CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50739

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: December 3, 1997

TO: David W. Feigal, Jr., M.D., M.P.H.
Acting Director, Office of Drug Evaluation IV
Center for Drug Evaluation and Research

FROM: Gary K. Chikami, M.D. /S/ 12/4/97
Acting Director, Division of Anti-Infective Drug Products

SUBJECT: NDA 50-739 OMNICEF (cefdinir) Capsules
NDA 50-749 OMNICEF (cefdinir) for Oral Suspension

ASSESSMENT

Parke-Davis Pharmaceuticals has submitted NDA 50-739 and NDA 50-749 for two formulations of a new semi-synthetic cephalosporin antibiotic, OMNICEF (cefdinir) for oral administration in the treatment of following clinical indications: community acquired pneumonia; acute exacerbation of chronic bronchitis; secondary bacterial infections of acute bronchitis; acute maxillary sinusitis; pharyngitis/tonsillitis; and uncomplicated skin and skin structure infections.

CMC

An Environmental Assessment has been completed and a Finding of No Significant Impact has been issued. Deficiencies identified in the initial CMC review were resolved during the review process. A list of outstanding issues which the applicant has committed to resolving are detailed in the approval letter. The final CMC review has recommended approval.

Pharmacology

Data from nonclinical pharmacology, pharmacokinetic and ADME, acute and chronic toxicity, reproductive toxicity and genotoxicity studies were submitted. Data from carcinogenicity studies were not submitted. Based on these studies, the Pharmacology review has recommended approval. Pregnancy Category B is recommended.

Microbiology

The Microbiology Review recommended approval. There were no outstanding microbiology issues.

BIOPHARMACEUTICS

The Biopharmaceutics Review has recommended approval. During the review an issue in vitro dissolution testing for OMNICEF for Oral Suspension was identified, however this issues was resolved. There are no outstanding Biopharmaceutics issues.

CLINICAL

Data from adequate and well controlled studies in adults support the safety and effectiveness of OMNICEF for the treatment community acquired pneumonia, acute exacerbation of chronic bronchitis, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infection. Data from adequate and well controlled studies in pediatric patients support the safety and effectiveness of OMNICEF for the treatment of acute bacterial otitis media, pharyngitis/tonsillitis and uncomplicated skin and skin structure infections in that patient population. Data from adequate and well controlled studies in adults for the treatment of acute maxillary sinusitis demonstrating safety and effectiveness and supportive information including pharmacokinetic data in pediatric patients and pathophysiologic and microbiologic information that would support extrapolation of efficacy data from studies in adults to pediatric patients, support the inclusion of a pediatric use statement for acute maxillary sinusitis in the Pediatric Use subsection of the Precautions section.

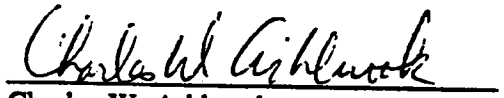
Data submitted did not support requested indication for treatment of [redacted]. The recommendation from the review team is nonapproval for this indication.

ACKNOWLEDGMENT

The entire review team Dr. Hamilton, Dr. Bonwit, Dr. Viragahavan, Dr. Blank, Dr. Pagay, Dr. Katague, Dr. Adeyemo, Dr. Osterberg, Dr. Colangelo, Dr. Pelsor, Dr. Altaie, Dr. Sheldon, Dr. Chakravary and Dr. Lin are to be congratulated on doing an excellent job of reviewing these applications and bringing them to an action within the PDUFA goal date. In particular, Dr. Janis Soreth, the Medical Team Leader, and Ms. Beth Duvall-Miller and Mr. Carmen DeBellas, the project managers, have done an outstanding job of providing both scientific and administrative oversight for the review of this project.

Patent Statement:	**US Patent Number:**	**4,935,507**
	Expiration Date:	**August 8, 2008**
	Patent Type:	**Crystalline form of cefdinir**
	Assignee:	**Fujisawa Pharmaceutical Co, Ltd**
	US Agent:	**Warner-Lambert Company**
	US Patent Number:	**4,559,334**
	Expiration Date:	**December 17, 2002**
	Patent Type:	**Chemical entity and pharmaceutical formulation**
	Assignee:	**Fujisawa Pharmaceutical Co, Ltd**
	US Agent:	**Warner-Lambert Company**
	US Patent Number:	**4,585,860**
	Expiration Date:	**November 10, 2000**
	Patent Type:	**Chemical entity, pharmaceutical formulation, and method for treating infectious disease**
	Assignee:	**Fujisawa Pharmaceutical Co, Ltd**
	US Agent:	**Warner-Lambert Company**

The undersigned declares that Patent Numbers 4,559,334 and 4,585,860 cover the formulation of cefdinir and 4,585,860 covers the method of treatment using cefdinir. This product is the subject of this application for which approval is sought.



Charles W. Ashbrook
Patent Counsel

EXCLUSIVITY SUMMARY for NDA # 50-739/749 SUPPL # _____

Trade Name OMNICEF **Generic Name** cefdinir capsules and powder for oral suspension
Applicant Name Parke-Davis **HFD-**520

Approval Date 12/4/97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES /X/ NO /__/

b) Is it an effectiveness supplement?

YES /__/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /__/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if

known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # ____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/s/ 12/3/97

Signature Date

Title: Project Manager

/s/ 12/3/97

Signature of Division Director Date

cc: Original NDA
Division File
HFD-85/Mary Ann Holovac

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 50-739/749 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF D-520 Trade and generic names/dosage form: Omnicef (cefdinir) Capsules and Powder for Oral Suspension Action: AP AE NA

Applicant Parke-Davis Therapeutic Class 1S

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate x inadequate ___

Indication in this application CAP, AECB, Sinusitis, Phar/Tons., SSSI, AOM (For supplemen answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

x 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Project Manager 12/3/97
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA #50-739, 50-749
HF D-520 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

NDA 50-739
Cefdinir Suspension
Amendment

Item 13.3 Certification for Generic Drug Enforcement Act of 1992.

Warner-Lambert Company certifies that it is not debarred; the Company did not and will not use in any capacity, the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetics Act in connection with this application.

NDA 50-749
Cefdinir Suspension
Amendment

Item 13.3 Certification for Generic Drug Enforcement Act of 1992.

Warner-Lambert Company certifies that it is not debarred; the Company did not and will not use in any capacity, the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetics Act in connection with this application.

Consult #770 (HFD-530)

OMNICEF cefdinir oral suspension and capsules

This consult is a resubmission of an IND consult which has now reached the NDA stage. The Committe had narrowly found the name acceptable in the original consult. However, upon closer examination at this consultation, the Committee feels there is a significant potential for confusion with OMNIPEN, an ampicillin product. This concern is amplified by similar indications, strengths and dosage regimens between the products which could lead to an unintended mix-up.

In view of the abov,e the Committee finds the proposed proprietary name unacceptable.

/S/ 5/22/97, Chair
CDER Labeling and Nomenclature Committee

OMNICEF AS A PROPRIETARY NAME FOR CEFDINIR

Cefdinir is a broad spectrum, third generation cephalosporin for oral administration, and is under development for the outpatient treatment of several types of community-acquired infections in adults and children. A request for a review of the proposed tradename, "Omnicef", was made on April 8, 1994 (SN 193, IND[ ]. The name was reviewed at a meeting of CDER's Nomenclature and Labeling Committee on May 9, and Parke-Davis was informed that the Committee was unable to recommend the name to the Anti-Infective Division.

The Committee first commented on the potential for confusion with the names of the following approved drugs: Ancef (cefazolin sodium) is a parenteral product and must be reconstituted from vials, primarily for hospital use, while cefdinir is an oral product that will be used to treat outpatient infections. Omniflox (temafloxacin) is no longer marketed anywhere in the world. Omnipen (ampicillin) is provided as an injection, as 250 and 500 mg violet/pink capsules, and as a white powder to make a salmon (125 mg/5 mL) or pink (250 mg/5 mL) suspension (generic ampicillin products are also available, and may be different in appearance to the Omnipen products). Omnipen is no longer promoted or sampled. Also, the use of ampicillin is quite low in comparison with other anti-infective agents (less than 1% of total), and has been decreasing (18% decrease in last year alone). Five branded ampicillin products, including Omnipen, compete for 18% of the small ampicillin market; 82% of prescriptions are generics. In fact, Omnipen oral suspension prescriptions do not even appear in the IMS National Prescription Audit database for July 1993-July 1994 because the number was less than the cut-off limit. Estimates are that[ ] prescriptions for the oral suspension were written during this time period.

