CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 201355Orig1s000

Name: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL

Sponsor: Nostrum Laboratories Inc.
(formerly Caraco Pharmaceutical Laboratories, Ltd.)

Approval Date: August 14, 2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201355Orig1s000

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Other Action Letters	X
Labeling	X
Labeling Review(s)	X
Medical Review(s)	
Chemistry Review(s)	X
Pharm/Tox Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	X
Other Review(s)	X
Administrative & Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201355Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 201355

Caraco Pharmaceutical Laboratories, Ltd.
Attention: Robert Kurkiewicz
Senior Vice President, Regulatory Affairs
705 East Mulberry Street
Bryan, OH 43506

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 4, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Nitrofurantoin Oral Suspension USP, 25 mg/5 mL.

Reference is also made to your amendments dated May 6, September 29, and October 7, 2010; April 7, May 20, and December 21, 2011; February 3, and May 30, 2012; and May 10, 2013.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Nitrofurantoin Oral Suspension USP, 25 mg/5 mL, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Furadantin® Oral Suspension, 25 mg/5 mL, of Shionogi Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

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 directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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 Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting 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

08/14/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201355Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 201355

COMPLETE RESPONSE

Sun Pharmaceutical Industries, Inc.
Attention: Robert Kurkiewicz
705 East Mulberry Street
Bryan, OH 43512

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated March 4, 2010, received March 8, 2010, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitrofurantoin Oral Suspension USP, 25 mg/5 mL.

We acknowledge receipt of your amendments dated May 6, September 29, and October 7, 2010; April 7, May 20, and December 21, 2011; and February 3, and May 30, 2012.

We have completed our review of this ANDA and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below represent Minor deficiencies.

Deficiency:

Please revise the drug product release and stability dissolution specification as per DBE recommendation and provide supporting data.

BIOEQUIVALENCE

Your dissolution testing data comparing your test product, Nitrofurantoin Oral Suspension USP, 25 mg/5 mL, with the reference product, Shionogi Pharma's FURADANTIN® (nitrofurantoin) Oral Suspension USP, 25 mg/5 mL, using the FDA-recommended dissolution method, are acceptable. However, your proposed specifications [NLT (b) (4)% (Q) in (b) (4) minutes] are not acceptable. Based on the data submitted, the DBI recommends a more appropriate

specification. Please acknowledge your acceptance of the following dissolution method and specification for your test product:

Medium:	Phosphate Buffer, pH 7.2
Volume:	900 mL
Apparatus:	USP apparatus II (Paddle)
Speed:	50 rpm

Specification: NLT (b)(4)% (Q) of labeled amount of nitrofurantoin in the dosage form is dissolved in 30 minutes.

LABELING

The Division of Labeling has no further questions at this time since their last review dated November 8, 2010.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a **MINOR AMENDMENT**. The designation as a **RESUBMISSION/AFTER ACTION MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Product Quality (CMC), Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

If you have any questions, call Christina Kirby, Regulatory Project Manager, at (240) 276-8519.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
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 on behalf of GREGORY P GEBA

02/19/2013

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

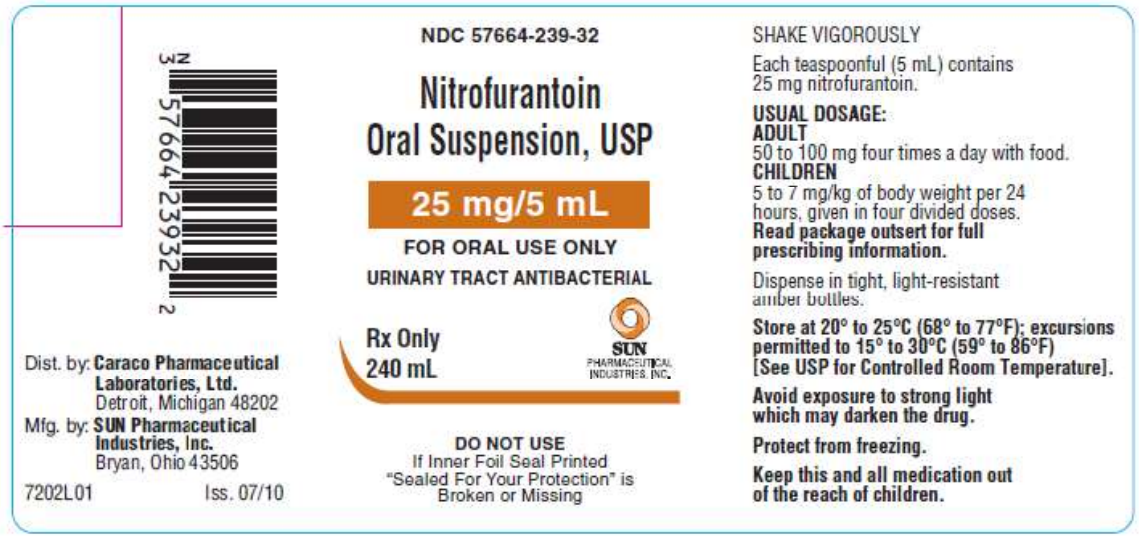
APPLICATION NUMBER:

ANDA201355Orig1s000

LABELING

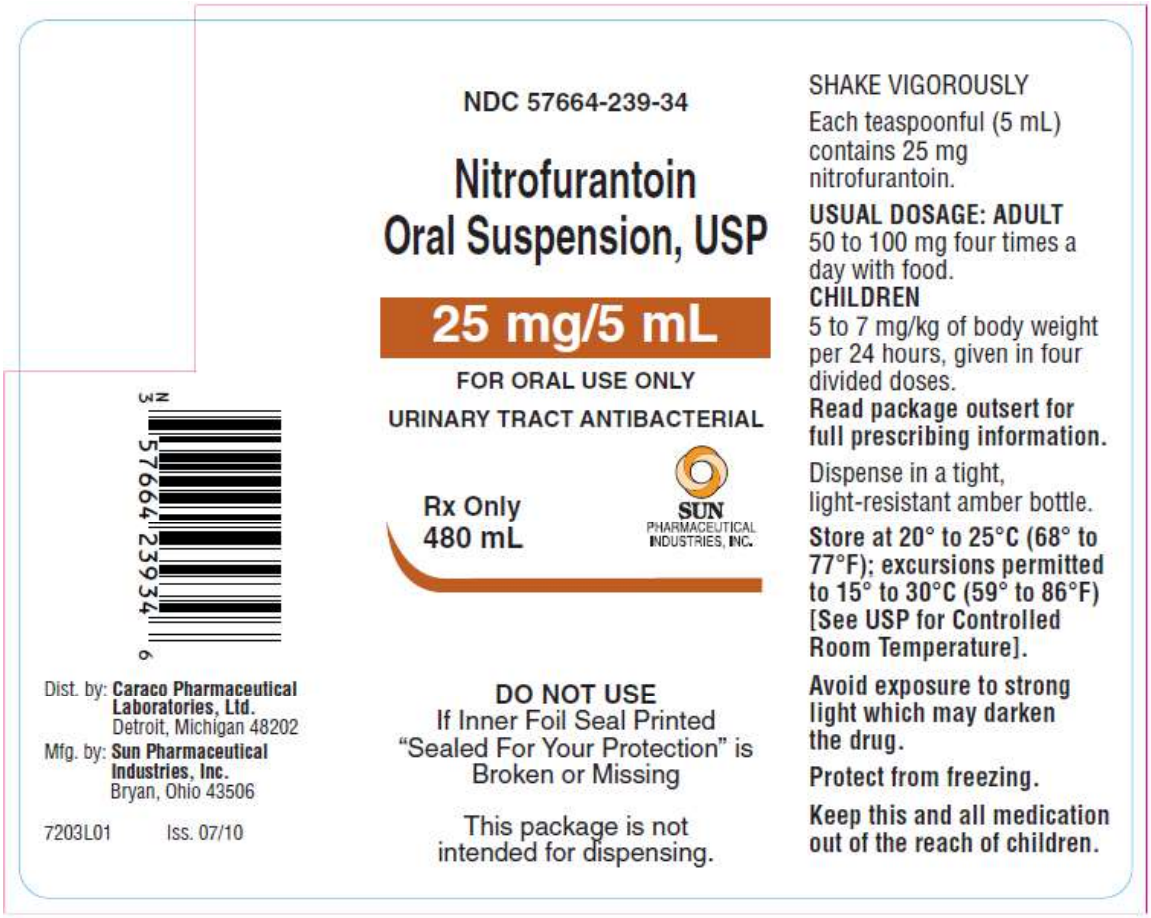
SUN Pharmaceuticals Industries, Inc.

ANDA for Nitrofurantoin Oral Suspension, USP, 25 mg/ 5 mL
ANDA Number: 201355



SUN Pharmaceuticals Industries, Inc.

ANDA for Nitrofurantoin Oral Suspension, USP, 25 mg/ 5 mL
ANDA Number: 201355

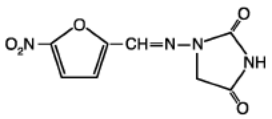


NITROFURANTOIN ORAL SUSPENSION, USP

FOR ORAL USE ONLY
Rx Only

DESCRIPTION:

Nitrofurantoin, a synthetic chemical, is a stable, yellow, crystalline compound. Nitrofurantoin Oral Suspension, USP is an antibacterial agent for specific urinary tract infections. Nitrofurantoin Oral Suspension, USP is available in 25 mg/5 mL liquid suspension for oral administration.



1-[[(5-nitro-2-furanyl)methylene]amino]-2, 4-imidazolidinedione

Inactive Ingredients:

Nitrofurantoin Oral Suspension, USP contains carboxymethylcellulose sodium, citric acid, glycerin, magnesium aluminum silicate, methylparaben, N&A fruit gum flavor #960 (MN72), propylparaben, purified water, sodium citrate, sorbitol, and sucralose.

CLINICAL PHARMACOLOGY

Orally administered Nitrofurantoin Oral Suspension, USP is readily absorbed and rapidly excreted in urine. Blood concentrations at therapeutic dosage are usually low. It is highly soluble in urine, to which it may impart a brown color.

Following a dose regimen of 100 mg q.i.d. for 7 days, average urinary drug recoveries (0 to 24 hours) on day 1 and day 7 were 42.7% and 43.6%.

Unlike many drugs, the presence of food or agents delaying gastric emptying can increase the bioavailability of Nitrofurantoin Oral Suspension, USP, presumably by allowing better dissolution in gastric juices.

Microbiology:

Nitrofurantoin is bactericidal in urine at therapeutic doses. The mechanism of the antimicrobial action of nitrofurantoin is unusual among antibacterials. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of such inactivations, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis, and cell wall synthesis are inhibited. The broad-based nature of this mode of action may explain the lack of acquired bacterial resistance to nitrofurantoin, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria. Development of resistance to nitrofurantoin has not been a significant problem since its introduction in 1953. Cross-resistance with antibiotics and sulfonamides has not been observed, and transferable resistance is, at most, a very rare phenomenon.

Nitrofurantoin, in the form of Nitrofurantoin Oral Suspension, USP, has been shown to be active against most strains of the following bacteria both *in vitro* and in clinical infections: (See **INDICATIONS AND USAGE**).

Gram-Positive Aerobes

- *Staphylococcus aureus*
- Enterococci (e.g., *Enterococcus faecalis*)

Gram-Negative Aerobes

- *Escherichia coli*

Note: Some strains of *Enterobacter* species and *Klebsiella* species are resistant to nitrofurantoin.

Nitrofurantoin also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance of these data with respect to treatment with Nitrofurantoin Oral Suspension, USP is unknown:

Gram-Positive Aerobes

- Coagulase-negative staphylococci (including *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*)
- *Streptococcus agalactiae*
- Group D streptococci
- Viridans group streptococci

Gram-Negative Aerobes

- *Citrobacter amalonaticus*
- *Citrobacter diversus*
- *Citrobacter freundii*
- *Klebsiella oxytoca*
- *Klebsiella ozaenae*

Nitrofurantoin is not active against most strains of *Proteus* species or *Serratia* species. It has no activity against *Pseudomonas* species.

Antagonism has been demonstrated *in vitro* between nitrofurantoin and quinolone antimicrobial agents. The clinical significance of this finding is unknown.

Susceptibility Tests

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standard procedure.

Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of nitrofurantoin powder. The MIC values should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation	
≤ 32	Susceptible	(S)
65	Intermediate	(I)
≥ 128	Resistant	(R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body site where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard nitrofurantoin powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
E. *coli* ATCC 25922	4 to 16
S. *aureus* ATCC 29213	8 to 32
E. *faecalis* ATCC 29212	4 to 16

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 300 mcg of nitrofurantoin to test the susceptibility of microorganisms to nitrofurantoin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 300 mcg nitrofurantoin disk should be interpreted according to the following criteria.

Zone diameter (mm)	Interpretation	
≥ 17	Susceptible	(S)
15 to 16	Intermediate	(I)
≤ 14	Resistant	(R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC nitrofurantoin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 300 mcg nitrofurantoin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone diameter (mm)
E. *coli* ATCC 25922	20 to 25
S. *aureus* ATCC 25923	18 to 22

INDICATIONS & USAGE

Nitrofurantoin Oral Suspension, USP is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses.

Nitrofurantoins lack the broader tissue distribution of other therapeutic agents approved for urinary tract infections. Consequently, many patients who are treated with Nitrofurantoin Oral Suspension, USP are predisposed to persistence or reappearance of bacteriuria. Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy. If persistence or reappearance of bacteriuria occurs after treatment with Nitrofurantoin Oral Suspension, USP, other therapeutic agents with broader tissue distribution should be selected. In considering the use of Nitrofurantoin Oral Suspension, USP, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antimicrobial resistance when agents with broader tissue distribution are utilized.

CONTRAINDICATIONS:

Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug.

Because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability), the drug is contraindicated in pregnant patients at term (38 to 42 weeks gestation), during labor and delivery, or when the onset of labor is imminent. For the same reason, the drug is contraindicated in neonates under one month of age.

Nitrofurantoin Oral Suspension, USP is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin. Nitrofurantoin Oral Suspension, USP is also contraindicated in those patients with known hypersensitivity to nitrofurantoin.

WARNINGS:

Pulmonary reactions:

ACUTE, SUBACUTE, OR CHRONIC PULMONARY REACTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH NITROFURANTOIN. IF THESE REACTIONS OCCUR, NITROFURANTOIN ORAL SUSPENSION, USP SHOULD BE DISCONTINUED AND APPROPRIATE MEASURES TAKEN. REPORTS HAVE CITED PULMONARY REACTIONS AS A CONTRIBUTING CAUSE OF DEATH.

CHRONIC PULMONARY REACTIONS (DIFFUSE INTERSTITIAL PNEUMONITIS OR PULMONARY FIBROSIS, OR BOTH) CAN DEVELOP INSIDIOUSLY. THESE REACTIONS OCCUR RARELY AND GENERALLY IN PATIENTS RECEIVING THERAPY FOR SIX MONTHS OR LONGER. CLOSE MONITORING OF THE PULMONARY CONDITION OF PATIENTS RECEIVING LONG-TERM THERAPY IS WARRANTED AND REQUIRES THAT THE BENEFITS OF THERAPY BE WEIGHED AGAINST POTENTIAL RISKS. (SEE RESPIRATORY REACTIONS.)

Hepatotoxicity:

Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Fatalities have been reported. The onset of chronic active hepatitis may be insidious, and patients should be monitored periodically for changes in biochemical tests that would indicate liver injury. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken.

Neuropathy:

Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance the occurrence of peripheral neuropathy. Patients receiving long-term therapy should be monitored periodically for changes in renal function.

Optic neuritis has been reported rarely in postmarketing experience with nitrofurantoin formulations.

Hemolytic anemia:

Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Nitrofurantoin Oral Suspension, USP; hemolysis ceases when the drug is withdrawn.

Clostridium difficile-associated diarrhea:

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Nitrofurantoin Oral Suspension, USP, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

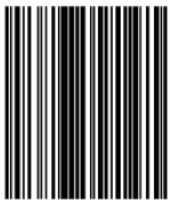
PRECAUTIONS

Information for Patients:

Patients should be advised to take Nitrofurantoin Oral Suspension, USP with food to further enhance tolerance and improve drug absorption. Patients should be instructed to complete the full course of therapy; however, they should be advised to contact their physician if any unusual symptoms should occur during therapy.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

7204T01
Nitrofurantoin Oral Suspension, USP



7204T01
Nitrofurantoin Oral Suspension, USP

Patients should be advised not to use antacid preparations containing magnesium trisilicate while taking Nitrofurantoin Oral Suspension, USP.

DRUG INTERACTIONS

Antacids containing magnesium trisilicate, when administered concomitantly with nitrofurantoin, reduce both the rate and extent of absorption. The mechanism for this interaction probably is adsorption of nitrofurantoin onto the surface of magnesium trisilicate.

Uricosuric drugs, such as probenecid and sulfinpyrazone, can inhibit renal tubular secretion of nitrofurantoin. The resulting increase in nitrofurantoin serum levels may increase toxicity, and the decreased urinary levels could lessen its efficacy as a urinary tract antibacterial.

DRUG/LABORATORY TEST INTERACTIONS

As a result of the presence of nitrofurantoin, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions but not with the glucose enzymatic test.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

Nitrofurantoin was not carcinogenic when fed to female Holtzman rats for 44.5 weeks or to female Sprague-Dawley rats for 75 weeks.

Two chronic rodent bioassays utilizing male and female Sprague-Dawley rats and two chronic bioassays in Swiss mice and in BDF1 mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female $B6C3F_1$ mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary. In male F344/N rats, there were increased incidences of uncommon kidney tubular cell neoplasms, osteosarcomas of the bone, and neoplasms of the subcutaneous tissue. In one study involving subcutaneous administration of 75 mg/kg nitrofurantoin to pregnant female mice, lung papillary adenomas of unknown significance were observed in the F1 generation.

Nitrofurantoin has been shown to induce point mutations in certain strains of *Salmonella typhimurium* and forward mutations L5178Y mouse lymphoma cells. Nitrofurantoin induced increased numbers of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells but not in human cells in culture. Results of the sex-linked recessive lethal assay in Drosophila were negative after administration of nitrofurantoin by feeding or by injection. Nitrofurantoin did not induce heritable mutation in the rodent models examined.

The significance of carcinogenicity and mutagenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown.

The administration of high doses of nitrofurantoin to rats causes temporary spermatogenic arrest; this is reversible on discontinuing the drug. Doses of 10 mg/kg/day or greater in healthy human males may, in certain unpredictable instances, produce a slight to moderate spermatogenic arrest with a decrease in sperm count.

PREGNANCY:

Teratogenic effects:

Pregnancy Category B. Several reproduction studies have been performed in rabbits and rats at doses up to six times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to nitrofurantoin. In a single published study conducted in mice at 68 times the human dose (based on mg/kg administered to the dam), growth retardation and a low incidence of minor and common malformations were observed. However at 25 times the human dose, fetal malformations were not observed; the relevance of these findings to humans is uncertain. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic effects:

Nitrofurantoin has been shown in one published transplacental carcinogenicity study to induce lung papillary adenomas in the F1 generation mice at doses 19 times the human dose on a mg/kg basis. The relationship of this finding to potential human carcinogenesis is presently unknown. Because of the uncertainty regarding the human implications of these animal data, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY:

See **CONTRAINDICATIONS.**

NURSING MOTHERS:

Nitrofurantoin has been detected in human breast milk in trace amounts. Because of the potential for serious adverse reactions from nitrofurantoin in nursing infants under one month of age, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See **CONTRAINDICATIONS.**)

PEDIATRIC USE:

Safety and effectiveness of Nitrofurantoin Oral Suspension, USP in neonates below the age of one month have not been established. (See **CONTRAINDICATIONS.**)

ADVERSE REACTIONS:

Respiratory:

CHRONIC, SUBACUTE, OR ACUTE PULMONARY HYPERSENSITIVITY REACTIONS MAY OCCUR.

CHRONIC PULMONARY REACTIONS MAY OCCUR GENERALLY IN PATIENTS WHO HAVE RECEIVED CONTINUOUS TREATMENT FOR SIX MONTHS OR LONGER. MALAISE, DYSPNEA ON EXERTION, COUGH, AND ALTERED PULMONARY FUNCTION ARE COMMON MANIFESTATIONS WHICH CAN OCCUR INSIDIOUSLY. RADIOLOGIC AND HISTOLOGIC FINDINGS OF DIFFUSE INTERSTITIAL PNEUMONITIS OR FIBROSIS, OR BOTH, ARE ALSO COMMON MANIFESTATIONS OF THE CHRONIC PULMONARY REACTION. FEVER IS RARELY PROMINENT.

THE SEVERITY OF CHRONIC PULMONARY REACTIONS AND THEIR DEGREES OF RESOLUTION APPEAR TO BE RELATED TO THE DURATION OF THERAPY AFTER THE FIRST CLINICAL SIGNS APPEAR. PULMONARY FUNCTION MAY BE IMPAIRED PERMANENTLY, EVEN AFTER CESSATION OF THERAPY. THE RISK IS GREATER WHEN CHRONIC PULMONARY REACTIONS ARE NOT RECOGNIZED EARLY.

In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form. Upon cessation of therapy, recovery may require several months. If the symptoms are not recognized as being drug-related and nitrofurantoin therapy is not stopped, the symptoms may become more severe.

Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation of pleural effusion on x-ray, and eosinophilia. Acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution often is dramatic. (See **WARNINGS.**)

Changes in EKG (e.g., non-specific ST/T wave changes, bundle branch block) have been reported in association with pulmonary reactions.

Cyanosis has been reported rarely.

Hepatic:

Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic neurosis, occur rarely. (See **WARNINGS.**)

Neurologic:

Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating diseases may increase the possibility of peripheral neuropathy. (See **WARNINGS.**)

Asthenia, vertigo, nystagmus, dizziness, headache, and drowsiness have also been reported with the use of nitrofurantoin.

Benign intracranial hypertension (pseudotumor cerebri), confusion, depression, optic neuritis, and psychotic reactions have been reported rarely. Bulging fontanels, as a sign of benign intracranial hypertension in infants, have been reported rarely.

Dermatologic:

Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson syndrome) have been reported rarely. Transient alopecia also has been reported.

Allergic:

A lupus-like syndrome associated with pulmonary reactions to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous, or eczematous eruptions; pruritus; urticaria; anaphylaxis; arthralgia; myalgia; drug fever; and chills have been reported.

Hypersensitivity reactions present the most frequent spontaneously-reported adverse events in world-wide postmarketing experience with nitrofurantoin formulations.

Gastrointestinal:

Nausea, emesis, and anorexia occur most often. Abdominal pain and diarrhea are less common gastrointestinal reactions. These dose-related reactions can be minimized by reduction of dosage. Sialadenitis and pancreatitis have been reported. There have been sporadic reports of pseudomembranous colitis with the use of nitrofurantoin. The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment. (See **WARNINGS.**)

Hematologic:

Cyanosis secondary to methemoglobinemia has been reported rarely.

Miscellaneous:

As with other antimicrobial agents, superinfections caused by resistant organisms, e.g., *Pseudomonas* species or *Candida* species, can occur. There are sporadic reports of *Clostridium difficile* superinfections, or pseudomembranous colitis, with the use of nitrofurantoin.

Laboratory Adverse Events:

The following laboratory adverse events have been reported with the use of nitrofurantoin; increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, glucose-6-phosphate dehydrogenase deficiency anemia (see **WARNINGS**), agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.

OVERDOSAGE:

Occasional incidents of acute overdosage of Nitrofurantoin Oral Suspension, USP have not resulted in any specific symptoms other than vomiting. Induction of emesis is recommended. There is no specific antidote, but a high fluid intake should be maintained to promote urinary excretion of the drug. It is dialyzable.

DOSAGE AND ADMINISTRATION:

Nitrofurantoin Oral Suspension, USP should be given with food to improve drug absorption and, in some patients, tolerance.

Adults:

50 to 100 mg four times a day — the lower dosage level is recommended for uncomplicated urinary tract infections.

Pediatric Patients:

5 to 7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).

The following table is based on an average weight in each range receiving 5 to 6 mg/kg of body weight per 24 hours, given in four divided doses. It can be used to calculate an average dose of Nitrofurantoin Oral Suspension, USP (25 mg/5 mL) for pediatric patients (one 5 mL teaspoon of Nitrofurantoin Oral Suspension, USP contains 25 mg of nitrofurantoin):

Body Weight		No. Teaspoonfuls
Pounds	**Kilograms**	**4 Times Daily**
15 to 26	7 to 11	1/2 (2.5 mL)
27 to 46	12 to 21	1 (5 mL)
47 to 68	22 to 30	1 1/2 (7.5 mL)
69 to 91	31 to 41	2 (10 mL)

Therapy should be continued for one week or for at least 3 days after sterility of the urine is obtained. Continued infection indicates the need for reevaluation.

For long-term suppressive therapy in adults, a reduction of dosage to 50 to 100 mg at bedtime may be adequate. For long-term suppressive therapy in pediatric patients, doses as low as 1 mg/kg per 24 hours, given in a single dose or in two divided doses, may be adequate. **SEE WARNINGS SECTION REGARDING RISKS ASSOCIATED WITH LONG TERM THERAPY.**

HOW SUPPLIED:

Nitrofurantoin Oral Suspension, USP is a lemon yellow liquid with a fruity scent available in:

NDC 57664-239-32 240 mL amber PET bottle
NDC 57664-239-34 480 mL amber PET bottle

Avoid exposure to strong light which may darken the drug. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP for Controlled Room Temperature]. Protect from freezing. Dispense in tight, light-resistant amber bottles.

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

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* - Seventh Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January, 1997.
2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.

Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
Detroit, Michigan 48202

Manufactured by:
SUN Pharmaceutical Industries, Inc.
Bryan, Ohio 43506

7204T01 Iss: 07/10

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA201355Orig1s000

LABELING REVIEWS

APPROVAL SUMMARY

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

ANDA Number: 201355

Date of Submission: October 7, 2010 (original)

Applicant's Name: Sun Pharmaceutical Industries, Inc.

Established Name: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL

APPROVAL SUMMARY:

REMS required? (checked November 3, 2010)
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

Do you have Final Printed Labels and Labeling? Yes

1. CONTAINER (240 mL and 480 mL amber PET bottles)
   Satisfactory in final print as submitted October 7, 2010.

2. INSERT
   Satisfactory in final print as submitted October 7, 2010.

Revisions required post-approval: Yes. The following comments will be emailed to anne.toland@sunpharmausa.com after the review has been signed off. Revised labeling may be submitted in the annual report. SPL should be submitted within 14 days after the full approval of the ANDA.

CONTAINER (480 mL amber PET bottles): relocate "ADULT" to appear on a new line.

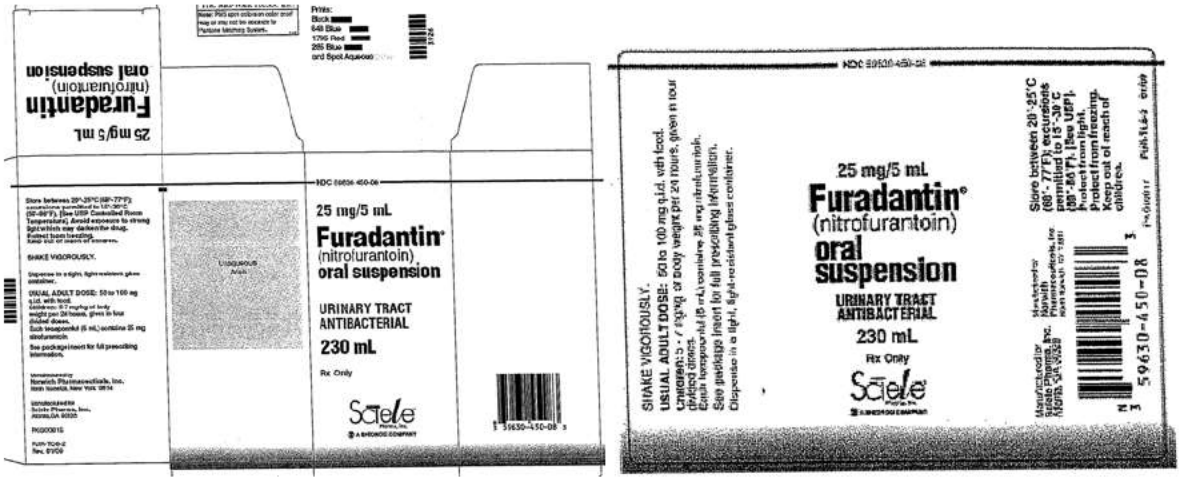
SPL Data Elements, Inactive Ingredients: Please specify "Fruit Flavor"

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of Furadantin® (nitrofurantoin) Oral Suspension NDA 009175/S-037 approved February 6, 2009. This "Changes Being Effected" supplemental new drug application provides for changes to the Furadantin® package insert to more adequately characterize and communicate the risk for nitrofurantoin–associated hepatotoxicity.

   NDA 009175/S-038 approved October 27, 2010 provides for a change in bottle size for the drug product from (b) (4) mL to 230 mL. (b) (4)

   (b) (4)



NDA 009175/S-039 approved October 14, 2010 provides for the addition of the statement "(four times daily)" to the abbreviation QID. In the approval letter, the agency requested a minor editorial change: deletion of the abbreviation "QID" from the 230 mL carton and bottle labels, as it is redundant and confusing. The statement should be revised to read: "USUAL ADULT DOSE: 50 to 100 mg four times daily with food."

(b) (4)

[redacted]

Note: CIII has been deleted from DailyMed posting (checked July 19, 2010)

From: *Wu, Ruby (Chi-Ann)*
Sent: *Tuesday, June 08, 2010 9:27 AM*
To: *Davi, Christopher; Samanta, Susmita*
Subject: *NDA 9175 Furadantin*

Good morning Chris and Susmita,

(Chris...sorry for the previous email...I accidently pressed "send").

I'm writing regarding NDA 9175. In the firm's SPL submissions, the product is listed as CIII. Is this accurate?

Thanks,

Ruby
OGD labeling reviewer

FURADANTIN
(nitrofurantoin) suspension
[Sciele Pharma, Inc.]

RxNorm Names
Review RxNor

Category	DEA Schedule	M S
HUMAN PRESCRIPTION DRUG LABEL	CIII	

(b) (4)

2. PATENTS AND EXCLUSIVITIES FOR NDA 009175

   There are no unexpired patents for this product in the Orange Book Database.

