

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-222**

**ADMINISTRATIVE DOCUMENTS**

SPECTRACEF™ (cefditoren 200 mg tablets as cefditoren pivoxil)  
December 21, 1999

#### 14.0 Certification Under 21 C.F.R. § 314.53(c)

Pursuant to 21 C.F.R. § 314.53(c), TAP Holdings Inc. submits the following patent information for SPECTRACEF™ (cefditoren pivoxil):

<u>U.S. Patent No.</u>	<u>Expiration Date</u>	<u>Type of Patent</u>
4,839,350	June 13, 2006	Drug Substance
4,918,068	June 13, 2006	Drug Substance
5,958,915	October 14, 2016	Drug Product

The undersigned declares that Patents Nos. 4,839,350, 4,918,068 and 5,985,915 cover the formulation and composition of SPECTRACEF™ (cefditoren pivoxil). This product is the subject of the application for which approval is being sought. The owner of these patents is Meiji Seika Kaisha Ltd., Tokyo, Japan, which has licensed them to TAP Holdings Inc.

By:



Donna K. Helms  
Associate Director, Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # 21-222 SUPPL # \_\_\_\_\_

Trade Name Spectracef Generic Name cefditern pivoxil

Applicant Name TAP Pharmaceuticals HFD # 520

Approval Date If Known August 29, 2001

**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 question about the submission.

a) Is it an original NDA? YES /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

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 /  / 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 /  /

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

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

no

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? (Rx to OTC switches should be answered NO-please indicate as such)

YES /  / NO /  /

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 /  /

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 /  /

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.

(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:

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(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:  
\_\_\_\_\_  
\_\_\_\_\_

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /\_\_\_/

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

\_\_\_\_\_

\_\_\_\_\_

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 /\_\_\_/

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

\_\_\_\_\_

\_\_\_\_\_

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"):

\_\_\_\_\_

\_\_\_\_\_



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 _____
_____	!	_____
_____	!	_____
	!	





# PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

**NDA Number:** N 021222  
**Trade Name:** SPECTRACEF(CEFDTOREN PIVOXIL)200MG TABS  
**Generic Name:** CEFDTOREN PIVOXIL  
**Supplement Number:** 000 **Supplement Type:** N  
**Dosage Form:**  
**Regulatory Action:** AE **Action Date:** 10/27/00  
**COMIS Indication:** UNCOMPLICATED SKIN/SKIN STRUCTURE INFECTIONS. ACUTE BACTERIAL EXACERBATION OF CHRONIC BRONCHITIS. ACUTE MAXILLARY SINUSITIS. PHARYNGITIS/TONSILLITIS

**Indication #1: Uncomplicated Skin and Skin Structure Infections**

**Label Adequacy:** Adequate for some pediatric age groups  
**Formulation Needed:** New formulation needed, applicant has agreed to provide it  
**Comments (if any)** 10/26/00 - Indication is Approvable. Sponsor is developing a suspension formulation for pediatric patients.

Lower Range	Upper Range	Status	Date
12 years	Adult	Completed	
10/26/00			

**Comments:** Pediatric patients 12 years and older were included in phase 3 trials for this indication.

0 months	3 months	Waived	
10/26/00			

**Comments:** Waived in this age range because oral antibiotics not typically used for this age range and lower carnitine levels in neonatal/infant age group may pose a risk for use of this drug.

3 months	12 years	Deferred	1/1/01
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**Comments:** The sponsor is developing pediatric suspension formulation, and safety and pharmacokinetic information for this age group has not yet been provided.

**Indication #2: Streptococcal Pharyngitis**

**Label Adequacy:** Adequate for some pediatric age groups  
**Formulation Needed:** New formulation needed, applicant has agreed to provide it  
**Comments (if any)**

Lower Range	Upper Range	Status	Date
12 years	Adult	Completed	
10/26/00			

**Comments:** Pediatric patients 12 years and older were included in phase 3 trials for this indication.

0 months	3 months	Waived	
10/26/00			

**Comments:** Waived in this age range because oral antibiotics not typically used for this age range and lower carnitine levels in neonatal/infant age group may pose a risk for use of this drug.

