CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-012

***Name*:** Cefoxitin for Injection USP,
1 g/20 mL vial, 1 g/100 mL vial,
2 g/20 mL vial, and 2 g/10 mL vial

***Sponsor*:** American Pharmaceutical Partners

***Approval Date*:** July 3, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-012

APPROVAL LETTER

ANDA 65-012

JUL 3 2000

American Pharmaceutical Partners
Attention: Genny Cruz
2045 N. Cornell Avenue
Melrose Park, IL 60160

Dear Madam:

This is in reference to your abbreviated new drug application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cefoxitin for Injection USP, 1 g/20 mL vial, 1 g/100 mL vial, 2 g/20 mL vial, and 2 g/100 mL vial. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated March 22, April 26, June 1 and June 12, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Cefoxitin for Injection USP, 1 g/vial and 2 g/vial to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Mefoxin® Injection, 1 g/vial and 2 g/vial, respectively, of Merck and Co.).

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

Post-marketing reporting requirements for this abbreviated application 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 7/3/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-012
Division File
Field Copy
HFD-610/R. West
HFD-210/B. Poole
HFD-330
HFD-205

Endorsements:
643/S.Rosencrance/6/14/00 S Rosencrance 6/19/00
643/R.Adams/6/15/00 R.C. Adams 6/21/00
617/M.Anderson/6/9/00 M Anderson 6/21/00
640/P.DeLeo/ Paul Chorlied 6/23/2000
640/A.High/ AHL 6/21/00
613/J.Council/6/9/00 No BS in RLD labeling 6/21/00 CL for CH & JC
613/C.Hoppes/

V:\firmsam\app\ltrs&rev\65012.APD.DOC
F/T by smr/6/19/00

APPROVAL

CMC Satisfactory. Vilayat A Sayeed 6/28/00

Robert L West 6/30/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

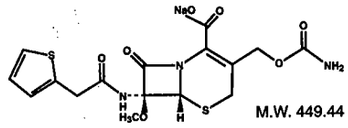
ANDA 65-012

LABELING

45647B/Revised: June 2000

CEFOXITIN
FOR INJECTION, USP APPROVED

DESCRIPTION:
Cefoxitin for Injection, USP contains cefoxitin sodium a semi-synthetic, broad-spectrum cephalosporin antibiotic for parenteral administration. It is derived from cephalosporin C, which is produced by *Cephalosporium Acremonium*. It is the sodium salt of 3-(hydroxymethyl)-7α-methoxy-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate carbamate (ester). The molecular formula is $C_{16}H_{16}N_3NaO_7S_2$, and the structural formula is:



M.W. 449.44

Cefoxitin for Injection, USP contains cefoxitin sodium with approximately 53.8 mg (2.3 mEq) of sodium per gram of cefoxitin activity. Solutions of Cefoxitin for Injection, USP range from colorless to light amber in color. The pH of freshly constituted solutions usually ranges from 4.2 to 7.0.

Each conventional vial contains sterile cefoxitin sodium, USP equivalent to 1 or 2 g cefoxitin. Each infusion bottle contains sterile cefoxitin sodium, USP equivalent to 1 or 2 g cefoxitin.

CLINICAL PHARMACOLOGY:
Clinical Pharmacology
Following an intravenous dose of 1 gram, serum concentrations were 110 mcg/mL at 5 minutes, declining to less than 1 mcg/mL at 4 hours. The half-life after an intravenous dose is 41 to 59 minutes. Approximately 85% of cefoxitin is excreted unchanged by the kidneys over a 6-hour period, resulting in high urinary concentrations. Probenecid slows tubular excretion and produces higher serum levels and increases the duration of measurable serum concentrations.

Cefoxitin passes into pleural and joint fluids and is detectable in antibacterial concentrations in bile.

Microbiology
The bactericidal action of cefoxitin results from inhibition of cell wall synthesis. Cefoxitin has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. The methoxy group in the 7α position provides cefoxitin with a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative bacteria.

Cefoxitin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms
Staphylococcus aureus[a] (including penicillinase-producing strains)
Staphylococcus epidermidis[a]
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
[a]Staphylococci resistant to methicillin/oxacillin should be considered resistant to cefoxitin.

Most strains of enterococci, e.g. *Enterococcus faecalis*, are resistant.

Aerobic gram-negative microorganisms
Escherichia coli
Haemophilus influenzae
Klebsiella spp. (including *K. pneumoniae*)
Morganella morganii
Neisseria gonorrhoeae, (including penicillinase-producing strains)
Proteus mirabilis
Proteus vulgaris
Providencia spp. (including *Providencia rettgeri*)

Anaerobic gram-positive microorganisms
Clostridium spp.
Peptococcus niger
Peptostreptococcus spp.

Anaerobic gram-negative microorganisms
Bacteroides distasonis
Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides spp.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Cefoxitin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 8 mcg/mL or less for aerobic microorganisms and 16 mcg/mL or less for anaerobic microorganisms against most (>90%) strains of the following microorganisms; however, the safety and effectiveness of cefoxitin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms
Eikenella corrodens (non-β-lactamase producers)
Klebsiella oxytoca

Anaerobic gram-positive microorganisms
Clostridium perfringens

Anaerobic gram-negative microorganisms
Prevotella bivia (formerly *Bacteroides bivius*)

Cefoxitin is inactive *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci and many strains of *Enterobacter cloacae*.

Susceptibility Tests
Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimum 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 standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefoxitin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms[a,b,c] other than *Neisseria gonorrhoeae*:

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

[a]Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefoxitin despite apparent *in vitro* susceptibility.

[b]For testing *Haemophilus influenzae* these interpretative criteria applicable only to tests performed by broth microdilution method using Haemophilus Test Medium (HTM)[1].

[c]For testing streptococci these interpretative criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth

in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms
Staphylococcus aureus[a] (including penicillinase-producing strains)
Staphylococcus epidermidis[a]
Streptococcus agalactiae
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[a]Staphylococci resistant to methicillin/oxacillin should be considered resistant to cefoxitin.
Most strains of enterococci, e.g. *Enterococcus faecalis*, are resistant.

Aerobic gram-negative microorganisms
Escherichia coli
Haemophilus influenzae
Klebsiella spp. (including *K. pneumoniae*)
Morganella morganii
Neisseria gonorrhoeae, (including penicillinase-producing strains)
Proteus mirabilis
Proteus vulgaris
Providencia spp. (including *Providencia rettgeri*)

Anaerobic gram-positive microorganisms
Clostridium spp.
Peptococcus niger
Peptostreptococcus spp.

Anaerobic gram-negative microorganisms
Bacteroides distasonis
Bacteroides fragilis
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Bacteroides thetaiotaomicron
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Klebsiella oxytoca

Anaerobic gram-positive microorganisms
Clostridium perfringens

Anaerobic gram-negative microorganisms
Prevotella bivia (formerly *Bacteroides bivius*)
Cefoxitin is inactive *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci and many strains of *Enterobacter cloacae.*

Susceptibility Tests
Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimum 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 standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefoxitin powder. The MIC values should be interpreted according to the following criteria:
For testing aerobic microorganisms[a,b,c] other than *Neisseria gonorrhoeae*:

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

[a]Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefoxitin despite apparent *in vitro* susceptibility.
[b]For testing *Haemophilus influenzae* these interpretative criteria applicable only to tests performed by broth microdilution method using Haemophilus Test Medium (HTM)[1].
[c]For testing streptococci these interpretative criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood[1].
For testing *Neisseria gonorrhoeae*[d]:

MIC (mcg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

[d]Interpretative criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement and incubated in 5% CO_2[1].
A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations 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 sites 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 cefoxitin powder should provide the following MIC values:

Microorganism		MIC (mcg/mL)
Escherichia coli	ATCC 25922	1–4
Neisseria gonorrhoeae[a]	ATCC 49226	0.5–2
Staphylococcus aureus	ATCC 29213	1–4

[a]Interpretative criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement and incubated in 5% CO_2[1].

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 30-mcg cefoxitin to test the susceptibility of microorganisms to cefoxitin.
Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-mcg cefoxitin disk should be interpreted according to the following criteria:
For testing aerobic microorganisms[a,b,c] other than *Neisseria gonorrhoeae*:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
15-17	Intermediate (I)
≤ 14	Resistant (R)

[a]Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefoxitin despite apparent *in vitro* susceptibility.
[b]For testing *Haemophilus influenzae* these interpretative criteria applicable only to tests performed by disk diffusion method using Haemophilus Test Medium (HTM)[1].
[c]For testing streptococci these interpretative criteria applicable only to tests performed by disk diffusion

method using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2[2].

For testing *Neisseria gonorrhoeae*[d]:

Zone Diameter (mm)	Interpretation
≥ 28	Susceptible (S)
24-27	Intermediate (I)
≤ 23	Resistant (R)

[d]Interpretative criteria applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement and incubated in 5% CO_2[2].

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 for cefoxitin.

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 30-mcg cefoxitin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	23–29
Neisseria gonorrhoeae[a]	ATCC 49226	33–41
Staphylococcus aureus	ATCC 25923	23–29

[a]Interpretative criteria applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement and incubated in 5% CO_2[2].

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to cefoxitin as MIC's can be determined by standardized test methods[2]. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 16	Susceptible (S)
32	Intermediate (I)
≥ 64	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standard cefoxitin powder should provide the following MIC values:

Using either an Agar Dilution Method[a] or Using a Broth[b] Microdilution Method:

Microorganism		MIC (mcg/mL)
Bacteroides fragilis	ATCC 25285	4–16
Bacteroides thetaiotaomicron	ATCC 29741	8–32

[a]Range applicable only to tests performed using either Brucella blood or Wilkins-Chalgren agar.

[b]Range applicable only to tests performed in the broth formulation of Wilkins-Chalgren agar[3].

INDICATIONS AND USAGE:

Treatment

Cefoxitin for Injection, USP is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

(1) Lower respiratory tract infections, including pneumonia and lung abscess, caused by *Streptococcus pneumoniae,* other streptococci (excluding enterococci, e.g., *Enterococcus faecalis* [formerly *Streptococcus faecalis*]), *Staphylococcus aureus* (including penicillinase-producing strains), *Escherichia coli, Klebsiella* species, *Haemophilus influenzae,* and *Bacteroides* species.

(2) Urinary tract infections caused by *Escherichia coli, Klebsiella* species, *Proteus mirabilis, Morganella morganii, Proteus vulgaris* and *Providencia* species (including *P. rettgeri*).

(3) Intra-abdominal infections, including peritonitis and intra-abdominal abscess, caused by *Escherichia coli, Klebsiella* species, *Bacteroides* species including *Bacteroides fragilis,* and *Clostridium* species.

(4) Gynecological infections, including endometritis, pelvic cellulitis, and pelvic inflammatory disease caused by *Escherichia coli, Neisseria gonorrhoeae* (including penicillinase-producing strains), *Bacteroides* species including *B. fragilis, Clostridium* species, *Peptococcus niger, Peptostreptococcus* species, and *Streptococcus agalactiae.* Cefoxitin for Injection, USP, like cephalosporins, has no activity against *Chlamydia trachomatis.* Therefore, when Cefoxitin for Injection, USP is used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added.

(5) Septicemia caused by *Streptococcus pneumoniae, Staphylococcus aureus* (including penicillinase-producing strains), *Escherichia coli, Klebsiella* species, and *Bacteroides* species including *B. fragilis.*

(6) Bone and joint infections caused by *Staphylococcus aureus* (including penicillinase-producing strains).

(7) Skin and skin structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and other streptococci (excluding enterococci e.g., *Enterococcus faecalis* [formerly *Streptococcus faecalis*]), *Escherichia coli, Proteus mirabilis, Klebsiella* species, *Bacteroides* species including *B. fragilis, Clostridium* species, *Peptococcus niger,* and *Peptostreptococcus* species.

Appropriate culture and susceptibility studies should be performed to determine the susceptibility of the causative organisms to Cefoxitin for Injection, USP. Therapy may be started while awaiting the results of these studies.

In randomized comparative studies, Cefoxitin for Injection, USP and cephalothin were comparably safe and effective in the management of infections caused by gram-positive cocci and gram-negative rods susceptible to the cephalosporins. Cefoxitin for Injection, USP has a high degree of stability in the presence of bacterial beta-lactamases, both penicillinases and cephalosporinases.

Many infections caused by aerobic and anaerobic gram-negative bacteria resistant to some cephalosporins respond to Cefoxitin for Injection, USP. Similarly, many infections caused by aerobic and anaerobic bacteria resistant to some penicillin antibiotics (ampicillin, carbenicillin, penicillin G) respond to treatment with Cefoxitin for Injection, USP. Many infections caused by mixtures of susceptible aerobic and anaerobic bacteria respond to treatment with Cefoxitin for Injection, USP.

Prevention

Cefoxitin for Injection, USP is indicated for the prophylaxis of infection in patients undergoing uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, or cesarean section.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate treatment may be instituted.

CONTRAINDICATIONS:

Cefoxitin for Injection is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

WARNINGS:

BEFORE THERAPY WITH CEFOXITIN FOR INJECTION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMON-

species (including *P. magnus*).

(3) **Intra-abdominal infections,** including peritonitis and intra-abdominal abscess, caused by *Escherichia coli, Klebsiella* species, *Bacteroides* species including *Bacteroides fragilis*, and *Clostridium* species.

(4) **Gynecological infections,** including endometritis, pelvic cellulitis, and pelvic inflammatory disease caused by *Escherichia coli, Neisseria gonorrhoeae* (including penicillinase-producing strains), *Bacteroides* species including *B. fragilis, Clostridium* species, *Peptococcus niger, Peptostreptococcus* species, and *Streptococcus agalactiae*. Cefoxitin for Injection, USP, like cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when Cefoxitin for Injection, USP is used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added.

(5) **Septicemia** caused by *Streptococcus pneumoniae, Staphylococcus aureus* (including penicillinase-producing strains), *Escherichia coli, Klebsiella* species, and *Bacteroides* species including *B. fragilis*.

(6) **Bone and joint infections** caused by *Staphylococcus aureus* (including penicillinase-producing strains).

(7) **Skin and skin structure infections** caused by *Staphylococcus aureus* (including penicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and other streptococci (excluding enterococci e.g., *Enterococcus faecalis* [formerly *Streptococcus faecalis*]), *Escherichia coli, Proteus mirabilis, Klebsiella* species, *Bacteroides* species including *B. fragilis, Clostridium* species, *Peptococcus niger,* and *Peptostreptococcus* species.

Appropriate culture and susceptibility studies should be performed to determine the susceptibility of the causative organisms to Cefoxitin for Injection, USP. Therapy may be started while awaiting the results of these studies.

In randomized comparative studies, Cefoxitin for Injection, USP and cephalothin were comparably safe and effective in the management of infections caused by gram-positive cocci and gram-negative rods susceptible to the cephalosporins. Cefoxitin for Injection, USP has a high degree of stability in the presence of bacterial beta-lactamases, both penicillinases and cephalosporinases.

Many infections caused by aerobic and anaerobic gram-negative bacteria resistant to some cephalosporins respond to Cefoxitin for Injection, USP. Similarly, many infections caused by aerobic and anaerobic bacteria resistant to some penicillin antibiotics (ampicillin, carbenicillin, penicillin G) respond to treatment with Cefoxitin for Injection, USP. Many infections caused by mixtures of susceptible aerobic and anaerobic bacteria respond to treatment with Cefoxitin for Injection, USP.

Prevention

Cefoxitin for Injection, USP is indicated for the prophylaxis of infection in patients undergoing uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, or cesarean section.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate treatment may be instituted.

CONTRAINDICATIONS:

Cefoxitin for Injection is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

WARNINGS:

BEFORE THERAPY WITH CEFOXITIN FOR INJECTION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN FOR INJECTION OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefoxitin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS:

General

The total daily dose should be reduced when Cefoxitin for Injection is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see **DOSAGE AND ADMINISTRATION**), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

Antibiotics (including cephalosporins) should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

As with other antibiotics, prolonged use of Cefoxitin for Injection may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Laboratory Tests

As with any potent antibacterial agent, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Drug Interactions

Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Drug/Laboratory Test Interactions

As with cephalothin, high concentrations of cefoxitin (>100 mcg/mL) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction, and produce false increases of modest degree in the levels of creatinine reported. Serum samples from patients treated with cefoxitin should not be analyzed for creatinine if withdrawn within 2 hours of drug administration.

High concentrations of cefoxitin in the urine may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction, and produce false increases of modest degree in the levels reported.

A false-positive reaction for glucose in the urine may occur. This has been observed with CLINITEST® reagent tablets.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed with cefoxitin to evaluate carcinogenic or mutagenic

potential. Studies in rats treated intravenously with 400 mg/kg of cefoxitin (approximately three times the maximum recommended human dose) revealed no effects on fertility or mating ability.

Pregnancy

Pregnancy Category B. Reproduction studies performed in rats and mice at parenteral doses of approximately one to seven and one-half times the maximum recommended human dose did not reveal teratogenic or fetal toxic effects, although a slight decrease in fetal weight was observed.

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.

In the rabbit, cefoxitin was associated with a high incidence of abortion and maternal death. This was not considered to be a teratogenic effect but an expected consequence of the rabbit's unusual sensitivity to antibiotic-induced changes in the population of the microflora of the intestine.

