6.1.5.3.4 Statistical Considerations

The Applicant's sample size calculation assumed a 90% favorable response rate (clinical and microbiologic) at the TOC visit in the microbiologically evaluable population (the primary efficacy analysis) for both groups and a significance level of 0.025 (one-sided). Based on this assumption, 150 evaluable patients per group were needed to have an 80% probability that the lower limit of the 95% (two-sided) CI for the difference in the response rates between the 2 groups did not exceed -10 percentage points.

According to the Applicant, "this study was designed to show equivalence (non-inferiority for MK-0826) of the 2 treatment groups. The definition of equivalence is that the 95% (two-sided) CI for the difference in response rates between the 2 treatment groups (test drug group minus control group) contains zero and the lower limit of the CI is not less than -10 percentage points if a 90% or better response rate is observed for the control group, -15 percentage points if a response rate <90% and ≥80% is observed for the control group, and –20 percentage points if a response rate <80% and ≥70% is observed for the control group."

Medical Officer's Comment: ***At the time the protocol was reviewed by the Division this definition of equivalence was considered acceptable, however, the Applicant has been told at multiple teleconferences since that time that the Division has moved away from this definition in the 1992 FDA Points to Consider. The Applicant has been informed that the Division is revisiting the approach to definitions of non-inferiority. One such definition is that of a "fixed" delta of 10%, regardless of response rate to demonstrate equivalence. The Division recognizes that the Applicant based their development plan on earlier guidances and the Applicant was informed that the determination of approvability for this indication would be based on the overall package provided for review.***

The efficacy variables were analyzed using an evaluable population only approach and a modified intent-to-treat (MITT) approach. The evaluable population approach was specified as the primary efficacy analysis. The primary endpoints were analyzed by stratum (diagnosis of complicated appendicitis without generalized peritonitis versus all other sites of infection including complicated appendicitis with generalized peritonitis) and APACHE II score ≤15 or >15. A test of treatment-by-stratum interaction (Breslow-Day Test of Homogeneity of Odds-Ratios) was performed. When the nominal p-value of the test was >0.05, it was concluded that the odds ratios were similar across the strata and that strata could be combined. Results were then displayed combined over strata for each treatment group.

The 2 treatment groups were compared for each of the efficacy parameters and the differences in proportions (MK-0826 minus piperacillin/tazobactam) were calculated, along with the corresponding 95% confidence intervals (CIs). CIs were calculated using the normal approximation to the binomial distribution. The estimated CIs for the difference between treatment groups account for stratification based on the Cochran-Mantel-Haenszel (CMH) approach. The observed proportions and the corresponding CIs are displayed. The CIs around the individual proportions were calculated using the CMH approach applied to

one sample. The observed differences between the treatment groups were computed by pooling data across the strata.

For MITT analyses, the proportion of clinical MITT evaluable patients with a favorable clinical response assessment, and the proportion of clinical and microbiological MITT evaluable patients with a favorable clinical and microbiological response assessment, were displayed, along with their corresponding 95% CIs. For the Applicant's MITT analysis, for patients missing a TOC assessment, the last evaluation before TOC was used.

Medical Officer's Comment: ***During the January 28, 2000 pre-NDA teleconference between the Applicant and the Division, the Applicant was informed that patients with missing or indeterminate outcomes were generally considered failures in the MITT analyses by the Division and that additional sensitivity analyses using this approach should be performed. These sensitivity analyses were not provided in the original NDA and were requested again at the March 12, 2001 teleconference between the Applicant and the Division. The Applicant provided the requested analyses in an April 4, 2001 amendment to the NDA.***

It is also notable that in all of the Applicant's MITT analyses, the piperacillin/tazobactam patients from both the 1 gm and 1.5 gm cohorts were combined into one group for analysis and display. In all revised analyses displays, based on the MO's criteria for evaluability and outcome, only the piperacillin/tazobactam patients from the 1 gm cohort will be used. (Revised demographic displays will also display only the piperacillin/tazobactam patients enrolled in the 1 gm cohort.)

The Applicant also performed subgroup analyses for stratum (diagnosis of complicated appendicitis without generalized peritonitis versus all other sites of infection including complicated appendicitis with generalized peritonitis) and APACHE II score ≤15 or >15, age (≤65 years versus >65 years, <75 years versus ≥75), race, and gender for the primary efficacy endpoint in the per-protocol "evaluable-patients-only" population. (The minimum sample size needed in order for the analysis to be performed was at least 10 patients in either subgroup.) In addition, the primary efficacy endpoint was displayed for the groups of evaluable patients randomized before and after new blinding procedures for infusion bags were implemented.

6.1.5.4 Study Results

6.1.5.4.1 Evaluability

A total of 665 patients from 51 study sites (of the 57 sites receiving study drug supplies, 51 study sites enrolled 1 or more patients) were randomized into 1 of 3 treatment groups in 2 sequential cohorts: the MK-0826 1.5gm cohort and the MK-0826 1 gm cohort. All patients enrolled prior to implementation of the dose reduction were considered the 1.5 gm cohort; those patients enrolled after implementation of the dose reduction were considered the 1 gm cohort. [The study was initiated with a 1.5 gm daily dose of MK-0826. When preliminary data became available from the dose-finding Phase IIa study in complicated IAI (Protocol 004), the dose of MK-0826 was changed from 1.5 to 1.0 gm daily for all patients assigned to the MK-0826 treatment group.] In the 1.5 gm cohort, 14

patients were randomized to receive 1.5 gms MK-0826 and 18 patients were randomized to receive piperacillin/tazobactam.

The primary efficacy analysis approach was the microbiologically evaluable population (note that to be microbiologically evaluable a patient had to be clinically evaluable, therefore the microbiologically evaluable population may also be considered a "fully evaluable" population) analysis in the MK-0826 1 gm cohort. In the 1 gm cohort, 323 patients were randomized to receive 1 gm MK-0826 and 310 patients were randomized to receive piperacillin/tazobactam. Three hundred ninety-six patients were considered evaluable for the primary efficacy analysis: 203 received MK-0826 1 gm daily and 193 received 3.375 gms piperacillin/tazobactam every 6 hours. The Applicant's accounting of patients randomized into the study and the reasons patients discontinued from study therapy and study are in Appendix 2. A figure displaying the Applicant's profile of study enrollment and summarizing the number of patients in each of the evaluable populations, according to the Applicant, is in Appendix 3.

In the overall study population, the most common reason for patients not being randomized to study medication was that the patients' primary diagnoses were considered ineligible for study (58/93 patients) and/or that at the time of surgery the patient was found to have a primary diagnosis that was specifically excluded from study (25/93 patients).

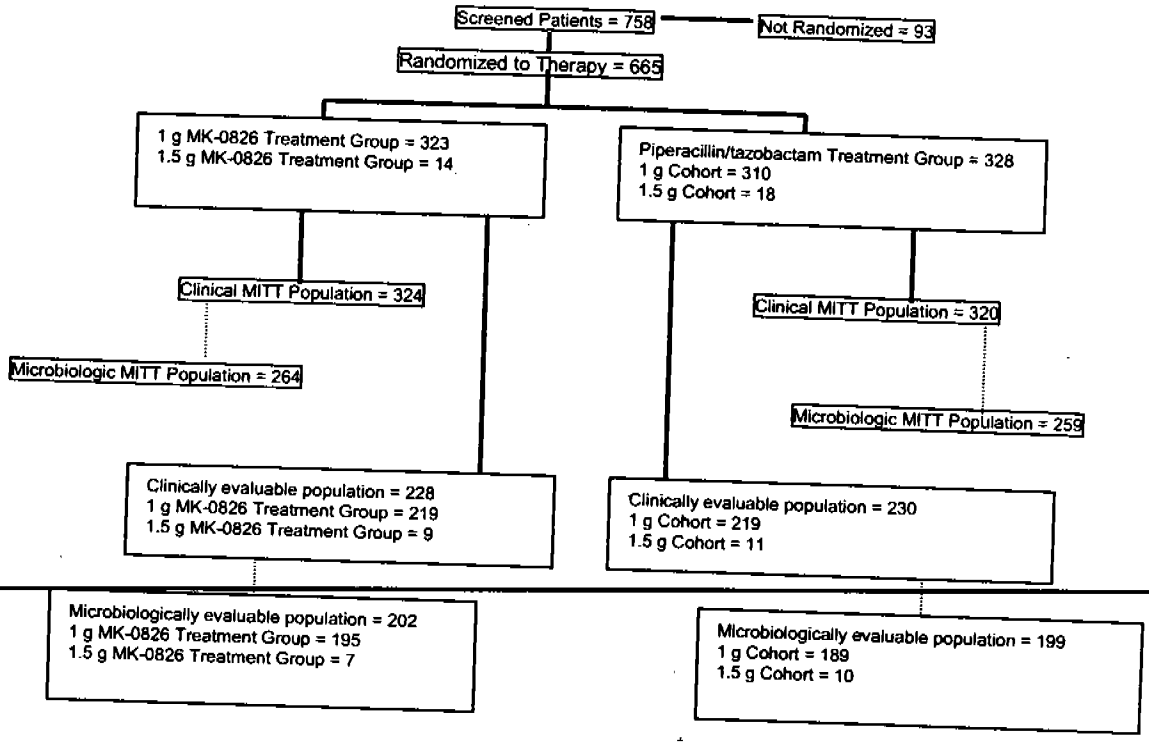
Medical Officer's Comment: ***Based on the MO's blinded, random sample review of 10% of the CRFs for P017 and the subsequent review of 188 additional CRFs for a subset of patients that received concomitant antibiotics, the MO has made the following changes to the Applicant's evaluable populations:***

- ***32 patients (17 in the MK-0826 1 gm group, 1 in the MK-0826 1.5 gm group, and 14 in the piperacillin/tazobactam group) were changed to clinically unevaluable.***
- ***26 patients (13 in the MK-0826 1 gm group, 1 in the MK-0826 1.5 gm group, and 12 in the piperacillin/tazobactam group) were changed to microbiologically unevaluable.***
- ***10 patients (5 in the MK-0826 1 gm group, 1 in the MK-0826 1.5 gm group, and 4 in the piperacillin/tazobactam group) were changed to clinically evaluable.***
- ***10 patients (5 in the MK-0826 1 gm group, 1 in the MK-0826 1.5 gm group, and 4 in the piperacillin/tazobactam group) were changed to microbiologically evaluable.***

The most common reason a patient was changed from evaluable to unevaluable was that the patient had received non-study antibiotics for an infection unrelated to their entry IAI prior to the TOC visit (25 patients). The most common reason a patient was changed from unevaluable to evaluable was that the patient had received non-study antibiotics (usually as oral therapy at the end of IV study therapy) as continued therapy for IAI (9 patients). A table is provided in Appendix 4 that provides a summary for the reason(s) that changes were made by patient.

The following figure displays the MO's profile of study enrollment and summarizes the number of patients in each of the evaluable populations according to the MO. The changes made have resulted in a small decrease in the percentage of evaluable patients in each group overall, but, the specific patients contained within each group has changed significantly.

MO's Profile of Patient Enrollment



The number and percent of patients in each study population and the reasons that patients were considered to be non-evaluable for the per-protocol, MITT and other efficacy analyses, according to the Applicant, are displayed in Appendix 5.

Medical Officer's Comment: ***Sites 017007 (Dr. Yellin, Los Angeles, CA) and 017060 (Dr. Fernandez, Guatemala) were the sites that enrolled the most patients, with each site enrolling 50 patients. The microbiologic evaluability rate at site 017007 was 54% and at site 017060 was 92%. Based on the Applicant's assessment of evaluability, US sites enrolled 33% of the microbiologically evaluable patients in the MK-0826 1 gm group and 42% of the microbiologically evaluable patients in the piperacillin/tazobactam group (combined 1 gm and 1.5 gm cohorts). The number of the Applicant's microbiologically evaluable patients in each treatment group that was entered by each Investigator is displayed in Appendix 6.***

The number and percent of patients in each study population and the reasons that patients were considered to be non-evaluable for the per-protocol, MITT and other efficacy analyses, according to the MO, are displayed in the table below. Within each population, the treatment groups were similar with respect to the reasons that patients were not evaluable and not included in the MITT populations.

Evaluability of Randomized Population According to the MO

Reasons not Evaluable	Number of Subjects	
	Invanz 1g (N=323)	Piperacillin/ Tazobactam (N=310)
Clinically Evaluable Population		
Clinical protocol evaluable	219 (67.8%)	219 (70.6%)
Clinical protocol nonevaluable	104 (32.2%)	91 (29.4%)
Disease definition not met	9 (2.8%)	8 (2.6%)
Test-of-cure window violation	24 (7.4%)	25 (8.1%)
Inadequate/inappropriate study therapy	28 (8.7%)	20 (6.5%)
Prior antibiotics violation	6 (1.9%)	5 (1.6%)
Concomitant antibiotics violation	25 (7.7%)	16 (5.2%)
Baseline/intercurrent medical events	11 (3.4%)	9 (2.9%)
Baseline microbiology-resistant pathogen	6 (1.9%)	6 (1.9%)
Other	0 (0)	2 (0.6%)
Inadequate/inappropriate source control	9 (2.8%)	13 (4.2%)
Micorbiologically Evaluable Population		
Microbiologic protocol evaluable	195 (60.4%)	189 (61.0%)
Microbiologic protocol nonevaluable	128 (39.6%)	121 (37.7%)
Not clinical evaluable	109 (33.7%)	94 (30.3%)
Baseline microbiology not performed/inadequate	5 (1.5%)	1 (0.3%)
Baseline microbiology-no pathogen isolated	42 (13.0%)	48 (15.5%)
Clinical MITT Population		
Clinical MITT evaluable	310 (96.0%)	303 (97.7%)
Clinical MITT nonevaluable	13 (4.0%)	7 (1.9%)
Patient didn't receive at least 1 dose of study therapy	7 (2.2%)	3 (1.0%)
Minimal disease definition not met	4 (1.2%)	3 (1.0%)
Pharmacy dispensing errors preclude evaluability	2 (0.6%)	1 (0.3%)
Microbiologic MITT Population		
Microbiologic MITT evaluable	256 (79.3%)	244 (78.7%)
Microbiologic MITT nonevaluable	67 (20.7%)	66 (21.3%)
Not clinical MITT evaluable	12 (3.7%)	6 (1.9%)
Baseline microbiology not performed/inadequate	4 (1.2%)	1 (0.3%)
Baseline microbiology-no pathogen isolated	47 (14.6%)	51 (16.5%)
Follow-up microbiology inadequate	8 (2.5%)	11 (3.5%)

This table contains counts of patient evaluability. Therefore, although a patient may have one or more reasons for being nonevaluable, the patient was counted only once in the non-evaluable category.

(Modified from Applicant's Table 13, Volume 13 of 22, page 92)

Data for 155 patients (considered failures) was reviewed to determine the adequacy of source control of initial surgical intervention by an expert panel that was blinded to treatment group. This was performed according to a prespecified procedure. If source control was considered inadequate by the panel, the patient was considered not clinically evaluable. Nine (9) patients (2.8%) in the MK-0826 1-g group and 13 patients (4.0%) in the combined piperacillin/tazobactam group were considered to have inadequate surgical source control, and were therefore considered not clinically evaluable. In addition, patients with a second surgical procedure and an outcome of cure were reviewed by the panel to ensure that there was no evidence of failure at the time of the second procedure. If the panel concluded there was evidence of failure at the time of the subsequent intervention, these patients were downgraded to failures for all analyses. Of the patients reviewed, 2 patients (ANs 0285, 5790) in the MK-0826 1-g groups, 2 patients (ANs 5050, 5167) in the MK-0826 1.5-g group, and 3 patients (ANs 0454, 0529, 0623) in the piperacillin/tazobactam group were downgraded to failure by the panel. None of the 7

patients (ANs 0285, 0454, 0529, 0623, 5050, 5167, and 5790) whose outcomes were downgraded from cure to failure by the panel were clinically evaluable, so the downgraded outcomes were not included in the Applicant's efficacy analyses of evaluable patients. They were, however, included in the MITT analyses as having unfavorable outcomes. The proportion of randomized patients whose cases went to the expert panel review of surgical source control in failures and outcome in cases considered "cure" with subsequent surgical intervention are displayed in the following table.