3 months	12 years	Deferred	1/1/01
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**Comments:** The sponsor is developing pediatric suspension formulation, and safety and pharmacokinetic information for this age group has not yet been provided.

Cefditoren Pivoxil 200 mg. Tablets  
New Drug Application  
September 15, 1999

### DEBARMENT CERTIFICATION

TAP Holdings Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the *Federal Food, Drug and Cosmetic Act* in connection with this application.



\_\_\_\_\_  
Signature

Harold Cohen

\_\_\_\_\_  
Name

Director, Quality Assurance

\_\_\_\_\_  
Title

September 15, 1999

\_\_\_\_\_  
Date

#### **4.1.6 ENVIRONMENTAL ASSESSMENT**

The Sponsor confirms that SPECTRACEF™ (cefditoren pivoxil) meets the criteria listed under 21 CFR 25.31(b) and thereby requests a categorical exclusion. In particular, the Expected Introduction Concentration (EIC) of active moiety (cefditoren) into aquatic environment will be less than 1 part per billion (ppb). This information was generated in accordance with the FDA Guidance for Industry, entitled: *Environmental Assessment of Human Drug and Biologic Applications*.

Per 21 CFR 25.15(d), the Sponsor admits that to the best of our knowledge, no extraordinary circumstances exist that would affect this conclusion.

HFD-520  
B. Duvall-Miller

## REQUEST FOR TRADEMARK REVIEW

**To:** Labeling and Nomenclature Committee  
**Attention:** Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

<b>From:</b> Division of Anti-Infective Drug Products		<b>HFD-520</b>
<b>Attention:</b> Beth Duvall-Miller, Project Manager		<b>Phone:</b> (301) 827-2207
<b>Date:</b> June 17, 1999		
<b>Subject:</b> Request for Assessment of a Trademark for a Proposed New Drug Product		
<b>Proposed Trademark:</b> Spectracef		<b>IND#</b> 53,866
<b>Established name, including dosage form:</b> cefditoren pivoxil, tablets		
<b>Other trademarks by the same firm for companion products:</b> Spectracef Powder for Oral Suspension		
<b>Indications for Use (may be a summary if proposed statement is lengthy):</b> [redacted] acute bacterial exacerbation of chronic bronchitis, [redacted] pharyngitis/tonsillitis, and uncomplicated skin and skin-structure infections		
<b>Initial Comments from the submitter (concerns, observations, etc.):</b> Request submitted by sponsor June 7, 1999 (N-013).		

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

cc:

HFD-520/Division file  
 HFD-520/CSO/B. Duvall-Miller  
 HFD-520/Chem/B.V. Shetty  
 HFD-530/Chem/D. Boring

/S/ 6/17/99

## CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

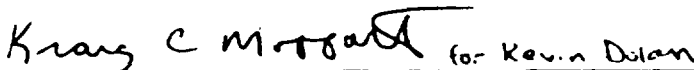
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Section 8.2 for list of	
	Investigators.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Kevin Dolan	TITLE Controller
FIRM/ORGANIZATION TAP Holdings, Inc.	
SIGNATURE  (for Kevin Dolan)	DATE 12 21 99

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

### Medical Team Leader's Memorandum

Review of clinical trials of anti-infectives for treatment of AECB involves a number of difficult issues. AECB has a high placebo response rate and patients with AECB, by definition, have chronic symptoms that may not completely resolve with antibiotic therapy, making cure or improvement difficult to assess. Furthermore, microbiological 'responses' to anti-infective therapy of AECB are difficult to interpret because of chronic colonization of the respiratory tract, making clinical response a better measure of outcome, although one that may be hard to assess on a background of chronic symptoms.

As Temple and Ellenberg have noted (*Ann. Intern. Med.* (2000) **133**:455-463), defects in conduct and analysis of active-control equivalence (ACE) trials are likely to result in a finding of equivalence even if there are true differences between therapeutic regimens. Furthermore, a finding of equivalence in an ACE trial does not demonstrate efficacy for a new regimen. To quote Temple and Ellenberg,

"Equivalence" could mean that the treatments were both effective in the study, but it could also mean that both treatments were ineffective in the study. To conclude from an ACET that a new treatment is effective on the basis of its similarity to the active control, one must make the critical (and untestable within the study) assumption that the active control had an effect in that particular study. In other words, one must assume that if a placebo group had been included, the placebo would have been inferior to the active control (15-33). Support for this assumption must come from sources external to the trial."

