CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-078

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: February 16, 2000

TO:

ADDRESS:

FROM: Valerie Jensen RPh., Project Manager
Division of Special Pathogen and Immunologic Drug Products

SUBJECT: Requests regarding chemistry review of amendments to DMF
DMF contains data on the manufactured by Company. This is used by Glaxo Wellcome for manufacture of Malarone (NDA 21-078).

Dr.

After review of the amendments submitted to DMF for we have the following comments and requests:

1. In order to avoid a potential inconsistency with Glaxo Wellcome's specification for the drug substance, please establish a limit on total impurities at NMT

2. The failure to obtain drug substance free of the impurity at the conclusion of the second step for the batch (# 491) suggests that this purification process remains unoptimized. Please consider the following points:

   a. The prevailing theory concerning the origin of the is that it forms from of the drug substance and that the amount of this impurity can be kept to acceptable levels by If this reasoning is sound, the detection of after the for batch 491 and after the step in batches 487, 488, and 491 suggests that the is still being exceeded. Please revise the

; method to aim for a that is units lower than the current target.

b. Assuming that the proposed mechanism for the formation of the is correct, has it been established whether the largest amount of the contamination is produced during the when the seems to be units lower than the or during the period of time prior to when the is at its maximum value? Have any experiments been conducted to determine if it is feasible to add to the before the adjustment? (This alternate procedure might have some benefit if a significant amount of the is produced prior to

3. Please describe (by page number) where the data may be found that was used to develop graphs 1 and 2 as found in the master batch records for process edition 5.1. For any page containing more data than was actually used in the development of these graphs, please also specify which portion of the data on that page was used.

4. Please explain the basis for setting the variation limit at plus/minus for the two optical density determinations.

5. It is stated in volume 1.4 that proguanil HCl treated with is "free" of and after a in Please provide the data that showed that the material was "free" of

6. The table of contents of the January 26, 2000 submission identifies it as "supplement 5" to the DMF. The Central Document Room only has record of the original DMF and two prior amendments in May and July, 1999. What were the dates of submission of the other "supplements," or weren't all of these "supplements" actually submitted to the DMF?

Please contact Valerie Jensen RPh., Project Manager, at (301) 827-2374 with any questions related to this correspondence.

Sincerely,

Valerie Jensen R.Ph., Project Manager, DSPIDP

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: July 11, 2000

TO: Thomas Shumaker
Project Director, Regulatory Affairs

ADDRESS: Glaxo Wellcome
PO Box 13398
Research Triangle Park, NC 27709
(919) 483-9324
(919) 483-5756 (fax)

FROM: Valerie Jensen RPh., Project Manager
Division of Special Pathogen and Immunologic Drug Products

SUBJECT: Container labeling for MALARONE™ which was submitted July 29, 1999.

We refer to your planned correspondence which will relate to committing to work with the Division to modify the container labeling and advertising for MALARONE™ within a six month time frame. Based on the particular changes we are referring to which involve moving the word Pediatric on the container containing the 62.5 mg/25 mg tablets, increasing the font of the text description of the strength on both containers, and decreasing the prominence of the text identifying the quantity of tablets on both containers, we do not foresee the need for a "Dear Doctor" or "Dear Pharmacist" letter to be sent regarding these changes. We also have asked that you address the issue of possible medication errors due to the two MALARONE™ tablets being the same color in this planned correspondence. We look forward to receiving your correspondence.

If there are any questions relating to the contents of this correspondence, please contact Valerie Jensen R.Ph., Project Manager at (301) 827-2374.

HFD-590 / JENSEN

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: 16 December 1999

TO: Tom Shumaker
Project Director, Regulatory Affairs

ADDRESS: Glaxo Wellcome
PO Box 13398
Research Triangle Park, NC 27709
(919) 483-9324
(919) 483-5756 (fax)

FROM: Valerie Jensen RPh., Project Manager
Division of Special Pathogen and Immunologic Drug Products

SUBJECT: Comments regarding methods validation relating to NDA 21-078 for Malarone™

NOTE: We are providing the following information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

1. Please revise the procedure for the drug substance assay to clarify the determination of two of the system suitability parameters. The proposed procedure states that the LOQs of proguanil HCl and [redacted] should be NLT [redacted] and [redacted] respectively, in the [redacted] of the LOQ [redacted] However, the method used to calculate the LOQs is not precisely defined. Please specify what the relative magnitude of the LOQ [redacted] responses should be, compared to [redacted] in order to meet this requirement.

2. Please revise the procedure for the determination of impurities in the drug product. The proposed procedure directs that process impurities controlled in the drug substance should be identified by [redacted] However, identification by [redacted] can be unreliable, and in this case it was shown to be so during methodvalidation studies by the FDA field laboratory assigned to evaluate these methods. Please revise the procedure to provide for identification of these impurities by [redacted] containing the impurities to be identified.

Please call Valerie Jensen R.Ph., Project Manager at (301) 827-2374 with any questions relating to this correspondence.

