

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50749

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 50-749**Submission Date:** August 13, 1996**Drug Product:** Cefdinir Powder for Oral Suspension 125 mg/5 ml**Trade Name:** OMNICEF® Oral Suspension**Sponsor:** Parke-Davis Pharmaceutical Research
Ann Arbor, MI**Type of Submission:** Amendment to Pending NDA**OCPB Reviewer:** Philip M. Colangelo, Pharm.D., Ph.D.**OCPB Log In Date:** August 20, 1997

I. BACKGROUND

The sponsor has provided the proposed methods and specification for the *in vitro* dissolution test of cefdinir powder for oral suspension as an amendment to the pending NDA 50-749. | The NDA 50-749 for this formulation is currently being reviewed within the Division of Anti-Infective Drug Products (DAIDP, HFD-520). The proposed dissolution methods and specifications were provided for review following discussions between the sponsor and Division's co-located representatives from the Offices of Clinical Pharmacology and Biopharmaceutics (OCPB, HFD-880) and New Drug Chemistry (ONDC, HFD-800).

II. RECOMMENDATION

The proposed dissolution methods and specifications for cefdinir powder for oral suspension have been reviewed by OCPB and were found to be acceptable.

ISI

9/3/97

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Office Clinical Pharmacology/Biopharmaceutics,
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RD/FT signed by Frank Pelsor, Pharm.D., TL

ISI

cc:

Div. File: NDA 50-749

HFD-590 (J. Soreth, TL/MO; H. Hamilton, MO)

~~HFD-590 (B. DuVall-Miller, PM/CSO)~~

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HFD-340 (Viswanathan)

HFD-205 (FOI)

~~HFD-880 (Division File)~~

~~HFD-880 (F. Pelsor, TL; P. Colangelo)~~

~~ODR (Barbara Murphy)~~

AUG 12 1997

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Duvall-Miller

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 50-739;
50-749

Submission Date: 50-739 - September 4, 1996;
50-749 - December 30, 1996

Drug Products: 50-739 - Cefdinir (CI-983) 300 mg Capsules;
50-749 - Cefdinir Oral Suspension 125 mg/5 ml

Trade Name: OMNICEF® Capsules and Oral Suspension

Sponsor: Parke-Davis Pharmaceutical Research
Ann Arbor, MI

Type of Submission: New NDA

Category: 1S

OCPB Reviewer: Philip M. Colangelo, Pharm.D., Ph.D.

OCPB Log In Dates: 50-739 - 9/96;
50-749 - 1/24/97

I. SYNOPSIS

The Human Pharmacokinetics and Bioavailability Section (Section 6) of capsule NDA 50-739, was comprised of 20 volumes that included studies which adequately characterized the pharmacokinetics of cefdinir in healthy adult subjects (capsules and suspension), pediatric subjects aged 6 months to 12 years (suspension), and adult special populations (i.e., elderly, renal impairment, and hemodialysis patients). Bioequivalence between clinical trials capsule and suspension formulations (i.e., used in Phases I/II/III) and between the market image capsules and Phase III clinical trials capsules (i.e., pivotal bioequivalence) was established. The effect of a high fat meal and timing of the meal on the bioavailability of the capsules was determined to be minimal. Drug interactions were significant for coadministration with probenecid, Maalox® TC, and oral iron supplements (i.e., either as ferrous sulfate tablets or iron-containing multivitamins). Cefdinir tissue penetration was evaluated by relating drug concentrations measured in blister, tonsil, lung, sinus, and middle ear fluids/tissues of infection following clinical doses of either 300 or 600 mg of the capsules or 7 and 14 mg/kg of the suspension with the MIC₉₀ values for the causative organisms. The description, validation, and performance of the bioanalytical methods used to assay drug concentrations in various biological matrices were provided with each study and

were found to be acceptable.

Although no formal studies were conducted to evaluate the influence of gender or ethnic background (i.e., race), meta analyses were performed using data from the pharmacokinetic studies to evaluate the predictive influence of several adult and pediatric subject/patient covariates on cefdinir pharmacokinetics. Furthermore, a population pharmacokinetics analysis was conducted from the PK database that was created to determine the mean population pharmacokinetic (PPK) parameter values for adults and children. In addition to the usual PPK parameters, the population bioavailability estimates for the capsule and suspension were also determined to be 16-21% and 25%, respectively.

The *in vitro* plasma protein binding of cefdinir was determined to be moderate (60-70%) and linear over clinically relevant plasma concentrations in both adult and pediatric subjects. Although no *in vitro* metabolism studies were provided as part of Section 6, a limited metabolism study in rat liver microsomes was reviewed from Section 5: Pharmacology / Toxicology. Also, *in vitro/in situ* G.I. absorption studies in animal models were conducted to investigate the apparent lack of dose proportionality from 300 to 600 mg and poor oral bioavailability of the capsules observed in humans and were reviewed from Section 5. The methods and specifications for *in vitro* dissolution testing of the capsules provided in NDA 50-739 were adequate.

In suspension NDA 50-749, Section 6 contained only the pivotal *in vivo* bioequivalence study establishing equivalence between the market image and clinical trials suspension formulations. The remaining PK studies for the suspension in children and adults were referenced with and reviewed from capsule NDA 50-739.

Overall, there were no outstanding deficiencies with capsule NDA 50-739. However, for suspension NDA 50-749, the proposed methods and specifications for the *in vitro* dissolution testing of the market image formulation were not provided. Although NDA 50-749 is currently deficient in this requirement, it is acceptable since the sponsor has agreed to provide the proposed dissolution methods, specifications, and data from the pilot scale batches of the market image suspension as interim data. The sponsor has also agreed to subsequently provide dissolution results for the full scale production batches of the suspension manufactured at the contract facility in Puerto Rico as a Phase IV commitment.

II. RECOMMENDATION

Section 6: Human Pharmacokinetics and Bioavailability of NDA 50-739 for cefdinir capsules has been reviewed and was found to be acceptable. The studies that pertained to cefdinir suspension in Section 6 of NDA 50-739 and Section 6 of suspension NDA 50-749 were also reviewed and were found to be acceptable. However, suspension NDA 50-749 was deficient in the provision of any *in vitro* dissolution methods, specifications, and data for the to be marketed suspension

formulation. As such, suspension NDA 50-749 is acceptable, provided that the requested dissolution information, as outlined in Comment 2 below, is obtained by the Agency from the sponsor. Both Comments 1 and 2 (Section III. below) should be conveyed to and adequately addressed by the sponsor, while Comments 3 and 4 (Section III.a. below) are to be conveyed to the sponsor for consideration. In addition, Labeling Comments 1 through 11 (Section IV. below) are intended to be suggested changes to various sections of the proposed labeling (v: 12/26/96) and serve as a starting point for dialogue between the sponsor and the Agency.

III. COMMENTS TO BE SENT TO SPONSOR

Capsule NDA 50-739

1. The proposed *in vitro* dissolution specification for the 300 mg capsules (Formulation 34) is a Q value of % at minutes. Based on the dissolution results provided for Formulation 34, it is recommended that the specification for the cefdinir capsules be changed to a Q value of % at minutes.

Suspension NDA 50-749

2. The sponsor did not provide a proposed method and specification for the *in vitro* dissolution testing of the to be marketed suspension formulation. In a 90 day NDA status meeting between the Agency and the sponsor (held Feb. 12, 1997), it was agreed upon that the sponsor would provide the dissolution method, proposed specifications, and the data from the pilot scale batches of the market image suspension as interim data. The sponsor agreed to provide the final methods, specifications, and dissolution results for the full scale production batches manufactured at the contract facility in Puerto Rico as a Phase IV commitment.

Upon review and discussion with the sponsor of the interim dissolution report, it was agreed upon that the sponsor will perform Phase IV dissolution testing of the 3 NDA stability lots of the powder for oral suspension (i.e., Lots D40115, D40116, and D40117) over the shelf-life of the product (i.e., at 15 and 18 months). These lots are full scale production batches of the market image formulation and full dissolution profiles on the constituted powder for oral suspension will be obtained with these batches (i.e., from minutes). The interim dissolution method is USP Apparatus II at 50 rpm at 37 °C in 900 ml phosphate buffer at pH 6.8 and the interim specification is a Q value of % at minutes. It was also agreed that single point dissolution testing at minutes will be conducted on subsequent commercial lots.

III.a. COMMENTS FOR THE SPONSOR TO CONSIDER

3. At the Clinical Pharmacology / Biopharmaceutics NDA briefing for cefdinir held on July 10, 1997, concern was expressed by Drs. Shiew-Mei Huang (OCPB, HFD-850) and Jerry Collins (OTR, HFD-900) over the lack of evaluation of the potential for cefdinir to inhibit the metabolism of other drugs that undergo biotransformation by human

hepatic CYP450 enzymes as their primary route of systemic elimination. Although it was understood that cefdinir itself does not appear to undergo hepatic metabolism to any significant extent, the potential for cefdinir to inhibit the metabolism of other drugs may still exist. Reference for this type of evaluation was made with respect to the recently published April 1997 Guidance for Industry entitled "Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro". As suggested by Dr. Huang, the sponsor should consider performing metabolic inhibition studies using known substrates for the 5 "major" human CYP450 enzymes, i.e., 1A2, 2C9/19, 2D6, 2E1, 3A4. In lieu of these studies, the sponsor may provide to the Agency the rationale for why these studies would not be relevant for cefdinir.

