CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-017

CHEMISTRY REVIEW(S)

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch size for each potency is capsules. The manufacturing process described in the master production record is different from that described in the exhibit batch record. In the revised master batch record the and the agent are removed from the capsule shell formulation.

CHEMIST: Ruth Ganunis /S/ **DATE:** 11/15/99 11/22/99
SUPERVISOR: Richard Adams **DATE:** 11/19/99 11/22/99

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMIST'S REVIEW NO. 3

2. ANDA # 65-017

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413

Headquarters:
Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413

Manufacturing Facility:

Testing Facility:
Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413

4. LEGAL BASIS for ANDA SUBMISSION
Reference listed drug is Neoral® (cyclosporine capsules for microemulsion) by Novartis (Sandoz NDA #50-715).

Appropriate patent certification and exclusivity statements provided on pp. 3-4: no effective patents or exclusivity associated with NDA 50-715.

5. SUPPLEMENT(s)
N/A

6. NAME OF DRUG
Cyclosporine Capsules USP, (Modified)

7. NONPROPRIETARY NAME
Cyclosporine Capsules USP, (Modified)

8. SUPPLEMENT(s) PROVIDE(s) FOR
N/A

9. AMENDMENTS AND OTHER DATES

Firm:

1.	Original submission	6/8/98
2.	Response to telecon request for additional information	6/26/98
3.	Submission of reformatted disk with biostudy results	9/11/98
4.	Telephone Bioequivalence Amendment	11/12/98
5.	General Communication: Request for waiving pre-approval inspections at 2 labs	2/5/99
6.	Chemistry and Labeling Amendment	3/30/99
7.	Chemistry and Labeling Amendment	10/21/99

FDA:

1.	Telecon asking for revisions in order to be acceptable to file	6/23/98
2.	Acknowledgment Letter	7/2/98
3.	EER request for all facilities	7/6/98
4.	Division of Bioequivalence Review #1	9/11/98
5.	Labeling Review #1 - Deficient	9/29/98
6.	Division of Bioequivalence communication of deficiencies via telecon	10/30/98
7.	Pharmacologist's consult re: Vit.E TPGS: OK	11/5/98
8.	Division of Bioequivalence Rev.#2-Acceptable	11/17/98
9.	Chemistry Review #1 - Deficient	2/16/99
10.	Division of Bioequivalence Amend-Acceptable	5/10/99
11.	Chemistry and Labeling Review #2 - Deficient	10/5/99

10. PHARMACOLOGICAL CATEGORY

Immunosuppressive antibiotic

11. HOW DISPENSED

Soft Gelatin Capsules

12. RELATED IND/NDA/DMF(s)

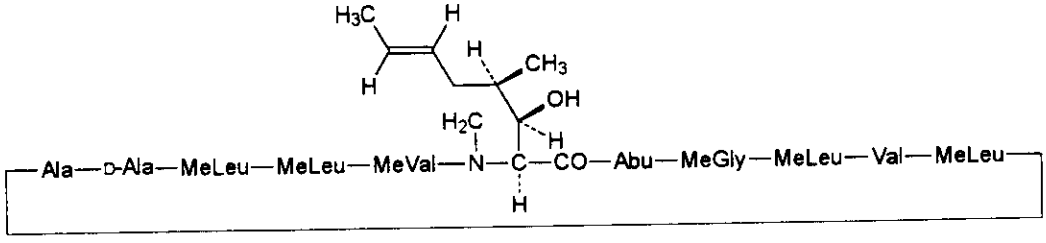
DMF#(type)	**Holder**	**Subject**	**LOA page**

13. DOSAGE FORM

Soft Gelatin Capsule

14. POTENCY
25 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE
Cyclosporine. Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl].
$C_{62}H_{111}N_{11}O_{12}$. 1202.64. 59865-13-3. Immunosuppressive.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application was the second application received, and is the first generic application recommended for approval for Cyclosporine Capsules USP (modified). The first generic application received was ANDA
The reference listed drug for this application is Neoral® (Cyclosporine Capsules for Microemulsion) by Novartis (formerly Sandoz), which is a soft gelatin capsule. Specifications for Neoral® Capsules (NDA #50-715) are provided in this review.

The only generic cyclosporine approved is Sangstat's ANDA 64-195 for oral solution. Biostudies for Sangstat's application were run against and found equivalent to Neoral® Oral Solution for Microemulsion (Novartis).

Proposed new monographs for cyclosporine dosage forms for microemulsion were published in *Pharmaceutical Forum* (No. 3, May-June 1998, page 6155) which include tests specific for cyclosporine drug products which form a microemulsion upon contact with water. The proposed new monographs and other, related issues were the subjects of various petitions filed by Novartis, the innovator of Neoral® and Sandimmune®. These petitions were denied (see Nov. 2, 1998

96P-0459/CP1, PSA1 and CP2, SA2) wherein the FDA reached the following conclusions:

1. It is appropriate to designate Neoral® as a second RLD for cyclosporine.
2. The microemulsion-forming properties of Neoral do not constitute a unique "dosage form."
3. FDA expects to revise the *Orange Book* promptly to consolidate the listing of the Neoral® and Sandimmune® products under the same dosage form and route of administration subheadings.
4. FDA intends to recommend the following labeling for Neoral and for generic applications, when they are approved, "Cyclosporine Capsules USP (Modified)" or "Cyclosporine for Oral Solution USP, (Modified)" to differentiate them from Sandimmune, ("Cyclosporine Capsules USP, (Unmodified)"), since the drug products are bioinequivalent.

In terms of chemistry, the only difference between Neoral® and Sandimmune® is the formulation. Neoral® contains emulsifiers not present in the Sandimmune® formulation. Neoral® forms a microemulsion upon mixing in water, Sandimmune® does not.

The Division of Bioequivalence requested Eon to run the dissolution testing cited in the proposed new monograph and this product passed. Eon states that they are petitioning the USP to remove the dissolution testing. The Division of Labeling has requested that the firm rename the drug product from Cyclosporine Soft Gelatin Capsules, USP 100 mg to Cyclosporine Capsules USP (Modified) to conform to the FDA finding, summarized above.

Process:

Summary:

Stability data were submitted.

Status/Summary:

The firm has addressed the remaining CMC issues. The Division of Labeling found the application acceptable on 11/8/99. The Division of Bioequivalence found the 100 mg strength approvable on 11/17/98, and accepted the waiver for the 25 mg strength on 5/10/99. EER was found acceptable 5/17/99.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended.

19. REVIEWER
Ruth M. Ganunis /S/

DATE COMPLETED
11/15/99 11/15/99

TABLES

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Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #3

#20 - #37

OCT - 5 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 65-017 Applicant: Eon Labs Manufacturing, Inc.

Drug Product: Cyclosporine Capsules USP (Modified), 25 mg and 100 mg

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Please provide updated room temperature stability data in your next amendment. Please include results for the tests for Ethanol Content, Microbial Limits Testing and Dissolution according to your current Stability Testing Procedure.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 16 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 65-017 Applicant: Eon Labs Manufacturing, Inc.

Drug Product: Cyclosporine Capsules USP (Modified), 100 mg

The deficiencies presented below represent MAJOR deficiencies.

Deficiencies:

Page(s) 1

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Commercial/Confidential

Information and are not

releasable.

2/16/09

#38

Chemistry Review

5. We note that the Certificate of Analysis on page 479 contains several "unspecified" entries. Please clarify.

Sincerely yours,

/S/

Florence Fang
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research