CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 40-621

Name: Extended Phenytoin Sodium Capsules, USP 100 mg

Sponsor: Sun Pharmaceutical Industries Ltd.

Approval Date: December 11, 2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-621

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-621

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 40-621

A.A.C. Consulting Group, Inc.
U.S. Agent for: Sun Pharmaceutical Industries Ltd.
Attention: Anthony C. Celeste
7361 Calhoun Place, Suite 500
Rockville, MD 20817

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 20, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Extended Phenytoin Sodium Capsules USP, 100 mg.

Reference is also made to your amendments dated May 5, 2005; and June 6 and September 18, 2006.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Extended Phenytoin Sodium Capsules USP, 100 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Dilantin Kapseals, 100 mg, of Parke Davis Div Warner Lambert Co.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Dissolution Testing should be conducted in 900 mL of water using apparatus 1 (basket) at 50 rpm.

Time (minutes)	Percent Dissolved
30	(b) (4)
60	
120	

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert L. West
12/11/2006 02:11:45 PM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-621

LABELING

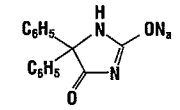
SUN PHARMACEUTICAL INDUSTRIES LIMITED

EXTENDED PHENYTOIN SODIUM CAPSULES, USP

Barcode

DESCRIPTION

Phenytoin Sodium is an antiepileptic drug. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is sodium 5,5-diphenyl-2,4-imidazolidinedione, having the following structural formula:



Each Extended Phenytoin Sodium Capsule, USP contains 100 mg phenytoin Sodium, USP. Also contains lactol monohydrate, NF; sodium lauryl sulfate, NF; talc, USP; magnesium stearate, NF. The capsule shell contains gelatin, NF; and black printing ink, which contains black iron oxide, FD & C Blue No. 2, FD & C Red No. 40, FD & C Blue No. 1, D & C Yellow No.10 shellac glaze and SDA 3A alcohol or N-butyl alcohol and propylene glycol. Product *in vivo* performance is characterized by a slow and extended rate of absorption with peak blood concentrations expected in 4-12 hours as contrasted to *Prompt Phenytoin Sodium Capsules*, USP with a rapid rate of absorption with peak blood concentration expected in 1½ to 3 hours.

CLINICAL PHARMACOLOGY

Phenytoin is an antiepileptic 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 tonic-clonic (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. Steady-state therapeutic levels are achieved at least 7 to 10 days (5-7 half-lives) after initiation of therapy with recommended doses of 300 mg/day.

When serum level determinations are necessary, they should be obtained at least 5-7 half-lives after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. For Extended phenytoin sodium capsules, USP peak serum levels occur 4-12 hours after administration.

Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 and 20mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or 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. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

Most 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. Because phenytoin is hydroxylated in the liver by an enzyme system, which is saturable at high plasma levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

INDICATIONS AND USAGE

Extended Phenytoin Sodium Capsules, USP are indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments.

(see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY sections).

CONTRAINDICATIONS

Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

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 alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg. fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effor t should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels, while chronic alcohol use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy:

Clinical:

A. Risks to Mother. An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see PRECAUTIONS, Laboratory Tests). However, postpartum restoration of the original dosage will probably be indicated.

B. Risks to the Fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mother received phenytoin during pregnancy. The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or two-to three-fold that in the general population. However, the relative contribution of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most case it has not been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during pregnancy.

C. Postpartum Period. A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin in utero. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Preclinical:

Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/kg or higher (approximately 120% of the maximum human loading dose or higher on a mg/m² basis) to pregnant rabbits.

PRECAUTIONS

General:

The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, 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 should be discontinued if a skin rash appears (see WARNINGS section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See ADVERSE REACTIONS section.) If the rash is of 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 phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see CONTRAINDICATIONS). Additionally, caution should be exercised if using structurally similar compounds (eg. barbiturates, succinimides, oxazolidinediones, and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See WARNINGS section.)

Information for the Patients:

Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg. surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

EXTENDED PHENYTOIN SODIUM CAPSULES, USP

Do not use capsules which are discolored.

Laboratory Tests:
Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions:
There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below:

1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, cimetidine, diazepam, dicumarol, disulfiram, estrogens, ethosuximide, fluoxetine, H2-antagonist, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, ticlopidine, tolbutamide, trazodone.
2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban® (Moban is a registered trademark of Endo Pharmaceuticals, Inc.) brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.
3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.
4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.
5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, paroxetine, quinidine, rifampin, theophylline, vitamin D.

Drug-Enteral Feeding/Nutritional Preparations Interaction: Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin plasma levels. It is therefore suggested that phenytoin not be administered concomitantly with an enteral feeding preparation. More frequent serum phenytoin level monitoring may be necessary in these patients.

Drug/Laboratory Test Interactions:
Phenytoin may decrease serum concentrations of T_4. It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis:
See WARNINGS section for information on carcinogenesis.

Pregnancy:
Pregnancy Category D; See WARNINGS section.

Nursing Mothers:
Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

Pediatric Use:
See DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed.
There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

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. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see PRECAUTIONS section.)

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 with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have been reported (see WARNINGS section).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's disease.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, periarteritis nodosa and immunoglobulin abnormalities.

OVERDOSAGE

The lethal dose in pediatric patients is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur.

Nystagmus, on lateral gaze, usually appears at 20mcg/mL, ataxia at 30mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40mcg/mL, but as high a concentration as 50mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100mcg/mL with complete recovery.

Treatment:
Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in pediatric patients.

In acute overdosage, the possibility of other CNS depressants, including alcohol, should be borne in mind.

DOSAGE AND ADMINISTRATION

Serum concentrations should be monitored in changing from Extended Phenytoin Sodium Capsules, USP to Prompt Phenytoin Sodium Capsules, USP, and from the sodium salt to the free acid form.

Extended Phenytoin Sodium Capsules, USP are formulated with the sodium salt of phenytoin. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt and vice versa.

General:
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 10-20mcg/mL. With recommended dosage, a period of seven to ten days may be required to achieve steady-state blood levels with phenytoin and changes in dosage (increase or decrease) should not be carried out at intervals shorter than seven to ten days.

Adult Dosage:
Divided daily dosage:
Patients who have received no previous treatment may be started on one 100-mg Extended Phenytoin Sodium Capsule, USP three times daily and the dosage then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be one capsule three to four times a day. An increase up to two capsules three times a day may be made, if necessary.

Once-A-Day dosage:
In adults, if seizure control is established with divided doses of three 100-mg Extended Phenytoin Sodium Capsules, USP daily, once-a-day dosage with 300 mg of extended phenytoin sodium capsules may be considered. Studies comparing divided doses of 300 mg with a single daily dose of this quantity indicated absorption, peak plasma levels, biologic half-life, difference between peak and minimum values, and urinary recovery were equivalent. Once-a-day dosage offers a convenience to the individual patient or to nursing personnel for institutionalized patients and is intended to be used only for patients requiring this amount of drug daily. A major problem in motivating noncompliant patients may also be lessened when the patient can take this drug once a day. However, patients should be cautioned not to miss a dose, inadvertently.

Only extended phenytoin sodium capsules are recommended for once-a-day dosing. Inherent differences in dissolution characteristics and resultant absorption rates of phenytoin due to different manufacturing procedures and/or dosage forms preclude such recommendation for other phenytoin products. When a change in the dosage form or brand is prescribed, careful monitoring of phenytoin serum levels should be carried out.

Loading Dose:
Some authorities have advocated use of an oral loading dose of phenytoin in adults who require rapid steady-state serum levels and where intravenous administration is not desirable. This dosing regimen should be reserved for patients in a clinic or hospital setting where phenytoin serum levels can be closely monitored. Patients with a history of renal or liver disease should not receive the oral loading regimen.

Initially, one gram of phenytoin capsules is divided into three doses (400 mg, 300 mg, 300 mg) and administered at two-hour intervals. Normal maintenance dosage is then instituted 24 hours after the loading dose, with frequent serum level determinations.

Pediatric Dosage:
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 old and adolescents may require the minimum adult dose (300 mg/day).

HOW SUPPLIED

Extended Phenytoin Sodium Capsules, USP, 100 mg are supplied as follows:

Transparent # 3 capsule filled with white to off-white powder, with the code '402' imprinted on the cap and body.

Bottles of 100: NDC 62756-402-01

Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP.

Rx only

PXPI 0795 April 2005

Manufactured by:
M.J.Pharmaceuticals Ltd.
Halol-Baroda Highway,
Halol-389 350, Gujarat, India

Manufactured for:
Sun Pharmaceutical Industries Ltd.
Acme Plaza, Andheri-Kurla Road,
Andheri (East), Mumbai- 400 059, India

Each capsule contains 100 mg phenytoin sodium, USP.

Usual Dosage - Adults, 1 capsule three or four times daily or as directed.

See package insert for complete prescribing information.

Keep this and all drugs out of the reach of children.

NOTE TO PHARMACIST - Do not dispense capsules which are discolored.

Exp date and Batch No.

NDC 62756-402-01

Extended Phenytoin Sodium Capsules, USP

100 mg

Rx only

100 CAPSULES

PXLB 0106

SUN PHARMACEUTICAL IND. LTD.

Dispense in a tight, light resistant container as defined in the USP.

Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USPControlled Room Temperature].
Protect from light and moisture.

Manufactured by:
M.J. Pharmaceuticals Ltd.
Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

Manufactured For:
Sun Pharmaceutical Ind. Ltd.
Acme Plaza, Andheri-Kurla Road,
Andheri (East), Mumbai-400 059, India.

8 901127 003452

38 mm

89 mm

Final Size: 89 x 38 mm

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-621

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-621

Date of Submission: August 20, 2004

Applicant's Name: Sun Pharmacetuical Industries, Ltd.

Established Name: Extended Phenytoin Sodium Capsules USP, 100 mg

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Labeling Deficiencies:

1. CONTAINER -100s

   a. Revise storage temperature recommendation to:
   Store at 20°-25°C (68°- 77°F [see USP controlled room temperature]. Protect from light and moisture.

   b. Please clarify the meaning of "PXLB 0106" appearing on your main panel of your container label.

   c. It is difficult to read your container labels. Please improve the print quality on your label (especially on the side panel.

2. INSERT

   a. DESCRIPTION

      List the dyes in your imprinting ink with your inactive ingredients.

Due to changes in the labeling for Dilantin® Kapseals, ANDA 84-349/S-040, approved December 9, 2003, please make the following revisions:

b. WARNINGS:
Usage in Pregnancy: replace your subsection with the following paragraphs:

Clinical:
A. Risks to Mother. An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see PRECAUTIONS, Laboratory Tests). However, postpartum restoration of the original dosage will probably be indicated.

B. Risks to the Fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among

children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or two- to three-fold that in the general population. However, the relative contribution of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most cases it has not been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during pregnancy.

C. Postpartum Period. A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin in utero. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Preclinical:
Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/kg or higher (approximately 120% of the maximum human loading dose or higher on a mg/m2 basis) to pregnant rabbits.

c. PRECAUTIONS

(1). General: fourth paragraph, first sentence-revise to"...hypersensitivity (see CONTRAINDICATIONS).

(2) Drug Interactions- revise number 1 to read - ...chlordiazepoxide, cimetidine, diazapam, dicumarol, disulfiram, estrogens, ethosuximide, fluoxetine, H2-antagonist, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, ticlopidine, tolbutamide, trazodone.

(3) Drug Interactions-revise number 5 to read"...oral contraceptives, paroxetine, quinidine..."

(4) Insert the following paragraph to appear after Drug Interactions number 5;

Drug-Enteral Feeding/Nutritional Preparations Interaction: Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin plasma levels. It is therefore suggested that phenytoin not be administered concomitantly with an enteral feeding preparation. More frequent serum phenytoin level monitoring may be necessary in these patients.

(5) Drug/Laboratory Test Interactions- revise first sentence to read-"Phenytoin may decrease serum concentrations of T_4."

(6) Pregnancy:revise to read-"Pregnancy:Pregnancy Category D; See WARNINGS section.