Concurrence:
Dr. SchmuffCTL/
Dr. SmithCR/

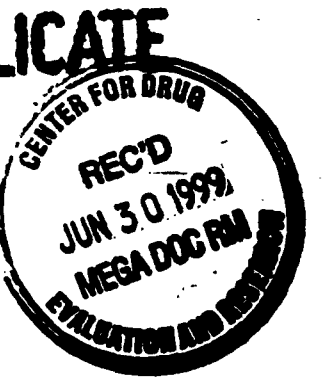
Distribution:
HFD-590/Division File
HFD-590/Smith/Chem reviewer
HFD-590/Jensen/PM

NDA 21-078

WITHHOLD 4 PAGE (S)

GlaxoWellcome

NEW CORRES DUPLICATE



June 29, 1999

NC

Mark Goldberger, M.D., Director
Division of Special Pathogens & Immunologic Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
HFD-590
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-078; MALARONE™ (atovaquone and proguanil hydrochloride) Tablets for the Treatment and Prevention of Malaria
Phase IV Commitments

Dear Dr. Goldberger:

Reference is made to NDA 21-078 for MALARONE (atovaquone and proguanil hydrochloride) Tablets, i.e., an application under active review in your Division. Please also refer to the telephone conferences on May 24 and June 16, 1999, in which we discussed several recommendations for Phase IV activities with this product. In view of the Division's recommendations, the purpose of this letter is to provide a statement of our commitment to Phase IV activities with MALARONE Tablets.

Background Information

This letter provides a straightforward list of Phase IV activities, recognizing the need for such a list that can be quoted in the action letter. The letter provides expanded information on each Phase IV activity; which enables us to summarize some work that is already ongoing and to explicitly state our understanding of key operational aspects of the activities. Please note that our intent is to keep FDA informed on a regular basis of our progress toward completion of these activities. Specifically, we intend to include a progress report on these Phase IV activities in our Annual Reports to NDA 21-078.

As we proceed toward an action for this NDA, this list represents the agreements made to date between Glaxo Wellcome and the Agency.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

List of Phase IV Activities

1. Glaxo Wellcome will continue to study and report the clinical safety and efficacy of MALARONE Tablets to demonstrate the utility of this drug product in the non-immune patient population, by initiating or completing the following clinical trials:

   - An international, randomized, double-blind study to compare the safety and efficacy of MALARONE (atovaquone and proguanil hydrochloride) versus mefloquine for chemoprophylaxis against malaria in non-immune travelers (this study is currently on-going),
   - An international, randomized, double-blind study to compare the safety and efficacy of MALARONE (atovaquone and proguanil hydrochloride) versus chloroquine/proguanil hydrochloride for chemoprophylaxis against malaria in non-immune travelers (this study is currently on-going),
   - An international, randomized, open-label study to compare the safety and efficacy of MALARONE (atovaquone and proguanil hydrochloride) versus chloroquine/proguanil hydrochloride for chemoprophylaxis against malaria in non-immune pediatric travelers (this study is currently on-going).

   We will commit to be diligent in our enrollment and follow-up on these studies. We commit to submit the final study reports for these studies to the Division in a timely manner after they are prepared, and prior to February 2001.

2. Glaxo Wellcome will conduct and report the results of a study to provide additional evidence that MALARONE Tablets has causal prophylactic activity:

   - A randomized, double-blind, placebo-controlled study of MALARONE (atovaquone and proguanil hydrochloride) as a causal prophylactic agent against mosquito-transmitted *P. falciparum* malaria in healthy non-immune volunteers.

   This study will provide additional data on the causal prophylactic activity of MALARONE Tablets. We commit to submit the final study report for this study to the Division in a timely manner after it is prepared, and prior to February 2001.

3. Glaxo Wellcome will conduct and report the results of a study using MALARONE Tablets manufactured at the Mississauga, Canada site, containing proguanil hydrochloride from .

   - An Uncontrolled Study to Evaluate the Safety and Efficacy of MALARONE (atovaquone and proguanil hydrochloride) for Treatment of Adults with Acute *Plasmodium falciparum* Malaria in Thailand Using Tablets Manufactured in Canada

   This study will provide additional data on the efficacy of the to-be-marketed MALARONE Tablets manufactured in Canada. We further commit to submit the final study report for this study to the Division in a timely manner after it is prepared, and prior to April 2001.

   If the lower bound of the two-sided 95% confidence interval for efficacy is 90% or greater, If the lower bound of the two-sided 95% confidence interval for efficacy is less than 90%,

4. Glaxo Wellcome will conduct and report the results of a study using MALARONE Pediatric Tablets manufactured at Canada containing proguanil hydrochloride from

   - A randomized, double-blind, placebo-controlled, parallel group study to evaluate the suppressive prophylactic activity of MALARONE (atovaquone/proguanil hydrochloride) in children at risk of developing *P. falciparum* malaria.

   This study will provide additional data on the protective efficacy of the to-be-marketed MALARONE Pediatric Tablets manufactured in Canada. We further commit to submit the final study report for this study to the Division in a timely manner after it is prepared, and prior to April 2001.

   If the lower bound of the two-sided 95% confidence interval for protective efficacy is 60% or greater in the per protocol population, then a bioequivalence study will not be needed. If the lower bound of the two-sided 95% confidence interval for protective efficacy is less than 60% in the per protocol population, then the need for a bioequivalence study will be evaluated in the context of all of the efficacy data provided.

5. Glaxo Wellcome will conduct a study that evaluates the pharmacokinetics of MALARONE in patients with renal impairment.

   - MAL10908 - An open label, parallel group, single oral dose study to investigate the pharmacokinetics of MALARONE in subjects with severe renal impairment compared to healthy subjects.

