The following table summarizes the sponsor's eradication numbers for the atypical pathogens requested in the NDA:

Eradication Rates for Identified Atypical Pathogens
Clinically and Bacteriologically Evaluable Subjects*
Treated with Trovafloxacin
Community Acquired Pneumonia

Pathogen	Study number, N				Totals
	Study 110 N = 64	**Study 111** N = 68	**Study 112** N = 53	**Study 134** N = 56	N = 241
Mycoplasma pneumoniae	8/8	9/10	4/5	16/17	37/40
Chlamydia pneumoniae	2/4	2/2	1/1	5/6	10/13
Legionella pneumophila#	2/2	7/10	--	--	9/12

* A subject could have more than one pathogen at baseline.
\# Sponsor actually shows 10/13, but this includes one subject (111-56070186) who was not assessable.

This table does not include study 102; that study included an additional two *Chlamydia pneumoniae* patients who were treated with 200 mg of Trovan for 10 days and were evaluable at EOS; both of these were considered cured.

The above numbers do not take completely into account the definitions of a 'positive test' as provided in the package inserts to the assays utilized in this NDA. The following table examines these numbers more carefully by the precise serologic basis for the diagnosis of each organism in each study:

Clinically and Bacteriologically Evaluable Subjects
Treated with Trovafloxacin
Community Acquired Pneumonia
Atypical pathogens according to method of diagnosis

	# Cures / Total Clinical & Micro Evaluable at EOS					TOTALS
Pathogen and method of diagnosis	Study 110 N = 64	Study 111 N = 68	Study 112 N = 53	Study 134 N = 56	Study 102 N = 16	N = 241
Mycoplasma pneumoniae						**36/40 (90%)**
4X rise in IgG and IgM	2/2	1/2		3/3		6/7
4X rise in IgG	5/5	8/8	5/6	12/13		30/32
4X rise in IgM	0/1					0/1
Legionella pneumophila [$]						**6/11 (55%)**
4X rise in IFA to 1:128*	1/2	3/4				4/6
4X rise in IFA*	1/2	4/7		1/1		6/10
Urinary antigen ⊕		0/1				0/1
Chlamydia pneumoniae [#]						**9/14 (64%)**
4X rise in IgG and IgM						
4X rise in IgG [@]	1/4	2/2	1/1	0/2		4/9
4X rise in IgM				3/3	2/2	5/5

footnotes:

$ Excludes two patients included in sponsor's final tally of N=13:
111-56070186, who was 'Not Assessable' (received 2 weeks of erythromycin at EOT)
111-56271159, who did not have a fourfold rise in titer documented and had *Streptococcus pneumoniae* bacteremia

* These two categories are not additive; those whose rose at least to 1:128 are a subset of those who had any sort of 4X rise in titer.

Of the 19 patients listed by the sponsor in table 5.3a of each study, the following were excluded to arrive at the denominator of 14:
102-50170247 (Not Evaluable)
110-50460304 (Not Evaluable)
111-51690166 (Not Assessable)
111-51900151 (Not Assessable)
134-52520242 (diagnosed on basis of isolated IgA rise only)

@ Includes two patients (110-52240357 and 110-55340447) who had single IgG titers of 1:1024 in the presence of a fourfold rise in IgA.

The efficacy of the comparator regimens for Atypical CAP is shown in the following table:

Clinically and Bacteriologically Evaluable Patients at EOS
Combined Comparator Regimens
CAP due to atypical agents

	# Cures / Total Clinical & Micro Evaluable at EOS					TOTALS
Pathogen and method of diagnosis	Study 110 N = 64	Study 113 N = 68	Study 112 N = 53	Study 134 N = 56	Study 102 N = 16	N = 241
Mycoplasma pneumoniae	cipro + amp	ctx-ceftin ± erythro	amox ± erythro	clari	ceclor	**23/27 (85%)**
4X rise in IgG and IgM	1/1			3/4	1/1	5/6
4X rise in IgG	6/7		1/2	11/12		18/21
4X rise in IgM						
Legionella pneumophila						**12/13 (92%)**
4X rise in IFA to 1:128*	2/2	3/3				5/5
4X rise in IFA*	3/3	6/6				9/9
Urinary antigen ⊕	1/1	2/3				3/4
Chlamydia pneumoniae#						**17/21 (81%)**
4X rise in IgG and IgM	3/3		1/1		0/1	4/5
4X rise in IgG	4/4	4/4		3/4		11/12
4X rise in IgM		1/3		1/1		2/4

footnotes:

* These two categories are not additive; those whose IFA rose at least to 1:128 are a subset of those who had any sort of 4X rise in titer.

Excludes five patients diagnosed by sponsor on basis of IgA alone: 110-52240319; 110-55560118; 112-55560921; 134-50320097; and 111-51900001

Medical Officer comments:

1. **Regarding *Mycoplasma pneumoniae***: from the above table, it would appear that there is an adequate number of *Mycoplasma* patients to warrant inclusion of this organism in the CAP indication for trovafloxacin. Any of the three seroconversion definitions are acceptable for the diagnosis of this infection, as they conform to the diagnostic kit product labeling.

2. **Regarding *Chlamydia pneumoniae***: the numbers are substantially lower than those accrued for *Mycoplasma*. Although greater than 10, the total of 14 accumulated cases falls short of the '10% rule', which would in this case require a minimum of 28 (10% of 283) accumulated subjects in order to consider approval of this pathogen for this indication. It should also be kept in mind that the diagnostic test kit utilized in this assay is not FDA approved; the labeling provided by the sponsor states that it is "For Investigational Use Only". Although this fact does not preclude the use of this test in the context of a clinical study filed as part of an NDA, the sponsor must present evidence to support the contention that this test is acceptable for use in this situation.

(It is readily acknowledged that there are no currently FDA-approved diagnostic tests for this pathogen.)

(It is also acknowledged that several recent product approvals for this organism were based on this same serological test, so it is reasonable to allow its use in this NDA as well.)

The eradication rate of 64% for trovafloxacin in *Chlamydia pneumoniae* pneumonia compares with an overall eradication rate of 81% (17/21) for the various comparator regimens utilized in these five studies.

Other factors to consider might include the efficacy of trovafloxacin against other Chlamydial infections in other requested indications (NGU, PID) in which other species of Chlamydia may be present; the in vitro activity of the drug against the pathogen, and what regulatory precident exists.

The NDA for trovafloxacin also requests approval for nongonococcal urethritis due to *Chlamydia trachomatis*. Although this indication may appear to be approvable, it is difficult extrapolating the results of such studies to the CAP situation (different organisms and distinctly different anatomical sites).

Although there is not standardized in vitro susceptibility testing methodology for the chlamydiae, trovafloxacin is reported to have an MIC_{90} of 0.25 μg/mL against *C. pneumoniae* (identical to the reported MIC_{90} for *Mycoplasma pneumoniae*).

As mentioned above, recent product approvals for Sparfloxacin, Levofloxacin, azithromycin IV, and Grepafloxacin have all considered Chlamydia pneumoniae as a pathogen in community acquired pneumonia. The following regulatory actions were taken:

Recent regulatory experience with Chlamydia pneumoniae

Drug	Number eradicated / total evaluable	Number clincally & microbiologically evaluable for CAP indication (all pathogens)	Approval granted?
Sparfloxacin	19/22 (86%) eradicated	197	✓
Levofloxacin*	154/161 (96%)	370	✓
Azithromycin IV	19/21 (90%)	?	✓

* The number of patients in this application is extremely high because the case definition allowed for the inclusion of subjects who did not necessarily have serologic evidence of active infection.