   There is no unexpired exclusivity for this product.

   ANDA firm filed PI

3. MANUFACTURING FACILITY
   SUN Pharmaceutical Industries, Inc.
   705 East Mulberry Street
   Bryan, Ohio 43506

4. STORAGE CONDITIONS:
   NDA: Avoid exposure to strong light which may darken the drug. It is stable when stored between 20°-25°C (68°77 °F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. Protect from freezing.
   ANDA: Avoid exposure to strong light which may darken the drug. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP for Controlled Room Temperature]. Protect from freezing.

5. DISPENSING RECOMMENDATIONS:
   NDA: It should be dispensed in glass amber bottles.
   ANDA: Dispense in a tight, light-resistant container amber bottles.

6. PRODUCT LINE:
   NDA: glass amber bottle of 230mL (60 mL and 470 mL no longer marketed)
   ANDA: 240 mL and 480 mL

7. CONTAINER/CLOSURE SYSTEM:

TYPE	DESCRIPTION
Bottle	480 mL PET (b) (4) Amber Bottles
	240 mL PET Amber Bottles
	(b) (4)

The components used for packaging Nitrofurantoin Oral Suspension, USP 25 mg/5 mL, meet all the requirements as per USP <661> (containers) and <671> permeation.

October 7, 2010 amendment:

b. Please confirm (b) (4)

(b) (4)

(b) (4)

8. PRODUCT DESCRIPTION:
A lemon yellow liquid with a fruity scent

9. 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.

Ingredient	Percentage (w/w %)	Percentage (w/v %)	mg/5 mL	Each gram Contains (mg)	Batch Contains (kg)
Nitrofurantoin, USP (b) (4)					(b) (4)
Carboxymethylcellulose Sodium, USP (b) (4)					
Magnesium Aluminum Silicate, (b) (4)					
Methylparaben, NF					
Propylparaben, NF					
Sorbitol (b) (4)					
Glycerin, USP					
Sucralose, NF (b) (4) (b) (4)					
Sodium Citrate (b) (4) USP					
(b) (4) Citric Acid, USP (b) (4)					
N&A Fruit Gum Flavor # 960 (MN 72)					
Purified Water, USP					
THEORETICAL TOTAL					

10. EXPEDITED REVIEW ANDA

From: West, Robert L
Sent: Tuesday, June 08, 2010 6:57 AM
To: Young, Johnny; CDER-DDR600
Cc: Shimer, Martin; Howard, Eda; Washington, Edward; Danso, Benjamin; Bykadi, Gururaj; Wu, Ruby (Chi-Ann); Sanchez, Aida L
Subject: RE: ANDA 201679 (Nitrofurantoin Oral Suspension USP, 25 mg/5 mL)

Johnny:

I agree that Amneal's ANDA 201679 for Nitrofurantoin Oral Suspension meets the criteria specified in CDER MaPP 5240.3 for "expedited review".

However, I note that we also have the following additional ANDAs for this drug product in queue:

201355 Sun
(b) (4)

Thus, "expedited review" status is granted to each of (b) (4) ANDAs for Nitrofurantoin Oral Suspension. This designation should be deleted upon the approval of one of these ANDAs.

Thank you,

Bob

From: Young, Johnny
Sent: Monday, June 07, 2010 2:29 PM
To: West, Robert L
Cc: Shimer, Martin
Subject: ANDA 201679 (Nitrofurantoin Oral Suspension USP, 25 mg/5 mL)

Dear Bob,

Amneal Pharmaceuticals is requesting "Expedited Review" status for their drug product, pursuant to MaPP 5240.3. There are currently no blocking patents or exclusivities protecting the RLD. May we grant the firm's request?

Sincerely,
Johnny

11. SPL Data Elements: revision requested post-approval.

Date of Review: November 3, 2010 Date of Submission: October 7, 2010

Primary Reviewer: Ruby Wu

Team Leader: Koung Lee

ANDA 201355

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

/s/

CHI-ANN Y WU
11/03/2010

KOUNG U LEE
11/08/2010
For Wm. Peter Rickman

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

ANDA Number: 201355

Date of Submission: March 4, 2010 (original)

Applicant's Name: Sun Pharmaceutical Industries, Inc.

Established Name: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL

Labeling Deficiencies:

1. CONTAINER (240 mL and 480 mL amber PET bottles)
   a. Revise "Dispense in a tight, light-resistant [redacted] (b) (4) amber PET." to read "Dispense in tight, light-resistant amber bottles."
   b. Please confirm [redacted] (b) (4)
   c. Adult dosage: revise [redacted] (b) (4) to read "four times a day"

2. INSERT: (review based on insert submitted in Word)
   a. File "PI.pdf" submitted in the original submission is image based. Please note that insert labeling submitted in pdf should be TEXT based, not image based.
   b. CLINICAL PHARMACOLOGY, first sentence: "…Suspension…"
   c. CLINICAL PHARMACOLOGY, Microbiology: correct the spelling of "nitrofurantoin" [2 occurrences]
   d. INDICATIONS AND USAGE, second paragraph: "abscesses" [spelling]
   e. INDICATIONS AND USAGE, third paragraph, fourth sentence: "bacteriuria" [spelling]
   f. WARNINGS, first paragraph, second sentence: "APPROPRIATE" [adjective]
   g. WARNINGS, second paragraph, last sentence: "RISKS" [plural]
   h. WARNINGS, Hepatotoxicity, first sentence: "Hepatic" [spelling]
   i. PRECAUTIONS, Information for patients, second paragraph, second sentence: "…develop watery and bloody stools (with or without stomach cramps…"
   j. PRECAUTIONS, Drug Interactions, first paragraph, second sentence: "…is adsorption of…"
   k. PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility, Fourth paragraph, second sentence: "…human cells in…"
   l. ADVERSE REACTIONS, Neurologic, third paragraph, second sentence: "fontanels" [spelling]
   m. ADVERSE REACTIONS, Allergic, second sentence: "erythematous" [spelling]
   n. ADVERSE REACTIONS, Allergic, third sentence: "…spontaneously reported…"
   o. ADVERSE REACTIONS, Laboratory Adverse Events: "…dehydrogenase deficiency…" [delete comma]
   p. DOSAGE AND ADMINISTRATION: "…Oral Suspension, USP…" [2 occurrences]
   q. HOW SUPPLIED: Please include information on the color, scent and flavor of the oral suspension.
   r. Revise "Dispense in a tight, light-resistant [redacted] (b) (4) amber PET." to read "Dispense in tight, light-resistant amber bottles."

3. SPL Data Elements: Please include the flavor

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

NOTES/QUESTIONS TO THE CHEMIST:

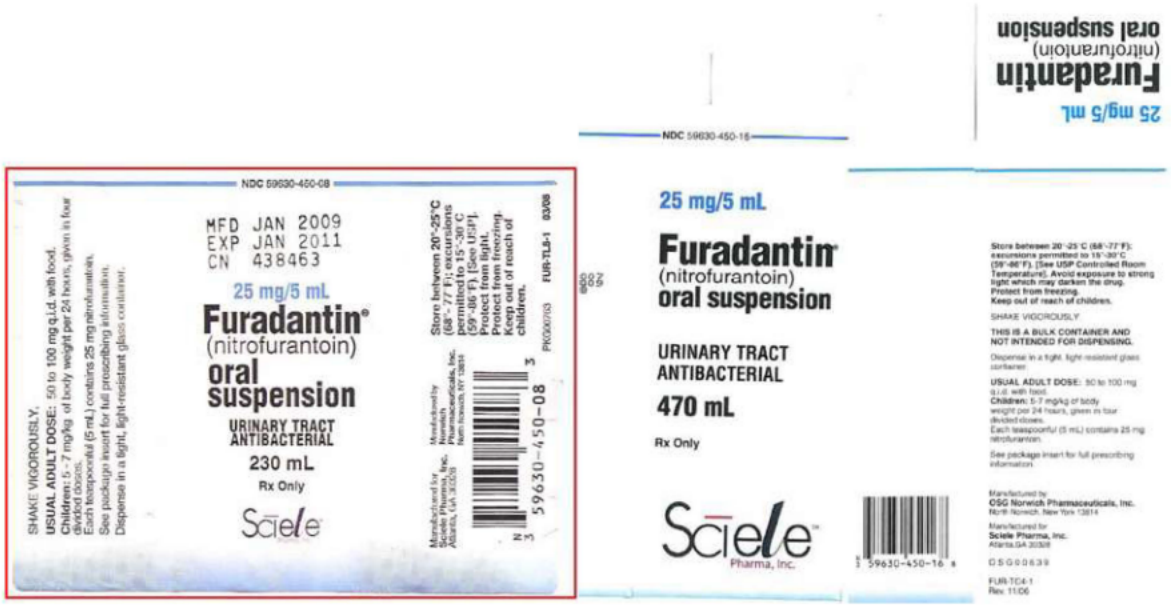
During the course of the review of this application, if there are any questions or comments, please do not hesitate to contact me via telephone at (609) 495-2823, via facsimile at (609) 495-2711 or e-mail: anne.toland@SUNpharmausa.com.

FOR THE RECORD:

REMS required? (checked June 8, 2010)
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

1. MODEL LABELING - This review is based on the labeling of Furadantin® (nitrofurantoin) Oral Suspension NDA 009175/S-037 approved February 6, 2009. This "Changes Being Effected" supplemental new drug application provides for changes to the Furadantin® package insert to more adequately characterize and communicate the risk for nitrofurantoin–associated hepatotoxicity.



From: *Wu, Ruby (Chi-Ann)*
Sent: *Tuesday, June 08, 2010 9:27 AM*
To: *Davi, Christopher; Samanta, Susmita*
Subject: *NDA 9175 Furadantin*

Good morning Chris and Susmita,

(Chris...sorry for the previous email...I accidently pressed "send").

I'm writing regarding NDA 9175. In the firm's SPL submissions, the product is listed as CIII. Is this accurate?

Thanks,

Ruby
OGD labeling reviewer

FURADANTIN
(nitrofurantoin) suspension
[Sciele Pharma, Inc.]

RxNorm Names

Review RxNor

Category	DEA Schedule	M S
HUMAN PRESCRIPTION DRUG LABEL	CIII	

(b) (4)

2. PATENTS AND EXCLUSIVITIES FOR NDA 009175

   There are no unexpired patents for this product in the Orange Book Database.

   There is no unexpired exclusivity for this product.

   ANDA firm filed PI

3. MANUFACTURING FACILITY
   SUN Pharmaceutical Industries, Inc.
   705 East Mulberry Street
   Bryan, Ohio 43506

4. STORAGE CONDITIONS:
   NDA: Avoid exposure to strong light which may darken the drug. It is stable when stored between 20˚-25˚C (68˚77 ˚F); excursions permitted to 15˚-30˚C (59˚-86˚F) [See USP Controlled Room Temperature]. Protect from freezing.
   ANDA: Avoid exposure to strong light which may darken the drug. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP for Controlled Room Temperature]. Protect from freezing.

5. DISPENSING RECOMMENDATIONS:
   NDA: It should be dispensed in glass amber bottles.
   ANDA: Dispense in a tight, light-resistant (b) (4) amber PET.
   4. Added the statement "**Dispense in a tight, light-resistant** (b) (4) **amber PET.**" SUN's product was packaged in amber PET.

6. PRODUCT LINE:
   NDA: glass amber bottle of 230mL (60 mL and 470 mL no longer marketed)
   ANDA: 240 mL and 480 mL

7. CONTAINER/CLOSURE SYSTEM:

TYPE	DESCRIPTION
Bottle	480 mL PET (b) (4) Amber Bottles
	240 mL PET Amber Bottles
(b) (4)	

The components used for packaging Nitrofurantoin Oral Suspension, USP 25 mg/5 mL,

meet all the requirements as per USP <661> (containers) and <671> permeation.

8. PRODUCT DESCRIPTION:
A lemon yellow liquid with a fruity scent

9. 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.

Ingredient	Percentage (w/w %)	Percentage (w/v %)	mg/5 mL	Each gram Contains (mg)	Batch Contains (kg)
Nitrofurantoin, USP (b) (4)					(b) (4)
Carboxymethylcellulose Sodium, USP (b) (4)					
Magnesium Aluminum Silicate, NF (b) (4)					
Methylparaben, NF					
Propylparaben, NF					
Sorbitol (b) (4)					
Glycerin, USP					
Sucralose, NF (b) (4) (b) (4)					
Sodium Citrate (b) (4) USP					
(b) (4) Citric Acid, USP (b) (4)					
N&A Fruit Gum Flavor # 960 (MN 72)					
Purified Water, USP					
THEORETICAL TOTAL					

10. EXPEDITED REVIEW ANDA

From: West, Robert L
Sent: Tuesday, June 08, 2010 6:57 AM
To: Young, Johnny; CDER-DDR600
Cc: Shimer, Martin; Howard, Eda; Washington, Edward; Danso, Benjamin; Bykadi, Gururaj; Wu, Ruby (Chi-Ann); Sanchez, Aida L
Subject: RE: ANDA 201679 (Nitrofurantoin Oral Suspension USP, 25 mg/5 mL)

Johnny:

I agree that Amneal's ANDA 201679 for Nitrofurantoin Oral Suspension meets the criteria specified in CDER MaPP 5240.3 for "expedited review".

However, I note that we also have the following additional ANDAs for this drug product in queue:

201355 Sun
(b) (4)

Thus, "expedited review" status is granted to each of (b) (4) ANDAs for Nitrofurantoin Oral Suspension. This designation should be deleted upon the approval of one of these ANDAs.

Thank you,

Bob

From: Young, Johnny
Sent: Monday, June 07, 2010 2:29 PM
To: West, Robert L
Cc: Shimer, Martin
Subject: ANDA 201679 (Nitrofurantoin Oral Suspension USP, 25 mg/5 mL)

Dear Bob,

Amneal Pharmaceuticals is requesting "Expedited Review" status for their drug product, pursuant to MaPP 5240.3. There are currently no blocking patents or exclusivities protecting the RLD. May we grant the firm's request?

Sincerely,
Johnny

11. SPL Data Elements: deficient.

Date of Review: June 8, 2010 Date of Submission: March 4, 2010

Primary Reviewer: Ruby Wu

Team Leader: Koung Lee

ANDA 201355

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201355	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES INC	NITROFURANTOIN

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

/s/

CHI-ANN Y WU
06/08/2010
for Wm Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201355Orig1s000

CHEMISTRY REVIEWS

ANDA 201355

Nitrofurantoin Oral Suspension USP, 25mg/ 5mL

Caraco Pharmaceutical Laboratories

(SUN Pharmaceutical Industries, Inc.)

Aijin Shen, Ph.D.
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: # 201355

2. REVIEW: #4

3. REVIEW DATE: June 25, 2013

4. REVIEWER: Aijin Shen

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original Acceptable for Filing Telephone Amendment	March 04, 2010 March 08, 2010 May 06, 2010
Gratuitous Amendment	May 20, 2011
Amendment	April 07, 2011
Amendment	December 21, 2011
Telephone Amendment	February 3, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Complete Response Amendment	May 10, 2013
General Correspondence	May 14, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Caraco Pharmaceutical Laboratories, Ltd.
Address:	705 East Mulberry Street Bryan, Ohio 43506
US Agent:	N/A
Representative:	N/A
Telephone:	313-556-4105
Fax:	248-926-0231

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nitrofurantoin Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Reference Product: Furadantin (nitrofurantoin) Oral Suspension
Manufacturer by: (b) (4) Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Manufacturer for: Shionogi Pharma (formerly named Sciele Pharma, Inc.)
Atlanta, Georgia 30328

NDA #: 009175
Approved Date: December 23, 1953
The basis for submission of this application is the reference-listed drug, Furadantin (nitrofurantoin)

a. The firm has provided the following certifications for the for the patents:
Firm claims that there are no unexpired patents for this product in the Orange Book Database. Firm provided Paragraph II Certification.

The firm states that the proposed drug product contains information and data to show that the ANDA product is the same as the reference listed drug in: (i) conditions of use, (ii) active ingredient, (iii) dosage form, (iv) strength, (v) route of administration, and (vi) labeling except for the differences annotated in the side-by-side comparison in Section 1.14 (labeling), the changes as allowed for in 314.94(a)(9)(ii).

Basis of submission:
This ANDA for Nitrofurantoin Oral Suspension USP, 25mg/5 mL refers to the listed drug Furadantin (Nitrofurantoin) Suspension, NDA# 009175 by Shionogi Pharma published in the electronic version of Approved Drug Products with Therapeutic Equivalence Evaluations.

10. PHARMACOL. CATEGORY: Indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 25 mg/ 5mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

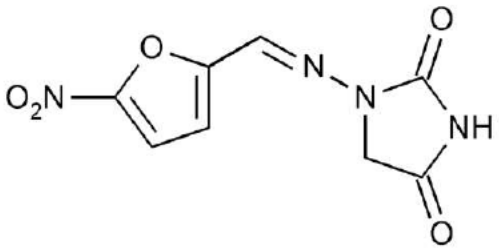
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

NITROFURANTOIN
Molecular Formula: $C_8H_6N_4O_5$
Formula Weight: 238.16
Chemical Name: 2,4 – Imidazolidinedione, 1-[[(5-nitro-2-furanyl) methylene] amino] (**or**) 1-[(5-Nitrofurfurylidene)amino]hydantoin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	A. Shen 07/03/2013	
	III			4			
	III			4			

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	IV			4			
	IV			4			

* Checked DARRTS; No new submission to review as of July 3, 2013. DMF is adequate.

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS*:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable for Overall Recommendation	07/18/2013	C. Capacci-daniel
Methods Validation	N/A		
Labeling	Approved	11/08/2010	R. Wu
Bioequivalence	Adequate	07/03/2013	C. Mahadevan
EA	Categorical Exclusion		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 201355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 201355 is approvable,

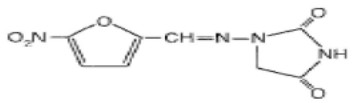
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

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

Nitrofurantoin, a synthetic chemical, is a stable, yellow, crystalline compound. Nitrofurantoin Oral Suspension, USP is an antibacterial agent for specific urinary tract infections. Nitrofurantoin Oral Suspension, USP is available in 25 mg/5mL liquid suspension for oral administration.



Inactive Ingredients:

Nitrofurantoin Oral Suspension, USP contains carboxymethylcellulose sodium, citric acid, glycerin, magnesium aluminum silicate, methylparaben, N&A fruit gum flavor #960 (MN72), propylparaben, purified water, sodium citrate, sorbitol, and sucralose.

Nitrofurantoin Oral Suspension, USP is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses.

DOSAGE AND ADMINISTRATION:

Nitrofurantoin Oral Suspension, USP should be given with food to improve drug absorption and, in some patients, tolerance.

Adults:

50 to 100 mg four times a day – the lower dosage level is recommended for uncomplicated urinary tract infections.

Pediatric Patients:

5 to 7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).

The following table is based on an average weight in each range receiving 5 to 6 mg/kg of body weight per 24 hours, given in four divided doses. It can be used to calculate an average dose of Nitrofurantoin Oral suspension, USP (25 mg/5 mL) for pediatric patients (one 5 mL teaspoon of Nitrofurantoin Oral suspension, USP contains 25 mg of nitrofurantoin):

Body Weight		No. Teaspoonfuls
Pounds	**Kilograms**	**4 Times Daily**
15 to 26	7 to 11	½ (2.5 mL)
27 to 46	12 to 21	1 (5 mL)
47 to 68	22 to 30	1 ½ (7.5 mL)
69 to 91	31 to 41	2 (10 mL)

IT and QT based on MDD (400 mg /day)
Note: The MDD is 50-100 mg four times a day; therefore 400 mg is used as MDD dose.

	IT	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Store at 20° to 25°C (68° to 77°F.

- HOW SUPPLIED

Nitrofurantoin Oral suspension, USP is available in:

NDC 57664-239-32 240 mL amber PET bottle
NDC 57664-239-34 480 mL amber PET bottle

Avoid exposure to strong light which may darken the drug. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP for Controlled Room Temperature]. Protect from freezing. Dispense in a tight, light-resistant container made of (b) (4) amber PET.

C. Basis for Approvability or Not-Approval Recommendation

Approvable with Labeling, CMC, BIO, and EES – AC.

Part I

Part I

Review of Complete Response Amendment dated May 10, 2013 and General Correspondence dated May 14, 2013

PRODUCT QUALITY

Please revise the drug product release and stability dissolution specification as per DBE recommendation and provide supporting data.

Response:

Caraco has revised the drug product release and stability dissolution specifications as per the DBE recommendations. The drug product release specification is included in Section 3.2. P.5.1. The revised post approval stability protocols are included in Section 3.2.P.8.2. Caraco has provided supporting data for the DBE recommended dissolution specification. The data reported is from the testing of the exhibition batch, **lot # B1127**. The tables included in **Attachment 1** contain the data collected at the 30 minute time point for the S1 dissolution test. At the time of the testing, Caraco's specification was NLT (b)(4)% (Q) in (b)(4) minutes. The data provided was taken at the 30 minute time point. In reviewing the data, Caraco has statistically evaluated the reported data and has concluded that it will conform to the revised specification.

Based on the data submitted, the DBI recommends a specification.
Medium: Phosphate Buffer, pH 7.2
Volume: 900 mL
Apparatus: USP apparatus II (Paddle)
Speed: 50 rpm
Specifications: NLT (b)(4)% (Q) of labeled amount of nitrofurantoin in the dosage form is dissolved in 30 minutes.
The dissolution specification is adequate based on DBE review.

Firm provided data to support the specification.

III. List Of Deficiencies To Be Communicated

ANDA is approval.

APPEARS THIS WAY ON ORIGINAL

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block
HFD-620/Aijin Shen, Ph.D./ July 03, August 07, 2013
HFD-620/Raj Bykadi, Ph.D./
HFD-617/Rinku Patel, Pharm. D / Danbi Lee/August 07, 2013

C. CC Block

C:\Documents and Settings\Shenai\My Documents\ANDAs\201355-Nitrofurantoin-Sun\201355R4.doc

TYPE OF LETTER: CMC - SATISFACTORY

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

/s/

AIJIN SHEN
08/07/2013

DANBI LEE
08/07/2013

GURURAJ BYKADI
08/07/2013

BING CAI
08/07/2013

ANDA 201355

Nitrofurantoin Oral Suspension USP, 25mg/ 5mL

SUN Pharmaceutical Industries, Inc.

Aijin Shen, Ph.D.
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: # 201355

2. REVIEW: #3 Addendum

3. REVIEW DATE: January 24, 2013

4. REVIEWER: Aijin Shen

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original Acceptable for Filing Telephone Amendment	March 04, 2010 March 08, 2010 May 06, 2010
Gratuitous Amendment	May 20, 2011
Amendment	April 07, 2011
Amendment	December 21, 2011
Telephone Amendment	February 3, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone call during August 6, 2012	

7. NAME & ADDRESS OF APPLICANT:

Name:	SUN Pharmaceutical Industries, Inc.
Address:	705 East Mulberry Street Bryan, Ohio 43506
US Agent:	N/A
Representative:	N/A
Telephone:	313-556-4105
Fax:	248-926-0231

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nitrofurantoin Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Reference Product: Furadantin (nitrofurantoin) Oral Suspension
Manufacturer by: (b) (4) Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Manufacturer for: Shionogi Pharma (formerly named Sciele Pharma, Inc.)
Atlanta, Georgia 30328

NDA #: 009175
Approved Date: December 23, 1953
The basis for submission of this application is the reference-listed drug, Furadantin (nitrofurantoin)

a. The firm has provided the following certifications for the for the patents:
Firm claims that there are no unexpired patents for this product in the Orange Book Database. Firm provided Paragraph II Certification.

The firm states that the proposed drug product contains information and data to show that the ANDA product is the same as the reference listed drug in: (i) conditions of use, (ii) active ingredient, (iii) dosage form, (iv) strength, (v) route of administration, and (vi) labeling except for the differences annotated in the side-by-side comparison in Section 1.14 (labeling), the changes as allowed for in 314.94(a)(9)(ii).

Basis of submission:
This ANDA for Nitrofurantoin Oral Suspension USP, 25mg/5 mL refers to the listed drug Furadantin (Nitrofurantoin) Suspension, NDA# 009175 by Shionogi Pharma published in the electronic version of Approved Drug Products with Therapeutic Equivalence Evaluations.

10. PHARMACOL. CATEGORY: Indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 25 mg/ 5mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

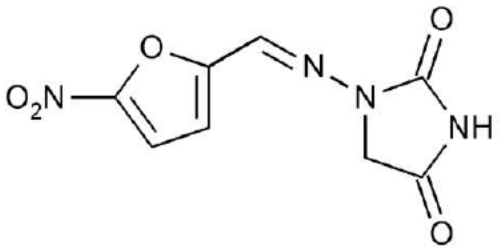
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

NITROFURANTOIN
Molecular Formula: $C_8H_6N_4O_5$
Formula Weight: 238.16
Chemical Name: 2,4 – Imidazolidinedione, 1-[[(5-nitro-2-furanyl) methylene] amino] (**or**) 1-[(5-Nitrofurfurylidene)amino]hydantoin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	A. Shen 02/07/2012	
	III			4			
	III			4			

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	IV			4			
	IV			4			

* Checked DARRTS; No new submission to review as of March 13, 2012. DMF is adequate.

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	12/05/2012	
Methods Validation	N/A		
Labeling	Approved	11/08/2010	R. Wu
Bioequivalence	Deficient	06/12/2012	K. Ren
EA	Categorical Exclusion		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 201355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 201355 is not approvable; CMC, Bio NA.
EES is pending.

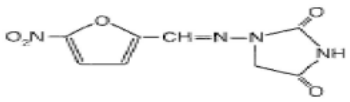
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

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

Nitrofurantoin, a synthetic chemical, is a stable, yellow, crystalline compound. Nitrofurantoin Oral Suspension, USP is an antibacterial agent for specific urinary tract infections. Nitrofurantoin Oral Suspension, USP is available in 25 mg/5mL liquid suspension for oral administration.



Inactive Ingredients:

Nitrofurantoin Oral Suspension, USP contains carboxymethylcellulose sodium, citric acid, glycerin, magnesium aluminum silicate, methylparaben, N&A fruit gum flavor #960 (MN72), propylparaben, purified water, sodium citrate, sorbitol, and sucralose.

Nitrofurantoin Oral Suspension, USP is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses.

DOSAGE AND ADMINISTRATION:

Nitrofurantoin Oral Suspension, USP should be given with food to improve drug absorption and, in some patients, tolerance.

Adults:

50 to 100 mg four times a day – the lower dosage level is recommended for uncomplicated urinary tract infections.

Pediatric Patients:

5 to 7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).

The following table is based on an average weight in each range receiving 5 to 6 mg/kg of body weight per 24 hours, given in four divided doses. It can be used to calculate an average dose of Nitrofurantoin Oral suspension, USP (25 mg/5 mL) for pediatric patients (one 5 mL teaspoon of Nitrofurantoin Oral suspension, USP contains 25 mg of nitrofurantoin):

Body Weight		No. Teaspoonfuls
Pounds	**Kilograms**	**4 Times Daily**
15 to 26	7 to 11	½ (2.5 mL)
27 to 46	12 to 21	1 (5 mL)
47 to 68	22 to 30	1 ½ (7.5 mL)
69 to 91	31 to 41	2 (10 mL)

IT and QT based on MDD (400 mg /day)
Note: The MDD is 50-100 mg four times a day; therefore 400 mg is used as MDD dose.

	IT	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Store at 20° to 25°C (68° to 77°F.

- HOW SUPPLIED

Nitrofurantoin Oral suspension, USP is available in:

NDC 57664-239-32 240 mL amber PET bottle

NDC 57664-239-34 480 mL amber PET bottle

Avoid exposure to strong light which may darken the drug. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP for Controlled Room Temperature]. Protect from freezing. Dispense in a tight, light-resistant container made of (b) (4) amber PET.

C. Basis for Approvability or Not-Approval Recommendation

Not Approvable due to CMC and BIO deficient and EES pending

\\fdswv04385\documents\23537-201355.doc

This is an addendum for review #3.

DBE sent a DL to firm's proposed dissolution specification [*NLT* (b) (4) *% (Q) in* (b) (4) *minutes*]. Based on the data submitted by the firm, the DBE recommended the following a more appropriate and a final dissolution specification.

Medium: Phosphate Buffer, pH 7.2
Volume: 900 mL
Apparatus: USP apparatus II (Paddle)
Speed: 50 rpm

Specification: NLT (b) (4) *% (Q) of labeled amount of nitrofurantoin in the dosage form is dissolved in 30 minutes.*

August 06, 2012, the Chemistry reviewer called firm to update the CMC with revised dissolution specification along with supporting data. No response was received as of today. Therefore, we are sending a deficiency letter to the firm and close the CMC.

Deficiency:
Please revise the drug product release and stability dissolution specification as per DBE recommendation and provide supporting data.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201355 APPLICANT: SUN Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25mg/ 5mL

The deficiencies presented below represent Minor deficiencies.

Deficiency:

Please revise the drug product release and stability dissolution specification as per DBE recommendation and provide supporting data.

Sincerely yours,
(see appended electronic signature page)

Andre Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block
HFD-620/Aijin Shen, Ph.D./ January 24, 2013
HFD-620/Raj Bykadi, Ph.D./ January 24, 2013
HFD-617/Rinku Patel, Pharm. D/ 2/4/2013

C. CC Block

\\fdswv04385\documents\23537-201355.doc

TYPE OF LETTER: Not Approval

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

/s/

AIJIN SHEN
02/05/2013

RINKU PATEL
02/05/2013

GURURAJ BYKADI
02/06/2013

BING CAI
02/06/2013

Chem Comp, PN EES ONLY

ANDA 201355

Nitrofurantoin Oral Suspension USP, 25mg/ 5mL

SUN Pharmaceutical Industries, Inc.