   This study is being conducted in [redacted] We will commit to be diligent in our enrollment and follow-up on this study. We commit to submit the final study report for this study to the Division in a timely manner after it is prepared, and prior to February 2001.

6. Glaxo Wellcome will conduct a study that evaluates the pharmacokinetics of MALARONE in patients with hepatic impairment.

   - MAL10909 - An open label, parallel group, single oral dose study to investigate the pharmacokinetics of MALARONE in subjects with mild to moderate hepatic impairment compared to healthy subjects.

   This study is being conducted in [redacted] We will commit to be diligent in our enrollment and follow-up on this study. We commit to submit the final study report for this study to the Division in a timely manner after it is prepared, and prior to February 2001.

7. Glaxo Wellcome will collaborate with the CDC to prepare and submit an annual [redacted] report [redacted] MALARONE Tablets. This report will include data on [redacted]

   This report will be prepared for the first 5 years following approval of the NDA, at which time we will consult with the Agency as to the usefulness of continuing this reporting mechanism.

8. Glaxo Wellcome agrees to continue to study and report the non-clinical safety profile of MALARONE Tablets to demonstrate the utility of this drug product for chronic administration, by initiating or completing the following non-clinical pharmacology and toxicology studies and submitting the reports in a timely manner:

- A Segment I (Fertility) reproductive toxicology study with proguanil in rats,
- A Segment III (Pre- and post-natal development) reproductive toxicology study with proguanil in rats,
- A 90-day pre-oncogenicity study with proguanil in mice,
- A carcinogenicity study with proguanil in mice,
- A carcinogenicity study with proguanil in rats.

Reports of Segment I (fertility) and Segment III (pre- and post-natal development) studies with proguanil in rats will be submitted by [redacted] respectively.

Reports of completed carcinogenicity studies with proguanil in mice and rats will be submitted by the [redacted] of 2002.

9. [redacted]

10. Glaxo Wellcome agrees to develop a dissolution method that avoids using [redacted] as the dissolution medium for the atovaquone component for MALARONE. This method will be developed and reported to the Agency within [redacted] of the approval date of the NDA.

Our understanding is that this list of items will be quoted in the action letter, if issued based on discussions of June 28, 1999.

This letter is submitted in duplicate. Seven desk copies have been provided directly to Ms. Mary Dempsey for use by the review team. Please contact me at (919)-483-9324 for any matters regarding this application. Thank you.

Sincerely,

Thomas K. Shumaker
Project Director
Regulatory Affairs

Jeffrey M. Chulay, M.D.
Principal Clinical Program Head
HIV and Opportunistic Infections
Clinical Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE

DATE: June 28, 1999

TO: Tom Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Regulatory Project Manager

THROUGH: Robert Hopkins, M.D., M.P.H., T.M., Medical Team Leader
Kenneth Hastings, Ph.D., Team Leader Pharmacology/Toxicology
Andrea Meyerhoff, M.D., M.Sc., DTMH, Medical Officer
Leonard Sacks, M.D., Medical Officer
Steve Kunder, Ph.D., Pharm/Tox

APPLICANT: Glaxo Wellcome

NDA: 21-078

INDICATION: Treatment and prophylaxis of *P. falciparum* malaria

Related Document: Original NDA

SUBJECT: Labeling

Please revise the Pregnancy section of the labeling as follows:

INFORMATION FOR PATIENTS:

in 6/21/99 draft, line ~~144~~, add an additional bullet point that says

- that falciparum malaria carries a higher risk of death and serious complications in pregnant women than in the general population. Pregnant women anticipating travel to malarious areas should discuss risks and benefits of such travel with their physicians.

Pregnancy: Pregnancy Category C: Falciparum malaria carries a higher risk of morbidity and mortality in pregnant women than in the general population. Maternal death and fetal loss are both known complications of falciparum malaria in pregnancy. In pregnant women who must travel to malaria endemic areas, personal protection against mosquito bites should always be employed (see Information for Patients) in addition to antimalarials.

Atovaquone was not teratogenic and did not cause reproductive toxicity in rats at maternal plasma concentrations up to 5 to 6.5 times the estimated human exposure during the treatment of malaria. Following single dose administration of ^{14}C-labeled atovaquone to pregnant rats, concentrations of radiolabel in rat fetuses were 18% (mid-gestation) and 60% (late gestation) of concurrent maternal plasma concentrations. In rabbits, atovaquone caused maternal toxicity at plasma concentrations that were approximately 0.6 to 1.3 times the estimated human exposure during treatment of malaria. Adverse fetal effects in rabbits, including decreased fetal body lengths and weights and increased early resorptions and post-implantation losses, were observed only in the presence of maternal toxicity. Concentrations of atovaquone in rabbit fetuses averaged 30% of concurrent maternal plasma concentrations.

The combination of atovaquone and proguanil hydrochloride was not teratogenic in rats at plasma concentrations up to 1.7 and 0.10 times, respectively, the estimated human exposure during treatment of malaria. In rabbits, the combination of atovaquone and proguanil hydrochloride was not teratogenic or embryotoxic to rabbit fetuses at plasma concentrations up to 0.34 and 0.82 times, respectively, the estimated human exposure during treatment of malaria.

