

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 76-699**

**BIOEQUIVALENCE REVIEW(S)**

---



---

**DIVISION OF BIOEQUIVALENCE REVIEW**


---



---

**ANDA No.** 76-699  
**Drug Product Name** Carbidopa and Levodopa Orally Disintegrating Tablets  
**Strength** 10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg  
**Applicant Name** Schwarz Pharma, Inc.  
**Address** 6140 W. Executive Drive, Mequon, WI 53092  
**Submission Date(s)** March 28, 2003  
**Amendment Date(s)** NA  
**Reviewer** James E. Chaney  
**First Generic** Yes  
**File Location** V:\firmsnz\schwarzpharma\ltrs&rev\76699n0303

---



---

**I. Executive Summary**

This ANDA for Carbidopa and Levodopa Orally Disintegrating Tablets, 10 mg/100 mg, 25 mg/100 mg and 25 mg/250 mg is based on a suitability petition (Docket #02P-0033/CP1) filed on 1/18/02 and approved on 9/25/02. The suitability petition requested a dosage form change from immediate release tablets to orally disintegrating tablets. The submission includes: 1) a fasting BE study on the 25 mg/250 mg strength with measurement of parent carbidopa and levodopa, 2) comparative dissolution data on all strengths and 3) waiver requests for the lower strengths. The BE study is a replicated 4-way crossover study (ABAB and BABA sequences) using 48 normal healthy subjects (28 males and 20 females) each of which was administered carbidopa/levodopa 25 mg/250 mg. The results (point estimate and 90% CI) of the BE study for carbidopa are LAUC<sub>t</sub> of 0.899, 84.7-95.4%; LAUC<sub>i</sub> of 0.903, 85.2-95.6%; and LC<sub>max</sub> of 0.884, 82.4-94.8%. The results (point estimate and 90% CI) for Levodopa are LAUC<sub>t</sub> of 0.959, 93.5-98.3%; LAUC<sub>i</sub> of 0.958, 93.5-98.2%; and LC<sub>max</sub> of 0.965, 91.2-102.1%. The biostudy is incomplete due to analytical deficiencies. The dissolution testing is incomplete. The FDA recommended dissolution method was not used. The firm used apparatus 2 (paddle) at 50 rpm in 750 mL of 0.1N HCl. DBE recommends dissolution testing using USP apparatus 1 (basket) at 50 rpm in 750 mL of 0.1N HCl and additional methodology to optimize the dissolution testing for this dosage form. The application is incomplete.

**II. Table of Contents**

I. Executive Summary.....	1
II. Table of Contents.....	1
III. Submission Summary.....	2
A. Drug Product Information.....	2
B. PK/PD Information.....	2
C. Contents of Submission.....	4
D. Pre-Study Bioanalytical Method Validation.....	4
E. In Vivo Studies.....	5
1. Single-dose Fasting Bioequivalence Study.....	5
F. Formulation.....	6
G. In Vitro Dissolution.....	6
H. Waiver Request(s).....	7
I. Deficiency Comments.....	7

J. Recommendations .....	8
IV. Appendix .....	10
A. Individual Study Reviews.....	10
1. Single-dose Fasting Bioequivalence Study .....	10
a) Study Design .....	10
b) Clinical Results .....	12
c) Bioanalytical Results.....	15
d) Pharmacokinetic Results .....	16
B. Formulation Data.....	25
C. Dissolution Data.....	26
D. Consult Reviews.....	27
E. SAS Output.....	28
F. Additional Attachments.....	40

### III. Submission Summary

#### A. Drug Product Information

<b>Test Product</b>	Carbidopa and Levodopa Orally Disintegrating Tablets 10 mg/100 mg, 25 mg/100 mg and 25 mg/250 mg
<b>Reference Product</b>	Sinemet <sup>®</sup> (carbidopa and levodopa) Tablets, 10 mg/100 mg, 25 mg/100 mg and 25 mg/250 mg, Bristol Myers Squibb
<b>RLD Manufacturer</b>	Merck & Co., Inc. (as noted in submitted reference labeling)
<b>NDA No.</b>	17-555
<b>RLD Approval Date</b>	3/13/80
<b>Indication</b>	Sinemet <sup>®</sup> is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication.

#### B. PK/PD Information

<b>Bioavailability</b>	Carbidopa and levodopa each have about 99% bioavailability.
<b>Food Effect</b>	Sinemet <sup>®</sup> labeling does not make any statements about the effect of food on the drug absorption.
<b>T<sub>max</sub></b>	1 hour for levodopa and 2 hours for carbidopa.
<b>Metabolism</b>	When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system. Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain.
<b>Excretion</b>	Carbidopa and levodopa are eliminated renally as dopamine metabolites and small amounts of unchanged drug.
<b>Half-life</b>	1.5 hours for levodopa and 2 hours for carbidopa

**Relevant OGD or  
DBE History**

The following approved ANDAs are in the Orange Book for immediate release carbidopa/levodopa tablets:

- Teva's ANDAs 73-618, 73-589 and 73-607 for the 10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg strengths, respectively
- Sandoz's ANDAs 73-586, 73-587 and 73-620 for the 10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg strengths, respectively
- Purepac's ANDA 74-260 for the 10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 strengths.

Additionally, DBE has reviewed the following submissions on carbidopa/levodopa:

- Protocol - \_\_\_\_\_ for conducting a biostudy on orally disintegrating tablets
- Control - Ranbaxy (01-404) seeking bioequivalence recommendations on its proposed tablets for oral suspension
- ANDA - Ranbaxy (76-643) on its tablets for oral suspension 10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg strengths (found acceptable by DBE).

For documentation of bioequivalence for 10 mg/100 mg, 25/100 mg and 25 mg/250 mg carbidopa/levodopa immediate release tablets, orally disintegrating tablets and tablets for oral suspension DBE has recommended:

- A fasting bioequivalence study on the 25 mg/250 mg against Sinemet<sup>®</sup> to establish bioequivalence based on plasma levels of carbidopa and levodopa with measurement of the parent drugs only
- Biowaivers for the generic carbidopa and levodopa Tablets, 10 mg/100 mg and 25/100 mg, may be considered if the following conditions are met: 1) results of the fasting bioequivalence study conducted on the 25 mg/250 mg tablet are acceptable, 2) comparative dissolution testing conducted on the three strengths of the generic carbidopa/levodopa tablets is acceptable and 3) formulations among the three strengths of generic tablets are proportionally similar.

**Agency Guidance  
Drug Specific  
Issues (if any)**

None  
NA

**APPEARS THIS WAY  
ON ORIGINAL**

### C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	Yes	3*
Waiver requests	Yes	2
BCS Waivers	No	--
Vasoconstrictor Studies	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

\*Dissolution testing was conducted in 0.1N HCl on the three strengths using the paddle apparatus at 50 rpm. Also, the firm attempted testing in pH 4.5 acetate buffer and pH 6.8 phosphate and found decomposition problems at these higher pHs.

### D. Pre-Study Bioanalytical Method Validation

Analyte name	Carbidopa	Levodopa
Internal Standard	3,4-Dihydroxybenzylamine	3,4-Dihydroxybenzylamine
Method description	HPLC with Fluorescence Detection	HPLC with Fluorescence Detection
QC range	10.23 to 409.39 ng/mL	25.65 to 2154.60 ng/mL
Standard curve range	4.30 to 537.2 ng/mL	10.46 to 3033.40 ng/mL
Limit of quantitation	4.30 ng/mL	10.46 ng/mL
Average recovery of Drug (%)	Low QC: 67.8 High QC: 51.5	Low QC: 80.6 High QC: 67.8
Average Recovery of Int. Std (%)	79.3	79.3
QC Intraday precision range (%)	5.5 to 11.0	2.7 to 5.1
QC Intraday accuracy range (%)	99.1 to 103.1	98.7 to 104.8
QC Interday precision range (%)	5.2 to 8.7	2.4 to 5.4
QC Interday accuracy range (%)	97.7 to 98.3	96.8 to 100.7
Bench-top stability (hrs)	13.7 hours in cold water	13.7 hours in cold water
Stock stability (days)	270 days at -80°C	206 days at -80°C
Processed stability (hrs)	131.6 hrs at 4°C	131.6 hrs at 4°C
Freeze-thaw stability (cycles)	4 cycles at -80°C	5 cycles at -80°C
Long-term storage stability (days)	154 days at -80°C	154 days at -80°C
Dilution integrity	Dilution of 993.44 ng/mL by 10X gave 111.6 % accuracy. Meets firm's acceptance criteria.	Dilution of 9964 ng/mL by 10X gave 85.4 & 116.1 % accuracy. Meets firm's acceptance criteria.
Specificity	None of the 20 blank plasma lots evaluated showed significant interference with analyte or internal standard.	None of the 20 blank plasma lots evaluated showed significant interference with analyte or internal standard.
SOPs submitted	No SOPs were submitted, only a list. No effective dates were included. See Section IV.F (Additional Attachments of Appendix) on page 40.	
Bioanalytical method is acceptable	Incomplete	Incomplete
20% Validation Chromatograms included (Y/N)	No	No
Random or Serial Selection of Chrom	NA	NA

## E. In Vivo Studies

### 1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	
Study Design	Single-dose, randomized, open-label, 2-treatment, 2-sequence (ABAB & BABA), 4-period, replicate design.
No. of subjects enrolled	A total of 50 subjects, 29 males and 21 females, were enrolled in the study.
No. of subjects completing	Forty-nine (49) subjects, 29 males and 20 females, completed the study.
No. of subjects analyzed	49
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 29      Female: 20
Test product	Carbidopa and Levodopa Orally Disintegrating Tablets
Reference product	Sinemet <sup>®</sup> Tablets
Strength tested	25 mg/250 mg Carbidopa/Levodopa
Dose	25 mg/250 mg Carbidopa/Levodopa

Summary of Statistical Analysis, Fasting Bioequivalence Study		
Parameter	Point Estimate	90% Confidence Interval
<b>Carbidopa</b>		
AUC <sub>0-t</sub>	0.899	84.7-95.4
AUC <sub>∞</sub>	0.903	85.2-95.6
C <sub>max</sub>	0.884	82.4-94.8
<b>Levodopa</b>		
AUC <sub>0-t</sub>	0.959	93.5-98.3
AUC <sub>∞</sub>	0.958	93.5-98.2
C <sub>max</sub>	0.965	91.2-102.1

Analysis was conducted on 2547 samples for carbidopa and levodopa.