During discussions with the sponsor regarding the CAP indication, the issue of relatively small numbers of evaluable *Chlamydia* patients was mentioned. The sponsor requested that the medical officer take into consideration a completed CAP study (154-136) that had been compiled but not submitted to the NDA. A Final Study Report for this study was provided to this medical officer during the final stages of the CAP review. This study was a randomized, double-blind, double-dummy trial comparing 7-10 days of trovafloxacin at a dose of 200 mg qd with high-dose amoxicillin at a dose of 1000 mg tid. The design and conduct of the study appeared to be similar to that of the CAP studies previously reviewed. During the conduct of this multicenter, international study, a total of 22 patients were enrolled in the trovafloxacin arm who were considered by the sponsor to have demonstrated serologic evidence of infection with *C. pneumoniae*. The medical officer reviewed these cases (although the CRFs and patient profiles were not available) to apply the same serologic criteria delineated above (i.e., a change in serum IgA titer alone was not sufficient for diagnosis). This resulted in the following additional cases:

Chlamydia pneumoniae cases reported from non-NDA CAP study 154-136 Trovafloxacin-treated patients

SPID#	(b)(4)	Evaluable at EOS?	Clinical response	Coinfection?
50340810		yes	cure	
50340814		no	--	--
50340833		yes	cure	
52120286		--	--	--
54130315		yes	cure	Strep pneumoniae (blood)
55550389		no	--	--
55550403		--	--	--
55700017		yes	cure	
55900096		yes	cure	
55900269		yes	cure	
55960297		yes	failure	Mycoplasma pneumoniae
56270334		yes	failure	
56270381		yes	cure	
56290425		yes	failure	
59920167		--	--	--
59920170		yes	failure	Strep pneumoniae
60430325		yes	cure	
63570191		yes	cure	
64160943		--	--	--
65480885		yes	cure	Staph aureus
65570904		--	--	--
65690905		yes	cure	Mycoplasma pneumoniae
65880410		yes	cure	

Thus it can be seen that there are an additional 15 evaluable *Chlamydia pneumoniae* patients (diagnosed serologically by IgG titer rise only) in Study 136 who were treated with trovafloxacin and considered evaluable at the EOS timepoint. Of these 15 subjects, 11 (73%) were clinical cures. If these numbers are added to those tallied above (9/14), the total becomes 20/29 (69%) cured at EOS following 7-10 days of trovafloxacin therapy.

It should be noted that the medical officer only tallied 'cures' in the numerator (as indicated in the table for NDA studies 102, 110, 111, 112, and 134). If 'improvements' are also counted as a favorable outcome, an additional two patients should be added to the numerator, making the total 22/29 or 76%. This should be compared with efficacy rates of 86% for sparfloxacin and 90% for IV azithromycin. (Because of the inadequate case definition used in the levofloxacin review, this will be disregarded.)

The total of 29 accrued patients with Chlamydia pneumoniae appears to fulfill the '10% rule'; however, if one is to include these additional patients from study 136 to achieve a denominator of 29, this should also raise the total number of microbiologically evaluable subjects from which the 10% is calculated. If one disregards this for the moment and simply considers the relative efficacy rates, it remains troublesome that the trovafloxacin efficacy rate was only 76% while that of the various comparators in studies 102, 110, 111, 112, and 134 was a cumulative 17/21 or 81% *cures* (not cure + improved). It is also of note that in the European study 136, the sponsor tallies 22/26 (85%) *cures* for the amoxicillin arm.

These numbers, however, are too small to say with any statistical confidence that they are NOT equivalent

Regarding *Legionella pneumophila*: once again, the sponsor has accrued a relatively small number of such patients. Using the broadest definition of infection, the sponsor has provided clinical outcomes on eleven evaluable patients infected with this organism. Since the '10% rule' in this situation would indicate that somewhere in the order of 28 patients need to be studied in order grant such labeling for trovafloxacin, it would appear that there is insufficient information here to warrant approval. *Legionella pneumophila* is a respiratory tract pathogen which, along with the Gram-negative bacilli, is associated with severe disease. In a study of passive surveillance data on 3254 patients diagnosed with legionellosis from 1980 to 1989, Marston and colleagues [Arch Int Med 154(21): 2417-22, Nov 94] at the CDC found an overall mortality rate of 24%. Similar to Gram-negative bacillary pneumonia, this study found that risk of death was higher in patients with cancer, renal disease, immunosuppression, or advanced age. Thus, for legionellosis as well as Gram negative bacillary CAP, the need to study adequate numbers of patients is essential.

Although the small numbers make statements of equivalence problematic, the number of evaluable cures at end-of-study for the trovafloxacin arm (6/11 or 55%) appears to be less than that for the combined comparators (12/13 or 92%). The sponsor's tally, as provided in table CAP.X.2a (Attachment 1), shows 8 cures out of 13 subjects, or 62%.

The following table shows recent regulatory experience in granting the indication of CAP due to Legionella pneumophila:

Recent regulatory experience with Legionella pneumophila

Drug	Number eradicated / total evaluable	Number clincally & microbiologically evaluable for CAP indication (all pathogens)	Approval granted?
Sparfloxacin	not requested		
Levofloxacin	7/10	370	✓
Azithromycin IV	13/16	??	✓
Grepafloxacin	8/9	96	NO

As can be seen from the above table, approval has been granted for levofloxacin with relatively low numbers of patients. This fact was brought forward by the sponsor in the process of discussing the approvability of the CAP indication. This precedent notwithstanding, it is the opinion of this medical officer that given the gravity of community-acquired pneumonia due to *Legionella pneumophila*, it is unacceptable to grant approval on a total of eleven evaluable patients, only six of which were deemed to be clinically cured at the end of study, particularly when the same double-blinded, double-dummy studies accrued a similar number of cases in the comparator arms (13) and 12 of these patients were cured.

The sponsor then requested that the legionellosis cases from a recently-completed European study (154-136), which had not been submitted to the NDA, be considered in addition to those tallied above. A Final Study Report for this study was provided to this medical officer during the final stages of the CAP review. This study was a randomized, double-blind, double-dummy trial comparing 7-10 days of trovafloxacin at a dose of 200 mg qd with high-dose amoxicillin at a dose of 1000 mg tid. The design and conduct of the study appeared to be similar to that of the CAP studies previously reviewed. During the conduct of this multicenter, international study, a total of 6 cases of legionellosis were accrued at five separate study sites. The following is a compilation of the *Legionella* cases from study 154-136:

Legionella cases from non-NDA CAP study 154-136

PID# (b)(4)	Evaluable at EOS?	Clinical response
trovafloxacin patients		
5627-0372	yes	cure
5627-0381	yes	cure
5627-0433	yes	cure
5992-0166	yes	cure
6043-0322	yes	cure
6116-0081	yes	cure
amoxicillin patients		
5573-0022	yes	failure (NB: also showed 4X rise in *Chlamydia pneumoniae* IgG)
5627-0336	yes	cure
5627-0382	yes	failure (NB: also showed 4X rise in *Chlamydia pneumoniae* IgM)
5627-0435	yes	failure
6043-0321	yes	cure
6043-0326	yes	cure

According to the sponsor, the serologies done in this European study were performed in a manner identical to those done for the previously-reviewed CAP studies: the Zeus test kit was utilized, and was performed by the contracted central laboratory service, Scicor. Recall from the previous discussion of this test that the definition of a positive IgG rise, according to the product labeling, was:

> *"a four-fold rise in titer between serum taken during the acute phase of illness (within the first week) and convalescent phase (3 to 6 weeks after onset). The rise in titer must be to ≥ 1:128 to be considered as evidence of recent infection."*

Using this definition, the last two trovafloxacin subjects listed above cannot be diagnosed as having Legionella as the cause of their acute illness. In the previously reviewed CAP studies, there were no serum samples obtained at days 9-10, so these two patients would never have been called positive in those studies to begin with. Furthermore, one of these two (6116-0081) also had Strep pneumo grown from a sputum sample.