Nursing Mothers

Cefoxitin for Injection is excreted in human milk in low concentrations. Caution should be exercised when Cefoxitin for Injection is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients from birth to three months of age have not yet been established. In pediatric patients three months of age and older, higher doses of Cefoxitin for Injection have been associated with an increased incidence of eosinophilia and elevated SGOT.

ADVERSE REACTIONS:

Cefoxitin for Injection is generally well tolerated. The most common adverse reactions have been local reactions following intravenous injection. Other adverse reactions have been encountered infrequently.

Local Reactions

Thrombophlebitis has occurred with intravenous administration.

Allergic Reactions

Rash (including exfoliative dermatitis and toxic epidermal necrolysis), pruritus, eosinophilia, fever, dyspnea, and other allergic reactions including anaphylaxis, interstitial nephritis and angioedema have been noted.

Cardiovascular

Hypotension.

Gastrointestinal

Diarrhea, including documented pseudomembranous colitis which can appear during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Neuromuscular

Possible exacerbation of myasthenia gravis.

Blood

Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hemolytic anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may develop in some individuals, especially those with azotemia.

Liver Function

Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase; and jaundice have been reported.

Renal Function

Elevations in serum creatinine and/or blood urea nitrogen levels have been observed. As with the cephalosporins, acute renal failure has been reported rarely. The role of Cefoxitin for Injection in changes in renal function tests is difficult to assess, since factors predisposing to prerenal azotemia or to impaired renal function usually have been present.

In addition to the adverse reactions listed above which have been observed in patients treated with Cefoxitin for Injection, the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:

Urticaria, erythema multiforme, Stevens-Johnson syndrome, serum sickness-like reactions, abdominal pain, colitis, renal dysfunction, toxic nephropathy, false-positive test for urinary glucose, hepatic dysfunction including cholestasis, elevated bilirubin, aplastic anemia, hemorrhage, prolonged prothrombin time, pancytopenia, agranulocytosis, superinfection, vaginitis including vaginal candidiasis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. (See **DOSAGE AND ADMINISTRATION.**) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE:

The acute intravenous LD_{50} in the adult female mouse and rabbit was about 8 g/kg and greater than 1 g/kg, respectively. The acute intraperitoneal LD_{50} in the adult rat was greater than 10 g/kg.

DOSAGE AND ADMINISTRATION:

Treatment

Adults

The usual adult dosage range is 1 gram to 2 grams every six to eight hours. Dosage should be determined by susceptibility of the causative organisms, severity of infection, and the condition of the patient (see Table 1 for dosage guidelines).

If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefoxitin sodium has no activity against this organism.

Cefoxitin for Injection may be used in patients with reduced renal function with the following dosage adjustments:

In adults with renal insufficiency, an initial loading dose of 1 gram to 2 grams may be given. After a loading dose, the recommendations for *maintenance dosage* (Table 2) may be used as a guide.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: $$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Females: 0.85 x above value

In patients undergoing hemodialysis, the loading dose of 1 to 2 grams should be given after each hemodialysis, and the maintenance dose should be given as indicated in Table 2.

Antibiotic therapy for group A beta-hemolytic streptococcal infections should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Pediatric Patients

The recommended dosage in pediatric patients three months of age and older is 80 to 160 mg/kg of body weight per day divided into four to six equal doses. The higher dosages should be used for more severe or serious infections. The total daily dosage should not exceed 12 grams.

At this time no recommendation is made for pediatric patients from birth to three months of age (see **PRECAUTIONS**).

In pediatric patients with renal insufficiency, the dosage and frequency of dosage should be modified consistent with the recommendations for adults (see Table 2).

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In addition to the adverse reactions listed above which have been observed in patients treated with Cefoxitin for Injection, the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:

Urticaria, erythema multiforme, Stevens-Johnson syndrome, serum sickness-like reactions, abdominal pain, colitis, renal dysfunction, toxic nephropathy, false-positive test for urinary glucose, hepatic dysfunction including cholestasis, elevated bilirubin, aplastic anemia, hemorrhage, prolonged prothrombin time, pancytopenia, agranulocytosis, superinfection, vaginitis including vaginal candidiasis.

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When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Females: 0.85 x above value

In patients undergoing hemodialysis, the loading dose of 1 to 2 grams should be given after each hemodialysis, and the maintenance dose should be given as indicated in Table 2.

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The recommended dosage in pediatric patients three months of age and older is 80 to 160 mg/kg of body weight per day divided into four to six equal doses. The higher dosages should be used for more severe or serious infections. The total daily dosage should not exceed 12 grams.

At this time no recommendation is made for pediatric patients from birth to three months of age (see **PRECAUTIONS**).

In pediatric patients with renal insufficiency, the dosage and frequency of dosage should be modified consistent with the recommendations for adults (see Table 2).

Prevention

Effective prophylactic use depends on the time of administration. Cefoxitin for Injection usually should be given one-half to one hour before the operation, which is sufficient time to achieve effective levels in the wound during the procedure. Prophylactic administration should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection.

For prophylactic use in uncontaminated gastrointestinal surgery, vaginal hysterectomy, or abdominal hysterectomy, the following doses are recommended:

Adults:

2 grams administered intravenously just prior to surgery (approximately one-half to one hour before the initial incision) followed by 2 grams every 6 hours after the first dose for no more than 24 hours.

Pediatric Patients (3 months and older):

30 to 40 mg/kg doses may be given at the times designated above.

Cesarean section patients:

For patients undergoing cesarean section, either a single 2 gram dose administered intravenously as soon as the umbilical cord is clamped OR a 3-dose regimen consisting of 2 grams given intravenously as soon as the umbilical cord is clamped followed by 2 grams 4 and 8 hours after the initial dose is recommended. (See **CLINICAL STUDIES.**)

Table 1 – Guidelines for Dosage of Cefoxitin for Injection

Type of Infection	Daily Dosage	Frequency and Route
Uncomplicated forms* of infections such as pneumonia, urinary tract infection, cutaneous infection	3-4 grams	1 gram every 6-8 hours IV
Moderately severe or severe infections	6-8 grams	1 gram every 4 hours or 2 grams every 6-8 hours IV
Infections commonly needing antibiotics in higher dosage (e.g., gas gangrene)	12 grams	2 grams every 4 hours or 3 grams every 6 hours IV

*Including patients in whom bacteremia is absent or unlikely.

Table 2 – Maintenance Dosage of Cefoxitin for Injection in Adults with Reduced Renal Function

Renal Function	Creatinine Clearance (mL/min)	Dose (grams)	Frequency
Mild impairment	50-30	1-2	every 8-12 hours
Moderate impairment	29-10	1-2	every 12-24 hours
Severe impairment	9-5	0.5-1	every 12-24 hours
Essentially no function	<5	0.5-1	every 24-48 hours

Table 3 – Preparation of Solution for Intravenous Administration

Strength	Amount of Diluent to be Added (mL)**	Approximate Withdrawable Volume (mL)	Approximate Average Concentration (mg/mL)
1 gram Vial	10	10.5	95
2 gram Vial	10 or 20	11.1 or 21	180 or 95
1 gram Infusion Bottle	50 or 100	50 or 100	20 or 10
2 gram Infusion Bottle	50 or 100	50 or 100	40 or 20

**Shake to dissolve and let stand until clear.

Preparation of Solution

Table 3 is provided for convenience in constituting Cefoxitin for Injection for intravenous administration.

For Vials

One gram should be constituted with at least

10 mL, and 2 grams with 10 or 20 mL, of Sterile Water for Injection, Bacteriostatic Water for Injection, 0.9 percent Sodium Chloride Injection, or 5 percent Dextrose Injection. These primary solutions may be further diluted in 50 to 1000 mL of the diluents listed under the ***Vials*** portion of the **COMPATIBILITY AND STABILITY** section.

Benzyl alcohol as a preservative has been associated with toxicity in neonates. While toxicity has not been demonstrated in pediatric patients greater than three months of age, in whom use of Cefoxitin for Injection may be indicated, small pediatric patients in this age range may also be at risk for benzyl alcohol toxicity. Therefore, diluent containing benzyl alcohol should not be used when Cefoxitin for Injection is constituted for administration to pediatric patients in this age range.

For Infusion Bottles
One or 2 grams of Cefoxitin for Injection for infusion may be constituted with 50 or 100 mL of 0.9 percent Sodium Chloride Injection, or 5 percent or 10 percent Dextrose Injection.

ADMINISTRATION:
Cefoxitin for Injection may be administered intravenously after constitution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Intravenous Administration
The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For intermittent intravenous administration, a solution containing 1 gram or 2 grams in 10 mL of Sterile Water for Injection can be injected over a period of three to five minutes. Using an infusion system, it may also be given over a longer period of time through the tubing system by which the patient may be receiving other intravenous solutions. However, during infusion of the solution containing Cefoxitin for Injection, it is advisable to temporarily discontinue administration of any other solutions at the same site.

For the administration of higher doses by continuous intravenous infusion, a solution of Cefoxitin for Injection may be added to an intravenous bottle containing 5 percent Dextrose Injection, 0.9 percent Sodium Chloride Injection, or 5 percent Dextrose and 0.9 percent Sodium Chloride Injection. BUTTERFLY[††] or scalp vein-type needles are preferred for this type of infusion.

Solutions of Cefoxitin for Injection, like those of most beta-lactam antibiotics, should not be added to aminoglycoside solutions (e.g., gentamicin sulfate, tobramycin sulfate, amikacin sulfate) because of potential interaction. However, Cefoxitin for Injection and aminoglycosides may be administered separately to the same patient.

COMPATIBILITY AND STABILITY:
Vials
Cefoxitin for Injection, as supplied in vials and constituted to 1 gram/10 mL with Sterile Water for Injection, Bacteriostatic Water for Injection, (see ***Preparation of Solution***), 0.9 percent Sodium Chloride Injection, or 5 percent Dextrose Injection, maintains satisfactory potency for 6 hours at room temperature or for one week under refrigeration (below 5°C).

These primary solutions may be further diluted in 50 to 1000 mL of the following diluents and maintain potency for an additional 18 hours at room temperature or an additional 48 hours under refrigeration:

- 0.9 percent Sodium Chloride Injection
- 5 percent or 10 percent Dextrose Injection
- 5 percent Dextrose and 0.9 percent Sodium Chloride Injection
- 5 percent Dextrose Injection with 0.2 percent or 0.45 percent saline solution
- Lactated Ringer's Injection
- 5 percent Dextrose in Lactated Ringer's Injection
- 10 percent invert sugar in water
- 10 percent invert sugar in saline solution
- 5 percent Sodium Bicarbonate Injection
- M/6 sodium lactate solution
- Mannitol 5% and 10%

Infusion Bottles
Cefoxitin for Injection, as supplied in infusion bottles and constituted with 50 to 100 mL of 0.9 percent Sodium Chloride Injection, or 5 percent or 10 percent Dextrose Injection, maintains satisfactory potency for 24 hours at room temperature or for 1 week under refrigeration (below 5°C).

After the periods mentioned above, any unused solutions should be discarded.

HOW SUPPLIED:
Cefoxitin for Injection, USP is a dry white to off-white powder supplied in conventional vials and infusion bottles containing cefoxitin sodium as follows:

Product No.	NDC No.	
304120	63323-341-20	Sterile cefoxitin sodium, USP equivalent to 1 g cefoxitin in a 20 mL vial (tray of 25).
304220	63323-342-20	Sterile cefoxitin sodium, USP equivalent to 2 g cefoxitin in a 20 mL vial (tray of 25).
304165	63323-341-65	Sterile cefoxitin sodium, USP equivalent to 1 g cefoxitin in a 100 mL infusion bottle (tray of 10).
304265	63323-342-65	Sterile cefoxitin sodium, USP equivalent to 2 g cefoxitin in a 100 mL infusion bottle (tray of 10).

Special storage instructions
Cefoxitin for Injection, USP in the dry state should be stored between 2°-25°C (36°-77°F). Avoid exposure to temperatures above 50°C. The dry material as well as solutions tend to darken, depending on storage conditions; product potency, however, is not adversely affected.

CLINICAL STUDIES:
A prospective, randomized, double-blind, placebo-controlled clinical trial was conducted to determine the efficacy of short-term prophylaxis with cefoxitin in patients undergoing cesarean section who were at high risk for subsequent endometritis because of ruptured membranes. Patients were randomized to receive either three doses of placebo (n=58), a single dose of cefoxitin (2 g) followed by two doses of placebo (n=64), or a three-dose regimen of cefoxitin (each dose consisting of 2 g) (n=60), given intravenously, usually beginning at the time of clamping of the umbilical cord, with the second and third doses given 4 and 8 hours post-operatively. Endometritis occurred in 16/58 (27.6%) patients given placebo, 5/63 (7.9%) patients given a single dose of cefoxitin, and 3/58 (5.2%) patients given three doses of cefoxitin. The differences between the two groups treated with cefoxitin and placebo with respect to endometritis were statistically significant ($p<0.01$) in favor of cefoxitin. The differences between the one-dose and three-dose regimens of cefoxitin were not statistically significant.

Two double-blind, randomized studies compared the efficacy of a single 2 gram intravenous dose of cefoxitin to a single 2 gram intravenous dose of cefotetan in the prevention of surgical site-related infection (major morbidity) and non-site-related infections (minor morbidity) in patients following cesarean section. In the first study, 82/98 (83.7%) patients treated with cefoxitin and 71/95 (74.7%) patients treated with cefotetan experienced no major or minor morbidity. The difference in the outcomes in this study (95% CI: -0.03, +0.21) was not statistically significant. In the second study, 65/75 (86.7%) patients treated with cefoxitin and 62/76 (81.6%) patients treated with cefotetan experienced no major or minor morbidity. The difference in the outcomes in this study (95% CI: -0.08, +0.18) was not statistically significant.

In clinical trials of patients with intra-abdominal infec-

5 percent Dextrose Injection with 0.2 percent or 0.45 percent saline solution
Lactated Ringer's Injection
5 percent Dextrose in Lactated Ringer's Injection
10 percent invert sugar in water
10 percent invert sugar in saline solution
5 percent Sodium Bicarbonate Injection
M/6 sodium lactate solution
Mannitol 5% and 10%

Infusion Bottles
Cefoxitin for Injection, as supplied in infusion bottles and constituted with 50 to 100 mL of 0.9 percent Sodium Chloride Injection, or 5 percent or 10 percent Dextrose Injection, maintains satisfactory potency for 24 hours at room temperature or for 1 week under refrigeration (below 5°C).

After the periods mentioned above, any unused solutions should be discarded.

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304165	63323-341-65	Sterile cefoxitin sodium, USP equivalent to 1 g cefoxitin in a 100 mL infusion bottle (tray of 10).
304265	63323-342-65	Sterile cefoxitin sodium, USP equivalent to 2 g cefoxitin in a 100 mL infusion bottle (tray of 10).

Special storage instructions
Cefoxitin for Injection, USP in the dry state should be stored between 2°-25°C (36°-77°F). Avoid exposure to temperatures above 50°C. The dry material as well as solutions tend to darken, depending on storage conditions; product potency, however, is not adversely affected.

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In clinical trials of patients with intra-abdominal infections due to *Bacteroides fragilis* group microorganisms, eradication rates at 1 to 2 weeks posttreatment for isolates were in the range of 70% to 80%. Eradication rates for individual species are listed below:

Bacteroides distasonis	7/10	(70%)
Bacteroides fragilis	26/33	(79%)
Bacteroides ovatus	10/13	(77%)
B. thetaiotaomicron	13/18	(72%)

REFERENCES:

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fourth 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.
3. National Committee for Clinical Laboratory Standards, Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Third Edition. Approved Standard NCCLS Document M11-A4, Vol. 17, No. 26, NCCLS, Villanova, PA, December 1997.

