products used for leg cramps and one action to remove products for OTC malaria use). The Agency responded that action is being considered and that all regulatory history is taken into account, but that it is not possible to propose a timeline for action. Mutual requested another telecon be held in a few weeks to discuss any updates.

**Minutes Preparer:** Kristen Miller, Pharm.D., Project Manager, DSPIDP

**Chair Concurrence:** John Loh, M.D. Team Leader, DNDLC

**APPEARS THIS WAY  
ON ORIGINAL**

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Kristen Miller  
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CSO



## Teleconference Minutes

**Teleconference Date:** July 27, 2005  
**Application Numbers:** NDA 21-799 (Quinine Sulfate)  
**Sponsor:** Mutual Pharmaceuticals  
**Attendees:**

**Mutual Pharmaceuticals**

Robert Dettery, Ph.D. Regulatory Affairs

---

**Division of Special Pathogen and Immunologic Drug Products**

Eileen Navarro, M.D.	Medical Officer Team Leader
Mary Singer, M.D.	Medical Officer Reviewer
Karen Higgins, Sc.D.	Statistics Team Leader
LaRee Tracy, M.A.	Statistics Reviewer
Steve Kunder, Ph.D.	Pharmacology/Toxicology Reviewer
Philip Colangelo, Pharm.D., Ph.D.	Team Leader, Clinical Pharmacology/Biopharmaceutics
Shukal Bala, Ph.D.	Microbiology Team Leader
Kalavati Suvama, Ph.D.	Microbiology Reviewer
Sheetal Patel	Intern
Kristen Miller, Pharm.D.	Regulatory Project Manager

**BACKGROUND:** On October 14, 2004, Mutual submitted a new drug application (NDA) 21-799 for quinine sulfate. On July 22, 2005, the Review Team sent Mutual revisions to the proposed labeling. A telecon was scheduled for July 27, 2005 to further discuss the proposed changes. On July 27, 2005, Mutual submitted a proposal to add:

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(A)

1 Page(s) Withheld

       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

5. The Review Team will send labeling with the discussed revisions, the Clinical Pharmacology and Drug Interaction section proposals, and the proposed patient package insert to Mutual on July 29, 2005.

**Minutes Preparer:** Kristen Miller, Pharm.D., Project Manager

**Chair Concurrence:** Eileen Navarro, M.D., Medical Officer Team Leader

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Kristen Miller  
8/8/05 12:34:57 PM  
CSO

Eileen Navarro  
8/8/05 01:26:28 PM  
MEDICAL OFFICER



*product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES  NO   
 If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO   
 If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
 If yes, explain.
- If yes, has OC/DMPQ been notified of the submission?  N/A YES  NO
- Does the submission contain an accurate comprehensive index?  YES  NO
- Was form 356h included with an authorized signature?  YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50?  YES  NO   
 If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A  YES  NO   
**If an electronic NDA, all certifications must be in paper and require a signature.**  
 Which parts of the application were submitted in electronic format? **All parts are electronic.**
- Additional comments:
- If in Common Technical Document format, does it follow the guidance?  N/A YES  NO
- Is it an electronic CTD? N/A YES  NO   
**If an electronic CTD, all certifications must be in paper and require a signature.**  
 Which parts of the application were submitted in electronic format?
- Additional comments:
- Patent information submitted on form FDA 3542a?  YES  NO
- Exclusivity requested?  YES  NO  7 years

**NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature?  YES NO  
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature?  YES NO  
**(Forms 3454 and 3455 NEEDED must be used and must be signed by the APPLICANT.)**
- Field Copy Certification (that it is a true copy of the CMC technical section)?  YES NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS?  YES NO  
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.  YES
- List referenced IND numbers: 67,012
- End-of-Phase 2 Meeting(s)? Date: July 15, 2003 NO  
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date: May 25, 2004 NO  
 If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?  YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS?  N/A YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS?  N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?  N/A YES NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?  N/A YES NO

- Has DOTCDP been notified of the OTC switch application?  N/A YES NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  N/A YES NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment?  YES NO  
If no, did applicant submit a complete environmental assessment?  N/A YES NO  
If EA submitted, consulted to Florian Zielinski (HFD-357)?  N/A YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ?  YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)?  N/A YES NO

ATTACHMENT

MEMO OF FILING MEETING

**DATE:** December 3, 2004

**BACKGROUND:**

Quinine sulfate was approved in 1939 for multiple indications and was withdrawn as a result of DESI. There are multiple manufacturers with quinine products currently on the market; however, none of these is approved. On January 21, 2004, IND 67,012 was submitted for quinine sulfate capsules for treatment for uncomplicated Plasmodium falciparum (P. falciparum) malaria

On October 13, 2004, Mutual Pharmaceuticals submitted quinine sulfate for the treatment of uncomplicated *Plasmodium falciparum* malaria (NDA 21-799). The product is available as immediate release capsules for oral administration in a 324-mg dosage strength. This has been granted orphan drug status.

