CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 84-349/S-045

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	84-349
Drug Product Name	Dilantin Kapseals® (Phenytoin Sodium Extended-Release Capsules, USP)
Strength	100 mg
Applicant Name	Parke-Davis Pharmaceutical Research
Address	235 East 42nd Street, New York, NY 10017
Submission Date(s)	December 15, 2005
Amendment Date(s)	February 13, 2006
Reviewer	Devvrat Patel
First Generic	Yes
File Location	v:\firmsnz\parkedav\ltrs&rev\84349S1205.doc

Review of a Supplement

I. Executive Summary

Park-Davis' Dilantin 100 mg extended release capsules are listed as the reference listed drug in the Orange Book. Parke-Davis manufactured its drug product using a new manufacturing process. The new process uses sodium phenytoin manufactured using (b) (4). The firm has compared its drug product manufactured using the new process with its currently marketed drug product. Fasting and fed studies were conducted and the results are provided in this submission. The Division of Bioequivalence does not request fed study for this drug product.

The fasting study was a single-dose, replicate, 4 period crossover study in 21 healthy male (20) and female (1) subjects given a dose of 1 x 100 mg capsule. The subjects were dosed in 2 groups but grp*trt was not significant. The results (point estimate, 90% CI) of the fasting study are $LAUC_{0-t}$ 1.04, 100.73-107.17%; $LAUC_{0-\infty}$ 1.04, 100.85-107.53%; LC_{max} 1.11, 103.20-118.39%.

The fed study was a single-dose, two-way crossover study in 29 healthy male (27) and female (2) subjects given a dose of 1 x 100 mg capsule. The subjects were dosed in 2 groups but grp*trt was not significant. The results (point estimate, 90% CI) of the fed study are $LAUC_{0-t}$ 1.06, 99.87-112.04%; $LAUC_{0-\infty}$ 1.05, 99.02-111.06%; LC_{max} 1.01, 92.23-111.08%. It is noted that subject #10011030 had plasma phenytoin concentrations in Period 2 following administration of the test treatment that were zero in all samples through 48 hours postdose, with a single quantifiable concentration at 72 hours post-dose. The study remains acceptable with or without this subject.

The bioequivalence studies are incomplete because the firm did not provide manufacture date, batch size, production batch size, potency, and content uniformity of the test product. Additionally, the firm did not provide expiration date and potency of the reference product used in bioequivalence studies. The firm did not provide details of bio-analytical method validation.

It is noted that the optimized manufacturing process formulation of the test product has the same composition as the current commercial product (reference product). Additionally, the firm states that the manufacturing process change applies only to the 100 mg strength capsule, and not 30 mg strength capsule.

The firm conducted dissolution testing using USP 29 method [900 mL of water using USP Apparatus 1 (Basket) at 50 rpm]. The test products meet USP specifications. For dissolution testing, the firm used lot no. 01615C for the test and lot no. 01095F for the reference products. However, the firm used lot nos. 05-026235 and 05-026268 for the test and reference products, respectively, in the in vivo bioequivalence studies. The dissolution testing should be conducted on the lots used in the bioequivalence studies. Therefore, the dissolution testing is incomplete.

The application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Phenytoin Sodium Extended Release Capsule (Dilantin®)
Reference Product	Phenytoin Sodium Extended Release Capsule (Dilantin Kapseal®)
RLD Manufacturer	Parke Davis
NDA No.	84-349
RLD Approval Date	Approved prior to January 1, 1982
Indication	Indicated for the control of generalized tonic-clonic (grand mal) and complex partial seizures.

B. PK/PD Information

Bioavailability	According to Micromedex, oral phenytoin sodium capsules have bioavailability of 70% to 100%.
Food Effect	There is no mention of food effect in the labeling. As per the Micromedex, the food increases the absorption of phenytoin.
Tmax	Peak serum levels occur 4 to 12 hours after administration.
Metabolism	Since phenytoin is hydroxylated in the liver by an enzyme system that is saturable, small incremental doses may increase the half-life and produce very substantial increases in serum levels.
Excretion	Most of the drug is excreted in the bile as inactive metabolites that are then reabsorbed from the intestinal tract and excreted in the urine.
Half-life	The plasma half-life after oral administration averages 22 hours, with a range of 7 to 42 hours.

C. Supplement Summary

The innovator has optimized the current manufacturing process including using (b) (4) (b) (4) for both the active ingredient and drug product for the 100 mg strength capsule. The new process also uses sodium phenytoin manufactured using (b) (4) this process (b) (4) (b) (4) compared to material used in the current manufacturing process. The optimized manufacturing process formulation has the same composition as the current commercial product.

These enhancements were developed primarily to address manufacturing concerns that were the subject of the consent decree entered into by the FDA and Warner-Lambert in 1993 (Warner Lambert Co. merged with Pfizer in 2000) and to fulfill the intent of a Remedial Action Plan, dated 15 October 1993, agreed upon by Pfizer and FDA.

The supplement contains the following changes that are applicable to the 100 mg capsule:

- Addition of a manufacturing process for the drug substance (also referred to as active pharmaceutical ingredient).
- Modification of the manufacturing process for the drug product, the 100 mg capsule, including a change in market image from the Kapseal"' (a banded capsule) to an interlocked capsule.
- Addition of a new packaging configuration.
- Addition of a packaging site, Vega Baja PR, for the 100 mg capsule.

The firm conducted fasting and fed bioequivalence studies using Dilantin 100 mg capsules prepared using (b) (4) sodium phenytoin (new optimized manufacturing process) and currently marketed Dilantin 10 mg Kapseal® .

D. Pre-Study Bioanalytical Method Validation

Information Requested	Data
	Study A4121001 and A4121002
Bioanalytical method validation report location	On file with Sponsor
Analyte	Phenytoin
Internal standard (IS)	(b) (4)
Method description	Plasma was separated by centrifugation at 3000 rpm for 15 minutes in a refrigerated centrifuge. Plasma samples were frozen in an upright position at approximately -20°C within 60 minutes of sample collection. Plasma samples were assayed using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method.
Limit of quantitation (ng/mL)	20
Average recovery of drug (%)	88.0%
Average recovery of IS (%)	126%
Standard curve concentrations (ng/mL)	20, 40, 80, 200, 400, 800, 2000, 4500, 5000
QC concentrations (ng/mL)	60, 600, 1250, 4000
QC Intraday precision range (%)	1.68% to 6.31%
QC Intraday accuracy range (%)	-1.67% to 8.57%
QC Interday precision range (%)	3.15% to 7.41%
QC Interday accuracy range (%)	2.17% to 3.18%
Bench-top stability (hrs)	24
Stock stability (days)	9
Processed stability (hrs)	79
Freeze-thaw stability (cycles)	3
Long-term storage stability (days)	92
Dilution integrity	2- and 10-fold
Selectivity	The selectivity was documented during sample analysis by assaying a blank standard with and without internal standard with each batch run. No interfering peaks that significantly impacted quantitation were observed at the retention time of phenytoin or the internal standard.

The firm provided only this summary table but not the method validation report in the submission. Therefore, it is not known if the method was validated properly. The recovery of the analyte (phenytoin) is 88% and that of IS ((b) (4)) is 126%. The

firm should explain high % recovery of the IS ((b) (4)) and also the reasons for such differences in the recovery of the analyte and IS.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	A4121001
Study Design	Randomized, single-dose, replicate, 2 sequence, 4 period study.
No. of subjects enrolled	24
No. of subjects completing	22
No. of subjects analyzed	21*
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 20 Female: 1
Test product	Dilantin capsule containing (b) (4) sodium phenytoin manufactured using a new optimized process
Reference product	Dilantin Kapseal containing the currently marketed phenytoin sodium formulation
Strength tested	100 mg
Dose	1 x 100 mg capsule

*One subject (#10011023 in Periods 2, 3, and 4) had pre-dose concentrations of 83.58 ng/mL, 82.38 ng/mL, and 111.6 ng/mL, respectively. The subject was excluded from analysis since pre-dose concentrations in periods 3 and 4 are greater than 5% of subject's Cmax values (1335 ng/mL, and 1950 ng/mL, respectively).

Statistical Summary of the Comparative Bioavailability Studies (Provided by the Firm)

Phenytoin Sodium Dose (1 100 mg capsule) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t} (µg·hr/mL)	36.7	35.2	104	101.22 to 107.54
AUC8 (µg·hr/mL)	38.1	36.6	104	101.17 to 107.52
C_{max} (µg/mL)	1.41	1.27	111	103.78 to 118.61
Fed Bioequivalence Study (all subjects)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t} (µg·hr/mL)	29.3	30.3	96.6	81.80 to 114.18
AUC8 (µg·hr/mL)	33.5[a]	31.8	105	99.29 to 111.47
C_{max} (µg/mL)	1.19	1.26	94.8	81.95 to 109.62
Fed Bioequivalence Study (subject 10011030 excluded)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t} (µg·hr/mL)	32.5	30.7	106	99.85 to 112.10
AUC8 (µg·hr/mL)	33.8	32.2	105	99.01 to 111.14
C_{max} (µg/mL)	1.29	1.28	101	92.51 to 110.75

[a]Subject 10011030's AUC_∞ data from the test treatment were not include in the analysis as there was insufficient data to calculate half-life and AUC_∞.

