CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

84-427

Trade Name: Dilantin Infatabs Tablets, 50mg

Generic Name: Phenytoin

Sponsor: Warner-Lambert Co.

Approval Date: February 26, 1979

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84-427

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84-427

APPROVAL LETTER

FEB 26 1979

NDA 84-427

Warner-Lambert Co.
Pharmaceutical Division
Parke Davis & Co.
Attention: Dr. E.A. Timm
201 Tabor Road
Morris Plains, NJ 07950

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dilantin Infatabs (Phenytoin) Tablets, 50 mg.

We acknowledge receipt of the following communications:

Date (in 1979)	Purpose
January 10	revised labeling in accord with Agency recommendation requests
January 26	full manufacturing and control information in accord with our previous request
February 22	packaging specifications

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Any significant change in the conditions outlined in this abbreviated new drug application, requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.8 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

Promotion of a product marketed under an abbreviated new drug application must not convey theimpression that the product is a new entity.

The enclosures summarize the conditions relating to the approval of this application.

In addition, we would appreciate your submitting in duplicate, the advertising copy which you intend to use in your immediate or proposed promotional or advertising campaign. Please submit one copy directly to the Division of Drug Advertising (HFD-170).

Sincerely yours,

Marvin Seife 2/26/79

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosures:
Conditions of Approval of a New Drug Application
Records & Reports Requirements

NWK-DO DUP HFD-614
MSeife/JLMeyer/GMillar
prepared by GMillar
R/DinitJMeyer/MSeife 2/23/79
ft/cjb/2-23-79 approved

JMeyer 2/23/79

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84-427

FINAL PRINTED LABELING

Dilantin
(Phenytoin)

Pediatric Dose: Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years may require the minimum adult dose (300 mg/day). If the daily dosage cannot be divided equally, the larger dose should be given before retiring.

MANAGEMENT OF OVERDOSAGE

The mean lethal dose in adults is estimated to be 2 to 5 grams. The cardinal initial symptoms are nystagmus, ataxia, and dysarthria. The patient then becomes comatose, the pupils are unresponsive and hypotension occurs. Death is due to respiratory depression and apnea. Treatment is nonspecific since there is no known antidote. First, the stomach should be emptied. If the gag reflex is absent, the airway should be supported. Oxygen, vasopressors, and assisted ventilation may be necessary for central nervous system, respiratory, and cardiovascular depression. Finally, hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been utilized in the treatment of severe intoxication in children.

HOW SUPPLIED

N 0071-0007 (Tablet 7)-Dilantin Infatabs each contain 50 mg phenytoin; 100's, and unit dose 100's.

Also available as:

N 0071-0362 (Kapseal 362)-Dilantin (phenytoin sodium capsules, USP) 100 mg; in 100's, 1000's and unit dose 100's.

N 0071-0365 (Kapseal 365)-Dilantin (phenytoin sodium capsules, USP) 30 mg; in 100's, 1000's and unit dose 100's.

N 0071-2214 Dilantin-125® Suspension (phenytoin oral suspension, NF), 125 mg phenytoin/5 ml with maximum alcohol content not greater than 0.6 percent; available in 8-oz bottles and individual unit dose foil pouches which deliver 5 ml (125 mg phenytoin). The minimum sales unit is 100 pouches.

N 0071-2315 Dilantin-30® Pediatric Suspension (phenytoin oral suspension, NF), 30 mg phenytoin/5 ml with a maximum alcohol content not greater than 0.6 percent; available in 8-oz bottles and individual unit dose foil pouches which deliver 5 ml (30 mg phenytoin). The minimum sales unit is 100 pouches.

N 0071-0375 (Kapseal 375)-Dilantin with Phenobarbital each contain 100 mg phenytoin sodium with 16 mg (1/4 gr) phenobarbital; in 100's and 1000's.

N 0071-0531 (Kapseal 531)—Dilantin with Phenobarbital each contain 100 mg phenytoin sodium with 32 mg (1/2 gr) phenobarbital; in 100's, 1000's and unit dose 100's.

N 0071-1801-13 Dilantin (phenytoin sodium, USP) powder, 1-oz bottles.

N 0071-0394-24 (Kapseal 394)-Phelantin® each contain 100 mg phenytoin, 30 mg phenobarbital, and 2.5 mg methamphetamine hydrochloride, 100's.

For Parenteral Use:

N 0071-4488-05 (Ampoule 1488) Dilantin ready-mixed solution containing 50 mg phenytoin sodium per milliliter is supplied in 2-ml ampoules. Packages of ten.

N 0071-4488-41 (Steri-Dose® 4488) Dilantin ready-mixed solution containing 50 mg phenytoin sodium per milliliter is supplied in a 2-ml sterile disposable syringe (22 gauge x 1¼ inch needle). Packages of ten individually cartoned syringes.

N 0071-4475-35 (Ampoule 1475) Dilantin ready-mixed solution containing 50 mg phenytoin sodium per milliliter is supplied in 5-ml ampoules with one 6-ml sterile disposable syringe (22 gauge x 1¼ inch needle). Packages of ten.

N 0071-4475-08 (Ampoule 1475) Dilantin ready-mixed solution containing 50 mg phenytoin sodium per milliliter is supplied in packages of ten 5-ml ampoules without syringes.

May 1978

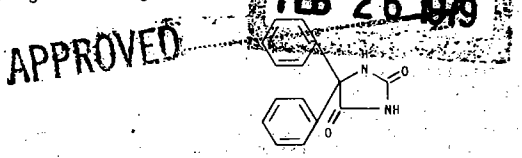
Parke, Davis & Co/Detroit, Mi 48232 USA 121 866300/WE

INFATABS®

Dilantin®
(Phenytoin Tablets, USP)

DESCRIPTION

Dilantin (phenytoin) is related to [illegible] barbiturates in chemical structure, but has a five-membered ring. The chemical name is 5,5-diphenyl-2,4-imidazolidinedione, having the following structural formula:



CLINICAL PHARMACOLOGY

Phenytoin is an anticonvulsant drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of posttetanic potentiation at synapses. Loss of posttetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of grand mal seizures.

The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7 to 42 hours.

Clinical studies using Dilantin Infatabs have shown an average plasma half-life of 14 hours with a range of 7 to 29 hours.

Steady state therapeutic levels are achieved 7 to 10 days after initiation of therapy with recommended doses. The clinically effective serum level is usually 10 to 20 mcg/ml.

The majority of the drug is excreted in the bile as inactive metabolites, which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but more importantly, by tubular secretion.

In most patients maintained at a steady dosage, a stable drug blood level is achieved. Some patients manifest a large variation in plasma levels despite equivalent doses. Patients with unusually low levels may not be absorbing the drug, may be noncompliant, or are hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem and may benefit from serum level determinations.

Clinical studies show that chewed and unchewed Dilantin Infatabs are bioequivalent, yield approximately equivalent plasma levels, and are more rapidly absorbed than 100-mg Dilantin Kapseals®.

INDICATIONS

Dilantin is indicated for the control of grand mal and psychomotor seizures.

PARKE-DAVIS

121 866300/WE

CONTRAINDICATION

Dilantin is contraindicated in those patients with a history of hypersensitivity to hydantoin products.

WARNINGS

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When in the judgment of the clinician the need for dosage reduction, discontinuation, or substitution of other anticonvulsant medication arises, this should be done gradually. Phenytoin is not indicated in seizures due to hypoglycemia or other causes which may be immediately identified and corrected. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin metabolism may be significantly affected by the concomitant use of other drugs such as:

a. Barbiturates may enhance the rate of metabolism of phenytoin. This effect, however, is variable and unpredictable. It has been reported that in some patients the concomitant administration of carbamazepine resulted in an increased rate of phenytoin metabolism.

b. Coumarin anticoagulants, disulfiram, phenylbutazone, and sulfaphenazole may inhibit the metabolism of phenytoin, resulting in increased serum levels of the drug. This may lead to an increased incidence of nystagmus, ataxia, or other toxic signs. The effect of dicumarol in inhibiting the metabolism of phenytoin in the liver has been well documented.

c. Isoniazid inhibits the metabolism of phenytoin so that with combined therapy, patients who are slow acetylators may suffer from phenytoin intoxication.

d. Tricyclic antidepressants in high doses may precipitate seizures, and the dosage of phenytoin may have to be adjusted accordingly.

Phenytoin may interfere with the metyrapone and the 1-mg dexamethasone tests. It may also suppress the protein-bound iodine. However, this has not been associated with any clinical signs of hypothyroidism, the T-3 is normal.

Usage in Pregnancy: The effects of Dilantin in human pregnancy and nursing infants are unknown.

Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, e.g., genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of child-bearing potential.

PRECAUTIONS

The liver is the chief site of biotransformation of phenytoin: patients with impaired liver function may show early signs of toxicity. Elderly patients or those who are gravely ill may show early signs of toxicity. A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin has been associated with reversible lymph node hyperplasia. If lymph node enlargement occurs in patients on phenytoin, every effort should be made to substitute another anticonvulsant drug or drug combination.

Drugs that control grand mal are not effective for absence (petit mal) seizures. Therefore, if both conditions are present, combined drug therapy is needed.

The drug should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric, or bullous, use of the drug should not be resumed. If the rash is a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further medication is contraindicated.

Osteomalacia has been associated with anticonvulsant therapy, including phenytoin.

Hyperglycemia, resulting from the drug's inhibitory effect on insulin release, has been reported. Phenytoin may also raise the blood sugar level in persons already suffering from hyperglycemia.

ADVERSE REACTIONS

Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system. These include nystagmus, ataxia, slurred speech, and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headache have also been observed. These side effects may disappear with continuing therapy at a reduced dosage level.

Gastrointestinal System: Phenytoin may cause nausea, vomiting, and constipation. Administration of the drug with or immediately after meals may help prevent gastrointestinal discomfort.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Rashes are more frequent in children and young adults. Other more serious forms which may be fatal have included bullous, exfoliative, or purpuric dermatitis, lupus erythematosus, and Stevens-Johnson syndrome.

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia. While macrocytosis and megaloblastic anemia have occurred; these conditions usually respond to folic acid therapy. The occasional occurrence of lymphadenopathy indicates the need to differentiate such a condition from other lymph gland pathology.

Other: Gingival hyperplasia occurs frequently; this incidence may be reduced by good oral hygiene including gum massage, frequent brushing and appropriate dental care. Polyarthropathy and hirsutism occur occasionally. Hyperglycemia has been reported. Toxic hepatitis, liver damage, and periarteritis nodosa may occur and can be fatal.

DOSAGE AND ADMINISTRATION

Dosage should be individualized to provide maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments—the clinically effective serum level is usually 10-20 mcg/ml. Serum blood level determinations are especially helpful when possible drug interactions are suspected. With recommended dosage, a period of seven to ten days may be required to achieve therapeutic blood levels with Dilantin.

Dilantin Infatabs can be either chewed thoroughly before being swallowed or swallowed whole.

When given in equal doses, Dilantin Infatabs yield higher plasma levels than Dilantin Kapseals.® For this reason, care should be taken when switching a patient from one dosage form to the other.

Adult Dose: Patients who have received no previous treatment may be started on two Infatabs three times daily, and the dose is then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be six to eight Infatabs daily, an increase to twelve Infatabs daily may be made, if necessary.

NDA 84-427

Labeling: Orig
NDA No: 84-427 Rc'd. 1-10-79
Reviewed by:

APPROVED FEB 26 1979

Pediatric Dosage—Initially, 5 mg/kg daily in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily.

Dilantin Infatabs can be either chewed thoroughly before being swallowed or swallowed whole.

See package insert for complete prescribing information.

N 0071-0007-24

INFATABS®
Dilantin®

(Phenytoin Tablets,USP)
50 MG
Caution—Federal law prohibits dispensing without prescription.

