CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-017

ADMINISTRATIVE DOCUMENTS

AADA APPROVAL SUMMARY

AADA: 65-017

DRUG PRODUCT: Cyclosporine Capsules USP (Modified)

FIRM: Eon Labs Manufacturing, Inc.

DOSAGE FORM: Capsules **STRENGTH:** 25 mg, 100 mg

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certifications provided on pages 269A, 274, and 284, Vol. 1.2. Acceptable EER dated 5/17/99.

BIO STUDY: The bio-study conducted on the applicant's product and Novartis' Neoral® capsules (100 mg) was found acceptable by the Division of Bioequivalence on 11/17/98. The waiver for bio-study for the 25 mg capsule was found acceptable on 5/10/99.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and drug product are both USP. The applicant is using USP methods in testing the bulk drug and finished product. An exception is dissolution testing on the finished product, which at the request of the Division of Bioequivalence is performed according to the Pharmaceutical Forum (No. 3, May-June, p. 6155).

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Accelerated and room temperature stability data support the proposed 24 month expiration date. Containers used in the stability studies were identical to those described in the container section.

LABELING: See "Approval Summary" dated 11/8/99.

STERILIZATION VALIDATION (IF APPLICABLE): Not-applicable to this drug product.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): Exhibit batch #711243 (100 mg) used for stability and bio-studies and exhibit batch #801218 (25 mg) used for stability studies were manufactured with bulk drug substance from
Each batch consisted of capsules.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): See above

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

ANDA Number: 65-017

Date of Submission: March 30, 1999

Applicant's Name: Eon Labs Manufacturing, Inc.

Proposed Established Name: Cyclosporine Capsules USP (Modified), 25 mg & 100 mg
Labeling Deficiencies:

1. Blister Card

   a. Alcohol must be declared in terms of percent volume (v/v) of absolute alcohol rather than as "dehydrated alcohol". Please revise accordingly. You are referred to section 502(e) of the Act and 21 CFR 201.10(d)(2) for guidance.

   b. As stated earlier, please be aware that for your labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

2. Carton - 30 Unit-dose

   a. Please revise the boxed WARNING statement to read as follows:

      WARNING: Cyclosporine Capsules, USP (Modified) is **NOT BIOEQUIVALENT** to Sandimmune® [Cyclosporine Capsules, USP (Non-modified)]. Do not...

   b. See comment (a) under Blister Card above.

   c. We note that you have included alcohol in the listing of the inactive ingredients. It is not necessary since you have listed alcohol in conjunction with the active ingredient.

   d. 25 mg

      We note that your Components and Composition statement includes However, it is not included in the listing of inactive ingredients for 25 mg strength. In addition, the HOW SUPPLIED section describes your 25 mg drug product as clear capsules. Please comment.

   e. Revise the storage requirement statement to read as follows:

      ... 86°F) [See USP]

   f. We ask you to describe the ingredients in your imprinting ink, dyes at the minimum if any. Please revise and/or comment.

   g. Include a statement as to whether or not the unit-dose package is child-resistant. We offer the following as an example:

      This unit-dose package is not child-resistant. If dispensed for outpatient use, a

child-resistant container should be used. [NOTE: The second sentence is optional]

3. INSERT

a. General

i. Your package insert labeling is difficult to read. We believe that the readability of your insert labeling should be improved.

ii. When referring to information associated with your specific dosage form [*i.e.*, Cyclosporine Capsules, USP (Modified)] such as an indication or specific dose of your product, use the established name [*i.e.*, Cyclosporine Capsules, USP (Modified)] rather than the general term "Cyclosporine USP, (Modified)" throughout the text. This is particularly true with the INDICATION AND USAGE and DOSAGE AND ADMINISTRATION sections.

iii. Delete the term "USP" associated with "Cyclosporine" throughout text including tables except when referring to the established name of your drug products.

b. BOXED WARNING

Replace "Cyclosporine, USP (Modified)" with Cyclosporine Capsules, USP (Modified)" and "Cyclosporine, USP (Non-modified)" with "*Sandimmune® [Cyclosporine Capsules, USP (Non-modified)]", respectively throughout this section.

c. DESCRIPTION

i. We encourage you to increase the prominence of the "NOTE:... " statement.