NOTES:
†Registered trademark of Ames Company, Division of Miles Laboratories, Inc.
††Registered trademark of Abbott Laboratories, Inc.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024

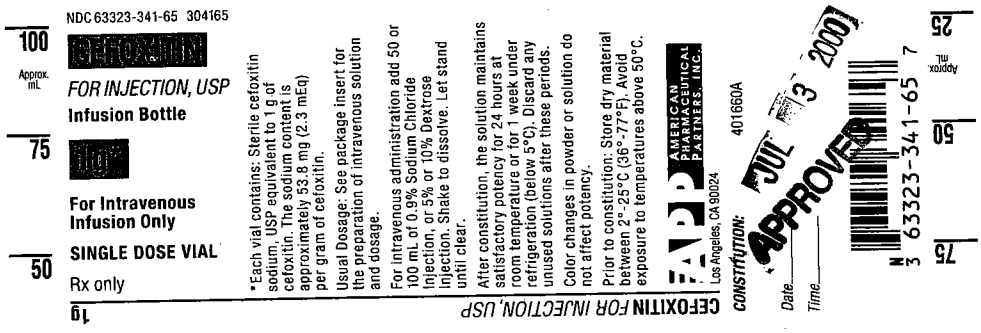
45647B
Revised: June 2000

ANDA 65-012
Cefoxitin for Injection, USP (SDV) **Labeling Amendment**

Cefoxitin for Injection, USP (SDV)
1g/20 mL Container Label (Conventional Vial)
Product Code: 304120

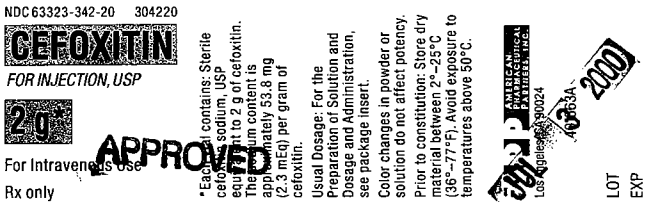
ANDA 65-012
Cefoxitin for Injection, USP (SDV) **Labeling Amendment**

Cefoxitin for Injection, USP (SDV)
1g/100mL Container Label (Piggyback Vial)
Product Code: 304165



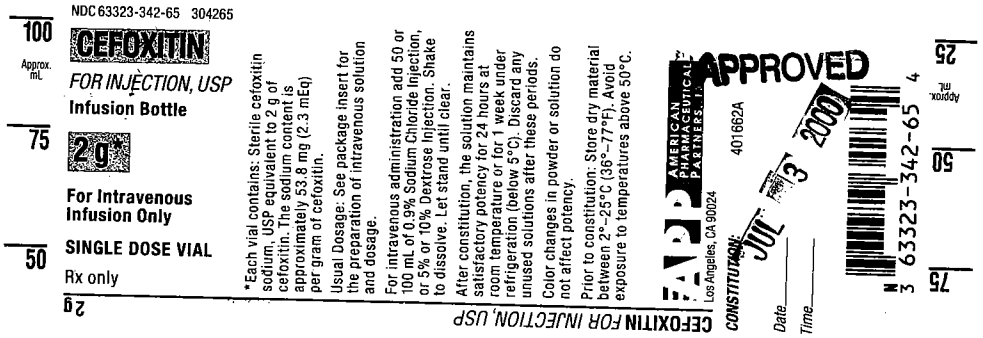
ANDA 65-012
Cefoxitin for Injection, USP (SDV) **Labeling Amendment**

Cefoxitin for Injection, USP (SDV)
2g/20mL Container Label (Conventional Vial)
Product Code: 304220



ANDA 65-012
Cefoxitin for Injection, USP (SDV) **Labeling Amendment**

Cefoxitin for Injection, USP (SDV)
2g/100mL Container Label (Piggyback Vial)
Product Code: 304265



APPROVED
JUL 13 2000

1 g*

FOR INJECTION, USP

CEFOXITIN

*Each vial contains: Sterile cefoxitin sodium, USP equivalent to 1 g of cefoxitin. The sodium content is approximately 53.8 mg (2.3 mEq) per gram of cefoxitin.

Usual Dosage: For the Preparation of Solution and Dosage and Administration, see package insert.

Color changes in powder or solution do not affect potency.

Prior to constitution: Store dry material between 2°- 25°C (36°-77°F). Avoid exposure to temperatures above 50°C.

62527A

APP AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024

63323-341-20

304120

CEFOXITIN

FOR INJECTION, USP

1 g*

travenous Use

y

25 Vials

AMERICAN PHARMACEUTICAL PARTNERS, INC.

AMERICAN PHARMACEUTICAL PARTNERS, INC.

CEFOXITIN
FOR INJECTION, USP

Infusion Bottle

1 g*

*Each vial contains: Sterile cefoxitin sodium, USP equivalent to 1 g of cefoxitin. The sodium content is approximately 53.8 mg (2.3 mEq) per gram of cefoxitin.

Usual Dosage: See package insert for the preparation of intravenous solution and dosage.

For intravenous administration add 50 or 100 mL of 0.9% Sodium Chloride Injection, or 5% or 10% Dextrose Injection. Shake to dissolve. Let stand until clear. See accompanying package insert.

After constitution, the solution maintains satisfactory potency for 24 hours at room temperature or for 1 week under refrigeration (below 5°C). Discard any unused solutions after these periods.

Prior to constitution: Store dry material between 2°–25°C (36°–77°F). Avoid exposure to temperatures above 50°C. Color changes in powder or solution do not affect potency.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024
62528A

NDC 63323-341-65

304165

CEFOXITIN

FOR INJECTION, USP

Infusion Bottle

For Intravenous Infusion Only.
SINGLE DOSE VIAL

1 g*

Rx only

10 Infusion Bottles

AMERICAN PHARMACEUTICAL PARTNERS, INC.

BLACK 1565C

[redacted]

FOR INJECTION, USP

[redacted]

*Each vial contains: Sterile cefoxitin sodium, USP equivalent to 2 g of cefoxitin. The sodium content is approximately 53.8 mg (2.3 mEq) per gram of cefoxitin.

Usual Dosage: For the Preparation of Solution and Dosage and Administration, see package insert.

Color changes in powder or solution do not affect potency.

Prior to constitution: Store dry material between 2°-25°C (36°-77°F). Avoid exposure to temperatures above 50°C.

62529A

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024

NDC 63323-342-20

304220

[redacted]

FOR INJECTION, USP

[redacted]

For Intravenous Use

Rx only

25 Vials

FAPP AMERICAN PHARMACEUTICAL PARTNERS, INC.

FAPP AMERICAN PHARMACEUTICAL PARTNERS, INC.

BLACK 3262C

[redacted]

Infusion Bottle

FOR INJECTION, USP

[redacted]

*Each vial contains: Sterile cefoxitin sodium, USP equivalent to 2 g of cefoxitin. The sodium content is approximately 53.8 mg (2.3 mEq) per gram of cefoxitin.

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AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024

NDC 63323-342-65

[redacted]

FOR INJECTION, USP

Infusion Bottle

[redacted]

For Intravenous Infusion Only
SINGLE DOSE VIAL

Rx only

10 Infusion Bottl

AMERICAN PHARMACEUTICAL PARTNERS, INC.

BLACK 3262C

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-012

LABELING REVIEWS

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

ANDA Number: 65-012

Date of Submission: March 20, 1998

Applicant's Name: American Pharmaceutical Partners, Inc.

Established Name: Cefoxitin for Injection USP,
1 g and 2 g conventional vials, and
1 g and 2 g infusion bottles

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Replace the "Caution: Federal law..." statement with "**Rx only**" or "**℞ only**" on labels and labeling. A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

   b. Revise your labels and labeling to reflect the transfer of ownership.

2. CONTAINERS:

   a. 1 g and 2 g conventional vials

      i. We encourage you to differentiate your drug product strengths by using contrasting colors and/or boxing.

      ii. Front panel

         A) Add an asterisk following the strength, "___ g*".

B) Delete the text ——————————.

iii. Side panel

Revise to read as follows:

A) *Each vial contains: Sterile cefoxitin sodium, USP equivalent to ___ g of cefoxitin. The sodium content ...

B) Usual Dosage: For the preparation ...

C) Prior to constitution: Store dry ...

b. 1 g and 2 g infusion bottles:

i. See comments 2(a)(i, ii and iii) and 2(a)(iv)(A) under CONTAINER.

ii. Front panel

A) Revise the text "————————" to read **"For IV Infusion Only"** in bold print.

B) Add the following statement in uppercase bold print:

SINGLE DOSE VIAL

iii. Side panel

Revise to read as follows:

A) Usual Dosage: See package insert for the preparation of intravenous solution and dosage.

B) Prior to constitution: Store dry ...

iv. Delete the text ——————————— from the upside-down statement.

3. CARTON:

a. 1 g and 2 g conventional vials: 25s

See comments 2(a)(i, ii and iii) and 2(a)(iv)(A) under CONTAINER.

b. 1 g and 2 g infusion bottles: 10s

See comments 2(b)(i), 2(b)(ii)(A and B), 2(b)(iii) (A and B) and comment 3(a) under CARTON.

4. INSERT

a. General Comment

Delete "USP" following the established name except in the TITLE and in the DESCRIPTION, INDICATIONS AND USAGE and HOW SUPPLIED sections.

b. DESCRIPTION

i. Revise the first sentence to read, "Cefoxitin for Injection, USP contains cefoxitin sodium a semi-synthetic, ...".

ii. You may delete the text "sealed under nitrogen", which is no longer required in the DESCRIPTION section.

iii. We acknowledge that you have deleted the text, "... administration. It is derived from cephamycin C, which is produced by *Streptomyces lactamdurans*" because your firm uses a different synthetic route. In the first paragraph please include the synthetic route used by your firm.

iv. Revise the chemical name to read, "...-7∝-methoxy-8-...".

v. Revise " ——————— " to "molecular formula".

vi. Revise the first sentence of the second paragraph to read, "Cefoxitin for Injection, USP contains cefoxitin sodium with approximately ...".

vii. Add the following as the last paragraph:

> Each conventional vial contains ... cefoxitin. Each infusion bottle contains ... cefoxitin.

c. PRECAUTIONS (Pediatric Use)

Revise to read as follows:

Safety and efficacy in infants from birth to three months ... established. In pediatric patients three months of age and older, ...elevated SGOT.

d. ADVERSE REACTIONS (Liver function)

Revise to read, "... in SGOT, SGPT, serum LDH, ...".
[Delete ————————].

e. OVERDOSAGE

Delete the terminal zero following the decimal point, i.e., "1" instead of "1.0".

f. DOSAGE AND ADMINISTRATION

i. To be in accord with 21 CFR 201.57 revise "DOSAGE" to read "DOSAGE AND ADMINISTRATION".

ii. In patients undergoing hemodialysis

Delete ———————————— .

iii. Revise the subsection heading "Pediatric Patients" to read "Infants and Pediatric Patients".

iv. See comment under OVERDOSAGE.

v. Please note "Preparation of Solution" is a subsection of the "DOSAGE AND ADMINISTRATION" section. Therefore, revise the title format to be consistent with your other subsection headings.

vi. Preparation of Solution

A) For IV Use

- In the second paragraph revise "———————" to read "infants", (two locations).

- In the last sentence of second paragraph revise "———————— ———————" to read

"infants".

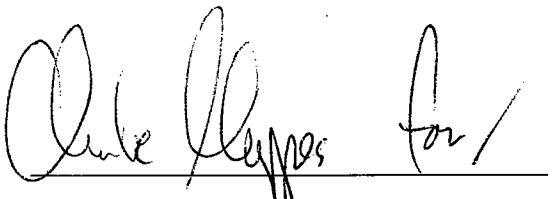
g. Notes

Delete the number 5 and the corresponding text. We refer you to comment 4(f)(ii) under DOSAGE AND ADMINISTRATION.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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



Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.	X		
Is this name different than that used in the Orange Book? *Cefoxitin Sodium Injection	x*		
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis	–	–	–
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR	–	–	–
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	

Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. *See NOTES TO THE CHEMIST	*		
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR	-	-	-
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)	-	-	-
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?			x

Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)	-	-	-
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. * Not listed in the RLD.	x*		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. Do you concur with the following labeling comment?

   > We acknowledge that you have deleted the text, "... administration. It is derived from cephamycin C, which is produced by *Streptomyces lactamdurans*" because your firm uses a different synthetic route. In the first paragraph please include the synthetic route used by your firm.

2. Has the firm submitted adequate compatibility and stability studies to support the claims which appear in the insert labeling under the DOSAGE AND ADMINISTRATION (Compatibility and stability) section?

FOR THE RECORD:

1. Mefoxin, NDA 50-517 by Merck & Co., Inc., revised 2/95 and approved 2/27/97.

   50-517/S-039 approved 4/24/97, is for instructions for the ADD Vantage Vial.

   NOTE. This is a combined conventional vial and infusion bottle insert that references the pharmacy bulk package (ANDA 65-011).

2. The firm's composition statement is consistent with the DESCRIPTION section.
   [Vol. 1.1, p. 00094]

3. The formulated drug product is packaged in Type I USP flint, glass tubing (20 mL) and molded glass vials (100 mL) with gray rubber stoppers and flip-off ——— seals.
   [Vol. 1.1, p. 00094]

4. Package sizes:

   NDA - 1 g x 25, 1 g infusion bottles x 10
   2 g x 25, 2 g infusion bottles x 10
   10 g PBP x 6
   1 g ADD-vantage x 25
   2 g ADD-vantage x 25

   65012 - 1 g x 25, 1 g infusion bottles x 10
   2 g x 25, 2 g infusion bottles x 10

5. Bioavailability/Bioequivalence - pending

   - A bio. *in vivo* bioequivalence study waiver was granted

on 7/23/98 for intravenous administration only.

- A waiver was not granted for intramuscular use.

- The bio. reviwer reported that the reference listed drug was for intravenous use only [Physicians Desk Reference, 1998]. NOTE: The reference listed drug, "Mefoxin" packaged in conventional vials is for intravenous and intramuscular use. The infusion bottles are for intravenous use only. The bio. reviewer most likely saw labeling for premixed plastic mini-bags, which are for intravenous use only.

6. Storage:

Dry powder

NDA - Mefoxin in dry state should be stored below 30°C. Avoid exposure to temperatures above 50°C. The dry material as well as solutions tend to darken, depending on storage conditions; product potency, however, is not adversely affected.

ANDA - Same as NDA

After constitution

NDA - 24 hours at room temperature, one week under refrigeration(below 5°C) and 30 weeks frozen

ANDA - Same as NDA

After further dilution in intravenous solution

NDA - 24 hours at room temperature, 48 hours under refrigeration

ANDA - same as NDA

7. Labeling Issues:

a. ADVERSE REACTIONS

ANDA 62182 approved on 4/8/98 has three paragraphs at the end of the ADVERSE REACTIONS section that are missing from NDA 50517 approved on 2/27/97. I would like to know if there is a FTR regarding this issue.

b. Dosage AND ADMINISTRATION (Compatibility and Stability /Intravenous)

I noticed that bacteriostatic water for injection is listed as a diluent. There should be follow-up with the Project Manager in the new drug division.

Date of Review: 8/21/98

Primary Reviewer
Jacqueline White, Pharm.D. *

10/16/98
Date

Team Leader

10/16/98
Date

cc:

ANDA: 65012
DUP/DIVISION FILE
HFD-613/JWhite/CHoppes (no cc)
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Review

Endorsements: HFD-613/JWhite
HFD-613/CHoppes

* Reviewer @ a distant site

APPROVAL SUMMARY

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

ANDA Number: **65-012**

Date of Submission: **December 4, 1998**

Applicant's Name: **American Pharmaceutical Partners, Inc.**

Established Name: **Cefoxitin for Injection USP, 1 g and 2 g Conventional vials, and 1 g and 2 g Infusion bottles**

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: **1 g and 2 g Conventional vials, and 1 g and 2 g Infusion bottles**

Satisfactory in FPL (12/4/98 submission)

Carton Labeling: 25's (Conventional vials)
10's (Infusion bottles)

Professional Package Insert Labeling:

Satisfactory in FPL (12/4/98 submission)

Revisions needed post-approval:

1. GENERAL

   Add storage requirement in Fahrenheit as well [e.g., 30°C (86°F), 50°C (122°F)]

2. CONTAINER

   Encourage the relocation of Rx Only" to the principal display panel.

3. CARTON

See the comment under CONTAINER.

4. INSERT

a. Use lower case letters for the established name throughout the text except at the beginning of the sentence.

b. Encourage the inclusion of "Rx Only" beneath the title.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Mefoxin®

NDA Number: 50-517/S-031

NDA Drug Name: Mefoxin®

NDA Firm: Merck Co.

Date of Approval of NDA Insert and supplement #: 2/27/97 (S-031)

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Other Comments:

The firm's product is derived from a different source as compared to the innovator's product. (See FTR)

FOR THE RECORD:

1. Mefoxin, NDA 50-517 by Merck & Co., Inc., revised 2/95 and approved 2/27/97.

50-517/S-039 approved 4/24/97, is for instructions for the ADD Vantage Vial.

NOTE. This is a combined conventional vial and infusion bottle insert.

2. The firm has deleted the reference to the [redacted] from the H.S. section.

3. The ownership of this product has been transferred from Fujisawa to APP.

4. The firm's product is derived from "cephalosporin C, which is produced by *Cephalosporium Acremonium*" as opposed to "*Streptomyces lactamdurans*" of the RLD.

5. The firm's composition statement is consistent with the DESCRIPTION section.
[Vol. 1.1, p. 00094]

6. The formulated drug product is packaged in Type I USP flint, glass tubing (20 mL) and molded glass vials (100 mL) with gray rubber stoppers and flip-off [redacted] seals.
[Vol. 1.1, p. 00094]

7. Package sizes:

NDA - 1 g x 25, 1 g infusion bottles x 10
2 g x 25, 2 g infusion bottles x 10
10 g PBP x 6
1 g ADD-vantage x 25
2 g ADD-vantage x 25

65012 - 1 g vials x 25, 1 g infusion bottles x 10
2 g vials x 25, 2 g infusion bottles x 10

8. Storage:

Dry powder

NDA - Mefoxin in dry state should be stored below 30°C. Avoid exposure to temperatures above 50°C. The dry material as well as solutions tend to darken, depending on storage conditions; product potency, however, is not adversely affected.

ANDA - Same as NDA

After constitution

NDA - 24 hours at room temperature, one week under refrigeration(below 5°C) and 30 weeks frozen

ANDA - Same as NDA

After further dilution in intravenous solution

NDA - 24 hours at room temperature, 48 hours under refrigeration

ANDA - same as NDA

9. **Labeling Issues (From previous record):**

a. ADVERSE REACTIONS

ANDA 62182 approved on 4/8/98 has three paragraphs at the end of the ADVERSE REACTIONS section that are missing from NDA 50517 approved on 2/27/97. I would like to know if there is a FTR regarding this issue.

b. Dosage AND ADMINISTRATION (Compatibility and Stability /Intravenous)

I noticed that bacteriostatic water for injection is listed as a diluent. There should be follow-up with the Project Manager in the new drug division.