100 TABLETS
PARKE-DAVIS

Store so that children cannot eat these flavored tablets as candy.

Store at a room temperature below 86° F.

Chewable, flavored for children.

Exp date and lot

02 0007 24 01 4

Stock 36-7-4
Parke, Davis & Co
Detroit, Mi 48232 USA

APPROVED FEB 26 1979

Pediatric Dosage—Initially, 5 mg/kg daily in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily.

Dilantin Infatabs can be either chewed thoroughly before being swallowed or swallowed whole.

See package insert for complete prescribing information.

N 0071-0007-24

INFATABS®
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(Phenytoin Tablets,USP)
50 MG
Caution—Federal law prohibits dispensing without prescription.

100 TABLETS
PARKE-DAVIS

Store so that children cannot eat these flavored tablets as candy.

Store at a room temperature below 86° F.

Chewable, flavored for children.

Exp date and lot

02 0007 24 01 4

Stock 36-7-4
Parke, Davis & Co
Detroit, Mi 48232 USA

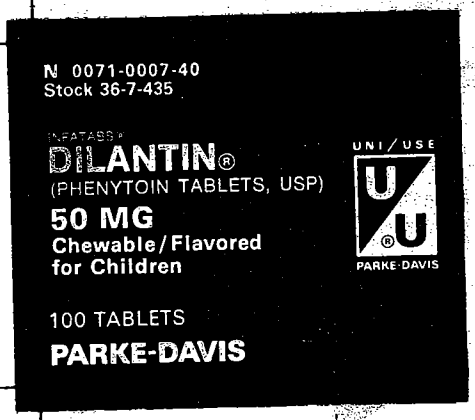
PMS 216 brown

REDUCE 50%

NDA 84-427

Labeling: Orig
NDA No: 84-427 Rec'd. 1-11-79
Reviewed by:

APPROVED FEB 26 1979



Caution—Federal law prohibits dispensing without prescription.

Pediatric Dosage—Initially, 5 mg/kg/daily in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily.

See package insert for complete prescribing information.

Dilantin Infatabs can be either chewed thoroughly before being swallowed or swallowed whole.

Store at Controlled Room Temperature (59° to 86° F). Protect From Moisture.

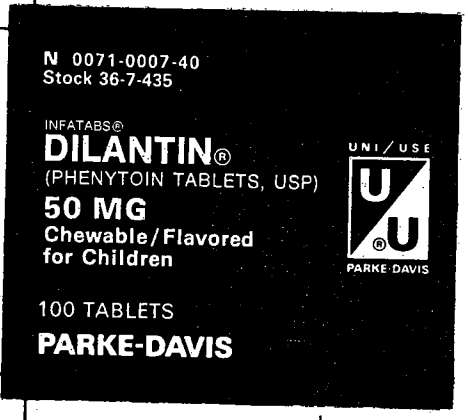
Store so that children cannot eat these flavored tablets as candy.

Expiration date and lot

Parke, Davis & Co/Detroit, Mi 48232 USA

01 0007 40 01 2

APPROVED FEB 26 1979



Caution—Federal law prohibits dispensing without prescription.

Pediatric Dosage—Initially, 5 mg/kg/daily in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily.

See package insert for complete prescribing information.

Dilantin Infatabs can be either chewed thoroughly before being swallowed or swallowed whole.

Store at Controlled Room Temperature (59° to 86° F). Protect From Moisture.

Store so that children cannot eat these flavored tablets as candy.

Expiration date and lot

Parke, Davis & Co/Detroit, Mi 48232 USA

01 0007 40 01 2

20,000 Tablets

APPROVED FEB 26 1979

INFATABS®

Dilantin®

(Phenytoin Tablets, USP)

50 MG

Caution—Federal law prohibits dispensing without prescription.

Pediatric Dosage—Initially, 5 mg/kg/daily in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily.

Dilantin Infatabs can be either chewed thoroughly before being swallowed or swallowed whole.

Caution—For manufacturing, processing or repacking.

See package insert for complete prescribing information.

Store so children cannot eat these flavored tablets as candy.

Store at a Room Temperature below 86° F.

Stock 36-7-9585

N 0071-0007-34 [91]

PARKE-DAVIS

Parke, Davis & Co / Detroit, Mi 48232 USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84-427

CSO LABELING REVIEW(S)

REVIEW OF AMENDMENT

DATE COMPLETED: 3-30-78

ANDA #: 84-427

CO. NAME: Parke, Davis & Company
Box 118, G.P.O.
Detroit, MI 48232

NAME OF DRUG: Trade: Dilantin Infatabs 50 mg.

Generic: Phenytoin Chewable Tablets, 50 mg.
(in containers of 100 and unit dose 100s)

DATE OF SUBMISSION: 11-1-77

TYPE OF SUBMISSION: Amendment

CLINICAL EVALUATION:

1. Review of Studies: The bioavailability data has been reviewed by the Division of Biopharmaceutics (see review signed 1/10/78 by R.P. Gural, Ph.D).

2. Review of Labeling:

   a) Draft labeling - immediate container - added by the firm is the statement "Chew tablets thoroughly before swallowing them". This phrase is incompatible with the word "Infatabs" in the products name since infants (0-2 years) are usually unable to do so because of lack of teeth. A request of clarification by the firm should be obtained.

   b) Draft labeling - unit dose - the term "chewable Infatab" has been added. Clarification of this revision should be requested as per above.

   c) Draft labeling - unit dose container - phrase "Chew tablets thoroughly before swallowing them" has been added. Again, clarification of this addition should be requested from the firm.

   d) Package insert - the package insert with minor modifications is satisfactory. However, the point of chewing the tablet thoroughly and the name "Infatabs" has to be clarified.

CONCLUSION:
1. Include Dr. Gural's comments on dissolution and labeling of the product in a letter to the firm.
2. Request clarification of the term "Infatabs" in the products name in light of the labeling addition "Chew Tablets thoroughly before swallowing them".

RECOMMENDATIONS: See above.

Marvin Seife

Marvin Seife, M.D.

cc:dup:MS/wlb/3-30-78

REVIEW OF AMENDMENT

DATE COMPLETED: 2-8-79

ANDA #: 84-427

CO. NAME: Parke, Davis & Co.
Morris Plains, NJ 07950

NAME OF DRUG: Trade: Dilantin Infatabs, 50 mg.

Generic: Phenytoin Chewable Tablets, 50 mg. (in containers of 100 and unit dose 100's)

DATE OF SUBMISSION: 1-10-79

TYPE OF SUBMISSION: Amendment

CLINICAL EVALUATION:

1. Review of Studies: none submitted

2. Review of Labeling:

FPL's, package insert, immediate container labels and bulk labels are now satisfactory.

The labels now state the following - "Dilantin Infatabs can be either chewed thoroughly before being swallowed or swallowed whole". Bioavailability studies submitted by the company have substantiated the statement.

The package insert ——— section has been removed in favor of a "CLINICAL PHARMACOLOGY" section which now provides extensive information to the prescribing physician and clearly states that clinical studies show that chewed and unchewed "Dilantin Infatabs" are bioequivalent.

CONCLUSION: FPL's are satisfactory.

RECOMMENDATIONS: Approve the ANDA.

Marvin Seife

Marvin Seife, M.D.

cc:dup
MS/wlh/2-9-79

Addendum 2/16/79
The immediate container "Proof copy" are exact replicas of the firms FPL, for bottle containers of 100 (reduced to half of the original size and quite ledgible to the reader) and unit dose packages of 100, are satisfactory.

Marvin Seife

Marvin Seife, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84-427

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-530

2. NDA NUMBER: 84-427

3. NAME AND ADDRESS OF APPLICANT *(City and State)*:
parke davis & co
detroit, MI 48232

4. DATE NDA APPROVED:

5. IF PRIOR TO OCT 10, 1962, DATE APPROVED FOR EFFICACY:

6. NAME OF DRUG: dilantin infatabs

7. NONPROPRIETARY NAME: phenytoin

8. SUPPLEMENT NUMBER / DATE:

9. PURPOSE OF SUPPLEMENT:

10. AMENDMENT DATE(s): as per letter to issue

11. OTHER DATE *(Report, etc.)*:

12. PHARMACOLOGICAL CATEGORY: anti-convulsant

13. AF NUMBER:

14. DOSAGE FORM: tablet(chewable)

15. HOW DISPENSED: [XX] Rx [ ] OTC

16. RELATED IND/NDA/MF(s): 84-349 = kapseals, 30 & 100 mg.

17. POTENCY(ies): 50 mg.

18. NAS/NRC: [ ] UNDER REVIEW [XX] REVIEWED

19. CHEMICAL NAME:

20. RECORDS AND REPORTS

CURRENT		REVIEWED	
[ ] YES	[ ] NO	[ ] YES	[ ] NO

21. CHEMICAL FORMULA

APPEARS THIS WAY
ON ORIGINAL

22. REMARKS: as per letter to issue

23. CONCLUSIONS: rev w/f

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
gmillar	4/3/78	3/30/78

DISTRIBUTION: [X] ORIGINAL JACKET [ ] DUPLICATE JACKET [ ] REVIEWER

Enter evaluation or comments for each item. If necessary, continue on 8½" x 10½" paper. Key continuation to item by number. Enter "NC" if no change or "NA" if not applicable.

NDA NUMBER 84-427

25. COMPONENTS AND COMPOSITION (6, 7)

submitted
composition listed in Vol 3.1, pg ¢ of NOH filing

26. FACILITIES AND PERSONNEL (8a,b)

submitted

27. SYNTHESIS (8c)

manufactured at Holland, MI laboratory of Parke DAvis

28. RAW MATERIAL CONTROLS (8d,e)

a. NEW DRUG SUBSTANCE

needed & requested

b. OTHER INGREDIENTS

as per addendum

29. OTHER FIRM(S) (8f)

30. MANUFACTURING AND PROCESSING (8g,h,i,j,k) pg 46 of filing refers to "Quality Control Approval"

additional information requested

31. CONTAINER (8l)

requested

32. PACKAGING AND LABELING (8l,m)

submitted

33. LABORATORY CONTROLS (In-Process and Finished Dosage Form) (8n)

additional information requested
pg 31 reveals changed content uniformity & no assay.

34. STABILITY (8p)

data submitted on pg 70 of original NDA & in 3.1 vol
as per dddndum

35. CONTROL NUMBERS (8q)

submitted

36. SAMPLES AND RESULTS (9)

a. VALIDATION NA

b. MARKET PACKAGE

37. LABELING (4)

as per MO(mseife).

38. ESTABLISHMENT INSPECTION

requested

39. RECALLS

requested; pg 2 of 314.200 (3)iii in 9/27/84 filing

addendum to chemist's review:

NB: this filing was received for HFD-530 review in late January 1978 since previous reviews/evaluations had been done by Biopharmaceutics

the Notice of Hearing is still pending
(as pew 3/27/78 conversation + CPrettyman of HFD-120

28: no data on phenytoin mfg has been submitted--it is requested
revisions to needed data on other components is requested

34: stability

[ ]

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION

2. NDA NUMBER: 84-427

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Warner-Lambert Pharmaceutical Div.
Parke-Davis
Morris Plains, NJ 07950

4. DATE NDA APPROVED

5. IF PRIOR TO OCT 10, 1962, DATE APPROVED FOR EFFICACY

6. NAME OF DRUG: Dilantin Infatabs

7. NONPROPRIETARY NAME: Phenytoin

8. SUPPLEMENT
NUMBER | DATE

9. PURPOSE OF SUPPLEMENT
a) Acknowledges need for updating; submits FPL
b) submits updating re: mfg, controls, etc.
c) packaging specs

10. AMENDMENT DATE(s)
1/10/79
1/26/79

11. OTHER DATE *(Report, etc.)*

12. PHARMACOLOGICAL CATEGORY
anti-convulsant; cardiac depressant

13. AF NUMBER

16. RELATED IND/NDA/MF(s)

14. DOSAGE FORM: tablet-chewable

15. HOW DISPENSED
☒ Rx ☐ OTC

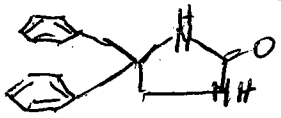
17. POTENCY(ies): 50 mg.