While there are no adequate and well controlled studies of atovaquone and/or proguanil hydrochloride in pregnant women, Malarone may be used if the potential benefit justifies the potential risk to the fetus. The proguanil component of Malarone acts by inhibiting parasitic dihydrofolate reductase. However there are no data indicating that folate supplementation diminishes drug efficacy, and for women of childbearing age receiving folate supplements to prevent neural tube birth defects, such supplements may be continued while taking Malarone.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 22, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078

Dissolution issues

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE

DATE: June 22, 1999

TO: Tom Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Regulatory Project Manager

THROUGH: Robert Hopkins, M.D., M.P.H., T.M., Medical Team Leader
Funmilayo Ajayi, Ph.D., Team Leader, DPE III, Office of Clinical Pharmacology and Biopharmaceutics email 6-22-99
John Smith, Ph.D., Act Chemistry Team Leader email 6-22-99
Houda Mahayni, Pharm.D., Biopharm Reviewer

APPLICANT: Glaxo Wellcome

NDA: 21-078

INDICATION: Treatment and prophylaxis of *P. falciparum* malaria

Related Document: Original NDA

SUBJECT: Dissolution issues

1) Prior to this date, Glaxo has removed the [redacted] dissolution method from the NDA.

2) Glaxo will add to the Phase 4 commitments the following: [redacted]

3) The Glaxo proposal for scale changes is considered a level 1 SUPAC-IR change. They are able to make this change (within one year of the approval date of the NDA) without a dissolution method for [redacted] The dissolution method will be adequate during this interim period.

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey DATE: June 29, 1999
COMPANY: DSPIDP, CDER, FDA FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 14 PHONE NO.:

MESSAGE: NDA 21-078
Malarone NDA: Clean PI

Ms. Dempsey,

Attached is the clean PI, as discussed earlier today.

Please contact me at 919-483-9324 or Robert Watson at 919-483-6972 regarding this information and for any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

FROM:

Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO:

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey
DATE: June 29, 1999
COMPANY: DSPIDP, CDER, FDA
FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 15
PHONE NO.:

MESSAGE: NDA 21-078
Malarone NDA: Revision-marked PI

Ms. Dempsey,

Attached is the revision-marked PI, as discussed earlier today.

Please contact me at 919-483-9324 or Robert Watson at 919-483-6972 regarding this information and for any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

FROM:

Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO:

27 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 28, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078

Labeling

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

********** -COMM. JOURNAL- ********** DATE JUN-28-1999 ***** TIME 17:05 *** P.01

MODE = MEMORY TRANSMISSION START=JUN-28 17:03 END=JUN-28 17:05

FILE NO.= 247

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-FOOD & DRUG ADMIN.

********** - ***** - 301 827 2474- **********

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 28, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078

Labeling

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

MODE = MEMORY TRANSMISSION START=JUN-22 16:30 END=JUN-22 16:32

FILE NO.= 149

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-FOOD & DRUG ADMIN. -

********** - ***** - 301 827 2474- *********

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 22, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078

Dissolution issues

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

GlaxoWellcome **FACSIMILE**

DATE	JUNE 17, 1999	**TOTAL PAGES**	2
TO	Ms. Mary Dempsey Food and Drug Administration	**FAX** **PHONE**	(301) 827-2520 (301) 827-2127
FROM	Ms. Kimberley Jessup-Crippen	**FAX** **PHONE**	(919) 483-5381 (919) 483-9804

Re: **NDA 21-078; MALARONE™ (atovaquone and proguanil hydrochloride) Tablets for the Treatment and Prevention of Malaria**
Response to FDA Request/Comment: CMC

Reference is made to the telephone conversation between John Smith (reviewing chemist), and Ian Buxton and Kimberley Jessup-Crippen of Glaxo Wellcome on June 16, 1999, in which John Smith questioned the in-process control limits for individual tablet weight for NDA 21-078. This fax contains Glaxo Wellcome's response on the in-process control limits for individual tablet weight.

A complete response, with copies sent to the Division and District Offices, will be forthcoming.

Should you have any questions regarding the contents of this submission, please feel free to contact me directly at (919) 483-9804 or via fax at (919) 483-5381.

Regards,

Kimberley Jessup-Crippen

Kimberley Jessup-Crippen
US CMC Submissions
Chemistry, Pharmacy and Manufacturing Regulatory Affairs and Quality Division

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park, NC
27709-3398

U. S. Regulatory Affairs
Phone 919-483-2100

LIMITS FOR INDIVIDUAL TABLET WEIGHTS FOR MALARONE TABLETS AND MALARONE PEDIATRIC TABLETS

A verbal supplementary question has been asked by FDA Reviewing Chemist John Smith and is summarized as:

"The limits proposed in NDA 21-078 for individual tablet weight are wider than those applied during the manufacture of the batches. The proposed NDA limits would action adjustment of the when two tablets exceed , and the batches were manufactured with limits in place of for MALARONE Tablets and , for MALARONE PEDIATRIC Tablets. The expansion of the limits should be justified and supported with data."

In-process limits on individual tablet weight of , and were applied during the manufacture of batches manufactured at the site in Mississauga, Canada only. The batches and batches manufactured at Dartford UK had no limits applied to the individual tablets during manufacture, however, a limit of was applied to the mean tablet weight for both strengths.