Expert Panel Review of Surgical Source Control in Failures and Outcome in Cases Considered "Cure" With Subsequent Surgical Intervention (All Randomized Patients)

	MK-0826 1 g (N=323)		MK-0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=328)		Total (N=665)	
Surgical Panel Review	n	(%)	n	(%)	n	(%)	n	(%)
Total cases reviewed by panel	71	(22.0)	5	(35.7)	79†	(24.1)	155†	(23.3)
Panel findings:								
In failures: inadequate surgical source control	9	(2.8)	0	(0.0)	13	(4.0)	22	(3.3)
In cures with second procedure: outcome downgraded to failure	2	(0.6)	2	(14.3)	3	(0.9)	7	(1.1)

† AN 5919 was "cure with second procedure" and should have been counted in the total number cases reviewed by panel.
n = The total number of patients reviewed by surgical panel

(Applicant's Table 21, Volume 13 of 22, page 106)

Medical Officer's Comment: ***In the MO's blinded review of 188 CRFs for a subset of patients that received concomitant antimicrobials, the MO considered three additional patients, ANs 5109, 5250, and 5760, to have had a high likelihood of inadequate initial surgical intervention and considered these 3 patients to be unevaluable. ANs 5109 and 5760 had inadequate initial CT guided aspiration and drainage procedures to drain intra-abdominal abscesses and AN 5250 had a retained common bile duct stone post cholecystectomy and developed cholangitis.***

6.1.5.4.2 Demographics

The table below displays the baseline characteristics for the Applicant's microbiologically evaluable group.

Baseline Patient Characteristics by Treatment Group
(Microbiologically Evaluable Population)

	MK-0826 1 g (N=203)	MK-0826 1.5 g (N=7)	Piperacillin/ Tazobactam (N=207)	Total (N=417)
	n (%)	n (%)	n (%)	n (%)
Gender				
Male	133 (65.5)	4 (57.1)	137 (66.2)	274 (65.7)
Female	70 (34.5)	3 (42.9)	70 (33.8)	143 (34.3)
Race				
Armenian	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Asian	3 (1.5)	0 (0.0)	4 (1.9)	7 (1.7)
Black	5 (2.5)	1 (14.3)	6 (2.9)	12 (2.9)
Caucasian	107 (52.7)	6 (85.7)	113 (54.6)	226 (54.2)
Colored	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.5)
Hispanic	72 (35.5)	0 (0.0)	67 (32.4)	139 (33.3)
Mestizo	3 (1.5)	0 (0.0)	2 (1.0)	5 (1.2)
Mixed	10 (4.9)	0 (0.0)	12 (5.8)	22 (5.3)
Native American	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Unknown	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.5)
Age (Years)				
<18	1	0	1	2
18 to 40	96	1	99	196
41 to 64	73	2	64	139
65 to 74	18	4	26	48
≥75	15	0	17	32
Mean	44.9	56.9	45.0	45.2
SD	18.6	18.6	18.7	18.7
Median	42.0	65.0	42.0	42.0
Range	17 to 89	20 to 73	17 to 89	17 to 89
Stratum†				
Complicated Appendicitis APACHE II ≤15	105 (51.7)	3 (42.9)	103 (49.8)	211 (50.6)
Complicated Appendicitis APACHE II >15	2 (1.0)	0 (0.0)	5 (2.4)	7 (1.7)
Other Diagnoses APACHE II ≤15	86 (42.4)	3 (42.9)	88 (42.5)	177 (42.4)
Other Diagnoses APACHE II >15	10 (4.9)	1 (14.3)	11 (5.3)	22 (5.3)
Apache Score‡				
APACHE II Score ≤15	192 (94.6)	6 (85.7)	192 (92.8)	390 (93.5)
APACHE II Score >15	11 (5.4)	1 (14.3)	14 (6.8)	26 (6.2)
Unknown	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)

† Includes patients as they were stratified by the study site (stratification errors are not corrected in this table).
‡ Includes patients who were counted according to APACHE II score reported (irrespective of stratification errors).
SD = Standard deviation.

(Applicant's Table 15, Volume 13 of 22, page 95)

Medical Officer's Comment: ***The groups (MK-0826 1 gm and piperacillin/tazobactam) appear to be similar with respect to gender, race, age, stratum, and APACHE II score. A revised table of baseline characteristics based on the MO's evaluability criteria is displayed below. The 2 treatment groups remained well balanced using the evaluability reassignments made by the MO.***

**APPEARS THIS WAY
ON ORIGINAL**

**Baseline Patient Characteristics by Treatment Group
Microbiologically Evaluable Population - According to the MO
(Observed Data)**

	Treatment Group			
	MK-0826 1 g (A) (N=195)		Piperacillin/Tazobactam (B) (N=189)	
	Observed Response		Observed Response	
	n	%	n	%
Gender				
Female	70	35.9	60	31.7
Male	125	64.1	129	68.3
Age Category (years)				
<65	167	85.6	162	85.7
≥65	28	14.4	27	14.3
<75	182	93.3	178	91.3
≥75	13	6.7	11	5.6
Race				
Armenian	1	0.5	0	-
Asian	3	1.5	4	2.1
Black	5	2.6	6	3.2
Caucasian	99	50.8	96	50.8
Colored	1	0.5	1	0.5
Hispanic	73	37.4	67	35.4
Mestizo	3	1.5	2	1.1
Mixed	10	5.1	12	6.3
Not specified	0	-	1	0.5
Stratum				
Complicated Appendicitis, APACHE II score ≤15	87	44.6	88	46.6
Complicated Appendicitis, APACHE II score >15	2	1.0	3	1.6
All Other Diagnoses, APACHE II score ≤15	100	51.3	91	48.1
All Other Diagnoses, APACHE II score >15	6	3.1	7	3.7
APACHE II				
≤15	187	95.9	179	94.7
>15	8	4.1	10	5.3

N = Number of microbiologically evaluable patients in each treatment group.
n = Number of patients with assessment.

The anatomic site of specific intra-abdominal infection diagnoses, in the randomized population, is displayed in the following table.

Anatomic Site of Infection
(Randomized Population)

	MK-0826 1 g (N=323)		MK-0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=328)		Total (N=665)	
	n	(%)	n	(%)	n	(%)	n	(%)
Anatomic Site*								
Appendix	154	(47.7)	4	(28.6)	152	(46.3)	310	(46.6)
Biliary-Cholangitis	0	(0.0)	0	(0.0)	3	(0.9)	3	(0.5)
Biliary-Cholecystitis	27	(8.4)	0	(0.0)	21	(6.4)	48	(7.2)
Colon	56	(17.3)	5	(35.7)	72	(22.0)	133	(20.0)
Kidney-Related Infection	1	(0.3)	0	(0.0)	1	(0.3)	2	(0.3)
Parenchymal Liver	3	(0.9)	0	(0.0)	7	(2.1)	10	(1.5)
Parenchymal Spleen	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.2)
Pelvic Inflammatory Disease	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.2)
Small Bowel	30	(9.3)	2	(14.3)	26	(7.9)	58	(8.7)
Stomach/Duodenum	28	(8.7)	0	(0.0)	23	(7.0)	51	(7.7)
Other	21	(6.5)	3	(21.4)	22	(6.7)	46	(6.9)

*Only one anatomic site was recorded per patient.
In the 1 g MK-0826 treatment group: Randomized patients, AN 1417 and AN 0307 were not included, as no study drug was given and no primary diagnosis data was submitted.
n = The total number of patients with the diagnosis.

(May 24, 2001 submission, Applicant's Table 1)

Medical Officer's Comment: ***When the MO performed a blinded review of 10% of the CRFs, a number of errors were detected in the Applicant's data sets regarding the correct recording of the anatomic site of infection. The Applicant was asked to review the CRFs for all patients in this study and correct the anatomic site of infection appropriately in the data sets and to provide new analyses and tables that were dependent on this variable. The Applicant provided these corrected analyses in the May 24, 2001 amendment to the NDA. In that amendment the Applicant noted that a total of 54 corrections were made to the "anatomic site code". In the table below the Applicant's revised "anatomic site" codes are incorporated to display the number of infections at each anatomic site in the MO's microbiologically evaluable population.***

Anatomic Site of Infection
According to the MO
(Microbiologically Evaluable Population)

Infection Site/Process	MK-0826 1 g (N=195)		Piperacillin/ Tazobactam (N=189)	
	n	(%)	n	(%)
Anatomic Site				
Appendix	118	60.5	113	59.8
Biliary-cholangitis	0	-	2	1.1
Biliary-cholecystitis	12	6.2	10	5.3
Colon	35	18.0	32	16.9
Parenchymal liver	1	0.5	2	1.1
Parenchymal spleen	0	-	1	0.5
Pelvic inflammatory disease	1	0.5	0	-
Small bowel	13	6.7	11	5.8
Stomach/duodenum	8	4.1	7	3.7
Other	7	3.6	11	5.8

*Patients could have had more than 1 infectious process recorded.
n = The total number of patients with the diagnosis.

The following table displays the extent of exposure to all study drugs (duration) by treatment group for all patients who received at least 1 dose of therapy. In order to determine the number of days that study therapy was missed, it was assumed that the number of days from the first to the last dose of study therapy was the duration of therapy planned by the investigator. A calendar day in which a patient received no active study therapy was counted as a day of missed study therapy. If the patient received only placebo dose on the last day of study therapy, then this day was counted as a day in which the patient missed study therapy. This situation only pertained to the MK-0826 treatment group, for which the last 3 doses of each 24-hour period were placebo doses, and not to the piperacillin/tazobactam group, for which each infusion was an active dose. Thus, it appears that 86 patients in the MK-0826 group and 1 patient in the 1.5-g MK-0826 group missed a day of study therapy, but seventy-seven (77) patients who actually received the full duration of therapy were included in this count because they received only placebo doses on the last day of study therapy.

Extent of Exposure (Duration of Therapy) by Dose and Treatment Group
(Treated Population)

	MK-0826 1 g (N=316)	MK-0826 1.5 g (N=14)	Piperacillin/ Tazobactam (N=325)	Total (N=655)
Days on Parenteral Therapy				
n	316	14	325	655
Mean	7.3	9.1	7.6	7.5
SD	3.7	4.6	3.0	3.4
Median	6.0	9.0	7.0	6.0
Range				
Days Missed Therapy				
n	86†	1	0	87†
Mean	1.0	1.0	0.0	1.0
SD	0.2			0.2
Median	1.0	1.0	0.0	1.0
Range				

† Includes 77 patients who did not actually miss any days of study therapy, but were counted in the total because the last day of study infusions were placebos.
n = Number of patients in category.
SD = Standard deviation.

(Applicant's Table 26, Volume 13 of 22, page 121)

Medical Officer's Comment: ***The mean and median values for days on parenteral therapy are similar between the MK-0826 1 gm and piperacillin/tazobactam groups.***

The mean and median values for days on parenteral therapy in the Applicant's microbiologically evaluable population were similar to those in the treated population. These values were not recalculated for the MO's microbiologically evaluable population.

6.1.5.4.3 Efficacy

6.1.5.4.3.1 Clinical

The primary efficacy analysis was the proportion of microbiologically evaluable patients with a favorable clinical and microbiologic response assessment at the TOC visit in the 1 gm cohort. According to the Applicant, 86.7% of patients in

the MK-0826 1 gm group and 81.2% of patients in the piperacillin/tazobactam group (only those piperacillin/tazobactam patients enrolled with the 1 gm cohort were considered) had a favorable clinical and microbiologic response assessment at the TOC visit. The difference in the clinical and microbiologic response rates between the 2 treatment groups (adjusted for stratum) was 5.5%, with a 95% CI of (-2.2%, 13.1%). A table displaying the results of the Applicant's analysis for the primary efficacy parameter at the DCIV, EFU, and TOC timepoints is displayed in Appendix 7.

The Applicant also performed an analysis of the clinical response rates in the microbiologic MITT to support the primary protocol analyses. The Applicant's microbiologic MITT population included all patients in the clinical MITT population in whom a microbiologic outcome could be assessed, and included patients randomized to both the 1- and 1.5-g MK-0826 cohorts, combined. Of the 665 patients randomized in the study, 523 (78.6%) patients were included in the microbiologic MITT population: 264/337 patients (78.3%) randomized to the MK-0826 group, and 259/328 patients (79%) randomized to the piperacillin/tazobactam group. The clinical MITT outcome (from Applicant's revised analysis included in April 4, 2001 amendment to the NDA) was favorable in 76.9% of patients in the MK-0826 group and in 70.7% of patients in the piperacillin/tazobactam group. The difference in the clinical MITT response rates between the 2 treatment groups adjusted for stratum was 6.2%, with a 95% CI of (-1.4, 13.8%). Tables (Applicant's original and revised) demonstrating the proportion of patients with favorable clinical response assessments for the microbiological MITT population, according to the Applicant, are displayed in Appendix 8.

Medical Officer's Comment: *A blinded, 10% random sample of CRFs for patients enrolled in this study was reviewed by the MO. Based on the bootstrap analysis performed by Dr. Joel Jiang, Biometrics, for the results of the MO's 10% review it was concluded that the Applicant's efficacy analyses for this study could not be accepted. The results of the "bootstrap" analysis suggested that the confidence level was only 32.7% that the lower bound of the CI was > -10% delta and that the p-value for the null hypothesis ("lower bound ≤ delta" versus alternate "lower bound > delta") was 0.80. When the MO's results of the 10% sample were compared with the Applicant's data set for these patients it appeared that the primary reason for discrepancies related to evaluability and outcome assignments for patients that had received concomitant antimicrobials. Therefore, the MO used the Applicant's data sets to define a subset of 188 additional CRFs, for further blinded review, for patients who received concomitant antimicrobials. These CRFs were chosen based on the following criteria:*

1. *The patient received the concomitant antimicrobial during the IV treatment phase or the post IV treatment phase, but if given during the IV treatment phase it was given beyond the first day of study therapy (to exclude patients that had potentially received one dose of non-study antimicrobial post-operatively since this was allowed in the protocol).*
2. *The concomitant antimicrobial was not: a) vancomycin (since vancomycin use was allowed per protocol to treat resistant gram positive organisms or C. difficile associated disease), b) usually used as an antitubercular, an antiviral, an antifungal, an antimalarial, a topical antimicrobial product, or c) a product that is commonly used orally for selective bowel decontamination as a pre-operative agent.*

Based on the MO's blinded review (using criteria previously stated) of these 188 CRFs (17 had already been reviewed in the initial 10% random sample), the MO determined that the evaluability and/or outcomes for 55 patients should be reassigned. Details regarding patients with evaluability reassignments have been previously reviewed in section 6.1.5.4.1 above. The MO has made changes to the Applicant's outcome assignments as follows:

- ***14 patients (9 in the MK-0826 1 gm group, 1 in the MK-0826 1.5 gm group, and 4 in the piperacillin/tazobactam group) were changed from favorable clinical response to unfavorable clinical response.***
- ***30 patients (16 in the MK-0826 1 gm group and 14 in the piperacillin/tazobactam group [12/14 in the 1 gm cohort]) were changed from favorable clinical response to indeterminate clinical response.***
- ***6 patients (2 in the MK-0826 1 gm group and 4 in the piperacillin/tazobactam group) were changed from unfavorable clinical response to indeterminate clinical response.***

The most common reason a patient's response status was changed was that the patient had received non-study antibiotics for an infection unrelated to their entry IAI prior to the TOC visit (24 patients). A table is provided in Appendix 4 that provides a summary for the reason(s) that changes were made by patient.

The results of the MITT and primary efficacy analyses, incorporating the MO's changes to the evaluability and/or outcome status for these 55 patients, are displayed in the following tables. In contrast to the Applicant's MITT analysis, the piperacillin/tazobactam group contains only patients that were enrolled with the 1 gm cohort.

Proportion of Patients With Favorable Clinical and Microbiological Response Assessments (According to the MO)—Microbiologically Evaluable Population (Observed Data)

Time Point	Treatment Group				Observed† Difference (A-B)	
	Ertapenem (A) (N=195)		Piperacillin/Tazobactam (B) (N=189)			
	Observed Response		Observed Response			
	n	%	n	%	%	(95% CI)
TOC	163	83.6	152	80.4	3.2	(-5.0%, 11.4%)

N = Number of microbiologically evaluable patients in each treatment group.
n = Number of patients with favorable clinical and microbiologic response assessments.
CI = Confidence interval.
TOC = Test of cure.