ii. Please note that the molecular weight of your drug product is 1202.64, not 1202.63 per USP 23 as mentioned in the last deficiency letter. Please revise accordingly.

iii. Refer to the comment (a) under Blister Card.

iv. We note that you have included alcohol in the listing of the inactive ingredients. You may delete alcohol from the listing since you have listed alcohol separately.

v. See comments (d) & (f) under CARTON.

vi. Second paragraph:

... principle in Cyclosporine capsules, USP (Modified), is a ...

d. CLINICAL PHARMACOLOGY

i. Absorption – Revise the first paragraph to read as follows:

Cyclosporine (Modified) has increased bioavailability compared to *Sandimmune®. The absolute bioavailability of cyclosporine administered as *Sandimmune® is dependent on the patient population, estimated to

be less than 10% in liver transplant patients and as great as 89% in some renal transplant patients. The absolute bioavailability of cyclosporine administered as cyclosporine (Modified) has not been determined in adults. In studies of renal transplant, rheumatoid arthritis and psoriasis patients, the mean cyclosporine AUC was approximately 20% to 50% greater and the peak blood cyclosporine concentration (C_{max}) was approximately 40% to 106% greater following administration of cyclosporine (Modified) compared to following administration of *Sandimmune®. The dose normalized AUC in *de novo* liver transplant patients administered cyclosporine (Modified) 28 days after transplantation was 50% greater and C_{max} was 90% greater than in those patients administered *Sandimmune®. AUC and C_{max} are also increased [cyclosporine (Modified) relative to *Sandimmune®] in heart patients, but data are very limited. Although the AUC and Cmax values are higher on cyclosporine (Modified) relative to *Sandimmune®, the pre-dose trough concentrations (dose-normalized) are similar for the two formulations.

ii. Metabolism – Add the following text as the last sentence.

Based on blood concentration data from stable renal transplant patients [13 patients administered cyclosporine (Modified) and cyclosporine (Non-modified) in a crossover study], and bile concentration data from *de novo* liver transplant patients [4 administered cyclosporine (Modified); 3 administered cyclosporine (Non-modified)], the percentage of dose present as M1, M9, and M4N metabolites is similar when either cyclosporine (Modified) or cyclosporine (Non-modified) is administered.

iii. Special Populations (Pediatric population) – Revise this subsection to read as follows:

... (Modified) or cyclosporine (Non-modified) are very limited. In 15 renal transplant patients aged 3 to 16 years, cyclosporine whole blood clearance after IV administration of cyclosporine was 10.6±3.7 mL/min/kg (assay: Cyclo-trac specific RIA). In a study of 7 renal transplant patients aged 2 to 16, the cyclosporine clearance ranged from 9.8 to 15.5 mL/min/kg. In 9 liver transplant patients aged 0.6 to 5.6 years, clearance was 9.3±5.4 mL/min/kg (assay: HPLC).

In the pediatric population, cyclosporine (Modified) also demonstrates an increased bioavailability as compared to cyclosporine (Non-modified). In 7 liver *de novo* transplant patients aged 1.4 to 10 years, the absolute bioavailability of cyclosporine (Modified) was 43% (range 30% to 68%) and for cyclosporine (Non-modified) in the same individuals absolute bioavailability was 28% (range 17% to 42%).

e. CLINICAL TRIALS

i. Rheumatoid Arthritis – First paragraph:

...(Modified) and cyclosporine (Non-modified) in the treatment...

ii. Graph

A) Title – "Numbers" rather than "numbers"
[note the upper case "N"]

B) 10th column – Revise the legend to read as follows:

**CsA vs. CsA (MOD.)[1]

C) Include the following legend immediately underneath the graph:

[1]Cyclosporine (Modified)

f. WARNINGS

i. All Patients – Include the following as the last paragraph.

Because Cyclosporine Capsules, USP [Modified] is not bioequivalent to *Sandimmune® [Cyclosporine, (Non-modified)], conversion from Cyclosporine Capsules, USP [Modified] to *Sandimmune® [Cyclosporine, (Non-modified)] using a 1:1 ratio (mg/kg/day) may result in lower cyclosporine blood concentrations. Conversion from Cyclosporine Capsules, USP [Modified] *Sandimmune® [Cyclosporine, (Non-modified)] should be made with increased monitoring to avoid the potential of underdosing.

ii. Kidney, Liver, and Heart Transplant

A) First paragraph:

... ingredient of Cyclosporine Capsule, (Modified), can...

