CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-017

CORRESPONDENCE

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

October 21, 1999

NDA ORIG AMENDMENT
N/FA

Douglas Sporn
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

Re: FACSIMILE AMENDMENT — Chemistry and Labeling
Cyclosporine Capsules, USP (Modified), 100 mg and 25 mg
ANDA 65-017

Dear Mr. Sporn;

Reference is made to your correspondence of October 5, 1999 commenting on our Abbreviated New Drug Application for Cyclosporine Capsules, USP (Modified), 100 mg and 25 mg, **ANDA 65-017**. In addition to our responses noted below, please note that we have included an outside laboratory certification for the facility we intend to use to perform microbial testing which we committed to in our March 30, 1999 amendment. This facility is within cGMP compliance. Information relevant the outside facility immediately follows this letter.

A. Deficiencies:

Page(s) 3

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Division

LABELING COMMENTS AND RESPONSES:

1. **Blister Card:**

   Comments:

   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.**

   Response:

   The blister cards have been revised according to your comments. We are submitting 12 copies of final printed labeling (computer generated) which represent the true color, size, text, and specifications of the actual blister card, ***ATTACHMENT 7.***

2. **Carton-30 Unit-dose**:

   Comment:

   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 . . .

   Response:

   The boxed WARNING statement was revised according to your comment.

Comment:

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

Response:

The alcohol content statement was revised according to your comment.

Comment:

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.**

Response:

Alcohol was removed from the listing of ingredients as per your comment.

Comment:

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.

Response:

The components/composition statement in the March 30, 1999 amendment included ' because it reflected the composition of the actual **Executed Batch Record**. ' is no longer in the formulation and has been removed in accordance with the commitments made in the March 30, 1999 amendment. A revised components/composition statement and product labeling has been amended and submitted in ***ATTACHMENT 1*** and ***ATTACHMENT 7*** respectively.

Comment:

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

. . .86°F) [See USP].

Response:

The storage requirement statement was revised as recommended.

Comment:

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

Response:

The imprinting is done using a laser that "scars" or "etches" the gelatin capsule surface leaving an " imprint" on the capsule shell. There are no inks or additives used in the laser technology.

Comment:

g. **Included 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].

Response:

The boxes were revised to include the following statement: **"THIS UNIT-DOSE PACKAGE IS NOT CHILD-RESISTANT."**

3. INSERT

Comments:

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 indicator or specific dose of your product, use the established name [i.e., Cyclosporine Capsules, USP (Modified)] rather than the general term "Cyclosporine 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 . . ."

ii. Please not that the molecular weigh 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 your have included alcohol in the listing of the inactive ingredients. You may delete alcohol form 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

vii. Absorption - Revise the first paragraph to read as follows:

Cyclosporine (Modified) has increased bioavailability compared to *Sandimmune®. The absolute of cyclosporine bioavailability 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 C_{max} 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. <u>CLINICAL TRIALS</u>

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 - Revised 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 Capsules, (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 . . ." - Relocated 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-section heading to read "Other Drug Interactions". [note the upper case "I"]

h. ADVERSE REACTIONS

iii. 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-section "Autonomic Nervous System".

. . . In 1% to <3% of the rheumatoid . . . [rather than1-3%]

i. <u>DOSAGE AND ADMINISTRATION</u>

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 Novartis Pharmaceuticals Corporation.

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

Response:

The insert has been revised according to your comments. Twelve (12) final printed inserts are provided, ***ATTACHMENT 7***. An additional revision was also made to include the correct name of the cyclosporine source in the Description section. The source of cyclosporine is "Tolypocladium infantum" and not "Beauveria nivea". We emphasize that this is not a change in source of cyclosporine but merely a correction to the insert to reflect the source of cyclosporine used in this ANDA submission.

To facilitate review of this submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), a side-by-side comparison of the proposed labeling as compared to the labeling in the previous submission is provided, ***ATTACHMENT 7*** and an annotated reference table summarizing the differences highlighted on the side-by-side comparison is provided. In addition, we have compared internally our insert labeling to the innovator's and found it satisfactory.

We hope that our responses satisfactorily address the deficiencies noted in your letter. If you need further clarification or information, do not hesitate to call at (718) 276-8607 x 393.

Sincerely,
Eon Labs Manufacturing, Inc.,

Zohra E. Lomri
Manager, Regulatory Affairs

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

March 30, 1999

Douglas Sporn
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

NDA ORIG AMENDMENT
N/Ac

Re: MAJOR AMENDMENT — Chemistry and Labeling
Cyclosporine Capsules, USP (Modified), 100 mg
ANDA 65-017

Dear Mr. Sporn,

We refer to your letter of February 16, 1999 commenting on our Abbreviated New Drug Application submitted on June 8, 1999 for Cyclosporine Capsules, USP (Modified), 100 mg. In addition to responding to your comments, we are amending this application with an additional strength, Cyclosporine Capsules, USP (Modified), 25 mg. Both products use the same bulk solution in the soft gelatin capsule process. All the manufacturing and controls data filed in the original application for the 100 mg will also apply to the 25 mg. The responses submitted herein have incorporated both dosage strengths.

