Registration Trials of Antibacterial Drugs for the Treatment of Nosocomial Pneumonia

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Since 1989, 12 registration trials have been submitted to the US Food and Drug Administration to support the clinical efficacy of 8 antibacterial drugs for the treatment of nosocomial pneumonia. Six trials used noninferiority designs, whereas the others were equivalence trials or lacked a prespecified hypothesis. Patients with nosocomial pneumonia and ventilator-associated pneumonia were frequently enrolled in the same clinical trials. Enrolled patients were predominantly male and had mean Acute Physiology and Chronic Health Evaluation II scores of 12–18. The investigator’s assessment of clinical response was the primary end point, which was usually measured 7–14 days after study drug completion. Clinical cure rates among the intent-to-treat population for nosocomial pneumonia and ventilator-associated pneumonia ranged from 37% to 69% and 25% to 58%, respectively. All-cause mortality ranged from 8% to 28%. Pseudomonas aeruginosa, Acinetobacter species, and methicillin-resistant Staphylococcus aureus were common bacterial pathogens. The design, implementation, and limitations of the clinical trials and implications for future clinical research are discussed.

Overview of clinical registration trials

Clinical trial design. Twelve phase 3 registration trials conducted from 1989 through 2006 were submitted to...
the FDA to support new drug applications for 8 antibacterial drug products for the treatment of NP. The clinical trials were randomized, multicenter, and comparative in design; 7 were open label, and 5 were double blind (Table 1). The trials compared either new molecular entities or marketed antibacterial drugs previously approved for other indications with marketed active control antibacterial drugs that were indicated for the treatment of NP, pneumonia, or lower respiratory tract infection. Nine trials coenrolled patients with NP and VAP, 1 trial enrolled patients with VAP exclusively, 1 trial enrolled patients with either NP or acute bronchitis, and 1 trial enrolled patients with NP, including VAP and community-acquired pneumonia. In some trials, patients were stratified at randomization by whether they had VAP or by baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) score (≤15 or >15). Four clinical trials used study centers located in the United States and Canada only, whereas the remaining trials used both US and international sites.

Six trials used a noninferiority design, and 6 were either equivalence trials or lacked a prespecified study hypothesis. Coprimary analysis populations were used to assess noninferiority in these trials, including an intent-to-treat (ITT) or modified ITT population and a per-protocol or microbiologically evaluable population. This approach ensured consistency of results across both analysis populations before concluding noninferiority.

Statistically, noninferiority of the new antibacterial drug, compared with the active control, was established if the 2-sided 95% confidence interval for the difference in clinical cure rates between the new antibacterial drug and the active control drug excluded a prespecified margin. Noninferiority margins of 15% or 20%, based on either a sliding delta as described in the 1992 FDA “Points to Consider” [7] or clinical judgment, were used in the 6 noninferiority trials. The sliding delta criteria for noninferiority margin determination are no longer in use.

**Treatment regimens.** The 12 trials used the following active control comparator antibacterial drugs: imipenem-cilastatin, ceftazidime, vancomycin, ciprofloxacin, and piperacillin-tazobactam. Various durations of study treatment were used, including 7–14 days (4 trials), 10–14 days (2 trials), 5–12 days (4 trials), 5–14 days (1 trial), and 7–21 days (1 trial). On the basis of prespecified criteria, a switch from intravenously administered study drug to an oral antibacterial agent was permitted in 4 trials.

Concomitant nonstudy antibacterial therapy was permitted during the initial 48–72 h of study participation if drug-resistant bacteria, such as *P. aeruginosa* or MRSA, were suspected pathogens. Aminoglycosides (amikacin, gentamicin, and tobramycin), ceftazidime, aztreonam, and piperacillin-tazobactam were permitted concomitant antibacterial drugs in 10 trials to provide empirical or continued antipseudomonal coverage. Concomitant vancomycin therapy was permissible in 7 trials when MRSA was a suspected or confirmed pathogen.

