CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 074650

CHEMISTRY REVIEWS

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.: 1 (one)

2. ANDA #: 74-650 (Date of Application - 3-20-95)

3. NAME AND ADDRESS OF APPLICANT:

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

Tel: (516 789-8228

4. LEGAL BASIS for ANDA SUBMISSION:

Bactrim™ Oral Suspension (Sulfamethoxazole and Trimethoprim Oral Suspension); NDA 17-560 001. Bactrim Oral Suspension is now a discontinued drug product of Hoffmann LaRoche, Inc.
(Note: Bactrim™ Pediatric Suspension (NDA 17-560 002 remains on the current approved list of drugs.)

Patent Certification (page 008) and Exclusivity (page 009) statements have been included.

Satisfactory.

5. SUPPLEMENT(s):

Not applicable.

6. NAME OF DRUG:

Sulfamethoxazole and Trimethoprim Oral Suspension USP; 200 mg/40 mg per 5 mL

7. NONPROPRIETARY NAME:

Sulfamethoxazole and Trimethoprim Oral Suspension USP; 200 mg/40 mg per 5 mL

8. SUPPLEMENT(s) PROVIDE(s) FOR:

Not applicable.

9. AMENDMENTS AND OTHER DATES:

None.

10. PHARMACOLOGICAL CATEGORY:

Antibacterial, Antipneumocystis

11. HOW DISPENSED:

℞

12. RELATED IND/NDA/DMF(s):

DMF [redacted] (b) (4)
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM:

Suspension

14. POTENCY:

Sulfamethoxazole, 200 mg/5 mL
Trimethoprim, 40 mg/5 mL

15. CHEMICAL NAME AND STRUCTURE:

(Sulfamethoxazole) 4-amino-N-(5-methyl-3-isoxazolyl)benzenesulfonamide,

(Trimethoprim) 5-[(3,4,5-Trimethoxyphenyl)methyl]-2,4-pyrimidinediamine

16. RECORDS AND REPORTS:

None

17. COMMENTS:

The following is provided for your information:

1. The bioequivalence information which you have provided is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

2. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

18. CONCLUSIONS AND RECOMMENDATIONS:

This application is deficient (Major Amendment) for the following reasons:

1. (b) (4)

2.

3.

4.

Following this page, 2 pages withheld in full (b)(4)

19. REVIEWER: 19A. DATE COMPLETED:

A.J. Mueller, Ph.D. August 15, 1995

Endorsed by P.Schwartz, Ph.D. September 22, 1995

Following this page, 13 pages withheld in full (b)(4)

[redacted] (b)(4)

The submitted stability test data supports Hi-Tech's request for a tentative 24 month expiry date and is satisfactory.

30. CONTROL NUMBERS:

Control Numbers for both raw materials and production batches of the drug product are explained on pages 1622-1626, Vol 1.6 and are satisfactory.

31. SAMPLES AND RESULTS:

Samples for validation testing are not required. The drug product is a USP compendial drug product. Additional tests submitted in this application are adequately validated through submitted data.

32. LABELING:

Proposed labeling is given in Section V (pages 032-085, Vol. 1.1) of this application and any comments by labeling review will be added to the CMC review.

33. ESTABLISHMENT INSPECTION:

An EER will be submitted to the DMPQ at the appropriate time.

34. BIOAVAILABILITY:

Hi-Tech has submitted a clinical evaluation in support of the bioequivalence of their drug product. See pages 086 through 1067, Volumes 1.2, 1.3 and 1.4 of this application. This study has been submitted to the Division of Bioequivalence for evaluation (7-10-95).

Because of [redacted] (b)(4) *current inability to supply the* [redacted] (b)(4)*, you will need to supply 3-way dissolution data from a new executed batch using new source* [redacted] (b)(4)*, your current executed batch (Lot No. 401 824) and the innovator product to support a waiver of bioequivalence study using the new source* [redacted] (b)(4)*. Refer to our Tel-Con of June 21, 1995 between the Office of Generic Drugs (OGD) and your company. Your sould consult OGD's Division of Bioequivalence on any aspect of needed information to support bioequivalence requirements for this*

application.