4. In patients with estimated CLcr values of <30 ml/min (i.e., defined by the sponsor as "severe" renal insufficiency), the capsule dosage is to be reduced to 300 mg daily. For patients with end stage renal disease requiring routine hemodialysis, the dosage is further reduced to 300 mg every other other day, with 300 mg administered at the end of each dialysis session. For those patients with estimated CLcr values between 30 and 60 ml/min (i.e., defined by the sponsonor as "moderate" renal insufficiency), the dosage remains unadjusted from that in patients with CLcr values >60 ml/min (i.e., defined by the sponsonor as "normal" renal function) at 300 mg q. 12 hours. The sponsor should consider post-approval monitoring of the appropriateness of these proposed dosage regimens, with safety and toleration as the primary focus, in each of these 3 renal insufficiency groups.

IV. LABELING COMMENTS

Redacted

3

pages of trade

secret and/or

confidential

commercial

information

Suggested Change: As with other β -lactam antibiotics, probenecid inhibits the renal excretion of cefdinir, resulting in an approximate doubling in AUC, a 54% increase in peak plasma levels, and a 50% prolongation in the apparent elimination half-life.

- ▶ Additional wording to quantify the increase in $T_{1/2}$.

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8/12/97

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Div. File: NDA 50-739;
NDA 50-749

HFD-520 (J. Soreth, TL, MO; H. Hamilton, MO)

HFD-520 (B. DuVall-Miller, CSO)

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HFD-340 (Viswanathan)

HFD-205 (FOI)

✓ HFD-880 (Division File)

✓ HFD-880 (F. Pelsor, TL; P. Colangelo)

✓ CDR (Barbara Murphy)

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V. BACKGROUND

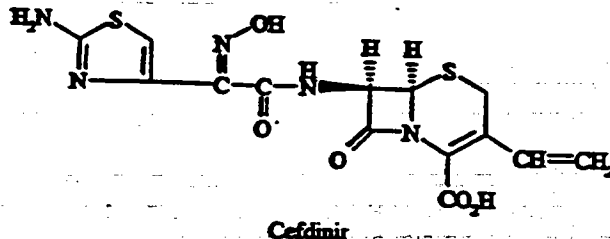
Cefdinir is a semisynthetic, extended spectrum, β -lactam cephalosporin developed in the U.S. for oral administration as 300 mg capsules and 125 mg/5 ml pediatric suspension for the treatment of mild to moderate bacterial infections. The drug was originally developed in _____ and is currently being licensed from _____ by the sponsor. The 200 mg capsule formulation has been approved in Japan since 1991 and a pediatric sachet (i.e., fine granule) formulation was approved in 1993. Besides the U.S., the sponsor also plans to submit marketing applications for cefdinir in Canada, Europe, Australia, and South Africa.

None of the studies used to register the drug in Japan were used to support submission of the current NDA's for the capsule (NDA 50-739) and suspension (NDA 50-749) since cefdinir was evaluated at different doses/regimens, and in infections not commonly defined as indications in the U.S. It appears to have *in vitro* activity against many strains of bacteria that are resistant to penicillins and other first and second generation cephalosporins. The capsule NDA seeks approval for 6 indications in adults and adolescents (i.e., ≥ 13 yrs) and are outlined in the proposed labeling in Appendix 1. Capsule doses of 300 mg bid or 600 mg qd for 5-10 days were used in the Phase III clinical efficacy and safety trials for these indications. The suspension NDA seeks approval for 4 indications in pediatrics (i.e., 6 months-12 yrs), 3 of which are common to the adult/adolescent indications, and are also outlined in the proposed labeling (Appendix 1). Suspension doses of 7 mg/kg bid or 14 mg/kg qd for 5-10 days were used in the efficacy and safety trials. The sponsor applied the "Pediatric Rule" for the acute maxillary sinusitis indication in children and provided the rationale for this as part of the suspension NDA.

VI. DRUG CHARACTERISTICS AND FORMULATIONS

1. Physcial/Chemical Characteristics

Cefdinir is a semisynthetic cephalosporin containing aminothiazole and oxime moieties. The chemical structure is shown below. There are 2 chiral centers (C-6 and C-7) and cefdinir is prepared and marketed as the 6R-[6 α , 7 β (Z)] isomer. The absolute configuration of cefdinir and the Z-configuration of the oxime moiety have been established through NMR studies. Stereochemistry issues are addressed in more detail in the Chemist's review of the capsule NDA.



a. Dissociation

The cefdinir molecule has 3 ionizable groups with the following pKa's assigned to each:

- COOH group of the cephem moiety = 1.9;
- NH₂ group of the aminothiazole moiety = 3.3;
- =N-OH group of the oxime moiety = 9.9

b. Solubility

The solubility of Cefdinir is highly dependent upon pH. It is insoluble in water (0.46 mg/ml) and other common organic solvents (e.g., acetonitrile <0.01 mg/ml, methanol 0.19 mg/ml), except for DMSO (>350 mg/ml). It is slightly soluble in 0.1M HCl (1.56 mg/ml). In buffered media, it is insoluble in pH 4.0 acetate (0.72 mg/ml), sparingly soluble in pH 7.4 phosphate (21 mg/ml), and freely soluble in sodium bicarbonate (83 mg/ml). These latter results were consistent with the J-shaped pH-solubility profile for cefdinir, with minimum solubility at pH ~3-4 and maximum solubility at pH ~6-7.

c. pH Stability

The stability of cefdinir in aqueous solutions buffered from pH 1 to 9 was determined at constant temperature and ionic strength. The pH-degradation rate profile was V-shaped, with maximum stability at pH 3 to 7 and minimum stability at the extremes, i.e., at pH 1 and 9. These findings appeared to be consistent with those from the *in situ* gastrointestinal stability studies in animals which showed cefdinir stability to be greatest in the stomach and small intestine

2. Formulations and Dissolution

a. Capsule Formulation and Dissolution

The proposed commercial formulation, designated as Formulation No. 34, will be a 300 mg hard gelatin capsule (No. 1). The commercial capsules will be manufactured, tested, and packaged under contract by Eli Lilly Industries in Puerto Rico. The bulk drug substance will be supplied from

(The composition of the proposed commercial product is as follows:

Formulation No. 34; Label Claim: 300 mg

Ingredients	Amount per Capsule (mg)
Cefdinir	
Carboxymethylcellulose Calcium, NF	
Polyoxyl 40 Stearate, NF	
Magnesium Stearate, NF	

Target Fill Weight

- *Quantity adjusted based on the assay of cefdinir
- **Actual quantity adjusted based on amount cefdinir used

This proposed formulation is compositionally identical to the 300 mg capsule used in the pivotal clinical trials, i.e., Formulation No. 24. In order to provide double blinded capsules for these clinical trials, the Formulation 24 capsules were over-encapsulated into a larger sized shell (No. 0) and this formulation was subsequently designated as Formulation No. 25. The *in vivo* bioequivalence between the over-encapsulated Formulation 25 and the full-scale production lot of the market image Formulation 34 was demonstrated in the pivotal BE study 983-066 (see Appendix 2.B.9 for details). In some of the Phase I and II clinical studies, the sponsor used cefdinir capsule strengths of 50, 100, and 200 mg which were obtained from [redacted]. These capsules were identical in ingredients and compositionally proportional to the proposed commercial product. In addition, the *in vivo* bioequivalence between the 200 mg [redacted] capsules and 200 mg Parke-Davis capsules was demonstrated in study 983-021 (see Appendix 2.B.8 for details).

The proposed *in vitro* dissolution method and specification for the capsules is as follows:

Apparatus:	USP Apparatus II (paddle)
Paddle Speed:	50 rpm
Medium:	900 ml Phosphate Buffer pH 6.8
Temperature:	37 ± 0.5°C
Analytical Method:	
Specification:	Q value of % dissolved at minutes

The dissolution results for the production scale batch of Formulation 34 (Lot D40021; capsules) used in the pivotal BE study 983-066 were provided in Table 1 immediately at the end of this section. The mean dissolution at [redacted] minutes was [redacted] % (%RSD 0.99%). Based on these results, the specification for the cefdinir capsules should be changed to a Q value of [redacted] % dissolved at [redacted] minutes.

b. Suspension Formulation and Dissolution

The proposed to be marketed suspension product, designated as Formulation No. 37, will be a strawberry-creme flavored powder for oral suspension containing 125 mg cefdinir per 5 ml upon constitution with water. Similar to the capsules, the proposed commercial suspension product will also be manufactured, tested, and packaged under contract by/Eli Lilly Industries in Puerto Rico. (

The quantitative composition for Formulation 37 and of the two formulations used in clinical trials, i.e., Formulation Nos. 21 and 27, are compared in Table 2 immediately at the end of this section. The proposed commercial suspension differs mainly from that of the clinical trials formulations in the flavoring agents (i.e., strawberry-creme vs raspberry) and in the increase in the amount of sucrose (i.e., 2.867 g vs. 1.5 g) per teaspoonful (5 ml). The sponsor provided a statement in the proposed labeling for the suspension indicating that if the patient is diabetic, he/she or the guardian should be aware that the product contains 2.86 g of sucrose per teaspoonful. The *in vivo* bioequivalence between the clinical trials suspension Formulation 27 and proposed market image suspension Formulation 37 was demonstrated in the pivotal BE study 983-067 (see Appendix 3.24 for details).