Aijin Shen, Ph.D.
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: # 201355

2. REVIEW: #3

3. REVIEW DATE: January 03, and February 13, 2012

4. REVIEWER: Aijin Shen

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original Acceptable for Filing Telephone Amendment	March 04, 2010 March 08, 2010 May 06, 2010
Gratuitous Amendment	May 20, 2011
Amendment	April 07, 2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	December 21, 2011
Telephone Amendment	February 3, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	SUN Pharmaceutical Industries, Inc.
Address:	705 East Mulberry Street Bryan, Ohio 43506
US Agent:	N/A
Representative:	N/A
Telephone:	313-556-4105
Fax:	248-926-0231

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nitrofurantoin Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Reference Product: Furadantin (nitrofurantoin) Oral Suspension
Manufacturer by: (b) (4) Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Manufacturer for: Shionogi Pharma (formerly named Sciele Pharma, Inc.)
Atlanta, Georgia 30328

NDA #: 009175
Approved Date: December 23, 1953
The basis for submission of this application is the reference-listed drug, Furadantin (nitrofurantoin)

a. The firm has provided the following certifications for the for the patents:
Firm claims that there are no unexpired patents for this product in the Orange Book Database. Firm provided Paragraph II Certification.

The firm states that the proposed drug product contains information and data to show that the ANDA product is the same as the reference listed drug in: (i) conditions of use, (ii) active ingredient, (iii) dosage form, (iv) strength, (v) route of administration, and (vi) labeling except for the differences annotated in the side-by-side comparison in Section 1.14 (labeling), the changes as allowed for in 314.94(a)(9)(ii).

Basis of submission:
This ANDA for Nitrofurantoin Oral Suspension USP, 25mg/5 mL refers to the listed drug Furadantin (Nitrofurantoin) Suspension, NDA# 009175 by Shionogi Pharma published in the electronic version of Approved Drug Products with Therapeutic Equivalence Evaluations.

10. PHARMACOL. CATEGORY: Indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 25 mg/ 5mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

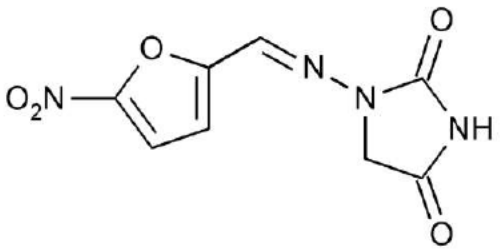
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

NITROFURANTOIN
Molecular Formula: $C_8H_6N_4O_5$
Formula Weight: 238.16
Chemical Name: 2,4 – Imidazolidinedione, 1-[[(5-nitro-2-furanyl) methylene] amino] (**or**) 1-[(5-Nitrofurfurylidene)amino]hydantoin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	A. Shen 02/07/2012	
	III			4			
	III			4			
	III			4			

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	IV			4			
	IV			4			

* Checked DARRTS; No new submission to review as of March 13, 2012. DMF is adequate.

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS*:

Chemistry Review Data Sheet

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	PENNDING	3/27/2012	
Methods Validation	N/A		
Labeling	Approved	11/08/2010	R. Wu
Bioequivalence	Deficient	07/19/2010	K. Ren
Bioequivalence	Clinical consult pending	6/20/2011	K. Ren
EA	Categorical Exclusion		
Radiopharmaceutical	N/A		

DARRTS checked on March 13, 2012.

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 201355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 201355 is approvable; EES is PENNDING.

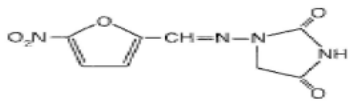
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

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

Nitrofurantoin, a synthetic chemical, is a stable, yellow, crystalline compound. Nitrofurantoin Oral Suspension, USP is an antibacterial agent for specific urinary tract infections. Nitrofurantoin Oral Suspension, USP is available in 25 mg/5mL liquid suspension for oral administration.



Inactive Ingredients:

Nitrofurantoin Oral Suspension, USP contains carboxymethylcellulose sodium, citric acid, glycerin, magnesium aluminum silicate, methylparaben, N&A fruit gum flavor #960 (MN72), propylparaben, purified water, sodium citrate, sorbitol, and sucralose.

Nitrofurantoin Oral Suspension, USP is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses.

DOSAGE AND ADMINISTRATION:

Nitrofurantoin Oral Suspension, USP should be given with food to improve drug absorption and, in some patients, tolerance.

Adults:

50 to 100 mg four times a day – the lower dosage level is recommended for uncomplicated urinary tract infections.

Pediatric Patients:

5 to 7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).

The following table is based on an average weight in each range receiving 5 to 6 mg/kg of body weight per 24 hours, given in four divided doses. It can be used to calculate an average dose of Nitrofurantoin Oral suspension, USP (25 mg/5 mL) for pediatric patients (one 5 mL teaspoon of Nitrofurantoin Oral suspension, USP contains 25 mg of nitrofurantoin):

Body Weight		No. Teaspoonfuls
Pounds	**Kilograms**	**4 Times Daily**
15 to 26	7 to 11	½ (2.5 mL)
27 to 46	12 to 21	1 (5 mL)
47 to 68	22 to 30	1 ½ (7.5 mL)
69 to 91	31 to 41	2 (10 mL)

IT and QT based on MDD (400 mg /day)
Note: The MDD is 50-100 mg four times a day; therefore 400 mg is used as MDD dose.

	IT	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Store at 20° to 25°C (68° to 77°F.

- HOW SUPPLIED

Nitrofurantoin Oral suspension, USP is available in:

NDC 57664-239-32 240 mL amber PET bottle
NDC 57664-239-34 480 mL amber PET bottle

Avoid exposure to strong light which may darken the drug. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP for Controlled Room Temperature]. Protect from freezing. Dispense in a tight, light-resistant container made of (b) (4) amber PET.

C. Basis for Approvability or Not-Approval Recommendation

Labeling, CMC, BIO – AC. EES (withhold (OAI alert))

C:\Documents and Settings\Shenai\My Documents\ANDAs\201355-Nitrofurantoin-Sun\201355R3.doc

(b) (4)

[redacted]

Additional information complied by the Reviewer:

R REGIONAL INFORMATION

R1 Executed Batch Records (3.2.R)

R2 Comparability Protocols: N/A

R3 Methods Validation Package:

The DS and DP are compendial articles. Method validation package is provided. MV from FDA laboratory will not be requested based on the current OGD guideline for method validation.
The method validation request selection criteria:

	DS	DP
USP item	Yes	Yes
First generic	No	No
New technology	No	No

	DS	DP
Low dose drug		No
Multiple drug components		No
Multiple drug impurities or degradants		No

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The labeling is approved.

B. Environmental Assessment Or Claim Of Categorical Exclusion

It is satisfactory.

III. List Of Deficiencies To Be Communicated

ANDA is approval with EES withhold.

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

HFD-620/Aijin Shen, Ph.D./ February 14, March 15, 2012
HFD-620/Raj Bykadi, Ph.D./ March 13, 16, 2012
HFD-617/Benjamin Danso, Pharm.D/ 3-27-12

C. CC Block

C:\Documents and Settings\Shenai\My Documents\ANDAs\201355-Nitrofurantoin-Sun\201355R3.doc

TYPE OF LETTER: CMC - SATISFACTORY

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

/s/

AIJIN SHEN
03/28/2012

GURURAJ BYKADI
03/28/2012

BENJAMIN DANSO
03/30/2012

EXPEDITED REVIEW

ANDA 201355

Nitrofurantoin Oral Suspension USP, 25mg/ 5mL

SUN Pharmaceutical Industries, Inc.

Aijin Shen, Ph.D.
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: # 201355

2. REVIEW: #2

3. REVIEW DATE: June 1, 2011

4. REVIEWER: Aijin Shen

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original Acceptable for Filing Telephone Amendment	March 04, 2010 March 08, 2010 May 06, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Gratuitous Amendment	May 20, 2011
Amendment	April 07, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	SUN Pharmaceutical Industries, Inc.
Address:	Attn : Ann Toland, Director of Reg Affairs 705 East Mulberry Street Bryan, Ohio 43506
US Agent:	N/A
Representative:	N/A
Telephone:	609-495-2823
Fax:	609-495-2711

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Nitrofurantoin Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Reference Product: Furadantin (nitrofurantoin) Oral Suspension
Manufacturer by: (b) (4) Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Manufacturer for: Shionogi Pharma (formerly named Sciele Pharma, Inc.)
Atlanta, Georgia 30328

NDA #: 009175
Approved Date: December 23, 1953
The basis for submission of this application is the reference-listed drug, Furadantin (nitrofurantoin)

a. The firm has provided the following certifications for the for the patents:
Firm claims that there are no unexpired patents for this product in the Orange Book Database. Firm provided Paragraph II Certification.

The firm states that the proposed drug product contains information and data to show that the ANDA product is the same as the reference listed drug in: (i) conditions of use, (ii) active ingredient, (iii) dosage form, (iv) strength, (v) route of administration, and (vi) labeling except for the differences annotated in the side-by-side comparison in Section 1.14 (labeling), the changes as allowed for in 314.94(a)(9)(ii).

Basis of submission:
This ANDA for Nitrofurantoin Oral Suspension USP, 25mg/5 mL refers to the listed drug Furadantin (Nitrofurantoin) Suspension, NDA# 009175 by Shionogi Pharma published in the electronic version of Approved Drug Products with Therapeutic Equivalence Evaluations.

10. PHARMACOL. CATEGORY: Indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 25 mg/ 5mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

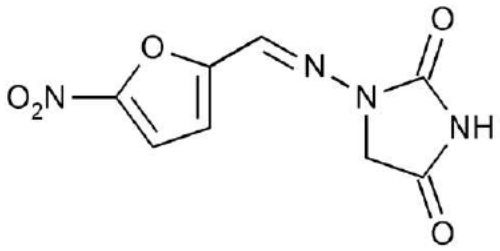
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x__Not a SPOTS product

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

NITROFURANTOIN
Molecular Formula: $C_8H_6N_4O_5$
Formula Weight: 238.16
Chemical Name: 2,4 – Imidazolidinedione, 1-[[(5-nitro-2-furanyl) methylene] amino] (**or**) 1-[(5-Nitrofurfurylidene)amino]hydantoin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	P. Onyimba 06/06/2011	
	III			4			
	III			4			
	III			4			

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	IV			4			
	IV			4			

* Checked DARRTS; No new submission as of June 24, 2011 DMF is adequate

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS*:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Withhold (Withhold status as of 25-Aug-2010/Warning letter issued)		A. Inyard
Methods Validation	N/A		
Labeling	Approved	11/03/2010	R. Wu
Bioequivalence	Deficient	07/14/2010	K. Ren
Bioequivalence	Clinical consult pending	6/20/2011	K. Ren
EA	Categorical Exclusion		
Radiopharmaceutical	N/A		

* DARRTS checked on June 24, 2011

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 201355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 201355 is not approvable.

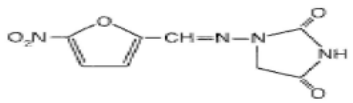
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

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

Nitrofurantoin, a synthetic chemical, is a stable, yellow, crystalline compound. Nitrofurantoin Oral Suspension, USP is an antibacterial agent for specific urinary tract infections. Nitrofurantoin Oral Suspension, USP is available in 25 mg/5mL liquid suspension for oral administration.



Inactive Ingredients:

Nitrofurantoin Oral Suspension, USP contains carboxymethylcellulose sodium, citric acid, glycerin, magnesium aluminum silicate, methylparaben, N&A fruit gum flavor #960 (MN72), propylparaben, purified water, sodium citrate, sorbitol, and sucralose.

Nitrofurantoin Oral Suspension, USP is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses.

DOSAGE AND ADMINISTRATION:

Nitrofurantoin Oral Suspension, USP should be given with food to improve drug absorption and, in some patients, tolerance.

Adults:

50 to 100 mg four times a day – the lower dosage level is recommended for uncomplicated urinary tract infections.

Pediatric Patients:

5 to 7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).

The following table is based on an average weight in each range receiving 5 to 6 mg/kg of body weight per 24 hours, given in four divided doses. It can be used to calculate an average dose of Nitrofurantoin Oral suspension, USP (25 mg/5 mL) for pediatric patients (one 5 mL teaspoon of Nitrofurantoin Oral suspension, USP contains 25 mg of nitrofurantoin):

Body Weight		No. Teaspoonfuls
Pounds	**Kilograms**	**4 Times Daily**
15 to 26	7 to 11	½ (2.5 mL)
27 to 46	12 to 21	1 (5 mL)
47 to 68	22 to 30	1 ½ (7.5 mL)
69 to 91	31 to 41	2 (10 mL)

IT and QT based on MDD (400 mg /day)
Note: The MDD is 50-100 mg four times a day; therefore 400 mg is used as MDD dose.

	IT	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Store at 20° to 25°C (68° to 77°F.

- HOW SUPPLIED

Nitrofurantoin Oral suspension, USP is available in:

NDC 57664-239-32 240 mL amber PET bottle
NDC 57664-239-34 480 mL amber PET bottle

Avoid exposure to strong light which may darken the drug. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP for Controlled Room Temperature]. Protect from freezing. Dispense in a tight, light-resistant container made of (b) (4) amber PET.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

1. MINOR Chemistry issues
2. Bioequivalence review – Deficient
3. EES-withhold (OAI alert) (EES Status checked on 6/22/2011)

C:\Documents and Settings\Shenai\My Documents\ANDAs\201355-Nitrofurantoin-Sun\201355CR2. NA.doc

(b) (4)

[redacted]

Additional information complied by the Reviewer:

R REGIONAL INFORMATION

R1 Executed Batch Records (3.2.R)

R2 Comparability Protocols: N/A

R3 Methods Validation Package:

The DS and DP are compendial articles. Method validation package is provided. MV from FDA laboratory will not be requested based on the current OGD guideline for method validation.
The method validation request selection criteria:

	DS	DP
USP item	Yes	Yes
First generic	No	No
New technology	No	No
Low dose drug		No
Multiple drug components		No
Multiple drug impurities or degradants		No

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The labeling is approved.

B. Environmental Assessment Or Claim Of Categorical Exclusion

It is satisfactory.

III. List Of Deficiencies To Be Communicated

See the section below for details.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201355 APPLICANT: SUN Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25 mg/5mL

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6. (b) (4)

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph. D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

HFD-620/Aijin Shen, Ph.D./June 23, 2011, July 05 2011
HFD-620/Raj Bykadi, Ph.D./ July 5, 2011
HFD-617/Benjamin Danso, Pharm.D/ 7-6-11

C. CC Block

C:\Documents and Settings\Shenai\Application Data\eRoom\eRoom Client\V7\EditingFiles\201355CR2. NA.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

AIJIN SHEN
07/19/2011

GURURAJ BYKADI
07/19/2011

BENJAMIN DANSO
07/22/2011

EXPEDITED REVIEW

ANDA 201355

Nitrofurantoin Oral Suspension USP, 25mg/ 5mL

SUN Pharmaceutical Industries, Inc.

Aijin Shen, Ph.D.
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: # 201355

2. REVIEW: #1

3. REVIEW DATE: July 30, 2010

4. REVIEWER: Aijin Shen

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Acceptable for Filing Telephone Amendment	March 04, 2010 March 08, 2010 May 06, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	SUN Pharmaceutical Industries, Inc.
Address:	Attn : Ann Toland, Director of Reg Affairs 705 East Mulberry Street Bryan, Ohio 43506
US Agent:	N/A
Representative:	N/A
Telephone:	609-495-2823
Fax:	609-495-2711

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Nitrofurantoin Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Reference Product: Furadantin (nitrofurantoin) Oral Suspension
Manufacturer by: (b) (4) Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Manufacturer for: Shionogi Pharma (formerly named Sciele Pharma, Inc.)
Atlanta, Georgia 30328

NDA #: 009175

Approved Date: December 23, 1953

The basis for submission of this application is the reference-listed drug, Furadantin (nitrofurantoin)

a. The firm has provided the following certifications for the for the patents:
Firm claims that there are no unexpired patents for this product in the Orange Book Database. Firm provided Paragraph II Certification.

The firm states that the proposed drug product contains information and data to show that the ANDA product is the same as the reference listed drug in: (i) conditions of use, (ii) active ingredient, (iii) dosage form, (iv) strength, (v) route of administration, and (vi) labeling except for the differences annotated in the side-by-side comparison in Section 1.14 (labeling), the changes as allowed for in 314.94(a)(9)(ii).

Basis of submission:
This ANDA for Nitrofurantoin Oral Suspension USP, 25mg/5 mL refers to the listed drug Furadantin (Nitrofurantoin) Suspension, NDA# 009175 by Shionogi Pharma published in the electronic version of Approved Drug Products with Therapeutic Equivalence Evaluations.

10. PHARMACOL. CATEGORY:

Indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 25 mg/ 5mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

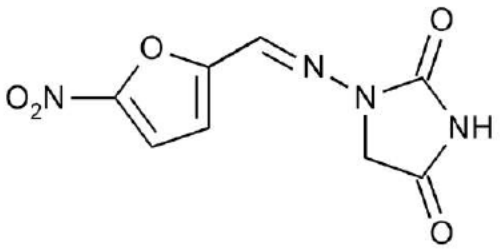
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

NITROFURANTOIN
Molecular Formula: $C_8H_6N_4O_5$
Formula Weight: 238.16
Chemical Name: 2,4 – Imidazolidinedione, 1-[[(5-nitro-2-furanyl) methylene] amino] (**or**) 1-[(5-Nitrofurfurylidene)amino]hydantoin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	09/22/2010 by A. Shen	
	III			4			
	III			4			
	III			4			

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	IV			4			
	IV			4			

* Checked DARRTS; No new submission as of Sept 9, 2010 DMF is adequate with informational request

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS*:

Chemistry Review Data Sheet

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending (Withhold status as of 25-Aug-2010/Warning letter issued)		S. Adams
Methods Validation	N/A		
Labeling	Deficient	06/08/2010	R. Wu
Bioequivalence	Deficient	07/14/2010	K. Ren
EA	Categorical Exclusion		
Radiopharmaceutical	N/A		

* DARRTS checked on Sept 13, 2010

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 201355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 201355 is not approvable.

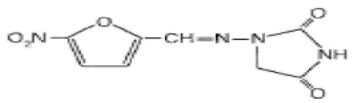
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

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

Nitrofurantoin, a synthetic chemical, is a stable, yellow, crystalline compound. Nitrofurantoin Oral Suspension, USP is an antibacterial agent for specific urinary tract infections. Nitrofurantoin Oral Suspension, USP is available in 25 mg/5mL liquid suspension for oral administration.



Inactive Ingredients:

Nitrofurantoin Oral Suspension, USP contains carboxymethylcellulose sodium, citric acid, glycerin, magnesium aluminum silicate, methylparaben, N&A fruit gum flavor #960 (MN72), propylparaben, purified water, sodium citrate, sorbitol, and sucralose.

Nitrofurantoin Oral Suspension, USP is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses.

DOSAGE AND ADMINISTRATION:

Nitrofurantoin Oral Suspension, USP should be given with food to improve drug absorption and, in some patients, tolerance.

Adults:

50 to 100 mg four times a day – the lower dosage level is recommended for uncomplicated urinary tract infections.

Pediatric Patients:

5 to 7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).

The following table is based on an average weight in each range receiving 5 to 6 mg/kg of body weight per 24 hours, given in four divided doses. It can be used to calculate an average dose of Nitrofurantoin Oral suspension, USP (25 mg/5 mL) for pediatric patients (one 5 mL teaspoon of Nitrofurantoin Oral suspension, USP contains 25 mg of nitrofurantoin):

Body Weight		No. Teaspoonfuls
Pounds	**Kilograms**	**4 Times Daily**
15 to 26	7 to 11	½ (2.5 mL)
27 to 46	12 to 21	1 (5 mL)
47 to 68	22 to 30	1 ½ (7.5 mL)
69 to 91	31 to 41	2 (10 mL)

IT and QT based on MDD (400 mg /day)
Note: The MDD is 50-100 mg four times a day; therefore 400 mg is used as MDD dose.

	IT	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Store at 20° to 25°C (68° to 77°F.

- HOW SUPPLIED

Nitrofurantoin Oral suspension, USP is available in:

NDC 57664-239-32 240 mL amber PET bottle
NDC 57664-239-34 480 mL amber PET bottle

Avoid exposure to strong light which may darken the drug. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP for Controlled Room Temperature]. Protect from freezing. Dispense in a tight, light-resistant container made of (b) (4) amber PET.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

1. MINOR Chemistry issues
2. Bioequivalence review – Deficient
3. Labeling – Deficient

C:\Documents and Settings\dansob\Application Data\eRoom\eRoom Client\V7\EditingFiles\201355 Nitrofurantoin.CR1A. NA.doc

Following this page, 61 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

Additional information complied by the Reviewer:

R REGIONAL INFORMATION

R1 Executed Batch Records (3.2.R)

R2 Comparability Protocols: N/A

R3 Methods Validation Package:

The DS and DP are compendial articles. Method validation package is provided. MV from FDA laboratory will not be requested based on the current OGD guideline for method validation.
The method validation request selection criteria:

	DS	DP
USP item	Yes	Yes
First generic	No	Yes
New technology	No	No
Low dose drug		No
Multiple drug components		No
Multiple drug impurities or degradants		No

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The labeling is deficient.

B. Environmental Assessment Or Claim Of Categorical Exclusion

Categorical exclusion from the requirement to prepare an Environmental Assessment is requested (1.12.14).
It is satisfactory.

III. List Of Deficiencies To Be Communicated

See the section below for details.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201355 APPLICANT: SUN Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25 mg/5mL

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

A. Deficiencies:

Drug Substance:

1. (b) (4)

2.

3.

Drug Product:

2. (b) (4)

3.

4.

5.

6.

Following this page, 1 Page Withheld in Full as (b)(4)

19. (b) (4)

20.

21.

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

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. (b) (4)

3.

4.

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph. D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

HFD-620/Aijin Shen, Ph.D./August 25, 2010, September 14, 28, 2010
HFD-620/Raj Bykadi, Ph.D./ Spet 13, 15, 28, 2010
HFD-617/Benjamin Danso, Pharm.D/9-22-10

C. CC Block

C:\Documents and Settings\dansob\Application Data\eRoom\eRoom Client\V7\EditingFiles\201355 Nitrofurantoin.CR1A. NA.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

AIJIN SHEN
09/28/2010

RAMNARAYAN S RANDAD on behalf of GURURAJ BYKADI
09/29/2010

BENJAMIN DANSO
09/29/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA201355Orig1s000

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	201355
Drug Product Name	Nitrofurantoin Oral Suspension, USP
Strength	25 mg/5 mL
Applicant Name	Caraco Pharmaceutical Laboratories, Ltd.
Submission Date	May 10, 2013 (SD-14)
Reviewer	Chitra Mahadevan, Pharm.D.
Outcome	ADEQUATE

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm, dated May 10, 2013.

The firm has accepted the FDA-recommended dissolution method and specifications.

The bioequivalence section of this application is now adequate.

COMMENTS:

The application was found to be incomplete pending the firm's acknowledgement of its acceptance of the FDA-recommended dissolution method and specifications.

On May 10, 2013, Caraco Pharmaceutical Laboratories, Ltd. acknowledged the FDA-recommended dissolution method and specifications listed below:

Medium:	Phosphate Buffer, pH 7.2
Volume:	900 mL
Apparatus:	USP II (Paddle)
Speed:	50 rpm
Specification:	NLT (b) (4) % (Q) of the labeled amount of nitrofurantoin is dissolved in 30 minutes

Based on the acceptability of the dissolution acknowledgement, ANDA 201355 is now acceptable.

DEFICIENCY COMMENTS:

N/A

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for in-vitro dissolution testing and in-vivo bioequivalence. Therefore, the bioequivalence section of the application is **ADEQUATE**.

I. Completed Assignment for 201355 ID: 20118

Reviewer: Mahadevan, Chitra **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Nitrofurantoin Suspension Dissolution Acknowledgement

---

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
20118	5/10/2013	Dissolution Data (REGULAR)	Dissolution Acknowledgement	1	0
				Total:	0

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

/s/

CHITRA MAHADEVAN
07/03/2013

AARON W SIGLER
07/03/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	201355		
Drug Product Name	Nitrofurantoin Oral Suspension USP		
Strength(s)	25 mg/5 mL		
Applicant Name	Sun Pharmaceutical Industries, Inc.		
Address	705 East Mulberry Street Bryan, Ohio 43506		
Applicant's Point of Contact	Anne Toland		
Contact's Telephone Number	1-609-495-2823		
Contact's Fax Number	1-609-495-2711		
Original Submission Date(s)	March 4, 2010		
Submission Date(s) of Amendment(s) Under Review	September 29, 2010 May 30, 2012 (telephone amendment- individual dissolution data)		
First Generic	Yes		
Reviewer	Ke Ren, Ph.D.		
Study Number (s)	PKD_09_521		
Study Type (s)	Fed Study		
Strength (s)	25 mg/5 mL		
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Near R.C. Patel Estate Akota Road, Akota Vadodara- 390 020 (India)		
Analytical Site	Sun Pharmaceutical Industries Ltd.		
Analytical Site Address	Tandalja, Vadodara -390020 Gujarat, India		
Overall Review Result	**INADEQUATE (pending the firm's acceptance to FDA-recommended dissolution specification)**		
DSI Inspection Status	**ADEQUATE**		
Bioequivalence Study Tracking/Supporting Document #	**Study /Test Type**	**Strength**	**Review Result**
#1, #4 and #10	Dissolution	25 mg/5 mL	**INADEQUATE**
#1 and #4	Fed Study	25 mg/5 mL	**ADEQUATE**

REVIEW OF AN AMENDMENT

1 EXECUTIVE SUMMARY

In the current submission dated September 29, 2010, Sun Pharmaceutical Industries Inc. submitted its response to the deficiencies issued by the Division of Bioequivalence I (DBI) in its letter of July 22, 2010[1]. The deficiency comments were related to (b) (4) (b) (4) amount of glycerin in the test product's formulation based on the maximum daily dose, detailed information for the formulation, lack of individual dissolution data and unusual high drug release during the dissolution testing.

In response, the firm has provided the detailed information for the formulation. Also, the Division of Clinical Review has determined the amount of glycerin contained in the test product is acceptable. Therefore, the firm's formulation is acceptable. The firm's dissolution data with FDA-recommended dissolution method in the original submission (submission date: March 4, 2010) is acceptable. However, the firm proposed specifications [NLT (b) (4) % (Q) in (b) (4) minutes] are not acceptable. Based on the data submitted, the DB I recommends a more appropriate specification [NLT (b) (4) % (Q) in 30 minutes]. The firm should accept and acknowledge the FDA-recommended speciation. Therefore, the firm's dissolution testing is **inadequate.**

Currently, no Office of Scientific Investigation (OSI) inspection is pending for either the clinical[2] or analytical site[3].

The application is **inadequate** with a deficiency.

---

[1] DARRTS ANDA 201355 Ramson, Teresa V 07/22/2010 FAX 07/22/2010 COR-ANDADE-01 (Bio Incomplete Deficiencies) Archive

[2] The routine OSI inspection of the clinical site was finished on April 23, 2010 and the outcome was NAI (No Action Indicated) Please see DARRTS ANDA 091552 Biswas, Gopa 06/17/2010 N/A 06/17/2010 CONSULT REV_DSI-05 (Bioequivalence Establishment Inspection Report Review) Archive

[3] The analytical site was last inspected for the ANDA 090178 due to a 'for cause" request and the outcome of VAI [DARRTS ANDA 090178 Kassim, Sean Y 06/08/2010 N/A 06/08/2010 CONSULT REV-BIOEQ-01 (General Consult Review) Archive]. The reviewer deems the OSI finding would have no impact on the BE study outcome. Please see DARRTS ANDA 201355 Ren, Ke 07/19/2010 N/A 07/19/2010 REV-BIOEQ-01 (General Review) Archive.

2 BACKGROUND

- There is a Draft Guidance on this drug product on a public website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM148222.pdf (posted on October 2011). As per this guidance the DB requests only **a fed BE study** on this drug product (no fasting BE study).

- There was **No** "dissolution only" review for this application. The dissolution data was reviewed with the "full ANDA" review.

- In the original submission (submission date March 4, 2010)[4], the firm submitted the results of a single dose fed BE study (# PKD_09_521) comparing its Nitrofurantoin Oral Suspension USP, 25 mg/5 mL, to the reference-listed drug product, FURADANTIN® (Nitrofurantoin) Oral Suspension USP, 25 mg/5 mL, manufactured by Shionogi Pharma (formerly Sciele Pharma Inc, NDA 009175). The DB I reviewed the submission [**DARRTS ANDA 201355 Ren, Ke 07/19/2010 N/A 07/19/2010 REV-BIOEQ-01 (General Review) Archive**]. The study was incomplete due to (b) (4) amount of glycerin used in the formulation based on the maximum daily dose, detailed information for the formulation, lack of individual dissolution data and unusual high drug release in the dissolution test. The result of the fed study is summarized in the table below[5].

Nitrofurantoin Oral Suspension Dose (1 x 25 mg/5 mL) Fed Bioequivalence Study No. PKD_09_521, N=28 (male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	883.09	868.88	1.02	98.51	104.86
AUC∞ (ng·hr/mL)	915.62	893.56	1.02	99.57	105.46
Cmax (ng/mL)	371.79	372.31	1.00	90.44	110.26

The firm was requested to provide the information on the deficiencies identified by the DB I. In this current amendment, the firm submitted its responses for each of the deficiencies issued by the DB I (dated July 22, 2010).

- On June 20, 2011, the reviewer requested a clinical consultation to the OGD Clinical Team for the safety and clinical significance of (b) (4)

[4] DARRTS ANDA 201355, New/ANDA. Submitted 03/04/2008. Last accessed 05/23/2012.
[5] DARRTS ANDA 201355 Ren, Ke 07/19/2010 N/A 07/19/2010 REV-BIOEQ-01 (General Review) Archive

amount of glycerin in firm's formulation of the test product[6]. The detail information will be discussed further in the review.

APPEARS THIS WAY ON ORIGINAL

[6] DARRTS ANDA 201355 Ren, Ke 06/20/2011 N/A 06/20/2011 FRM-CONSULT-01 (General Consult Review) Archive

3 TABLE OF CONTENTS

4 SUBMISSION SUMMARY

4.1 Drug Product Information, PK/PD Information, and Relevant DBE History

- For more information, please refer to the following reviews:
  - DARRTS ANDA 201355 Ren, Ke 07/19/2010 N/A 07/19/2010 REV-BIOEQ-01 (General Review) Archive
  - DARRTS ANDA 201355, Ramson, Teresa V 07/22/2010 FAX 07/22/2010 COR-ANDADE-01 (Bio Incomplete Deficiencies) Archive
  - DARRTS ANDA 201355 Ren, Ke 06/20/2011 N/A 06/20/2011 FRM-CONSULT-01 (General Consult Review) Archive
  - DARRTS ANDA 201355 Forsyth, Linda M 05/15/2012 N/A 05/15/2012 CONSULT REV-CLINICAL-01 (General Consult Review) Archive
- There is a Draft Guidance on this drug product on a public website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM148222.pdf (posted on October 2011). As per this guidance the DB requests only **a fed BE study** on this drug product (no fasting BE study).
- On October 27, 2010, there were some changes made on the carton labeling[7].