Proportion of Patients With Favorable Clinical Response Assessment According to the MO—Microbiologic MITT Population (Observed Data)

Time Point	Treatment Group				Observed† Difference (A-B)	
	MK-0826 1g (A) (N=256)		Piperacillin/Tazobactam (B) (N=244)			
	Observed Response		Observed Response			
	n	%	n	%	%	(95% CI)
TOC	184	71.9	167	68.4	3.4	(-5.0%, 11.9%)

N = Number of microbiologically evaluable patients in each treatment group.
n = Number of patients with favorable clinical and microbiologic response assessments.
CI = Confidence interval.
TOC = Test of cure.

A revised table displaying response by old or new blinding procedure, based on the MO's evaluability and outcome reassignments, is displayed below. The Applicant's table is displayed in Appendix 6.1-G.

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments at Test of Cure Displayed by Blinding Procedure According to the MO— Microbiologically Evaluable Population (Observed Data)

Enhanced Blinding Procedure	Treatment Group				Observed Difference (A-B)	
	MK-0826 1 g (A) (N=195)		Piperacillin/Tazobactam (B) (N=189)			
	Observed Response		Observed Response			
	n/m	%	n/m	%	%	95% CI
No	102/124	82.3	98/123	79.7	2.6	(-8.0%, 13.2%)
Yes	61/71	85.9	54/66	81.8	4.1	(-9.7%, 17.9%)

N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

The Applicant also provided an analysis of efficacy by entry infection stratum. At TOC, in patients with localized complicated appendicitis (without generalized peritonitis), 85/94 patients (90.4%) in the MK-0826 1 gm group and 82/91 patients (90.1%) in the piperacillin/tazobactam group (1 gm cohort only) had a favorable clinical and microbiologic response assessment. In patients with other sites of infection (including complicated appendicitis with generalized peritonitis), 91/109 patients (83.5%) in the MK-0826 group and 75/102 patients (73.5%) in the piperacillin/tazobactam group (1 gm cohort only) had a favorable clinical and microbiologic response assessment. The difference in the clinical and microbiologic response rates between the 2 treatment groups was 0.3% in patients with localized complicated appendicitis (without generalized peritonitis) and 10.0% in patients with all other sites of infection (including complicated appendicitis with generalized peritonitis). A table displaying the Applicant's results may be found in Appendix 7.

Medical Officer's Comment: ***A revised table, based on the MO's evaluability and outcome reassignments is displayed below.***

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments At Test of Cure Displayed by Site of Infection Stratum According to the MO— Microbiologically Evaluable Population (Observed Data)

Site of Infection	Treatment Group				Observed Difference (A-B)	
	MK-0826 1 g (A) (N=195)		Piperacillin/Tazobactam (B) (N=189)			
	Observed Response		Observed Response			
	n/m	%	n/m	%	%	95% CI
Complicated Appendicitis*	80/89	89.9	81/91	89.0	0.9	(-9.2%, 11.0%)
All Other Diagnoses	83/106	78.3	71/98	72.5	5.9	(-7.0%, 18.7%)
Overall	163/195	83.6	152/189	80.4	3.2	(-5.0%, 11.4%)

* Without generalized peritonitis.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

The Applicant also provided an analysis of efficacy by entry by the APACHE II score stratum. At TOC, patients with an APACHE II score of ≤15, 169/192 patients (88.0%) in the MK-0826 group and 147/181 patients (81.2%) in the piperacillin/tazobactam group had a favorable clinical and microbiologic response assessment. In patients with APACHE II score of >15, 7/11 patients (63.6%) in the MK-0826 group and 10/12 patients (83.3%) in the piperacillin/tazobactam group had a favorable clinical and microbiologic response assessment. The difference in the clinical and microbiologic response rates between the 2 treatment groups was 6.8% in patients with APACHE II score of ≤15, and –19.7% in patients with APACHE II score of >15. A table displaying the Applicant's results may be found in Appendix 7.

Medical Officer's Comment: ***The trend, in the Applicant's analysis, for patients in the APACHE II score >15 MK-0826 group to have done worse is concerning, however, the small number of evaluable patients with APACHE II scores >15 make it difficult to conclude the trend is significant. A revised table, based on the MO's evaluability and outcome reassignments, is displayed below. An analysis for the microbiologic MITT population is also presented.***

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments At Test of Cure
Displayed by APACHE II Score Stratum According to the MO—
Microbiologically Evaluable and MITT Populations
(Observed Data)

APACHE II Score	Treatment Group				Observed Difference (A-B)	
	MK-0826 1 g (A)		Piperacillin/Tazobactam (B)			
	Observed Response		Observed Response			
	n/N	%	n/N	%	%	95% CI
Micro MITT						
≤15	176/238	73.9	157/227	69.2	4.8	(-3.8%, 13.3%)
>15	7/18	38.9	10/17	58.8	-19.9	(-58.1%, 18.3%)
Overall	183/256	71.5	167/244	68.4	3.0	(-5.4%, 11.5%)
Micro Eval						
≤15	158/187	84.5	144/179	80.4	4.0	(-4.3%, 12.4%)
>15	5/8	62.5	8/10	80.0	-17.5	(-70.5%, 35.5%)
Overall	163/195	83.6	152/189	80.4	3.2	(-5.0%, 11.4%)

n/N = Number of patients with favorable assessment/number of patients in microbiologic population (MITT or evaluable)
CI = Confidence interval.

A revised table containing combined site of infection and APACHE II strata, based on the MO's evaluability and outcome reassignments, is displayed below. The Applicant's table is displayed in Appendix 7.

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments at Test of Cure
Displayed by Site of Infection and APACHE II Score Strata According to the MO—Microbiologically Evaluable Population
(Observed Data)

Stratum	Treatment Group: MK-0826 1 g (A) (N=195) Observed Response n/m	%	Piperacillin/Tazobactam (B) (N=189) Observed Response n/m	%	Observed Differences (A-B) %	95% CI
Complicated Appendicitis‡, APACHE II score ≤15	78/87	89.7	78/88	88.6	1.1	(-9.3%, 11.
Complicated Appendicitis‡, APACHE II score >15	2/2	100	3/3	100	0	(-41.7%, 41.
All Other Diagnoses, APACHE II score ≤15	80/100	80.0	66/91	72.5	7.5	(-5.6%, 20.(
All Other Diagnoses, APACHE II score >15	3/6	50	5/7	71.4	-21.4	(-89.1%, 46.

‡ Without generalized peritonitis.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

A table displaying response by site of infection, based on the MO's evaluability and outcome reassignments, is displayed below. While there appear to be relatively few patients with infections of the hepatobiliary system, all major sites associated with complicated intra-abdominal infections were represented and outcomes were similar between the 2 treatment groups. The Applicant's table is displayed in Appendix 7.

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments at Test of Cure
Displayed by Primary Site of Infection According to the MO—Microbiologically Evaluable Population
(Observed Data)

Primary Site of Infection†	MK-0826 1g (N=195) n/m	(%)	Piperacillin/Tazobactam (N=189) n/m	(%)
Stomach/Duodenum	8/8	100	6/7	85.7
Biliary-Cholecystitis	10/12	83.3	10/10	100
Biliary-Cholangitis	0	-	0/2	0.0
Small Bowel	9/13	69.2	8/11	72.7
Appendix	104/118	88.1	101/113	89.4
Colon	26/35	74.3	22/32	68.8
Parenchymal (liver)	0/1	0	1/2	50.0
Parenchymal (spleen)	0/0	-	0/1	0.0
Pelvic Inflammatory Disease	1/1	100	0	-
Other	5/7	71.4	4/11	36.4

† Only 1 site indicated per patient.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
- = No observation
* Patients with intra-abdominal infection (abscess) for whom site could not be attributed.

A revised table displaying responses by gender, race, and age category, based on the MO's evaluability and outcome reassignments, is displayed below. The clinical and microbiologic responses by gender in the microbiologically evaluable population were similar in the 2 treatment groups. The response rates for patients ≥65 or ≥75 in the MK-0826 group (17/28 [60.7%] and 7/13 [53.9%]) was lower than that in the piperacillin/tazobactam group (25/27 [92.6%] and 11/11 [100%], respectively). Although the number of patients in the older age groups was limited, this finding is concerning and was not explained by the Applicant. The response rate for Caucasian and Hispanic patients was similar in the 2 treatment

groups; however, the number of patients of other races that were enrolled is insufficient to make a meaningful comparison. The Applicant's table is displayed in Appendix 7.

Proportion of Patients With Favorable Clinical and Microbiologic Response Assessments at Test of Cure Displayed by Gender, Age Category, and Race According to the MO—Microbiologically Evaluable Population (Observed Data)

	Treatment Group			
	MK-0826 1 g (A) (N=195)		Piperacillin/Tazobactam (B) (N=189)	
	Observed Response		Observed Response	
	n/m	%	n/m	%
Gender				
Female	57/70	81.4	45/60	75.0
Male	106/125	84.8	107/129	83.0
Age Category				
<65	146/167	87.4	127/162	78.4
≥65	17/28	60.7	25/27	92.6
<75	156/182	85.7	141/178	79.2
≥75	7/13	53.9	11/11	100
Race				
African	0/0	-	0/0	-
Armenian	1/1	100	0/0	-
Asian	2/3	66.7	2/4	50.0
Black	5/5	100	4/6	66.7
Caucasian	80/99	80.8	76/96	79.2
Colored	1/1	100	1/1	100
Hispanic	65/73	89.0	57/67	85.1
Mestizo	1/3	33.3	2/2	100
Mixed	8/10	80.0	9/12	75.0
Not specified	0/0	-	1/1	100

N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

6.1.5.4.3.2 Microbiologic

The Applicant determined microbiologic outcome for all unique baseline pathogens from intra-abdominal sites and/or blood at DCIV and follow-up study visits. If no specimen was obtained for culture at a follow-up visit, the microbiologic outcome was presumed based on the clinical outcome; eradication was presumed for favorable clinical outcomes and persistence was presumed for unfavorable clinical outcomes. A baseline pathogen isolated both from the primary infection site and from the blood was counted once in the overall list of pathogens and once in the list of bacteremic pathogens. A baseline pathogen isolated only from blood and presumed to be associated with the primary infection was counted once in the overall list and once in the bacteremic list. If a patient received vancomycin for treatment of gram-positive infection, all gram-positive baseline pathogens were considered to have indeterminate microbiologic outcomes. If these patients were otherwise microbiologically evaluable, their clinical, overall microbiological outcomes and other per-pathogen microbiologic outcomes were considered valid. A favorable overall microbiologic response

assessment required that all baseline pathogens had an outcome of eradication or presumed eradication. Any single per-pathogen outcome of persistence or presumed persistence or persistence-acquiring resistance resulted in an overall unfavorable microbiologic assessment.

The proportion of microbiologically evaluable patients with a favorable overall microbiologic response assessment at the DCIV visit, at EFU, and at TOC, according to the Applicant is displayed in Appendix 7. According to the Applicant, 89.1% of patients in the MK-0826 group and 84.4% of patients in the piperacillin/tazobactam group had a favorable overall microbiologic response assessment at the TOC visit. The difference in the overall microbiologic response rates between the 2 treatment groups at TOC adjusted for stratum was 4.8% with a 95% CI of (-2.4%, 11.9%).

Medical Officer's Comment: ***A revised table displaying the overall microbiologic response in the microbiologically evaluable population at the TOC visit, based on the MO's evaluability and outcome reassignments, is displayed below.***

Proportion of Patients With Favorable Overall Microbiologic Response Assessments in the Microbiologically Evaluable Population According to the MO (Observed)

	Treatment Group				Observed† Difference (A-B)	
	MK-0826 1 g (A) (N=195)		Piperacillin/Tazobactam (B) (N=189)			
Time Point	Observed Response n	%	Observed Response n	%	%	(95% CI)
TOC	163	83.6	152	80.4	3.2	(-5.0%, 11.4%)

N = Number of microbiologically evaluable patients in each treatment group.
n = Number of microbiologically evaluable patients with assessment at each time point included in the analysis.
CI = Confidence interval.
TOC = Test of cure.

6.1.5.4.3.3 By Pathogen

The Applicant compared the microbiologic response rates in microbiologically evaluable patients between the 2 treatment groups (in the 1 gm cohort) for all unique baseline pathogens obtained from intra-abdominal cultures or blood cultures (if the same pathogen was isolated from both blood and intra-abdominal cultures it was only counted once in the overall list.) The most common species identified, in the Applicant's analysis, were *E. coli, B. fragilis, B. thetaiotaomicron, B. wadsworthia*, and *P. aeruginosa*, each with at least 50 isolates in the microbiologically evaluable population. Also common in both treatment groups were 11 other species: *E. faecalis, K. pneumoniae, C. clostridiiforme, C. innocuum, C. perfringens, E. lentum, P. micros, B. distasonis, B. ovatus, B. uniformis*, and *B. vulgatus*, each with at least 10 isolates having response assessments at TOC in 1 of the treatment groups. The Applicant's table displaying the difference in the microbiologic per-pathogen response rates (MK-0826 minus piperacillin/tazobactam) between the 2 treatment groups for these

species is displayed in Appendix 7 anaerobic pathogens. For patients that received vancomycin per protocol, gram-positive pathogens that were isolated from intra-abdominal or blood cultures were not included in the per-pathogen analysis in the microbiologically evaluable population. Failure to obtain a blood culture in the setting of a clinical failure was not used to presume persistent bacteremia. Rather, in this setting, the outcome of these pathogens was excluded from the Applicant's per-pathogen analysis.

Medical Officer's Comment: ***The 1992 FDA Points-to-Consider document discussed when an organism should be included in a granted indication. This document recommended the following criteria when making this determination:***

1. ***Only those microorganisms considered to be an etiologic agent (pathogen) in at least 10% of the evaluable cases of the specific infection successfully treated with the investigative agent should be included.***
2. ***The "at least 10%" should be understood to mean "at least 10% of the evaluable cases meeting both clinical and microbiological evaluability criteria or 10 total cases (as just defined), whichever is higher."***
3. ***The eradication rate of the pathogen should be clinically acceptable in order for that pathogen to be included in this section of the labeling.***

The Points-to-Consider document goes on to discuss how pathogens might be included in the label when <10% of cases were associated with the pathogen and states that "in such situations, explicit labeling to inform the physician of the actual extent of data available should be included in the product labeling." The situations in which the Points-to-Consider document suggests it is appropriate to consider this approach are when pathogens:

1. ***Are generally accepted as pathogens at the site of infection under investigations (however in numbers less than 10%) and the number of such infections studied in the clinical trials is consistent with the percentage of such infection due to these pathogens in the general population.***
2. ***Have in vitro activity that is at least similar to that of other pathogens more substantially evaluated in the clinical trials.***
3. ***Have a mechanism(s) of resistance that is similar to other pathogens more substantially evaluated in the clinical trials.***
4. ***Have no scientific data to suggest any differences in the management of the infection due to these pathogens or in the prognosis of patients with the infection due to these pathogens.***

Although not stated in the Points-to-Consider document, it seems reasonable to extrapolate pathogen data from other treatment indications, such as acute pelvic infections, to support efficacy in the treatment indication under review as long as that extrapolation is clinically and pharmacodynamically reasonable. In addition, if data are to be extrapolated between studies for different indications, the MO believes that the severity of illness, dose, and duration of therapy should be similar between the indications.

A revised table displaying the difference in the microbiologic per-pathogen response rates in the microbiologically evaluable population at the TOC visit, based on the MO's evaluability and outcome reassignments, is displayed below. Highlighted pathogens are those that the MO feels should be granted for this indication in the label based on the comments above. Because of variability in MIC data for Bacteriodes spp., Prevotella spp., Clostridia spp., and Eubacterium spp., only those pathogens identified to the species level that have been demonstrated in adequate numbers with adequate efficacy in this study should be granted in the label.

Because the severity of illness and duration of therapy for patients treated in Protocol 023 (acute pelvic infections) was not comparable to Protocol 017, the MO does not believe pathogen data from Protocol 023 should be considered in determining which pathogens will be granted for the complicated IAI indication.

