

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-699**

**CHEMISTRY REVIEW(S)**



**ANDA 76-699** ✓

**Carbidopa and Levodopa Orally Disintegrating Tablets  
10 mg/100 mg, 25 mg/100mg, and 25mg/250 mg**

**Schwarz Pharma, Inc.**

**Karen Bernard, Ph.D.  
Office of Generic Drugs/Division of Chemistry II**



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    A. Reviewer's Signature .....

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    C. CC Block.....

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**APPEARS THIS WAY  
ON ORIGINAL**



# Chemistry Review Data Sheet

1. ANDA: #76-699
2. REVIEW #: 1
3. REVIEW DATE: 9/5/03
4. REVIEWER: Karen A. Bernard, Ph.D.

## 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None	

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	March 28, 2003

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Schwarz Pharma, Inc  
6140 W.Executive Drive  
Mequon, WI 53092

Representative: Donna K. Multhauf  
Telephone: (262)-238-5171  
Fax: (262)-238-0957

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: PARCOPA®
- b) Non-Proprietary Name (USAN): Carbidopa-Levodopa ODT

## 9. LEGAL BASIS FOR SUBMISSION:

The basis for Schwarz Pharma's proposed Carbidopa/Levodopa Orally Disintegrating Tablets, 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg, is the approved application for SINEMET® Tablets, 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg, NDA #17-555 held by Bristol Myers Squibb. A suitability petition was filed for the change in

Chemistry Review Data Sheet

dosage form from a tablet to a Orally Disintegrating Tablet. There are no unexpired patents or exclusivites for this product. The firm filed a Paragraph I certification

- 10. PHARMACOL. CATEGORY:           Antiparkinsonian
- 11. DOSAGE FORM:                   Orally Disintegrating Tablets
- 12. STRENGTH/POTENCY:           10 mg/100 mg, 25 mg/100 mg and 25 mg/250 mg
- 13. ROUTE OF ADMINISTRATION:   Oral
- 14. Rx/OTC DISPENSED:            \_X\_ Rx        \_\_\_ OTC
- 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

      \_\_\_ SPOTS product – Form Completed

      \_X\_ Not a SPOTS product

- 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

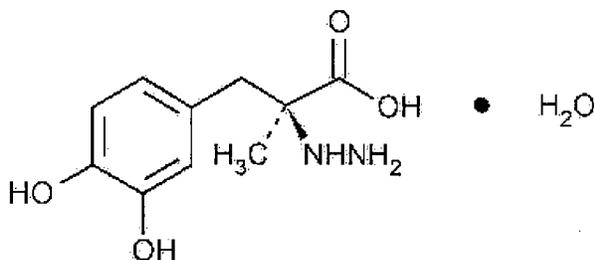
Carbidopa

$C_{10}H_{14}N_2O_4 \cdot H_2O$  244.24

Benzenepropanoic acid, a-hydrazino-3,4-dihydroxy-a-methyl-, monohydrate, (S)-.

(-)- L-a-Hydrazino-3,4-dihydroxy-a-methylhydrocinnamic acid monohydrate [38821-49-7].

Anhydrous 226.23 [28860-95-9].



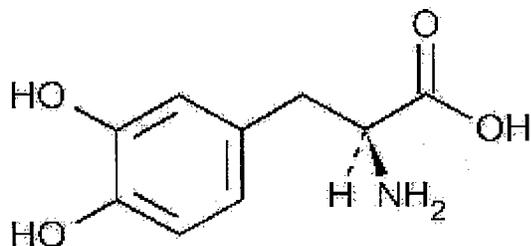
Chemistry Review Data Sheet

Levodopa

C<sub>9</sub>H<sub>11</sub>NO<sub>4</sub> 197.19

L-Tyrosine, 3-hydroxy-

(-)-3-(3,4-Dihydroxyphenyl)- L-alanine [59-92-7].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	3	adequate	3/13/03	By ER
	II			3	adequate	6/25/03	By RR
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

<sup>1</sup> Action codes for DMF Table:

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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	8/25/03	
Methods Validation	Pending		
Labeling	Deficient	8/8/03	
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

**APPEARS THIS WAY  
ON ORIGINAL**

# The Chemistry Review for ANDA 76-699

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Not approvable – The firm will be requested to address the minor deficiencies identified in the review.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

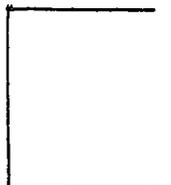
#### A. Description of the Drug Product(s) and Drug Substance(s)

Carbidopa (Benzenepropanoic acid, alpha-methyl, monohydrate (S)) is a potent inhibitor of dopa-decarboxylase. Levodopa (3-Hydroxy-L-tyrosine) is an Antiparkinsonian in combination with Levodopa.