Cefdinir will be provided as a 300 mg lavender/turquoise capsule and as a white powder to make a white suspension of 125 or 250 mg/5 mL. We believe it unlikely that anyone filling, dispensing, or using prescriptions for cefdinir and the drugs described above would confuse the names and dosage forms.

We also believe the Committee should also consider that the Patent and Trademark Office (PTO) has completed the substantive review of the trademark and that a certificate of Registration will issue once actual use of the tradename has been accomplished. As indicated in our submission of April 8, application for the trademark Omnicef was made to the PTO on August 14, 1992; the trademark was published in the Official Gazette on May 18, 1993, and allowed on December 7, 1993. By statute, the PTO must determine whether there is a likelihood of confusion with any prior trademark registrations or pending trademark applications before it can grant an applicant a certificate of registration. The PTO did not cite a single trademark during the examination process as a potential impediment. The application was passed to publication in the Official Gazette, which is a significant action in the review process, in that there are no further substantive reviews by the PTO before a registration is granted. This is also significant because the PTO is obligated by law to reject applications for

trademark registration that are likely to cause confusion with any prior applications or registrations. Further, unrelated third parties had an opportunity to file an opposition to registration of the mark after it was published in the Official Gazette, and no action was taken by any party (the statutory period to oppose has long since lapsed).

The Committee's second, and primary, concern was the use of the prefix "omni", with respect to 21 CFR 201.10(c)(3). This regulation states that "The labeling of the drug may be misleading by reason of the employment of a fanciful proprietary name for a drug or ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition when, in fact, the drug or ingredient is a common substance, the limitations of which are recognized when the drug or ingredient is listed by its established name." While acknowledging that "omni" has been allowed in numerous drug proprietary names, the Committee felt this has been without prior due consideration of the puffery nature of the term.

The concern with "omni" as puffery is unclear to us. As stated above, 21 CFR. 201.10(c)(3) addresses names that imply that the drug "has some unique effectiveness or composition when...the drug...is a common substance, the limitations of which are readily recognized [through] its...established name." The term "omni" should not be viewed in a vacuum. It is axiomatic that a trademark should not be split up into its component parts then compared with another to determine likelihood of confusion; rather, it is the impression that the mark as a whole creates, and not the parts of the mark, that is critical to the analysis. Even if an argument were made that the "omni" term has some meaning in the minds of consumers, it is well established that a combination of arguably descriptive or even generic words can and often does result in an arbitrary unitary term that functions independently as a trademark. It is unlikely that the product will ever be referred to as "Omni." When the name Omnicef is considered in its entirety, clearly the product is a cephalosporin, i.e., Omni "cef", but we do not believe that a physician or other prescriber is likely to think that Omnicef has any unique effectiveness or composition. Even if considered in isolation, the prefix "omni" does not imply unique effectiveness or composition. This is particularly true given the wide usage of "omni" in other contexts, including in the names of other drug products. Our recent review of the use of "omni" in trademarks revealed 71 uses, including several in FDA-approved products. In fact, as recently as 1992 and 1993, two CDER-regulated products were approved with a name using the prefix, "Omniflox" (temafloxacin) and "Omniscan" (gadodiamide). Whatever ability the term "omni" may have had to imply unique effectiveness or composition has clearly been eliminated through wide usage.

The Committee also commented on the undesirability of the term "cef" in Omnicef, but acknowledges the ubiquitous use of the term in cephalosporin proprietary names. The inclusion of the "cef" portion in the Omnicef trademark should also not be the basis upon which to recommend against allowing the Omnicef trademark for cefdinir. If the objection to the inclusion of "cef" anywhere in the trademark is on the ground that it will likely lead to

confusion, that concern has been addressed above. If the objection is because the non-proprietary name for the compound, cefdinir, also includes the "cef" component, we similarly do not believe this to be an appropriate basis upon which to recommend against Omnicef as a trademark, especially in light of the clear phonetic and visual differences between the two names. This is particularly true given that "cef" has already been included in numerous cephalosporin proprietary names. There are also numerous trademark registrations containing "cef" in the suffix. We believe that Omnicef poses no danger to the integrity of the name cefdinir given the phonetic and visual difference between cefdinir and Omnicef, and the numerous existing trademark registrations that contain the "cef" and "omni" component.

Finally, we would like to note that we have expended considerable time and resources in adopting the name Omnicef, a name chosen based on names previously considered acceptable by the Agency. Given the wide usage and adoption of names with similar prefixes and suffixes, it is difficult to understand how Omnicef is now being interpreted as confusing, puffery and inappropriate vis-a-vis its nonproprietary name. This is especially true given the lack of any recognizable violation of generally applicable guidelines, principles or historical practice of the Committee or Agency. Based on recent NDA approvals with proprietary names containing "omni", the dilution of the meaning of this term via extensive trademark use over many years, and the registration of the trademark by the PTO, we ask that the Committee reconsider its prior recommendation regarding Omnicef as a tradename for cefdinir.

Consult #298 (HFD-520)
(revisit)

OMNICEF

Cefdinir Capsules 300 mg
Cefdinir Oral Suspension
125 mg/5 mL or 250 mg/5 mL

In the last review (May 1994), the Committee set forth 3 comments/concerns and recommended that the Division reviewers consider these issues before deciding on the acceptability of the name. Based on the firm's letter of November 10, 1994, it appears as if all the Committee's comments and concerns were shared with the firm. Two of the issues have been responded to satisfactorily by the firm, the sound-alike/look-alike potential with Ancef (different dosage forms) and the use of "cef" in the name (already in numerous cephalosporin products).

With regards to the puffery issue concerning the use of "Omni" in the proposed name, the Committee believes that the implied meaning of the component parts of a trademark is an important part of the impression the name creates as a whole. Indeed, it is reasonable to assume that "omni" was intentionally selected over some other term with a less desirable meaning. In the May 1994 review of this name, the Committee noted that the proposed name had the potential to be considered misleading as defined in 21 CFR 201.10(c)(3). At the same time, it was noted that the Division had the responsibility for determining whether "omni" was appropriate for the product considering the benefits, spectrum of activity, potency and past use of "omni" in other product names. Based on the firm's letter of November 10, 1994, we are unable to determine if the review Division was opposed to the use of the name "Omnicef" or merely passed along all of the Committee's comments. The Committee re-reviewed the proposed name in light of the firm's comments. As previously noted "Omni" appears in the proprietary name of numerous drug products, therefore, as long as there are no apparent safety concerns, the Committee will not oppose the proposed name on this basis. However, the Committee suggests that the firm be advised against differentiating or increasing the prominence of "Omni" on the label in a manner that would place emphasis on this portion of the name. The Committee also suggests that the Division reviewers consult with the Division of Drug Marketing, Advertising, and Communications to determine if they have any suggestions regarding the use or portrayal of this name.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

/S/, Chair 4/11/95

COMPLETED

(770)

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-611) MPN II

FROM: Division of Anti-Infective HFD-520
Attention: S.N.P/A SAY Phone 827-2179

DATE: 3/18/97

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: OMNICEF TM NDA/ANDA# 50-749

Company Name: Parke Davis/ Warner Lambert

Established name, including dosage form: Cefdinir - 125 mg/5 ml oral suspension

Other trademarks by the same firm for companion products: None

Indications for Use (may be a summary if proposed statement is lengthy):
Cefdinir is an extended-spectrum semisynthetic cephalosporin for oral administration in the treatment of mild to moderate bacterial infections.

Initial comments from the submitter: (concerns, observations, etc.)
The cover letter from the firm states that at your 4/11/95 meeting, the CDER labeling & nomenclature committee would not object to this trademark

Omnipen
OmnisCan
Omni Paque

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev May.94

(770)

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-611) MPN II

FROM: Division of Anti-Infective HFD-520
Attention: S.N. PRAGAY Phone 827-2179

DATE: 3/18/97

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: OMNICEF™ NDA/ANDA# 50-739

Company Name: Parke Davis/ Warner Lambert

Established name, including dosage form: Cefdinir - 300 mg Capsules,

Other trademarks by the same firm for companion products: None

Indications for Use (may be a summary if proposed statement is lengthy):
Cefdinir is an extended-spectrum semisynthetic cephalosporin for oral administration in the treatment of mild to moderate bacterial infections.