(7) Pediatric Use- add the following to appear as the next subsection to follow Nursing Mothers;

Pediatric Use: See DOSAGE AND ADMINISTRATION

d. ADVERSE REACTIONS

(1) Delete (b) (4)

(2) Immunologic:revise to ...systemic lupus erythematosus, periarteritis nodosa....

e. HOW SUPPLIED

(1) Revise storage temperature recommendation to:
Store at 20°-25°C (68°- 77°F [see USP controlled room temperature]. Protect from light and moisture

(2) Include the following statement to appear following your storage recommendation:
" Dispense in a tight, light-resistant container as defined in the USP".

(3) Include a disclaimer for Moban;
(Moban is a registered trademark of Endo Pharmaceuticals, Inc.)

Please revise your container and insert labeling as instructed above and submit in final print to be in accord with the electronic labeling rule published December 11, 2003, (68 FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/cdernew/listserv.html or http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER Labels: (

Professional Package Insert Labeling:

Revisions needed post-approval: None.

BASIS OF APPROVAL:

Patent Data – NDA 84-349

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 84-349

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Extended Phenytoin Sodium Capsules USP (Dilantin®)
ANDA Number: 84-349
ANDA Drug Name: Extended Phenytoin Sodium Capsules USP (Dilantin®)
ANDA Firm: Parke Davis
Date of Approval of ANDA Insert and supplement #: 12-9-03 (S-040)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? Yes
Basis of Approval for the Container Labels: side by side

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 28	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Review based on the labeling of the referenced listed drug, Dilantin Kapseals®; NDA 84-349/S-040 approved on December 9, 2003.

2.

Patent Data – NDA 84-349

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 84-349

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage Conditions:
RLD – Store below 30°C (86°F). Protect from light and moisture.
ANDA - Store (b) (4) . Protect from light and moisture

The firm has been requested to revise storage temperature recommendation to: Store at 20°-25°C (68°- 77°F [see USP controlled room temperature]. Protect from light and moisture.

4. Dispensing Recommendations:
NDA – Dispense in a tight, light-resistant container as defined in the USP.
ANDA - none
USP- Preserve in tight, light-resistant containers. Store at controlled room temperature

The firm has been requested to include the following statement on their container and insert labeling: Preserve in tight, light-resistant containers.

5. Product Line:
The innovator markets their product in 100s, 1000s, and UD 100s
The applicant proposes to market their product in 100s,

6. The capsule description and imprint has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). (Vol 1.4 pg. 1249)

7. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert is not consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1005-1013 (Volume 1.4).
The firm has been requested to list dyes in the imprinting ink.

8. M.J. Pharmaceuticals Ltd, India is the manufacturer - page 1192 (Vol 1.4)

9. Container/Closure – pg. 1436 (Vol 1.5)

Bottles – Round HDPE 75 cc bottle
Caps- 33 mm CRC

Date of Review: March 30, 2005 **Date of Submission:** August 20, 2004

Primary Reviewer: Michelle Dillahunt **Date:** 4/11/05

Team Leader: Lillie Golson **Date:** 4/11/05

cc: ANDA: 40-621
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\SUN\LTRS&REV\40621na1.Labeling.doc
Review

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-621

Date of Submissions: May 5, August 3 and September 28, 2005

Applicant's Name: Sun Pharmacetuical Industries, Ltd.

Established Name: Extended Phenytoin Sodium Capsules USP, 100 mg

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APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No, electronic

1. CONTAINER -100s

Satisfactory in FPL as of the August 3, 2005 submission. (Vol 4.1)

2. INSERT

Satisfactory in FPL as of the May 5, 2005 submission.
file:///\\Cdsesubogd1\n40621\N_000\2005-05-05\Package insert .pdf

BASIS OF APPROVAL:

Patent Data – NDA 84-349

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 84-349

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Extended Phenytoin Sodium Capsules USP (Dilantin®)
ANDA Number: 84-349
ANDA Drug Name: Extended Phenytoin Sodium Capsules USP (Dilantin®)
ANDA Firm: Parke Davis
Date of Approval of ANDA Insert and supplement #: 12-9-03 (S-040)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? Yes
Basis of Approval for the Container Labels: side by side

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 28	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Review based on the labeling of the referenced listed drug, Dilantin Kapseals®; NDA 84-349/S-040 approved on December 9, 2003.

2 .

Patent Data – NDA 84-349

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 84-349

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage Conditions:
RLD – Store below 30°C (86°F). Protect from light and moisture.
ANDA - Store at 20°-25°C (68°- 77°F [see USP controlled room temperature]

4. Dispensing Recommendations:
NDA – Dispense in a tight, light-resistant container as defined in the USP.
ANDA - Dispense in tight, light-resistant containers
USP- Preserve in tight, light-resistant containers. Store at controlled room temperature

5. Product Line:
The innovator markets their product in 100s, 1000s, and UD 100s
The applicant proposes to market their product in 100s.

6. The capsule description and imprint has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). (Vol 1.4 pg. 1249)

7. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert is consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1005-1013 (Volume 1.4).

8. M.J. Pharmaceuticals Ltd, India is the manufacturer - page 1192 (Vol 1.4)

9. Container/Closure – pg. 1436 (Vol 1.5)
Bottles – Round HDPE 75 cc bottle
Caps- 33 mm CRC

10. The firm submitted samples of their final printed insert labeling in the 9/28/05 amendment. The insert in its final format is not front and back. Anthony Celeste confirmed this with a voice mail message on 10/13/05. The firm did not submit 12 copies of the insert, therefore I will use the electronic submission dated 5/5/05 for the final printed labeling.

Date of Review: October 11, 2005 **Date of Submissions:** May 5 , August 3 and September 28, 2005

Primary Reviewer: Michelle Dillahunt **Date:** 10/17/05

Team Leader: Lillie Golson **Date:** 10/17/05

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cc: ANDA: 40-621
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\SUN\LTRS&REV\40621ap1.Labeling.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-621

CHEMISTRY REVIEWS

ANDA 40-621

Extended Phenytoin Sodium Capsules, USP
100 mg

Sun Pharmaceutical Industries Ltd.

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

Table of Contents

Chemistry Review Data Sheet

1. ANDA: #40-621

2. REVIEW #: 1

3. REVIEW DATE: 1/16/05

4. REVIEWER: Karen A. Bernard, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	August 20, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	A.A.C. Consulting Group, Inc. US Agent for: Sun Pharmaceutical Industries Ltd. Acme Plaza, Andheri-Kurla Road, Andheri(East), Mumbai-400059, India
Representative:	Anthony C. Celeste 7361 Calhoun Place, Suite 500 Rockville, MD 20855-2765
Telephone:	(301)-838-3120
Fax	(301)-838-3182

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Extended Phenytoin Sodium Capsules USP

9. LEGAL BASIS FOR SUBMISSION:

Pharmaceuticals. There are no unexpired patents or exclusivities. The firm filed a Paragraph I patent certification.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

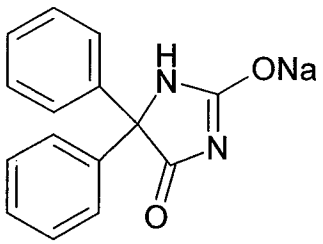
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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



Chemical Name: 5,5-Diphenylhydantoin sodium salt
Molecular Formula: $C_{15}H_{11}N_2O_2Na$
Molecular Weight: 274.25

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	2/20/04	By N Ya
	III			4			
	III			4			

(b) (4)	III	(b) (4)	(b) (4)		4			
	III				4			
	III				4			
	III				4			
	III				4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	AC Dissolve Testing	11/29/04	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 40-621

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

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

N/A

II. Summary of Chemistry Assessments

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

Phenytoin Sodium USP is 5,5-Diphenylhydantoin sodium salt that acts as an anti-convulsant and anti-epileptic.

Phenytoin Sodium is a white fine odorless powder. It is freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide, soluble in alcohol; practically insoluble in ether and in chloroform It is very sensitive to light and moisture. It also exhibits known polymorphism. The proposed source for Phneytoin Sodium is (b) (4).

The extended release transparent colorless capsule of Extended Phenytoin Sodium Capsules is available in a 100 mg strength.

Extended Phenytoin Sodium Capsules 100 mg is manufactured using (b) (4). The finished drug product is required to meet specifications for description, identification, assay, related substances, dissolution and water.

The drug product is supplied in an HDPE bottle of 100 capsules with a CRC closure. The proposed expiration dating period is 24 months.

There is a USP monograph for both the active drug substance and the drug product..

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

Extended Phenytoin Sodium is indicated for the treatment of convulsions and it is an anti-epileptic. It is recommended that Phenytoin Sodium treatment should be administered at a dose of 100 mg 3-4 times a day.

Following this page, 13 pages withheld in full (b)(4)- Chemistry review #1

(b) (4)

[redacted]

30. MICROBIOLOGY N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
Both drug substance and drug product are compendial. Method validation is no longer performed by the field laboratory under normal circumstances.

32. LABELING
Pending.

33. ESTABLISHMENT INSPECTION
Pending

34. BIOEQUIVALENCE
Dissolve Testing AC 11/29/05

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
The firm requests a categorical exclusion from the requirement of an Environmental Assessment Statement or Environmental Impact Statement in accord with 21 CFR 25.31(a). This is on page 2117.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-621
APPLICANT: Sun Pharmaceutical Industries Ltd.
DRUG PRODUCT: Extended Phenytoin Sodium Capsules USP, 100 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.

(b) (4)

8.

9.

10.

11.

12.

13.

14.

15.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

The bioequivalence review comments are provided to you under separate cover. If the Office of Bioequivalence recommends a different Dissolution test or specification for the drug product from the one proposed in this application, please revise the Dissolution testing method and specification for the finished drug products release and stability protocols accordingly and resubmit the comparative drug release profile data if necessary.

Sincerely yours,

Brenda J. Gannine /for 2/22/05

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-621
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/KBernard 1/20/05
HFD-640/BArnwine/2/17/05
HFD-617/YKong/2/17/05

K Bernard 2/22/05
B Arnwine 2/22/05
Y 2-22-05

F/T by: rad2/18/05

V:\Firmsnz\sun\Ltrs&Rev\40-621c1

TYPE OF LETTER: NOT APPROVABLE – MINOR AMENDMENT

ANDA 40-621

Extended Phenytoin Sodium Capsules USP, 100 mg

Sun Pharmaceutical Industries Ltd.

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

Table of Contents

Chemistry Review Data Sheet

1. ANDA: #40-621

2. REVIEW #: 2

3. REVIEW DATE: 12/13/05

4. REVIEWER: Karen A. Bernard, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	August 20, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	May 5, 2005
CMC t-con	November 23, 2005
Labeling Amendments	May 5, August 3 and September 28, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	A.A.C. Consulting Group, Inc. US Agent for: Sun Pharmaceutical Industries Ltd. Acme Plaza, Andheri-Kurla Road, Andheri (East), Mumbai-400059, India
U.S. Agent:	Anthony C. Celeste, A.A.C. Consulting Group, Inc. 7361 Calhoun Place, Suite 500 Rockville, MD 20855-2765
Telephone:	(301)-838-3120
Fax	(301)-838-3182

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Extended Phenytoin Sodium Capsules USP

9. LEGAL BASIS FOR SUBMISSION:
The basis for Sun's proposed Extended Phenytoin Sodium Capsules, USP 100 mg is the approved application for DILANTIN®, NDA #84-349 held by Parke Davis Pharmaceuticals. There are no unexpired patents or exclusivities. The firm filed a Paragraph I patent certification.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

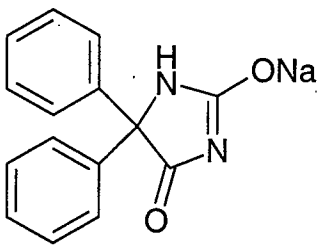
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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



Chemical Name: 5,5-Diphenylhydantoin sodium salt
Molecular Formula: $C_{15}H_{11}N_2O_2Na$
Molecular Weight: 274.25

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	5/4/05	By S. Dhanesar
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	NA		
Labeling	Acceptable	10/17/05	M.Dillahunt
Bioequivalence	Acceptable	7/29/05	J. Lee
EA	AC Dissolve Testing	11/29/04	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 40-621

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable (MINOR)

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

N/A

II. Summary of Chemistry Assessments

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

Phenytoin Sodium USP is 5,5-Diphenylhydantoin sodium salt that acts as an anti-convulsant and anti-epileptic.