If these four additional cases are added to the tally for all the CAP studies submitted to the NDA, the resulting numbers are 10/15 (67%) clinical cures at EOS. This number remains well below the 28 called for by the '10% rule' of the Points to Consider document, but approximates the 16 that were tallied in the NDA submission for intravenous azithromycin, another Pfizer product recently reviewed and subsequently approved by FDA.

(The efficacy of amoxicillin in this study was interesting. If one discounts the two patients who had evidence of infection with *Chlamydia pneumoniae*, amoxicillin in this study cured 3/4 *Legionella* patients. If one uses the serologic criteria applied above, the one evaluable amoxicillin patient was cured.)

Because these numbers are so small, it cannot be determined with any reasonable degree of confidence that 10/15 is equivalent to [or inferior to] 13/16 (the numbers tallied in the IV azithromycin NDA). (NB: since these azithromycin numbers include 'cures' plus 'improvements' in the numerator of 13, it should be pointed out that there were two trovafloxacin subjects called 'improvement' who were not tallied in the above table, which is entitled "# Cures/total…". The appropriate comparison is 12/15 for trovafloxacin, to 13/16 for IV azithromycin.)

When discussing this issue with the entire Trovan review team, it was pointed out by Dr. Alivasatos that there were a few cases of legionellosis in the two Nosocomial Pneumonia studies. The study reports from studies 154-113 and 154-137 were examined and the following trovafloxacin-treated subjects were found: (NB: these studies both utilized IV doses of 300 mg qd, followed by 200 mg PO when changed to oral therapy.)

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Synopses of trovafloxacin-treated subjects in nosocomial pneumonia studies diagnosed with Legionellosis

113-53860200 61 female received 5 days of Trovan for nosocomial pneumonia. Initial sputum showed an adequate Gram stain for culture; a pathogen (Haemophilus parainfluenzae) was isolated. Trovan was discontinued due to an adverse event (Hallucinations) that was considered study drug-related. Therapy changed to ampicillin. Patient called an evaluable cure at EOS by sponsor. Serologies showed a fourfold rise in Legionella titer from .

Comment: although the protocol allowed patients with at least five days on study drug to be considered evaluable, it is difficult to ascribe the clinical outcome to drug exposure here. Most references call for diagnosed cases of legionellosis to be treated with 21 days of erythromycin.

113-53860249 65 year old male ex-smoker s/p CABG, admitted to ICU for management of nosocomial pneumonia. Initial sputum called 'normal respiratory flora' on CRF but the following organisms all described ~~as~~ pathogens: H. influenzae, Klebsiella oxytoca, and Staphylococcus aureus. Received 3 days of IV therapy, then changed to PO trovafloxacin to complete 12 days of therapy. Serologies noted to show rise in Legionella titers from Called an evaluable cure at EOS.

Comment: aside from the issue of the diagnostic test needing to rise to or above 1:128, this case appears to be appropriate for inclusion. The issue of sputum co-pathogens has been discussed previously.

137-59450136 62 year old Australian male ex-smoker with underlying hepatic disease (baseline SGOT/PT 149/102) admitted to this open study and randomized to Trovan. Given 8 days IV therapy (at 300 mg qd), then switched to PO to complete a total of 23 days of Trovan therapy. Initial sputum showed normal flora; initial CXR read as "minimal atelectasis left base, lungs otherwise clear". No followup CXR obtained. Called evaluable cure at EOS.

Comment: unimpressive radiograph would make eligibility for entry into study questionable. Nonetheless, patient has serology consistent with diagnosis of legionellosis, and has no other sputum pathogens. Rationale for duration of therapy not provided by investigator.

137-59780398 48 year old German male smoker admitted to ICU for treatment of nosocomial pneumonia. Initial sputum culture grew Acinetobacter baumannii and Escherichia coli. Patient treated with 300 mg IV Trovan for XX days then changed to 200 mg orally to complete 10-day course. Called evaluable EOS cure by sponsor; presumed eradication of A. baumannii, E. coli, and Legionella pneumophila based on a baseline serology showing a titer of 1:1024 and a negative urinary antigen. The convalescent , and thus the diagnosis of legionellosis was made on a >4X drop in titer.

Comment: a drop in titer is not considered diagnostic. This is not mentioned in the product labeling nor is it discussed in the standard Infectious Disease reference text (Mandell's Principles and Practice of Infectious Diseases). A single titer of such magnitude may be used as an indicator of acute infection. However, since this antibody test may give false positives in the presence of concomitant gram negative bacillary disease, it is quite possible that the serology may represent a false positive in this case. If the sputum had not shown other pathogens, this case would have been considered acceptable for inclusion.

The medical officer will consider patients 113-53860249 and 137-59450136 as acceptable additions to the tally for cases of legionellosis for the CAP indication. Since both of these subjects are cures, this brings the total tally for this organism in this indication to 14 cured or improved out of 17 evaluable cases.

The medical officer is asked to make a recommendation concerning approval of this indication not on the basis of 'adequate' numbers of evaluable subjects and a comparable rate of clinical response, but on the basis of precedent within the agency (not all of it consistent with the tenants of the Points to Consider document) and in the face of an apparently similar response rate (12/13) in the pooled comparator arms (many of whom were not treated with the gold standard comparator, erythromycin).

Since the *in vitro* activity of trovafloxacin against *Legionella pneumophila* indicates that this drug should be clinically efficacious in this infection, and since the number of accumulated evaluable cases (17) is at least as large as the number of cases described in the medical officer's review of the IV azithromycin NDA (16), and since the efficacy was similar (82% for trovafloxacin and 81% for IV azithromycin), it is the opinion of this medical officer that the CAP indication in the INDICATIONS AND USAGE section of the product labeling should include *Legionella pneumophila*. However, since patients treated with the nosocomial pneumonia dosage (300 mg IV qd) were included in this analysis, the DOSAGE AND ADMINISTRATION section will need to reflect this fact.

C. Recommended action

The medical officer recommends inclusion of the following language in the INDICATIONS AND USAGE section of the Trovan® product labeling:

"**Community acquired pneumonia** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Moraxella catarrhalis*, *Legionella pneumophila*, or *Chlamydia pneumoniae.*"

Under DOSAGE AND ADMINISTRATION:

The column heading "Infection/location and type" should include an entry entitled "Community Acquired Pneumonia";

The column heading "Daily unit dose and route of administration" should read "200 mg oral or 200 mg IV followed by 200 mg oral";

The column heading "Total duration" should read "7-14 days".

(Please see attached addendum to this conclusion.)

/S/

Philip E. Coyne, Jr., MD
Medical Officer
HFD-590

concurrence: HFD-590/DivDir/Goldberger /S/
HFD-590/TL/Leis[illegible] /S/

cc:
original NDA 20-759, 20-760
HFD-590
HFD-590/DepDivDir/Albrecht
HFD-590/MO/Alivasatos
HFD-590/Pharm/Ellis
HFD-590/Biopharm/Colangelo
HFD-590/Stats/Silliman
HFD-590/CSO/

Medical officer addendum to review of Community Acquired Pneumonia

Date: 16 December 1997

The sponsor has taken issue with the stated intention of the agency to deny the inclusion of *Klebsiella pneumoniae* as a listed organism in the CAP indication. An electronic communication was received on 12 December which read, in part, as follows:

Klebsiella pneumoniae

--Across nosocomial pneumonia and CAP, 18/24 *Klebsiella pneumoniae* isolates were successfully treated. Eight were from Nosocomial pneumonia with 4 clinical successes, while 16 were from double blind, randomized, controlled trials in CAP, with 14/16 successfully treated (EOS). From p. 407 of the medical officer's review of levofloxacin, it appears that there were only 6 clinically evaluable subjects with this isolate, several of which appear to have originated in the non-comparative trial #M92-075. The medical officer did not recommend approval for this organism, however, there is a reference on p. 427 to additional data from supportive trials in an 'addendum', which is not available to Pfizer.