The clinical circumstances in which nonstudy antibacterials could be administered to patients before trial enrollment varied. In several trials, systemic nonstudy antibacterial therapy was...

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**Table 1. Selected Characteristics of Clinical Trials Reviewed**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Noninferiority design</th>
<th>Blinded</th>
<th>Duration of study therapy, days</th>
<th>Percentage of patients with VAP (ITT or MITT)</th>
<th>No. of ITT patients</th>
<th>Age, mean years ± SDa</th>
<th>Mean Apache II score ± SDb</th>
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<td></td>
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<td>Control arm</td>
<td>No. of ITT patients</td>
<td>Control arm</td>
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<td>137</td>
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<tr>
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<td>No</td>
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<td>140</td>
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<td>53 ± 19</td>
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<td>220</td>
<td>218</td>
<td>56 ± 20</td>
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<td>7–21</td>
<td>58</td>
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<td>193</td>
<td>63 ± 18</td>
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<td>223</td>
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<td>58 ± 20</td>
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<td>52 ± 20</td>
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<td>7–14</td>
<td>27</td>
<td>467</td>
<td>467</td>
<td>58 ± 18</td>
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</table>

**NOTE.** ITT, intent-to-treat; MITT, modified ITT; NR, not reported; RS, reported by stratum only; SD, standard deviation; VAP, ventilator-associated pneumonia.

a As provided in reports.
b Median (range).
c Median.
d Mean (range).

*In the test arm, 357 patients (78%) had a mean APACHE II score <15, and 100 (22%) had a mean APACHE II score >15; in the control arm, 349 patients (75%) had a mean APACHE II score <15, and 118 (25%) had a mean APACHE II score >15.*
The exclusion criteria varied across trials. However, some of the noteworthy exclusions included presence of symptoms of bronchitis and wheezing alone, need for concomitant nonstudy antibiotics, presence of a pulmonary infiltrate that was unlikely to be the result of an infection, high likelihood of an anaerobic infection, APACHE II score >25, septic shock, prior nonpermissible antibacterial therapy, and presence of drug-resistant baseline bacterial pathogens.

Clinical trial end points. The primary endpoint in all trials was the investigator’s assessment of clinical response (ie, cure, indeterminate, or failure) at the test-of-cure (TOC) visit. The timing of the TOC visit varied across trials. Although the TOC visit was conducted 7–14 days after completion of study drug therapy in the majority of the trials, other TOC visits occurred 12–28 days, 10–21 days (±2 days), or 3–15 days after the end of study therapy. Various secondary endpoints were also assessed in the trials, including all-cause mortality.

Clinical and microbiological outcome definitions. Most of the clinical trials defined clinical cure and clinical failure on the basis of a composite of clinical and radiographical criteria. One trial (trial 9) defined clinical cure on the basis of a composite of clinical and microbiological criteria.

In general, clinical cure referred to the resolution or improvement of all signs and symptoms of pneumonia in addition to improvement or lack of progression of chest radiographic findings at the TOC visit. Clinical failure was frequently defined as the persistence or worsening of clinical signs and symptoms with progression of radiographic findings after at least 48 h of study drug administration.

In most trials, microbiological response was classified as documented eradication (defined as the absence of the baseline pathogens found in respiratory tract culture samples obtained at the TOC visit), presumed eradication (defined as clinical cure at the TOC visit for which a respiratory tract specimen was not available), persistence (baseline isolate was present in a respiratory tract culture specimen obtained at TOC visit), or presumed persistence (defined as clinical failure at the TOC visit for which a respiratory tract specimen was not available). Documented or presumed eradication was classified as microbiological success, and persistence or presumed persistence was classified as microbiological failure.

Statistical analysis populations. The primary or coprimary analyses populations varied across trials. In the 6 non-inferiority trials, the primary end point was evaluated on the basis of the consistency of results obtained from 2 coprimary populations: (1) the ITT population (or an ITT population that was modified on the basis of clinical or microbiological criteria) and (2) the per-protocol, clinically evaluable (CE), or microbiologically evaluable population. Patients in the ITT population were excluded from the per-protocol or clinically evaluable populations because of major protocol violations, withdrawal

limited to a duration of ≦24 h within the 72 h before enrollment unless the baseline pathogen was resistant to the previous antibacterial drug regimen, the patient was experiencing therapy failure, or the patient developed a new pneumonia despite treatment.