**ATTENDEES:**

Mark Goldberger, M.D., M.P.H.	Deputy Director (ODEIV)
Renata Albrecht, M.D.	Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP)
Steven Gitterman, M.D., Ph.D.	Deputy Director, DSPIDP
Leonard Sacks, M.D.	Medical Officer Team Leader
Eileen Navarro, M.D.	Medical Officer Team Leader
Mary Singer, M.D.	Medical Officer Reviewer
Karen Higgins, Sc.D.	Statistics Team Leader
LaRee Tracy, M.A.	Statistics Reviewer
Stephen G. Hundley, Ph.D., DABT	Pharmacology/Toxicology Team Leader
Steve Kunder, Ph.D.	Pharmacology/Toxicology Reviewer
Philip Colangelo, Pharm.D., Ph.D.	Team Leader, Clinical Pharmacology/Biopharmaceutics
Gerlie De Los Reyes, Ph.D.	Clinical Pharmacology/Biopharmaceutics Reviewer
Gene Holbert, Ph.D.	Chemistry Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
David Roeder, M.S.	Associate Director for Regulatory Affairs (ODEIV)
Diana Willard	Chief, Project Management Staff
Kristen Miller, Pharm.D.	Regulatory Project Manager

**ASSIGNED REVIEWERS:**

**Discipline**

Medical:  
Statistical:  
Pharmacology:  
Chemistry:  
Biopharmaceutical:  
Microbiology, clinical:  
Regulatory Project Management:

**Reviewer**

Mary Singer  
LaRee Tracy  
Steve Kunder  
Gene Holbert  
Gerlie De Los Reyes  
Kalavati Suvarna  
Kristen Miller

Per reviewers, are all parts in English or English translation?  YES  NO  
 If no, explain:

CLINICAL FILE  X REFUSE TO FILE

- Clinical site inspection needed: YES  NO
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_  NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?  N/A YES  NO

CLINICAL MICROBIOLOGY NA  FILE  X REFUSE TO FILE

STATISTICS FILE  X REFUSE TO FILE

BIOPHARMACEUTICS FILE  X REFUSE TO FILE   
 • Biopharm. inspection needed:  YES  NO

PHARMACOLOGY NA  FILE  X REFUSE TO FILE   
 • GLP inspection needed: YES  NO

CHEMISTRY FILE  X REFUSE TO FILE

- Establishment(s) ready for inspection?  YES  NO
- Microbiology  NA YES  NO

ELECTRONIC SUBMISSION: Yes  
 Any comments: No

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. Document filing issues/no filing issues conveyed to applicant by Day 74.

\_\_\_\_\_  
 Kristen Miller, Pharm.D.  
 Regulatory Project Manager, HFD-590

### Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

N/A

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO  
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

**NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES  NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

There is no listed drug for this product. This product was approved in 1939 for multiple indications (these are different from the indication currently under review) and was withdrawn as a result of DESI. There are multiple manufacturers with quinine products currently on the market; however, none of these is approved.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES  N/A  NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under YES  N/A  NO

21 CFR 314.101(d)(9).

10. Are there certifications for each of the patents listed for the listed drug(s)?  N/A YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

21 CFR 314.50(i)(1)(ii): No relevant patents.

\_\_\_\_\_ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

\_\_\_\_\_ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

\_\_\_\_\_ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?  YES      NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  N/A      YES      NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  N/A      YES      NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?  N/A      YES      NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).  
Sponsor notified to submit this.  N/A      YES      NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.  YES      NO
- EITHER  
 The number of the applicant's IND under which the studies essential to approval were conducted. IND #   67,012        NO  
 OR  
 A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted? YES      NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES      NO

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/s/

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Kristen Miller  
7/27/05 11:21:33 AM  
CSO