--The only other recent reference to *Klebsiella pneumoniae* is the levofloxacin package insert clinical trials section, where a figure of 10 isolates, all successfully treated, is cited.

--We regard this as a 'level playing field issue'. The primary source of *the Klebsiella pneumoniae* for the levofloxacin label was from an unblinded study (vs. ceftriaxone/cefuroxime) which was justly criticized by the medical officer because of this and other deficiencies. The only further data seem to have come from a non-comparative study, as reported in the clinical trials section. The trovafloxacin CAP data on *Klebsiella pneumoniae* are from much more robust double blind studies. More *Klebsiella pneumoniae* were studied in the trovafloxacin CAP program, by a considerable margin than in the levofloxacin program.

--The agency may fairly take the position that it has made an egregious error in the levofloxacin label and will not include organisms on such flimsy data in the future. However, the trovafloxacin data are much more robust and much greater in quantity. To not include *Klebsiella pneumoniae* would be unfair.

Medical officer comments:

1. The sponsor's total of 16 patients in combined CAP clinical studies apparently includes 5 from study 136, which was not submitted formally as part of the NDA. (The matter of this study and its applicability to NDA 20-759/760 was not raised until final discussions were underway regarding the approvability of the CAP indication. The final study report for 136 was submitted to the NDA on 3 December 1997, two weeks before the PDUFA due date.) It was agreed, in previous discussions with the sponsor, to consider this European study only in the context of discussions regarding the approval of atypical agents of CAP, specifically *Legionella*. (The sponsor made the appropriate observation that legionellosis is a respiratory disease which occurs as small epidemics, and the only way to capture cases in the context of an NDA-driven clinical trial is by being lucky enough to catch an epidemic while conducting the trial. Study 136 did so.) If the study in its entirety is to be taken into consideration, in order to consider additional organisms such as *Klebsiella pneumoniae*, it would most likely be considered as a major clinical amendment to the NDA, mandating an additional 3 months of review time.

2. The sponsor's total minus study 136 would then be 11. In looking over Tables 5.3.1 and 5.4.1 for each study report of the 5 studies (102, 110, 111, 112, and 134) in the electronic NDA submission, and noting that only the 200 mg arm of study 102 is of interest here, the following numbers are found:

Clinical Response at End Of Study
Clinically and Bacteriologically Evaluable CAP patients with *Klebsiella pneumoniae*
(Source: table 5.4.1, studies 102, 110, 111, 112 and 134)

Study	number clinical successes/number evaluable
102	4/4
110	1/1
111	2/2
112	1/1
134	0/1
Total	8/9

Clinical Response by Baseline Pathogen
Clinically Evaluable CAP patients with *Klebsiella pneumoniae*
(Source: table 5.3.1, studies 102, 110, 111, 112 and 134)

Study	number clinical successes/number evaluable
102	6/6
110	1/1
111	2/2
112	0/1
134	0/1
Total	9/11

The sponsor was asked to explain the difference in these numbers. Specifically:

- how the one *Klebsiella pneumoniae* patient is study 112 could be a failure in the analysis presented in table 5.3.1, and a success in table 5.4.1; and
- how an additional two patients in study 102 were included as successes in table 5.3.1, as compared to table 5.4.1.

The sponsor (Dr. Debra Williams, phone conversation 17 Dec 97) that the patient in study 112 was a clinical failure but had a f/u sputum culture done which did not grow *Klebsiella pneumoniae*; therefore this patient was counted as a bacteriologic eradication even though a clinical failure. The two patient difference in study 102 was due to the fact that two patients were considered (by the sponsor) to have persistent productive cough at EOS, and therefore a f/u sputum should have been obtained. They were considered to have clinically successful outcomes, and were so counted in table 5.3.1; however, they were considered bacteriologically unevaluable on this basis and thus do not appear in table 5.4.1.

It would seem reasonable to allow inclusion of the additional two patients from study 102 who were considered clinical cures, even though they had some residual productive cough (not at all unusual in this population of patients, many of whom have underlying chronic bronchitis). Thus, the 9/11 numbers are accepted.

Is it reasonable to take the *Klebsiella pneumoniae* patients from Dr. Alivasatos' review of the nosocomial pneumonia indication (studies 113 and 137) into consideration? The two diseases are pathophysiologically quite similar; the basis for their distinction as separate clinical entities is, to a large degree, based on the difference in microbial etiologies between the two clinical syndromes. There are differences in the patient populations (nosocomial pneumonia patients generally being more ill, with higher degree of comorbidity) that make the application of CAP clinical trial subjects to consideration of the nosocomial pneumonia indication quite problematic. However, it would seem reasonable to apply the results of nosocomial pneumonia studies to the setting of the CAP indication.

According to Dr. Alivasatos, by her analysis there were a total of 4/8 *Klebsiella pneumoniae* patients in studies 113 and 137 who were clinically and bacteriologically cured at EOS.

If these additional patients are added to the 9/11 noted above from cumulative tables 5.3.1 of the CAP studies, the total *Klebsiella pneumoniae* experience then becomes 13/19, for an eradication rate of 69%.

The medical officer considers these revised numbers to be adequate, and an eradication rate of nearly 70% to be acceptable for this indication, particularly in light of the higher rate in those patients from the actual CAP studies. Therefore, the inclusion of *Klebsiella pneumoniae* to the organism list for CAP is acceptable.

In the same electronic communication of 12 December, the sponsor also took issue with the division's stance that *Staph aureus* had not been studied in adequate numbers to warrant inclusion in the CAP indication:

Staphylococcus aureus

--In Nosocomial pneumonia alone, there were 21 *S. aureus* isolated and 14 successfully clinically treated at EOS (67%) in the two trovafloxacin protocols, results equal to the overall outcomes. The figures for the comparators are 10/21 (48%). The somewhat better efficacy with trovafloxacin is not surprising since trovafloxacin is at least an order of magnitude more active than ciprofloxacin or ceftazidime. In CAP, 18/18 were successfully treated in the trovafloxacin arms.

--*S. aureus* was included in the levofloxacin CAP indication, apparently on the basis of successful outcomes in 15/17 cases, as reported in the clinical trials section of the package insert. As noted below however, the levofloxacin CAP studies were very weak in key design areas (one was unblinded and the other non-comparative).

--*S. aureus* was included in the recent Zosyn label for Nosocomial pneumonia apparently on the sole basis of organisms acquired in the single pivotal trial vs. ceftazidime in which 155 patients were randomized to Zosyn. From the medical officer's review (p. 75), it is apparent that approval was gained on the basis of 13 successful courses out of 16 isolates.

--We regard this as a 'level playing field' issue. We believe we have studied adequate numbers that are at least equal to those studied in recent approvals. We do not believe the sponsors of levofloxacin and Zosyn were required to specially 'prove the validity' of this particular isolate as Pfizer was, for an organism that is generally regarded as a pathogen in these infections.