Any comments will be communicated to Hi-Tech under separate cover.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Hi-Tech has submitted a request for waiver of environment assessment (see page 1629), together with a certification statement of compliance to all local, state and federal environmental regulations. Satisfactory.

36. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt:
Yes___XXX___ No _____

If no, explain reason(s) below:

cc: ANDA #74-650
ANDA #74-650/Division File
Field Copy

Endorsements:

HFD-629/A.Mueller/8-15-96 A Mueller 7-29-96

HFD-629/P.Schwartz, Ph.D./9-22-96 PS 7/29/96

X:\WPFILE\MAJORS\MUELLER\74650N00.R01
F/T MM 2-22-96
Not Approvable - Major

37. **DMF CHECKLIST FOR ANDA 74-650 REVIEW # 1**

Date: August 15, 1995

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted] (b) (4)		3	SAT	3-21-95
	Comments: [redacted] (b) (4)			
[redacted] (b) (4)		1	DEF	8-14-95
	Comments: [redacted] (b) (4)			
[redacted] (b) (4)		3	SAT	12-20-93
	Comments: Acceptable [redacted] (b) (4) (C-H. Kim)			
[redacted] (b) (4)		6		
	Comments: DMF volumes unavailable at this time. This application currently a major deficiency (first review).			
[redacted] (b) (4)		1	DEF	8-8-95
	Comments: Wrong company referenced on LoA.			
[redacted] (b) (4)		3	SAT	10-13-94
	Comments: Found satisfactory (S. Rosencrance).			

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

A. J. Mueller — Signature — 2-29-96 Date

1. CHEMISTRY REVIEW NO. 2

2. ANDA #74-650

3. NAME AND ADDRESS OF APPLICANT
Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

4. LEGAL BASIS for ANDA SUBMISSION
Approved application for Bactrim™ Oral Suspension (Sulfamethoxazole and Trimethoprim Oral Suspension) of Roche Laboratories.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sulfamethoxazole and Trimethoprim Oral Suspension USP, 200 mg/40 mg per 5 mL

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

9. AMENDMENTS AND OTHER DATES
Original Application Submission Date March 20, 1995
Amendment Date May 8, 1995
Major Amendment Date October 4, 1996
Major Amendment Date November 27, 1996

10. PHARMACOLOGICAL CATEGORY
Antibacterial, Antipneumocystis

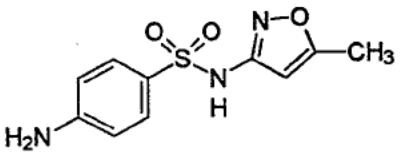
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
See DMF Section (37)

13. DOSAGE FORM
Suspension

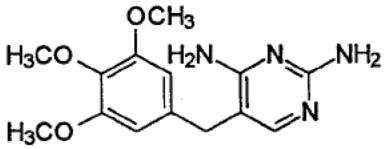
14. POTENCY
Sulfamethoxazole, 200 mg/5 mL
Trimethoprim, 40 mg/5 mL

15. CHEMICAL NAME AND STRUCTURE
Sulfamethoxazole. $C_{10}H_{11}N_3O_3S$. 253.28. Benzensulfonamide, 4-amino-*N*-(5-methyl-3-isoxazolyl)-. 723-46-6. USP 23, page 1461.



and

Trimethoprim. $C_{14}H_{18}N_4O_3$. 290.32. 2,4-Pyrimidinediamine,5-[(3,4,5-trimethoxyphenyl)methyl]-. 738-70-5. USP 23, page 1602.



