

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)
ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE
Sheraton College Park Hotel

April 1-2, 2008

DRAFT ADVISORY COMMITTEE QUESTIONS

1. Does the committee concur that evidence provided from the “historical” studies and more recent studies support non-inferiority studies of CAP due to *S. pneumoniae*? In your response please discuss whether this evidence is applicable to current clinical trials of CAP.
2. If the committee concurs that there is evidence to support a non-inferiority margin from earlier studies, what non-inferiority margin is supported by this information?
 - a. Please discuss the population to which this margin would apply, specifically addressing severity of illness.
 - b. Please discuss how the evidence which showed a treatment effect based on mortality can be generalized or modified to the endpoints which are used in current non-inferiority trials, (i.e. clinical response or other endpoints).
 - c. If the available evidence for setting a non-inferiority margin in current CAP trials is limited to treatment of *S. pneumoniae*, should non-inferiority studies enroll patients with other etiologies for CAP? If not, what additional data/studies are needed to show that antibacterial drugs are effective for specific organisms? Please specifically address this question with regard to the following organisms:
 - *Chlamydophila pneumoniae*
 - *Haemophilus influenzae*
 - *Klebsiella pneumoniae*
 - *Legionella pneumophila*
 - *Mycoplasma pneumoniae*
 - *Staphylococcus aureus*
3. Can placebo-controlled trials be performed safely in patients with CAP?
 - a. If yes, what selection criteria or study procedures are needed to minimize risk for study participants?

- b. If no, what alternative study designs can be used to measure the treatment effect of antibacterial drugs in these patients?
4. Please discuss the following issues in CAP trial design for antibacterials available as only oral or intravenous formulations:
 - a. Should only patients with more severe pneumonia be enrolled in studies of intravenous antibacterial therapy, and if so, how should severity be defined (e.g., clinical exam, CURB-65, or PORT scores)?
 - b. Should a microbiological diagnosis be necessary for enrollment in CAP trials, and if so, what organisms should be permitted for enrollment (or analysis)?
 - c. Since the historical evidence for a treatment effect was based on studies which evaluated penicillin and sulfonamides, are these the only appropriate comparators for CAP studies? If no, then what information is needed to extrapolate the treatment effect for other antibacterial drugs?
 - d. What primary endpoint should be used for clinical studies of CAP?
 - e. What secondary endpoints should be included?
5. For a drug with both an IV and oral formulation, is study of inpatients with the IV formulation sufficient to support approval of the oral formulation for outpatient use? Alternatively, would separate studies using oral therapy alone be necessary to demonstrate safety and/or effectiveness of the oral drug?