These considerations apply with particular force to AECB trials. Given the high placebo response rate and the finding that antibiotics are of benefit only in a subset of AECB patients (Anthoniesen *et al.* *Ann. Intern. Med.* (1987) **106**:196-204), careful adherence to entry criteria and criteria for outcome assessment are important to avoid an incorrect finding of efficacy based on ACE trials; deviation from these will blur distinctions between treatment regimens and almost guarantee that 'equivalence' is demonstrated.

One particularly problematic area is that of 'improvement' in AECB. Patients who do not show resolution of symptoms but who are considered 'improved' by the investigator will increase the cure rate if they are considered as cures. Because inflation of the cure rate will normally drive a trial towards equivalence, it is important that assessments of 'improvement' be based on well-defined criteria; in other words, there needs to be a bright line between what is considered true improvement and what is not. Failure to follow this principle will lead to a finding of equivalence regardless of real differences between regimens. Previous NDA reviews of anti-infectives for AECB (e.g., cefprozil, cefepime, moxifloxacin, grepafloxacin) have typically accepted 'improved' patients as cures **only** if there was improvement in all specific signs and symptoms, and have not let this be a matter for investigator interpretation based on concepts such as 'gestalt' or 'the whole clinical picture'. The rationale is that if there is no improvement in specific signs and symptoms, there is no basis for stating that that the patient's clinical status has improved. In the absence of such symptomatic improvement, the 'gestalt' concept does not answer the question of what exactly it is that has improved about the patient. The 'gestalt' concept thus makes ACE trials vulnerable to the sort of problems that Temple and Ellenberg describe.



Given this, Dr. Mulinde's reassessment of 'improved' patients in the AECB portion of the Spectracef NDA according to the criteria set forth in the protocol seems to me to be fundamentally sound, and results in response rates for Spectracef that are clinically unacceptable (i.e., no greater than would be expected from placebo), and are lower than in other NDAs for this indication. The same is true for her analysis of patients assessed as cures by the investigators. The finding that approved agents (cefuroxime and clarithromycin) gave similar response rates simply demonstrates that the trials as designed lacked assay sensitivity; in other words, they focused on an overly broad set of patients and could not show a drug treatment effect. This problem is exacerbated by the applicant's failure to apply entry and evaluability criteria as outlined in the protocol. (This is consistent with analyses Dr. Mulinde has done showing that cure rates for both Spectracef and comparator rise if one analyzes patients who had at least two signs and symptoms, i.e., those patients with Anthoniesen type I or II AECB, who are most likely to show benefit from antibiotics.)

With respect to the question of 'readjudication' of outcomes by the reviewer, the issue to my mind is not one of whether the reviewer is substituting her judgement for that of the investigators, but rather whether the investigators (and sponsor) adhered to pre-defined criteria for outcome assessment. Although there is no question that in clinical practice there is the 'art' of deciding whether or not a patient is better, in this situation we are dealing with the science of clinical trials and assessing efficacy in a rigorous, quantitative fashion. This requires consistent application of clear protocol-specified definitions of evaluability and outcome.

For these reasons, I concur with Dr. Mulinde that the applicant has not provided substantial evidence of efficacy for cefditoren in the treatment of acute exacerbations of chronic bronchitis.

/s/

David Ross, M.D., Ph.D.

Medical Team Leader/HFD-520

112510  
R. Hills

## MEMORANDUM OF TELECONFERENCE

**Meeting Date:** March 22, 2000

**Time:** 1:00 p.m.

**Application:** NDA 21-222 for SPECTRACEF® (cefditoren pivoxil)

**Type of Meeting:** Information Request

**Meeting Chair:** Dr. Daphne Lin, Team Leader, Bio-Statistics

**Meeting Recorder:** Mr. R. Grant Hills, Regulatory Project Manager

**Agency Attendees:** Dr. Daphne Lin, Team Leader, Bio-Statistics  
Dr. Thamban Valappil, Bio-Statistician  
Mr. R. Grant Hills, Regulatory Project Manager

**TAP Attendees:** Mr. Jesse Siedman, Associate, Regulatory Affairs  
Dr. Barbara Hunt, Statistician  
Dr. Nancy Seidman, Assistant Director, Statistics

### **Background**

TAP Holdings, Inc. filed this NDA with the Agency on December 29, 1999. The application is now nearing the end of its third month of review. The Action Performance Goal Date is October 29, 2000. And the PDUFA Goal Date is December 29, 2000.