**REQUEST FOR CONSULTATION**

TO (Division/Office): **Office of Drug Safety – Division of Surveillance, Research and Communication Support (DSRCS)**

FROM: **Division of Special Pathogen and Immunologic Drug Products, HFD-590; 301-827-2127**  
**Kristen Miller, Pharm.D., Regulatory Project Manager**

DATE  
**July 15, 2005**

IND NO.  
**N/A**

NDA NO.  
**21-799**

TYPE OF DOCUMENT  
**N-000 Original NDA**

DATE OF DOCUMENT  
**October 13, 2004**

NAME OF DRUG  
**Quinine Sulfate Capsules**

PRIORITY CONSIDERATION  
**Standard (Goal- August 12, 2005)**

CLASSIFICATION OF DRUG  
**Antimalarial (4050120)**

DESIRED COMPLETION DATE  
**August 1, 2005**

NAME OF FIRM: **Mutual Pharmaceuticals**

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- |  |   |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

Mutual Pharmaceuticals submitted a new NDA for quinine sulfate capsules 324mg. They have submitted this as a 505(b)2. The proposed indication is for the treatment of uncomplicated *Plasmodium falciparum* malaria (NDA 21-799). This application was submitted electronically on October 13, 2004. The network path location is: [\\CDSESUB1\N21799\N\\_000\2004-10-13](\\CDSESUB1\N21799\N_000\2004-10-13). The product is available as immediate release capsules for oral administration in a 324-mg dosage strength. This has been granted orphan drug status. The Division intends to take an approval action during the week of August 8, 2005 on this NDA. Quinine has been around for centuries and there are currently many unapproved quinine products on the market (prescription only but still can be found OTC). In 1998, a FR Notice stated that all OTC products containing quinine are misbranded and not regarded as safe <http://www.fda.gov/ohrms/dockets/98fr/032098a.pdf>. There are many adverse events relevant to unregulated off label use for nocturnal leg cramps; the areas of most concern for quinine are QTc prolongation, arrhythmia, and cardiovascular toxicity, and other known toxicities (hematologic, CNS, etc.).

We are interested in pursuing the \_\_\_\_\_ as a postmarketing commitment with the sponsor. We would like your guidance regarding the \_\_\_\_\_

Your input will be very valuable in the design of such a study. Please feel free to We are happy to discuss any questions you may have ([millerk@cder.fda.gov](mailto:millerk@cder.fda.gov)). Thank you very much!

SIGNATURE OF REQUESTER <b>Kristen Miller, July 15, 2005</b>	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> E-MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Kristen Miller  
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## Teleconference Minutes

**Teleconference Date:** May 16, 2005  
**Application Numbers:** NDA 21-799 (Quinine Sulfate)  
**Sponsor:** Mutual Pharmaceuticals  
**Attendees:**

**Mutual Pharmaceuticals**

Robert Dettery, Ph.D. Regulatory Affairs

**Division of Special Pathogen and Immunologic Drug Products**

Mary Singer, M.D. Medical Officer Reviewer  
Eileen Navarro, M.D. Medical Officer Team Leader  
Kristen Miller, Pharm.D. Regulatory Project Manager

**BACKGROUND:** On October 14, 2004, Mutual submitted a new drug application (NDA) 21-799 for quinine sulfate. On April 29, 2005, Mutual submitted a proposal

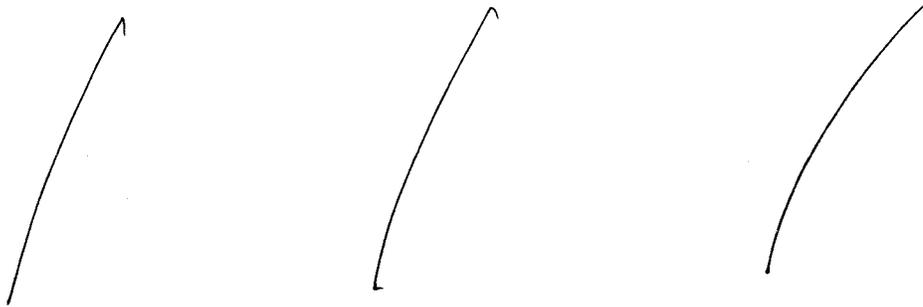
Additionally, Mutual requested

Mutual also wished to discuss enforcement of unauthorized quinine products following approval of NDA 21-799, and to update the Division that a pediatric supplement is being planned. On May 13, 2005, the Review Team sent Mutual a response to this submission, and a telecon was scheduled for May 16, 2005 to further discuss these topics.