10. The ADVERSE section of the applicant is identical to that of the innovator's

Date of Review: December 9, 1998

Primary Reviewer — Date 12/10/98

Team Leader — Date 12/10/98

12/10/98

cc:

ANDA: 65012
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
X:\NEW\FIRMSAM\AMERICAN\LTR&REV\65012AP.L
Review

Endorsements: HFD-613/Cpark
HFD-613/CHoppes

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

ANDA Number: 65-012

Date of Submission: April 26, 2000

Applicant's Name: American Pharmaceutical Partners, Inc.

Established Name: Cefoxitin for Injection, USP
65-012 - 1 g and 2 g Conventional vials, and
1 g and 2 g Infusion bottles

Labeling Deficiencies:

1. CONTAINER:

   General Comment

   Please note that the "Intramuscular Route of Administration [IM]" is no longer approved in the labeling of the reference listed drug, Mefoxin®. Therefore, delete all text referring to this route of administration on your conventional vial container labels.

2. CARTON:

   See General Comment under CONTAINER.

3. INSERT

   a. General Comments

      i. Delete all text that refers to the "intramuscular route of administration" and revise your labeling to be consistent with the reference listed drug, Mefoxin® approved on February 14, 2000. See General Comment under CONTAINER.

      ii. Improve the readability of the superscripts and the text printed in each table by increasing the print size.

   b. DESCRIPTION

      Improve the readability of the molecular formula.

   c. CLINICAL PHARMACOLOGY (Pharmacokinetics)

      Delete the last paragraph, "[redacted]".

   d. INDICATIONS AND USAGE

      i. Revise the second Indication and Usage, "Genitourinary Infections" to read the same as the text of the reference listed drug, Mefoxin®, approved on February 14, 2000.

ii. Prevention

Relocate the paragraph, "Effective prophylactic use ...subsequent infection" to appear as the first paragraph under the DOSAGE AND ADMINISTRATION/Prevention section.

e. WARNINGS

Revise the last three paragraphs of this section to be consistent with the last three paragraphs found in the insert labeling of the reference listed drug, Mefoxin® approved on February 14, 2000.

f. PRECAUTIONS

Add the subsection, "Laboratory Tests ..." immediately prior to the subsection "Drug Interactions" as seen in the insert labeling of the reference listed drug, Mefoxin® approved on February 14, 2000.

g. ADVERSE REACTIONS

Renal function

Add the last three paragraphs, "In addition ... clinically indicated" as seen in the insert labeling of the reference listed drug, Mefoxin® approved on February 14, 2000.

h. OVERDOSAGE

Replace "IV" with "intravenous".

i. DOSAGE AND ADMINISTRATION

i. Prevention

Please refer to comment 3(d)(ii) above.

ii. Preparation of Solution

Revise as follows:

- *For Vials*
  For IV Use, 1 gram ... 20 mL
- *For Infusion Bottles*
  One or 2 grams ... Injection.
- In the last sentence, delete the text, " ———————
  ———
- Revise the third paragraph to be consistent with the insert labeling of the reference listed drug, Mefoxin® approved on February 14, 2000.

iii. COMPATIBILITY AND STABILITY (Intravenous)

Revise this subsection to be consistent with the insert labeling of the reference listed drug, Mefoxin® approved on February 14, 2000.

j. CLINICAL STUDIES

Add a third paragraph as seen in the insert labeling of the reference listed drug, Mefoxin® approved on February 14, 2000.

k. REFERENCES

Add a "REFERENCES" section immediately following "CLINICAL STUDIES" as seen in the insert labeling of the reference listed drug, Mefoxin® approved on February 14, 2000.

l. NOTES

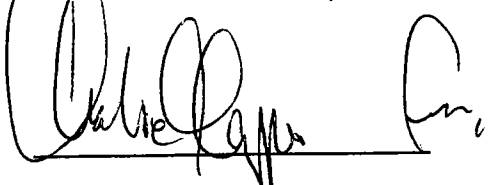
i. Renumber the list of NOTES, [due to the relocation of the first three references]. See comment 3(k).

ii. Delete note number 5, "[redacted]" and/or comment.

Please revise your container labels, carton and insert labeling, as instructed above, and submit twelve copies in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes, http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.

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



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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.	X		
Is this name different than that used in the Orange Book? *Cefoxitin Sodium Injection	*		
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis	-	-	-
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR	-	-	-
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR	-	-	-
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)	-	-	-
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?			x
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) *I do have the USP in this office. I plan to request it.	*		
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Not listed in the RLD.	*		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	

Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Labeling Model:

   Mefoxin®, NDA 50-517/S-038 by Merck & Co., Inc., issued 10/96 and approved . 2/14/2000. Also, S-031 approved 2/27/97 for text pertaining to the conventional vial and the IM route of administration.

2. Components and Composition:

   The firm's composition statement is consistent with the DESCRIPTION section.

   - [65-011-Vol. 1.1, p. 00080]

   - [65-012 [Vol. 1.1, p.00094]

3. CONTAINER/CLOSURE:

   -The formulated drug product is packaged in Type I USP flint, molded glass vials (100 mL) with gray rubber stoppers and flip-off ——— seals.
   [65-011-Vol. 1.1, p. 00080]

   -The formulated drug product is packaged in Type I USP flint,glass tubing (20 mL) and molded glass vials (100 mL) with gray rubber stoppers and flip-off ——— seals.
   [65-012-Vol. 1.1, p. 00094]

4. Package sizes:

   NDA - 1 g x 25, 1 g infusion bottles x 10
   2 g x 25, 2 g infusion bottles x 10
   10 g PBP x 6
   1 g ADD-vantage x 25
   2 g ADD-vantage x 25

   65-011 - 10 g x 10

   65-012 - 1 g vials x 25, 1 g infusion bottles x 10
   2 g vials x 25, 2 g infusion bottles x 10

5. This amendment was the result of up-dated insert labeling approved for the RLD Mefoxin®, NDA 50-517 on 2/14/2000. This review supersedes the approval summary for the firm's 12/4/98 submission for ANDA 65-012.

Date of Review: 5/1/2000

Primary Reviewer
Jacqueline Council, Pharm.D.

5-15-2000
Date

Team Leader

5/11/00
Date

cc:

ANDA: 650-12

DUP/DIVISION FILE
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Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY

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

ANDA Number: 65-012

Date of Submission: June 1, 2000

Applicant's Name: American Pharmaceutical Partners, Inc.

Established Name: Cefoxitin for Injection, USP
65-012 - 1 g and 2 g Conventional vials, and
1 g and 2 g Infusion bottles

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

Do you have 12 Final Printed Labels and Labeling? Yes.

Container Labels: 1 g and 2 g conventional vials, and
1 g and 2 g infusion bottles
Satisfactory in final print as of the June 1, 2000 submission.

Carton Labeling: 1 g and 2 g Conventional vials –25s, and
1 g and 2 g Infusion bottles – 10s
Satisfactory in final print as of the June 1, 2000 submission.

Professional Package Insert Labeling:
Satisfactory in final print as of the June 1, 2000 submission.

Future revisions/post-approval:

1. INSERT

   - DOSAGE AND ADMINISTRATION (Compatibility and Stability)
     Vials
     Revise to read, "...in vials may be constituted ...".
   - REFERENCES:
     Revise the third reference to read, "...Bacteria – Third Edition, ...No. 26, NCCLS, Wayne, PA. ...".

2. CONTAINER

   - 1 g and 2 g infusion bottles
     Revise "...maintains satisfactory potency for 24 hours ..." to read "...maintains satisfactory potency for 6 hours ...".

3. CARTON

   - 1 g and 2 gram infusion bottles – 10s
     See comment under CONTAINER.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Mefoxin®

NDA Number: 50-517

NDA Drug Name: Cefoxitin for Injection, USP

NDA Firm: Merck & Co.

Date of Approval of NDA Insert and supplement #: S-038 approved 2/14/2000

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: RLD

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	**Yes**	**No**	**N.A.**
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.	X		
Is this name different than that used in the Orange Book? *Cefoxitin Sodium Injection	*		
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis	-	-	-
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR	-	-	-
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR	-	-	-
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)	-	-	-
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?			x
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) *I do have the USP in this office. I plan to request it.	*		
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Not listed in the RLD.	*		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	

Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling Model:

   a. Mefoxin®, NDA 50-517/S-038 by Merck & Co., Inc., issued 10/96 and approved . 2/14/2000.

   b. The firm is being requested to update reference #7 in the REFERENCES section to be in accord with the approval letter dated 2/14/2000. These revisions are terms of the approval for the draft insert labeling of the RLD, Mefoxin®.

2. Components and Composition:

   The firm's composition statement is consistent with the DESCRIPTION section.

   [Vol. 1.1, p. 00094]

3. CONTAINER/CLOSURE:

   The formulated drug product is packaged in Type I USP flint,glass tubing (20 mL) and molded glass vials (100 mL) with gray rubber stoppers and flip-off ——— seals.
   [65-012-Vol. 1.1, p. 00094]

4. Package sizes:

   NDA - 1 g x 25, 1 g infusion bottles x 10
   2 g x 25, 2 g infusion bottles x 10
   10 g PBP x 6
   1 g ADD-vantage x 25
   2 g ADD-vantage x 25

   65-012 - 1 g vials x 25, 1 g infusion bottles x 10
   2 g vials x 25, 2 g infusion bottles x 10

5. Prior to approval the firm will be requested to commit to making the revisions listed under "Future revisions/post-approval" to their container labels and carton labeling.

Date of Review: 6/8/2000

Jacqueline Council, Pharm.D.
Primary Reviewer

Team Leader

NDA is on RLD labeling as of 6/22/00

6-9-2000
Date

6/9/00
Date

cc:

ANDA: 65-012
DUP/DIVISION FILE
HFD-613/JCouncil/CHoppes (no cc)
v:\firmsams\American\ltrs&rev\65012ap.l
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-012

CHEMISTRY REVIEWS

Office of Generic Drugs
Chemistry, Manufacturing and Controls Review

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 65-012

3. NAME AND ADDRESS OF APPLICANT
As received on 3/20/98:
Fujisawa USA, Inc.
3 Parkway North, 3rd Floor
Parkway North Center
Deerfield, IL 60015-2548

Change in ownership 6/1/98 to:
Corporate Address
American Pharmaceutical Partners
Mitchall Clark, Senior Director, Reg. Affairs
2825 Santa Monica Boulevard
Santa Monica, CA 90404
Phone: 310-264-7768

Correspondence Address
Mitchall Clark, Senior Director, Reg. Affairs
or
Genny Cruz, Senior Regulatory Scientist
American Pharmaceutical Partners
2045 N. Cornell Avenue
Melrose park, IL 60160
Phone: 708-343-6100

Manufacturing Facility
Fujisawa USA, Inc. (Lyphomed Division)
3159 Staley Road
Grand Island, NY 14072

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies that there is patent information submitted to the Agency with respect to Cefoxitin for Injection, USP, for which clearance is sought and that there is no marketing exclusivity in effect for the listed drug. (See page 7, Vol. 1)

Innovator: Merck Sharp Dohme Mefoxin®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Cefoxitin for Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
1. Original submission 3/20/98
2. Change of Ownership 6/1/98
3. NC: revised LOA for DMF # [redacted]
7/1/98
FDA:
1. Telecon re: exhibit batch size 4/2/98
2. Acknowledgment letter 4/9/98

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

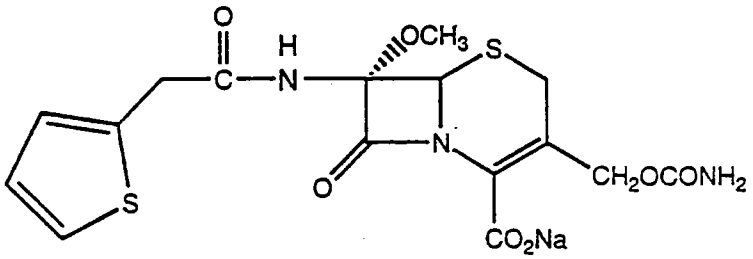
TABLE 1: RELATED NDA'S/DMF'S

Firm	ANDA/ DMF No.	Type	LOA Page	Function
[redacted]	DMF	II	109 + 7/1/98 NC	[redacted]
	DMF	V	148	
	DMF	III	622	
	DMF	III	626	
	DMF	III	627	
	DMF	III	629	
	DMF	III	630	

13. DOSAGE FORM
For Injection

14. POTENCY
1 g/20 mL
2 g/20 mL
1 g/100 mL piggyback
2 g/100 mL piggyback

15. CHEMICAL NAME AND STRUCTURE



Cefoxitin Sodium

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The CMC aspects of this submission are generally adequate. Minor deficiencies are noted with regard to the proposed Finished Product Specifications protocol and limits for impurities, as well as a very minor deficiency in the testing protocol for the stability program.

Outstanding issues with this application are:

- DMF for the Drug Substance under first review.
- EER (to be requested)
- Microbiology review pending
- Labelling review pending
- Review of request for waiver of *in vivo* bioequivalence study is ~~pending~~. acceptable 7/29/98 mAdams 8/4/98

19. REVIEWER: R. C. Adams
DATE COMPLETED: 7/31/98

Redacted 18 page(s)

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information from

CHEMISTRY REVIEW #1

cc: ANDA #65-102
DUP
Division File
Field Copy

Endorsed:
HFD-643/RAdams/7/31/98
HFD-643/JHarrison/7/31/98
HFD-600/MAnderson/7/31/98
X:\new\firmsam\american\ltrs&rev\65012.naf

7/31/98
R.C. adams
7/31/98
8/4/98

Facsimile Amendment

APPEARS THIS WAY
ON ORIGINAL

Office of Generic Drugs
Chemistry Manufacturing and Controls Review

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 65-012 mA

3. NAME AND ADDRESS OF APPLICANT
As received on 3/20/98:
Fujisawa USA, Inc.
3 Parkway North, 3rd Floor
Parkway North Center
Deerfield, IL 60015-2548

Change in ownership 6/1/98 to:
Corporate Address
American Pharmaceutical Partners
Mitchall Clark, Senior Director, Reg. Affairs
2825 Santa Monica Boulevard
Santa Monica, CA 90404
Phone: 310-264-7768

Correspondence Address
Mitchall Clark, Senior Director, Reg. Affairs
or
Genny Cruz, Senior Regulatory Scientist
American Pharmaceutical Partners
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: 708-343-6100

Manufacturing Facility
Fujisawa USA, Inc. (Lyphomed Division)
3159 Staley Road
Grand Island, NY 14072

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies that there is patent information submitted to the Agency with respect to Cefoxitin for Injection, USP, for which clearance is sought and that there is no marketing exclusivity in effect for the listed drug. (See page 7, Vol. 1)

Innovator: Merck Sharp Dohme Mefoxin®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Cefoxitin for Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

1. Original submission 3/20/98
2. Change of Ownership 6/1/98
3. NC: revised LOA for DMF #_____ 7/1/98
4. * Minor amendment response to deficiencies faxed on 8/18/98 9/10/98

FDA:

1. Telecon re: exhibit batch size 4/2/98
2. Acknowledgment letter 4/9/98
3. Fax transmission of minor CMC deficiencies. 8/18/98
3. Fax transmission granting waiver of *in vivo* bioequivalence studies 8/18/98

***Amendment being reviewed.**

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

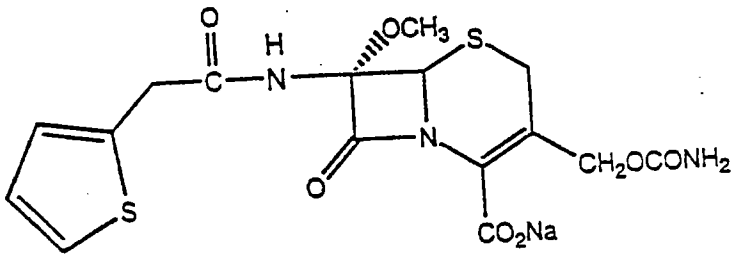
TABLE 1: RELATED NDA'S/DMF'S

Firm	ANDA/ DMF No.	Type	LOA Page	Function
	DMF	II	109 + 7/1/98 NC	
	DMF	V	148	
	DMF	III	622	
	DMF	III	626	
	DMF	III	627	
	DMF	III	629	
	DMF	III	630	

13. DOSAGE FORM
For Injection

14. POTENCY
10 g/100 mL Pharmacy Bulk Package

15. CHEMICAL NAME AND STRUCTURE



Cefoxitin Sodium

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The CMC aspects of this submission are generally adequate. Minor deficiencies were noted with regard to the proposed Finished Product Specifications protocol and limits for impurities, as well as a very minor deficiency in the testing protocol for the stability program.