Subjects were dosed in two groups. The firm did not test for the treatment*group interaction. The statistical results provided above by the firm assume that the subjects were dosed in one group.

The reviewer analyzed data to include group term in statistical model. After including the group factor in statistical analyses, the treatment*group interaction was not statistically significant for any of the log-transformed pharmacokinetic parameters. Therefore, the statistical analyses on combined groups 1 and 2 data are provided below:

Summary of Statistical Analysis, Fasting Bioequivalence Study*		
Parameter	**Point Estimate**	**90% Confidence Interval**
$LAUC_{0-t}$	1.04	100.73 – 107.17
$LAUC_{0-\infty}$	1.04	100.85 – 107.53
LCmax	1.11	103.20 – 118.39

* Subject #10011023 was excluded from statistical analyses because this subject had pre-dose plasma concentrations that were more than 5% of the corresponding Cmax values in periods 3 and 4.

Reanalysis of Study Samples

Study No. A4121001 Additional information in electronic submission N84-349-S90\hpbio\bio\a4121001.pdf in Appendix A8								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	Test	Ref.	T	R	T	R	T	R
Low internal standard	2	0	0.1	0	2	0	0.1	0
Total	2	0	0.1	0	2	0	0.1	0

Did use of recalculated plasma concentration data change study outcome? No.

The study protocol states that bioequivalence of the Dilantin capsule lots compared in this study would be concluded if all of the following criteria are met:

Cmax criteria: The 90% confidence interval for the ratio of the test-to-reference least-squares mean Cmax values, based on log transformed Cmax data, is within the interval of 80% to 125%.

AUC criteria: The 90% confidence interval for the ratio of the test-to-reference least-squares mean AUC values, based on log transformed AUC data, is within the interval of 92% to 109%.

The test product met the protocol-defined criteria of bioequivalence. The Division of Bioequivalence uses 80-125% criteria for AUC as well as Cmax.

2. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	A4121002
Study Design	Randomized, single-dose, two-way crossover
No. of subjects enrolled	32
No. of subjects completing	30
No. of subjects analyzed	29*
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 27 Female: 2
Test product	Dilantin capsule containing (b) (4) sodium phenytoin manufactured using a new optimized process
Reference product	Dilantin Kapseal containing the currently marketed phenytoin sodium formulation
Strength tested	100 mg
Dose	1 x 100 mg capsule

* Subject #10011030 had plasma phenytoin concentrations in Period 2 following administration of the test treatment that were zero in all samples through 48 hours postdose, with a single quantifiable concentration of 97.65 ng/mL at 72 hours postdose. Pharmacokinetic parameters were not determined for this subject due to insufficient data.

Summary of statistical analysis provided by the firm is provided above (given under fasting study). The firm analyzed data of all subjects completing the study and also analyzed data excluding data for subject #10011030. Subject #10011030 had plasma phenytoin concentrations in Period 2 following administration of the test treatment that were zero in all samples through 48 hours postdose, with a single quantifiable concentration at 72 hours post-dose.

Subjects were dosed in two groups. The firm did not test for treatment*group interaction. The reviewer analyzed the data including treatment*group term in the model. The treatment*group interaction was not statistically significant for any of the log-transformed pharmacokinetic parameters. Therefore, the statistical analyses on combined groups 1 and 2 data are provided below:

Summary of statistical analysis by the reviewer is provided below:

Summary of Statistical Analysis, Fed Bioequivalence Study*		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	99.87 – 112.04
$AUC_{0-\infty}$	1.05	99.02 – 111.06
Cmax	1.01	92.23 – 111.08

* Excluding data for Subject #10011030.

Summary of Statistical Analysis, Fed Bioequivalence Study*		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.97	82.03 – 114.70
$AUC_{0-\infty}$	1.05	99.11 – 110.95
Cmax	0.95	81.85 – 110.03

* Includes data from all subjects.

Reanalysis of Study Samples

Study No. A4121002 Additional information in electronic submission N84-349-890\hpbio\bio\a4121001.pdf in Appendix A8								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	Test	Ref.	T	R	T	R	T	R
Incongruous with the concentration-time profile, and >45% different from both adjacent samples	0	4	0	0.4	0	0	0	0
All of this subject's samples had assayed values less than the lower limit of quantitation except for the 72 h sample requested to ensure that values were not in error.	15	15	1.6	1.6	0	2	0	0.2
Total	15	19	1.6	2.0	0.0	2.0	0	0.2

Did use of recalculated plasma concentration data change study outcome? No

The study protocol states that bioequivalence of the Dilantin capsule lots compared in this study would be concluded if all of the following criteria are met:

Cmax criteria: The 90% confidence interval for the ratio of the test-to-reference least-squares mean Cmax values, based on log transformed Cmax data, is within the interval of 80% to 125%.

AUC criteria: The 90% confidence interval for the ratio of the test-to-reference least-squares mean AUC values, based on log transformed AUC data, is within the interval of 92% to 109%.

Dilantin 100 mg capsules containing (b) (4) sodium phenytoin met the protocol-defined criterion for Cmax but did not meet protocol-defined criterion for AUC, relative to marketed Dilantin 100 mg Kapseals. The Division of Bioequivalence uses 80-125% criteria for AUC as well as Cmax.

F. Formulation

Location in appendix	Section IV.B, Page 37
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	USP (Test 1)
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	USP Apparatus 1 (Basket)
Rotation (rpm)	50 rpm
Firm's proposed specifications	NMT 45% (Q) in 30 minutes NMT 60% (Q) in 60 minutes NLT 70% (Q) in 120 minutes
FDA-recommended specifications	Same as the firm's specifications.
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	Yes
If not then why?	N/A

F_2 metric, test compared to reference	
Strength	**F_2 metric**
100 mg	61.50

H. Waiver Request(s)

Strengths for which waivers are requested	N/A
Regulation cited	N/A
Proportional to strength tested *in vivo*?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	No waiver requests.

I. Deficiency Comments

1. The firm did not provide the following information for the test lot no. 05-026235 used in bioequivalence studies: manufacture date, batch size, production batch size, potency, and content uniformity.

   The firm did not provide the following information for the reference lot no. 05-026268 used in bioequivalence studies: expiration date, and potency.

2. The firm did not provide the test article inventory data (records of the test and reference drugs received and dispensed) for the fasting and fed studies.

3. The firm provided only the summary table for bioanalytical method validation. The firm should provide the complete bioanalytical method validation report.

4. According to the summary table for bioanalytical method validation, the recovery of the Analyte (phenytoin) is 88% and that of internal standard ((b) (4)) is 126%. The firm should explain the high percent recovery of the internal standard and also the reasons for such differences in the recovery of the analyte and internal standard.

5. The firm did not provide bioanalytical method SOPs, and SOPs dealing with analytical repeats of study samples.

6. The firm conducted comparative dissolution testing using the USP method [900 mL of water using USP Apparatus 1 (Basket) at 50 rpm]. In dissolution testing, the firm used lot no. 01615C for the test and lot no. 01095F for the reference products. However, in the in vivo bioequivalence studies, the firm used lot nos. 05-026235 and 05-026268 for the test and reference products, respectively. The firm should note that the dissolution testing should be conducted on the lots used in the bioequivalence studies.

7. Subjects in the fasting and fed bioequivalence studies were enrolled in two groups. The firm should note that in the future if the subjects in the studies are dosed in more than one group, appropriate terms for group should be included in the model for statistical analysis.

8. The firm may note that the FDA does not request a fed BE study for this drug product. Also, a bioequivalence limit of 80-125% for AUC and Cmax is used by the FDA for this drug product. Of note is that the firm's fed BE study does not pass their protocol proposed limits for AUC, although it passes the accepted FDA limit for 90% confidence intervals.

J. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Parke-Davis on its Dilantin Capsule (phenytoin sodium extended-release capsule manufactured using a new optimized process), 100 mg (lot # 05-026235) comparing it to the reference product Dilantin Kapseal® (phenytoin sodium extended release capsule currently marketed), 100 mg (lot # 05-026268) is incomplete due to deficiencies noted above.

2. The *in vivo* bioequivalence study conducted under fed conditions by Parke-Davis on its Dilantin Capsule (phenytoin sodium extended-release capsule manufactured using a new optimized process), 100 mg (lot # 05-026235) comparing it to the reference product Dilantin Kapseal® (phenytoin sodium extended release capsule currently marketed), 100 mg (lot # 05-026268) is incomplete due to deficiencies noted above.