The sponsor did not provide a proposed method and specification for the in vitro dissolution testing of the to be marketed formulation in the suspension NDA. In a 90 day NDA status meeting between the Agency and the sponsor (held Feb. 12, 1997), it was agreed upon that the sponsor would provide the dissolution method, proposed specifications, and the data from pilot scale batches of the market image suspension as interim data. The sponsor also agreed to provide the dissolution results for the full scale production batches manufactured at the contract facility in Puerto Rico as a Phase IV commitment.

Upon review and discussion with the sponsor of the interim dissolution report, it was agreed upon that the sponsor will perform Phase IV dissolution testing of the 3 NDA stability lots of the powder for oral suspension (i.e., Lots D40115, D40116, and D40117) over the shelf-life of the product (i.e., 18 months). These lots are full scale production batches of the market image formulation and full dissolution profiles will be obtained with these batches (i.e., from minutes). It was also agreed that single point dissolution testing at minutes will be conducted on subsequent commercial lots. The interim dissolution method and specification is as follows:

Apparatus:	USP Apparatus II (paddle)		
Paddle Speed:	50 rpm		
Medium:	900 ml Phosphate Buffer pH 6.8		
Temperature:	37 ± 0.5 °C		
Analytical Method:			
Specification:	Q value of	% dissolved at	minutes

TABLE 1

Dissolution Profiles of Formulations Used in Bioequivalence Study (983-66)

Formula	Lot No.	Conditions	Dosage Unit	Percent of Label Claim Dissolved				
				10 Min	20 Min	30 Min	40 Min	50 Min
First Set -34, 300-mg Cap (D400021)	CX 1400995 6.8 Phosphate Buffer 37°C ± 0.5°C	USP Apparatus II Paddles - Speed 50 rpm	1					
			2					
			3					
			4					
			5					
			6					

Mean	96	98	100	101	101
%RSD	2.23	1.78	1.33	1.40	1.02

Second Set
USP Apparatus II Paddles - Speed 50 rpm
6.8 Phosphate Buffer
37°C ± 0.5°C

1
2
3
4
5
6

Mean	95	98	100	101	102
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%RSD 0.54 0.42 0.55 0.74 0.74

Notebook Reference: 53596X12, Method 939-00690

Grand Mean 96 98 100 101 102
%RSD 1.57 1.26 0.99 1.07 0.89
(N = 12)

RR-REG 959-00034

Cefdinir

Clinical Trial Formulations

TABLE 2

Cefdinir Powder for Suspension 125 mg/5 mL

Formula	21 (mg/5 mL)	27 (mg/5 mL)	37 (mg/5 mL)
Cefdinir Milled			
Sucrose, NF			
Citric Acid, USP, Anhydrous			
Sodium Citrate, USP, Anhydrous			
Xanthan Gum, NF			
Guar Gum, NF			
Artificial Raspberry Flavor 57.801/AP 05.51			
Van-O-Plus No. 10293 (Art Vanilla flavor)			
FD&C Red No. 40			
Maltrin QD M500 (Maltodextrin)			
Aerosil 200, NF			
Sodium Benzoate, NF			
Artificial Cream Flavor 610979U PFW			
Artificial Strawberry Flavor DY04359			
Artificial Strawberry Flavor FD-9581-S			
Magnesium Stearate, NF			

VII. ANALYTICAL METHODS

VIII. IN VITRO STUDIES

The following is a synopsis of the relevant *in vitro* metabolism and absorption studies included in the capsule NDA. A more detailed description of these studies and the protein binding study can be found in Appendix 2.E.17 to 19.

***In Vitro* Metabolism (Corresponds to Appendix 2.E.18)**

No *in vitro* human hepatic metabolism studies were included with this NDA submission. Presumably, this was because of the apparent lack of evidence for hepatic metabolism as a major route of cefdinir elimination. A limited study of the effect(s) of cefdinir on rat liver microsomal CYP450 enzymes was previously conducted by _____ while cefdinir was undergoing development in Japan. After single oral daily doses of 10 and 100 mg/kg cefdinir for 3 days to 6 male Sprague-Dawley rats, no effects on total CYP450 content or on aminopyrine demethylase, aniline hydroxylase, and ethoxyresorufin deethylase were observed. Due the limited nature of the data, no inferences to the human metabolic enzymes can be made.

Absorption Studies (Corresponds to Appendix 2.E.19)

The gastrointestinal (GI) stability, site, and mechanism of GI absorption of cefdinir was examined through several studies utilizing animal models for absorption (previously conducted by _____ and human CaCO-2 cells (conducted by Parke-Davis). These studies were conducted to explore the apparent lack of dose proportionality and poor oral bioavailability of cefdinir observed in humans.

The site and extent of GI absorption was studied using the *in situ* rat absorption model and following the appearance of parent cefdinir in the urine for 3 hrs after each GI instillation. GI stability was also evaluated over 24 hrs post instillation using an established microbiological assay of the homogenized GI

segments for the determination of cefdinir concentration. The order of absorption was as follows: jejunum 21%; duodenum 7.8%; large intestine 7.6%; ileum 5%; stomach 0.4%. In general, cefdinir stability progressively declined from the stomach to the large intestine. Cefdinir was most stable in the stomach and all regions of the small intestine through 4 hrs post instillation, with ~92-99% of the instilled dose remaining. Only ~50% remained in the large intestine at 4 hrs post instillation and continued to decline to 35% at 6 hrs. At 24 hrs post instillation, residual amounts of cefdinir were (in decreasing order): duodenum 83%, stomach 69%, jejunum 66%, ileum 54%, and large intestine 1.7%. These results suggested that cefdinir absorption was greatest from the small intestine, preferably the jejunum, and was most stable in the stomach and upper regions of the small intestine. Absorption from the stomach was negligible and cefdinir appeared to be rapidly degraded in the large intestine.

The mechanism of cefdinir GI absorption was investigated through the use of rabbit intestinal brush border membrane vesicles (BBMV) and human intestinal CaCO-2 cells. Experiments of cefdinir uptake from these two models were conducted using specific substrates and inhibitors for dipeptide and monocarboxylic acid transport systems. Reference cephalosporins known to undergo active transport (e.g., cefixime) and/or with similar partition coefficients (e.g., cefaclor) were also used. In both models, it appeared that the major component of cefdinir absorption was through active transport processes rather than a passive process. In BBMV studies, passive diffusion accounted for ~15%, while active transport via both proton-independent (~62%) and proton-dependent carrier (~23%) systems accounted for ~85% of cefdinir absorption. The CaCO-2 studies suggested a carrier-mediated dipeptide transport process that may have both saturable and non-saturable components.

In summary, the results from these absorption studies suggested that a window of absorption for cefdinir exists in the gastrointestinal tract, primarily in the jejunum, and that cefdinir also undergoes absorption mainly via active processes.

IX. HUMAN PHARMACOKINETIC (PK)/PHARMACODYNAMIC (PD) STUDIES

The following is a synopsis of the clinical pharmacokinetic studies for cefdinir capsules and suspension. Refer to Appendices 2.A-D, 3, and 4 for more detailed summaries of each study. The pharmacokinetic parameters were summarized in Table 3 immediately at the end of this section.

CAPSULES (Corresponds to Appendix 2.A.1 through 2.D.16)

A. Basic Pharmacokinetics

1. 983-050: [¹⁴C]-Cefdinir Mass Balance and Metabolism; 300 mg [¹⁴C]-cefdinir dosing solution; N = 6 male subjects, age 28-62 yrs.

Recovery of total radioactivity from urine and feces was nearly complete for all 6 subjects studied (i.e., mean recovery ~95%) after 120 hrs (5 days) following the dose. Approximately 56% of the radioactive dose was excreted in the feces and ~38% was excreted in the urine. Analysis of plasma and urine samples collected for metabolite profiling showed a predominant contribution of parent [¹⁴C]-cefdinir relative to total radioactivity in both plasma (i.e., ~80%) and urine (i.e., ~90%). Although other small analytical peaks were detected in the plasma and urine samples collected for metabolic profiling, they were quantitatively negligible compared to that of parent cefdinir. The data from this and other preclinical and clinical studies indicated that cefdinir undergoes minimal systemic metabolism and is eliminated predominantly by the kidneys.

2. 983-035: Single Dose Proportionality; 200, 300, 400, 600 mg; N = 20 male and female subjects, age 20-43 yrs; 4-way crossover design.

3. 983-001: Single and Repeated Dose Escalation; 50, 100, 200, 400, 600 mg qd and bid x 14 days; N =

30 male and female subjects, age 23-45 yrs; placebo controlled, parallel groups design.

4. 983-025: Single Dose Proportionality and Suction Blister Penetration; 200, 300, 400, 600 mg; N = 16 male subjects, age 19-29 yrs; 4-way crossover design.

These studies defined cefdinir plasma pharmacokinetics, particularly after 300 and 600 mg doses. Mean C_{max} and $AUC(0-inf)$ after 300 mg were ~ 1.6 mcg/ml and ~ 7 ug.hr/ml; after 600 mg these same estimates were ~ 2.7 mcg/ml and ~ 10.5 mcg.hr/ml. Rate of absorption was moderate for all doses studied, as indicated by mean T_{max} of 3-4 hrs. Apparent elimination $T_{1/2}$ was short for all doses studied at ~ 1.5 -1.8 hrs., and thus, cefdinir accumulation in plasma following repeated bid doses was negligible. Renal clearance of cefdinir was high and approached or exceeded creatinine clearance (i.e., Cl_r generally greater than 120 ml/min) at all doses. Because of rapid elimination, cefdinir plasma concentrations generally fell below the limit of assay quantitation at 10-12 hrs postdose and at predose. Thus, steady-state concentrations after repeated bid doses were not attainable. The apparent elimination $T_{1/2}$ and renal clearance values were constant across all doses, indicating that the kinetics of elimination were linear (i.e., independent of dose).

