Applicant therefore concludes that "these data confirm that the enrolled patients met criteria for a diagnosis of chronic bronchitis and an acute exacerbation of their chronic disease."

Medical Officer's Comment: ***The MO did not question the supportive data provided in the CRFs documenting patients had a history of chronic bronchitis. The MO does not believe, however, it is appropriate to use signs and symptoms from post-therapy and follow-up visits to define patients who appropriately met entry inclusion criteria. Therefore the MO's requirement for an increase in two or more signs and symptoms consistent with AECB, between the patient's baseline pre-exacerbation status and pre-therapy assessment, is appropriately used to define patients for inclusion in the MO's MITT population. Although the literature suggests that purulent sputum, increased sputum production, and increased dyspnea (Winnipeg Type I) or two of these three criteria (Winnipeg Type II) are most predictive of patients that will benefit over placebo from antimicrobial therapy, the MO accepted an increase in any two of the Applicant's 10 signs and symptoms recorded on the pre-therapy assessment as evidence to document an acute exacerbation. Of note, this requirement is*** *considerably less stringent than what has been applied in reviews of other recently approved antimicrobials for the treatment of AECB. If modified* ***Winnipeg criteria (CRFs did not contain information regarding patient's pre-exaccerbation level of dyspnea) are applied to the Applicant's data base to attempt to define a population that would be most likely to benefit from antimicrobial therapy, then 92% and 93% of patients meet criteria for modified Winnipeg Type I or II in studies CEF97-003 and CEF97-005, respectively. The breakdown of patients by Winnipeg group for each study is displayed in Table 7.***

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Table 7. Breakdown of Patients by Modified^ Winnipeg Type

	Type I*^		Type II*^		Type III*^	
	n/N	(%)	n/N	(%)	n/N	(%)
CEF97-003	419/618	(68%)	151/618	(24%)	48/618	(8%)
CEF97-005	602/903	(67%)	245/903	(27%)	52/903	(6%)

*[2]Type I=Patient has increased sputum purulence, increased sputum volume and increased dyspnea from baseline (patients treated with antimicrobial demonstrated a significantly better cure rate than those treated with placebo, 63% vs 43%).
Type II=Patient demonstrates 2 of 3 criteria listed for Type III (patients treated with antimicrobial demonstrated a significantly better cure rate than those treated with placebo, 70% vs 60%).
Type III=Patient demonstrates 1 of 3 criteria listed for Type III and at least 1 of the following: upper respiratory infection (sore throat, nasal discharge), within the past 5 days: fever without other cause: increased wheezing: increase cough: or increased in respiratory rate or heart rate by 20% as compared with baseline (patients treated with antimicrobial did not demonstrate a significantly better cure rate than those treated with placebo, 74% vs 70%).
^Documentation that dyspnea has increased from pre-exacerbation baseline is not available in CRFs, therefore if any degree of dyspnea was present on study day 1 it was assumed to be an increase from the patient's pre-exacerbation baseline.

In addition, the Applicant also stated in the October 2, 2000 telecon between the Applicant and the DAIDP that they felt the MO's requirement that ALL signs and symptoms be improved at the Follow-Up visit compared to the Pre-Therapy visit to consider a patient a cure was too stringent for this type of infection.

Medical Officer's Comment: ***The MO was simply following outcome criteria stated by the Applicant in the original study protocol and in the study report when this criteria was applied in the MO's analyses. However, the MO agrees that the requirement for every sign and symptom to be resolved may be too stringent and additional sensitivity analyses in which patients were only required to show 1) improvement of 7 of 10 signs and symptoms or 2)no worsening or new signs and symptoms, at post-therapy and follow-up, to be considered a cure are provided in Tables 8 and 9.***

[2] Anthonisen NR, Manfreda J, Warren CPW et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987; 106:196-204.

Table 8. CEF97-003 Clinical Response at the Post-Therapy and Follow-Up Visits According to the MO

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Original MO Analysis						
Post-Therapy						
MITT Cures	71/96	(74%)	71/95	(75%)	85/112	(75%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-14.6, 12.6]			
CDTR-PI 400 mg vs CXM-AX			[-13.8, 13.3]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-14.9, 13.4]			
Post-Therapy						
Evaluable Cures	66/87	(76%)	66/83	(80%)	78/102	(77%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-14.6, 13.3]			
CDTR-PI 400 mg vs CXM-AX			[-10.6, 16.7]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-18.0, 10.6]			
Follow-Up						
MITT Cures	38/96	(40%)	46/95	(48%)	50/112	(45%)
Comparison of Cure Rates			97.5% CI for Difference in Cure Rate[b]			
CDTR-PI 200 mg vs CXM-AX			[-20.4, 10.3]			
CDTR-PI 400 mg vs CXM-AX			[-11.8, 19.4]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-24.9, 7.2]			
Follow-Up						
Evaluable Cures	37/87	(43%)	46/83	(55%)	46/102	(45%)
Comparison of Cure Rates			97.5% CI for Difference in Cure Rate[b]			
CDTR-PI 200 mg vs CXM-AX			[-18.8, 13.7]			
CDTR-PI 400 mg vs CXM-AX			[-6.2, 26.8]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-29.9, 4.2]			
CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil n/N = number of evaluable patients with clinical response/total number of evaluable patients [b] The 97.5% CI for the difference in clinical cure rates was used to adjust for multiple comparisons						
If require adequate gram stain, increase in two signs and symptoms for study entry, target pathogen on entry culture, no worsening of symptoms at EOT and no more than three symptoms are unimproved at TOC						
Follow-Up						
MITT	59/96	(61%)	67/95	(71%)	71/112	(63%)
Evaluable Cures	57/87	(66%)	64/83	(77%)	66/102	(65%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
			MITT		**Eval**	
CDTR-PI 200 mg vs CXM-AX			[-17.0, 13.2]		[-14.8, 16.4]	
CDTR-PI 400 mg vs CXM-AX			[-7.5, 21.8]		[-2.4, 27.2]	
If require adequate gram stain, increase in two signs and symptoms for study entry, target pathogen on entry culture, no worsening of symptoms at EOT and TOC						
Follow-Up						
MITT		(63%)		(71%)		(65%)
Evaluable Cures		(67%)		(77%)		(67%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
			MITT		**EVAL**	
CDTR-PI 200 mg vs CXM-AX			[-17.7, 12.3]		[-15.4, 15.4]	
CDTR-PI 400 mg vs CXM-AX			[-9.2, 19.9]		[-4.3, 25.1]	

Table 9. CEF97-005 Clinical Response at the Post-Therapy and Follow-Up Visits According to the MO

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Original MO Analysis						
Post-Therapy						
MITT Cures	129/165	(78%)	102/156	(65%)	134/173	(78%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-9.4, 10.9]			
CDTR-PI 400 mg vs CLA			[-23.2, -1.0]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[1.6, 24.0]			
Post-Therapy						
Evaluable Cures	115/146	(79%)	95/135	(70%)	122/154	(79%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-11.0, 10.1]			
CDTR-PI 400 mg vs CLA			[-20.3, 2.6]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.2, 20.0]			
Follow-Up						
MITT Cures	78/165	(47%)	60/156	(39%)	90/173	(52%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-16.9, 7.4]			
CDTR-PI 400 mg vs CLA			[-25.8, 1.4]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.2, 21.2]			
Follow-Up						
Evaluable Cures	74/146	(51%)	58/135	(43%)	84/154	(55%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-16.8, 9.1]			
CDTR-PI 400 mg vs CLA			[-24.7, 1.5]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-5.6, 21.0]			
CDTR-PI = cefditoren pivoxil; CLA = clarithromycin n/N = number of evaluable patients with clinical response/total number of evaluable patients [b] The 97.5% CI for the difference in clinical cure rates was used to adjust for multiple comparisons						
If also require adequate gram stain, increase in two signs and symptoms for study entry, target pathogen on entry culture, no worsening of symptoms at EOT and no more than three symptoms are unimproved at TOC						
Follow-Up						
MITT	114/165	(69%)	90/156	(58%)	119/173	(69%)
Evaluable Cures	107/146	(73%)	86/135	(64%)	110/154	(71%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
			MITT		**EVAL**	
CDTR-PI 200 mg vs CLA			[-11.0, 11.6]		[-9.7, 13.4]	
CDTR-PI 400 mg vs CLA			[-23.0, 0.8]		[-20.1,4.6]	
If also require adequate gram stain, increase in two signs and symptoms for study entry, target pathogen on entry culture, no worsening of symptoms at EOT and TOC						
Follow-Up						
MITT		(53%)		(44%)		(57%)
Evaluable Cures		(58%)		(50%)		(58%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
			MITT		**Eval**	
CDTR-PI 200 mg vs CLA			[-15.4, 8.8]		[-13.7, 11.9]	
CDTR-PI 400 mg vs CLA			[-24.7, -0.1]		[-22.0, 4.3]	

Medical Officer's Comment: ***During the October 20, 2000 face to face meeting with the Applicant, additional evidence suggesting sampling error and reader***

variability may logically account for discrepancies between the investigators' and central labs interpretation of gram stains. At an internal meeting between Dr. Murphy and the clinical review team that followed, Dr. Murphy requested additional sensitivity analyses be performed for study CEF97-005 using the investigators' gram stain results with other criteria defined by the MO. The results of these analyses are presented in Tables 10 and 11.