3. The dissolution testing conducted by the firm on phenytoin extended-release capsules, 100 mg, is incomplete. The dissolution testing should be conducted in 900 mL of water using USP Apparatus 1 (Basket) at 50 rpm. The test product should meet the following specifications:

   Not more than 45% (Q) in 30 minutes
   Not more than 60% (Q) in 60 minutes
   Not less than 70% (Q) in 120 minutes

Devvrat Patel 3/27/2006

Devvrat Patel, Pharm.D. Date Signed
Division of Bioequivalence, Branch V

Dhariwal 3/27/2006

Kuldeep R. Dhariwal, Ph.D. Date Signed
Team Leader, Division of Bioequivalence, Branch V

Dale P. Conner 3/28/06

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

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	A4121001
Study Title	A Single-Dose Bioequivalence Study in Healthy Volunteers Comparing 100-mg Dilantin® Capsules Containing (b) (4) Sodium Phenytoin and Manufactured Using a New Optimized Process to Currently Marketed 100-mg Dilantin Kapseals®
Clinical Site	Pfizer Global Research and Development, 2800 Plymouth Rd, Ann Arbor, MI 48105
Principal Investigator	Thomas Charles Stock, MD
Study/Dosing Dates	**Group1 (Subjects 10011001-10011012):** Period 1: June 27, 2005 Period 2: July 11, 2005 Period 3: July 25, 2005 Period 4: August 8, 2005 **Group 2 (Subjects 10011013-1011024):** Period 1: July 8, 2005 Period 2: July 22, 2005 Period 3: August 5, 2005 Period 4: August 19, 2005
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	8/18/2005 to 08/31/2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	65 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Dilantin Capsule (Optimized product contains (b) (4) phenytoin sodium and manufactured using a new optimized process)	Dilantin Kapseal (Commercial product contains the currently marketed phenytoin sodium formulation)
Manufacturer	Parke Davis	Parke Davis
Batch/Lot No.	05-026235	05-026268
Manufacture Date	Not provided	N/A
Expiration Date	N/A	Not provided
Strength	100 mg	100 mg
Dosage Form	Capsule	Capsule
Batch Size	Not provided	N/A
Production Batch Size	Not provided	N/A
Potency	Not provided	Not provided
Content Uniformity (mean, %CV)	Not provided	Not provided
Formulation	See Appendix Section B	
Dose Administered	100 mg x 1 capsule	
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	2
Washout Period	14 days
Randomization Scheme	ABBA: 10011001, 10011004, 10011006, 10011008, 10011011, 10011012, 10011013, 10011014, 10011017, 10011020, 10011021, 10011022 BAAB: 10011002, 10011003, 10011005, 10011007, 10011009, 10011010, 10011015, 10011016, 10011018, 10011019, 10011023, 10011024
Blood Sampling Times	0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post-dose.
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	The blood samples were collected in vacuum blood collection tubes containing K3 EDTA. The samples were centrifuged, and the plasma was transferred into tubes and stored in a freezer at -20 °C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	All subjects fasted for 8 hours before dosing and remained fasted for 4 hours post-dose.
Length of Confinement	Overnight for at least 10 hours before dosing and for 24 hours after dosing. Subjects returned to clinic for the 36, 48, 72, and 96 hours blood samples.
Safety Monitoring	Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead ECG, and safety laboratory tests. Subjects were monitored throughout the confinement for adverse reactions.

Comments on Study Design:

In the protocol and clinical study report, the firm did not mention anything about subjects being dosed in two groups. The firm analyzed data as if subjects were dosed in one group. However, according to the Administration Schedule, subjects were dosed in two groups as noted in above table.

The study design is appropriate.

b) Clinical Results

Table 1 Demographics of Study Subjects

	Study No.: A4121001 (Fasted Study)	
	Treatment Groups	
	Test Product N=24	Reference Product Same as for test product. This was a cross-over study.
Age (years)		
Mean ± SD	37.6 ± 12.6	
Range	18-55	
Groups		
<18	0	
18-44	15	
45-64	9	
65-75	0	
>75	0	
Sex		
Female	1	
Male	23	
Race		
Asian	NR	
Black	5	
Caucasian	17	
Hispanic	NR	
Other	2	
Other Factors		

NR = not recorded, recorded categories were Caucasian, Black and Other

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
10011004	Subject was withdrawn due to lack of compliance (positive drug screen).	Prior to start of Period 2	N
10011017	Subject withdrew consent.	During Period 2	N

Table 3 Study Adverse Events

Adverse events table for both fasting and fed bioequivalence studies is provided below.

Body System/Adverse Event (All Causalities)	Reported Incidence by Treatment Groups			
	Fasted Bioequivalence Study Study No.: A4121001		Fed Bioequivalance Study Study No.: A4121002	
	Test (100 mg capsule)	Reference (100 mg Kapseal)	Test (100 mg capsule)	Reference (100 mg Kapseal)
	N (%)			
Renal and urinary	-	-	0 (0)	1 (3)
Eye Disorders	-	-	1 (3)	0 (0)
Investigations	-	-	1 (3)	0 (0)
Metabolism and nutrition disorders	-	-	0 (0)	1 (3)
Ear and labyrinth disorders	1 (4)	1 (4)	-	-
Gastrointestinal disorders	1 (4)	1 (4)	5 (16)	4 (13)
General disorders and administration site conditions	0 (0)	1 (4)	-	-
Immune system disorders	1 (4)	1 (4)	-	-
Infections and infestations	2 (8)	2 (9)	2 (6)	1 (3)
Injury, poisoning, and procedural complications	1 (4)	3 (13)	2 (6)	2 (7)
Musculoskeletal and connective tissue disorders	2 (8)	3 (13)	1 (3)	1 (3)
Nervous system disorders	3 (13)	4 (17)	8 (25)	8 (27)
Respiratory, thoracic and mediastinal disorders	1 (4)	1 (4)	-	-
Skin and subcutaneous tissue disorders	1 (4)	1 (4)	1 (3)	2 (7)
Surgical and medical procedures	0 (0)	1 (4)	-	-
Total	9 (38)	13 (57)	14 (44)	13 (43)

- = None reported

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
None		

Comments on Dropouts/Adverse Events/Protocol Deviations:

According to Clinical Study Report, a total of 34 adverse events were reported: 21 following administration of Dilantin Kapseal (Reference treatment) and 13 following administration of Dilantin capsule (Test treatment). In the adverse events table provided by the firm, the firm provided number of subjects experiencing adverse events, not the total number of adverse events reported.

No serious adverse events were reported during the entire course of the study.

The firm's calculated pharmacokinetic parameters (using the actual sampling times) were similar to the reviewer's calculated parameters (using the scheduled sample collection times).

The protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Parent				Metabolite			
QC Conc. (ng/mL)	60.00	600.0	1250	4000	N/A			
Inter day Precision (%CV)	6.10	4.09	4.73	5.60				
Inter day Accuracy (%)	102.17	103.98	102.05	101.36				

Cal. Standards Conc (ng/mL)	20.00	40.00	80.00	200.0	400.0	800.0	2000	4500	5000	
Inter day Precision (%CV)	5.28	3.74	2.90	2.76	4.10	4.81	3.07	3.37	3.11	
Inter day Accuracy (%)	100.16	100.75	98.98	100.72	97.94	99.86	99.64	99.50	100.62	
Linearity Range (range of R^2 values)	0.9972 to 0.9999									

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Randomly

Comments on Chromatograms:

Chromatograms submitted by the firm are acceptable.

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

SOP No.	Date of SOP	SOP Title
Not provided		

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	SOPs not provided.
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

The firm did not provide analytical method and sample re-assay SOPs.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

Replicate 1

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	ng/mL	1.40	23.84	1.23	18.50
Tmax	hour	4.00	64.20	4.30	40.96
AUCT	ng·hr/mL	36.44	36.38	35.30	37.04
AUCI	ng·hr/mL	38.46	45.85	36.77	41.54
Kel	$hour^{-1}$	0.05	24.33	0.05	23.87
THALF	hour	14.78	53.08	14.03	34.51

Replicate 2

Parameter	Units	Test		Reference	
		Mean	CV%	Mean	CV%
Cmax	ng/mL	1.45	16.67	1.33	16.92
Tmax	hour	3.40	37.69	4.67	63.20
AUCT	ng·hr/mL	37.80	32.32	36.58	33.95
AUCI	ng·hr/mL	39.78	40.50	38.44	40.82
Kel	$hour^{-1}$	0.05	27.14	0.05	25.08
THALF	hour	15.12	50.86	14.95	46.13

Comments on Pharmacokinetic and Statistical Analysis:

- One subject (Subject 10011023) had quantifiable predose plasma concentration in period 2, which was less than 5% of the corresponding Cmax value. This subject had predose plasma concentrations that were more than 5% of the corresponding Cmax values in periods 3 and 4. Therefore, this subject was excluded from the statistical analysis. Summary of these predose samples is provided below:

Table 5. Predose Samples With Quantifiable Plasma Phenytoin Concentrations, Protocol A4121001

Subject	Period	Treatment	Predose Concentration (µg/mL)	Cmax (µg/mL)	Predose % of Cmax[a]
10011023	2	100-mg (b) (4) Capsules (test)	0.0836	1.81	4.62
10011023	3	100-mg Capsules (test)	0.0824	1.34	6.15
10011023	4	100-mg Dilantin Kapseals (Ref)	0.112	1.95	5.74

[a] (Predose/Cmax) * 100%

- Since the study was performed in two groups, the data were analyzed with the group effect incorporated in the PROC MIXED model. After including the group factor in the statistical analyses, the treatment*group interaction was not statistically significant for any of the log-transformed pharmacokinetic parameters. Therefore, the reviewer performed statistical analysis on combined groups 1 and 2 data as recommended by DBE in Control Document #98-392 ((b) (4) , 9/10/1999). The document is attached in Section F.