### **Meeting Objective**

Today's meeting was called in order to clarify with the sponsor the exact nature of the Division's recent requests regarding randomly selected patients and the subsequent submission of their Case Report Forms (CRF's).

### **Discussion Points** (See Attachment)

1. The Division noted that the sponsor had excluded some sites from analysis. For example, under the indication of AECB/study number 007, 27 patients were excluded. TAP acknowledged that some sites were indeed excluded. The Division asked TAP to submit a letter, as a formal submission, specifying which sites were excluded from analysis, as well as the reasons for the exclusion. TAP acknowledged.
2. The Division asked TAP to also provide annotated CRF's along with the associated Code Book for the purpose of generating the randomized list of patients that the Division would use to request the specific CRF's from TAP. TAP agreed.
3. The Division also asked TAP to provide SAS programs including the macros, along with a separate decoding list. TAP agreed.

4. The Division asked TAP to explain how the missing data were evaluated. TAP stated that these data sets were considered as failures in the Intent-To-Treat analysis.
5. The Division asked TAP if the analysis distinguished missing values, such as patients lost-to-follow-up, from those who died. TAP stated that for those patients who died, the clinical response would be missing; although, it would have been included if there was an Adverse Event in the evaluable analysis. The Division responded that we may need to have another teleconference to discuss this issue in the future.

**Agreements Reached**

1. TAP agreed to fax the site numbers of those whose data was excluded from analysis.
2. TAP agreed to forward a copy of the Code Book by the end of the week.
3. TAP agreed to submit SAS programs with the Annotated CRF's for the [redacted] [redacted] indication, as well as other indications, as soon as possible.

Minutes Preparer:

ISI 4/5/02  
R. Grant Hills  
Regulatory Project Manager

Chair Concurrence:

ISI 4/10/02  
Dr. Daphne Lin  
Team Leader, Bio-Statistics



# MEMO OF TELECONFERENCE

Date: August 25, 2000

Time: 10:00 a.m.

Application: NDA 21-222: SPECTRACEF® (cefditoren pivoxil) Tablets

TAP Attendees: Donna Helms, Associate Director, Regulatory Affairs  
Richard Homme, Clinical Director  
Sarah Kidd, M.T., Assistant Director, Clinical Development  
Barbara Hunt, Ph.D., Statistician  
Nancy Seidman, Ph.D., Assistant Director, Statistics

FDA Attendees: John Alexander, M.D., Medical Officer  
James Blank, Ph.D., Clinical Reviewer  
Sumathi Nambiar, M.D., Medical Officer  
R. Grant Hills, B.S.N., Regulatory Project Manager

## **Background**

TAP Pharmaceutical Associates (TAP) submitted this New Drug Application (NDA) on October 29, 1999.

## **Purpose**

This teleconference was held to clarify the Division's request that TAP provide revised SAS programs for the Skin & Skin Structure Infection and Streptococcal Pharyngitis indications.

## **Discussion**

### *Pharyngitis*

1. In the final study report for pharyngitis, differences in outcome by various concomitant factors (e.g., severity of illness) were tabulated for patients in the cefditoren treatment arm. However, similar tables were not provided for patients in the penicillin treatment arm.

### *Skin and skin structure infections (SSSI)*

2. There are two major issues involving the data for SSSI.

The first issue concerns patients who were evaluated as clinical improvements by the investigator at the follow-up visit. These evaluations were then over-ridden by TAP

to either a clinical cure or a failure. In most instances, they were over-ridden to a cure. There were 271 of these patients. TAP was asked to re-evaluate these patients and reconsider their clinical outcomes as follows: at the follow-up visit, if the patient has three (3) or more signs/symptoms present, he or she should be listed as a clinical failure. Patients who have two (2) or fewer signs/symptoms present should be considered clinical cures.