Although plasma concentrations, C_{max} and $AUC(0-inf)$ all tended to increase as the doses were increased, the magnitude of these increases from 400 mg to 600 mg and from 300 mg to 600 mg were less than dose proportional. Dose proportional increases in C_{max} and $AUC(0-inf)$ were observed from doses of 200 to 300 to 400 mg. The systemic exposure to cefdinir from the 600 mg capsule doses was estimated to be ~ 75 -80% of that predicted from an ideal dose proportional model using doses from 200 to 400 mg (i.e., relative bioavailability from 600 mg doses ~ 75 -80%). In addition, the percentage of the dose excreted in the urine as parent cefdinir ($A_e\%$) decreased as the dose was increased (i.e., from $\sim 20\%$ at 200 mg to $\sim 12\%$ at 600 mg). This reduction in the systemic availability of cefdinir appeared to be due to a decrease in the extent of absorption, rather than an alteration in the elimination kinetics of cefdinir, with the increase in dose. Although not addressed by the sponsor in the submission, one potential explanation for the reduction in extent of absorption may be due to the saturation of the active transport processes responsible for cefdinir absorption at higher doses. Approximately 85% of cefdinir absorption from the GIT has been shown in *in vitro* animal models to occur by saturable, active transport processes, with the remaining 15% absorbed by passive diffusion.

The apparently slower rates of diffusion into (i.e., $T_{max} \sim 4.8$ hrs) and out of (i.e., $T_{1/2} \sim 3.5$ hrs) the interstitial space resulted in mean blister fluid C_{max} values that were $\sim 50\%$ of those in plasma while mean blister $AUC(0-inf)$ estimates were similar to those in plasma over a 12 hr period following single dose administration at all doses (i.e., overall mean blister fluid : plasma AUC ratio $\sim 90\%$). This suggested that while the rate of diffusion of cefdinir into the interstitial spaces may lag behind that which was observed in plasma, the extent to which the drug penetrates into the interstitial spaces appeared to be similar to that observed in plasma.

5. Plasma and Tissue Distribution Studies

The mean population estimate for cefdinir volume of distribution (i.e., $V_{d_{area}}$) was ~ 0.35 L/kg for both 300 and 600 mg doses, which suggested that the volume of distribution exceeded the extracellular fluid volume by almost 2-fold (i.e., ~ 0.2 L/kg). The *in vitro* binding of cefdinir to plasma proteins was determined to be moderate, i.e., 60-70%, and independent over a range of plasma drug concentrations that would be observed clinically, and also independent of age. Thus, alterations that would normally produce a change in plasma protein binding (e.g., drug displacement interactions; renal failure) would not be expected to significantly alter the unbound concentrations of cefdinir.

In addition to blister fluid (Protocol 983-025), cefdinir concentrations were measured at ~ 4 hrs following single 300 or 600 mg doses in tonsil (Protocol 983-024); lung, i.e., bronchial mucosa and epithelial lining fluid (ELF) (Protocol 983-049); and sinus (Protocol 983-053) tissue in male and female adult subjects who underwent tonsillectomy, diagnostic fiberoptic bronchoscopy, or surgery of the ethmoid/maxillary sinuses, respectively. The mean tissue to plasma ratios, a measure of drug tissue penetration, were

comparable between the 300 and 600 mg doses for tonsil tissue (i.e., 0.27 ± 0.09 and 0.21 ± 0.06 , respectively). Overall (i.e., 300 and 600 mg data combined), mean drug levels in tonsil tissue were ~24% of the corresponding plasma concentrations.

Mean tissue to plasma penetration ratios for bronchial mucosa and ELF appeared to be higher at the 300 mg dose (i.e., 0.37 ± 0.21 ; 0.65 ± 0.18) when compared to the 600 mg dose (i.e., 0.25 ± 0.12 ; 0.09 ± 0.06). However, the quality of the individual tissue concentration data was relatively poor, with at least 2 subjects in each dose group having drug levels below the quantitation limit of the microbiological assay and other subjects for which tissue sample collection was not possible or inadequate for accurate concentration determination. Overall (i.e., 300 and 600 mg data combined), mean drug levels in bronchial mucosa and ELF were ~30% and ~35%, respectively, of the corresponding plasma concentrations.

The mean sinus tissue to plasma penetration ratio appeared to be higher for the 600 mg (i.e., 0.20 ± 0.22) compared to 300 mg (i.e., 0.12 ± 0.17). Because of problems with sinus sample collection and labeling, no distinction could be made between sinus mucosa and fluid. Thus, mucosa and fluid were collectively referred to as sinus tissue. In addition, 5 of the 11 samples collected from the 300 mg dose group and 5 of the 10 samples collected for the 600 mg group were noted to be either dehydrated or blood stained, and the effect of these conditions on the determination of cefdinir concentrations in these samples was not known by the sponsor. Overall (i.e., 300 and 600 mg data combined), mean drug levels in sinus tissue were ~16% of the corresponding plasma concentrations.

Although the total variability (as %CV) in plasma concentrations, tissue levels, and penetration ratios was high for all tissues and for both doses, it was especially high for ELF tissue levels and ratios at 300 mg and for sinus tissue levels and ratios at both 300 and 600 mg.

The mean cefdinir concentrations achieved in these various tissues/fluids at 4 hrs postdose were also compared with the MIC_{90} values for the common pathogens isolated from patients with infections for which the sponsor is seeking market approval. The results, which were provided in Table 4 immediately following this section, indicated that cefdinir tissue levels at 4 hrs following single 300 and 600 mg doses were adequate for the majority of pathogens listed. The notable exception was in sinus tissue following the 300 mg dose, where the mean drug concentration of 0.12 mcg/ml fell below the MIC_{90} for *S. aureus*, *H. influenzae*, *M. catarrhalis*, *E. coli*, and *K. pneumoniae*.

B. Bioavailability and Bioequivalence

6. 983-017: Food Effect and Effect of Timing of the Meal on Cefdinir Pharmacokinetics; 400 mg x 1; N = 10 male subjects, age 22-51 yrs; 4-way crossover design (i.e., fasting, 1 hr before, with, and 1 hr after high fat meal).

In general, the pharmacokinetic parameters resulting from single 400 mg dose administration of cefdinir under either fasting conditions (Trt 1), and at 1 hour before (Trt 2), with (Trt 3), or 1 hour after (Trt 4) a high fat meal were consistent with those observed in other studies at the same dose level.

A high fat meal (Trt 3) appeared to slightly reduce the systemic exposure to cefdinir when compared to fasting conditions (Trt 1). The least squares mean differences and associated 95% confidence intervals for the with food vs fasting C_{max} and $AUC(0-inf)$ comparison were -16% (-26.9% to -6.9%) and -10% (-20.4% to -0.1%), respectively. Although the reduction in C_{max} was statistically significant when cefdinir was administered with the high fat meal vs fasting (i.e., 1.9 mcg/ml vs 2.3 mcg/ml), no significant difference was detected in $AUC(0-inf)$ (i.e., 9.6 mcg.hr/ml vs 10.7 mcg.hr/ml). Food significantly prolonged the mean T_{max} by 35% compared to fasting (i.e., 4.7 hrs vs 3.5 hrs). The results suggested that while the rate of cefdinir absorption was significantly reduced by food, the extent of absorption was not. The sponsor concluded that the reduction in cefdinir systemic availability with food was not likely to be clinically significant, and thus, cefdinir may be given without regards to meals. This conclusion was deemed to be acceptable.

7. 983-018: Bioequivalence Study Between Blinded (i.e., Over-Encapsulated) vs Capsules; 200 mg x 1; N = 17 male and female subjects, age 21-64 yrs; 2-way crossover design.

8. 983-021: Bioequivalence Study Between Parke-Davis Capsules and Parke-Davis Suspension vs Capsules; 400 mg x 1; N = 22 male and female subjects, age 21-63 yrs; 3-way crossover design.

These studies evaluated bioequivalence of cefdinir capsule formulations prepared or manufactured by the sponsor in the U.S. with the capsules manufactured in The over-encapsulated 200 mg capsules tested in study 983-018 were used in various PK studies and in Phase II/III clinical efficacy trials and were prepared at the sponsor's U.S. facility by over-encapsulating No. 2 cefdinir capsules manufactured by with No. 0 Parke-Davis blinded capsules. Since this repackaging may affect the systemic availability of the drug, the pharmacokinetics of cefdinir were compared after single 200 mg dose administration of the No. 2 capsule and the blinded capsule. In study 983-021, the Parke-Davis capsule and suspension formulations were manufactured at the sponsor's U.S. facility. These Parke-Davis and capsules were primarily used in early PK studies. The Parke-Davis raspberry flavored suspension formulation was used in all PK and clinical efficacy trials in pediatric subjects.

In study 983-018, the rate and extent of cefdinir absorption following single 200 mg doses of the blinded over-encapsulated test capsule and the reference capsule were similar. The 90% confidence intervals on the difference between the test and reference least square mean C_{max} and AUC(0-inf) values were (83.3%-119.0%) and (81.7%-112.2%), respectively. The sponsor concluded that the blinded Parke-Davis capsules and cefdinir capsules were bioequivalent and that the blinded capsules were suitable for use in clinical trials. These conclusions were deemed to be acceptable.