- The reviewer calculated 90% confidence intervals for the test to reference ratios for the natural log transformed parameters, AUC_{0-t} $AUC_{0-\infty}$ and C_{max} are within acceptable limits of 80%-125%. The DBE uses 80-125% limits as acceptance criteria.

- Dilantin 100 mg capsules containing (b) (4) sodium phenytoin met the firm's protocol-defined criteria (80-125% for Cmax and 92-109% for AUC) for Cmax as well as AUC. The DBE uses 80-125% criteria for bioequivalence of this drug product.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study is incomplete.

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Replicate 1

TIME (HR)	TEST (N=21)		REFEREENCE (N=21)	
	MEAN1 (ng/mL)	%CV	MEAN2 (ng/mL)	%CV
0	0.00	.	0.00	.
0.5	188.07	111.56	144.92	112.30
1	712.28	83.26	558.69	71.18
2	1144.58	42.55	954.03	39.66
3	1236.09	27.17	1089.54	24.71
4	1265.96	20.86	1125.27	18.75
5	1184.51	21.35	1119.37	17.49
6	1157.11	17.98	1072.43	19.53
8	1090.98	18.86	1016.36	19.79
12	995.61	17.90	964.26	19.89
16	848.89	23.04	833.29	21.99
24	643.65	32.71	620.37	28.83
36	379.75	53.16	380.37	51.70
48	222.42	70.44	214.91	61.23
72	79.69	139.59	71.61	107.45
96	30.45	271.58	13.45	200.09

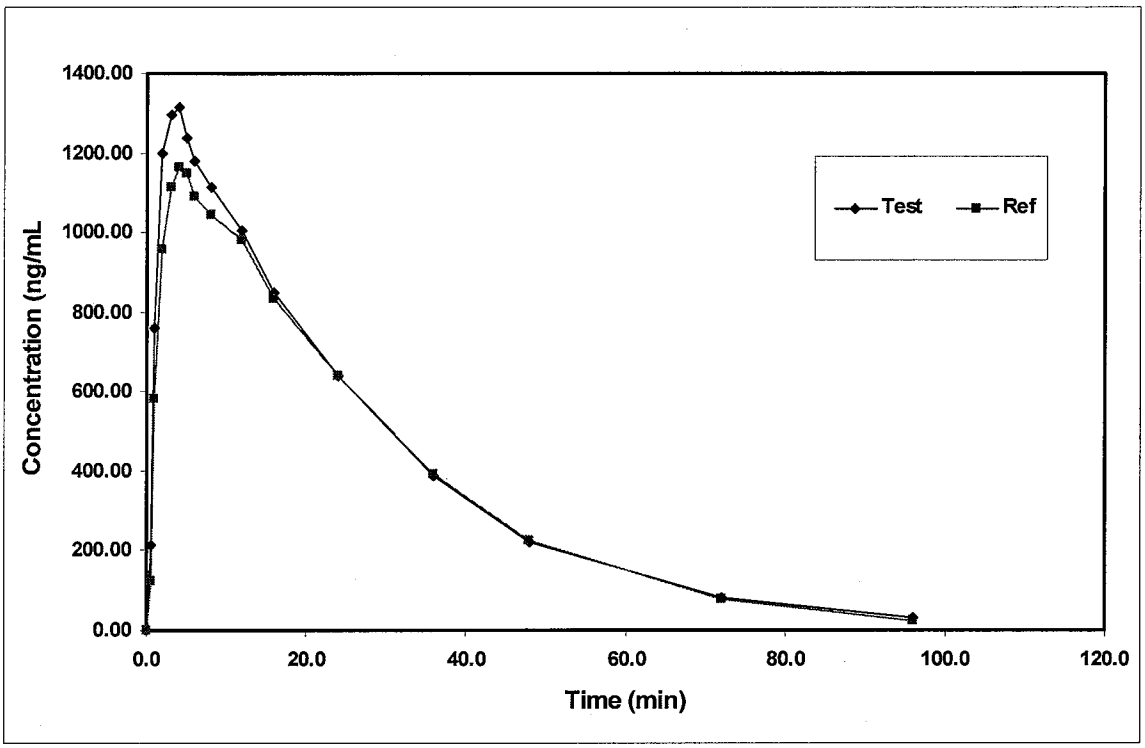
Replicate 2

TIME (HR)	TEST (N=21)		REFEREENCE (N=21)	
	MEAN1 (ng/mL)	%CV	MEAN2 (ng/mL)	%CV
0	0.00	.	0.00	.
0.5	235.85	90.55	106.06	109.03
1	810.41	62.26	607.67	68.89
2	1255.31	28.70	961.01	43.44
3	1354.77	16.94	1133.20	29.21
4	1367.28	16.69	1199.74	19.47
5	1287.43	13.92	1175.57	23.36
6	1202.41	16.81	1107.02	18.48
8	1136.45	16.27	1067.72	16.71
12	1013.59	20.35	1001.80	15.86
16	845.94	24.36	832.73	22.54
24	634.60	29.72	657.04	29.52
36	393.61	49.96	402.36	46.78
48	220.67	66.60	233.06	66.80
72	84.58	132.73	86.43	123.66
96	31.11	247.02	31.44	233.89

Composite Plasma Values for Both Replicates

TIME (HR)	TEST (N=21)		REFEREENCE (N=21)	
	MEAN1 (ng/mL)	%CV	MEAN2 (ng/mL)	%CV
0	0.00	.	0.00	.
0.5	211.96	99.31	125.49	112.22
1	761.35	71.73	583.18	69.28
2	1199.95	35.57	957.52	41.10
3	1295.43	22.42	1111.37	26.89
4	1316.62	18.92	1162.51	19.19
5	1235.97	18.01	1147.47	20.67
6	1179.76	17.28	1089.72	18.83
8	1113.71	17.47	1042.04	18.19
12	1004.60	18.98	983.03	17.80
16	847.41	23.41	833.01	21.99
24	639.12	30.89	638.71	29.00
36	386.68	50.93	391.36	48.66
48	221.54	67.72	223.99	63.70
72	82.14	134.42	79.02	116.79
96	30.78	256.00	22.66	246.85

Figure 1 Mean Composite Plasma Concentrations for Both Replicates, Single-Dose Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	A4121002
Study Title	A Single-Dose Bioequivalence Study in Healthy Volunteers Comparing 100-mg Dilantin® Capsules Containing (b) (4) Sodium Phenytoin and Manufactured Using a New Optimized Process to Currently Marketed 100-mg Dilantin® Kapseals® Under Fed Conditions
Clinical Site	Pfizer Global Research and Development, 2800 Plymouth Rd, Ann Arbor, MI 48105
Principal Investigator	Thomas Charles Stock, MD
Study/Dosing Dates	**Group 1 (Subjects 10011001 to 10011016):** Period 1: August 22, 2005 Period 2: September 6, 2005 **Group 2 (Subjects 10011017 to 10011032):** Period 1: August 24, 2005 Period 2: September 7, 2005
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	September 14, 2005 to October 18, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	57 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Dilantin Capsule (Optimized product contains (b) (4) phenytoin sodium and manufactured using a new optimized process)	Dilantin Kapseal (Commercial product contains the currently marketed phenytoin sodium formulation)
Manufacturer	Parke Davis	Parke Davis
Batch/Lot No.	05-026235	05-026268
Manufacture Date	Not provided	N/A
Expiration Date	N/A	Not provided
Strength	100 mg	100 mg
Dosage Form	Capsule	Capsule
Batch Size	Not provided	N/A
Production Batch Size	Not provided	N/A
Potency	Not provided	Not provided
Content Uniformity(mean, %CV)	Not provided	Not provided
Formulation	See Appendix Section B	
Dose Administered	100 mg x 1 capsule	
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	14 days (15 days for Group 1 subjects #10011001 to 10011016)
Randomization Scheme	AB: 10011001, 10011002, 10011005, 10011008, 10011009, 10011010, 10011014, 10011016, 10011018, 10011019, 10011022, 10011024, 10011025, 10011028, 10011029, 10011032 BA: 10011003, 10011004, 10011006, 10011007, 10011011, 10011012, 10011013, 10011015, 10011017, 10011020, 10011021, 10011023, 10011026, 10011027, 10011030, 10011031
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 12**
Blood Sampling Times	0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours post-dose.
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	The blood samples were collected in vacuum blood collection tubes containing K3 EDTA. The samples were centrifuged, and the plasma was transferred into tubes and stored in a freezer at -20 °C until analysis.
Length of Confinement	Overnight for at least 10 hours before dosing and for 24 hours after dosing. Subjects returned to clinic for the 36, 48 and 72 hours blood samples.
Safety Monitoring	Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead ECG, and safety laboratory tests. Subjects were monitored throughout the confinement for adverse reactions.
Length of Fasting before Meal	Overnight for at least 10 hours before receiving standard breakfast and for 4 hours post-dose.
Standard FDA Meal Used?	Yes
If no, then meal is listed in table below	N/A

Comments on Study Design:

The dose was administered with 4 oz of whole milk within 5 minutes of completing breakfast.