B) Third paragraph (First sentence) – Revise to read as follows.

Based on the historical *Sandimmune® [Cyclosporine, (Non-modified)] experience with oral solution, nephrotoxicity associated...

C) The paragraph starting "Hepatotoxicity associated..." – Relocate the fourth sentence (As in patients...) to be a new paragraph.

iii. Psoriasis – Penultimate paragraph:

Relocate the seventh sentence (There were two...) to be a new paragraph.

g. PRECAUTIONS

i. General (Hypertension)- First sentence:

... ingredient of Cyclosporine Capsules, USP (Modified)...

ii. Drug Interactions (Other Drug Interactions):

Revise the sub-subsection heading to read "Other Drug Interactions". [note the upper case "I"]

h. ADVERSE REACTIONS

i. Kidney, Liver, and Heart Transplantation

A) First table:

Revise the heading "Cyclosporine, USP (Non-modified) Patients" to read "Cyclosporine Patients [Cyclosporine, USP (Non-modified)]".

B) Second table:

"(N=228)" rather than "(N=2288)"

ii. Rheumatoid Arthritis

A) Table:

Revise the heading "Cyclosporine, USP (Modified/Non-modified) Rheumatoid Arthritis" to read "Cyclosporine (Modified)/Cyclosporine (Non-modified) Rheumatoid Arthritis".

B) The paragraph immediately prior to the sub-subsection "Autonomic Nervous System":

...in 1% to <3% of the rheumatoid... [rather than □3%□]

i. DOSAGE AND ADMINISTRATION

i. Include the following text in bold face type as the first paragraph.

Cyclosporine Capsules, USP (Modified) has increased bioavailability in comparison to Cyclosporine, (Non-modified) e.g., *Sandimmune®. Cyclosporine, USP (Modified) is not bioequivalent to *Sandimmune® [Cyclosporine (Non-modified)] and cannot be used interchangeably without physician supervision.

ii. Newly Transplanted Patients

A) First paragraph – Include the following text as the third sentence:

In newly transplanted patients, initial oral dose of cyclosporine (Modified) is the same as the initial oral dose of cyclosporine (Non-modified).

B) Second paragraph – Revise the last two sentences to read as follows:

... below) If cyclosporine trough blood concentrations are used, the target range is the same for cyclosporine (Modified) as for cyclosporine (Non-modified). Using the same trough concentration target range for cyclosporine (Modified) as for cyclosporine (Non-modified) results in greater cyclosporine exposure when cyclosporine (Modified) is administered (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). Dosing should...

iii. Transplant Patients...(Non-modified) – First sentence:

... absorption of cyclosporine from Cyclosporine Capsules, USP (Non-modified).

j. HOW SUPPLIED – Include the following as the last sentence in this section.

i. *Sandimmune® is a registered trademark of Norvatis Pharmaceuticals Corporation.

ii. Refer to the comments (d) & (e) under CARTON.

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

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following the website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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 the innovator labeling with all differences annotated and explained.

/S/

Robert L. West, R.Ph., M.S.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION

DATE: October 30, 1998

DRUG PRODUCT: Cyclosporine Soft Gelatin Capsules, USP 100 mg

ANDA NUMBER: 65-017

COMPANY: Eon Labs

NAME OF COMPANY REPRESENTATIVE(S): Pat Kaufold

NAME OF OGD REPRESENTATIVE(S): Nasser Mahmud
Moheb Makary

Telecon initiated by: Nasser Mahmud

COMPANY TELEPHONE: 718-276-8600

Upon completion of the review, it was decided by Division of Bioequivalence to communicate deficiencies to the firm via telecon as opposed to a deficiency letter. Following deficiencies were relayed to the firm and a response was requested within ten business days.

1. In the Statistical Report No. ANA-97-132 (the single dose bioequivalence fasting study), it was stated that 36 subjects and 2 alternates were initially enrolled in the study. Of these, 29 subjects completed the study. Hence, an additional 7 subjects were enrolled and 6 subjects completed. In the Clinical Report No. ANA-97-132, it was stated that a total of 38 subjects were enrolled and 35 completed the study. Reasons were provided only for the withdrawal of subjects 15 and 18. Please clarify this discrepancy and provide the reasons for <u>each</u> of the 9 subjects who did not complete the study from the initial enrollment and the one subject from the second enrollment.