Medical officer comment:

The sponsor is correct in noting that the levofloxacin NDA was approved for *Staph aureus* in CAP on the basis of 15 successes out of 17 cases. It should also be noted that there was no analysis done in the levofloxacin review that looked specifically at how many of those 17 cases were instances in which *Staph aureus* was the sole pathogen identified. Thus, the sponsor makes a valid observation. The total number of *Staph aureus* isolates, again from the two tables noted above for the five studies submitted for the CAP indication in the NDA, were as follows:

Clinical Response at End Of Study
Clinically and Bacteriologically Evaluable CAP patients with *Staphylococcus aureus*
(Source: table 5.4.1, studies 102, 110, 111, 112 and 134)

Study	number clinical successes/number evaluable
102	0/0
110	3/3
111	3/3
112	1/1
134	7/7
Total	14/14

Clinical Response by Baseline Pathogen
Clinically Evaluable CAP patients with *Staphylococcus aureus*
(Source: table 5.3.1, studies 102, 110, 111, 112 and 134)

Study	number clinical successes/number evaluable
102	0/0
110	3/3
111	3/3
112	1/1
134	7/7
Total	14/14

In the text of the sponsor's comments, the number 18 is used for the number of *Staph aureus* CAP isolates. The difference between 14 and 18 is the 4 *Staph aureus* isolates from study 136. It is the opinion of this medical officer that full consideration of this study, in the absence of its designation as a 'major amendment', sets an undesirable precedent which would allow a sponsor to submit additional last-minute clinical information with no impact on the PDUFA-mandated action date.

The sponsor's claim that their numbers (14/14) are somehow qualitatively 'better' than the 15/17 successes in the levofloxacin CAP indication, because of differences in study design, is difficult to factor into consideration.

Returning to the discussion in the overall CAP conclusions in this Medical Officer's review, the following observations were made:

> *Staphylococcus aureus*: the revised numbers bring the total from 6 to 14 patients, of whom 100% were reported to have a successful outcome (actually 12 cures out of 14). Again, these numbers fall in between the absolute '10' and the number mandated by the 'rule of 10%' (i.e., 28). The MIC_{90} for this organism is less than that for *S. pneumoniae*, but one dilution greater than that of *Klebsiella pneumoniae*. If this organism appeared to be approvable for a related respiratory indication, this would be of interest.... CAP caused by *S. aureus* is adequately severe to warrant the absolute requirement that it be studied in adequate numbers (i.e., 10% or 28 in this situation) such that efficacy has been undisputably demonstrated rather than partially inferred from other respiratory indications. There were a total of 8 trovafloxacin-treated CAP patients who had *S.aureus* isolated as the sole respiratory pathogen; of these, 6 were cured and 2 were improved.

Since the recommendation has now been made that the nosocomial pneumonia indication should include *Staph aureus* (see Dr. Alivasatos' review), the situation now exists in which a closely related respiratory indication (in fact, one in which the patients are, in general, sicker) has been approved for this pathogen. This medical officer thus concludes that it is reasonable to allow the inclusion of this organism to the list of pathogens for the CAP indication as well. The overall numbers (14/14) are essentially identical to those of the levofloxacin review (15/17); this conclusion is based neither on a judgment of the 'quality' of these numbers based on underlying trial design, nor on the basis of additional numbers from a study that was never submitted as a major clinical amendment to this NDA.

Philip E. Coyne, Jr., MD
Medical Officer
HFD-590

concurrence: HFD-590/DivDir/Goldberger
HFD-590/TL/Leissa

NOV 4 1998

Medical Officer's Review of NDAs 20-759 and 20-760

Complicated Intra-abdominal Infections

1.1 NDAs : 20-759 (oral tablets) and 20-760 (injection)

1.2 Applicant identification
- 1.2.1 Pfizer Central Research
- 1.2.2 Address and telephone number:
  Eastern Point Road
  Groton, CT 06340

1.3 Submission/review dates
- 1.3.1 Date of submission : 27 December 1996
- 1.3.2 CDER stamp date : 30 December 1996
- 1.3.3 Date submission received by reviewer : 6 January 1997
- 1.3.4 Date review begun : 4 June 1998
- 1.3.5 Date review completed : 12 December 1997

1.4 Drug identification
- 1.4.1 Generic name : trovafloxacin mesylate (tablets)
  alatrofloxacin mesylate (solution for injection)
- 1.4.2 Proposed trade name : **TROVAN™**
- 1.4.3 Other names used during development: CP-99,219 (tablet)
  CP-116,517 (IV)

1.5 Pharmacologic Category : fluoronaphthyridone

1.6 Dosage form : See 1.1 above

1.7 Route of Administration : intravenous (20-760) and oral (20-759)

1.8 Proposed Indication & Usage section :

COMPLICATED INTRA-ABDOMINAL INFECTIONS, including post-surgical infections caused by *Escherichia coli, Bacteroides fragilis, Streptococcus viridans, Bacteroides thetaiotaomicron, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis, Streptococcus agalactiae, Streptococcus anginosus, Staphylococcus aureus, Beta Streptococcus* Group B, *Peptostreptococcus* species, *Prevotella* species, *Enterobacter* species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species or *Bacteroides* species.

1.9 Proposed Dosage and Administration section :

300 mg I.V. followed by 200 mg oral for a total of 7-14 days.

NOTE: Where the BernhardMod BT font is used in this document, this represents text copied from the applicant's submission.

1.10 Related Drugs : See 1.4.3 above.

1.11 Material Reviewed : NDAs and amendments

1.12 Regulatory Background

A) Anti-Infective Drug Products Approved For This Indication

The following products are approved for "**INTRA-ABDOMINAL INFECTIONS**" (NOTE: some labels specify "including peritonitis"):

amikacin, aztreonam, cefoperazone, cefotaxime, cefoxitin, ceftazidime, clindamycin, imipenem/cilastatin (PRIMAXIN®), metronidazole, mezlocillin, netilmicin, ticarcillin, ticarcillin/clavulanate (TIMENTIN®), tobramycin,

Piperacillin/tazobactam (ZOSYN) is approved for "**Appendicitis (complicated by rupture or abscess) and peritonitis** caused by piperacillin resistant, beta-lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragilis* group; *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, Or *B. vulgatus*. The individual members of this group were studied in less than 10 cases."

Parenteral ciprofloxacin (CIPRO) is approved for "**Complicated Intra-Abdominal Infections** (used in conjunction with metronidazole) caused by *E. coli, P. aeruginosa, P. mirabilis, K. pneumoniae*, or *B. fragilis*" at a dose of 400 mg q12 hrs.

****

Owing to the recent approval (1996) of meropenem (MERREM; NDA 50-706) for CIAI, the MO reviewed the original MOR. In piecing together the MERREM history, this MO noted the following highlights from the MOR:

In the original NDA submission (1993), clinical experience for CIAI included a single North American and three foreign studies:

- 3591US/0007 -- considered by the original MO as a single adequate and well-controlled study for complicated appendicitis - meropenem 1g q8h vs. clindamycin + tobramycin (double-blind study)
- 194660/0300
- 194660/0301
- 194660/0402

The original MO concluded that a confirmatory trial was needed for intra-abdominal/pelivc cavity infections. Submitted data from foreign studies were considered inadequate. Therefore, the indication was considered not approvable.

The MERREM resubmission consisted of three foreign, open-label studies (conducted between 1989-1991):

- 14660/0300 - meropenem 1g q8h vs. cefotaxime + metronidazole (Europe and S. Africa)
- 14660/0301 - meropenem 1g q8h vs. imipenem/cilastatin (Europe)
- 14660/0402 - same as 301 (Europe)

In the company's presentation of the data, they pooled data across studies.

As discussed in the original MOR, to be considered evaluable, the following criteria were used:

- Documentation that the operative site was evaluated.
- Follow-up ≥7 days post-therapy.
- For failure: Received a minimum of 48 hours of study drug.