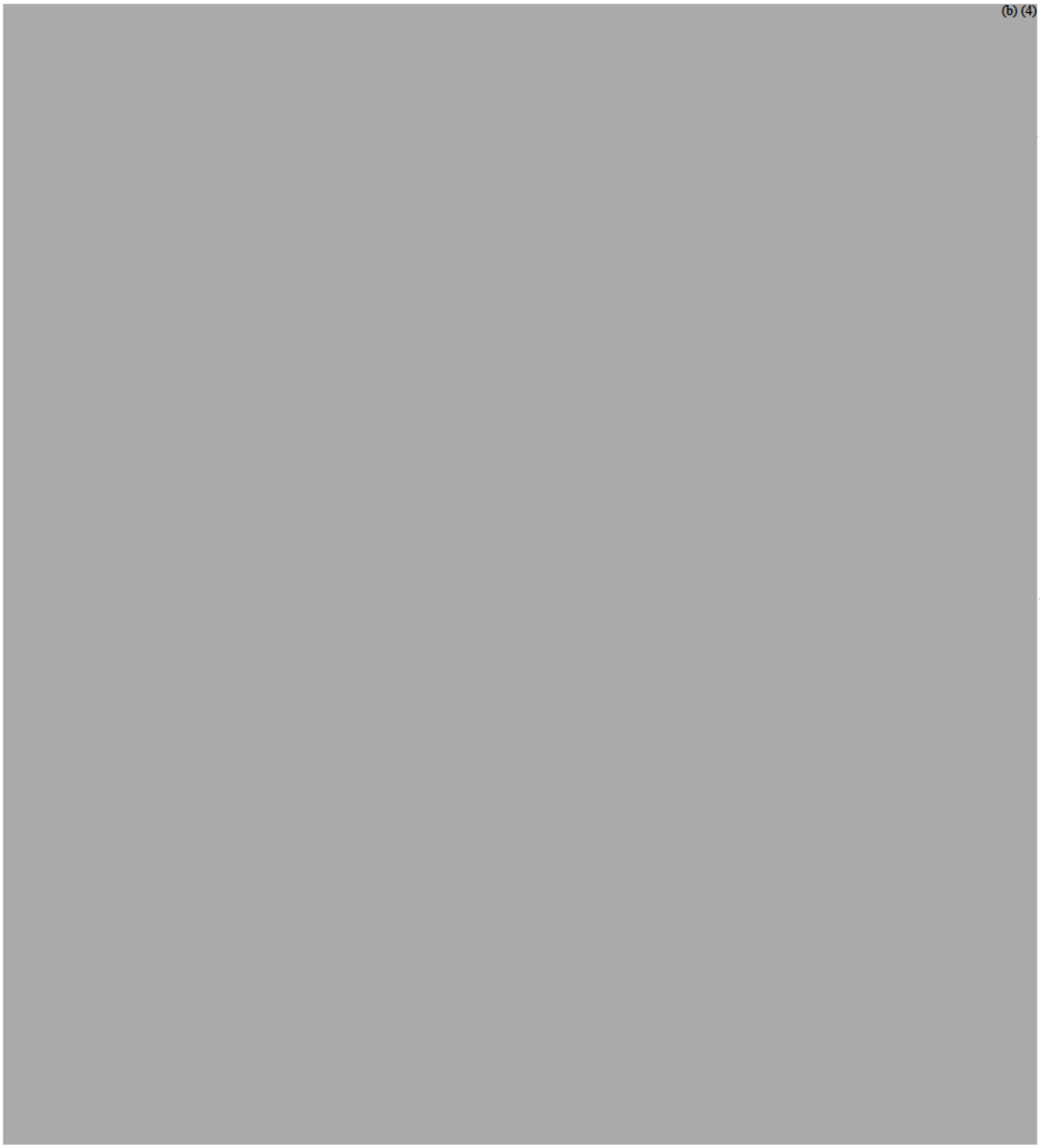
16. RECORDS AND REPORTS
N/A

17. COMMENTS
In Major Deficiency Letter dated 4/4/96, firm was notified, in addition to other deficiencies, the need to supply a 3-way dissolution data from a new executed batch using new sources of [redacted](b)(4). Firm's Major Amendment dated 11/27/96 relates to the new executed batch; Major amendment dated 10/4/96 relates to other deficiencies notified to the firm in the deficiency letter. This chemistry review covers both the Major Amendments referenced above.
See Individual Sections for Comments.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable, Major

19. REVIEWER: U.S. Atwal
DATE COMPLETED: April 8, 1997

Following this page, 12 pages withheld in full (b)(4)



30. CONTROL NUMBERS **Satisfactory**
Control Numbers for both raw materials and production batches of the drug product are explained in original application on pages 1622-1626, Vol 1.6.

31. SAMPLES AND RESULTS
Samples for validation testing are not required. The drug product is a USP compendial drug product. Additional tests submitted in this application are adequately validated

through submitted data.