Phenytoin Sodium is a white fine odorless powder. It is freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide, soluble in alcohol; practically insoluble in ether and in chloroform It is very sensitive to light and moisture. It also exhibits known polymorphism. The proposed source for Phneytoin Sodium is (b) (4).

The extended release transparent colorless capsule of Extended Phenytoin Sodium Capsules is available in a 100 mg strength.

Extended Phenytoin Sodium Capsules 100 mg is manufactured using (b) (4). The finished drug product is required to meet specifications for description, identification, assay, related substances, dissolution and water.

The drug product is supplied in an HDPE bottle of 100 capsules with a CRC closure. The proposed expiration dating period is 24 months.

There is a USP monograph for both the active drug substance and the drug product.

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

Extended Phenytoin Sodium is indicated for the treatment of convulsions and it is an anti-epileptic. It is recommended that Phenytoin Sodium treatment should be administered at a dose of 100 mg 3-4 times a day.

C. Basis for Approvability or Not-Approval Recommendation

Not-Approvable (MINOR)

Following this page, 19 pages withheld in full (b)(4)- Chemistry review #2

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-621 APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Extended Phenytoin Sodium Capsules USP, 100 mg

The deficiencies presented below represent MINOR deficiencies:

1. (b) (4)

2.

3.

(b) (4)

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-621
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/KBernard/7/12/05 /1. Bernard for 12/22/05

HFD-640/SFurness/12/5/05 /1. Bernard 12/22/05

HFD-617/YKong/11/3/05/12/22/05 YKong 12/22/05

F/T by: rad12/8/05;12/13/05

V:\Firmsnz\sun\Ltrs&Rev\40-621c2

TYPE OF LETTER: NOT APPROVABLE

ANDA 40-621

Extended Phenytoin Sodium Capsules USP, 100 mg

Sun Pharmaceutical Industries Ltd.

Suhas Patankar, Ph.D.
Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 40-621

2. REVIEW #: 3

3. REVIEW DATE: 4/12/06

4. REVIEWER: Suhas Patankar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	August 20, 2004
Amendment	May 5, 2005
CMC t-con	November 23, 2005
Labeling Amendment	May 5, August 3 and September 28, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	February 1, 2006

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Sun Pharmaceutical Industries Ltd. Acme Plaza, Andheri-Kurla Road, Andheri (East), Mumbai-400059, India
U.S. Agent:	A.A.C. Consulting Group, Inc. 7361 Calhoun Place, Suite 500 Rockville, MD 20855-2765
Representative:	Anthony C. Celeste
Telephone:	(301)-838-3120
Fax	(301)-838-3182

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Extended Phenytoin Sodium Capsules USP

9. LEGAL BASIS FOR SUBMISSION:

This section is Satisfactory as per Review #2.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

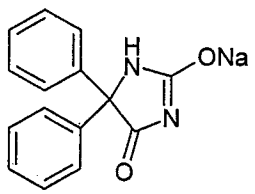
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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



Chemical Name: 5,5-Diphenylhydantoin sodium salt
Molecular Formula: $C_{15}H_{11}N_2O_2Na$
Molecular Weight: 274.25

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	1/10/06	By S. Patankar
	III			4			
	III			4			

(b) (4)	III	(b) (4)	(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12/16/05	
Methods Validation	NA		
Labeling	Acceptable	10/17/05	M.Dillahunt
Bioequivalence	Acceptable	7/29/05	J. Lee
EA	AC Dissolve Testing	11/29/04	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 40-621

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable (MINOR)

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

N/A

II. Summary of Chemistry Assessments

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

Phenytoin Sodium USP is 5,5-Diphenylhydantoin sodium salt that acts as an anti-convulsant and anti-epileptic. Phenytoin Sodium is white fine odorless powder. It is freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide, soluble in alcohol; practically insoluble in ether and in chloroform. It is very sensitive to light and moisture. It also exhibits known polymorphism. The proposed source for Phneytoin Sodium is (b) (4).

The transparent colorless Extended Phenytoin Sodium Capsules is available in a 100 mg strength.

Extended Phenytoin Sodium Capsules 100 mg is manufactured using (b) (4) (b) (4).

The drug product is supplied in an HDPE bottle of 100 capsules with a CRC closure. The proposed expiration dating period is 24 months.

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

Extended Phenytoin Sodium is indicated for the treatment of convulsions and it is an anti-epileptic. It is recommended that Phenytoin Sodium treatment should be administered at a dose of 100 mg 3-4 times a day.

C. Basis for Approvability or Not-Approval Recommendation

Not-Approvable (MINOR)

Following this page, 10 pages withheld in full (b)(4)- Chemistry review #3

This section is Satisfactory as per Review #2.

30. MICROBIOLOGY N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Both drug substance and drug product are compendial. Method validation is no longer performed by the field laboratory under normal circumstances.

32. LABELING ***Satisfactory***

Acceptable 10/17/05

33. ESTABLISHMENT INSPECTION ***Satisfactory***

Acceptable 12/16/05

34. BIOEQUIVALENCE ***Satisfactory***

Acceptable 7/19/05

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

This section is Satisfactory as per Review #2.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-621 APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Extended Phenytoin Sodium Capsules USP, 100 mg

The deficiencies presented below represent MINOR deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

9. (b) (4)

10.

Sincerely yours,

Vilayat A. Sayeed
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-621
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/S. Patankar, Ph.D./4/21/06; 5/1/06 Suhas Patankar 5/2/06

HFD-630/H. Khorsidi, Ph.D./5/2/06 H. Khorsidi 5/3/06

HFD-617/J. Skanchy, Ph.D./5/3/06 JS Skanchy 5/5/06

F/T by: EW 5/3/06

V:\FIRMSNZ\SUN\LTRS&REV\40621.CR03.DOC

TYPE OF LETTER: NOT APPROVABLE

ANDA 40-621

Extended Phenytoin Sodium Capsules USP, 100 mg

Sun Pharmaceutical Industries Ltd.

Suhas Patankar, Ph.D.
Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 40-621

2. REVIEW #: 4

3. REVIEW DATE: 8/09/06
   Revised: 10/13/06

4. REVIEWER: Suhas Patankar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	August 20, 2004
Amendment	May 5, 2005
CMC t-con	November 23, 2005
Labeling Amendments	May 5, August 3, and September 28, 2005
Amendment	February 1, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	June 6, 2006
Telephone Amendment	September 18, 2006

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Sun Pharmaceutical Industries Ltd. Acme Plaza, Andheri-Kurla Road, Andheri (East), Mumbai-400059, India
U.S. Agent:	A.A.C. Consulting Group, Inc. 7361 Calhoun Place, Suite 500 Rockville, MD 20817
Representative:	Anthony C. Celeste
Telephone:	(301)-838-3120
Fax	(301)-838-3182

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Extended Phenytoin Sodium Capsules USP

9. LEGAL BASIS FOR SUBMISSION:

This section is Satisfactory as per Review #2.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

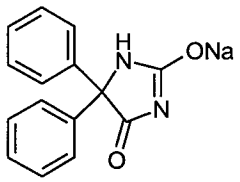
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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



Chemical Name: 5,5-Diphenylhydantoin sodium salt
Molecular Formula: $C_{15}H_{11}N_2O_2Na$
Molecular Weight: 274.25

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	7/3/06	By S. Patankar
	III			4			

(b) (4)	III	(b) (4)		(b) (4)	4			
	III				4			
	III				4			
	III				4			
	III				4			
	III				4			

[1] Action codes for DMF Table:
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6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12/16/05	
Methods Validation	NA		
Labeling	Acceptable	10/17/05	M.Dillahunt
Bioequivalence	Acceptable	7/29/05	J. Lee
EA	AC Dissolve Testing	11/29/04	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 40-621

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

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

N/A

II. Summary of Chemistry Assessments

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

Phenytoin Sodium USP is 5,5-Diphenylhydantoin sodium salt that acts as an anti-convulsant and anti-epileptic. Phenytoin Sodium is white fine odorless powder. It is freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide, soluble in alcohol; practically insoluble in ether and in chloroform. It is very sensitive to light and moisture. It also exhibits known polymorphism. The proposed source for Phneytoin Sodium is (b) (4).

The transparent colorless Extended Phenytoin Sodium Capsules is available in a 100 mg strength.

Extended Phenytoin Sodium Capsules 100 mg is manufactured using (b) (4) (b) (4).

The drug product is supplied in an HDPE bottle of 100 capsules with a CRC closure. The proposed expiration dating period is 24 months.

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

Extended Phenytoin Sodium is indicated for the treatment of convulsions and it is an anti-epileptic. It is recommended that Phenytoin Sodium treatment should be administered at a dose of 100 mg 3-4 times a day.

C. Basis for Approvability or Not-Approval Recommendation

Approvable

Following this page, 13 pages withheld in full (b)(4)- Chemistry review #4

This section is Satisfactory as per Review #2. **The applicant has provided RT stability data up to 18 months and results for Free Phenytoin @ 22 months. The data is acceptable.**

C. Expiration Dating period:

The firm proposes an expiration dating period of 24 months. The data submitted support this expiration.

D. Stability Commitment:

This section is Satisfactory as per Review #2.

30. MICROBIOLOGY N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Both drug substance and drug product are compendial. Method validation is no longer performed by the field laboratory under normal circumstances.

32. LABELING ***Satisfactory***

Acceptable 10/17/05

33. ESTABLISHMENT INSPECTION ***Satisfactory***

Acceptable 12/16/05

34. BIOEQUIVALENCE ***Satisfactory***

Acceptable 7/29/05

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

This section is Satisfactory as per Review #2.

cc: ANDA 40-621
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/S. Patankar, Ph.D./8/28/06; 10/16/06

HFD-630/H. Khorshidi, Ph.D./8/31/06

HFD-617/J. Skanchy, R.Ph./9/5/06

F/T by:

V:\FIRMSNZ\SUN\LTRS&REV\40621.CR04.DOC

TYPE OF LETTER: APPROVABLE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suhas Patankar
12/12/2006 10:14:52 AM
CHEMIST

Hossein Khorshidi
12/14/2006 03:18:09 PM
CHEMIST

Jeanne Skanchy
12/18/2006 03:17:07 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-621

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-621
Drug Product Name	Extended Phenytoin Sodium Capsules, USP
Strength	100 mg
Applicant Name	Sun Pharmaceutical Industries, Ltd.
Address	U.S. Agent: A.A.C Consulting Group, Inc. 47361 Calhoun Place, Suite 500. Rockville, MD 20855
Submission Date(s)	August 20, 2004
Amendment Date(s)	N/A
Reviewer	Phelicia B. Bush, Pharm.D.
First Generic	No
File Location	v:\firmsnz\sun\ltrs&rev\40621D0804

Review of Dissolution Data

I. Executive Summary

This submission consisted of a single-dose, replicate, 4-way, crossover fasting bioequivalence (BE) study comparing the test product, Extended Phenytoin Sodium Capsules USP, 100 mg with the RLD product, Parke-Davis' Dilantin® (Extended Phenytoin Sodium Capsules USP), 100 mg and *in vitro* dissolution data.

The firm conducted comparative dissolution testing on the test and reference products using the USP method. The dissolution data were reviewed. The dissolution data are acceptable. The fasting BE study is pending review by the DBE.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Extended Phenytoin Sodium Capsules USP, 100 mg
Reference Product	Dilantin® Kapseals® (Extended Phenytoin Sodium Capsules USP), 100 mg (also available in 30 mg strength capsules)
RLD Manufacturer	Parke-Davis
NDA No.	84-349
RLD Approval Date	August 27, 1976
Indication	Indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Strength	Test Extended Phenytoin Sodium Capsules USP		Reference Dilantin® Capsules	
	Lot Number	Exp. Date	Lot Number	Exp. Date
100 mg	JK40265	2/16/2004	02463F	05/2005

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting*	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests*	No	

*Note: the single-dose fasting study will be reviewed at a later date.

C. Relevant OGD or DBE History

The USP method is recommended for dissolution testing for Extended Phenytoin Sodium Capsules USP.

