Complicated Intra-Abdominal Infections: Developing Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2018
Clinical/Antimicrobial
Revision 1

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Contains Nonbinding Recommendations

Complicated Intra-Abdominal Infections: Developing Drugs for Treatment Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of complicated intra-abdominal infections (cIAIs).[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for the treatment of cIAI.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[3]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2012-D-0973-0009 (available at https://www.regulations.gov/document?D=FDA-2012-D-0973-0009).

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

Intra-abdominal infections are common in clinical practice and comprise a wide variety of clinical presentations and differing sources of infection. A cIAI extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis (Solomkin et al. 2010). Different bacterial pathogens are responsible for cIAIs, including gram-negative aerobic bacteria, gram-positive bacteria, and anaerobic bacteria, and there are also mixed infections. *Uncomplicated* intra-abdominal infections and *complicated* intra-abdominal infections may be difficult to distinguish, but in general cIAIs extend beyond local viscera into peritoneal or retroperitoneal spaces and are associated with systemic signs and symptoms of illness. When patients are diagnosed with cIAI, antibacterial drug therapy is recommended before, during, and after the planned surgical procedure (e.g., open laparotomy, laparoscopy, percutaneous drainage of an abscess).

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

The wide variety of bacterial pathogens responsible for cIAIs represents a challenging aspect for clinical development. Before sponsors start phase 3 clinical trials, an investigational drug's antibacterial activity should be characterized (e.g., information on the spectrum of activity of the investigational drug against bacteria that cause cIAIs).

2. Drug Development Population

The clinical diagnoses and brief descriptions that define the population of patients with cIAIs include, but are not limited to, the following:

- **Intra-abdominal abscess:** one or more abscesses surrounding diseased or perforated viscera often characterized by nonspecific abdominal pain
- **Perforation of intestine:** an acute perforation of the intestine associated with diffuse infection of the peritoneum, often characterized by nonspecific abdominal pain
- **Peritonitis:** a diffuse infection of the peritoneum, often characterized by nonspecific abdominal pain
- **Appendicitis with perforation or periappendiceal abscess:** an acute infection of the appendix characterized by colicky abdominal pain often localized to the right lower quadrant
- **Cholecystitis with perforation or abscess:** an acute infection extending beyond the gallbladder wall, often accompanied by right upper quadrant abdominal pain

- **Diverticulitis with perforation, peritonitis, or abscess:** an acute infection of a diverticula (herniation of mucosa or submucosa through the muscularis propria of the colon), most often characterized by left lower quadrant abdominal pain

3. Efficacy Considerations

Noninferiority trials are interpretable and appropriate for the indication of the treatment of cIAI. A showing of superiority is also readily interpretable.

A single adequate and well-controlled trial supported by other independent evidence, such as a trial in another infectious disease indication, can provide evidence of effectiveness.[4] Sponsors should discuss with the FDA the other independent evidence that would be used to support the findings from a single trial in cIAI.

4. Safety Considerations

In general, we recommend a preapproval safety database of approximately 700 patients. If the same dose and duration of therapy for treatment of cIAI were used in clinical trials for other infectious disease indications, the safety information from those clinical trials can be part of the overall preapproval safety database. For new drugs that have an important clinical benefit compared to existing therapies, a smaller preapproval safety database may be appropriate. Sponsors should discuss the appropriate size of the preapproval safety database with the FDA during clinical development.

B. Specific Efficacy Trial Considerations

1. Trial Design

Trials in cIAI should be randomized, double blind, and active controlled using a noninferiority or superiority design. Placebo-controlled trials are not appropriate for this indication except when they are add-on superiority trials in which patients receive either placebo or investigational drug added to standard-of-care antibacterial drug treatment.

2. Trial Population

Trials should have a patient population with a variety of cIAI diagnoses as described in section III.A.2., Drug Development Population. The proportion of patients who have cIAI caused by appendicitis with perforation or periappendiceal abscess should not exceed approximately 50 percent in a cIAI trial.

3. Inclusion and Exclusion Criteria

The following are recommendations for inclusion criteria:

[4] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

- Operative procedure for the current diagnosis and management of cIAI planned or completed within 24 hours of the first dose of an antibacterial drug

  – Procedures include open laparotomy, laparoscopy, and percutaneous drainage of intra-abdominal abscess

- One or more systemic signs or symptoms that accompany cIAI, such as fever, hypotension, abdominal pain, nausea/vomiting, abdominal mass on clinical examination, altered mental status

The following are recommendations for exclusion criteria:

- Receipt of effective antibacterial drug therapy for cIAI for a continuous duration of more than 24 hours during the previous 72 hours[5]

- Upper gastrointestinal perforations unless clear evidence exists of an established secondary infection within the abdominal cavity