4.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	No	0
Waiver requests	No	0
BCS Waivers	No	0
Vasoconstrictor Studies	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	1

4.3 Review of Submission

The firm's responses to the three (3) deficiencies and the reviewer's evaluations of those responses are provided in this section of the review:

[7] Drug@ FDA, search term: Nitrofurantoin. Last accessed: May 29, 2012

Deficiency 1: *Based on the data available to the Agency, the maximum daily intake of Glycerin calculated from approved oral drug products is* (b) (4) *For your formulation, based on the maximum daily dose of 400 mg of nitrofurantoin recommended for the drug product (as stated in the labeling of the Reference Listed Drug (RLD) product, Furadantin® (Nitrofurantoin Oral Suspension), the total daily intake of Glycerin from your test formulation* (b) (4) *the approved daily intake amount mentioned above. Please provide justifications for the amount of Glycerin used in the test formulation, and additional data and/or evidence demonstrating that the proposed amount of this excipient in your test formulation is safe.*

Firm's Response: *Glycerin, USP, is an inactive ingredient, used as a* (b) (4) *in Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL. The concentration of Glycerin, USP, in Sun's formulation is* (b) (4) [redacted] *The data for the above mentioned study can be found in the Pharmaceutical Development Report included in the original application as Module 3, Section 3.2.P.2. In addition, accelerated stability studies on the finished product showed no deleterious interaction of the excipients, which included Glycerin, USP,* (b) (4)

Glycerin is generally recognized as safe and occurs naturally in fats and oils from animals and plant origins. Glycerin is consumed as part of a normal diet and is readily absorbed from the intestine. The absorbed glycerin is either metabolized to carbon dioxide and glycogen or used in the synthesis of body fats. Glycerin is used in a wide variety of approved pharmaceutical formulations, including oral, ophthalmic, parenteral, and topical preparations. When glycerin is used as a pharmaceutical excipient or a food additive, it is rarely associated with adverse effects and is generally regarded as nontoxic and a nonirritant. (b) (4) [redacted]

(b) (4) [redacted]

(b) (4)

Reviewer's Comments: The firm's response to Deficiency #1 is **acceptable.**

- The reviewer realized an error in evaluating glycerin in the test product. The excipients present in the reference product formulation were not considered in the original full ANDA review. The RLD formulation is listed in the following table[8].

NOT FOR RELEASE UNDER FOAI

Components	mg per 5 mL dose	Type
Nitrofurantoin	25 mg	Active
Glycerin	(b) (4)	Inactive
Magnesium Aluminum		Inactive
(b) (4) Methylparaben		Inactive
Carboxymethylcellulose		Inactive
Flavor		Inactive
Propylparaben		Inactive
Saccharin		Inactive
Sodium Citrate		Inactive
Sorbitol		Inactive
Citric Acid		Inactive
Water, Purified		Inactive

(b) (4)

(b) (4) Therefore, the test product formulation is acceptable.

[8] Review of Controlled Correspondence 08-0029. Doc Date: 12/21/2007. \\cdsnas\OGDS6\CONTROLS\2008-docs\08-0029.pdf.
[9] http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?id=19082

Clinical Consult:

- On June 20, 2011, the reviewer requested a clinical consultation to the OGD Clinical Team for the safety and clinical significance of the (b) (4) amount of glycerin in firm's formulation of the test product.

- The clinical review was complete May 15, 2012[10]. The Division of Clinical Review (DCR) concluded that "*the amount of glycerin contained in the proposed generic product is not a range know to product toxic effects. The amount of glycerin used in the reference listed drug is* (b) (4) *at the maximal daily dose. The amount of glycerin contained in ANDA is* (b) (4) *as the maximal daily dose. Therefore, the amount of glycerin contained in current ANDA is acceptable.* (b) (4)

- Therefore, the firm's response to Deficiency #1 is **acceptable.**

Deficiency 2: *Please provide the quantitative composition of N&A Fruit Gum Flavor #960 used in your formulation.*

Firm's Response: (b) (4)*, the manufacturer of N&A Fruit Gum FL #960, provided the requested information to the Agency on August 20, 2010. A copy of the communication sent to the Agency is included in the DMF Letters of Authorization in Module 1, section 1.4.1.*

Reviewer's Comments: The firm's response to Deficiency #2 is **acceptable**. The firm submitted the information as the agency requested. In addition, the amount of color additives in N&A Fruit Gum Flavor # 960 is (b) (4) and is considered insignificant.

Deficiency 3: *Your dissolution testing is incomplete. You did not submit the individual dissolution data for the 12 dosage units of the test and reference product. Please submit these data. In addition, the dissolution data showed* (b) (4) *drug release for the test and RLD products (i.e., many values were* (b) (4) *Please explain* (b) (4) *dissolution values for the test and RLD products, and provide complete validation data and report for the analytical method used in the dissolution testing. Also, please conduct additional dissolution testing using the FDA recommended dissolution method for both the*

[10] ANDA 201355 Forsyth, Linda M 05/15/2012 N/A 05/15/2012 CONSULT REV-CLINICAL-01 (General Consult Review) Archive

test and RLD products to confirm the accuracy and reproducibility of the dissolution results.

Firm's Response: The FDA-recommended dissolution method of pH 7.2 Phosphate Buffer was submitted in the original submission as part of the proposed drug specification. This dissolution was validated accordingly and the FDA-recommended dissolution method validation report was submitted in the original submission in Module 3, Section 3.2.P.5.3, as file Validation 1. In addition, individual product bioequivalence requirements for individual dissolution data of 12 dosage units using the FDA recommended dissolution method was submitted in Module 2 as part of Table 5 in Section 2.7 Clinical Summary. Upon further review of this data, typographical errors were noted in Table 5, the revised tables for Module 2 have included in Module 2, section 2.7.

Table 1: Test Product:

Dissolution Conditions	**Method:**	II (Paddles)
	Speed of Rotation:	50 rpm
	Medium:	pH 7.2
Firm's Proposed Specifications	Must conform to current USP acceptance criteria S_1, S_2 or S_3. Q = (b) (4)% at (b) (4) minutes, acceptance (S_1) = Q + 5%	
Dissolution Test Site	Sun Pharmaceutical Industries, Inc. 705 East Mulberry Street, Bryan, Ohio 43506	
Test Product	Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL, Sun Pharmaceutical Industry Inc. Manufacture Date: 12/2009	
Lot & Package	B1127 (b) (4)	
Dosage Strength & Form	25 mg/5 mL Oral Suspension	

Units	**Collection Times**				
	15 min	**30 min**	**60 min**	**120 min**	**180 min**
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	84.8	99.9	104.6	106.8	106.7
Min	(b) (4)				
Max					

%RSD, CV	7.8	3.2	1.7	1.1	0.5

Table 2: Reference Product:

Dissolution Conditions	**Method:**	II (Paddles)
	Speed of Rotation:	50 rpm
	Medium:	pH 7.2
Firm's Proposed Specifications	Must conform to current USP acceptance criteria S1, S2 or S3. Q = [redacted]% at [redacted] minutes, acceptance (S1) = Q + 5%	
Dissolution Test Site	Sun Pharmaceutical Industries, Inc. 705 East Mulberry Street Bryan, Ohio 43506	
Test Product	Furandantin Oral Suspension, 25 mg/5 mL, [redacted] Expiry Date: 08/2010	
Lot & Package	437034 8 oz (Units 1-6) & 435328 16 oz (Units 7-12)	
Dosage Strength & Form	25 mg/5 mL Oral Suspension	

Units	**Collection Times**				
	15 min	**30 min**	**60 min**	**120 min**	**180 min**
1	[redacted]				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	98.3	103.3	104.2	104.7	107.9
Min	[redacted]				
Max					
%RSD, CV	7.7	3.9	3.7	3.4	3.4

To demonstrate accuracy and reproducibility of the FDA recommended dissolution method, recovery was performed in triplicate. The validation demonstrated that the % mean recovery was within the specification of 80% to 120% for each concentration at each time point. In addition, the standard deviation of the % recoveries was within the stated specification ≤ 15%. The average recoveries of the three accuracy studies performed are listed in the table below and were represented on page 20 of the method validation report

submitted in the original submission in Module 3, Section 3.2.P.5.3. Therefore, the method demonstrated to be accurate and reproducible.

(b) (4)

In addition to the 12 dosage units, the FDA recommended dissolution method was performed throughout the submitted stability conditions on Sun's proposed formula and the RLD. The overall range summary of stability testing is listed in the table below as original reported in Module 3, Section 3.2.P.8.1 of the original submission. The stability data is in line with the data submitted in Module 5.

Table 4: Stability Data

Dissolution Comparison of Sun Formulation vs. Shionogi Pharma			
Parameter	**Limits**	**Sun-240 mL**	**Shionogi**
Stability Condition	**Dissolution:**	**Range Results:**	**Range Results**
40°C ±2°C/25% ±5% RH	**120 min.**	S1, (b) (4) %	S1, (b) (4) %
	180 min.	S1, %	S1, %
30°C ±2°C/65% ±5% RH	**120 min.**	S1, %	S1, %
	180 min.	S1, %	S1, %

Reviewer's Comments: The firm's response to Deficiency #3 is **adequate**.

- The firm stated that individual dissolution data of 12 dosage units using the FDA recommended dissolution method was submitted in Module 2 as part of Table 5 in Section 2.7 Clinical Summary. The reviewer went through all of the submission and was unable to locate the individual dissolution data. It appeared as though the firm only submitted comparative dissolution summary results. Therefore, on May 24, 2012, our Project Manger contacted the firm for individual dissolution data[11]. The

[11] DARRTS ANDA 201355 Ramson, Teresa V 05/24/2012 Verbal 05/24/2012 COR-ANDAIR-01 (Advice/Information Request)

firm submitted this information on May 30, 2012[12] which is the information provided in the above tables (Table 1 and Table 2).

- The firm has proposed to manufacture the Nitrofurantoin Oral Suspension 25 mg /5 mL [redacted] All bottles came from the same lot (Lot # B1127).

- There is no USP dissolution method for this product but there is an FDA-recommended method [900 mL of phosphate buffer, pH 7.2 using Apparatus II (Paddle) at 50 rpm]. The firm's dissolution testing data with the FDA-recommended dissolution method demonstrated [redacted] dissolution at the early time point for both the test and reference products [redacted] of the drug was released, respectively). Both products completely released the drug within [redacted] min. In addition, the dissolution testing data of both products were released more than [redacted]% at 30 min, 45 min, 60 min, 120 min and 180 min sampling time points (range: [redacted]% for the test product and [redacted]%). In the current amendment submission (submission date September 29, 2010), the stability data also showed [redacted] drug release for the test and reference products at [redacted] min. The firm did not identify the source for [redacted] dissolution values in its dissolution testing. Please note DB I does not set dissolution specification based on stability data.

- The firm provided its method validation report for "Nitrofurantoin Oral Suspension-Dissolution". The % label claim amount of nitrofurantoin in Nitrofurantoin Oral Suspension was determined by UV analysis [redacted]. The method has been demonstrated to be linear, precise, accuracy, system suitability, solution stability and robust for nitrofurantoin.

- According to the USP potency for Nitrofurantoin Oral Suspension, it allows a potency of not less than 92% and not more than 108% of labeled amount of nitrofurantoin[13]. [redacted]

- [redacted]

[12] DARRTS ANDA 201355 05/30/2012 Bioequivalence/Response to Information Request
[13] http://www.uspnf.com/uspnf/pub/index?usp=35&nf=30&s=0&officialOn=May%201,%202012; search term: nitrofurantoin; last accessed: June 8, 2012.
[14] [redacted]

(b) (4)

- Please see the summary of the particle size specifications of nitrofurantoin among in-house ANDAs: (NOT TO BE RELEASED UNDER FOIA)

ANDAs	ANDA 201355 (Current)[16]	ANDA 201693[17]	Approved ANDA 201679[18]
D10	(b) (4)		
D50			
D90			

The CMC reviewers have requested the particle size specification of nitrofurantoin for the two other submitted applications, ANDAs (b) (4)

- Dissolution profiles using the FDA-recommended method for the all in-house ANDAs are presented in Figure 1. It shows that dissolution released rate is directly correlated with the particle size of nitrofurantoin. (b) (4)

(b) (4)

[15] (b) (4)

[16] DARRTS ANDA 201355 Shen, Aijun 07/22/2011 N/A 07/22/2011 REV-Quality-03 (General Review) Archive

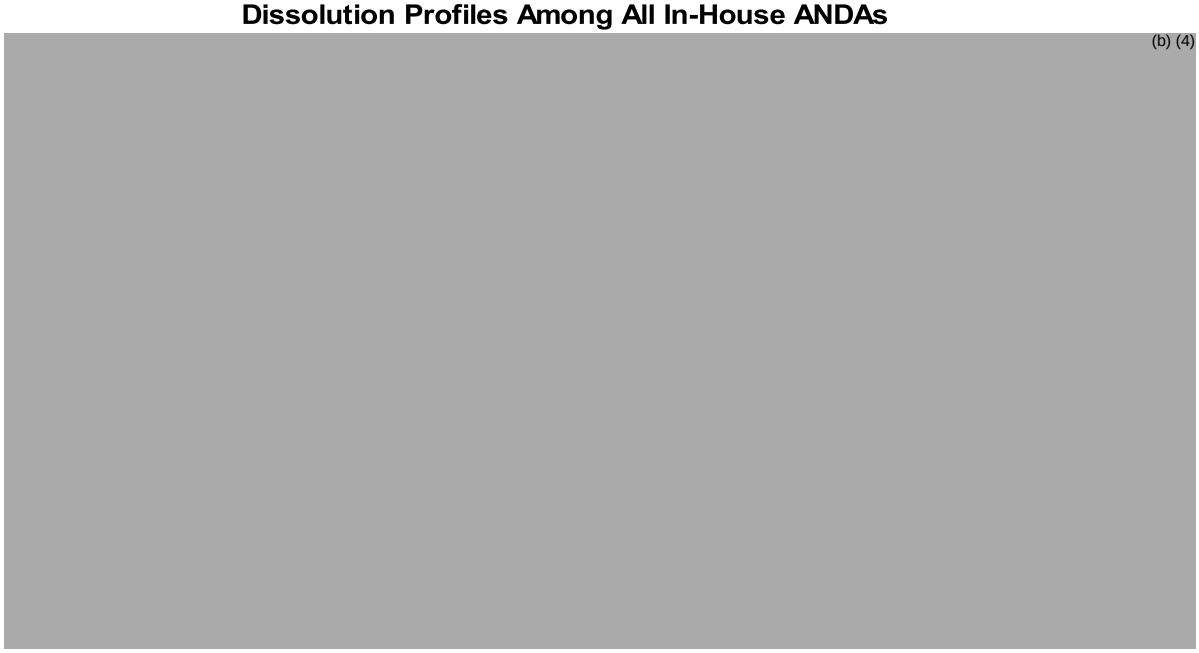
[17] DARRTS ANDA 201693 Onyimba, Patricia I 05/02/2012 N/A 05/02/2012 REV-Quality-03 (General Review) Archive

[18] DARRTS ANDA 201679 Onyimba, Patricia I 05/11/2011 N/A 05/11/2011 REV-Quality-03 (General Review) Archive

[19] (b) (4)

[20] (b) (4)

Figure 1. Dissolution profiles comparison using FDA-recommended method among all in-house ANDAs



- Based on the previous comments, the DB reviewer has determined the firm's dissolution testing with the FDA-recommended is acceptable. However, the firm proposed specifications [NLT (b) (4)% (Q) in (b) (4) minutes] are not acceptable. Based on the data submitted, DB I recommends a more appropriate specification [NLT (b) (4)% (Q) in 30 minutes]. The firm should accept and acknowledge the FDA-recommended speciation.

- (b) (4)

- Please note that the dissolution data reported for the reference product in ANDA (b) (4) are similar to those reported in the current application, (b) (4) (b) (4)

(b) (4)

APPEARS THIS WAY ON ORIGINAL

[21] (b) (4)

Following this page, 2 Pages Withheld in Full as (b)(4)

4.4 Waiver Request(s)

None.

4.5 Deficiency Comment

The firm's dissolution data with FDA-recommended dissolution method is acceptable. However, the firm proposed specifications [NLT (b)(4)% (Q) in (b)(4) minutes] are not acceptable. Based on the data submitted, DB I recommends a more appropriate specification [NLT (b)(4)% (Q) in 30 minutes]. The firm should accept and acknowledge the FDA-recommended speciation.

Medium: Phosphate Buffer, pH 7.2
Volume: 900 mL
Apparatus: USP apparatus II (Paddle)
Speed: 50 rpm
Specification: NLT (b)(4)% (Q) of labeled amount of nitrofurantoin in the dosage form is dissolved in 30 minutes.

4.6 Recommendations

1. The Division of Bioequivalence accepts the fed BE study (study # PKD_09_521) conducted by Sun Pharmaceutical, Nitrofurantoin Oral Suspension, 25 mg/5 mL, lot # B1127, comparing it to Shionogi Pharma's Furadantin® (nitrofurantoin) Oral Suspension, 25 mg/mL, lot #437034.

2. The dissolution testing conduct by Sun Pharmaceutical on its Nitrofurantoin Oral Suspension, 25 mg/5 mL, lot # B1127, comparing it to Furadantin® (nitrofurantoin) Oral Suspension, 25 mg/mL by Shionogi Pharma, is **inadequate** due to the reason cited in the deficiency comment.

The firm should be informed of the above deficiency comment and recommendations.

BIOEQUIVALENCE DEFICIENCY

ANDA: 201355

APPLICANT: Sun Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Your dissolution testing data comparing your test product, Nitrofurantoin Oral Suspension USP, 25 mg/5 mL, with the reference product, Shionogi Pharma's FURADANTIN® (nitrofurantoin) Oral Suspension USP, 25 mg/5 mL, using the FDA-recommended dissolution method, are acceptable. However, your proposed specifications [NLT (b) (4)% (Q) in (b) (4) minutes] are not acceptable. Based on the data submitted, the DBI recommends a more appropriate specification. Please acknowledge your acceptance of the following dissolution method and specification for your test product:

Medium: Phosphate Buffer, pH 7.2
Volume: 900 mL
Apparatus: USP apparatus II (Paddle)
Speed: 50 rpm
Specification: NLT (b) (4)% (Q) of labeled amount of nitrofurantoin in the dosage form is dissolved in 30 minutes.

Sincerely yours,

{See appended electronic signature page}

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

4.7 Outcome Page

ANDA: 201355

Reviewer: Ren, Ke **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL, Sun Pharmaceutical Industries, Inc.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
17025	9/29/2010	Other	Study Amendment	1	1
17025	5/30/2012	Other	Study Amendment Without Credit (WC)	0	0
17025	3/4/2010	Other	Study Amendment (Review of Consult Response)	1	1
				Total:	2

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

/s/

KE REN
06/12/2012

APRIL C BRADDY
06/13/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
06/13/2012

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	201355		
Drug Product Name	Nitrofurantoin Oral Suspension USP		
Strength(s)	25 mg/5 mL		
Applicant Name	Sun Pharmaceutical Industries, Inc.		
Address	705 East Mulberry Street Bryan, Ohio 43506		
Applicant's Point of Contact	Anne Toland		
Contact's Telephone Number	1-609-495-2823		
Contact's Fax Number	1-609-495-2711		
Original Submission Date(s)	March 4, 2010		
Submission Date(s) of Amendment(s) Under Review	N/A		
Reviewer	Ke Ren, Ph.D.		
Study Number (s)	PKD_09_521		
Study Type (s)	Fed Study		
Strength (s)	25 mg/5 mL		
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Near R.C. Patel Estate Akota Road, Akota Vadodara- 390 020 (India)		
Analytical Site	Sun Pharmaceutical Industries Ltd.		
Analytical Site Address	Tandalja, Vadodara -390020 Gujarat, India		
Overall Review Result	**INADEQUATE**		
DSI Inspection Status	**INADEQUATE pending DSI inspection for clinical site**		
Bioequivalence Study Tracking/Supporting Document #	**Study /Test Type**	**Strength**	**Review Result**
1	Dissolution	25 mg/5 mL	**INADEQUATE**
1	Fed Study	25 mg/5 mL	**INADEQUATE**

1 EXECUTIVE SUMMARY

This is a First Generic Application.

There is a Draft Guidance on this drug product on a public website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM148222.pdf (posted on April 2009). As per this guidance the DBE requests only **a fed BE study** on this drug product (no fasting BE study).

This application contains the result of a fed BE study comparing a test product, Sun Pharmaceutical's Nitrofurantoin Oral Suspension USP, 25 mg/5 mL, to the corresponding reference product, FURADANTIN® (Nitrofurantoin) Oral Suspension USP, 25 mg/5 mL, manufactured by Shionogi Pharma (formerly Sciele Pharma Inc). The fed BE study was designed as a single-dose, two-way crossover study in healthy male subjects. The results of the fed study are summarized in the table below.

Nitrofurantoin Oral Suspension Dose (1 x 25 mg/5 mL) Fed Bioequivalence Study No. PKD 09 521, N=28 (male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	883.09	868.88	1.02	98.51	104.86
AUC∞ (ng·hr/mL)	915.62	893.56	1.02	99.57	105.46
Cmax (ng/mL)	371.79	372.31	1.00	90.44	110.26

However, the firm's fed BE study on the 25 mg/5 mL Nitrofurantoin Oral Suspension is **inadequate** due to (b) (4) amount of Glycerin used in the formulation, based on the maximum daily dose of 400 mg. In additional, the firm did not provide breakdown of N&A Fruit Gum Flavor # 960.

There is no "dissolution only" review on this ANDA. There is no USP dissolution method for the test product (Nitrofurantoin Oral Suspension, USP, 25 mg / 5 mL) but there is an FDA-recommended method [900 mL of phosphate buffer, pH 7.2 using Apparatus II (Paddle) at 50 rpm]. The firm conducted its dissolution testing using the FDA-recommended method. However, the firm did not submit individual dissolution data for the 12 dosage units of the test and reference product.

In addition, the dissolution data showed (b) (4) drug release for the test and reference products, indicating possible lack of specificity in the analytical assay. The firm is recommended to do the following: 1) The firm should explain why many of the dissolution data points for the test and reference products are (b) (4) release; 2) To conduct additional dissolution testing using the FDA-recommended dissolution method for both the test and RLD products to confirm the accuracy and reproducibility of the dissolution results.

The inspection for the clinical site was requested by ANDA 091552 (routine inspection) on February 11, 2010. The analytical site was last inspected on June 8, 2010 for ANDA 090178 due to a "for cause" request and the outcome was VAI. During the DSI inspection, form 483 was issued. The reviewer went through the ANDA 090178 DSI inspection report and the firm's responses to the form 483. Those issues are not related to our current ANDA. Therefore, this DSI outcome for analytical site is valid. The application is **incomplete** pending clinical site.
The application is **incomplete**.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Nitrofurantoin Oral Suspension USP, 25 mg/5 mL
Reference Product	Furadantin® Oral Suspension, USP, 25 mg/mL
RLD Manufacturer	Shionogi Pharma
NDA No.	009175
RLD Approval Date	December 23, 1953
Indication[1]	Furadantin is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

3.2 PK/PD Information[1,2]

Bioavailability	Nitrofurantoin is readily absorbed following oral administration. The macrocrystalline form is more slowly absorbed due to a slower rate of dissolution. This form can produce fewer adverse GI effects. Bioavailability, especially of the macrocrystals, can be increased by the presence of any substance that delays gastric emptying such as food.
Food Effect	The RLD labeling states that the presence of food or agents delaying gastric emptying can increase the bioavailability of Furadantin, presumably by allowing better dissolution in gastric juices. Patients should be advised to take Furadantin with food to further enhance tolerance and improve drug absorption.
Tmax	Peak urinary concentrations occur within about 30 minutes after administration of microcrystals, while dosage with macrocrystals takes slightly longer.
Distribution	Protein binding of nitrofurantoin is approximately 20—60%. Nitrofurantoin crosses the placenta and is distributed into breast milk. High concentrations of nitrofurantoin are found in urine.
Metabolism	Oral administered Furadantin is rapidly excreted in urine. Blood concentrations at therapeutic dosage are usually low. It is highly soluble in urine. Nitrofurantoin is bactericidal in urine at therapeutic doses.
Excretion	Urinary concentrations in patients with normal renal function range from 50—250 mcg/ml. Although there is some hepatic metabolism, about 30—50% of the drug is excreted unchanged in the urine within 24 hours of dosage. Nitrofurantoin is eliminated by glomerular filtration and tubular secretion, with some reabsorption.
Half-life	In patients with normal renal function, the plasma half-life is roughly 20 minutes.

[1] http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?id=19082
[2] http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=438&sec=monphar

Drug Specific Issues (if any)	1. **Pulmonary reactions**: Acute, subacute, or chronic pulmonary reactions have been observed in patients treated with Nitrofurantoin. If these reactions occur, Furadantin should be discontinued and appropriate measures taken; Reports have cited pulmonary reactions as a contributing cause of death. Chronic pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) can develop insidiously. These reactions occur rarely and generally in patients receiving therapy for six months or longer. Close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted and requires that the benefits of therapy be weighted against potential risks. 2. **Respiratory:** Chronic, subacute, or acute pulmonary hypersensitivity reactions may occur. Chronic pulmonary reactions may occur generally in patients who have received continuous treatment for six months or longer. Malaise, dyspnea on exertion, cough, and altered pulmonary function are common manifestations which can occur insidiously. Radiologic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations of the chronic pulmonary reaction. Fever is rarely prominent. The severity of chronic pulmonary reactions and their degrees of resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be impaired permanently, even after cessation of therapy. The risk is greater when chronic pulmonary reactions are not recognized early. 3. Furadantin is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Nitrofurantoin. 4. Furadantin is also contraindicated in those patients with known hypersensitivity to Nitrofurantoin. 5. The FDA pregnancy risk category of nitrofurantoin is B.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fed

1.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	25 mg/5 mL Nitrofurantoin Oral Suspension
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	None

Analytes to measure (in plasma/serum/blood):	Nitrofurantoin in plasma
Bioequivalence based on:	90% CI for Nitrofurantoin

Waiver request of in-vivo testing:	Not Applicable
Source of most recent recommendations:	Control # 08-0029 (Sun, letter date:12/21/2007) NOTE: **Draft Guidance for the current drug product is found at the end of this review.**
Summary of OGD or DBE History:	According to the current Orange Book, there are no approved generic products for Nitrofurantoin Oral Suspension. The OGD has received and under review the following ANDAs: (b) (4) ANDA 201679 (Amneal Pharma) (b) (4) The OGD has received and reviewed the following control documents for Nitrofurantoin Oral Suspension: 08-0029 and 08-0616 (Sun, 12/21/2007 and 5/23/2008), 08-0738 (b) (4) (b) (4) and 08-1099 (b) (4) Per control correspondence 08-0029 (Sun, letter date:12/21/2007), OGD recommends the following for BE requirements of the drug product: 1. A single-dose fed *in-vivo* bioequivalence study comparing Nitrofurantoin Suspension, 25 mg/5 mL, to the reference listed drug (RLD), Furadantin® Suspension, 25 mg/5 mL. 2. Only the parent drug, nitrofurantoin, should be measured in plasma. 3. DBE recommends that the firm uses the FDA-recommended method for comparative dissolution testing using 12 dosage units each of the test and reference product.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	0
Single-dose fed	No	1
Steady-state	No	0
In vitro dissolution	Yes	1
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical Method Validation Report location	**Report No.: MV_NFT_199A; 5-3-1-4 (method-validation-report); Page: 1 – 72**
Analyte	Nitrofurantoin
Internal Standard (IS)	(b) (4)
Method Description	Extraction method: Refer Method Validation report (MV_NFT_199A); Page No.14 (Solid Phase Extraction); Analytical method: LC-MS/MS
Limit of quantitation	LLOQ : 10.0ng/mL ULOQ : 1003.9ng/mL
Average recovery of analyte (%)	QC Low A: 47.2%, %CV: 11.5 QC Low B: 56.4%, %CV: 5.9 QC Med A: 59.6%, %CV: 8.3 QC Med B: 56.5%,%CV: 5.4 QC High : 66.7%, %CV: 2.3
Average recovery of IS (%)	90.4%, %CV: 6.4
Standard curve concentrations (ng/mL)	10.0, 20.1, 80.3, 175.7, 451.8, 652.6, 803.2, 1003.9
QC Concentrations (ng/mL)	Low QC A: 29.9 Low QC B: 89.8 Medium QC A : 249.5 Medium QC B : 474.0 High QC : 823.3
QC Intraday precision range (%)	3.2% to 12.9%
QC Intraday accuracy range (%)	92.2% to 108.1%
QC Interday precision range (%)	1.4% to 12.9% & 1.7% to 10.3%
QC Interday accuracy range (%)	92.2% to 109.7% & 86.6% to 108.4%
Bench-top stability (hrs)	6 hours at room temperature
Stock solution stability (days)	18 days @ 2-8°C
Post-Processed stability (hrs)	71 hours @ 10°C ± 2°C
Post Extraction Bench Top Stability	6 hours at room temperature
Freeze-thaw stability (cycles)	03 cycles
Long term storage stability (Days)	59 days @ -20°± 5°C
Dilution Integrity	3 – 4 times of CS8 Concentration (2993.9ng/mL) diluted 10 folds.
	% Accuracy : 1/5th : 105.3
	% Precision : 1/5th : 4.5
Selectivity	No interference observed in blank plasma samples

SOPs submitted	SOP No. ATP_02_NFT Determination of Nitrofurantoin in human plasma using liquid chromatography method with tandem mass spectrometry, effective date November 20, 2009. SOP No. PKD/S/010 Evaluation of stability of drugs in biological matrix and solutions, effective date March 7, 2009. SOP No. PKD/S/013 Bioanalytical method validation, effective date March 7, 2009. SOP No. PKD/S/015 Verification of chromatograms, peak integration and chromatographic acceptance criteria, effective date December 21, 2009. SOP No. PKD/S/019 Sample reanalysis and reporting of final concentrations, effective date August, 10, 2009. SOP No. PKD/S/033 Chromatographic analysis of study sample, effective date November 25, 2009. SOP No. PKD/S/034 Preparation, identification and acceptance criteria of stock solutions, calibration standards, quality control samples, effective date July 3, 2009. SOP No. PKD/S/035 Identification and analysis of incurred sample, effective date July 15, 2009.
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation:

- In the pre-study method validation, human plasma containing the anticoagulant, **K_3EDTA** was used to prepare the calibration standards and quality control (QC) samples. In the fed BE study, the firm used **K_3EDTA** for the collection of the biological samples.
- The firm's long term storage data of 59 days is sufficient to cover the storage period for the fed (28 days) bioequivalence study.
- The pre-study validations data are **complete.**

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Pharmacokinetic Parameters[1] (+/- SD) (Nitrofurantoin) (N=28)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng-hr/mL)	AUC_{0-inf} (ng-hr/mL)	$T_{1/2}$ (hr)	Kel (1/hr)	
PKD_09_521	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Nitrofurantoin 25mg/5ml Oral Suspension of Sun Pharmaceutical Industries Inc., Bryan, OH 43506 and Furadantin® (Nitrofurantoin) 25mg/5ml Oral Suspension of Sciele Pharma, Inc. Atlanta, GA 30328, in 30 healthy human adult subjects, under fed conditions.	A Randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study with 9 days washout period between each drug administration under fed conditions	Test: Nitrofurantoin 25mg/5ml / Oral Suspension /Oral Lot No.: B1127	28 healthy male subjects (28/0) Mean age (Range) : 29.8 (22 – 44)	387.45 +/- 126.223 (32.6)	1.62 (0.25 – 4.25)	898.8058 +/- 127.96007 (14.2)	925.3354 +/- 127.49995 (13.8)	0.8107 +/- 0.23555 (29.1)	0.91741 +/- 0.237731 (25.9)	Section 5.3.1.2 (Section 2 Synopsis)
			Reference: Furadantin® (Nitrofurantoin) 25mg/5ml / Oral Suspension /Oral Lot No.: CN 437034		380.15 +/- 100.354 (26.4)	1.00 (0.50 – 2.25)	881.0540 +/- 139.76824 (15.9)	901.9114 +/- 142.36217 (15.8)	0.7546 +/- 0.16531 (21.9)	0.95625 +/- 0.183527 (19.2)	

[1]**Arithmetic mean ± standard deviations (% CV) except for Tmax (Range) for which the median are reported**

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer using CALKE.