Carbidopa (USP) is a white powder that is slightly soluble in water and freely soluble in 3N HCl, insoluble in alcohol, acetone, chloroform and ether. Levodopa (USP) is a white to off white crystalline powder. It is slightly soluble in water, freely soluble in 3N HCl, and insoluble in alcohol. The proposed source for both Carbidopa and Levodopa is

The orally disintegrating Carbidopa and Levodopa tablets (PARCOPA®), are available in 3 strengths: 25 mg/100 mg, 10 mg/100 mg, and 25 mg/250 mg. The 25/250 mg and the 10 mg/100 mg strength are dose proportional to the 25 mg/250 mg strength. The 25 mg/100 mg strength is not dose proportional. The 25 mg/250 mg strength was used for the bioequivalence lot, a waiver was requested for the other 2 strengths.

Carbidopa-Levodopa Orally Disintegrating Tablets are manufactured using a



The drug products are supplied in HDPE bottles of 100 tablets with screw cap and blister packages. The proposed expiration dating period is 24 months.



Executive Summary Section

Currently, there is no USP monograph for Carbidopa/Levodopa Orally Disintegrating Tablets. A USP monograph, does exist, however for the immediate release tablets, which the firm utilizes as a reference point for their analytical methods development

**B. Description of How the Drug Product is Intended to be Used**

Carbidoap/Levodopa Orally Disntegrating Tablets are indicated for the treatment of Parkinsons Disease.

**C. Basis for Approvability or Not-Approval Recommendation**

The ANDA is not recommended for approval due to minor deficiencies. There are minor issues regarding drug substance specifications, in-process and release testing specifications, manufacturing and processing, laboratory controls, and stability.

APPEARS THIS WAY  
ON ORIGINAL

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1



# CHEMISTRY REVIEW



## Chemistry Assessment Section

cc: ANDA 76-699  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/KBernard 9/5/03 *K Bernard 9/9/03*  
HFD-640/BArnwine/9/5/03 *(B) Arnwine 9/10/03*  
HFD-617/NPark/9/4/03 *N Park 9/12/03*

F/T by: EW 9/8/03

V:\Firmsnz\schwarzpharma\Ltrs&Rev\76-699c1

**TYPE OF LETTER: NOT APPROVABLE – MINOR AMENDMENT**

**APPEARS THIS WAY  
ON ORIGINAL**



## **ANDA 76-699**

**Carbidopa and Levodopa Orally Disintegrating Tablets  
10 mg/100 mg, 25 mg/100mg, and 25mg/250 mg**

**Schwarz Pharma, Inc.**

**Karen Bernard, Ph.D.  
Office of Generic Drugs/Division of Chemistry II**



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**Chemistry Assessment** ..... 9

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**APPEARS THIS WAY  
ON ORIGINAL**



# Chemistry Review Data Sheet

1. ANDA: #76-699
2. REVIEW #: 2
3. REVIEW DATE: 4/30/04
4. REVIEWER: Karen A. Bernard, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	March 28, 2003
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 002	March 8, 2004
Amendment 001	April 15, 2004
7. NAME & ADDRESS OF APPLICANT:

Name: Schwarz Pharma, Inc  
6140 W.Executive Drive  
Mequon, WI 53092

Representative: Donna K. Multhauf  
Telephone: (262)-238-5171  
Fax: (262)-238-0957
8. DRUG PRODUCT NAME/CODE/TYPE:
  - a) Proprietary Name: PARCOPA®
  - b) Non-Proprietary Name (USAN): Carbidopa-Levodopa ODT
9. LEGAL BASIS FOR SUBMISSION:

The basis for Schwarz Pharma's proposed Carbidopa/Levodopa Orally Disinetgrating Tablets, 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg, is the approved application for SINEMET® Tablets, 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg, NDA #17-555 held by Bristol Myers Squibb. A suitability petition was filed for the change in

## Chemistry Review Data Sheet

dosage form from a tablet to a Orally Disintegrating Tablet. There are no unexpired patents or exclusivities for this product. The firm filed a Paragraph I certification