The firm listed the following reporting codes: B for sample lost in processing, C for poor chromatography, D for anomalous sample values, F for above the curve limit, and G for highest standard missing or lowest standard missing. However, it did not submit a listing of the repeat and original assay values of any repeat assays.

**Did use of recalculated plasma concentration data change study outcome?** NA. The firm did not indicate if its reported data consisted of data obtained from repeat analyses. The firm will be advised to submit a complete tabular summary on its repeat assays if any, including (1) the reason(s) for re-assay, (2) the original and re-assayed values of the involved samples, (3) identification of which value was selected for PK analysis and (4) the associated subjects,

treatments, and sampling times. It will be requested to submit copies of SOPs (including effective dates) for its repeat assays.

## F. Formulation

<b>Location in appendix</b>	Section IV.B, Page 25
<b>Are inactive ingredients within IIG limits?</b>	Yes
<b>If no, list ingredients outside of limits</b>	NA
<b>If a tablet, is the product scored?</b>	Yes
<b>If yes, which strengths are scored?</b>	10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg
<b>Is scoring of RLD the same as test?</b>	Yes
<b>Is the formulation acceptable?</b>	Yes
<b>If not acceptable, why?</b>	NA

## G. In Vitro Dissolution

<b>Source of Method (USP, FDA or Firm)</b>	Firm
<b>Medium</b>	The selected medium was 0.1N HCl. Also, the firm attempted testing in pH 4.5 acetate buffer and pH 6.8 phosphate and found decomposition problems at these higher pHs.
<b>Volume (mL)</b>	750 mL
<b>USP Apparatus type</b>	2 (paddle)
<b>Rotation (rpm)</b>	50
<b>Firm's proposed specifications</b>	Same as USP specifications for RLD: Not less than 80% (Q) of the labeled amounts of carbidopa and levodopa are dissolved in 30 minutes.
<b>FDA-recommended specifications</b>	N/A
<b>F2 metric calculated?</b>	Yes
<b>If no, reason why F2 not calculated</b>	Firm reported $f_2$ results but the information is of limited value in that both carbidopa and levodopa dissolve too rapidly. For the lower strengths of test and reference —% or more of each active ingredient in all strengths is dissolved by 5 minutes (2 <sup>nd</sup> time point. For the reference product —% or more of each active ingredient in the lower strengths is dissolved by 5 minutes. The highest strength of the reference shows —% & —% dissolution for levodopa & carbidopa, respectively.
<b>Is method acceptable?</b>	No.
<b>If not then why?</b>	The firm used apparatus 2 (paddle). For the RLD (a USP product) the FDA recommended using 750 mL of 0.1N HCl with USP apparatus 1 (basket) at 50 rpm.

### Dissolution History from Previous Applications

- There is a USP method for *in vitro* dissolution testing of immediate-release carbidopa/levodopa tablets (RLD) but there is no compendial method for the orally disintegrating tablets. The USP recommends use of 750 mL of 0.1N HCl and the basket apparatus at 50 rpm with a dissolution specification of NLT 80% (Q) within 30 minutes for both carbidopa and levodopa.
- In a review of correspondence from \_\_\_\_\_, on its proposed carbidopa/levodopa tablets for oral suspension, 10 mg/100 mg, 25 mg/100 mg and 25 mg/250 mg, DBE recommended that since this was a new dosage form the firm should develop an optimal dissolution method for conducting the dissolution testing.
- For Ranbaxy Laboratories' ANDA 76-643 on carbidopa and levodopa tablets for oral suspension DBE found Ranbaxy's use of the USP method and specifications for the RLD acceptable.
- For the orally disintegrating tablet dosage form \_\_\_\_\_, was advised in Protocol letter \_\_\_\_\_ as follows: "Since this is a new dosage form, the DBE recommends that you develop an optimal dissolution method. The comparative *in vitro* dissolution testing should be conducted on 12 dosage units of all strengths of the test and reference products."

### H. Waiver Request(s)

Strengths for which waivers are requested	10 mg/100 mg and 25 mg/100 mg
Regulation cited	21 CFR 320.22
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No. Firm did not use the FDA recommended apparatus 1
Waivers granted?	No
If not then why?	Incomplete dissolution testing

### I. Deficiency Comments

1. The dissolution testing is incomplete. The firm did not use the FDA dissolution testing method. The firm used apparatus 2 (paddle) at 50 rpm in 750 mL of 0.1N HCl. The firm should be advised to conduct comparative dissolution testing on all strengths in 750 mL of 0.1 N HCl at 37°C using USP apparatus 1 (basket) at 25 rpm and 50 rpm. Also, it should conduct the comparative dissolution testing on all strengths in 750 mL of 0.1 N HCl at 37°C using USP apparatus 2 (paddle) at 25 rpm. The recommended sampling times are 2.5, 5, 10 and 30 minutes.
2. The report on sample assays is incomplete. The firm submitted a listing of SOPs used in its analytical work, but none of them contained effective dates and none addressed repeat assays. A complete list of all SOPs used in the study including those that describe objective criteria for identifying and re-assaying samples believed to have anomalous pharmacokinetic results should be submitted. The submission should include the dates

on which all SOPs were implemented. Actual copies of SOPs for repeat assays should be submitted.

3. The firm should submit a complete tabular summary on its repeat assays if any, including (1) the reason(s) for re-assay, (2) the original and re-assayed values of the involved samples, (3) identification of which value was selected for PK analysis and (4) the associated subjects, treatments, and sampling times.
4. The firm did not submit 20% of serially selected chromatograms. It should be advised to submit them and refer to the Guidance for Industry Bioanalytical Method Validation issued in May 2001.

#### **J. Recommendations**

1. The single-dose, fasting bioequivalence study conducted by Schwarz Pharma, Inc. on its carbidopa and levodopa orally disintegrating tablets 25 mg/250 mg, lot # 920238, comparing them to Bristol Myers Squibb's Sinemet® Tablets, 25 mg/250 mg, lot K5015 has been found incomplete by the Division of Bioequivalence per Deficiencies Comments 2-4.
2. The dissolution testing is incomplete. The firm should be advised to conduct comparative dissolution testing on all strengths in 750 mL of 0.1 N HCl at 37°C using USP apparatus 1 (basket) at 25 rpm and 50 rpm. Also, it should conduct additional comparative dissolution testing on all strengths in 750 mL of 0.1 N HCl at 37°C using USP apparatus 2 (paddle) at 25 rpm. Recommended sampling times are 2.5, 5, 10 and 30 minutes.
3. The formulations of the 10 mg/100 mg and 25 mg/100 mg carbidopa and levodopa orally disintegrating tablets are proportionally similar to that of the 25 mg/250 mg carbidopa and levodopa disintegrating tablets of the test product. The waivers of *in vivo* bioequivalence study requirements for the 10 mg/100 mg and 25 mg/100 mg tablets of the test product are pending an acceptable fasted bioequivalence study on the 25 mg/250 strength and acceptable dissolution testing on all three strengths.
4. From the bioequivalence point of view the application is incomplete.

The firm should be informed of the above recommendations.

*James E. Chaney* 4/29/2004

James E. Chaney, Review Branch 1, Date signed

*Yih-Chain Huang* 4/29/2004

Yih-Chain Huang, Review Branch 1, Date signed

*Barbara M Davitt* 4/29/04

*for*

Dale P. Conner, Pharm. D.  
Director, Division of Bioequivalence  
Office of Generic Drugs

<b>ANDA No.</b>	76-699
<b>Drug Product Name</b>	Carbidopa and Levodopa Orally Disintegrating Tablets
<b>Strength</b>	10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg
<b>Applicant Name</b>	Schwarz Pharma, Inc.

**APPEARS THIS WAY  
ON ORIGINAL**

## IV. Appendix

## A. Individual Study Reviews

## 1. Single-dose Fasting Bioequivalence Study

## a) Study Design

Study Information	
Study Number	AA03139
Study Title	A Pharmacokinetic Study to Compare the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT), of Carbidopa 25 mg/Levodopa 250 mg to a Marketed Immediate Release Carbidopa 25 mg/Levodopa 250 mg Formulation (Reference), Sinemet <sup>®</sup> , DuPont Pharmaceuticals, Inc.
Clinical Site	[ ]
Principal Investigator	[ ]
Study/Dosing Dates	Group 1 (Subject #s 1-25) Period 1, 11/9/02; Period 2, 11/16/02; Period 3, 11/23/02; Period 4, 11/30/02 Group 2 (Subject #s 26-50) Period 1, 11/10/02; Period 2, 11/17/02; Period 3, 11/24/02; Period 4, 12/1/02
Analytical Site	[ ]
Analytical Director	[ ]
Analysis Dates	Extracted 12/16/02 - 1/17/03
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	The maximum time samples were stored frozen (-80°C) from the first day of collection (11/9/02) to the last day of analysis (1/17/03) was 68 days. The validated frozen plasma stability for carbidopa and levodopa was 154 days at -80°C.