The study design is appropriate.

b) Clinical Results

Table 12 Demographics of Study Subjects

	Study No.: A4121002 (Fed Study)	
	Treatment Groups	
	Test Product N=32	Reference Product Same as for test product. This was a cross-over study.
Age (years)		
Mean ± SD	38.2 ± 11.8	
Range	19-55	
Groups		
<18	0	
18-44	19	
45-64	13	
65-75	0	
>75	0	
Sex		
Female	2	
Male	30	
Race		
Asian	1	
Black	1	
Caucasian	28	
Hispanic	NR	
Other	2	
Other Factors		

NR = Not reported, recorded race categories did not include Hispanic

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
10011010	Subject was discontinued from the study due to adverse event (blurred vision right eye and headache)	During Period 1	N
10011032	Subject dropped.	Prior to start of Period 2	N

Table 14 Study Adverse Events

Adverse events information is provided in Table 3.

Table 15 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
No sample was collected for subject 10011018 at the 16-hour time point on Day 15 due to difficulty gaining venous access.	--	10011018
The inclusion criteria in the protocol stated that subject with BMI of approximately 18 to 30 kg/m2 were eligible. Subjects in Group B (last 16 subjects enrolled) were accepted with BMI's of approximately ≤ 32 kg/m2 in order to complete the targeted enrollment.	10011017 – 10011032	10011017 – 10011032
Study Day 15 dosing was moved to Day 16 for subjects in Group A (the first 16 enrolled) in order to accommodate a national holiday.	1011001 – 10011016	1011001 – 10011016

Comments on Adverse Events/Protocol Deviations:

Adverse events table is provided as part of Table 3.

According to Clinical Study Report, a total of 46 adverse events were reported: 20 following administration of Dilantin Kapseal (Reference treatment) and 26 following administration of Dilantin capsule (Test treatment). In the adverse events table provided by the firm, the firm provided number of subjects experiencing adverse events, not the total number of adverse events reported.

No serious adverse events were reported during the course of the study.

The firm's calculated pharmacokinetic parameters (using the actual sampling times) were similar to the reviewer's calculated parameters (using the scheduled sample collection times).

The protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Parent				Metabolite			
QC Conc. (ng/mL)	60.00	600.0	1250	4000	N/A			
Inter day Precision (%CV)	4.16	3.90	5.25	4.44				
Inter day Accuracy (%)	103.10	102.34	104.43	103.72				

Cal. Standards Conc (ng/mL)	20.00	40.00	80.00	200.0	400.0	800.0	2000	4500	5000	
Inter day Precision (%CV)	6.13	3.50	2.93	3.13	3.37	3.30	2.72	2.31	2.73	
Inter day Accuracy (%)	102.35	99.70	98.58	99.50	99.96	100.12	99.63	99.56	100.55	
Linearity Range (range of R^2 values)	0.9988 to 0.9999									

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Randomly

Comments on Chromatograms:

Chromatograms submitted by the firm are acceptable.

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
Not provided		

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	SOPs not provided
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

The firm did not provide analytical method and sample re-assay SOPs.

d) Pharmacokinetic Results

Note: The pharmacokinetic results exclude data for Subject #10011030.

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 22 and Figure 2.

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
AUC_{0-t}	ng·hr/mL	33.84	25.30	31.83	25.23	1.06
$AUC_{0-\infty}$	ng·hr/mL	35.35	27.05	33.43	25.72	1.06
CMAX	ng/mL	1.36	29.88	1.31	23.37	1.04
TMAX	hour	8.33	61.22	8.49	45.13	0.98
KE	$hour^{-1}$	0.05	19.19	0.06	19.88	0.94
THALF	hour	13.55	19.63	12.87	22.65	1.05
$LAUC_{0-t}$	ng·hr/mL	32.63	0.88	30.77	0.89	1.06
$LAUC_{0-\infty}$	ng·hr/mL	33.95	0.89	32.29	0.85	1.05
LCMAX	ng/mL	1.29	25.63	1.28	18.68	1.01

Table 20 Geometric Means and 90% Confidence Intervals

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$LAUC_{0-t}$	32.68	30.90	1.06	99.87	112.04
$LAUC_{0-\infty}$	34.02	32.44	1.05	99.02	111.06
LCMAX	1.29	1.28	1.01	92.23	111.08

* Excluding data for Subject #10011030.

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$LAUC_{0-t}$	29.50	30.41	0.97	82.03	114.70
$LAUC_{0-\infty}$	33.49	31.94	1.05	99.11	110.95
LCMAX	1.19	1.26	0.95	81.85	110.03

* Includes data from all subjects.

Table 21 Additional Study Information

Root mean square error, AUC_{0-t}	0.1282	
Root mean square error, $AUC_{0-\infty}$	0.1279	
Root mean square error, Cmax	0.2074	
Mean ratio $AUC_{0-t}/AUC_{0-\infty}$	T = 0.96	R = 0.95
Range of values, ratio $AUC_{0-t}/AUC_{0-\infty}$	T = 0.90 – 0.99	R = 0.82 – 0.99
Kel and $AUC_{0-\infty}$ determined for how many subjects?	29	
Do you agree or disagree with firm's decision?	Ke and $AUC_{0-\infty}$ were determined for all subjects used in analysis.	
Indicate the number of subjects with the following:		
-measurable drug concentrations at 0 hr	None	
-first measurable drug concentration as Cmax	None	
Were the subjects dosed as more than one group?	Yes	

Comments on Pharmacokinetic and Statistical Analysis:

- Since the study was performed in two groups, the data were analyzed with the group effect incorporated in the model. After including the group factor in the statistical analyses, the treatment*group interaction was not statistically significant for any of the log-transformed pharmacokinetic parameters. Therefore, the reviewer performed statistical analysis on combined groups 1 and 2 data as recommended by DBE in Control Document #98-392 ((b) (4) , 9/10/1999). The document is attached in Section F.

- Subject 10011030 had plasma phenytoin concentrations in Period 2 following administration of the test treatment that were zero in all samples through 48 hours postdose, with a single quantifiable concentration of 97.65 ng/mL at 72 hours postdose. Cmax and AUC0-t values were reported for this subject based on the single observed concentration. AUC0-inf could not be estimated. The firm states that the FDA guidance on Statistical Approaches to Establishing Bioequivalence suggests several possibilities, including problems occurring during study conduct and sample analysis, product failure, or a subject-by-formulation interaction. The explanation provided by the firm is included in Section F.

- The reviewer calculated 90% confidence intervals for the test to reference ratios for the natural log transformed parameters, AUC_{0-t} $AUC_{0-\infty}$ and C_{max} are in agreement with the firm's reported values and are within 80%-125%.

- The protocol states that bioequivalence of the Dilantin capsule lots compared in this study would be concluded if all of the following criteria are met:

  Cmax criteria: The 90% confidence interval for the ratio of the test-to-reference least-squares mean Cmax values, based on log transformed Cmax data, is within the interval of 80% to 125%.

  AUC criteria: The 90% confidence interval for the ratio of the test-to-reference least-squares mean AUC values, based on log transformed AUC data, is within the interval of 92% to 109%.

- Dilantin 100 mg capsules containing (b) (4) sodium phenytoin met the protocol-defined criterion for Cmax but did not meet protocol-defined criterion for AUC, relative to marketed Dilantin 100 mg Kapseals.

- The firm states that considering that bioequivalence was established under fasted conditions and that there is no relevant food effect with the marketed product, and that in vitro performance relative to marketed product was shown to be very similar, the in vivo performance of the optimized product is considered acceptable for commercialization.

- The 90% confidence interval limits recommended by the DBE are 80-125% for all three pharmacokinetic parameters. Parke Davis submitted a correspondence and a protocol and advocated narrowing the confidence interval for AUC from 80-125% to 92-109% in May 2000. The OGD did not change the confidence interval limits for phenytoin AUC.

- The DBE will use 80-125% criteria for assessing the bioequivalence and using this criterion, the study passes.