These deficiencies were communicated to the firm in our facsimile transmission of August 18, 1998:

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CHEMISTRY REVIEW #2

cc: ANDA #65-012
Division File
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Endorsed:
HFD-643/RAdams/9/20/98 R. C. Adams, 11/2/98
HFD-643/JHarrison/9/21/98 J Harrison 11/2/98
HFD-617/MAnderson/10/28/98 Mark Anderson 11/2/98

F/T by tic 10/29/98
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NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

Office of Generic Drugs
Chemistry Manufacturing and Controls
Minor Amendment Review

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1. CHEMISTRY REVIEW NO. 3

2. ANDA # 65-012

3. NAME AND ADDRESS OF APPLICANT
As received on 3/20/98:
Fujisawa USA, Inc.
3 Parkway North, 3rd Floor
Parkway North Center
Deerfield, IL 60015-2548

Change in ownership 6/1/98 to:
Corporate Address
American Pharmaceutical Partners
Mitchall Clark, Senior Director, Reg. Affairs
2825 Santa Monica Boulevard
Santa Monica, CA 90404
Phone: 310-264-7768

Correspondence Address
Mitchall Clark, Senior Director, Reg. Affairs
or
Genny Cruz, Senior Regulatory Scientist
American Pharmaceutical Partners
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: 708-343-6100

Manufacturing Facility
Fujisawa USA, Inc. (Lyphomed Division)
3159 Staley Road
Grand Island, NY 14072

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies that there is patent information submitted to the Agency with respect to Cefoxitin for Injection, USP, for which clearance is sought and that there is no marketing exclusivity in effect for the listed drug. (See page 7, Vol. 1)

Innovator: Merck Sharp Dohme Mefoxin®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Cefoxitin for Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

1. Original submission 3/20/98
2. Change of Ownership 6/1/98
3. NC: revised LOA for DMF # [redacted] 7/1/98
4. Minor amendment response to deficiencies faxed on 8/18/98 9/10/98
5. Microbiology Review #1 ??????
6. Response to 11/12/98 fax deficiencies 12/15/98
7. Minor amendment: response to 11/12/fax deficiencies 3/9/99

FDA:

1. Telecon re: exhibit batch size 4/2/98
2. Acknowledgment letter 4/9/98
3. Chemistry Review #1 and fax transmission of minor CMC deficiencies. 8/18/98
4. Fax transmission granting waiver of *in vivo* bioequivalence studies 8/18/98
5. Fax transmission of labelling, micro deficiencies, Chemistry Review #2 (CMC OK) 11/12/99
6. Labeling approval summary 1/12/99
7. Microbiology Review #2 - unacceptable 5/19/99

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

TABLE 1: RELATED NDA'S/DMF'S

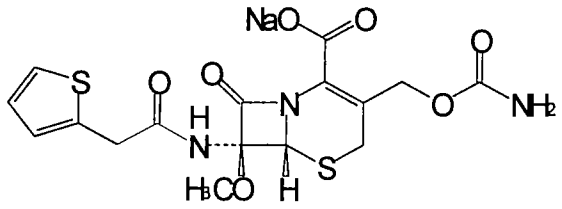
Firm	ANDA/ DMF No.	Type	LOA Page	Function
	DMF	II	109	
	DMF	II	auth. in # [redacted]	
	DMF	V	148	
	DMF	III	622	
	DMF	III	626	
	DMF	III	627	
	DMF	III	629	
	DMF	III	630	

13. DOSAGE FORM
For Injection

14. POTENCY
1 g and 2 g/vial

15. CHEMICAL NAME AND STRUCTURE

Cefoxitin Sodium. $C_{16}H_{16}N_3NaO_7S_2$. 449.44. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-methyl-8-oxo-7-[(2-thienylacetyl)amino]-, sodium salt (6*R-cis*)-. 33564-30-6, 35607-66-0. Antibacterial.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
All CMC issues in this application were acceptable as of the second review (11/18/98 fax deficiency date) except for the drug substance DMF's. Both the primary and secondary DMF's have since been amended and were reviewed and found acceptable.

A question was raised by the labeling reviewer regarding supporting data for the labeling claims for primary diluents and LVP diluent compatibilities. This had been reviewed earlier but had not been specifically commented upon in the reviews. These data are included in Attachment 30 and 31 of the application and a discussion is now incorporated in this review (Section 29). The claims were found to be adequately supported with data. However, the firm should provide a rationale for the unsupported LVP diluent compatibility claims.

Summary of Application Issues:

- DMF's for the Drug Substance (DMF #[redacted], acceptable with regard to CMC issues after amendment response to deficiency letters.
- EER acceptable 6/30/98
- Labelling review acceptable: approval summary 1/12/99.
- Biowaiver granted 8/18/98.
- Microbiology Review #2: DMF #[redacted] still not acceptable.
- In the minor amendment notice for the microbiology deficiencies, we will ask the firm for justification for the unsupported LVP diluent compatibility claims.

18. CONCLUSIONS AND RECOMMENDATIONS:
Microbiology review of DMF for drug substance remains unacceptable; firm will also be asked to provide a rationale for the unsupported diluent compatibility claims.

Application **NOT APPROVABLE, MINOR AMENDMENT** required.

19. REVIEWER: R. C. Adams
DATE COMPLETED: 6/10/99

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CHEMISTRY REVIEW #3

cc: ANDA #65-012
Division File
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HFD-643/RAdams/6/15/99 R. C. adams, 6/15/99
HFD-643/MShih/6/16/99 M. S. 6/16/99
HFD-617/MAnderson/6/16/99 6/17/99

F/T by:ps/6/14/99

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NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

Office of Generic Drugs
Chemistry Manufacturing and Controls
Minor Amendment Review

---

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 65-012

3. NAME AND ADDRESS OF APPLICANT
As received on 3/20/98:
Fujisawa USA, Inc.
3 Parkway North, 3rd Floor
Parkway North Center
Deerfield, IL 60015-2548

Change in ownership 6/1/98 to:
Corporate Address
American Pharmaceutical Partners
Mitchall Clark, Senior Director, Reg. Affairs
2825 Santa Monica Boulevard
Santa Monica, CA 90404
Phone: 310-264-7768

Correspondence Address
Mitchall Clark, Senior Director, Reg. Affairs
or
Genny Cruz, Senior Regulatory Scientist
American Pharmaceutical Partners
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: 708-343-6100

Manufacturing Facility
Fujisawa USA, Inc. (Lyphomed Division)
3159 Staley Road
Grand Island, NY 14072

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies that there is patent information submitted to the Agency with respect to Cefoxitin for Injection, USP, for which clearance is sought and that there is no marketing exclusivity in effect for the listed drug. (See page 7, Vol. 1)

Innovator: Merck Sharp Dohme Mefoxin®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Cefoxitin for Injection USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

1.	Original submission	3/20/98
2.	Change of Ownership	6/1/98
3.	NC: revised LOA for DMF #———	7/1/98
4.	Minor amendment	9/10/98
5.	Microbiology Review #1	9/28/98
6.	Response to 11/12/98 fax deficiencies	12/15/98
7.	Minor amendment	3/9/99
8.	Minor amendment	7/23/99

FDA:

1.	Telecon re: exhibit batch size	4/2/98
2.	Acknowledgment letter	4/9/98
3.	Chemistry Review #1 - CMC deficiencies	8/18/98
4.	Fax transmission: bio waiver granted	8/18/98
5.	Fax transmission of (labeling & micro)	11/12/99
6.	Labeling approval summary	1/12/99
7.	Microbiology Review #2 - unacceptable	5/19/99
8.	Chemistry Review #3 - CMC deficiencies	6/18/99

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

TABLE 1: RELATED NDA'S/DMF'S

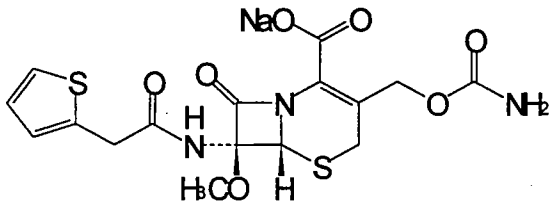
Firm	ANDA/ DMF No.	Type	LOA Page	Function
	DMF	II	109	
	DMF	II	auth. in #———	
	DMF	V	148	
	DMF	III	622	
	DMF	III	626	
	DMF	III	627	
	DMF	III	629	
	DMF	III	630	

13. DOSAGE FORM
For Injection

14. POTENCY
1 g and 2 g/vial

15. CHEMICAL NAME AND STRUCTURE

Cefoxitin Sodium. $C_{16}H_{16}N_3NaO_7S_2$. 449.44. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-methyl-8-oxo-7-[(2-thienylacetyl)amino]-, sodium salt (6*R-cis*)-. 33564-30-6, 35607-66-0. Antibacterial.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
All CMC issues in this application were acceptable as of the second review (11/18/98 fax deficiency date) except for the drug substance DMF's. Both the primary and secondary DMF's have since been amended and were reviewed and found acceptable.

A question was raised by the labeling reviewer regarding supporting data for the labeling claims for primary diluents and LVP diluent compatibilities. This had been reviewed earlier but had not been specifically commented upon in the reviews. These data are included in Attachment 36 and 37 of the application and a discussion is now incorporated in this review (Section 29). Most claims were adequately supported with data. For those not supported with data the firm provided an acceptable scientific rationale in their minor amendment dated 7/23/99.

Summary of Application Issues:

- DMF's for the Drug Substance (DMF #————————) acceptable with regard to CMC issues after amendment response to deficiency letters.

- EER was re-requested since firm added a new contract facility to perform diluent compatibility studies (———————). Results remain pending.
- Labeling review acceptable: approval summary 1/12/99.
- Biowaiver granted 8/18/98.
- Microbiology Review #3: DMF # ——— still not acceptable.
- Firm's justification for the unsupported LVP diluent compatibility claims found acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS:
Microbiology review of DMF for drug substance remains unacceptable. EER re-requested due to the addition of a new contract facility (———————). Results remain pending.

Application **NOT APPROVABLE, MINOR AMENDMENT** required.

19. REVIEWER: DATE COMPLETED:
R.C. Adams (Reviews 1-3) 9/21/99
S.M. Rosencrance (Review 4)

S M Rosencrance 9/22/99

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ON ORIGINAL

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CHEMISTRY REVIEW #4

cc: ANDA #65-012
Division File
Field Copy

Endorsed:
HFD-643/SRosencrance/9/21/99 S M Rosencrance 9/22/99
HFD-643/RAdams/9/22/99 R.C. adams, 9/22/99
HFD-617/MAnderson/9/22/99 M Anderson 9/22/99

F/T by smr/9/22/99

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NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

Office of Generic Drugs
Chemistry Manufacturing and Controls
Minor Amendment Review

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 65-012

3. NAME AND ADDRESS OF APPLICANT
As received on 3/20/98:
Fujisawa USA, Inc.
3 Parkway North, 3rd Floor
Parkway North Center
Deerfield, IL 60015-2548

Change in ownership 6/1/98 to:
Corporate Address
American Pharmaceutical Partners
Mitchall Clark, Senior Director, Reg. Affairs
2825 Santa Monica Boulevard
Santa Monica, CA 90404
Phone: 310-264-7768

Correspondence Address
Mitchall Clark, Senior Director, Reg. Affairs
or
Genny Cruz, Senior Regulatory Scientist
American Pharmaceutical Partners
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: 708-343-6100

Manufacturing Facility
Fujisawa USA, Inc. (Lyphomed Division)
3159 Staley Road
Grand Island, NY 14072

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies that there is patent information submitted to the Agency with respect to Cefoxitin for Injection, USP, for which clearance is sought and that there is no marketing exclusivity in effect for the listed drug. (See page 7, Vol. 1)

Innovator: Merck Sharp Dohme Mefoxin®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Cefoxitin for Injection USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

1.	Original submission	3/20/98
2.	Change of Ownership	6/1/98
3.	NC: revised LOA for DMF #———	7/1/98
4.	Minor amendment	9/10/98
5.	Microbiology Review #1	9/28/98
6.	Response to 11/12/98 fax deficiencies	12/15/98
7.	Minor amendment	3/9/99
8.	Minor amendment	7/23/99
9.	Minor amendment	11/24/99

FDA:

1.	Telecon re: exhibit batch size	4/2/98
2.	Acknowledgment letter	4/9/98
3.	Chemistry Review #1 - CMC deficiencies	8/18/98
4.	Fax transmission: bio waiver granted	8/18/98
5.	Fax transmission of (labeling & micro)	11/12/99
6.	Labeling approval summary	12/9/98
7.	Microbiology Review #2 - unacceptable	5/19/99
8.	Chemistry Review #3 - CMC deficiencies	6/18/99
9.	Microbiology Review #3 - unacceptable	8/27/99
10.	Chemistry Review #4 - unacceptable	9/21/99

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

TABLE 1: RELATED NDA'S/DMF'S

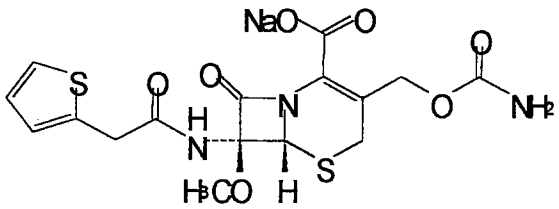
Firm	ANDA/ DMF No.	Type	LOA Page	Function
	DMF	II	109	
	DMF	II	auth. in #———	
	DMF	V	148	
	DMF	III	622	
	DMF	III	626	
	DMF	III	627	
	DMF	III	629	
	DMF	III	630	

13. DOSAGE FORM
For Injection

14. POTENCY
1 g and 2 g/vial

15. CHEMICAL NAME AND STRUCTURE

Cefoxitin Sodium. $C_{16}H_{16}N_3NaO_7S_2$. 449.44. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-methyl-8-oxo-7-[(2-thienylacetyl)amino]-, sodium salt (6*R-cis*)-. 33564-30-6, 35607-66-0. Antibacterial.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
All CMC issues in this application were acceptable as per the 4th review cycle.

Summary of Application Issues:

- DMF's for the Drug Substance (DMF # [redacted]) acceptable with regard to CMC issues after amendment response to deficiency letters.
- EER acceptable as of 9/30/99
- Labeling review acceptable: approval summary 12/9/98.
- Biowaiver granted 8/18/98.
- Microbiology Review #4: DMF #[redacted] continues to be unacceptable.

18. CONCLUSIONS AND RECOMMENDATIONS:
Microbiology review of DMF ——— remains unacceptable.

Application **NOT APPROVABLE, MINOR AMENDMENT** required.

19. REVIEWER: DATE COMPLETED:
R.C. Adams (Reviews 1-3) 1/28/00
S.M. Rosencrance (Review 4-5)

S M Rosencrance 1/31/00

APPEARS THIS WAY
ON ORIGINAL

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CHEMISTRY REVIEW #5

cc: ANDA #65-012
Division File
Field Copy

Endorsed:
HFD-643/SRosencrance/1/28/00 S M Rosencrance 1/31/00
HFD-643/RAdams/1/28/00 R. C. Adams 1/31/00
HFD-617/MAnderson/1/29/00 M Anderson 1/31/00

F/T by MDA/1/29/00

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NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

Office of Generic Drugs
Chemistry, Manufacturing, and Control Review

---

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 65-012

3. NAME AND ADDRESS OF APPLICANT
As received on 3/20/98:
Fujisawa USA, Inc.
3 Parkway North, 3rd Floor
Parkway North Center
Deerfield, IL 60015-2548

Change in ownership 6/1/98 to:
Corporate Address
American Pharmaceutical Partners
Mitchall Clark, Senior Director, Reg. Affairs
2825 Santa Monica Boulevard
Santa Monica, CA 90404
Phone: 310-264-7768

Correspondence Address
Mitchall Clark, Senior Director, Reg. Affairs
or
Genny Cruz, Senior Regulatory Scientist
American Pharmaceutical Partners
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: 708-343-6100

Manufacturing Facility
Fujisawa USA, Inc. (Lyphomed Division)
3159 Staley Road
Grand Island, NY 14072

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies that there is patent information submitted to the Agency with respect to Cefoxitin for Injection, USP, for which clearance is sought and that there is no marketing exclusivity in effect for the listed drug. (See page 7, Vol. 1)

Innovator: Merck Sharp Dohme Mefoxin®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Cefoxitin for Injection USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

1.	Original submission	3/20/98
2.	Change of Ownership	6/1/98
3.	NC: revised LOA for DMF # ———	7/1/98
4.	Minor amendment	9/10/98
5.	Microbiology Review #1	9/28/98
6.	Response to 11/12/98 fax deficiencies	12/15/98
7.	Minor amendment	3/9/99
8.	Minor amendment	7/23/99
9.	Minor amendment	11/24/99
10.	Minor amendment	3/22/00
11.	Labeling amendment	4/26/00
12.	Labeling amendment	6/1/00
13.	Commitment	6/12/00

FDA:

1.	Telecon re: exhibit batch size	4/2/98
2.	Acknowledgment letter	4/9/98
3.	Chemistry Review #1 - CMC deficiencies	8/18/98
4.	Fax transmission: bio waiver granted	8/18/98
5.	Fax transmission of (labeling & micro)	11/12/99
6.	Labeling approval summary	12/9/98
7.	Microbiology Review #2 - unacceptable	5/19/99
8.	Chemistry Review #3 - CMC deficiencies	6/18/99
9.	Microbiology Review #3 - unacceptable	8/27/99
10.	Chemistry Review #4 - unacceptable	9/21/99
11.	Microbiology Review #4 - unacceptable	1/21/00
12.	Chemistry Review #5 - unacceptable	1/31/00
13.	Microbiology Review #5 - acceptable	4/4/00
14.	Labeling Review - unacceptable	5/11/00
15.	Labeling Review - acceptable	6/9/00

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

TABLE 1: RELATED NDA'S/DMF'S

Firm	ANDA/ DMF No.	Type	LOA Page	Function
———	DMF ———	II	109	———

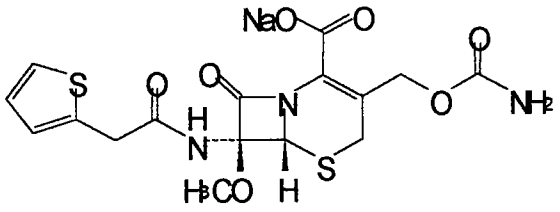
DMF	II	auth. in # [redacted]
DMF	V	148
DMF	III	622
DMF	III	626
DMF	III	627
DMF	III	629
DMF	III	630

13. DOSAGE FORM
For Injection

14. POTENCY
1 g and 2 g/vial

15. CHEMICAL NAME AND STRUCTURE

Cefoxitin Sodium. $C_{16}H_{16}N_3NaO_7S_2$. 449.44. 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-methyl-8-oxo-7-[(2-thienylacetyl)amino]-, sodium salt (6*R-cis*)-. 33564-30-6, 35607-66-0. Antibacterial.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
All CMC issues in this application were acceptable as per the 4th review cycle.