4. Clinical Microbiology Considerations

An adequate clinical specimen for microbiologic evaluation should be obtained from all patients and sent to the laboratory for microscopic evaluation (e.g., Gram stain), culture, and in vitro antibacterial susceptibility testing performed on appropriate bacteria isolated from the specimen. Specimens should be processed according to recognized methods.[6] The FDA also recommends that aerobic and anaerobic blood cultures be taken at two separate venipuncture sites before initiation of antibacterial drug therapy for cIAI. All isolates considered to be possible pathogens should be saved in the event that additional testing of an isolate is needed (e.g., pulse field gel electrophoresis for strain identification). Bacterial pathogens should have in vitro susceptibility testing using standardized methods.[7]

Even though most patients will have a bacterial pathogen identified on routine cultures, development of new rapid diagnostic tests may facilitate future clinical trial design and potentially benefit patients by providing earlier diagnosis of causative organisms. Clinical trials of a new antibacterial drug for treatment of cIAI may provide an opportunity to contribute to the evaluation of a new diagnostic test. Sponsors interested in the development of a new rapid diagnostic test should discuss this with the FDA.

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[5] Patients who received an antibacterial drug for surgical prophylaxis and then developed cIAI, or patients who have objective documentation of clinical progression of cIAI while on antibacterial drug therapy, may be appropriate for enrollment.

[6] For examples, see the most current editions of the publications from the American Society for Microbiology, such as *Manual of Clinical Microbiology* and *Clinical Microbiological Procedures Handbook*.

[7] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute, Wayne, PA.

5. Randomization, Stratification, and Blinding

Trials should be randomized, multicenter, and double-blind unless there is a compelling reason for single-blind or open-label trials. If trials are single-blind or open-label, sponsors should discuss potential biases with the FDA and how these biases will be addressed. Sponsors should consider a stratification strategy to avoid enrollment of an excessive number of patients with cIAI associated with appendicitis (see section III.B.2., Trial Population).

6. Specific Populations

The trials should include patients of both sexes and all races, as well as geriatric patients.[8] Patients with renal or hepatic impairment can be enrolled, provided the pharmacokinetics of the drug have been evaluated in these patients and appropriate dosing regimens have been defined.

The FDA encourages sponsors to begin discussions about their pediatric clinical development plans as early as is feasible because pediatric studies are a required part of the overall drug development program and sponsors are required to submit pediatric study plans no later than 60 days after an end-of-phase 2 meeting.[9]

7. Dose Selection

To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics, safety and tolerability information from phase 1 clinical trials, and safety and efficacy information from phase 2 dose-ranging clinical trials. An assessment of drug penetration into certain tissues can be used as supportive evidence that the selected doses are likely to achieve drug concentrations sufficient to exert both an antimicrobial and clinical effect for cIAI.

In general, patients with cIAI will begin treatment with an antibacterial drug given by intravenous (IV) administration. Guidelines recommend 4 to 7 days of therapy for cIAI (Solomkin et al. 2010). Because nausea and vomiting are frequently associated with cIAI and patients may require complete bowel rest for several days, patients are often hospitalized and cannot eat food or take oral mediations (e.g., a physician order for *nil per os* or *NPO*) while being treated for cIAI. Therefore, it may be possible to conduct clinical trials using IV antibacterial drug therapy for 4 to 7 days without a switch to oral drug therapy. However, patients who demonstrate improvement and can tolerate an oral diet may have completion of treatment with an orally administered drug (Solomkin et al. 2010). Sponsors should discuss with

[8] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics: Questions and Answers.*

[9] See the Pediatric Research Equity Act (Public Law 108-155; section 505B of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355c) as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (Public Law 112-144) and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the FDA the timing of a switch from an investigational IV drug to oral drug during therapy for cIAI or the development of an oral drug for treatment of cIAI.

8. Choice of Comparators

In general, the active comparator used in clinical trials should be considered standard of care in the United States for this indication. When evaluating the current standard of care, we consider recommendations by authoritative scientific bodies (e.g., the Surgical Infection Society, Infectious Diseases Society of America) based on clinical evidence and other reliable information that reflects current clinical practice.

9. Concomitant Antibacterial Therapy

An investigational drug's in vitro antibacterial activity can encompass the full spectrum of bacterial pathogens implicated in cIAI. However, an investigational drug may not have a full spectrum of activity and the addition of concomitant antibacterial therapy may be necessary to complete the antibacterial spectrum for empirical treatment of cIAI. The spectrum of antibacterial activity of the investigational drug should not be similar to the spectrum of the concomitant drug, so that the effect of the investigational antibacterial drug can be isolated and fully assessed.