Initial comments from the submitter: (concerns, observations, etc.)
The cover letter from the firm states that at your 4/11/95 meeting, ~~the~~ the CDER labeling & nomenclature committee would not object to this trademark

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev May.94

Revisit #298

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Mr. Kent Johnson, Chair, (HFD-600) MPN II

FROM: Division of Anti-Infective Drug Products HFD-520
Attention: Carmen DeBellas Phone: 443-6797

DATE: 3/1/95

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Omnicef IND ~~NDA/ANDA~~ # :

Established name, including dosage form:
Cefdinir capsules And Suspension

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy):
Pneumonia
Bronchitis
Skin & Skin Structure
Pharyngitis
Otitis Media

Initial comments from the submitter: (concerns, observations, etc.)

This a reconsider correspondence the May 9, 1994 review of the Omnicef name.

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Dec. 1990

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEWS FOR INTERNAL DISTRIBUTION ONLY)

NDA:	50-739
Drug Class:	
Generic Drug Name:	Cefdinir 300 mg capsules/oral suspension
Drug Trade Name:	Omnicef
Applicant:	Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company
Indication:	1. Community Acquired Pneumonia 2. Acute Exacerbations of Chronic Bronchitis 3. 4. Acute Maxillary Sinusitis 5. Pharyngitis/Tonsillitis 6. Uncomplicated Skin and Skin Structure Infections
Statistical Reviewer:	Dr. Alaka G. Chakravarty
45-day review done by:	Dr. Alaka G. Chakravarty
Clinical Reviewer:	Dr. Andrew Bonwit Dr. Roopa Viraraghavan Dr. Holli Hamilton Dr. James Blank
Project Manager:	Mr. Carmen DeBellas Ms. Beth Duvall-Miller
Submission Date:	September 3, 1996
Date Received:	September 4, 1996
45 Day Meeting Date:	November 14, 1996
User Fee Date:	September 4, 1997

Primary Controlled Clinical Efficacy Studies:

Table 1 summarizes the pivotal and supportive studies.

Table 1: Summary of Pivotal and Supportive Clinical Studies

Indication	Study number	Study Design	Comparator	Sample size
Capsules				
Community Acquired Pneumonia	983-4	active-controlled, randomized, double-blind, parallel-group, multicenter, US	cefaclor	
	983-26	active-controlled, randomized, investigator-blind, parallel-group, multicenter, Canada, Europe, S.Africa, Australia	Amoxicillin/ Clavulanate	
Acute Exacerbations of Chronic Bronchitis	983-5	active-controlled, randomized, double-blind, parallel-group, multicenter, U.S, Europe, S.Africa, Australia	Cefuroxime	
Acute Maxillary Sinusitis	983-6	active-controlled, randomized, investigator-blind, parallel-group, multicenter, U.S.	Amoxicillin/ Clavulanate	
	983-37	active-controlled, randomized, investigator-blind, parallel-group, multicenter, Europe	Amoxicillin/ Clavulanate	
Pharyngitis/Tonsillitis	983-7	active-controlled, randomized, double-blind, parallel-group, multicenter, U.S. and Canada	Penicillin	
	983-58	active-controlled, randomized, double-blind, parallel-group, multicenter, U.S	Penicillin	
Uncomplicated Skin and Skin Structure	983-8	active-controlled, randomized, double-blind, parallel-group, multicenter, U.S	Cephalexin	
Oral Suspension				
Acute Suppurative Otitis Media	983-10	active-controlled, randomized, investigator-blind, parallel-group, multicenter, U.S	Amoxicillin/ Clavulanate	
	983-11	active-controlled, randomized, investigator-blind, parallel-group, multicenter, Europe, S.Africa, Australia	Amoxicillin/ Clavulanate	

Indication	Study number	Study Design	Comparator	Sample size
Pharyngitis/Tonsillitis	983-51	active-controlled, randomized, investigator-blind, parallel-group, multicenter, U.S. and Canada	Penicillin	
	983-56	active-controlled, randomized, investigator-blind, parallel-group, multicenter, U.S.	Penicillin	
Uncomplicated Skin and Skin Structure Infections	983-13	active-controlled, randomized, investigator-blind, parallel-group, multicenter, U.S.	Cephalexin	

Items below marked with a * which are not included or are unacceptable are reasons to consider not filing the NDA.

I. ORGANIZATION AND DATA PRESENTATION

	YES	NO	N/A
*A. Is there an overall table of contents for the entire NDA?	✔	—	—
*B. Is each NDA volume adequately indexed and paginated?	✔	—	—
C. Are all lists of tables, figures, and appendices indexed paginated?	✔	—	—
D. Do the titles of tables and figures clearly and adequately describe their contents?	✔	—	—
*E. Are the original protocols, protocol amendments and the proposed label provided?	✔	—	—
*F. Are the following summary tables provided in each study report by treatment for all patients and by center:		-	
1. Number and percentage of patients included in the intent to treat (ITT) or modified ITT efficacy analysis population.	✔	—	—
2. Number and percentage of patients included in the efficacy evaluable or per-protocol efficacy analysis population.	✔	—	—
3. Number and percentage of patients included in the safety analysis population.	✔	—	—
4. For each analysis population, the number and percentage of lost (not included) patients by reason	✔	—	—
5. Efficacy results on the patient level for each efficacy analysis population	✔	—	—

	YES	NO	N/A
6. Efficacy results on the pathogen level for each efficacy analysis population (where applicable)	✔	—	—
7. Clinical and laboratory adverse events by severity and relationship to treatment in the safety population	✔	—	—
G. Are the summary tables listed in item F above provided by treatment for age, race (B, W, O), and sex (M,F) subgroups?	✔	—	—
*H. Are the following data listings provided electronically or in hard copy:			
1. Clinical and laboratory adverse events with patient id, treatment, center, age, race, sex, time of occurrence, severity, and relationship to treatment?	✔	—	—
2. Lost (non-evaluable) patients with patient id, treatment, center, age, race, sex, reason and time of dropout or discontinuation.	✔	—	—
*I. Has an adequate integrated summary of safety (ISS) been provided, which includes summary data from all foreign and cited sources?	✔	—	—
*J. Does the ISS include subpopulation analyses by age, race, sex, and indication (where applicable)?	✔	—	—
K. Is it necessary for the data to be submitted electronically?	✔	—	—
L. Have the data been submitted electronically?	✔	—	—
*M. If the data have been submitted electronically, does the electronic submission meet the following criteria:			
1. Are the electronic files in a useful format which can be read by your computer?	✔	—	—
2. Have all the pertinent efficacy and safety data been provided?	✔	—	—
3. Are the data files adequately documented with a data dictionary including file contents, sample printouts, detailed variable definitions, and variable codes?	✔	—	—
4. Are the data files for each study in a format which allows for uncomplicated merging across studies (if necessary)?	✔	—	—
5. Have the final study reports (including tables) and protocols (if available) been provided in word processing files?	✔	—	—

II. STATISTICAL METHODOLOGY
(preliminary evaluation based applicant's summary analyses)

	YES	NO	N/A
*A. Are the efficacy and safety analyses appropriate for the type of data collected, the study design, and the study objectives (based on protocol and proposed label claims)?	✔	—	—
B. Have sufficient and appropriate references been included for novel statistical approaches?	—	—	✔
*C. Were the ITT or modified ITT analyses performed properly?	✔	—	—
*D. Given the number of non-evaluable patients, has the integrity of each study with respect to power and sample size been maintained?	✔	—	—
*E. If the study reports contain interim analyses, were they planned in the protocol and were appropriate significance level adjustments made?	—	—	✔
*F. Are there studies which are incomplete or ongoing?	—	✔	—
*G. Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	✔	—	—

Reviewer's note: No novel statistical approaches were submitted.

III. FILEABILITY CONCLUSIONS

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

Yes.

