*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**

# QUESTIONS

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**For questions 1 and 2:**

**To rely on noninferiority studies for new drugs to treat CAP, we must be able to estimate the effect size a control drug would have on the primary endpoint used in the current trial. The Agency has presented information on the historical experience that suggest a reduction in mortality with point estimates ranging from 18 to 25% in the observational studies and from approximately 10 to 19% in controlled trials. These data are derived from patients with pneumococcal / lobar pneumonia.**

**1. Can these data be utilized to select a noninferiority margin for a contemporary CAP study for an IV drug in hospitalized patients?**
**Vote- YES/NO**

**a) To what severity of pneumonia or type of patients would it apply and how should severity be defined?**

**b) Should a microbiological diagnosis be necessary for inclusion in the primary analysis population for the trial, and if so, what organisms should be included (e.g., *S. pneumoniae*, other microbes)?**

**c) Should strategies be utilized to enrich the population for patients with a particular microbial etiology (e.g., *S. pneumoniae*, or other microbes)?**

**d) Please discuss whether the evidence which shows a treatment effect based on mortality can be linked to endpoints which are used in current non-inferiority CAP trials (i.e. clinical success/failure). If so, how? (Note: the possible components of the clinical failure endpoint might include some of the following mortality, receiving rescue therapy, lack of resolution of clinical signs and symptoms such that additional antibacterial therapy is administered, lack of resolution of signs and symptoms at the time the primary endpoint is assessed.)**

**e) The historical evidence for a treatment effect is based on studies which evaluated penicillin, sulfonamides, and tetracyclines. Given the need to preserve the treatment effect (the effect of the comparator agent over placebo or no treatment) in a future study, what are appropriate choices for comparator agents? Please explain the basis and information that supports the recommendation for comparator agents for a future study.**

**f) What is your best estimate of the treatment effect size (M1) that the historical data support for treatment of hospitalized CAP (based on severity selected in part a of this question, above) in a future CAP trial and what is your recommendation for a noninferiority margin that preserves a portion of the treatment effect (i.e., M2) for a CAP trial in this population with the endpoints discussed above?**

**2. Given the information presented, mostly from historical data on the treatment effect of drugs for CAP in patients with pneumococcal / lobar pneumonia, please address the following questions on trials of outpatient CAP (studies using an oral drug).**

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**a) Can a treatment effect be reliably quantified for a noninferiority study of outpatient CAP (i.e., for an oral drug)?**
**Vote- YES/NO**

**i. To which patient population would this information apply with regards to disease severity and microbiological etiology?**

**ii. What endpoint(s) should be utilized?**

**iii. What is the proposed noninferiority margin and what data support the proposed noninferiority margin?**

**b) Can placebo-controlled trials be carried out in less severely ill patients with CAP?**
**Vote- YES/NO**

**i. If yes, how can risk to patients be minimized? What patient population could be enrolled? What endpoints should be evaluated?**

**c) Can you suggest any alternative study designs that could be utilized which would allow for an informative trial of outpatient CAP (i.e., an oral drug) to be conducted? Please describe.**

**3. In a setting of hospitalized CAP as described in question 1 (above), one could study therapy with an intravenous formulation administered initially with subsequent "step down" therapy to an oral formulation as a means to support the use of the oral and IV formulations for severe disease. This leaves the question of whether the finding of efficacy for severe CAP would provide evidence of efficacy that could be used to support efficacy of the oral formulation for less severe (i.e., mild and moderate CAP). Do you believe the finding of efficacy in more severe CAP supports the drug's effect in less severe CAP, even though the drug has not been directly studied in less severe CAP?**
**Vote- YES/NO**

**4. If the available evidence for setting a noninferiority margin in current CAP trials is derived primarily from studies of patients with CAP due to *S.pneumoniae*, should noninferiority studies include patients with other etiologies of CAP?**
**Vote- YES/NO**

**If not, what additional data/studies are needed to show that antibacterial drugs are effective for specific organisms? When addressing this question please consider the following organisms:**

- ***Chlamydophila pneumoniae***
- ***Haemophilus influenzae***
- ***Legionella pneumophila***
- ***Mycoplasma pneumoniae***
- ***Staphylococcus aureus***
- ***Klebsiella pneumoniae***