In study 983-021, the results showed that the Parke-Davis cefdinir capsules were bioequivalent to the cefdinir capsules. However, the Parke-Davis oral suspension was not bioequivalent to the capsules, with the 90% confidence interval for the log-transformed AUC(0-inf) falling outside the acceptance limits by 5.6%, i.e., (99.1-130.6%). The relative bioavailability of the Parke-Davis suspension was 120% when compared to the capsules (i.e., mean AUC(0-inf) ratio of suspension capsule = 1.20). The P-D suspension was found not to be bioequivalent to the P-D capsules, with the 90% confidence interval for the log-transformed AUC(0-inf) falling outside the acceptance limits by 8%, i.e., (102-133%). The relative bioavailability of the P-D suspension was also higher than that of the P-D capsules at 117%. The sponsor used the relative bioavailability estimate of 1.2 to extrapolate the dosage of the capsules in adults to the equivalent suspension dosage in children aged 6 months to 12 years.

9. 983-066: Pivotal Bioequivalence Study Between the 300 mg Market Image (Formulation No. 34) and the Clinical Trials Capsules (Formulation No. 25, Over- Encapsulated); 300 mg x 1; N = 36 male and female subjects, age 21-67 yrs; 2-way crossover design.

The ratios (i.e., Test/Reference) for C_{max} and AUC(0-inf) were 93.9% and 95.4%, respectively, and the 90% confidence intervals (CI) on the ratios were (85.3%-104%) and (87.5%-104%), respectively. These results demonstrated that the 90% confidence intervals for C_{max} and AUC(0-inf) fell within the acceptance criteria of (80% -125%), and therefore, the market image capsule was deemed to be bioequivalent to the clinical capsule. The results and sponsor's conclusion were acceptable.

C. Drug Interaction Studies

10. 983-029: Probenecid - Cefdinir Interaction; CefD 300 mg x 1, Prob 1000 mg x 1; N = 12 male and female subjects, age 22-47 yrs; 2-way crossover design.

Mean cefdinir C_{max} and AUC(0-inf) were increased by ~1.5 and ~2-fold, respectively, with probenecid. The least square mean increases were 53.5% (range 13.9%-132%) for C_{max} and 113% (range 35%-306%) for AUC(0-inf). Mean renal clearance (CL_r) was reduced ~65%, from 192 ml/min following cefdinir alone to 67.6 ml/min following cefdinir with probenecid, and mean cefdinir T_{1/2} was increased 1.5-fold from

1.4 hrs to 2.1 hrs with probenecid coadministration. There were no serious adverse events or serious laboratory abnormalities reported for either treatment. Headache was the most common adverse event reported for both treatments. The sponsor noted that cefdinir was well tolerated either alone or coadministered with probenecid.

The results suggested that coadministration of probenecid with cefdinir approximately doubled systemic exposure to cefdinir, reduced cefdinir renal clearance, and substantially increased cefdinir $T_{1/2}$. The reduction in renal clearance appeared to be due to inhibition of active renal tubular secretion of cefdinir by probenecid.

11. 983-030: Maalox - Cefdinir Interaction; Cefd 300 mg x 1, Maalox 30 ml x 1; N = 16 male and female subjects, age 23-62 yrs; 4-way crossover design (Cefd alone, with, 2 hrs before, 2 hrs after Maalox).

The results indicated substantial reductions in cefdinir C_{max} , T_{max} , $AUC(0-inf)$, and $A_e\%$ (the percent of the cefdinir dose excreted in the urine as unchanged drug) of 38%, 30.3%, 44.4%, and 40%, respectively, when cefdinir was administered with Maalox TC[®]. Only slight, if any, reductions in these parameters for the before and after Maalox TC[®] treatments were observed (i.e., range of mean differences of ~3% increase to ~16% decrease). No alterations in cefdinir renal clearance or $T_{1/2}$ were observed for any of the three treatments vs. cefdinir alone. Thus, the decrease in $A_e\%$ when cefdinir was administered with Maalox TC[®] appeared to be due to a reduction in systemic availability (i.e., $AUC(0-inf)$). The sponsor recommended that, if an aluminum or magnesium-containing antacid is to be taken with cefdinir therapy, cefdinir should be given at least 2 hrs before or after the antacid. These results and conclusions were acceptable.

12. 983-034: Oral Iron - Cefdinir Interaction; Cefd 300 mg x 1, FeSO₄ Tablet x 1 (60 mg elemental Fe), Multivitamin Tablet x 1 (10 mg elemental iron); N = 15 males, age 19-48 yrs; 3-way crossover design (Cefd alone, with FeSO₄, with Multivitamin).

13. 983-043: Effect of Timing of Oral Iron Therapy on Cefdinir Pharmacokinetics; Cefd 300 mg x 1, FeSO₄ Tablet x 1 (60 mg elemental Fe); N = 11 male and female subjects, age 25-52 yrs; 4-way crossover design (Cefd alone, with, 2 hrs after, 2 hrs before FeSO₄).

In both studies, coadministration of iron with cefdinir substantially reduced systemic exposure to the antibiotic and the magnitude of the reduction appeared to be dependent on the dose of elemental iron. Mean cefdinir C_{max} , $AUC(0-inf)$, and $A_e\%$ were decreased by 30-38% following coadministration with the multivitamin tablet containing 10 mg elemental iron when compared to cefdinir given alone. Following coadministration with the FeSO₄ tablet containing 60 mg elemental iron, mean cefdinir C_{max} , $AUC(0-inf)$, and $A_e\%$ were decreased by 79-83% when compared to cefdinir given alone. In general, the elimination of cefdinir appeared to not be substantially effected by multivitamin or ferrous sulfate coadministration, as indicated by nonsignificant changes in renal clearance and $T_{1/2}$.

When cefdinir was taken at 2 hrs before or after FeSO₄, the reduction in systemic exposure to cefdinir was smaller in magnitude than that when given with iron (i.e., C_{max} and AUC decreased in the range of ~14% to ~30%), and were not significantly different when compared to cefdinir administered alone.

The results suggested that iron reduces the absorption of cefdinir from the gastrointestinal tract, and thereby, reducing systemic availability. The sponsor postulated that this effect was mediated by the formation of nonabsorbable iron-cefdinir complexes in the gut, with increasing iron doses producing greater reductions in the amount of cefdinir available for absorption. The sponsor recommended to avoid coadministration of cefdinir with iron supplements, and if iron supplements are needed during cefdinir therapy, cefdinir should be administered at least 2 hrs before or after the supplement. These results and conclusions are acceptable.

D. Special Populations

14. 983-040: Effect of Age on Cefdinir Pharmacokinetics; Cefd 300 mg x 1; N = 16 young males and

females - age 20-27 yrs, 16 elderly males and females - age 65-91 yrs; parallel groups design.

Systemic exposure to cefdinir following a single 300 mg dose to the 16 elderly subjects was substantially increased when compared to that of the younger subjects, as evidenced by statistically significant increases in C_{max} and $AUC(0-inf)$ of 43.5% and 86.3%, respectively, (i.e., mean C_{max} 3.0 mcg/ml vs 2.1 mcg/ml; mean $AUC(0-inf)$ 19.0 mcg.hr/ml vs 10.2 mcg.hr/ml). The percent of the dose excreted in the urine as unchanged cefdinir ($A_e\%$) was only modestly increased from 17.4% in the young to 20.9% in the elderly, which suggested that the increase in systemic availability/exposure in the elderly was not due to age related changes in cefdinir oral bioavailability, but rather to a reduction in cefdinir clearance.

Cefdinir renal clearance (CL_r), apparent oral clearance (CL/F), and apparent volume of distribution ($V_d\beta/F$) were significantly reduced in the elderly group by 34.6%, 48.1%, and 38.9%, respectively. The reduction in $V_d\beta/F$ may be expected due to an age related reduction in total body water. Because of the decreases in both CL/F and $V_d\beta/F$, only modest changes in the apparent elimination $T_{1/2}$ of cefdinir were observed in the elderly subjects (i.e., ~20% increase in mean $T_{1/2}$ from 1.8 hrs in the young to 2.2 hrs in the elderly). Based on the range of $T_{1/2}$ values in the elderly group (i.e., 1.3 to 3.3 hrs), the predicted accumulation of cefdinir in plasma would be minimal (i.e., <10%) with either repeated bid or qd dosing.

Creatinine clearance (CL_{Cr}) in the elderly subjects was significantly decreased by 42.6% versus the young subjects (i.e. mean CL_{Cr} 54 ml/min vs 94 ml/min). This reduction in renal function in the elderly group was another expected finding since age related reductions in renal function have been documented in the literature. Correlation and regression analyses indicated that reductions in cefdinir renal clearance in the elderly appeared to be primarily due to decreases in CL_{Cr} , whereas reductions in apparent oral clearance (i.e., total clearance) in the elderly appeared to be preferably related to changes in age rather than to changes in CL_{Cr} .

From the results of these correlation and regression analyses and a meta analysis of PK data, the sponsor concluded that the pharmacokinetic differences observed between the elderly and young subjects, were largely attributable to reduced cefdinir elimination secondary to the expected age related decline in renal function. From this conclusion, the proposed labeling indicates that elderly patients do not require dosage adjustment unless they have intrinsic renal dysfunction (i.e., CL_{Cr} <30 ml/min). This conclusion was acceptable.