<b>Treatment ID</b>	A	B
<b>Test or Reference</b>	Test	Reference
<b>Product Name</b>	Carbidopa 25 mg/Levodopa 250 mg	Sinemet® (Immediate Release Carbidopa 25 mg/Levodopa 250 mg tablet)
<b>Manufacturer</b>	CIMA LABS, INC.	Merck & Co., Inc.
<b>Batch/Lot No.</b>	920238	K5015
<b>Manufacture Date</b>	July 2002	--
<b>Expiration Date</b>	July 2004	April 2004
<b>Strength</b>	25 mg/250 mg	25 mg/250 mg
<b>Dosage Form</b>	Orally Disintegrating Tablet	Tablet
<b>Batch Size</b>	[ ]	--
<b>Production Batch Size</b>	[ ]	--
<b>Potency</b>	Carbidopa, 98.1% Levodopa, 97.9%	Carbidopa, 98.4% Levodopa, 99.0%
<b>Content Uniformity (mean, % CV)</b>	Carbidopa, 98.4, 1.3%CV Levodopa, 99.0, 1.3%CV	Carbidopa, Not submitted Levodopa, Not submitted
<b>Formulation</b>	See Appendix Section B	
<b>Dose Administered</b>	25 mg/250 mg	25 mg/250 mg
<b>Route of Administration</b>	Oral. One tablet was placed on the tongue. After total tablet disintegration 240 mL of water was administered.	Oral. One tablet was taken with 240 mL of water.

<b>No. of Sequences</b>	2
<b>No. of Periods</b>	4
<b>No. of Treatments</b>	2 (Test Replicates 1 & 2, Reference Replicates 1 & 2)
<b>No. of Groups</b>	Dosed as two groups. The firm combined the two groups in its reported statistical analysis. (See "Comments on Group Analysis" at the end of in Section IV.A.1.d).
<b>Washout Period</b>	7 days
<b>Randomization Scheme</b>	<p><b>SEPARATE GROUPS</b></p> <p>GRP1 ABAB: 1, 3, 5, 8, 9, 11, 13, 15, 18, 20, 22, 23, 25</p> <p>GRP1 BABA: 2, 4, 6, 7, 10, 12, 14, 16, 17, 19, 21, 24</p> <p>GRP2 ABAB: 27, 30, 32, 34, 36, 37, 39, 41, 44, 46, 47, 50</p> <p>GRP2 BABA: 26, 28, 29, 31, 33, 35, 38, 40, 42, 43, 45, 48, 49</p> <p><b>GROUPS COMBINED</b></p> <p>ABAB: 1, 3, 5, 8, 9, 11, 13, 15, 18, 20, 22, 23, 25, 27, 30, 32, 34, 36, 37, 39, 41, 44, 46, 47, 50</p> <p>BABA: 2, 4, 6, 7, 10, 12, 14, 16, 17, 19, 21, 24, 26, 28, 29, 31, 33, 35, 38, 40, 42, 43, 45, 48, 49</p>

<b>Blood Sampling Times</b>	0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 4, 6, 8, 10 & 12 hours
<b>Blood Volume Collected/Sample</b>	A total of 52 blood samples (520 mL) were drawn during the study for drug analysis.
<b>Blood Sample Processing/Storage</b>	Samples were collected in pre-chilled tubes, processed under yellow lighting, and placed in an ice bath. Plasma samples were separated by centrifugation, frozen at -70°, packed in dry ice & sent to the analytical site.
<b>IRB Approval</b>	Yes
<b>Informed Consent</b>	Yes
<b>Subjects Demographics</b>	See Table 1
<b>Length of Fasting</b>	10 hours
<b>Length of Confinement</b>	About 24 hours (about 12 hours before dosing until just after the 12 hours post-dose blood sample collection)
<b>Safety Monitoring</b>	Sitting vital signs (blood pressure and pulse) were assessed each morning prior to dosing. A clinical laboratory evaluation (hematology, serum chemistries, and urinalysis), a brief physical examination (including vital signs), and 12-lead electrocardiograms were performed at the completion of the study. Subjects were instructed to inform the study physician and/or nurses of any adverse events that occurred during the study.

### Comments on Study Design:

The study design is acceptable.

### b) Clinical Results

**Table 1 Demographics of Study Subjects Enrolled**

Age		Weight (lbs)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	88
Mean	31.9	Mean	163.7	18-40	74	Male	58	Afr. Amer.	2
SD	10	SD	26	41-64	26	Female	42	Hispanic	10
Range	19-49	Range	123-229	65-75	0			Asian	0
				>75	0			Others	0

<b>Demographics Table Continued</b>									
<b>Table 1b. Group 1 (N=25)</b>									
Age		Weight (lbs)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	96
Mean	33.6	Mean	169.0	18-40	68	Male	60	Afr. Amer.	4
SD	11	SD	28.6	41-64	32	Female	40	Hispanic	0
Range	19-49	Range	124-229	65-75	0			Asian	0
				>75	0			Others	0

<b>Table 1c. Group 2 (N=25)</b>									
Age		Weight (lbs)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	80
Mean	30.2	Mean	158.3	18-40	80	Male	56	Afr. Amer.	0
SD	9	SD	22	41-64	20	Female	44	Hispanic	20
Range	19-49	Range	123-202	65-75	0			Asian	0
				>75	0			Others	0

**Table 2 Dropout Information**

Subject No	Reason	Period	Replaced?
36	Subject withdrew due to adverse events & conflict with work.	1	No

**Table 3 Study Adverse Events**

Adverse Event Description	# in Test Group	# in Ref. Group
Aphthae	1	0
Bites on inside right cheek	1	0
Clammy	3	0
Diaphoresis	1	0
Dizzy	3	4
Drowsy	1	2
Dry heaves	1	1
Elevated ALT	1	0
Elevated calcium in blood	1	0
Elevated glucose in blood	3	2
Elevated glucose in urine	1	0
Elevated leukocyte esterase	3	1
Elevated PLT	0	1
Elevated WBC in urine	1	2
Feels hot	0	4

Feels warm	1	2
Headache	15	13
Hot feeling	0	1
Lightheaded	6	10
Low HCT	0	2
Low HGB	0	1
Nausea	17	31
Pale	1	0
Petechiae across soft palate	1	0
Petechiae inside cheeks	1	5
Pressure in head	1	1
Tired	1	1
Vomited	9	20
Weak	0	1
<b>Total</b>	<b>74</b>	<b>105</b>

**Table 4 Protocol Deviations**

Type	Subject #s (Test)	Subject #s (Reference)
According to the protocol, 1.2 mL plasma was to be added to a transfer tube already containing 0.025 mL preservative. On Day 1, Period 1 (Treatment B), at the 1.67-hour time-point, all of the plasma was added to a transfer tube containing 0.025 mL preservative. Preservative (0.050 mL) was then added to compensate for the approximate 3:3 ratio. The sample was then divided into 3 aliquots.		14
All blood samples were to be collected and processed under yellow lights. The samples for the 8-hour time point during Period 3 were taken to the wrong processing room and sat under white lights for 15 minutes	7, 14-25	7, 14-25
At least 2 to 3 aliquots were to be obtained from blood processing. Only 1 aliquot was obtained at the 0.33-hour time point during Period 2 (Treatment B for both subjects) because of a processing error.		27, 32
On Day I, Period 1 (Treatment B), the predose blood draw sample was lost during processing because of a processing error.		43
All females were to provide a blood sample for serum pregnancy testing (4 mL). Also, according to the protocol, at check-in for Periods 2, 3, and 4, all subjects were to provide a blood sample for determination of hemoglobin and hematocrit (4 mL). At Period 2 check-in, all subjects provided a total of 8 mL of blood each; therefore, all males provided an extra 4 mL of blood.	3, 6, 8, 9, 10, 13, 14, 15, 16, 18, 19, 22, 23, 24, 25, 26, 28, 30, 34, 37, 38, 39, 40, 42,45, 46, 48, 49, 50	3, 6, 8, 9, 10, 13, 14, 15, 16, 18, 19, 22, 23, 24, 25, 26, 28, 30, 34, 37, 38, 39, 40, 42,45, 46, 48, 49, 50

**Comments on Dropouts/Adverse Events/Protocol Deviations:**

There were no serious adverse events.

The dropout, adverse events and protocol deviations did not compromise the integrity of the study.

## c) Bioanalytical Results

**Table 5 Assay Quality Control – Within Study**

	<b>Carbidopa</b>	<b>Levodopa</b>
<b>QC Concentrations (ng/mL)</b>	10.23, 204.7, 409.39	25.65, 820.80, 2154.60
<b>Interday Precision (% CV)</b>	10.0, 6.7, 8.2	6.2, 4.7, 5.9
<b>Interday % Accuracy</b>	97.1, 97.3, 98.8	99.0, 100.3, 101.0
<b>Calibration Standards (ng/mL)</b>	4.30 – 537.21	10.46 – 3033.40
<b>Interday Precision (% CV)</b>	4.7 – 7.9	3.3 - 5.4
<b>Interday % Accuracy</b>	95.6-103.1	97.2 - 102.7
<b>Linearity Range (range of r<sup>2</sup>)</b>	0.9908 - 0.9998	0.9917 - 0.9999
<b>Linearity Range (ng/mL)</b>	4.30 – 537.21	10.46 – 3033.40

**Comments on Study Assay Quality Control:**

<b>Any interfering peaks in chromatograms?</b>	NA. Chromatographs were not submitted for evaluation.
<b>Were 20% of chromatograms included?</b>	No
<b>Were chromatograms serially or randomly selected?</b>	NA

**Comments on Chromatograms:**

NA. Chromatographs were not submitted for evaluation.

**Table 6 SOP's dealing with analytical repeats of study samples**

<b>SOP No.</b>	<b>Date of SOP</b>	<b>SOP Title</b>
NA*		

\*The firm did not submit any SOPs on analytical repeats. One is on file at the analytical facility. The firm only submitted a flow sheet summary of the re-assay procedure and acceptance criteria for samples that were reanalyzed for reasons of pharmacokinetic incongruity.