The active ingredients comprise a large proportion of the MALARONE Tablet granule formulation: atovaquone , proguanil hydrochloride . With such ratios of active to excipients, it may be expected that there will be a very strong correlation between the uniformity of tablet weight and uniformity of active content. If the tablet cores comply with the requirements for uniformity of weight USP, there will be a high degree of confidence that they will also comply with content uniformity USP, as specified in the NDA.

The USP limits for both uniformity of weight and active content are 85-115% of the **label claim** and relative standard deviation does not exceed 6%, determined on 10 tablets. The current weight uniformity limits proposed in the NDA are that no more than tablets must deviate from the **average** by more than and none by more than determined on tablets. However, if the average is allowed to vary within or for MALARONE PEDIATRIC Tablets), this may theoretically allow tablets to fall outside active content uniformity limits.

It is proposed therefore that the in-process limits on individual tablets should be modified to state:

tablets selected at random ( ) and determine the **individual weights**. Not more than of the individual weights deviate from the **label claim** by more than and none deviates by more than

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE

DATE: June 16, 1999

TO: Tom Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Regulatory Project Manager

THROUGH: Kenneth Hastings, Ph.D., Team Leader Pharmacology/Toxicology
Shukal Bala, Ph.D., Microbiologist

APPLICANT: Glaxo Wellcome

NDA: 21-078

INDICATION: Treatment and prophylaxis of *P. falciparum* malaria

Related Document: Original NDA

SUBJECT: Telecon follow up

The following are recommendations considered to be important studies, but not Phase 4 commitments. These will be cited in the action letter as recommendations.

ADDITIONAL REQUESTS COMMUNICATED TO GLAXO DURING TELECON 6-16-99

MICROBIOLOGY

1. [redacted]

2. [redacted]

3. [redacted]

PHARM/TOX

4. Please conduct a nonclinical study to determine the immunotoxic potential of proguanil. It is recommended that a functional assay such as the [redacted], be included in this determination. This study is requested due to the observation of pneumonia in proguanil-treated dogs.

5. Please conduct additional genotoxicity studies with proguanil. It is recommended that a [redacted] These studies are requested since results of life-time rodent carcinogenicity studies will not be known for at least three years and long-term clinical use (prophylaxis) is likely.

6. Please conduct a battery of genotoxicity assays to determine the potential hazard of the proguanil contaminant [redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 16, 1999 Number of Pages (including cover sheet): 3
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078

Recommendations to be included in an action letter

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

MODE = MEMORY TRANSMISSION START=JUN-16 14:06 END=JUN-16 14:07

FILE NO.= 071

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
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-FOOD & DRUG ADMIN.

********** ***** 301 827 2474- *********

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 16, 1999 Number of Pages (including cover sheet): 3
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078

Recommendations to be included in an action letter

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE

DATE: June 16, 1999

TO: Tom Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Regulatory Project Manager

THROUGH: Robert Hopkins, M.D., M.P.H., T.M., Medical Team Leader
Kenneth Hastings, Ph.D., Team Leader Pharmacology/Toxicology
Funmilayo Ajayi, Ph. D., Team Leader, DPE III
Office of Clinical Pharmacology and Biopharmaceutics
Leonard Sacks, M.D., Medical Officer
Steve Kunder, Ph.D., Pharm/Tox
Houda Mahayni, Pharm.D., Biopharm Reviewer

APPLICANT: Glaxo Wellcome

NDA: 21-078

INDICATION: Treatment and prophylaxis of *P. falciparum* malaria

Related Document: Original NDA

SUBJECT: Phase 4 commitments

In preparation for our teleconference this morning, June 16, 1999, the reviewers have drafted specific wording for the proposed Phase 4 commitments. Please be prepared to discuss the following:

CLINICAL PHASE 4

Studies in non-immune travelers:

- International, randomized, double-blind studies to evaluate the safety and efficacy of Malarone versus _____ for the chemoprophylaxis against malaria in non-immune travelers. Three such studies (_____) have been described by the sponsor in a letter of May 27,1999.

_____ Pediatric patients should be included in the study population.

(These study concepts have been outlined in a submission of May 14, 1999.)

Final reports for these studies must be submitted by February 2001.

PHARM/TOX PHASE 4

- The sponsor agrees to conduct Segment I and III reproductive toxicology studies with proguanil in rats. The final study reports should be submitted to the Agency by respectively. In addition,

- The sponsor agrees to conduct rodent carcinogenicity bioassays. The final study reports should be submitted by the quarter of 2002. In addition, it is recommended that the sponsor submit results of the 90 day pre-carcinogenicity study in mice and to seek concurrence from the CDER Executive Carcinogenicity Assessment Committee on study design and doses selected for the rodent bioassays."

BIOPHARM PHASE 4

- Under most situations, the Agency requires bioequivalence to be demonstrated between to-be-marketed products and products used in clincial trials when these are not identical. For NDA 21-078, the Division will defer this requirement as allowed under CFR 320.22 (e) due to the public health need for malarone in the treatment and prophylaxis of P. falciparum malaria. As part of your phase 4 commitments, you should

- Please develop a dissolution methodology that avoid using [redacted] as dissolution medium for the atovaquone component of malarone.
- [redacted]
- [redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 16, 1999 — Number of Pages (including cover sheet): 4
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078

Phase 4

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 — FAX NUMBER:(301) 827-2475

********** -COMM. JOURNAL- ********** DATE JUN-16-1999 ***** TIME 08:20 *** P.01

MODE = MEMORY TRANSMISSION START=JUN-16 08:19 END=JUN-16 08:20

FILE NO.= 054

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-FOOD & DRUG ADMIN.