15. 983-031: Effect of Renal Impairment on Cefdinir Pharmacokinetics; Cefd 300 mg x 1; Grp 1 - 8 subjects, normal renal fxn (CL_{Cr} >60 ml/min), mean CL_{Cr} 99 ml/min, age 22-48 yrs; Grp 2 - 4 subjects, moderate renal impairment (CL_{Cr} 30-60 ml/min), mean CL_{Cr} 44 ml/min, age 24-61 yrs; Grp 3 - 9 subjects, severe renal impairment (CL_{Cr} <30 ml/min), mean CL_{Cr} 20 ml/min, age 26-67 yrs; parallel groups design.

Plasma concentrations of cefdinir following single 300 mg doses were higher and persisted longer in subjects with moderate to severe renal impairment when compared to subjects with normal renal function, i.e., quantifiable drug levels at 24-48 hrs postdose with renal impairment vs 12-14 hrs postdose with normal renal function. As a result, systemic exposure to cefdinir was substantially greater in those subjects with renal impairment, as evidenced by significant increases in mean $AUC(0-inf)$ by ~3.5-fold for the moderate impairment (i.e., 33 mcg.hr/ml vs 9.5 mcg.hr/ml) and ~6.5-fold for the severe impairment groups (i.e., 61 mcg.hr/ml vs 9.5 mcg.hr/ml). Mean cefdinir C_{max} was also significantly increased over the normal renal function group by 2-fold in both the moderate (i.e., 4.5 mcg/ml vs 2.0 mcg/ml) and severe renal impairment groups (i.e., 4.1 mcg/ml vs 2.0 mcg/ml). The occurrence of the higher C_{max} was significantly prolonged only in the severe renal impairment group by ~1 hr (i.e., mean T_{max} 5.2 hrs vs 3.9 hrs), while T_{max} for the moderate impairment group was similar to subjects with normal renal function (i.e., 4.0 hrs vs 3.9 hrs).

The increase in systemic exposure was due to the significant reduction in cefdinir elimination, as indicated by the decreases in both renal and apparent oral clearances of ~70-80% for the moderate impairment group and ~85-90% for the severe impairment group. However, the reduction in clearance resulted in a

significant prolongation of $T_{1/2}$ only for the subjects with severe impairment from a mean of 2.2 hrs in normals to 11.4 hrs in this group. Mean $T_{1/2}$ for the moderately impaired group increased to 3.9 hrs.

Significant correlations were observed for the following linear regression relationships: λ_z vs CL_{cr} ($r^2 = 0.803$), CL_r vs CL_{cr} ($r^2 = 0.943$), and CL/F vs CL_{cr} ($r^2 = 0.846$). A significant linear relationship was also observed for CL/F vs. CL_r ($r^2 = 0.906$). These results suggested that renal function was the primary factor influencing cefdinir elimination in the subjects evaluated in this study.

The sponsor concluded by recommending the dose of cefdinir be reduced to 300 mg once daily in patients with severe renal impairment, i.e., $CL_{cr} < 30$ ml/min. Although clearance was significantly reduced in both moderate and severe impairment, the predicted systemic drug exposure (i.e., AUC) determined from the regression equation relating CL/F and CL_{cr} (i.e., $CL/F = 7.93 \times CL_{cr} - 86.4$; and $AUC = F \times Dose/CL$) for the moderate group at a dose of 600 mg / day and the severe group at 300 mg / day was consistent with that of subjects with normal renal function. Thus, it would appear that the dosage reduction to 300 mg qd for $CL_{cr} < 30$ ml/min and the usual recommended dosage of 300 mg q12 hours (or 600 mg qd) for CL_{cr} between 30 and 60 ml/min are appropriate. The sponsor's conclusions and dosage recommendation were acceptable.

16. 983-068: Effect of Hemodialysis on Cefdinir Pharmacokinetics; Cefd 300 mg x 1; N = 8 male and female patients requiring chronic hemodialysis 3 times per week at ~4 hrs/dialysis session for end stage renal disease; age 30-48 yrs; open-label design.

Following a single 300 mg dose of cefdinir to 8 hemodialysis patients, systemic drug exposure while not on dialysis was substantially increased in these patients over that of subjects with no renal impairment, as indicated by a 3-fold increase in C_{max} (i.e., mean C_{max} 4.7 mcg/ml vs 1.6 mcg/ml) and a 17-fold increase in $AUC(0-inf)$ (i.e., mean $AUC(0-inf)$ 121 mcg.hr/ml vs 7.1 mcg.hr/ml). The apparent elimination of cefdinir while not on dialysis was decreased substantially, as indicated by $T_{1/2}$ estimates ranging from 13 to 24 hrs, with a mean of 15.9 hrs, in the hemodialysis patients compared to a mean $T_{1/2}$ of 1.5 hrs in subjects with no renal impairment.

Cefdinir appeared to be effectively removed from the systemic circulation with the first hemodialysis treatment, as indicated by the relatively short dialysis $T_{1/2}$ of ~3 hrs. Based on the mean apparent elimination rate constant estimated during dialysis (i.e., $\lambda_d = 0.246 \text{ hr}^{-1}$), the sponsor determined that a 4-hr dialysis treatment would be expected to remove ~63% of cefdinir from the systemic circulation (i.e., $\%loss = (1 - e^{-(\lambda_d \times t)}) \times 100\%$).

The sponsor recommended that the initial dosage regimen of cefdinir in hemodialysis patients be adjusted to 300 mg given every other day, with 300 mg administered at the end of each dialysis session. Subsequent doses of 300 mg are to be administered every other day. These results and conclusions were acceptable.

SUSPENSION (Corresponds to Appendix 3.20-24)

20. Pharmacokinetic Rationale for Cefdinir Dose Selection in Pediatric Subjects

The sponsor provided documentation of the methods used to define the doses for the Phase III pediatric studies with cefdinir suspension that would result in systemic drug exposure comparable to that observed in adults following the 300 mg and 600 mg capsule doses. The adult 300 mg doses were extrapolated to pediatric doses on a mg/m² basis (using 1.73 m² for adult BSA) and adjusting for the relative bioavailability of the suspension compared to the capsule ($F_{rel} = 1.2$). Standard body weights and heights at the 50th percentile for pediatric ages ranging from 6 months to 12 years were used to calculate body surface area and the average mg/kg dose.

The target pediatric suspension doses equivalent to a 300 mg capsule dose in adults ranged from 4.64 to

6.94 mg/kg in children 6 months to 12 years. The final recommended pediatric dose was rounded up to 7 mg/kg. The corresponding pediatric suspension dose equivalent to the 600 mg adult dose was 14 mg/kg. The methods provided by the sponsor to extrapolate the adult cefdinir capsule doses to equivalent pediatric suspension doses were found to be acceptable. The sponsor conducted a pharmacokinetic study in pediatric subjects (see Protocol 983-023 below and Appendix 3.21) with the recommended doses of the suspension resulting from this analysis.

21. 983-023: Single Dose Pharmacokinetics; 7 mg/kg x 1 or 14 mg/kg x 1; N = 12 boys and girls 6 mos - 2 yrs (mean 1.4 yrs), 12 boys and girls 2 - 12 yrs (mean 8.7 yrs); parallel groups design (i.e., younger group and older group), with 6 children receiving 7 mg/kg per group and 6 receiving 14 mg/kg per group.

Following single suspension doses of 7 and 14 mg/kg cefdinir to healthy children aged 6 mos - 2 yrs (younger group), dose proportional increases in mean C_{max} (i.e., 2.0 and 4.1 mcg/ml, respectively) and AUC(0-inf) (i.e., 6.8 and 13.0 mcg.hr/ml, respectively) were observed. However, less than proportional increases in mean C_{max} (i.e., 2.6 and 3.6 mcg/ml, respectively) and AUC(0-inf) (i.e., 9.8 and 13.7 mcg.hr/ml, respectively) were observed following the same suspension doses to healthy children aged 2 yrs - 12 yrs (older group). Overall, the increases in mean C_{max} and AUC(0-inf) for all children 6 mos - 12 yrs were less than proportional to the increase in the dose from 7 to 14 mg/kg. The reason(s) for this was(were) not provided by the sponsor in the present study, but less than dose proportional increases in C_{max} and AUC(0-inf) were also observed in adults at higher capsule doses of 600 mg.

Both mean T_{max} and T_{1/2} were not substantially different between the two age groups at the two suspension doses. Overall mean T_{max} was 2.2 hrs at 7 mg/kg and 1.8 hrs at 14 mg/kg for children 6 mos - 12 yrs. Overall mean T_{1/2} for the 7 mg/kg and 14 mg/kg doses were 1.5 and 1.4 hrs, respectively. For all PK parameters, there was a substantial amount of overlap in the individual values between the younger and older children at the 7 and 14 mg/kg doses. In general, it appeared that cefdinir pharmacokinetics were similar between the two age groups following single doses of 7 mg/kg and 14 mg/kg.