**Table 7 Additional Comments on Repeat Assays**

Were all SOPs followed?	NA*
Did recalculation of plasma concentrations change the study outcome?	NA**
Does the reviewer agree with the outcome of the repeat assays?	NA**
If no, reason for disagreement	NA**

\*The firm did not submit any SOPs on analytical repeats.

\*\*The firm did not indicate that its report included or did not include the results of reanalysis. So, no judgment can be made as to the impact of repeat assays.

### Summary/Conclusions, Study Assays:

The report on sample assays is incomplete. The firm did not submit any SOPs. It did submit a listing of SOPs used in its analytical work, but none of them contained effective dates and none addressed repeat assays. A complete list of all SOPs used in the study including those that describe objective criteria for identifying and re-assaying samples that are believed to exhibit anomalous pharmacokinetic values should be submitted. The submission should include the dates on which all SOPs were implemented. Actual copies of SOPs for repeat assays should be submitted.

#### d) Pharmacokinetic Results

**Table 8 Arithmetic Mean Pharmacokinetic Parameters - Separate Replicates**

(Mean plasma concentrations are presented in Table 11 and Figure 1.)

Parameter	Test (Replicate 1)			Test (Replicate 2)			Reference (Replicate 1)			Reference (Replicate 2)		
	Mean	%CV	N	Mean	%CV	N	Mean	%CV	N	Mean	%CV	N
<b>Carbidopa</b>												
AUC <sub>t</sub> (ng*hr/mL)	543	36	43	547	34	45	591	33	43	643	32	39
AUC <sub>∞</sub> (ng*hr/mL)	572	33	38	577	31	43	622	30	41	662	32	39
C <sub>max</sub> (ng/mL)	108.3	37	43	111.7	35	45	122.6	39	43	128.7	34	39
T <sub>max</sub> (hr.)	2.85	39	43	2.84	37	45	2.79	49	43	2.88	38	39
T <sub>1/2</sub> (hr)	1.78	19	38	1.73	20	43	1.70	21	41	1.69	14	39
Kel (1/hr)	0.401	16	38	0.416	19	43	0.424	19	41	0.417	14	39
<b>Levodopa</b>												
AUC <sub>t</sub> (ng*hr/mL)	4897	27	44	5041	28	46	5244	27	43	5362	28	40
AUC <sub>∞</sub> (ng*hr/mL)	4942	27	43	5082	28	46	5282	27	43	5415	28	39
C <sub>max</sub> (ng/mL)	1965	26	44	1964	30	46	2027	29	43	2071	29	40
T <sub>max</sub> (hr.)	0.90	69	44	1.13	67	46	1.08	71	43	1.28	54	40
T <sub>1/2</sub> (hr)	1.56	22	43	1.44	15	46	1.53	22	43	1.46	16	39
Kel (1/hr)	0.461	18	43	0.491	14	46	0.469	17	43	0.486	14	39

Table 8 Continued. Arithmetic Mean Pharmacokinetic Parameters - Combined Replicates

Parameter	Test (Replicates 1 & 2)		Reference (Replicates 1 & 2)		T/R Ratio
	Mean	% CV	Mean	% CV	
<b>Carbidopa</b>					
AUC <sub>t</sub> (ng*hr/mL)	545	35	616	33	0.89
AUC <sub>∞</sub> (ng*hr/mL)	575	32	642	31	0.90
C <sub>max</sub> (ng/mL)	110.0	36	125.5	37	0.88
T <sub>max</sub> (hr.)	2.84	38	2.83	44	1.00
T <sub>1/2</sub> (hr)	1.75	19	1.69	17	1.03
Kel (1/hr)	0.409	18	0.421	17	0.97
<b>Levodopa</b>					
AUC <sub>t</sub> (ng*hr/mL)	4971	27	5301	27	0.94
AUC <sub>∞</sub> (ng*hr/mL)	5014	27	5345	27	0.94
C <sub>max</sub> (ng/mL)	1964	28	2048	28	0.96
T <sub>max</sub> (hr.)	1.02	69	1.17	62	0.87
T <sub>1/2</sub> (hr)	1.50	20	1.49	20	1.00
Kel (1/hr)	0.476	16	0.477	15	1.00

Table 9 Least Squares Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
<b>Carbidopa</b>				
AUC <sub>0-t</sub>	509.85	567.33	0.899	84.7-95.4
AUC <sub>∞</sub>	550.14	609.53	0.903	85.2-95.6
C <sub>max</sub>	103.05	116.57	0.884	82.4-94.8
<b>Levodopa</b>				
AUC <sub>0-t</sub>	4889.3	5100.5	0.959	93.5-98.3
AUC <sub>∞</sub>	4924.1	5138.1	0.958	93.5-98.2
C <sub>max</sub>	1906.6	1976.1	0.965	91.2-102.1

**Table 10 Additional Study Information**

<b>Carbidopa</b>	
*Root mean square errors, AUC <sub>0-t</sub>	Test, 0.21864; Reference, 0.17909
*Root mean square errors, AUC <sub>∞</sub>	Test, 0.19861; Reference, 0.16949
*Root mean square errors, C <sub>max</sub>	Test, 0.25482; Reference, 0.22543
Variance, AUC <sub>0-t</sub>	Within Test, 0.04902; Within Reference, 0.03169
Variance, AUC <sub>∞</sub>	Within Test, 0.03863; Within Reference, 0.02803
Variance, C <sub>max</sub>	Within Test, 0.06438; Within Reference, 0.05110
Kel and AUC <sub>∞</sub> determined for how many subjects?	Test Replicate #1: N=38 Reference Replicate #1: N=41 Test Replicate #2: N=43 Reference Replicate #2: N=39
Do you agree with firm's decision?	Agree
Indicate number of subjects with following:	
-measurable drug concentrations at 0 hr	Subj #8, Test, 2 <sup>nd</sup> replicate (Per 3) Subj #23, Ref, 2 <sup>nd</sup> replicate (Per 4) Both > 5% of respective C <sub>max</sub> values.
-first measurable concentration as C <sub>max</sub>	None
Were subjects dosed as more than one group?	Yes. See subsequent "Comments on Group Analysis".

\*Calculated by reviewer using the Proc GLM procedure comparing test in replicate 1 with test in replicate 2 and reference in replicate 1 with reference in replicate 2.

**Table 10 Continued**

<b>Levodopa</b>	
*Root mean square errors, AUC <sub>0-t</sub>	Test, 0.10111; Reference, 0.09476
*Root mean square errors, AUC <sub>∞</sub>	Test, 0.09209; Reference, 0.09535
*Root mean square errors, C <sub>max</sub>	Test, 0.18165; Reference, 0.21450
Variance, AUC <sub>0-t</sub>	Within Test, 0.00983; Within Reference, 0.00869
Variance, AUC <sub>∞</sub>	Within Test, 0.00858; Within Reference, 0.00925
Variance, C <sub>max</sub>	Within Test, 0.03305; Within Reference, 0.04627
Kel and AUC <sub>∞</sub> determined for how many subjects?	Test Replicate #1: N=43 Reference Replicate #1: N=43 Test Replicate #2: N=46 Reference Replicate #2: N=39
Do you agree with firm's decision?	Agree
Indicate number of subjects with following:	
-measurable drug concentrations at 0 hr	None
-first measurable concentration as C <sub>max</sub>	None
Were subjects dosed as more than one group?	Yes. See subsequent "Comments on Group Analysis".

\*Calculated by reviewer using the Proc GLM procedure comparing test in replicate 1 with test in replicate 2 and reference in replicate 1 with reference in replicate 2.

**Comments on Pharmacokinetic and Statistical Analysis:**Carbidopa

- The reviewer agrees with the firm's decision not to calculate kel for those subjects reported without the kel results.
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for AUC<sub>t</sub>, AUC<sub>i</sub>, C<sub>max</sub> are within the acceptable limits of 80-125%.

Levodopa

- The reviewer agrees with the firm's decision not to calculate kel for those subjects reported without the kel results.
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for AUC<sub>t</sub>, AUC<sub>i</sub>, C<sub>max</sub> are within the acceptable limits of 80-125%.

Excluded Subjects

Fifty subjects were enrolled in the study. Subject #36 dropped out in the first period due to adverse events & conflict with work.

Some of the remaining 49 subjects who completed the study were excluded from statistical analysis. Each was excluded due to 1) vomiting within two times the median T<sub>max</sub> in its period or 2) pre-dose concentrations were higher than 5% of their C<sub>max</sub> values. The list of subjects that were excluded from each of the four periods: test of replicate 1 (A1); reference of replicate 1 (B1); test of replicate 2 (A2); reference of replicate 2 (B2) follows.

Trt	N	Subject Exclusion	
		Reason	Subj #s Excluded
<b>Carbidopa</b>			
A1	43	Vomiting <sup>1</sup>	4, 29, 31, 35, 38, 39
B1	43	Vomiting <sup>1</sup>	26, 27, 29, 33, 38, 39
A2	45	Vomiting <sup>1</sup>	4, 39, 43
		Pre-dose Conc. <sup>2</sup>	8
B2	39	Vomiting <sup>1</sup>	3, 6, 27, 29, 31, 33, 38, 39, 44
		Pre-dose Conc. <sup>2</sup>	23
<b>Levodopa</b>			
A1	44	Vomiting <sup>1</sup>	4, 29, 31, 38, 39
B1	43	Vomiting <sup>1</sup>	26, 27, 29, 33, 38, 39
A2	46	Vomiting <sup>1</sup>	4, 39, 43
B2	40	Vomiting <sup>1</sup>	3, 6, 27, 29, 31, 33, 38, 39, 44

<sup>1</sup> Vomiting occurred within two times the median T<sub>max</sub>.