********** - - ***** - 301 827 2474- **********

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 16, 1999 Number of Pages (including cover sheet): 4
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078

Phase 4

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

MEMORANDUM OF FACSIMILE

Food and Drug Administration
Rockville MD 20857

DATE: June 16, 1999

TO: Tom Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Regulatory Project Manager

THROUGH: Kenneth Hastings, Ph.D., Team Leader Pharmacology/Toxicology

APPLICANT: Glaxo Wellcome

NDA: 21-078

INDICATION: Treatment and prophylaxis of *P. falciparum* malaria

Related Document: Original NDA

SUBJECT: **Labeling**

Please consider the revised recommendation to the Pharm/Tox section of the labeling as follows:

ANIMAL [redacted] TOXICOLOGY: Fibrovascular proliferation in the right atrium, pyelonephritis, bone marrow hypocellularity, lymphoid atrophy, and gastritis/enteritis were observed in dogs treated with proguanil hydrochloride for 6 months at a dose of 12 mg/kg per day (approximately 3.9 times the recommended daily human dose for malaria prophylaxis on a mg/m^2 basis). Bile duct hyperplasia, gall bladder mucosal atrophy, and interstitial pneumonia were observed in dogs treated with proguanil hydrochloride for 6 months at a dose of 4 mg/kg per day (approximately 1.3 times the recommended daily human dose for malaria prophylaxis on a mg/m^2 basis). Mucosal hyperplasia of the cecum and renal tubular basophilia were observed in rats treated with proguanil hydrochloride for 6 months at a dose of 20 mg/kg per day (approximately 1.6 times the recommended daily human dose for malaria prophylaxis on a mg/m^2 basis). Adverse heart, lung, liver, and gall bladder effects observed in dogs and kidney effects observed in rats were not shown to be reversible.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 16, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078

Animal Pharmacology and Toxicology Labeling

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey DATE: June 16, 1999
COMPANY: DSPIDP, CDER, FDA FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 6 PHONE NO.:

MESSAGE: NDA 21-078
Treatment Study Concept Sheet

Ms. Dempsey,

Attached is the concept sheet for the [redacted] study comparing MALARONE Tablets manufactured at two different locations. We propose this as an alternative to the

We can discuss this further at the telecon on Thursday. Sent by e-mail also.

The phone number for the telecon on Thursday will be (805) 240-9483.
The code is 890561.

Please contact me at 919-483-9324 regarding this information and for any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

FROM:
Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO:
Dr. Robert Hopkins
Biopharm Reviewers
Medical Reviewers

WITHHOLD 5 PAGE (S)

HFD-5[illegible]R

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 21-078

Food and Drug Administration
Rockville MD 20857

JUN 15 1999

Glaxo Wellcome Inc.
PO Box 13398
Research Triangle Park, NC 27709
Attention: Thomas Shumaker
Project Director, Regulatory Affairs

Dear Mr. Shumaker:

Please refer to your New Drug Application (NDA) submission dated May 24, 1999, received May 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Malarone (atovaquone and proguanil hydrochloride) Tablets.

We also refer to your submission dated April 21, 1999 and to our facsimile dated April 12, 1999.

We have reviewed your submission and generally agree, for reasons outlined in your May 24, 1999 submission, that the likelihood of confusion of the name MALARONE with the nomenclature of other prescription drug products does not pose a substantial risk.

In the event of post-marketing reports of medication errors, as a result of similarities in nomenclature with other products, we may be compelled to reevaluate this decision.

If you have any questions, contact Mary Dempsey, Regulatory Project Manager, at 301-827-2127.

Sincerely.

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

GlaxoWellcome **FACSIMILE**

DATE JUNE 15, 1999 **TOTAL PAGES** 4

TO Ms. Mary Dempsey
Food and Drug Administration
FAX (301) 827-2520
PHONE (301) 827-2127

FROM Ms. Kimberley Jessup-Crippen
FAX (919) 483-5381
PHONE (919) 483-9804

Re: **NDA 21-078; MALARONE™ (atovaquone and proguanil hydrochloride) Tablets for the Treatment and Prevention of Malaria**
Response to FDA Request/Comment: CMC

This facsimile communication is in response to the June 15, 1999 teleconference between John Smith (reviewing chemist); and Ian Buxton, Tom Shumaker and Kimberley Jessup-Crippen of Glaxo Wellcome.

A complete copy of this response, with copies sent to the Division and District Offices, will be forthcoming.

If there are any comments regarding this document, please feel free to contact me directly at (919) 483-9804 or via fax at (919) 483-5381.

Sincerely,

Kimberley Jessup-Crippen

Kimberley Jessup-Crippen
US CMC Submissions
Chemistry Pharmacy and Manufacturing Regulatory Affairs and Quality Division

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park, NC
27709-3398

U. S. Regulatory Affairs
Phone 919-483-2100

WITHHOLD 3 PAGE (S)

GlaxoWellcome FACSIMILE

DATE	JUNE 14, 1999	TOTAL PAGES	11
TO	Ms. Mary Dempsey Food and Drug Administration	FAX PHONE	(301) 827-2520 (301) 827-2127
FROM	Ms. Kimberley Jessup-Crippen	FAX PHONE	(919) 483-5381 (919) 483-9804

Re: **NDA 21-078; MALARONE™ (atovaquone and proguanil hydrochloride) Tablets for the Treatment and Prevention of Malaria**
Response to FDA Request/Comment: CMC

Reference is made to the facsimile communications from you on June 8, 1999 and June 11, 1999, the labeling teleconference on June 10, 1999, and a teleconference on June 11, 1999, requesting additional CMC information for NDA 21-078. This submission contains Glaxo Wellcome's complete response to the CMC questions received on June 8, 1999.