/S/
11/12/96

Alaka G. Chakravarty, Ph.D.
Biomedical Statistician, Division of Biometrics IV

/S/ 11/12/96

Concur: Daphne Lin, Ph.D.
Acting Team Leader, Division of Biometrics IV

cc:
Orig. NDA 50-739
HFD-520
HFD-520/Dr. Feigal
HFD-520/Dr. Soreth
HFD-520/Dr. Bonwit
HFD-520/Dr. Viraraghavan
HFD-520/Dr. Hamilton
HFD-520/Dr. Blank
HFD-520/Mr. Debellas
HFD-520/Ms. Duvall-Miller
HFD-725/Dr. Harkins
HFD-725/Dr. Lin
HFD-725/Dr. Chakravarty
Chron.

45 DAY MEETING CHECKLIST

NOV 7 1996

EABILITY:

n initial overview of the NDA application:

	YES	NO
BIOPHARMACEUTICAL:		
(1) On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin?	✓	
(2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	✓	
(3) On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin?	✓	
(4) Are the Phase 1 studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	✓	
(5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparison between the product to be marketed and the product(s) used in the clinical development?	✓	
(6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not?	✓	

/S/

eviewing Biopharmaceutics Officer

/S/

ervisory Biopharmaceutics Officer

OMNICEF, NDA 50-739

- cefdinir -

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:	YES	NO

MANUFACTURING AND CONTROLS:

(1)	On its face, is the M&C section of the NDA organized in a manner to allow substantive review to begin?	X	
(2)	Is the M&C section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X	
(3)	On its face, is the M&C section of the NDA legible so that substantive review can begin?	X	
(4)	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X Requested - to confirm the listed facilities.	will respond by 12/11/96
(5)	Has the applicant submitted a complete environmental impact assessment?	X	submitted 11/14/96
(6)	Has the applicant developed appropriate controls assessment procedures that are presently ready for FDA verification?	X	
(7)	For an antibiotic, has the applicant submitted an appropriate validation package and committed to the readiness of exhibit samples?	X	
(8)	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	NA	
(9)	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package? (Volume 1.11, page 150)	X	
(10)	Has the applicant submitted stability data to support and justify the proposed expiry? 12 mo at 25/60 RH 6 mo 45/75 RH	X	
(11)	Has the applicant stated that they are ready now (Priority Drugs) for inspections of the facilities or that they will be ready within the next 6 months (Standard Drugs)?	X	

(12) From a manufacturing and controls perspective, is this NDA fileable? If "no", please state on reverse why it is not. *

The CMC portion of the NDA is acceptable for review.

/S/ 11/11/96
Reviewing Chemistry Officer

/S/ 11/12/96
Supervisory Chemistry Officer

NDA 50-739
Omnicef 300 mg capsules
(Cefdinir)
Parke-Davis Pharm. Research

11/14/96

45 DAY MEETING CHECKLIST

FILEABILITY: NDA 50-739 Cefdinir 300 mg capsules (OMNICEF)

On initial overview of the NDA application: YES NO

PHARMACOLOGY:

(1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin? Yes

(2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review begin? Yes

(3) On its face, is the pharmacology section of the NDA legible so that substantive review can begin? Yes

(4) Are all required(*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? Yes

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? N/A as formulation is same as that to be marketed

(6) Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? Yes used both mg/m2 and mg/kg/day

(7) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? Yes

	YES	NO
(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	Yes	
(9) Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	Yes	
(10) Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	Yes	
(11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.	Yes	

/S/ 11/13/96

Reviewing Pharmacology Officer

/S/ 11/14/96

Supervisory Pharmacology Officer

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:	YES	NO

MICROBIOLOGY:

(1) On its face, is the microbiologic section of the NDA organized in a manner to allow substantive review to begin?	✓	
(2) Is the microbiologic section of the NDA indexed and paginated in a manner to allow substantive review to begin	✓	
(3) On its face, is the microbiologic section of the NDA legible so that substantive review can begin?	✓	
(4) On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains, and using necessary numbers of approved laboratories to meet current divisional standard for approvability of the submitted draft labeling?	✓	
(5) Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓	
(6) Has the applicant submitted draft breakpoint and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	✓	
(7) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓ Microbiological only	
(8) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policy, and the design of the development package?	✓	

(9) If necessary for this product, has the applicant submitted the sterilization procedures and documentation required for approval of the manufacturing and controls elements of this NDA? N/A

(9) From a microbiology perspective, is this NDA fileable? If "no", please state on reverse why it is not. ✓

/S/

Reviewing Microbiology Officer

/S/ 11/13/96

Supervisory Microbiology Officer

45 DAY MEETING CHECKLIST
Date: November 14, 1996

NDA: 50-739
Drug: Omnicef (cefdinir)
Sponsor: Parke Davis
Indication: Community Acquired Pneumonia (Adults and Peds)
Acute Exacerbations of Chronic Bronchitis

Acute Maxillary Sinusitis
Uncomplicated Skin and Skin Structure (Adults and Peds)

Type: 1S
Receipt Date: 9/4/96
Filing Date: 11/4/96
Regulatory Due Date: 9/4/97
User Fee Date: 9/4/97

FILEABILITY	YES	NO
On initial overview of the NDA application:	√	

PROJECT MANAGEMENT:

(1)	Do any of the following apply to this application (i.e., if YES, the application MUST BE REFUSED TO FILE under 314.101 (e) and there is no filing over protest):		
	(a)	Is the drug product already covered by an approved application?	√
	(b)	Does the submission purport to be an abbreviated application under 314.55; However the drug is not one for which the FDA has made a finding that an abbreviated application is acceptable under 314.44(b)?	√
	(C)	Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?	√
(2)	Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.101(d) and there is the potential for filing over protest):		
	(a)	Does the application contain a completed application form as required under 314.50 or 314.55?	√

NDA
45 DAY MEETING CHECKLIST

		YES	NO
(b)	On its face, does the application contain the sections of an application required by regulation and Center guidelines?	√	
(c)	Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is under 25.24 of the CFR?	√	
(d)	On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries?		
(e)	Is the NDA indexed and paginated?	√	
(f)	On its face, is the NDA legible?	√	
(g)	Has the applicant submitted all required copies of the submission and various sections of the submission?	√	
(h)	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	√	
(I)	Does the application contain a statement that all clincial trials were Conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those Requirements ?	√	
(j)	If required, has the applicant submitted carcinogenicity studies?	√	
(k)	On its face, does the application contain at least two adequate and well-controlled clinical trials?	√	
(l)	Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?	√	
(m)	Have all articles/study reports been submitted whether in English or translated into English?	√	
(n)	Has the applicant submitted draft labeling in compliance with 201.56 and 201.57 of the CFR?	√	

NDA
45 DAY MEETING CHECKLIST

		YES	NO
(o)	Has the applicant submitted the required FRAUD POLICY notice?	√	
(p)	Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated?	√	
(q)	Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS?	√	
(r)	If this is a CANDA submission, has the applicant submitted a statement to the archival NDA that the text, tables, and data in the CANDA and the archival hardcopy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions?	√	
(3)	From a project management perspective, is this NDA fileable? If "no", please state why it is not.	Yes	

/S/
Carmen L. DeBellas, R.Ph.
Project Manager

/S/
James D. Bona, R. P.h., M.P.H.
Chief, Project Management Staff

MEMORANDUM OF TELECON

DATE: July 15 and 17, 1997

APPLICATION NUMBER: NDA 50-749; Omnicef (cefdinir) Powder for Oral Suspension

BETWEEN:

Name: Dr. Paul Chen, Senior Manager, Regulatory Affairs
Dr. Sean Brennan, Senior Director, Regulatory Affairs
Dr. Robert Guttendorf, Section Director, Pharmacokinetic and Drug Metabolism
Dr. Thomas Julian, Director, Pharmaceutical Delivery System
Dr. John Murtha, Research Associate, Pharmaceutical Delivery System
Dr. Galen Radendaugh, Pharmaceutical Delivery System
Phone: (313) 998-3200
Representing: Parke-Davis and Pharmaceutical Delivery System

AND

Name: Ms. Beth Duvall-Miller, Project Manager
Dr. Phil Colangelo, Biopharmaceutics Reviewer
Dr. Frank Pelsor, Team Leader Biopharmaceutics
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Dissolution study

NDA 50-749, Omnicef (cefdinir) Powder for Oral Suspension, is currently under active review in the Division. It is being concurrently reviewed with the capsule formulation, NDA 50-739. On February 12, 1997, a 90-day meeting was held with Parke-Davis to discuss the review of both applications. At the time, Dr. Paul Chen had discussed conducting dissolution testing on both the capsule and the suspension. In a facsimile dated July 3, 1997, Parke-Davis presented information to support their request to not perform dissolution testing on the powder for oral suspension. This telecon, and the follow-up telecon held on July 17, 1997, were held to discuss the dissolution testing requested by the Division.

