

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**40-274**

**ADMINISTRATIVE DOCUMENTS**

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: 40-274

Date of Submission: August 28, 1997

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Hydroxychloroquine Sulfate Tablets USP, 200 mg

Labeling Deficiencies:

1. CONTAINER (100s)

- a. On your label, you instruct the pharmacist to attach a "KEEP OUT OF THE REACH OF CHILDREN" warning sticker when dispensing. We note that the innovator supplies these stickers. We believe you should do the same. Please comment.
- b. Please ensure that the established name and strength is the most prominent information appearing on the label.
- c. Include the following on the main panel:

KEEP OUT OF THE REACH OF CHILDREN

2. INSERT

a. DESCRIPTION

- i. Revise the first sentence of the first paragraph to read, "Hydroxychloroquine Sulfate is a white or practically white crystalline...".
- ii. Revise to include the structural formula, molecular weight, and molecular formula of the drug product.
- iii. Revise the first sentence of the second paragraph to read, "Each tablet for oral administration contains 200 mg hydroxychloroquine sulfate (equivalent to 155 mg hydroxychloroquine). Inactive..."

b. ACTIONS

Revise this section heading throughout your labeling to read, "CLINICAL PHARMACOLOGY:".

c. INDICATIONS

Revise this section heading throughout your labeling to read, "INDICATIONS AND USAGE:".

d. WARNINGS

Revise section heading to read "WARNINGS, General". "General" is not a subsection but rather is meant to distinguish these "WARNINGS" from the "WARNINGS" specific to Malaria and Lupus.

e. PRECAUTIONS

See Item (d) above regarding "General".

f. OVERDOSAGE

Revise the penultimate sentence of the first paragraph to read, ...tracheal intubation or...

g. MALARIA

i. See Comments (2) (b) and (c).

ii. Revise "Warning" to read "Warnings".

iii. Adverse Reactions

Add the following as the ultimate paragraph:

Cardiomyopathy has been rarely reported with high daily dosages of hydroxychloroquine.

h. LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

i. See Comment (2) (c).

ii. Revise the first sentence of paragraph 2 to read, "Other *fundus* changes...". (italicize)

iii. Miscellaneous Reactions

Revise the ultimate sentence to read like (g) (iii) above.

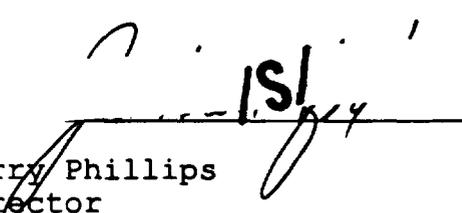
i. HOW SUPPLIED

- i. We encourage you to include "USP" with the established name.
- ii. Indicate whether or not your tablets are scored.

Please revise your labels and labeling, as instructed above, and submit in final print, or draft if you prefer.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

  
Jerry Phillips  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: 40-274

Date of Submission: August 28, 1997

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Hydroxychloroquine Sulfate Tablets USP, 200 mg

Labeling Deficiencies:

1. CONTAINER (100s)

- a. On your label, you instruct the pharmacist to attach a "KEEP OUT OF THE REACH OF CHILDREN" warning sticker when dispensing. We note that the innovator supplies these stickers. We believe you should do the same. Please comment.
- b. Please ensure that the established name and strength is the most prominent information appearing on the label.
- c. Include the following on the main panel:

KEEP OUT OF THE REACH OF CHILDREN

2. INSERT

a. DESCRIPTION

- i. Revise the first sentence of the first paragraph to read, "Hydroxychloroquine Sulfate is a white or practically white crystalline...".
- ii. Revise to include the structural formula, molecular weight, and molecular formula of the drug product.
- iii. Revise the first sentence of the second paragraph to read, "Each tablet for oral administration contains 200 mg hydroxychloroquine sulfate (equivalent to 155 mg hydroxychloroquine). Inactive..."

b. ACTIONS

Revise this section heading throughout your labeling to read, "CLINICAL PHARMACOLOGY:".

c. INDICATIONS

Revise this section heading throughout your labeling to read, "INDICATIONS AND USAGE:".

d. WARNINGS

Revise section heading to read "WARNINGS, General". "General" is not a subsection but rather is meant to distinguish these "WARNINGS" from the "WARNINGS" specific to Malaria and Lupus.

e. PRECAUTIONS

See Item (d) above regarding "General".

f. OVERDOSAGE

Revise the penultimate sentence of the first paragraph to read, ...tracheal intubation or...

g. MALARIA

i. See Comments (2) (b) and (c).

ii. Revise "Warning" to read "Warnings".

iii. Adverse Reactions

Add the following as the ultimate paragraph:

Cardiomyopathy has been rarely reported with high daily dosages of hydroxychloroquine.

h. LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

i. See Comment (2) (c).

ii. Revise the first sentence of paragraph 2 to read, "Other *fundus* changes...". (italicize)

iii. Miscellaneous Reactions

Revise the ultimate sentence to read like (g) (iii) above.

i. ---HOW SUPPLIED

- i. We encourage you to include "USP" with the established name.
- ii. Indicate whether or not your tablets are scored.

Please revise your labels and labeling, as instructed above, and submit in final print, or draft if you prefer.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

# REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAM stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
<b>Packaging</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.	x		
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	x		
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	

Labeling (continued)	Yes	No	N.A.
Does NLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of NLD and applicant (page #) in the FTR			
Is the scoring configuration different than the NLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C <sub>max</sub> , T <sub>max</sub> , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

**NOTES/QUESTIONS TO THE CHEMIST:**

The USP recommends that this product be stored in tight light resistant containers. Do the proposed containers and closures satisfy this recommendation?

yw KPW 3/9/98

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**FOR THE RECORD:**

1. Labeling review was based on the labeling of the listed drug PLAQUENIL® (Approved May 26, 1994; Revised April 1992).

2. Packaging  
The RLD packages its product in bottles of 100.

The applicant is proposing to package its product in beige, HDPE bottles of 100 tablets with CRCs.