**DISCUSSION POINTS:**

Following introductions, the Review Team

( ) ( ) ( ) ( )

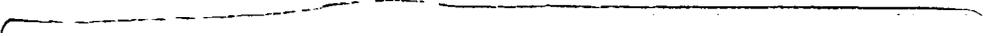


Mutual agreed to consider and address those issues.

Mutual asked if a teleconference could be scheduled with the Division and Office of Compliance to discuss the enforcement issues regarding the marketing of unauthorized quinine products following approval of 21-799. The Review Team will contact the Office of Compliance and will then be in touch with Mutual to discuss this possibility.

Finally, Mutual asked about the progress of the review and the possibility of an early action. The Review Team stated that the review is progressing, but that an early action is unlikely. Mutual thanked the Review Team and the telecon was ended.

#### **ACTION ITEMS**

1. 
2. The Review Team will discuss enforcement issues with the Office of Compliance prior to action on this NDA and touch base with Mutual regarding a potential meeting regarding the enforcement issues of unauthorized quinine products.

**Minutes Preparer:** Kristen Miller, Pharm.D., Project Manager

**Chair Concurrence:** Mary Singer, M.D., Medical Officer Reviewer

Eileen Navarro, M.D., Medical Officer Team Leader

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/s/  
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Kristen Miller  
5/24/05 07:34:40 PM  
CSO

Mary Singer  
6/24/05 02:59:28 PM  
MEDICAL OFFICER

Eileen Navarro  
7/5/05 09:28:47 AM  
MEDICAL OFFICER



United Research Laboratories, Inc.  
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street  
Philadelphia, PA 19124

215-288-6500  
www.urlmutual.com

**REQUEST FOR EXCLUSION FROM REQUIREMENT FOR  
ENVIRONMENTAL ASSESSMENT**

Pursuant to 21 CFR §§25.15(d) and 25.31(a), Mutual Pharmaceutical Company, Inc. hereby claims a categorical exclusion from the requirement of an Environmental Assessment.

Under 21 CFR §§25.31(a), a categorical exclusion exists for:

Action on an NDA, abbreviated application, application for marketing, approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.

Mutual Pharmaceutical Company is requesting FDA to take action by approving its application for Quinine Sulfate Capsules, 324 mg. Mutual Pharmaceutical Company, Inc. meets the requirements of 21 CFR §25.31(a) because Mutual Pharmaceutical's Quinine Sulfate Capsules, 324 will not increase the use of the product beyond that which is already commercially sold in the United States.

Mutual Pharmaceutical Company certifies that it is unaware of any extraordinary circumstances that indicate the proposed action may significantly affect the quality of the human environment.

Mutual Pharmaceutical Company also certifies that, to the best of its knowledge and in its opinion, it is in compliance with all federal, state and local environmental protection requirements and that it has a waste disposal program.

On the basis of the foregoing, Mutual Pharmaceutical Company submits that an Environmental Assessment is not required with this application and, therefore, requests that it be categorically excluded from the requirement to submit an Environmental Assessment.

A handwritten signature in cursive script that reads "Robert Dettery".

Robert Dettery  
Vice-President, Regulatory Affairs

July 5, 2005  
Date



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** June 23, 2005

<b>To:</b> Robert Dettery	<b>From:</b> Kristen Miller
<b>Company:</b> Mutual Pharmaceutical Company	Division of Special Pathogen and Immunologic Drug Products
<b>Fax Number:</b> 215-807-1095	<b>Fax Number:</b> 301-827-2475
<b>Phone Number:</b> 215-807-1044	<b>Phone Number:</b> 301-827-2127

**Subject:** Chemistry information request for NDA 21-799

**Total no. of pages including cover:**

**Comments:** Concur:  
Gene Holbert, Ph.D.

Chemistry Reviewer

**Document to be mailed:**  YES  NO

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Please refer to your new drug application (NDA) 21-799 for quinine sulfate. The Review Team has the following comments and requests to assist in the review of this application.