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Table 10. CEF97-005 Clinical Response at the Follow-Up Visit According to the MO

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Original MO Analysis						
Follow-Up MITT Cures	78/165	(47%)	60/156	(39%)	90/173	(52%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-16.9, 7.4]			
CDTR-PI 400 mg vs CLA			[-25.8, 1.4]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.2, 21.2]			
Follow-Up Evaluable Cures	74/146	(51%)	58/135	(43%)	84/154	(55%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-16.8, 9.1]			
CDTR-PI 400 mg vs CLA			[-24.7, 1.5]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-5.6, 21.0]			
CDTR-PI = cefditoren pivoxil; CLA = clarithromycin n/N = number of evaluable patients with clinical response/total number of evaluable patients [b] The 97.5% CI for the difference in clinical cure rates was used to adjust for multiple comparisons						
If require adequate gram stain at central lab, increase in two signs and symptoms for study entry, target pathogen on entry culture, no worsening of symptoms at EOT and no more than three symptoms are unimproved at TOC						
Follow-Up MITT Cures	114/165	(69%)	90/156	(58%)	119/173	(69%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-11.0, 11.6]			
CDTR-PI 400 mg vs CLA			[-23.0,0.8]			
Follow-Up Evaluable Cures	107/146	(73%)	86/135	(64%)	110/154	(71%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-9.7, 13.4]			
CDTR-PI 400 mg vs CLA			[-20.1,4.6]			
[redacted], **increase in two signs and symptoms for study entry, target pathogen on entry culture, no worsening of symptoms at EOT and no more than three symptoms are unimproved at TOC**						
Follow-Up MITT Cures	149/233	(64%)	133/227	(59%)	159/240	(66%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-12.1, 7.5]			
CDTR-PI 400 mg vs CLA			[-17.7, 2.4]			
Follow-Up Evaluable Cures	138/205	(67%)	125/198	(63%)	147/212	(69%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-12.2, 7.5]			
CDTR-PI 400 mg vs CLA			[-16.7, 4.3]			

Table 11. CEF97-005 Clinical Response at the Follow-Up Visit According to the MO

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Original MO Analysis						
Follow-Up MITT Cures	78/165	(47%)	60/156	(39%)	90/173	(52%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-16.9, 7.4]			
CDTR-PI 400 mg vs CLA			[-25.8, 1.4]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.2, 21.2]			
Follow-Up Evaluable Cures	74/146	(51%)	58/135	(43%)	84/154	(55%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-16.8, 9.1]			
CDTR-PI 400 mg vs CLA			[-24.7, 1.5]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-5.6, 21.0]			
CDTR-PI = cefditoren pivoxil; CLA = clarithromycin n/N = number of evaluable patients with clinical response/total number of evaluable patients [b] The 97.5% CI for the difference in clinical cure rates was used to adjust for multiple comparisons						
If require adequate gram stain at central lab, increase in two signs and symptoms for study entry, target pathogen on entry culture, no worsening of symptoms at EOT and TOC						
Follow-Up MITT Cures	(53%		(44%)		(57%)	
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-15.4, 8.8]			
CDTR-PI 400 mg vs CLA			[-24.7, -0.1]			
Follow-Up Evaluable Cures	(58%)		(50%)		(58%)	
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-13.7, 11.9]			
CDTR-PI 400 mg vs CLA			[-22.0, 4.3]			
[redacted], **increase in two signs and symptoms for study entry, target pathogen on entry culture, no worsening of symptoms at EOT and TOC**						
Follow-Up MITT Cures	(50%)		(46%)		(53%)	
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-13.0, 7.6]			
CDTR-PI 400 mg vs CLA			[-16.6, 4.1]			
Follow-Up Evaluable Cures	(53%)		(51%)		(55%)	
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-13.0, 8.9]			
CDTR-PI 400 mg vs CLA			[-15.7, 6.3]			

If only modified Winnipeg Type I and II patients are included in the analyses results are displayed in Table 12.

Table 12. Clinical Outcome for Patients Who Are Modified Winnipeg Type I or II

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		Comparator n/N (%)	
If require adequate gram stain at central lab, patient meets Winnipeg Type I or II criteria for entry, patient has no worsening of symptoms at EOT visit, and patient shows improvement in dyspnea, sputum volume and sputum purulence at TOC visit						
CEF97-003						
Follow-Up						
MITT		(56%)		(58%)		(55%)
Evaluable Cures	48/80	(60%)	54/81	(67%)	52/95	(55%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
			MITT		**Eval**	
CDTR-PI 200 mg vs CXM			[-14.7, 17.7]		[-11.5, 22.0]	
CDTR-PI 400 mg vs CXM			[-12.6, 19.1]		[-4.5, 28.3]	
CEF97-005						
Follow-Up						
MITT		(61%)		(53%)		(59%)
Evaluable Cures	93/139	(67%)	78/133	(59%)	90/146	(62%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
			MITT		**Eval**	
CDTR-PI 200 mg vs CLA			[-10.2, 14.2]		[-7.4, 18.0]	
CDTR-PI 400 mg vs CLA			[-18.7, 6.3]		[-16.1, 10.2]	
[redacted], **patient meets Winnipeg Type I or II criteria for entry, patient has no worsening of symptoms at EOT visit, and patient shows improvement in dyspnea, sputum volume and sputum purulence at TOC visit**						
CEF97-005						
Follow-Up						
MITT	126/218	(58%)	119/218	(55%)	126/225	(56%)
Evaluable Cures	120/193	(62%)	112/191	(59%)	118/199	(59%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
			MITT		**Eval**	
CDTR-PI 200 mg vs CLA			[-8.7, 12.3]		[-8.2, 13.9]	
CDTR-PI 400 mg vs CLA			[-12.0, 9.2]		[-11.8, 10.5]	

6. Applicant's Statistical Analyses

In their September 6, 2000 submission the Applicant has provided the following justification for not applying a multiple comparison adjustment to analyses:

"In the protocol(s), the comparison to the higher dose was designated as primary with additional comparison to be done subsequently. Standard practice being followed was that the primary comparison must be successful for subsequent comparisons to be valid. Thus while not formally specified in the protocol, it was implicitly implied and intended that the results of the comparison of the lower dose (200 mg) to the comparator would be considered only if the higher dose (400 mg) was found to be equivalent to the comparator in the primary comparison.

Since the comparison of the higher dose (400 mg) versus the comparator was shown to be equivalent in our studies, the next logical test to perform using a closed testing procedure is the comparison of the lower dose (200 mg) versus the comparator. Since using this closed testing procedure only provides one opportunity for success at each step, no multiple comparison adjustment is needed."

Medical Officer's Comment: ***While the logic of the Applicant is understood, if the Applicant planned to make such a step-wise approach to analysis it should have been specified in the original protocol. In addition, if it was the intention of the Applicant to perform such a step-wise comparison in order to avoid the need for a multiple comparison adjustment, then the reason that additional analyses of the 200 mg versus 400 mg arms were performed is unclear.***

7. Conclusion

After review of additional sensitivity analyses, the MO recommends that cefditoren-pivoxil 200 mg PO BID x 10 days not be approved for the indication of AECB. The MO's recommendation is based on the following findings (in addition to those cited in the original MO's review):

- The Applicant has not presented data of equivalent regulatory quality to that provided by other Applicant's who have sought and were granted the indication of AECB. The primary difference between the current Applicant's data and that of prior Applicant's was documentation that the patient's study entry signs and symtoms had resolved to an adequate degree to consider the patient a clinical cure.
- If the criterion for a "good" gram stain at the central lab is removed from the MO's evaluability and efficacy criteria the overall outcomes are not significantly changed from the MO's original analyses.

- If the criterion for resolution of all signs and symptoms at the Follow-Up visit is changed to no more than 3 signs and symptoms may be unimproved or no sign or symptom may be worsened for the patient to be considered a clinical cure, then the overall outcomes are not significantly changed from the MO's original analyses.
- Despite additional sensitivity analyses the results of the studies remain discordant: CDTR-PI 400 mg appears to show equivalence in study CEF97-003, but does not show equivalence in study CEF97-005: CDTR-PI 200 mg does not show equivalence in study CEF97-003, but does show equivalence in study CEF97-005.
- Surprisingly low cure rates, consistent with historical placebo rates (43-60%), are observed for both the study drug and the comparator in many of the sensitivity analyses.

The MO recommends the Applicant perform an additional statistically adequate and well controlled study comparing cefditoren-pivoxil 400 mg PO BID x 10 days to an approved comparator, if they wish to further pursue this indication.