The studies were designed with the end-of-therapy visit as the primary efficacy endpoint. However, since the original MO wanted a minimum of 7 days post-therapy follow-up to be considered evaluable, the FDA evaluable population dropped to 30%.

The MO concluded that MERREM was equivalent to Primaxin but inferior to cefotaxime/metronidazole. Furthermore, efficacy was considered too low (5/11) to include *E. faecalis* in the listing of approved pathogens in the INDICATIONS AND USAGE section. In addition to that shown above, the following labeling eventually was approved in 1996:

B) Regulatory Guidance

1992 DAIDP "Points to Consider" document (PTC)

The PTC states that for the treatment indication "complicated intra-abdominal infections" (CIAI):

- only a single study is needed
- only patients that require surgical intervention, including penetrating and blunt trauma should be studied.
- at least 80% of clinically evaluable patients should be microbiologicaly evaluable
- for an anaerobic claim, the drug product under review needs to establish effectiveness in either at least one other infection (with anaerobes) or establish in-vitro susceptibility and animal data effectiveness.

- need a reasonable mix of intra-abdominal infections – if not, a labeling restriction may be necessary
- it is expected for this indication to be granted, that efficacy also must be established in gynecologic infections at the same dosing and duration.
- tissue distribution studies are expected. (PK/PD)

IDSA/FDA Guidelines (*Clinical Infectious Diseases*; 15, Suppl. 1; Nov. 1992)

The guidelines make the following points about CIAI:

- Appropriate diseases for CIAI: where surgical intervention is needed (including percutaneous drainage). viscous perforation frequently resulting in peritonitis and/or abscess (including liver, pancreas, & spleen), periappendiceal abscess, perforated appendicitis, following emergency or elective operation with associated problems noted above.

- Inappropriate diseases for CIAI: diverticulitis, acute cholecystitis, non-operative management of acute appendicitis, Crohn's, ulcerative colitis (NOTE: w/o perforation), postoperative abdominal wound infections, spontaneous bacterial peritonitis, and CAPD-associated peritonitis perinephric infections, female genital tract infections, acute appendicitis, suppurative appendicitis

The IDSA/FDA Guidelines go on to comment on specific CIAIs:

- Acute gastric and duodenal perforations: if perforation occurs <24 hours prior to surgery, mostly gram-positive organisms and cultures only reflect intraluminal flora and therefore NOT appropriate for CIAI. However, if >24 hours, then gram-negative facultative and obligate anaerobes are present and culture results should correlate well with the isolation of this organism as a true pathogen.

- Traumatic perforations and transmural necrosis of the intestine: appropriate to include in CIAI study if surgery occurs >12 hours after perforation.

- Infections arising from the distal small bowel, appendix, and colon/rectum: need abscess or peritoneal fluid with WBCs and isolation of organisms from the infected site.

- Infections that occur following emergency or elective operation: constitute approx. 25% of intra-abdominal infections. May include resistant pathogens due to the failure of prophylaxis. Activity against resistant bugs (e.g., *P. aeruginosa* and *Enterobacteriaceae*) is important here.

The Guidelines discuss the following miscellaneous points:

- Parenteral therapy is usually continued until the patient is afebrile, WBC <12,500/mm^3, and return of bowel function - generally after a 7-day course.

- Infection must be documented at the time of surgery or during radiographically-directed drainage procedure.

- Patients should not be enrolled if the APACHE score >35

- Minimum total treatment duration (IV + PO) is typically 5 days; maximum is 14 days. If patients require >14 days of treatment, they should be considered failures. The minimum parenteral therapy is typically 3 days prior to switching to oral therapy.

- Patients who receive additional antimicrobial agents for nosocomial infections outside of the abdomen ≥5 days into the trial should be evaluated on the day on which therapy these agents are initiated. If there is no evidence of intra-abdominal sepsis at this time and there is no evidence of recurrent intra-abdominal infection during the subsequent clinical course, the patients should be considered clinically cured.

Clinical evaluability summarized (per IDSA/FDA Guidelines)

- Appropriate diagnosis (abscess, peritonitis, etc.) - diagnosed and treated via laparotomy or radiographically-directed drainage procedure.
- Survive >48 hours
- APACHE score <35 at entry
- For gastric & duodenal perforations: Need >24 hours since perforation prior to defining surgery
- For traumatic perforation, need >12 hours since perforation prior to defining surgery

Microbiological evaluability summarized (per IDSA/FDA Guidelines)

- Clinically evaluable AND
- (+) culture within 24 hours of defining surgery -- blood and/or site culture

Clinical outcomes summarized (per IDSA/FDA Guidelines):

Cure

- Minimum duration of therapy to be considered a cure is 5 days (first 3 days of therapy should be IV)
- To be evaluable for cure, the patient needs a valid 4-6 week follow-up visit after study entry

Failure

- additional surgical procedures needed
- treatment prolonged >14 days

- Any modification of therapy

2. Table of Contents: not applicable

3. Chemistry/Manufacturing Controls:

4. Animal Pharmacology/Toxicology:

CP-99,219 was found efficacious in a rat abscess model relative to control animals and comparable in effect with animals treated with clindamycin/gentamicin. (SOURCE: Onderdonk AB, BWH, Channing Labs; personal communication.) The preliminary data from this study are presented in the following table. This experimental model of intra-abdominal sepsis has been shown to consist of two phases: early peritonitis and abscess development in surviving recipients of a fecal inoculum. During the early, acute peritonitis stage, *Escherichia coli* and other Gram-negative organisms are numerically dominant and appear to be responsible for mortality. The second and more chronic stage of the disease, abscess formation, requires the presence of obligate anaerobes, such as *Bacteroides fragilis*. Quinolones, such as ciprofloxacin, do not prevent abscess formation when used alone in this animal model. Thus, the finding of only 2 of a possible 17 abscess formations in animals treated with CP-99,219 is further evidence suggesting the potential of this agent as sole treatment of intra-abdominal infections.

	Control	CP-99,219	Clindamycin-gentamicin
Mortality (%)	13/19 (68.4%)	1/18 (5.6%)	0/19 (0.0%)
Abscess (%)	6/6 (100%)	2/17 (12%)	3/19 (16%)
Organisms recovered	*E. coli* *Gr. D. Strept* *Lactobacillus* *C. perfringens* *B. fragilis* *Fusobacterium*	*E. coli* *Lactobacillus*	*E. coli* *Gr. D. Strept* *Lactobacillus*

Table : Preliminary data from rat abscess model treated with CP-99,219 (20 mg SC three times daily for 7 days), clindamycin (15 mg SC three times daily for 7 days) and gentamicin (2 mg IM three times daily for 7 days), or placebo (Control).