Proportion of Favorable Microbiologic Response Assessments at Test of Cure Displayed by Baseline Pathogen in the Microbiologically Evaluable Population According to the MO—Total Isolates (Observed Data)

	Treatment Group				Observed Difference (A-B)	
	MK-0826 1 g (A) (N=195)		Piperacillin/Tazobactam (B) (N=189)			
Total Isolates	Observed Response n/m	%	Observed Response n/m	%	%	95% CI
Gram-Positive Aerobic Cocci	**111/129**	**(86.1%)**	**94/115**	**(81.7%)**	**4.3%**	**(-5.8%, 14.4%)**
Enterococcus	14/16	(87.5%)	9/10	(90.0%)		
Enterococcus avium	8/10	(80.0%)	3/4	(75.0%)		
Enterococcus casseliflavus	0/0	-	1/1	(100%)		
Enterococcus faecalis	22/25	(88.0%)	11/12	(91.7%)		
Enterococcus faecium	6/7	(85.7%)	1/5	(20.0%)		
Enterococcus gallinarum	1/1	(100%)	0/1	(0)		
Gemella morbillorum	1/1	(100%)	0/0	-		
Micrococcus	0/0	-	1/1	(100%)		
Staphylococcus	1/1	(100%)	1/1	(100%)		
Staphylococcus aureus[#]	4/6[#]	(66.7%)[#]	3/3	(100%)		
Staphylococcus epidermidis	3/3	(100%)	3/4	(75.0%)		
Staphylococcus haemolyticus	3/3	(100%)	0/0	-		
Staphylococcus, coagulase negative	3/4	(75.0%)	5/7	(71.4%)		
Streptococcus	5/6	(83.3%)	7/8	(87.5%)		
Streptococcus (alpha-hemolytic)	4/5	(80.0%)	5/6	(83.3%)		
Streptococcus (beta-hemolytic)	5/5	(100%)	2/4	(50.0%)		
Streptococcus (Group C)	0/0	-	1/1	(100%)		
Streptococcus (Group D)	5/5	(100%)	4/5	(80.0%)		
Streptococcus (Group F)	2/2	(100%)	0/0	-		
Streptococcus (microaerophilic)	0/0	-	0/0	-		
Streptococcus (nonhemolytic)	0/1	(0)	0/0	-		
Streptococcus agalactiae	1/1	(100%)	1/2	(50.0%)		
Streptococcus anginosus	1/1	(100%)	1/1	(100%)		
Streptococcus bovis	1/1	(100%)	3/3	(100%)		
Streptococcus constellatus	1/1	(100%)	3/3	(100%)		
Streptococcus intermedius	2/2	(100%)	4/4	(100%)		
Streptococcus milleri group	5/6	(83.3%)	4/6	(66.7%)		
Streptococcus mitis	1/1	(100%)	0/0	-		
Streptococcus pneumoniae	0/0	-	4/4	(100%)		
Streptococcus pyogenes	0/0	-	2/2	(100%)		
Streptococcus salivarius	2/2	(100%)	0/0	-		
Streptococcus sanguinis	1/1	(100%)	0/0	-		
Streptococcus viridans group	9/12	(75.0%)	15/17	(88.2%)		
Gram-Negative Aerobic Rods	**220/241**	**(91.3%)**	**199/222**	**(89.6%)**	**1.6%**	**(-4.1%, 7.4%)**
Acinetobacter	0/0	-	2/2	(100%)		
Acinetobacter baumannii	2/2	(100%)	0/0	-		
Acinetobacter calcoaceticus	5/5	(100%)	2/3	(66.7%)		
Acinetobacter lwoffi	1/1	(100%)	1/1	(100%)		
Aeromonas hydrophila	1/1	(100%)	0/0	-		
Alcaligenes faecalis	1/1	(100%)	0/0	-		
Campylobacter gracilis	0/1	(0)	3/3	(100%)		
Citrobacter	0/0	-	0/0	-		

Citrobacter amalonaticus	0/0	-	1/1	(100%)		
Citrobacter freundii	0/0	-	1/2	(50.0%)		
Citrobacter koseri	0/0	-	0/1	(0)		
Comamonas testosteroni	0/0	-	0/1	(0)		
Eikenella corrodens	1/1	(100%)	1/1	(100%)		
Enterobacter	1/2	(50.0%)	2/2	(100%)		
Enterobacter aerogenes	1/1	(100%)	3/3	(100%)		
Enterobacter cloacae	3/3	(100%)	6/6	(100%)		
Enterobacter gergoviae	1/1	(100%)	0/0	-		
Enterobacter intermedius	0/0	-	1/1	(100%)		
Enterobacter sakazakii	1/1	(100%)	0/0			
[redacted]	138/149‡	(92.6%)‡	116/128	(90.6%)		
Gram-negative aerobic rods	1/1	(100%)	0/0	-		
Haemophilus parainfluenzae	0/0	-	1/2	(50.0%)		
Hafnia alvei	0/0	-	1/1	(100%)		
Klebsiella	4/5	(50.0%)	2/2	(100%)		
Klebsiella oxytoca	6/6	(100%)	4/4	(100%)		
Klebsiella ozaenae	1/1	(100%)	3/3	(100%)		
Klebsiella pneumoniae	13/14	(92.9%)	12/16	(75.0%)		
Morganella morganii	2/2	(100%)	1/1	(100%)		
Pantoea agglomerans	2/2	(100%)	4/4	(100%)		
Proteus mirabilis	6/7	(85.7%)	3/3	(100%)		
Proteus vulgaris	6/6	(100%)	1/1	(100%)		
Pseudomonas	0/0	-	1/1	(100%)		
Pseudomonas aeruginosa	21/26	(80.7%)	23/25	(92.0%)		
Pseudomonas alcaligenes	0/0	-	1/1	(100%)		
Pseudomonas fluorescens	0/0	-	1/1	(100%)		
Pseudomonas mendocina	0/0	-	1/1	(100%)		
Pseudomonas stutzeri	0/0	-	1/1	(100%)		
Serratia marcescens	0/0	-	1/1	(100%)		
Shewanella putrefaciens	1/1	(100%)	0/0	-		
Sphingomonas paucimobilis	1/1	(100%)	0/0	-		
Gram-Negative Aerobic Cocci	**0/0**	-	**1/1**	**(100%)**	-	-
Neisseria	0/0	-	1/1	(100%)		
Gram-Positive Anaerobic Rods	**131/141**	**(92.9%)**	**102/111**	**(91.9%)**	**1.0%**	**(-6.4%, 8.4%)**
Actinomyces	1/1	(100%)	0/0	-		
Actinomyces naeslundii	1/1	(100%)	0/0	-		
Actinomyces odontolyticus	0/0	-	1/1	(100%)		
Bifidobacterium breve	1/1	(100%)	0/0	-		
Clostridium	3/4	(75.0%)	5/7	(71.4%)		
Clostridium barati	1/1	(100%)	0/0	-		
Clostridium bifermentans	2/2	(100%)	1/1	(100%)		
Clostridium butyricum	3/3	(100%)	1/1	(100%)		
Clostridium cadaveris	3/3	(100%)	1/1	(100%)		
[redacted]	18/19	(94.7%)	21/21	(100%)		
Clostridium cochlearium	0/0	-	1/1	(100%)		
Clostridium innocuum	17/17	(100%)	9/9	(100%)		
Clostridium leptum	1/1	(100%)	0/0	-		
Clostridium perfringens	13/15	(86.7%)	10/13	(76.9%)		
Clostridium ramosum	8/8	(100%)	4/4	(100%)		
Clostridium sordellii	2/2	(100%)	0/2	(0)		
Clostridium sphenoides	0/0	-	1/1	(100%)		
Clostridium sporogenes	1/1	(100%)	0/0	-		
Clostridium symbiosum	2/4	(50.0%)	1/1	(100%)		
Clostridium tertium	1/1	(100%)	1/1	(100%)		
Collinsella aerofaciens	1/3	(33.3%)	0/0	-		
Eubacterium	19/20	(95.0%)	16/16	(100%)		
Eubacterium contortum	1/1	(100%)	0/0	-		
[redacted]	20/21	(95.2%)	12/12	(100%)		
Eubacterium limosum	0/0	-	1/1	(100%)		
Gram-positive anaerobic rods‡	4/4	(100%)	6/7	(85.7%)		

Lactobacillus	3/3	(100%)	2/3	(66.7%)		
Lactobacillus casei	1/1	(100%)	0/0	-		
Lactobacillus catenaformis	0/0	-	2/2	(100%)		
Lactobacillus fermentum	1/1	(100%)	0/0	-		
Lactobacillus plantarum	1/1	(100%)	1/1	(100%)		
Propionibacterium	1/1	(100%)	2/2	(100%)		
Propionibacterium acnes	1/1	(100%)	2/2	(100%)		
Weissella confusa	0/0	-	1/1	(100%)		
Gram-Positive Anaerobic Cocci	**34/39**	**(87.2%)**	**27/29**	**(93.1%)**	**-5.9%**	**(-22.9%, 11.1%)**
Gram-positive anaerobic cocci‡	3/3	(100%)	1/3	(33.3%)		
[redacted]	11/13	(84.6%)	10/10	(100%)		
Peptostreptococcus anaerobius	4/5	(80.0%)	2/2	(100%)		
Peptostreptococcus asaccharolyticus	1/1	(100%)	0/0	-		
Peptostreptococcus magnus	2/2	(100%)	3/3	(100%)		
Peptostreptococcus micros	10/12	(83.3%)	10/10	(100%)		
Peptostreptococcus prevotii	1/1	(100%)	1/1	(100%)		
Peptostreptococcus tetradius	1/1	(100%)	0/0	-		
Ruminococcus productus	1/1	(100%)	0/0	-		
Gram-Negative Anaerobic Rods	**284/309**	**(91.9%)**	**272/289**	**(94.1%)**	**-2.2%**	**(-6.6%, 2.2%)**
Bacteroides	4/5	(80.0%)	10/12	(83.3%)		
Bacteroides caccae	8/9	(88.9%)	10/12	(83.3%)		
Bacteroides capillosus	2/2	(100%)	1/1	(100%)		
[redacted]	16/19	(84.2%)	25/25	(100%)		
Bacteroides eggerthii	1/1	(100%)	0/0	-		
[redacted]	65/74	(87.8%)	60/65	(92.3%)		
Bacteroides merdae	1/1	(100%)	2/2	(100%)		
[redacted]	20/21	(95.2%)	22/22	(100%)		
Bacteroides putredinis	1/4	(25.0%)	1/1	(100%)		
Bacteroides splanchnicus	2/2	(100%)	5/5	(100%)		
Bacteroides stercoris	5/5	(100%)	3/3	(100%)		
[redacted]	44/46	(95.7%)	32/33	(97.0%)		
[redacted]	21/22	(95.5%)	20/21	(95.2%)		
Bacteroides ureolyticus	0/0	-	1/1	(100%)		
Bacteroides vulgatus	8/9	(88.9%)	19/19	(100%)		
Bilophila	2/2	(100%)	0/0	-		
Bilophila wadsworthia	28/29	(96.6%)	24/26	(92.3%)		
Desulfovibrio	1/1	(100%)	0/0	-		
Dialister pneumosintes	2/2	(100%)	0/0	-		
Fusobacterium	2/2)	(100%	1/1	(100%)		
Fusobacterium gonidiaformans	1/1	(100%)	0/0	-		
Fusobacterium mortiferum	2/2	(100%)	2/2	(100%)		
Fusobacterium necrophorum	6/6	(100%)	3/3	(100%)		
Fusobacterium nucleatum	3/3	(100%)	2/2	(100%)		
Fusobacterium varium	2/2	(100%)	2/2	(100%)		
Gardnerella vaginalis	0/0	-	1/1	(100%)		
Gram-negative anaerobic rods‡	5/5	(100%)	3/6	(50.0%)		
Porphyromonas	1/1	(100%)	1/1	(100%)		
Porphyromonas asaccharolytica	5/5	(100%)	5/6	(83.3%)		
Porphyromonas gingivalis	2/2	(100%)	0/0	-		
Prevotella	4/4	(100%)	5/5	(100%)		
Prevotella bivia	0/0	-	2/2	(100%)		
Prevotella buccae	5/5	(100%)	3/3	(100%)		
Prevotella corporis	1/1	(100%)	0/0	-		
Prevotella denticola	0/1	(0)	0/0	-		
Prevotella disiens	0/0	-	1/1	(100%)		
Prevotella heparinolytica	0/0	-	1/1	(100%)		
Prevotella intermedia^	8/9^	(88.9%)^	3/3	(100%)		
Prevotella melaninogenica	4/4	(100%)	2/2	(100%)		
Prevotella oris	1/1	(100%)	0/0	-		
Tissierella praeacuta	1/1	(100%)	0/0	-		

Gram-Negative Anaerobic Cocci	**2/2**	**(100%)**	**3/3**	**(100%)**	- - -
Veillonella	1/1	(100%)	2/2	(100%)	
Acidaminococcus fermentans	1/1	(100%)	1/1	(100%)	
Bacteria	**0/0**	-	**1/1**	**(100%)**	- - -
Bacteria	0/0	-	1/1	(100%)	
Other Bacteria	**5/5**	**(100%)**	**3/4**	**(75.0%)**	- -
Aerobic gram-variable rods‡	0/0	-	1/1	(100%)	
Anaerobes, gram-negative‡	1/1	(100%)	0/0	-	
Gram-negative bacteria‡	1/1	(100%)	0/0	-	
Gram-negative rods‡	1/1	(100%)	1/2	(50.0%)	
Gram-positive bacteria‡	1/1	(100%)	0/0	-	
Gram-positive rods‡	1/1	(100%)	1/1	(100%)	

‡ These organisms were not further categorized by the investigative site.
N = Number of microbiologic evaluable patients in each treatment group.
n/m = Number of pathogens with associated favorable assessment/number of pathogens with an assessment.
CI = Confidence interval.
# If the one patient (AN) with *S.aureus* on entry blood culture who was a presumed micro failure is included then the n/m = 4/7 with a 57% favorable response.
! If the one patient (AN) with *E.coli* on entry blood culture who was a presumed micro failure is included then the n/m = 138/150 with a 92% favorable response.
^ If the one patient (AN) with *P. intermedia* on entry blood culture who was a presumed micro failure is included then the n/m = 8/10 with a 80% favorable response.

Blood Isolates

The Applicant also compared the microbiologic response rates in the 2 treatment groups by baseline blood isolates. In this analysis a microbiologically evaluable patient had to have a baseline blood pathogen (presumed at least partially responsible for IAI) to be included. In the Applicant's analysis of microbiologic responses for blood isolates, the only presumed outcome that was considered valid was presumed eradication; presumed persistence was not considered a valid outcome by the Applicant. (Failure to obtain a blood culture in the setting of a clinical failure was not used to presume persistent bacteremia. Rather, in this setting, the outcome of these pathogens was excluded from the Applicant's per-pathogen analysis of blood isolates.) A table displaying the proportion of favorable microbiologic response assessments in patients with baseline blood isolates, according to the Applicant, is displayed in Appendix 7.

Medical Officer's Comment: ***The MO did not feel that patients who were otherwise evaluable failures should be excluded from this analysis based on the absence of repeat blood cultures, but that they should be considered to have presumed persistence and be considered to have an unfavorable outcome.***

Five patients (3 in the MK-0826 1 gm group: ANs 0722, 0801, and 5340 and 2 in the piperacillin/tazobactam group: ANs 0362 and 0789) with positive entry blood cultures were therefore considered failures based on presumed persistence by the MO. In addition, based on the MO's evaluability and outcome criteria, one additional patient (AN 0285) with E. coli, in the MK-0826 group, was considered an evaluable failure. The MO's revised table for outcome of patients with baseline pathogen blood isolates is provided below.

Proportion of Favorable Microbiologic Response Assessments At Test of Cure Displayed by Baseline Pathogen in the Microbiologically Evaluable Population According to the MO—Blood Isolates (Observed Data)

Blood Isolates	Treatment Group: MK-0826 1 g (A) (N=13) n/m	Observed %	Response (95% CI)	Piperacillin/Tazobactam (B) (N=19) n/m	Observed %	Response (95% CI)	Observed Difference (A-B) %
Gram-Positive Aerobic Cocci	**1/2**	**50**		**7/7**	**100**		**-50**
Enterococcus faecalis	-	-		1/1	100		-
Micrococcus	-	-		1/1	100		-
Staphylococcus, coagulase negative	-	-		3/3	100		-
Streptococcus (Group D)	-	-		1/1	100		-
Streptococcus pneumoniae	-	-		1/1	100		-
Viridans Streptococcus group	1/1	100		-	-		-
S. aureus	0/1	0					-
Gram-Negative Aerobic Rods	**7/8**	**88**		**7/8**	**88**		**0**
Acinetobacter	-	-		1/1	100		-
Acinetobacter calcoaceticus	2/2	100		1/2	50		50
Escherichia coli	3/4	75		3/3	100		30
Klebsiella oxytoca	1/1	100		-	-		-
Klebsiella pneumoniae	-	-		1/1	100		-
Pantoea agglomerans	-	-		1/1	100		-
Proteus vulgaris	1/1	100		-	-		-
Gram-Positive Anaerobic Rods	-	-		**1/1**	**100**		-
Propionibacterium	-	-		1/1	100		-
Gram-Negative Anaerobic Rods	**1/3**	**33**		**1/2**	**50**		**-17**
Bacteroides spp.	1/2	50		1/2	50		0.0
Prevotella intermedia	0/1	0					
Other Bacteria	-	-		**1/1**	**100**		-
Gram-negative rods[1]	-	-		1/1	100		-

[1] These organisms were not further categorized by the investigative site.
N = Number of microbiologically evaluable patients with baseline pathogens isolated from blood in each treatment group.
n/m = Number of pathogens with associated favorable microbiologic response assessment/number of pathogens with an assessment.
CI = Confidence interval.