1. According to the Merck Index Thirteenth Edition, the solubility of quinine sulfate dihydrate is 1 g in 810 mL of water (1.23 mg/mL), not \_\_\_\_\_ (page 04 000025). Please explain this discrepancy.
2. Compliance inspected / \_\_\_\_\_ (CFN \_\_\_\_\_) in December 2004. The profile was acceptable and no action was indicated. However, the inspector was informed that the facility has no contract with the applicant and does not intend to test the product. Please withdraw this facility as an alternate testing site.
3. Limits of Detection and Quantitation for \_\_\_\_\_ cannot be located in the drug substance HPLC method for Related Substances/Degradation Products. Please provide those limits and describe how they were determined.
4. Please clarify what in-process controls are applied to every commercial batch of product.
5. Please request categorical exclusion from environmental assessment and certify that you are not aware of any extraordinary circumstances. See "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications" (July 1998), section II.
6. Please provide \_\_\_\_\_
7. Please verify the accuracy of the following statement from the draft package insert: \_\_\_\_\_  
\_\_\_\_\_
8. Please add "Dosage and Use" information to the container labels.
9. With reference to the Amendment of 30-MAR-2005:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

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Kristen Miller, Pharm.D.  
Regulatory Project Manager

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/s/

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Kristen Miller  
6/23/05 12:41:57 PM  
CSO

## REQUEST FOR CONSULTATION

TO (Office/Division): Kathleen Uhl, M.D.  
Marsha Holloman, B.S. Pharm, J.D.  
CDER/OND/ Pregnancy and Lactation Team, HFD-020

FROM (Name, Office/Division, and Phone Number of Requestor):  
Kristen Miller, Pharm.D.  
CDER/OND/Division of Special Pathogen and  
Transplant Products  
301-827-2374

DATE  
June 16, 2005

IND NO.  
N/A

NDA NO.  
21-799

TYPE OF DOCUMENT  
N-000

DATE OF DOCUMENT  
October 12, 2004

NAME OF DRUG  
Quinine Sulfate

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-malarial

DESIRED COMPLETION DATE  
July 20, 2005

NAME OF FIRM: Mutual Pharmaceuticals

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input checked="" type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input checked="" type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|--|--|

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG SAFETY

- |  |   |
|--|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input checked="" type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Mutual Pharmaceuticals has submitted quinine sulfate for the treatment of uncomplicated Plasmodium falciparum malaria (NDA 21-799). The product is available as immediate release capsules for oral administration in a 324-mg dosage strength. This has been submitted primarily in electronic format; the network path location is: \\CDSESUB1\N21799\N\_000\2004-10-13, and the proposed package insert is available.

The Division requests that you provide feedback on the pregnancy section of the labeling. Mutual has proposed a \_\_\_\_\_ based on two submitted studies in pregnant patients. Mary Singer, the medical officer for this application, will be providing additional information via email. Please contact me or Mary if you have any questions. We have labeling discussions scheduled for July 1 and July 12 if you would like to attend. Thank you!

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

Kristen Miller, Pharm.D.	<input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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ON ORIGINAL**

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Kristen Miller  
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**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** June 14, 2005

<b>To:</b> Robert Dettery	<b>From:</b> Kristen Miller
<b>Company:</b> Mutual Pharmaceutical Company	Division of Special Pathogen and Immunologic Drug Products
<b>Fax Number:</b> 215-807-1095	<b>Fax Number:</b> 301-827-2475
<b>Phone Number:</b> 215-807-1044	<b>Phone Number:</b> 301-827-2127

**Subject:** Labeling information request for NDA 21-799

**Total no. of pages including cover:**

**Comments:** Concur:

Mary Singer, M.D.

Kala Suvarna, Ph.D.

Gerlie Gieser, Ph.D.

Medical Officer Reviewer

Microbiology Reviewer

Clinical Pharmacology Reviewer

**Document to be mailed:**

YES

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CSO



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** June 2, 2005

<b>To:</b> Robert Dettery	<b>From:</b> Kristen Miller
<b>Company:</b> Mutual Pharmaceutical Company	Division of Special Pathogen and Immunologic Drug Products
<b>Fax Number:</b> 215-807-1095	<b>Fax Number:</b> 301-827-2475
<b>Phone Number:</b> 215-807-1044	<b>Phone Number:</b> 301-827-2127

**Subject:** Request for information for labeling for NDA 21-799

**Total no. of pages including cover:** 3

**Comments:** Concur:

Mary Singer, M.D.

Eileen Navarro, M.D.