Jean M. Mulinde, M.D.
Medical Officer/HFD-520

HFD-520
HFD-520/ActingDivDir/JSoreth
HFD-520/DepDivDir/LGavrilovich
HFD-520/ClinTeamLeader/DRoss
HFD-520/MedOfficer/JAlexander
HFD-520/Pharm/ToxTeamLeader/ROsterberg
HFD-520/Pharm/ToxReviewer/KSeethaler
HFD-520/MicroTeamLeader/ASheldon
HFD-520/MicroReviewer/JUnowsky
HFD-520/ChemTeamLeader/DKatague
HFD-520/ChemReviewer/VShetty
HFD-520/BiopharmTeamLeader/Fpelsor
HFD-520/BiopharmReviewer/CBonapace
HFD-725/Biometrics/DivDir/MHuque
HFD-725/BiometricsTeamLeader/DLin
HFD-520/BiometricsReviewer/TValappil
HFD-520/ProjManLeader/FLeSane
HFD-520/ProjMan/BDuvall-Miller
HFD-520/DSI/MThomas

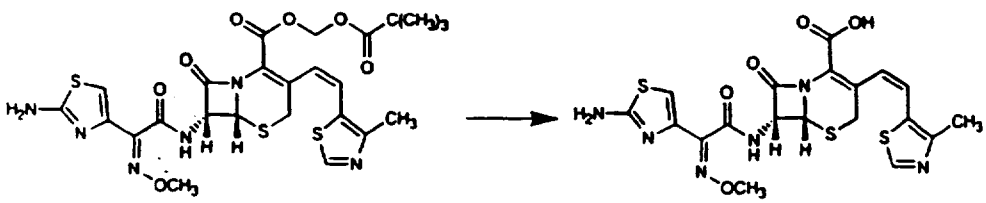
concurrence:
HFD-520/ActingDivDir/JSoreth
HFD-520/ClinTeamLeader/DRoss

Medical Officer's and Biostatisticians's Review of NDA 21,222
Acute Exacerbation of Chronic Bronchitis Indication

1. General Information
   - 1.1 NDA 21,222
   - 1.2 Applicant Identification
     - 1.2.1 TAP Holdings, Inc.
     - 1.2.2 675 N. Field Drive
       Lake Forest, IL 60045
       Phone: (847) 236-2524
       Fax: (847) 3 17-5795
     - 1.2.3 Jesse Kai Seidman, M.S.
       Regulatory Affairs Specialist

   - 1.3 Submission/Review Dates
     - 1.3.1 Date of Submission: December 28, 1999
     - 1.3.2 CDER Stamp Date: December 29, 1999
     - 1.3.3 Date Submission Received by Reviewer: April 4, 2000
     - 1.3.4 Date Review Begun: April 21, 2000
     - 1.3.5 Date Review Completed: September 27, 2000

   - 1.4 Drug Identification
     - 1.4.1 Generic Name: Cefditoren pivoxil
     - 1.4.2 Proposed Trade Name: Spectracef TM
     - 1.4.3 Chemical Name: (-)-(6R,7R)-2,2-dimethylpropionyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
     - 1.4.4 Chemical Structure:



Cefditoren Pivoxil (CDTR-PI) Cefditoren (CDTR)

     - 1.4.5 Molecular Formula: $C_{25}H_{28}N_6O_7S_3$
     - 1.4.6 Molecular Weight: 620.73

   - 1.5 Pharmacologic Category: Cephalosporin antibiotic

   - 1.6 Dosage Form: Tablet

   - 1.7 Route of Administration: Oral

1.8 Proposed Indication & Usage section [for Acute Exacerbation of Chronic Bronchitis (AECB) indication]

The Applicant's proposed label includes (Volume 2 of 322, page 15):
"**Acute Bacterial Exacerbation of Chronic Bronchitis** caused by the following:
Haemophilus influenzae (including β-lactamase-producing strains)
Haemophilus parainfluenzae (including β-lactamase-producing strains)
Streptococcus pneumoniae (penicillin-susceptible strains only)
Moraxella catarrhalis (including β-lactamase-producing strains)
[redacted]

1.9 Proposed Dosage & Administration section (for AECB indication)

The Applicant's proposed label includes the following table and text (Volume 2 of 322, pages 24-25):

Table 1. Dosage and Administration Instructions From Label Submitted by Applicant

SPECTRACEF Dosage and Administration* **Adults and Adolescents (≥12 Years)**		
Type of Infection	**Dosage**	**Duration (days)**
Acute Bacterial Exacerbation of Chronic Bronchitis [redacted] Pharyngitis/Tonsillitis Uncomplicated Skin and Skin Structure Infections	200 mg BID	10

*Should be taken with food

"**Patients with Renal Insufficiency**
[redacted]

Patients with Hepatic Disease
No dose adjustments are necessary for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B)."

1.10 Proposed Clinical Studies section (for AECB indication)

The Applicant's proposed label includes (Volume 2 of 322, page 28):

"Acute Exacerbation of Chronic Bronchitis

[redacted]

1.11 Materials Reviewed

1.11.1 NDA volumes reviewed:
NDA 21,222 volumes 2, 4, 213-222, and 246-252 of 322, December 28, 1999 submission

1.11.2 Other documents reviewed:

- NDA 21,222 General Correspondence, March 31, 2000 submission (annotated Case Report Forms)
- NDA 21,222 Response to Request for Information, August 8, 2000 (additional SAS data sets for the bronchitis and sinusitis studies)
- FAX March 27, 2000 (Code lists for ISS and ISE data sets)
- FAX June 13, 2000 (Sputum gram stain procedures for studies CEF-97-003 and CEF-97-005)
- FAX June 15, 2000 (Decision tree analysis for Skin and Skin structure studies)
- FAX June 26, 2000 (Decision tree analyses for all clinical studies)
- FAX June 26, 2000 (Sputum gram stain procedures for studies CEF-97-003 and CEF-97-005)
- FAX June 29, 2000 (Case Report Form for patient #6520, CEF-97-005, AECB study)
- FAX July 25, 2000 (additional annotated Case Report Forms for AECB studies)
- NDA 21,222, September 13, 2000 submission (missing tables from CEF97-005 study report)

1.11.3 Amendments reviewed:

- NDA 21,222 Amendment 004 Volume 1 of 1, May 3, 2000 submission
- NDA 21,222 Amendment 016 Volume 1 of 1, June 13, 2000 submission

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Appendices

Appendix 1: Case Report Forms
Appendix 2: June 13, 2000 Fax/Gram stain processing
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3. Clinical Studies

3.1 Introduction

In 1997, TAP Holdings Inc., initiated a program to collect data on the efficacy and safety of cefditoren pivoxil for the treatment of uncomplicated skin and skin structure infections, acute exacerbation of chronic bronchitis, [redacted] streptococcal pharyngitis [redacted] The Applicant has submitted data from 8 of 10 phase III trials in support of this NDA [redacted] Table 2. lists pivotal Phase III studies submitted in NDA 21,222 (Applicant Table 3.7.3a., Volume 4 of 322, pages 85-86):

3.2 Acute Exacerbation of Chronic Bronchitis Indication

The Applicant has provided results from the following two pivotal Phase III studies in support of obtaining an indication for AECB:

- **Study CEF-97-003** "Comparative Safety and Efficacy of Cefditoren Pivoxil and Cefuroxime Axetil in the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis"
- **Study CEF-97-005** "Comparative Safety and Efficacy of Cefditoren Pivoxil and Clarithromycin in the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis"

The Applicant has also provided results from the following foreign Phase II study as supportive evidence for the efficacy and safety of cefditoren pivoxil for the treatment of AECB. This study was an unblinded, non-comparative, European study of 107 patients. Of the 107 patients, 20 were bacteriologically evaluable. According to the Applicant, in the bacteriologically evaluable population, the Investigator's Overall Clinical Efficacy Assessment was: 35% cure, 55% improvement, and 10% relapse. Diarrhea occurred in 7.5% of patients and is the only adverse event that occurred in more than 2% of the patients. Given the limited sample size and study design issues, this study does not provide data of regulatory quality and will not be further reviewed.

- GBHA-248 "An Open, Multicenter Study to Evaluate the Safety and Efficacy of ME1207 Taken Orally as 200 mg Twice Daily for Ten Days, In Patients With Acute Bacterial Exacerbations of Chronic Bronchitis"

Table 2. Completed Phase III Studies Submitted in NDA 21,222.

Table 3.7.3a. Completed Phase III Studies of Cefditoren Pivoxil Sponsored by TAP Holdings Inc.							
Protocol #/ # of Investigators/ Country	Study Design	Treatment Groups	# of Patients Analyzed for Safety	Mean Age (Range)	Gender	Race	CRFs Available/ Full Report (Vol.)
Indication: Acute Exacerbation of Chronic Bronchitis							
CEF-97-003/ 58 investigators (data from 2 additional sites -- 225 patients -- were excluded)/ USA	Randomized, double-blind, active-control, parallel-group, multicenter	CDTR-PI 200 mg BID x 10 Days	203	52.1 (14-90)	43%M; 57%F	90%C; 5%B; 3%H; <1%A; 1%O	Yes/ v.1.212 v.1.280
		CDTR-PI 400 mg BID x 10 Days	208	50.3 (13-87)	46%M; 54%F	90%C; 5%B; 3%H; 1%A; <1%O	
		CXM-AX 250 mg BID x 10 Days	207	52.1 (15-86)	41%M; 59%F	89%C; 7%B; 2%H; 1%A; <1%O	
CEF-97-005/ 73 investigators (data from 2 additional sites -- 88 patients -- were excluded)/ USA	Randomized, double-blind, active-control, parallel-group, multicenter	CDTR-PI 200 mg BID x 10 Days	297	49.4 (13-85)	49%M; 51%F	89%C; 7%B; 3%H; 1%O	Yes/v.1.217, v.1.285
		CDTR-PI 400 mg BID x 10 Days	302	49.5 (14-86)	46%M; 54%F	89%C; 7%B; 3%H; 1%O	
		CLA 500 mg BID x 10 Days	304	50.2 (17-89)	47%M; 53%F	92%C; 4%B; 4%H; 1%O	
Indication: Streptococcal Pharyngitis							
CEF-97-008/ 38 investigators/ USA	Randomized, double-blind, active-control, parallel-group, multicenter	CDTR-PI 200 mg BID x 10 Days	256	28.5 (12-67)	37%M; 63%F	84%C; 9%B; 5%H; <1%A; 1%O	Yes/ v.1.223, v.1.291
		PCN-VK 250 mg QID x 10 Days	247	29.1 (12-80)	39%M; 61%F	89%C; 6%B; 4%H; <1%A; <1%O	
CEF-97-010/ 47 investigators/ USA	Randomized, double-blind, active-control, parallel-group, multicenter	CDTR-PI 200 mg BID x 10 Days	254	26.4 (11-74)	38%M; 62%F	86%C; 4%B; 8%H; <1%A; 2%O	Yes/ v.1.227, v.1.295
		PCN-VK 250 mg QID x 10 Days	254	27.1 (12-72)	33%M; 67%F	89%C; 4%B; 7%H; <1%A; <1%O	
AMOX/CLAV = amoxicillin/clavulanate potassium; CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; CFDX-MN = cefadroxil monohydrate; CXM-AX = cefuroxime axetil; PCN-VK = penicillin VK; BID = twice daily; TID = three times daily; QID = four times daily; M = Male; F = Female; C = Caucasian; B = Black; H = Hispanic; A = Asian; O = Other							

