

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65003

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 65-003

Date of Submission: May 28, 1999

Applicant's Name: Abbott Laboratories

Established Name: Cyclosporine Capsules USP (Modified), 25 mg, 50 mg, & 100 mg

Labeling Deficiencies:

1. General Comments

- a. Revise the labels and labeling to include the alcohol content of your product in terms of percent volume (v/v) of absolute alcohol, not dehydrated alcohol. In addition to be consistent with the reference listed drug, include the alcohol content on a (w/v) basis in parenthesis following the (v/v) percentage. We refer you to section 502(e) of the Act and 21 CFR 201.10(d)(2) for further guidance.
- b. Following your storage temperature range add the statement, "(See USP)".

2. CONTAINER: Blisters – 25 mg, 50 mg and 100 mg

- a. See General Comment 1(a).
- b. You may delete the text, "Each capsule manufactured with" prior to the alcohol...".

3. CARTON: 25 mg, 50 mg and 100 mg – 1 x 30 blisters

- a. See comments under CONTAINER.
- b. Print the established name in the same format as the Title of your insert labeling, "(Cyclosporine Oral Solution, USP [MODIFIED])". Note the location of the parenthesis and the brackets.
- c. Delete the text "AB rated to *Neoral®" from your container label. This next is not approved.
- d. Add the following as instruction #3, "Push out capsule".
- e. Delete the text "OR ALTERNATE OPENING METHOD...".
- f. Add the following statements:

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

[Note: The second sentence is optional].

- g. Delete "Neoral®" from the asterisked statement on the side panel and/or comment. In addition, revise "are" to read "is".

4. INSERT

a. General Comments

- i. We note that your capsule insert labeling differs from your oral solution insert labeling for ANDA 65-025 submitted on July 15, 1999. Please update your capsule insert labeling accordingly, in addition to the revisions listed below.
- ii. When using your proprietary name "Gengraf™", include make consistent use of the inclusion of the symbol "™".
- iii. Please assure that the requirements of 21 CFR 201.10(g) are met throughout the text. The established name must appear in certain sections in association with the proprietary name, i.e., "Gengraf™ (Cyclosporine Oral Solution, USP [MODIFIED])". Please revise your labeling accordingly.
- iv. When printing the innovator's proprietary name include the symbol "®", i.e., Sandimmune® (cyclosporine [non-modified]).

b. DESCRIPTION

We note that your trade name, "Gengraf™" appears to represent the drug substance. This is not consistent with the container labels and carton labeling. Does your trade name represent the drug product or the drug substance? Please comment and revise your labels and labeling accordingly.

c. CLINICAL PHARMACOLOGY

i. Pharmacokinetics

The second paragraph of the Absorption subsection differs from your oral solution formulation. Please comment.

We note you have included as the second paragraph, "Gengraf™ Capsules (cyclosporine capsules, USP [MODIFIED]) are bioequivalent to Gengraf™ Oral Solution (cyclosporine oral solution [MODIFIED])". We note that your capsule formulation differs from your oral solution formulation. Has your firm demonstrated that one formulation is bioequivalent to the other?

ii. Absorption

Revise the first sentence to read, "Cyclosporine [MODIFIED] has increased bioavailability compared to cyclosporine, [NON-MODIFIED]."

d. PRECAUTIONS

i. General

Special Monitoring of Rheumatoid Arthritis Patients

Revise the third sentence to read, "... after an increase of the...".

ii. Information for Patients

Second paragraph, first sentence:

... receiving cyclosporine. Patients...

iii. Drug Interactions

Drugs That May Potentiate Renal Dysfunction

Revise "sulindrec" to read "sulidac".

iv. Pediatric Use - Last sentence:

... treatment in pediatric patients with...

e. ADVERSE REACTIONS

i. Rheumatoid Arthritis - Table:

Please rewrite headings of the table on each page when you prepare final print.

ii. Psoriasis

Second paragraph, first sentence:

... in U.S. controlled clinical studies...

f. DOSAGE AND ADMINISTRATION

i. General Comment

Include the section headings wherever a reference is made to a subsection in the text throughout this section, [e.g., "(see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption)"].

ii. First paragraph

A) Delete the first and second sentences, "Gengraf Capsules (cyclosporine capsules, USP [MODIFIED]) and Gengraf Oral Solution (cyclosporine oral solution, USP [MODIFIED]) are bioequivalent to Neoral Soft Gelatin Capsules (cyclosporine capsules, USP [MODIFIED]) and Neoral Oral Solution (cyclosporine oral solution, USP [MODIFIED])".

iii. Conversion from Sandimmune® (Cyclosporine [NON-MODIFIED]) to "Gengraf™" in Transplant Patients

Throughout this subsection retain the innovator's proprietary name, as follows:

Sandimmune® (cyclosporine [NON-MODIFIED]).

iv. Transplant Patients with Poor Absorption of Sandimmune® (cyclosporine [NON-MODIFIED])

Throughout this subsection retain the innovator's proprietary name, Sandimmune® (cyclosporine [NON-MODIFIED]).

v. Rheumatoid Arthritis – Second paragraph:

... (See WARNINGS...) [plural]

g. HOW SUPPLIED

i. Gengraf Oral Solution

... 100 mg/mL with dispensing syringe (NDC...).

ii. Revise the last statement to read as follows:

*Sandimmune® is registered trademark of Novartis Pharmaceuticals Corporation.

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

Please revise your labels and labeling, as instructed above, and submit in draft or in final print, 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 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 enclosed innovator's labeling with all differences annotated and explained.



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

MEETING TO DISCUSS BIOEQUIVALENCE DISSOLUTION REQUIREMENTS
FOR ABBOTT'S CYCLOSPORINE CAPSULES (ANDA 65-003)

Meeting held 2:00 P.M., April 17, 2000

Attendees:

Rabi Patnaik
Barbara Davit
Zakaria Wahba
Mamata Gokhale
Richard Adams
Maria Shih
Mark Anderson

The group met to come to an agreement as to what dissolution parameters should be recommended to Abbott Laboratories for their pending application for Cyclosporine Capsules USP (Modified).

Based on the review of the submitted data dated March 30, 2000 it has been determined that _____ of the capsules is the likely cause of the change in dissolution seen over time. The use of Tier 2 testing using _____ reversed the declining dissolution rate.

Rabi Patnaik said it was his recommendation that Tier I testing be recommended for release testing of the product because it is more discriminatory than Tier 2 testing. Richard Adams asked what purpose using Tier 1 testing would serve since _____ had been identified as the cause of the problem. Rabi explained that _____ is a non specific hydrolyzing agent which would negate _____ effects but could also affect dissolution in other ways due to its being a non specific hydrolyzing agent. For this reason use of _____ has not previously been recommended on a routine basis for any other capsule applications. Because of this non specificity, if it was used as the only dissolution media it would not be able to detect any changes to the product caused by things other than _____

Barbara Davit raised the issue that supplement number 1 to USP XXIV had provided for a reduction in the amount of _____ to be used in Tier 2 testing - now limited to _____ u/liter. Abbott should be required to follow this new limitation.

Agreement was reached that the Division of Bioequivalence will recommend acceptance of Abbott's dissolution data. Bioequivalence acceptable comments will be prepared recommending the firm follow Tier 1 testing parameters and be allowed to use _____

Tier 2 testing only when Tier 1 test result begin falling out of specification (for stability testing purposes). Appropriate language recommended in USP XXIV, Supplement 1 for Tier 2 testing will be used.

/S/

4/17/00

Notes prepared by: Mark Anderson, Project Manager
4/17/00

Concur: HFD-651/R.Patnaik/
HFD-643/R.Adams/

/S/

4/17/00