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Guidance for Industry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

INTERIM GUIDANCE[1]

MAR 4 1994

PHENYTOIN/PHENYTOIN SODIUM

CAPSULES, TABLETS AND SUSPENSION

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Phenytoin is an antiepileptic drug indicated for the control of generalized tonic-clonic seizures and complex partial seizures. The primary site of action appears to be the cerebral motor cortex where spread of seizure activity is inhibited. The mechanism of action may involve a promotion of sodium efflux from neurons and stabilization of the depolarization threshold against hyperexcitability caused by excessive stimulation or environmental changes (1).

Phenytoin dosages should be individualized to optimize seizure control relative to side effects. Serum level determinations may be necessary for optimal dosage adjustments to maintain concentrations in the therapeutic range of 10-20 mcg/ml. In general, the initial adult dosage of phenytoin is 100 mg three times daily. For most adults, a satisfactory maintenance dose will be 300 mg or 400 mg a day. In some patients, an increase up to 600 mg (200 mg three times a day) may be necessary. If seizure control is established with divided doses of 300 mg daily, once-a-day dosage with three 100 mg extended phenytoin sodium capsules may be considered. The usual initial dosage recommended for children is 5 mg/kg or 250 mg/m^2 daily administered in two or three equally divided doses. Maintenance dosage may range from 4 to 8 mg/kg a day, and a total daily dose should not exceed 300 mg (1,2). Children over 6 years old may require the minimum adult dose of 300 mg/day (1).

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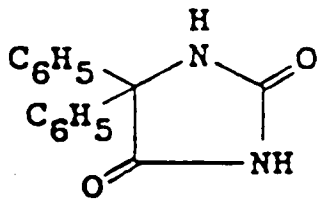
[1]This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, please contact the Division of Bioequivalence, HFD-650, Office of Generic Drugs, 7500 Standish Place, Metro Park North II, Rockville, MD 20855 (Phone: 301-594-0315; Fax: 301-594-0181). For copies of this guidance, please contact the Executive Secretariat Staff, HFD-8, Center for Drug Evaluation and Research, 7520 Standish Place, Metro Park North I, Rockville, MD 20855 (Phone: 301-594-1012).

B. Chemistry

The chemical name of phenytoin is 5,5-diphenyl-2,4-imidazolidinedione or 5,5-diphenylhydantoin (Figure). The drug is related to barbiturates in chemical structure, but has a five-membered ring.



Phenytoin is a relatively weak acid (pKa = 8.3) with limited aqueous solubility (3). Both phenytoin and its sodium salt occur as a white powder. The free acid is practically insoluble in water, soluble in hot alcohol, and slightly soluble in cold alcohol. The sodium salt is soluble in alcohol, and is freely soluble in water and warm propylene glycol. Phenytoin sodium is hygroscopic in nature and is reported to absorb atmospheric CO_2 with liberation of free acid (2,4).

C. Pharmacokinetics

Phenytoin and its sodium salt are readily absorbed from the GI tract. The rate of absorption differs substantially between extended and prompt phenytoin sodium capsules. Phenytoin from prompt capsules is rapidly absorbed and generally produces peak serum levels in 1.5-3 hours. Phenytoin from extended capsules is more slowly absorbed with peak serum levels achieved in 4-12 hours (1,2).

Phenytoin is 90% bound to plasma protein, primarily albumin. The volume of distribution of the drug is about 0.6-0.7 L/Kg. Phenytoin appears to be rapidly distributed to the brain (5,6). Small amounts of the drug have been found in milk (2). The reported half-life in man after oral administration of 300 mg phenytoin averages 22 hours with a range of 7 to 42 hours (1). Because of non-linear pharmacokinetics, the clearance of phenytoin is a function of plasma concentration, as is phenytoin half-life (3).

The major route of phenytoin metabolism is oxidation by the liver to an inactive metabolite, 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH). The urinary recovery of p-HPPH and its glucuronide accounts for 60-90% of an oral dose of phenytoin. Only 1-5% of the administered dose is recovered unchanged in the urine (7,8).