10. Prior Nontrial Antibacterial Drugs

Patients who have cIAIs should receive effective antibacterial drug therapy before, during, and after the operative procedure as part of standard of care (Solomkin et al. 2010; Bratzler et al. 2013). Based on available data, we were not able to determine the effect that prior antibacterial drug therapy would have on the assessment of an investigational drug's efficacy. Attempts should be made to minimize prior nontrial antibacterial drug therapy to the extent possible. Patients who receive up to 24 hours of prior nontrial antibacterial drug therapy should be eligible for enrollment. For patients who are enrolled in the trial after the surgical procedure, only one dose of effective antibacterial drug therapy should be administered postoperatively before randomization. The results in the subgroups of patients who did and did not receive prior effective antibacterial drug therapy should be analyzed.

11. Efficacy Endpoints

The primary endpoint of clinical success is defined as resolution of the baseline signs and symptoms of cIAI based on objective assessments of events from randomization until approximately day 28. A patient should be characterized as having a primary endpoint of clinical failure based on any of the following events that occur from randomization until approximately day 28:

- Death
- Surgical site wound infection

- Unplanned surgical procedures or percutaneous drainage procedures for complication or recurrence of cIAI based on documented worsening symptoms or signs of cIAI

- Initiation of nontrial antibacterial drug therapy for treatment of cIAI based on documented worsening symptoms or signs of cIAI

12. Trial Procedures and Timing of Assessments

a. Entry visit

At the entry visit, baseline demographic and clinical information should be collected and should include clinical signs and symptoms, microbiologic specimens (Gram stain and culture of intra-abdominal specimen and/or blood), radiographic or ultrasound imaging results, and laboratory tests, as appropriate.

b. On-therapy and end-of-therapy visit

Patients should be evaluated at least once during therapy and at the end of prescribed therapy. Clinical and laboratory assessments for safety should be performed as appropriate. If it is possible that the trial drug would need to be continued beyond the protocol-specified duration, objective criteria for extending the therapy should be prespecified in the protocol.

c. Visit at day 28

At approximately day 28 following randomization, patients should be evaluated for safety and for the occurrence of an event at or before the visit at day 28 that characterizes clinical failure (see section III.B.11., Efficacy Endpoints).

13. Statistical Considerations

In general, sponsors should provide a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before trial initiation. The primary efficacy analysis should be based on the difference in the proportions of patients achieving a successful clinical response.

a. Analysis populations

The FDA considers the following to be the definitions for the statistical analysis populations:

- Intent-to-treat (ITT) population — All patients who were randomized

- Safety population — All patients who received at least one dose of drug during the trial

- Microbiological intent-to-treat (micro-ITT) population — All patients randomized to treatment who have a baseline bacterial pathogen known to cause cIAI

- Per-protocol populations — Patients who follow important components of the trial can then be defined as part of a per-protocol population

- Microbiologically evaluable population — Patients who follow important components of the trial and who have a baseline bacterial pathogen known to cause cIAI

In general, a bacterial pathogen (or bacterial pathogens) should be identifiable in a majority of enrolled patients such that the ITT and micro-ITT populations will be similar. The micro-ITT population should be considered as the primary analysis population. Generally, it is not appropriate to consider analyses of the per-protocol population as primary because that population is based on postrandomization events or characteristics of patients. However, consistency of the results should be evaluated in all populations.

b. Noninferiority margins

Noninferiority trials are considered appropriate and recommended if there is reliable and reproducible evidence of a treatment effect for the comparator drug.[10] For a cIAI trial, a noninferiority margin of 10 percent is supported by the historical evidence (see Appendix A). Sponsors should discuss with the FDA the selection of a proposed margin greater than 10 percent.

c. Sample size

An estimate of an appropriate sample size for the primary micro-ITT analysis population for a noninferiority trial with 1:1 randomization is approximately 337 patients per group based on a noninferiority margin selection of 10 percent and a clinical success rate of 80 percent in the control group. Approximately 90 percent of patients enrolled in the trial should have a bacterial pathogen identified by culture (the ITT population would consist of approximately 375 patients per group). The trial should rule out a greater than 10 percent inferiority of the investigational drug to control drug (upper bound of the two-sided 95 percent confidence interval for the clinical success rate of control drug minus investigational drug).

C. Other Considerations

1. PK/PD Considerations

The pharmacokinetic/pharmacodynamic (PK/PD) characteristics of the drug should be evaluated using in vitro models or animal models of infection. The results from PK/PD assessments should be integrated with the findings from phase 1 PK assessments to help identify appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials.

Sponsors should consider a sparse sampling strategy in all patients in phase 2 and phase 3 clinical trials to allow for the estimation of drug exposure in each patient. Collection of PK data in phase 2 clinical trials can be used to explore the exposure-response relationship and to confirm that the proper dose and dosing regimen are selected for further evaluation in phase 3 clinical

[10] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*.

trials. Collection of PK data in phase 3 clinical trials may help to address potential questions regarding efficacy or safety that might arise from the clinical trials.