2. Please provide the content uniformity data for the test and the reference products.

3. Please submit comparative dissolution testing data on the Cyclosporine Soft Gelatin Capsules, USP 100 mg, using the method published in Pharmacopeial Forum, May-June 1998, Volume 24, Number 3.

Pat Kaufold said that she would send the response via fax followed by a hard copy within ten business days.

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

ANDA Number: 65-017

Date of Submission: June 8, 1998

Applicant's Name: Eon Labs Manufacturing, Inc.

Proposed Established Name: Cyclosporine Capsules USP (modified), 100 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. We acknowledge that your firm has forwarded an established name (Cyclosporine Soft Gelatin Capsules, USP) for your drug product for our review and comment. However, there is no USP monograph for Cyclosporine Soft Gelatin Capsules, USP. Please revise your established name to read "Cyclosporine Capsules, USP (Modified)" throughout your labels and labeling.

   b. Alcohol must be declared in conjunction with the active ingredients. We refer you to 502(e)(1) of the Federal Food, Drug, and Cosmetic Act. In addition, revise to include the alcohol content of your product in terms of percent volume (v/v) of absolute alcohol. You are referred to section 502(e) of the Act and 21 CFR 201.10(d)(2) for guidance.

   c. We ask the deletion of the following statement from your labels and labeling.

      ATTENTION: Eon's Cyclosporine... for microemulsion).

   d. When referring to Neoral® Soft Gelatin Capsules (cyclosporine capsules for microemulsion) use the established name "cyclosporine capsules, USP (Modified)".

   e. When referring to Neoral® Oral Solution (cyclosporine oral solution for microemulsion) use the established name "cyclosporine oral solution,

USP (Modified)".

f. When referring to Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) use the established name "cyclosporine capsules, USP (Non-modified)".

g. When referring to Sandimmune® Oral Solution (cyclosporine oral solution, USP) use the established name "cyclosporine oral solution, USP (Non-modified)".

2. Blister Card

a. See first general comments, as applicable.

b. Please note that for your labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

3. CARTON - 30 Unit-dose

a. See general comments, as applicable.

b. Revise the boxed WARNING statement to read as follows:

WARNING: Cyclosporine capsules, USP (Modified) is **NOT BIOEQUIVALENT** to cyclosporine capsules, USP (Non-modified). Do not...

c. Side Panel

We encourage the inclusion of the net quantity statement.

4. INSERT

a. General

i. See general comments, as applicable.

ii. It is preferable to use the term "to" rather than a "hyphen" to express a range. Revise accordingly throughout the text of the insert labeling.

iii. We acknowledge that you have omitted most references to Sandimmune® Capsules

(Cyclosporine Capsules, USP) in terms of making comparison to your drug product throughout the text. However, we ask you to include these references to Sandimmune® Capsules (Cyclosporine Capsules, USP) in the text including the tables in the ADVERSE REACTIONS section.

iv. When referring to information associated with your specific dosage form [*i.e.*, Cyclosporine Capsules, USP (Modified)], use the established name rather than the general term "cyclosporine" throughout the text including the tables and figures.

v. Throughout the text of the innovator's insert labeling where the term "cyclosporine" is appearing alone, do NOT revise.

vi. Due to the difficulty in determining the dosage form utilized during clinical studies (oral solution or capsule), we request that you make the following revisions throughout the text of the insert (including the tables):

Where "Neoral" appears in the innovator's package insert labeling without reference to specific dosage form, revise to read "Cyclosporine (Modified)".

Where "Sandimmune" appears in the innovator's package insert labeling without reference to specific dosage form, revise to read "Cyclosporine (Non-Modified)".

b. Boxed WARNINGS

Delete the first box and revise the second Boxed WARNING to be in accordance with the innovator's labeling.

c. DESCRIPTION

i. Include the following as the first paragraph in this section:

NOTE: The nomenclature "Cyclosporine Capsules for Microemulsion" has been changed throughout the insert to read "Cyclosporine

Capsules, USP (Modified)".

ii. You may delete "purified water" from the listing of inactive ingredients.

iii. We note that you have listed the molecular formula and molecular weight in two places. You may delete one of these. Please note that the molecular weight of your drug product is 1202.64, not 1202.63 per USP 23.

iv. Last paragraph

Revise "chemical structure" to read "structural formula".

d. CLINICAL PHARMACOLOGY

i. Pharmacokinetics - Last paragraph, second sentence:

The intersubject... [spelling]

ii. Absorption (Table):

A) First column, last row:

Include superscript "6" to read "*De novo* psoriasis[6]".