D. In Vitro Dissolution

Sun has provided dissolution data for Extended Phenytoin Sodium Capsules USP, 100 mg as well as for Dilantin® (Extended Phenytoin Sodium Capsules USP), 100 mg. The Official USP Monograph for Extended Phenytoin Sodium capsules provides dissolution method, dissolution specifications and Acceptance Tables (for 30 mg and for 100 mg capsules). The dissolution specifications for 100 mg capsules (based on USP's acceptance table) are as follows:

USP Dissolution Specifications for Extended Phenytoin Sodium Capsules USP, 100 mg (per acceptance table)		
Dissolution (%)	**Stage S1 (%)**	**Stage S2 (%)**
NMT 45% (Q) in 30 minutes	20-45	25-45 (none outside 15-55)
60% (Q') in 60 minutes	40-80	45-75 (none outside 35-85)
NLT 70% (Q") in 120 minutes	NLT 75	NLT 70 (none less than 60)

Source of Method (USP, FDA or Firm)	USP (Test 1)
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	USP apparatus I (Basket)
Rotation (rpm)	50 rpm
Firm's proposed specifications	Same as above (USP specifications)
FDA-recommended specifications	(b) (4)
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	Yes

F2 metric, test compared to reference	
Strength	F2 metric
100 mg	57.00

Comment: The dissolution testing is acceptable. See section Appendix for details.

E. Deficiency Comments

None

F. Recommendations

1. The *in vitro* dissolution testing conducted by Sun Pharmaceutical on its test product, Extended Phenytoin Sodium Capsules USP, 100 mg (batch # JK40265) comparing it to Parke-Davis' Dilantin® (Extended Phenytoin Sodium Capsules USP), 100 mg (Lot # 02463F) is **acceptable**. The firm has conducted the dissolution testing using the USP dissolution method [Test 1: 900 mL of water, Apparatus I (Basket) at 50 rpm] and the test meets the following USP specifications:

   (b) (4)

The firm should be informed of the above recommendations.

Phelicia B. Bush

Phelicia B. Bush, Pharm. D., Reviewer, Branch III — 11/22/04 Date

Yih-Chain Huang

Yih-Chain Huang, Ph. D., Team Leader, — 11/23/2004 Date

for Barbara M. Davit

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs — 11/23/04

ANDA 40-621
Extended Phenytoin Sodium Capsules USP, 100 mg
Sun Pharmaceuticals Industries, Ltd.
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IV. Appendix

A. Dissolution Data and Dissolution Profiles

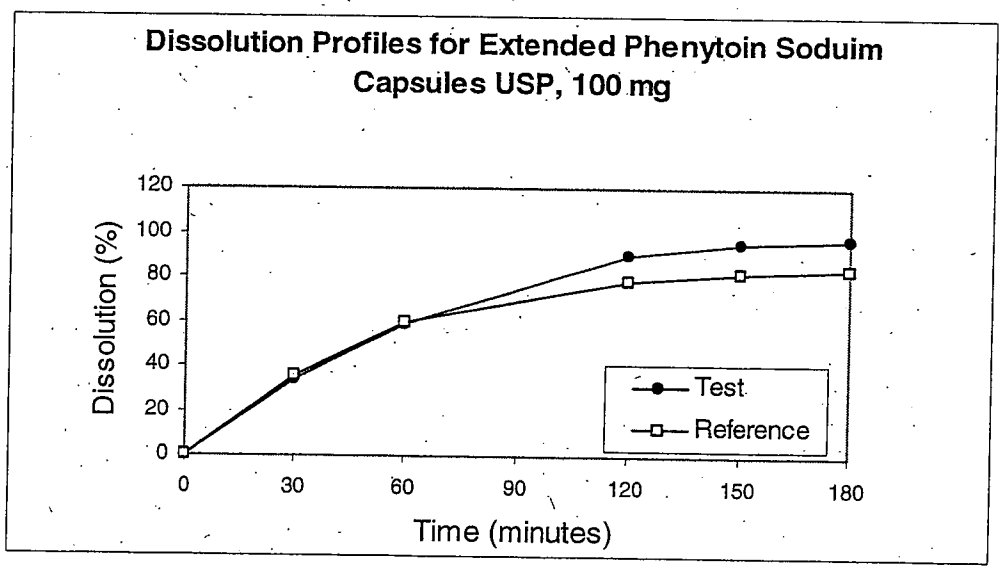
Testing Conditions: USP (Test 1)

Medium: Water at 37°C ± 0.5°C
Volume: 900 mL
Apparatus: USP apparatus I (Basket)
Speed: 50 rpm
Specification: (b) (4)

Table 1: *In Vitro* Comparative Drug Release

Sampling Time (Minutes)	Test Product, Extended Phenytoin Sodium Capsules USP Strength 100 mg Lot No. JK40265			Reference Product Dilantin® (Extended Phenytoin Sodium Capsules USP) Strength 100 mg Lot No. 02463F		
	Mean	%CV	Range	Mean	%CV	Range
0	0	--	--	0	--	--
30	33.48	7.79	29.7-37.5	35.85	8.70	32.1-44.0
60	58.62	6.37	52.9-65.5	59.67	6.46	55.3-69.3
120	89.62	4.23	82.7-94.1	78.26	7.72	70.0-88.1
150	94.85	3.59	89.3-98.5	81.69	4.84	75.2-89.1
180	96.80	3.22	91.3-99.9	83.29	4.47	77.1-90.0

Figure 1: Dissolution Profiles



BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-621 APPLICANT: Sun Pharmaceutical

DRUG PRODUCT: Extended Phenytoin Sodium Capsules USP, 100 mg

The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later.

We acknowledge that the dissolution testing has been conducted as specified in USP.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the in vivo study.

Sincerely yours,

for Barbara M. Davit

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

CC: ANDA 40-621
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-650/ P. Bush PBush 11/22/04
HFD-658/ YC Huang YCH 11/23/2004
HFD-650/ D. Conner DCnd 11/23/04

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Printed in final on 11/22/03

BIOEQUIVALENCE – Acceptable Submission Date: August 20, 2004

[NOTE: The dissolution method and specification are acceptable. The fasting BE study is pending review.]

1. **Dissolution** (Dissolution Data) VR Strength: 100 mg
Outcome: **AC**

Outcome Decisions: AC - Acceptable
WinBio Comments: AC

JUL 29 2005

DEV

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-621
Drug Product Name	Extended phenytoin sodium capsules USP
Strength	100 mg
Applicant Name	Sun Pharmaceutical Industries Ltd.
Address	Mumbai, India
Submission Date(s)	20 Aug 2004
Amendment Date(s)	7 Jul 2005
Reviewer	J. Lee
First Generic	no
File Location	**V:\\firmsnz\Sun\ltrs&rev\40621N804.doc**

I. Executive Summary

This submission pertains to extended phenytoin sodium capsules and includes one fasting BE study on the 100 mg strength capsule. The fasting study is a single-dose, replicate design study using 24 healthy normal male and female volunteers given a dose of 100 mg. The results (point estimate, 90% CI) of the fasting BE study are LAUCt of 98.8, 93.2-105%, LAUCi of 94.0, 89.8-98.5 and LCmax of 101, 91.6-112%.

Dissolution testing data was submitted using the USP method and was found acceptable.

From the bioequivalence viewpoint, this application is acceptable

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II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Extended phenytoin sodium capsules
Reference Product	Dilantin® Kapseals®
RLD Manufacturer	Parke-Davis Pharmaceuticals
NDA No.	84-349
RLD Approval Date	27 Aug 1976
Indication	Antiepileptic drug - control of generalized tonic-clonic and complex partial seizures and prevention and treatment of seizures occurring during or following neurosurgery.

B. PK/PD Information

Bioavailability	70-100% (Micromedex)
Food Effect	Not indicated in product labeling
Tmax	4 - 12 hrs
Metabolism	Hydroxylation in the liver
Excretion	Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine.
Half-life	22 hrs, with a mean of 7-42 hrs
Relevant OGD or DBE History	Approved ANDAs: 40-435 (Barr), 40-298 (Mylan); protocols: P00-021 All of the above contained or recommended a fasted BE study (replicate design) only per the Guidance cited below. There was one submission (b) (4) from (b) (4) that included two single dose fasted studies (four-way and three-way crossovers) that tried to establish a relationship between phenytoin bioavailability and dissolution characteristics for their (b) (4) capsules. The deficiencies were never responded to and that submission remains incomplete [submission date: (b) (4)].
Agency Guidance	Yes. Phenytoin/Phenytoin Sodium (capsules, tablets, suspension) In Vivo Bioequivalence and In Vitro Dissolution Testing (Issued 3/4/1994)
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	y	1
Single-dose fed	n	
In vitro dissolution	y	1
Waiver requests	n	

D. Pre-Study Bioanalytical Method Validation

	Phenytoin
Analyte name	Phenytoin
Internal Standard	(b) (4)
Method description	RP-HPLC; liq-liq extraction; UV absorbance
QC range	250.0 to 6500 ng/ml
Standard curve range	250.0 to 8000 ng/ml
Limit of quantitation	250.0 ng/ml
Average recovery of Drug (%)	100%
Average Recovery of Int. Std (%)	100%
QC Intraday precision range (%)	4.4 to 7.8%
QC Intraday accuracy range (%)	95.9 to 104%
QC Interday precision range (%)	5.4 to 7.9%
QC Interday accuracy range (%)	98.1 to 102%
Bench-top stability (hrs)	4.5
Stock stability (days)	N/A
Processed stability (hrs)	24 hr (RT); 48 hr (refrigerated)
Freeze-thaw stability (cycles)	4
Long-term storage stability (days)	14 months
Dilution integrity	Y
Specificity	Y
SOPs submitted	Y
Bioanalytical method is acceptable	Y*

* The firm should note that the QC sample concentrations are to be within the calibration curve range, but different from those of the calibration standards.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	AAI-US-232
Study Design	2 treatment, 4 period, 2 sequence
No. of subjects enrolled	24
No. of subjects completing	22
No. of subjects analyzed	22
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 16 Female: 8
Test product	Phenytoin sodium capsule
Reference product	Dilantin® Kapseals® capsule
Strength tested	100 mg
Dose	1 x 100 mg

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	98.8	93.2; 105
AUCi	94.0	89.8; 98.5
C_{max}	101	91.6; 112

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
faulty instrument setting	**7**	**16**	**0.46**	**1.0**	**0**	**0**	**0**	**0**
poor chromatography	**12**	**15**	**0.78**	**0.98**	**0**	**0**	**0**	**0**
insufficient spl volume	**-**	**4**	**-**	**0.26**	**0**	**0**	**0**	**0**
IS outside acceptance range	**3**	**2**	**0.20**	**0.13**	**0**	**0**	**0**	**0**
spl lost during extraction	**4**	**1**	**0.26**	**0.07**	**0**	**0**	**0**	**0**
Total	**26**	**34**	**1.7**	**2.2**	**0**	**0**	**0**	**0**

Did use of recalculated plasma concentration data change study outcome? No.
The analytical repeats followed the SOP. There were no PK repeats.

F. Formulation

The test product formulation is detailed in Table 1 of the Appendix.

G. In Vitro Dissolution (USP method)

USP apparatus I (basket) @ 50 rpm
900 ml of water @ 37°C

Tolerances for the 100 mg capsule:
(b) (4)

H. Waiver Request(s)

N/A

I. Deficiency Comments

None

J. Recommendations

1. The bioequivalence study conducted by AAI Clinic for Sun Pharmaceutical Industries Ltd. on its extended phenytoin sodium 100 mg capsule has been found acceptable.