Phenytoin exhibits Michaelis-Menten kinetics at therapeutic doses. The capacity-limited or saturable metabolism of the drug results in a disproportionate increase in serum concentrations at steady state as the daily dose of phenytoin is increased. The time required to attain steady state levels also increases with the rate of administration and varies with individual V_{max} and K_m values (9,10). In addition, due to low solubility and capacity-limited metabolism, the time to achieve peak concentration after a single dose increases with the dose (11,12).

Because of the nonlinear pharmacokinetics of phenytoin, a small difference in average absorbed dose can result in a large difference in serum concentrations at steady state (13). To ensure the therapeutic efficacy and safety of the drug, the USP has recently proposed that the assay specification for extended phenytoin sodium capsules be tightened from 93-107% to 95-105% (14).

Food effects on the bioavailability of phenytoin free acid have been studied in healthy volunteers (15,16). In one study, concurrent intake of a standard breakfast with three 100 mg phenytoin tablets appeared to enhance drug absorption. A mean increase of 27% and 40% in AUC and C_{max}, respectively, was found during the postprandial state as opposed to the fasting condition (15). In another study, carbohydrate and protein were shown to reduce the absorption of phenytoin, whereas fat had no measurable influence (16).

The effect of food on the bioavailability of phenytoin sodium salt is less well documented. An increase in the rate and extent of absorption of phenytoin from an investigational dosage form of 300 mg extended phenytoin sodium capsules has been reported (17).

D. Phenytoin Drug Products

Phenytoin is currently available in the U.S. as capsules, chewable tablets, oral suspension, and parenteral solution. Phenytoin formulations are marketed by the innovator, Warner-Lambert/Parke-Davis, under the brand name, Dilantin®.

a. Phenytoin Sodium Capsules

Two classes of phenytoin sodium capsules (extended versus prompt) were established by FDA/USP in 1980.

1. Extended Phenytoin Sodium Capsules

Extended phenytoin sodium capsules are available in strengths of 30 and 100 mg. The reference listed drug for extended phenytoin sodium capsules is Dilantin® Kapseals®. "Extended" capsules exhibit slower dissolution with prolonged absorption of the drug substance compared to "prompt" capsules. In the absence of a specific rate-controlling mechanism, this

formulation is not classified as a true extended release dosage form.

2. Prompt Phenytoin Sodium Capsules

Several prompt phenytoin sodium capsules are available in strengths of 30 and 100 mg. These products release the drug substance immediately and are thus not recommended for substitution with extended phenytoin sodium capsules.

b. Phenytoin Chewable Tablets

Phenytoin free acid chewable tablets are available in a single strength of 50 mg. Labeling for this formulation indicates that it may be chewed thoroughly and swallowed or swallowed whole. The reference listed drug product is Dilantin^{R} Infatabs^{R}, which is considered an immediate release dosage form.

c. Phenytoin Suspension

Phenytoin free acid suspension is available in strengths of 30 mg/5 mL and 125 mg/5 mL. The reference listed drug product is Dilantin-30^{R}-Pediatric and Dilantin-125^{R} Suspension, which is considered an immediate release dosage form. Literature reports (18) have suggested delayed absorption of free acid from the formulation.

d. Phenytoin Sodium Injection

Phenytoin sodium injection is available in a single strength of 50 mg/mL. The reference listed drug product is Dilantin^{R} Parenteral, which is a ready-mixed solution of phenytoin sodium in a vehicle containing 40% propylene glycol and 10% alcohol in water for injection, adjusted to pH 12 with sodium hydroxide.

II. Documentation of Bioequivalence

Because of the nonlinear pharmacokinetics of phenytoin, questions have been raised as to whether single-dose or multiple-dose studies should be used for demonstration of bioequivalence for generic phenytoin/phenytoin sodium products. This issue was discussed at an open public session of the Generic Drugs Advisory Committee meeting in February 1993. The Committee concluded that the use of single-dose, replicate design studies may be more appropriate than multiple-dose, steady-state studies for bioequivalence assessment of phenytoin/phenytoin sodium formulations for the following reasons:

1. Single-dose studies are more sensitive in detecting the rate differences, if any, between formulations.

2. The disparities, if any, in bioavailability parameters (e.g., AUC) observed with multiple doses reflect, to a large extent, the nonlinear characteristics of the drug substance, rather than a true difference between formulations.