In response to the additional comments received on June 11, 1999 on our initial responses to questions 1 - 6 of the June 8, 1999 facsimile, responses to the comments concerning the modification of the [redacted] and to the differences between the in-process controls listed in Volume 3, Section D2 relative to those listed in the Batch Records, have been incorporated into this response in question 6.

In response to the comments on storage statements raised in the labeling teleconference on June 10, 1999, the storage statement has been revised to the following:

Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

A replacement page for the corresponding section of the NDA (Volume 3, Section F2.3) will be provided if requested.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park, NC
27709-3398

U. S. Regulatory Affairs
Phone 919-483-2100

A complete copy of this response, with copies sent to the Division and District Offices, will be forthcoming.

If there are any comments regarding this document, please feel free to contact me directly at (919) 483-9804 or via fax at (919) 483-5381.

Sincerely,

Kimberley Jessup-Crippen

Kimberley Jessup-Crippen
US CMC Submissions
Chemistry Pharmacy and Manufacturing Regulatory Affairs and Quality Division

WITHELD 9 PAGE(S)

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey
DATE: June 14, 1999
COMPANY: DSPIDP, CDER, FDA
FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 7
PHONE NO.:

MESSAGE: NDA 21-078
Response to Child-Resistance Questions

Ms. Dempsey,

Attached is a response to Dr. Smith, in regards to the questions and comments regarding the packaging and carton labeling for MALARONE Tablets.

The phone number for the telecon on Wednesday will be (805) 240-9483. The code is 733299.

Please contact me at 919-483-9324 regarding this information and for any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

FROM:
Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO: Dr. John Smith

GlaxoWellcome

June 14, 1999

Mark Goldberger, M.D., Director
Division of Special Pathogens & Immunologic Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
HFD-590
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-078; MALARONE™ (atovaquone and proguanil hydrochloride) Tablets for the Treatment and Prevention of Malaria
Response to FDA Request/Comment: CMC, Child Resistant Packaging

Dear Dr. Goldberger:

Reference is made to the comment received by telephone from Dr. John Smith, the Reviewing Chemist for the MALARONE NDA, through Ms. Mary Dempsey of your Division, on June 8 and 11, 1999. Dr. Smith commented on June 8, 1999, that since the proposed packaging of MALARONE Tablets . the standards for "special [*i.e.*, child resistant and senior friendly] packaging" set forth in 16 CFR Part 1700, that Glaxo Wellcome should

Glaxo Wellcome does not agree that an . is necessary to allow use of the proposed package. The position of Glaxo Wellcome is that the proposed packaging of MALARONE Tablets serves both as a pharmacy bulk package and an institutional pack, neither of which is subject to the requirement of '

Consistent with long-standing CPSC guidance and an explicit policy statement printed in the *Federal Register* (see 16 CFR Part 1701), prescription drugs packaged in pharmacy bulk packs are not subject to the special packaging requirements because they are not intended to be dispensed to patients in their original packaging. To the contrary, they represent a pool of pharmacy inventory that can be drawn on to fill individual prescriptions requiring repackaging. Given the expected conditions of use of Malarone as a preventative, a carton of can certainly be expected to be drawn on to fill multiple prescriptions. While the exact number of tablets dispensed will vary for each patient, depending on their duration of travel, the expected duration of travel in a malaria endemic area is two weeks for most travelers, and so 23 tablets are sufficient for a single

Glaxo Wellcome Research and Development
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A Division of Glaxo Wellcome Inc.

patient at the proposed dosing schedule (one tablet ~~qd-1-tc~~ 2 days before traveling, one tablet qd during 14 day stay in endemic area, one tablet qd for 7 days upon return). Each carton will thus likely contribute to the filling of several different prescriptions.

Moreover, the proposed package is also designed to serve the needs of in-patients who will be receiving MALRONE tablets for treatment. The legislation that authorizes "special packaging" requirements (*viz.*, the Poison Prevention Packaging Act of 1970) is limited in its coverage of drugs to those that are "household substances," *i.e.*, that are to be used in or about the household. Drugs dispensed for use in institutional settings are thus outside the coverage of the requirements.

The dispensing information we have proposed on the exterior of each carton:

is an additional step we propose to take voluntarily, in recognition of the possibility that some pharmacists dispensing for out-patient use may , that the is, child-resistant.

Following the discussion of the points listed above with Dr. Smith on June 11, 1999, Glaxo Wellcome has taken another look at the carton labeling to determine is alternative wording would be desirable. We have also reviewed the similar wording used on a number of other marketed products (see attachment and two representative samples). While we believe that the proposed wording is fully appropriate to the circumstance and is a product not subject to improvement by the change, we propose to substitute the wording below for that originally submitted:

We request that the word be retained in favor of " " as requested by Dr. Smith. If a doctor or patient specifically requests that the drug be provided in a non-child-resistant package, we do not want to mislead or confuse the dispensing pharmacist in thinking that MALARONE is somehow different from other drugs with similar wording and that they are no longer free to respond to such a request. We would be willing to discuss the carton labeling further during the telephone conference scheduled for Wednesday, June 16.