Nitrofurantoin Oral Suspension Dose (1 x 25 mg/5 mL) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. PKD_09_521				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	883.09	868.88	1.02	98.51- 104.86
AUC∞ (hr *ng/ml)	915.62	893.56	1.02	99.57- 105.46
Cmax (ng/ml)	371.79	372.31	1.00	90.44- 110.26

Table 3. Reanalysis of Study Samples

Study No. PKD_09_521 Nitrofurantoin								
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[2]**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Unacceptable internal standard response	4	5	0.30	0.37	4	4	0.30	0.30
Incomplete analysis	3	1	0.22	0.07	3	1	0.22	0.07
Sample reanalyzed to obtain confirming value	1	0	0.07	0.00	1	0	0.07	0.00
Inconsistent Profile	1	1	0.07	0.07	0	1	0.00	0.07
Rejected analytical run	96	96	7.15	7.15	95	96	7.07	7.15
Total	**105**	**103**	**7.82**	**7.67**	**103**	**102**	**7.67**	**7.59**

Did use of recalculated plasma concentration data change study outcome?

No.

Comments from the Reviewer:

- Nine samples for nitrofurantoin were reanalyzed due to "unacceptable internal standard response" from the fed study. The SOP (Sample reanalysis and reporting of final concentrations) defines the unacceptable internal standard response as following: *any study sample analysis presenting an internal standard response beyond ± 30% (for HPLC methods) and ± 50% (for LC/MS/MS method) of mean internal standard response of accepted calibration standards and with in acceptance quality control samples shall be repeat, if sample volume is sufficient to carry out repeat analysis.* . The reviewer checked the reassays for those subjects coded with this reason. All of the reanalysis samples met this criterion.

- There are total 192 samples (T + R) that were re-analyzed under the reason of "rejected analytical run" from fed study. They were all from 4 runs: subject No. (b) (6) The reasons for rejected analytical runs were: 67% of total QCs did not meet acceptance criteria or both MQC did not meet acceptance criteria.

- Two samples (T + R) were re-analyzed under the reason "inconsistent profile" and one sample was re-analyzed under the reason "sample reanalyzed to obtain confirming value" are deemed PK repeats by the reviewer. For those two "inconsistent profile" values, the firm used the one of the original value and one re-analyzed value in the statistical analysis in the fed study. This reviewer conducted statistical analysis using the original value as shown below in the table.

Detailed PK Repeat Information for Nitrofurantoin

Subject	Period	Time	Original Assay Conc	Repeat Assay Conc	Final Reported Conc
(b) (6)	2	4.25 h	617.0 ng/mL	37.9 ng/mL	37.9 ng/mL
	1	1.0 h	0	572.6 ng/mL	572.6 ng/mL

The reviewer did the SAS analysis using the original value of those two samples. The CIs of the PK parameters are still within the 80-125% limit. The PK repeats did not alter the outcome of the study. Please see the table below for details:

Nitrofurantoin Oral Suspension Dose (1 x 25 mg/5 mL) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. PKD_09_521				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	887.60	872.02	1.02	98.77- 104.89
AUC∞ (hr *ng/ml)	919.66	897.06	1.03	99.66- 105.46
Cmax (ng/ml)	379.24	382.08	0.99	89.75- 109.76

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION INCOMPLETE**
If not acceptable, why?	Pending justifications for its (b) (4) amount of Glycerin and breakdown of N&A Fruit Gum Flavor # 960.

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	There is NO "dissolution only" review for this application. The dissolution data are reviewed in the current application.
Source of Method (USP, FDA or Firm)	FDA
Medium	Phosphate buffer, pH 7.2
Volume (mL)	900 mL
USP Apparatus type	II (paddle)
Rotation (rpm)	50 rpm
Tolerances	(b) (4)
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Incomplete dissolution data
Is method acceptable?	**INADEQUATE**
If not then why?	Pending individual dissolution data for the 12 dosage units

Dissolution Review:

- There is no USP dissolution method for the test product (Nitrofurantoin Oral Suspension, USP, 25 mg / 5 mL) but there is an FDA-recommended method [900 mL of phosphate buffer, pH 7.2 using Apparatus II (Paddle) at 50 rpm]. The firm conducted its dissolution testing using the FDA-recommended method.

- The firm is proposed to manufacture the Nitrofurantoin Oral Suspension 25 mg / 5 mL (b) (4) All bottles came from the same lot (Lot #. B1127). However, the firm did not submit individual dissolution data for the 12 dosage units of the test and reference product. The dissolution testing is **incomplete**.

- Based on the Dissolution Summary Table, the dissolution testing data of the test and reference product show that the both products release more than (b) (4)% at 30 min, 45 min, 60 min, 120 min and 180 min sampling time points (range: (b) (4) (b) (4)% for the test product and (b) (4)%). (b) (4) The reviewer noticed another application (ANDA 201679[3]) shows a different (b) (4) dissolution profiles for the RLD product than that reported in current ANDA. The firm is asked to explain the (b) (4) dissolution results of the test and reference products.

(b) (4)

3.9 Waiver Request(s)

Strengths for which waivers are requested	None
Proportional to strength tested in vivo?	Not Applicable
Is dissolution acceptable?	Not Applicable
Waivers granted?	Not Applicable
If not then why?	

3.10 Deficiency Comments

1. The firm is asked to provide justifications for its (b) (4) amount of **Glycerin** used in the formulation, based on the maximum daily dose of 400 mg.

2. The firm should provide breakdown of N&A Fruit Gum Flavor # 960 use in its formulation.

3. The dissolution data showed (b) (4) drug release for the test and reference products, indicating possible lack of specificity in the analytical assay. The firm is recommended to do the following: 1) The firm should explain why many of the dissolution data points for the test and reference products are (b) (4) (b) (4); 2) To conduct additional dissolution testing using the FDA-recommended dissolution method for both the test and RLD products to confirm the accuracy and reproducibility of the dissolution results; and 3) In the original submission, the firm did not submit the individual dissolution data. Therefore, the firm should submit individual dissolution data for the 12 dosage units of the test and reference product using FDA-recommended dissolution method.

[3] DARRTS ANDA 201679 Dehaven, Wayne I, 07/07/2010 N/A 07/07/2010 REV-BIOEQ-01 (General Review) Archive.

3.11 Recommendations

1. The Division of Bioequivalence finds the fed BE study No. PKD_09_521 **inadequate** due to the reason cited in the Deficiency Comments #1 and 2. The Sun Pharmaceutical conducted the fed BE study on its Nitrofurantoin Oral Suspension, 25 mg/5 mL, lot # B1127, comparing it to Shionogi Pharma's Furadantin® Oral Suspension, 25 mg/mL, lot #437034.

2. The dissolution testing conducted by Novast Sun Pharmaceutical on its Nitrofurantoin Oral Suspension, 25 mg/5 mL comparing them to Furadantin® Oral Suspension, 25 mg/mL, manufactured by Shionogi Pharma, is **incomplete** for the reason provided in the Deficiency Comments #3.

   The firm should conduct and submit dissolution testing on twelve (12) dosage units of test and reference products using the following FDA-recommended method:

USP Apparatus:	II (Paddle)
Speed (rpm):	50
Medium:	pH 7.2 phosphate buffer
Volume (mL):	900

3.12 Comments for Other OGD Disciplines

Discipline	Comment
	The application is incomplete pending DSI inspection for clinical site.

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fed Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	PKD_09_521
Study Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Nitrofurantoin 25mg/5ml Oral Suspension of Sun Pharmaceutical Industries Inc., Bryan, OH 43506 and Furadantin® (Nitrofurantoin) 25mg/5ml Oral Suspension of Sciele Pharma, Inc. Atlanta, GA 30328, in 30 healthy human adult subjects, under fed conditions.
Clinical Site	Sun Pharmaceutical Industries Ltd. Near R.C. Patel Estate, Akota Road, Akota Vadodara – 390 020 (India) Phone No.: 91-265-2339103, 91-265-2330815
Clinical Investigator	Dr. Aman Khanna
Dosing Dates	Period I: 29th December 2009; Period II: 7th January 2010
Analytical Site	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, Gujarat, India. Tel: 91-265-2350789, 91-265-6615500
Analysis Date	From 17th January, 2010 to 25th January, 2010
Analytical Director	Dr. K. Shivram
Storage Period of Biostudy Samples	From 29th December 2009 to 25th January 2010 (28 days)

Table 5. Product information

Product	**Test**	**Reference**
Treatment ID	Treatment A	Treatment B
Product Name	Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL	Manufactured by: Norwich Pharmaceuticals, Inc. North Norwich, New York, 13814 Manufactured for (Applicant): Shionogi Pharma (formerly Sciele Pharma, Inc.
Manufacturer	Sun Pharmaceutical Industries, Inc.	Sciele Pharma, Inc.
Batch/Lot No.	B1127	437034

Manufacture Date	November 6, 2009	N/A
Expiration Date	TBD	August 2010
Strength	25 mg/5 mL	25 mg/5 mL
Dosage Form	Oral Suspension	Oral Suspension
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	101.0%	100.5%
Content Uniformity (mean, %CV)	N/A	N/A
Dose Administered	25 mg (5 mL suspension)*	25 mg (5 mL suspension)*
Route of Administration	Oral	Oral

* - Amneal administered a single dose of 100 mg Nitrofurantoin (20 mL suspension) for it's fed BE study
[See page 17 of DARRTS review for ANDA 201679 DEHAVEN, WAYNE I 07/07/2010 N/A 07/07/2010 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive].

Table 6. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	30(enrolled)/ 28(completed)/28(analyzed)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	9 days
Randomization Scheme	TR: RT: (b) (6)
Blood Sampling Times	Pre-dose and post-dose at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 5.00, 6.00, 8.00, 10.00 and 12.00 hours post-dose.
Blood Volume Collected/Sample	During each study period, 24 blood samples (5 mL each) were collected from each subject by direct vein puncture using pre-labeled Vacutainers® containing **K3EDTA** as an anticoagulant.
Blood Sample Processing/Storage	Samples were collected by direct vein puncture, cooled by an ice bath until processes, and centrifuged within 1.5 hours of collection at approximately 3000 rpm and 4ºC for 10 minutes. Plasma sample were divided in to two aliquots and stored within 2 hours of the blood sampling in suitably labeled polypropylene tubes at -20 ºC± 5 ºC or colder pending sample shipment for sample analysis. Upon completion of the study, the plasma samples were shipped to the bioanalytical laboratory at Sun Pharmaceutical Industries Limited for analysis.
IRB Approval	Protocol approved on November 13, 2009.
Informed Consent	Informed Consent Form approved on November 13, 2009.
Length of Fasting	At least 10 hour prior to breakfast, subjects started the high-calorie high-fat breakfast 30 minutes prior to administration of the study drug. Subjects subsequently fasted for a period of at least 5 hours post dose. Dosing and dispensing was done under sodium lamp light.

Length of Confinement	At least 10 hours prior to dosing until 12 hour post dose in each period
Safety Monitoring	Clinical examinations were performed at the time of screening and during check in and check out of each period of the study. Seated blood pressure, pulse rate were noted at check in, prior to dosing and at 1.0, 2.0, 4.0, 8.0, 12.0 hours (± 30 minutes) post-dosing and at the time of check out in each period. Oral temperature recording were noted at the time of check-in, at pre-dose, 4.0, 12.0 (± 30 minutes) hours post dose and at checkout. Throughout the study, subjects were monitored for adverse events. A physical examination was conducted at the end of the study. At study exit, blood samples were collected for hematology testing, clinical chemistry testing

Standard FDA Meal Used?	No	
If No, then meal components and composition is listed in the tables below		
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat	57.39	577.35
Carbohydrate	27.5	276.60
Protein	15.07	150
Total		1006

Sr. No.	Ingredients	Cooked Wt. (Gms.)	Fat (Gms.)	Carbs. (Gms.)	Protein (Gms.)	Food Energy (Calorie)
1	3 boiled Eggs	297 gm	15	3	18	225
2	Cheddar Cheese 1 Cubic Inch		6	0	4	70
3	2 slices of toast with 2 tbsp butter		24	24	6	330
4	4 Oz. (120 gm) hash brown potatoes		13.9	33.9	3.9	261.5
5	180 mL Milk		5.25	8.25	6	105
	TOTAL		**64.15**	**69.15**	**37.9**	**~1006***
	Calorie (Approx.)		**577.35**	**276.60**	**151.60**	
	FDA Recommended		**500-600**	**250**	**150**	**800-1000**

* Additional 23 Kcal was given in the form of 15 gm sauce (Tomato ketchup) to all the subjects in both the period of study. Hence the total caloric content of fed breakfast was ~ 1029.

Comments on Study Design:

- All subjects completed breakfast within 30 minutes except subject (b) (6) who did not consume complete high-calorie high-fat breakfast. Subject (b) (6) was withdrawn from the study.
- According to the FDA's Guidance for Industry: Food-effect bioavailability and fed bioequivalence studies (posted December 2002), the fed bioequivalence study should be conducted using a high-fat and high-calorie meal. "*A high-fat*

(approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat respectively."

- The firm provided the caloric breakdown and total caloric of the test meal. The firm's test meal met the FDA high-fat and high-calorie meal criteria.
- The study design is adequate.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

		Study No. PKD_09_521 (Fed)	
		Treatment Groups	
		Test Product N= 28	Reference Product N=28
Age (Years)	Mean ± SD	29.8 +/- 5.68	29.8 +/- 5.68
	Range	22 – 44	22 – 44
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18-40	26 (92.86%)	26 (92.86%)
	41-64	2 (7.14%)	2 (7.14%)
	65-75	0 (0.00%)	0 (0.00%)
	>75	0 (0.00%)	0 (0.00%)
Sex	Female	0 (0.00%)	0 (0.00%)
	Male	28 (100%)	28 (100%)
Race	Asian	28 (100%)	28 (100%)
	Black	0 (0.00%)	0 (0.00%)
	Caucasian	0 (0.00%)	0 (0.00%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)
BMI	Mean ± SD	21.62+/- 1.851	21.62+/- 1.851
	Range	19.1 – 24.8	19.1 – 24.8
Other factors		-	-

Subject (b) (6) was withdrawn as subject failed to comply with the requirements of the protocol (Not consumed complete high-calorie high-fat breakfast in Period I).
Subject (b) (6) did not appear for period II.□

Table 8. Dropout Information, Fed Bioequivalence Study

Subject No	Reason for dropout/replacement*	Period	Replaced?	Replaced with
(b) (6)	Not appeared for period II	II	NO	NA
	Fails to comply with the requirements of the	I	NO	NA

	protocol (Not consumed complete high-calorie high-fat breakfast in Period I)			

Table 9. Study Adverse Events, Fed Bioequivalence Studies

	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study No.: PKD_09_521	
Med DRA System Organ Class Preferred Terms	Adverse Events	
	Test n (%)	Reference n (%)
Adverse event considered for both formulation*		
Investigations		
Platelet count decreased	1 (100.0)	
Total	**1 (100.0)**	

* Since laboratory assessment (hematology) was not done after period I until post study assessments and adverse event observed during post study assessment, this adverse event was considered for both the formulation.

Table 10. Protocol Deviations, Fed Bioequivalence Study

Study No.: PKD_09_521		
Type	**Subject(Test)**	**Subject(Reference)**
Additionally 23 Kcal was given in the form of sauce (Tomato ketchup). So the total calorie given was ~1029 Kcal which is more than calorie content defined in the protocol.	(b) (6)	

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. There was no adverse event occurred during the study. Only subject (b) (6) experienced a single post-dose adverse event which was decrease in platelet count. Since laboratory assessment was not done after period I until post study assessments and adverse events observed during post study assessment, this adverse event was considered for both test and reference products.

2. Subject (b) (6) was withdrawn as subject failed to comply with the requirements of the protocol (Not consumed complete high-calorie high-fat breakfast in period I). Subject (b) (6) did not appear for period II. The dropouts are adequate.

3. The handlings of AE and protocol deviations are acceptable.

4. There were some blood sampling time deviations during fed bioequivalence study. The firm used actual sampling times for its PK calculation. The reviewer used schedule sampling times for PK calculation.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. PKD_09_521 (Fed) Analyte Name : Nitrofurantoin								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	10.0	20.1	80.3	175.7	451.8	652.6	803.2	1003.9
Inter Day Precision (% C.V.)	2.4	4.2	4.2	3.6	3.6	4.0	4.2	5.5
Inter Day Accuracy (% Bias)	98.3	103.8	97.6	102.1	102.9	98.0	98.7	98.6
Linearity	0.9950 to 0.9998 (r value)							
Linearity range (ng/mL)	10.0 to 1003.9							
Limit Of Quantitation (ng/mL)	10.0							

Bioequivalence Study No. PKD_09_521 (Fed) Analyte Name : Nitrofurantoin					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	29.6	90.4	251.0	476.9	828.3
Inter Day Precision (% C.V.)	6.6	7.0	8.1	10.6	10.0
Inter Day Accuracy (% Bias)	106.5	108.3	104.7	102.9	106.3

Comments on Study Assay Validation:

These data are acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected (subject (b) (6) (b) (6)

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
PKD/S/019	10-08-2009	Sample reanalysis and Reporting of Final concentrations. (Revision No.: 03)

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Acceptable.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated

Mean plasma concentrations are presented in Table 18 and Figure 1

Fed Bioequivalence Study, Study No. PKD_09_521									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	891.199	14.62	636.47	1148.38	876.470	15.92	645.50	1160.21	1.02
AUC∞ (hr *ng/ml)	923.121	14.20	664.64	1164.89	901.677	15.96	658.73	1174.57	1.02
Cmax (ng/ml)	387.454	32.58	238.80	782.00	380.150	26.40	233.50	636.80	1.02
Tmax* (hr)	1.625	.	0.25	4.25	1.000	.	0.50	2.25	1.63
Kel (hr^{-1})	0.851	31.74	0.26	1.55	0.865	28.51	0.35	1.51	0.98
T1/2 (hr)	0.916	44.20	0.45	2.65	0.879	35.86	0.46	1.99	1.04

* Tmax values are presented as median, range.

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Nitrofurantoin Oral Suspension Dose (1 x 25 mg/5 mL) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. PKD_09_521				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	891.39	873.46	102.05	98.84 - 105.38
AUC∞ (hr *ng/ml)	918.54	893.95	102.75	99.73 - 105.86
Cmax (ng/ml)	371.79	372.31	99.86	90.44 - 110.26

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Nitrofurantoin Oral Suspension Dose (1 x 25 mg/5 mL) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. PKD_09_521				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	883.09	868.88	1.02	98.51- 104.86
AUC∞ (hr *ng/ml)	915.62	893.56	1.02	99.57- 105.46
Cmax (ng/ml)	371.79	372.31	1.00	90.44- 110.26

Table 17. Additional Study Information, Fed Study No. PKD_09_521

Root mean square error, AUC0-t	0.0683	
Root mean square error, AUC∞	0.0629	
Root mean square error, Cmax	0.2168	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	Firm used 28 Reviewer used 28	Firm used 28 Reviewer used 28
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	28	0.97	0.80	0.99
Reference	28	0.97	0.90	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer used a calke SAS program to calculate Kel.
- The arithmetic mean and 90% CI of Cmax calculated by the reviewer agree with firm's calculations.
- 90% CI of AUC0-t and AUC∞ calculated by the review slightly differs from the firm's calculations because the firm used the actual collection time for the calculation of AUC0-t and AUC. The reviewer used the schedule sampling time for the calculation of AUC0-t and AUC.
- In summary, the 90% confidence intervals for lnAUC0-t, lnAUC∞ and lnCmax calculated by both the reviewer and the firm met the criteria for bioequivalence.

Summary and Conclusions, Single-Dose Fed Bioequivalence Study:

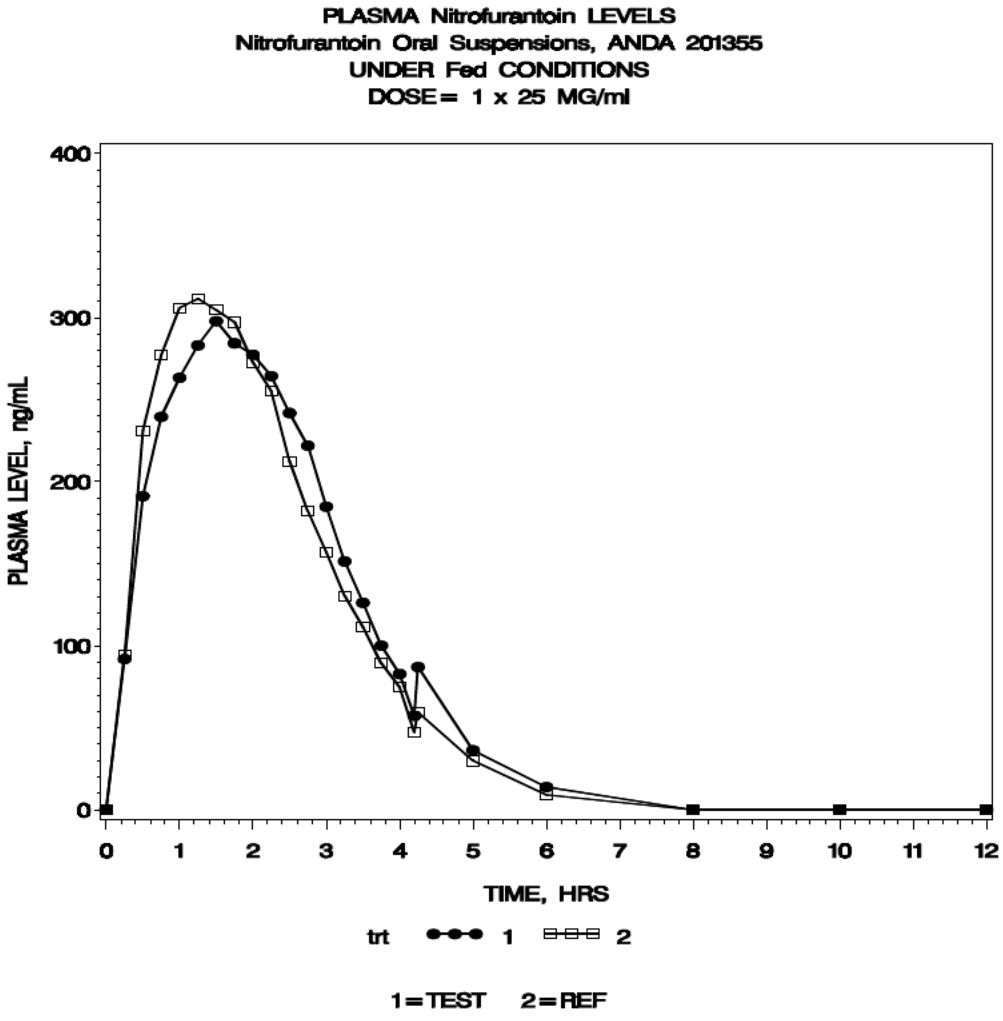
The firm's *in vivo* BE study under fed condition is **incomplete** due to (b) (4) amount of Glycerin in the formulation and lack of individual dissolution data.

Table 18. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Nitrofurantoin					
Time (hr)	Test (n=28)		Reference (n=28)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	91.82	110.67	94.54	107.69	0.97
0.50	191.08	66.47	231.11	62.54	0.83
0.75	239.46	54.29	277.06	45.40	0.86
1.00	263.26	43.68	305.88	34.01	0.86
1.25	283.07	41.19	311.50	26.73	0.91
1.50	297.80	41.34	304.54	25.29	0.98
1.75	284.30	22.99	297.14	28.60	0.96
2.00	277.33	22.22	272.65	29.47	1.02
2.25	264.27	23.78	255.00	34.69	1.04
2.50	241.75	23.06	212.42	35.12	1.14
2.75	221.86	38.51	181.84	35.17	1.22
3.00	184.66	31.79	157.05	34.58	1.18
3.25	151.38	34.01	130.27	36.97	1.16
3.50	126.12	37.47	111.25	42.69	1.13
3.75	100.02	37.53	89.26	43.04	1.12
4.00	82.71	42.98	74.62	45.98	1.11
4.20	57.25	51.48	47.35	49.93	1.21
4.25	86.95	100.46	59.30	43.60	1.47
5.00	36.24	65.45	29.86	54.65	1.21
6.00	13.85	104.86	9.14	115.01	1.52
8.00	0.00	.	0.00	.	.

10.00	0.00	.	0.00	.	.
12.00	0.00	.	0.00	.	.

Figure 1. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Ingredient	Percentage (w/w %)	Percentage (w/v %)	mg/5 mL	Each gram Contains (mg)	Batch Contains (kg)
Nitrofurantoin, USP (b) (4)					(b) (4)
Carboxymethylcellulose Sodium, USP (b) (4)					
Magnesium Aluminum Silicate, NF (b) (4)					
Methylparaben, NF					
Propylparaben, NF					
Sorbitol (b) (4) USP (b) (4)					
Glycerin, USP					
Sucralose, NF (b) (4)					
Sodium Citrate (b) (4) USP					
(b) (4) Citric Acid, USP (b) (4) (b) (4)					
N&A Fruit Gum Flavor # 960 (MN 72)					
Purified Water, USP					
THEORETICAL TOTAL					

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	See comments below

Reviewer's Comments on formulation:

- Per the current RLD label for Nitrofurantoin Oral Suspension, the maximum daily dose is 50- 100 mg four times a day. Therefore, 400 mg of Nitrofurantoin will take per day.
- The amounts of eight inactive ingredients in the formulation are below those used in the approved drug products based on CDER's Inactive Ingredient Guide (IIG) for Approved Drug Products based on MDD. However, the amount of one inactive ingredient, **Glycerin**, in the test formulation (b) (4) based on the basis of MDD of the approved drug products (see table below).

Inactive Ingredient	Maximum amount/day based on MDD of Nitrofurantoin Oral Suspension Amount (mg)	Maximum Level Listed in the FDA IIG Database for Approved Drug Product /Unit	Test formulation Below or Exceed FDA IIG
Carboxymethylcellulose Sodium		(b) (4)	
Magnesium Aluminum Silicate			
Methylparaben, NF			
Propylparaben, NF			
Sorbitol (b) (4)			
Glycerin			
Sucralose			
Sodium Citrate (b) (4)			
(b) (4) Citric Acid			
(b) (4)			

- The firm is asked to provide justifications for its (b) (4) amount of **Glycerin** used in the formulation, based on the maximum daily dose of 400 mg.

- The amount of color additives in N&A Fruit Gum Flavor # 960 is [redacted] (b) (4) and is considered insignificant. However, the firm still needs to provide breakdown of N&A Fruit Gum Flavor # 960.

- The formulation is **incomplete**.