Table 3.73a. Completed Phase III Studies of Cefditoren Pivoxil Sponsored by TAP Holdings Inc. (continued)

Protocol #/ # of Investigators/ Country	Study Design	Treatment Groups	# of Patients Analyzed for Safety	Mean Age (Range)	Gender	Race	CRFs Available/ Full Report (Vol.)
Indication: Acute Maxillary Sinusitis							
CEF-97-004/ 61 investigators/ USA	Randomized, investigator-blind, active-control, parallel-group, multicenter	CDTR-PI 200 mg BID x 10 Days	257	40.7 (12-82)	41%M; 59%F	91%C; 7%B; 2%H; <1%A	Yes/ v.1.231, v.1.299
		CDTR-PI 400 mg BID x 10 Days	261	39.8 (12-80)	40%M; 60%F	88%C; 9%B; 2%H; 1%O	
		AMOX/CLAV 875 mg BID x 10 Days	257	39.0 (13-78)	37%M; 63%F	87%C; 10%B; 3%H; <1%O	
CEF-97-007/ 70 investigators (data from 1 additional site -- 27 patients -- were excluded)/ USA	Randomized, investigator-blind, active-control, parallel-group, multicenter	CDTR-PI 200 mg BID x 10 Days	281	39.9 (13-82)	43%M; 57%F	78%C; 7%B; 11%H; 2%A; 1%O	Yes/ v.1.237, v.1.305
		CDTR-PI 400 mg BID x 10 Days	279	38.9 (13-80)	35%M; 65%F	76%C; 8%B; 13%H; 2%A; 1%O	
		AMOX/CLAV 500 mg TID x 10 Days	277	40.7 (12-84)	44%M; 56%F	79%C; 8%B; 10%H; 2%A; 1%O	
Indication: Uncomplicated Skin and Skin Structure Infection							
CEF-97-009/ 63 investigators/ USA	Randomized, double-blind, active-control, parallel-group, multicenter	CDTR-PI 200 mg BID x 10 Days	291	40.9 (13-87)	53%M; 47%F	78%C; 14%B; 5%H; 1%A; 1%O	Yes/ v.1.202, v.1.270
		CDTR-PI 400 mg BID x 10 Days	283	40.8 (12-93)	50%M; 50%F	83%C; 13%B; 3%H; 1%O	
		CXM-AX 250 mg BID x 10 Days	283	41.2 (12-92)	47%M; 53%F	81%C; 12%B; 5%H; <1%A; 1%O	
CEF-97-011/ 69 investigators (data from 1 additional site -- 30 patients -- were excluded)/ USA	Randomized, double-blind, active-control, parallel-group, multicenter	CDTR-PI 200 mg BID x 10 Days	278	42.6 (12-95)	50%M; 50%F	81%C; 7%B; 10%H; 1%A; 1%O	Yes/ v.1.207, v.1.275
		CDTR-PI 400 mg BID x 10 Days	277	40.7 (12-85)	52%M; 48%F	80%C; 4%B; 13%H; 1%A; 3%O	
		CFDX-MN 500 mg BID x 10 Days	273	40.6 (13-93)	53%M; 47%F	79%C; 7%B; 10%H; 1%A; 2%O	

AMOX/CLAV = amoxicillin/clavulanate potassium; CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; CFDX-MN = cefadroxil monohydrate; CXM-AX = cefuroxime axetil; PCN-VK = penicillin VK; BID = twice daily; TID = three times daily; QID = four times daily; M = Male; F = Female; C = Caucasian; B = Black; H = Hispanic; A = Asian; O = Other

3.2.1 **Study CEF-97-003** "Comparative Safety and Efficacy of Cefditoren Pivoxil and Cefuroxime Axetil in the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis"

Enrollment Period
Start: November 4, 1997
Completion: August 19, 1998

3.2.1.1 Objective

"To compare the safety and efficacy of orally administered cefditoren pivoxil 200 mg BID and 400 mg BID and cefuroxime 250 mg BID in the treatment of patients with an acute bacterial exacerbation of chronic bronchitis or chronic asthmatic bronchitis who are suitable candidates for oral antibiotic therapy." (Volume 214 of 322, page 017)

3.2.1.2 Design

Study CEF-97-003 was a randomized, double-blind, comparative, multiple dose, multicenter trial that was conducted in the United States. The randomization ratio was 1:1:1 (cefditoren pivoxil 200 mg BID:cefditoren pivoxil 400 mg BID:cefuroxime axetil 250 mg BID). Although two dosage regimens for cefditoren pivoxil were included in this study, the study was not designed specifically as a dose-ranging study.

MO Comments: ***The Applicant has stated that "the doses of cefditoren pivoxil tablets, 200 mg BID and 400 mg BID, for 10 days were chosen for the treatment of bacterial exacerbation of chronic bronchitis or chronic asthmatic bronchitis based on the in vitro susceptibility data of respiratory pathogens (i.e., S. pneumoniae, H. influenzae, and M. catarrhalis) to cefditoren pivoxil and the time that serum levels of cefditoren exceeded the MIC of these pathogens." They also stated that "the primary comparison for efficacy endpoints will be made between the cefditoren 400 mg BID treatment group and the cefuroxime axetil treatment group." (Volume 212 of 322, page 029 and Volume 214 of 322, page 046) Based on these statements the MO presumes the expectation of the Applicant was that the 400 mg treatment group would do better (provided the adverse event profile was not higher in this group) than the 200 mg treatment group.***

Patients who were at least 12 years old and presented with the clinical signs and symptoms of an acute bacterial exacerbation of chronic bronchitis or chronic asthmatic bronchitis, who had a chest x-ray demonstrating the absence of pneumonia, who had a sputum qualified by Gram stain at the investigator site, and who met the selection criteria were eligible for entry into the study. Patients

who met the selection criteria were randomly assigned to receive one of three treatment regimens for 10 days:

cefditoren 200 mg BID as cefditoren pivoxil
or
cefditoren 400 mg BID as cefditoren pivoxil
or
cefuroxime axetil 250 mg BID

Patients returned to the investigator's office for an On-Therapy Visit, if it was felt necessary based on telephone contact during Study Days 3 to 5. All patients returned to the investigator's office for a Post-Therapy Visit within 48 hours after the last dose of study medication and a Follow-Up Visit 7 to 14 days after the last dose of study medication. Microbiologic evaluation (if sputum was available) and assessment of the clinical signs and symptoms of infection were performed at each study visit. Safety was evaluated by laboratory tests, physical examination, and monitoring of adverse events at each study visit.

3.2.1.3 Protocol Review

3.2.1.3.1 Population

3.2.1.3.1.1 Inclusion Criteria

The inclusion criteria as defined in the original protocol and study report are nearly identical, with the exception that the study report defines the following additional criteria: "Was not seriously ill and had acute bacterial exacerbation of chronic bronchitis or chronic asthmatic bronchitis that was suitable for oral antibiotic therapy." (Volume 212 of 322, page 026)

Noteworthy inclusion criteria include (Volume 212 of 322, pages 025-026):

- Diagnosis of chronic bronchitis or chronic asthmatic bronchitis "was confirmed by history of recurrent productive cough that had been present on most days during at least 3 consecutive months in more than 2 successive years."
- "Signs and symptoms were consistent with an acute bacterial infection of the lower respiratory tract and included a productive cough supported by <u>two or more</u> of the following:
    - Increased cough;
    - Increased sputum production;
    - Change in sputum color of consistency suggestive of an acute bacterial infection (e.g., change to yellow or green color; increased tenacity of sputum);
    - Increased chest discomfort and/or congestion;

- Development of, or increase in, dyspnea, rales, rhonchi, or cyanosis."

MO Comment: ***Based on the paper by Anthonisen[1], the criteria used allowed some patients to be enrolled that would have been predicted have no benefit from antimicrobial therapy (Winnipeg type III).***

The Case Report Form (CRF) records the patient's signs and symptoms from study day 1, on therapy (if this visit occurred), at the end of therapy, and at the follow-up visit. The patient's baseline chronic bronchitic signs and symptoms are also recorded in the CRF. Increases in cough and sputum and change in sputum character from the patient's baseline to study day 1 are documented in the CRF. However, documentation that there has been an increase in chest discomfort, congestion, dyspnea, rales, rhonchi, or cyanosis from baseline is not provided in the CRF (See Appendix 1).

- "A specimen of bronchopulmonary secretions was obtained within 48 hours prior to initiation of study drug therapy for culture and Gram stain; the pretreatment Gram stain qualified the specimen for microbiologic evaluation."