2. The in-vitro dissolution data is also acceptable. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XXVIII apparatus I (basket) at 50 rpm. The test product should meet the following specifications:

(b) (4)

3. From the bioequivalence viewpoint, this application is acceptable.

R. Lee 7-29-05
J. Lee, Branch II

Gurjaspal Singh 7-29-05
GJPSingh, Ph.D., Team Leader, Branch II

Barbara M Davit 7/29/05
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	AAI-US-232
Study Title	Single dose four-way fully-replicated crossover fasted bioequivalence study of phenytoin sodium 100 mg capsules in healthy volunteers
Clinical Site	AAI clinic; Chapel Hill, North Carolina
Principal Investigator	Evin H. Sides, III, M.D.
Study/Dosing Dates	per I - 18 May 04; per II - 25 May 04; per III - 1 Jun 04; per IV - 8 Jun 04
Analytical Site	AAI clinic
Analytical Director	(b) (6)
Analysis Dates	2 Jun 04 - 28 Jun 04
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	41 days

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Phenytoin sodium capsules	Dilantin® Kapseals®
Manufacturer	Sun Pharmaceutical Industries	Parke-Davis
Batch/Lot No.	JK40265A	02463F
Manufacture Date	Feb 2004	N/A
Expiration Date	N/A	May 2005
Strength	100 mg	100 mg
Dosage Form	Capsule	Capsule
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	98.5%	99.6%
Content Uniformity (mean, %CV)	100.6%, 1.68%	100.2%, 1.48%
Dose Administered	1 x 100 mg	1 x 100 mg
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	ABAB - subj #1, 4, 9, 10, 11, 14, 15, 18, 19, 21, 22, 23 BABA - subj #2, 3, 5, 6, 7, 8, 12, 13, 16, 17, 20, 24
Blood Sampling Times	0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hrs
Blood Volume Collected/Sample	7 ml
Blood Sample Processing/Storage	cool centrifuged; plasma stored at -20°
IRB Approval	Y
Informed Consent	Y
Subjects Demographics	See Table 1
Length of Fasting	10 hrs prior to dosing
Length of Confinement	Through the 24 hr blood draw
Safety Monitoring	Vital signs obtained prior to each dosing period. Additional safety measures as needed by the Medical Director.

Comments on Study Design: none

b) Clinical Results

Table 1 Demographics of Study Subjects

Age (yrs)		Weight (lb)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	36
Mean	26	Mean	171	18-40	91	Male	68	Afr. Amer.	50
SD	9.4	SD	28	41-64	9	Female	32	Hispanic	14
Range	18-56	Range	110-226	65-75				Asian	
				>75				Others	

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
8	withdrawn by PI due to development of fever and sore throat	before per II	N
20	withdrawn by PI due to a positive drug screen at per II check-in	II	N

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
drowsiness	-	2
tingling sensation in hand	1	-
Total:	1	2

Table 4 Protocol Deviations

There were some blood sampling time deviations. However, these were time-adjusted in the AUC calculations.

Comments on Dropouts/Adverse Events/Protocol Deviations: All adverse events were mild in nature.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

QC Conc. (ng/ml)	750 - 6500
Inter day Precision (%CV)	4.4 - 5.8%
Inter day Accuracy (%)	102%
Cal. Standards Conc. (ng/ml)	250 - 8000 (7 pts)
Inter day Precision (%CV)	4.8 - 6.3%
Inter day Accuracy (%)	99.0 - 101%
Linearity Range (r^2)	≥0.9874

Comments on Study Assay Quality Control: none

Any interfering peaks in chromatograms?	N
Were 20% of chromatograms included?	Y
Were chromatograms serially or randomly selected?	serial

Comments on Chromatograms: none

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

SOP No.	Date of SOP	SOP Title
20-010-01.11	**2 Jun 03**	**Calibration, calculations, and acceptance criteria for HPLC**

Table 7 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: acceptable

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	%CV	
AUC_{0-t}	(ng*hr)/ml	31135	39	31134	33	100
AUC_{∞}	(ng*hr)/ml	40544	32	43060	29	94.2
Cmax	ng/ml	1408	27	1418	32	99.3
Tmax	hr	3.98	76	5.02	94	79.3
$T_{1/2}$	hr	18.0	26	20.0	34	90.0
Kel	1/hr	0.0407	22	0.0381	29	107

Table 9 Geometric Means and 90% Confidence Intervals

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCI	38094.312	40513.075	0.94	89.789	98.471
LAUCT	28702.95	29063.456	0.99	93.156	104.700
LCMAX	1349.9982	1332.4139	1.01	91.572	112.105

Table 10 Additional Study Information

	Trt A	Trt B
Within subject variance, AUC	0.03373	0.01933
Within subject variance, Cmax	0.02850	0.03716
Ke and AUCi determined for how many subjects?	all except for two subjects; #16, trt B, per I and trt A, per II; and #1, trt A, per III	
Do you agree or disagree with firm's decision?	Y	
Indicate the number of subjects with the following:		
-measurable drug concentrations at 0 hr	0	
-first measurable drug concentration as Cmax	0	
Were the subjects dosed as more than one group?	N	

Comments on Pharmacokinetic Analysis: The data was analyzed by the reviewer using the SAS Proc Mixed procedure for this replicate design study. The 90% CIs were exactly the same as reported by the sponsor.

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

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

Replicate 1

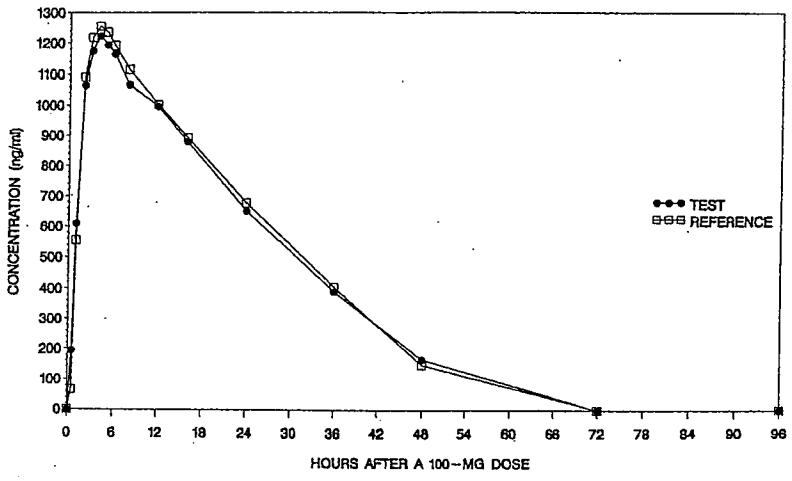
	Treatment A		Treatment B	
Time	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%
0	0.00	.	0.00	.
0.5	148.21	203.25	33.42	315.89
1	562.66	86.37	618.07	86.10
2	1035.17	56.10	1171.95	60.04
3	1210.62	43.42	1246.59	47.04
4	1249.17	32.31	1270.82	40.53
5	1221.77	29.21	1263.49	33.56
6	1204.59	32.80	1266.97	32.70
8	1081.64	32.18	1169.70	28.47
12	1053.73	31.76	1074.92	27.74
16	911.71	30.49	947.31	27.48
24	688.52	34.03	711.44	28.12
36	408.13	68.69	420.08	49.71
48	192.43	110.56	137.26	150.78
72	24.23	324.15	0.00	.
96	0.00	.	0.00	.

Replicate 2

	Treatment A		Treatment B	
Time	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%
0	0.00	.	0.00	.
0.5	245.74	193.23	103.21	214.66
1	670.38	92.91	507.59	77.67
2	1101.87	44.35	1036.29	54.23
3	1129.97	37.29	1208.74	40.86
4	1213.84	30.31	1251.91	32.54
5	1178.35	30.67	1211.82	27.67

	Treatment A		Treatment B	
Time	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%
6	1176.42	29.14	1128.44	26.60
8	1063.25	30.75	1074.00	26.98
12	937.47	29.41	932.46	25.93
16	842.84	26.94	850.23	24.85
24	624.48	34.46	653.31	26.72
36	370.40	43.59	397.09	45.98
48	147.70	114.24	172.48	116.05
72	0.00	.	0.00	.
96	0.00	.	0.00	.

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



B. Formulation Data

Ingredient	Mg/Cap
(b) (4)	
Phenytoin Sodium USP	100.00
Magnesium Stearate NF	(b) (4)
Lactitol Monhydrate NF	
Talc USP	
(b) (4)	
Sodium Lauryl Sulfate NF	
Total Weight	250.00

extended phenytoin sodium 100 mg - transparent #3 capsule filled with white to off-white powder, with the code '402' imprinted on the cap and body.

Dilantin® Kapseal 100 mg - transparent #3 capsule with an orange band - imprinted Dilantin 100 mg.

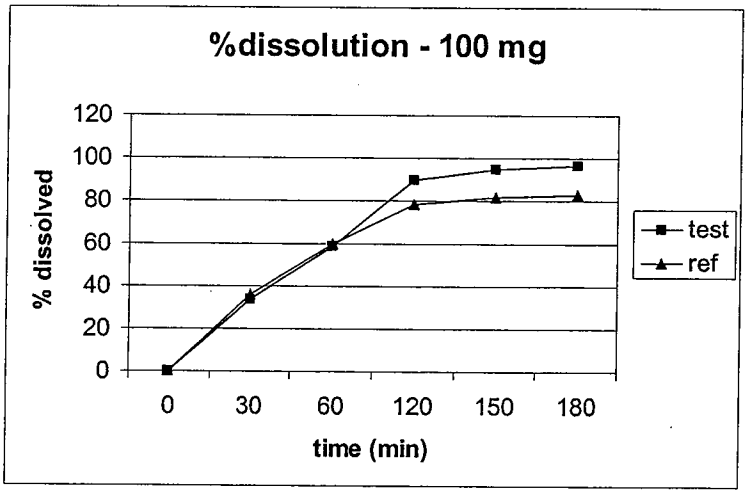
C. Dissolution Data

Dissolution testing has been reviewed previously.

phenyt11dis.doc

The f_2 value is 57.00.

Figure 2 Dissolution Profiles



D. Consult Reviews

N/A

E. SAS Output

phenytoin	Phenyt11.txt

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-621 APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Extended phenytoin sodium capsules USP, 100 mg

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

The dissolution testing should be conducted per USP 28.

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

Sincerely yours,

Barbara W. Gavit

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

CC: ANDA 40-621
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

V:\\firmsnz\Sun\ltrs&rev\40621N804.doc

Endorsements:
HFD-655/ Reviewer E.S. 7-29-05
HFD-655/ Bio team Leader [illegible] 7-29-05
HFD-650/ D. Conner [illegible] 7/29/05

BIOEQUIVALENCE - ACCEPTABLE

submission date: 20 Aug 2004

1. **FASTING STUDY** (STF)
Clinical: AAI Clinic
Analytical: same

Strengths: 100 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:
Fasted study acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 40-621 **SPONSOR:** Sun Pharmaceutical Industries Ltd..

DRUG & DOSAGE FORM: Extended phenytoin sodium capsule

STRENGTH(S): 100 mg

TYPES OF STUDIES: Fasted

CLINICAL STUDY SITE(S): AAI Clinic; Chapel Hill, NC

ANALYTICAL SITE(S): Same

STUDY SUMMARY: Fasted study acceptable.

DISSOLUTION: OK per USP

DSI INSPECTION STATUS

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

Proposed Dissolution Method and Specifications from Original Submission Acceptable?
Yes x No ____ (If no, project Manager should verify and sign below when acknowledgement amendment is received)

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

AMENDMENT DATE: _____

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: JLee **BRANCH:** II
INITIAL: E.S. DATE: 29 Jul 05

TEAM LEADER: GJPSingh **BRANCH:** II
INITIAL: GJPS DATE: 7-29-05

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: DPC DATE: 7/29/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-621

PHARMACOLOGY TOXICOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office) DE I, Colleen LoCicero HFD--101 please fwd to HFD-120 ivision of Neuropharmacological Drug Products for review of Pharm-Tox Study			FROM: OGD/Regulatory Support Branch HFD--617	
DATE: 10/25/04	IND NO. 84-349	ANDA NO. [redacted]	TYPE OF DOCUMENT New Correspondence	DATE OF DOCUMENT August 20, 2004
NAME OF DRUG Extended Phenytoin Sodium Capsules USP, 100 mg		PRIORITY CONSIDERATION low	CLASSIFICATION OF DRUG Anti-seizure	DESIRED COMPLETION DATE December 25, 2004

NAME OF FIRM Sun Pharmaceutical Industries Ltd.

