SUPPLEMENT ARTICLE

Registration Trials of Antibacterial Drugs for the Treatment of Nosocomial Pneumonia

Alfred Sorbello,[1] Scott Komo,[2] Thamban Valappil,[2] and Sumati Nambiar[1]

[1]Office of Antimicrobial Products and [2]Division of Biometrics IV, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland

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.

Nosocomial pneumonia (NP), which occurs ⩾48 h after hospital admission, is the third most common cause of health care–associated infection [1]. Ventilator-associated pneumonia (VAP) develops in patients requiring mechanical ventilation for ⩾48 h and is associated with substantial morbidity and mortality [2]. The initial empirical treatment of NP and VAP frequently comprises broad-spectrum combination antibacterial therapy, followed by de-escalation based on the susceptibilities of the identified respiratory tract pathogens [3]. However, emerging multidrug antibacterial resistance has become a substantial problem underscoring the need for new antibacterial drugs. Methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Pseudomonas aeruginosa* and *Acinteobacter baumanii,* and carbapenemase-producing *Klebsiella pneumoniae* can be difficult bacterial pathogens to treat in patients with VAP [4–6].

Currently, piperacillin-tazobactam, levofloxacin, ciprofloxacin, and linezolid are the only antibacterial drugs approved by the US Food and Drug Administration (FDA) for the treatment of NP. No antibacterial drugs are labeled specifically for the treatment of VAP. Other antibacterials commonly used in the treatment of NP and VAP (eg, vancomycin, imipenem-cilastatin, ceftazidime, and aztreonam) are labeled for pneumonia or the broader indication of lower respiratory tract infection.

This article describes the design, conduct, and results of the 12 registration trials conducted from 1989 through 2006 that were submitted to the FDA to support new drug applications for the indication of NP. Data from these clinical trials, their limitations, and insights gained with respect to future clinical trials of antibacterial drugs in the treatment of NP and VAP are discussed.

OVERVIEW OF CLINICAL REGISTRATION TRIALS

Clinical trial design. Twelve phase 3 registration trials conducted from 1989 through 2006 were submitted to

The views expressed in this article are those of the authors and do not necessarily represent the views of the US Food and Drug Administration.

Reprints or correspondence: Dr Alfred Sorbello, US Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Ave, Silver Spring, MD 20993 (alfred.sorbello@fda.hhs.gov).

Clinical Infectious Diseases 2010; 51(S1):S36–S41

1058-4838/2010/5103S1-0007
DOI: 10.1086/653038

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 ($\leqslant$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

Table 1. Selected Characteristics of Clinical Trials Reviewed

Trial	Noninferiority design	Blinded	Duration of study therapy, days	Percentage of patients with VAP (ITT or MITT)	No. of ITT patients		Age, mean years ± SD[a]		Mean Apache II score ± SD[a]	
					Test arm	Control arm	Test arm	Control arm	Test arm	Control arm
1	No	No	5–14	NR	155	145	56	54	NR	NR
2	No	Yes	5–21	82	156	156	59	58	18	18
3	No	No	5–21	NR	213	217	67 (18–93)[b]	68 (18–89)[b]	14[c]	14[c]
4	No	Yes	10–14	NR	127	137	68 (23–98)[d]	71 (20–95)[d]	13	13
5	No	No	10–14	NR	135	140	62 (18–94)[d]	64 (18–90)[d]	12	14
6	No	No	5–21	NR	83	83	68 (18–90)[b]	69 (18–89)[b]	14[c]	13[c]
7	Yes	Yes	5–21	69	222	215	53 ± 19	53 ± 21	14 ± 6	13 ± 5
8	Yes	No	7–14	71	220	218	56 ± 20	56 ± 20	15 ± 6	15 ± 6
9	Yes	Yes	7–21	58	203	193	63 ± 18	61 ± 19	16 ± 6	15 ± 7
10	Yes	No	7–14	30	223	221	58 ± 20	59 ± 19	13 ± 4	13 ± 4
11	Yes	No	7–14	100	262	263	52 ± 20	52 ± 19	16 ± 5	16 ± 5
12	Yes	Yes	7–14	27	467	467	58 ± 18	58 ± 18	RS[e]	RS[e]

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).

[e] In the test arm, 357 patients (78%) had a mean APACHE II score $\leqslant$15, and 100 (22%) had a mean APACHE II score >15; in the control arm, 349 patients (75%) had a mean APACHE II score $\leqslant$15, and 118 (25%) had a mean APACHE II score >15.

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).

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 end point 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 end points 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 radiograph 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 noninferiority 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

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 evaluability data were available.