3.2.1.3.1.2 Exclusion Criteria

The exclusion criteria defined in the original protocol and in the study report are identical. Noteworthy exclusion criteria are listed below (Volume 212 of 322, pages 026-027):

- "Acute infection considered mild in severity that did not require antimicrobial therapy."
- "Radiographic evidence of pneumonia, active tuberculosis, or present tumor involving the lung."
- "Any infection that necessitated the use of a concomitant antibiotic or a parenteral antibiotic therapy."
- "Treatment with a systemic antibiotic within 7 days prior to study drug administration or treatment with a long-acting injectable antibiotic (e.g. penicillin G benzathine) within 30 days prior to study drug administration."
- "Treatment with an investigational drug within 4 weeks prior to study drug administration."
- "Treatment with azithromycin within 2 weeks prior to study drug administration."
- "Receiving systemic steroids in a dose of > 10 mg per day of prednisone (or the equivalent)."
- "Previous treatment in the current study."
- "Currently receiving or likely to require other concomitant oral or systemic antimicrobial therapy or any other investigational agent during the period between the Pre-

[1] Anthonisen NR, Manfreda J, Warren CPW et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987; 106:196-204.

Therapy Visit (initial presentation to office/clinic) and the Follow-Up Visit (7 to 14 days post treatment)."

MO Comment: ***Of note the Exclusion Criteria did not specifically exclude a patient from entering this study if they had been been previously enrolled in another cefditoren pivoxil study.***

3.2.1.3.2 Procedures

3.2.1.3.2.1 Summary of Study Procedures and Timing of Visits

Study procedures and timing of study visits are summarized in Table 3.

Table 3. Summary of Study Procedures. (modified from Applicant Table 9.5a., Volume 312 of 322, page 033)

Study Procedure	Pretreatment	During Treatment	Posttreatment**		Unscheduled Visit
	Pre-Therapy Visit Study Day 1*	Telephone Contact On-Therapy Visit+ Study Day 3 to 5	Post-Therapy Visit (Within 48 hours after last dose)	Follow-Up Visit (7 to 14 days after last dose)	
Informed Consent	X				
Medical History	X				
Physical Examination	X		X	X	X#
Signs/Symptoms	X	X	X	X	X
Vital Signs	X	X	X	X	X#
Chest X-Ray	X				
Lower Respiratory Tract Culture	X	X$	X@	X@	X#
Laboratory Tests***	X	X	X		X#
Dispense Medication	X				
Evaluate Study Drug Compliance		X+	X		
Adverse Event Assessment		X+	X	X	X
Assess Clinical Response to Therapy			X	X	

* Study Day 1 was the day the first dose was administered.
** Patients who were prematurely discontinued from the study drug therapy were to complete Post-Therapy and Follow-Up Visit evaluations. Patients who were clinical failures were not required to return for the Follow-Up Visit.
*** Hematology and Coagulation, Chemistry, Urinalysis, Urine Pregnancy Test
$ If clinically indicated and culturable material was available.
@ If culturable material was available.
+ Telephone contact to assess patient's status and schedule the On-Therapy Visit if clinically indicated. If an On-Therapy Visit was clinically indicated, all procedures were to be performed.
# If deemed necessary.

3.2.1.3.2.2 Assessment of Clinical Signs and Symptoms (Volume 214 of 322, pages 026-027)

Clinical signs and symptoms were assessed at each visit according to the following 11 criteria:

1. Sputum appearance

   Absent (None-Not applicable pretreatment)

Mucoid	(Clear mucous material with egg white appearance that may have contained isolated flecks or traces of pus)
Mucopurulent	(Mucoid material with many thick opaque purulent areas, ≤1/2 pus)
Purulent	(Almost uniform yellow or green thick opaque material with the appearance of pus, > 1/2 pus)

2. Blood in sputum? Yes or no

3. Amount of sputum produced in 24 hours
   - ≤ 1 tablespoon
   - 1-2 tablespoons
   - 2-4 tablespoons
   - 1/4 cup

4. Cough

Absent	(None)
Mild	(Not enough to interfere with normal activities)
Moderate	(Interfered with normal activities or sleep to some degree)
Severe	(Caused considerable interference with normal activities or sleep)

5. Cough frequency in 24-hour interval

6. Dyspnea

Absent	(None)
Mild	(Not enough to interfere with normal activities)
Moderate	(Interfered with normal activities to some degree)
Severe	(Prevented normal activities)

7. Rales	Absent or present
8. Rhonchi	Absent or present
9. Wheezes	Absent or present
10. Cyanosis	Absent or present
11. Fever	Absent or present (≥ 100.4°F [oral] or ≥ 101.2°F [tympanic])

3.2.1.3.2.3 Culture and Susceptibility Testing (Volume 212 of 322, pages 035-036)

The procedures described regarding microbiologic specimens stated that a specimen of bronchopulmonary secretions was obtained within 48 hours prior to the initiation of study drug therapy for Gram stain, culture and susceptibility testing. The investigator was to perform a Gram stain to qualify the specimen. The specimen was considered adequate for bacterial culture and to enroll the patient in the study if it contained > 25 WBC per field and < 10 squamous epithelial cells at 100x magnification. The investigator had the option of obtaining a second specimen if the Gram stain from the first was not adequate; however, if the investigator was still unable to obtain an adequate specimen, the patient was not to be enrolled in the study.

Although patients could be enrolled based on clinical evidence of AECB and a qualifying Gram stain at the investigator site, all sputum material was forwarded to [redacted] for confirmatory Gram stain, culture and susceptibility determination of pathogens.

MO Comment: ***Because of discrepancies in the investigator and central laboratory readings on Gram stains observed in a sampling of CRFs reviewed by the MO, the MO requested further detailed information on the instructions that had been given to the investigators regarding Gram stain preparation and the manner in which specimens were submitted to the central lab. In the Applicant's Fax of June 13, 2000 they stated that:***

> ***"Clinical sites were instructed to prepare two Gram stain slides for each sputum specimen. The slides were air dried. One slide was sent with the culture swab to [redacted] for staining and evaluation. The person processing and reading the Gram slide at the clinical sites varied by site. Depending on the expertise of the individual site, it may have been the investigator or a member of his staff or, in some cases, the slide was sent to a nearby laboratory. The investigators entered their Gram stain assessments on the case report form. The [redacted] assessment was part of the laboratory database and was used when determining the evaluability of the microbiologic data. The purpose of the slide processed by the clinical site was to evaluate if the specimen was suitable to forward to [redacted] for culture."(See Appendix 2)***

Additional instructions from the investigator manual and a presentation by Dr. Paul Oefinger during investigator meetings were received in a June 26, 2000 Fax from the Applicant. Specific instructions regarding the manner in which Gram stains were to be made included(See Appendix 3):

- ***"Use sterile swab supplied by [redacted] to sample purulent material in specimen"***
- ***"Spread evenly on two slides supplied by [redacted]"***
- ***"Air dry slides"***
- ***"Place one in transport packet for stain at central laboratory"***

Although one would expect the investigator's and central lab's gram stain readings to be in agreement, given the manner in which they were made, they were frequently discordant; the central lab read pre-therapy gram stains from 166 of 618 (CEF97-005: 181 of 903) patients as inadequate. The MO believes that the Gram stain read by the central lab was more accurate than the one read at investigator sites and the one that should be used to determine evaluability because the central laboratory was a CLIA certified laboratory and certification was not required at the Investigators' facilities.

3.2.1.3.3 Evaluability Criteria

3.2.1.3.3.1 Intent-to-Treat (Volume 212 of 322, pages 060-061)

The original protocol and study report defined the Intent-to-Treat population as "all patients who were enrolled in the study and had at least one causative respiratory pathogen isolated at pretreatment were included in the intent-to-treat data set. Patients who did not return for a particular visit or did not have a particular procedure performed were included in the analyses as treatment failures."

The study report defines causative respiratory pathogens as: "*H. influenzae, H. parainfluenzae, M. catarrhalis, S. pneumoniae, S. aureus,* and *S. pyogenes*, and any organism >3+ and not defined as normal flora" (Volume 312 of 322, page 035).

MO Comment: ***This population would more exactly be defined as Modified Intent-to-Treat.***

Given that patients with chronic bronchitis are frequently colonized with common respiratory pathogens, the requirement that sputum cultures be positive for a "respiratory pathogen," for a patient to be included in the MITT population, without first requiring that the sputum be defined as a "good" (>25 WBC and <10 squamous epithelial cells per field at 100x magnification) specimen is illogical.

To validate the Applicant's data base, the MO reviewed, in a blinded manner, 90 CRFs from each of the pivotal studies. The MO determined that two patients in CEF97-003 and two patients in CEF97-005 did not meet the inclusion criteria for adequate gram stain at investigator site (or at central lab) as defined by the Applicant. In addition, two patients in CEF97-003 had identical responses for sputum appearance, sputum volume, cough severity and cough frequency on the pre-exacerbation and study day 1 information sheets. An increase in signs/symptoms and a "good" Gram stain were required for enrollment on the study. These inclusion criteria are essential to the diagnosis of AECB. Based on the MO's findings in the random sampling, an estimated 2% - 4% of patients were inappropriately enrolled in each study and included in the MITT populations. Therefore, the MO has also required the following for patients to be included in the MITT population:

- ***Two or more of the following signs and symptoms (defined in inclusion criteria):***
  - ***Increased cough***
  - ***Increased sputum production***
  - ***Change in sputum color of consistency suggestive of an acute bacterial infection (e.g., change to***

yellow or green color; increased tenacity of sputum)
- ***Increased chest discomfort and/or congestion***
- ***Development of, or increase in, dyspnea, rales, rhonchi, or cyanosis.***

- ***Gram stain at central lab read as "good" (>25 WBC and <10 squamous epithelial cells per field at 100x magnification)***

For the MO's primary analyses, the MO will consider only patients with the target respiratory pathogens defined in the Applicant's original protocol (H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus, S. pneumoniae, and S. pyogenes) as qualifying for inclusion in the MITT population.