18. DRUG REGUIRES
☐ NDA ☒ ANDA

19. CHEMICAL NAME

20. RECORDS AND REPORTS
CURRENT: ☐ YES ☐ NO
REVIEWED: ☐ YES ☐ NO

21. CHEMICAL FORMULA



22. REMARKS

1) the 2/22/79 submission was outlined in a phone conversation with Milton Kaplan of WL/PD, with his commitment that a formal submission is being submitted; material pertains to packaging of drug product as it is being marketed.

2) for bio evaluation note 9/30/77 letter based upon 8/10/77 review of HFD-522

23. CONCLUSIONS

APPEARS THIS WAY
ON ORIGINAL

24. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
GMillar	[signature] 2/23/79	2/22/79

DISTRIBUTION ☐ ORIGINAL JACKET ☐ DUPLICATE JACKET ☐ REVIEWER

FORM FDH 2266 (11/73) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

Redacted 2

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84-427

BIOEQUIVALENCE REVIEW(S)

Dilantin Infatabs 50 mg
ANDA 84-427

Parke-Davis Company
Submission Dated:
November 1, 1977

REVIEW OF DISSOLUTION AND LABELLING

DISSOLUTION:

The Division of Biopharmaceutics agrees with the sponsor that it would not be fruitful to perform additional dissolution studies.

LABELLING:

The sponsor has submitted revised labelling for the Infatabs. In general the Division of Biopharmaceutics concurs with the labelling, however a paragraph should be included under "Clinical Pharmacology" which describes the results of the bioavailability study on the chewed vs unchewed tablets. This paragraph should describe the fact that chewed and unchewed tablets results in approximately equivalent plasma levels, and that they are more rapdily absorbed than the 100 mg Kapseals.

The sponsor should be advised that the labelling may be subject to future revisions promulgated in a Federal Register announcement.

Approval of this application is recommended with the above comments sent to the firm.

Richard P. Gural 1/10/78

Richard P. Gural, Ph.D.
Biopharmaceutics Review Branch

cc: ANDA orig., dupl., trip., hfd-530, hfd-520, hfd-522, chronological file, hfd-500, hfd-501, hfd-525, hfd-120, hfd-32

RPGURAL/lj 1/10/78
RD INITIALED BY BECABANA
FINAL TYPE INITIALED BY B.C. Cabana 1/10/78

APPEARS THIS WAY
ON ORIGINAL

Diphenylhydantoin Chewable
50 mg tablets infatabs
ANDA 84-427

Parke-Davis & Company
Detroit, Michigan
AF #12-757
Submission Dated:
August 12, 1974

REVIEW OF THREE BIOAVAILABILITY STUDIES

I PROTOCOL 73-62:

PURPOSE:

Studies previously completed (see sections II & III, this review) suggested to the firm that Dilantin Suspension was bio-inequivalent to the Infatab and Kapseal. This study was conducted to clarify any differences between these drug products by giving doses of 10 mg/kg to nine children confined to the

RECOMMENDATIONS:

This study is not acceptable as definitive evidence of either bioequivalency or a documented difference between dosage forms (pharmaceutical alternatives) because of the deficiencies listed below. While the rate of absorption cannot be observed it does seem from this study that the suspension may be more extensively absorbed than the other two dosage forms.

1. It is, therefore, recommended that the firm perform a new bioavailability study comparing the Infatabs, Suspension, and Kapseals using sufficient subjects and sufficient sampling times to describe the absorption and elimination phases of the plasma--concentration curve.

2. A protocol should be submitted prior to commencing the study so the Agency and the firm can agree on a mutual approach.

3. Any significant differences shown by the resultant study should be included in the package insert.

DEFICIENCIES:

1. The number of sampling times was insufficient to adequately describe the plasma concentration-time curve. The peak value was missed on the Infatab and probably even the Kapseals.

2. After concluding that 10 subjects were too few for acceptable variation, the firm intended to use 12 subjects, but only 9 were actually used. As in prior studies the variation (as reflected by the coefficient of variation) was excessive being over 50.1% at 1/2 the sampling times.

3. The laboratory which performed the analyses of drug in plasma failed to validate the assay. Since the study was completed in 1970, it is doubtful any validation at this time would prove useful.

RESUME:

The conclusion from Protocol 73-29 stated that the wide variations in blood concentrations could be a result of the small number of subjects in that study. This study (73-62) conducted in February 1970 therefore called for 12 children between the ages of 2-12 years. The subjects were to be divided into 6 groups of 2 and each group would receive the three dosage forms in its own order. To more completely describe the curve, groups, 1, 2, and 3 were to be sampled at 2, 4, 8, and 12 hours post dosing while groups 4, 5, and 6 were to have samples drawn at 1, 3, 6, and 10 hours post dosing. None of these procedures were actually followed, however. Only 9 subjects were used compared to 5 younger and 5 older children in the previous study where this was deemed as too few. The subjects were all given the same dosage form at the same time, and apparently blood samples were taken at hours, 1, 3, 6, and 10. While no patient received medication concurrently during the 48 hours of the trial, 8 out of the 9 patients received some concurrent medication between phases and 7 out of 9 received medication within the 3 weeks prior to the study. Other conditions were similar to protocol 73-21.

COMMENTS:

1. The method of analysis of diphenylhydantoin (DPH) was by Dill, et. al., but was not validated by the laboratory performing the analyses.

2. Rough Estimates of the elimination half-life were made and show great variations in the half-life.

	SUSPENSION	KAPSEAL	INFATAB
Kel (h^{-1})	.004	0.002	.006
T 1/2 (hr)	15.36	25.77	11.5
AUC in beta phase	227	201	208

Further refinement of these curves is not possible primarily due to the failure to collect sufficient samples to adequately describe the curve.

II PROTOCOL 73-21:

PURPOSE:

The purpose of this study was to compare the blood levels resulting from a single administration of:

a. Dilantin Half-Strength Suspension
b. Dilantin Kapseals
c. Dilantin Infatabs

at a dose of 10 mg/kg, in 10 children inpatients. The children were divided into 2 groups of 5 by age: 3 years and 8-12 years.

RECOMMENDATION:

This study is not acceptable as a definitive proof of bioequivalency for the reasons listed as deficiencies below.

DEFICIENCIES:

1. The commercial drug product was not tested since the drug product was given in applesauce - presumably not intact, and this would destroy the integrity of the drug product.

2. Since the children were divided into an older group and a younger group, the number of subjects needed to describe each response should be greater than 5 in each group. The coefficient of variation showed this in fluctuating between 31% and 113%.

3. Comparison of the three dosage forms within the older group revealed that the elimination rate constant for the Infatabs might be different than for the suspension and the Kapseals. The data, however, was too incomplete for a conclusive statement.

RESUME:

1. The study was conducted in 1966 by _____ The subjects were institutionalized children, diagnosed as retardates with no known metabolic disease and no acute or chronic systems illness.

These children had normal hematology and clinical chemistry values. Two groups were formed by age and each group received all medications; although it is not clear, it appears all individuals received the same medication at the same time. Subjects were given Paladac Vitamins with Minerals, 1 teaspoonful per day; no other medicine but the Dilantin was permitted.

2. The blood samples (? ml) were taken at 0, 1, 2, 4, 6, 8, and 12 hours post dosing. The plasma was analyzed for diphenylhydantoin by an extraction and spectrophotometric analysis described by Svensmark and Kristensen, J. Lab. and Clin. Med. 61: 501, 1963. The working standards were from 10-100 mcg/ml.

COMMENTS:

1. Identical doses were not given to each child, but a dose calculated on weight to give 10 mg/kg. In the medical interpretation of protocol 73-21, Dr. Charles Weiss states "Due to weight ranges and dosage schedule, the most precise dosing was accomplished with the suspension form since it was measured and administered in increments of 18 mg, whereas, Infatabs and Kapseals could be administered in increments of 25 mg and 50 mg respectively."

COMMENT:

It should be noted that the Preliminary Statistical Evaluation performed by the Company (page 88 volume 2) concludes that the high degree of variation of blood levels between treatment groups may be due to the small number of subjects in this study.

Michael R. Scheffler
Biopharmaceutics Review Branch

cc: ANDA orig., dupl., trip., hfd-520, hfd-522, hfd-106, af file, pharmacokinetic file, chronological file, hfd-530 (Dr. Seife)

MRSCHEFFLER/lj 4/1/75
RD INITIALED BY HRMURJDOCK
FINAL TYPE INITIALED BY HRM

Dilantin Infatabs (Phenytoin)
50 mg
Dilantin Kapseals (Phenytoin Sodium)
30 mg
NDA 84-427

Parke-Davis
Detroit, Michigan
AF #12-757
Submission dated:
November 21, 1975

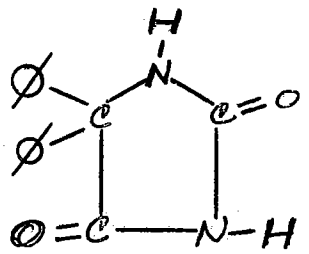
noted RBS 2/6/76

REVIEW OF BIOAVAILABILITY STUDY NO. 73-116

INTRODUCTION:

As an anticonvulsant, phenytoin appears to stablize rather than raise normal seizure threshold and to prevent spread of seizure activity rather than abolish the primary focus of seizure discharges.

STRUCTURE:



STUDY OBJECTIVE:

The objective of this study was to compare the bioavailability of Dilantin Infatabs 50 mg (lot RK-333) to Dilantin Kapseals 30 mg (lot RE-464).

STUDY DESIGN:

The study consisted of 11 male volunteers in a randomized crossover trial. The volunteers had an average age of 31 years (range 22 to 43 years), average weight of 72 kg (range 60.5 to 85.6 kg) and average height of 174 cm (range 168 to 183 cm) selected from the prisoner population of the _____ The study was conducted by _____ Each fasted subject received each of the following treatments with 200 ml of water separated by a two week rest period.

TREATMENT	DOSE (PHENYTOIN EQUIVALENT)
Dilantin Infatabs, 50 mg* (5 tablets, Phenytoin)	250 mg
Dilantin Kapseals, 30 mg (9 Kapseals, Phenytoin Sodium)	248.36 mg**

*Dilantin Infatabs were thoroughly chewed before swallowing.
**The M.W. of phenytoin is 91.98% of that of the sodium SALT.

Blood samples of 15 mls were obtained at 0, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, and 96 hours into heparinized tubes. The plasma was harvested and kept frozen until assayed. Urine samples were collected at 0, 1-12 and 12-24 hours as well as on days 2, 3, 4, 5, 6, and 7.

RESULTS:

Plasma samples were assayed for intact DPH and the urine assayed for total HPPH (free plus conjugated). The assay has sufficient specificity and linearity for both DPH and HPPH.