This product is light sensitive. Chemist will be asked to verify that the proposed containers are light resistant.

3. Labeling  
Mylan has been asked to ensure that the established name and strength appear as the most prominent information on their label.

There are 4 red "KEEP OUT OF THE REACH OF CHILDREN" adhesive warning stickers on the innovator's product. Applicant has not included any information concerning such labeling for their product. They have been asked to comment on their intent.

There is a statement that is to be added to the Adverse Reactions section. In referring back to the approval letter of May 26, 1994, it was noted that the statement we have been requesting generic firms to include differs from that requested in the approval letter. We have requested the inclusion of "Cardiomyopathy has been rarely reported and the relationship to hydroxychloroquine is unclear" which is the wording that was used in the Lupus, Adverse Reactions section of the proposed labeling of the innovator. However, new drugs asked that the following be used in all ADVERSE REACTIONS sections, as a condition of approval, "Cardiomyopathy has been rarely reported with high daily dosages of hydroxychloroquine." The change was requested in this review.

Mylan has been asked to describe the scoring configuration of its tablet in the HOW SUPPLIED section of the insert labeling.

4. **Inactive ingredients**  
There is no discrepancy in the listing of inactives between the DESCRIPTION and the C&C Statements.
5. **USP Issues**  
USP - Preserve in tight, light resistant containers.  
RLD - Dispense in tight light resistant containers as defined in the USP/NF.  
ANDA - Dispense in tight light resistant containers as defined in the USP using a child resistant closure. Store at CRT 15-30°C (59-86°F).
6. **Bioequivalence Issues - Pending**
7. **Patent/Exclusivity Issues - None pending.**

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**Date of Review:**  
December 30, 1997

**Date of Submission:**  
August 28, 1997

**Primary Reviewer:**

**Date:**

*Phillip N. Nelson*  
Team Leader:

12/31/97

*John Year*

**Date:**

1/5/98

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**APPROVAL SUMMARY**

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: 40-274                      Date of Submission: February 27, 1998

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Hydroxychloroquine Sulfate Tablets USP, 200 mg

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?    Yes

Container Labels: (100s)  
Satisfactory as of February 27, 1998, submission

Professional Package Insert Labeling:  
Satisfactory as of February 27, 1998, submission

**BASIS OF APPROVAL:**

Was this approval based upon a petition?    No

What is the RLD on the 356(h) form: Plaquenil®

NDA Number: 9-768

NDA Drug Name: Hydroxychloroquine Sulfate Tablets, 200 mg

NDA Firm: Sanofi Winthrop Pharmaceuticals

Date of Approval of NDA Insert and supplement #029: May 26, 1994

Has this been verified by the MIS system for the NDA?    Yes

Was this approval based upon an OGD labeling guidance?    No

Basis of Approval for the Container Labels: 9-768

# REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the FT?			x
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FT, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
<b>Packaging</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FT.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.	x		
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FT: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASEP guidelines)		x	

Labeling (continued)	Yes	No	N.E.
Does NLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufacturer/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
<b>Scoring:</b> Describe scoring configuration of NLD and applicant (page #) in the FTR			
Is the scoring configuration different than the NLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
<b>Inactive Ingredients:</b> (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzy alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

**NOTES/QUESTIONS TO THE CHEMIST:**

The USP recommends that this product be stored in tight light resistant containers. Do the proposed containers and closures satisfy this recommendation?

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**FOR THE RECORD:**

1. Labeling review was based on the labeling of the listed drug PLAQUENIL® (Approved May 26, 1994; Revised April 1992).

2. Packaging

The RLD packages its product in bottles of 100.

The applicant is proposing to package its product in beige, HDPE bottles of 100 tablets with CRCs.

This product is light sensitive. Chemist has been asked to verify that the proposed containers are light resistant.

3. Labeling

The established name and strength does appear as the most prominent information on their label.

There are 4 red "KEEP OUT OF THE REACH OF CHILDREN" adhesive warning stickers on the innovator's product. Applicant has included samples of the stickers to be used with their product.

There is a statement that is to be added to the Adverse Reactions section. In referring back to the approval letter of May 26, 1994, it was noted that the statement we have been requesting generic firms to include differs from that requested in the approval letter. We have requested the inclusion of "Cardiomyopathy has been rarely reported and the relationship to hydroxychloroquine is unclear" which is the wording that was used in the Lupus, Adverse Reactions section of the proposed labeling of the innovator. However, new drugs asked that the following be used in all ADVERSE REACTIONS sections, as a condition of approval, "Cardiomyopathy has been rarely reported with high daily dosages of hydroxychloroquine." The change was requested in this review.

Firm committed to revising its labeling prior to printing their production quantities to comply with section 126 of FDAMA which deals with "Rx only".

4. **Inactive Ingredients**  
There is no discrepancy in the listing of inactives between the DESCRIPTION and the C&C Statements.
5. **USP Issues**  
USP - Preserve in tight, light resistant containers.  
RLD - Dispense in tight light resistant containers as defined in the USP/NF.  
ANDA - Dispense in tight light resistant containers as defined in the USP using a child resistant closure. Store at CRT 15-30°C (59-86°F).
6. **Bioequivalence Issues** - Waiver granted January 2, 1998
7. **Patent/Exclusivity Issues** - None pending.

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Date of Review:  
March 6, 1998

Date of Submission:  
February 27, 1998

Primary Reviewer:

Date:

*John Boh*

3/6/98

Team Leader:

Date:

*John Boh*

3/6/98

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CC: