

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
65003

CORRESPONDENCE

ANDA 65-003

Abbott Laboratories
Attention: Rebecca A. Welch
D-491/AP6B-1
100 Abbott Park Road
Abbott Park, IL 60064-3500

MAR 19 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 also made to our refuse to file letter dated February 3, 1998 and your amendment dated March 3, 1998.

NAME OF DRUG: Cyclosporine Capsules USP, 25 mg, 50 mg, and
100 mg

DATE OF APPLICATION: December 19, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 4, 1998

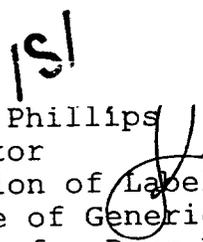
We will correspond with you further after we have had the opportunity to review the application.

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,


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

Abbott Laboratories
Attention: Rebecca Welch
100 Abbott Park Road
Abbott Park, IL 60064-3500

FEB 3 1998



Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated December 19, 1997 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Cyclosporine Capsules USP, 25 mg, 50 mg, and 100 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(2) for the following reasons:

The concentration of the inactive ingredient, _____ in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral dosage form. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range. The information to demonstrate safety should include, but is not limited to examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range.

It appears that your proposed formulation contains an inactive ingredient that has not been approved in a drug product for human use by the same route of administration [21 CFR 314.127(a)(8)(ii)]. According to the regulation, there is reasonable basis to conclude that the inactive ingredient in your proposed product may raise safety questions because of the lack of information that you have provided regarding the use of _____

Therefore, the Office of Generic

Drugs (OGD) will not file this application as an ANDA since new inactive ingredients must be the subject of a new drug application. Please provide additional information to support the safety of the use of this inactive ingredient in your proposed drug product, including a more detailed identification of

You have failed to submit complete comparative *in vitro* dissolution data between your proposed drug product and the reference listed drug. Comparative dissolution data profiles should include individual tablet data as well as the mean, range, and standard deviation at each point for twelve tablets. The lot numbers of the tablets tested should also be identified. The comparative dissolution data, as presented (section VI, p. 3216), does not include all of the data necessary for a complete evaluation by the reviewer. A complete dissolution report should contain the individual data for twelve capsules, including means, range and relative standard deviation (RSD) at each time point, a description of the methodology being used, and the lot numbers being tested.

Each ANDA must have a dedicated test batch manufactured specifically to support approval of the ANDA. This same test batch must be used for the chemistry, manufacturing and controls of the proposed drug product, for the bioequivalence data, *in vitro* and *in vivo*, and the stability studies. The lot numbers of the product used in your bioequivalence study do not correspond with the lot numbers in your dedicated test batch. Please explain.

Please provide a Certificate of Analysis (COA) for the inactive ingredient,

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act. Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Nasser Mahmud
Project Manager
(301) 827-5862

Sincerely yours,

/S/

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

ANDA 65-003
cc: DUP/Jacket
Division File
HFD-92
Field Copy
HFD-600/Reading File
HFD-610/JPhillips
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, /S/ date 2/3/98
HFD-615/NMahmud, CSO, // date 1/30/98
HFD-643/JHarrison/Chem. Sup, date
WP File x:\new\firmSAM\abbott\ltrs&rev\65003.rtf
FT/njg/1/30/98
ANDA Refuse to File!



Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

March 30, 2000

RECEIVED
AB

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Dale P. Conner, Pharm. D.

**Re: ANDA 65-003
Cyclosporine Capsules, USP (modified)**

**BIOEQUIVALENCY
AMENDMENT**

Dear Dr. Conner:

Reference is made to the Bioequivalency Amendment facsimile of deficiencies that we received from the Agency on March 15, 2000. We have addressed the deficiencies listed in the facsimile. In addressing the deficiencies, we have incorporated the verbal guidance received from the Agency in response to our request for clarification on the bioequivalence deficiencies. The following items are enclosed:

- Attachment 1: Table of Contents
- Attachment 2: A copy of the Bioequivalency Amendment facsimile received on 3/15/2000
- Attachment 3: A Product History Overview
- Attachment 4: Our responses to the deficiencies (the deficiencies are restated in bold, and our responses follow each deficiency)
- Attachment 5: Appendix 1 - Tier 1 and Tier 2 dissolution data for stability samples of Cyclosporine Capsules
- Attachment 6: Appendix 2 - Dissolution profiles of Cyclosporine Capsules



March 30, 2000
Office of Generic Drugs (HFD-600)
Page Two

Attachments (Continued):

Attachment 7: References:

Pharmaceutical Research, Vol. 10, No. 9, 1295-1300, 1993

Pharmaceutical Technology, March, 72-86, 1989

Pharmaceutical Technology, June, 76-83, 1993

Please contact me at 847-935-2448 or Dr. Lawrence E. Roebel at 847- 937-7495 if you have any questions concerning this submission.

Sincerely,



Alexa L. Chun, Ph.D.
Associate Director
Regulatory Affairs, Pharmaceutical Products Division
Abbott Laboratories

Sent by Federal Express

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

March 30, 2000

NEW 208555

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room (facsimile no. 301-827-4337)
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Florence Fang

**Re: ANDA 65-003
Cyclosporine Capsules, USP (modified)**

**FAX AMENDMENT
CHEMISTRY**

Dear Ms. Fang:

Reference is made to the Fax Amendment of minor chemistry deficiencies that we received from the Agency on March 17, 2000. We have addressed the deficiencies listed in the facsimile. The following items are included with this letter:

- Attachment 1: Third Copy Certification
- Attachment 2: A copy of the Fax Amendment received on March 17, 2000
- Attachment 3: A Product History Overview
- Attachment 4: Our responses to the minor deficiencies (the deficiencies are restated in bold, and our responses follow each deficiency)

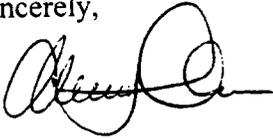
The available samples from different batches (Lots: 45-001-AR-03; 45-998-AR-03; 45-999-AR-03; 59-479-AF-22; 60-500-AF-22; 60-503-AF-22; 59-478-AF-22; 60-501-AF-22; 60-504-AF-22) will be sent under separate cover. In addition, a copy of this submission is being sent to the Chicago District Office.



March 30, 2000
Office of Generic Drugs (HFD-600)
Page Two

Please contact me at 847-935-2448 or Dr. Lawrence E. Roebel at 847- 937-7495 if you have any questions concerning this submission.

Sincerely,

A handwritten signature in black ink, appearing to read 'Alexa L. Chun', with a large, stylized flourish at the end.

Alexa L. Chun, Ph.D.
Associate Director
Regulatory Affairs, Pharmaceutical Products Division
Abbott Laboratories

Sent by facsimile and Federal Express



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

March 17, 2000

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

*Noted.
N/AE
Mark Anderson
3/22/00*

**Re: ANDA 65-003
Gengraf™
(Cyclosporine Capsules, USP [MODIFIED])**

Amendment

Dear Madam/Sir:

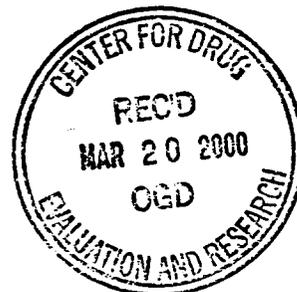
The sponsor is providing a hard copy of two amendments previously provided by facsimili. These include dissolution data provided to Dr. Barbara Davitt from BioPharm on February 10 and February 17, 2000.

Thank you for your attention to this matter. Please contact me at the number provided below if you have any questions or concerns regarding this information.

Sincerely,

Rebecca A. Welch

Rebecca A. Welch
Regulatory Affairs
D491, Building AP6B
Pharmaceutical Products Division
Abbott Laboratories
(847) 937-8971



*REC'D
3-27-00*

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
110 Abbott Park Road
D 491 AP66-1 SW
Abbott Park, Illinois 60064-6108

February 17, 2000

ORIG AMENDMENT

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Attention: Barbara Davitt

N/A B

**Re: ANDA 65-003
Gengraf™
Cyclosporine Capsules, USP (MODIFIED)**

**Bioequivalence
Fax Amendment**

Dear Sir:

On February 10, 2000 the sponsor provided an amendment which included dissolution data on lot 45-001-AR-03 and 28-687-AR-03. These are both lots of Cyclosporine capsules, 100 mg strength. Lot 45-001-AR-03 was submitted in support of the May 1999 amendment. Lot 28-687-AR-03 was submitted in the original ANDA submission in December, 1997. These data were submitted to address the request received from Dr. Barbara Davitt and Dr. Zakaria Wahba on February 8th and 9th, 2000.

At this time the sponsor would also like to provide dissolution data for both the 25mg and 50mg capsules. These data further support that the capsules submitted in the May 1999 amendment, which are now 12 months old, have similar profiles to the original capsules which were 18 months old when first tested by the current dissolution method using the LDAO media.

These data also confirm that the use of the Tier 2 dissolution media for both the original and new capsules after aging results in a dissolution profile more representative of the fresh capsule. The _____ used for Tier 2 testing reduces the effect of the capsule shell

ANDA 65-003
Gengraf Capsules
Page 2 of 2
February 17, 2000

In addition, the sponsor is providing the synopsis of a clinical study which demonstrates the bioequivalence of Gengraf to Neoral in a stable renal transplant population. The study report has been submitted to the Division of Special Pathogens & Immunologic Drug Products (HFD590) under IND _____ as serial no. 026 on November 10, 1999. The drug product dosed in this study was the 100 mg capsule, lot 28-687-AR-03, and the 25 mg capsule, lot 28-686-AR-03. At the time this study was dosed, between April '98 to April '99, these capsules were between 12 and 24 months old.

Thank you for your attention to this matter. Please contact me at the number provided below if you have any questions or concerns regarding this information.

Sincerely,



Rebecca A. Welch
Regulatory Affairs
D491, Building AP6B
Pharmaceutical Products Division
Abbott Laboratories
(847) 937-8971

The following review provides dissolution data for each lot of Gengraf Capsules after storage at 25°C/60%RH (label storage condition). Table 1 provides data for the original capsule lots after storage for 24 months, the proposed product shelf-life. All lots met the product specification. Two of the nine samples required Tier 2 testing due to low individual values during Tier 1 testing - Tier 1 mean values met the product specification.

Table 2 provides data for the capsule lots manufactured under low humidity conditions (i.e., modified capsules) after storage for 12 months. All lots met the product specification. Two samples required Tier 2 testing due to low individual values during Tier 1 testing - Tier 1 mean values met the product specification.

Data for the original capsule lots (blister package) and the modified lots are compared in Figure 1. The variability is high at 10 minutes, reflecting the variability in the time required for capsule shell opening. After 10 minutes, results for capsules tested with the Tier 2 methods are very similar across the dosage strengths regardless of age. Results are lower and more variable for capsules tested with the Tier 1 methods.

A direct comparison of dissolution profiles for the Tier 1 and Tier 2 dissolution methods is provided in Table 3 for the 100 mg dosage strength. Capsules were tested specifically to compare the two methods and were not part of routine stability testing. Capsules were approximately 13.5 months old at the time of testing. Tier 2 release was faster and less variable than for the Tier 1 test method. The results also show that the samples met the dissolution specification for the Tier 1 method.

Table 1

Dissolution data on original lots of Gengraf Capsules after 24 months at 25°C/60%RH

Sample		% Released					
		10	20	30	45	60	90 min.
25mg Lot 28-686-AR-03							
Aclar Blister	Mean	45.9	82.4	87.0	94.7	97.6	98.1
	sd	27.6	29.5	13.3	8.2	5.5	3.3
HDPE Bottles of 30	Mean	48.4	77.9	87.8	98.8	101.1	99.7
	sd	31.8	31.7	22.2	3.6	3.7	2.3
HDPE Bottles of 100	Mean	61.2	85.7	87.9	94.3	100.1	101.5
	sd	46.0	32.6	29.8	17.6	3.8	1.7
50 mg Lot Lot 29-719-AR-03							
Aclar Blisters (Tier 2)	Mean	48.3	82.8	96.0	101.3	102.8	104.3
	sd	24.0	19.5	10.6	7.1	5.7	4.1
HDPE Bottles of 30	Mean	44.9	83.4	94.6	97.5	99.9	98.9
	sd	15.9	13.6	10.0	5.2	1.4	2.1
HDPE Bottles of 100	Mean	38.8	84.5	93.0	98.8	101.2	100.9
	sd	24.7	18.0	10.2	4.3	0.5	0.7
100 mg Lot Lot 28-687-AR-03							
Aclar Blisters (Tier 2)	Mean	23.4	83.1	98.2	102.8	104.1	104.2
	sd	5.5	10.2	3.1	1.6	0.8	0.6
HDPE Bottles of 30	Mean	16.0	47.6	69.5	92.9	99.8	101.7
	sd	7.3	16.9	14.1	12.3	5.3	4.2
HDPE Bottles of 100	Mean	14.2	35.1	56.0	90.2	95.6	100.2
	sd	5.7	13.8	19.3	10.5	9.3	4.0

Table 2

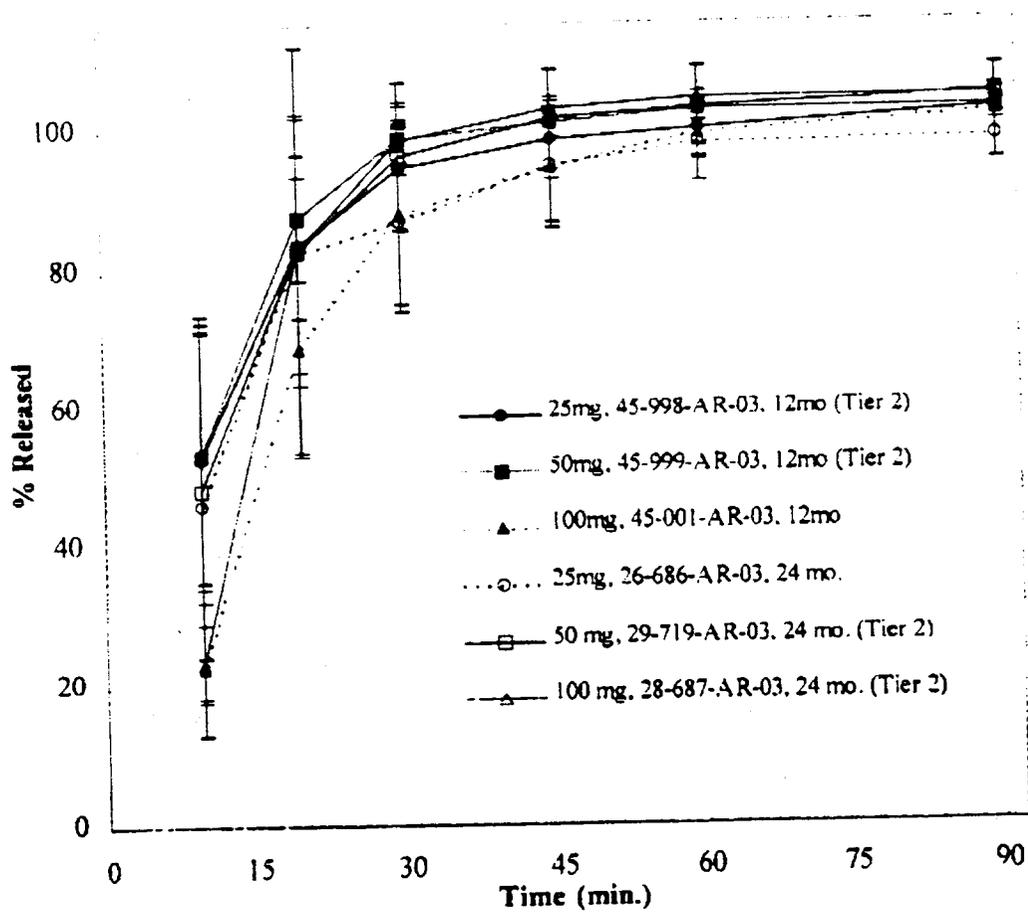
Dissolution data on modified lots of Gengraf Capsules after 12 months at 25°C/60%RH

Sample		% Released					
		10	20	30	45	60	90 min.
25mg. 45-998-AR-03 (Tier 2)	Mean	52.6	83.4	94.5	98.3	99.8	102.2
	sd	18.3	18.3	8.8	5.7	4.2	1.2
50mg. 45-999-AR-03 (Tier 2)	Mean	53.3	87.4	98.7	100.7	102.5	102.5
	sd	18.1	9	5.2	2	1.7	1.2
100mg. 45-001-AR-03	Mean	22.7	68.5	87.9	94.4	99.2	101.6
	sd	9.7	14.9	13.0	8.6	4.1	1.4

Table 3

Tier 1 and Tier 2 dissolution data for Gengraf Capsules, 100 mg, Lot 45-001-AR-03

		% Released					
		10	20	30	45	60	90 min.
Tier 1	Mean	28.9	72.7	87.3	95.3	97.4	99.6
	sd	13.3	17.1	14.4	10.4	7.8	2.4
Tier 2	Mean	49.6	91.3	100.8	102.8	102.8	102.9
	sd	10.6	5.5	2.4	1.6	1.3	1.1

Figure 1. Gengraf Capsule Dissolution Profiles for Product Stored at 25°C/60%RH

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
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Abbott Park, Illinois 60064-6108

February 10, 2000

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/AR

Attention: Dr. Barbara Davitt

Re: ANDA 65-003
Gengraf™
(Cyclosporine Capsules, USP [MODIFIED])

BioPharm Amendment

Dear Madam:

The sponsor is providing this amendment to address the questions raised by Dr. Barbara Davitt and Dr. Zakaria Wahba during a teleconference on February 8th and 9th, 2000.

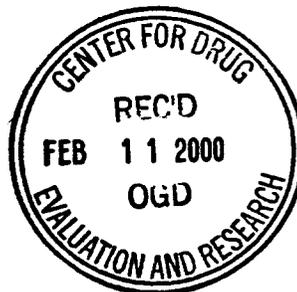
The questions concerned the dissolution profiles for Gengraf Capsule lots 28-687-AR-03 and 45-001-AR-03. The attached report and data compares the dissolution data from these two lots at various timepoints. This information was provided by fax on 2/10/00.

Thank you for your attention to this matter. Please contact me at the number provided below if you have any questions or concerns regarding this information.

Sincerely,

Rebecca A. Welch

Rebecca A. Welch
Regulatory Affairs
D491, Building AP6B
Pharmaceutical Products Division
Abbott Laboratories
(847) 937-8971





Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

February 1, 2000

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AB

Attention: Mark Anderson

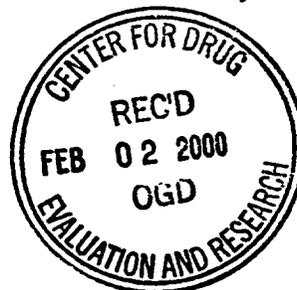
Re: **ANDA 65-003**
GengrafTM
Cyclosporine Capsules, USP (MODIFIED)

Bioequivalence
Fax Amendment

Dear Sir:

The sponsor is providing this amendment to address the request received from Mark Anderson on January 31, 2000. The request was for additional information regarding the lots manufactured in support of the May 28, 1999 amendment. The requested information is attached.

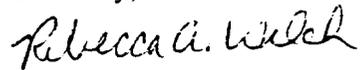
The May amendment included dissolution data for three lots of cyclosporine capsules (one lot each of the 25 mg, 50 mg and 100 mg strength). The data was included in section VI, pages 373 to 376. This dissolution data had been previously submitted in the March 31, 1999 amendment in report R&D/99/053. The attached information includes the lot #, strength, date of manufacture, date of dissolution testing, assay results and content uniformity results for these lots. These lots were all manufactured with white capsule shells and clear gelatin bands, which is the same configuration as the commercial product. The specifications for the capsule shells were included in section VIII of the May 28, 1999 amendment on pages 445 to 464.



ANDA 65-003
Gengraf Capsules
Page 2 of 2
February 1, 2000

Thank you for your attention to this matter. Please contact me at the number provided below if you have any questions or concerns regarding this information.

Sincerely,



Rebecca A. Welch
Regulatory Affairs
D491, Building AP6B
Pharmaceutical Products Division
Abbott Laboratories
(847) 937-8971



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

January 27, 2000

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

N/A

Attention: Mark Andersen

**Re: ANDA 65-003
Cyclosporine Capsules USP (modified)**

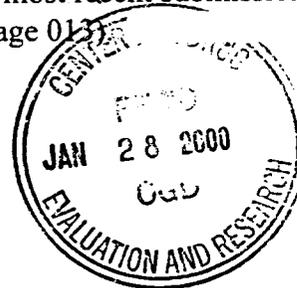
Fax Amendment

Dear Sir:

The sponsor is providing this amendment to address the deficiencies identified during a telephone conversation with Dr. Maria Shih. held on January 27, 2000. The comments concerned the in-process moisture requirements for the capsule and the dissolution testing required for release and stability. The following clarification describes the testing and specification required for these quality control parameters. The sponsor commits to an in-process moisture specification and a dissolution specification for release and shelf-life.

Regarding the in-process moisture requirements, on page 513 of the amendment dated May 28, 1999, the requirement states,

Justification of the specified limits can be found on pages 1712 and 1713 of the May 28 amendment. The most recent submission of the specification was provided December 7, 1999 (starting on page 013) are as follows:



Capsule Strength	List #	Page # (12/7/99 amendment)	Specification Requirement (2-P)
25 mg	6463	014	
50 mg	6477	031	
100 mg	6479	048	

Capsule Strength	List #	Page # (12/7/99 amendment)	Specification Requirement (3-P and 6-F, Process Control Limit)
25 mg	6463	015	
50 mg	6477	032	
100 mg	6479	049	

Capsule Strength	List #	Page # (12/7/99 amendment)	Specification Requirement (6-F, Acceptance Limit)
25 mg	6463	015	
50 mg	6477	032	
100 mg	6479	049	

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314 & 601)</i>	Form Approved: OMB No. 0910-0338 Expiration Date: April 30, 2000 See OMB Statement on page 2.
	FOR FDA USE ONLY
	APPLICATION NUMBER

APPLICANT INFORMATION	
NAME OF APPLICANT Abbott Laboratories	DATE OF SUBMISSION January 27, 2000
TELEPHONE NO. (Include Area Code) (847) 937-8971	FACSIMILE (FAX) Number (Include Area Code) (847) 937-8002
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): D-491/AP6B-1 100 Abbott Park Road Abbott Park, IL 60064-3500	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)		65-003
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Cyclosporine Capsules, USP (MODIFIED)	PROPRIETARY NAME (trade name) IF ANY Gengraf	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Cyclosporine	CODE NAME (If any)	
DOSAGE FORM: Capsule	STRENGTHS: 25 mg, 50 mg, 100 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Solid organ transplant		

APPLICATION INFORMATION		
APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input checked="" type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507		
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <i>Neoral</i> Holder of Approved Application <i>Novartis</i>		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
REASON FOR SUBMISSION <i>Amendment regarding a response to the bioequivalency deficiency letter</i>		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC.	

ESTABLISHMENT INFORMATION	
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.	
DMF	
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)	
DMF	

This application contains the following items: (Check all that apply)		
<input type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input type="checkbox"/>	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
<input type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
<input type="checkbox"/>	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (k) (3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input checked="" type="checkbox"/>	19. OTHER (Specify) Response to Deficiency	
CERTIFICATION		
<p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:</p> <ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202. 5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81. 7. Local, state and Federal environmental impact laws. <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision. The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Rebecca A Welch</i>	TYPED NAME AND TITLE Rebecca A. Welch Associate Director	DATE 1/27/00
ADDRESS (Street, City, State, and ZIP Code) 100 Abbott Park Road Abbott Park, IL 60064-3500		Telephone Number (847) 937-8971
<p>Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p>DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0338) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. Washington, DC 20201</p> <p>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</p>		
Please DO NOT RETURN this form to this address.		



Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

December 7, 1999

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
Document Control Room, Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

RECEIVED
DEC 10 1999

Attention: Mr. Mark Anderson.

**Re: ANDA 65-003
Gengraf™ Capsules
(cyclosporine capsules USP [MODIFIED])**

Fax Amendment

Dear Sir:

The sponsor is providing this amendment to address the deficiencies identified in the letter dated November 15, 1999. The letter included comments on the CMC, Labeling and Bioequivalence sections.

The CMC comments are addressed behind the "Responses" tab and supporting documentation is included as Reference 1 and Reference 2.

The responses to the labeling comments are also included behind the "Responses" tab. The FPL for the blister, carton and package insert are included as references 3, 4, and 5. The review copy has 12 mounted copies of each label. The archival copy includes one copy of each label. In addition, the annotated labeling is provided behind the last tab, "Annotated Labels". In order to perform a side by side comparison, a copy of the innovator labeling for the 25 and 100 mg blister and carton are included. (Please note the innovator is not currently marketing a 50 mg strength capsule so this labeling is not available.) The Gengraf and Neoral cartons are provided on two pages due to size. The annotation of the Gengraf carton has been completed on a copy of the carton, and for the 100 mg strength has been reduced to ~85%. The annotated package insert is provided on a side by side label format, where any changes to the innovator

DEC 08 1999
CDR

Page 2
ANDA 65-003
December 7, 1999

text has been reflected in the right hand column. This format has been used because it provides a high quality copy and is easier to review. A current version of the innovator insert (June '97) is also provided for the reviewer, however the copy quality is poor due to the original package insert being blue print and oversized. This is being provided as an aid to the reviewer and is not expected to be used for the review.

The Gengraf package insert has been provided on disk in Word '97 and is included in the archival copy. This label has been verified to be an exact copy of the FPL but is in an 8 1/2 x 11 " format. This is being provided as a reviewer aid.

The response to the Bioequivalency issue is also included. Supportive documentation is included as reference 6.

This submission consists of one volumes. Two copies (archival and review copies) are being provided to the Office of Generic Drugs.

Thank you for your attention to this matter. Please contact me at the number provided below if you have any questions or concerns regarding this information.

Sincerely,



Rebecca A. Welch
Regulatory Affairs
D491, Building AP6B
Pharmaceutical Products Division
Abbott Laboratories
(847) 937-8971



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

May 28, 1999

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
NAC

Attention: Frank O. Holcombe, Jr., Ph.D.

Re: ANDA 65-003
Cyclosporine Capsules USP (modified)

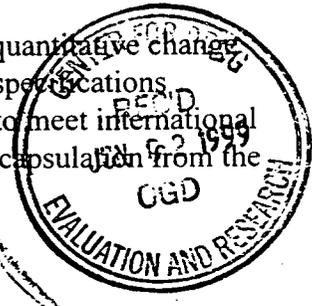
Amendment

Dear Sir:

The sponsor is providing this amendment to address the deficiencies identified in the letter dated August 19, 1998. In that letter it was stated that the cosmetic defect of capsule dimpling noted on stability was unacceptable. The recommendation was that the product and/or package be revised and new batches be manufactured to demonstrate that the problem has been eliminated. Capsule dimpling can be defined as a dented appearance in the capsule shell.

Extensive studies have been conducted to understand the cause of the capsule dimpling.

The lots produced in support of this amendment had no qualitative or quantitative change in the composition of the capsule formulation, no change in excipient specifications (except for the capsule shell which has had the _____ eliminated to meet international requirements), and no change in the manufacturing process through encapsulation from the original application dated December 19, 1997.



Page 2
ANDA 65-003
May 28, 1999

The product manufactured with the stricter environmental controls and the new package has been shown through the stability program to have equivalent chemical stability, disintegration and dissolution characteristics to the original ANDA lots and to be equivalent to the innovator's product (Neoral Capsules). The additional controls will minimize moisture gain and enhance physical stability. Three months of both room temperature and accelerated stability data is being submitted on one lot of each strength manufactured with these improved controls.

In addition, the sponsor is responding to the issues raised in the letter from Labeling Review, dated September 30, 1998. These items have been addressed and the modified, draft label text is included in section V. One of the items addressed is the change in the established name to cyclosporine capsules, USP (modified). Throughout this ANDA amendment the sponsor's product is identified as GengrafTM Capsules (cyclosporine capsules, USP [MODIFIED]), cyclosporine capsules, USP or SSF21 (the developmental formulation name). These terms are all in reference to the capsules produced in support of this application.

Because this is an amendment, there are sections of the application which refer to the original application submitted on December 19, 1997. Those sections which support the new lots produced under the modified process are included. These include revised labeling, information on the raw material lots used to produce the new capsule lots, modified manufacturing and processing instructions, in-process controls including executed batch records, modified specifications and new test methods, stability data, and sample information.

This submission consists of seven volumes. A full copy is also being provided to the sponsor's district office (Chicago district). Two copies of each volume (archival and CMC review copies) are being provided to the Office of Generic Drugs. In addition, volume two has an additional copy for biopharm review. Although no additional bioequivalence studies were performed, the dissolution data for the new lots is provided. In addition, two extra copies of volume six are being provided. This volume contains the analytical methods section. Samples are not being included with this submission, but a list of samples is included in XIX and will be provided upon request.



Attachment

The following action plan has been implemented to address and eliminate dimpling of the Cyclosporine capsules:

- 1) There will be stricter control of environmental conditions during the process.
- 2) An _____ specification for water content of the capsule has been established. The capsules will be _____ specification is reached. Excursions in the _____ will not impact material quality but may _____ A maximum _____ has been established.
- 3) To prevent any _____ packaged into an HDPE drum. Direct product contact (PE liner) is unchanged from the original application.
- 4) To prevent moisture uptake during product shelf life, the final product will be packaged into a foil/foil blister. The HDPE bottle and Aclar blister are no longer being considered as a commercial package.
- 5) As requested in the letter dated August 19, 1998, finished capsule and stability specifications are in place for _____ substances. In addition, a specification for moisture has been established for _____ product release, and stability.



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

April 23, 1999

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Lizzy Sanchez
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/AB

**Re: ANDA 65-003
Cyclosporine Capsules USP (modified)**

**AMENDMENT
BIOEQUIVALENCY**

Dear Sir/Madam:

The sponsor, Abbott Laboratories, submits this amendment to an abbreviated new drug application, submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act for Cyclosporine 25 mg, 50 mg, and 100 mg Capsules .

The purpose of this amendment is to provide the additional information requested during a telephone conversation with Ms. Jeanne Fox held on April 14, 1999. Responses to the original observations were provided March 31, 1999 to address the deficiencies identified in the letter dated October 9, 1998 and signed by Dale P. Conner, Pharm. D. The referenced letter raised concerns regarding stability data for the blood samples, the status of the soft gelatin capsule formulation, the dissolution test method, and the lots of Neoral used as reference in the two bioequivalence studies.

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APR 26 1999

GENERIC DRUGS

Page 2
ANDA 65-003
April 23, 1999

This submission includes additional information regarding the long term stability of the frozen blood samples, and dissolution data for the innovator 25 and 50 mg product (Neoral®, Cyclosporine capsules, USP (modified)).

Thank you for your attention to this matter. Please contact me at the number provided below if you have any questions or concerns regarding this information.

Sincerely,



Rebecca A. Welch
Regulatory Affairs Pharmaceutical Products Division
D491, Building AP6B
100 Abbott Park, IL
Abbott Laboratories
(847) 937-8971

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

March 31, 1999

ORIG AMENDMENT

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Lizzy Sanchez
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

AB

**Re: ANDA 65-003
Cyclosporine Capsules USP (modified)**

**AMENDMENT
BIOEQUIVALENCY**

Dear Sir/Madam:

The sponsor, Abbott Laboratories, submits this amendment to an abbreviated new drug application, submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act for Cyclosporine 25 mg, 50 mg, and 100 mg Capsules .

The purpose of this amendment is to respond to the letter dated October 9, 1998 and signed by Dale P. Conner, Pharm. D. The referenced letter raised concerns regarding stability data for the blood samples, the status of the soft gelatin capsule formulation, the dissolution test method, and the lots of Neoral used as reference in the two bioequivalence studies. In response, the sponsor is providing additional information with regards to each of these observations.

Thank you for your attention to this matter. Please contact me at the number provided below if you have any questions or concerns regarding this proposal.

Sincerely,

Rebecca A. Welch

Rebecca A. Welch
Regulatory Affairs, Pharmaceutical Products Division
D491, Building AP6B
100 Abbott Park, IL
Abbott Laboratories
(847) 937-8971

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APR 01 1999

GENERIC DRUGS



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

August 5, 1998

Office of Generic Drugs
Food and Drug Administration
HFD 601 Room 286
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ANDA DRUG AMENDMENT

N/AE

**Subject: Cyclosporine Capsules, USP
ANDA 65-003**

Information Amendment

Attention: Lizzy Sanchez:

The following is being provided in response to a telephone communication held on Friday, July 31, 1998. The information included is plasma and PK data on a floppy diskette in ASC II Space Delimited Format. The files included are data from study M97-685 (fasting) and Study M97-686 (fed). Printouts of the data are also provided.

If you have any questions regarding the information, please call me at the number provided below.

Sincerely,

Rebecca A. Welch
Sr. Reg Affairs Administrator
Pharmaceutical Products Division
Abbott Laboratories
(847) 937-8971

RECEIVED

AUG 06 1998

GENERIC DRUGS



ABBOTT

*Noted - Copy to
Ted to Control
M. Anderson
5/29/98*

Pharmaceutical Products Division

Roland T. Catherall
Vice President
Regulatory Affairs and
Research Quality Assurance

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

Phone No.: (847) 937-7495
Fax: No.: (847) 937-8002

May 13, 1998

Mr. Gordon R. Johnston
Deputy Director
Office of Generic Drugs
Food and Drug Administration
HFD 601 Room 286
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

*NEW PRODUCT
No*

Subject: ANDA 65-003

Dear Mr. Johnston:

Reference is made to a May 8, 1998 telephone conversation between yourself, Fred Gustafson and myself of Abbott Laboratories. The subject of our discussion centered around the 6 month room temperature stability results in which Capsule dimpling was identified.

Attached is a brief outline of the issue, cause and how we plan to resolve the issue. As agreed in our telephone conversation a meeting should be held with the review staff and members of our development team. At the meeting more details will be provided on each of the specific areas listed on the attachment. Discussion centered around a tentative meeting in early June. After reviewing calendars, early in the week of June 22nd would be more desirable.

Rebecca Welch of our group will be contacting you or a member of your staff in approximately one week to finalize arrangements. Thank you for your consideration of this matter.

Sincerely,

Roland T. Catherall
Vice President, Regulatory Affairs and Quality Assurance

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MAY 19 1998
GENERIC DRUGS

RTC:adw
Attachments



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

December 19, 1997

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**Re: Gengraf™
Cyclosporine Capsules, USP
ANDA**

Original Submission

Dear Madam or Sir:

The sponsor, Abbott Laboratories, submits the following information under the provision of section 505 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94. This information consists of Chemistry, Manufacturing, and Controls information and two bioequivalence studies comparing Abbott Cyclosporine Capsules to the innovator product, Neoral 100 mg.

This submission consists of 14 volumes. A complete set of the volumes has been provided as the archival copy. Sections I-VII are being provided for bioavailability/bioequivalence review. Sections I-V and VII-XXI are being provided for chemistry review. In addition, a complete copy of the chemistry, manufacturing and controls sections (I-V, and VII-XXI) have been provided to our FDA District Office as required in 21 CFR 314.70.

Two additional copies of the Methods Validation information are included. Although the product is a USP monograph item, the test methods have been modified in order to assure the degradants are separated from the Cyclosporine A main peak. The Abbott Cyclosporine Capsules do meet all USP requirements for Cyclosporine Capsules, USP.

A complete list of the available samples is included in section XIX. The actual samples of the drug substance and drug product are not included in this submission, but will be provided upon request.

For ease of review, a copy of the "Checklist for Completeness and Acceptability for Filing Abbreviated Applications" has been provided behind FDA form 356h (pages 0011 and 0012) with the appropriate page numbers identified where the items are located.

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DEC 23 1997

GENERIC DRUGS



Page 2

Cyclosporine Capsules, USP

This application was originally planned to be an Abbreviated Antibiotic Drug Application (AADA) since the innovator product, Neoral, was approved under section 507. However, with the signing of The Food and Drug Administration Modernization and Accountability Act of 1997, and after discussion with Mr. Harvey Greenberg of the Office of Generic Drugs, the application is being submitted as an Abbreviated New Drug Application (ANDA). As an ANDA, Section II. (Basis for ANDA Submission), and Section III. (Patent Certification), are being included. Regarding the patent certification, the Modernization and Accountability Act of 1997, identifies sections of 505 which are exempted under this Act. An exception is provided for the requirements of section (j.)(2.)(A)(vii) regarding patent certification. Therefore, this statement is included on the Patent Certification, found on page 0017. Because this change in application type/title was not made until early December, many of the reports identify the application as an AADA. This has no impact on the accuracy of the data and information provided in these reports.

This application meets the requirements for a categorical exclusion for an environmental assessment, under 21 CFR 25.24 because the formulation will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect.

There are no user fees associated with this application.

A petition to modify CFR 448.123(b) has been submitted under separate cover to the attention of Office Director, Doug Sporn.

As always, should you have any questions regarding this information, please call me at the number provided below.

Rebecca A. Welch

Rebecca A. Welch
Sr. Administrator, PPD Regulatory Affairs
Abbott Laboratories
Dept. 491, Bldg. AP6B-1
(847) 937-8971
100 Abbott park Road
Abbott Park, IL 60064