The second issue concerns patients with skin pathogens present at pre-therapy, who were listed as clinical failures or relapses at the follow-up visit, but considered microbiological cures. In the Division's guidelines, SSSI is both a clinically and microbiologically driven indication. That is, efficacy for both is needed for drug approval. Therefore, these patients are considered microbiological failures. TAP was requested to change the microbiological results to failures, for all of the patients who were either clinical failures or relapses, where a skin pathogen was present at baseline. The evaluations for the clinical and microbiological outcomes for these patients should be identical.

#### **Agreements**

1. TAP agreed to re-evaluate the patients in the SSSI indication studies who were listed as clinical improvements by the investigator and subsequently changed to cures or failures by TAP, according to criteria discussed during the meeting.
2. TAP agreed to provide a re-analysis where microbiological outcomes are changed from cures to failures for all patients who were either clinical failures or relapses at the follow-up visit where a skin pathogen was present at baseline.
3. TAP agreed to provide tables of outcome by concomitant factors for the patients in the penicillin treatment arm in the pharyngitis studies, similar to those provided for the cefditoren treatment arm.
4. TAP agreed to provide the Division with a timeline for submitting the requested analyses.
5. The Division agreed to submit a fax of the Clinical Reviewer's written comments relating to the discussion above.

*Prepared by: R. Grant Hills*

**MEMORANDUM**

Center for Drug Evaluation and Research  
Food and Drug Administration  
Public Health Service

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**Date:** October 26, 2000

**To:** Janice Soreth, M.D.  
Acting Director  
Division of Anti-Infective Drug Products; HFD-520

**From:** James Blank, Ph.D.  
Division of Anti-Infective Drug Products; HFD-520

**Through:** David Ross, MD, Ph.D.  
Acting Medical Team Leader  
Division of Anti-Infective Drug Products; HFD-520

**Subject:** Disqualified Patients in Spectracef Study Cef-97-011.

The 30 additional patients enrolled by Dr. Aldrich were excluded by the company from all analyses when it was determined that important study procedures were not being followed, rendering the information gathered unreliable.

## MEMO OF TELECONFERENCE

Date: November 17, 2000

Time: 1:30 p.m.

Application: NDA 21-222 for SPECTRACEF® (cefditoren pivoxil)

TAP Attendees: Donna Helms, Associate Director, Regulatory Affairs  
Richard Homme, Clinical Director  
Sarah Kidd, M.T., Assistant Director, Clinical Development  
Dr. Barbara Hunt, Statistician  
Dr. Nancy Seidman, Assistant Director, Statistics

FDA Attendees: Dr. Janice M. Soreth, Acting Division Director, DAIDP  
Dr. David Ross, Clinical Team Leader, DAIDP  
Dr. Jean Mulinde, Medical Officer, DAIDP  
Dr. Thamban Valappil, Statistician, DAIDP  
Dr. Joel Unowsky, Microbiologist, DAIDP  
Cdr. R. Grant Hills, Regulatory Project Manager, DAIDP

### **Background**

TAP Pharmaceutical Associates (TAP) submitted this New Drug Application (NDA) October 29, 1999. An approvable action was taken on this NDA on October 27, 2000. The approval for the indication of Acute Exacerbation of Chronic Bronchitis (AECB) was contingent upon the applicant supplying supportive additional analyses of AECB studies or a supportive final study report for their completed [REDACTED]

### **Purpose**

To discuss the requirements for resubmission of data to support the AECB indication.

### **Discussion**

1. TAP referred to its November 8, 2000 proposal for performing a reanalysis of AECB according to the Winnepeg Criteria. The Agency stated that this post-hoc analysis may result in the introduction of bias into the study.
2. Another problem with the proposed reanalysis is the Sponsor's assumption that the degree of dyspnea at follow-up is equivalent to that for dyspnea present at pre-exacerbation. The Agency believes that this assumption is not scientifically sound given that, in prior sensitivity analyses, a significant number of signs and symptoms did not return to study entry levels, nor to pre-exacerbation baseline levels. The Division stated that supportive data for efficacy in AECB must be robust.