The following results for the concentration (mcg/ml) of DPH in plasma were reported:

	TREATMENT	
TIME (hrs)	INFATABS (Mean, C.V.)	KAPSEALS (Mean, C.V.)
0.5	0.9, 0.47	1.1, 0.55
1.0	1.6, 0.33	1.9, 0.37
2.0	2.4, 0.26	2.5, 0.33
4.0	3.2, 0.21	2.7, 0.25
8.0	3.1, 0.20	2.6, 0.18
12.0	3.0, 0.23	2.5, 0.19
24.0	2.1, 0.44	1.8, 0.41
48.0	0.6, 0.83	0.6, 0.80
72.0	0.2, 1.09	0.2, 0.89
96.0	0.1, 1.26	0.1, 1.59

The cumulative urinary excretion of HPPH expressed as percent of the dose is given in the following table:

	TREATMENT	
TIME (hrs)	INFATABS (Mean, C.V.)	KAPSEALS (Mean, C.V.
0-12	15.1, 0.46	11.6, 0.21
12-24	31.8, 0.34	29.1, 0.13
24-48	50.6, 0.25	51.0, 0.24
48-72	59.4, 0.21	61.4, 0.25
72-96	61.6, 0.21	64.6, 0.28
96-120	62.1, 0.22	65.7, 0.29
120-144	62.4, 0.22	65.8, 0.29
144-168	62.5, 0.22	65.9, 0.29

From the data herein reported the following parameters were computed using the SAAM 23 program.

Parameter	TREATMENT Infatabs	Kapseals
Absorption rate (1/hr)	0.41	0.54
Absorption half life (hr)	1.65	1.28
Elimination rate (1/hr)	0.0415	0.0382
Elimination half life (hr)	16.7	18.13
T Peak (hr)	6.1	5.3
Cmax (mcg/ml)	3.4	2.9
AUC (mcg/ml/hr)	104.2	92.5

Dissolution data was obtained on both the Infatabs and Kapseals. The Infatabs were crushed and a ——— fraction was used in the test. The dissolution was carried out in ——— The time for —— dissolution for the Infatabs was 7.5 minutes and for the Kapseals was 25 minutes.

COMMENTS:

1. Dissolution data that was supplied by the firm is not adequate. The complete dissolution profile for the Infatabs both crushed and intact should be supplied as well as dissolution data for the Kapseals.

2. The firm has compared the bioavailability of two drugs products for which they have no previous bioavailability data. The firm's largest data base is composed of the 100 mg Kapseals not the 30 mg Kapseals.

3. The Infatabs were thoroughly chewed prior to swallowing, the question arises as to why this was done. According to the PDR labelling for Infatabs, chewing of the tablet is not required. The firm should perform a bioavailability study in which the Infatab is chewed prior to ingestion and is swallowed intact compared to the 100 mg Kapseal or a solution of phenytoin. If chewing is required the labelling should reflect this or a disintegrant added to the Formulation.

RECOMMENDATION:

See comments 1 to 3. Based on these comments the study is not approvable at this time.

Richard P. Gural

Richard Gural, Ph.D.
Biopharmaceutics Review Branch

cc: NDA Orig., Dup., Trip., HFD-520, HFD-522, AF File, Chron, HFD-530(Dr. Seife)

R/D init. by JPSkelly/HRMurdock
Final init. 7HM

Noted
I concur as above
RBarsular 2/6/76

RGural/mjm 1/22/76

OK
RS

Dilantin Infatabs
Phenytoin)
ANDA 84-427

Parke-Davis
Detroit, Michigan
AF #12-757
Submission dated:
May 7, 1976

7/29/76

REVIEW OF PROTOCOL

The firm has submitted a protocol designed to evaluate the necessity of a chewing Dilantin Infatabs. The study will be conducted by [redacted] and will involve 20 normal male volunteers. Each volunteer will receive each of the following treatment at weekly intervals in a fasted cross-over fashion: 1) 2 *50 mg Dilantin Infatabs thoroughly chewed, prior to ingestion. 2) 2 *50mg Dilantin Infatabs swallowed intact and 3) 1 * 100mg Dilantin Kapseal.

Ten ml blood samples will be obtained at 0, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours after dosing. The plasma will be harvested for subsequent phenytoin concentration determinations by Parke-Davis. In addition urine specimens will be collected at zero, 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours after dosing. These samples will be assayed for the content of the major metabolite of phenytoin, HPPH.

RECOMMENDATION:

This protocol is approved.

Richard P. Gural

Richard P. Gural, Ph.D.
Biopharmaceutics Review Branch

cc: ANDA [redacted], HFD-520, HFD-522, chron., HFD-530

ROUGH DRAFT INITIALED BY JPS

FINAL DRAFT INITIALED BY RPG

RPGural/pas 7/22/76

noted as above
Abangular
7/29/76

Infatabs (Phenytoin)
50 mg Tablets
ANDA 84-427

Parke-Davis Company
Submission Dated:
December 7, 1976

REVIEW OF A BIOEQUIVALENCY STUDY

BACKGROUND:

The sponsor has submitted the results of a bioequivalency study which was requested by the Division of Biopharmaceutics. The purpose of this study was to compare the bioavailability of chewed Infatabs versus unchewed Infatabs relative to Dilantin Kapseals.

STUDY DESIGN:

The study was carried out at the [redacted] with 21 healthy male volunteers. The subjects received on a randomized, non-blind, three-way crossover basis, each of the following preparations at a weekly interval.

TREATMENTS	DOSE	ROUTE
A Dilantin Infatabs, 50 mg 2 Tablets (phenytoin), Lot TE 319	100 mg	P.O. (chewed)
B Dilantin Infatabs, 50 mg 2 Tablets (phenytoin), Lot TE 319	100 mg	P.O. (unchewed and swallowed whole)
C Dilantin Kapseals, 100 mg (phenytoin sodium), Lot TB 479 RS	100 mg	P.O.

The dose was administered to subjects after an overnight fast with 200 ml water. Subjects were not fed and did not have coffee for four hours after the dose.

Ten ml heparinized blood samples were collected Pre-Rx and at 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after the dose. The plasma were separated and kept frozen until assay.

RESULTS:

The assay procedure employed was a — method which has been shown to be linear, reproducible and specific.

The results of the plasma levels and pertinent pharmacokinetic parameters are given in Table I. The urinary excretion data is represented in Table II.

The dissolution data submitted by the firm dealing with both Infatabs or Kapseals is unacceptable, the use of ——————— is unwarrented.

RECOMMENDATION:

The firm has adequately demonstrated that the intact and chewed Infatabs result in equivalent plasma and urinary excretion profiles. It should be noted that the Infatabs give higher plasma levels than the Kapseals, and this fact should be reflected in the labelling of the product. In addition it should be stressed that once-a-day dosing of the Infatabs can not be recommended without clinical data supporting such a claim.

The sponsor should be requested to perform dissolution studies on both products which reflects the results of the bioequivalency study, before approval of the application is granted.

Richard P. Gural 8/11/77

Richard P. Gural, Ph.D.
Biopharmaceutics Review Branch

cc: ANDA orig., dupl., trip., hfd-530, hfd-520, hfd-522, chronological file

RPGURAL/lj 8/10/77
RD INITIALED BY HRMURDOCK
FINAL TYPE INITIALED BY HRM

APPEARS THIS WAY
ON ORIGINAL

PLASMA LEVELS AND PERTINENT PHARMACOKINETIC PARAMETERS OF DILANTIN INFATABS CHEWED VS UNCHEWED RELATIVE TO DILANTIN KAPSEALS

Mean (% C.V.)

	Treatments		
	A	B	C
Plasma Levels (mcg/ml)			
Time (hours)			
0	0.00 (00)	0.00 (00)	0.00 (00)
1	1.10 (53)	0.76 (68)	0.81 (70)
2	1.72 (29)	1.45 (40)	1.12 (53)
3	1.95 (20)	1.71 (26)	1.23 (46)
4	2.00 (22)	1.83 (28)	1.27 (48)
6	1.80 (17)	1.76 (29)	1.23 (35)
8	1.68 (23)	1.63 (23)	1.20 (38)
12	1.31 (29)	1.37 (30)	1.02 (39)
24	0.73 (46)	0.77 (47)	0.68 (47)
48	0.25 (87)	0.23 (76)	0.26 (85)
72	0.08 (162)	0.09 (141)	0.09 (158)
Tpeak (hour)	3.70 (36)	4.80 (58)	4.50 (60)
Cmax (mcg/ml)	2.15 (18)	1.99 (28)	1.39 (39)
$T_{\frac{1}{2}}$ (hour)	14.40 (38)	14.10 (32)	16.9 (34)
AUC_0^{72} (mcg/ml/hr)	47.10 (35)	46.31 (36)	38.84 (47)
Fraction Absorbed (dose corrected)	1.17 (21) 1.04 (18)	1.14 (21) --	--

TREATMENT

A	2 * 50 mg Infatabs Chewed
B	2 * 50 mg Infatabs Unchewed
C	1 * 100 mg Dilantin Kapseal

CUMMULATIVE URINARY EXCRETION OF HPPH
FOLLOWING ADMINISTRATION DILANTIN
INFATABS CHEWED VS UNCHEWED RELATIVE
TO DILANTIN KAPSEALS

Mean (% C.V.)

	Treatments		
	A	B	C
Time (hours)			
0	0.00 (--)	0.00 (--)	0.00 (--)
2	1.03 (58)	0.84 (83)	0.86 (68)
4	4.11 (48)	3.32 (62)	2.84 (54)
8	11.25 (40)	10.10 (44)	7.74 (42)
12	20.46 (33)	18.43 (37)	14.72 (35)
24	42.73 (23)	40.33 (25)	33.08 (40)
48	62.98 (20)	59.53 (20)	54.17 (38)
72	68.69 (19)	66.78 (17)	62.17 (37)
96	70.47 (19)	68.29 (17)	63.95 (35)
120	71.34 (19)	68.63 (17)	64.55 (35)
Fraction Absorbed	1.10 (25)	1.05 (26)	--
(dose corrected)	1.05 (18)	---	--

TREATMENT

A	2 * 50 mg Infatabs Chewed
B	2 * 50 mg Infatabs Unchewed
C	1 * 100 mg Dilantin Kapseal

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84-427

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : HFD- 530
ATTN: 16-69

DATE: Feb. 23, 1979

PLEASE HANDCARRY RESPONSE TO HFD-322, & PLACE IN BOX MARKED "STABILITY RESPONSES" LOCATED NEXT TO GWQAP CONTROL DESK (ROOM 9B09)

FROM : Manufacturing Review Branch (HFD-322)
Div. of Drug Manufacturing

SUBJECT: Pre-Award GWQAP

FDA Control # (File)

NDA/ANDA # 84-427

DRUG: Phenytoin Infatabs, 50 mg., Tabs, 100's and other sizes

FIRM: Parke Davis, Morris Plains, NJ

Unit/Package Size(s) Requested: _____

Requested Expiration Date: _____ months.

ADDITIONAL INFORMATION:

*PLEASE CALL Wayne Matthews at x35307 IMMEDIATELY if your response will be delayed past the indicated due date, or if the information available is not sufficient to complete a response.

********** RESPONSE **********

RESPONSE DUE 2/28/79

STABILITY DATA SUPPORTS:

Maximum Exp. Date (mos)	Container/ Closure System	Package Size
60 mo	HDPE	100s

COMMENTS:

If you want Htastes pls send up another request

cc: HFD-
HFD-322(OAP)
HFD-322(ECK)

Prepared by: O.M.MILLER
Date: 2/23/79

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 3/30/77
FROM: Marvin Seife, M.D.		OFFICE
TO: Division of Biopharmaceutics		DIVISION HFD-530
SUBJECT:		

SUMMARY

Attention: Dr. Harold Murdock

NDA 84-427
Dilantin Infatabs
Parke-Davis

Please review the bioavailability study on the above drug.

FINAL REPORT

Thank you,

Marvin Seife

Marvin Seife, M.D.