10. PHARMACOL. CATEGORY: Antiparkinsonian
11. DOSAGE FORM: Orally Disintegrating Tablets
12. STRENGTH/POTENCY: 10 mg/100 mg, 25 mg/100 mg and 25 mg/250 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

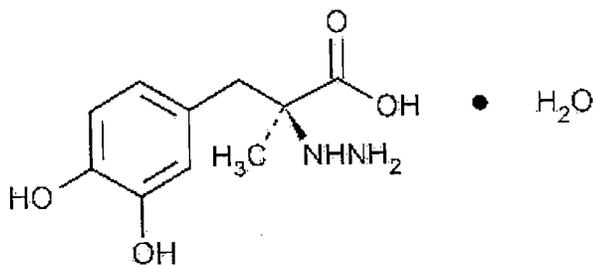
Carbidopa

$C_{10}H_{14}N_2O_4 \cdot H_2O$  244.24

Benzenepropanoic acid,  $\alpha$ -hydrazino-3,4-dihydroxy- $\alpha$ -methyl-, monohydrate, (S)-.

(-)- L- $\alpha$ -Hydrazino-3,4-dihydroxy- $\alpha$ -methylhydrocinnamic acid monohydrate [38821-49-7].

Anhydrous 226.23 [28860-95-9].



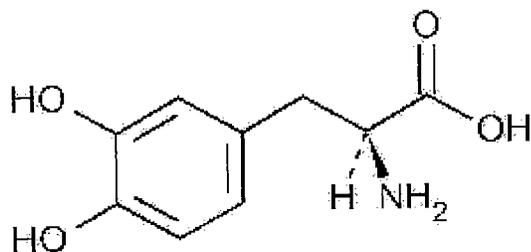
## Chemistry Review Data Sheet

Levodopa

 $C_9H_{11}NO_4$  197.19

L-Tyrosine, 3-hydroxy-

(-)-3-(3,4-Dihydroxyphenyl)- L-alanine [59-92-7].



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
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/	III	/	/	4			
/	III	/	/	4			
/	III	/	/	4			
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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	8/25/03	
Methods Validation	NA-Discontinued program		
Labeling	Deficient	8/8/03	
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

**APPEARS THIS WAY  
ON ORIGINAL**

# The Chemistry Review for ANDA 76-699

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Not approvable – The firm will be requested to address some minor deficiencies identified in the review.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Carbidopa (Benzenepropanoic acid, alpha-methyl, monohydrate (S)) is a potent inhibitor of dopa-decarboxylase. Levodopa (3-Hydroxy-L-tyrosine) is an Antiparkinsonian in combination with Levodopa.

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Carbidopa-Levodopa Orally Disintegrating Tablets are manufactured using a



The drug products are supplied in HDPE bottles of 100 tablets with screw cap and blister packages. The proposed expiration dating period is 24 months.



## Executive Summary Section

Currently, there is no USP monograph for Carbidopa/Levodopa Orally Disintegrating Tablets. A USP monograph, does exist, however for the immediate release tablets, which the firm utilizes as a reference point for their analytical methods development

**B. Description of How the Drug Product is Intended to be Used**

Carbidopa/Levodopa Orally Disintegrating Tablets are indicated for the treatment of Parkinsons Disease.

**C. Basis for Approvability or Not-Approval Recommendation**

The ANDA is not recommended for approval due to minor deficiencies. There are minor issues regarding in-process control, release testing specifications, manufacturing clarification, laboratory controls, and stability.

**APPEARS THIS WAY  
ON ORIGINAL**

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

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# CHEMISTRY REVIEW



## Chemistry Assessment Section

cc: ANDA 76-699  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/KBernard 5/3/04

HFD-640/BArnwine/5/10/04

HFD-617/NPark/5/10/04

F/T by: EW 5/10/04

V:\Firmsnz\schwarzpharma\Ltrs&Rev\76-699c2

**TYPE OF LETTER:** NOT APPROVABLE – MINOR AMENDMENT

**APPEARS THIS WAY  
ON ORIGINAL**



# CHEMISTRY REVIEW



Chemistry Assessment Section

**APPEARS THIS WAY  
ON ORIGINAL**

## ANDA 76-699

**Carbidopa and Levodopa Orally Disintegrating Tablets  
10 mg/100 mg, 25 mg/100mg, and 25mg/250 mg**

**Schwarz Pharma, Inc.**

**Karen Bernard, Ph.D.  
Office of Generic Drugs/Division of Chemistry II**

(37) 8/24/04

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C. Basis for Approvability or Not-Approval Recommendation .....	8
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B. Endorsement Block .....	
C. CC Block.....	
<b>Chemistry Assessment .....</b>	<b>9</b>
III. List Of Deficiencies To Be Communicated.....	