REASON FOR REQUEST

I. GENERAL

9 NEW PROTOCOL
9 PROGRESS REPORT
9 NEW CORRESPONDENCE
9 DRUG ADVERTISING
9 ADVERSE REACTION REPORT
9 MANUFACTURING CHANGE/ADDITION
9 MEETING PLANNED BY _____
9 PRE NDA MEETING
9 END OF PHASE II MEETING
9 RESUBMISSION
9 SAFETY/EFFICACY
9 PAPER NDA
9 CONTROL SUPPLEMENT
9 RESPONSE TO DEFICPENCY LETTER
9 FINAL PRINTED LABELING
9 LABELING REVISION
9 ORIGINAL NEW CORRESPONDENCE
9 FORMULATIVE REVIEW
X OTHER ('specify below)

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
9 TYPE A OR B NDA REVIEW 9 END QF PHASE II MEETING 9 CONTROLLED STUDI ES 9 PROTOCOL REVIEW OTHER	9 CHEMISTRY 9 PHARMACOLOGY 9 BIOPHARMACEUTICS 9 OTHER

III.BIOPHARMACEUTICS

□ DISSOLUTION
□ PROTOCOL-- BIOPHARMACEUTICS
□ IN--VIVO WAIVER REQUEST
□ DEFICIENCY LETTER RESPONSE
□ BIOAVAILABILITY STUDIES
□ PHASE IV STUDIES

IV.DRUG EXPERIENCE

□ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
□ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
□ CASE REPORTS OF SPECIFIC REACTIONS(List below)
□ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
□ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
□ SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

x□ CLINICAL
□ PRECLINICAL

COMMENTS

OGD is requesting a Pharm/Tox Review. Please comment on the acceptability of the enclosed Toleran Toxicological Studies which intend to demonstrate the safety of Lactitol Monohydrate.

Thank you,

Kojo

Please provide as electronic transfer of the completed review and return to Cuthbert (Ted) Palat--HF

SIGNATURE OF REQUESTER Kojo Awuah	METHOD OF DE LIVERY (Check one) □ MAIL □ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA 40-681

COMPLETED JAN - 3 2005

Barry N. Rosloff, Ph.D.
12/21/04

CONSULT # 9290

This consult is for an evaluation of the animal toxicology data on lactitol, an inactive ingredient proposed for use in phenytoin ER capsules, which is not listed in our Inactive Ingredient guide. It is stated that the maximum daily intake of lactitol through this dosage form is expected to be "around (b) (4) mg/day."

Lactitol is a disaccharide sugar alcohol (galactosidyl sorbitol). It is proposed for use here since the structurally similar and more commonly used excipient lactose (galactosidyl glucose) has a potential for interaction with the drug substance (phenytoin). According to the Handbook of Pharmaceutical Excipients, 4th Ed., lactitol is used as a diluent in solid dosage forms, a noncariogenic replacement for sucrose, therapeutically in the treatment of hepatic encephalopathy, and as a laxative; it is stated that it is GRAS listed.

Summaries of a variety of animal toxicology studies of lactitol were provided. There is not enough information for independent review (e.g. no protocols, summary tables, or individual animal data), although the narrative summaries are fairly comprehensive and the studies performed appear to have encompassed most of those normally required for a compound with intended chronic use in humans. The studies described included acute and 3 and 12 month toxicity in rats, 6 month toxicity in dogs, lifetime carcinogenicity in rats and mice, reproduction studies in rats, and genotoxicity assays. The most prominent effects occurred in the rat carcinogenicity study which used lactitol doses, as % of diet, of 2, 5, and 10%; a comparator group given 20% lactose was also used. These effects included (1) increased calcareous deposits in kidney (mainly pelvis) at 5 and 10% , (2) increased bile duct proliferation at 5 and 10%, (3) increased incidence of hyperplasia and "neoplasia" of testicular Leydig cells at 10%, and (4) increased incidence of adrenomedullary "proliferative changes" in males at 10%. All of the above were also seen in the lactose group. It was suggested that the kidney effect was secondary to hyperabsorption of calcium. An unspecified effect on calcium homeostasis was suggested as a mechanism for the adrenal effects. No mechanism was suggested for the Leydig cell tumors, although it was noted that there is absence of evidence for an association between lactose consumption and such tumors in humans. None of the above effects were seen in the mouse carcinogenicity study (high dose 10% lactitol). Lactitol was said to be non-genotoxic, and given the fact that it is not absorbed intact after oral administration, but rather hydrolyzed to galactose and sorbitol and subsequently fermented (with subsequent formation of short chain volatile fatty acids) in the colon, it is likely that any carcinogenic effect was produced by an indirect epigenetic mechanism and has a threshhold. In this regard, it is not clear if the effects seen only at high dietary concentrations of lactitol (10%) have any relevance for the proposed human usage (up to (b) (4) mg/day).

One area of potential concern which was not addressed (at least in the material provided to me) is the possibility of lactitol causing symptoms similar to those of lactose intolerance; lactitol is thought not to be hydrolyzed in the small intestine and thus the entire dose reaches the colon. (In the case of lactose intolerance, a large amount of lactose reaches the colon in people who lack the ability to hydrolyze it in the small intestine). However, it is noted that the amount of lactitol in the

proposed product is relatively low (maximum (b) (4) mg/day); it was stated that the laxative threshhold of lactitol in humans in one study was 6.3 grams/day; it was also stated that doses up to 50 grams/day (in 4-6 divided portions), after a 4 day adaptation period, caused little discomfort.

Barry Rosloff

Benton, Sandra J

From: Temple, Robert
Sent: Friday, January 07, 2005 11:41 AM
To: Rosloff, Barry N; Benton, Sandra J; Katz, Russell G
Subject: RE: Consult from Generics re phenytoin ER capsules

Sandy, let's add that to the consult and send forward.

-----Original Message-----
From: Rosloff, Barry N
Sent: Friday, January 07, 2005 10:18 AM
To: Benton, Sandra J; Katz, Russell G
Cc: Temple, Robert
Subject: RE: Consult from Generics re phenytoin ER capsules

I thought I was just being asked to evaluate the animal tox info submitted. As noted, the substance appears to have shown some unspecified neoplastic/proliferative effects at high doses (10% of diet) in rats. Considering the facts that it was said that these effects occurred only at a high dose, that the substance is not genotoxic, and that the effects did not occur in mice, it is likely that the effects are not relevant to humans at the proposed dose. It was also noted that the same effects were produced by lactose, a commonly used excipient. If I am being asked if it is OK to include lactitiol in the drug product at the proposed level, my conclusion is yes, with the caveat that I did not receive or review any of the actual studies.

Barry

-----Original Message-----
From: Benton, Sandra J
Sent: Friday, January 07, 2005 9:16 AM
To: Katz, Russell G; Rosloff, Barry N
Cc: Temple, Robert
Subject: Consult from Generics re phenytoin ER capsules

Hi! I gave the above consult to RT to sign off and he wrote the following -

> Russ, Barry: I don't see any conclusion.

I've attached a copy of the review. If you need the package back, please let me know and I'll put it in interoffice mail.

Thanks much!

Sandy
301-443-5296

<< File: Rosloff_Lacitol_Jan3,05.pdf >>

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-621

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Sun Pharma Advanced Research Centre (SPARC)
Akota Road, Akota, Baroda 390 020, INDIA.
Tel. : 91-265-2330815/9257/9674/2340547/1400
Fax : 91-265-2339103.

SUN PHARMACEUTICAL INDUSTRIES LTD.

505(j)(2)(A)(i)
3200 SEQ

August 20, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: ANDA Submission for Extended Phenytoin Sodium Capsules, USP, 100mg.

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

Sun Pharmaceutical Industries Ltd. hereby submits this Original Abbreviated New Drug Application, which provides for **Extended Phenytoin Sodium Capsules, USP, 100mg**, in accordance with section 505 (j) of the Federal Food Drug and Cosmetic Act. The subject drug is a prescription drug formulated as an extended release oral capsule. Sun Pharmaceutical Industries Ltd. will manufacture the Extended Phenytoin Sodium Capsules, USP, 100mg, in 100-count bottle pack with child resistant cap, as a final drug product at M J Pharmaceuticals Ltd. located at Halol-Baroda Highway, Halol-389 350, and Gujarat, India. The Active Raw Material is manufactured by (b) (4). Please refer to Drug Master File (DMF) # (b) (4) for a full description of the facility and the Active raw material details.

Please refer to the accompanying Table of Contents for a list of the data supporting this submission. These data have been presented in 7 volumes consistent with the Office of Generic Drugs Guidance for Industry entitled "Organization of an ANDA" dated February 1999.

The Pharmacokinetics section is separately bound and consists of 2 volumes. The Pharmacokinetics section includes sections I through VI from volume 1 of the Archival copy. The Review copy contains the Chemistry, Manufacturing and Controls information, corresponding to Volumes 1, 4, 5, 6 and 7 of the Archival copy.

Sun's proposed product, **Extended Phenytoin Sodium Capsules, USP, 100mg**, has undergone, "A Single Dose Four-Way Fully-Replicated Crossover Fasted Bio-equivalence study of Phenytoin Sodium 100 mg Capsules in Healthy Volunteers" (AAI-US-232), to demonstrate its bioequivalence to the listed drug Dilantin® Capsules, 100 mg. This biostudy was conducted by AAI Pharma Inc.

RECEIVED
SEP 0 1 2004
OGD/CDER

Corporate Office : ACME PLAZA, Andheri - Kurla Road, Andheri (E); Mumbai - 400 059, INDIA.
Tel : (91-22) 8230102/8212128/8211288, Fax : (91-22) 8212010. Tlx : 78249 SUN IN, Sprint Mail ID : sunmumiø.cor@smp.sprintrpg.ems.vsnl.net.in

Sun Pharma Advanced Research Centre (SPARC)
Akota Road, Akota, Baroda 390 020, INDIA.
Tel. : 91-265-2330815/9257/9674/2340547/1400
Fax : 91-265-2339103.

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PHARMACEUTICAL
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Sun Pharmaceutical Industries, **Extended Phenytoin Sodium Capsules, USP, 100mg** are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same standards of strength, quality, purity and identity as the listed drug Dilantin® Capsules,100 mg.

We are requesting twenty-four months expiration dating for this product based on the 3 months accelerated stability and 3 month controlled room temperature data enclosed herein in section XVI subpart 4. At the FDA's request we will provide samples of the bulk drug substance and finished dosage form.

A copy of the Table of Contents has been provided in the front of each volume of the archival and review copies of this original abbreviated new drug application.

Following this letter is a letter authorizing A.A.C Consulting group Inc. to act as the U.S. agent for this ANDA.

Thank you

Sincerely,

Dr. Abhay Muthal
Dy. General Manager, Regulatory Affairs

Corporate Office : ACME PLAZA, Andheri - Kurla Road, Andheri (E), Mumbai - 400 059, INDIA.
Tel : (91-22) 8230102/8212128/8211288, Fax : (91-22) 8212010, Tlx : 78249 SUN IN, Sprint Mail ID : sunmumiø.cor@smp.sprintrpg.ems.vsnl.net.in

Hand Delivery

September 19, 2004

Attention: Dr. Kojo Awuah
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Pl (MPN2)
Rockville, MD 20855

AAC
CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

Reference: Response to Request for Additional Information ANDA#40-621, Extended Phenytoin Sodium Capsules USP

Dear Dr. Awuah,

This comes in follow-up to our telephone conversation regarding the additional information need for Sun Pharmaceutical's ANDA#40-621, Extended Phenytoin Sodium Capsules USP:

1. A side by side comparison of the box label for the RLD and the Sun product.
2. The quantitative formula of (b) (4) black (ink) from (b) (4).
3. A revised 356h adding USP after the product name.

We wish to thank you for your assistance concerning this matter.

If you have any questions, please let me know.

Sincerely,

Anthony C. Celeste
Senior Consultant

Enclosures

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 40-621 **FIRM NAME**: SUN PHARMACEUTICAL INDUSTRIES LTD.