APPEARS THIS WAY IN ORIGINAL

4.3 Dissolution Data

Dissolution Review Path	There is NO "dissolution only" review for this application. **The dissolution data are reviewed in section 3.8.**

Table 19. Dissolution Data

FDA-recommended dissolution method:

Dissolution Conditions	**Method:**	II (Paddles)
	Speed of Rotation:	50 rpm
	Medium:	pH 7.2 Phosphate Buffer
Firm's Proposed Specifications	Must conform to current USP acceptance criteria S_1, S_2 or S_3. Q = (b) (4)% at (b) (4) minutes, acceptance (S_1) = Q + 5%	
Dissolution Testing Site	Sun Pharmaceutical Industries, Inc. 705 East Mulberry Street Bryan, Ohio 43506	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (Minutes) 15	30	60	120	180	Study Report Location
N/A	2/12/2010	**Test Product**: Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL, (b) (4) Sun Pharmaceutical Industries Inc. Lot Number: B1127 Manufacture Date: 12/2009	25 mg/5 mL Oral Suspension	6	% Mean	88.2	101.5	105.0	106.7	106.7	
					% Range	(b) (4)					
					% RSD	7.5	3.9	1.6	1.5	0.7	
	11/19/2009	**Reference Product**: Furandantin Oral Suspension, 25 mg/5 mL Sceile Inc. Lot Number: 437034 Expiry Date: 08/2010			% Mean	98	105.3	107.5	107.8	109.6	
					% Range	(b) (4)					
					% RSD	11.2	2.3	1.1	0.5	1.0	

FDA-recommended dissolution method:

Dissolution Conditions	**Method:**	II (Paddles)
	Speed of Rotation:	50 rpm
	Medium:	pH 7.2 Phosphate Buffer
Firm's Proposed Specifications	Must conform to current USP acceptance criteria S_1, S_2 or S_3. Q = 75% at 120 and 180 minutes, acceptance (S_1) = Q + 5%	
Dissolution Testing Site	Sun Pharmaceutical Industries, Inc. 270 Prospect Plains Road Cranbury, NJ 08512	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Minutes)**					**Study Report Location**
						5	**10**	**15**	**30**	**45**	
N/A	2/12/2010	**Test Product**: Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL, (b) (4) Sun Pharmaceutical Industries Inc. Lot Number: B1127 Manufacture Date: 12/2009	25 mg/5 mL Oral Suspension	6	% Mean	81.5	98.3	104.2	106.9	106.7	
					% Range	73.9-86.5	96.4-99.5	101.3-106.4	106.2-108.6	106.3-107.3	
					% RSD	6.1	1.1	1.8	0.8	0.3	
	2/12/2010	**Reference Product**: Furandantin Oral Suspension, 25 mg/5 mL, 470 mL Sceile Inc. Lot Number: 435328 Expiry Date: 03/2010			% Mean	98.6	101.2	100.9	101.5	106.2	
					% Range	95.1-100.6	95.7-107.8	98.4-104.0	98.7-103.9	102.4-115.3	
					% RSD	2.1	4.4	2.2	2.0	4.4	

Following this page, 2 Pages Withheld in Full as (b)(4)

4.4 Detailed Regulatory History

Contains Nonbinding Recommendations

Draft Guidance on Nitrofurantoin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Nitrofurantoin

Form/Route: Suspension/Oral

Recommended studies: 1 study

Type of study: Fed
Design: Single-dose, two-way, crossover *in-vivo*
Strength: 25 mg/5 mL
Subjects: Healthy males and nonpregnant females, general population.
Additional comments:

Analytes to measure: Nitrofurantoin in plasma

Bioequivalence based on (90% CI): Nitrofurantoin

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please note that a dosage unit is based on the labeled concentration of the suspension product. Please use the dosage unit (5 ml). A total of 12 units from 12 different bottles should be used. Specifications will be determined upon review of the application.

4.5 SAS Output

4.5.1 Fed Study Data

Fed Concentrations Dataset

Obs	sub	per	seq	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17
1	(b) (6)	1	1	A	1	0	175.4	331.0	348.0	371.0	332.0	307.8	261.1	227.2	214.3	185.0	145.4	126.3	91.1	83.2	67.8	54.8
2		2	1	B	1	0	38.6	159.2	224.3	292.3	334.7	358.2	339.8	287.3	387.3	256.6	179.5	147.0	123.4	163.7	133.3	113.7
3		1	1	A	1	0	0.0	24.4	42.5	82.4	113.4	156.0	235.5	313.3	331.4	302.6	262.7	244.8	203.3	186.5	138.3	103.5
4		2	1	B	1	0	0.0	34.3	126.4	268.9	361.1	423.4	406.6	353.8	302.2	242.6	184.6	137.1	94.7	68.5	52.1	46.6
5		1	2	B	1	0	74.6	306.9	379.8	381.6	320.3	297.1	363.7	215.1	323.8	297.9	250.2	208.4	177.2	151.9	134.3	115.5
6		2	2	A	1	0	179.3	358.0	455.6	433.5	450.8	485.9	374.4	292.3	270.5	212.0	186.5	131.1	105.0	83.2	48.1	39.3
7		1	2	B	1	0	30.8	89.5	135.6	159.3	234.8	289.8	352.7	343.0	333.8	325.3	264.0	265.6	220.9	173.9	132.0	93.1
8		2	2	A	1	0	46.6	111.9	199.0	161.6	155.8	259.2	194.3	238.0	328.7	343.1	543.8	339.7	284.7	232.8	153.9	121.4
9		1	1	A	1	0	495.1	473.2	430.1	380.9	302.2	265.5	197.0	169.8	139.1	149.4	120.6	122.9	105.5	90.8	74.2	59.0
10		2	1	B	1	0	516.4	636.8	509.3	450.0	361.7	249.7	213.6	180.0	151.1	110.6	94.8	72.6	58.3	60.8	43.1	30.0
11		1	2	B	1	0	103.3	236.6	255.6	230.8	193.9	195.4	301.7	252.1	212.4	220.2	228.4	210.3	179.4	189.6	150.2	142.1
12		2	2	A	1	0	168.6	314.5	413.1	319.3	320.4	268.3	282.3	342.7	371.8	323.1	223.0	193.3	151.7	124.6	91.9	75.9
13		1	1	A	1	0	33.8	118.5	183.2	239.7	235.7	245.4	265.1	225.8	218.3	207.8	184.2	174.0	142.6	107.2	96.9	75.5
14		2	1	B	1	0	146.5	327.2	370.7	389.4	324.2	260.5	233.0	231.6	179.1	158.2	116.5	97.6	66.8	49.6	48.3	37.0
15		1	2	B	1	0	16.2	117.2	138.1	190.7	261.2	294.4	272.2	296.5	257.8	236.3	205.9	193.8	172.1	149.4	127.4	102.7
16		2	2	A	1	0	139.9	268.8	267.7	261.1	332.6	382.2	361.6	266.9	261.6	235.4	349.9	160.9	138.3	99.2	88.4	62.9
17		1	2	B	1	0	164.7	474.8	555.6	569.2	422.3	350.2	289.4	225.4	162.5	110.9	97.7	79.4	66.6	55.7	46.1	38.8
18		2	2	A	1	0	111.7	268.9	318.0	334.8	400.4	404.0	354.3	296.0	237.4	231.0	198.4	139.6	94.9	83.0	66.5	54.7
19		1	2	B	1	0	51.3	213.0	232.3	214.6	253.5	305.3	335.8	277.1	270.2	240.2	194.6	202.0	162.2	143.8	117.1	90.4
20		2	2	A	1	0	95.2	239.7	297.5	386.9	399.7	358.1	300.0	281.4	244.8	204.5	185.3	142.3	131.4	96.3	81.1	68.9
21		1	1	A	1	0	60.8	288.6	330.5	306.6	240.8	202.2	180.8	170.7	142.6	141.0	104.5	107.7	73.3	78.1	62.9	51.0

Obs	sub	per	seq	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17
22	(b) (6)	2	1	B	1	0	22.7	71.6	140.0	314.5	277.3	314.2	293.3	287.7	287.8	166.4	162.5	145.3	112.0	72.8	55.9	43.8
23		1	2	B	1	0	54.1	232.3	233.5	204.5	146.8	218.0	177.8	164.3	138.2	144.0	112.8	100.7	90.2	84.1	76.3	111.3
24		2	2	A	1	0	159.1	233.4	293.3	257.8	311.2	223.4	193.3	214.3	166.7	166.9	132.3	128.0	100.0	82.3	78.1	64.0
25		1	2	B	1	0	19.1	217.2	243.1	237.1	238.1	230.1	215.2	177.9	155.2	136.1	122.7	123.4	114.0	92.4	79.6	66.3
26		2	2	A	1	0	0.0	50.8	115.1	241.2	288.6	344.2	316.7	278.6	289.5	232.4	252.8	197.8	179.2	159.7	120.2	84.8
27		1	2	B	1	0	29.4	150.5	219.2	246.5	217.3	181.0	198.4	183.8	165.1	136.5	126.8	125.2	119.2	115.0	93.0	79.1
28		2	2	A	1	0	45.7	111.7	158.8	206.1	235.3	277.2	262.6	234.4	234.1	215.2	198.2	163.7	146.6	118.2	109.7	117.8
29		1	1	A	1	0	40.4	83.9	113.5	103.1	107.9	138.7	220.6	315.2	294.9	295.2	295.2	295.1	228.2	217.9	187.8	152.4
30		2	1	B	1	0	15.0	48.6	113.0	177.7	264.3	443.0	524.1	481.0	423.8	352.3	256.7	209.2	214.1	213.0	174.8	139.2
31		1	1	A	1	0	37.6	145.9	185.9	175.8	193.2	226.4	226.3	238.8	230.6	221.8	203.5	196.1	147.4	133.2	106.7	97.1
32		2	1	B	1	0	50.8	217.0	375.3	385.5	459.4	353.6	288.0	247.0	219.2	188.5	154.0	142.4	107.8	92.2	64.3	54.7
33		1	1	A	1	0	33.1	114.0	256.7	244.2	331.0	341.8	376.1	317.9	331.3	344.9	315.3	291.9	236.2	189.0	176.4	167.7
34		2	1	B	1	0	28.1	90.8	197.6	336.0	449.0	476.4	480.0	451.6	471.9	413.0	345.4	241.1	181.5	128.1	91.2	72.6
35		1	2	B	1	0	111.4	228.2	287.5	323.5	275.5	279.1	222.8	205.4	171.9	162.7	129.8	117.7	99.1	82.0	69.3	54.4
36		2	2	A	1	0	110.4	220.6	251.1	268.8	225.5	209.2	225.6	220.0	194.4	175.6	173.8	160.0	139.4	113.8	105.8	77.3
37		1	1	A	1	0	21.5	90.4	114.7	141.2	179.1	252.0	305.4	283.9	272.6	264.0	228.3	184.0	179.4	178.9	144.5	129.0
38		2	1	B	1	0	75.4	361.1	468.8	439.3	389.1	292.9	271.1	275.3	264.4	226.1	206.3	175.6	157.6	129.2	90.4	62.7
39		1	1	A	1	0	0.0	27.8	52.8	139.0	213.7	237.5	276.2	247.2	213.3	217.5	195.3	222.8	201.2	186.6	145.9	151.2
40		2	1	B	1	0	0.0	29.8	71.6	166.0	265.6	272.1	304.6	361.6	352.2	272.6	226.9	191.2	179.7	154.5	117.7	121.1
41		1	2	B	1	0	192.0	326.0	287.9	269.4	.	217.0	251.2	287.2	269.0	252.1	238.0	194.5	165.7	145.2	113.6	93.7
42		2	2	A	1	0	38.3	42.0	85.1	133.9	202.1	227.0	278.2	375.2	320.4	337.2	312.6	266.7	223.4	187.3	137.7	106.5
43		1	2	B	1	0	123.0	234.6	297.8	296.4	303.5	228.6	194.5	190.4	159.6	148.7	127.7	109.3	80.7	44.6	36.7	26.4
44		2	2	A	1	0	15.8	86.7	131.3	113.6	152.5	176.1	246.8	245.8	270.0	244.4	218.9	165.1	149.7	111.9	63.6	47.3
45		1	1	A	1	0	43.5	240.0	304.8	325.4	302.9	279.9	341.3	274.2	278.9	242.0	214.4	179.8	159.9	130.9	92.6	65.7
46		2	1	B	1	0	140.8	233.9	337.4	434.0	405.2	399.2	279.7	257.2	200.0	165.2	126.6	89.0	64.3	47.0	33.4	28.9
47		1	2	B	1	0	107.8	150.3	170.2	184.4	259.1	308.0	309.7	270.5	272.1	217.1	195.7	155.5	132.2	114.4	96.2	71.0

Obs	sub	per	seq	treat	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17
48	(b) (6)	2	2	A	1	0	17.8	69.6	104.5	287.9	285.0	346.9	403.0	440.1	399.4	276.0	184.1	152.1	105.6	80.9	62.2	43.9
49		1	2	B	1	0	142.1	264.8	260.4	236.8	220.2	231.1	190.7	193.9	195.7	190.1	172.1	168.1	152.2	153.7	125.8	95.0
50		2	2	A	1	0	31.9	108.4	162.8	206.2	264.1	268.2	247.5	277.4	294.4	249.7	220.4	234.0	184.2	127.8	97.0	70.8
51		1	1	A	1	0	221.3	393.7	405.9	415.4	351.7	782.0	392.1	379.5	296.3	248.5	174.6	126.1	98.6	67.6	59.7	51.3
52		2	1	B	1	0	161.5	480.4	477.5	414.6	404.6	403.2	362.4	314.8	216.8	163.6	131.2	100.4	70.3	49.9	40.3	29.0
53		1	2	B	1	0	188.1	377.0	350.4	367.6	348.5	283.7	259.8	240.2	243.2	150.2	142.2	132.7	101.7	85.1	74.4	69.4
54		2	2	A	1	0	98.0	133.7	165.4	261.4	311.6	361.8	355.2	341.5	299.7	279.1	208.5	165.7	119.3	86.0	68.3	54.3
55		1	1	A	1	0	150.2	400.0	518.0	572.6	686.7	311.5	287.1	257.2	252.7	223.7	179.5	159.0	118.5	94.4	74.4	68.0
56		2	1	B	1	0	43.5	161.5	298.7	384.0	419.4	371.8	388.1	382.5	353.7	263.8	297.9	262.2	183.7	105.0	82.5	60.8

Obs	c18	c19	c20	c21	c22	c23	c24	KE_FIRST	KE_LAST	trt
1	45.5	32.5	18.9	10.3	0	0	0	18	21	1
2	86.6	59.5	33.5	17.0	0	0	0	18	21	2
3	68.5	54.6	35.7	12.5	0	0	0	18	21	1
4	39.5	28.8	18.0	0.0	0	0	0	17	20	2
5	87.2	86.4	48.0	17.0	0	0	0	18	21	2
6	24.4	19.7	16.3	0.0	0	0	0	17	20	1
7	68.0	50.7	26.1	0.0	0	0	0	17	20	2
8	81.0	60.0	28.1	0.0	0	0	0	17	20	1
9	48.0	39.6	25.5	0.0	0	0	0	17	20	1
10	28.2	23.2	17.0	0.0	0	0	0	17	20	2
11	104.7	94.9	62.6	42.8	0	0	0	18	21	2
12	58.2	48.1	32.0	17.4	0	0	0	18	21	1
13	73.4	50.8	29.9	17.7	0	0	0	18	21	1
14	30.3	25.5	15.1	0.0	0	0	0	17	20	2
15	89.8	76.8	41.2	18.3	0	0	0	18	21	2

Obs	c18	c19	c20	c21	c22	c23	c24	KE_FIRST	KE_LAST	trt
16	50.4	40.3	28.0	11.5	0	0	0	18	21	1
17	37.5	32.1	23.6	11.7	0	0	0	18	21	2
18	49.0	42.8	29.6	17.9	0	0	0	18	21	1
19	78.2	64.1	54.1	15.8	0	0	0	18	21	2
20	49.5	40.3	21.5	0.0	0	0	0	17	20	1
21	492.8	30.9	19.6	11.4	0	0	0	18	21	1
22	37.9	24.3	15.3	0.0	0	0	0	17	20	2
23	74.0	61.7	40.6	12.4	0	0	0	18	21	2
24	58.4	42.7	28.8	13.2	0	0	0	18	21	1
25	65.8	40.8	29.9	10.0	0	0	0	18	21	2
26	78.0	55.5	32.6	11.3	0	0	0	18	21	1
27	87.2	78.1	61.4	20.0	0	0	0	18	21	2
28	114.4	106.4	55.3	26.0	0	0	0	18	21	1
29	147.4	130.9	89.1	34.9	0	0	0	18	21	1
30	104.3	80.9	39.7	14.3	0	0	0	18	21	2
31	83.7	81.7	55.7	53.2	0	0	0	18	21	1
32	41.2	32.8	33.3	0.0	0	0	0	17	20	2
33	134.2	83.9	45.7	18.2	0	0	0	18	21	1
34	53.2	35.5	25.0	11.0	0	0	0	18	21	2
35	40.3	34.0	21.7	0.0	0	0	0	17	20	2
36	61.3	50.3	16.3	0.0	0	0	0	17	20	1
37	99.3	75.2	50.1	36.1	0	0	0	18	21	1
38	57.2	44.8	24.4	0.0	0	0	0	17	20	2
39	172.3	134.1	108.8	39.0	0	0	0	18	21	1
40	92.2	88.0	49.0	14.3	0	0	0	18	21	2
41	75.8	56.7	46.9	26.4	0	0	0	18	21	2

Obs	c18	c19	c20	c21	c22	c23	c24	KE_FIRST	KE_LAST	trt
42	115.1	94.7	87.6	33.8	0	0	0	18	21	1
43	19.5	16.0	0.0	0.0	0	0	0	16	19	2
44	34.5	38.9	21.4	0.0	0	0	0	17	20	1
45	63.7	51.1	31.5	13.0	0	0	0	18	21	1
46	19.8	15.4	0.0	0.0	0	0	0	16	19	2
47	63.7	42.8	24.5	12.4	0	0	0	18	21	2
48	32.8	23.8	15.1	0.0	0	0	0	17	20	1
49	60.9	42.1	28.7	0.0	0	0	0	17	20	2
50	53.6	39.5	25.7	0.0	0	0	0	17	20	1
51	45.8	54.2	18.5	0.0	0	0	0	17	20	1
52	24.1	17.3	11.1	0.0	0	0	0	17	20	2
53	53.3	40.2	24.7	12.5	0	0	0	18	21	2
54	36.9	34.3	20.2	0.0	0	0	0	17	20	1
55	62.4	46.3	27.1	10.3	0	0	0	18	21	1
56	39.9	32.3	20.7	0.0	0	0	0	17	20	2

4.5.2 Fed Study Output

Fed STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	28	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	56
Number of Observations Used	56

Fed STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	1.16456889	0.04015755	8.62	<.0001
Error	26	0.12117610	0.00466062		
Corrected Total	55	1.28574499			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.905754	1.007971	0.068269	6.772884

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.06464093	0.06464093	13.87	0.0010
sub(seq)	26	1.07593164	0.04138199	8.88	<.0001
per	1	0.02032641	0.02032641	4.36	0.0467
trt	1	0.00366991	0.00366991	0.79	0.3830

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.06464093	0.06464093	13.87	0.0010
sub(seq)	26	1.07593164	0.04138199	8.88	<.0001
per	1	0.01901073	0.01901073	4.08	0.0538
trt	1	0.00366991	0.00366991	0.79	0.3830

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.06464093	0.06464093	1.56	0.2225

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01623209	0.01829231	0.89	0.3830

Fed STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	1.19065719	0.04105714	10.39	<.0001
Error	26	0.10277242	0.00395279		
Corrected Total	55	1.29342961			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.920543	0.923935	0.062871	6.804721

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.07867272	0.07867272	19.90	0.0001
sub(seq)	26	1.09264142	0.04202467	10.63	<.0001
per	1	0.01105976	0.01105976	2.80	0.1064
trt	1	0.00828329	0.00828329	2.10	0.1597

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.07867272	0.07867272	19.90	0.0001
sub(seq)	26	1.09264142	0.04202467	10.63	<.0001
per	1	0.00968174	0.00968174	2.45	0.1297
trt	1	0.00828329	0.00828329	2.10	0.1597

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.07867272	0.07867272	1.87	0.1829

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.02438643	0.01684606	1.45	0.1597

Fed STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	2.81439300	0.09704803	2.06	0.0327
Error	26	1.22232213	0.04701239		
Corrected Total	55	4.03671513			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.697199	3.667261	0.216823	5.912407

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.47864919	0.47864919	10.18	0.0037
sub(seq)	26	2.06120533	0.07927713	1.69	0.0947
per	1	0.27451163	0.27451163	5.84	0.0230
trt	1	0.00002685	0.00002685	0.00	0.9811

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.47864919	0.47864919	10.18	0.0037
sub(seq)	26	2.06120533	0.07927713	1.69	0.0947
per	1	0.27349803	0.27349803	5.82	0.0232
trt	1	0.00002685	0.00002685	0.00	0.9811

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.47864919	0.47864919	6.04	0.0210

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.00138838	0.05809689	-0.02	0.9811

ANDA 201355 Fed Firm to Reviewer Ratio

Obs	sub (b) (6)	per	seq	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1		1	1	1	1	869.25	885.98	371.0	A	873.24	885.51	371.0	1.00459	0.99948	1
2		2	1	1	2	954.35	1004.29	387.3	B	962.31	980.18	387.3	1.00835	0.97599	1
3		1	1	1	1	750.86	821.27	331.4	A	755.78	768.62	331.4	1.00655	0.93589	1
4		2	1	1	2	797.68	833.66	423.4	B	800.90	818.35	423.4	1.00404	0.98164	1
5		1	2	1	2	1092.40	1136.14	381.6	B	1098.28	1114.06	381.6	1.00538	0.98056	1
6		2	2	1	1	1042.72	1065.21	485.9	A	1043.94	1059.55	485.9	1.00116	0.99468	1
7		1	2	1	2	897.28	1069.73	352.7	B	903.56	924.13	352.7	1.00700	0.86389	1
8		2	2	1	1	970.47	1217.64	543.8	A	978.40	997.82	543.8	1.00818	0.81947	1
9		1	1	1	1	923.68	965.42	495.1	A	927.05	957.23	495.1	1.00365	0.99152	1
10		2	1	1	2	953.02	973.92	636.8	B	954.70	975.27	636.8	1.00176	1.00139	1
11		1	2	1	2	949.30	1136.67	301.7	B	955.61	1033.37	301.7	1.00665	0.90912	1
12		2	2	1	1	1057.48	1091.85	413.1	A	1061.41	1086.69	413.1	1.00372	0.99528	1
13		1	1	1	1	750.58	808.17	265.1	A	757.10	780.23	265.1	1.00869	0.96542	1
14		2	1	1	2	777.68	800.43	389.4	B	779.96	796.62	389.4	1.00293	0.99525	1
15		1	2	1	2	841.99	932.79	296.5	B	849.28	870.06	296.5	1.00866	0.93275	1
16		2	2	1	1	970.45	992.16	382.2	A	973.81	987.48	382.2	1.00346	0.99527	1
17		1	2	1	2	970.20	987.13	569.2	B	972.29	989.83	569.2	1.00215	1.00274	1
18		2	2	1	1	954.94	988.96	404.0	A	957.85	988.54	404.0	1.00305	0.99958	1
19		1	2	1	2	914.30	962.05	335.8	B	917.91	937.49	335.8	1.00395	0.97447	1
20		2	2	1	1	906.94	951.90	399.7	A	911.14	929.90	399.7	1.00463	0.97689	1
21		1	1	1	1	719.73	746.06	492.8	A	790.71	808.33	492.8	1.09862	1.08346	1

Obs	sub	per	seq	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
22	(b) (6)	2	1	1	2	710.97	752.97	314.5	B	714.36	728.37	314.5	1.00477	0.96733	1
23		1	2	1	2	645.50	681.55	233.5	B	650.51	662.24	233.5	1.00776	0.97167	1
24		2	2	1	1	755.40	782.22	311.2	A	759.84	776.71	311.2	1.00588	0.99295	1
25		1	2	1	2	670.67	697.62	243.1	B	676.05	685.81	243.1	1.00803	0.98306	1
26		2	2	1	1	851.50	879.87	344.2	A	858.31	868.97	344.2	1.00800	0.98761	1
27		1	2	1	2	699.77	784.25	246.5	B	703.64	724.94	246.5	1.00553	0.92438	1
28		2	2	1	1	822.94	952.91	277.2	A	831.80	861.22	277.2	1.01077	0.90378	1
29		1	1	1	1	933.97	6348.13	315.2	A	942.71	981.96	315.2	1.00936	0.15468	1
30		2	1	1	2	1096.10	1180.42	524.1	B	1105.79	1118.35	524.1	1.00884	0.94741	1
31		1	1	1	1	807.31	1139.05	238.8	A	811.51	929.45	238.8	1.00520	0.81598	1
32		2	1	1	2	879.66	952.37	459.4	B	880.85	925.38	459.4	1.00135	0.97166	1
33		1	1	1	1	1111.99	1188.19	376.1	A	1125.26	1143.38	376.1	1.01194	0.96228	1
34		2	1	1	2	1160.21	1186.10	480.0	B	1164.44	1178.42	480.0	1.00365	0.99352	1
35		1	2	1	2	730.54	774.66	323.5	B	733.33	757.83	323.5	1.00382	0.97827	1
36		2	2	1	1	749.34	791.10	268.8	A	756.09	767.37	268.8	1.00901	0.97000	1
37		1	1	1	1	843.50	1202.54	305.4	A	850.88	912.83	305.4	1.00875	0.75908	1
38		2	1	1	2	1003.61	1055.65	468.8	B	1008.53	1029.79	468.8	1.00490	0.97551	1
39		1	1	1	1	866.94	2512.11	276.2	A	876.46	923.26	276.2	1.01099	0.36752	1
40		2	1	1	2	865.27	921.37	361.6	B	871.75	883.53	361.6	1.00749	0.95893	1
41		1	2	1	2	970.68	1037.50	326.0	B	975.01	1013.30	326.0	1.00447	0.97667	1
42		2	2	1	1	961.16	1621.85	375.2	A	965.29	1017.63	375.2	1.00429	0.62745	1
43		1	2	1	2	652.18	676.89	303.5	B	657.50	672.41	303.5	1.00816	0.99338	1
44		2	2	1	1	636.47	748.04	270.0	A	638.44	658.81	270.0	1.00309	0.88072	1

Obs	sub	per	seq	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
45	(b) (6)	1	1	1	1	929.43	959.77	341.3	A	934.26	948.54	341.3	1.00520	0.98830	1
46		2	1	1	2	812.05	833.11	434.0	B	817.33	830.62	434.0	1.00650	0.99701	1
47		1	2	1	2	804.22	833.13	309.7	B	810.10	824.25	309.7	1.00731	0.98934	1
48		2	2	1	1	833.00	876.16	440.1	A	835.65	848.56	440.1	1.00319	0.96850	1
49		1	2	1	2	781.53	862.83	264.8	B	786.36	810.37	264.8	1.00618	0.93920	1
50		2	2	1	1	791.65	899.95	294.4	A	795.84	818.40	294.4	1.00529	0.90938	1
51		1	1	1	1	1148.38	1176.97	782.0	A	1152.48	1171.77	782.0	1.00357	0.99558	1
52		2	1	1	2	968.46	982.22	480.4	B	970.41	980.37	480.4	1.00201	0.99812	1
53		1	2	1	2	902.44	924.13	377.0	B	906.73	922.55	377.0	1.00475	0.99828	1
54		2	2	1	1	852.01	897.29	361.8	A	854.51	873.52	361.8	1.00294	0.97351	1
55		1	1	1	1	1141.52	1158.11	686.7	A	1146.81	1157.14	686.7	1.00464	0.99916	1
56		2	1	1	2	1039.16	1087.46	419.4	B	1042.04	1065.64	419.4	1.00277	0.97993	1

ANDA 201355 fed reviewer-calculated pharmacokinetic dataset

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
1	(b) (6)	1	1	1	1	869.25	885.98	371.0	1.00	1.126	0.61575
2		2	1	2	1	954.35	1004.29	387.3	2.25	2.036	0.34037
3		1	1	1	1	750.86	821.27	331.4	2.25	3.904	0.17753
4		2	1	2	1	797.68	833.66	423.4	1.50	1.386	0.50025
5		1	2	2	1	1042.72	1065.21	485.9	1.50	0.956	0.72480
6		2	2	1	1	1092.40	1136.14	381.6	1.00	1.784	0.38858
7		1	2	2	1	970.47	1217.64	543.8	2.75	6.097	0.11368
8		2	2	1	1	897.28	1069.73	352.7	1.75	4.580	0.15135
9		1	1	1	1	923.68	965.42	495.1	0.25	1.135	0.61090
10		2	1	2	1	953.02	973.92	636.8	0.50	0.852	0.81354
11		1	2	2	1	1057.48	1091.85	413.1	0.75	1.369	0.50634
12		2	2	1	1	949.30	1136.67	301.7	1.75	3.035	0.22842
13		1	1	1	1	750.58	808.17	265.1	1.75	2.256	0.30729
14		2	1	2	1	777.68	800.43	389.4	1.00	1.044	0.66388
15		1	2	2	1	970.45	992.16	382.2	1.50	1.309	0.52969
16		2	2	1	1	841.99	932.79	296.5	2.00	3.439	0.20153
17		1	2	2	1	954.94	988.96	404.0	1.50	1.317	0.52624
18		2	2	1	1	970.20	987.13	569.2	1.00	1.003	0.69129
19		1	2	2	1	906.94	951.90	399.7	1.25	1.450	0.47813
20		2	2	1	1	914.30	962.05	335.8	1.75	2.095	0.33085
21		1	1	1	1	719.73	746.06	492.8	4.25	1.601	0.43301
22		2	1	2	1	710.97	752.97	314.5	1.00	1.903	0.36431
23		1	2	2	1	755.40	782.22	311.2	1.25	1.409	0.49205
24		2	2	1	1	645.50	681.55	233.5	0.75	2.015	0.34401
25		1	2	2	1	851.50	879.87	344.2	1.50	1.740	0.39833
26		2	2	1	1	670.67	697.62	243.1	0.75	1.868	0.37098
27		1	2	2	1	822.94	952.91	277.2	1.50	3.465	0.20003
28		2	2	1	1	699.77	784.25	246.5	1.00	2.928	0.23674
29		1	1	1	1	933.97	6348.13	315.2	2.00	107.530	0.00645
30		2	1	2	1	1096.10	1180.42	524.1	1.75	4.087	0.16958
31		1	1	1	1	807.31	1139.05	238.8	2.00	4.322	0.16037
32		2	1	2	1	879.66	952.37	459.4	1.25	1.513	0.45804
33		1	1	1	1	1111.99	1188.19	376.1	1.75	2.902	0.23883

Obs	sub (b) (6)	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
34		2	1	2	1	1160.21	1186.10	480.0	1.75	1.632	0.42484
35		1	2	2	1	749.34	791.10	268.8	1.00	1.776	0.39028
36		2	2	1	1	730.54	774.66	323.5	1.00	1.410	0.49175
37		1	1	1	1	843.50	1202.54	305.4	1.75	6.894	0.10054
38		2	1	2	1	1003.61	1055.65	468.8	0.75	1.478	0.46885
39		1	1	1	1	866.94	2512.11	276.2	1.75	29.240	0.02371
40		2	1	2	1	865.27	921.37	361.6	2.00	2.719	0.25492
41		1	2	2	1	961.16	1621.85	375.2	2.00	13.549	0.05116
42		2	2	1	1	970.68	1037.50	326.0	0.50	1.755	0.39505
43		1	2	2	1	636.47	748.04	270.0	2.25	3.614	0.19182
44		2	2	1	1	652.18	676.89	303.5	1.25	1.071	0.64731
45		1	1	1	1	929.43	959.77	341.3	1.75	1.618	0.42847
46		2	1	2	1	812.05	833.11	434.0	1.00	0.948	0.73109
47		1	2	2	1	833.00	876.16	440.1	2.00	1.981	0.34985
48		2	2	1	1	804.22	833.13	309.7	1.75	1.616	0.42886
49		1	2	2	1	791.65	899.95	294.4	2.25	2.921	0.23731
50		2	2	1	1	781.53	862.83	264.8	0.50	1.963	0.35304
51		1	1	1	1	1148.38	1176.97	782.0	1.50	1.071	0.64710
52		2	1	2	1	968.46	982.22	480.4	0.50	0.859	0.80675
53		1	2	2	1	852.01	897.29	361.8	1.50	1.554	0.44608
54		2	2	1	1	902.44	924.13	377.0	0.50	1.203	0.57609
55		1	1	1	1	1141.52	1158.11	686.7	1.25	1.117	0.62071
56		2	1	2	1	1039.16	1087.46	419.4	1.25	1.617	0.42855

BIOEQUIVALENCE DEFICIENCIES

ANDA: 201355

APPLICANT: Sun Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL

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

1. Based on the data available to the Agency, the maximum daily intake of Glycerin calculated from approved oral drug products is [redacted] (b) (4) For your formulation, based on the maximum daily dose of 400 mg of nitrofurantoin recommended for the drug product (as stated in the labeling of the Reference Listed Drug (RLD) product, Furadantin® (Nitrofurantoin) Oral Suspension), the total daily intake of Glycerin from your test formulation [redacted] (b) (4) the approved daily intake amount mentioned above. Please provide justifications for the amount of Glycerin used in the test formulation, and additional data and/or evidence demonstrating that the proposed amount of this excipient in your test formulation is safe.