A retrospective exposure-response analysis based on the population PK model from patients in phase 3 clinical trials should be performed to assess the relationship between PK/PD indices and observed clinical and microbiologic outcomes. The relationship between drug exposure or different dosing regimens and clinically relevant adverse events also should be explored to identify potential risks. Additionally, these relationships should be explored for specific patient populations (e.g., patients with renal impairment).

2. Labeling Considerations

The labeled indication should be for the treatment of cIAI caused by specific bacteria identified in patients in the clinical trials. For example:

"Drug X is indicated for the treatment of complicated intra-abdominal infections due to…."

REFERENCES

Altemeier, WA, 1949, The Treatment of Acute Peritonitis, JAMA, 139(6):347–352.

Bratzler, DW, EP Dellinger, KM Olsen, et al., 2013, Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery, Am J Health Syst Pharm, 70:195–283.

DerSimonian, R and N Laird, 1986, Meta-Analysis in Clinical Trials, Control Clin Trials, 7:177–187.

Donovan, IA, D Ellis, D Gatehouse, et al., 1979, One-Dose Antibiotic Prophylaxis Against Wound Infection After Appendectomy: A Randomized Trial of Clindamycin, Cefazolin Sodium and a Placebo, Br J Surg, 66:193–196.

Maluch, RW and RM Simon, 1980, Sample Size Considerations for Non-Randomized Comparative Studies, J Chron Dis, 33:175–181.

Montravers, P, R Gauzit, C Muller, et al., 1996, Emergence of Antibiotic-Resistant Bacteria in Cases of Peritonitis After Intra-abdominal Surgery Affects the Efficacy of Empirical Antimicrobial Therapy, Clin Infect Dis, 23:486–94.

Morris, WT, DB Innes, RA Richardson, AJ Lee, and RB Ellis-Pegler, 1980, The Prevention of Post-Appendectomy Sepsis by Metronidazole and Cefazolin: A Controlled Double-Blind Trial, Aust NZ J Surg, 50:429–433

Mosdell, DM, DM Morris, A Voltura, et al., 1991, Antibiotic Treatment for Surgical Peritonitis, Ann Surg, 214:543–549.

Solomkin, JS, JE Mazuski, JS Bradley et al., 2010, Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Disease Society of America, Clin Infect Dis, 50:133–164.

APPENDIX A: JUSTIFICATION FOR NONINFERIORITY MARGIN FOR COMPLICATED INTRA-ABDOMINAL INFECTIONS

A literature search found no placebo-controlled trials in patients with complicated intra-abdominal infections (cIAIs). Observational-cohort and retrospective chart-review studies show that effective antibacterial drugs for treatment of cIAIs are associated with shorter hospital stays, fewer unplanned re-operations, and lower mortality rates (Montravers et al. 1996; Mosdell et al. 1991), but an estimate of a treatment effect of an antibacterial drug could not be derived from these nonrandomized studies. Because all patients in these studies had appropriate surgical procedures for cIAIs, the studies suggest that effective antibacterial drugs have an added benefit to the benefits of the surgical procedures for cIAIs.