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

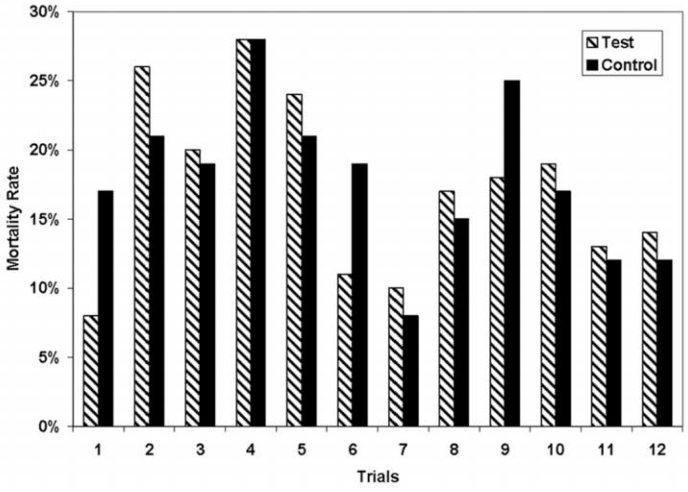

Figure 1. All-cause mortality rates (intent-to-treat or modified intent-to-treat populations)

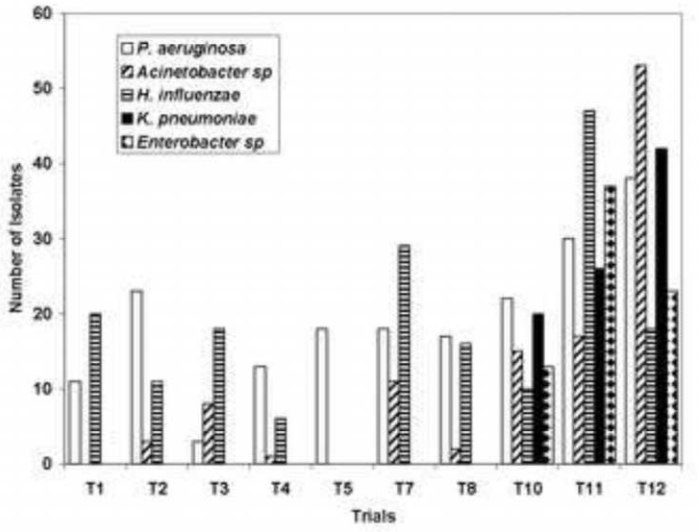

Figure 2. Frequency of baseline gram-negative bacterial pathogens.

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

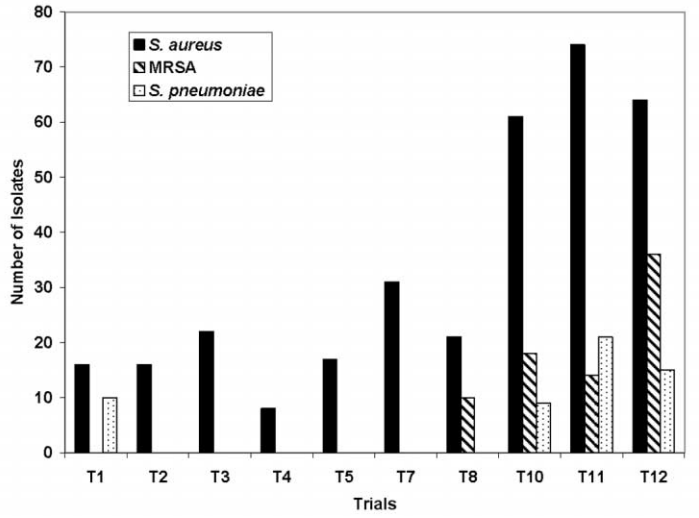

Figure 3. Frequency of baseline gram-positive bacterial pathogens. MRSA, methicillin-resistant *Staphylococcus aureus*.

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.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Supplement sponsorship. This article was published as part of a supplement entitled "Workshop on Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia," sponsored by the US Food and Drug Administration, Infectious Diseases Society of America, American College of Chest Physicians, American Thoracic Society, and the Society of Critical Care Medicine, with financial support from the Pharmaceutical Research and Manufacturers of America, AstraZeneca Pharmaceuticals, and Forest Pharmaceuticals.

References

1. Klevens RM, Edwards JR, Richards CL, et al. Estimating health care-associated infections and deaths in US hospitals, 2002. Public Health Rep **2007**; 122:160.
2. Ostendorf U, Ewig S, Torres A. Nosocomial pneumonia. Curr Opin Infect Dis **2006**; 19:327–338.
3. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med **2005**; 171:388–416.
4. Hidron AI, Edwards JR, Patel J, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol **2008**; 29:996–1011.
5. Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. Lancet Infect Dis **2009**; 9:228–236.
6. Munoz-Price LS, Quinn JP. The spread of *Klebsiella pneumoniae* carbapenemases: a tale of strains, plasmids, and transposons. Clin Infect Dis **2009**; 49:1739–1741.
7. US Food and Drug Administration. Points to consider: clinical development and labeling of anti-infective drug products. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070975.pdf. Accessed 4 November 2009.
8. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med **1985**; 13(10): 818–829.
9. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. I. Ethical and scientific issues. Ann Intern Med **2000**; 133:455–463.
10. Hung HMJ, Wang SJ, O'Neill R. A regulatory perspective on choice of margin and statistical inference in non-inferiority trials. Biometrical J **2005**; 47(1):28–36.
11. Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. Ann Intern Med **2006**; 145:62–69.
12. US Food and Drug Administration. Guidance for industry: E 10 choice of control group and related issues in clinical trials, 2001. http://www.fda.gov/RegulatoryInformation/Guidances/ucm125802.htm. Accessed 26 October 2009.
13. US Food and Drug Administration (2007). Guidance for industry—antimicrobial drug products: use of noninferiority studies to support approval (draft guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070951.pdf. Accessed 26 October 2009.
14. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. Crit Care Med **1999**; 27(5):887–892.
15. McDonald LC. Trends in antimicrobial resistance in health care–associated pathogens and effect on treatment. Clin Infect Dis **2006**; 42(suppl 1):S65–S71.