2. Please provide the quantitative composition of N&A Fruit Gum Flavor # 960 used in your formulation.

3. Your dissolution testing is incomplete. You did not submit the ***individual*** dissolution data for the 12 dosage units of the test and reference product. Please submit these data. In addition, the dissolution data showed unusually high drug release for the test and RLD products (i.e., many values were substantially greater than 100%), indicating a possible lack of specificity in the analytical assay. Please explain the unusually high dissolution values for the test and RLD products, and provide complete validation data and report for the analytical method used in the dissolution testing. Also, please conduct additional dissolution testing using the FDA-recommended dissolution method for both the test and RLD products to confirm the accuracy and reproducibility of the dissolution results.

Sincerely yours,

{See appended electronic signature page}

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

4.6 Outcome Page

ANDA 0201355

Reviewer: Ren, Ke **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL, Sun Pharmaceutical Industries, Inc.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11561	3/4/2010	Bioequivalence Study	Fed Study	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201355	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES INC	NITROFURANTOIN

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

/s/

KE REN
07/14/2010

SHRINIWAS G NERURKAR
07/14/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/19/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201355Orig1s000

OTHER REVIEWS

Medical Consultation
Nitrofurantoin Oral Suspension 25 mg/5mL

RLD:	Furadantin® (nitrofurantoin) Oral Suspension 25 mg/5 mL NDA 009175 Shionogi Inc
Sponsor:	ANDA 201355 Sun Pharmaceuticals
To:	Ke Ren, PhD Reviewer, Division of Bioequivalence I (DBI) Office of Generic Drugs Hoainhon Nyugen, PhD Acting Deputy Director, DBI Office of Generic Drugs
Thru:	John Peters, M.D. Director, Division of Clinical Review (DCR) Office of Generic Drugs
Reviewer:	Linda Forsyth, M.D. Medical Officer, DCR Office of Generic Drugs (OGD)
Drug Class:	Antibacterial agent
Chemical Name:	1-[[(5-nitro-2-furanyl)methylene]amino]-2,4-imidazolidinedione
Date Received:	March 1, 2012
Review Completion Date:	May 10, 2012

Reason for Consultation: "Request opinion on the safety and clinical significance of the (b) (4) amount of the inactive ingredient[i] glycerin used in the test formulation of ANDA 201355, nitrofurantoin oral suspension, 25 mg/5mL."

Recommendation: The amount of glycerin contained in ANDA 201355 is acceptable.

Regulatory Background: A consultation request from the Division of Bioequivalence (DB) I was submitted in DARRTS on June 20, 2011 by Ken Re to the Division of Clinical Review (DCR). DCR assigned this consultation request on January 13, 2012.

A letter was issued to the sponsor on July 22, 2010 from the Division of Bioequivalence. The sponsor response regarding the excessive amount of the inactive ingredient is submitted is located in the electronic document room under October 1, 2010, under Supporting Document 4, eCTD Sequence Number 0002.

Furadantin under NDA 009175 was approved on December 23, 1953. There is already one approved generic for nitrofurantoin oral suspension, approved on May 11, 2011, under ANDA 201679.

Medical Officer's Comment: The only approved ANDA for nitrofurantoin oral suspension provides (b) (4) ***of glycerin at maximal daily dose (MDD) as opposed to*** (b) (4) ***for this proposed formulation. The reference listed drug (RLD) by comparison contains*** (b) (4)

Table 1 Orange Book

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Priority Name	Applicant
201679	AB	No	NITROFURANTOIN	SUSPENSION; ORAL	25MG/5ML	NITROFURANTOIN	Amneal Pharm
009175	AB	Yes	NITROFURANTOIN	SUSPENSION; ORAL	25MG/5ML	FURADANTIN	Shionogi Inc

Labeling: Current product labeling was approved on October 27, 2010.
Indications and Usage: Furadantin is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella sp.* and *Enterobacter sp.*

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses. Nitrofurantoins lack the broader tissue distribution of other therapeutic agents approved for urinary tract infections. Consequently, many patients who are treated with Furadantin are predisposed to persistence or reappearance of bacteriuria. Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy. If persistence or reappearance of bacteriuria occurs after treatment with Furadantin, other therapeutic agents with broader tissue distribution should be selected. In considering the use of Furadantin, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antimicrobial resistance when agents with broader tissue distribution are utilized.

Dosage and Administration: Furadantin should be given with food to improve drug absorption and, in some patients, tolerance.

Adults: 50-100 mg four times a day-the lower dosage level is recommended for uncomplicated urinary tract infections.

Medical Officer's Comment: This product is indicated for the treatment of urinary tract infection. The lower dosage of 50 mg is recommended for uncomplicated urinary tract infection, but up to 100 mg can be administered four times daily in adults. The normal course of a treatment is 7 days. However, the label also mentions long-term suppressive therapy in adults. The site of action is the urinary bladder[ii] and the concentration of active drug and active metabolites in the urine is critical to the efficacy of the drug. (b) (4)

Pediatric Patients: 5-7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under one month of age).

(b) (4)

The following table is based on an average weight in each range receiving 5 to 6 mg/kg of body weight per 24 hours, given in four divided doses. It can be used to calculate an average dose of Furadantin oral suspension (25 mg/5 mL) for pediatric patients (one 5-mL teaspoon of Furadantin oral suspension contains 25 mg of nitrofurantoin).

Table 2 Furadantin Pediatric Dosage

Body Weight		Number of Teaspoons
Pounds	**Kilograms**	**4 Times Daily**
15-26	7-11	½ (2.5 ml)
27-46	12-21	1 (5 ml)
47-68	22-30	1 ½ (7.5 ml)
69-91	31-41	2 (10 ml)

Therapy should be continued for one week or for at least 3 days after sterility of the urine is obtained. Continued infection indicates the need for reevaluation.

For long-term suppressive therapy in adults, a reduction of dosage to 50-100 mg at bedtime may be adequate. For long-term suppressive therapy in pediatric patients, doses as low as 1 mg/kg per 24 hours, given in a single dose or in two divided doses, may be adequate. See Warnings section regarding risks associated with long term therapy.

Contraindications:

- Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum

creatinine) are contraindications. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug.

- Because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability), the drug is contraindicated in pregnant patients at term (38-42 weeks gestation), during labor and delivery, or when the onset of labor is imminent. For the same reason, the drug is contraindicated in neonates under one month of age.
- Furadantin is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin. Furadantin is also contraindicated in those patients with known hypersensitivity to nitrofurantoin.

Warnings and Precautions: There are bolded warnings.

- **Pulmonary reactions: ACUTE, SUBACUTE, OR CHRONIC PULMONARY REACTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH NITROFURANTOIN. IF THESE REACTIONS OCCUR, FURADANTIN SHOULD BE DISCONTINUED AND APPROPRIATE MEASURES TAKEN. REPORTS HAVE CITED PULMONARY REACTIONS AS A CONTRIBUTING CAUSE OF DEATH.**
- **CHRONIC PULMONARY REACTIONS (DIFFUSE INTERSTITIAL PNEUMONITIS OR PULMONARY FIBROSIS, OR BOTH) CAN DEVELOP INSIDIOUSLY. THESE REACTIONS OCCUR RARELY AND GENERALLY IN PATIENTS RECEIVING THERAPY FOR SIX MONTHS OR LONGER. CLOSE MONITORING OF THE PULMONARY CONDITION OF PATIENTS RECEIVING LONG-TERM THERAPY IS WARRANTED AND REQUIRES THAT THE BENEFITS OF THERAPY BE WEIGHED AGAINST POTENTIAL RISKS**.
- Hepatotoxicity: Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Fatalities have been reported. The onset of chronic active hepatitis may be insidious, and patients should be monitored periodically for changes in biochemical tests that would indicate liver injury. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken.
- Neuropathy: Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance the occurrence of peripheral neuropathy. Patients receiving long-term therapy should be monitored periodically for changes in renal function.
- Optic neuritis has been reported rarely in postmarketing experience with nitrofurantoin formulations.

- Hemolytic anemia: Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Furadantin; hemolysis ceases when the drug is withdrawn.
- Clostridium difficile-associated diarrhea.
- Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic.
- Patients should be advised not to use antacid preparations containing magnesium trisilicate while taking Furadantin as reduce both the rate and extent of absorption.
- Safety and effectiveness of Furadantin in neonates below the age of one month have not been established.

Adverse Reactions:

Respiratory: CHRONIC, SUBACUTE, OR ACUTE PULMONARY HYPERSENSITIVITY REACTIONS MAY OCCUR. CHRONIC PULMONARY REACTIONS MAY OCCUR GENERALLY IN PATIENTS WHO HAVE RECEIVED CONTINUOUS TREATMENT FOR SIX MONTHS OR LONGER. MALAISE, DYSPNEA ON EXERTION, COUGH, AND ALTERED PULMONARY FUNCTION ARE COMMON MANIFESTATIONS WHICH CAN OCCUR INSIDIOUSLY. RADIOLOGIC AND HISTOLOGIC FINDINGS OF DIFFUSE INTERSTITIAL PNEUMONITIS OR FIBROSIS, OR BOTH, ARE ALSO COMMON MANIFESTATIONS OF THE CHRONIC PULMONARY REACTION. FEVER IS RARELY PROMINENT.

THE SEVERITY OF CHRONIC PULMONARY REACTIONS AND THEIR DEGREES OF RESOLUTION APPEAR TO BE RELATED TO THE DURATION OF THERAPY AFTER THE FIRST CLINICAL SIGNS APPEAR. PULMONARY FUNCTION MAY BE IMPAIRED PERMANENTLY, EVEN AFTER CESSATION OF THERAPY. THE RISK IS GREATER WHEN CHRONIC PULMONARY REACTIONS ARE NOT RECOGNIZED EARLY.

Hepatic: Hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic neurosis, occur rarely.

Neurologic: Peripheral neuropathy, which may become severe or irreversible. Fatalities (renal impairment, anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating diseases may increase the possibility). Asthenia, vertigo, nystagmus, dizziness, headache, and drowsiness, benign intracranial hypertension, confusion, depression, optic neuritis, psychotic reactions, and bulging fontanels in infants.

Dermatologic: Exfoliative dermatitis, erythema multiforme (including Stevens-Johnson syndrome), transient alopecia.
Allergic: Lupus-like syndrome associated with pulmonary reactions, angioedema, maculopapular, erythematous, or eczematous eruptions, pruritus, urticaria, anaphylaxis, arthralgia, myalgia, drug fever, chills, hypersensitivity.
Gastrointestinal: Nausea, emesis, anorexia, abdominal pain, diarrhea, sialadenitis, pancreatitis, pseudomembranous colitis symptoms.
Hematologic: Cyanosis secondary to methemoglobinemia.
Miscellaneous: Superinfections caused by resistant organisms, e.g., *Pseudomonas* species or *Candida; Clostridium difficile* superinfections, or pseudomembranous colitis.
Laboratory Adverse Events: Increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, glucose-6-phosphate dehydrogenase deficiency anemia, agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia (most resolved following cessation of therapy), aplastic anemia.

Pregnancy Category: B
Nursing Mothers: Nitrofurantoin has been detected in human breast milk in trace amounts. Because of the potential for serious adverse reactions from nitrofurantoin in nursing infants under one month of age, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Inactive Ingredients: Furadantin oral suspension contain carboxymethylcellulose sodium, citric acid, flavors, glycerin, magnesium aluminum silicate, methylparaben, propylparaben, purified water, saccharin, sodium citrate, and sorbitol.

Medical Officer's Comment: The formulation is shown in the table below (P. 8).

How Supplied: Furadantin oral suspension is available in: NDC 59630-450-08 glass amber bottle of 230mL.

Mechanism of Action: The antibiotic nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of such inactivations, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis, and cell wall synthesis are inhibited. The broad-based nature of this mode of action may explain the lack of acquired bacterial resistance to nitrofurantoin, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria.

Pharmacokinetics: Orally administered Furadantin is readily absorbed and rapidly excreted in urine. Blood concentrations at therapeutic dosage are usually low. It is highly soluble in urine, to which it may impart a brown color. Following a dose regimen of 100 mg four times daily (q.i.d). for 7 days, average urinary

drug recoveries (0-24 hours) on day 1 and day 7 were 42.7% and 43.6%. Unlike many drugs, the presence of food or agents delaying gastric emptying can increase the bioavailability of Furadantin, presumably by allowing better dissolution in gastric juices.

Discussion:

Glycerin is also known as glycerol. [redacted] (b) (4)

The Division of Bioequivalence (DBE) consultation requests states:
"DBE requests a clinical consult to determine whether the [redacted] (b) (4) amount of glycerin used in the formulation of Sun Pharmaceuticals nitrofurantoin oral suspension should be of a safety concern."

The formulation comparison is displayed in the tables below.

Table 3 Nitrofurantoin Oral Suspension and the RLD, Furadantin (Nitrofurantoin) Oral Suspension

Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL (Sun Pharmaceutical Industries, Inc.)	**Furadantin (nitrofurantoin) Oral Suspension, 25 mg/5 mL (Sciele Pharma, Inc.)**
Ingredient	**Ingredient**
Nitrofurantoin [redacted] (b) (4) USP	Nitrofurantoin
Sodium Carboxymethylcellulose, USP	Carboxymethylcellulose Sodium
Citric Acid, USP	Citric Acid
Fruit Gum Flavor #960	Flavors
Magnesium Aluminum Silicate, NF	Magnesium Aluminum Silicate
Glycerin, USP	Glycerin
Methylparaben, NF	Methylparaben
Propylparaben, NF	Propylparaben
Sucralose, NF	
	Saccharin Sodium
Sodium Citrate, USP	Sodium Citrate
Sorbitol [redacted] (b) (4) USP	
	Sorbitol
Purified Water, USP	Purified Water, USP

From the Chemistry review, DARRTS, Aijin Shen, 9/29/10, page 33 of 77.

Table 4 Unit composition: The unit composition for Test (Nitrofurantoin Oral Suspension, USP) 25 mg/5 mL

Ingredient	Percentage (w/w %)	Percentage (w/v %)	mg/5 mL	Each gram Contains (mg)	Batch Contains (kg)
Nitrofurantoin, USP (b) (4)					(b) (4)
Carboxymethylcellulose Sodium, USP (b) (4) (b) (4)					
Magnesium Aluminum Silicate, NF (b) (4)					
Methylparaben, NF					
Propylparaben, NF					
Sorbitol (b) (4) USP (b) (4)					
Glycerin, USP					
Sucralose, NF (b) (4) (b) (4)					
Sodium Citrate (b) (4) USP					
(b) (4) Citric Acid, USP (b) (4)					
N&A Fruit Gum Flavor # 960 (MN 72)					
Purified Water, USP					
THEORETICAL TOTAL					(b) (4)

Table 5 Formulation Comparison

Ingredient	Test		Reference	
	mg/5 ml	% w/w	mg/5 ml	Active/Inactive Ingredient
Nitrofurantoin	[redacted] (b) (4)			Active
Carboxymethylcellulose Sodium				Inactive
Magnesium Aluminum Silicate				Inactive
Methylparaben, NF				Inactive
Propylparaben, NF				Inactive
Sorbitol [redacted] (b) (4)				Inactive
Glycerin				Inactive
Sucralose				Inactive
Sodium Citrate [redacted] (b) (4)				Inactive
[redacted] (b) (4) Citric Acid				Inactive
Fruit Gum Flavor #960				Inactive
Purified Water				Inactive

RLD formulation (from Control Correspondence 08-0029 Doc Date: 12/21/2007. \\cdsnas\OGDS6\CONTROLS\2008-docs\08-0029.pdf

Medical Officer's Comment: DCR discussed with DB2 the conversion of the amount of glycerin contained in the reference listed drug in milligrams. This was calculated to be [redacted] (b) (4) in 5 ml of the RLD suspension.

Table 6 Maximal Intake Based on MDD of Nitrofurantoin Oral Suspension

Inactive Ingredient	Maximum amount/day based on MDD of Nitrofurantoin Oral Suspension Amount (mg)	Maximum Level Listed in the FDA IIG Database for Approved Drug Product /Unit (mg)	Test formulation Below or Exceed FDA IIG
Carboxymethylcellulose Sodium	[redacted]	[redacted]	[redacted]
Magnesium Aluminum Silicate	[redacted]	[redacted]	[redacted]
Methylparaben, NF	[redacted]	[redacted]	[redacted]
Propylparaben, NF	[redacted]	[redacted]	[redacted]
Sorbitol [redacted]	[redacted]	[redacted]	[redacted]
Glycerin	[redacted]	[redacted]	[redacted]
Sucralose	[redacted]	[redacted]	[redacted]
Sodium Citrate [redacted]	[redacted]	[redacted]	[redacted]
[redacted] Citric Acid	[redacted]	[redacted]	[redacted]

The BE reviewer, Ke Ren, for ANDA 201355 calculated a single 5 ml dose of the test product contains (b) (4) glycerin and according to the dosage administration up to 16 doses a day could be given. (b) (4)

(b) (4)

(b) (4)

Following this page, 6 Pages Withheld in Full as (b)(4)

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

/s/

LINDA M FORSYTH
05/15/2012

JOHN R PETERS
05/15/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20852

To:	Dena Hixon, M.D., Director for Medical Affairs, Office of Generic Drugs
From:	Ke Ren, Reviewer, Division of Bioequivalence I, Office of Generic Drugs
Through:	Hoainhon Nguyen, Acting Deputy Director, Division of Bioequivalence (DBE) 1, Office of Generic Drugs
Re:	Request opinion on the safety and clinical significance of the excessive amount of the inactive ingredient Glycerin used in the test formulation of ANDA 201355, Nitrofurantoin Oral Suspension, 25 mg/ 5mL.

Introduction:

Sun Pharmaceuticals submitted the result of a fed bioequivalence (BE) study comparing its test product, Nitrofurantoin Oral Suspension USP, 25 mg/5 mL (Lot # B1127), to the corresponding reference product, FURADANTIN® (Nitrofurantoin) Oral Suspension USP, 25 mg/5 mL (Lot # 437034).

The fed (n=28; male) BE study used a single-dose, two-way crossover study design in healthy male subjects. The fed study results met the BE acceptance criteria for the AUCs and Cmax (**DARRTS ANDA 201355 Ren, Ke 07/19/2010 N/A 07/19/2010 REV-BIOEQ-01 (General Review) Archive**). However, one of the inactive ingredients, **Glycerin**, used in the test product formulation, when based on the maximum daily dose of 400 mg of Nitrofurantoin Oral Suspension, (b) (4) the maximum daily intake of Glycerin found in approved drug products (See the table below).

Issue:

DBE requests a clinical consult to determine whether (b) (4) amount of Glycerin used in the formulation of Sun Pharmaceuticals Nitrofurantoin Oral Suspension should be of a safety concern. The amount of Glycerin used in the test formulation and the (b) (4) CDER's Inactive Ingredient Guidance (IIG) for Approved Drug Products are summarized in the following table:

Inactive Ingredient	Maximum amount/day based on MDD of Nitrofurantoin Oral Suspension Amount (mg)	Maximum Level Listed in the FDA IIG Database for Approved Drug Product /Unit	Test formulation Below or Exceed FDA IIG
Carboxymethylcellulose Sodium		(b) (4)	
Magnesium Aluminum Silicate			
Methylparaben, NF			
Propylparaben, NF			
Sorbitol (b) (4)			
Glycerin			
Sucralose			
Sodium Citrate (b) (4)			
(b) (4) Citric Acid			

(b) (4)

Background:

Section I:

The results of fed BE study comparing its test product, Nitrofurantoin Oral Suspension USP, 25 mg/5 mL (Lot # B1127), to the corresponding reference product, FURADANTIN® (Nitrofurantoin) Oral Suspension USP, 25 mg/5 mL (Lot # 437034) are summarized below:

Nitrofurantoin Oral Suspension Dose (1 x 25 mg/5 mL) Fed Bioequivalence Study No. PKD_09_521, N=28 (male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	883.09	868.88	1.02	98.51	104.86
AUC∞ (ng·hr/mL)	915.62	893.56	1.02	99.57	105.46
Cmax (ng/mL)	371.79	372.31	1.00	90.44	110.26

However, there was an (b) (4) amount of Glycerin used in the test formulation based on the Maximum Daily Dose (MDD) of the drug (See inactive ingredient table above). In response to the DBE's deficiency letter dated 07/22/10, the firm has submitted information on the safety of Glycerin in its current amendment (located at the EDR ANDA 201355 submission date September 29, 2010). The submitted safety information is attached in this consult request (Please refer to the Appendix for details).

Section II: OGD History of This Drug Product

To this date, OGD approved one ANDA for Nitrofurantoin Oral Suspension (ANDA 201679, approved on May 11, 2011). Based on the formulation of this approved product, the maximum daily intake of Glycerin from this product is (b) (4)

Comparative Maximum Daily Intakes of Glycerin from Two Pending ANDAs of Nitrofurantoin Oral Suspension

	ANDA 201355	ANDA 201693
Glycerin (Daily amount taken based on MDD)	(b) (4)	(b) (4)

Section III: Additional Drug Product Information

Test Product	Nitrofurantoin Oral Suspension USP, 25 mg/5 mL
Reference Product	Furadantin® Oral Suspension, USP, 25 mg/mL
RLD Manufacturer	Shionogi Pharma
NDA No.	009175
RLD Approval Date	December 23, 1953
Indication[1]	Furadantin is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

PK/PD Information

Bioavailability	Nitrofurantoin is readily absorbed following oral administration. The macrocrystalline form is more slowly absorbed due to a slower rate of dissolution. This form can produce fewer adverse GI effects. Bioavailability, especially of the macrocrystals, can be increased by the presence of any substance that delays gastric emptying such as food.
Food Effect	The RLD labeling states that the presence of food or agents delaying gastric emptying can increase the bioavailability of Furadantin, presumably by allowing better dissolution in gastric juices. Patients should be advised to take Furadantin with food to further enhance tolerance and improve drug absorption.
Tmax	Peak urinary concentrations occur within about 30 minutes after administration of microcrystals, while dosage with macrocrystals takes slightly longer.
Distribution	Protein binding of nitrofurantoin is approximately 20—60%. Nitrofurantoin crosses the placenta and is distributed into breast milk. High concentrations of nitrofurantoin are found in urine.
Metabolism	Oral administered Furadantin is rapidly excreted in urine. Blood concentrations at therapeutic dosage are usually low. It is highly soluble in urine. Nitrofurantoin is bactericidal in urine at therapeutic doses.
Excretion	Urinary concentrations in patients with normal renal function range from 50—250 mcg/ml. Although there is some hepatic metabolism, about 30—50% of the drug is excreted unchanged in the urine within 24 hours of dosage. Nitrofurantoin is eliminated by glomerular filtration and tubular secretion, with some reabsorption.
Half-life	In patients with normal renal function, the plasma half-life is roughly 20 minutes.
Drug Specific Issues (if any)	1. **Pulmonary reactions**: Acute, subacute, or chronic pulmonary reactions have been observed in patients treated with Nitrofurantoin. If these reactions occur, Furadantin should be

[1] http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?id=19082

	discontinued and appropriate measures taken; Reports have cited pulmonary reactions as a contributing cause of death. Chronic pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) can develop insidiously. These reactions occur rarely and generally in patients receiving therapy for six months or longer. Close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted and requires that the benefits of therapy be weighted against potential risks. 2. **Respiratory:** Chronic, subacute, or acute pulmonary hypersensitivity reactions may occur. Chronic pulmonary reactions may occur generally in patients who have received continuous treatment for six months or longer. Malaise, dyspnea on exertion, cough, and altered pulmonary function are common manifestations which can occur insidiously. Radiologic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations of the chronic pulmonary reaction. Fever is rarely prominent. The severity of chronic pulmonary reactions and their degrees of resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be impaired permanently, even after cessation of therapy. The risk is greater when chronic pulmonary reactions are not recognized early. 3. Furadantin is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Nitrofurantoin. 4. Furadantin is also contraindicated in those patients with known hypersensitivity to Nitrofurantoin. 5. The FDA pregnancy risk category of nitrofurantoin is B.

Section VI: Conclusion:

The amount **Glycerin** in the formulation of Sun Pharmaceuticals' test product, Nitrofurantoin Oral Suspension USP, 25 mg/5 mL, [redacted] (b) (4) of CDER's Inactive Ingredient Guidance (IIG) for Approved Drug Products, when justified with the maximum daily dose of the active ingredient. The DBE requests the clinical and safety evaluation of the proposed amount of Glycerin in the test product.

References:

Location of the original review: DARRTS ANDA 201355 Ren, Ke 07/19/2010 N/A 07/19/2010 REV-BIOEQ-01 (General Review) Archive

Sun Pharmaceuticals' Formulation:

Ingredient	Percentage (w/w %)	Percentage (w/v %)	mg/5 mL	Each gram Contains (mg)	Batch Contains (kg)
Nitrofurantoin, USP (b) (4)					(b) (4)
Carboxymethylcellulose Sodium, USP (b) (4)					
Magnesium Aluminum Silicate, NF (b) (4)					
Methylparaben, NF					
Propylparaben, NF					
Sorbitol (b) (4) USP (b) (4)					
Glycerin, USP					
Sucralose, NF (b) (4)					
Sodium Citrate (b) (4) USP					
(b) (4) Citric Acid, USP (b) (4) (b) (4)					
N&A Fruit Gum Flavor # 960 (MN 72)					
Purified Water, USP					
THEORETICAL TOTAL					

(b) (4)

Appendix: Firm's Submitted Safety Information of Glycerin
(EDR ANDA 201355 submission date September 29, 2010)

Glycerin, USP, is an inactive ingredient, used as a (b) (4) in Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL. The concentration of Glycerin, USP, in Sun's formulation is (b) (4) The data for the above mentioned study can be found in the Pharmaceutical Development Report included in the original application as Module 3, Section 3.2.P.2. In addition, accelerated stability studies on the finished product showed no deleterious interaction of the excipients, which included Glycerin, USP, (b) (4)

Glycerin is generally recognized as safe and occurs naturally in fats and oils from animals and plant origins. Glycerin is consumed as part of a normal diet and is readily absorbed from the intestine. The absorbed glycerin is either metabolized to carbon dioxide and glycogen or used in the synthesis of body fats. Glycerin is used in a wide variety of approved pharmaceutical formulations, including oral, ophthalmic, parenteral, and topical preparations. When glycerin is used as a pharmaceutical excipient or a food additive, it is rarely associated with adverse effects and is generally regarded as nontoxic and a nonirritant. (b) (4)

(b) (4)

Following this page, 17 Pages Withheld in Full as (b)(4)

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

/s/

KE REN
06/17/2011

SHRINIWAS G NERURKAR
06/17/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
06/20/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201355Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

BIOEQUIVALENCE AMENDMENT

ANDA 201355

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Sun Pharmaceutical Industries, Inc. TEL: 1-313-556-4105

ATTN: Robert Kurkiewicz FAX: 1-248-926-0231

FROM: Teresa Ramson FDA CONTACT PHONE: (240) 276-8782

Dear Sir or Madam:

This facsimile is in reference to the bioequivalence data submitted on March 4, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitrofurantoin Oral Suspension USP, 25 mg/5 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 201355

APPLICANT: Sun Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Your dissolution testing data comparing your test product, Nitrofurantoin Oral Suspension USP, 25 mg/5 mL, with the reference product, Shionogi Pharma's FURADANTIN® (nitrofurantoin) Oral Suspension USP, 25 mg/5 mL, using the FDA-recommended dissolution method, are acceptable. However, your proposed specifications [NLT (b) (4) % (Q) in (b) (4) minutes] are not acceptable. Based on the data submitted, the DBI recommends a more appropriate specification. Please acknowledge your acceptance of the following dissolution method and specification for your test product:

Medium: Phosphate Buffer, pH 7.2
Volume: 900 mL
Apparatus: USP apparatus II (Paddle)
Speed: 50 rpm
Specification: NLT (b) (4) % (Q) of labeled amount of nitrofurantoin in the dosage form is dissolved in 30 minutes.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence I
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/

DALE P CONNER
06/18/2012

Electronic Log Book

Electronic Log Book ID	2264
Contact:	Sun Pharmaceutical Industries, Inc.
Contact Person:	Robert Kurkiewicz
Reason:	Outgoing, FDA Request for Information
Contact Type:	Email
Category:	ANDA
ANDA/Control/Protocol #:	201355
FDA Contact:	Teresa Ramson
Contact Time and Date	5/24/2012 at 11:28:34 AM

Subject: Bioequivalence

Query
Hello Mr. Kurkiewicz,

Please see the attached telephone amendment request for ANDA 201355. Please respond to this request within 7 business days. You can send a copy to me via fax or email and also send in a formal copy our document room.