B) Legend #2:

...was measured over... [rather than "measure"]

C) Legend #4:

Revise to read "[4]Assay: TDx specific... [rather than "Tdx"]

iii. Metabolism - Last sentence:

... oral administration of cyclosporine capsules, the mean...

iv. First and second tables:

"ng•hr/mL" rather than "ng.hr/mL"

e. CLINICAL TRIALS (Rheumatoid Arthritis) - Table:

Please assure that the legends of the table be legible. In general, please increase the readability of the table.

f. WARNINGS (Kidney, Liver, and Heart Transplant)

i. First paragraph:

Relocate the second sentence to begin as a new second paragraph.

ii. Table:

Revise the text in the last column and last row to read as follows:

...steroids or antilymphocyte globulin [note two spaces included]

g. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, and Impairment of Fertility - Fourth paragraph, third sentence (An increased incidence...):

Let this sentence begin a new fifth paragraph.

ii. Pediatric Use

Revise "children" to read "pediatric patients".

h. ADVERSE REACTIONS - Rheumatoid Arthritis:

i. Table:

A) Revise to read "≥3%" in the title rather than ">3%".

B) Central and Peripheral Nervous System Disorders, Headache - Last column:

"9 %" rather than "9"

C) Gastrointestinal System Disorders - Abdominal pain:

Relocate the numbers so that they are in alignment with corresponding columns.

D) Renal:

Increase the prominence of the symbol "≥" in two places.

ii. Last paragraph:

...in 1% to <3% of the rheumatoid... [rather than "3%"]

i. DOSAGE AND ADMINISTRATION (Newly Transplanted Patients) - Second paragraph:

Include the following text as the last sentence:

Lower doses of cyclosporine capsules (modified) may be sufficient as maintenance therapy.

j. HOW SUPPLIED

We encourage the relocation of the "Rx only" to the TITLE section.

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

Please note that we reserve 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 the innovator labeling with all differences annotated and explained.

/S/

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

ANDA Number: 65-017

Date of Submission: June 8, 1998

Applicant's Name: Eon Labs Manufacturing, Inc.

Proposed Established Name: Cyclosporine Capsules USP (modified), 100 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. We acknowledge that your firm has forwarded an established name (Cyclosporine Soft Gelatin Capsules, USP) for your drug product for our review and comment. However, there is no USP monograph for Cyclosporine Soft Gelatin Capsules, USP. Please revise your established name to read "Cyclosporine Capsules, USP (Modified)" throughout your labels and labeling.

   b. Alcohol must be declared in conjunction with the active ingredients. We refer you to 502(e)(1) of the Federal Food, Drug, and Cosmetic Act. In addition, revise to include the alcohol content of your product in terms of percent volume (v/v) of absolute alcohol. You are referred to section 502(e) of the Act and 21 CFR 201.10(d)(2) for guidance.

   c. We ask the deletion of the following statement from your labels and labeling.

      ATTENTION: Eon's Cyclosporine... for microemulsion).

   d. When referring to Neoral® Soft Gelatin Capsules (cyclosporine capsules for microemulsion) use the established name "cyclosporine capsules, USP (Modified)".

   e. When referring to Neoral® Oral Solution (cyclosporine oral solution for microemulsion) use the established name "cyclosporine oral solution,

USP (Modified)".

f. When referring to Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) use the established name "cyclosporine capsules, USP (Non-modified)".

g. When referring to Sandimmune® Oral Solution (cyclosporine oral solution, USP) use the established name "cyclosporine oral solution, USP (Non-modified)".

2. Blister Card

a. See first general comments, as applicable.

b. Please note that for your labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

3. CARTON - 30 Unit-dose

a. See general comments, as applicable.

b. Revise the boxed WARNING statement to read as follows:

WARNING: Cyclosporine capsules, USP (Modified) is **NOT BIOEQUIVALENT** to cyclosporine capsules, USP (Non-modified). Do not...

c. Side Parel

We encourage the inclusion of the net quantity statement.