After review of the data submitted in the facsimile dated July 3, 1997, Dr. Colangelo and Dr. Pelsor reiterated their request for dissolution data on full-scale production batches, at a recommended specification of not less than % (Q) at minutes for the powder for oral suspension. They explained that the data collected at minutes is not critical. The data collected from minutes is acceptable and an adequate method has been established using pH 6.8 phosphate buffer at 50 rpm with Apparatus II.

Parke-Davis pointed out that this testing has not been required on other currently approved powder for oral suspension drug products. Dr. Pelsor explained that the FDA does not require sponsors to go back and conduct dissolution testing on these older products. However, the

current FDA practice is to request dissolution data on suspension products. Parke-Davis then pointed out that the Omnicef product is different from other suspension products in that it is reconstituted at the time of use, not stored as a ready made suspension product. Therefore, there are no crystallization concerns with the storage of this product. Parke-Davis believes that the 50 rpm data is not meaningful data but rather is an artifact of inadequate mixing. Parke-Davis does not believe that the data is an accurate indicator of product quality.

Dr. Colangelo reminded Parke-Davis of the discussions that were held at the 90-day meeting on February 12, 1997 and that the FDA still requests that dissolution data be submitted. Any further discussions on this issue would require a higher level of discussion with the Office of Clinical Pharmacology and Biopharmaceutics management.

Parke-Davis proposed to commit to dissolution testing on the 3 existing NDA stability lots (i.e. D40115, D40116, and D40117) through their storage shelf-life (i.e. 15 and 18 months). Dissolution profiles would be obtained using the same method described previously. If accepted, Parke-Davis would address discontinuation of the dissolution testing on subsequent production batches through a supplemental application, post-approval. This proposal was accepted by the FDA.

Following this telecon, Dr. Sean Brennan, Parke-Davis, phoned to request a second telecon to clarify the commitments made in the first telecon. The same personnel listed above, with the exception of Drs. Radendaugh and Guttendorf, reconvened on July 17, 1997 to finalize comments.

Parke-Davis opened the second telecon to clarify that the dissolution data mentioned in the July 15, 1997 telecon were conducted on 15% of the commercial batch size, not the entire batch. Parke-Davis asked if this changes the FDA's evaluation of the requirements presented in the July 15, 1997 telecon. Drs. Pelsor and Colangelo responded that this difference had no effect on their previously stated requirements.

The following commitments were confirmed between the FDA and Parke-Davis:

- Parke-Davis commits to conducting dissolution testing of the 3 existing NDA stability batches.
- Parke-Davis commits to submitting full profiles (at minutes) on the 3 NDA batches, at 15- and 18- month storage stations.
- Parke-Davis also commits to continue to conduct single-point testing on all commercial batches at minutes and 50 rpm.

Parke-Davis will submit the full dissolution profiles on the 3 NDA stability lots and the single-point dissolution determinations on commercial batches as the basis for their future supplement to 1) propose the final dissolution method and specification; and 2) propose the discontinuation of dissolution testing on subsequent production batches of the powder for oral suspension.

Parke-Davis noted that they would not have Methods Validation completed by the projected

approval time of the application (December 4, 1997 dual action projected for both NDA 50-739 and NDA 50-749). Dr. Colangelo responded that he would need the supervisory chemist's input to discuss this aspect of NDA requirements. The FDA agreed to follow-up with an internal meeting with the chemistry reviewer and supervisor to discuss this issue.

/S/

Beth Duvall-Miller
Project Manager

cc:

Original NDA 50-749
HFD-520/Div. File
HFD-520/CSO/B. Duvall-Miller
HFD-520/BioPharm/P. Colangelo
HFD-880/TLBioPharm/F. Pelsor
HFD-520/Chem/S. Pagay

Concurrence:

HFD-520/SCSO/J. Bona 8/4/97
HFD-880/BioPharm/P. Colangelo 8/4/97
HFD-880/TLBioPharm/F. Pelsor 8/5/97
HFD-520/ActDivDir/G. Chikami 8/5/97

drafted: bdm/July 23, 1997/M:\TELECON\N50749.DIS
r/d Initials:
final: 8/4/97

TELECON

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 29, 1997

FROM: Beth Duvall-Miller

SUBJECT: NDA 50-749; Methods validation requirements for dissolution method

TO: Original NDA 50-749
HFD-520/Div. Files
HFD-520/CSO/B. Duvall-Miller
HFD-880/BioPharm/P. Colangelo
HFD-880/TLBioPharm/F. Pelsor
HFD-520/Chem/S. Pagay
HFD-520/TLChem/D. Katague

On July 15 and 17, 1997, Ms. Beth Duvall-Miller, Dr. Frank Pelsor, and Dr. Phil Colangelo participated in teleconferences with Parke-Davis to discuss the requirements for dissolution testing on the Omnicef (cefdinir) Powder for Oral Suspension, NDA 50-749. In the latter teleconference, Parke-Davis agreed to conduct dissolution testing but noted that methods validation of the dissolution method was not likely to be completed by the action date of the application (projected December 4, 1997). Dr. Pelsor responded that he would follow-up with an internal meeting with the supervisory and review chemists to discuss the requirements for dissolution method validation. This meeting was held to resolve that issue.

Dr. Katague explained that it would depend upon what type of process the dissolution testing is considered to be. If the dissolution testing is considered a regulatory specification, then the review of the method must be complete by the time of action on the application. The submission of dissolution data would also be required before the action date, however, the FDA validation would not necessarily have to be complete by that time. However, if the dissolution testing is considered an in-process quality control test, then the testing may continue as a Phase IV commitment. The Division recommends that in-house methods validation be conducted by the sponsor and that subsequent submission of the results be reviewed, however the methods validation would not be a requirement for approval.

Dr. Pelsor agreed to research the historical precedence set for methods validation as a regulatory specification for other approved oral suspension products (i.e. either ready-made or powders for suspension). His findings will determine what response will be provided for Parke-Davis regarding the requirements for methods validation of dissolution testing.

On August 6, 1997, the above attendees reconvened to reach a final decision regarding the

requirements for validation of the dissolution method. Dr. Pelsor determined that there was a precedence for requiring methods validation as a regulatory specification for both ready-made suspension and powder for oral suspension drug products. Therefore, the decision of the Division was to require that Parke-Davis submit their dissolution method and validation as a regulatory specification, thereby disallowing future discontinuation of the dissolution testing on their commercial batches. All future commercial batches would require single-point dissolution testing at minutes through the recommended shelf-life.

Ms. Duvall-Miller communicated this decision to Dr. Paul Chen, Senior Manager, Regulatory Affairs, Parke-Davis, following the internal meeting on August 6, 1997. Dr. Chen followed-up to the Divisions' decision with a facsimile dated August 8, 1997 (attached), which outlined their proposal to address the requirement of a regulatory specification of the dissolution method. Dr. Pagay reviewed this facsimile and responded via email (attached) that he found Parke-Davis' proposal acceptable. Dr. Pagay also requested, in his email response, that Parke-Davis include the details of the sample preparation including the method of transfer of the sample to the dissolution vessel. Ms. Duvall-Miller communicated this acceptance and additional comment to Dr. Chen on August 11, 1997.

drafted: bdm/August 5, 1997/M:\MEMOS\N50749.1

MEMORANDUM OF A TELEPHONE CONVERSATION

Date October 3, 1997

Between: Dr.Paul Chen
Parke-Davis
(313)-996-2623

And: Shrikant Pagay, Ph. D.
Review Chemist, HFD-520

10/6/97

Subject: NDA 50-749 - Cefdinir 125 mg/5 mL Powder for Oral Suspension - Request by the Firm to include an additional package size.

The package sizes included in the original NDA are Physician's Sample (5 mL suspension in 1 oz bottle size) and a commercial package of (100 mL suspension in 6 oz bottle size). The firm has submitted 15 months stability data for the 1 oz and 6 oz bottle sizes (Amendment, September 29, 1997).