Summary of Application Issues:

- DMF's for the Drug Substance (DMF # [redacted]) acceptable with regard to CMC issues after amendment response to deficiency letters.

- EER acceptable as of 9/30/99
- Labeling review acceptable: approval summary 6/9/00
- Biowaiver granted 8/18/98
- Microbiology Review #5: DMF #——— found acceptable

18. CONCLUSIONS AND RECOMMENDATIONS:
Microbiology review of DMF ——— found acceptable. All labeling issues resolved.

Application is ready for **APPROVAL**

19. REVIEWER:
R.C. Adams (Reviews 1-3)
S.M. Rosencrance (Review 4-6)

DATE COMPLETED:
6/14/00

S M Rosencrance
6/19/00

APPEARS THIS WAY
ON ORIGINAL

Redacted 19 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #6

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA #65-012
Division File
Field Copy

Endorsed:
HFD-643/SRosencrance/6/14/00
HFD-643/RAdams/6/15/00
F/T by smr/6/19/00

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APPROVAL

R.C. Adams 6/21/00

APPEARS THIS WAY
ON ORIGINAL

ANDA APPROVAL SUMMARY

ANDA: 65-012

DRUG PRODUCT: Cefoxitin for Injection USP

FIRM: American Pharmaceutical Partners (APP)

DOSAGE FORM: Sterile Powder (IM/IV)

STRENGTHS/CONFIGURATIONS: 1 g/20 mL vial, 2 g/20 mL vial, 1 g/100 mL piggyback vial, 2 g/100 mL piggyback vial

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification provided on page 136 (3/20/98 submission). Acceptable EER dated 9/30/99.

BIO STUDY: Bio-study waiver request under CFR 320.22(b) was granted by the Division of Bioequivalence (8/18/98).

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and product are USP. The applicant is using the USP method with slight modification for assaying the bulk drug and finished product. The firm's method was validated and shown to yield comparable results with the USP method.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): The container/closure system used in the stability study was identical to that described in the container section.

LABELING: FPL found acceptable 6/9/00 (see approval summary)

STERILIZATION VALIDATION (IF APPLICABLE): Application recommended for approval on the basis of sterility assurance (see Micro Review #5; 4/4/00).

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): A waiver was granted for a bio-study (no bio batches available).

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): The exhibit batches were manufactured with bulk drug from [redacted]. The batches produced yields that were 10% of full scale production. Samples from the batches were used in generating accelerated and room temperature stability data to support the 24 month expiry date. The submission included data or justification to support

stability claims made in the package insert regarding reconstitution, dilution and admixture.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch sizes are 10% greater than the yield from the exhibit batches. The manufacturing process described in the master production record is comparable to that described in the exhibit batch record.

CHEMIST: Susan Rosencrance **DATE:** S M Rosencrance 6/17/00

TEAM LEADER: Richard Admas **DATE:** R. C. adams 6/21/00

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-012

BIOEQUIVALENCE REVIEWS

Cefoxitin for Injection
Sterile Powder
1 g/20 mL Vial, 2g/20 mL Vial,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial
ANDA 65-012
Reviewer: James E. Chaney
WP #65012w.398

Fujisawa USA, Inc.
Deerfield, Illinois
Submission Date
March 20, 1998

Review of a Waiver Request for a Sterile Powder for Injection

The firm has requested that the *in-vivo* bioequivalence requirements for its Cefoxitin for Injection, USP (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial) be waived under the provisions of 21 CFR 320.22(b)(1). The drug is a broad-spectrum cepha antibiotic.

Comments:

1. The test products are identical in formulation to the reference strengths of Mefoxin®, manufactured by Merck Sharp and Dohme.

2. The reference and test dosage forms each contain sterile Cefoxitin Sodium, USP equivalent to the label strengths of Cefoxitin and each contains no inactive ingredients except for head space nitrogen.

3. The firm claims that the reference products are approved for intravenous or intramuscular administration after reconstitution, depending on the amounts of diluents used. Similarly, the firm reports that the test products are intended for intravenous or intramuscular administration after reconstitution.

   It should be noted that according to current labeling the reference products are only for intravenous administration.

   If the products are intended for intramuscular administration the powder upon reconstitution must be completely dissolved as a requirement to receive a waiver of bioequivalence study requirements.

   The Division of Labeling should be made aware of this matter.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Fujisawa USA, Inc. demonstrates that Cefoxitin for Injection, (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial) falls under 21 CFR Section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of the *in-vivo* bioequivalence study requirements on Cefoxitin for Injection, (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial) is granted for intravenous administration only. From the bioequivalence point of view, the Division of Bioequivalence deems the test Cefoxitin for Injection (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial) to be bioequivalent to the approved Mefoxin®, (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial) manufactured by Merck, Sharp and Dohme.

The waiver is granted for intravenous administration only, since the current labeling of the listed reference drug does not include intramuscular administration (Physicians Desk Reference, 1998).

If the test products are intended for intramuscular administration the powder upon reconstitution must be completely dissolved as a requirement to receive a waiver of bioequivalence study requirements.

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang Date 7/23/98

Concur: Dale P. Conner Date 7/23/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/072398
X:\NEW\FIRMSAM\FUJISAWA\LTRS&REV\65012W.398

cc: ANDA # 65-012 (original, duplicate), Chaney HFD-652, Drug File, Division File

ANDA: 65-012 APPLICANT: Fujisawa USA, Inc.

DRUG PRODUCT: Cefoxitin for Injection, USP (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial)

The Division of Bioequivalence has completed its review and has no further questions at this time assuming per currently approved labeling that the products are for intravenous administration only.

In general, a waiver of bioequivalence study requirements for a drug powder intended for intramuscular administration requires complete dissolution of the drug powder upon reconstitution.

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

Sincerely yours,

Dale P. Conner

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

CC: ANDA 65-012
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Secretary - Bio Drug File
HFD-652/ J. Chaney
HFD-652/ Y. Huang
BIO DRUG FILE

HFD-652/ J. Chaney J. Chaney 7/23/98
HFD-652/ Y. Huang 7/23/98
HFD-617/ L. Sanchez
HFD-650/ D. Conner 7/23/98

X:\NEW\FIRMSAM\FUJISAWA\LTRS&REV\65012W.398
07/21/98

BIOEQUIVALENCY - ACCEPTABLE

1. **WAIVER** (WAI) Strengths: Cefoxitin for Injection, USP (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial)

submission date: 03-20-98

OUTCOME DECISIONS: **AC** - Acceptable

WINBIO COMMENTS:

Waiver of the bioequivalence study requirements is granted provided the products are for intravenous injection only.

OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 65-012 **SPONSOR:** Fujisawa USA, Inc.

DRUG & DOSAGE FORM: Cefoxitin for Injection, Sterile Powder

STRENGTH(s): 1 g/20 mL Vial, 2g/20 mL Vial,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial

TYPE OF STUDIES: Waiver request

STUDY SITES: Not applicable

STUDY SUMMARY: The test products are identical in formulation to the reference products, Mefoxin®, manufactured by Merck Sharp and Dohme. Waiver is granted for i.v. administration.

DISSOLUTION: Not applicable

PRIMARY REVIEWER: James E. Chaney, Ph.D. **BRANCH:** I

INITIAL: James E. Chaney **DATE:** 7/23/98

BRANCH CHIEF: Yih Chain Huang, Ph.D. **BRANCH:** I

INITIAL: [signature] **DATE:** 7/23/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: DPC **DATE:** 7/23/98

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: _____ **DATE:** _____

Cefoxitin for Injection, USP
Sterile Powder
1 g/20 mL Vial, 2g/20 mL Vial
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial
ANDA 65-012
Reviewer: James E. Chaney
V:\FIRMSAM\FUJISAWA\LTRS&REV\65012adm.398

Fujisawa USA, Inc.
Deerfield, Illinois
Submission Date
March 20, 1998

Addendum to Review of a Waiver Request for A Sterile Powder for Injection

In the original March 20, 1998 submission the firm requested that the *in-vivo* bioequivalence requirements for its cefoxitin for injection, USP (1 g/20 mL vial, 2 g/20 mL vial, 1 g/100 mL piggyback vial, and 2 g/100 mL piggyback vial) be waived under the provisions of 21 CFR 320.22(b)(1). The waiver request was denied for intramuscular administration and granted for intravenous administration (review of July 23, 1998). The bioequivalence review is herein revised to grant a waiver for both routes of administration.

Comments:

1. The test products are identical in formulation to the reference strengths of Mefoxin®, manufactured by Merck Sharp and Dohme.

2. The reference and test dosage forms each contain sterile cefoxitin sodium, USP equivalent to the labeled strength of cefoxitin and each contains no inactive ingredients except for head space nitrogen.

3. Formerly, the listed reference drug labeling provided for intramuscular administration of the 1 and 2 gram doses reconstituted in 2 mL and 4 mL of water (or aqeuous 0.5% lidocaine hydrochloride solution), respectively. The generic applicant has included the former RLD labeling which provides for its proposed intramuscular or intravenous administration (Volume 1.1, p 43).

4. As noted in the July 23, 1998 bioequivalence review, according to the then current labeling (1998 PDR) the reference products were for intravenous administration only. Also, according to the 1999 PDR these products are for

intravenous administration only. The Division of Labeling reviewer, Jacqueline White, suggests that the package insert should include both routes of administration (see her attached email of January 4, 2000, Attachment 1).

5. According to policy of the Division of Bioequivalence if a powdered drug product for injection is intended for intramuscular administration the drug substance upon reconstitution must be completely dissolved as a requirement for a waiver of bioequivalence study requirements to be granted.

   The Division of Bioequivalence has recently been advised *via* the attached email (Attachment 1) from Susan Rosencrance (reviewer in the Division of Chemistry) to Lizzie Sanchez of the Division of Bioequivalence that there should be no problem concerning the complete dissolution of this drug at the proposed IM concentrations (1 and 2 gram doses reconstituted in 2 ml and 4 mL of diluent, respectively) based on solubility information derived from the Merck Index and the U.S. Pharmacopeia.

   Also, AHFS Drug Information 1999 reports that 1 and 2 grams of sterile cefoxitin sodium reconstituted in 2 mL and 4 mL of water, respectively, yield solutions containing 400 mg of cefoxitin per mL.

6. The waiver may be granted for both intravenous and intramuscular administration.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Fujisawa USA, Inc. demonstrates that cefoxitin for injection, (1 g/20 mL vial, 2 g/20 mL vial, 1 g/100 mL piggyback vial, and 2 g/100 mL piggyback vial) falls under 21 CFR Section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of the *in-vivo* bioequivalence study requirements on cefoxitin for injection, (1 g/20 mL vial, 2 g/20 mL vial, 1 g/100 mL piggyback vial, and 2 g/100 mL piggyback vial) is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test cefoxitin for injection (1 g/20 mL vial, 2 g/20 mL vial, 1 g/100 mL piggyback vial, and 2 g/100 mL piggyback vial) to be bioequivalent to the approved Mefoxin®, (1

g/20 mL vial, 2 g/20 mL vial, 1 g/100 mL piggyback Vial, and 2 g/100 mL piggyback vial) manufactured by Merck, Sharp and Dohme.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang Date 1/12/00

Concur Date 1/24/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/011100
V:\FIRMSAM\FUJISAWA\LTRS&REV\65012adm.398

Attachment 1
T 1/5012 adm. 398

Printed by James Chaney

Electronic Mail Message

Date: 05-Jan-2000 10:41am
From: Susan Rosencrance
ROSENCRANCES
Dept: HFD-643 MPN2 E240
Tel No: 301-827-5779 FAX 301-594-3839

Subject: Cefoxitin Sodium for IM use

Lizzie: Based on the Merck and USP definitions cefoxitin sodium is very soluble in water. From chemistry's standpoint we don't have a concern about the drug not forming a solution when diluted to the IM concentrations.

Susan

APPEARS THIS WAY
ON ORIGINAL

Attachment 2 to
5012 adm. 398

Printed by James Chaney

Electronic Mail Message

Date: 04-Jan-2000 05:06pm
From: Jacqueline White
WHITEJ
Dept: HFD-613 MPN2 200N
Tel No: 301-827-5846 FAX 301-594-0183

Subject: FWD: RE: ESI's Cefoxitin for Injection, ANDA 65-051

Good afternoon,

This ANDA's package insert labeling should contain both the IV and IM routes of administration. Most likely the IM dosage form is a suspension. Therefore, I thought we should notify bio., since a bio. waiver was granted for the IV route of administration. In addition, chemistry should be notified since additional stability tests by be required. We plan to request the firm to add the IM routes of administration to their labeling to be consistent with our Office policy.

Jacqueline

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS

ANDA: 65-012 APPLICANT: Fujisawa USA, Inc.

DRUG PRODUCT: Cefoxitin for Injection, USP (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial)

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

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

Sincerely yours,

Dale P. Conner

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

CC: ANDA 65-012
ANDA DUPLICATE
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DRUG FILE

HFD-652/ J. Chaney J. Chaney 1/13/00
HFD-652/ Y. Huang a/l for Y.C. Huang
HFD-617/ J. Fan J. Fan 1/28/00
HFD-650/ D. Conner DR 1/24/00

V:\FIRMSAM\FUJISAWA\LTRS&REV\65012ADM.398

BIOEQUIVALENCY - ACCEPTABLE Submission date: October 12, 1999

1. **WAIVER** (WAI) Strengths: 1 g/20 mL Vial, 2 g/20 mL Via, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial AC

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:

Waiver of the bioequivalence study requirements is granted.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 65-012 SPONSOR : Fujisawa USA, Inc.

DRUG & DOSAGE FORM: Cefoxitin for Injection, Sterile Powder

STRENGTH(s): 1 g/20 mL Vial, 2g/20 mL Vial,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial

TYPE OF STUDIES: Waiver request

STUDY SITES: Not applicable

STUDY SUMMARY: Waiver of bioequivalence testing is granted.

DISSOLUTION: Not applicable

~~DSI INSPECTION STATUS~~

Inspection needed: NO (Not applicable)	Inspection status:	Inspection results:
First Generic_____ New facility_____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : James Chaney BRANCH : I
INITIAL : JEC DATE : 1/13/00

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : a/f for Y.C. Huang DATE : 1/14/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : _____ DATE : 1/27/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-012

MICROBIOLOGY REVIEWS

OFFICE OF GENERIC DRUGS, HFD-640

Microbiology Review #1

September 22, 1998

A. 1. ANDA 65-012

APPLICANT APP (American Pharmaceutical Partners) Inc
[formerly Fujisawa USA Inc]
2045 North Cornell
Melrose Park Il 60160

2. PRODUCT NAME: Cefoxitin for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 g/20 mL Vial, 2 g/20 mL vial, 1 g/100 mL Piggyback Vial, 2 g/100 mL Piggyback Vial, Intravenous, Intramuscular (20 mL Vials only)

4. METHOD(S) OF STERILIZATION: ———————

5. PHARMACOLOGICAL CATEGORY: Anti-Infective

B. 1. DATE OF INITIAL SUBMISSION: March 20, 1998
Subject of this Review (Received, March 24, 1998)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: DMF ——
DMF ——
DMF ——
DMF ——

4. ASSIGNED FOR REVIEW: 9/9/98

C. REMARKS: The subject drug product is [redacted]

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant". The referenced DMF ——— is deficient. The DMF holder will be notified.

9/28/98
Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\65-012 10/5/98
Initialed by M. Fanning, R. Patel, F. Fang/F. Holcombe, Jr.

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #1

Microbiology Comments to be Provided to the Applicant

ANDA: 65-012 APPLICANT: American Pharmaceutical Partners

DRUG PRODUCT: Cefoxitin Sodium USP, **1 g/20 mL Vial, 2 g/20 mL vial, 1 g/100 mL Piggyback Vial, 2 g/100 mL Piggyback Vial**

Microbiology Deficiency:

The ———— DMF ———— is deficient.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCY". The "RESPONSE TO MICROBIOLOGY DEFICIENCY" should also be noted in your cover page/letter.

Sincerely yours,

MD, PhD for.