32. LABELING **Pending**
Firm's response to labeling comments from deficiency letter, dated 3/4/96, needs to be reviewed.

33. ESTABLISHMENT INSPECTION **Pending**
EER filing Date April 9, 1997.

34. BIOEQUIVALENCY STATUS **Pending**
Bioequivalence review of the new exhibit batch, batch #601 824 is needed.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION
Hi-Tech has submitted a request for waiver of environment assessment (see page 1629 of original ANDA, and page 407 of major amendment dated 11/27/96), together with a certification statement of compliance to all local, state and federal environmental regulations. **Satisfactory.**

36. ORDER OF REVIEW
The application submission(s) covered by this review was taken in the date order of receipt:
Yes_____ No ____x____

Note: This ANDA was transferred from Branch II to Branch I and had a status of 160 days waiting.

37. **DMF CHECKLIST FOR ANDA 74-650 REVIEW # 2**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted] (b) (4)		1	Adequate	4-4-97
	Comments: Reviewed by U.S. Atwal			
[redacted] (b) (4)		1	Inadequate	4-8-97
	Comments: Reviewed by U.S. Atwal			
[redacted] (b) (4)		3	Adequate	12-20-93
	Comments: Reviewed by C.H. Kim			
[redacted] (b) (4)		3	Adequate	5/22/96
	Comments: Reviewed by M. Adams			
[redacted] (b) (4)		4		
	Comments: L.O.A. Date 3/14/96			
[redacted] (b) (4)		3	Adequate	10/13/94
	Comments: Reviewed by S. Rosencrance.			
[redacted] (b) (4)		3	Adequate	4/15/96
	Comments: Reviewed by S.S. Brown			
[redacted] (b) (4)		4		
	Comments:			

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Reviewer Signature

10/10/97
Date

38. Chemistry Comments to be Provided to the Applicant

ANDA: #74-650 APPLICANT: Hi-Tech Pharmacal Co., Inc.

DRUG PRODUCT: Sulfamethoxazole and Trimethoprim Oral Suspension USP 200 mg/40 mg per 5 mL

The deficiencies presented below represent Major deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6.

7.

8. [redacted] (b) (4)

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

1. Please commit to update the specifications for all inactive compendial ingredients to meet current requirements established in the USP/NF.

2. All DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA. Some of the DMF holders may have to be inspected by our Division of Manufacturing and Product Quality. Any unsatisfactory review/evaluation will delay the approval of the ANDA.

3. The facilities referenced in the application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval. We have requested an evalution from the Division of Manufacturing and Product Quality.

4. The DMF number listed on form FDA 356h for [redacted] (b) (4) is incorrect. Please revise the form to reflect the correct number.

Sincerely yours,

4/15/97

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-650
Division File
DUP Jacket
Field Copy

Endorsements:
HFD-623/U. Atwal, Ph.D./4-8-97
HFD-623/V. Sayeed, Ph.D./4-9-97
HFD-617/J. Wilson, PM/4-9-97
X:\NEW\FIRMSAM\HITECH\74650.RV2
F/t by: bc/4-10-97

4/10/97 4/14/97.

NOT APPROVABLE - MAJOR

1. CHEMISTRY REVIEW NO. 3

2. ANDA #74-650

3. NAME AND ADDRESS OF APPLICANT
Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

4. LEGAL BASIS for ANDA SUBMISSION
Approved application for Bactrim™ Oral Suspension (Sulfamethoxazole and Trimethoprim Oral Suspension) of Roche Laboratories.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sulfamethoxazole and Trimethoprim Oral Suspension USP, 200 mg/40 mg per 5 mL

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

9. AMENDMENTS AND OTHER DATES
Original Application Submission Date March 20, 1995
Amendment Date May 8, 1995
Major Amendment Date October 4, 1996
Major Amendment Date November 27, 1996
Major Amendment Date April 30, 1997 (This Review)
New Correspondence Date May 1, 1997 (Request to Change Deficiencies from Major to Minor)
Telephone Amendment Date September 3, 1997 (This Review)
Telephone Amendment Date September 4, 1997 (This Review)