3. Due to the nonlinear kinetics of phenytoin, the time required to reach steady state may be prolonged to several weeks or months. Documentation of attainment of steady state is difficult for the drug if a multiple-dose, steady-state study were to be conducted.

On the basis of the above considerations, the Division of Bioequivalence, at the present time, recommends that single-dose, replicated-treatment designs be employed in pivotal bioequivalence studies for phenytoin/phenytoin sodium products. Recognizing the importance of nonlinear kinetics and the degree of intrasubject/intralot variability of the drug, the Division may adjust the bioequivalence criteria pending the results of further studies.

III. *IN VIVO* BIOEQUIVALENCE STUDIES[2]

A. Product Information

1. FDA designated reference products: 1) Dilantin^{R} Kapseals^{R}, 100 mg and 30 mg, for respective strengths of extended phenytoin sodium capsule; 2) Dilantin^{R} Infatabs^{R}, 50 mg, for phenytoin chewable tablet; and 3) Dilantin-125^{R}, 125 mg/5 mL, and Dilantin-30^{R}-Pediatric, 30 mg/5 mL, for respective strengths of phenytoin oral suspension.

2. Batch size: The test batch or lot must be manufactured under production conditions and must be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, whichever is greater.

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 3%.

[2]The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1).

B. Types of Studies Required

1. Capsules

A single-dose, randomized, fasting, two-treatment, two-sequence (or four-sequence), four-period crossover study with replication of identical lots of test and reference products.

2. Chewable Tablets

a. A single-dose, randomized, fasting, two-treatment, two-sequence (or four-sequence), four-period crossover study with replication of identical lots of test and reference products, swallowed whole.

b. A single-dose, randomized, fasting, three-treatment, six-sequence, three-period crossover study comparing equal doses of the test and reference products, chewed thoroughly and swallowed.

3. Suspension

A single-dose, randomized, fasting, two-treatment, two-sequence (or four-sequence), four-period crossover study with replication of identical lots of test and reference products.

C. Protocols for *In Vivo* Fasting Bioequivalence Studies

1. Capsules

Objective: To compare the rate and extent of absorption of a generic formulation of extended phenytoin sodium capsule, 100 mg or 30 mg, with the corresponding strength of reference product, Dilantin^{R} Kapseals^{R}, 100 mg or 30 mg, when given as equal single labeled doses.

Design: The study design is a single-dose, two-treatment, two-sequence (or four-sequence)[3], four-period crossover with a washout interval of at least one-week between phases (i.e., 7 days after the last blood sampling). The recommended two sequences are TRTR and RTRT

[3]Two possible study designs are currently recommended due to unresolved issues regarding phenytoin pharmacokinetics. The sponsoring firm is advised to make its best judgement for the choice of study design. A two-treatment, four-sequence, four-period crossover design is preferred in the event that residual effects occur in the study. The disadvantage of using such a design is that there is more than one "reasonable" estimator for the ratio of the test over reference average, and each possible estimator produces a different confidence interval. However, if the firm believes that residual effects will not occur with the washout period planned, a two-sequence study is preferred for demonstration of bioequivalence.

(or TRRT and RTTR), where T and R represent test and reference product, respectively. The recommended four sequences are TTRR, RRTT, TRRT and RTTR. Equal numbers of subjects should be randomly assigned to each of the two or four possible dosing sequences. Before the study begins, the proposed protocols should be approved by an institutional review board.

Facilities: The clinical and analytical laboratories used for the study should be identified along with the names, titles and curriculum vitae of the medical and scientific/analytical directors.

Selection of Subjects: The sponsor should enroll a sufficient number of volunteers to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. Subjects should be healthy male volunteers aged 18 to 50 years and within 10% of ideal body weight for their heights and builds (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical testing. Subjects with any current or past medical condition which might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study participants before they are accepted into the studies.

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single 100 mg (1 x 100 mg capsule) or 90 mg (3 x 30 mg capsule) dose of the test or reference product with 240 mL of water.