4. INSERT

a. General

i. See general comments, as applicable.

ii. It is preferable to use the term "to" rather than a "hyphen" to express a range. Revise accordingly throughout the text of the insert labeling.

iii. We acknowledge that you have omitted most references to Sandimmune® Capsules

(Cyclosporine Capsules, USP) in terms of making comparison to your drug product throughout the text. However, we ask you to include these references to Sandimmune® Capsules (Cyclosporine Capsules, USP) in the text including the tables in the ADVERSE REACTIONS section.

iv. When referring to information associated with your specific dosage form [*i.e.*, Cyclosporine Capsules, USP (Modified)], use the established name rather than the general term "cyclosporine" throughout the text including the tables and figures.

v. Throughout the text of the innovator's insert labeling where the term "cyclosporine" is appearing alone, do NOT revise.

vi. Due to the difficulty in determining the dosage form utilized during clinical studies (oral solution or capsule), we request that you make the following revisions throughout the text of the insert (including the tables):

Where "Neoral" appears in the innovator's package insert labeling without reference to specific dosage form, revise to read "Cyclosporine (Modified)".

Where "Sandimmune" appears in the innovator's package insert labeling without reference to specific dosage form, revise to read "Cyclosporine (Non-Modified)".

b. Boxed WARNINGS

Delete the first box and revise the second Boxed WARNING to be in accordance with the innovator's labeling.

c. DESCRIPTION

i. Include the following as the first paragraph in this section:

NOTE: The nomenclature "Cyclosporine Capsules for Microemulsion" has been changed throughout the insert to read "Cyclosporine

Capsules, USP (Modified)".

ii. You may delete "purified water" from the listing of inactive ingredients.

iii. We note that you have listed the molecular formula and molecular weight in two places. You may delete one of these. Please note that the molecular weight of your drug product is 1202.64, not 1202.63 per USP 23.

iv. Last paragraph

Revise "chemical structure" to read "structural formula".

d. CLINICAL PHARMACOLOGY

i. Pharmacokinetics - Last paragraph, second sentence:

The intersubject... [spelling]

ii. Absorption (Table):

A) First column, last row:

Include superscript "6" to read "*De novo* psoriasis[6]".

B) Legend #2:

...was measured over... [rather than "measure"]

C) Legend #4:

Revise to read "[4]Assay: TDx specific... [rather than "Tdx"]

iii. Metabolism - Last sentence:

... oral administration of cyclosporine capsules, the mean...

iv. First and second tables:

"ng•hr/mL" rather than "ng.hr/mL"

e. CLINICAL TRIALS (Rheumatoid Arthritis) - Table:

Please assure that the legends of the table be legible. In general, please increase the readability of the table.

f. WARNINGS (Kidney, Liver, and Heart Transplant)

i. First paragraph:

Relocate the second sentence to begin as a new second paragraph.

ii. Table:

Revise the text in the last column and last row to read as follows:

...steroids or antilymphocyte globulin [note two spaces included]

g. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, and Impairment of Fertility - Fourth paragraph, third sentence (An increased incidence...):

Let this sentence begin a new fifth paragraph.

ii. Pediatric Use

Revise "children" to read "pediatric patients".

h. ADVERSE REACTIONS - Rheumatoid Arthritis:

i. Table:

A) Revise to read "≥3%" in the title rather than ">3%".

B) Central and Peripheral Nervous System Disorders, Headache - Last column:

"9 %" rather than "9"

C) Gastrointestinal System Disorders - Abdominal pain:

Relocate the numbers so that they are in alignment with corresponding columns.

D) Renal:

Increase the prominence of the symbol "≥" in two places.

ii. Last paragraph:

...in 1% to <3% of the rheumatoid... [rather than "3%"]

i. DOSAGE AND ADMINISTRATION (Newly Transplanted Patients) - Second paragraph:

Include the following text as the last sentence:

Lower doses of cyclosporine capsules (modified) may be sufficient as maintenance therapy.

j. HOW SUPPLIED

We encourage the relocation of the "Rx only" to the TITLE section.

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

Please note that we reserve 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 the innovator labeling 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

NOTES/QUESTIONS TO THE CHEMIST:

The RLD has a storage requirement to read "Store at controlled room temperature 68°-77°F (20°-25°C)." whereas the sponsor has "Store at controlled room temperature 15° - 30°C (59° - 86°F). ". Is it acceptable?