3.2.1.3.3.2 Clinically Evaluable Population

The Clinical Evaluability criteria as stated in the original protocol were (Volume 214 of 322, pages 044-045):

"The following criteria must be met for a patient to be evaluable for clinical efficacy analysis:

- The diagnosis of acute bacterial exacerbation of chronic bronchitis or chronic asthmatic bronchitis was sufficiently supported by clinical signs and symptoms.
- The pretreatment x-ray findings did not demonstrate pneumonia, active tuberculosis, or present tumor involving the lung.
- The pretreatment bronchopulmonary specimen for routine bacterial culture was obtained within 48 hours prior to initiation of study drug therapy and at least one target pathogen was isolated.
- To be evaluable as a clinical failure, the patient must have received at least three consecutive days of study drug therapy.
- At least 80% of the scheduled medication was taken.
- No other systemic antimicrobial agent was taken during the Follow-Up Visit unless the patient was considered a study treatment failure.
- A clinical evaluation was made at the Follow-Up Visit, unless the patient was a "clinical failure" at the Post-Therapy Visit in which case the patient will also be considered a "clinical failure" at the Follow-Up Visit.

Patients who received additional antimicrobials for the current infection will be considered evaluable if the patient received at least three consecutive days of study drug. The patient will be considered a "clinical failure" at the Follow-Up Visit. If a

patient prematurely discontinued from study drug therapy due to lack of efficacy or due to an adverse event possibly, probably or definitely related to study drug, a clinical response of "clinical failure" will be assigned if the patient did not have a clinical evaluation made at the Follow-Up Visit.".

The criteria presented in the study report are essentially the same with the following exceptions (Volume 212 of 322, pages 058-059):

- The first bulleted statement above has been replaced by the statement, "the patients pretreatment (within 4 days prior to the start of study drug) signs and symptoms included at least cough and sputum production."
- The timing of collection of the bronchopulmonary specimen has been changed to "within 4 days prior to the initiation of study drug therapy and at least one causative respiratory pathogen was isolated"
- The statement excluding other systemic antimicrobials has been changed to "no more than one oral dose of another systemic antimicrobial agent that was known to have activity against lower respiratory tract pathogens was taken during the period from the start of study drug to the Follow-Up Visit (at least 5 days after the end of treatment), unless the patient was considered a study treatment failure."

MO Comment: ***The subtle change to the criterion regarding required clinical signs and symptoms would allow patients with chronic bronchitis, but not necessarily an acute exacerbation, to be considered evaluable. This issue is resolved in the MO analysis by the requirement for signs and symptoms to be met in order to be included in the MO's MITT population.***

The criteria regarding required pathogens on the bronchopulmonary specimen has also changed. In the protocol "target pathogens" are defined as H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus, S. pneumoniae, or S. pyogenes (Volume 214 of 322, page 042). Although not stated in the study report, review of the Applicant's data revealed that patients with H. parahaemolyticus, K. pneumoniae, P. mirabilis, and S agalctiae were also considered evaluable in the Applicant's clinical and microbiologic analyses.

The clinical evaluability criteria presented in the study report include the following two additional criteria (Volume 212 of 322, page 059):

- "The study treatment blind was not broken prior to a clinical evaluation."
- "In order to be considered clinically evaluable at the Post Therapy Visit (2 days before to 4 days after the end of treatment), a clinical evaluation was made at the Post-Therapy Visit, unless the patient was a "clinical failure" prior to this visit, in which case the patient was also considered to be a "clinical failure" at the Post-Therapy Visit."

In addition, in the study report the Applicant also defined a population as clinically "evaluable with variation." This population included patients that the Applicant considered to have "minor deviations from the protocol." The following are the Applicant's reasons for categorization as "evaluable with variation" [FAX June 26, 2000 (Decision tree analyses for all clinical studies), page19. See Appendix 4]:

#	Defined
- 201	"Admission criteria not met"
- 203	"Mistiming of visit"
- 303	"Received an oral dose of another antimicrobial agent after the start of treatment"
- 304	"Received another antimicrobial agent pretreatment"
- 305	"Received an oral dose of another antimicrobial agent before the start of treatment"

MO Comment: ***The MO agrees with reason 201 given that certain minor protocol deviations, such as β-lactam allergy, should not make a patient unevaluable if they have entered and completed the study. The MO also agrees with reason 203, given the short half-life of cefditoren, so long as the Follow-Up Visit occurred at least 5 days after completion of study drug and not more than 21 days after the completion of study drug. Reasons 303, 304, and 305 are problematic in that the MO suspects patients falling into these categories might better be considered treatment failures or unevaluable; however since only one patient in each study (CEF-97-003 and CEF-97-005) fell into these categories the MO will not further pursue this issue.***

3.2.1.3.3.3 Microbiologically Evaluable Population

The Microbiologic Evaluability criteria as stated in the original protocol were (Volume 214 of 322, page 045):

"The following criteria must be met for a patient to be evaluable for microbiologic efficacy analysis:

- The patient is clinically evaluable.
- A specimen of bronchopulmonary secretions for routine bacterial culture was obtained or no culturable material was available at the Follow-Up Visit, unless the microbiologic response at the Post-Therapy Visit was 'persistence' in which case the microbiologic response at the Follow-Up Visit will also be 'persistence.'

  Patients who received additional antimicrobials for the current infection will be considered evaluable if the patient received at least three consecutive days of study drug, a microbiologic response of 'persistence' will be assigned at the Follow-Up Visit. If a patient prematurely discontinued from study drug therapy due to lack of efficacy or due to and adverse event possibly, probably or definitely related to study drug, a microbiologic response of 'persistence' will be assigned if the patient did not have a microbiologic evaluation made at the Follow-Up Visit."

The microbiologic evaluability criteria defined in the study report are similar, but also include the following statement defining evaluability at the Post-Therapy Visit (Volume 212 of 322, page 060):

> "In order to be considered microbiologically evaluable at the Post-Therapy Visit (2 days before to 4 days after the end of treatment), a specimen of bronchopulmonary secretions for routine bacterial culture was obtained or no culturable material was available at the Post-Therapy Visit, unless the microbiologic response prior to this visit was 'persistence,' in which case the microbiologic response at the Post-Therapy Visit was also 'persistence.'"

In addition, in the study report the Applicant also defined a population as microbiologically "evaluable with variation." This population included patients that the Applicant considered to have "minor deviations from the protocol." The following are the Applicant's reasons for categorization as "evaluable with variation" [FAX June 26, 2000 (Decision tree analyses for all clinical studies), page19. See Appendix 4]:

#	Defined
201	"Admission criteria not met"
203	"Mistiming of visit"
303	"Received an oral dose of another antimicrobial agent after the start of treatment"

- 304 "Received another antimicrobial agent pretreatment"
- 305 "Received an oral dose of another antimicrobial agent before the start of treatment"
- 405 "Pre-therapy gram stain result at central lab not adequate"

MO Comment: ***For MO comments regarding reasons 201, 203, 303, 304, and 305 please see prior MO comment under clinical "evaluable with variation" section.***

The MO does not agree with "evaluable with variation" reason 405, "pre-therapy gram stain at central lab not adequate." As previously noted in the MO Comment in Section 3.2.1.3.2.3 Culture and Susceptibility Testing, the gram stain performed at investigator sites may be unreliable due to the potential for it to be performed and read by poorly qualified individuals. The gram stain performed by the central lab was described by the Applicant as the one on which evaluability decisions were to be made and is more likely to have been performed and read by qualified individuals. As previously noted the MO required the gram stain at the central lab to be "good" in order for the patient to be included in the MO's MITT analyses and thus also in the MO's Evaluable analyses.

A summary of TAP versus the MO evaluability criteria is provided in Table 4.