Now, they want to include a 4 oz bottle size. The 4 oz package will contain 60 mL suspension. They have provided in support of this request, a justification for bracketing which includes the dimensional analysis and head space analysis to demonstrate that the contents of the 4 oz bottles are in proportion to 1 oz and 6 oz bottle sizes. The package components and the product formulation contained in the 3 bottle sizes are identical (Attachment 4, August 13, 1997 Amendment). The stability data after storage for 15 months for the 1 oz and 6 oz bottles is satisfactory. The concept of bracketing has been justified in the ICH document (ICH Q1A).

Based on the stability data for the 1 oz and 6 oz bottle sizes, the dimentional analysis to show the similarity of the 3 package sizes, same packaging components and formulation, the firm was informed that 4 oz bottle size can be included in the original NDA with commitments to place 3 manufacturing scale batches on stability studies under the same protocol as the NDA batches for the 1 oz and 6 oz sizes.

cc: Ori. NDA 50-749
HFD/520/Division File
HFD/520/S.Pagay
HFD-520/Duval-Miller
HFD-520/Soreth
HFD/520/D. Katague Init by: DBK 10/6/97

SJC
Duvall
Miller

MEMORANDUM OF MEETING MINUTES

Meeting Date: Tuesday, May 20, 1997
Time: 11:00 a.m. - 12:20 p.m.
Location: CORP S400

Application: NDAs 50-739 and 50-749, Omnicef® (cefdinir) Capsules and Suspension

Type of Meeting: Informal meeting with applicant to discuss clinical review

Meeting Chair: Janice Soreth

Meeting Recorder: Beth Duvall-Miller

FDA Attendees, titles, and Office/Division:

Ms. Beth Duvall-Miller, Project Manager, HFD-520
Dr. Janice Soreth, Team Leader Medical Officer, HFD-520
Dr. Roopa Viraraghavan, Medical Officer, HFD-520
Dr. Andy Bonwit, Medical Officer, HFD-520
Dr. Jim Blank, Clinical Reviewer, HFD-520
Dr. Holli Hamilton, Medical Officer, HFD-520
Dr. Aloka Chakravarty, BioStatistician, HFD-725

External Constituent Attendees and titles:

Dr. Drusilla Scott, Director FDA Liaison, Parke-Davis
Dr. Kenneth Tack, Senior Director, Anti-Infectives, Parke-Davis

Background:

Parke-Davis submitted new drug applications 50-739 and 50-749 on September 4, 1996 and February 14, 1997 respectively. The Division is reviewing the two applications concurrently with the goal of completing action on both applications by September 4, 1997. This meeting was held to discuss the status of the clinical reviews with respect to the Division's requests for revised data sets from Parke-Davis.

Meeting Objectives:

1. To discuss the status of the clinical review of the cefdinir applications.

2. To determine what revised data sets are needed by the applications' reviewers.

Discussion Points:

1. Revised data sets
2. Chemistry review time line
3. Worldwide marketing
4. Data sets for microbiology review
5. Statistical analysis used on data sets
6. Labeling meetings

Decisions (agreements) reached:

1. A facsimile was sent to Parke-Davis on May 15, 1997 summarizing the reviewers' requests for revised data sets. These requests were discussed and confirmed by each reviewer at the meeting.
2. Parke-Davis expressed their concerns over Dr. Shrikant Pagay's (chemistry reviewer) timeline with regards to the intended concurrent review of the two NDA's.
3. Parke-Davis confirmed that Omnicef was approved in the United Kingdom for the same indications included in the NDA's
4. The Division requested that the revised data sets also be sent to Dr. Sousan Altaie (microbiology reviewer).
5. Dr. Aloka Chakravarty asked what method was used in the confidence interval calculations by Parke-Davis and whether a continuity correction was used in the analysis.
6. The review team reminded Parke-Davis of the upcoming internal labeling meetings that are scheduled for June 17, 1997, 10:00 a.m. and July 10, 1997, 11:00 a.m. Parke-Davis was asked to add these dates to their calendars for potential teleconference or face-to-face inclusion in these meetings.

Unresolved issues or issues requiring further discussion:

1. The numbers of microbiologically evaluable patients will need to be closely

examined by individual indications relative to the guidelines set forth in the Points to Consider document.

Action Items:

Item	Responsible Person	Due Date
1. Revised data sets micro and clinical	Parke-Davis	ASAP
2. Chemistry time line	Duvall-Miller/Pagay	ASAP
3. Statistical analysis info	Parke-Davis	ASAP

Minutes Preparer: /S/

Chair Concurrence /S/

cc:
Original NDA's 50-739, 50-749
HFD-520/Div. Files
HFD-520/Meeting Minutes files
HFD-520/CSO/B. Duvall-Miller
HFD-520/SMO/J. Soreth
HFD-520/MO/R. Viraraghavan RV 7/22/97
HFD-520/MR/J. Blank 7/22/97
HFD-520/MO/H. Hamilton 7/21/97
HFD-520/MO/A. Bonwit
HFD-725/BioStat/A. Chakravarty 7/22/97

Concurrence:
HFD-520/SCSO/J. Bona 7/14/97
HFD-520/SMO/J. Soreth 7/17/97
HFD-520/ActDivDir/G. Chikami 8/12/97

Drafted by: bdm/June 10, 1997/M:\MEETMIN\N50739.2
Initialed by:
final: 7/15/97

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Date: Tuesday, September 23, 1997
Time: 9:30-11:30 AM
Location: CRP2 S300

Application: NDA's 50-739, 50-749; Omnicef® (cefdinir) Capsules and Powder for Oral Suspension

Type of Meeting: Labeling meeting

Meeting Chair: Gary Chikami, M.D.

Meeting Recorder: Beth Duvall-Miller

FDA Attendees, titles, and Office/Division:

Ms. Beth Duvall-Miller, Project Manager, Division of Anti-Infective Drug Products
Dr. Janice Soreth, Medical Team Leader, Division of Anti-Infective Drug Products
Dr. Roopa Viraraghavan, Medical Officer, Division of Anti-Infective Drug Products
Dr. Jim Blank, Clinical Reviewer, Division of Anti-Infective Drug Products
Dr. Holli Hamilton, Medical Officer, Division of Anti-Infective Drug Products (by phone)
Dr. Shrikant Pagay, Chemistry Reviewer, Division of Anti-Infective Drug Products
Dr. Phil Colangelo, Biopharmaceutics Reviewer, Division of Pharmaceutical Evaluation III
Dr. Frank Pelsor, Biopharmaceutics Team Leader, Division of Pharmaceutical Evaluation III
Dr. Sousan Altaie, Microbiology Reviewer, Division of Anti-Infective Drug Products
Dr. Aloka Chakravarty, Biostatistics Reviewer, Division of Biometrics IV
Dr. Gary Chikami, Acting Director, Division of Anti-Infective Drug Products

External Constituent Attendees and titles:

Ms. Karen Lewis, Project Manager, Biometrics, Parke-Davis
Dr. Drusilla Scott, Director, FDA Liaison, Regulatory Affairs, Parke-Davis
Dr. Kenneth Tack, Senior Director, Clinical Anti-Infectives, Parke-Davis
Ms. Connie Keyserling, Director, Clinical Anti-Infectives, Parke-Davis
Ms. Lori Weaver, Clinical Scientist, Clinical Anti-Infectives, Parke-Davis
Dr. Robert Guttendorf, Section Director, Pharmacokinetics/Drug Metabolism, Parke-Davis
Dr. Irwin Martin, Vice President, FDA Liaison, Regulatory Affairs, Parke-Davis
Mr. Brian Zorn, Director, U.S. Anti-Infective Marketing, Parke-Davis
Dr. Paul Chen, Senior Manager, CMC Regulatory Affairs, Parke-Davis

Background:

Parke-Davis submitted new drug applications (NDA's) 50-739 and 50-749 on September 4, 1996 and December 31, 1996 respectively, for Omnicef® (cefdinir) Capsules and Powder for Oral Suspension, respectively. The applications were reviewed concurrently by a team of clinical reviewers including Dr. Andy Bonwit, Dr. Jim Blank, Dr. Holli Hamilton, and Dr. Roopa Viraraghavan for the claimed indications of CAP, AECB, Sinusitis, Pharyngitis/Tonsilitis, Acute Otitis Media, and Uncomplicated Skin and Skin Structure Infections. A major clinical amendment (revised clinical data sets for all indications removing fraudulent investigator data) was received on June 24, 1997, extending the PDUFA due date to December 4, 1997. The Division of Anti-Infective Drug Products intends to take a concurrent action on the applications by the December 4, 1997 due date. The labeling is a combined package insert for both the capsule and powder for oral suspension formulations. This meeting was the first labeling meeting held that involved both FDA and Parke-Davis personnel.