6.1.5.5 Reviewer's Comments/Conclusions of Study

In adult patients with complicated intra-abdominal infections (IAI) treated for 5 to 14 days with intravenous administration of MK-0826 1gm per day, the following conclusions can be drawn:

1. MK-0826 1 gm IV once daily is clinically and microbiologically as effective as piperacillin/tazobactam 3.375 gm every 6 hours in treating complicated IAI.
2. Based on the results of Protocol 017, the Applicant has provided adequate data to substantiate the inclusion of the following organism list in the INDICATIONS AND ADMINISTRATION section of the label for complicated intra-abdominal infections: "*Escherichia coli, Clostridium clotridiiforme, Eubacterium lentum, Peptostreptococcus* species, *Bacteroides fragilis, Bacteriodes distasonis, Bacteriodes ovatus, Bacteriodes thetaiotaomicron,* or *Bacteriodes uniformis.*"
3. Based on the results of Protocol 017, the Applicant has not provided adequate data to substantiate the inclusion of a statement regarding patients with

bacteremia due to *E. coli* in the INDICATIONS AND ADMINISTRATION or CLINICAL STUDIES sections of the label for this indication.

4. For conclusions regarding the safety and tolerability of MK-0826, in this study, see section 7.1.1 of this review.

6.1.6 Indication Conclusion

The Applicant has provided adequate data to support the granting of the **Complicated Intra-Abdominal Infections** indication for MK-0826 1 gm IV once daily for 5 to 14 days.

In adult patients with complicated intra-abdominal infections treated for 5 to 14 days with intravenous administration of MK-0826 1gm per day, the following conclusions can be drawn:

1. The results of Protocol 017 support the conclusion that MK-0826 1 gm IV once daily was clinically and microbiologically as effective as piperacillin/tazobactam 3.375 gms every 6 hours in treating complicated intra-abdominal infections in adults.
2. The results of the pivotal Phase III Protocol 023 (acute pelvic infections protocol) provide supportive evidence for the efficacy of MK-0826 in the treatment of complicated intra-abdominal infections in adults.
3. Based on the results of Protocol 017, the Applicant has provided adequate data to substantiate the inclusion of the following list of organisms in the INDICATIONS AND ADMINISTRATION section of the label for this indication: "*Escherichia coli, Clostridium clotridiiforme, Eubacterium lentum, Peptostreptococcus* species, *Bacteroides fragilis, Bacteriodes distasonis, Bacteriodes ovatus, Bacteriodes thetaiotaomicron,* or *Bacteriodes uniformis*."
4. Based on the results of Protocol 017, the Applicant has not provided adequate data to substantiate the inclusion of a statement regarding patients with bacteremia due to *E. coli* in the INDICATIONS AND ADMINISTRATION or CLINICAL STUDIES sections of the label for this indication.
5. The CLINICAL STUDIES section of the label should be revised to include overall efficacy results and results by disease site stratum and severity of infection to reflect key study design features and outcome findings. A table of efficacy by-pathogen should not be included in the CLINICAL STUDIES section of the label for this indication.
6. MK-0826 1 gm IV once daily for 5 to 14 days was generally safe and well tolerated in adult patients with complicated intra-abdominal infections; however, the statistically significant greater percentage of deaths during parenteral therapy and the trend toward a greater percentage of deaths in the entire study period in the MK-0826 group is concerning. A comparison of death rate between MK-0826 and comparator agents will be further explored in the Integrated Summary of Safety.

6.2 Acute Pelvic Infections (API) Indication

6.2.1 Reviewer: Jean M. Mulinde
Medical Officer, HFD-520

6.2.2 Indication Review Dates

6.2.2.1 Received by reviewer:	December 5, 2000
6.2.2.2 Review begun:	March 15, 2001
6.2.2.3 Review completed:	July 22, 2001
6.2.2.4 Review revised:	September 18, 2001

6.2.3 Indication Specific Proposed Label Claims and Critical Differences From Applicant's Proposed Claims

The Applicant has proposed the following label claims in reference to the acute pelvic infections indication:

- In the **INDICATIONS AND USAGE** section of the label:

"Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections due to *Streptococcus agalactiae, Escherichia coli,* *Peptostreptococcus* species,

And at the end of the entire section, as a separate paragraph:

Medical Officer's Comment: ***Based on the MO review that follows the MO recommends that this section be amended to the following:***

"Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections due to *Escherichia coli, Streptococcus agalactiae, Bacteroides fragilis, Porphyromonas asaccharolytica, Prevotella bivia,* and *Peptostreptococcus* species."

The separate paragraph above should be completely removed from the label. The Applicant has not provided adequate data to support bacteremia claims for complicated intra-abdominal infections or acute pelvic infections. Statements regarding E. coli bacteremia in patients with complicated urinary tract infections and S. pneumoniae in patients with community acquired pneumonia should be incorporated into the specific indication statements.

- In the **DOSAGE AND ADMINISTRATION** section of the label:

[redacted] dose of INVANZ in adults is 1 gram (g) given once a day.

INVANZ may be administered by intravenous infusion or intramuscular injection. When administered intravenously, INVANZ should be infused over a period of 30 minutes.

Intramuscular administration of INVANZ may be used as an alternative to intravenous administration in the treatment of those infections for which intramuscular therapy is appropriate.

DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

Table 7 presents dosage guidelines for INVANZ.

Table 7
Dosage Guidelines for Adults With Normal Renal Function* and Body Weight

Infection†	Daily Dose (IV or IM)	Recommended Duration of Total Antimicrobial Treatment
Complicated intra-abdominal infections	1 g	5 to 14 days
Complicated skin and skin structure infections [redacted]	1 g	7 to 14 days
Community acquired pneumonia	1 g	10 to 14 days‡
Complicated urinary tract infections, including Pyelonephritis	1 g	10 to 14 days‡
Acute pelvic infections including postpartum Endomyometritis, septic abortion and post surgical Gynecologic infections	1 g	3 to 10 days

* defined as creatinine clearance >90 mL/min/1.73 m^2

† due to the designated pathogens (see INDICATIONS AND USAGE)

‡ duration includes a possible switch to an appropriate oral therapy once clinical improvement has been demonstrated.

[redacted]

Medical Officer's Comment: ***Many of the statements in the text and table are repetitive. In the first sentence of the "Dosage and Administration" section, the statement "usual dose" is too vague to provide meaningful dosing instructions. The paragraph that follows Table 7 provides limited information beyond that in the table and is therefore not needed. In Table 7, the footnote "‡" should be revised to state "duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated." This change will reflect the design of the studies used to support the indications for which an oral switch was allowed.***

Based on the MO review that follows and the prior MO comment, the MO recommends that the "Dosage and Administration" section be amended to the following:

"The dose of INVANZ in adults with normal renal function is 1 gram (g) given once a day.

INVANZ may be administered by intravenous infusion for up to 14 days or by intramuscular injection for up to 7 days. When administered intravenously, INVANZ should be infused over a period of 30 minutes.

DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

Table 7 presents dosage guidelines for INVANZ.

Table 7
Dosage Guidelines for Adults With Normal Renal Function* and Body Weight

Infection†	Daily Dose (IV or IM)	Recommended Duration of Total Antimicrobial Treatment
Complicated intra-abdominal infections	1 g	5 to 14 days
Complicated skin and skin structure infections	1 g	7 to 14 days
Community acquired pneumonia	1 g	10 to 14 days‡
Complicated urinary tract infections, including Pyelonephritis	1 g	10 to 14 days‡
Acute pelvic infections including postpartum Endomyometritis, septic abortion and post surgical gynecologic infections	1 g	3 to 10 days

* defined as creatinine clearance >90 mL/min/1.73 m^2
† due to the designated pathogens (see INDICATIONS AND USAGE)
‡ duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.

- In the **CLINICAL STUDIES** section of the label:

"Acute Pelvic Infections including endomyometritis, septic abortion and post surgical gynecologic infections

Ertapenem was evaluated in adults for the treatment of acute pelvic infections [redacted] clinical trial. This study compared ertapenem (1 g IV once a day) with piperacillin/tazobactam (3.375 g IV every 6 hours) for 3 to 10 days and enrolled 412 patients including 350 patients with obstetric/postpartum infections and 45 patients with septic abortion. The clinical success rates at 2 to 4 weeks posttherapy (test of cure) were 93.9% (153/163) for ertapenem and 91.5% (140/153) for piperacillin/tazobactam.

[redacted]

Medical Officer's Comment: ***Based on the recently published draft Guidance for Industry on the clinical studies section of labels[5] and on the MO review that follows the MO recommends that this section be amended to the following:***

- In the **CLINICAL STUDIES** section of the label:

"Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections

Ertapenem was evaluated in adults for the treatment of acute pelvic infections in a clinical trial. This study compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 3 to 10 days and enrolled 412 patients including 250 patients with obstetric/postpartum infections and 45 patients with septic abortion. The clinical success rates in the clinically evaluable population at 2 to 4 weeks posttherapy (test of cure) were 93.9% (153/163) for ertapenem and 91.5% (140/153) for piperacillin/tazobactam.

6.2.4 General Review Approach to Review of the Efficacy of the Drug for the Acute Pelvic Infections Indication

The Phase IIb/III program conducted by the Applicant in support of the acute pelvic infection indication included a pivotal, statistically adequate, noninferiority study (Protocol 023) that compared MK-0826 to piperacillin/tazobactam. The pivotal Phase IIB study of complicated intra-abdominal infections (Protocol 017) is intended to be used as supportive evidence of the efficacy of MK-0826 in the treatment of acute pelvic infections. The efficacy results of studies 017 and 023 are reviewed in detail in the sections 6.1.5 and 6.2.5, respectively, of this review.

The following table displays summary data for the clinical studies conducted in patients with intra-abdominal infections (Protocols 004 and 017) and the single clinical study conducted in patients with acute pelvic infections (Protocol 023).

[5] Guidance for Industry. Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format. Published 6/29/01.

Summary of Clinical Studies
Relating to Complicated Intra-Abdominal Infections Indication

Protocol	Location†	Pivotal/ Supportive	Study Regimens						Oral Switch?	IM Therapy?	Primary Analysis	
			Ertapenem	N (n)‡		Comparator	N (n)‡				Evaluable Population	Primary Analysis Response
Complicated Intra-Abdominal Infection												
004	US/Int	IIa	ETP 1 g q.d.	59	(31)	CRO* 2 g q.d.*	110	(72)	Yes	No	Clinical and Microbiologic	Clinical and microbiologic response
			ETP 1.5 g q.d.	51	(29)							
017	US/Int	Pivotal	ETP 1 g q.d.¶	323	(203)	P/T 3.375 g q6h¶	328	(207)	No	No	Microbiologic	Clinical and microbiologic response
			ETP 1.5 g q.d.¶	14	(7)							
Acute Pelvic Infection												
023	US/Int	Pivotal	ETP 1 g q.d.¶	216	(163)	P/T 3.375 g q6h¶	196	(153)	No	No	Clinical	Clinical response

† Abbreviations used in this table: CRO, ceftriaxone; ETP, ertapenem; IIa, Phase IIa study; Int, International; P/T, piperacillin/tazobactam; US, United States.
‡ N, number of patients randomized to each regimen; n, number of patients in primary analysis evaluable population.
*Patients on CRO also received blinded metronidazole therapy for anaerobic coverage.
¶ Patients could have received optional open vancomycin therapy for resistant gram-positive bacterial infections.

(Modified from Applicant's Table 1, Volume 1 of 22, Worldwide Clinical Summary, page 5)

APPEARS THIS WAY
ON ORIGINAL

6.2.5 PROTOCOL 023: A PROSPECTIVE, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, COMPARATIVE STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF MK-0826 VERSUS PIPERACILLIN/TAZOBACTAM IN THE TREATMENT OF ACUTE PELVIC INFECTION IN HOSPITALIZED WOMEN

6.2.5.1 Objective/Rationale

The objectives of the study, as stated by the Applicant, were:

Primary Objectives

1. To compare the efficacy of intravenous MK-0826 and piperacillin/tazobactam with respect to the clinical response assessment profile in the treatment of patients with acute pelvic infection at the 2- to 4- week posttreatment follow-up visit.
2. To evaluate the safety profile of MK-0826 versus piperacillin/tazobactam with respect to the proportion of patients with any drug-related adverse experiences leading to discontinuation of study drug and also with respect to the proportion of patients with any drug-related serious adverse experience.

Secondary Objectives

1. To compare the efficacy of MK-0826 and piperacillin/tazobactam with respect to both the clinical response assessment and the microbiologic assessment profile in the treatment of patients with acute pelvic infections at the follow-up visit 2- to 4- weeks posttreatment.
2. To evaluate and compare the tolerability profile of the intravenous MK-0826 and piperacillin/tazobactam in patients with acute pelvic infections.

Medical Officer's Comment: ***The primary efficacy objective is consistent with the IDSA's 1992 Guideline for the Evaluation of New Anti-Infective Drugs for the Treatment of Acute Pelvic Infections in Hospitalized Women [6] and the 1992 FDA Points to Consider for Clinical Development and Labeling of Anti-Infective Drug Products.***

6.2.5.2 Design

This was a prospective, randomized, multicenter, double-blind, active-treatment-controlled, comparative equivalence study conducted at 47 centers in the United States and 19 centers internationally. Thirty centers in the United States and 17 centers internationally (10 from Latin America, 4 from Eastern and Western Europe, and 3 from Canada) actually enrolled patients between November 3, 1998 and May 9, 2000.

[6] Hemsell et al., Clinical Infectious Diseases 1992;15(Suppl.1):S43-52.

Patients who met all of the entry criteria and had a clearly defined pelvic infection, characterized by the investigator as severe enough to require parenteral therapy for 3-10 days, were randomized to 1 of the 2 study regimens in a 1:1 ratio. Allocations were stratified for balance based upon the diagnosis of obstetric/postpartum infection (included patients postvaginal delivery, postcesarean section, and with septic abortion) or gynecologic/postoperative infection. MK-0826 was given as a single daily 1-g dose of intravenously infused over a 30-minute interval. Piperacillin/tazobactam was given every 6 hours, 3.375 g per IV dose, infused over a 30-minute interval. In order to maintain blinding, a piperacillin/tazobactam placebo was administered intravenously at Hours 6, 12, and 18 of the daily dosing intervals to patients randomized to receive MK-0826. The recommended duration of therapy was between 3 and 10 days.

Patients had an initial screening evaluation within 24 hours of enrollment. Prestudy pelvic cultures were to be obtained within 24 hours of enrollment for all patients. If no admission pathogen was isolated, the patient remained in the study for clinical evaluation only. If the admission culture was known prior to enrollment to contain a pathogen resistant to either study drug, the patient should not have been enrolled in the study. If the admission pathogen (unknown at admission) was found during the study to be resistant to either of the study drugs, it was left to the investigator's judgment whether to discontinue the patient. If the patient showed no clinical improvement, the patient should have been discontinued as a failure. An evaluation of clinical signs and symptoms of infection, including a pelvic examination with detailed description of extent of the infection, abnormal vaginal discharge, presence of a pelvic mass, and wound condition (if applicable), a targeted physical exam, and microbiological cultures (if clinically indicated) were performed at baseline, at the discontinuation of intravenous therapy (DCIV) visit, and at the test-of-cure (TOC) visit, 2 to 4 weeks posttreatment. Vital signs were performed at each study visit and daily while the patient was on parenteral therapy.