Table 4. TAP versus MO Evaluability Criteria

	TAP	MO
TAP "All" Or MO "ITT"	• Patient received at least one dose of study drug.	• Patient received at least one dose of study drug.
TAP "ITT" Or MO "MITT"	• Meets criteria for "All" population • Had pre-treatment sputum culture with at least one causative respiratory pathogen (*H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus, S. pneumoniae, S. pyogenes,* and any organism ≥3+ and not defined as normal flora)	• Meets criteria for "ITT" population • Had pre-treatment sputum culture with at least one protocol defined respiratory pathogen (*H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus, S. pneumoniae, or S. pyogenes)* • Had "good" pre-treatment sputum gram stain at central lab • Had at least two pre-treatment signs and symptoms of AECB that were greater than the patients baseline values
Clinically Evaluable	• Meets criteria for "ITT" poulation • At pre-treatment the patient's signs and symptoms included cough and sputum production • x-ray was negative for pneumonia, active tuberculosis, and lung tumor • sputum specimen obtained within 4 days prior to start of drug therapy and at least one causative respiratory pathogen was isolated (*H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus, S. pneumoniae, S. pyogenes, H parahhaemolyticus, K. pneumoniae, P. mirabilis, and S agalctiae)* • Took at least 80% of study drug, unless patient was considered a clinical failure in which case they were still evaluable if they had taken at least 3 consecutive days of study drug • No more than one oral dose of another systemic antimicrobial, that was known to have activity against lower respiratory tract pathogens, was taken during study period • Blind was not broken • To be evaluable for Post-Therapy analyses, had a visit between 2 days before to 4 days after the end of treatment (unless earlier treatment failure-then carried forward as evaluable failure) • To be evaluable for Follow-Up analyses, had a visit at least 5 days after the end of treatment (unless	• Meets criteria for "MITT" population • At pre-treatment the patient's x-ray was negative for pneumonia, active tuberculosis, and lung tumor • sputum specimen obtained within 4 days prior to start of drug therapy • Took at least 80% of study drug, unless patient was considered a clinical failure in which case they were still evaluable if they had taken at least 3 consecutive days of study drug • No more than one oral dose of another systemic antimicrobial, that was known to have activity against lower respiratory tract pathogens, was taken during study period • Blind was not broken • To be evaluable for Post-Therapy analyses, had a visit between 2 days before to 4 days after the end of treatment (unless earlier treatment failure-then carried forward as evaluable failure) • To be evaluable for Follow-Up analyses, had a visit at least 5 days after the end of treatment (unless earlier treatment failure-then carried forward as evaluable failure) • If a patient prematurely discontinued from study due to an adverse event considered possibly, probably, or definitely related to study drug, a clinical response of "clinical failure" was assigned and the patient was

	earlier treatment failure-then carried forward as evaluable failure) • If a patient prematurely discontinued from study due to an adverse event considered possibly, probably, or definitely related to study drug, a clinical response of "clinical failure" was assigned and the patient was considered evaluable	considered evaluable
Micro-Biologically Evaluable	• Patient was clinically evaluable • To be evaluable for Post-Therapy analyses had a sputum specimen obtained or no culturable material was evaluable at Post-Therapy visit between 2 days before to 4 days after the end of treatment (unless earlier micro response of "persistence," then carried forward as "persistence") • To be evaluable for Follow-Up analyses had a sputum specimen obtained or no culturable material was evaluable at Follow-Up visit, at least 5 days after the end of treatment (unless earlier micro response of "persistence," then carried forward as "persistence") • If a patient prematurely discontinued from study due to an adverse event considered possibly, probably, or definitely related to study drug, a micro response of "persistence" was assigned and the patient was considered evaluable • If a patient was a clinical failure at a particular visit, a micro response of "persistence" was assigned in the abscense of a repeat sputum at that and subsequent visits and the patient was considered evaluable	• Patient was clinically evaluable • To be evaluable for Post-Therapy analyses had a sputum specimen obtained or no culturable material was evaluable at Post-Therapy visit between 2 days before to 4 days after the end of treatment (unless earlier micro response of "persistence," then carried forward as "persistence") • To be evaluable for Follow-Up analyses had a sputum specimen obtained or no culturable material was evaluable at Follow-Up visit, at least 5 days after the end of treatment (unless earlier micro response of "persistence," then carried forward as "persistence") • If a patient prematurely discontinued from study due to an adverse event considered possibly, probably, or definitely related to study drug, a micro response of "persistence" was assigned and the patient was considered evaluable • If a patient was a clinical failure at a particular visit, a micro response of "persistence" was assigned in the abscense of a repeat sputum at that and subsequent visits and the patient was considered evaluable

3.2.1.3.3.4 Safety

All patients who received at least one dose of study drug were included in the safety analysis.

3.2.1.3.4 Endpoints (Volume 212 0f 322, page 004)

In summary, "the primary efficacy endpoints used to summarize clinical and microbiological outcomes at Post-Therapy and Follow-Up Visits included:

- Clinical Cure Rate (percentage of patients who had a clinical response of "cure").

- Patient Microbiologic Cure Rate (percentage of patients for whom all pretreatment causative respiratory pathogens were eradicated).
- Pathogen Eradication Rate (percentage of pathogens that were eradicated for each pretreatment causative respiratory pathogen and combined over all pretreatment causative respiratory pathogens).

The secondary efficacy endpoints included changes in clinical signs and symptoms from the Pre-Therapy Visit to the Post-Therapy and Follow-Up Visits.

Safety endpoints included adverse events, clinical laboratory variables, and vital signs."

3.2.1.3.4.1 Clinical Response Definitions

The investigator compared the clinical signs and symptoms at the Post-Therapy and Follow-Up Visits to those obtained at the Pre-Therapy Visit and classified the clinical response for each patient using to the following definitions (Volume 212 of 322, page 041 and Volume 214 of 322, pages 041-042):

Clinical Cure	**The pretreatment signs and symptoms of the infection resolved or returned to preinfection baseline.**
Clinical Improvement	**The pretreatment signs and symptoms of the infection improved but did not return to preinfection baseline.**
Clinical Failure	**(Applicable for the Post-Therapy Visit only) The pretreatment signs and symptoms of the infection did not improve or worsened.**

Clinical Relapse	**(Applicable for the Follow-Up Visit only) The signs and symptoms of the infection improved at the Post-Therapy Visit and worsened or reappeared during the Follow-Up period.**
Indeterminate	**Clinical response to therapy could not be determined.**

The Applicant states that they reassessed clinical responses of "Clinical Improvement" as either "Clinical Cure" or "Clinical Failure" in order to analyze the data according to the July 1998 FDA draft guidance for AECB. The reassessments were based on the following definitions (Volume 212 of 322, page 042):

Clinical Cure	**The pretreatment signs and symptoms of the infection resolved, returned to preinfection baseline, or improved without the need for additional antimicrobial therapy for the treatment of the acute exacerbation of chronic bronchitis.**
Clinical Failure	**(Applicable for the Post-Therapy Visit only) The pretreatment signs and symptoms of the infection improved with the need for additional antimicrobial therapy for treatment of acute exacerbation of chronic bronchitis, did not improve, or worsened.**
Clinical Relapse	**(Applicable for the Follow-Up Visit only) The signs and symptoms of the infection improved without the need for additional antimicrobial therapy at the Post-Therapy Visit and worsened or reappeared during the Follow-Up period.**
Indeterminate	**Clinical response to therapy could not be determined.**

MO Comment: ***In validating the random samples of CRFs for each pivotal study (90 per study), in a blinded manner, the MO disagreed with the Applicant's clinical outcomes at the Follow-Up visit for three patients in study CEF97-003 and seven patients in study CEF97-005. The MO considered these patients failures due to persistence or increase in signs and symptoms from study day 1. Therefore, the MO has required that at the Follow-Up visit ALL signs and symptoms be improved in comparison to the enrollment visit for a patient to be categorized as a "clinical cure" in the MO's efficacy analyses. Of note this criteria is less strict than those recommended in the FDA Guidance for Industry for AECB or IDSA guidelines, which recommend that all signs and symptoms return to the patient's pre-exacerbation baseline before a patient is called a clinical cure. At the Post-Therapy Visit the MO has required only that all signs and symptoms be no worse or improved in comparison to the enrollment visit.***

Although the Applicant states they have reassigned patients classified as "Clinical Improvement" according to the July 1998 FDA draft guidance for AECB, the definitions provided above are not in accordance with this guidance. The guidance states "The category of clinical improvement should be avoided for purposes of drug development. If it is unclear whether the patient meets either the cure or failure category, further follow-up should be planned. If the improved symptoms persist and additional antimicrobials are added, then the patient is a failure. If the patient returns to baseline condition without additional antimicrobial therapy, the patient should be classified as a cure." This study was not designed to follow improved patients beyond the Follow-Up Visit to determine if they returned to baseline and a strict interpretation of the guidance would therefore result in all "improved" patients being considered

"failures." Since this study was designed and begun prior to issuance of the AECB guidance the Reviewer believes it would be unreasonable to consider all "improved" patients as "failures." Therefore, the MO has required that at the Follow-Up visit ALL signs and symptoms be improved in comparison to the enrollment visit and that no additional antimicrobial therapy was administered for an "improved" patient to be recategorized as a "clinical cure" in the MO's efficacy analyses (TAP only required that the investigator called the patient "improved" and that no further antimicrobials were given – see Appendix 4, page 16 of 51).

The July 1998 draft guidance for AECB also states that there is no distinction between failure and relapse. Therefore, patients classified as "clinical failure" and "clinical relapse" by the Applicant are all considered as "clinical failures" in the Reviewer's analyses.

3.2.1.3.4.2 Microbiologic Response Definitions

The Applicant assigned a microbiologic response at Post-Therapy and Follow-Up for each respiratory pathogen identified at in the Pre-Therapy Visit bronchopulmonary specimen using the following definitions (Volume 212 of 322, page 043):

Eradication	**Absence of the initial pathogen or the infection cleared to such an extent that no culturable material was available.**
Persistence	**(Applicable for the Post-Therapy Visit only) Presence of the initial pathogen.**
Recurrence	**(Applicable for the Follow-Up Visit only) Absence of the initial pathogen or the infection cleared to such an extent that no culturable material was available at the Post-Therapy Visit with reappearance of the same pathogen during the follow-up period.**
Reinfection	**Presence of a new pathogen.**
Indeterminate	**Microbiologic response to therapy could not be assigned.**

Although not defined above under "persistence," the statistical analysis plan also defined the following additional guideline for patients with "presumed persistence" (Volume 212 of 322, page 054):

Persistence	**If a patient was considered a clinical failure at a particular visit, in the absence of a repeat sputum culture, a microbiologic response of "persistence" was assigned at that and subsequent visits.**

MO Comment: ***Patients with persistence, presumed persistence, and recurrence are placed into the category "failed eradication" in the Reviewer's analyses.***

3.2.1.3.5 Statistical Considerations

3.2.1.3.5.1 Determination of Sample Size (Volume 212 of 322, page 050)

According to the Applicant, "A sample size of 140 evaluable patients per treatment group would have at least 80% power to meet the criteria that the absolute value of the lower bound of a two-sided 95% confidence interval for the difference in clinical cure rates between the cefditoren 400 mg BID treatment group and the cefuroxime axetil 250 mg BID treatment group did not exceed 10%. This calculation assumed that the true clinical cure rates of both treatment groups were 90%. Assuming an evaluability rate of at least 50%, it was calculated that approximately 840 patients would be needed for enrollment to obtain 420 evaluable patients (140 patients per treatment group)."