We are also amending the Master Batch Records for commercial manufacturing to remove the coloring agent. red iron oxide, from the formulation. This applies to both the 25 mg and 100 mg dosage strengths. We are bringing to your attention that the manufacturing process and testing methods have not been affected otherwise by this minor change.

With regards to labeling, the package insert has been revised to reflect the addition of the 25 mg strength, and the removal of the coloring agent from the capsule shell. All other label changes have been made in accordance with your comments in the deficiency letter.

For your convenience, we have included as **ATTACHMENT 1** all the review documents necessary to support our responses to the deficiencies for Cyclosporine Capsules, USP (Modified), 100 mg, and in **ATTACHMENT 2**, you will find the supporting documentation required to file the additional strength of Cyclosporine Capsules, USP (Modified), 25 mg. In the case of documents pertaining to both strengths, they will be included in **ATTACHMENT 2**.

RECEIVED
APR 0 2 1999

GENERIC DRUGS

If additional information is required, please contact me at (718) 276-8607, extension 393.

Sincerely,

Zohra E. Lomri
Sr. Regulatory Affairs Associate

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

February 5, 1999

Mr. Mark Anderson
Consumer Safety Officer
Division of Chemistry II
Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

General Correspondence

Re: ***Cyclosporine Soft Gelatin Capsules, USP, 100 mg***
ANDA 65-017

Dear Mr. Anderson;

Reference is made to our Abbreviated New Drug Application for Cyclosporine Soft Gelatin Capsules, USP, 100 mg, ANDA 65-017. The application provides for five foreign contractors to perform manufacturing, packaging, and/or testing as indicated below:

Firm	Responsibility
	API Manufacturer
	Contract Manufacturer
	Contract Packager
	Outside Testing Laboratory
	Outside Testing Laboratory

Eon Labs was recently advised by the Office of Compliance that a satisfactory cGMP status has been granted to however, outstanding foreign inspection notices are still pending for

Eon Labs was not aware that inspection notices were still pending for these two laboratories. Our understanding was that an agreement had been reached between FDA and n October1998, to waive the pre-approval inspections. Since the compliance status of must be satisfied before approval of our ANDA, we would like to clarify the relationship of these two firms with regards to the chemistry and manufacturing controls for the Cyclosporine Soft Gelatin Capsules and the role they play in our ANDA application.

contract laboratory used occasionally by for performing limited tests of **inactive ingredients** only. They **ARE NOT** contracted directly by Eon Labs for laboratory testing nor do they perform any tests for either the cyclosporine active pharmaceutical ingredient or finished product. The limited tests that performs for the **inactive ingredients** follow compendial standards and test methods and are considered non-pivotal to the application.

The majority of analytical testing for the **inactive ingredients** is currently performed at according to compendial test methods and specifications filed in the cyclosporine application. The acility has undergone an extensive pre-approval inspection in October 1998, which included an in-depth evaluation of the Quality Control Laboratory and Manufacturing Department. FDA concluded that vas found acceptable and within CGMP compliance. Jointly and Eon Labs has the capability of performing all the analytical tests done by and intend to conduct all future release testing for **inactive ingredients** in-house.

government owned and operated facility. nas used this laboratory in the past to test specifically for water conductivity. All other compendial tests required for QC release of water is done internally by For the future, also intends do all water testing in-house including conductivity.

Based on the information provided herein, and the future intention to perform all release testing at either r Eon Labs, please consider waiving the pre-approval inspections for and withdraw the outstanding inspection notices. Both these laboratories have perform limited testing non-pivotal to the Cyclosporine application. I will be more than happy to provide you with additional information if needed to aid in you decision. I can be reached at (718) 276-8607 X330. I look forward to hearing from you at the earliest regarding the CGMP status of these two firms.

Regards,

Sadie M. Ciganek

Vice President Regulatory Affairs

CC:

ANDA 65-017

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

JUL - 2 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated June 23, 1998 and your correspondence dated June 26, 1998.

NAME OF DRUG: Cyclosporine Capsules USP, 100 mg

DATE OF APPLICATION: June 8, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 10, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

/S/

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

5-017
DUP/Jacket

Enclosure:

/S/

Letter!

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

NAI 7/1/98
Greg S. Davis

June 26, 1998

Greg Davis
Regulatory Branch
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Reference: General Correspondence
CYCLOSPORINE SOFT GELATIN CAPSULES, USP, 100 MG

Dear Mr. Davis;

We refer to your phone conversation of June 23, 1998 requesting the following:

1. English Translation for pages 184, 199, 287, and 545.
2. List of address of manufacturer/suppliers' for all the inactive ingredients.