When compared to the equivalent capsule doses in adults, i.e., 7 mg/kg suspension vs 300 mg capsule and 14 mg/kg suspension vs 600 mg capsule, the greatest differences were observed in mean C_{max} and T_{max}. Mean cefdinir C_{max} was ~25-30% lower following the capsule doses in adults vs the suspension doses in children (i.e., 1.6 mcg/ml @300 mg vs 2.3 mcg/ml @7mg/kg; 2.9 mcg/ml @600 mg vs 3.9 mcg/ml @14 mg/kg) and mean T_{max} was ~1 hr longer (i.e., cap ~3 hrs vs susp ~2 hrs). In general, this would be expected for a capsule vs suspension formulation. However, systemic exposure, i.e., mean AUC(0-inf), and mean T_{1/2} were comparable between doses of 300 mg of the capsule and 7 mg/kg of the suspension and 600 mg of the capsule and 14 mg/kg of the suspension. The sponsor's projected equivalency of the suspension and capsule doses appeared to be acceptable, based on similarities in overall systemic exposure and the elimination T_{1/2} between children and adults.

22. 983-048: Cefdinir Concentrations in Middle Ear Fluid and Plasma in Pediatric Patients with Acute Otitis Media (AOME); 7 mg/kg bid or 14 mg/kg qd x 10 days; N = 14 boys and girls, age 1-12 yrs; parallel groups design, with 6 children receiving 7 mg/kg bid and 8 receiving 14 mg/kg qd.

Cefdinir concentrations in middle ear effusion fluid and plasma were determined at 3 hrs after the first doses of each the 10-day suspension regimens. After the first dose of 7 mg/kg, plasma concentrations ranged from 0.8-3.2 mcg/ml and middle ear fluid levels ranged from 0-0.94 mcg/ml (mean±sd 0.23±0.37 mcg/ml). After the first dose of 14 mg/kg, plasma concentrations ranged from 2.36-5.54 mcg/ml and middle ear fluid levels ranged from 0-1.42 mcg/ml (mean±sd 0.63±0.50 mcg/ml). At 7 mg/kg, middle ear fluid concentrations fell below the quantitation limit of the microbiological assay (i.e., <0.016 mcg/ml) for 3 of the 6 pediatric patients studied, and in 1 of the 8 patients receiving 14 mg/kg.

The mean cefdinir middle ear fluid : plasma ratio, a measure of cefdinir tissue penetration, after 14 mg/kg was ~2-fold higher than the corresponding mean ratio for the 7 mg/kg dose. The mean ratio at 14 mg/kg

was 0.20 (range 0-0.35); at 7 mg/kg, the mean ratio was 0.10 (range 0-0.40). There appeared to be no relationship between the concentration of cefdinir in middle ear fluid and in plasma, and the ratios also appeared to be independent of plasma drug concentrations over the range of doses studied.

At 14 mg/kg, the mean middle ear fluid concentration of 0.63 mcg/ml was above the MIC₉₀ values for the 5 common pathogens associated with AOME (see Table 4 immediately at end of this section). At 7 mg/kg, the mean middle ear fluid concentration of 0.23 mcg/ml was above the MIC₉₀ values for *Strep. pneumoniae* and *pyogenes*, but below those for *Staph. aureus*, *H. influenzae* and *Moraxella catarrhalis*.

23. 983-041: Effect of Iron-Fortified Infant Formula on Cefdinir Pharmacokinetics in Healthy Infants; Cefd 7 mg/kg, 6 oz Iron-Fortified (IF) Similac (~2.7 mg elemental Fe), 6 oz Non-Iron Fortified (NIF) Similac; N = 15 healthy infants, age 6-12 mos; 2-way crossover design (i.e., Cefd + IF; Cefd + NIF).

Coadministration of a single 7 mg/kg dose of cefdinir suspension with an iron fortified infant formula to healthy infants significantly reduced mean C_{max} by ~20% (i.e., 0.98 mcg/ml vs 1.22 mcg/ml; p=0.043), but did not significantly alter T_{max}, AUC(0-inf), or the apparent elimination T_{1/2} of cefdinir when compared to coadministration with the non-iron fortified formula. The sponsor concluded that iron supplementation in an infant formula has little effect on the rate and extent of cefdinir absorption. In light of the borderline statistical significance in the reduction in only C_{max} with the IF formula, the sponsor's conclusion of no effect of the IF treatment was acceptable.

24. 983-067: Pivotal Bioequivalence Study Comparing Market Image Suspension (Formulation 37, 125 mg/5 ml) to Clinical Trials Suspension (Formulation 27, 125 mg/5 ml); 400 mg; N = 36 male and female adult subjects; 2-way crossover design.

The ratios (i.e., Market Image/Clinical Trials) for C_{max} and AUC(0-inf) were 102% and 100%, respectively, and the 90% confidence intervals (CI) on the ratios were (96.3%-108%) and (94.7%-106%), respectively. These results demonstrated that the 90% confidence intervals for C_{max} and AUC(0-inf) fell within the acceptance criteria, and therefore, the market image suspension was bioequivalent to the clinical trials suspension.

META/POPULATION PK ANALYSES for CEFDINIR In ADULTS (CAPSULES) and In CHILDREN (SUSPENSION) (Corresponds to Appendix 4)

Meta analyses of data from various clinical PK and efficacy trials were performed to identify relevant covariates that may be predictive of cefdinir pharmacokinetics in adult and pediatric subjects, and adult patients. Population pharmacokinetic (PPK) parameters were determined in adults and children, which also included estimation of oral bioavailability of both the capsules and suspension, and inter- and intra-subject variability in C_{max} and AUC. All covariate, PPK, and variability analyses were performed using SAS. Covariate analyses employed the use of linear regression models in a stepwise fashion to evaluate the influence of various subject/patient characteristics on cefdinir pharmacokinetic parameters. The method used to determine oral bioavailability (F) of the capsules at doses of 400 mg or less was reported in the literature by Hinderling and Shi (*J. Pharm. Sci.*, **84**:385-386, 1995). Bioavailability of the 600 mg capsule dose and the suspension were estimated by adjusting F at ≤400 mg for the respective relative bioavailabilities that were determined in previous PK studies.

The results are summarized as follows:

In adults (N = 217), CL_{cr} appeared to be the most relevant covariate to predict cefdinir pharmacokinetics and dosage adjustments would be needed in individuals with renal impairment (i.e., CL_{cr} <30 ml/min). Other covariates, i.e., weight, height, body surface area (BSA), gender, and age appeared to have relatively little impact on cefdinir pharmacokinetics, and thus, no dosage adjustments would be needed due to these adult patient characteristics. Although not formally evaluated because of limited data, race also did not appear to have any significant

influence on cefdinir pharmacokinetics.

In children (N = 39), BSA appeared to be the best predictor of cefdinir pharmacokinetics over other covariates such as weight, height, and CL_{cr}. Subject classification by age (i.e., adult vs pediatric) had no substantial impact in predicting cefdinir pharmacokinetics. Thus, differences in cefdinir pharmacokinetics between adults and children appeared to be mainly attributed to differences in body size.

No significant correlation was detected in the cefdinir plasma concentrations at 4 hrs postdose between adult patients (N = 158) and healthy adult subjects (N = 154) receiving capsule doses of either 300 or 600 mg. CL_{cr} was the only relevant covariate for the 4 hr postdose plasma concentrations between patients and healthy subjects. This suggested that the pharmacokinetic profiles in patients would be similar to those in healthy subjects.

The population estimate of cefdinir bioavailability from the capsules at doses \leq 400 mg was 21% and ~16% at doses of 600 mg. For the suspension, the population mean bioavailability was estimated at ~25%.

The total variability (as %RSD) in C_{max} and AUC(0-inf) was 36.2% and 34.4%, respectively. This variability in C_{max} and AUC(0-inf) was mainly due to the variance within rather than between subjects, with the intrasubject variability for both parameters at 27%. The intersubject variances in C_{max} and AUC(0-inf) were 24% and 21%, respectively. The sponsor noted that cefdinir may be considered as a highly variable drug since the intrasubject variances approached 30%.

There were no apparent deficiencies with the methods of analyses. In general, very little new information had surfaced from this work, and thus, it mainly served to confirm the sponsor's previous findings from the individual pharmacokinetic studies.

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TABLE 3

Summary of In Vivo Data: Cefdinir Pharmacokinetic Parameters^a
(Page 1 of 5)

Protocol	Study Day/ Treatment	Dose (mg)	C _{max} (µg/mL)	t _{max} (hr)	t _{1/2} (hr ⁻¹)	AUC(0-∞) (µg-hr/mL)	Results			
Basic Pharmacokinetics										
983-001	Day 1	50	0.233	2.7	NC	NC	Plasma concentrations increased approximately proportional to dose and were similar on Days 1 and 17.			
		100	0.422	3.5	NC	NC				
		200	0.474	3.0	3.2	2.63				
		400	1.76	3.5	1.2	6.49				
		600	2.42	3.5	1.9	11.2				
		50	0.366	3.7	NC	NC				
	Day 17	100	0.396	3.0	NC	NC				
		200	0.725	3.5	1.9	3.65				
		400	1.11	3.5	1.5	5.10				
		600	1.70	3.7	1.9	8.04				
		983-17	Fasting	400	2.29	3.5		1.5	10.7	Food does not effect cefdinir availability.
				400	1.89	2.7		1.7	8.11	
400	1.92			4.7	1.7	9.58				
2-12 yr (S)	400		2.05	4.1	1.7	10.2				
	7 mg/kg		2.56	2.3	1.6	9.83				
	14 mg/kg		3.60	1.7	1.6	13.7				
983-23	6 mo - 2 yr (S)	7 mg/kg	2.04	2.0	1.3	6.79	Plasma concentrations increased with dose and were similar between age groups.			
		14 mg/kg	4.11	2.0	1.3	13.0				

NC = Not calculated; S = Cefdinir suspension.
^a Cefdinir administered as capsules unless otherwise noted.