The safety of parenteral MK-0826 and of parenteral piperacillin/tazobactam was evaluated by determining the presence or absence of clinical or laboratory adverse experiences. Patients were monitored for adverse experiences on a daily basis during the parenteral study antimicrobial period and for at least 14 days after the last dose of study drug. Adverse events of special interest, as identified by the Applicant, included: seizures (regardless of prior seizure history), elevated transaminases, neutropenia, and rash of sufficient severity to require discontinuation of study therapy. The schedule of clinical observations and laboratory measurements is in Appendix 9.

At the follow-up (TOC) visit 2- to 4-weeks posttherapy, clinical efficacy was determined based upon the investigator's assessment of clinical response to therapy. Microbiological efficacy was determined based upon the results of bacterial cultures, or was presumed based upon clinical response if cultures were not repeated.

In addition to the primary study, the protocol was amended during the course of the study to include a lactation substudy that was conducted at selected U.S. study sites. The objective of the substudy was to determine the penetration of MK-0826 into the breast milk when administered intravenously to lactating women and to examine the time to clearance from breast milk over a 5-day period after the last dose of study therapy. Blood samples were assayed for total MK-0826 drug concentration along with breast milk samples collected at prestudy and once within the first 12 hours after the last "A" dose (the bag that always contained active drug, either MK-0826 or piperacillin/tazobactam) of IV study drug. Another breast milk sample was collected between Hours 12 and 24 after the last "A" dose of IV study drug. On Days 2 through 5 posttreatment, a morning breast milk sample was collected. All samples were frozen immediately after collection and were shipped to MRL for analysis.

Medical Officer's Comment: ***According to the protocol the minimum duration of therapy was specified as 3 days, which is not consistent with the recommendation for a minimum duration of 4 days specified in the 1992 IDSA guidelines[7] for clinical trials for this indication. However, since this concern was not communicated to the Sponsor at the time the protocol was initially submitted to the Agency for review, a minimum duration of therapy of 3 days was accepted in this review to consider a patient clinically evaluable.***

The protocol also allowed the TOC visit to be conducted as a telephone interview provided a DCIV visit had been conducted and the patient's responses to the phone interview were adequately documented. Although the IDSA guidelines suggest such an approach is acceptable for up to 20% of enrolled patients, in general this is not considered an adequate assessment for the purposes of providing data of regulatory quality. Since only a small percentage of TOC visits were actually conducted in this manner, the MO accepted patients with TOC phone assessments as evaluable provided the interview was within the TOC time window and was conducted with the patients themselves.

It is also notable that the protocol was amended during the course of the study to provide additional blinding procedures when it was recognized that a slight color difference could sometimes be detected between MK-0826 and placebo. Measures implemented by the Applicant to assure the study drug blind was maintained included: limits on the time of reconstitution; limits on the choice of the final infusion container; prompt disposal of study infusion bags after use; and the use of amber-colored translucent bag covers.

6.2.5.3 Protocol Overview

6.2.5.3.1 Population/Procedures

Inclusion and exclusion criteria were applied in order to enroll patients with appropriate pelvic infections that were likely to be treatable with 3 to 10 days of parenteral therapy. The following are the Applicant's noteworthy inclusion and exclusion criteria:

Noteworthy Inclusion Criteria

1. At entry, patient must have had:

---

[7] Hemsell et al., Clinical Infectious Diseases 1992;15(Suppl.1):S43-52.

a. Oral temperature >38°C (100.4°F),

AND EITHER

b. White blood cell (WBC) count >10,500/mm^3,

OR

WBC differential indicating >10% immature granulocytes (band forms)

2. And at least one of the following:

   a. Pelvic, abdominal, or uterine pain, or cramping.
   b. b. Pelvic, abdominal, or uterine tenderness.
   c. Sonographic or other imaging study that suggested pelvic abscess or infection.

3. Patients were required to have had a vaginal delivery, cesarean section, or gynecologic surgery from at least 24 hours up to 1 month prior to enrollment. (Patients having signs or symptoms of acute pelvic infection in inclusion criterion 2. above within the first 24 hours following any of the above procedures may have been enrolled if their temperature was at least 101.5°F [38.6°C] in this time period.) Although it was anticipated that most patients would have been enrolled postoperatively or postpartum, patients who presented with a well-documented (radiologically or surgically confirmed) pelvic infection without a recent history of gynecologic surgery or delivery (for example, in association with appendicitis or diverticulitis) were permitted, and were grouped with the stratum of postoperative infections.
4. Patients with a diagnosis of septic abortion were allowed to enroll if the severity of their illness required a minimum of 3 full days of IV therapy. These patients were grouped with the stratum of postpartum infections. No more than 15% of those enrolled should have had a diagnosis of septic abortion.
5. Specimens from the endometrium or other infected site were taken within 24 hours of enrollment into the study and prior to administration of study antibiotic using a method to avoid vaginal contamination (e.g., Unimar Pipelle™). These specimens were sent for culture and susceptibility testing.
6. Patient was a female ≥16 years of age. (Patients <16 years of age were enrolled by specific waiver.)
7. Females of childbearing potential were required to have had a negative serum pregnancy test (β-human chorionic gonadatropin [β-hCG]) prior to enrollment into the study (or must have delivered within 2 weeks) and, subsequently, for at least 1 month following study treatment patients were to have used adequate birth control measures as discussed with the investigator. Hormonal contraceptives were not to be used as the sole method of birth control, because

the effect of MK-0826 on the efficacy of hormonal contraceptives had not yet been established.

8. Nursing women were allowed to participate if they agreed to defer breast feeding until 5 days after completion of therapy to allow elimination of the drug from breast milk.
9. The patient's infection was expected to require at least 3 full days of antibiotic therapy.

Noteworthy Exclusion Criteria

1. Patients with a diagnosis of pelvic inflammatory disease, tubo-ovarian abscess, or postoperative abdominal wall infection. Patients were tested for Chlamydia infection if appropriate, as judged by the investigator.
2. The need for concomitant systemic antimicrobials (other than vancomycin or antifungal agents) in addition to those designated in the 2 study groups.
3. Patients with active gynecologic malignancy were excluded, unless the tumor had been adequately resected by surgery. However, patients who were receiving chemotherapy or radiation therapy were excluded.
4. Concurrent infection that would have interfered with evaluation of response to the study antibiotic.
5. Patients with renal or hepatic dysfunction as indicated below:

   a. Patients requiring hemodialysis, peritoneal dialysis, or hemofiltration were excluded. For patients with renal insufficiency and not requiring dialysis, the dose of study drug was adjusted based upon the degree of renal function impairment as determined by the estimated or actual creatinine clearance.

   b. Liver function tests:

      1) Alanine transaminase [ALT], aspartate transaminase [AST] >6 times the upper limit of the normal range (ULN) of values used by the laboratory performing the test. Patients with elevations of AST and/or ALT up to 10 times ULN were allowed if these elevations were acute and directly related to the infectious process being treated.
      2) Bilirubin >3.0 times ULN, unless isolated hyperbilirubinemia was directly related to the acute infection.
      3) Alkaline phosphatase >3.0 times ULN. Patients with values >3.0 times ULN and up to 5.0 times ULN were eligible if this value was historically stable.

   c. Patients with acute hepatic failure or acute decompensation of chronic hepatic failure were excluded.

6. Hematocrit <20% or hemoglobin <6 g/dL.

7. Neutropenia with absolute neutrophil count (ANC) <1000/mm^3. Patients with neutrophil counts as low as 500 cells/mm^3 were permitted if this reduction was due to the acute infectious process.
8. Platelet count <75,000/mm^3. Patients with platelet counts as low as 50,000/mm^3 were permitted if this reduction was historically stable.
9. Coagulation tests >1.5 times ULN (prothrombin time [PT] and partial thromboplastin time [PTT] and/or international normalized ratio [INR]). Patients who were on anticoagulant therapy with values >1.5 times ULN were enrolled, provided these values were stable and within the therapeutic range.
10. Patients who had hypotension with acute hemodynamic instability (such as a systolic BP <90 mm Hg that required pressor support). The requirement of volume repletion (but not pressors) for support of blood pressure (maintaining systolic BP >90 mm Hg) was allowed.
11. Patient had received more than 1 dose of an effective systemic antimicrobial regimen for the infection within the 72-hour period prior to study entry unless the patient was considered to have failed the previous treatment regimen. (Surgical or intrapartum prophylaxis was allowed.)
12. Immunosuppressive therapy, or use of high-dose corticosteroids (e.g., 40 mg or more of prednisone or equivalent per day).
13. Diagnosis of acquired immunodeficiency syndrome (AIDS), according to current Center for Disease Control (CDC) criteria.

Medical Officer's Comment: ***The Applicant's inclusion and exclusion criteria are acceptable and in general accordance with recommendations in the 1992 FDA Points to Consider for Clinical Development and Labeling of Anti-Infective Drug Products and with the IDSA's 1992 Guidelines for the Evaluation of New Anti-Infective Drugs for the Treatment of Acute Pelvic Infections[8].***

The Applicant's inclusion criteria for temperature and WBC were amended after the start of the study to require patients to meet both minimal criteria as opposed to one or the other; therefore some patients were enrolled that met only the minimal temperature elevation criterion or the minimal WBC elevation criterion. The MO accepted patients that met the minimal disease definition so long as they met either of these criteria in addition to the remaining criteria.

6.2.5.3.2 Evaluability Criteria

According to the Applicant, determinations of evaluability for the per protocol and MITT populations were made prior to unblinding using the prespecified criteria stated in the Data Analysis Plan (DAP). The following criteria were used by the Applicant to define study populations for analysis:

Screened population

All patients who signed consent for the study. This population includes those patients who were not randomized to therapy and those patients who were randomized to therapy.

[8] Hemsell et al., Clinical Infectious Diseases 1992;15(Suppl.1):S43-52.

Randomized population
A subset of the screened population comprising patients who were randomized to a study regimen, irrespective of whether the patient actually received therapy. Patients randomized to 1 treatment group who, due to dispensing errors, mistakenly received study therapy with the other study treatment for the entire parenteral study period were analyzed and displayed throughout based on the study therapy actually received. Patients who, due to dispensing errors, received both parenteral study drugs at any time during the course of the study were analyzed based on the treatment group to which they were originally randomized.

Treated population
A subset of the randomized population comprising patients who received at least 1 dose of study therapy. Only treated patients are included in the analysis of safety.

Clinical MITT population
A subset of the treated population comprising patients that met the minimal disease definition.

Microbiologic MITT population
A subset of the clinical MITT population, comprised those clinical MITT patients who had a baseline pathogen identified, regardless of susceptibility to study agents, and a microbiologic response assessed.

Clinically evaluable population
A subset of the clinical MITT population comprising patients in whom sufficient information was available to determine the patients' outcome and no confounding factors were present that interfered with the assessment of that outcome; furthermore, it was required that if baseline pathogens were identified, one or more of these pathogens were susceptible to both parenteral study therapies.

Study specific criteria for the API indication that were provided in the Applicant's DAP required that the patient meet the clinical and microbiologic criteria as specified in the inclusion criteria. The following additional criteria were also provided in the DAP:

1) The test-of-cure visit is 12-42 days after the end of study therapy. A telephone follow-up is acceptable for test-of-cure provided there is adequate documentation.
2) Patients should have received ≥80% of the intended doses to be considered evaluable. MK-0826 is administered once per day as dose "A" and piperacillin/tazobactam is administered four times a day as doses "A", "B", "C", and "D". Therefore, in the blinded preliminary assessment patients must receive ≥80% of the intended "A" doses and ≥80% of the intended "A", "B", "C", and "D" doses. In the unblinded confirmatory assessment, patients must receive ≥80% of the intended doses of randomized therapy.

3) Patients must receive ≥3 and ≤12 days of total study therapy to be considered an evaluable success. Patients must receive >48 hours of parenteral therapy to be considered an evaluable failure.

The DAP also included the following "Evaluability exclusions" for the API study:

1) Exclusions resulting from prior antimicrobials
   a) Patients who have failed surgical/obstetrical prophylaxis are evaluable. For other patients, no more than one dose of "appropriate" non-study therapy allowed within 72 hours of study entry unless there is evidence of clinical failure with a persistent pathogen. Patients who have been treated for chorioamnionitis during delivery and meet criteria for study entry will be considered to have failed therapy for chorioamnionitis, and will be evaluable if a pathogen is demonstrated from specimens obtained at study entry. Similarly, patients who have received parenteral antibiotics in order to delay preterm delivery will be acceptable if they otherwise meet entry criteria.
   b) More than one dose of antimicrobials (either single agent or regimen) following the procedure at which the entry culture was obtained.
2) Exclusions resulting from concomitant antimicrobials
   a) Use of more than one dose of a non-study systemic antimicrobial with activity against the pathogen under study for reasons other than clinical failure. If a non-study systemic antimicrobial with activity against the pathogen under study is used after study therapy is completed and the patient is subsequently a clinical failure prior to or at the test-of-cure visit, then the patient can still be a "protocol-evaluable" failure. Vancomycin for MRSA or enterococci in mixed infections is acceptable but renders all gram positive pathogens of the mixed infection indeterminate. Similarly, use of dicloxacillin for the treatment of mastitis will be acceptable but renders all gram positive pathogens of the mixed infection indeterminate. A switch to non-study therapy will be considered an evaluable failure if clinical signs of pelvic infection are present or non-evaluable if there are no signs of ongoing pelvic infection.
3) Exclusion due to baseline or intercurrent medical events
   a) Patients must not have any of the following at the time of study entry or within 48 hours of admission:
      i) infections excluded at baseline:
         a) PID
         b) TOA
         c) post-operative abdominal wall infection
      ii) No evidence of intra-abdominal and/or intra-pelvic infection
      iii) Absolute neutrophil counts <500 cells/mm^3 prior to therapy
   b) Patients must not have had any of the following at study entry through the test-of-cure visit if they interfere with evaluation of the response to study therapy:
      i) concurrent surgical or medical condition

ii) active gynecologic malignancy or use of chemotherapy or radiotherapy
iii) chronic immunosuppressive therapy (chemotherapy/immunosuppressants or prednisone >40 mg/d or its equivalent) or AIDS; HIV-infection without AIDS is acceptable

4) Exclusion due to base-line microbiology
   a) isolation of a sole aerobic pathogen not susceptible (I or R) to either parenteral study drug.

Microbiologically evaluable population
A subset of the clinically evaluable population, comprised of those clinically evaluable patients who had a baseline pathogen identified and a microbiologic response assessed.

The Applicant's DAP also required that for Protocol 023 microbiologic evaluability that "patients must have an aerobic pathogen isolated form a pre-study culture taken either by protected endometrial sampling, percutaneous procedure, ot other method that minimizes contamination by vaginal flora, that is susceptible to both MK-0826 and comparator, or an anaerobe isolated, in which case susceptibility data are not required. Patients must have at test-of-cure either a microbiology specimen collected or be presumed eradicated/persistent."

Medical Officer's Comment: ***The MO accepted the Applicant's criteria for determining evaluability and used them in the MO's blinded reviews of CRFs with the following additions:***

- ***For those patients who had a TOC assessment via phone, phone contact had to be made directly with the patient in order to consider the patient clinically evaluable.***
- ***If the patient was treated with a non-study antimicrobial (with more than one dose) for an infection unrelated to the index infection prior to the TOC visit, then the patient was considered clinically unevaluable (and with indeterminate outcome).***

6.2.5.3.3 Endpoints

The Applicant provided the following endpoint definitions:

Clinical Response
A "favorable" clinical response assessment was "cure" at the DCIV visit and "cure" or "presumed cure" at the TOC visit. Once a patient had an "unfavorable" clinical assessment, the patient was counted as having that "unfavorable" response at all subsequent time points.

The definitions of the Applicant's clinical responses assigned at the DCIV visit and the TOC visit are provided in the following tables:

Clinical Response Definitions at Discontinuation of Intravenous Therapy (DCIV) Visit

Clinical Response at DCIV Therapy	
Cure[1]	a. Afebrile (T<100.4°F or 38°C orally) for at least 24 hours (or at least 48 hours for documented abscess) without the influence of antipyretic agents. b. Resolution or substantial improvement in signs and symptoms of acute pelvic infection. c. No further antibiotic therapy was required for pelvic infection.
Failure	a. Death due to active infection; or b. Persistence, incomplete resolution, or worsening of entry signs and symptoms, or emergence of new signs or symptoms of pelvic infection requiring additional antimicrobial treatment. c. Surgical intervention for pelvic infection more than 24 hours after study entry. d. Surgical site infection requiring additional antibiotic therapy.
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: a. Death occurred during the study period and the index infection was clearly noncontributory; b. Extenuating circumstances precluded classification as cure or failure.
[1] The definition of cure required all criteria (a, b, and c) to be met.	