Patient demographic characteristics. In 11 of the 12 trials, 127–467 patients per treatment arm were enrolled in the ITT population, whereas in 1 trial, 83 patients were enrolled in each treatment arm (Table 1). The patients enrolled in the clinical trials were predominantly male. The cross-trial mean age was 52–71 years. In most trials, severity of illness was reported on the basis of APACHE II scores [8]. The APACHE II scores varied across trials, and the cross-trial mean scores were 12–18. The frequencies of concomitant medical illnesses, such as diabetes mellitus, chronic obstructive pulmonary disease, heart failure, and renal failure, were reported in only a few trials. With the exception of one clinical trial (trial 11) that enrolled only patients with VAP, all of the other trials enrolled patients with either NP or NP and VAP; the proportion of patients with VAP ranged from 21% to 82%.

Entry criteria. In general, for patients to be eligible for enrollment with NP, they had to have been hospitalized for ≧48 h before the onset of pneumonia. For patients to be considered as having VAP, they had to have been receiving mechanical ventilation for ≧48 h before the development of pneumonia.

The specific clinical, microbiological, and radiographical inclusion and exclusion criteria varied across the 12 clinical trials. However, most of the trials required evidence of at least 2 of the following clinical and laboratory findings: fever (oral temperature, 38°C), leukocytosis, and purulent sputum or respiratory tract secretions. Other clinical findings described for entry into some of the trials included cough, dyspnea, pleuritic chest pain, auscultatory abnormalities (eg, rales), and hypoxemia.

All trials required that an adequate respiratory tract specimen be obtained for culture to identify baseline bacterial pathogens and to determine the antimicrobial drug susceptibilities of these pathogens. Various methods for respiratory tract specimen collection were used, including obtainment of expectorated sputum samples, bronchoscopy with bronchoalveolar lavage or protected-brush sampling, pleurocentesis with pleural fluid culture, and endotracheal aspiration. Interpretative Gram stain criteria for sputum specimens (>25 polymorphonuclear leukocytes per high power field and <10 squamous epithelial cells per high power field) were described in only a few trials. In several trials, baseline blood cultures were also performed.

All trials required evidence of a new, persistent, or progressive lung infiltrate on a chest radiograph. Confirmation of the investigators’ chest radiograph interpretations by a radiologist was required in only a single trial (trial 12).
of consent, loss to follow-up, inadequate study drug dosing, insufficient signs and symptoms of pneumonia, use of nonstudy concomitant antibacterial drugs, death not attributable to NP or VAP, the TOC visit occurring outside a prespecified visit window, and indeterminate clinical outcomes. The clinically evaluable rates were 45%–77% in the trials for which evalua-

**Efficacy.** Clinical cure rates in an ITT or modified ITT population were available for only 9 trials and were 37%–69% across the test and comparator arms. Clinical cure rates in VAP subgroups in the ITT population were 25%–58%. In the single clinical trial that enrolled only patients with VAP (trial 11), the proportion of patients with satisfactory clinical response was 59% for the test drug and 58% for the comparator in the clinical modified ITT populations.

All-cause mortality was reported in all 12 trials and ranged from 8% to 28% in both the test and comparator arms (Figure 1). The timing of the mortality assessment was not uniform across trials. Eight trials did not specify a reporting period for all-cause mortality, whereas mortality was reported at 28 or 30 days after study initiation in the other 4 trials.