APPEARS THIS WAY
ON ORIGINAL

SIGNATURE	DOCUMENT NUMBER

FD FORM 2034 (2/72)

MEMO RECORD	*AVOID ERRORS PUT IT IN WRITING*	DATE November 15, 1976
FROM: Ronald Kartzinel, M.D. HFD-120		OFFICE
TO: Jean Mansur/HFD-30		DIVISION DNDP

SUBJECT: Request for Hearing, Re: Dilantin Infatabs; DESI 5856

SUMMARY

The data submitted in this response to the N.O.H. is identical to that originally submitted August 8, 1974, ANDA # 84-427. Since there has been no question raised as to the safety and efficacy of Dilantin Infatabs, and the only obstacle to the approval of the ANDA is the biopharmaceutics studies, this data would be more appropriately handled by Dr. Cabana, who has reviewed this data several times before.

cc:
Ronald L. Wilson/HFD-32
H.M. Postman/HFD-120

APPEARS THIS WAY
ON ORIGINAL

SIGNATURE Ronald Kartzinel MD	DOCUMENT NUMBER

FD FORM 2034 (2/72)

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : DESI Project Manager (HFD-501)

DATE: SEP 26 1977

FROM : Deputy Assistant Director for
Regulatory Affairs (HFD-30)

SUBJECT: Hearing Request on Dilantin Infatabs (ANDA 84-427) (Related to DESI 5856)

After publication in July 1976 of a followup notice on the phenytoin single entity oral suspension product that was in the DESI study, Parke, Davis submitted requests for hearing for several of their phenytoin-containing products that were marketed but not approved. Among the products was Dilantin Infatabs, a tablet containing phenytoin, 50 mg.

About two years prior to that, Parke, Davis had submitted an abbreviated new drug application, based on DESI 5856, for the Infatabs product. Correspondence with the firm pointed out inadequacies in the bioavailability/bioequivalence studies. In its hearing request, the company cites as the sole issue of fact whether the drug product is approvable as safe and effective regardless of whether it is bioequivalent to other Dilantin products.

When the company submitted data in support of its hearing request the material was forwarded to the Division of Neuropharmacologic Drug Products (DNDP). There was a question of whether, in the absence of adequate bioequivalence data, a full NDA would be required. At any rate, that Division sent the material back to this office with the comment that no question of safety or efficacy of this product had been raised; the issue was the biopharmaceutics studies.

I do not know the current status of the ANDA for the Infatabs (ANDA 84-427). At any rate, our office should not be holding the hearing request data that needs review. Therefore, I am sending this on to you for two purposes: (1) so that the material can be provided to the appropriate review unit and (2) so that unresolved issues can be referred to the Hearings Committee. If the firm has not yet submitted bioequivalence data considered adequate by the Division of Biopharmaceutics, then the request for hearing raises policy questions that need to be addressed by the Committee (and Dr. Crout). As I see it the basic questions are:

1. Is there adequate bioequivalence data?

2. If not, may the ANDA be approved anyway provided there are adequate safety and efficacy data?

3. If the answer to #2 is yes, then is there in fact adequate evidence of safety and efficacy?

4. If approval, if granted, must be based on clinical evidence of safety and efficacy, should the application be a "full" NDA rather than an ANDA?

Jean Mansur

Attachment

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Division of Generic Drug Monographs (HFD-530) Attn: Gerry Millar

DATE: December 13, 1978

FROM : Product Surveillance Branch (HFD-333)

SUBJECT: Report of Drug Product Problem Reports on Phenytoin Sodium Products

This is in reference to your request for information from our computerized files on Phenytoin Sodium Drug Products. A search of our files has resulted in the attached report. The large proportion of the reports on Dilantin products is probably a reflection of Park-Davis's (PD) market position and the range of their available dosage forms. No reports were found on Diphenylan (Lannett Co.).

Among the generic distributors, [redacted] appears to distribute [redacted] product and several reports on each cite possible problems of drug bioavailability. [redacted]

[redacted]. There appears to have been a [redacted] over the period 71-74, but no recent reports have cited this problem. Also several reporters cited [redacted] Products. The reports of [redacted] do not appear to be indicative of a significant problem.

I trust this information proves useful to you. If we can be of further assistance, please do not hesitate to contact us.

Ernest S Moyer
for Courtney Michael Kerwin, Ph.D.
Consumer Safety Officer

Attachment: Printout

cc:
HFD-330 (2)
HFD-333 (RF)
HFD-333 (Mark IV file)
HFA-224 (2)
CMKerwin/djw:12-13-78

Memorandum of Telephone Conversation

January 5, 1979

Between:

Dr. E. A. Timms
Director of Regulatory Affairs
Parke Davis

and

J. Richard Crout, M.D.
Director
Bureau of Drugs

Subject: Phenytoin Infatabs (ANDA 84-427)

I called Dr. Timms to request him to reply to our letter of April 4, 1978 as soon as possible. In this letter we set out some remaining deficiencies in the above referenced ANDA, and Parke-Davis has not responded. The purpose of my call was to indicate that this was a drug product for which an ANDA was clearly required and yet we cannot credibly take enforcement action against it because it is the sole product of its type for use in treating children with epilepsy. Its non-approved status, however, is testing the credibility of our enforcement programs and giving us a real problem in responding to Parke-Davis' contract bid to DoD.

Dr. Timms explained that he had talked with Dr. Seife about this application yesterday, that he was aware of the urgency of the matter, and that he regretted the delay. He said that assignment for responding to the April 4 letter in his own staff has been mishandled and he would now attempt to correct it as soon as possible. He said he would be in Washington next week with a partial response and confer with Dr. Seife about a complete response.

J. Richard Crout

J. Richard Crout, M.D.

cc:
Mr. Michels (HFD-300)
Dr. Seife (HFD-520)
ANDA 84-427
HFD-1, HFD-2, HFD-4

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Jerome P. Skelly, Ph.D., Chief
Biopharmaceutics & Pharmacokinetics Branch

DATE: March 24, 1976

FROM : Chemist, Biopharmaceutics
Review Branch

SUBJECT: Agenda of Meeting with Parke-Davis

The meeting with the Parke-Davis Company on March 26, 1976 at 11:00 will concern itself with the dilantin pediatric formulations, namely Dilantin Infatabs, Dilantin 30 mg Kapseals and Dilantin 125 mg Suspension. Concern has arisen due to submissions by the firm where the various dosage forms did not perform ideally. In addition concern has developed due to the need for chewing of Infatabs and the once a day dosing of Infatabs.

It is the purpose of this meeting to evaluate various protocols which would answer many questions concerning the various pediatric preparations. I propose that the firm perform a three-way cross-over trials. The first cross-over would evaluate the chewed and unchewed Dilantin Infatab relative to the Dilantin 100 mg Kapseal. The second trial would test the Dilantin 125 mg Suspension, and Dilantin 30 mg Kapseal against the Dilantin 100 mg Kapseal.

Richard P. Gural

Richard P. Gural, Ph.D.

cc: hfd-500 (GK), hfd-520 (BEC), hfd-522 (HRM), hfd-530 (MS), hfd-520, hfd-522, chronological file

RPGURAL/lj 3/24/76

Phenytoin Infatab
ANDA 84-427
ANDA 83-349

Parke-Davis
AF #12-757
3/36/76

MEMORANDUM OF A MEETING

BETWEEN:	Dr. Robert Buchanan	
	Dr. Aryln Kinkel	
	Dr. Salatore Fusari	
	Mr. Julius Hauser	Parke-Davis
	and	
	Dr. Bernard Cabana	HFD-520
	Dr. Jerome Skelly	HFD-525
	Dr. Harold Murdock	HFD-522
	Dr. Richard Gural	HFD-522
	Dr. R. Barzaili	HFD-530
	Dr. Marvin Seife	HFD-530

This meeting was called by myself to clarify the bioavailability of the various Dilantin Pediatric dosage forms, see attached memo.

The firm has agreed to perform a bioavailability study to determine if chewing of the Dilantin Infatab is necessary. This study will be a three-way crossover study in which the three treatments will be:

a) 2-50 mg Infatabs unchewed
b) 2-50 mg Infatabs chewed and
c) 1-100 mg Kapseal

This study will be completed and reported to the FDA by mid July.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

The issue of the Dilantin 300 mg Kapseal for once- a -day dosing was discussed. It was mentioned that a multi-dose steady state study of once-a-day dosing of Dilantin, 300 mg Kapseal may be necessary to resolve this issue. Further discussion along these lines is continuing.

R. Gural

Richard Gural, Ph.D.
Biopharmaceutics Review Branch

cc: ANDA orig., dupl., trip. HFD-520 (2), HFD-522 (2), HFD-525, HFD-530 (2), chron

RPGural/pas 4/5/76

ROUGH DRAFT INITIALED BY BEC 4/2/76
FINAL DRAFT INITIALED BY _____

APPEARS THIS WAY
ON ORIGINAL

ANDA drug 84-427

MEMORANDUM OF MEETING

November 25, 1975

AF 12-757

BETWEEN: Les Lueck, Ph.D., Parke-Davis
Julius Hauser, Parke-Davis

and

Marvin Seife, M.D., Division of Generic Drug Monographs
Gene G. Knapp, Associate Director for Drug Monographs
Bernard E. Cabana, Ph.D., Division of Biopharmaceutics

Subject: Bioavailability of Dilantin, ANDA 84-349, IND 1113, ANDA 84-427

This meeting was held with the firm at the request of Dr. Seife and myself in order to discuss the bioavailability problems associated with the various Dilantin products.

I pointed out to the firm that our review of 5 separate bioavailability studies (some of which were submitted by Parke-Davis) indicated unusual variability for the various Dilantin products. It was further pointed out to the firm that a recent FDA study of phenytoin (100 mg capsules) drug products, conducted at the _____, revealed that a given lot of Dilantin (selected at random) was the poorest of 11 generic phenytoin products in the study. The rate and extent of absorption of Dilantin differed significantly from several other generic drug products, the largest differences indicating a 55% difference in peak concentrations and a 30% difference in total area (total absorption).

I pointed out to the firm that the Agency was in the process of documenting phenytoin (diphenylhydantoin) bioinequivalence in preparation for establishing a bioequivalence requirement and that in light of these documented problems with Dilantin products, that the Agency may no longer be able to support the use of Dilantin Kapseal (100 mg) as the reference standard. I told the firm that this stand was further justified since there was no approved NDA for any of the solid dosage forms. In addition, the firm was told that the Agency may have no recourse but to use phenytoin-Na in solution (PEG 400-H_2O mixture 50:50 v/v) or a suspension previously approved (Abbotts) as the reference standard for immediate release dosage forms.

Dr. Lueck replied that this would be unfortunate since Parke-Davis had greater than 95% of phenytoin market in the U.S. and the physicians were using Dilantin to titrate their patients. He further indicated that PD has applied for an NDA (ANDA 84-349, and 84-427) on all of its

product, but that the Agency has not approved them as yet, possibly due to lack of in vitro specification (dissolution rate data). A discussion ensued concerning their in vitro methodology to assure lot to lot reproducibility. He further stated that the great variability observed in the studies could only be inscribed in his opinion, to patient variability.

I pointed out to Dr. Lueck, that in our opinion, the dissolution methodology was non-discriminating in that it utilized ———, a total unphysiological system. I further added that in vitro dissolution data would not suffice for approving their ANDA, but needed to be correlate or associated with good in vivo bioavailability data. The firm was also told that none of the submitted data had been approved due to unusual variability and inadequate design in certain instances. It was further pointed out that in several studies reviewed by the Division of Biopharmaceutics that the coefficient of variation of dilantin products was 2-4 times that of several test drug, and in certain instances ranged ———, and that in our opinion, this could be ascribed to the slow absorption of their product.

Dr. Lueck admitted that there may be a reproducibility problem with their dosage form, but that it was not advisable to have a fast absorbing product or more available form of the drug as the standard, because of potential increase side effects, he could not explain this. He was advised that perhaps the problem was due to differences in steady-state resulting from administration of less available form of Dilantin.

It was pointed out to the firm that the Agency was confronted with three basic problems:

1) issue of Dilantin reproducibility and unusual variability;

2) issue of obvious difference in rates of absorption of different forms of phenytoin;

3) the need for a common standard which is reproducible.