Meeting Objective:

To negotiate labeling for Omnicef® (cefdinir) Capsules and Powder for Oral Suspension

Discussion Points

1. **DESCRIPTION** section
2. **CLINICAL PHARMACOLOGY** section
3. **Microbiology** subsection
4. **INDICATIONS AND USAGE** section
5. **WARNINGS** section
6. **PRECAUTIONS** section
7. **ADVERSE EVENTS** section
8. **DOSAGE AND ADMINISTRATION** section
9. **HOW SUPPLIED** section
10. **CLINICAL STUDIES** section
11. **REFERENCES** section

Decisions (agreements) reached:

1. Revisions to the **DESCRIPTION** and **HOW SUPPLIED** sections were found acceptable by Dr. Pagay. Dr. Pagay reminded Parke-Davis that the established name must appear on all pages of the package insert (CFR 201.10(g)(1)) and that the date of issuance should be placed at the end of the package insert (CFR 201.56(e)). Parke-Davis intends to fulfill these requirements.

2. In the **CLINICAL PHARMACOLOGY** section, the following revised subsections, as shown in the working draft version of the label dated September 22, 1997, were accepted by Parke-Davis: **Absorption:** *Effect of Food*; **Special Populations:** *Patients with Renal Insufficiency*, *Hemodialysis*, and *Gender and Race*.

3. In the **CLINICAL PHARMACOLOGY** section, the following changes to the label were agreed upon: In the **Absorption:** *Oral Bioavailability* subsection, Parke-Davis agreed to supply an added statement indicating the bioavailability of the suspension relative to the capsules, in healthy adults, is approximately 120%. In the **Distribution** subsection, Parke-Davis agreed to report the median and range of cefdinir concentrations for skin blister, tonsil tissue, sinus tissue, lung tissue, and middle ear fluid, with a lower limit of quantitation accepted by the FDA in some instances. In the **Metabolism and Excretion** subsection, the FDA agreed to Parke-Davis' proposal to report oral clearance rather than plasma clearance. Parke-Davis will provide data for this revision. In the **Special Populations** *Hepatic Disease* subsection, Parke-Davis will provide a reworded last sentence that indicates that dosage adjustment would not be expected to be altered in this population. In the **Special Populations** *Geriatric Patients* subsection, the FDA agreed to change the word in the fourth sentence of the subsection.

4. In the **Microbiology** subsection of the **CLINICAL PHARMACOLOGY** section and where listed in the **INDICATIONS AND USAGE** section, the FDA agreed to include the parenthetic statement with *Moraxella catarrhalis* in the **Aerobic gram-negative microorganisms** list.

5. In the **INDICATIONS AND USAGE** section, Parke-Davis had no objections or comments on the FDA's revisions to the Acute Exacerbation of Acute Bronchitis indication.

6. In the **INDICATIONS AND USAGE** section, Parke-Davis agreed to the FDA's rationale for not granting the indication. The FDA's rationale was that the study, as designed (uncontrolled, supportive dose-ranging study that demonstrated dose was irrelevant to clinical response), was not sufficient to prove efficacy. Furthermore, an advisory committee panel had recently recommended that a clinical study to support labeling for should be placebo-controlled.

7. In the **INDICATIONS AND USAGE** section, Parke-Davis had no objections or comments on the FDA's revisions to the Sinusitis indication.

8. In the **INDICATIONS AND USAGE** section, the FDA agreed to revise the wording of the Pharyngitis/Tonsilitis indication to the previous version supplied by Parke-Davis, but excluding the second paragraph that describes the studies and including a reference to the **CLINICAL STUDIES** section in the first paragraph.

9. In the **INDICATIONS AND USAGE** section, Parke-Davis had previously agreed that the Otitis Media review was ongoing and that the wording of this section would not be discussed at this labeling meeting.

10. Revisions to the **WARNINGS** section were accepted by Parke-Davis.

11. In the **PRECAUTIONS** section, revisions to **Antacids** and **Probenecid** in the **Drug Interactions** subsection were accepted by Parke-Davis.

12. In the **PRECAUTIONS** section, the **Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy-Teratogenic Effects, Labor and Delivery,** and **Nursing Mothers** subsections were previously accepted by the FDA.

13. Regarding the **ADVERSE EVENTS** section, the FDA recently asked Parke-Davis to provide a breakdown of adverse events into b.i.d. versus q24h dosing. Parke-Davis noted that combined tables were agreed upon in the pre-NDA meeting provided there was no significant difference in the incidence of events noted between the two dosing regimens. Parke-Davis provided tables to the FDA depicting the breakdown in adverse events . The FDA agreed that the differences noted were insignificant and therefore, combined tables would be acceptable.

14. In the **ADVERSE EVENTS** section, Parke-Davis will include somnolence and insomnia in the "ADVERSE EVENTS ASSOCIATED WITH CEFDINIR CAPSULES, US TRIALS IN ADULT AND ADOLESCENT PATIENTS (N=3275)" table to follow pruritus, both at 0.2% incidence.

15. During the FDA review of cefdinir, the review team noted that in the sinusitis and AECB studies, q24h dosing demonstrated better efficacy compared to the b.i.d. regimen. The FDA reviewers, as well as Parke-Davis, expected the reverse would be demonstrated. Both parties could offer no explanation as to why this was demonstrated. Parke-Davis confirmed that the q24h studies on uSSSI and community-acquired pneumonia were discontinued due to concern over q24h dosing of patients with severe infections.

16. In the **REFERENCES** section, references 3-5 were erroneously deleted from the working draft version dated September 22, 1997. Whereas, references 1 and 2

should be reordered as noted in the working version dated September 22, 1997, references 3-5 should be reinserted in this section.

17. The FDA and Parke-Davis agreed to negotiate further labeling changes via telecon, fax, and if necessary, another face-to-face meeting.

Unresolved issues or issues requiring further discussion:

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Item	Responsible Person	Due Date
1. Provide revisions to **CLINICAL PHARMACOLOGY** section noted in #3 under Agreements	Parke-Davis	immediately
2. Submit listing of BLNAR strains and proposed notation	Parke-Davis	immediately
3. Determine if *Streptococcus agalactiae*, *Escherichia coli*, and *Klebsiella pneumoniae* belong on *in vitro* list of microorganisms	FDA/Altaie, Sheldon	immediately

Item	Responsible Person	Due Date
4. Refer to 1993 NDA Holder for algorithm requirements of excluded microorganisms	Parke-Davis	immediately
5. Provide rationale, repooled data, and case report forms for CAP caused by *Klebsiella pneumoniae*	Parke-Davis	immediately
6. Construct a scientific rationale for inclusion of *Streptococcus agalactiae* in uSSSI indication	Parke-Davis	immediately
7. Include somnolence and insomnia in adverse events table	Parke-Davis	immediately
8. Consider proposal to exclude pseudomembranous colitis from adverse event table	FDA/Clinical	immediately
9. Design **CLINICAL STUDIES** section for all indications	Parke-Davis	immediately
10. Propose plan to track medication errors	Parke-Davis/FDA	before action

11. Include revisions agreed to in "Decisions (agreements) reached" section in next working version of draft label	FDA/Duvall-Miller	immediately

Minutes Preparer: /S/

Chair Concurrence: /S/

cc:

Original NDA's 50-739, 50-749
HFD-520/Div. Files
HFD-520/Meeting Minutes files
HFD-520/CSO/B. Duvall-Miller
HFD-520/MO/H. Hamilton
HFD-520/ClinRev/J. Blank 1/13/98
HFD-520/MO/R. Viraraghavan
HFD-520/SMO/J. Soreth
HFD-520/Chem/S. Pagay
HFD-880/BioPharm/P. Colangelo
HFD-520/Micro/S. Altaie 1/13/98
HFD-725/Stats/A. Chakravarty