We are providing you with the following:

1. The translated pages, paginated 184a, 199a, 287a and 545a, **(ATTACHMENT 1)**.
2. Table containing the address list of manufacturer/suppliers' for all the inactive ingredients, **(ATTACHMENT 2)**.

Sincerely,
Eon Labs Manufacturing, Inc.

Zohra E. Lomri
Sr. Regulatory Affairs Associate

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

505(j)(2)(B) OK 7/1/98

June 8, 1998

Douglas L. Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ORIGINAL ANDA
Cyclosporine Soft Gelatin Capsules USP, 100 mg

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, enclosed is an original Abbreviated New Drug Application for Cyclosporine Soft Gelatin Capsules USP, 100 mg . This application consists of the following volumes:

Volume 1 Debarment, patent and exclusivity certifications, Section 505(j)(2)(A) information, labeling, dissolution profiles, certificates of analysis, and components and composition.

Volume 2 Raw material control data, manufacturing and packaging data including executed batch record.

Volume 3 Container/closure, finished product control, methods validation, stability data, control numbers, samples, and environmental impact statement.

Volume 4 through 9 Biostudy summaries and test results. Also included are diskettes of raw data and a validation package.

A full table of contents precedes each appropriately paginated volume.

In addition to the archival and review copies, we are submitting a certified true copy of the chemistry, manufacturing and controls data to the District Field Office, Brooklyn, New York. Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Field Office.

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

If there are any comments or questions about this application, please contact me at (718) 276-8600, extension 330.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie M. Ciganek
Vice President Regulatory Affairs

ANDA 65-017

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

JUL - 2 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated June 23, 1998 and your correspondence dated June 26, 1998.

NAME OF DRUG: Cyclosporine Capsules USP, 100 mg

DATE OF APPLICATION: June 8, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 10, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

/S/

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

-017
DUP/Jacket

/s/

m._____date
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File 65-017

MEDICAL OFFICER SUMMARY OF PHARM/TOX REVIEW
December 9, 1998

ANDA 65-017
Drug Product: Cyclosporine soft gelatin capsules, 100 mg
Sponsor: Eon Laboratories

The Pharm/tox reviewer has evaluated the inactive ingredient, d-alpha-tocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS) that present in this product at the request of the Office of Generic Drugs. He concludes that "This application is acceptable with regards to pharmacology/toxicology issues." Based on data presented, I agree with the conclusion.

/S/

Mary M. Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs

PHARMACOLOGIST'S REVIEW
CONSULTATION

ANDA 65-017
DATE SUBMITTED: 22 Sept 1998
DATE RECEIVED: 23 Sept 1998
DATE ASSIGNED: 29 Sept 1998
DATE REVIEW COMPLETED: 5 Nov 1998
SPONSOR: Eon Laboratories
DRUG: Cyclosporin soft gelatin capsules
HFD-590

RELATED DOCUMENTS:
INDICATION: Organ transplantation
INTRODUCTION: This submission was received for consultation from the Office of Generic Drugs, HFD-600, to evaluate the safety of an inactive ingredient, d-α tocopherol polyethylene glycol 1000 succinate (vitamin E TPGS). Both vitamin E and polyethylene glycol are GRAS substances individually but not listed as a conjugate. Vitamin E TPGS is used as an r ses consistent with those of the individual components.
The supplier of vitamin E TPGS, erformed GLP animal toxicology studies at the National Cancer Institute including one year chronic oral studies in both rats and dogs. Doses of 100, 300 and 1000 mg/kg/day were used in both studies. These doses convert to 16, 50 and 166 mg/kg human equivalent dose (rats) and 50, 150 and 500 mg/kg human equivalent dose (dogs). In rats no effects were related to the test substance. In the dog study, 2/8 dogs in the 300 mg/kg/day group were euthanized due to gavage errors. One dog (1000 mg/kg) was found dead on day 212, with red material in the refuse pan. Pathology studies attributed mortality to acute bronchopneumonia. A high dose female was euthanized on day 347. Pathology findings attributed morbidity to chronic active pyelonephritis. These findings do not appear to be test substance related.

Current usage of cyclosporin includes doses up to 15 mg/kg prior to transplantation. Based on this dose and the composition of the generic preparation (300 mg vitamin E TPGS/ 100 mg cyclosporin, or 900 mg total cyclosporin, for a total of 2700 mg vitamin E TPGS, or about 45 mg/kg), exposure to vitamin E TPGS would not exceed 45/mg/kg which did not produce toxicity in one year rat or dog studies at equivalent (body surface area corrected) doses or at doses in excess. Maintenance doses of cyclosporin would be lower than 15 mg/kg, resulting in even lower exposure to vitamin E TPGS.

This application is acceptable with regards to pharmacology/toxicology issues

/S/

Steven C. Kunder, Ph.D.
Reviewing Pharmacologist