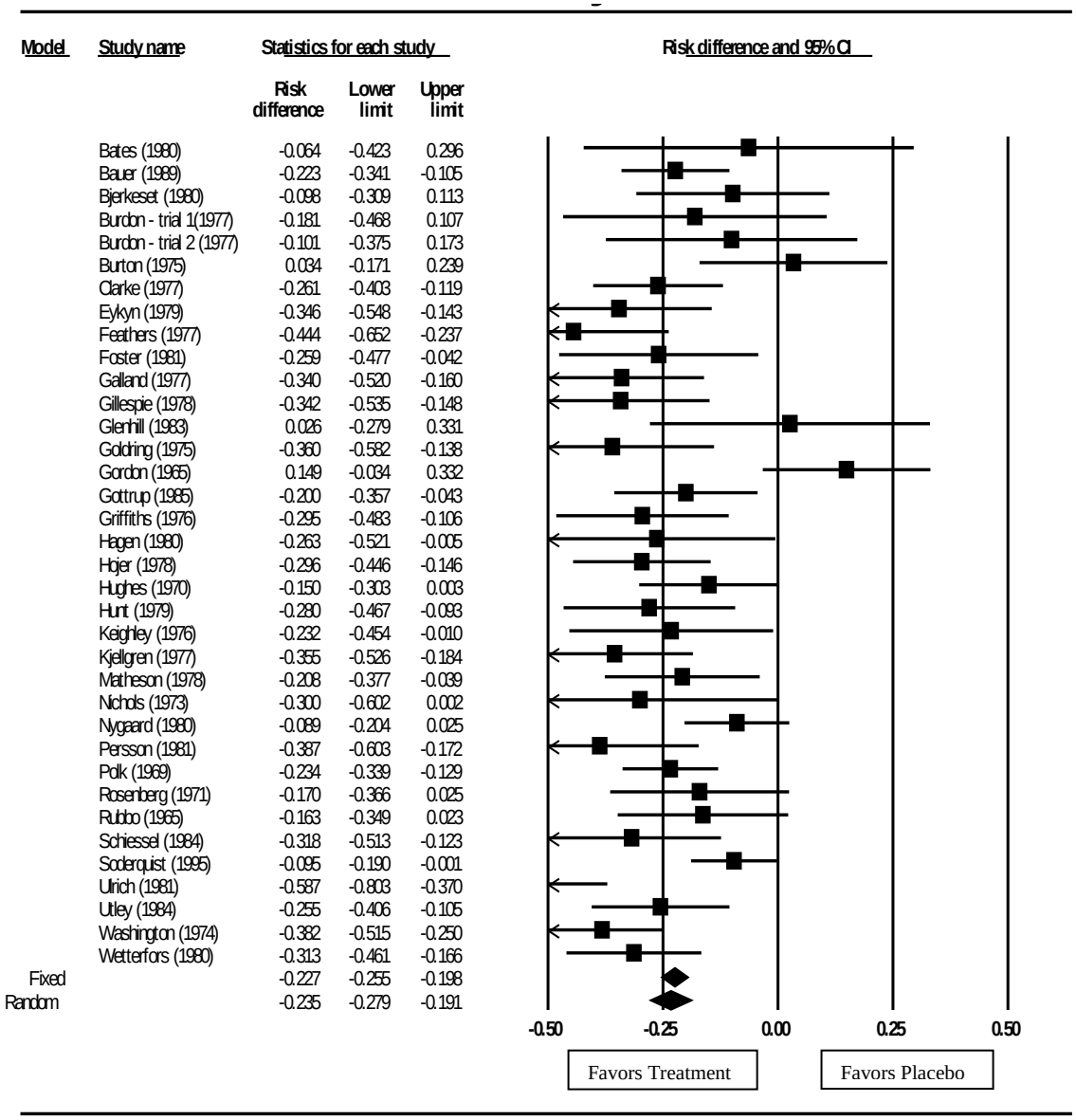
We evaluated a cross-study comparison of success rates described in recently conducted trials and success rates described before the availability of antibacterial drugs. However, in the historical papers before the availability of antibacterial drugs, there was uncertainty as to whether events labeled as clinical success were actual clinical successes (e.g., continued drainage of pus for more than 28 days following insertion of a drainage tube was considered a clinical success in one historical paper). Therefore, it was not possible to estimate the proportion of patients with a true clinical success before the availability of antibacterial drugs.

Approximately 40 placebo-controlled surgical prophylaxis trials are published in the more recent literature. These trials evaluated the effect of antibacterial drugs administered as prophylaxis; patients about to undergo elective intra-abdominal surgeries were randomized to antibacterial drug or to placebo/no treatment. Of these, 36 trials provided enough data to characterize the clinical events among patients who were randomized to placebo/no treatment or receiving antibacterial drug treatment. For these trials, we excluded patients who were undergoing procedures for simple appendicitis without abscess formation. In general, patients were followed postoperatively in a hospitalized setting and then evaluated in an outpatient clinic setting after trial completion, usually within a 1-month time period. Therefore, the event rates can be considered as events that occurred within approximately 1 month following the surgical procedure. In addition, the rates of day 28 clinical success outcomes were evaluated among recently conducted active-controlled clinical trials in patients who have cIAIs.

In this appendix, we describe two approaches to quantifying an estimate of the treatment effect of antibacterial drugs for cIAIs in patients who have appropriate surgical procedures.

The first approach to understanding the effect of an antibacterial drug for treatment of cIAIs is to evaluate the risk differences of event rates in the surgical prophylaxis trials. Figure 1 shows the forest plot of the differences in event rates of death or development of an intra-abdominal or surgical wound infection.

Figure 1. Forest Plot of the Risk Differences in Event Rates (Death or Intra-Abdominal or Surgical Infection) Between Recipients of Antibacterial Drug Prophylaxis and Recipients of Placebo/No Treatment in the Trials of Antibacterial Drug Prophylaxis[1]