<sup>2</sup> Pre-dose concentrations were higher than 5% of their C<sub>max</sub> values.

The above exclusions are acceptable per the General Guidance.

Discussion on Group Analysis (Carbidopa and Levodopa)

The subjects were dosed in two groups of 25 subjects each. The results reported by the firm are derived from combining the two groups. Discussion on the statistical analysis involving groups follows:

The following study information is considered by DBE as support for combining the groups for statistical analysis:

- The clinical study for the two groups was carried out at the same clinical facility.
- Study subjects in both groups were recruited from the same enrollment pool and have similar demographics. See demographics table (Table 1).
- The groups were dosed only one day apart.
- All enrolled subjects were randomly assigned to the study treatments.
- Plasma samples from both groups were analyzed by the same analytical facility.

The firm reported that its ANOVA model included group, sequence, period nested within group, treatment and treatment\*group interaction as fixed effects and subject nested within group\*sequence as a random effect. A 10% level of significance was used to test the sequence effect. The firm's plan for statistical analysis stated that if the treatment\*group interaction was not statistically significant at the 5% level, the interaction term would be dropped from the model. If a statistically significant interaction was found, results for those pharmacokinetic parameters that showed interaction were to be presented by group as well as combined. Because the treatment\*group interaction was not statistically significant for LAUC<sub>t</sub>, LAUC<sub>i</sub> or LC<sub>max</sub> the final selected model did not contain this term, and only the combined group statistical results were submitted in the PK tables.

The reviewer statistically analyzed the grouped data and found that the study would meet the criteria for bioequivalence in terms of point estimates and 90% confidence intervals if the group model had been used. The data was analyzed by the reviewer using a SAS Proc Mixed procedure with the following model considering "group" effect:  $Y = \text{GROUP SEQ GROUP*SEQ PER}(\text{GROUP}) \text{ TRT GROUP*TRT}$  wherein  $Y = \text{LAUC}_t, \text{LAUC}_i \text{ or LC}_{\text{max}}$ .

**Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:**

1. The report on sample assays is incomplete. The firm submitted a listing of SOPs used in its analytical work, but none of them contained effective dates and none addressed repeat assays. A complete list of all SOPs used in the study including those that describe criteria for identifying and re-assaying pharmacokinetically anomalous samples should be submitted. The submission should include the dates on which all SOPs were implemented. Actual copies of SOPs for repeat assays should be submitted.
2. The firm did not indicate that its report included or did not include the results of reanalysis. The firm should submit a complete tabular summary on its repeat assays if any, including (1) the reason(s) for re-assay, (2) the original and re-assayed values of the

involved samples, (3) identification of which value was selected for PK analysis and (4) the associated subjects, treatments, and sampling times.

3. The firm did not submit 20% of serially selected chromatograms. It should refer to the Guidance for Industry Bioanalytical Method Validation issued in May 2001.

**Table 11 Mean Plasma Concentrations (ng/mL) vs. Time, Single-Dose Fasting Bioequivalence Study**

Carbidopa - Separate Replicates								
Time (Hours)	Test (Replicate 1) (N=43)		Test (Replicate 2) (N=45)		Reference (Replicate 1) (N=43)		Reference (Replicate 2) (N=39)	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
0	0.0	--	0.0	--	0.0	--	0.0	--
0.33	16.1	155	11.8	74	9.8	120	7.0	133
0.67	42.3	39	43.1	55	50.0	72	37.6	54
1	55.9	41	53.4	54	68.9	61	64.4	51
1.33	67.1	44	63.4	49	84.5	55	78.6	49
1.67	74.5	47	77.2	46	91.9	48	92.4	46
2	82.8	38	85.1	44	97.9	36	100.7	45
2.5	90.1	42	93.5	38	98.8	35	109.2	38
4	92.1	42	90.0	41	94.6	47	107.1	39
6	54.4	46	57.1	46	58.4	47	66.3	44
8	22.1	53	23.5	54	24.4	46	26.9	46
10	9.9	55	9.2	60	9.2	58	11.0	57
12	3.0	122	3.9	88	3.6	100	4.8	87

**Table 11 (Continued). Arithmetic Mean Plasma Concentrations (ng/mL) vs. Time**

Levodopa - Separate Replicates								
Time (Hours)	Test (Replicate 1) (N=44)		Test (Replicate 2) (N=46)		Reference (Replicate 1) (N=43)		Reference (Replicate 2) (N=40)	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
0	0	--	0	--	0	--	0	--
0.33	1543	43	1602	45	1211	75	1064	77
0.67	1193	53	1068	43	1274	56	1158	56
1	951	50	945	53	1004	49	993	54
1.33	1030	53	1089	47	1113	51	1089	57
1.67	1157	48	1361	39	1320	41	1467	41
2	1229	41	1335	46	1359	45	1418	42
2.5	927	39	954	42	1041	43	1077	48
4	493	52	525	50	544	47	593	54
6	201	63	202	50	231	56	241	57
8	73	67	75	52	89	66	94	65
10	38	96	28	56	34	70	33	63
12	9	124	7	130	12	84	9	101

Table 11 (Continued). Arithmetic Mean Plasma Concentrations (ng/mL) vs. Time

Carbidopa - Combined Replicates					
Time (hrs)	Combined Test (Replicates 1 & 2)		Combined Reference (Replicates 1 & 2)		T/R Ratio
	Mean	%CV	Mean	%CV	
0	0.0	--	0.0	--	--
0.33	14.0	134	8.5	126	1.65
0.67	42.7	48	44.0	68	0.97
1	54.6	48	66.7	57	0.82
1.33	65.2	47	81.7	52	0.80
1.67	75.9	46	92.2	47	0.82
2	84.0	41	99.3	40	0.85
2.5	91.8	39	103.8	37	0.89
4	91.0	42	100.6	44	0.91
6	55.8	46	62.1	46	0.90
8	22.8	53	25.6	46	0.89
10	9.6	57	10.1	58	0.95
12	3.5	102	4.1	94	0.84

Table 11 (Continued). Arithmetic Mean Plasma Concentrations (ng/mL) vs. Time

Levodopa - Combined Replicates					
Time (hrs)	Combined Test (Replicates 1 & 2)		Combined Reference (Replicates 1 & 2)		T/R Ratio
	Mean	%CV	Mean	%CV	
0	0	--	0	--	--
0.33	1573	44	1140	76	1.38
0.67	1128	49	1217	56	0.93
1	948	51	999	51	0.95
1.33	1060	50	1102	54	0.96
1.67	1264	43	1391	41	0.91
2	1284	44	1388	43	0.93
2.5	941	40	1058	45	0.89
4	509	51	568	51	0.90
6	202	56	236	57	0.85
8	74	59	92	65	0.81
10	33	86	33	67	0.98
12	8	127	11	92	0.72