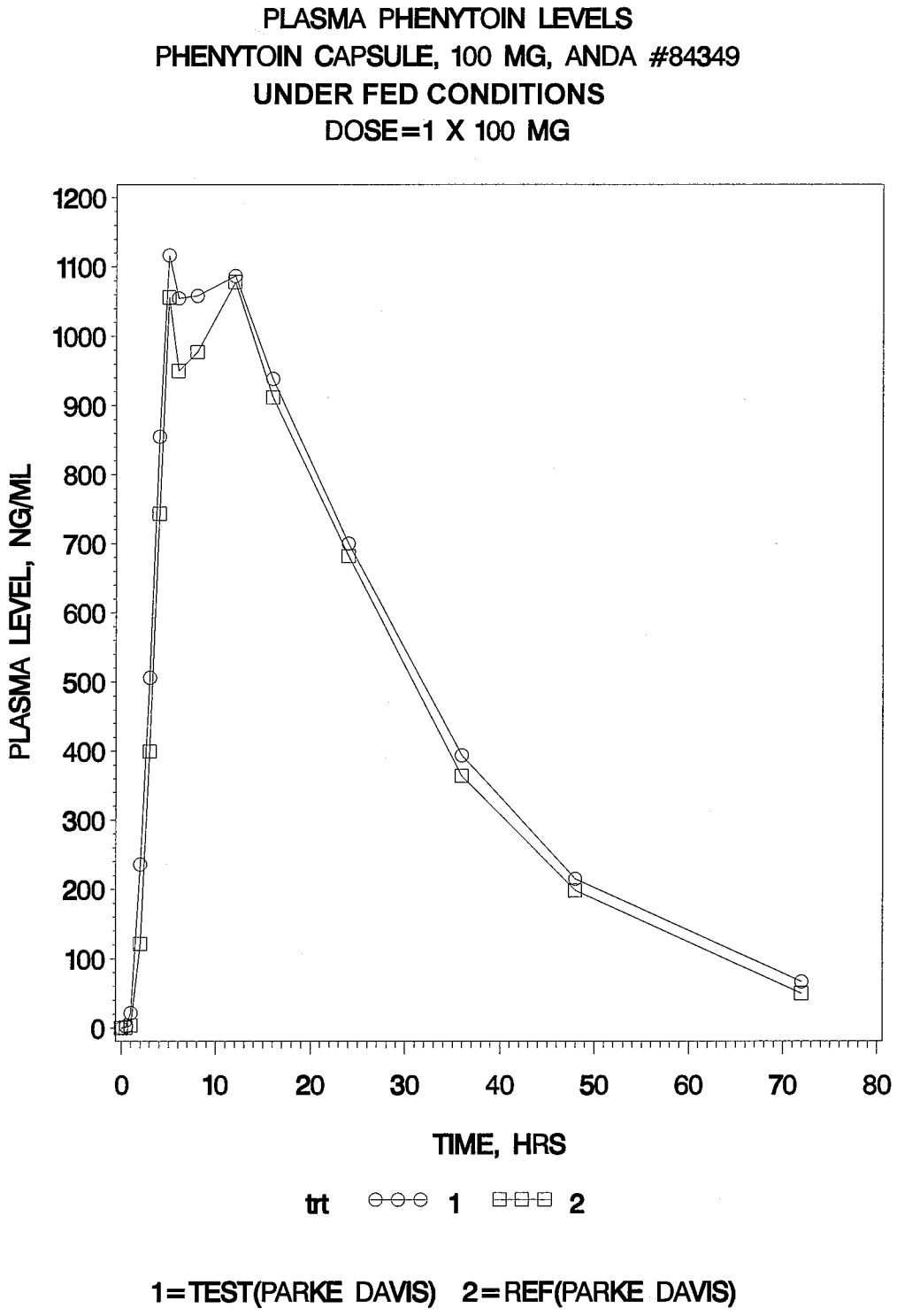
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study is incomplete.

Table 22 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

TIME (HR)	TEST (N=29)		REFEREENCE (N=29)		RATIO T/R
	MEAN1 (ng/mL)	%CV	MEAN2 (ng/mL)	%CV	
0	0.00	.	0.00	.	.
0.5	2.57	305.03	0.97	538.52	2.65
1	21.78	176.57	4.07	261.46	5.35
2	235.98	131.74	121.39	92.71	1.94
3	506.26	78.84	399.60	87.46	1.27
4	855.14	56.14	742.95	55.78	1.15
5	1116.73	49.29	1055.82	45.37	1.06
6	1054.69	46.70	950.14	43.79	1.11
8	1058.29	38.78	977.20	32.18	1.08
12	1086.79	23.96	1078.06	23.36	1.01
16	938.58	23.04	911.88	26.84	1.03
24	699.93	30.59	681.80	29.53	1.03
36	393.71	40.08	363.56	37.00	1.08
48	214.82	50.05	198.26	50.33	1.08
72	66.89	74.05	49.73	88.97	1.35

Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

Formulation of phenytoin sodium extended-release capsule, 100 mg is provided below:

Ingredient[1]	Typical Amount mg/Capsule	Approximate Amount (%) Capsule Contents
Phenytoin Sodium (b) (4), USP	100.00	43
Lactose Monohydrate, NF (b) (4)	(b) (4)	
Confectioner's Sugar, NF		
Talc (b) (4) USP		
Magnesium Stearate, NF		
Total	229.90	

Comments (Formulation)

The firm noted that the optimized manufacturing process formulation has the same composition as the current commercial product. The quality and grades of the excipients did not change.

Product Description

Strength	Test	Reference
100 mg	Hard filled No. 3 capsule containing a white powder. The medium orange cap has the Parke-Davis logo printed in black ink and white opaque body has "DILANTIN" over "100 mg" printed in black.	Hard, filled No. 3, natural transparent capsule with an orange band having "DILANTIN" printed in black ink on the cap and "100 mg" printed in black ink on the body and containing a white powder or Hard, filled No. 3, natural transparent capsule with an orange band having P-D 362 printed in black ink and containing a white powder.

C. Dissolution Data

The firm conducted dissolution testing using the following USP 29 method:

Medium:	Water
Volume:	900 mL at 37 °C ± 0.5 °C
Apparatus:	1 (Basket) at 50 rpm
Specifications:	Not more than 45% (Q) in 30 minutes Not more than 60% (Q) in 60 minutes Not less than 70% (Q) in 120 minutes

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range) of Label Claim			Study Report Location
					30 Min	60 Min	120 Min	
N/A	Dilantin extended phenytoin sodium capsules USP Kapseal/01095F	Capsule	Conducted according to proposed specifications found on page 1007 of submission described under Study Report Location in this table.	12	30 (b) (4)	52 (b) (4)	74 (b) (4)	A summary of the studies is found starting on page 36 of the CMC section of the electronic submission to ANDA 84-349, submitted on 12/15/2005. It can be found at n84349\cmc\cmc.pdf in the submission
N/A	Dilantin oral capsules/01615C	Capsule	Same as above	12	34 (b) (4)	59 (b) (4)	80 (b) (4)	

Comments (Dissolution):

The firm conducted dissolution testing using the USP method. The test product meets the USP specifications.

According to dissolution data, the firm used lot no. 01615C for the test and lot no. 01095F for the reference products. However, in the in vivo bioequivalence studies, the firm used lot nos. 05-026235 and 05-026268 for the test and reference products, respectively. The firm should note that dissolution testing should be conducted on the lots used in the bioequivalence studies. Therefore, the dissolution testing is incomplete.

D. Consult Reviews

None

E. SAS Output

	Fasting Study	Fed Study
SAS Program	Repl_dp2.txt	BE02dp4.txt
Statistical Output	Fast_STAT.txt	Fed_STAT.txt
Plasma Concentration Data	conc.txt	conc.txt
PK Data	pk.txt	pk.txt

F. Additional Attachments: Not to be Released Under FOI

- Control document #98-392 that discusses the Group-by-Treatment interaction is attached below.

98-392.pdf

- In the fed bioequivalence study, subject 10011030 had plasma phenytoin concentrations in Period 2 following administration of the test treatment that were zero in all samples through 48 hours postdose, with a single quantifiable concentration of 97.65 ng/mL at 72 hours postdose. The firm provided the following explanation:

> With respect to possible problems with study conduct and sample analysis, it is important to note the following. Trial treatments were administered under the supervision of investigator site personnel. The oral cavity of each subject was examined following dosing to assure the trial medication was taken. Subjects were under medical supervision for the first 24 hours after drug administration. This subject had no history or evidence of a clinically relevant gastrointestinal disease and the subject reported no AEs such as vomiting or diarrhea. The subject's plasma samples were reassayed for phenytoin concentrations and reassay values were nearly identical to the original values.

With respect to product failure it is important to note that every capsule undergoes a weight check during the packaging process. Further, the release mechanism does not rely on a single unit (such as an osmotic pump) that may be more sensitive to gastrointestinal transit time or problems with the release mechanism (ie, plugged orifice).