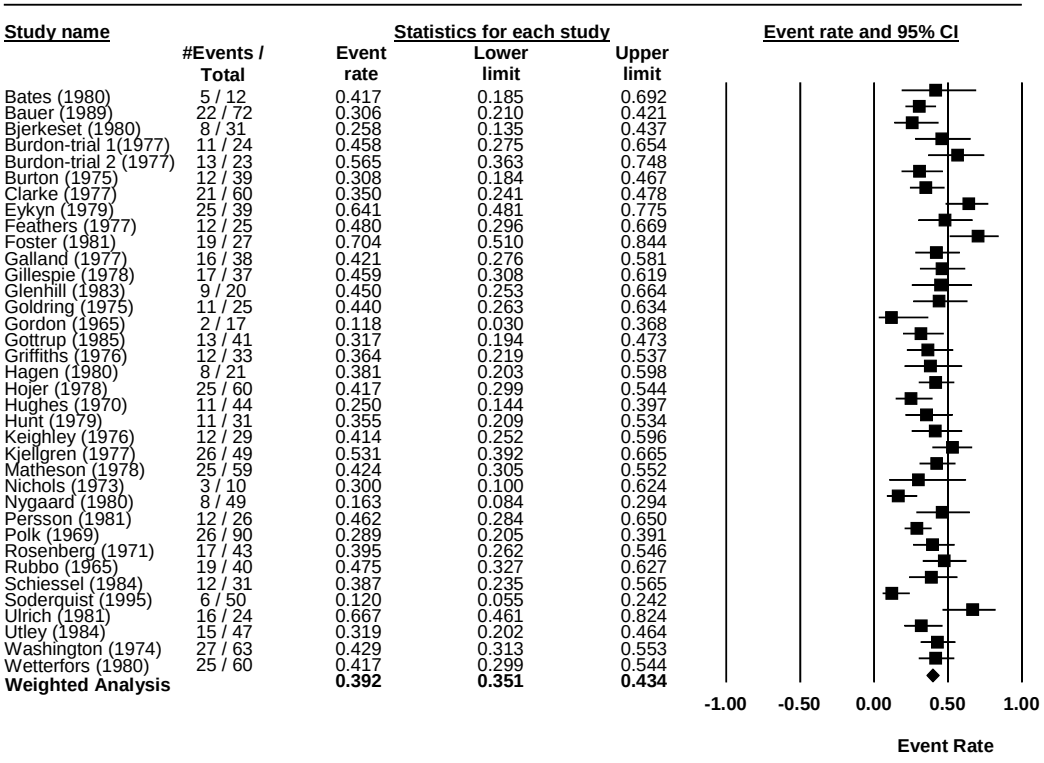
The random effects meta-analysis (DerSimonian and Laird 1986) shows a treatment benefit of antibacterial drug prophylaxis at 19.1 percent (the lowest absolute numerical value of the two-sided 95 percent confidence interval of the risk difference). At randomization, patients in these studies did not yet have an infection, and many patients undoubtedly did not develop an infection, limiting the potential benefit of an anti-infective agent. The treatment difference between treated and untreated patients who have established infection is likely to be larger than

[1] A list of these references can be found in Appendix B of the guidance for industry *Complicated Intra-Abdominal Infections: Developing Drugs for Treatment*.

the observed effect of prophylaxis. M_1 can be defined at 19.1 percent, a conservative estimate, using the prophylaxis results.

The second approach is to evaluate the event rates of death or development of an intra-abdominal or surgical wound infection among patients randomized to receive placebo/no treatment in the antibacterial drug prophylaxis trials, and compare these rates to the event rates in recently conducted trials among patients receiving appropriate antibacterial drug therapy for cIAIs. Figure 2 describes the event rates of death or development of an intra-abdominal or surgical wound infection.

Figure 2. Forest Plot of the Event Rates (Death or Intra-Abdominal or Surgical Infection) in the Trials of Antibacterial Drug Prophylaxis Among Recipients of Placebo or Randomized to Receive No Antibacterial Drug Treatment[2]



A random effects meta-analysis (DerSimonian and Laird 1986) showed the point estimate for the event rate among placebo/no treatment recipients at 39.2 percent, with a two-sided 95 percent confidence interval of 35.1 percent and 43.4 percent. The rate of a clinical success outcome was computed by 1 minus the event rate. Thus, an estimate of the placebo/no treatment successful response rate is 60.8 percent, with a two-sided 95 percent confidence interval of 56.6 percent and 64.9 percent.

[2] A list of these references can be found in Appendix B of the guidance for industry *Complicated Intra-Abdominal Infections: Developing Drugs for Treatment.*

We evaluated the rate of day 28 clinical success outcomes among recently conducted active-controlled clinical trials in cIAI. All trials evaluated patients during antibacterial drug treatment for cIAI and observed patients for differing periods of time after completion of antibacterial drugs (e.g., observations from day 14 to day 60).

The results from the datasets available for review at the FDA are displayed in Table 1.

Table 1. Clinical Response Cure Rate at Day 28 in the Micro-ITT Population

Trial	Study Group	Clinical Response Rate at Day 28 n/N (%)
1	A	157/194 (80.9)
1	B	159/191 (83.2)
2	C	157/199 (78.9)
2	D	157/186 (84.4))

The meta-analysis for the clinical response rates among patients treated with an antibacterial drug showed a point estimate of 81.7 percent and a two-sided 95 percent confidence interval of 78.8 percent and 84.3 percent (DerSimonian and Laird 1986).