**Figure 1 Mean Plasma Concentrations, Single-Dose Fasting, Replicate Design Bioequivalence Study**

Figure 1a. Mean Carbidopa Plasma Concentration vs. Time - Separate Replicates

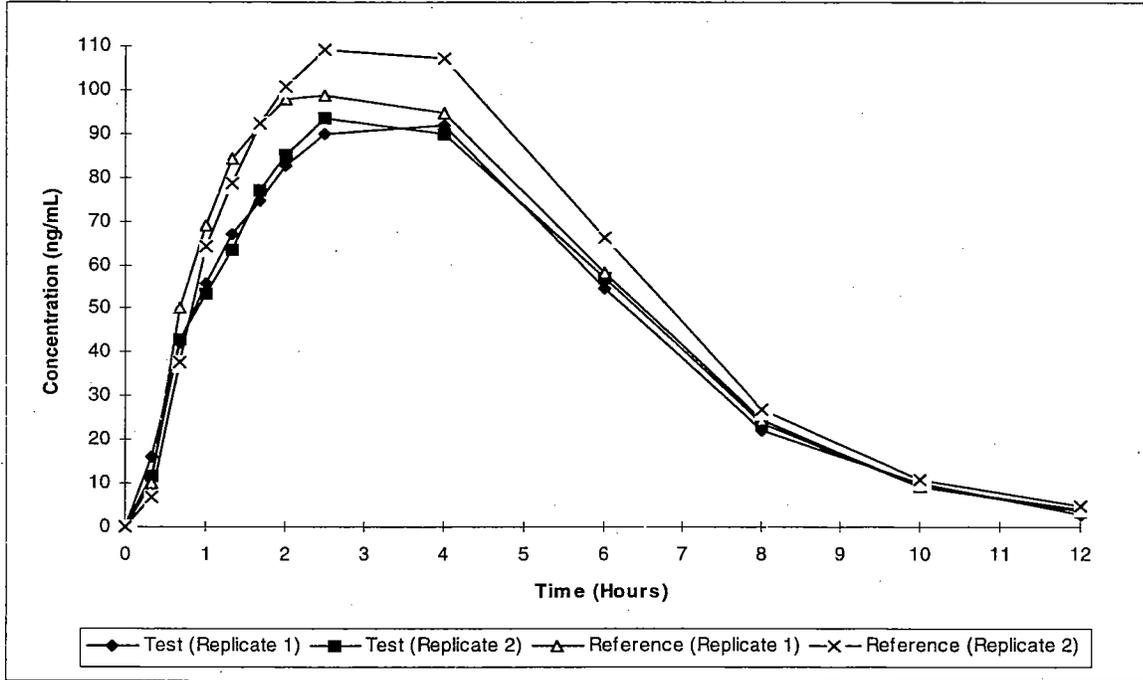


Figure 1b. Mean Levodopa Plasma Concentration vs. Time - Separate Replicates

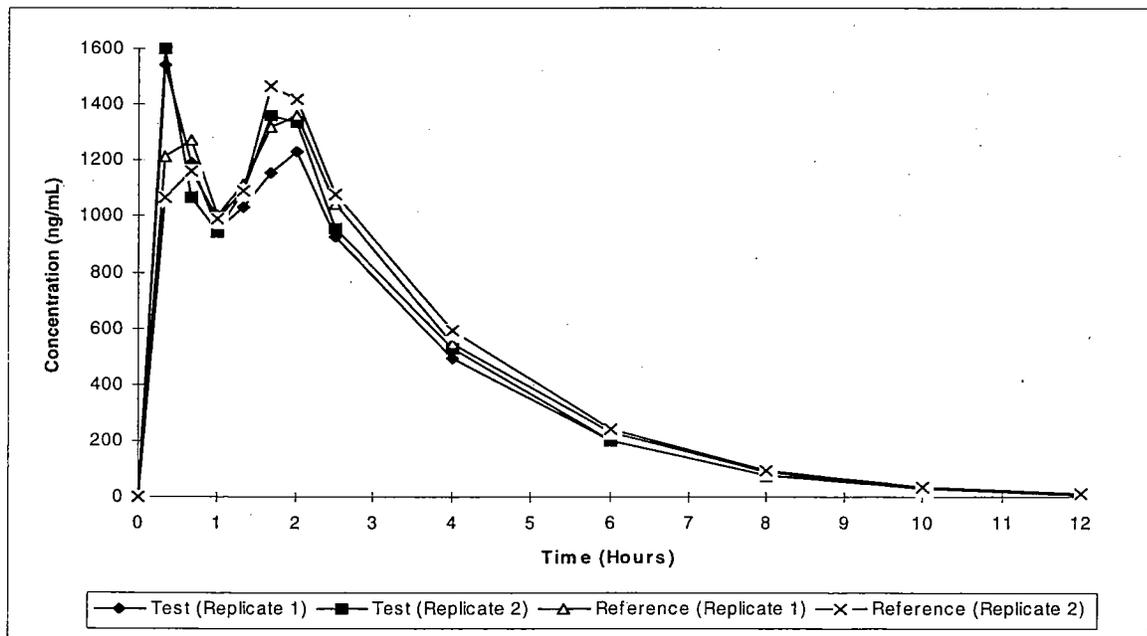


Figure 1c. Mean Carbidopa Plasma Concentration vs. Time (Combined Replicates)

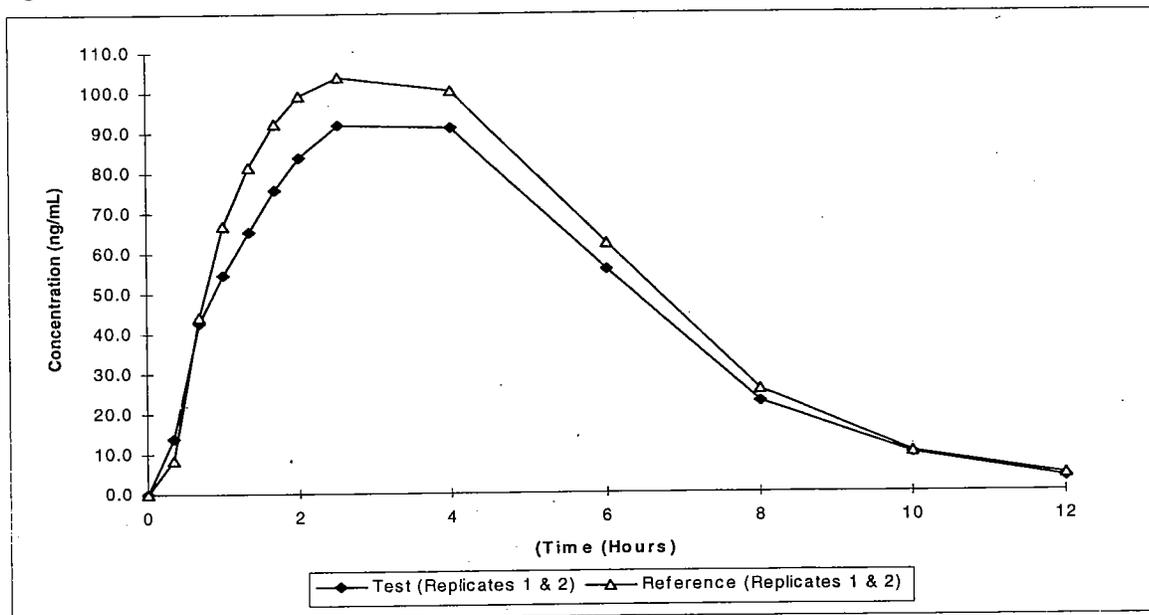
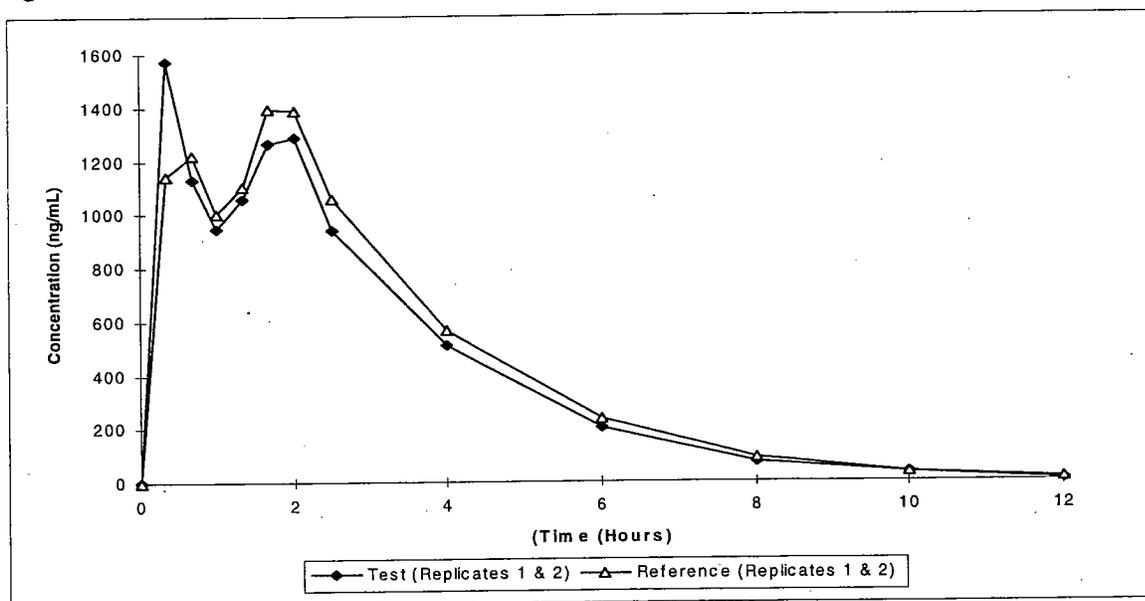


Figure 1d. Mean Levodopa Plasma Concentration vs. Time - Combined Replicates



**B. Formulation Data**

Ingredient	10 mg/100 mg		25 mg/100 mg		25 mg/250 mg	
	mg	%w/w	mg	%w/w	Mg	%w/w
Carbidopa USP (Monohydrate)	10.80*	2.70	27.00**	6.75	27.00**	2.70
Levodopa USP	100.00	25.00	100.00	25.00	250.00	25.00
Mannitol — USP						
Microcrystalline Cellulose, NF						
—— Mannitol —— USP						
Crospovidone NF						
Sodium Bicarbonate, —— USP						
Citric Acid, —— USP						
Aspartame NF						
Magnesium Stearate NF						
Natural & Artificial Mint Flavor ——						
FD&C Blue #2 HT Aluminum Lake						
—— Yellow 10 Iron Oxide	--	--	[	]	--	--
<b>TOTAL</b>	<b>400.00</b>	<b>100.00</b>	<b>400.00</b>	<b>100.00</b>	<b>1000.00</b>	<b>100.00</b>

\*The quantity of carbidopa in the 10 mg/100 mg tablet is equivalent to 10.0 mg of anhydrous carbidopa.

\*\*The quantities of carbidopa in the 25 mg/100 mg tablet and the 25 mg/250 mg tablets are equivalent to 25.0 mg of anhydrous carbidopa.

The formulations are proportionally similar. The ratios of inactive ingredients to total weight of the dosage form are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.

**APPEARS THIS WAY  
ON ORIGINAL**

### C. Dissolution Data

The firm used 750 mL of 0.1N HCl with USP apparatus 2 (paddle) at 50 rpm.

**Table 1**

Sampling Times (min)	Mean	%CV	Range	Mean	%CV	Range
	<b>Test 10 mg/100 mg Batch No. 920191</b>			<b>Reference 10 mg/100 mg Batch No. J4693</b>		
<b>Levodopa</b>						
2.5	78	8	/	70	5	/
5	96	2		89	3	
10	97	2		98	3	
30	98	2		101	2	
<b>Carbidopa</b>						
2.5	80	9	/	74	5	/
5	99	2		92	4	
10	100	1		98	3	
30	100	2		101	2	
	<b>Test 25 mg/100 mg Batch No. 920190</b>			<b>Reference 25 mg/100 mg Batch No. L5265</b>		
<b>Levodopa</b>						
2.5	66	10	/	71	5	/
5	90	5		91	4	
10	93	5		97	3	
30	95	4		98	2	
<b>Carbidopa</b>						
2.5	65	11	/	72	5	/
5	90	6		91	4	
10	93	5		96	3	
30	94	4		97	2	
	<b>Test 25 mg/250 mg Batch No. 920238</b>			<b>Reference 25 mg/250 mg Batch No. K5015</b>		
<b>Levodopa</b>						
2.5	61	11	/	48	6	/
5	91	2		78	4	
10	96	1		96	2	
30	97	1		99	1	
<b>Carbidopa</b>						
2.5	59	11	/	54	6	/
5	91	2		83	5	
10	95	2		97	2	
30	96	2		99	1	

**Figure 2 Dissolution Profiles**

Not applicable

**D. Consult Reviews**

No Consults

**APPEARS THIS WAY  
ON ORIGINAL**

Redacted 12 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW OF 3/28/2003 SUBMISSION

**F. Additional Attachments**

**SOPs used during analysis:**

<u>SOP No.</u>	<u>SOP Date</u>	<u>SOP Title</u>
AL-G-1506-13	Not given	Calibration Curve Preparation, Specifications and Acceptance Criteria
AL-G-1520-10	Not given	Reporting of Data Generated by the Analytical Laboratories
AL-G-1521-09.A01	Not given	Analytical Method Validation
AL-G-1527-02	Not given	System Suitability
AL-G-1543-05.A01	Not given	Chromatography Acceptance Criteria
CW-R-8745-01	Not given	Generation, Checking And Disposition of Raw Data, Calculations, Derived Data
SL-G-1857-01	Not given	Procedure to Submit/Request Material To/From The Archives

**APPEARS THIS WAY  
ON ORIGINAL**

## BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-699

APPLICANT: Schwarz Pharma, Inc.