5. Microbiology:

The MIC_{90}s of trovafloxacin for pathogens commonly associated with intra-abdominal infections are listed in the following table:

Pathogen	MIC_{90} range (μg/mL)	median MIC_{90} (μg/mL)
AEROBES		
Gram (+)		
S. agalactiae	0.12-0.5	0.25
S. aureus (MSSA + MRSA)	1-8	2.0
viridans group streptococci	0.06-0.5	0.25
E. faecalis (vanc S)	0.25-8	2.0
E. faecalis (vanc R)	8-16	8.0
E. faecium (vanc S)	0.78-4	2.0
E. faecium (vanc R)	4-32	8.0
Gram (-)		
Acinetobacter baumanii	>8	>8
C. freundii	0.25-4	0.375
E. coli	<0.015-4	0.06
E. cloacae	0.05-2	1.6
K. pneumoniae	0.06-1	0.12
M. morganii	0.12-2	0.5
Proteus mirabilis (indole -)	0.12-4	0.5
Proteus vulgaris (indole +)	0.25-1	0.5
Providencia stuartii	0.5-2	2.0
P. aeruginosa	1->16	2.0
STRICT ANAEROBES		
B. fragilis group	0.5-2	1.0
B. fragilis	≤0.25-2	0.5
B. thetaiotaomicron	0.5-4	1.0
B ovatus	1-2	2.0
B. distasonsis	0.5-1	1.0
B. vulgatus	0.5-4	4.0
B. uniformis	2-4	4.0
Prevotella spp.	1-2	1.0
P. bivia	1-2	1.0
P. intermedia	1	1.0
P. melaninogenica	1-2	1.5
C. perfringens	0.12-0.25	0.25
Peptostreptococcus spp.	0.25-1	1.0
Fusobacterium spp.	0.5-2	1.0
F. nucleatum	0.25-0.5	0.375

6. Human Pharmacokinetics/Pharmacodynamics: See biopharm review.

The peak blood level (C_{max}) of alatrofloxacin at the 300 mg intravenous dose (trovafloxacin equivalent dose) used for intra-abdominal infections is 4.4 μg/mL with a half-life of 10.8 hours. The fluid/serum concentration ratio of trovafloxacin in peritoneal fluid after IV administration of 200 mg alatrofloxacin was 0.39. Mean tissue/serum concentration ratios for gynecologic tissues (ovary, uterus, myometrium, cervix and fallopian tubes) ranged after single or multiple doses of oral trovafloxacin 200 mg. Thus, based upon its pharmacokinetic profile, single daily intravenous doses of 300 mg alatrofloxacin will exceed the MIC_{90} values of pathogens commonly involved in intra-abdominal and acute pelvic infections.

7. Human Clinical Experience: not applicable

8. Clinical Studies:

8.1 Protocol Overview:

APPEARS THIS WAY
ON ORIGINAL

Study: 154-124

Protocol Title: A Randomized, Double-Blind, Multicenter Trial Assessing The Safety and Efficacy of Intravenous CP-116,517 (alatrofloxacin) Followed by Oral CP-99,219 (trovafloxacin) Compared to Intravenous Imipenem/Cilastatin (PRIMAXIN®) Followed by Oral Amoxicillin/Clavulanic Acid (AUGMENTIN®) for the Treatment Of Complicated Intra-Abdominal Infections

Study Dates: 12 April 1995 - 20 June 1996

APPEARS THIS WAY
ON ORIGINAL

Study objective : To compare the safety and efficacy of alatrofloxacin (intravenous prodrug) followed by oral trovafloxacin with the combination of intravenous imipenem/cilastatin followed by oral amoxicillin/clavulanic acid in the treatment of subjects with complicated intra-abdominal infections.

Subjects with suspected complicated intra-abdominal infections were randomized in a double-blind fashion to receive either a regimen of intravenous alatrofloxacin and oral trovafloxacin (300 mg/day intravenously followed by 200 mg/day orally for a maximum of 14 days of total therapy) or a combined regimen of imipenem/cilastatin (maximum dose of 1 gram intravenously every 8 hours) followed by amoxicillin/clavulanic acid (500 mg orally every 8 hours). Switching from parenteral to oral medication was to be determined by the investigator when oral intake had been re-established.

APPEARS THIS WAY
ON ORIGINAL

Adequacy of comparator:

PRIMAXIN® (imipenem/cilastatin) is FDA-approved in the INDICATIONS AND USAGE section for the treatment of:

APPEARS THIS WAY
ON ORIGINAL

MO Comment : PRIMAXIN® is an adequate comparator.

Although AUGMENTIN® is not FDA-approved for intraabdominal infections, the applicant argues:

> Amoxicillin/clavulanic acid is clinically accepted as follow-up oral therapy in the treatment of severe infections, in particular those involving β-lactamase producing organisms and anaerobic organisms responsible for intra-abdominal infections (e.g. *Bacteroides* sp.).[1,2]

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[1]Ball P, Watson T, Mehtar S. Amoxycillin and clavulanic acid in intra-abdominal and pelvic sepsis. *J Antimicrob Chemother* 1981; 7:441-444.

[2]Yashioka K, Youngs DJ, Keighley MR. A randomised prospective controlled study of ciprofloxacin with metronidazole *versus* amoxicillin/clavulanic acid with metronidazole in the treatment of intra-abdominal infection. *Infection* 1991; 19:25-29.

MO Comment : Pfizer's rationale to use AUGMENTIN® as the follow-up oral therapy to PRIMAXIN® is acceptable.

Sample size: A total of 300 subjects were to be enrolled in this study. Recruitment was to cease when 300 subjects had been enrolled, even if some centers had not reached their projected recruitment targets.

MO Comment : The applicant enrolled a total of 414 patients instead.

Noteworthy Inclusion Criteria :

1) Subjects who are found to have one of the following infections requiring anti-infective therapy and an operative procedure or percutaneous drainage. Subjects must have physical examination findings consistent with an intra-abdominal infection (e.g. signs of peritoneal irritation, mass) as well as systemic evidence of inflammation (for example, fever [body temperature ≥ 38.5 °C], WBC > 12,500 cells/mm^3, hypotension [systolic blood pressure < 90 mmHg], etc.). Physical findings may also include clinically-documented serosal inflammation and/or presence of localized or diffuse abdominal wall rigidity, mass, or ileus. Where appropriate, imaging studies may support signs and symptoms of an intra-abdominal infection.

- intra-abdominal abscesses
- bacterial peritonitis
- appendicitis with evidence of a perforation or abscess; duration of symptoms ≥ 24 hours
- acute perforations of the stomach or duodenum only if not operated on within 24 hours of perforation
- traumatic perforations of the small bowel (excluding duodenum) or large bowel only if not operated on within 12 hours of perforation
- perforations unrelated to trauma of the small bowel (excluding duodenum) or large bowel
- intra-abdominal infections related to previous intra-abdominal surgery
- intra-abdominal infections following penetrating and blunt trauma.

MO Comment : The protocol specifies that "Findings at operation must confirm the presence of an intra-abdominal infection (e.g. presence of purulent exudate and inflamed or necrotic tissue)."

2) Duration of the treatment of the intra-abdominal infection is anticipated to be at least 3 days.

3) Subjects may be included into the study after receiving prior anti-infective therapy under the following conditions:

- the previous anti-infective therapy was given for < 24 hours of therapy with a drug which requires ≥ 7 days duration of therapy
- subjects with a known intra-abdominal abscess may be enrolled into the study despite receiving empirical therapy for several days if pre-treatment cultures at time of surgery or percutaneous drainage yield bacterial pathogens susceptible to the study drugs
- subjects infected with an organism that is resistant *in vitro* to the anti-infective drug initially used, provided that the organism causing the infection is recovered within before enrollment and is susceptible to the study drugs.

Noteworthy Exclusion Criteria :

1) Subjects with any of the following disease states:

- perinephric infections
- infections of the female genital tract (gynecological infections)
- spontaneous bacterial peritonitis
- peritonitis associated with chronic peritoneal dialysis
- acute (< 24 hours) perforations of the stomach or duodenum
- traumatic perforations of the small or large bowel and operated on within 12 hours of the perforation
- transmural necrosis of the intestine due to acute embolic or thrombotic occlusion
- acute cholecystitis with infection confined to the gallbladder
- early acute or suppurative (nonperforated) appendicitis unless there is evidence of an abscess or free peritoneal fluid containing leukocytes and microorganisms suggestive of regional contamination
- pancreatic and peripancreatic sepsis.

2) Baseline APACHE II score > 35 obtained within 48 hours prior to randomization into double-blind therapy.