Dr. Lueck agreed with the issue of reproducibility and the need for PD and the Agency to resolve this issue. He stated that with regards to rate of absorption, that PD had intentionally designed a "slow release" dosage form. With regards to a reference standard, he offered to provide the Agency a reference standard meeting any FDA requirement (fast, intermediate or slow release drug formulations) to be used by all manufacturers. He was advised that perhaps Dilantin Kapseal needed to be labelled as a timed-release or slow-release dosage form. He was further told of the time constraints of January 15, 1976 facing the

Agency and the need for having a well defined standard for the FR statement. I further told him that any reference standard provided by PD would need to be compared to the optimal dosage form (Drug in solution). I further advised him that there were many policy issues confronting the Agency that would require Dr. Crout's approval prior to any final decision be rendered. He was told that a second meeting would be called within 2 weeks.

B.E. Cabana

Bernard E. Cabana, Ph.D.

cc: IND, ANDA, NDA., Orig., Dup., trip., HFD-520, HFD-500, HFD-530, af file, chron

BECabana/mjm 11-28-75

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Edward Tocus, Ph.D.
Acting Director,
Division of Neuropharmacological Drug Products (HFD-120)_____
Through: Bruce Byer (HFD-120)_____

DATE: OCT 18 1976

FROM : Administrative Compliance Branch (HFD-32)
Office of the Assistant Director for Regulatory Affairs

SUBJECT: Data Submitted in Response to Notice of Opportunity for Hearing (Dilantin Infatabs - DESI 5856).

We are forwarding to you the attached data which has been submitted in response to the July 29, 1976 notice of opportunity for hearing.

When a medical analysis of the data has been prepared , send the medical review to (1) Dr. Finkel and (2) HFD-32 (Attention: R. Wilson). Our office is assisting General Counsel in preparation of the final order.

Ronald L. Wilson

Ronald L. Wilson

APPEARS THIS WAY
ON ORIGINAL

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 84-427

DATE APPROVAL LETTER ISSUED:

TO: Press Relations Staff (HFI-40)

FROM:
- [XX] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

ORIGINAL ABBREVIATED

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA
- [XX] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [XX] HUMAN
- [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

~~dilantin infatabs(phenytoin)~~

DOSAGE FORM: tablet

HOW DISPENSED
- [XX] RX
- [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

phenytoin, 50 mg.

NAME OF APPLICANT *(Include City and State)*

Warner-Lambert Pharmaceutical Division
Parke Davis
Morris Plains, NJ 07950

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

anti-convulsant; cardiac depressant

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

APPEARS THIS WAY
ON ORIGINAL

FORM PREPARED BY

NAME: G. Millar — DATE:

FORM APPROVED BY

NAME: J Meyer — DATE:

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84-427

CORRESPONDENCE

February 23, 1979

D. Wolfson (HFD-335)
Compendial Liaison Staff

Gerry Millar (HFD-530)
Chemist

Phenytoin Tablets

In Pharmacopeial Forum, Nov-Dec. 1978, Vol. 4, No. 6, p.639, there is an in-process revision for the above drug product.

The reference notes that the labeling should note that the tablets "...are to be chewed".

Our Division is presently reviewing Parke-Davis' Dilantin Infatabs (phenytoin tablets, 50 mg.), Parke-Davis' labeling maintains that the tablets "...can either be chewed thoroughly before being swallowed or swallowed whole".

A medical officer's review notes that bioavailability studies submitted by the company have substantiated the above statement.

Will you present this to USP and request (1) comment and (2) their plans for revising/not revising labeling directions.

2/23/79
Gerry Millar

cc:
JMeyer (HFD-530)
NDA 84-427 (orig.dup.)
GM:wh:2-23-79

Warner-Lambert COMPANY
Pharmaceutical Division
Parke-Davis Warner/Chilcott Texas Pharmacal

Rec'd 1/26 Drug

JAN 26 1979

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
Department of Health Education and Welfare
5600 Fishers Lane
Rockville Maryland 20857

RESUBMISSION
NDA ORIG AMENDMENT
RECEIVED
JAN 26 1979
GENERIC DRUGS

Dear Dr. Seife:

RE: ANDA 84-427
Dilantin® Infatabs® 50 mg
(Phenytoin Tablets, USP)

Reference is made to my recent January 10, 1979, letter which responded to your April 6, 1978 letter to the above Abbreviated New Drug Application.

As I indicated to you in my letter, the remaining responses (comments #2 thru #9) to your April 6, 1978, letter would be forthcoming as soon as all the requested information could be assembled from our records and the records of the Detroit Laboratories. We have completed this task and herewith submit to you the data you requested. For the convenience of your review, we will repeat your comment followed by our response. However, Comment #1, concerning Labeling, will not be repeated since we responded to it in our January 10, 1979 letter.

Comment 2. - For Ingredients

a. Phenytoin

1. Submit your specification sheets and analytical procedures.

Response - As stated in our Abbreviated New Drug Application

[ ]

201 Tabor Road Morris Plains, New Jersey 07950 (201) 540-2000

Redacted _8_

Page(s) of trade secret and /or confidential commercial information

there are any questions that you may have in connection with the above responses, please do not hesitate to contact me directly at my office at 201 Tabor Road, Morris Plains, NJ 07950, telephone (201) 540-4366.

Very truly yours,

E. A. Timm

E. A. Timm, Ph.D.
Vice President, Regulatory Affairs

EAT/WYJ/amj/i/a

APPEARS THIS WAY
ON ORIGINAL

Parke, Davis & Company

Joseph Campau at the River
Box 118—General Post Office
Detroit, Michigan 48232
Telephone (313) 567-5300

Quality Control and
Government Regulations Division

Drug

Recvd

PARKE-DAVIS

Janauary 10, 1979

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Seife:

Re: NDA-84-427
Dilantin Infatabs® 50 mg
(Phenytoin)

This is in response to your April 6, 1978 letter to the above abbreviated new drug application.

As I mentioned to you in our telephone discussion, the intervening activities of our organizational consolidation and relocation of our office and personnel from Detroit, Michigan to Morris Plains, New Jersey during the latter half of 1978 caused disruption and some delay to our normal handling of some of the communications with FDA. Unfortunately, your April 6th letter had been assigned to an individual who chose not to make the relocation move with us and, as a result, the gathering of the information and processing of an appropriate response suffered still added delay. We are now proceeding as expeditiously as possible and should have all of the requested information ready for forwarding in the very near future.

At this time, we are able to respond to the number one comment in your letter on labeling which, I believe, is the key issue remaining for this ANDA. For your convenience, we are repeating below the comment from your letter followed by our response:

1. For Labeling:

   a. Container Labels: We are requesting the rationale for your continued use of the trade name "Infatabs" since your label has added the statement "Chew tablets thoroughly before swallowing them". This phrase is incompatible with the word "Infatab" in the product's name since infants (0-2 years) are usually unable to chew because of the lack/immaturity of teeth.

Response - The product has been identified as Dilantin Infatabs® for over 26 years and is recognized by the medical profession as a flavored tablet which may be chewed and prescribed for those persons who desire this method of administration. However, we agree with your observation that there is a degree of incompatibility between the name Infatab and the direction to chew the tablet thoroughly before swallowing. Fortunately, the final report on our clinical protocol 73-121 submitted on March 21, 1977 and reviewed by the Division of Biopharmaceutics has shown conclusively that the stipulated limitation to chewing only is not necessary. Accordingly, our proposed revised labeling, which we have attached, indicates that the product may be either chewed or swallowed whole.

b. Package Insert: with minor modifications, as presented, it is satisfactory. However, you should:

1. Address yourself to a review of the trade name Infatab as presented above.

Response - Please refer to our response to 1.a. above.

2. Respond to the following comment for our review of labeling by our Division of Biopharmaceutics: The sponsor has submitted revised labeling for the Infatabs. In general the Division of Biopharmaceutics concurs with the labeling, however, a paragraph should be included under "Clinical Pharmacology" which describes the results of the bioavailability study on the unchewed tablet. This paragraph should describe the fact that chewed and unchewed tablets result in approximately equivalent plasma levels, and that they are more rapidly absorbed than the 100 mg Kapseals. The sponsor should be advised that the labeling may be subject to future revisions promulgated in a Federal Register announcement."

Response - We are in agreement with this recommendation and in this regard, please find attached twelve copies of final printed package inserts (Symbol WE) in which the "Clinical Pharmacology" section has been revised to include the recommendations by your Division of Biopharmaceutics. In addition, we are also attaching twelve revised copies of final printed bottle and Uni/Use carton labeling which indicate, in the pediatric dosage section, that the tablets can also be swallowed.

c. Define the expiration date to appear.

Response - The expiration dates that will appear on the marketed products are as follows:

Unit dose (Blister package): 36 months
Bottles of 100: 60 months

The stability data to support the above dating is being tabulated for your easier reference and will be forwarded in the following communication to be sent shortly.

d. Submit copies of bulk labels (used in shipping material to your [redacted]

Response - Twelve copies of the bulk labels used in shipping material to our [redacted] are attached.

Again, we are sorry for not responding earlier to your April 6, 1978 letter to our abbreviated new drug application for Dilantin Infatabs®. Response to the remaining comments in your letter will be forwarded to you as soon as all of the requested information can be assembled from our records here and in our Detroit laboratories.

Sincerely,

E. A. Timm

E. A. Timm, Ph.D.
Vice President
Regulatory Affairs

APR - 4 1978

NDA 84-427

Parke Davis & Co.
Attention: Dr. E.A. Timm
Joseph Campau at the River
Box 118 GPO
Detroit, MI 48232

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Dilantin Infatabs (Phenytoin) Tablets, 50 mg.

We acknowledge receipt of the following communications and filings:

August 8, 1974	submission of an original abbreviated new drug application (in two volumes)
November 21, 1975	submission of a bioavailability study (comparing Dilantin Infatabs with Dilantin Kapseals--in normal volunteers)
December 11, 1975	confirmation of arrangements (for a meeting with Agency personnel to discuss bioavailability studies for Dilantin---phenytoin and sodium phenytoin preparations)
May 7, 1976	response to queries from our Division of Biopharmaceutics--as raised in meetings and communications with Agency personnel
August 16, 1976	discussion, addressed to R. Crout, Bureau Director, of the implications of the Federal Register follow-up notice of July 29, 1976 on your ability to continue to market Dilantin (phenytoin-containing) preparations
August 30, 1976	filing, with the Agency's Hearing Clerk, of a request for "Opportunity of Hearing"---this submitted on your behalf by the Warner-Lambert Co.
September 27, 1976 (received for our review on September 29, 1977)	filing again with the Hearing Clerk of a resubmission containing (1) material filed in the above referenced communications (2) copies of Agency letters to you and (3) your evaluation of the need for this drug product to be bioequivalent to other Dilantin preparations.
November 1, 1977	enclosure of copies of draft labeling (container labels and package insert) revised in accord with comments from our Division of Biopharmaceutics.

We have reviewed the material submitted and have the following comments:

1. For Labeling:

   a. Container Labels: We are requesting the rationale for your continued use of the trade name "Infatabs" since your label has added the statement "Chew tablets thoroughly before swallowing them". This phrase is incompatible with the word "Infatabs" in the product's name, since infants (0-2 years) are usually unable to chew because of the lack/immaturity of teeth.

   b. Package Insert: with minor modifications, as presented, it is satisfactory. However, you should:

      1. address yourself to a review of the trade name "Infatabs", as presented above.

      2. respond to the following comment from our review of labeling by our Division of Biopharmaceutics:

         The sponsor has submitted revised labeling for the Infatabs. In general the Division of Biopharmaceutics concurs with the labeling, however a paragraph should be included under "Clinical Pharmacology" which describes the results of the bioavailability study on the unchewed tablets. This paragraph should describe the fact that chewed and unchewed tablets results in approximately equivalent plasma levels, and that they are more rapidly absorbed than the 100 mg. Kapseals.