DRUG PRODUCT: Carbidopa and Levodopa Orally Disintegrating Tablets  
10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your dissolution testing is incomplete. Please conduct comparative dissolution testing on all strengths in 750 mL of 0.1 N HCl at 37°C using USP apparatus 1 (basket) at 25 rpm and 50 rpm. Also, please conduct additional comparative dissolution testing on all strengths in 750 mL of 0.1 N HCl at 37°C using USP apparatus 2 (paddle) at 25 rpm. The recommended sampling times are 2.5, 5, 10 and 30 minutes.
2. You did not submit 20% of serially selected chromatograms. Please submit them. Refer to the Guidance for Industry Bioanalytical Method Validation issued in May 2001.
3. You submitted a listing of SOPs used in your analytical work on the bioequivalence study, but none of them contained effective dates and none addressed repeat assays. Please submit a complete list of all analytical SOPs used in the bioequivalence studies including those that describe objective criteria for identifying and re-assaying samples believed to have anomalous pharmacokinetic results. Please include the dates on which all SOPs were implemented. Actual copies of SOPs for repeat assays should be submitted.
4. Please submit a complete tabular summary on any repeat assays, including (1) the reason(s) for re-assay, (2) the original and re-assayed values of the involved samples, (3) identification of which value was selected for PK analysis and (4) the associated subjects, treatments, and sampling times.
5. In the current submission the plasma concentration data for all subjects was presented in one column.

In future submissions please submit your pharmacokinetic data on a diskette or CD in SAS Transport format in two separate files as described below:

- (1) SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE THalf
- (2) SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

Separate each field with a blank space and indicate missing values with a period (.).

Sincerely yours,

*for* 

Dale P. Conner, Pharm.D.

Director, Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

Carbidopa and Levodopa Orally Disintegrating Tablets, ANDA: 76-699

CC: ANDA 76-699  
ANDA DUPLICATE  
DIVISION FILE  
FIELD COPY  
DRUG FILE

HFD-652/ J. Chaney *J. Chaney 4/29/2004*  
HFD-652/ Y. Huang *YH 4/29/2004*  
HFD-650/ A. Sigler  
HFD-650/ D. Conner *BD 4/29/04*

*for*

V:\firmsnz\schwarzpharma\trs&rev\76699n0303

BIOEQUIVALENCE - DEFICIENCIES

Submission Date: March 28, 2003

FASTING STUDY (STF) *ok*

Strengths: 25 mg/250 mg  
Outcome: IC

Clinical Study Site: \_\_\_\_\_

Analytical Site: \_\_\_\_\_  
\_\_\_\_\_

DISSOLUTION DATA (DIW) *ok*

Strength: 10 mg/100 mg  
Outcome: IC

DISSOLUTION DATA (DIW) *ok*

Strength: 25 mg/100 mg  
Outcome: IC

Outcome Decision: Incomplete

WINBIO COMMENTS: The fasted study and dissolution testing are incomplete. The waivers are pending an acceptable biostudy and acceptable comparative dissolution testing.

---



---

**DIVISION OF BIOEQUIVALENCE REVIEW**


---



---

<b>ANDA No.</b>	76-699
<b>Drug Product Name</b>	Carbidopa and Levodopa Orally Disintegrating Tablets
<b>Strength</b>	10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg
<b>Applicant Name</b>	Schwarz Pharma, Inc.
<b>Address</b>	6140 W. Executive Drive, Mequon, WI 53092
<b>Submission Date(s)</b>	May 19, 2004
<b>Amendment Date(s)</b>	NA
<b>Reviewer</b>	James E. Chaney
<b>First Generic</b>	Yes
<b>File Location</b>	V:\firmsnz\schwarzpharma\trs&rev\76699a0504

---



---

**Review of an Amendment to an ANDA (Biostudy)**

**I. Executive Summary**

The original application for Carbidopa and Levodopa Orally Disintegrating Tablets, 10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg submitted May 19, 2003 included a fasted study and dissolution data. The ANDA was based on a suitability petition. The suitability petition requested a dosage form change from immediate release tablets to orally disintegrating tablets. The submission included: 1) a fasting BE study on the 25 mg/250 mg strength with measurement of parent carbidopa and levodopa, 2) comparative dissolution data on all strengths and 3) waiver requests for the lower strengths. The resulting pharmacokinetic data (point estimate and 90% CI) for levodopa and carbidopa was within the range of 80 to 125. However, the biostudy was incomplete in part due to analytical deficiencies regarding selection of chromatograms for submission, SOP information, deficient information on repeated sample assays and inappropriate PK data format. Also, the dissolution testing was incomplete. The application was considered incomplete. In the current amendment the firm has adequately addressed the deficiencies and the application is acceptable from the bioequivalence point of view. DBE has concluded that the firm's dissolution testing should be conducted in 750 mL of 0.1N HCl at 37°C using USP Apparatus 2 at 25 rpm. Not less than  $\bar{\%}$  (Q) of the labeled amounts of carbidopa and levodopa are dissolved in 10 minutes.

**II. Current Amendment**

The firm has responded to DBE's May 4, 2004 deficiency comments pertaining to the biostudy and dissolution testing on its Carbidopa and Levodopa Orally Disintegrating Tablets, 10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg originally submitted May 19, 2003. There were five deficiency comments (items) as follows:

- Incomplete dissolution testing
- Omission of selected assay chromatograms
- Inadequate SOP information
- Incomplete information on repeat assays
- Improper format of PK data submitted on diskette

**Item 1**

**Your dissolution testing is incomplete. Please conduct comparative dissolution testing on all strengths in 750 mL of 0.1 N HCl at 37°C using USP apparatus 1 (basket) at 25 rpm and 50 rpm. Also, please conduct additional comparative dissolution testing on all strengths in 750 mL of 0.1 N HCl at 37°C using USP apparatus 2 (paddle) at 25 rpm. The recommended sampling times are 2.5, 5, 10, and 30 minutes.**

**Firm's Response to Item 1**

As reported in the original submission the firm emphasizes that the basket apparatus is inappropriate for the test carbidopa/levodopa orally disintegrating tablets because in attempts to conduct testing using the basket method at 50 rpm the test tablets floated in the dissolution medium and formed non-dispersed masses of disintegrated tablets at the top of the basket under the spindle shaft, resulting in very inconsistent release of the active ingredients and a much slower dissolution rates for the test product relative to the RLD (Sinemet® an immediate release tablet). Given the observations of the failing attempts using the basket method at 50 rpm, the firm concluded that inconsistent release of active ingredients would also occur at the slower speed of 25 rpm. Therefore, the requested testing at 25 rpm using USP apparatus 1 was not performed.

Of the requested dissolution testing information the firm has submitted results obtained using the paddle method with a rotation speed of 25 rpm using USP apparatus 2 on all three strengths (25 mg/100 mg, 10 mg/100 mg and 25 mg/250 mg carbidopa/levodopa). The results are shown in Table 1 which also shows the results originally obtained from using the 50 rpm rotation speed initially reported. The sampling times were at 2.5, 5, 10 and 30 minutes. The discrimination is better at 25 rpm than at 50 rpm.

**DBE Comments on Firm's Response to Item #1:**

The firm's choice of paddle instead of basket (used by the RLD holder on its Sinemet® tablets) and the reasons for the choice are acceptable in view of the above problems encountered with the basket method involving floating of the test tablets accompanied by severely decreased dispersion and dissolution.

Based on the dissolution testing submitted the firm might experience difficulty in meeting the Q1= % dissolved at 10 minutes at S1 stage for all strengths employing the rotation speed of 25 rpm. Therefore, it is recommended that the dissolution testing should be conducted in 750 mL of 0.1N HCl at 37°C using USP Apparatus 2 at 50 rpm. The test product should meet the following specifications:

Not less than % (Q) of the labeled amounts of carbidopa and levodopa are dissolved in 10 minutes.