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #2
May 19, 1999

A. 1. **ANDA 65-012**

APPLICANT APP (American Pharmaceutical Partners) Inc
[formerly Fujisawa USA Inc]
2045 North Cornell
Melrose Park Il 60160

2. PRODUCT NAME: Cefoxitin for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 g/20 mL, 2g /20 mL, 1 g/ 100 mL and 2 g/100 mL, Intravenous

4. METHOD(S) OF STERILIZATION: ———————

5. PHARMACOLOGICAL CATEGORY: Anti-Infective

B. 1. DATE OF INITIAL SUBMISSION: March 20, 1998
(Received, March 24, 1998)

2. DATE OF AMENDMENT: March 9, 1999
Subject of this Review (Received, March 10, 1999)

3. RELATED DOCUMENTS: DMF ———

4. ASSIGNED FOR REVIEW: 5/19/99

C. REMARKS: The subject drug amendment is in response to the microbiology deficiency in the correspondence dated November 12, 1998.

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant". The referenced DMF ——— is deficient. The DMF holder will be notified.

Andrea S. High 5/19/99
Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:\wp\microrev\65-012a
Initialed by M. Fanning 6/7/99

E. REVIEW NOTES:

The applicant has responded to the microbiology deficiency in the correspondence dated November 2, 1999. The authorization to access DMF [redacted] for the [redacted] was provided.

Comment:

[redacted] DMF [redacted] is deficient.

APPEARS THIS WAY
ON ORIGINAL

Microbiology Comments to be Provided to the Applicant

ANDA: 65-012 APPLICANT: APP Inc

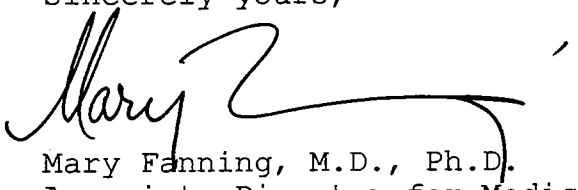
DRUG PRODUCT: Cefoxitin Sodium for Injection, 1 g/20 mL, 2 g/20 mL, 1 g/100 mL and 2 g/ 100 mL

Microbiology Deficiency:

_____ DMF _____ is deficient.

Please clearly identify your amendment as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,



Mary Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS, HFD-640

Microbiology Review #3

August 27, 1999

A. 1. **ANDA 65-012**

APPLICANT APP (American Pharmaceutical Partners) Inc
[formerly Fujisawa USA Inc]
2045 North Cornell
Melrose Park IL 60160

2. PRODUCT NAME: Cefoxitin for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 g/20 mL, 2g /20 mL, 1 g/ 100 mL and 2 g/100 mL, Intravenous

4. METHOD(S) OF STERILIZATION: ———————

5. PHARMACOLOGICAL CATEGORY: Anti-Infective

B. 1. DATE OF INITIAL SUBMISSION: March 20, 1998
(Received, March 24, 1998)

2. DATE OF AMENDMENT: July 23, 1999
Subject of this Review (Received, July 26, 1999)

3. RELATED DOCUMENTS: DMF ———

4. ASSIGNED FOR REVIEW: 8/26/99

C. REMARKS: The subject drug amendment is in response to the correspondence dated June 18, 1999.

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant". The referenced DMF——— is deficient. The DMF holder will be notified.

Andrea S. High 9/13/99
Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 v:microrev\65-012a2
Initialed by M. Fanning 9/14/99

E. REVIEW NOTES:

The applicant has responded to the correspondence dated June 18, 1999. The letter indicating the response to the microbiology deficiencies from the DMF Holder for DMF Type ——— for the ——————————— was provided.

Comment:

——————— DMF ——————— was reviewed and found deficient.

Microbiology Comments to be Provided to the Applicant

ANDA: 65-012 APPLICANT: APP Inc

DRUG PRODUCT: Cefoxitin Sodium for Injection, 1 g/20 mL, 2 g/20 mL, 1 g/100 mL and 2 g/ 100 mL

Microbiology Deficiency:

_____ DMF _____ was reviewed and found deficient.

Please clearly identify your amendment as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS, HFD-640
Microbiology Review #4
January 21, 2000

A. 1. **ANDA 65-012**

APPLICANT APP (American Pharmaceutical Partners) Inc
[formerly Fujisawa USA Inc]
2045 North Cornell
Melrose Park Il 60160

2. PRODUCT NAME: Cefoxitin for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 g/20 mL, 2g /20 mL, 1 g/ 100 mL and 2 g/100 mL, Intravenous

4. METHOD(S) OF STERILIZATION: ———————

5. PHARMACOLOGICAL CATEGORY: Anti-Infective

B. 1. DATE OF INITIAL SUBMISSION: March 20, 1998
(Received, March 24, 1998)

2. DATE OF AMENDMENT: November 24, 1999
Subject of this Review (Received November 26, 1999)

3. RELATED DOCUMENTS: DMF ———

4. ASSIGNED FOR REVIEW: 1/21/00

C. REMARKS: The subject drug amendment is in response to the correspondence dated September 23, 1999.

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant". The referenced DMF ——— is deficient. The DMF holder will be notified.

Andrea S. High 1/21/00
Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 v:microrev\65-012a3
Initialed by M. Fanning MF 1/24/00

E. REVIEW NOTES:

The applicant has responded to the correspondence dated September 23, 1999. The letter indicating the response to the microbiology deficiencies from the DMF Holder for DMF ——— for the ——— was provided.

Comment:

——— DMF ——— was reviewed and found deficient.

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS, HFD-640

Microbiology Review #5

April 4, 2000

A. 1. **ANDA:** **65-012**

APPLICANT: APP (American Pharmaceutical Partners), Inc.
[formerly Fujisawa USA Inc]
2045 North Cornell
Melrose Park, IL 60160

2. PRODUCT NAME: Cefoxitin for Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 1 g/20 mL, 2 g/20 mL, 1 g/100 mL and 2 g/100 mL; Intravenous injection

4. METHOD OF STERILIZATION: ———————

5. PHARMACOLOGICAL CATEGORY: Anti-Infective

B. 1. DATE OF INITIAL SUBMISSION: March 20, 1998 (Received, March 24, 1998)

2. DATE OF AMENDMENT: March 22, 2000 (Received March 23, 2000)

Subject of this Review

3. RELATED DOCUMENTS: DMF ——

4. ASSIGNED FOR REVIEW: March 29, 2000

C. REMARKS: The subject amendment is in response to the correspondence dated February 2, 2000.

D. CONCLUSIONS: The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes". The referenced Drug Master File (DMF ——→ is no longer deficient.

Paul C. DeLeo 4/4/2000
Paul C. DeLeo, Ph.D.

CSH 4/5/00

c: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by P. DeLeo HFD 600 V:\MICROREV\65-012A5.DOC
Initialed by A. High

E. REVIEW NOTES: The applicant responded to the letter dated February 2, 2000. A copy of the letter indicating the response to the microbiology deficiency was provided by the DMF Holder for DMF ——— for the ———.

Deficiency: ——— DMF ——— was reviewed and found deficient.

Response: The applicant reported that ——— responded to the deficiencies found in DMF ———.

Comment: The referenced Drug Master File (DMF ———) is no longer deficient.

ACCEPTABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-012

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

DATE: April 2, 1998

DRUG PRODUCT: Cefoxitin

ANDA NUMBER: 65-012

COMPANY: Fujisawa

NAME OF COMPANY REPRESENTATIVE(S): Genny Cruz

NAME OF OGD REPRESENTATIVE(S): Nasser Mahmud

Telecon initiated by: Nasser Mahmud

COMPANY TELEPHONE: 847-317-8679

I called Genny because the test batch for 2g/20mL and 2g/100mL was less than 10% of the proposed production batch. She said she would call back after looking into this. If an explanation can not be provided, revised production batch records would have to be submitted.

RECORD OF TELEPHONE CONVERSATION

DATE: April 3, 1998

DRUG PRODUCT: Cefoxitin

ANDA NUMBER: 65-012

COMPANY: Fujisawa

NAME OF COMPANY REPRESENTATIVE(S): Genny Cruz

NAME OF OGD REPRESENTATIVE(S): Nasser Mahmud

Telecon initiated by: Genny Cruz

COMPANY TELEPHONE: 847-317-8872

Genny called back to point out that the batch information requested is on pages 435 and 578.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-012

CORRESPONDENCE

FUJISAWA USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

March 20, 1998

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Park Building Room 2-14
12420 Parklawn Drive
Rockville, MD 20852

Re: Cefoxitin for Injection, USP (SDV)
1 g/20 mL Vial, 2 g/20 mL Vial ,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial
Manufacturing Site: Grand Island, NY
Number of Volumes: 3 Volumes

Dear Mr. Sporn:

Fujisawa USA, Inc. is submitting this application, in duplicate, as an Abbreviated New Drug Application in accordance with Section 505 of the Federal Food, Drug and Cosmetic Act to seek marketing clearance for Cefoxitin for Injection, USP. Enclosed, for your conveniences, are three copies of the analytical methods and validation section for the drug substance and finished dosage form.

Fujisawa USA, Inc. will manufacture this product at 3159 Staley Road, Grand Island, NY 14072. This application contains information describing the manufacturing and control of Cefoxitin for Injection, USP (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial) using ———— stopper and Type I USP glass vial. Applicable general procedural approaches and data may be cross-referenced to Fujisawa USA, Inc., Type V DMF # 11713. In addition, this application contains a request for the waiver of *in vivo* bioequivalence studies.

This application has been formatted according to the information in Office of Generic Drugs Policy and Procedure Guide #30-91, April 10, 1991 and letters to industry dated October 14, 1994 and December 24, 1996. An executive summary explaining the organization of this application is included after the cover letter.

An archival and review copy of this submission are provided for your review. Furthermore, a field copy has been sent to the FDA Buffalo District Office in accordance with 21 CFR §314.94(d)(5). Fujisawa USA, Inc. certifies that the field copy is a true copy of the Abbreviated New Drug Application submitted herewith. Also, note that the pharmacy bulk package application is being submitted to the FDA simultaneously with this single dose vial application.

Should you have any questions or require additional information, please do not hesitate to contact the undersigned at **(847) 317-8679** or Mr. Donald E. Baker, J.D. at **(847) 317-8872.** The facsimile number is **(847) 317-7286.**

Sincerely,

Genny Cruz
Senior Regulatory Scientist

L:\WP60\APP\ANDA\02.168

ANDA 65-012

Fujisawa USA, Inc.
Attention: Donald E. Baker
3 Parkway North, 3rd Floor
Parkway North Center
Deerfield, IL 60015-2548

APR 09 1998

Dear Sir:

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

Reference is also made to the telephone conversations dated April 2, 1998 and April 3, 1998.

NAME OF DRUG: Cefoxitin for Injection USP, 1g(base)/vial and 2g(base)/vial

DATE OF APPLICATION: March 20, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 24, 1998

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.

APPEARS THIS WAY
ON ORIGINAL

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 65-012
cc: DUP/Jacket
Division File
Field Copy
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett

Endorsement: HFD-615/PRickman, Chief, RSB _____ date 4/7/98
HFD-615/NMahmud, CSO _____ date 4/6/98
HFD-643/JHarrison, Sup. Chem. _____ date
WP File x:\new\firmsam\fujisawa\ltrs&rev\65012.ack
FT/njg/4/6/98
ANDA Acknowledgment Letter!

ARCHIVAL

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

June 1, 1998

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

RE: ANDA 65-012
Cefoxitin for Injection, USP (Single Dose Vial)
Pending Approval

CHANGE IN OWNERSHIP OF AN APPLICATION

Dear Mr. Sporn:

In accordance with the provisions of 21 CFR 314.72, the ownership of the above identified ANDA is being transferred in its entirety, effective June 1, 1998, from Fujisawa USA, Inc. (FUSA) to American Pharmaceutical Partners, Inc. (APP).

FUSA affirms that all of the rights to the referenced ANDA have been transferred to APP and that a complete copy of the ANDA including all amendments and FDA correspondence have been provided to APP.

The name and address of the new primary contact person at APP is:

CORPORATE ADDRESS
Mitchall Clark
Senior Director, Regulatory Affairs
American Pharmaceutical Partners, Inc.
2825 Santa Monica Boulevard
Santa Monica, CA 90404
Phone: (310)264-7768

CORRESPONDENCE ADDRESS
Mitchall Clark
Senior Director, Regulatory Affairs
American Pharmaceutical Partners, Inc.
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: (708)343-6100

All FDA correspondence should be forwarded to the correspondence address.

Please change your records to reflect this change in the ownership of the ANDA and acknowledge receipt of this letter. All future communications regarding this ANDA should be sent to APP.

Sincerely,

Jerry D. Johnson

Jerry D. Johnson, Ph.D.
Vice President, Regulatory Affairs and Pharmacovigilance

cc: Mitchall Clark
Senior Director, Regulatory Affairs (APP)

RECEIVED 1
JUN 0 2 1998
GENERIC DRUGS

L:\RA\WP60\TRANSFER\CEFOX.012

AMERICAN PHARMACEUTICAL PARTNERS, INC.

ARCHIVAL

July 1, 1998

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
NC

Re: ANDA 65-012
Cefoxitin for Injection, USP (SDV)
1 g/20 mL Vial, 2 g/20 mL Vial ,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial
Manufacturing Site: Grand Island, NY

GENERAL CORRESPONDENCE

Dear Mr. Sporn:

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment to the above mentioned product to provide a revised letter of authorization from——— permitting FDA to cross reference to their Drug Master File No. —— for ———

Please note that at the time of our ANDA submission on March 20, 1998, the AADA No. or DMF No. for ——— was not available yet due to the repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act. In light of this, a letter of authorization, with no assigned AADA or DMF No., from ——— has been included in the ANDA submission based on our February 11, 1998 telephone conversation with FDA.

Enclosed herewith in **Attachment 1** is——— revised letter of authorization to DMF—— on behalf of APP. A field copy of this amendment has been sent to the FDA Buffalo District Office in accordance with 21 CFR §314.94(d)(5). APP certifies that the field copy is a true copy of the amendment submitted herewith.

RECEIVED
JUL 02 1998
GENERIC DRUGS

2045 NORTH CORNELL
MELROSE PARK, ILLINOIS 60160

TEL (708) 343-6100
FACSIMILE (708) 343-4269
WWW.AMPHARMAPARTNERS.COM

Should you have any questions or require additional information, please do not hesitate to contact the undersigned at **(708) 547-3615**. You may also contact me via fax at **(708) 343-4269**.

Sincerely,

Genny Cruz
Senior Regulatory Scientist

H:\DATA\RA\SHARE\CEFOXIT\C06.248

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE AMENDMENT

AUG 18 1998

ANDA 65-012

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

TO: APPLICANT: American Pharmaceutical Partners, Inc. PHONE: 708-547-3615

ATTN: Genny Cruz FAX: 708-343-4269

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefoxitin Sodium for Injection USP, 1 g (base)/vial, 2 g (base)/vial; 20 mL vials and 100 mL piggy-back vials..

Attached are 2 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

We note that this product is subject to the exception provisions of Section 125(d) (2) of Title I of the FDA Modernization Act of 1997. CMC + Bioequivalence comments are attached.

PMAB 8/18/98

X:\new\ogdadmin\macros\faxfax.frm

AUG 18 1998

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 65-012   APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Cefoxitin For Injection, USP
1 g/20 mL, 2 g/20 mL,
1 g/100 mL piggyback,
2 g/100 mL piggyback

The deficiencies presented below represent FACSIMILE deficiencies.

Deficiencies:

1. The tentative specification limit of ____% for [ ] The proposed Specification Limits should be revised to more realistically reflect the values obtained from the tests on your exhibit batches.

2. Please report actual testing results for ____________ in the stability samples.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 65-012 APPLICANT: Fujisawa USA, Inc.

DRUG PRODUCT: Cefoxitin for Injection, USP (1 g/20 mL Vial, 2 g/20 mL Vial, 1 g/100 mL Piggyback Vial, and 2 g/100 mL Piggyback Vial)

The Division of Bioequivalence has completed its review and has no further questions at this time assuming per currently approved labeling that the products are for intravenous administration only.

In general, a waiver of bioequivalence study requirements for a drug powder intended for intramuscular administration requires complete dissolution of the drug powder upon reconstitution.

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

Sincerely yours,

Dale P. Conner

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

AMERICAN PHARMACEUTICAL PARTNERS, INC.

ARCHIVAL

September 10, 1998

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
NC
Fax

Re: ANDA 65-012
Cefoxitin for Injection, USP (SDV)
1 g/20 mL Vial, 2 g/20 mL Vial ,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial
Manufacturing Site: Grand Island, NY

FACSIMILE AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the above mentioned product. Reference is also made to FDA's facsimile amendment dated August 18, 1998 concerning CMC and Bioequivalence comments.

American Pharmaceutical Partners, Inc. (APP) is submitting this facsimile amendment in response to the minor deficiencies listed in your August 18, 1998 facsimile transmittal. For ease of review, both the FDA reviewer's comments and APP's responses are organized sequentially . Additional information concerning revised finished product specifications and SOP # 10-08-03-6057 are included in **Attachment 4** and **Attachment 5**, respectively.

A field copy of this facsimile amendment has been sent to the FDA Buffalo District Office in accordance with 21 CFR §314.96(b). APP certifies that the field copy is a true copy of the amendment submitted herewith.

Should you have any questions or require additional information, please do not hesitate to contact the undersigned at **(708) 547-3615** or via fax at **(708) 343-4269**.