Concurrence Only:

HFD-520/SCSO/J. Bona 1/15/98
HFD-520/ClinRev/J. Blank
HFD-520/MO/R. Viraraghavan 1/9/98
HFD-520/MO/H. Hamilton
HFD-520/Chem/S. Pagay 1/16/98
HFD-880/BioPharm/P. Colangelo 1/13/98
HFD-520/Micro/S. Altaie
HFD-520/SMO/J. Soreth 1/19/98
HFD-520/ActDivDir/G. Chikami 1/23/98

Drafted by: bdm/September 26, 1997/M:\MEETMIN\N50739.LB1
Initialed by:
final: 1/8/98

MEETING MINUTES

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

DESK COPY

July 21, 1997

NDA 50-749
Ref. No. 7
Omnicef® (cefdinir) Powder for Oral Suspension

Re: Meeting Minutes

Gary Chikami, M.D.
Acting Director
Division of Anti-Infective Drug
Products (HFD-520)
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20857

Dear Dr. Chikami:

Reference is made to our pending NDA 50-749 for Omnicef® (cefdinir) Powder for Oral Suspension, to the pre-meeting material (Ref. No. 5) submitted on July 3, 1997, and to teleconferences held on July 15 and 17, 1997, between representatives of Parke-Davis and Drs. Frank Pelsor and Philip Colangelo of Biopharmaceutics and Ms. Beth Duvall-Miller of your Division.

The meeting was conducted to discuss a request by Dr. Colangelo in the 90-day meeting on February 12, 1997, for a dissolution method and specification for the product.

After some discussion, Parke-Davis committed to obtained the dissolution profiles for the 3 NDA lots (D40115, D40116, and D40117) at 15- and 18-month stations to show that the dissolution performance had not changed from those presented in the pre-meeting materials. These data would be included in an NDA supplement to eliminate the test and specification as a regulatory requirement. Drs. Colangelo and Pelsor concurred with the proposal.

Attached are the meeting minutes from Parke-Davis. Please send us the minutes from the Agency for concurrence when they are available. If you have any questions or comments regarding this submission, please contact me at 313/996-2623 or FAX 313/996-7890.

Sincerely,

Paul R. Chen

Paul R. Chen, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

PC\rm
t:\nda\50-749\072197-7

Attachment

Desk Copies : Ms. Beth Duvall-Miller (HFD-520)
Dr. Phillip Colangelo (HFD-880)
Dr. Frank Pelsor (HFD-880)
Dr. Skricant Pagay (HFD-520)

Meeting Minutes of the Teleconferences on Omnicef Powder
for Suspension Dissolution (NDA 50-749)

The first meeting was held on July 15, 1997, from 11:00 AM to 11:45 AM and a follow-up meeting for clarification was held on July 17, 1997, at 2:40 PM. The representatives from FDA were Drs. Frank Pelsor and Phillip Colangelo, team leader and reviewer respectively, from the Biopharmaceutics Office and Ms. Beth Duvall-Miller, Project Manager of Anti-Infective Division. Participants from Parke-Davis were Drs. Sean Brennan, Paul Chen, Robert Guttendorf, Tom Julian and John Murtha. Dr. Galen Radebaugh of Parke-Davis participated in the 2nd meeting. Drs. Guttendorf and Murtha were not present in the meeting on July 17, 1997.

The purpose of the meeting was to review the request by FDA to add a dissolution method and specification for the product. Pre-meeting materials submitted by Parke-Davis proposed that a dissolution test was not necessary.

After some discussion, Drs. Colangelo and Pelsor still felt that a dissolution test and specification were required and recommended a specification of not less than [redacted]% (Q) at [redacted] minutes using the method (pH 6.8 phosphate buffer at 50 rpm) presented in the pre-meeting materials.

Parke-Davis committed to obtain the dissolution profiles (minimally 10, 20, 30 and 40-45 minutes) for the 3 NDA lots (D40115, D40116, D40117, pilot batches at 1/8 the full scale size) at 15- and 18-month stations to show that the dissolution performance had not changed from those presented in the pre-meeting materials. These data would be included in an NDA supplement to eliminate the dissolution test and specification as a regulatory requirement. Drs. Pelsor and Colangelo concurred with this proposal.

FDA also clarified that the dissolution test and specification [single point, [redacted]% (Q) in [redacted] minutes] applied to all lots produced for commercial distribution until approval of a supplement to eliminate the test was obtained.

Parke-Davis would also submit an amendment to the NDA with the specification and validation report of the dissolution method. As to the scope and extent of the validation, consultation would be sought with the Chemistry reviewers. Ms. Duvall-Miller would inform Parke-Davis of their expectations.

520
Duvall-Miller

NDA 50-739

AUG 5 1997

Parke-Davis Pharmaceutical Research
Attention: Drusilla Scott, Ph.D.
Director, Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Dr. Scott:

We acknowledge receipt on June 24, 1997 of your June 23, 1997 amendment to your new drug application for Omnicef® (cefdinir) Capsules.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is December 4, 1997.

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-739
HFD-520/Div. Files
HFD-520/B. Duvall-Miller
DISTRICT OFFICE

Concurrence:
HFD-520/SCSO/J. Bona 6/27/97
HFD-520/SMO/J. Soreth 7/4/97
HFD-520/ActDivDir/G. Chikami 7/31/97

Drafted by: bdm/June 26, 1997/M:\EXTENSIO\50739.WPD
Initialed by:
final: BDM 6/26/97

REVIEW EXTENSION

S20
Duvall-NAC

OCT 7 1997

NDA 50-739
NDA 50-749

Parke-Davis
Attention: Drusilla Scott, Ph.D.
Director, Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Dr. Scott:

Please refer to your pending September 3, 1996 and December 30, 1996 new drug applications submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Omnicef® (cefdinir) Capsules and Powder for Oral Suspension.

We also refer to your amendments dated September 24, November 13, December 16, December 20, December 30, and December 31, 1996; January 31, February 21, March 10, April 25, May 6, May 9, June 2, June 11, June 24, June 30, July 1, July 7, July 8, July 9, July 18, July 22, August 8, and August 13, 1997.

We have completed our review of the human pharmacokinetics and bioavailability section of your submissions and have the following recommendations and comments:

NDA 50-739; Omnicef® (cefdinir) Capsules

1. The proposed *in vitro* dissolution specification for the 300 mg capsules (Formulation 34) is a Q value of [redacted]% at [redacted] 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 [redacted]% at [redacted] minutes.

NDA 50-749; Omnicef® (cefdinir) Powder for Oral Suspension

2. A proposed method and specification for the *in vitro* dissolution testing of the suspension formulation was not provided. At a 90-day NDA review status meeting between the Agency and representatives of your firm (February 12, 1997), it was agreed upon that your firm would provide the dissolution method, proposed specifications, and the data from the pilot scale batches of the market image suspension and interim data. Your firm 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 your firm of the interim dissolution report, it was agreed upon that your firm would perform Phase IV dissolution testing of the three

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 from these batches (i.e. from [redacted] 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 [redacted]% at [redacted] minutes. It was also agreed that single point dissolution testing at [redacted] minutes would be conducted on subsequent commercial lots.

LABELING COMMENTS

1. In the Pharmacokinetics and Drug Metabolism subsection of the CLINICAL PHARMACOLOGY section, the following labeling changes are suggested:

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information

We would appreciate your prompt written response so we can continue our evaluation of your NDA's.

If you have any questions, please contact Ms. Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDAs 50-739, 50-749
HFD-520/Div. Files
HFD-520/CSO/B. Duvall-Miller
HFD-880/BioPharm/P. Colangelo
HFD-880/TLBioPharm/F. Pelsor
HFD-830/ONDC Division Director

Concurrence only:
HFD-520/SCSO/J. Bona 9/18/97
HFD-880/BioPharm/P. Colangelo 9/8/97
HFD-880/TLBioPharm/F. Pelsor 9/26/97
HFD-520/SMO/J. Soreth 9/26/97
HFD-520/ActDivDir/G. Chikami 9/10/97

Drafted by: bdm/August 22, 1997/M:\NDADEF\50739.1
Initialed by:
final: BDM 9/17/97

INFORMATION REQUEST (IR)