3) Subjects who require "open abdomen" techniques for management. However, when clinically-indicated, temporary closure of the abdominal incision using Marlex® (or equivalent) with a subsequent, *planned* surgical procedure to close the abdomen within 72 hours of the initial surgical procedure will be allowed.

4) Subjects with any infections that require treatment with an anti-infective agent other than the study drugs. Subjects requiring antibiotic irrigation of the abdominal cavity or surgical wound are not suitable for entry.

5) Immunocompromised patients

APPEARS THIS WAY ON ORIGINAL

MO Comment : The applicant's criteria are entirely consistent with the IDSA/FDA Guidelines. The MO agrees with the applicant's use of them.

Evaluation Visits :

Patients were to be evaluated at baseline (day 1; within 48 hours prior to the start of therapy), daily between days 1-14, at end of therapy (EOT), and long-term follow up (EOS; days 28-42). Clinical response to therapy was to be assessed by the investigator at the end of the double-blind treatment period as well as at follow-up (day 30).

MO Comment : From a practical standpoint, the applicant used EOS as ≥21 days of study. Although the IDSA Guidelines recommend a 4-6 weeks post-therapy test-of-cure follow up visit, the MO considers this visit window acceptable. Furthermore, MERREM was recently approved for this indication based on a minimum follow-up visit of 7 days post-therapy.

At entry into the study, based on the findings from the illness-defining procedure, the investigator was instructed to capture the following information on the CRF:

UNDERLYING DISEASE (check all that apply) :

◊ Appendicitis with perforation or abscess ≥24 hours
◊ Acute perforation of stomach or duodenum with surgery ≥24 hours
◊ Perforation (non-traumatic) of small or large bowel
◊ Traumatic perforation of small bowel or large bowel with surgery ≥12 hours
◊ Intra-abdominal infection following penetrating or blunt trauma
◊ Intra-abdominal infection related to previous intra-abdominal surgery
◊ Other (specify) _____

APPEARS THIS WAY ON ORIGINAL

SITES OF INTRA-ABDOMINAL INFECTION (check all that apply):

◊ Distal esophagus/stomach/duodenum
◊ Appendix
◊ Pancreas

◊ Biliary tree
◊ Colon
◊ Proximal small bowel
◊ Liver
◊ Distal small bowel
◊ Spleen
◊ Other (specify) _____

TYPE OF INFECTION (check all that apply):

◊ Single abscess
◊ Multiple abscesses
◊ Peritonitis

Protocol Prohibitions

- Intraluminal use of antibiotics was not allowed during the study.

Microbiology

The protocol stipulated,

- pre-treatment blood and peritoneal fluid specimens for culture were to be obtained within 48 hours prior to initiation of therapy or, with peritoneal fluid samples, up to 12 hours after the initiation of therapy. Each probable pathogen was to be identified to the species level."

- blood cultures (more than 1) must be obtained from all subjects.

The following susceptibility testing was employed for this study:

	CP-99,219[1]	Imipenem-cilastatin[2]		Amoxicillin-clavulanic acid[2]	
Criteria	MIC µg/mL	Zone 10-µg disk	MIC µg/mL	Zone 30-µg disk	MIC µg/mL
Susceptible	≤ 2	≥ 16	≤ 4	≥ 18	≤ 8
Intermediate	4	14 - 16	8	14 - 17	16
Resistant	≥ 8	≤ 13	≥ 16	≤ 13	≥ 32

[1]tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing
[2]NCCLS criteria

According to the protocol, subjects need not be discontinued from the study drug if they do not have a pathogen isolated at baseline or because the pathogen is

resistant to any of the study medications. Rather, the investigator could choose to continue the patient in the study if there was evidence of clinical improvement.

Outcome Definitions

APPEARS THIS WAY
ON ORIGINAL

Clinical response

At each visit, clinical response was assessed for the presence or absence of intra-abdominal pain/tenderness, abdominal rigidity, swelling, induration, surgical wound discharge, mass, ileus, bowel sounds, formed bowel movements, flatulence, hypotension and leukocytosis on the CRF. The following clinical response definitions were used by the applicant.

Cure : Typically, a successful outcome may be characterised by resolution of signs and symptoms of an inflammatory response (e.g. fever [body temperature ≥ 38.5 °C], elevated white blood cell count [WBC ≥ 12,500 cells/mm^3], hypotension [systolic blood pressure < 90 mmHg]) and intra-abdominal distress (localized or diffuse abdominal wall rigidity and/or mass and/or ileus, pain/tenderness, abdominal swelling, discharge, induration, and lack/presence of bowel sounds).

MO Comment : As stated above, the IDSA/FDA Guidelines state that the minimum duration of therapy to be considered a cure is 5 days and that the first 3 days of therapy should usually be administered parenterally. The MO asked the applicant to identify "clinically evaluable" patients in both treatment arms who transitioned from IV to oral within 3 days of study onset. The applicant responded that for the "cure" rate was 3/6 (50%) and 9/12 (75%) for the TROVAN and PRIMAXIN→AUGMENTIN treatment arms, respectively.

APPEARS THIS WAY
ON ORIGINAL

Improvement : Resolution of **some but not all** intra-abdominal symptoms and no requirement for additional antibiotic. The investigator will determine if the subject is improved from baseline, rather than cured or failed antibiotic therapy.

Failure will be defined by one or all of the following conditions:

- lack of resolution of **all** signs and symptoms of an intra-abdominal infection (as defined above).
- the need for additional antibacterial therapy for the treatment of the intra-abdominal infection. The reason for additional antibiotic therapy must be documented in the subject's Case Report Form.
- the need for greater than 14 days of antibiotic therapy.
- the need for more than one surgical procedure (with the exclusion of replacement of peritoneal drainage tubes). However, if assessed independently

by a blinded panel of investigators and the sponsor that the initial surgical procedure is considered inadequate, then the subject should be considered non-evaluable (see below). Subjects who require temporary closure of the abdominal incision using Marlex® (or equivalent) with a subsequent, *planned* surgical procedure to close the abdomen within 72 hours of the initial surgical procedure will be considered as having a single surgical procedure. Thus, this delayed closure procedure will not be considered a treatment failure.

The occurrence of any of the following conditions will supersede the evaluation of response as cure, improvement, or failure and will result in the reassignment of outcome by the sponsor as follows:

- for subjects who were previously assessed as failures, the outcome will always be failure at subsequent time points.
- for subjects who were given a concomitant systemic antibiotic prior to an evaluation time point, response will be classified as failure if the concomitant antibiotic was given for incomplete clinical response or failure.

According to an August 1995 protocol amendment: For subjects who stopped double-blind therapy because of no apparent response, response will be classified as failure.

According to a November 1995 protocol amendment : Clinical response will also be determined at initiation of concomitant antibiotic therapy. Patients who receive additional antimicrobial agents for any infections outside of the abdomen ≥ 5 days into the study must be evaluated on the day on which therapy with these agents is initiated.

MO Comment : The MO asked the applicant to identify patients in the clinically evaluable population considered "successes" (cure or improvement) who received a systemic anti-infective drug product ≥5 days into the study considered "unrelated" to the intra-abdominal infection. The applicant noted 19 and 14 patients in the TROVAN and PRIMAXIN→AUGMENTIN treatment arms, respectively, who met these criteria. Example reasons included pneumonia, UTI, wound suppuration, tooth abscess, change in therapy due to the development of an adverse event, and "prophylaxis".

APPEARS THIS WAY
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Bacteriologic Response

Bacteriologic response was usually presumptively determined based on the subject's clinical outcome. Possible responses included : **eradication**, **presumed eradication**, **persistence**, **superinfection** (new pathogen during therapy), and **presumed microbiological persistence**.

MO Comment : The MO agrees with the applicant's outcome definitions.