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
Error Prevention Analysis			
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? USAN stem present? Prefix or Suffix present?			x
	Yes	No	N.A.
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
Packaging			
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	
Labeling			
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	
Does RLD 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.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			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	
	Yes	No	N.A.
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.		x	

Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ 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.		x	

FOR THE RECORD:

1. MODEL LABELING - **Neoral®** (Cyclosporine Capsules for Microemulsion) soft Gelatin Capsules- Novartis Pharmaceutical Corporation (revised, June 1997,; approved, June 19, 1997). This is NDA 50-715/S-004.

2. There are two reference listed drugs found in the Orange Book for Cyclosporine Capsules, Sandimmune® (Cyclosporine Capsules) and Neoral® (Cyclosporine Capsules for Microemulsion). They are not bioequivalent to each other.

3. The firm's proposed established name "Cyclosporine Soft Gelatin Capsules, USP" is **not recognized** as an official USP monograph. A decision was reached to use the established name "Cyclosporine Oral solution USP (modified)" for the Neoral® Solution. To be consistent with this decision, we will request that the firm use the following established name for their product.

   Cyclosporine Capsules USP (modified)

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 135, vol.1.1. However, see comment (b) under GENERAL COMMENTS.

5. PATENTS/EXCLUSIVITIES - There is no Patent and Exclusivity issue. The firm's statement is accurate.

6. STORAGE AND DISPENSE

   RLD: In the Original unit-dose container at controlled room temperature 77°F (25°C).

   ANDA: In the Original unit-dose container at controlled room temperature 15° - 30°C (59° - 86°F).

7. PACKAGING CONFIGURATIONS

RLD: 30's unit-dose
ANDA -30's unit-dose

8. The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See 596, , Vol.1.3.

9. CONTAINER/CLOSURE

[illegible], [illegible] [illegible]. See p.[illegible].3, vol.1.3.

Date of Review: July 29, 1998 **Date of Submission: June 10, 1998**

Primary Reviewer: Chan park C Park **Date:** 9/29/98

Team Leader: Charlie Hoppes /S/ **Date:** 198

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cc:

/S/

:)
;5017NA1.L

Telecon

Date: 062398

Time: 1530 H

ANDA #: 65-017

Firm: Eon Labs

Drug: Cyclosporine Capsules USP, 100 mg

Participants: Gregg Davis, FDA and Sadie Ciganek, Eon

Phone #: 718-276-8600 ext. 330

Agenda:

I called Sadie and asked for some revisions. The first is a list of the addresses for all of the inactive ingredient suppliers. The second item involves an English translation of various pages. These include the COAs for the inactive suppliers of gelatin and purified water, page 287, and the DMF authorization for the container/closure system. She said she will fax the info and follow with a hard copy.

for July 06, 1998

Application: **ANDA 65017/000**
Stamp: **10-JUN-1998** Regulatory Due:
Applicant: **EON LABS MFG**
227-15 NORTH CONDUIT AVE
LAURELTON, NY 11413

Priority: Org Code: **600**
Action Goal: District Goal: **10-MAY-1999**
Brand Name:
Established Name: **CYCLOSPORINE**
Generic Name:
Dosage Form: **CAP (CAPSULE)**
Strength: **100 MG (SOFT GELATIN)**

FDA Contacts: **M. ANDERSON (HFD-617) 301-827-5848 , Project Manager**
J. HARRISON (HFD-643) 301-827-5849 , Team Leader

Overall Recommendation:

Establishment:

DMF No:
AADA No:

Profile: **CSG** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **06-JUL-1998**

Responsibilities: **FINISHED DOSAGE PACKAGER**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **06-JUL-1998**

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Establishment: **2431929**
EON LABORATORIES MANUFACTUI
227-15 NORTH CONDUIT AVE
LAURELTON, NY 11413

DMF No:
AADA No:

Profile: **CSG** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **06-JUL-1998**

Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment: **9692045**

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **06-JUL-1998**

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Establishment: **9611868**

DMF No:
AADA No:

Profile: **CFN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **06-JUL-1998**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CSG** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **06-JUL-1998**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division Office): HFD-635, Dr Mary Fleming

FROM: HFD-615/ Reg Support Branch

DATE: Dec 1, 1998

IND NO.: —

NDA NO.: 65-017

TYPE OF DOCUMENT: Original application

DATE OF DOCUMENT: June 5, 1998

NAME OF DRUG: Cyclosporine Soft Gelatin Capsules, 100mg

PRIORITY CONSIDERATION: —

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE:

NAME OF FIRM: Eon Labs

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICPENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
  - ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ *OTHER (specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDI ES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (*Attach additional sheets if necessary*) HFD 590 has completed their Safety review of an inactive ingredient. Please review + comment for DGP Chemistry Division.