Restrictions: Study volunteers should be subject to the following restrictions:

a. Water may be allowed except for one hour before and after drug administration when no liquid should be permitted other than that needed for drug dosing.

b. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

c. No alcohol or xanthine-containing food or beverage should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

d. Subjects should take no Rx medication beginning two weeks and OTC drug beginning one week before drug administration until after the study is completed.

Blood Sampling: Venous blood samples should be collected pre-dose (0 hours) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours post-dose. Plasma/serum should be promptly separated and frozen until assayed.

Subject Monitoring: During the study, subjects should be observed for signs and symptoms which would indicate intolerance to the study medication. In the event of a serious adverse reaction, study medication may need to be terminated.

Clinical Report and Adverse Reactions: Subject medical histories, physical examination results, and all incidents of possible adverse reactions to the study formulations should be reported.

Analytical Methods: Phenytoin should be assayed using a suitable method fully validated with respect to adequate sensitivity, specificity, linearity, recovery, accuracy and precision (both within and between days). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of unknown samples, including all associated standard curve and quality control chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

Statistical Analysis of Pharmacokinetic Data: See Division of Bioequivalence Guidance entitled "*Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*". Sponsors are encouraged to review statistical approaches for replicated-treatment design with staff of the Division of Bioequivalence in the Office of Generic Drugs, and Division of Biometrics in the Office of Epidemiology and Biostatistics as appropriate.

2. Chewable Tablets

The protocol for this study is identical to that described for capsules, with the following differences:

Objective: To compare the rate and extent of absorption of a generic formulation of phenytoin tablet, 50 mg, with the reference product, Dilantin^{R} Infatabs^{R}, 50 mg, when given as equal labeled doses.

Design: Two studies should be conducted for tablets; one full-scale, replicated-treatment study with both test and reference tablets swallowed whole, and the other limited chewing-effect study with both test and reference tablets chewed thoroughly and swallowed.

The replicated-treatment design for both test and reference tablets swallowed whole is the same as that described for capsules.

The limited chewing-effect study is a single-dose, three-treatment, six-sequence, three-period crossover with a washout interval of at least one-week between phases (i.e., 7 days after the last blood sampling). Equal numbers of subjects should be assigned to each of the six possible dosing sequences. Each subject will receive the following three treatments:

Treatment 1: Generic product, chewed thoroughly and swallowed

Treatment 2: Reference product, chewed thoroughly and swallowed

Treatment 3: Generic product, swallowed whole

The lots of the test and reference products used in both studies should be the same.

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single 100 mg dose (2 x 50 mg tablet) of the test or reference product with 240 mL of water.

Statistical Analysis: For the limited chewing-effect study, only the mean values of AUC_{0-T}, $AUC_{0-\infty}$ and C_{max} for the test product will be compared with the respective mean values for the reference product. The equivalence criteria for this study will be set in accordance with those established for the full-scale study.

3. Suspension

The protocol for this study is identical to that described for capsules, with the following differences:

Objective: To compare the rate and extent of absorption of a generic formulation of phenytoin oral suspension, 125 mg/5 mL or 30 mg/5 mL, with the corresponding strength of reference product, Dilantin-125^{R} or Dilantin-30^{R}-Pediatric Suspension, when given as equal labeled doses.

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single 125 mg dose (5 mL for adult strength) or 90 mg dose (15 mL for pediatric strength) of the test or reference product with 240 mL of water.

IV. *IN VITRO* TESTING REQUIREMENTS

A. Dissolution Testing

Dissolution testing is recommended to be conducted on 12 dosage units of the test product versus 12 units of the reference product. The lots used in the *in vitro* dissolution testing should be the same as those tested in the *in vivo* bioequivalence study. The following method and tolerances are currently recommended for extended phenytoin sodium capsules:

Apparatus:	USP XXII apparatus 1 (basket)
RPM:	50
Medium:	Distilled water (37°C)
Volume:	900 mL
Sampling Times:	15, 30, 60, 90 and 120 minutes
Analytical:	HPLC method
Tolerance (Q):	NMT 40% in 30 minutes; 55% in 60 minutes; and NLT 70% in 120 minutes

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXII.

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