**Microbiology.** Baseline lower respiratory tract bacterial pathogens reported in patients with NP included *P. aeruginosa, Acinetobacter species, Haemophilus influenzae, Klebsiella pneumoniae, Enterobacter species, MRSA, and Streptococcus pneumoniae* (Figures 2 and 3). In some trials, gram-negative bacteria were isolated more frequently from patients with VAP than from patients with non–ventilator-associated NP. The overall rates of recovery of bacterial pathogens from baseline respiratory tract cultures tended to be low across the 12 clinical trials. The low frequency of use of invasive modalities, compared with noninvasive modalities, to obtain microbiological specimens and the inconsistent use of specific interpretive criteria may have affected such results. Data on the prevalence of baseline pathogens that exhibited reduced susceptibility to the study drug or comparator were reported in some of the trials. Rates of positive baseline blood culture results were also reported in both treatment groups in some trials.

**LIMITATIONS AND CONCLUSIONS**

The results of 12 registration trials submitted to the FDA to support new drug applications for 8 antibacterial drugs for the treatment of NP were reviewed. Seven of the new drug applications included supportive clinical efficacy data for patients with NP and VAP who were coenrolled in the same clinical trials, whereas only one new drug application included data from separate NP and VAP clinical trials.

Blinding of the investigators and study patients was used in 5 of the 12 trials, thus protecting them from postrandomization confounding and biased assessment of outcomes. The reports from the remaining 7 trials described various logistical issues that appeared to make blinding difficult, such as use of multiple concomitant antibacterial drugs in the initial treatment regimen and local practice preferences. Although it may be more practical to conduct open-label clinical trials because of such considerations, additional end points based on objective measurements should be considered in future trials to minimize bias.

Enrollment of patients from the United States and international sites appeared to be feasible in many of the clinical trials. However, the number of study sites and the number of patients enrolled per site were quite variable, which could add complexities to the successful conduct and monitoring of the clinical trial. In addition, regional differences in the epidemiology of bacterial pathogens, clinical practice patterns, and the availability of advanced medical technology and diagnostic laboratory facilities may impact the assessments of study drug efficacy and safety. It is anticipated that these aspects of clinical

![Figure 1. All-cause mortality rates (intent-to-treat or modified intent-to-treat populations)](image-url)
trial conduct will become increasingly important in the future as patients are recruited from multiple study centers dispersed worldwide.

Some clinical trials were designed to show noninferiority in assessing antibacterial drug efficacy in treating NP and VAP. Six reviewed trials used noninferiority designs with prespecified noninferiority margins of 15% or 20%, based on clinical response end points. However, because the trials did not report the scientific evidence, statistical approach, and clinical considerations underpinning the chosen primary end points and noninferiority margins, there was uncertainty with regard to whether those clinical trials were informative in distinguishing effective from ineffective treatments. Administration of concomitant antibacterial drugs, such as aminoglycosides for gram-negative coverage, was permitted in many of the noninferiority trials. However, adjunctive systemic antibacterials with activity against the primary lower respiratory tract pathogens tended to confound assessments of study treatment effect, thereby increasing the probability of erroneously concluding noninferiority. The issues and challenges in the design and interpretation of noninferiority trials are described elsewhere [9–12]. The 2007 “Draft Guidance for Industry on Antibacterial Drug Products: Use of Non-inferiority Studies to Support Approval” specifically identified the need to provide adequate scientific evidence to support a predefined treatment effect for the active control so that the proposed noninferiority margin can be justified [13].

Detailed information about the bacterial etiology of NP and VAP varied among the 12 registration trials. Some trials did

![Figure 2. Frequency of baseline gram-negative bacterial pathogens.](image)

![Figure 3. Frequency of baseline gram-positive bacterial pathogens. MRSA, methicillin-resistant Staphylococcus aureus.](image)
not provide information distinguishing pathogens, such as MRSA, from the overall number of *S. aureus* isolates. In those trials, only aggregate data were reported for *S. aureus*, regardless of methicillin susceptibility. Other trials provided more-comprehensive data that revealed an increased number of infections due to MRSA, *P. aeruginosa*, and *Acinetobacter* species, which is analogous to the trends reported in the published medical literature [4, 14, 15]. Drug-resistant bacteria are likely to be encountered more frequently in future clinical antibacterial drug trials for NP and VAP.

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