**APPEARS THIS WAY  
ON ORIGINAL**



# Chemistry Review Data Sheet

1. ANDA: #76-699
2. REVIEW #: 3
3. REVIEW DATE: 7/29/04
4. REVIEWER: Karen A. Bernard, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	March 28, 2003
Amendment 002	March 8, 2004
Amendment 0001	April 15, 2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 003	June 4, 2004
Amendment 004	July 12, 2004
Amendment	August 24, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Schwarz Pharma, Inc  
6140 W.Executive Drive  
Mequon, WI 53092

Representative: Donna K. Multhauf  
Telephone: (262)-238-5171  
Fax: (262)-238-0957

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: PARCOPA®
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## Chemistry Review Data Sheet

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14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Carbidopa

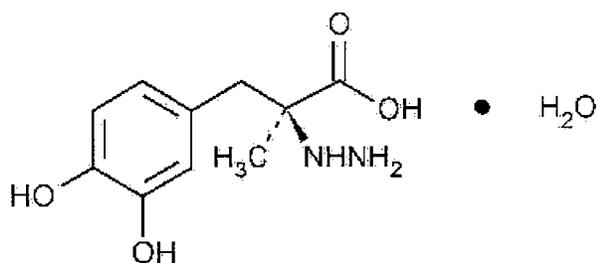
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Anhydrous 226.23 [28860-95-9].

## Chemistry Review Data Sheet

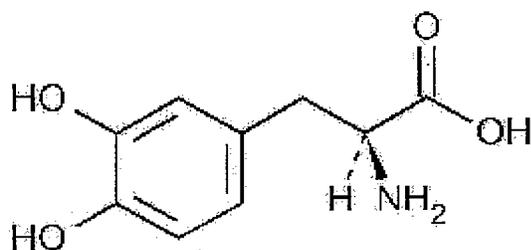


Levodopa

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L-Tyrosine, 3-hydroxy-.

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## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

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	II			3	adequate	3/26/04	DM
	III			4			
	III			4			
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	III			4			
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<sup>1</sup> Action codes for DMF Table:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

1 – DMF Reviewed.

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Methods Validation	NA-Discontinued program		
Labeling	Adequate	7/9/04	K.Lee
Bioequivalence	Acceptable	7/28/04	
EA	N/A		
Radiopharmaceutical	N/A		

### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

**APPEARS THIS WAY  
ON ORIGINAL**

# The Chemistry Review for ANDA 76-699

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Approval – The firm has addressed all minor deficiencies identified in the review.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

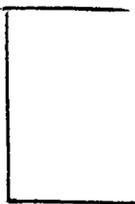
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This has been revised.

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## CHEMISTRY REVIEW



### Executive Summary Section

**B. Description of How the Drug Product is Intended to be Used**

Carbidopa/Levodopa Orally Disintegrating Tablets are indicated for the treatment of Parkinsons Disease.

**C. Basis for Approvability or Not-Approval Recommendation**

The ANDA is recommended for approval. All minor issues regarding in-process control, release testing specifications, manufacturing clarification, laboratory controls, and stability have been addressed satisfactorily.

**APPEARS THIS WAY  
ON ORIGINAL**

Redacted 27 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

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**33. ESTABLISHMENT INSPECTION**

Acceptable 8/25/03

**34. BIOEQUIVALENCE**

Acceptable. See Bio review dated 7/28/04

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

The firm requests a categorical exclusion from the requirement of an Environmental Assessment Statement or Environmental Impact Statement in accord with 21 CFR 25.31(a). This is on page 310 (Vol. 1.7).

**APPEARS THIS WAY  
ON ORIGINAL**



# CHEMISTRY REVIEW



## Chemistry Assessment Section

cc: ANDA 76-699  
ANDA DUP  
DIV FILE  
Field Copy

### Endorsements (Draft and Final with Dates):

HFD-640/KBernard 7/30/04

HFD-640/BArnwine/8/10/04

HFD-617/NPark/

F/T by: rad8/11/04

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*KBernard 8/12/04, 8/24/04*  
*B Arnwine 8/25/04*

**TYPE OF LETTER: APPROVAL**

**APPEARS THIS WAY  
ON ORIGINAL**