An estimate of the treatment effect based on the difference in the clinical response rates can be derived by comparing the rate of successful clinical responses of recently conducted clinical trials in infected patients and the rate of successful clinical responses of placebo or no treatment among patients undergoing intra-abdominal surgery. This gives a conservative estimate of the difference in rates because the patients undergoing surgery did not yet have an infection when randomized. Therefore, the difference between treated and untreated patients with an established infection should be larger than the difference observed here. Using an approach of the lower bound two-sided 95 percent confidence interval for antibacterial drug treatment estimate minus the upper bound of the two-sided 95 percent confidence interval for the placebo/no treatment estimate, a treatment difference is estimated to be 13.9 percent (78.8 percent minus 64.9 percent).

As noted, the comparison of the upper bound 95 percent confidence interval for the within-trial risk difference in the surgical prophylaxis trials, and the comparison of the lower bound 95 percent confidence interval for antibacterial drug therapy and the upper bound of the 95 percent confidence interval for placebo/no treatment are conservative estimates of the treatment difference. Therefore, there is little reason to consider discounting the treatment difference. M_1 is defined at 13.9 percent using this second approach and was defined at 19.1 percent using the first approach. Because it is important to preserve the treatment effect when selecting a noninferiority margin, regardless of either approach there is support for a noninferiority margin of 10 percent for active-controlled trials of cIAI for an endpoint of clinical success at 28 days. Sponsors should discuss with the FDA the choice of a noninferiority margin greater than 10 percent.

APPENDIX B: LIST OF REFERENCES USED IN THE NONINFERIORITY MARGIN JUSTIFICATION FOR THE ESTIMATE OF THE PLACEBO/NO TREATMENT RESPONSE RATE

Bates, T, VLR Touquet, MK Tutton, SE Mahmoud, and WA Reuther, 1980, Prophylactic Metronidazole in Appendectomy: A Controlled Trial, BrJ Surg, 67:547–550.

Bauer, T, BO Vennits, B Holm, et al., 1989, Antibiotic Prophylaxis in Acute Nonperforated Appendicitis, Ann Surg, 209(3):307–311.

Bjerkeset, T and A Digranes, 1980, Systemic Prophylaxis With Metronidazole (Flagyl) in Elective Surgery of the Colon and Rectum, Surgery, 87(5):560–566.

Burdon, JGW, PJ Morris, P Hunt, and JM Watts, 1977, A Trial of Cephalothin Sodium in Colon Surgery to Prevent Wound Infection, Arch Surg, 112:1169–1173-Trial 1.

Burdon, JGW, PJ Morris, P Hunt, and JM Watts, 1977, A Trial of Cephalothin Sodium in Colon Surgery to Prevent Wound Infection, Arch Surg, 112:1169–1173-Trial 2.

Burton, RC, ESR Hughes, and AM Cuthbertson, 1975, Prophylactic Use of Gentamycin in Colonic and Rectal Surgery, Med J Aust, 2:597–599.

Clarke, JS, RE Condon, JH Bartlett, SL Gorbach, RL Nichols, and S Ochi, 1977, Preoperative Oral Antibiotics Reduce Septic Complications of Colon Operations: Results of Prospective, Randomized, Double-Blind Clinical Study, Ann Surg, 186:251–259.

Eykyn, SJ, HE Lockhart-Mummery, BT Jackson, and II Phillips, 1979, Prophylactic Preoperative Intravenous Metronidazole in Elective Colorectal Surgery, Lancet, 2(8146):761–764.

Feathers, RS, AAM Lewis, GR Sagor, ID Amirak, and P Noone, 1977, Prophylactic Systemic Antibiotics in Colorectal Surgery, Lancet, 2:761–764.

Foster, GE, JB Bourke, J Bolwell, et al., 1981, Clinical and Economic Consequences of Wound Sepsis After Appendicectomy and Their Modification by Metronidazole or Povidone Iodine, Lancet, 1(8223):769–771.

Galland, RB, JH Saunders, JH Mosley, and JH Darrell, 1977, Prevention of Wound Infection in Abdominal Operations by Preoperative Antibiotics or Povidone-Iodine: A Controlled Trial, Lancet, 2:1043–1045.

Gillespie, G and W McNaught, 1978, Prophylactic Oral Metronidazole in Intestinal Surgery, J Antimicrob Chemother, 4(suppl c):29–32.

Glenhill, T, A Odurny, and PC Weaver, 1983, A Controlled Study of Single Dosage Cefamandole in the Prophylaxis of Wound Infections in Appendectomy, Surg Gynaecol Obstetr, 156(3):295–297.

Goldring, J, A Scott, W McNaught, and G Gillespie, 1975, Prophylactic Oral Antimicrobial Agents in Elective Colonic Surgery: A Controlled Trial, Lancet, 2:997–1000.