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: PHENYTON SODIUM EXTENDED
DOSAGE FORM: CAPSULES USP, 100 MG

Bio Assignments:	☐ **Micro Review**
☒ **BPH**	
☐ **BCE**	
☐ **BST**	

Random Queue: 10
Chem Team Leader: Rosencrance, Susan PM: Tom Hinchliffe Labeling Reviewer: Michelle Dillahunt

Letter Date: AUGUST 20, 2004	**Received Date**: SEPTEMBER 01, 2004
Comments: EC- 1 YES **On Cards:** YES **Therapeutic Code:** 2010300 ANTICONVULSANTS	
Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing **CSO/CST Kwadwo Awuah** **Date 10/21/04**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 22 Oct 2004
ADDITIONAL COMMENTS REGARDING THE ANDA: **Called Firm on 9/30/04 and asked them to provide:** **1. Revised 356H form with USP added to the name of the drug** **2. Provide box label comparison** **3. Provide Quantitative formulae for Opacodes** **4. Summary of the source of in-actives on one page**	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES – had to be revised (Statement regarding Rx/OTC Status) RX YES Contact Person: Anthony Celeste – Phone (301) 838-3120	☒
Sec. II	**Basis for Submission** **NDA# : 84-349** Ref Listed Drug: DILANTIN Firm: PARK DAVIS PHARMACEUTICALS ANDA suitability petition required? NO If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: I 2. Expiration of Patent: NA A. Pediatric Exclusivity Submitted? NO B. Pediatric Exclusivity Tracking System checked? YES **Exclusivity Statement:** YES	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as RLD 2. Active ingredients Phenytoin Sodium How Supplied 3. Route of administration Oral Bottles of 100 units each 4. Dosage Form Extended-Release Capsule 5. Strength 100 mg	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL YES – 4 copies of draft 2. 1 RLD label and 1 RLD container label YES 3. 1 side by side labeling comparison with all differences annotated and explained YES 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES (Page 52) **2. Request for Waiver of In-Vivo Study(ies): NA** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) N/A **4. Lot Numbers of Products used in BE Study(ies):** ANDA Lot # JK40265A / RLD Lot # 02463F **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING ON 100 MG – (based on control document (# 02-407)) a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES (Page 60 & 61)	☒

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation Copy in folder/jacket 2. Inactive ingredients as appropriate Pharm/Tox data for Lactitol Monohydrate sent on consult All other in-active ingredients OK per IIG database. Search Table attached to this checklist.	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers (Page 1017) b. Type II DMF authorization letters or synthesis DMF # (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) YES d. Applicant certificate of analysis e. Testing specifications and data from drug product manufacturer(s) YES f. Spectra and chromatograms for reference standards and test samples YES g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified (Page 1198) b. Testing specifications (including identification and characterization) YES c. Suppliers' COA (specifications and test results) YES d. Applicant certificate of analysis	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address YES 2. Functions YES 3. CGMP Certification/GLP YES 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement (Page 1328)	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation Strength Lot # Exhibit Batch Master Batch Quantity Made Quantity Packaged 100 mg JK40265 (b) (4) 2. In-process Controls - Specifications and data YES	☒

Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data (Type III DMF References) YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address (Page 1437)	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data YES 2. Certificate of Analysis for Finished Dosage Form YES	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted YES 2. Post Approval Commitments YES 3. Expiration Dating Period 24 months 4. Stability Data Submitted a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch YES	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance YES 2. Finished Dosage Form YES 3. Same lot numbers	☒
Sec. XVII	**Environmental Impact Analysis Statement**	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) (Page 2119) 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) YES	☒

INACTIVE INGREDIENT SEARCH TABLE

Extended Phenytoin Sodium Capsules USP, 100 mg
ANDA # 40-621, 09/28/04

MAGNESIUM STEARATE	ORAL; TABLET (IMMED./COMP. RELEASE), UNCOATED, CHEWABLE	(b) (4)
TALC	ORAL; CAPSULE, DELAYED ACTION	
SODIUM LAURYL SULFATE	ORAL; CAPSULE, SOFT GELATIN	

Firm provided Pharm/Tox data for Lactitol Monohydrate NF which has been sent on consult. (b) (4) and (b) (4) were used for imprinting capsules. Quantities of (b) (4) used are less than 0.01% of total capsule weight. Quantitative Formulae for the (b) (4) included in jacket.

ANDA 40-621 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. Dilantin Caps

N/A 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. Dilantin 84-349

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ✓ yes ____ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin H. Gruncz date 22 Oct 2004

ANDA 40-621

A.A.C Consulting Group, Inc.
U.S. Agent for: Sun Pharmaceutical Industries Ltd.
Attention: Mr. Anthony C. Celeste
7361 Calhoun Place, Suite 500
Rockville, MD 20855-2765

OCT 26 2004

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated September 30, 2004 and your correspondence dated October 14, 2004.

NAME OF DRUG: Extended Phenytoin Sodium Capsules USP, 100 mg

DATE OF APPLICATION: August 20, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 01, 2004

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Thomas Hinchliffe
Project Manager
(301) 827-5849

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-621

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/M. Shimer
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 25 Oct 2004
HFD-615/KAwuah, CSO _____ date 10/22/04
Word File
V:\FIRMSNZ\Sun\LTRS&REV\40621.ACK
F/T October 22, 2004

ANDA Acknowledgment Letter!

MINOR AMENDMENT

DCW

ANDA 40-621

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

FEB 23 2005

APPLICANT: A.A.C. Consulting Group, Inc.
U.S. Agent for Sun Pharmaceutical Industries Ltd.

TEL: 301-838-3120

FAX: 301-838-3182

ATTN: Anthony C. Celeste

PROJECT MANAGER: (301) 827-5791

FROM: Yoon Kong

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 20, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Extended Phenytoin Sodium Capsules USP, 100 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__3__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

a 2-23-05

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

FEB 2 3 2005

ANDA: 40-621
APPLICANT: Sun Pharmaceutical Industries Ltd.
DRUG PRODUCT: Extended Phenytoin Sodium Capsules USP, 100 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

(b) (4)

8.

9.

10.

11.

12.

13.

14.

15.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

The bioequivalence review comments are provided to you under separate cover. If the Office of Bioequivalence recommends a different Dissolution test or specification for the drug product from the one proposed in this application, please revise the Dissolution testing method and specification for the finished drug products release and stability protocols accordingly and resubmit the comparative drug release profile data if necessary.

Sincerely yours,

Brenda J. Cameron for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Hand Delivery

ORIG AMENDMENT
N/AF

May 5, 2005

Attention: Michelle Dillahunt
Office of Generic Drug
Division of Labeling & Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

AAC
CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

RE: Labeling Amendment for ANDA 40-621 – Extended Phenytoin Sodium Capsules, USP, 100 mg

Dear Ms. Dillahunt,

Acting as the U.S. Agent for Sun Pharmaceutical Industries LTD. please find enclosed the labeling amendment responding to FDA's letter dated April 11, 2005 providing labeling comments for ANDA 40-621 – Extended Phenytoin Sodium Capsules, USP, 100 mg. As requested please find enclosed paper copies of the revised labeling and a CD-ROM containing the electronic files (PDF).

If you have any questions or require additional information, please let us know.

Sincerely,

Anthony Celeste /cc

Anthony Celeste
Senior Vice President

RECEIVED
MAY 0 6 2005
OGD / CDER

Enclosures

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax : 91- 265 - 2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

April 27, 2005

Office of Generic Drugs
Center for Drug Evaluation and Research
Division of Labeling and Program Support
Labeling Review Branch
Rockville, Maryland 20855

Re: Labeling Amendment for Extended Phenytoin Sodium Capsules USP, 100 mg (ANDA # 40-621)

Dear Sir/Madam,

This is with reference to your Fax to our US agent AAC Consulting Group Inc (Dated 11, April'05) for the labeling deficiencies. Please note the following response to the deficiencies. The question and responses follows in the same order as in the letter:

Comment-1

1. **CONTAINER -100s**

   a. **Revise storage temperature recommendation to:**
   Store at 20°-25°C (68°- 77^{0}F [see USP controlled room temperature]. Protect from light and moisture.

   b. **Please clarify the meaning of "PXLB 0106" appearing on your main panel of your container label.**

   c. **It is difficult to read your container labels. Please improve the print quality on your label (especially on the side panel.**

Response-1

a. The container label of Extended Phenytoin Sodium Capsules USP, 100 mg has been revised to change the storage temperature recommendation to "Store at 20°-25°C (68°-77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]."

b. Please note that "PXLB 0106" is Sun Pharmaceutical's in-house reference number, which is specific for a product and pack.

c. We note the comment and shall ensure a good quality printing for the final printed labeling.

Four sets of revised container labels with above mentioned revision have been provided in ***Attachment-1.***

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax : 91- 265 - 2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

Comment-2

2. INSERT

a. DESCRIPTION

List the dyes in your imprinting ink with your inactive ingredients.

Response-2

Please note that dyes used in imprinting ink have already been mentioned in the package insert. In addition to this the other inactive ingredients of printing ink are added in the revised package insert, it includes shellac glaze, SDA 3A alcohol or N-butyl alcohol and propylene glycol.

Comment-3

Due to changes in the labeling for Dilantin® Kapseals, ANDA 84-349/S-040, approved December 9,2003, please make the following revisions:

b. WARNINGS:
Usage in Pregnancy: replace your subsection with the following paragraphs:

Clinical:

A. Risks to Mother. An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see PRECAUTIONS, Laboratory Tests). However, postpartum restoration of the original dosage will probably be indicated.

B. Risks to the Fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. The overall incidence of malformations for children of epileptic women treated with antlepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or two- to three-fold that in the general

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax : 91- 265 - 2354897

SUN PHARMACEUTICAL INDUSTRIES LTD.

population. However, the relative contribution of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most cases it has not been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during pregnancy.

C. Postpartum Period, A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin in utero. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Preclinical:
Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/kg or higher (approximately 120% of the maximum human loading dose or higher on a mg/m2 basis) to pregnant rabbits.

Response-3

In Warnings section, Usage in Pregnancy sub-section on insert has been revised as mentioned in comment 2(b).

Comment-4

c. PRECAUTIONS

(1) General: fourth paragraph, first sentence-revise to "...hypersensitivity (see CONTRAINDICATIONs).

(2) Drug Interactions- revise number 1 to read - . . .chlordiazepoxide, cimetidine, diazapam, dicumarol, disulfiram, estrogens, ethosuximide, fluoxetine, H2-antagonist, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, ticlopidine, tolbutamide, trazodone.

(3) Drug Interactions-revise number 5 to read"... oral contraceptives, paroxetine, quinidine..."

(4) Insert the following paragraph to appear after Drug Interactions number 5;

Drug-Enteral Feeding/Nutritional Preparations Interaction: Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than expected phenytoin plasma levels.

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax : 91- 265 - 2354897

SUN PHARMACEUTICAL INDUSTRIES LTD.

It is therefore suggested that phenytoin not be administered concomitantly with an enteral feeding preparation. More frequent serum phenytoin level monitoring may be necessary in these patients.

(5) Drug/Laboratory Test Interactions- revise first sentence to read-"Phenytoin may decrease serum concentrations of T_4."

(6) Pregnancy:revise to read-"Pregnancy:Pregnancy Category D; See WARNINGS section.

(7) Pediatric Use- add the following to appear as the next subsection to follow Nursing Mothers;

Pediatric Use: See DOSAGE AND ADMINISTRATION

Response-4

The Precautions section of insert for Extended Phenytoin Sodium Capsules USP, 100 mg has been revised as mentioned in comment 2(c)(1 to 7).

Comment-5

d. ADVERSE REACTIONS

(1) Delete " (b) (4) **"**

(2) Immunologic:revise to . . .systemic lupus erythematosus, periarteritis nodosa....

Response-5

1) In Adverse Reactions section, (b) (4) sub section has been deleted as mentioned in comment 2(d)(1).

2) Adverse Reactions section, Immunologic sub section of the insert has been revised as mentioned in comment 2(d)(2).

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax : 91- 265 - 2354897

SUN PHARMACEUTICAL INDUSTRIES LTD.

Comment-6

e. **HOW SUPPLIED**

(1) Revise storage temperature recommendation to:
Store at 20^0-25^0C (68°- 77^0F [see USP controlled room temperature].
Protect from light and moisture

(2) Include the following statement to appear following your storage recommendation:
"Dispense in a tight, light-resistant container as defined in the USP".

(3) Include a disclaimer for Moban;
(Moban is a registered trademark of Endo Pharmaceuticals, Inc.)

Response-6

1. In How Supplied section of insert, storage temperature recommendation has been revised to "Store at 20°- 25°C (68°-77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].".

2. The insert has been revised to include "Dispense in a tight, light-resistant container as defined in the USP." in How Supplied section.

3. Drug interactions subsection of Precautions section has been revised to include disclaimer "(Moban is registered trademark of Endo Pharmaceuticals, Inc.)"

Insert for Extended Phenytoin Sodium Capsules USP, 100 mg with above mentioned revisions has been provided in ***Attachment-2.***

Side-by side labeling comparison of the revised labeling and the labeling submitted previously has been provided in ***Attachment-3.***

Electronic copies of the below mentioned label and labeling for Extended Phenytoin Sodium Capsules USP, 100 mg are also provided.