RECEIVED
SEP 11 1998
GENERIC DRUGS

Sincerely,

Genny Cruz
Senior Regulatory Scientist

2045 NORTH CORNELL
MELROSE PARK, ILLINOIS 60160
TEL (708) 343-6100
FACSIMILE (708) 343-4269
WWW.AMPHARMAPARTNERS.COM

MINOR AMENDMENT

ANDA 65-012

NOV 12 1998

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

TO: APPLICANT: American Pharmaceutical Partners, Inc. PHONE: 708-547-3615

ATTN: Genny Cruz FAX: 708-343-4269

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefoxitin for Injection USP, 1 g/20 mL, 2 g/20 mL, 1 g/100 mL, 2 g/100 mL vials.

Reference is also made to your amendment dated September 10, 1998.

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

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

SPECIAL INSTRUCTIONS:

We note that this product is subject to the exception provisions of Section 125(d) (2) of Title I of the FDA Modernization Act of 1997. CMC and Microbiology comments are attached

PMSO 11/12/98

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NOV 12 1998

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 65-012 APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Cefoxitin For Injection, 1 g/20 mL, 2 g/20 mL, 1 g/100 mL piggyback, 2 g/100 mL piggyback

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File (DMF) # [redacted] was reviewed and found deficient. The DMF holder has been notified of the deficiencies. Please do not respond to this communication until you have been informed by the DMF holder that they have responded to their deficiencies.

Sincerely yours,

Frank O. Holcolme, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Microbiology Comments to be Provided to the Applicant

ANDA: 65-012 APPLICANT: American Pharmaceutical Partners

DRUG PRODUCT: Cefoxitin Sodium USP, **1 g/20 mL Vial, 2 g/20 mL vial, 1 g/100 mL Piggyback Vial, 2 g/100 mL Piggyback Vial**

Microbiology Deficiency:

The _____ DMF _____ is deficient.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCY". The "RESPONSE TO MICROBIOLOGY DEFICIENCY" should also be noted in your cover page/letter.

Sincerely yours,

MS, PhD for.

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

AMERICAN PHARMACEUTICAL PARTNERS, INC.

March 9, 1999

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

ARCHIVAL

Re: ANDA 65-012
Cefoxitin for Injection, USP (SDV)
1 g/20 mL Vial, 2 g/20 mL Vial ,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial
Manufacturing Site: Grand Island, NY

MINOR AMENDMENT
(RESPONSE TO MICROBIOLOGY DEFICIENCY)

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted on March 20, 1998 for Cefoxitin for Injection, USP, Single Dose Vials. Reference is also made to the attached FDA communication dated November 12, 1998 concerning Chemistry and Microbiology deficiencies found in ——————— Drug Master File (DMF) # ———————.

American Pharmaceutical Partners, Inc. (APP) has been notified by ———, on behalf of ——, that they have responded to the deficiencies observed in their DMF # —— for ——————— By copy of ——— 's transmittal dated March 3, 1999 provided in **Attachment 1**, APP has fully responded to the November 12, 1998 FDA communication.

In addition, please note that APP responded to the CMC and Labeling deficiencies for this application on September 10, 1998 and December 4, 1998, respectively.

RECEIVED
MAR 10 1999
GENERIC DRUGS

NW 3-12-98

2045 NORTH CORNELL AVENUE
MELROSE PARK, ILLINOIS 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
WWW.AMPHARMAPARTNERS.COM

In compliance with 21 CFR 314.96(b), a true and complete field copy of this amendment is being submitted to the District Director, Buffalo District, Food and Drug Administration, 300 Pearl Street, Buffalo, NY 14202.

Should you have any questions or require additional information concerning this amendment, please contact the undersigned at **(708) 547-3615** or via fax at **(708) 343-4269** or Mr. Mitchall G. Clark, Vice President of Regulatory Affairs at **(310) 470-4222.**

Sincerely,

Genny Cruz
Senior Regulatory Scientist

h:\data\ra\share\cefoxiti\65012.dmf

APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

JUN 18 1999

ANDA 65-012

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

TO: APPLICANT: American Pharmaceutical Partners, Inc. PHONE: 708-547-3615

ATTN: Genny Cruz FAX: 708-343-4269

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefoxitin for Injection USP, 1 g/20 mL, 2 g/20 mL, 1g/100 mL, and 2 g/100 mL vials..

Reference is also made to your amendment(s) dated March 9, 1999.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

We note that this product is subject to the exception provisions of Section 125(d) (2) of Title I of the FDA Modernization Act of 1997.

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CM 6/17/99

JUN 18 1999

Chemistry Comments to be Provided to the Applicant:

ANDA: 65-012 APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Cefoxitin For Injection, USP [redacted] 1g and 2g conventional vials and 1g and 2g Infusion bottles

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. Although all diluent compatibility claims are not required to be supported by data, please provide a justification for those for which no data was submitted.

2. The Drug Master File (DMF) #[redacted] was reviewed and found deficient. The DMF holder has been notified of the deficiencies. Please do not respond to this communication until you have been informed by the DMF holder that they have responded to their deficiencies.

Sincerely yours,

Vilayat A. Sayed

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

AMERICAN PHARMACEUTICAL PARTNERS, INC.

ARCHIVAL

ARCHIVAL

NDA ORIG AMENDMENT

N/Am1

July 23, 1999

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 65-012
Cefoxitin for Injection, USP (SDV)
1 g and 2 g Conventional Vials
1 g and 2 g Infusion Bottles
Manufacturing Site: Grand Island, NY

MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the above mentioned product. Reference is also made to FDA's facsimile dated June 18, 1999.

American Pharmaceutical Partners, Inc. (APP) is submitting this **MINOR AMENDMENT** in response to each of the comments made in your communication dated June 18, 1999. For ease of review, each of the reviewer's observation is provided in bold, followed by APP's response.

Also provided in this minor amendment is information concerning an additional contract testing laboratory (————————), which will be used to perform diluent compatibility testing on Cefoxitin for Injection, USP drug product. The full address, brief description of the function to be performed and current GMP/GLP certification of the facility are provided in the Additional Information section of this submission.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 26 1999
OGD

2045 NORTH CORNELL AVENUE
MELROSE PARK, ILLINOIS 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
WWW.AMPHARMAPARTNERS.COM

In compliance with 21 CFR § 314.96(b), we hereby certify that a true and complete field copy of this amendment is being simultaneously provided to the Buffalo district office.

Should you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 547-3615** or Mitchall G. Clark, Vice President, Regulatory Affairs at **(310) 470-4222**.

Sincerely,

Genny Cruz
Senior Regulatory Scientist

APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

SEP 23 1999

ANDA 65-012

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

TO: APPLICANT: American Pharmaceutical Partners, Inc. PHONE: 708-547-3615

ATTN: Genny Cruz FAX: 708-343-4269

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefoxitin for Injection USP, 1 g and 2 g conventional vials and 1 g and 2 g infusion bottles.

Reference is also made to your amendment dated July 23, 1999.

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

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

SPECIAL INSTRUCTIONS:

We note that this product is subject to the exception provisions of Section 125(d) (2) of Title I of the FDA Modernization Act of 1997.

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OK MA

Microbiology Comments to be Provided to the Applicant

ANDA: 65-012 APPLICANT: APP Inc

DRUG PRODUCT: Cefoxitin Sodium for Injection, 1 g/20 mL, 2 g/20 mL, 1 g/100 mL and 2 g/ 100 mL

Microbiology Deficiency:

_____ DMF _____ was reviewed and found deficient.

Please clearly identify your amendment as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 23 1999

Chemistry comments to be provided to the applicant:

ANDA: 65-012 APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Cefoxitin for Injection USP, 1g and 2g conventional vials and 1g and 2g infusion bottles

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

The Drug Master File (DMF) # _____ was reviewed and found deficient. The DMF holder has been notified of the remaining deficiencies. Please do not respond to this communication until you have been informed by the DMF holder that they have responded to their deficiencies.

Sincerely yours,

Vilayat Sayal

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

AMERICAN PHARMACEUTICAL PARTNERS, INC.

November 24, 1999

ARCHIVAL

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

Re: ANDA 65-012
Cefoxitin for Injection, USP (SDV)
1 g/20 mL Vial, 2 g/20 mL Vial ,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial
Manufacturing Site: Grand Island, NY

MINOR AMENDMENT
(RESPONSE TO MICROBIOLOGY DEFICIENCY)

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the above mentioned product. Reference is also made to FDA's facsimile dated September 23, 1999, which indicated the DMF of the manufacturer of the ——— was deficient.

American Pharmaceutical Partners, Inc.(APP) has been notified by ——— that they have responded to the deficiencies observed in their ——— DMF # ——— ——— DMF # ——— for the ——— . By copy of the attached transmittal letters both dated November 23, 1999 provided in **Attachment 1,** APP is fully responding to the September 23, 1999 FDA communication.

In compliance with 21 CFR § 314.96(b), we hereby certify that a true and complete field copy of this amendment is being simultaneously provided to the Buffalo district office.

Should you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 547-3615** or Mr. Mitchall G. Clark, Vice President, Regulatory Affairs at **(310) 470-4222.**

Sincerely,

NOV 26 1999

Genny Cruz
Senior Regulatory Scientist

11-29-99

2045 NORTH CORNELL AVENUE
MELROSE PARK, ILLINOIS 60160-1002

MAIN TELEPHONE(708) 343-6100
TELEFAX (708) 547-4429
WWW.AM-PP.COM

MINOR AMENDMENT

FEB 2 2000

ANDA 65-012

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

TO: APPLICANT: American Pharmaceutical Partners, Inc. PHONE: 708-547-3615

ATTN: Genny Cruz FAX: 708-343-4269

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefoxitin for Injection USP, 1 and 2 g conventional vials, and 1 and 2 g infusion bottles.

Reference is also made to your amendment dated November 24, 1999.

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

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

SPECIAL INSTRUCTIONS:

We note that this product is subject to the exception provisions of Section 125(d) (2) of Title I of the FDA Modernization Act of 1997.

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OK MA

Microbiology Comments to be Provided to the Applicant

ANDA: 65-012 APPLICANT: APP Inc

DRUG PRODUCT: Cefoxitin Sodium for Injection, 1 g/20 mL, 2 g/20 mL, 1 g/100 mL and 2 g/ 100 mL

Microbiology Deficiency:

_____ DMF _____ was reviewed and found deficient.

Please clearly identify your amendment as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry comments to be provided to the applicant:

ANDA: 65-012 APPLICANT: American Pharmaceutical Partners, Inc.

DRUG PRODUCT: Cefoxitin for Injection USP, 1g and 2g conventional vials and 1g and 2g infusion bottles

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

The Drug Master File (DMF) #_____ was reviewed and found deficient. The DMF holder has been notified of the remaining deficiencies. Please do not respond to this communication until you have been informed by the DMF holder that they have responded to their deficiencies.

Sincerely yours,

Vilayat J Sayal

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

AMERICAN PHARMACEUTICAL PARTNERS, INC.

March 22, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 65-012
Cefoxitin for Injection, USP (SDV)
1 g/20 mL Vial, 2 g/20 mL Vial ,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial
Manufacturing Site: Grand Island, NY

MINOR AMENDMENT
(RESPONSE TO MICROBIOLOGY DEFICIENCIES)

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the above mentioned product. Reference is also made to the attached FDA's facsimile dated February 2, 2000, which indicated the DMF of the manufacturer of the [redacted] was deficient.

American Pharmaceutical Partners, Inc.(APP) has been notified by [redacted]. that they have responded to the deficiencies observed in their [redacted] DMF # [redacted] DMF # [redacted]. By copy of the attached transmittal letters, both dated March 22, 2000, provided in **Attachment 1,** APP is fully responding to the February 2, 2000 FDA communication.

In compliance with 21 CFR § 314.96(b), we hereby certify that a true and complete field copy of this amendment is being simultaneously provided to the Buffalo district office.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 23 2000
OGD

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

Should you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 547-3615** or Nancy Bauer, Associate Director, Regulatory Affairs at **(708) 547-2381**.

Sincerely,

Genny Cruz
Senior Regulatory Scientist

APPEARS THIS WAY
ON ORIGINAL

AMERICAN PHARMACEUTICAL PARTNERS, INC.

April 26, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

ARCHIVAL

NDA ORIG AMENDMENT,
N/AP

Re: ANDA 65-012
Cefoxitin for Injection, USP (SDV)
1 g/20 mL Vial, 2 g/20 mL Vial,
1 g/100 mL Piggyback Vial, and
2 g/100 mL Piggyback Vial
Manufacturing Site: Grand Island, NY

LABELING AMENDMENT

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the above mentioned product. Reference is also made to the attached FDA's labeling comments dated April 17, 2000.

With this submission, American Pharmaceutical Partners, Inc. has revised the package insert in accordance with the changes noted in the innovator's (Merck & Co., Inc.) labeling provided in the FDA communication dated April 17, 2000. Twelve (12) copies of the Final Printed Labeling (FPL) for the package insert are provided in **Attachment 1**. A detailed annotation of the differences between the proposed labeling and existing labeling is included in **Attachment 2**.

Should you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 547-3615** or Nancy Bauer, Associate Director, Regulatory Affairs at **(708) 547-2381**.

Sincerely,

Genny Cruz
Senior Regulatory Scientist

desk copy: Mark Anderson, Project Manager, FDA

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 27 2000
OGD

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

AMERICAN PHARMACEUTICAL PARTNERS, INC.

June 1, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 65-012
Cefoxitin for Injection, USP (SDV)
1 g/20mL (Product Code: 304120)
2g/20mL (Product Code: 304220)
1g/100mL (ProductCode 304165)
2g/100mL (Product Code: 304265)
Manufacturing Site: Grand Island, NY

LABELING AMENDMENT

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the above mentioned product. Reference is made to our labeling amendment dated April 26, 2000, responding to the April 17, 2000 FDA communication.

With this submission, American Pharmaceutical Partners, Inc. (APP) has revised the Final Printed Labeling (FPL) for the container, carton and package insert based on the attached May 11, 2000 FDA communication. The revised FPL also incorporated changes based on the instruction received from Dr. Jacqueline White-Council on May 11, 2000. The instruction is to include all other revisions made in the February 14, 2000 innovator's (Merck & Co., Inc.) labeling that were not specifically asked from APP in the April 17, 2000 and May 11, 2000 FDA communications.

Twelve (12) copies of the Final Printed Labeling (FPL) for the package insert, container, and carton are provided in **Attachment 1** (separate binder). Based on the discussion with Dr. Jacqueline Council on May 11, 2000, a side-by side comparison of our proposed container and carton labeling with the FPL (container and carton) submitted on December 4, 1998, and additionally, the proposed package insert with the February 14, 2000 innovator's labeling, is provided in **Attachment 2**. The annotation format for the labeling was presented to Charles Hoppes on May 26, 2000, and was found acceptable.

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 344-2100
TELEFAX (708) 344-4429
www.apppartners.com

For clarification, please note that the "Current Labeling" contains only those changes that were highlighted in the February 14, 2000 innovator's labeling, and the "Proposed Labeling" contains all the changes included in the February 14, 2000 innovator's labeling and in the May 11, 2000 FDA comments.

Should you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 547-3615** or Nancy Bauer, Associate Director, Regulatory Affairs at **(708) 547-2381**.

Sincerely,

Genny Cruz
Senior Regulatory Scientist

desk copy: Mark Anderson, Project Manager, FDA

AMERICAN PHARMACEUTICAL PARTNERS, INC.

June 12, 2000

ARCHIVAL

Gary Buehler, Acting Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

Re: ANDA 65-012
Cefoxitin for Injection, USP (SDV)
1 g/20mL (Product Code: 304120)
2g/20mL (Product Code: 304220)
1g/100mL (ProductCode 304165)
2g/100mL (Product Code: 304265)
Manufacturing Site: Grand Island, NY

TELEPHONE MINOR AMENDMENT
(LABELING)

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated March 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the above mentioned product. References are also made to our labeling amendments dated April 26, 2000 and May 11, 2000.

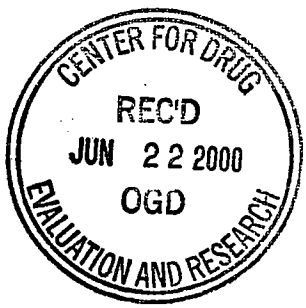
In response to the attached FDA facsimile dated June 9, 2000, American Pharmaceutical Partners, Inc. (APP) is hereby committing to make the following changes and submit as a Prior Approval Supplement.

CONTAINER:

1 g and 2 g infusion bottles
Revise "...maintains satisfactory potency for 24 hours...to read...maintains satisfactory potency for 6 hours..."

CARTON:

1 g and 2 gram infusion bottles – 10s
See comment under CONTAINER.



2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
www.appdrugs.com

It is our understanding from our discussion with Mark Anderson on June 9, 2000, that the above labeling changes will not be required for the approval of the ANDA (65-012), and that the FPL submitted on June 1, 2000 could be used in the distribution of the commercial batches.

Should you have any questions or require additional information concerning this amendment, please do not hesitate to contact the undersigned at **(708) 547-3615** or Nancy Bauer, Associate Director, Regulatory Affairs at **(708) 547-2381**.

Sincerely,

Genny Cruz
Senior Regulatory Scientist

desk copy: Mark Anderson, Project Manager, FDA