Thanks,

Reviewer Request:

In the amendment submission (submission date: September 29, 2010), the firm only submitted the comparative dissolution summary results which included the mean, range and % coefficient of variation (CV) at each time points. Please provide the individual dissolution data for the 12 dosage units of the test and reference products in the following format:

Unit	Collection Times (Minutes)				
	15	30	60	120	180
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean					

Min
Max
% RSD, CV

Response
The firm was requested to respond to the requested information within 7 business days.

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

/s/

TERESA V RAMSON
05/24/2012

TELEPHONE CONFERENCE FAX

ANDA 201355

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Sun Pharmaceutical Industries, Inc. TEL: 313-556-4105

ATTN: Robert Kurkiewicz FAX: 248-926-0231

FROM: Benjamin Danso FDA CONTACT PHONE: (240) 276-8527

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 4, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitrofurantoin Oral Suspension, 25 mg/5 mL.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Benjamin Danso at (240) 276-8527. Please submit documentation by fax to the attention of the Project Manager at 240-276-8504. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201355 APPLICANT: SUN Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25 mg/5mL

The deficiencies presented below represent Telephone deficiencies.

Deficiencies:

A. Deficiencies:

1. (b) (4)

2.

3.

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

/s/

BENJAMIN DANSO
01/27/2012

QUALITY DEFICIENCY - MINOR

ANDA 201355

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Sun Pharmaceutical Industries, Inc. TEL: 609-495-2823

ATTN: Anne Toland FAX: 609-495-2711

FROM: Benjamin Danso FDA CONTACT PHONE: (240) 276-8527

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 4, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitrofurantoin Oral Suspension, 25 mg/5 mL.

Reference is also made to your amendment dated April 7, and May 20, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS: Chemistry comments provided. Please include in response.

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201355 APPLICANT: SUN Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25 mg/5mL

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6. (b) (4) [redacted]

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph. D.
Acting Director
Division of Chemistry I
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/

GURURAJ BYKADI
07/22/2011
For Dr. P. Schwartz

QUALITY DEFICIENCY - MINOR

ANDA 201355

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Sun Pharmaceutical Industries, Inc. TEL: 609-495-2823

ATTN: Anne Toland FAX: 609-495-2711

FROM: Benjamin Danso FDA CONTACT PHONE: (240) 276-8527

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 4, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitrofurantoin Oral Suspension, 25 mg/5 mL.

Reference is also made to your amendment dated May 6, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS: Chemistry comments provided. Please include in response.

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201355 APPLICANT: SUN Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25 mg/5mL

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

A. Deficiencies:

Drug Substance:

1. (b) (4)

2.

3.

Drug Product:

1. (b) (4)

2.

3.

4.

5.

Following this page, 1 Page Withheld in Full as (b)(4)

18. (b) (4)

19.

20.

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

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. (b) (4)

3.

4.

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph. D.
Acting Director
Division of Chemistry I
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/

RAMNARAYAN S RANDAD on behalf of GURURAJ BYKADI
09/29/2010

BIOEQUIVALENCE AMENDMENT

ANDA 201355

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Sun Pharmaceutical Industries, Inc. TEL: (609) 495-2823

ATTN: Anne Toland FAX: (609) 495-2711

FROM: Teresa Ramson FDA CONTACT PHONE: (240) 276-8782

Dear Madam

This facsimile is in reference to the bioequivalence data submitted on March 4, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitrofurantoin Oral Suspension, 25 mg/5 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/*

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 201355

APPLICANT: Sun Pharmaceutical Industries, Inc.

DRUG PRODUCT: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL

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

1. Based on the data available to the Agency, the maximum daily intake of Glycerin calculated from approved oral drug products is (b) (4) For your formulation, based on the maximum daily dose of 400 mg of nitrofurantoin recommended for the drug product (as stated in the labeling of the Reference Listed Drug (RLD) product, Furadantin® (Nitrofurantoin) Oral Suspension), the total daily intake of Glycerin from your test formulation (b) (4) the approved daily intake amount mentioned above. Please provide justifications for the amount of Glycerin used in the test formulation, and additional data and/or evidence demonstrating that the proposed amount of this excipient in your test formulation is safe.

2. Please provide the quantitative composition of N&A Fruit Gum Flavor # 960 used in your formulation.

3. Your dissolution testing is incomplete. You did not submit the ***individual*** dissolution data for the 12 dosage units of the test and reference product. Please submit these data. In addition, the dissolution data showed (b) (4) drug release for the test and RLD products (i.e., many values were (b) (4) (b) (4). Please explain the (b) (4) (b) (4) dissolution values for the test and RLD products, and provide complete validation data and report for the analytical method used in the dissolution testing. Also, please conduct additional dissolution testing using the FDA-recommended dissolution method for both the test and RLD products to confirm the accuracy and reproducibility of the dissolution results.

Sincerely yours,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201355	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES INC	NITROFURANTOIN

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

/s/

DALE P CONNER
07/22/2010

Please send an email to the labeling reviewer (chi-ann.wu@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 201355

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8952)

TO: Sun Pharmaceutical Industries, Inc. TEL: 609-495-2823

ATTN: Anne Tolan (Agent) FAX: 609-495-2711

FROM: Ruby Wu

Dear Madam:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitrofurantoin Oral Suspension USP, 25 mg/5 mL.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT** **submit your ANDA Regulatory documents to this address prior to 01-Aug-2010**. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/*

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

ANDA Number: 201355

Date of Submission: March 4, 2010 (original)

Applicant's Name: Sun Pharmaceutical Industries, Inc.

Established Name: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL

Labeling Deficiencies:

1. CONTAINER (240 mL and 480 mL amber PET bottles)
   a. Revise "Dispense in a tight, light-resistant [redacted] (b) (4) amber PET." to read "Dispense in tight, light-resistant amber bottles."
   b. Please confirm [redacted] (b) (4)
   c. Adult dosage: revise [redacted] (b) (4) to read "four times a day"

2. INSERT: (review based on insert submitted in Word)
   a. File "PI.pdf" submitted in the original submission is image based. Please note that insert labeling submitted in pdf should be TEXT based, not image based.
   b. CLINICAL PHARMACOLOGY, first sentence: "…Suspension…"
   c. CLINICAL PHARMACOLOGY, Microbiology: correct the spelling of "nitrofurantoin" [2 occurrences]
   d. INDICATIONS AND USAGE, second paragraph: "abscesses" [spelling]
   e. INDICATIONS AND USAGE, third paragraph, fourth sentence: "bacteriuria" [spelling]
   f. WARNINGS, first paragraph, second sentence: "APPROPRIATE" [adjective]
   g. WARNINGS, second paragraph, last sentence: "RISKS" [plural]
   h. WARNINGS, Hepatotoxicity, first sentence: "Hepatic" [spelling]
   i. PRECAUTIONS, Information for patients, second paragraph, second sentence: "…develop watery and bloody stools (with or without stomach cramps…"
   j. PRECAUTIONS, Drug Interactions, first paragraph, second sentence: "…is adsorption of…"
   k. PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility, Fourth paragraph, second sentence: "…human cells in…"
   l. ADVERSE REACTIONS, Neurologic, third paragraph, second sentence: "fontanels" [spelling]
   m. ADVERSE REACTIONS, Allergic, second sentence: "erythematous" [spelling]
   n. ADVERSE REACTIONS, Allergic, third sentence: "…spontaneously reported…"
   o. ADVERSE REACTIONS, Laboratory Adverse Events: "…dehydrogenase deficiency…" [delete comma]
   p. DOSAGE AND ADMINISTRATION: "…Oral Suspension, USP…" [2 occurrences]
   q. HOW SUPPLIED: Please include information on the color, scent and flavor of the oral suspension.
   r. Revise "Dispense in a tight, light-resistant [redacted] (b) (4) amber PET." to read "Dispense in tight, light-resistant amber bottles."

3. SPL Data Elements: Please include the flavor

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the previously submitted labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201355	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES INC	NITROFURANTOIN

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

/s/

CHI-ANN Y WU
06/08/2010
for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
**** For more CTD and eCTD informational links see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ *****

ANDA #: 201355 **FIRM NAME**: SUN PHARMACEUTICAL INDUSTRIES, INC.

PIV: NO **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? YES No need to send to DBE see e-mail below from M. Shimer dated 4/3/10)

DRUG NAME: NITROFURANTOIN
DOSAGE FORM: ORAL SUSPENSION USP, 25 MG/5 ML

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC1 Team 5 ☒ ***Activity***	***Bio Team 10: April Braddy*** ☒ ***Activity***
ANDA/Quality RPM: Ben Danso ☒ ***FYI***	Bio PM: Diana Solana ☐ ***FYI***
Quality Team Leader: Bykadi, Raj No assignment needed in DARRTS	***Clinical Endpoint Team Assignment: (No)*** ☐ ***Activity***
Labeling Reviewer: Ruby Wu ☒ ***Activity***	***Micro Review (No)*** ☐ ***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: MARCH 4, 2010 **Received Date**: MARCH 8, 2010

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 4013100 ANTIBACTERIAL AGENTS - GENERAL

Archival copy: ELECTRONIC (ECTD FORMAT) **Sections** I
Review copy: NA E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

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 Saundra T. Middleton **Date 5/10/2010**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☒ Yes ☐ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☒ Yes ☐ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☐ Yes
4. Requested EER
   ☐ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

4/29/2010 – Sun was Advised that the incorrect DMF (b) (4) is listed throughout the ANDA for Nitrofurantoin and that a statement should be made to state the correct DMF number (b) (4) Submitted 5/6/2010.

Readable copy of the COA for Sorbitol from the supplier. Submitted 5/6/2010.

Ms. Toland was also advised that this ANDA could be eligible for expedite review. Since this was not addressed in their 5/6/2010 response, we will not honor it at this time.

Margand, Iain

From: Shimer, Martin
Sent: Friday, April 23, 2010 10:13 AM
To: Margand, Iain
Subject: RE: First Generic

Iain,

Based on what you have told me I don't see any need for this to go over to DBE.

Tx,

Marty

From: Margand, Iain
Sent: Friday, April 23, 2010 10:10 AM
To: Shimer, Martin
Subject: First Generic

Marty,

Eda and Eddie brought a Nitrofurantoin Oral Suspension first generic to me to send a review request to Bio. I checked the Bio online recommendations for this product and there is a draft stating to only perform a Fed study and dissolution. The firm has done this and the results are within the 80% to 125% CI. There are no patents attached to the RLD, 09175.

Should we still send the request to Bio or just put the application on the shelf for review? There are other applications for the same product I noted in DAARTS that have come in after this application.

Thanks,

Iain

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: MARCH 4, 2010	☒
1.2.1	**Form FDA 3674 (PDF) YES**	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☐
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☐
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) PI 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES No exclusivities	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES Type II DMF No. (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒

Following this page, 2 Pages Withheld in Full as (b)(4)

1.12.11	**Basis for Submission** NDA# : 00-9175 Ref Listed Drug: FURADATIN Firm: SHIONOGI PHARMA ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use **YES** 2. Active ingredients **YES** 3. Inactive ingredients **YES** 4. Route of administration **YES** 5. Dosage Form **YES** 6. Strength **YES**	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling** **(Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) E- SUBMISSION **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained **YES** **1.14.1.3** 1 package insert (content of labeling) submitted electronically **YES** ***Was a proprietary name request submitted? **NO** (If yes, send email to Labeling Reviewer indicating such.) **NDC 57664-239-32 240 mL amber PET bottle** **NDC 57664-239-34 480 mL amber PET bottle**	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained **YES** **1.14.3.3** 1 RLD label and 1 RLD container label **YES**	☒

MODULE 2
SUMMARIES

ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF YES** **Word Processed e.g., MS Word YES** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR) YES** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient) YES** **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product YES** **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF YES** **Word Processed e.g., MS Word YES** **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary **YES** Table 4. Bioanalytical Method Validation **YES** Table 6. Formulation Data **YES** **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **YES** **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies **YES** Table 3. Statistical Summary of the Comparative BA Data **YES** **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **YES** **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies **YES**	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) **YES** 2. Function or Responsibility **YES** 3. Type II DMF number for API **YES #** (b) (4) 4. CFN or FEI numbers **YES**	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) **YES** **3.2.S.4.2 Analytical Procedures YES** **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples **YES** 2. Samples-Statement of Availability and Identification of: a. Drug Substance **YES** b. Same lot number(s) **YES** **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) **YES** 2. Applicant certificate of analysis **YES** **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems – IN DMF**	☒
3.2.S.7	**Stability – IN DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

<table>
<tr><td>3.2.P.1</td><td>Description and Composition of the Drug Product
1. Unit composition YES
2. Inactive ingredients and amounts are appropriate per IIG YES</td><td>☐</td></tr>
<tr><td>3.2.P.2</td><td>Pharmaceutical Development
Pharmaceutical Development Report YES</td><td>☒</td></tr>
<tr><td>3.2.P.3</td><td>Manufacture
3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories)
1. Name and Full Address(es)of the Facility(ies) YES
2. CGMP Certification: YES
3. Function or Responsibility YES
4. CFN or FEI numbers YES
3.2.P.3.2 Batch Formula YES
3.2.P.3.3 Description of Manufacturing Process and Process Controls
1. Description of the Manufacturing Process YES
2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES
<table><tr><th></th><th>Exhibition</th><th>Validation / Commercial</th></tr><tr><td>Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL</td><td colspan="2">(b) (4)</td></tr></table>
3. If sterile product: Aseptic fill / Terminal sterilization NA
4. Reprocessing Statement YES
3.2.P.3.4 Controls of Critical Steps and Intermediates
3.2.P.3.5 Process Validation and/or Evaluation
1. Microbiological sterilization validation NA
2. Filter validation (if aseptic fill) NA</td><td>☒</td></tr>
<tr><td>3.2.P.4</td><td>Controls of Excipients (Inactive Ingredients)
Source of inactive ingredients identified YES
3.2.P.4.1 Specifications
1. Testing specifications (including identification and characterization) YES
2. Suppliers' COA (specifications and test results) YES
3.2.P.4.2 Analytical Procedures
3.2.P.4.3 Validation of Analytical Procedures
3.2.P.4.4 Justification of Specifications
Applicant COA</td><td>☒</td></tr>
</table>

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s) YES** **3.2.P.5.2 Analytical Procedures YES** **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form **YES** 2. Same lot numbers **YES** **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form **YES** **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) **YES** 2. Components Specification and Test Data **YES** 3. Packaging Configuration and Sizes **YES** 4. Container/Closure Testing **YES** 5. Source of supply and suppliers address **YES**	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted **YES** 2. Expiration Dating Period **YES – 24 MONTHS** **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments **YES** **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data **YES** 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S Comparability Protocols NO** **3.2.R.3.S Methods Validation Package NO** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation **YES – SEE BELOW** **3.2.R.1.P.2 Information on Components YES** **3.2.R.2.P Comparability Protocols NO** **3.2.R.3.P Methods Validation Package** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

What is the reconciliation of the exhibit batch?

Nitrofurantoin Oral Suspension, USP 25 mg/5 mL

MODULE 5
CLINICAL STUDY REPORTS ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) **YES** b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **NA** **2. Lot Numbers of Products used in BE Study(ies):** B1127 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) **YES** 2. Summary Bioequivalence tables: Table 10. Study Information **YES** Table 12. Dropout Information **YES** Table 13. Protocol Deviations **YES** **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information **YES** Table 16. Composition of Meal Used in Fed Bioequivalence Study **YES** **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples **YES** Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses **YES** Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **YES** **5.3.7** **Case Report Forms and Individual Patient Listing YES**	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FED STUDY ON 25 MG/5 ML only required 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) **YES – see below** 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: **YES**	☒

Table 3: Statistical Summary of the Comparative Bioavailability Data (Fed study)

Nitrofurantoin 25mg/5ml Oral Suspension Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals				
Study No. PKD_09_521 (Fed Bioequivalence data for Nitrofurantoin from Nitrofurantoin 25mg/5ml Oral Suspension) (N=28)				
Parameter	**Test**	**Reference**	**Ratio %**	**90% C.I**
AUC_{0-t} (ng*hr/mL)	891.39	873.46	102.05	98.84 to 105.38
AUC_{0-inf} (ng*hr/mL)	918.54	893.95	102.75	99.73 to 105.86
C_{max} (ng/mL)	371.79	372.31	99.86	90.44 to 110.26

Contains Nonbinding Recommendations

Draft Guidance on Nitrofurantoin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Nitrofurantoin

Form/Route: Suspension/Oral

Recommended studies: 1 study

Type of study: Fed
Design: Single-dose, two-way, crossover *in-vivo*
Strength: 25 mg/5 mL
Subjects: Healthy males and nonpregnant females, general population.
Additional comments:

Analytes to measure: Nitrofurantoin in plasma

Bioequivalence based on (90% CI): Nitrofurantoin

Waiver request of in-vivo testing: Not Applicable

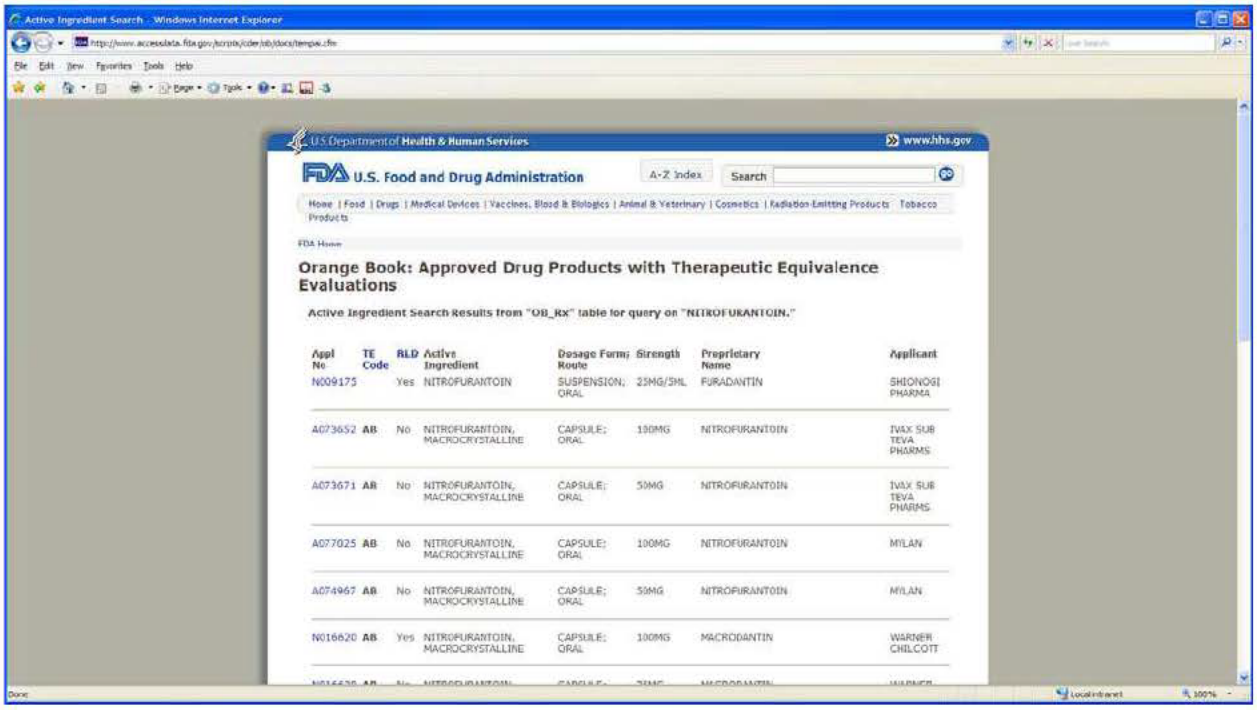
Dissolution test method and sampling times:

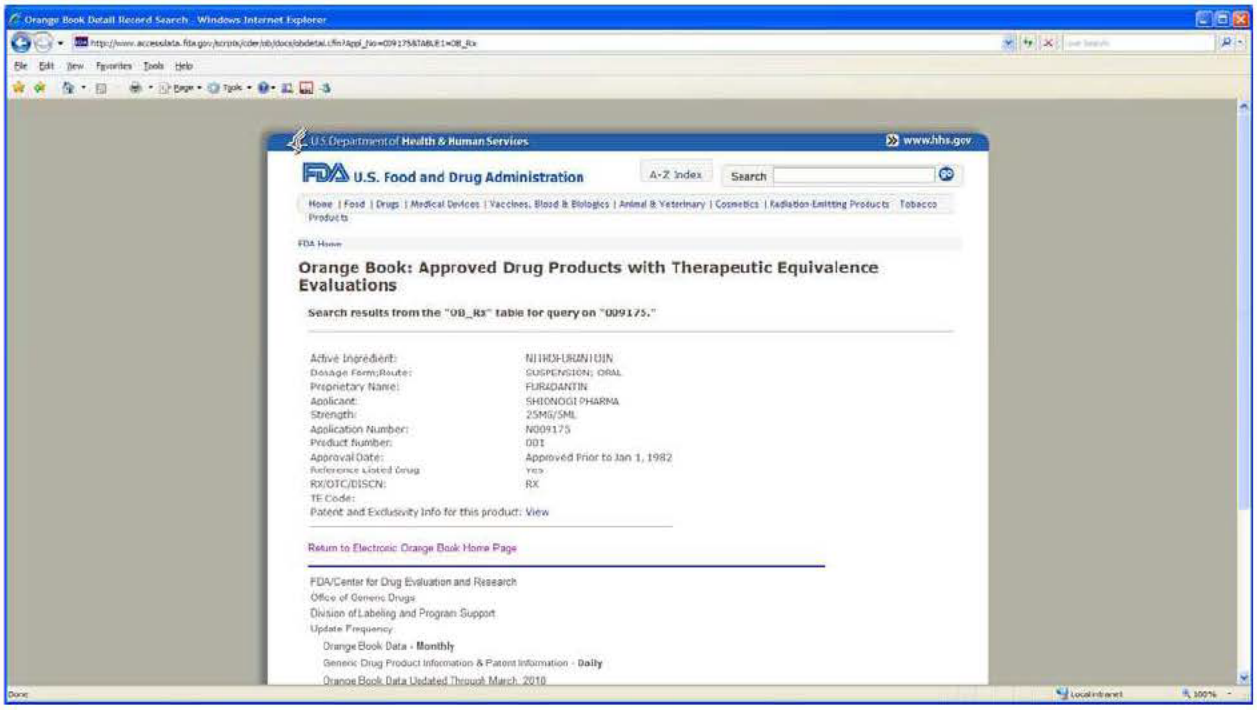
Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please note that a dosage unit is based on the labeled concentration of the suspension product. Please use the dosage unit (5 ml). A total of 12 units from 12 different bottles should be used. Specifications will be determined upon review of the application.

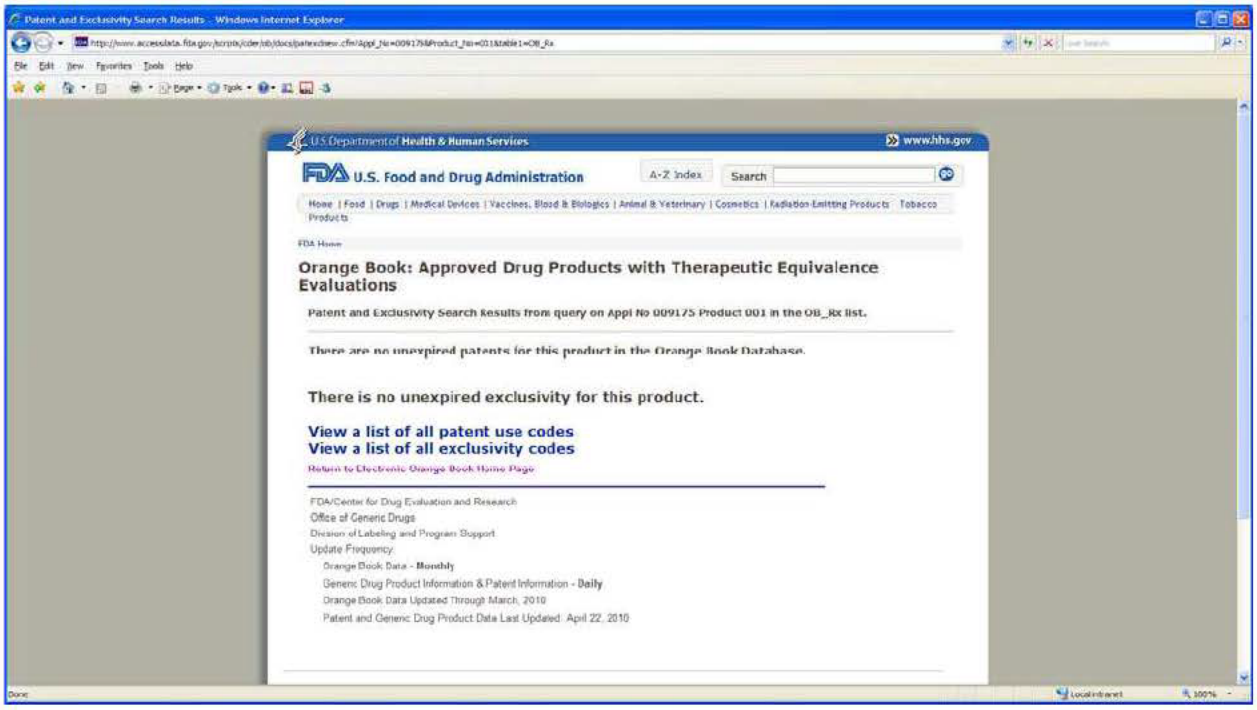
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐

Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009


Active Ingredient Search - Windows Internet Explorer
File Edit View Favorites Tools Help
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Active Ingredient Search Results from "OB_Rx" table for query on "NITROFURANTOIN."
Appl No | TE Code | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary Name | Applicant
N009175 | | Yes | NITROFURANTOIN | SUSPENSION; ORAL | 25MG/5ML | FURADANTIN | SHIONOGI PHARMA
A073652 | AB | No | NITROFURANTOIN, MACROCRYSTALLINE | CAPSULE; ORAL | 100MG | NITROFURANTOIN | IVAX SUB TEVA PHARMS
A073671 | AB | No | NITROFURANTOIN, MACROCRYSTALLINE | CAPSULE; ORAL | 50MG | NITROFURANTOIN | IVAX SUB TEVA PHARMS
A077025 | AB | No | NITROFURANTOIN, MACROCRYSTALLINE | CAPSULE; ORAL | 100MG | NITROFURANTOIN | MYLAN
A074967 | AB | No | NITROFURANTOIN, MACROCRYSTALLINE | CAPSULE; ORAL | 50MG | NITROFURANTOIN | MYLAN
N016620 | AB | Yes | NITROFURANTOIN, MACROCRYSTALLINE | CAPSULE; ORAL | 100MG | MACRODANTIN | WARNER CHILCOTT


Orange Book Detail Record Search - Windows Internet Explorer
File Edit View Favorites Tools Help
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Search results from the "OB_Rx" table for query on "009175."
Active Ingredient: NITROFURANTOIN
Dosage Form;Route: SUSPENSION; ORAL
Proprietary Name: FURADANTIN
Applicant: SHIONOGI PHARMA
Strength: 25MG/5ML
Application Number: N009175
Product Number: 001
Approval Date: Approved Prior to Jan 1, 1982
Reference Listed Drug: Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through March, 2010
Done
Local intranet
100%


Patent and Exclusivity Search Results - Windows Internet Explorer
File Edit View Favorites Tools Help
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Patent and Exclusivity Search Results from query on Appl No 009175 Product 001 in the OB_Rx list.
There are no unexpired patents for this product in the Orange Book Database.
There is no unexpired exclusivity for this product.
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through March, 2010
Patent and Generic Drug Product Data Last Updated: April 22, 2010
Done
Local intranet
100%

2.3.P.1 Description and Composition of the Drug Product

What are the components and composition of the final product? What is the function of each excipient?

Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL

***Unit composition*:** Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL, is packaged in two configurations: 240 mL and 480 mL PET round amber bottles. Both are sealed with CRC polypropylene cap.

Unit composition: **Nitrofurantoin Oral Suspension, USP, 25 mg/5 mL**

Ingredient	Percentage (w/w %)	Percentage (w/v %)	mg/5 mL	Each gram Contains (mg)	Batch Contains (kg)
Nitrofurantoin, USP (b) (4)					(b) (4)
Carboxymethylcellulose Sodium, USP (b) (4)					
Magnesium Aluminum Silicate, NF (b) (4)					
Methylparaben, NF					
Propylparaben, NF					
Sorbitol (b) (4) USP (b) (4)					
Glycerin, USP					
Sucralose, NF (b) (4) (b) (4)					
Sodium Citrate (b) (4) USP					
(b) (4) Citric Acid, USP (b) (4)					
N&A Fruit Gum Flavor # 960 (MN 72)					
Purified Water, USP					
THEORETICAL TOTAL					

Inactive ingredients confirmation per unit for ANDA 201335:

INGREDIENT	ROUTE;DOSAGE FORM	LAST NDA	APPROVAL DATE	DIV	MAXIMUM POTENCY/UNIT	
CARBOXYMETHYLCELLULOSE SODIUM	[redacted] (b) (4)					
MAGNESIUM ALIUMIN SILICATE						
METHYLPARABEN						
PROPYLPARABEN						
SORBITOL						
GLYCERIN						
SUCRALOSE						
SODIUM CITRATE [redacted] (b) (4)						
[redacted] (b) (4) CITRIC ACID						
N&A FRUIT GUM FLAVOR #960						

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201355	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES INC	NITROFURANTOIN

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

/s/

SAUNDRA T MIDDLETON
05/19/2010

IAIN MARGAND
05/21/2010
Signing for Martin Shimer

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 201355

Sun Pharmaceutical Industries, Inc.
Attention: Anne Toland
705 East Mulberry Street
Bryan, OH 43506

Dear Madam:

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 April 29, 2010 and your correspondence dated May 6, 2010.

NAME OF DRUG: Nitrofurantoin Oral Suspension USP, 25 mg/5 mL

DATE OF APPLICATION: March 4, 2010

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 8, 2010

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:

Benjamin Danso
Project Manager
(240) 276-8527

Sincerely yours,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201355	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES INC	NITROFURANTOIN

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

/s/

IAIN MARGAND
05/21/2010
Signing for Wm Peter Rickman