Gordon, HE, DW Gaylor, DM Richmond, et al., 1965, Operations on the Colon: The Role of Antibiotics in Preoperative Preparation, Calif Med, 103:243–246.

Gottrup, F, P Diederich, K Sorensen, et al., 1985, Prophylaxis With Whole Gut Irrigation and Antimicrobials in Colorectal Surgery: A Prospective, Randomized Double-Blind Clinical Trial, Am J Surg, 149(March):317–322.

Griffiths, DA, RA Simpson, BA Shorey, DCE Speller, and NB Williams, 1976, Single-Dose Preoperative Antibiotic Prophylaxis in Gastrointestinal Surgery, Lancet, 2(7981):325–328.

Hagen, TB, T Bergan, I Liavag, 1980, Prophylactic Metronidazole in Elective Colon-Rectal Surgery, Acta Chir Scand, 146:71–75.

Hojer, H and J Wetterfors, 1978, Systemic Prophylaxis With Doxycycline in Surgery of the Colon and Rectum, Ann Surg, 187(4):362–368.

Hughes, ESR, KJ Hardy, AM Cuthbertson, and SD Rubbo, 1970, Chemoprophylaxis in Large Bowel Surgery. 1. Effect of Intravenous Administration of Penicillin on Incidence of Postoperative Infection, Med J Aust, 1:305–308.

Hunt, PS, JK Francis, G Peck, et al., 1979, Tinidazole in the Prevention of Wound Infection After Elective Colorectal Surgery, Med J Aust, 1:107–109.

Keighley, MRB, AR Crapp, DW Burdon et al., 1976, Prophylaxis Against Anaerobic Sepsis in Bowel Surgery, Br J Surg, 63:538–541.

Kjellgren, K and H Sellstrom, 1977, Effect of Prophylactic Systemic Administration of Cephalothin in Colorectal Surgery, Acta Chir Scand, 143:473–477.

Matheson, DM, Y Arabi, D Baxter-Smith, et al., 1978, Randomized Multicentre Trial of Oral Bowel Preparations and Antimicrobials for Elective Colorectal Operations, Br J Surg, 65:597–600.

Nichols, RL, P Broido, RE Condon, et al., 1973, Effect of Preoperative Neomycin-Erythromycin Intestinal Preparation on the Incidence of Infectious Complications Following Colon Surgery, Ann Surg, 178:453–459.

Nygaard, K and J Hognestad, 1980, Infection Prophylaxis With Doxycycline in Colorectal Surgery, A Preliminary Report, Scand J Gastroenterol Suppl, 59:37–39.

Persson, S and H Gnarpe, 1981, Tinidazole as Preventive Treatment in Elective Colonic Surgery, Scand J Infect Dis, 13:137–140.

Polk, HC Jr and JF Lopez-Major, 1969, Postoperative Wound Infection: A Prospective Study of Determinant Factors and Prevention, Surgery, 66:97–103.

Rosenberg, IL, NG Graham, FT deDombal, and JC Goligher, 1971, Preparation of the Intestine in Patients Undergoing Major Large-Bowel Surgery, Mainly for Neoplasms of the Colon and Rectum, Br J Surg, 58:266–269.

Rubbo, SD, ESR Hughes, B Blainey, and IS Russell, 1965, Role of Preoperative Chemoprophylaxis in Bowel Surgery, Antimicrob Agents Chemother, 5:649–658.

Schiessel, R, I Huk, M Wunderlich, et al., 1984, Postoperative Infections in Colonic Surgery After Enteral Bacitracin-Neomycin-Clindamycin or Parenteral Mezlocillin-Oxacillin Prophylaxis, J Hosp Infect, 5:289–297.

Söderquist-Elinder, C, K Hirsch, S Bergdahl, et al., 1995, Prophylactic Antibiotics in Uncomplicated Appendicitis During Childhood — A Prospective Randomised Study, Eur J Pediatr Surg, 5:282–285.

Ulrich, C, 1981, 24-hour Systemic Antibiotic Prophylaxis in Large-Bowel Surgery, The Netherlands Journal of Surgery, 33(1):3–9.

Utley, RJ and WAAG Macbeth, 1984, Peroperative Cefoxitin, A Double-Blind Prospective Study in the Prevention of Wound Infection, J R Coll Surg Edinb, 29(3):143–146.

Washington, JA, WH Dearing, ES Judd, and LR Elveback, 1974, Effect of Preoperative Antibiotic Regimen on Development of Infection After Intestinal Surgery, Prospective, Randomized, Double-Blind Study, Ann Surg, 180(4):567–571.

Wetterfors, J and H Hoejer, 1980, Prophylaxis With Doxycycline (Vibramycin) in Colorectal Surgery, Scand J Gastroenterol, Suppl 59:12–16.