LaRee Tracy, M.A.

Cheryl Dixon, Ph.D.

Medical Officer Reviewer

Medical Officer Team Leader

Statistical Reviewer

Statistical Team Leader (Acting)

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Please refer to your October 14, 2004 new drug application (NDA) 21-799 for quinine sulfate. The Review Team has the following requests for information to assist in the review of this application.

1. Please provide evidence supporting the statement in the proposed label that \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_
2. Please provide the rationale and \_\_\_\_\_  
\_\_\_\_\_
3. Please provide evidence for \_\_\_\_\_  
\_\_\_\_\_ as stated in the proposed label \_\_\_\_\_

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Kristen Miller, Pharm.D.  
Regulatory Project Manager

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Renata Albrecht  
5/18/05 05:49:44 PM



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** May 13, 2005

<b>To:</b> Robert Dettery	<b>From:</b> Kristen Miller
<b>Company:</b> Mutual Pharmaceutical Company	Division of Special Pathogen and Immunologic Drug Products
<b>Fax Number:</b> 215-807-1095	<b>Fax Number:</b> 301-827-2475
<b>Phone Number:</b> 215-807-1044	<b>Phone Number:</b> 301-827-2127

**Subject:** Response regarding request new indication for NDA 21-799

**Total no. of pages including cover:** 3

**Comments:** Concur:

Mary Singer, M.D.

Eileen Navarro, M.D.

Renata Albrecht, M.D.

Medical Officer Reviewer

Medical Officer Team Leader

Division Director

**Document to be mailed:**

YES

NO

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Please refer to your October 14, 2004 new drug application (NDA) 21-799 for quinine sulfate. Please also refer to your April 29, 2005 submission proposing \_\_\_\_\_

\_\_\_\_\_ Additionally, we  
acknowledge your request \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Additionally, the Division will further discuss the enforcement issues regarding marketing of unauthorized quinine products addressed in your April 29, 2005 submission. Finally, we \_\_\_\_\_

\_\_\_\_\_

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\_\_\_\_\_  
Kristen Miller, Pharm.D.  
Regulatory Project Manager

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

DATE: May 9, 2005

TO: Renata Albrecht, M.D.  
Director  
Division of Special Pathogens and Immunologic Drug  
Products (HFD-590)

FROM: John A. Kadavil, Ph.D.  
Staff Fellow,  
  
Jacqueline A. O'Shaughnessy, Ph.D.  
Pharmacologist, and  
  
Michael F. Skelly, Ph.D.  
Pharmacologist

THROUGH: C.T. Viswanathan, Ph.D.  
Associate Director - Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-799, Quinine Sulfate  
Capsules

SPONSOR: Mutual Pharmaceutical Company

At the request of HFD-590, the Division of Scientific  
Investigations audited the following bioequivalence study:

**Protocol:** RA3-085  
**Study Title:** A Relative Bioavailability Study of Quinine  
Sulfate Capsules Under Fasting and Fed Conditions

The clinical portion of the study was conducted at \_\_\_\_\_  
\_\_\_\_\_ The  
analytical portion of the study was conducted at \_\_\_\_\_

Following the inspections at \_\_\_\_\_ (4/4 - 4/13/05) and at \_\_\_\_\_  
(4/25 - 4/28/05), no Form 483 was issued at either site.

Following the above inspections, DSI recommends that the data  
from this study can be considered for Agency review.



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/s/

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Amalia Himaya

5/9/05 03:34:03 PM

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Hard copy signed by Dr. Viswanathan on 5/9/05 and  
available upon request.



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV**

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** April 28, 2005

<b>To:</b> Robert Dettery	<b>From:</b> Kristen Miller
<b>Company:</b> Mutual Pharmaceutical Company	Division of Special Pathogen and Immunologic Drug Products
<b>Fax Number:</b> 215-807-1095	<b>Fax Number:</b> 301-827-2475
<b>Phone Number:</b> 215-807-1044	<b>Phone Number:</b> 301-827-2127

**Subject:** \_\_\_\_\_ request for NDA 21-799

**Total no. of pages including cover:** 3

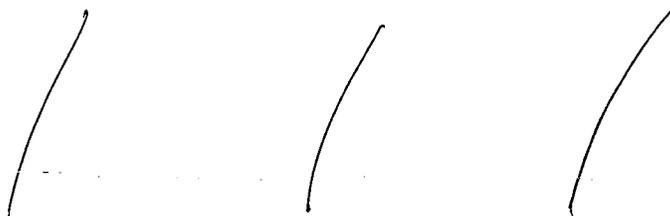
**Comments:** Concur:  
Mary Singer, M.D. Medical Officer Reviewer

**Document to be mailed:**                      • YES                       NO

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Please refer to your new drug application (NDA) 21-799 for quinine sulfate. The Review Team has the following request to assist in the review of this application.