         The sponsor should be advised that the labeling may be subject to future revisions promulgated in a Federal Register announcement.

   c. Define the expiration date to appear.

   d. Submit copies of bulk labels (used in shipping material to your ———

2. For Ingredients:

   a. Phenytoin:

      1. submit your specification sheets and analytical procedures

      2. clarify whether specifications provide for a determination of particle size

      3. submit your ——— certificate of analysis for lots used

4. discuss whether other (internal) specifications have been adopted

5. revise terminology in accord with current compendial and USAN titling

b. Other ingredients:

1. submit suppliers' certificates/protocols for non-compendial items

2. submit specifications/procedures performed by you on compendial items.
Here we note that these have NOT been updated to those official with the current editionsoof USP XIX and NF XIV.

3. we call to your attention the accompanying Federal Register proposal on _____

3. For the drug dosage form:

a. Submit information as to whether you have corresponded with USP regarding your revisions (simplifications) to the official monograph; here we cite (1) using TLC as an identification procedure and (2) using an alternate to the content uniformity procedure, and dropping the assay procedure.

b. Clarify whether you have refined the submitted content uniformity/ assay procedure so that a placebo no longer has to be added to the reference standard to insure method reliability.

c. Provide for a disintegration specification, since the "directions for use" call for the tablet to be chewed.

d. Submit in-process specifications

4. For stability:

a. Submit yourrprotocol

b. Clarify whether your program includes procedures for the detection of degradation products

c. Submit data at challenge conditions---in the container/closure system(s) in which the drug is to be marketed

d. Submit additional data in accord with your protocol, when available.

5. Update certification statements in accord with Parts 210 & 211 of the regulations (21 CFR) for:

   a. Your operations

   b. Other firms---those used in unit dose packaging

6. Submit full manufacturing records that include:

   a. Copies of master formula cards

   b. Precautions observed in operations

   c. In-process procedures

   d. Procedures to be used for _____ tablets, when/if necessary

   e. Procedures used to assure the integrity of the drug product, after unit dose packaging; here define what your "quality control approval" means

7. Include a full description of the container/closure(s) used, as follows:

   a. _____ data

   b. Methods for making these systems infant/child proof

   c. Testing results that assure that the methods do make the systems child-proof.

8. A commitment to submit analytical results for lots manufactured.

9. Full details of recalls (if effected) and other production problems/ complaints in view of the fact that you have been marketing since 1952.

Please let us have your response.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DET-DO DUP HFD-614
C.Prettyman/HFD-120
MSeife/JLMeyer/GMillar
R/DinitJMeyer/MSeife
ft/cjb/4-3-78 rev w/f

Enclosure: FR of 2-4-77 (yellow #5)

Parke, Davis & Company
Joseph Campau at the River
Box 118, General Post Office
Detroit, Michigan 48232
Telephone (313) 567-5300

Quality Control and
Government Regulations Division

Orig

PARKE-DAVIS

NOV 1 1977

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs (HFD-530)
Bureau of Drugs
Food and Drug Administration
Department of Health, Education and Welfare
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

Dear Dr. Seife:

Re: NDA 84-427
Dilantin (Phenytoin) Infatabs, 50 mg

Reference is made to your letter of August 19, 1977 which advised us that our bioavailability studies have adequately demonstrated that the intact and chewed Infatabs result in equivalent plasma and urinary excretion profiles.

Your letter went on to recommend that we revise our labeling to reflect the fact that the Infatabs give higher plasma levels than Dilantin Kapseals and that once-a-day dosing of the Infatabs cannot be recommended. We concur with these suggestions and four draft copies of the bottle label, unit dose, and package insert labeling (dated October 14, 1977), revised accordingly, are attached for your approval. It should be noted that this labeling also includes the Administration's anticonvulsant pregnancy warning statement and advises the prescribing physician of reports of osteomalacia and hyperglycemia associated with the use of anticonvulsant drug therapy.

The closing paragraph of your letter requested that we "perform dissolution studies on both products in order to reflect the results of the bioequivalency study."

Dissolution studies were performed on the "chewed" [redacted] and unchewed Dilantin Infatabs as well as the reference Dilantin Kapseals. These studies were reported and included with Volume 1 of 1 of our March 21, 1977, submission of the Final Report of Protocol 73-121.

They were presented in Appendix A as Attachment A-1, pages 45 and 46 of the March 21, 1977, submission. A copy of this is included for your convenience.

RECEIVED
NOV 03 1977
BUREAU OF DRUGS

The discussion of these studies, and their relationship to the plasma data, (please refer to page 21 of the submission) indicates that no meaningful correlation can be seen.

This analyses of the data leads us to believe that it would not be fruitful to perform additional dissolution studies designed to corroborate present data which already indicate that the in vitro dissolution behavior of Dilantin Infatabs bears no relationship to the in vivo drug bioavailability.

With this data in hand, we feel you will concur with this conclusion.

Very truly yours,

E. A. TIMM, Ph.D.
Vice President, Quality Control
and Government Regulations

EAT/JW/mh

APPEARS THIS WAY
ON ORIGINAL

NDA 84-427

SEP 30 1977

Parke, Davis & Company
Attention: Dr. E.A. Timm
Box 118-General Post Office
Detroit, MI 48232

Gentlemen:

Reference is made to the bioavailability studies you submitted for Dilantin (phenytoin) Infatabs Tablets, 50 mg.

The studies have been reviewed by our Division of Biopharmaceutics and they have the following comments:

The firm has adequately demonstrated that the intact and chewed infatabs result in equivalent plasma and urinary excretion profiles. It is noted that the Infatabs give higher plasma levels than the Kapseals, and this fact should be reflected in the labeling of the product. In addition, it must be stressed that once-a-day dosing of the Infatabs cannot be recommended without clinical data supporting such a claim.

The sponsor is requested to perform dissolution studies on both products (capsule and tablet) in order to complete the application.

Sincerely yours,

Marvin Seife 9/29/77

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DET-DO
DUP
HFD-614
HFD-520
HFD-530
MSeife/wlb/9-29-77
bio

NDA 84-427

Parke, Davis & Company
Attention: Dr. W.A. Timm
Box 118-General Post Office
Detroit, MI 48232

Gentlemen:

Reference is made to the bioavailability studies you submitted for Dilantin (phenytoin) Infatabs, 50 mg.

The studies have been reviewed by our Division of Biopharmaceutics and they have the following comments:

The firm has adequately demonstrated that the intact and chewed Infatabs result in equivalent plasma and urinary excretion profiles. It should be noted that the Infatabs give higher plasma levels than the Kapseals, and this fact should be reflected in the labeling of the product. In addition it should be stressed that once-a-day dosing of the Infatabs cannot be recommended without clinical data supporting such a claim.

The sponsor is requested to perform dissolution studies on both products in order to reflect the results of the bioequivalency study.

Sincerely yours,

Marvin Seife 8/18/77

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

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bio

ORIG

Parke, Davis & Company

Joseph Campau at the River
Box 118—General Post Office
Detroit, Michigan 48232
Telephone (313) 567-5300

PARKE-DAVIS

Quality Control and
Government Regulations Division

MAR 21 1977

Paul A. Bryan, M.D.
Deputy Associate Director for Drug Monographs
Bureau of Drugs (HFD-101)
Food and Drug Administration
Department of Health, Education and Welfare
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Bryan:

Re: ANDA 84-427
Dilantin Infatabs

We are submitting the Final Report for Protocol 73-121, a study designed to compare the bioavailability of single doses of Dilantin Infatabs, chewed and unchewed, and the standard Dilantin Kapseals.

An interim report for this study was submitted to this application on December 7, 1976.

Reference also is made to our letter of November 10, 1976 which responded to the Administration's October 20, 1976 letter. These communications discussed whether labeling revisions were necessary to assure proper drug dosing.

The attached data should resolve the issues which have been raised and should permit a conclusion that the application is approvable.

Very truly yours,

E. A. Timm

E. A. TIMM, Ph.D.
Vice President, Quality Control
and Government Regulations

EAT/CMH/mh

ORIG

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Joseph Campau at the River
Box 118—General Post Office
Detroit, Michigan 48232
Telephone (313) 567-5300

Quality Control and
Government Regulations Division

PARKE-DAVIS

DEC 7 1976

NDA ORIG AMENDMENT

Paul A. Bryan, M.D.
Deputy Associate Director for Drug Monographs
Bureau of Drugs (HFD-101)
Food and Drug Administration
Department of Health, Education and Welfare
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Bryan:

Re: ANDA 84-427
Dilantin® Infatabs®

Reference is made to our letter of November 10, 1976 in which we stated that we would submit, as soon as possible, the report on Protocol 73-121, A Clinical Bioavailability Study of Diphenylhydantoin Sodium Salt.

Attached are (1) an Interim Medical Interpretation for Protocol 73-121, authored by Dr. R. A. Buchanan and dated December 2, 1976, and (2) a report on the Bioavailability of Dilantin® Infatabs®, for Protocol 73-121, authored by Dr. A. W. Kinkel and dated November 10, 1976.

The complete protocol with final report will be submitted to this application as soon as it is available.

In our opinion, the attached clinical data demonstrate that the application is approvable with the current labeling. We trust you will concur with this conclusion.

Very truly yours,

PARKE, DAVIS & COMPANY

E. A. TIMM, Ph.D.
Vice President, Quality Control
and Government Regulations

EAT/CMH/evj

Attachment

Salmon Copy

ANDA-84-349

84-427

OCT 20 1976

L. M. Lueck, Ph.D.
Vice President, Quality & Regulatory Affairs
Warner-Lambert Company
Pharmaceutical Group for Parke-Davis & Company
Joseph Campau at the River
Detroit, MI 48232

Dear Dr. Lueck:

Your letter of August 16, 1976 to J. Richard Crout, M.D., Director, Bureau of Drugs, requested "prompt approval of the....new drug applications for Dilantin Capsules, 100 mg per capsule and 30 mg per capsule;" /ANDA 84-349/ "and Dilantin 'Infatabs' Tablets, 50 mg." /ANDA 84-427/.

ANDA 84-349 was approved by letter of August 27, 1976; therefore no further comments are required at this time regarding this application.

However, in regard to ANDA 84-427, Dilantin 'Infatabs' (phenytoin tablets, USP) 50 mg., we have the following comments:

Our Division of Biopharmaceutics cannot recommend approval for Dilantin Infatabs 50 mg (ANDA 84-427) at this time because of a potential bioavailability problem associated with this product. In particular, there is concern for the need of chewing such tablets prior to ingestion as indicated in Dr. Seife's letter dated February 12, 1976 to you. (Copy of letter is attached.) As a result, your firm reportedly has initiated a bioavailability study under protocol 73-121 to resolve these matters. To date, we have not received bioavailability data nor even a progress report on such specified studies comparing Dilantin Infatabs 50 mg to Dilantin Kapseals 100 mg., the complete dissolution profile for the Infatabs both crushed and intact, or dissolution data for the Kapseals.

Moreover, as we previously advised you, we also believe that labeling for the Infatab product should reflect whether or not complete chewing is required. All of this was requested in our February 12, 1976 letter.

In the absence of the requested final bioavailability data and because of the need to relabel the Infatab product, we are in no position at this time to consider the merits of approval on ANDA 84-427.