(Applicant's Table 8, volume 20 of 22, page 55)

Clinical Response Definitions at Follow-Up Test-of-Cure (TOC) Visit

Clinical Response at 2- to 4-Week Posttherapy Follow-Up Visit	
Cure[1]	a. Afebrile (T<100.4°F or 38°C orally) for at least 24 hours (or at least 48 hours for documented abscess) without the influence of antipyretic agents. b. Resolution or substantial improvement in signs and symptoms of acute pelvic infection. c. No further antibiotic therapy was required for pelvic infection. d. Additionally, postsurgical patients must have demonstrated WBC count <10,000/mm^3 and <10% immature granulocytes (band forms) on WBC differential (or within normal range).
Presumptive cure	Resolution of signs and symptoms of active infection based on phone contact. Patient did not return to the clinic for final visit.
Failure	a. Death due to active pelvic infection; or b. Persistence, incomplete resolution, or worsening of entry signs and symptoms, or emergence of new signs or symptoms of pelvic infection requiring additional antimicrobial treatment; c. Surgical intervention for pelvic infection more than 24 hours after study entry. d. Surgical site infection requiring additional antibiotic therapy.
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: a. Death occurred during the study period and the index infection was clearly noncontributory; b. Extenuating circumstances precluded classification as cure or failure.
[1] The definition of cure required all criteria (a, b, and c) to be met.	

(Applicant's Table 9, volume 20 of 22, page 56)

Microbiologic Response

At the TOC visit, an overall microbiological response was assessed as "favorable" or "unfavorable" for each patient. Favorable microbiological response assessments were "eradication" and "presumptive eradication". For patients from whom only 1 pathogen was isolated, the overall microbiological response assessment was based on the microbiological response assessment for that pathogen. For patients from whom more than 1 baseline pathogen was isolated, the overall microbiological response assessment reflected the worst microbiological outcome for all baseline pathogens. For a favorable overall microbiological assessment, each pathogen identified at baseline must have had a favorable or indeterminate response assessment.

The definitions of microbiological responses assigned by the Applicant at each study visit were:

Microbiological Response Definitions

Microbiological Response	Definitions
Eradication	Original pathogen was absent from the culture of an adequate specimen obtained from the original site of infection.
Presumptive eradication	No appropriate material was available for culture from the original site of infection, or collection of such a specimen would have caused the patient undue discomfort, in the setting of resolution of clinical signs and symptoms.
Persistence	The continued presence of the original pathogen in cultures from the original site of infection or surgical wound infection obtained during or after completion of therapy, up to the test-of-cure visit with or without clinical evidence of infection.
Persistence acquiring resistance	Continued presence of the original pathogen in cultures from the original site of infection obtained during or upon completion of therapy with or without clinical evidence of infection, and the pathogens that were susceptible, moderately susceptible, or intermediate to study drug pretreatment had become resistant to study drug posttreatment.
Presumed persistence	In patients who were judged to be clinical failures, and a culture was not possible or was not done, it was presumed that there was persistence of the original pathogen.
Superinfection	Emergence of new pathogen during therapy, either at the site of infection or at a distant site with emergence or worsening of signs and symptoms of infection.
New infection	Isolation of a new pathogen from a posttreatment culture from the same site in a patient with signs and symptoms of infection after completion of therapy. If a pathogen was isolated from a site distant to the primary infection after study therapy had been completed, then this was also designated as a new infection.
Indeterminate	a. Follow-up cultures were not available due to patient death (only if the primary infection was clearly noncontributory), or withdrawal from study (for reasons other than clinical failure); b. Any other circumstance that made it impossible to define the microbiological response.

(Applicant's Table 10, volume 20 of 22, page 57)

Medical Officer's Comment: ***The Applicant's endpoint definitions are acceptable and in general accordance with recommendations in the 1992 IDSA guidelines[9] and 1992 FDA Points to Consider for clinical trials for this indication.***

6.2.5.3.4 Statistical Considerations

The Applicant's sample size calculation assumed a 90% favorable response rate (clinical) at the TOC visit in the clinically evaluable population (the primary efficacy analysis) for both groups and a significance level of 0.025 (one-sided). Based on this assumption, 150 evaluable patients per group were needed to have an 80% probability that the lower limit of the 95% (two-sided) CI for the difference in the response rates between the 2 groups did not exceed -10 percentage points.

According to the Applicant, "this study was designed to show equivalence (non-inferiority for MK-0826) of the 2 treatment groups. The definition of equivalence is that the 95% (two-sided) CI for the difference in response rates between the 2 treatment groups (test drug group minus control group) contains zero and the lower limit of the CI is not less than -10 percentage points if a 90% or better response rate is observed for the control group, -15 percentage points if a response

[9] Hemsell et al., Clinical Infectious Diseases 1992;15(Suppl.1):S43-52.

rate <90% and ≥80% is observed for the control group, and –20 percentage points if a response rate <80% and ≥70% is observed for the control group."

Medical Officer's Comment: ***At the time the protocol was reviewed by the Division this definition of equivalence was considered acceptable, however, the Applicant has been told at multiple teleconferences since that time that the Division has moved away from this definition in the 1992 FDA Points to Consider. The Applicant has been informed that the Division is revisiting the approach to definitions of non-inferiority. One such definition is that of a "fixed" delta of 10%, regardless of response rate to demonstrate equivalence. The Division recognizes that the Applicant based their development plan on earlier guidances and that the determination of approvability for this indication would be based on the overall package provided for review.***

The efficacy variables were analyzed using an evaluable population only approach and a modified intent-to-treat (MITT) approach. The evaluable population approach was specified as the primary efficacy analysis. The primary endpoints were also displayed by stratum (obstetric infection versus gynecologic/postoperative infection) and by severity (severe infection was defined by entry blood culture positive for suspect pathogen or entry body temperature >39°C). A test of treatment-by-stratum interaction (Breslow-Day Test of Homogeneity of Odds-Ratios) was performed. When the nominal p-value of the test was >0.05, it was concluded that the odds ratios were similar across the strata and that strata could be combined. Results were then displayed combined over strata for each treatment group.

The 2 treatment groups were compared for each of the efficacy parameters and the differences in proportions (MK-0826 minus piperacillin/tazobactam) were calculated, along with the corresponding 95% confidence intervals (CIs). CIs were calculated using the normal approximation to the binomial distribution. The estimated CIs for the difference between treatment groups account for stratification based on the Cochran-Mantel-Haenszel (CMH) approach. The observed proportions and the corresponding CIs are displayed. The CIs around the individual proportions were calculated using the CMH approach applied to one sample. The observed differences between the treatment groups were computed by pooling data across the strata.

For MITT analyses, the proportion of clinical MITT evaluable patients with a favorable clinical response assessment, and the proportion of clinical and microbiological MITT evaluable patients with a favorable clinical and microbiological response assessment, were displayed, along with their corresponding 95% CIs. For the Applicant's MITT analysis, for patients missing a TOC assessment, the last evaluation before TOC was used.

Medical Officer's Comment: ***During the January 28, 2000 pre-NDA teleconference between the Applicant and the Division, the Applicant was informed that patients with missing or indeterminate outcomes were generally considered failures in the MITT analyses by the Division and that additional sensitivity analyses using this approach should be performed. These sensitivity analyses were not provided in the original NDA and were requested again at the March 12, 2001 teleconference between the Applicant and the Division. The Applicant provided the requested analyses in an April 4, 2001 amendment to the NDA.***

The Applicant also performed subgroup analyses for stratum (postpartum infection versus postoperative infection), severity, anatomic site of infection, age (≤65 years versus >65 years, <75 years versus ≥75), and race for the primary efficacy endpoint in the per-protocol "evaluable-patients-only" population. (The minimum sample size needed in order for the analysis to be performed was at least 10 patients in either subgroup.) In addition, the primary efficacy endpoint was displayed for the groups of evaluable patients randomized before and after new blinding procedures for infusion bags were implemented.

6.2.5.4 Study Results

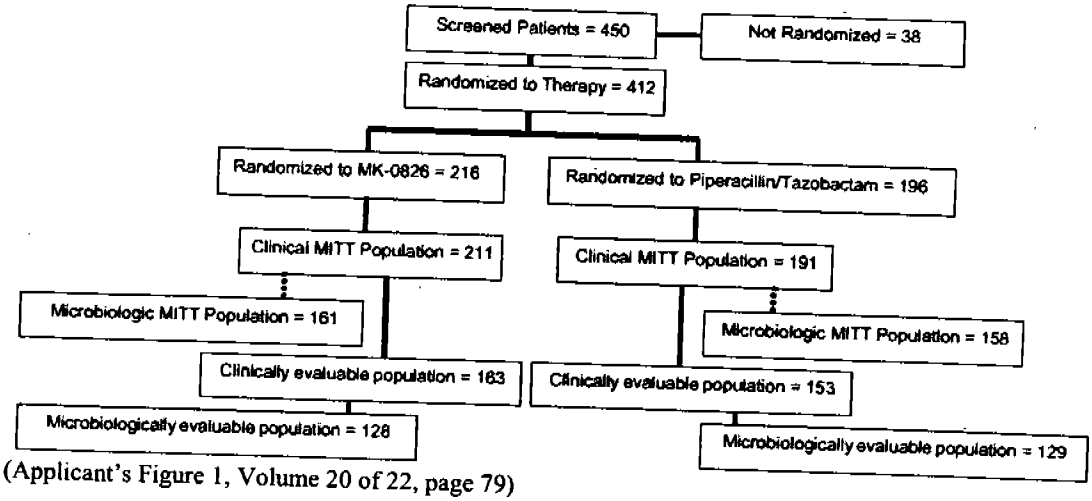
6.2.5.4.1 Evaluability

A total of 412 patients from 47 study sites (of the 66 sites receiving study drug supplies, 47 study sites enrolled 1 or more patients) were randomized into 1 of the 2 treatment groups: 216 patients were randomized to receive MK-0826 and 196 patients were randomized to receive piperacillin/tazobactam. The primary efficacy analysis approach was the clinically evaluable population analysis. Three hundred sixteen patients were considered evaluable for the primary efficacy analysis: 163 patients received MK-0826 and 153 received piperacillin/tazobactam.

A table with the accounting of randomized patients in the study as well as the reasons patients discontinued from the study drug therapy and from study observation is displayed in Appendix 10. A figure displaying the profile of study enrollment and summarizing the number of patients in each of the study populations is displayed below.

In the overall study population, the most common reasons for patients not being randomized to study medication were: primary infection diagnosis criteria not met as defined in protocol (47.4%), patient withdrew consent (13.2%), and concurrent infection would have interfered with evaluation of response to study antibiotic (10.5%).

Profile of Patient Enrollment



(Applicant's Figure 1, Volume 20 of 22, page 79)

The number and percent of patients in each study population and the reasons that patients were considered to be non-evaluable for the per-protocol and MITT analyses are displayed in the Applicant's table below.

Patient Accounting of Evaluability
(Randomized Population)

Reasons Not Evaluable	MK-0826 (N=216) n	(%)	Piperacillin/ Tazobactam (N=196) n	(%)
Clinical Protocol-Evaluable Population				
Clinical protocol evaluable	163	(75.5)	153	(78.1)
Clinical protocol non-evaluable	53	(24.5)	43	(21.9)
Disease definition not met	3	(1.4)	2	(1.0)
Test-of-cure window violation	19	(8.8)	12	(6.1)
Inadequate/inappropriate study therapy	27	(12.5)	14	(7.1)
Prior antibiotics violation	1	(0.5)	1	(0.5)
Concomitant antibiotics violation	8	(3.7)	8	(4.1)
Baseline/intercurrent medical events	12	(5.6)	7	(3.6)
Baseline microbiology–resistant pathogen	4	(1.9)	10	(5.1)
Microbiologic Protocol-Evaluable Population				
Microbiologic protocol evaluable	128	(59.3)	129	(65.8)
Microbiologic protocol non-evaluable	88	(40.7)	67	(34.2)
Not clinically evaluable	53	(24.5)	43	(21.9)
Baseline microbiology not performed/inadequate	5	(2.3)	2	(1.0)
Baseline microbiology–no pathogen isolated	40	(18.5)	27	(13.8)
Test-of-cure microbiology inadequate	2	(0.9)	2	(1.0)
Clinical MITT Population				
Clinical MITT evaluable	211	(97.7)	191	(97.4)
Clinical MITT non-evaluable	5	(2.3)	5	(2.6)
Patient did not receive at least 1 dose of study therapy	2	(0.9)	4	(2.0)
Minimal disease definition not met	1	(0.5)	1	(0.5)
Pharmacy dispensing errors preclude evaluability	2	(0.9)	0	(0.0)
Microbiologic MITT Population				
Microbiologic MITT evaluable	161	(74.5)	158	(80.6)
Microbiologic MITT non-evaluable	55	(25.5)	38	(19.4)
Not clinically evaluable	5	(2.3)	5	(2.6)
Baseline microbiology not performed/inadequate	5	(2.3)	2	(1.0)
Baseline microbiology–no pathogen isolated	40	(18.5)	27	(13.8)
Follow-up microbiology inadequate	6	(2.8)	5	(2.6)

This table contains counts of patient evaluability. Therefore, although a patient may have had one or more reasons for being non-evaluable, the patient was counted only once in the non-evaluable category.
MITT=Modified intent-to-treat approach.

(Applicant's Table 17, Volume 20 of 22, page 81)

Medical Officer's Comment: ***The primary reasons patients were discontinued from therapy in the randomized population were clinical adverse experience (12 in the MK-0826 group and 8 in the piperacillin/tazobactam group), clinical/microbiologic failure (6 in the MK-0826 group and 8 in the piperacillin/tazobactam group), and patient withdrew consent (4 in the MK-0826 group and 7 in the piperacillin/tazobactam group).***

Within each population, the treatment groups were similar with respect to reasons that patients were not evaluable.

The number of clinically evaluable patients in each treatment group that was entered by each investigator is in Appendix 11. Site 023006 (Dr. S. Roy, Los Angeles, CA) was the site that enrolled the most evaluable patients (33/37, 89% clinically evaluable). Of clinically evaluable patients, 47% and 53% were enrolled from US and non-US sites, respectively.

6.2.5.4.2 Demographics

The table below displays the baseline characteristics for the clinically evaluable group.

Baseline Patient Characteristics by Treatment Group
(Clinically Evaluable Population)

	MK-0826 (N=163)		Piperacillin/ Tazobactam (N=153)		Total (N=316)	
	n	(%)	n	(%)	n	(%)
Gender[1]						
Female	163	(100)	153	(100)	316	(100)
Race						
Asian	2	(1.2)	1	(0.7)	3	(0.9)
Black	42	(25.8)	38	(24.8)	80	(25.3)
Caucasian	34	(20.9)	32	(20.9)	66	(20.9)
Hispanic	57	(35.0)	55	(35.9)	112	(35.4)
Indian	0	(0.0)	1	(0.7)	1	(0.3)
Mestizo	28	(17.2)	26	(17.0)	54	(17.1)
Age (Years)						
<18	12		6		18	
18 to 40	140		129		269	
41 to 64	11		17		28	
65 to 74	0		1		1	
>74	0		0		0	
Mean	25.7		27.6		26.6	
SD	7.6		9.2		8.4	
Median	24.0		24.0		24.0	
Range	16 to 53		16 to 68		16 to 68	
Stratification						
Obstetric/postpartum infection	136	(83.4)	132	(86.3)	268	(84.8)
Gynecologic/postoperative infection	27[2]	(16.6)	21	(13.7)	48	(15.2)
Baseline Disease Characteristics						
Obstetric/postpartum infection						
Delivery procedure[3]						
Vaginal delivery	60	(36.8)	50	(32.7)	110	(34.8)
Cesarean section	60	(36.8)	68	(44.4)	128	(40.5)
Chorioamnionitis present	13	(8.0)	13	(8.5)	26	(8.2)
Severe infection present	38	(23.3)	27	(17.6)	65	(20.6)
Gynecologic/postoperative infection						
Severe infection present	4	(2.5)	8	(5.2)	12	(3.8)
Antibiotic prophylaxis given[4]	65	(39.9)	68	(44.4)	133	(42.1)
Diagnosis At Entry						
Abortion, septic	20	(12.3)	19	(12.4)	39	(12.3)
Abscess, pelvic	4	(2.5)	5	(3.3)	9	(2.8)
Adnexitis	2	(1.2)	0	(0.0)	2	(0.6)
Cellulitis, pelvic	6	(3.7)	9	(5.9)	15	(4.7)
Endomyometritis	120	(73.6)	115	(75.2)	235	(74.4)
Parametritis	6	(3.7)	4	(2.6)	10	(3.2)
Phlegmon, pelvic	1	(0.6)	0	(0.0)	1	(0.3)
Other	4	(2.5)	1	(0.7)	5	(1.6)

[1] All patients were female.
[2] AN 7020 was stratified incorrectly as postoperative infection, but is included in postpartum group for purposes of analysis in Table 31.
[3] Delivery procedure not identified for all patients.
[4] Includes prophylaxis for surgical procedures and obstetrical conditions.