Three handwritten checkmarks, each consisting of a single curved line starting from the bottom left and ending at the top right.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

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Kristen Miller, Pharm.D.  
Regulatory Project Manager

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Kristen Miller  
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- in vitro dissolution method and dissolution acceptance criteria
- Biopharmaceutics Classification System classification/characterization for quinine.

URL/Mutual noted that what is required for a comparator is a link with literature, i.e., a literature search should be conducted for formulations reported to be efficacious in the treatment of malaria and those formulations would be used as comparators. Mr. Rosen stated that URL/Mutual will review the literature to determine a suitable comparator and then may request to discuss their findings with the Division.

Dr. Colangelo stated that the answer to the second part of question 4 regarding *in vitro* studies would include protein binding studies and the human CYP450 microsomal studies already mentioned with regard to the evaluation of the drug interaction potential for quinine.

5. *URL/Mutual does not intend to seek pediatric labeling at this time. Does the Division agree with this approach?*

Dr. Sacks stated that the Division would very much like pediatric information but that it is not necessary to have in the NDA application. While the Division would definitely prefer pediatric information be submitted with the NDA, it is acceptable to consider submitting pediatric information at a later date, possibly as a supplement. URL/Mutual stated that there is some pediatric information in the literature and they will review what is available.

Dr. Goldberger asked whether URL/Mutual has given any consideration as to what would go into the geriatric section their quinine sulfate label. URL/Mutual stated there has been some internal discussion of the pharmacokinetics of quinine sulfate in older patients. URL/Mutual is not certain at this point in time how much data are available in the literature regarding geriatric patients. The concern will be the predisposition for QT prolongation and the frequent use of concomitant medications in geriatric patients. Dr. Goldberger stated that URL/Mutual should provide as much information regarding geriatric patients as possible. Dr. Sacks added that it may be possible for URL/Mutual to study QT prolongation in geriatric patients as part of a pharmacokinetic study.

Noting that the Division had requested an annotated label, Dr. Goldberger recommended that as URL/Mutual searches the literature they think about what they will use to support statements in their proposed quinine sulfate label.

6. *URL/Mutual believes that Quinine Sulfate for the indication stated above is eligible for Orphan Drug designation. Does the Division concur?*

Mr. Bona stated that the treatment of malaria would be an Orphan indication. If designated and then approved for the treatment of malaria, URL/Mutual could receive

seven years of exclusivity if their quinine sulfate product is the first approved for this indication.

Five years of Hatch-Waxman exclusivity is not an option as there have been previous approvals of quinine sulfate. For three years of Hatch-Waxman exclusivity, clinical studies would be needed.

**Other Questions:**

Noting that quinine sulfate is more heavily used in third world countries, URL/Mutual asked if the literature from these countries would be acceptable to support approval of an NDA. Dr. Sacks stated that the Division would accept literature reports from third world countries. Whether or not this literature will support approval depends on the quality of the data. Dr. Colangelo added that the literature needs to clearly demonstrate that there are no differences in how quinine sulfate is handled (ADME) among the Caucasians, Asians, Africans, and others who would receive the drug. The literature will need to convincingly demonstrate that there are no pharmacokinetic differences among races.

**Summary**

The meeting discussion addressed the sponsor's questions outlined in their June 26, 2003 meeting package. The only action item from the meeting was that Ms. Willard would send via facsimile transmission (FAX) a list of approved NDAs for quinine sulfate.

**Addendum**

A list of approved NDAs for quinine sulfate was FAXed to Mr. Rosen on July 16, 2003.

**Minutes Preparer:** \_\_\_\_\_  
**Diana Willard**

**Concurrence, Meeting Chair:** \_\_\_\_\_  
**Renata Albrecht, M.D.**

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/s/

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Diana Willard  
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Marc Cavaille Coll  
8/8/03 02:07:11 PM  
For Dr. Renata Albrecht, Division Director