1. Container Label.
2. Insert.

Hope you find these revised labeling in order. Kindly let us know if further information is required.

Sincerely,

Dr. Abhay Muthal
Dy. General Manager, Regulatory Affairs

ORIGINAL

Hand Delivery

ORIG AMENDMENT
N/AM

May 5, 2005

Attention: Dr. Yoon Kong
Office of Generic Drug
Division of Labeling & Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

AAC
CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

RE: Minor Chemistry Amendment for ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg

Dear Dr. Kong,

Acting as the U.S. Agent for Sun Pharmaceutical Industries LTD. please find enclosed the minor amendment responding to FDA's letter dated February 23, 2005 citing minor chemistry deficiencies for ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg.

If you have any questions or require additional information, please let us know.

Sincerely,

Anthony Celeste/CC

Anthony Celeste
Senior Vice President

Enclosures

RECEIVED
MAY 0 6 2005
OGD / CDER

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax : 91- 265 - 2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

April 29, 2005

Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855

Subject: Minor Amendment for Extended Phenytoin Sodium Capsules, USP, 100 mg (ANDA # 40-621)

Dear Sir/Madam:

This is with reference to your letter dated 23' February, 05 to A.A.C Consulting Group. Inc., U.S. Agent for Sun Pharmaceutical Industries Ltd. regarding ANDA # 40-621 for Extended Phenytoin Sodium Capsules, USP, 100 mg , submitted on September 1, 2004. Please find attached herewith our response to FDA's correspondence. The question and responses follows in the same order as in the letter:

Hope you find the responses in order. Kindly let us know if further information is required on the subject ANDA.

Sincerely,

Dr. Abhay Muthal
Dy. General Manager, Regulatory Affairs

Hand Delivery

August 3, 2005

ORIG AMENDMENT
N/AF

Attention: Michelle Dillahunt
Office of Generic Drug
Division of Labeling & Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

AAC
CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

RE: Labeling Amendment for ANDA 40-621 – Extended Phenytoin Sodium Capsules, USP, 100 mg

Dear Ms. Dillahunt,

Acting as the U.S. Agent for Sun Pharmaceutical Industries LTD. please find enclosed 12 set of the original labeling for ANDA 40-621 – Extended Phenytoin Sodium Capsules, USP, 100 mg.

If you have any questions or require additional information, please let us know.

Sincerely,

Anthony C. Celeste

Anthony Celeste
Senior Vice President

Enclosures

RECEIVED
AUG 0 3 2005
OGD / CDER

Hand Delivery

September 28, 2005

Attention: Michelle Dillahunt
Office of Generic Drug
Division of Labeling & Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/AF

AAC
CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

RE: Original Labeling for ANDA 40-621 – Extended Phenytoin Sodium Capsules, USP, 100 mg

Dear Ms. Dillahunt,

Acting as the U.S. Agent for Sun Pharmaceutical Industries Ltd. in follow-up to our June 14, 2005 telephone conversation please find enclosed the original labeling for ANDA 40-621 – Extended Phenytoin Sodium Capsules, USP, 100 mg.

If you have any questions or require additional information, please let us know.

Sincerely,

Anthony Celeste/cc
Anthony Celeste
Senior Vice President

Enclosures

RECEIVED
SEP 28 2005
OGD/CDER

Minor Amendment

Hand Delivery

November 23, 2005

Attention: Dr. Scott Furness
Office of Generic Drug
Division of Labeling & Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/Am

AAC CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

RE: Minor Amendment for ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg

Dear Dr. Furness,

Acting as the U.S. Agent for Sun Pharmaceutical Industries LTD. please find enclosed the minor amendment responding to our telephone discussion on November 17, 2005 regarding the revised drug product release specification, test procedure and pre-approval and post approval stability protocol for ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg. The Extended Phenytoin sodium capsules, 100 mg. Limit for total impurities has been revised to NMT (b) (4) %

If you have any questions or require additional information, please let us know.

Sincerely,

Anthony Celeste
Senior Vice President

Enclosures

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NOV 23 2005
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MINOR AMENDMENT

DW

ANDA 40-621

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

DEC 23 2005

APPLICANT: A.A.C. Consulting Group, Inc.
U.S. Agent for Sun Pharmaceutical Industries Ltd.

TEL: 301-838-3120

FAX: 301-838-3182

ATTN: Anthony C. Celeste

PROJECT MANAGER: (301) 827-5791

FROM: Yoon Kong

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 20, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Extended Phenytoin Sodium Capsules USP, 100 mg.

Reference is also made to your amendments dated May 5 and November 23, 2005.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

YK 12/22/05

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-621 APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Extended Phenytoin Sodium Capsules USP, 100 mg

The deficiencies presented below represent MINOR deficiencies: DEC 23 2005

1. (b) (4)

2.

3.

(b) (4)

[redacted]

Sincerely yours,

M. Scott Brewer for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Minor Amendment

Hand Delivery

February 1, 2006

ORIG AMENDMENT
N/Am

Attention: Dr. Yoon Kong
Office of Generic Drug
Division of Labeling & Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

AAC CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

RE: Minor Amendment for ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg

Dear Dr. Kong,

Acting as the U.S. Agent for Sun Pharmaceutical Industries LTD. please find enclosed the minor amendment (Archival, Review and Field copies) responding to FDA's letter dated December 23, 2005 citing deficiencies with ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg.

If you have any questions or require additional information, please let us know.

Sincerely,

Anthony Celeste /CP

Anthony Celeste
Senior Vice President

Enclosures

RECEIVED
FEB 0 1 2006
OGD / CDER

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax: 91- 265 - 2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

January 25, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855

Subject: Minor Amendment for Extended Phenytoin Sodium Capsules, USP, 100 mg (ANDA # 40-621)

Dear Sir/Madam:

This is with reference to your letter dated 23' December 05 to A.A.C Consulting Group. Inc., U.S. Agent for Sun Pharmaceutical Industries Ltd. regarding ANDA # 40-621 for Extended Phenytoin Sodium Capsules, USP, 100 mg , submitted on September 1, 2004. Please find attached herewith our response to FDA's correspondence. The question and responses follows in the same order as in the letter:

Hope you find the responses in order. Kindly let us know if further information is required on the subject ANDA.

Sincerely,

N M Daptardar

for Dr. Abhay Muthal
Dy. General Manager, Regulatory Affairs

MINOR AMENDMENT

Div

ANDA 40-621

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAY 0 9 2006

APPLICANT: A.A.C. Consulting Group, Inc. U.S. Agent for Sun Pharmaceutical Industries Ltd.

TEL: 301-838-3120

FAX: 301-838-3182

ATTN: Anthony C. Celeste

PROJECT MANAGER: (301) 827-5723

FROM: Jeanne Skanchy

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 20, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Extended Phenytoin Sodium Capsules USP, 100 mg.

Reference is also made to your amendment dated February 1, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

5/8/06

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

MAY 0 9 2006

ANDA: 40-621 APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Extended Phenytoin Sodium Capsules USP, 100 mg

The deficiencies presented below represent MINOR deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

9. (b) (4)

10.

Sincerely yours,

H Khorshid for

Vilayat A. Sayeed
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Minor Amendment

Hand Delivery

June 6, 2006

ORIG AMENDMENT
N/AM

Attention: Ms. Jeanne Skanchy
Office of Generic Drug
Division of Labeling & Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

AAC
CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

RE: Minor Amendment for ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg

Dear Ms. Skanchy,

Acting as the U.S. Agent for Sun Pharmaceutical Industries LTD. please find enclosed the minor amendment (Archival, Review and Field copies) responding to FDA's letter dated May 9, 2006 citing deficiencies with ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg.

If you have any questions or require additional information, please let us know.

Sincerely,

Anthony Celeste /cc.
Anthony Celeste
Senior Vice President

Enclosures

RECEIVED
JUN 0 6 2006
OGD / CDER

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax: 91- 265 - 2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

June 2, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Subject: Minor Amendment for Extended Phenytoin Sodium Capsules, USP, 100 mg (ANDA # 40-621)

Dear Sir/Madam:

This is with reference to your letter dated 09' May 06 to A.A.C Consulting Group. Inc., U.S. Agent for Sun Pharmaceutical Industries Ltd. regarding ANDA # 40-621 for Extended Phenytoin Sodium Capsules, USP, 100 mg , submitted on September 1, 2004. Please find attached herewith our response to FDA's correspondence. The question and responses follows in the same order as in the letter:

Hope you find the responses in order. Kindly let us know if further information is required on the subject ANDA.

Sincerely,

N N Daptardar

for Dr. Abhay Muthal
Dy. General Manager, Regulatory Affairs

Telephone Amendment

Hand Delivery

September 18, 2006

Attention: Ms. Jeanne Skanchy
Office of Generic Drug
Division of Labeling & Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/AM

AAC
CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

RE: Telephone Amendment for ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg

Dear Ms. Skanky,

Acting as the U.S. Agent for Sun Pharmaceutical Industries LTD. please find enclosed the telephone amendment (Archival, Review and Field copies) responding to FDA's letter dated September 6, 2006 citing telephone deficiencies with ANDA 40-621 – Extended Phenytoin Sodium Capsules USP, 100 mg.

If you have any questions or require additional information, please let us know.

Sincerely,

Anthony Celeste/cc.

Anthony Celeste
Senior Vice President
Kendle Regulatory Affairs/AAC Consulting Group

Enclosures

RECEIVED
SEP 18 2006
OGD / CDER

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax : 91- 265 - 2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

September 15, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Subject: Telephone Amendment for Extended Phenytoin Sodium Capsules, USP, 100 mg (ANDA # 40-621)

Dear Sir/Madam:

This is with reference to your letter dated 05' September 06 to A.A.C Consulting Group. Inc., U.S. Agent for Sun Pharmaceutical Industries Ltd. regarding ANDA # 40-621 for Extended Phenytoin Sodium Capsules, USP, 100 mg , submitted on September 1, 2004. Please find attached herewith our response to FDA's correspondence. The question and responses follows in the same order as in the letter:

Hope you find the responses in order. Kindly let us know if further information is required on the subject ANDA.

Sincerely,

Dr. Abhay Muthal
General Manager, Regulatory Affairs

OGD APPROVAL ROUTING SUMMARY

ANDA # 40-621 Applicant Sun Pharmaceutical Industries Ltd.
Drug Extended Phenytoin Sodium Capsules, USP Strength(s) 100 mg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 11/1/06 Initials MHS	Date _____ Initials _____

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes ☒ No ☐
Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary 10/17/05
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval
Comments: No patents or exclusivities remain on Dilantin. This ANDA eligible for Full Approval

2. Project Manager, Jeanne Skanchy Team 12 Review Support Branch	Date 10/30/2006 Initials js	Date _____ Initials _____

Original Rec'd date 8/20/2004
Date Acceptable for Filing 9/1/2004
Patent Certification (type) none
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 12/16/2005
Date of Office Bio Review 7/29/2005
Date of Labeling Approv. Sum 10/17/2005
Labeling Acceptable Email Rec'd Yes ☒ No ☐
Labeling Acceptable Email filed Yes ☒ No ☐
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☒ No ☒
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☒

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date 11/1/06	Date 11/1/06
Name/Initials md	Name/Initials Lillie Golson/lg

Comments:

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date _____
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials _____
Comments:

5. Div. Dir./Deputy Dir. Date 12/6/06
Chemistry Div. III Initials VAS

Comments: CMC Satisfactory

6. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)

7. Vacant Date_____
Deputy Dir., DLPS Initials_____

8. Peter Rickman Date12/8/06
Director, DLPS InitialsWPR
Para.IV Patent Cert: Yes☐ No☒;Pending Legal Action: Yes ☐ No ☒; Petition: Yes☐ No☒
Comments:no patents or exclusivity okay for full approval

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Jeanne Skanchy Team 12 Date12/12/2006
Review Support Branch Initials JS
_____Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
3:20 pm on 12/11/2006 Time notified of approval by phone11:39 am on 12/12/2006 Time approval letter faxed
FDA Notification:
12/12/2006Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/12/2006 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

REVIEWER:Suhas Patankar **FINAL ACTION: Approved on December 11,2006**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeanne Skanchy

12/18/2006 02:08:40 PM