Thanks,
Henry

SIGNATURE OF REQUESTER

METHOD OF DE LIVERY (*Check one*) ☐ MAIL ☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Controlled Correspondence Record

Date: 8 01:51:29 P

Log Number: A65-017

Received by ODEIV	9/22/9	Addressed To:	HFD-590
Received by Center	6/8/9	Correspondence From:	Greenberg
Document Date:	6/8/9	Document Type:	Intra-Government
RequestorDue Date	11/21/9	Sent upon completion to	
Division Goal Date:		Date sent:	

Subject: ANDA 65-017 - Cyclosporin (Eon Labs) - Inactive ingredient Vitamin E TPGS ([redacted]) - never before included in approved product

Instructions: TPGS is an inactive ingredient not part of any prior approved product. Material includes preclinical studies and an "abstract" of a clinical study of use of this product as a therapeut souce of oral Vitamin E in children. PLEASE SEND RESPONSE THROUGH T.HASSALL, ODE IV.

Assignments:

Name	Date Assigned:	Date Completed:	Comment Document:
Frank	9/23/98		

to Dempsey → let me know who you assign this to (ECF)

Biopharm - K Reynolds
P/T - Hunter (Hastings)
Chem - Siggel
mo — MC?

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO (Division/Office)	FROM:
Forward → HFD-530 Branch Petitions ODE II - Thomas Hassell	Office of Generic Drugs HFD-600

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Sept 21, 1998	—	ANDA 65-017	original application	June 5, 1998

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cyclosporine Soft gelatin capsules 100mg	High		Nov 21, 1998

NAME OF FIRM: Eon Labs

REASON FOR REQUEST

I. GENERAL

RECEIVED
SEP 22 1998
ODEIV 10

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ *OTHER (specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST
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- ☐ PHASE IV STUDIES

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (*Attach additional sheets if necessary*) The firm is using an inactive ingredient in their proposed formulation of Cyclosporin Soft gelatin capsules that has not been used in another approved drug product. The inactive ingredient is Vitamin E TPGS or TPGS. Please review & comment on the use of this inactive ingredient. Please return to and provide an electronic transfer of email of the completed review.

HARVEY A. GREENBERG, R.Ph.
Office of Generic Drugs
Ctr. for Drug Evaluation & Research
Metro Park North II, HFD-615
7500 Standish Place
Rockville, MD 20855-2773
(301) 827-5862
FAX (301) 594-1174

SIGNATURE OF RECEIVER: /S/ 827-5713

METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND

SIGNATURE OF DELIVERER

Controlled Correspondence Record

Date: 8 3:14:58 PM

Log Number: A65-017

Received by ODEIV	9/22/98	Addressed To:	HFD-590
Received by Center	6/8/98	Correspondence From:	Greenberg
Document Date	6/8/98	Document Type:	Intra-Government
RequestorDue Date	11/21/98	Sent upon completion t	Greenberg, Harvey
Division Goal Date		Date sent:	11/25/98

Subject: ANDA 65-017 - Cyclosporin (Eon Labs) - Inactive ingredient Vitamin E TPGS (to enhance - never before included in approved product

Instructions: TPGS is an inactive ingredient not part of any prior approved product. Material includes preclinical studies and an "abstract" of a clinical study of use of this product as a therapeutic souce of oral Vitamin E in children. PLEASE SEND RESPONSE THROUGH T.HASSALL, ODE IV. Comments conveyed to OGD via e-mail 11/20 by M. Dempsey. Signed written review to ODE IV 11/24; Written Review returned to OGD 11/25 - T.Hassall

Assignments:

Name	Date Assigned:	Date Completed:	Comment Document:
Frank	9/23/9		
Dempsey	9/25/9		