In closing, we believe that the Agency should view the proposed package for MALARONE Tablets as no different than any other institutional or pharmacy bulk pack, and to consider the questioned carton labeling as precautionary but ultimately elective information proposed as a supplement to the required dispensing information described for Rx drug labeling at 21 CFR 201.100(b)(7). We do not believe that involvement of the CPSC in the review process for the proposed packaging for MALARONE Tablets is either required and we ask the Agency complete their review in light of the comments we have provided above.

This submission is made in duplicate to NDA 21-078, with four additional desk copies of this submission provided directly to Ms. Mary Dempsey. If you have any questions regarding this submission, please contact me at (919) 483-9324. Thank you.

Sincerely,

Thomas K. Shumaker
Project Director
Regulatory Affairs

June 14, 1999

Lariam® (mefloquine hydrochloride) 250mg Tablets from Roche

- Box of 25 tablets in Tel-E-Dose unit dose foil
- "Tel-E-Dose® packaging is intended for institutional in-patient use. If dispensing this drug for out-patient use, an appropriate child-resistant package should be provided."

Fansidar® (pyrimethamine and sulfadoxine) Tablets from Roche

- Box of tablets in unit-dose foil
- "Individually packaged tablets should be dispensed in an appropriate child-resistant package."

Eulexin® (flutamide) Capsules from Schering Plough

- Box of 100 capsules in unit-dose foil
- "This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided."

Retrovir (zidovudine) Capsules

- Box of 100 capsules in unit-dose foil
- "This unit dose packaging is intended for institutional inpatient use. If dispensed for outpatient use, an appropriate safety closure should be provided."

Ceftin (cefuroxime axetil) Tablets

- Box of 100 tablets (125mg) in unit-dose foil
- "This package is intended for institutional use only. If dispensed for outpatient use, appropriate safety packaging must be provided."

Cipro® (ciprofloxacin hydrochloride) Tablets from Bayer

- Box of 100 tablets in unit dose strips
- **"For institutional use only"**

Coumadin® (warfarin sodium tablets, USP) Crystalline from DuPont Pharma

- Box of 100 tablets in unit dose strips
- "For Hospital Use Only"

TO OPEN LIFT THIS FLAP

USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.

STORE AT 59° TO 86° F (15° TO 30° C).

Distr. by: ROCHE LABORATORIES, a div. of Hoffmann-La Roche Inc., Nutley, NJ 07110
Mfd. by: F. HOFFMANN-LA ROCHE & CO. LTD., Basle, Switzerland

NDC 0004-0172-02 Tel-E-Dose® ITEM 74602

Roche

LARIAM®
(mefloquine HCl)

250 mg

Each tablet contains 250 mg mefloquine hydrochloride.

CAUTION: Federal law prohibits dispensing without prescription.

25 Tablets

LARIAM® (mefloquine HCl) 250 mg

EXP LOT

0004-0172-02 7

13-11-74602-0695

6505-01-315-1275

Tel-E-Dose® packaging is intended for institutional in-patient use. If dispensing this drug for out-patient use, an appropriate child-resistant package should be provided.

100 mg
Each capsule contains
Capsules
(zidovudine)
RETROVIR®

UNIT DOSE PACK

NDC 0173-0108-56

100 Capsules NDC 0173-0108-56
(10 blisterpacks of 10 capsules each)

UNIT DOSE PACK

RETROVIR®
(zidovudine)
Capsules

Each capsule contains
100 mg

This unit dose packaging is intended for institutional inpatient use. If dispensed for outpatient use, an appropriate safety closure should be provided.

For indications, dosage, precautions, etc., see enclosed package insert.

CAUTION: Federal law prohibits dispensing without prescription.

Store at 15° to 25°C (59° to 77°F) and protect from moisture.

U.S. Patent Nos. 4,914,534 and 4,888,939 (Product Patents); 4,724,232; 4,818,130; and 4,837,208 (Use Patents) Made in U.S.A.

4867967

180 Capsules
(10 blisterpacks of 10 capsules each)

NDC 0173-0108-56

UNIT
DOSE PACK

RETROVIR®
(zidovudine)
Capsules

For indications, dosage, precautions, etc., see enclosed package insert.
Store at 15° to 25°C (59° to 77°F) and protect from moisture.

100 Capsules NDC 0173-0108-56
(10 blisterpacks of 10 capsules each)

UNIT DOSE PACK

This unit dose packaging is intended for institutional inpatient use. If dispensed for outpatient use, an appropriate safety closure should be provided.

RETROVIR®
(zidovudine)
Capsules

Each capsule contains
100 mg

CAUTION: Federal law prohibits dispensing without prescription.

4867967
Rev. 8/97

180 Capsules
(10 blisterpacks of 10 capsules each)

NDC 0173-0108-56

UNIT
DOSE PACK

RETROVIR®
(zidovudine)
Capsules

For indications, dosage, precautions, etc., see enclosed package insert.
Store at 15° to 25°C (59° to 77°F) and protect from moisture.

WITHHOLD 2 PAGE (S)