10. PHARMACOLOGICAL CATEGORY
Antibacterial, Antipneumocystis

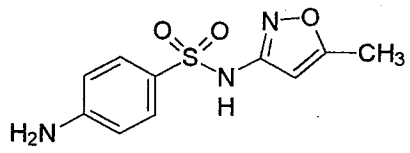
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
See DMF Section (37)

13. DOSAGE FORM
Suspension

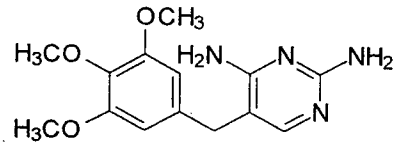
14. POTENCY
Sulfamethoxazole, 200 mg/5 mL
Trimethoprim, 40 mg/5 mL

15. CHEMICAL NAME AND STRUCTURE
Sulfamethoxazole. $C_{10}H_{11}N_3O_3S$. 253.28. Benzensulfonamide, 4-amino-*N*-(5-methyl-3-isoxazolyl)-. 723-46-6. USP 23, page 1461.



and

Trimethoprim. $C_{14}H_{18}N_4O_3$. 290.32. 2,4-Pyrimidinediamine,5-[(3,4,5-trimethoxyphenyl)methyl]-. 738-70-5. USP 23, page 1602.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
See Individual Sections; Comments from deficiency letter are followed by firm's response. The review also includes firm's response to the Tcon. between Mr. James Wilson and the firm (9/3/97), and to the Tcon. between Mr. James Wilson, Dr. Vilayat Sayeed, and the firm (9/4/97).

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER:
U.S. Atwal

DATE COMPLETED:
December 12, 1997

cc: ANDA 74-650
DUP File
Division File
Field Copy

Endorsements:
HFD-623/U.S. Atwal, Ph.D./ 12/16/97
HFD-623/V. Sayeed, Ph.D./ 12/17/97.
X:\NEW\FIRMSAM\HITECH\74650.RV3
F/T by: bc/12/18/97

CHEMISTRY REVIEW - APPROVABLE

Following this page, 13 pages withheld in full (b)(4)

Proposed Expiration Date: 24 months

30. CONTROL NUMBERS **N/A**

31. SAMPLES AND RESULTS **N/A**
The drug substances and the drug product are compendial.

32. LABELING **Satisfactory**
Labeling Approval Date 12/2/97.

33. ESTABLISHMENT INSPECTION **Satisfactory**
EER Acceptable Date 27-August-1997 by J.D Ambrogio

Comment from deficiency letter is followed by firm's response:

Comment:
The facilities referenced in the application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval. We have requested an evalution from the Division of Manufacturing and Product Quality.

Response:
Firm acknowledged the comment. **Response is Satisfactory.**

34. BIOEQUIVALENCY STATUS **Satisfactory**
Bio Acceptable Letter sent on June 12, 1997.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION
Satisfactory.

Hi-Tech has submitted a request for waiver of environment assessment (see page 1629 of original ANDA, and page 407 of major amendment dated 11/27/96), together with a certification statement of compliance to all local, state and federal environmental regulations.

36. ORDER OF REVIEW
The application submission(s) covered by this review was taken in the date order of receipt:
Yes___X___ No _____

37. **DMF CHECKLIST FOR ANDA 74-650 REVIEW # 3**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted] (b) (4)		1	Adequate	4/4/97
	Comments: Reviewed by U.S. Atwal			
[redacted] (b) (4)		1	Adequate	8/28/97
	Comments: Reviewed by U.S. Atwal			
[redacted] (b) (4)		3	Adequate	12/20/93
	Comments: Reviewed by C.H. Kim			
[redacted] (b) (4)		3	Adequate	5/22/96
	Comments: Reviewed by M. Adams			
[redacted] (b) (4)		4		
	Comments: L.O.A. Date 3/14/96			
[redacted] (b) (4)		3	Adequate	10/13/94
	Comments: Reviewed by S. Rosencrance.			
[redacted] (b) (4)		3	Adequate	4/15/96
	Comments: Reviewed by S.S. Brown			
[redacted] (b) (4)		4		
	Comments:			

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Reviewer Signature

12/16/97
Date