(Applicant's Table 19, Volume 20 of 22, pages 85-86)

Medical Officer's Comment: ***The 2 treatment groups appeared to be similar with respect to age, race, type of infection, and severity of infection in both the randomized and clinically evaluable populations.***

The table below displays the extent of exposure to study drugs (duration) by treatment group for the clinically evaluable population.

Extent of Exposure (Duration of Therapy) by Treatment Group
(Clinically Evaluable Population)

	MK-0826 (N=163)	Piperacillin/ Tazobactam (N=153)	Total (N=316)
Days on Study Therapy			
n	163	153	316
Mean	4.5	5.1	4.8
SD	1.8	1.8	1.8
Median	4.0	4.0	4.0
Range			
Days Missed Therapy			
n	43†		43†
Mean	1.0		1.0
SD	0.0		0.0
Median	1.0		1.0
Range			

N=Number of patients in each treatment group.
n=Number of patients in category.
† Forty-three (43) patients were counted as missing a dose of study therapy because they received only placebo doses on the last day of study therapy.
‡ AN 7387 received 3 doses of MK-0826 over 2 calendar days and was considered clinically evaluable.

(Applicant's Table 25, Volume 20 of 22, page 98)

Medical Officer's Comment: ***The 2 treatment groups appeared similar with respect to extent of exposure to study drug.***

6.2.5.4.3 Efficacy

6.2.5.4.3.1 Clinical

The primary efficacy analysis was clinical response in the clinically evaluable patient popultaion at the TOC visit. Additional secondary analyses were done on the microbiologically evaluable and MITT population groups. For the TOC analysis, 163/216 randomized patients (75.5%) in the MK-0826 group were clinically evaluable and 153/196 randomized patients (78.1%) in the piperacillin/tazobactam group were clinically evaluable. To address the primary hypothesis, the estimated proportion (adjusting for strata) of clinically evaluable patients with a favorable clinical response assessment was evaluated in both treatment groups. The following table displays the proportion of patients with a favorable clinical response assessment for the clinically evaluable population.

Proportion of Patients With a Favorable Clinical Response Assessment
in the Clinically Evaluable Population
(Estimated)

Time Point	Treatment Group: MK-0826 (A) (N=163) n	Estimated† Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=153) n	Estimated† Response %	(95% CI)	Estimated† Difference (A-B) %	(95% CI)
DCIV	163	95.1	(91.7, 98.4)	153	92.1	(87.8, 96.4)	2.9	(-3.1, 9.0)
Test of Cure	163	93.9	(90.2, 97.6)	153	91.5	(87.0, 95.9)	2.4	(-4.0, 8.8)

† Computed from a statistical model adjusting for strata.
N=Number of clinically evaluable patients in each treatment group.
n=Number of clinically evaluable patients included in the analysis.
CI=Confidence interval.
DCIV=Discontinuation of intravenous therapy.

(Applicant's Table 30, Volume 20 of 22, page 119)

Medical Officer's Comment: ***A blinded sample of 63 CRFs from this study was reviewed to validate the Applicant's analysis of the primary efficacy parameter. Based on the "bootstrap" analysis performed by Dr. Joel Jiang, Biometrics, for the results of the MO's review of these CRFs, it was concluded that the the Applicant's Analyses could not be accepted. The results of the "bootstrap" analysis suggested that based on this sample, the confidence level was only 54.3% that the lower bound of the CI was >-10% delta and that the p-value for the null hypothesis ("lower bound ≤ delta" versus alternate "lower bound > delta") was 0.457. When the MO's result for the sample were compared with the Applicant's data set for these patients, no predominant reason for discrepancies could be identified.***

Based on Dr. Jiang's recommendation, another random sample of 63 CRFs was generated and reviewed in a blinded manner by the MO. Dr Jiang then repeated the "bootstrap" analysis for the MO's results for the 2 groups combined (total of 126 CRFs, 30% total database). The results of the combined "bootstrap" analysis suggested that based on this sample, the confidence level was 99.95% that the lower bound of the CI was >-10% delta and that the p-value for the null hypothesis ("lower bound ≤ delta" versus alternate "lower bound > delta") was 0.0005. Therefore the Applicant's analyses for the efficacy parameters were accepted.

In the Applicant's revised clinical MITT population, the difference in the clinical response rates between the 2 treatment groups, adjusted for stratum, was -1.8% (82% of patients in the MK-0826 group and 83.8% of patients in the piperacillin/tazobactam group had a favorable clinical response) with a 95% CI of -9.7%, 6.1% (see Appendix 12).

The Applicant also assessed clinical response before and after institution of the enhanced blinding procedure. The results are displayed in the following table.

Proportion of Patients With a Favorable Clinical Response Assessment at Test of Cure
Displayed by Blinding Procedure
in the Clinically Evaluable Population
(Observed Data)

Enhanced Blinding Procedure	Treatment Group: MK-0826 (A) (N=163) n/m	Observed† Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=153) n/m	Observed† Response %	(95% CI)	Observed Difference (A-B) %
No	17/18	94.4	(72.7, 99.9)	15/16	93.8	(69.8, 99.8)	0.7
Yes	136/145	93.8	(88.5, 97.1)	125/137	91.2	(85.2, 95.4)	2.6

† Computed from an exact statistical model pooling across strata.
N=Number of clinically evaluable patients in each treatment group.
n/m=Number of clinically evaluable patients with favorable assessment/number of clinically evaluable patients with assessment at the visit.
CI=Confidence interval.

(Applicant's Table 36, Volume 20 of 22, page 129)

Medical Officer's Comment: ***The MO agrees with the Applicant that the results suggest that the enhanced procedure had no significant effect on the determination of clinical outcome.***

Patients were stratified at study entry for type of infection (Stratum I=obstetric/postpartum infections or septic abortion and Stratum II=gynecologic/postoperative infections). In addition the Applicant performed subgroup analyses by site of infection, severity of infection, age category, and race. The Applicant's results for these analyses are displayed in the following tables.

Proportion of Patients With a Favorable Clinical Response—Overall Assessment and Assessments by Stratum in the Clinically Evaluable Population
(Observed Data)

		Treatment Group				
		MK-0826 (N=163)		Piperacillin/Tazobactam (N=153)		
Time Point	Stratum	n/m	Observed[1] Response % (95% CI)	n/m	Observed[1] Response % (95% CI)	Observed Difference (A-B) %
Test of cure	Obstetric/postpartum infection	129/137[2]	94.2 (90.2, 98.1)	121/132	91.7 (86.9, 96.4)	2.5
	Gynecologic/ postoperative infection	24/26	92.3 (81.9, 100)	19/21	90.5 (77.6, 100)	1.8
	Overall	153/163	93.9 (90.2, 97.6)	140/153	91.5 (87.1, 95.9)	2.4

[1] For overall computed from a statistical model pooling across strata.
[2] AN 7020 was misstratified to postoperative stratum but for the purpose of the analysis was considered a postpartum infection.
N=Number of clinically evaluable patients in each treatment group.
n/m=Number of patients with favorable assessment/number of patients with assessment.
CI=Confidence interval.
DCTV=Discontinuation of intravenous therapy.

(Modified Applicant's Table 31, Volume 20 of 22, page 121)

Proportion of Patients With a Favorable Clinical Response Assessment at Test of Cure
Displayed by Infection Diagnosis
in the Clinically Evaluable Population
(Observed Data)

	Treatment Group						
	MK-0826 (A) (N=163)			Piperacillin/Tazobactam (B) (N=153)			Observed Difference (A-B) %
Primary Diagnosis	n/m	Observed[1] Response %	(95% CI)	n/m	Observed[1] Response %	(95% CI)	
Adnexitis	2/2	100	-	-	-	-	-
Appendicitis, acute	1/1	100	-	-	-	-	-
Cuff cellulitis	1/1	100	-	-	-	-	-
Endometritis	2/2	100	-	-	-	-	-
Endomyometritis	111/120	92.5	(86.2, 96.5)	104/115	90.4	(83.5, 95.1)	2.1
Parametritis	6/6	100	-	3/4	75.0	-	25.0
Pelvic abscess	3/4	75.0	-	4/5	80.0	-	-5.0
Pelvic cellulitis	6/6	100	-	9/9	100	-	0.0
Pelvic phlegmon	1/1	100	-	-	-	-	-
Salpingitis	-	-	-	1/1	100	-	-
Septic abortion	20/20	100	(83.2, 100)	19/19	100	(82.4, 100)	0.0

[1] Computed from an exact statistical model pooling across strata.
N=Number of clinically evaluable patients in each treatment group.
n/m=Number of clinically evaluable patients with favorable assessment/number of clinically evaluable patients with assessment at the visit.
CI=Confidence interval.

(Applicant's Table 32, Volume 20 of 22, page 123)

Proportion of Patients With a Favorable Clinical Response Assessment at Test of Cure Displayed by Severity in the Clinically Evaluable Population
(Observed Data)

Severity	Treatment Group: MK-0826 (A) (N=163) n/m	Observed[1] Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=153) n/m	Observed[1] Response %	(95% CI)	Observed Difference (A-B) %
Moderate	113/121	93.4	(87.4, 97.1)	110/118	93.2	(87.1, 97.0)	0.2
Severe	40/42	95.2	(83.8, 99.4)	30/35	85.7	(69.7, 95.2)	9.5

[1] Computed from a statistical model pooling across strata.
N=Number of clinically evaluable patients in each treatment group.
n/m=Number of clinically evaluable patients with favorable assessment/number of clinically evaluable patients with assessment at the visit.
CI=Confidence interval.

(Applicant's Table 33, Volume 20 of 22, page 125)

Proportion of Patients With a Favorable Clinical Response Assessment at Test of Cure
Displayed by Age and Race Category
in the Clinically Evaluable Population
(Observed Data)

Age Category	Treatment Group: MK-0826 (A) (N=163) n/m	Observed[1] Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=153) n/m	Observed[1] Response %	(95% CI)	Observed Difference (A-B) %
<65	153/163	93.9	(89.0, 97.0)	139/152	91.4	(85.8, 95.4)	2.4
≥65	-	-	-	1/1	100	-	-
Race							
Asian	2/2	100	-	1/1	100	-	0.0
Black	38/42	90.5	(77.4, 97.3)	33/38	86.8	(71.9, 95.6)	3.6
Caucasian	33/34	97.1	(84.7, 99.9)	29/32	90.6	(75.0, 98.0)	6.4
Hispanic	52/57	91.2	(80.7, 97.1)	50/55	90.9	(80.0, 97.0)	0.3
Indian	-	-	-	1/1	100	-	-
Mestizo	28/28	100	(87.7, 100)	26/26	100	(86.8, 100)	0.0

[1] Computed from a statistical model pooling across strata.
N=Number of clinically evaluable patients in each treatment group
n/m=Number of clinically evaluable patients with favorable assessment/number of clinically evaluable patients with assessment.
CI=Confidence interval.

(Applicant's Table 35, Volume 20 of 22, page 127)

Medical Officer's Comment: ***The response rates between the 2 treatment groups based on severity, race, age <65 years, and stratum (Stratum I=obstetric/postpartum infections or septic abortion and Stratum II=gynecologic/postoperative infections) were similar. Too few patients in the ≥65 year old age group (0 patients in the MK-0826 group and 1 patient in the piperacillin/tazobactam group) were enrolled to make any comparison.***

The only specific diagnoses, for which adequate numbers of patients were enrolled to make a direct comparison meaningful, were endomyometritis and septic abortion and the response rates for the 2 treatment groups were similar for patients with these diagnoses. Of the 120 clinically evaluable patients in the MK-0826 group with endomyometritis, 113 were postpartum patients (favorable clinical response = 105/113, 92.9%) and 7 were gynecologic postoperative patients (favorable clinical response = 6/7, 85.7%). Based on the MO's review of the Applicant's data a total of 25 clinically evaluable patients (7 with endomyometritis, 1 with endometritis, 5 with parametritis, 1 with cellulitis, 4 with pelvic abscess, and 6 with pelvic cellulitis) were enrolled in the gynecologic postoperative stratum and of these 23 patients (92.0%) had a favorable clinical response. The MO considered one patient (AN 7862), included in the Applicant's gynecologic postoperative clinically evaluable group, as unevaluable because the patient's diagnosis was acute appendicitis.

6.2.5.4.3.2 Microbiologic

Microbiological efficacy parameters were analyzed as secondary endpoints in this study. For the TOC analysis, 128/216 patients (59.3%) in the MK-0826 group were microbiologically evaluable and 129/196 patients (65.8%) in the piperacillin/tazobactam group were microbiologically evaluable.

The Applicant determined microbiologic outcome for all unique baseline pathogens from pelvic sites and/or blood at DCIV and follow-up study visits. If no specimen was obtained for culture at a follow-up visit, the microbiologic outcome was presumed based on the clinical outcome; eradication was presumed for favorable clinical outcomes and persistence was presumed for unfavorable clinical outcomes. A baseline pathogen isolated both from the primary infection site and from the blood was counted once in the overall list of pathogens and once in the list of bacteremic pathogens. A baseline pathogen isolated only from blood and presumed to be associated with the primary infection was counted once in the overall list and once in the bacteremic list. If a patient received vancomycin for treatment of gram-positive infection, all gram-positive baseline pathogens were considered to have indeterminate microbiologic outcomes. If these patients were otherwise microbiologically evaluable, their clinical, overall microbiological outcomes and other per-pathogen microbiologic outcomes were considered valid. A favorable overall microbiologic response assessment required that all baseline pathogens had an outcome of eradication or presumed eradication. Any single per-pathogen outcome of persistence or presumed persistence or persistence-acquiring resistance resulted in an overall unfavorable microbiologic assessment. The proportion of patients with a favorable overall microbiologic response at the TOC visit is displayed in the following table.

Proportion of Patients With a Favorable Overall Microbiological Response Assessment in the Microbiologically Evaluable Population (Estimated)

	Treatment Group							
	MK-0826 (A) (N=128)			Piperacillin/Tazobactam (B) (N=129)			Estimated[1] Difference (A-B)	
Time Point	n	Estimated[1] Response %	(95% CI)	n	Estimated[1] Response %	(95% CI)	%	(95% CI)
DCIV	127	95.3	(91.5, 99.0)	129	94.6	(90.7, 98.5)	0.7	(-5.5, 6.9)
Test of cure	128	93.7	(89.5, 98.0)	129	93.8	(89.6, 98.0)	-0.1	(-6.8, 6.6)

[1] Computed from a statistical model adjusting for strata.
N=Number of microbiologically evaluable patients in each treatment group.
n=Number of microbiologically evaluable patients included in the analysis.
CI=Confidence interval.
DCIV=Discontinuation of intravenous therapy.

(Applicant's Table 40, Volume 20 of 22, page 149)

Medical Officer's Comment: ***The proportion of patients with a favorable overall microbiologic response assessment in the 2 treatment groups supports the conclusion that the 2 treatments are equivalent in the population studied.***

In the Applicant's revised microbiologic MITT population, the difference in the clinical response rates between the 2 treatment groups, adjusted for stratum, was -0.9% (83.9% of patients in the MK-0826

group and 84.8% of patients in the piperacillin/tazobactam group had a favorable clinical response) with a 95% CI of -9.6%, 7.7% (see Appendix 12).

6.2.5.4.3.3 By Pathogen

The Applicant compared the microbiologic response rates in microbiologically evaluable patients between the 2 treatment groups for all unique baseline pathogens obtained from pelvic samples or blood (if the same pathogen was isolated from both blood and pelvic sample it was counted only once in the overall list). The following table displays the proportion of favorable microbiologic response assessments per pathogen in the microbiologically evaluable population at the TOC visit. The 95% CI was calculated for those bacterial species isolated in at least 10 patients in either treatment group.