As noted in the FDA guidance,[5] a subject-by-formulation interaction could occur when an individual is representative of subjects present in the general population in low numbers, for whom the relative bioavailability of the 2 products is markedly different than for the majority of the population, and for whom the 2 products are not bioequivalent, even though they might be bioequivalent in the majority of the population. However, given that the 2 formulations are compositionally equivalent and use the same method to control drug dissolution, it is difficult to theorize how a subject-by-formulation interaction could occur.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 84-349 APPLICANT: Parke-Davis Pharmaceutical

DRUG PRODUCT: Dilantin Kapseals® (Phenytoin Sodium Extended-Release Capsules, USP), 100 mg

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

1. Please provide the following information for the test lot no. 05-026235 (Dilantin® Extended Release Capsule containing (b) (4) phenytoin sodium and manufactured using a new optimized process) used in bioequivalence studies: manufacture date, batch size, production batch size, potency, and content uniformity.

   Additionally, please provide the following information for the reference lot no. 05-026268 (Dilantin Kapseal® containing the currently marketed phenytoin sodium) used in bioequivalence studies: expiration date, and potency.

2. Please provide the test article inventory data (records of the test and reference drugs received and dispensed) for fasting and fed bioequivalence studies. Additionally, please provide records of test and reference drug products administered to each subject.

3. Please submit the complete bioanalytical method validation report.

4. The recovery of the analyte (phenytoin) is 88% and that of internal standard ((b) (4)) is 126%. Please explain the high % recovery of the internal standard ((b) (4)) and also the reasons for such differences in the recovery of the analyte and internal standard.

5. You have not provided bioanalytical method Standard Operating Procedures (SOPs). Please submit all SOPs including those for sample reassays.

6. For dissolution testing, you have used lot no. 01615C for the test and lot no. 01095F for the reference products. However, in the in vivo bioequivalence studies, you have used lot nos. 05-026235 and 05-026268 for the test and reference products, respectively. Please note that the dissolution testing

should be conducted on the lots used in the bioequivalence studies. Please conduct dissolution testing using the USP method on both test and reference product lots used in the in vivo bioequivalence studies.

7. Subjects in the fasting and fed bioequivalence studies were enrolled in two groups. Please note that in the future if the subjects are dosed in more than one group, appropriate terms for group should be included in the model for statistical analysis.

8. Please note that the FDA does not request a fed BE study for this drug product. Also, a bioequivalence limit of 80-125% for AUC and Cmax is used by the FDA for this drug product. Of note is that your fed BE study does not pass your protocol proposed limits for AUC, although it passes the accepted FDA limit for 90% confidence intervals.

Sincerely yours,

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

CC: ANDA 84-349
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Patel

Printed in final on 3/27/2006
V:\FIRMSNZ\PARKEDAV\LTRS&REV\84349S1205.doc

Endorsements: (Final with Dates)
HFD-658/ Patel 3/27/06
HFD-658/ Dhariwal 3/27/06
HFD-658/ Thompson
HFD-650/ D. Conner 3/28/06

BIOEQUIVALENCE - INCOMPLETE Submission dates: 12/15/2005
02/13/2006

✓1. **FASTING STUDY (STF)** Strength: 100 mg
Outcome: IC
Clinical: Pfizer Global Research and Development, Ann Arbor, MI
Analytical: (b) (4)

✓2. **FED STUDY (STP)** Strength: 100 mg
Outcome: IC
Clinical: Pfizer Global Research and Development, Ann Arbor, MI
Analytical: (b) (4)

Outcome Decisions: **IC** - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	84-349
Drug Product Name	Dilantin Kapseals® (Phenytoin Sodium Extended-Release Capsules, USP)
Strength	100 mg
Applicant Name	Parke-Davis Pharmaceutical Research
Address	235 East 42nd Street, New York, NY 10017
Submission Date(s)	June 21, 2006
Amendment Date(s)	N/A
Reviewer	Devvrat Patel
First Generic	No
File Location	v:\Firmsnz\ParkeDav\ltrs&rev\84349A0606.doc

Review of Amendment

I. Executive Summary

Park-Davis' Dilantin 100 mg extended release capsules are listed as the reference listed drug in the Orange Book. Parke-Davis manufactured its drug product using a new manufacturing process. The new process uses sodium phenytoin manufactured using (b) (4). The firm has compared its drug product manufactured using the new process with its currently marketed drug product in fasting and fed bioequivalence studies. The bioequivalence studies were incomplete due to several deficiencies.

In the current amendment, the firm satisfactorily responded to all deficiencies. The fasting and fed bioequivalence studies are acceptable.

The dissolution testing conducted using USP 29 method [900 mL of water using USP Apparatus 1 (Basket) at 50 rpm] is acceptable.

From the DBE point of view, the application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Phenytoin Sodium Extended Release Capsule (Dilantin®)
Reference Product	Phenytoin Sodium Extended Release Capsule (Dilantin Kapseal®)
RLD Manufacturer	Parke Davis
NDA No.	84-349
RLD Approval Date	Approved prior to January 1, 1982
Indication	Indicated for the control of generalized tonic-clonic (grand mal) and complex partial seizures.

B. PK/PD Information

Please refer to the ANDA 84-349 review (84349S1205.doc) for PK/PD information.

IV. Background

Park-Davis' Dilantin 100 mg extended release capsules are listed as the reference listed drug in the Orange Book. Parke-Davis manufactured its drug product using a new manufacturing process. The new process uses sodium phenytoin manufactured using (b) (4). The firm has compared its drug product manufactured using the new process with its currently marketed drug product. Fasting and fed studies were conducted and the results are provided in this submission. The Division of Bioequivalence does not request fed study for this drug product.

The fasting study was a single-dose, replicate, 4 period crossover study in 21 healthy male (20) and female (1) subjects given a dose of 1 x 100 mg capsule. The subjects were dosed in 2 groups but grp*trt was not significant. The results (point estimate, 90% CI) of the fasting study are $LAUC_{0-t}$ 1.04, 100.73-107.17%; $LAUC_{0-\infty}$ 1.04, 100.85-107.53%; LC_{max} 1.11, 103.20-118.39%.

The fed study was a single-dose, two-way crossover study in 29 healthy male (27) and female (2) subjects given a dose of 1 x 100 mg capsule. The subjects were dosed in 2 groups but grp*trt

was not significant. The results (point estimate, 90% CI) of the fed study are $LAUC_{0-t}$ 1.06, 99.87-112.04%; $LAUC_{0-\infty}$ 1.05, 99.02-111.06%; LC_{max} 1.01, 92.23-111.08%.

The bioequivalence studies were incomplete because the firm did not provide manufacture date, batch size, production batch size, potency, and content uniformity of the test product. Additionally, the firm did not provide expiration date and potency of the reference product used in bioequivalence studies. The firm did not provide details of bio-analytical method validation.

It is noted that the optimized manufacturing process formulation of the test product has the same composition as the current commercial product (reference product). Additionally, the firm stated that the manufacturing process change applies only to the 100 mg strength capsule, and not 30 mg strength capsule.

The firm conducted dissolution testing using USP 29 method [900 mL of water using USP Apparatus 1 (Basket) at 50 rpm]. The test product meets USP specifications. For dissolution testing, the firm used lot no. 01615C for the test and lot no. 01095F for the reference products. However, the firm used lot nos. 05-026235 and 05-026268 for the test and reference products, respectively, in the in vivo bioequivalence studies. The dissolution testing should be conducted on the lots used in the bioequivalence studies. Therefore, the dissolution testing was incomplete.

V. Review of Submission

In the current amendment, the firm responded to the following deficiencies:

Deficiency 1: *Please provide the following information for the test lot no. 05-026235 (Dilantin® Extended Release Capsule containing* (b) (4) *phenytoin sodium and manufactured using a new optimized process) used in bioequivalence studies: manufacture date, batch size, production batch size, potency, and content uniformity.*

Additionally, please provide the following information for the reference lot no. 05-026268 (Dilantin Kapseal® containing the currently marketed phenytoin sodium) used in bioequivalence studies: expiration date, and potency.

Firm's Response: The firm provided the requested information. Information is provided below:

Product Name	Dilantin Capsules (Optimized Product)	Dilantin Kapseal (Currently Marketed Product)
BE Study Lot Number	05-026235	05-026268
Manufacturing date	04/26/2005	04/27/2005
Production batch size*	(b) (4)	(b) (4)
Potency (%)	100.4%	99.4%
Content Uniformity (%, %CV)	100.8% (0.9%)	99.6% (2.3%)
Expiration date	3/31/2007 (expected)	3/31/2007

* The firm noted that no special bio batch was made. Therefore, the bio batch size is same as the production batch size.

Reviewer's Comment: The firm's response is acceptable.

Deficiency 2: *Please provide the test article inventory data (records of the test and reference drugs received and dispensed) for fasting and fed bioequivalence studies. Additionally, please provide records of test and reference drug products administered to each subject.*

Firm's Response: The firm submitted test article inventory and drug administration records.

Reviewer's Comment: The firm's response is acceptable.