3.2.1.3.5.2 Demographic and Baseline Variables (Volume 212 of 322, page 045-046)

The Applicant analyzed and summarized demographic and baseline characteristics for all patients and for patients who were clinically evaluable at the Follow-Up Visit, as follows:

"The quantitative demographic variables, age, height and weight, were analyzed for differences among the treatment groups using a one-way analysis of variance (ANOVA) with treatment group as the factor. The categorical demographic variables, gender and race, were analyzed for differences among the treatment using a chi-square test.

The baseline characteristics of diagnosis, smoking status, alcohol consumption, and the number of lower respiratory tract infections (LRTIs) treated within the past 12 months were analyzed for differences among the treatment groups by a chi-square test. The baseline characteristics of infection status and clinical condition were compared among the treatment groups using Cochran-Mantel-Haenszel methodology for ordered response variables.

The percentage of patients with a history of each underlying pulmonary condition were compared among the treatment groups using a chi-square test.

The severity of clinical signs and symptoms at baseline was compared among the treatment groups using Cochran-Mantel-Haenszel methodology for ordered response variables."

3.2.1.3.5.3 Efficacy Analyses

3.2.1.3.5.3.1 Primary Endpoints (Volume 212 of 322, page 046-047)

According to the Applicant clinical cure rate, pathogen eradication rate and patient microbiologic cure rate were summarized by treatment group and analyzed with Fisher's exact test to perform pairwise comparisons of the treatment groups at the Post-Therapy Visit and at the Follow-Up Visit. Binomial 95% confidence intervals, based on normal approximation for the binomial distribution, were also calculated for the difference between each pair of treatment groups for the clinical cure rate and patient microbiologic cure rate. The Applicant then applied the following boundaries to establish equivalence:

If the observed cure rate for the better of two treatments is:	Then the lower bound of the confidence interval should not exceed:
>90%	10%
>80 and <90%	15%
<80%	20%

In addition the Applicant states "clinical cure rate and patient microbiologic cure rate were also summarized by investigator, age, race, gender, infection status, clinical condition, diagnosis, smoking status, alcohol consumption, inhaler use, steroid use, compliance, treatment duration, pretreatment pathogens, weight, and the number of lower respiratory tract infections treated with antimicrobials within the past year. Investigator by treatment interaction was tested using logistic regression. Investigative sites enrolling fewer than 6 patients were combined in this analysis. The Cochran-Mantel-Haenszel test was used as a supportive analysis to assess treatment group differences with the other factors as strata. The Breslow-Day test was used to assess the homogeneity of treatment group differences across the strata. The pathogen eradication rates were summarized for *S. pneumoniae* by pretreatment susceptibility to penicillin; for *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis* and *S. aureus* by penicillinase production; and for *S. aureus* by pretreatment susceptibility to penicillin and oxacillin."

MO Comment: ***Although the Applicant stated the primary comparison for efficacy would be between the cefditoren pivoxil 400 mg arm and the***

comparator arm, the Applicant has made multiple comparisons between the three treatment arms without apply an appropriate statistical adjustment for multiple comparisons (potentially inflating the Type I Error). In the Reviewer's efficacy analyses the alpha will be reduced to 2.5% to account for multiple comparisons between the three treatment arms.

Statistical Reviewer's Comments: The 1992 points to consider document has been phased out at FDA. Testing the equivalence of treatment difference with respect to the efficacy variables were assessed by computing a two-tailed 97.5% confidence interval (maintaining the overall significance level at 0.05) of the difference in reponse rates and using a delta of 10%.

3.2.1.3.5.3.2 Secondary Endpoints (Volume 212 of 322, page 047)

Pairwise comparisons of the treatment groups for each clinical sign/symptom from the Pre-Therapy Visit to the Post-Therapy Visit and to the Follow-Up Visit were made with respect to the percentage of patients who demonstrated either complete resolution or improvement in the sign/symptom using Fisher's exact test.

3.2.1.3.5.4 Safety Analyses

3.2.1.3.5.4.1 Adverse Events (Volume 212 of 322, page 048)

Adverse event incidence rates were calculated and summarized by treatment group during treatment (from the first day of study drug to 3 days after the last dose of study drug) and post-treatment (at least 4 days after the last dose of study drug) by COSTART term and body system. A patient with two or more adverse events with the same COSTART term was counted only once for that term. In addition, a patient who reported two or more different COSTART terms within the same body system was counted only once in the body system total, and a patient with two or more adverse events in different body systems was counted only once in the overall total. Incidence rates were summarized by treatment group for:

- all adverse events
- adverse events considered possibly, probably, or definitely study drug-related
- by severity (patients who had more than one designation of severity for the same event were counted only once based on the most severe occurrence of that event; patients with multiple events of varying severity

were counted only once in the overall total based on their most severe event)
- by relationship to drug (in the tabulations of adverse events by relationship to study drug, patients with multiple events of varying relation to study drug were counted only once in the overall total based on their most related event, i.e., greatest degree of relationship to study drug.
- by patient group (gender, race, age)

Fisher's exact test was used to assess treatment group differences in adverse event incidence rates.

Subgroup analyses of adverse event rates during treatment, adjusted for age, gender and race, were performed using Cochran-Mantel-Haenszel methodology.

3.2.1.3.5.4.2 Laboratory Data (Volume 212 of 322, page 049)
Per the Applicant, "mean baseline values were analyzed for differences among the treatment groups using a one-way ANOVA, with treatment group as the factor, for each laboratory test variable. Pairwise comparisons between the treatment groups of the mean change from baseline to the Post-Therapy Visit were based on contrasts within the one-way ANOVA. All negative (positive) changes from baseline represented decreases (increases) from baseline.

The laboratory data were summarized by shift tables which presented the number of patients who changed from low, normal, or high values at pretreatment with respect to the investigator's normal range to low, normal, or high values after treatment. The percentage of patients who had a change in the direction of concern was summarized by treatment group and analyzed with Fisher's exact test to perform pairwise comparisons between treatment groups. A change in the direction of concern was defined as either a change from a low or normal value pretreatment to a high value after treatment or as a change from a high or normal value pretreatment to a low value after treatment, depending on the laboratory test variable."

3.2.1.3.5.4.3 Vital Signs (Volume 212 of 322, page 049)
According to the Applicant "mean baseline values were analyzed for differences among the treatment groups using a one-way ANOVA, with treatment group as the factor, for sitting blood pressure, pulse rate, temperature, respiratory

rate, and body weight. Pairwise comparisons between the treatment groups of the mean change from baseline to the Post-Therapy and Follow-Up Visits were based on contrasts within the one-way ANOVA."

3.2.1.4 Study Results

3.2.1.4.1 Evaluability

A total of 60 principal investigators, at 59 US sites participated in this study. Data from two investigative sites (DeAbate, #4637 and Mathew, #13004) were excluded from all analyses, by the Applicant, because "important study procedures were not being followed, rendering the information gathered unreliable" (efficacy and safety data for these two investigators were presented separately by the Applicant). Exclusion of patients from these two sites resulted in a loss of data for 225 patients, leaving a total of 618 patients in the ITT population for analysis. Table 5. provides a summary of investigators, investigator sites, and distribution of enrolled and evaluable patients by site and treatment arm (modified from Table 6a., Volume 212 of 322, page 019).

Table 5. Distribution of Enrolled Patients by Investigator According to the Applicant

Investigator (Invest. #) Location	Treatment Group					
	@CDTR-PI 200 mg		@CDTR-PI 400 mg		+CXM-AX 250 mg	
	!Enrolled	^Eval(%)	!Enrolled	^Eval(%)	!Enrolled	^Eval(%)
Abrahams (#9535) Morgantown, WV	0	-	0	-	1	0 (0)
Albery (#9536) Phoenix, AZ	0	-	1	1 (100)	0	-
Armbruster (#12955) Tucson, AZ	1	1 (100)	1	1 (100)	0	-
Aven (#12992) Arlington Heights, IL	0	-	1	0 (0)	1	1 (100)
Bacon (#12997) Newark, DE	1	0 (0)	1	0 (0)	1	1 (100)
Baker (#7757) Portland, OR	4	3 (75)	5	5 (100)	5	5 (100)
Bensch (#7758) Stockton, CA	8	7 (88)	9	6 (67)	9	9 (100)
Bettis (#12571) Edmonds, WA	12	9 (75)	12	9 (75)	13	10 (77)
B. Christensen (#12971) Savannah, GA	4	3 (75)	4	3 (75)	4	3 (75)
S. Christensen (#13235) Salt Lake City, UT	9	9 (100)	9	6 (67)	9	8 (89)
Cohen (# 13536) San Diego, CA	5	5 (100)	5	2 (40)	5	5 (100)
*Coodley (#12970) Portland, OR	0	-	1	0 (0)	0	-