Summary of In Vivo Data: Cefdinir Pharmacokinetic Parameters*
(Page 2 of 5)

Protocol	Study Day/ Treatment	Dose (mg)	C _{max} (µg/mL)	t _{max} (hr)	t _{1/2} (hr ⁻¹)	AUC(0-∞) (µg·hr/mL)	Results
Baseline Pharmacokinetics (cont)							
983-24	Plasma	300	1.13	NC	NC	NC	Tissue/plasma cefdinir concentration ratio was 0.27 and 300 mg and 0.21 at 600 mg. Tonsil penetration is similar at both doses.
		600	2.17	NC	NC	NC	
	Tonsil	300	0.28	NC	NC	NC	
		600	0.44	NC	NC	NC	
983-25	Plasma	200	1.00	3.3	1.7	4.15	Plasma concentrations increased proportional to dose at 200 to 400 mg and were less than dose proportional at 400 to 600 mg. Blister fluid plasma concentrations, C _{max} and AUC(0-∞) were 48% and 91% of plasma concentrations, respectively.
		300	1.55	3.2	1.6	6.61	
		400	2.15	3.0	1.7	8.95	
		600	2.36	3.3	1.8	9.99	
	Blister	200	0.56	4.8	3.3	4.36	
		300	0.67	4.9	3.7	5.51	
		400	0.89	4.8	3.7	7.24	
		600	1.09	4.7	3.7	8.99	
983-35	Single dose	200	1.29	3.1	1.5	5.55	Plasma concentrations increased proportional to dose from 200 to 400 mg but are 75% to 85% of predicted at 600 mg.
		300	1.60	2.9	1.5	7.05	
		400	2.16	3.0	1.4	9.01	
		600	2.87	3.0	1.5	11.1	
983-48	Plasma	300	1.96	NC	NC	NC	Middle ear/plasma cefdinir concentration ratio was 0.10 at 300 mg and 0.20 at 600 mg.
		600	3.37	NC	NC	NC	
	Middle Ear	300	0.23	NC	NC	NC	
		600	0.63	NC	NC	NC	

NC = Not calculated.

* Cefdinir administered as capsules unless otherwise noted

Summary of In Vivo Data: Cefdinir Pharmacokinetic Parameters*
(Page 3 of 5)

Protocol	Study Day/ Treatment	Dose (mg)	C _{max} (µg/mL)	t _{max} (hr)	t _{1/2} (hr)	AUC(0-∞) (µg·hr/mL)	Results
Basic Pharmacokinetics (cont)							
983-49	Plasma	300	2.00	NC	NC	NC	Bronchial mucoosa/plasma cefdinir concentration ratio was 0.41 at 300 mg and 0.31 at 600 mg.
		600	4.20	NC	NC	NC	
		300	0.78	NC	NC	NC	
		600	1.14	NC	NC	NC	
983-50	[¹⁴ C]Cefdinir	300	2.31	2.7	1.8	11.7	[¹⁴ C]Cefdinir is minimally metabolized. Radioactivity is completely recovered in urine and feces.
983-52	Plasma Breast Milk	600	1.44	3.5	1.5	5.8	Cefdinir is not secreted in breast milk in detectable amounts.
		600	BLQ	BLQ	BLQ	BLQ	
983-53	Plasma Sinus	300	0.97	NC	NC	NC	Sinus tissue/plasma cefdinir concentration ratio was 0.116 at 300 mg and 0.195 at 600 mg.
		600	2.27	NC	NC	NC	
		300	0.12	NC	NC	NC	
		600	0.46	NC	NC	NC	
Bioequivalence							
983-18	Test Reference	200	0.812	3.7	1.6	3.46	Blinded capsules and capsules are bioequivalent.
		200	0.803	3.5	1.7	3.57	

NC = Not calculated; BLQ = Below limits of quantitation; S = Cefdinir suspension.
* Cefdinir administered as capsules unless otherwise noted

Summary of In Vivo Data: Cefdinir Pharmacokinetic Parameters*
(Page 4 of 5)

Protocol	Study Day/ Treatment	Dose (mg)	C _{max} (µg/mL)	t _{max} (hr)	t _{1/2} (hr ^h)	AUC(0-∞) (µg·hr/mL)	Results
Bioequivalence (cont)							
983-21	Test	400	1.40	3.7	1.7	6.36	Parke-Davis capsules, Parke-Davis pediatric suspension, and capsules are bioequivalent.
	Test (S)	400	1.44	3.3	1.9	7.43	
	Reference	400	1.34	3.6	1.9	6.21	
983-66	Market-Image Clinical Capsules	300 300	2.29 2.44	3.3 3.4	1.5 1.5	10.4 10.9	Market-image and clinical capsules are bioequivalent.
Drug Interaction							
983-29	Alone	300	1.06	3.3	1.4	4.44	Probenecid markedly inhibits cefdinir renal tubular secretion, reducing renal clearance, doubling exposure and prolonging t _{1/2} .
	w/ Probenecid	300	1.63	3.9	2.1	9.46	
983-30	Alone	300	1.71	3.3	1.7	7.84	Cefdinir bioavailability is significantly reduced when coadministered with Maalox.
	w/ Maalox	300	1.06	2.3	1.8	4.36	
	Before	300	1.76	3.1	1.7	6.79	
	After	300	1.44	3.3	1.7	6.72	
983-34	Alone	300	2.18	3.3	1.5	9.71	Iron reduces cefdinir absorption from the gastrointestinal tract. Cefdinir elimination remains unaffected.
	w/Multivitamin	300	1.36	3.8	1.7	6.74	
	w/Ferrous Sulfate	300	0.47	3.8	2.1	1.97	

S = Cefdinir suspension.

* Cefdinir administered as capsules unless otherwise noted

Summary of In Vivo Data: Cefdinir Pharmacokinetic Parameters*
(Page 5 of 5)

Protocol	Study Day/ Treatment	Dose (mg)	C _{max} (µg/mL)	t _{max} (hr)	t _{1/2} (hr ⁻¹)	AUC(0-∞) (µg-hr/mL)	Results
Drug Interactions (cont)							
983-41	w/ Formula (S)	7 mg/kg	1.22	2.6	1.9	5.55	Iron-fortified infant formula does not substantially alter the rate or extent of cefdinir absorption.
	w/ Iron-Fortified Formula (S)	7 mg/kg	0.982	3.2	1.9	5.14	
983-43	Alone	300	2.62	3.7	1.4	12.64	Cefdinir absorption is reduced when coadministered with iron.
	w/ Feratab Iron	300	0.49	3.2	1.8	2.36	
	Before	300	2.21	3.1	1.4	8.78	
	After	300	2.26	3.8	1.5	10.57	
Special Populations							
983-31 Renal Impairment							
	Normal	300	2.02	3.9	2.2	9.54	Cefdinir clearance is decreased in subjects with impaired renal function.
	Moderate	300	4.47	4.0	3.9	33.0	
	Severe	300	4.08	4.1	11.4	61.4	
983-40	Young	300	2.09	3.8	1.8	10.2	Cefdinir clearance is significantly lower in elderly patients, secondary to age-related decline in renal function. Based on pharmacokinetic parameters, doses should not be adjusted.
	Elderly	300	3.00	3.9	2.2	19.0	
983-68	Hemodialysis	300	4.72	5.0	3.2	NC	Cefdinir is removed by hemodialysis. Patients requiring dialysis should receive cefdinir immediately after dialysis and on an every-other-day schedule.

NC = Not calculated.

* Cefdinir administered as capsules unless otherwise noted

TABLE 4

Tissue/Fluid Cefdinir Concentrations Following Administration of Single 300-mg (7 mg/kg) and 600-mg (14 mg/kg) Doses Compared with MIC₉₀ Values for Causative Pathogens

Tissue/Fluid	Blister Fluid		Tonsil Tissue		Sinus Tissue		Bronchial Mucosa		Epithelial Lining Fluid		Middle Ear Effusion Fluid	
	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	7 mg/kg	14 mg/kg
Concentration, µg/mL	0.674	1.091	0.28	0.44	0.12	0.46	0.77	1.08	0.97	0.38	0.23	0.63
Pathogen	MIC ₉₀											
Gram-Positive Pathogens												
<i>Staphylococcus aureus</i> ^a	A	A	--	--	B	A	A	A	A	B	B	A
<i>Streptococcus pneumoniae</i> ^b	--	--	--	--	A	A	A	A	A	A	A	A
<i>Streptococcus pyogenes</i> (Group A)	A	A	A	A	A	A	A	A	A	A	A	A
<i>Streptococcus agalactiae</i> (Group B)	A	A	--	--	--	--	--	--	--	--	--	--
Gram-Negative Pathogens												
<i>Haemophilus influenzae</i>	--	--	--	--	B	A	A	A	A	B	B	A
<i>Haemophilus parainfluenzae</i>	--	--	--	--	A	A	A	A	A	A	--	--
<i>Moraxella catarrhalis</i>	--	--	--	--	B	A	A	A	A	A	B	A
<i>Escherichia coli</i>	--	--	--	--	B	A	A	A	A	B	--	--
<i>Klebsiella pneumoniae</i>	A	A	--	--	B	A	A	A	A	A	--	--

A = Adequate tissue/fluid concentrations; B = Inadequate tissue/fluid concentrations; -- = Pathogen not associated with infections related to tissue/fluid.

^a Methicillin/oxacillin-susceptible

^b Penicillin-susceptible