Deficiency 3: *Please submit the complete bioanalytical method validation report.*

Firm's Response: The firm provided the bioanalytical method validation report. Data provided in the report are consistent with the pre-study bioanalytical method validation table included in the original review (84349S1205.doc) except for the internal standard recovery. The report includes the correct value for the internal standard recovery, which is 78.4%. The firm explained the reason for this discrepancy as part of deficiency 4 response below.

Reviewer's Response: The firm's response is acceptable.

Deficiency 4: *The recovery of the analyte (phenytoin) is 88% and that of internal standard* (b) (4) *is 126%. Please explain the high % recovery of the internal standard* (b) (4) (b) (4) *and also the reasons for such differences in the recovery of the analyte and internal standard.*

Firm's Response: The firm stated that the original calculation of internal standard recovery was in error and represented the reciprocal of the correct value. The firm provided the correct internal standard recovery of 78.4%, which is similar to that for phenytoin.

Reviewer's Comment: The firm's response is satisfactory.

Deficiency 5: *You have not provided bioanalytical method Standard Operating Procedures (SOPs). Please submit all SOPs including those for sample reassays.*

Firm's Response: The firm provided the bioanalytical method SOPs. Additionally, the firm provided SOP for sample reassays.

Reviewer's Comment: The firm's response is satisfactory.

Deficiency 6: *For dissolution testing, you have used lot no. 01615C for the test and lot no. 01095F for the reference products. However, in the in vivo bioequivalence studies, you have used lot nos. 05-026235 and 05-026268 for the test and reference products, respectively. Please note that the dissolution testing should be conducted on the lots used in the bioequivalence studies. Please conduct dissolution testing using the USP method on both test and reference product lots used in the in vivo bioequivalence studies.*

Firm's Response: The firm stated that each of the product lots has two unique lot numbers: 01615C and 01095F represent lot numbers assigned by the manufacturing site; 05-026235 and 05-026268 represent lot numbers assigned by the clinical supply packaging system. Lot numbers 05-026235 and 01615C correspond to the test lot. Lot numbers 05-026268 and 01095F correspond to the reference lot. Thus, the dissolution testing was conducted on the product lots used in the bioequivalence studies.

For documentation of the connection between the manufacturing site lot numbers and the clinical supply packaging system lot numbers, the provided Material Review Reports.

Reviewer's Comment: The firm's response is satisfactory.

Deficiency 7: *Subjects in the fasting and fed bioequivalence studies were enrolled in two groups. Please note that in the future if the subjects are dosed in more than one group, appropriate terms for group should be included in the model for statistical analysis.*

Firm's Response: The firm acknowledged that group term should have been included in the model. The firm reanalyzed data from the fed study. The results are similar to those presented in the original review. The 90% confidence intervals for the test to reference ratios for the natural log transformed pharmacokinetic parameters, AUC_{0-t} $AUC_{0-\infty}$ and C_{max}, remained within acceptable limits of 80%-125%.

Reviewer's Comment: The firm's response is satisfactory.

Deficiency 8: *Please note that the FDA does not request a fed BE study for this drug product. Also, a bioequivalence limit of 80-125% for AUC and Cmax is used by the FDA for this drug product. Of note is that your fed BE study does not pass your protocol proposed limits for AUC, although it passes the accepted FDA limit for 90% confidence intervals.*

Firm's Response: The firm acknowledged that FDA does not request a fed bioequivalence study for this product. However, the firm feels that this study is warranted to assure adequate product performance. The firm provided data to illustrate the effect of food on various phenytoin or phenytoin sodium formulations.

The firm also recognizes that the fed study did not meet the protocol specified acceptance criteria. The rationale for the firm's choice of confidence interval criteria for AUC comes from

the reference: Ludden TM, Allerheiligen SR, Browne TR, Koup JR, Sensitivity analysis of the effect of bioavailability or dosage form content on mean steady state phenytoin concentration. Ther Drug Monit. 1991 Mar: 13(2):120-5.

Reviewer's Comment: The DBE does not change the study recommendations for this drug product at this time. The firm's response is satisfactory.

VI. Deficiency Comments

None

VII. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Parke-Davis on its Dilantin Capsule (phenytoin sodium extended-release capsule manufactured using a new optimized process), 100 mg (lot # 05-026235) comparing it to the reference product Dilantin Kapseal® (phenytoin sodium extended release capsule currently marketed), 100 mg (lot # 05-026268), is acceptable. The study demonstrates that under fasting conditions, Parke-Davis' Dilantin 100 mg Capsule manufactured using a new optimized process (lot # 05-0026235) is bioequivalent to the currently marketed Dilantin Kapseal 100 mg capsule (lot #05-026268).

2. The *in vivo* bioequivalence study conducted under fed conditions by Parke-Davis on its Dilantin Capsule (phenytoin sodium extended-release capsule manufactured using a new optimized process), 100 mg (lot # 05-026235) comparing it to the reference product Dilantin Kapseal® (phenytoin sodium extended release capsule currently marketed), 100 mg (lot # 05-026268), is acceptable. The study demonstrates that under fed conditions, Parke-Davis' Dilantin 100 mg Capsule manufactured using a new optimized process (lot # 05-0026235) is bioequivalent to the currently marketed Dilantin Kapseal 100 mg capsule (lot #05-026268).

3. The dissolution testing using USP 29 method is acceptable. The dissolution testing should be conducted in 900 mL of water using USP Apparatus 1 (Basket) at 50 rpm. The test product should meet the following specifications:

   Not more than 45% (Q) in 30 minutes
   Not more than 60% (Q) in 60 minutes
   Not less than 70% (Q) in 120 minutes

Devvrat Patel 8/7/2006

Devvrat Patel, Pharm.D. Date Signed
Division of Bioequivalence, Branch V

JMohariwal 8/7/2006

Kuldeep R. Dhariwal, Ph.D. Date Signed
Team Leader, Division of Bioequivalence, Branch V

Barbara M. Davit 8/8/06

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

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 84-349 APPLICANT: Parke-Davis Pharmaceutical Research

DRUG PRODUCT: Dilantin Kapseals®
(Phenytoin Sodium Extended-Release Capsules, USP)
100 mg

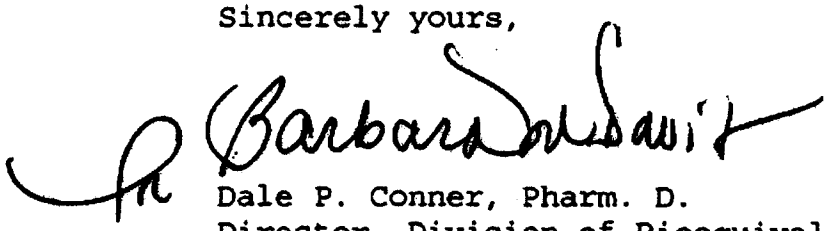
The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you have accepted the following dissolution method and specification specified in USP 29:

> The dissolution testing should be conducted in 900 mL of water at 37°C using USP Apparatus 1 (Basket) at 50 rpm. The test product should meet the following specifications:
>
> Not more than 45% (Q) in 30 minutes
> Not more than 60% (Q) in 60 minutes
> Not less than 70% (Q) in 120 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 84-349
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Patel

Printed in final on 08/07/2006
V:\FIRMSNZ\PARKEDAV\LTRS&REV\84349A0606.doc

Endorsements: (Final with Dates)
HFD-650/ Patel 8/7/06
HFD-650/ Dhariwal 8/7/06
HFD-650/ Thompson
HFD-650/ D. Conner 8/8/06

BIOEQUIVALENCE - ACCEPTABLE Submission dates: 06/21/2006

✓1. **STUDY AMENDMENT** (STA) Strength: 100 mg
Outcome: AC

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	84-349 **SPONSOR:** Parke-Davis
DRUG & DOSAGE FORM:	Dilantin Kapseals® (Phenytoin Sodium Extended-Release Capsules, USP)
STRENGTH(S):	100 mg
TYPES OF STUDIES:	Fasting and Fed
CLINICAL STUDY SITE(S):	Pfizer Global Research and Development, Ann Arbor, MI
ANALYTICAL SITE(S):	(b) (4)
STUDY SUMMARY:	The fasting and fed studies are acceptable.
DISSOLUTION:	The dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of water using USP Apparatus 1 (Basket) at 50 rpm [Specifications: NMT 45%(Q) in 30 min; NMT 60% (Q) in 60 min; NLT 70% (Q) in 120 min].

DSI INSPECTION STATUS

Inspection needed:	NO	**Inspection status:**	**Inspection results:**
First Generic	NO		
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?

Yes X No _____ (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes ___ No ___

AMENDMENT DATE: _____

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Devvrat Patel, Pharm.D. **BRANCH:** V
INITIAL: _____ **DATE:** 8/7/2006

TEAM LEADER: Kuldeep R. Dhariwal, Ph.D. **BRANCH:** V
INITIAL: _____ **DATE:** 8/7/2006

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, PharmD
INITIAL: _____ **DATE:** 8/8/06