Sincerely yours,

Paul A. Bryan, M.D.
Deputy Associate Director
for Drug Monographs
Bureau of Drugs

cc:
HFA-224
HFD-500 CF
HFD-500 SF
HFD-1
PABryan:ih/10/20/76

Approved by Dr. Leventhal 10/19/76

Parke, Davis & Company

Joseph Campau at the River
Box 118—General Post Office
Detroit, Michigan 48232
Telephone (313) 567-5300

Quality Control and
Government Regulations Division

PARKE-DAVIS

Miss Jennie C. Peterson
Hearing Clerk
Food and Drug Administration
Room 4-65
5600 Fishers Lane
Rockville, Maryland 20852

SEP 27 1976

Dear Miss Peterson:

Re: DESI 5856; Docket No. 76N-0245; NDA No. 84-427

Submitted herewith are the grounds, data, information and full factual analysis on which Parke-Davis relies to justify a hearing, as specified in 21 CFR 314.200(d). All the data and information (including all protocols and underlying raw data) relating to the studies on which Parke-Davis relies, are included in full, as required by 21 CFR 314.200 (c)(2). These data are identified as REQUEST FOR HEARING, Re: DILANTIN INFATABS; DESI 5856, Docket No. 76N-0245, NDA No. 84-427 which accompanies this letter.

We believe that Dilantin Infatabs are safe and effective for use as an anticonvulsant agent in accordance with the labeling. The FDA has not indicated any basic difference of opinion in this conclusion. We believe the sole issue of fact needed to be resolved at the Hearing is whether or not the NDA for Dilantin Infatabs should be approved irrespective of whether this product is bioequivalent to other Dilantin preparations. In this regard a prime factual consideration is that over 70,500 patients in the United States are currently, and for many years, have been successfully treated with this drug. Additionally, and of extreme importance, is the fact that to alter the formulation of this product, i.e., to alter its bioequivalence, would be to subject these patients to the need for retitration to a substitute phenytoin preparation under the close supervision of a physician. This could subject such patients to a serious health hazard.

In conclusion, the attached documents completely justify a request for hearing, or in the alternative they present substantial evidence upon which the FDA, upon re-evaluation, could properly conclude that the application is approvable.

Very truly yours,

PARKE, DAVIS & COMPANY

E. A. Timm

Rec'd 9/29/77

E. A. TIMM, Ph.D.
Vice President, Quality Control
and Government Regulations

EAT/CL/REK/evj

Parke, Davis & Company

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Detroit, Michigan 48232
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Quality Control and
Government Regulations Division

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Marvin Seife, M.D.
Director
Division of Generic Drug Monographs (HFD-530)
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
Department of Health, Education and Welfare
5600 Fishers Lane
Rockville, Maryland 20852

MAY 7 1976

Dear Dr. Seife:

Re: NDA 84-427, Phenytoin Tablets, U.S.P.
Dilantin Infatabs®

In response to the March 26, 1976 meeting held at the FDA Generic Drug Section (at HFD-520 with Dr. B. Cabana and our Dr. R. Buchanan present), we are forwarding the attached data for your review.

The discussion at the meeting lead to the development of the following questions:

A. Must INFATABS be chewed?

B. What data supports once daily administration of INFATABS?

C. Are 30 mg. capsules designed specifically for children?

D. Are there significant differences between the suspension, tablets, and capsules as possibly indicated in 73-21?

We have attached a copy of Dr. R. A. Buchanan's April 21, 1976 memo to Dr. L. M. Lueck. This document responds to those questions and indicates where in the attached information (protocols) further discussion of the questions can be found.

Our medical staff is particularly anxious to start work on protocol 73-121 as soon as possible. We would appreciate your comments concerning this protocol design at your earliest convenience.

Very truly yours,

PARKE, DAVIS & COMPANY

E. A. TIMM, Ph.D.
Vice President, Quality Control
and Government Regulations

EAT/REK/evj

Attachment:

cc: Dr. B. Cabana
Division of Biopharmaceutics (HFD-520)

NDA 84-427

Parke, Davis & Company
Attention: Dr. L. M. Leeck
Joseph Campau at the River
Detroit, MI 48232

Gentlemen:

Reference is made to the bioavailability studies you submitted on November 21, 1975 for Dilantin Infatabs (Phenytoin Tablets) 50 mg. and Dilantin Kapseals (Phenytoin Sodium Capsules) 30 mg.

The studies have been reviewed by our Division of Biopharmaceutics and they have the following comments:

1. The dissolution data supplied by the firm was inadequate. The complete dissolution profile for the Infatabs both crushed and intact should be supplied, as well as dissolution data for the Kapseals.
2. The firm has compared the bioavailability of two drug products for which they have no previous bioavailability data. The firm's largest data base is composed of the 100 mg Kapseals not the 30 mg Kapseals.
3. The Infatabs were thoroughly chewed prior to swallowing; the question arises as to why this was done. According to the PDR labeling for Infatabs, chewing of the tablet is not required. The firm should perform a five way crossover study utilizing chewed Infatabs, intact Infatabs, 30 mg Kapseals, 100 mg Kapseals and phenytoin solution. If chewing is required, the labeling should reflect this or a disintegrant added to the formulation.

CONCLUSION: The submitted study is not acceptable at this time.

Sincerely yours,

Marvin Seife 2/9/76

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

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MSeife/bho 2/9/76

NDA 84-427

AUG 0 2 1976

Parke, Davis and Company
Attention: Dr. E.A. Timm
Joseph Campau at the River
Detroit, MI 48232

Gentlemen:

Reference is made to the protocol you submitted for bioavailability studies for Dilantin Infatabs (Phenytoin Tablets) 50 mg.

The protocol has been reviewed by our Division of Biopharmaceutics and they have the following comments:

RECOMMENDATION: The submitted protocol is acceptable.

Sincerely yours,

Marvin Seife 8/2/76

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
DET-DO

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HFD-520
HFD-530 Meyer
MSeife/wlb/8-2-76
hrc letter

NDA 84-427

AF 12-757

APR 17 1975

Parke, Davis & Company
Attention: Dr. Les Lueck
Joseph Campau at the River
Detroit, MI 48232

Gentlemen:

Reference is made to the protocol you submitted for bioavailability studies for Dilantin (diphenylhydantoin hydrochloride) Chewable Infatabs, 50 mg.

The protocol has been reviewed by our Division of Biopharmaceutics and they have the following comments:

I. PROTOCOL 73-62:

RECOMMENDATIONS:

This study is not acceptable as definitive evidence of either bioequivalency or a documented difference between dosage forms (pharmaceutical alternatives) because of the deficiencies listed below. While the rate of absorption cannot be observed, it does seem, from this study, that the suspension may be more extensively absorbed than the other two dosage forms.

1. It is, therefore, recommended that the firm perform a new bioavailability study comparing the Infatabs, Suspension, and Kapseals using sufficient subjects and sufficient sampling times to describe the absorption and elimination phases of the plasma-concentration curve.

2. A protocol should be submitted prior to commencing the study so that the Agency and the firm can agree on a mutual approach.

3. Any significant differences shown by the resultant study should be included in the package insert.

APPEARS THIS WAY
ON ORIGINAL

II. PROTOCOL 73-21:

1. The commercial drug product was not tested since the drug product was given in applesauce - presumably not intact, and this would destroy the integrity of the drug product.

2. Since the children were divided into an older group and a younger group, the number of subjects needed to describe each response should be greater than 5 in each group. The coefficient of variation showed this in fluctuating between ———

3. Comparison of the three dosage forms within the older group revealed that the elimination rate constant for the Infatabs might be different than for the suspension and the Kapseals. The data, however, was too incomplete for a conclusive statement.

RECOMMENDATION:

This study is not acceptable as definitive proof of bioequivalency for the reasons listed above.

III. PROTOCOL 73-29:

RECOMMENDATION:

The study is unacceptable as proof of bioequivalence for the same deficiencies discussed in protocol 73-29. In addition, the one week washout period is insufficient to eliminate the drug before the next dose was given.

Sincerely yours,

Marvin Seife 4/17/75

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
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HFD-530 HFD-614 HFD-616 HFD-520
MSeife/rt/4-17-75

Joseph Campau at the River
Detroit, Michigan 48232
Telephone (313) 567-5300

December 11, 1975

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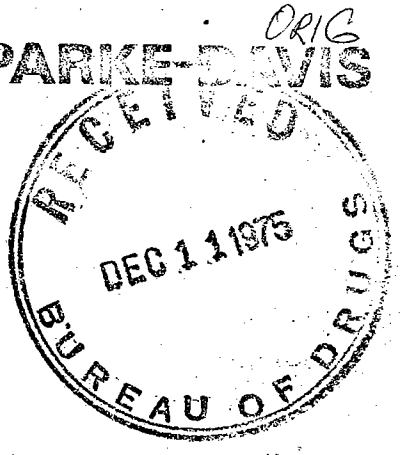
PARKE-DAVIS



ORIG NEW CORRES

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs (HFD-530)
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
Department of Health, Education and Welfare
5600 Fishers Lane
Rockville, Maryland 20852

Re: Dilantin IND 1113, ANDA 84-349, NDA 10-151, ANDA 8-762 and ANDA 84-427

Dear Dr. Seife:

Reference is made to the arrangements that have been made between you and our representative Mr. Julius Hauser for a meeting on December 15, 1975 between technical representatives of the Food and Drug Administration (FDA) and of Parke-Davis for discussion of bioavailability studies made with various preparations of phenytoin. We understand that one or more consultants to the FDA may also be present at this meeting.

The data to be discussed at the subject meeting includes information derived from studies conducted by Parke, Davis & Company at considerable expense and which were submitted to the Food and Drug Administration in the following IND and NDA submissions, which have not been the subject of an FDA "approvable" letter.

(1) IND 1113

(2) ANDA 84-349

(3) The July 23, 1975 supplement to NDA 10-151, and amendments thereto

(4) ANDA 8-762

(5) ANDA 84-427

In our opinion, data submitted in the subject IND and NDA's are valuable trade secrets and commercial information which are privileged or confidential within the meaning of section 4.61 of the regulations under the Freedom of Information Act. Further, we believe, that this information is required to be protected as confidential by 5 U.S.C. 552(b)(3) (4) and (6), and by section 301(j) of the Food, Drug and Cosmetic Act and

provisions of section 312.5 and 314.14 of the regulations concerning confidentiality of data and information in IND and NDA files. We wish again to note that FDA has not sent Parke-Davis an approvable or an approval letter based on the subject IND and NDA files. Further, data and information in these files have not heretofore been disclosed publicly by Parke, Davis & Company.

We will appreciate your confirmation that the information and data contained in the IND's and NDA's enumerated above, and which are to be discussed at our meeting on December 15, 1975, will be protected as confidential by FDA and any FDA consultants present in accord with the cited provisions of law and regulations.

Very truly yours,

PARKE, DAVIS & COMPANY

L.M. Lueck /lw

L.M. LUECK, Ph.D.
Vice President, Quality Control
and Government Regulations

APPEARS THIS WAY
ON ORIGINAL

Parke, Davis & Company

Joseph Campau at the River
Detroit, Michigan 48232
Telephone (313) 567-5300

PARKE-DAVIS

Quality Control and
Government Regulations Division

ORIG NEW CORRES

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs (HFD-530)
Office of Drug Monographs
Bureau of Drugs
Food and Drug Administration
Department of Health, Education and Welfare
5600 Fishers Lane
Rockville, Maryland 20852

NOV 21 1975

Dear Dr. Seife:

Re: NDA 84-427
Dilantin Infatabs, 50 mg.
(Phenytoin Tablets, U.S.P.)

We acknowledge receipt of your letter of April 17, 1975, which commented upon the bioavailability studies included in our above application.

Submitted herewith are additional clinical data from a recently completed study designed to compare the bioavailability of Dilantin Infatabs and Dilantin Kapseals in normal volunteers. These data, identified as Protocol 73-116, were filed under our Notice of Claimed Investigational Exemption on October 9, 1975 (IND 1113, Ref. No. 73/166).

We trust these additional data will allow you to complete your review of our application.

Very truly yours,

PARKE, DAVIS & COMPANY

L. M. LUECK, Ph.D.
Vice President, Quality Control
and Government Regulations

LML/CMH/evb
Attachment