**Table 1. Dissolution Testing Results on Test Product in 750 mL of 0.1N HCl Using Paddle Speeds of 25 rpm and 50 rpm**

Times (min)	Rotation Speed of 25 rpm			Rotation Speed of 50 rpm		
	Mean	% CV	Range	Mean	% CV	Range
<b>Test 10 mg/100 mg, Batch No. 920191</b>						
<b>Levodopa</b>						
2.5	61	17.1	/	78	8	/
5	85	12.4		96	2	
10	91	6.8		97	2	
30	94	4.5		98	2	
<b>Carbidopa</b>						
2.5	64	16.6	/	80	9	/
5	91	10.6		99	2	
10	96	5.3		100	1	
30	99	3.3		100	2	
<b>Test 25 mg/100 mg, Batch No. 920190</b>						
<b>Levodopa</b>						
2.5	53	14.5	/	66	10	/
5	77	12.4		90	5	
10	86	8.4		93	5	
30	92	5.4		95	4	
<b>Carbidopa</b>						
2.5	52	14.8	/	65	11	/
5	76	12.7		90	6	
10	87	7.9		93	5	
30	92	5.2		94	4	
<b>Test 25 mg/250 mg, Batch No. 920238</b>						
<b>Levodopa</b>						
2.5	51	12.1	/	61	11	/
5	85	7.3		91	2	
10	93	4.5		96	1	
30	97	2.1		97	1	
<b>Carbidopa</b>						
2.5	50	11.5	/	59	11	/
5	86	6.5		91	2	
10	94	2.8		95	2	
30	97	1.1		96	2	

## Item 2

**You did not submit 20% of serially selected chromatograms. Please submit them. Refer to the Guidance for Industry Bioanalytical Method Validation, issued in May 2001.**

## Firm's Response to Item 2

SPInc (Schwarz Pharma, Inc.) agrees that 20% of serially selected chromatograms for were inadvertently omitted from the original report. Attachment 2 of this response provides the serially selected chromatograms.

DBE Comment on Firm's Response to Item #2: The firm's response is acceptable in that 20% of serially selected chromatograms are included in this amendment.

## Item 3

**You submitted a listing of SOPs used in your analytical work on the bioequivalence study, but none of them contained effective dates and none addressed repeat assays. Please submit a complete list of all analytical SOPs used in the bioequivalence studies including those that describe objective criteria for identifying and re-assaying samples believed to have anomalous pharmacokinetic results. Please include the dates on which all SOPs were implemented. Actual copies of SOPs for repeat assays should be submitted.**

## Firm's Response to Item 3

Attachment 3 of the firm's response includes a list of the analytical SOPs used in the bioequivalence studies. This list includes the dates on which all of the SOPs were implemented. A copy of SOP AL-G-1520-11 for repeat assays was also included in the submitted Attachment 3.

The following SOPs were in place prior to initiation the study:

SOP TITLE	SOP NO	Effective dates of version cited
A High Performance Liquid Chromatographic Method Using Fluorescence Detection for the Determination of Carbidopa and Levodopa in Human Plasma	LC-M-6131-03	12/16/02-ongoing
Chromatographic and Spectrometric Methods: Calibration Curve Preparation, Specifications and Acceptance Criteria	AL-G-1506-15	4/25/02-1/31/03
Reporting of Data Generated from the Analysis of Biological Matrices	AL-G-1520-11	4/19/02-7/9/03
System Suitability	AL-G-1527-02	12/10/02-ongoing
Definition of the Units, Number of Digits and Rounding Procedures To Be Used In Reporting Study Data	CW-R-8701-02	12/9/99-5/1/03
Reports, Amendments and Addenda	CW-R-8729-04	8/14/00-6/20/03
Generation, Checking And Disposition of Raw Data, Calculations and Derived Data	SL-R-8745-03	5/31/02-Ongoing
Procedure to Submit/Request Material To/From The Archives	SL-G-1857-01	2/2202-4/16/04

Although SOP AL-G-1520-11 "Reporting of Data Generated from the Analysis of Biological Matrices" does not indicate in its title that the SOP applies to reassays of samples, it is part of the scope of the SOP.

DBE Comment on Firm's Response to Item #3:

The firm submitted effective dates for all of the SOPs used in its analytical work, demonstrating that they were in effect at the time of the analyses. A copy of SOP AL-G-1520-II was submitted which adequately addressed the repeat assays that were performed. No assays were repeated due to anomalous PK values. The firm's response is acceptable.

Item 4

**Please submit a complete tabular summary on any repeat assays, including (1) the reason(s) for re-assay, (2) the original and re-assayed values of the involved samples, (3) identification of which value was selected for PK analysis, and (4) the associated subjects, treatments, and sampling times.**

**Firm's Response to Item 4**

Attachment 4 of the firm's response includes a complete tabular summary of assays, including repeat assays, for both carbidopa and levodopa. No samples were re-assayed due to pharmacokinetic reasons. All re-assays were due to analytical reasons (refer to the codes noted at the bottom of each page of the table). The table also includes the identification of which value was selected (refer to the value listed in the "final" row for each subject), as well as the associated subjects, treatments, and sampling times.

DBE Comment on Firm's Response to Item #4: The firm's response is acceptable.

Item 5

**In the current submission the plasma concentration data for all subjects was presented in one column. In future submissions please submit your pharmacokinetic data on a diskette or CD in SAS Transport format in two separate files as described below:**

**(1) SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE THalf**

**(2) SUBJ SEQ PER TRT C1 C2 C3 Cn**

**Separate each field with a blank space and indicate missing values with a period (.).**

**Firm's Response to Item 5**

SPInc acknowledges the comment from the Agency. The pharmacokinetic data for future submissions will be submitted on a diskette or CD in SAS Transport format in two separate files, as noted above, with each field separated by a blank space and missing values indicated with a period (.).

DBE Comment on Firm's Response to Item #5: The firm's response is acceptable.

**III. Recommendations**

1. The single-dose fasted study conducted by Schwarz Pharma, Inc. on its Carbidopa and Levodopa Orally Disintegrating Tablets 25 mg/250 mg, lot 920238, comparing them to

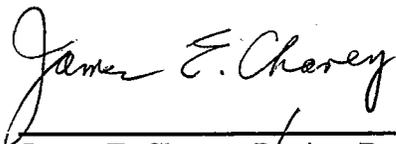
Sinemet® (Immediate Release Carbidopa 25 mg/Levodopa 250 mg tablet), Lot # K5015, manufactured by Merck & Co., Inc. have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Schwarz Pharma's Carbidopa and Levodopa Orally Disintegrating Tablets 25 mg/250 mg are bioequivalent to the reference product, Schwarz Pharma's Sinemet® (immediate release carbidopa 25 mg/levodopa 250 mg tablet) mg under fasting conditions.

2. The comparative dissolution testing conducted by the firm on its Carbidopa and Levodopa Orally Disintegrating Tablets 25 mg/250 mg (lot 920238), 25 mg/100 mg (lot 920190) and 10 mg/100 mg (Lot 920191) has been found acceptable.

The dissolution testing should be conducted in 750 mL of 0.1N HCl at 37°C using USP Apparatus 2 at 50 rpm. The test product should meet the following specifications:

Not less than ~ % (Q) of the labeled amounts of carbidopa and levodopa are dissolved in 10 minutes.

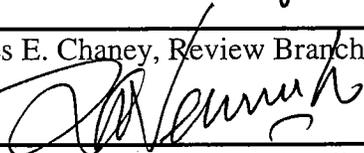
3. The formulations of the 10 mg/100 mg and 25 mg/100 mg carbidopa and levodopa orally disintegrating tablets are proportionally similar to that of the 25 mg/250 mg carbidopa and levodopa disintegrating tablets of the test product that underwent acceptable bioequivalence testing. The waivers of *in vivo* bioequivalence study requirements for the 10 mg/100 mg and 25 mg/100 mg tablets of the test product are granted.
4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.



7/28/2004

---

James E. Chaney, Review Branch 1, Date signed



7/28/2004

---

S. Nerurkar, Review Branch 1, Date signed



7/28/04

---

Dale P. Conner, Pharm. D.  
Director, Division of Bioequivalence  
Office of Generic Drugs

V:\firmsnz\schwarzpharma\trs&rev\76699a0504

BIOEQUIVALENCE - ACCEPTABLE

ANDA # 76-699

APPLICANT: Schwarz Pharma, Inc.  
Mequon, WI

DRUG PRODUCT:

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

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing should be conducted in 750 mL of 0.1N HCl at 37°C using USP Apparatus 2 at 50 rpm. The test product should meet the following specifications:

Not less than —% (Q) of the labeled amounts of carbidopa and levodopa are dissolved in 10 minutes.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm.D.  
Director  
Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

CC: ANDA 76-699  
ANDA DUPLICATE  
DIVISION FILE  
FIELD COPY  
DRUG FILE

HFD-652/ J. Chaney  
HFD-652/ S. Nerurkar  
HFD-650/ A. Sigler  
HFD-650/ D. Conner

*J. Chaney 7/28/2004*

*APC 7/28/04*

*[Signature] 7/28/04*

V:\firmsnz\schwarzpharma\ltrs&rev\76699a0504

BIOEQUIVALENCE – ACCEPTABLE

Submission date: May 19, 2004

1. STUDY AMENDMENT (STA)

Strengths:  
10 mg/100 mg, 25 mg/100 mg & 25 mg/250 mg  
Outcome: AC

Clinical Study Site: \_\_\_\_\_

Analytical Site: \_\_\_\_\_  
\_\_\_\_\_

Outcome Decision: Acceptable

WINBIO COMMENTS: The BE study under fasted conditions and the dissolution testing are acceptable. Waivers are granted for the 10 mg/100 mg & 25 mg/100 mg tablets.

OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE

ANDA # 76-699  
DRUG AND DOSAGE FORM: SPONSOR: Schwarz Pharma, Inc.  
STRENGTH(S): Carbidopa & Levodopa Orally Disintegrating Tablets  
10 mg/100 mg, 25 mg/100 mg, & 25 mg/250 mg  
TYPES OF STUDIES: Single-dose fasting

Clinical Study Site:  
Analytical Site:

STUDY SUMMARY: Acceptable fasting study

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: <u>NO</u>	Inspection status:	Inspection results:
First Generic <u>YES</u> New facility <u>NO</u> For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL: jc

DATE: 7/28/2004

TEAM LEADER: S. Nerurkar

BRANCH: I

INITIAL: [Signature]

DATE: 7/28/2004

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL: [Signature]

DATE: 7/28/04