

**Issues in the Design and Conduct of Clinical Trials of Antibacterial Drugs  
in the Treatment of Community-Acquired Pneumonia**

A workshop co-sponsored by the  
FDA and IDSA

January 17-18, 2008  
Silver Spring, Maryland

Co-Chairs:  
Tom Fleming  
David Gilbert  
Edward Cox

Rapporteur:  
Brad Spellberg

## **How will the workshop be conducted?**

- 1) Lectures on the current state of knowledge on
  - the condition of community-acquired pneumonia (CAP) including what we know about treatment effect
  - principles of clinical trial design and application no clinical trials of CAP
- 2) Presentation of prototypic clinical trial scenarios as a springboard for critical discussion of key elements of clinical trial designs for CAP intended to evaluate safety and efficacy of an antibacterial drug
- 3) Summation
  - What we know
  - What we don't know
  - What new approaches are worthy of further evaluation

IDSA/FDA-SPONSORED WORKSHOP  
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**Issues in the Design and Conduct of Clinical Trials of Antibacterial Drugs in the Treatment of Community-Acquired Pneumonia (CAP)**

**Goals:**

- 1) Examine critical issues in
  - The design and conduct of trials of the safety and efficacy of antibacterial drugs in the treatment of CAP
  - The implications of emerging scientific tools that assist in the diagnosis of the etiology of CAP.
- 2) Discuss clinical trial design and statistical considerations in demonstrating efficacy in clinical trials of CAP

## Thursday, January 17

- 7:45 – 8:00 a.m. Registration
- 8:00 – 8:15 a.m. Welcome by co-sponsors (Ed Cox, Tom Fleming, David Gilbert)  
(Goals and introduce morning panel)
- 8:15 – 8:45 a.m. How can current and emerging science improve clinical trials of  
antibacterials designed to determine safety and efficacy in the treatment of  
community-acquired pneumonia?  
*John Powers*
- 8:45 – 9:00 a.m. Q&A Panel
- 9:00 – 9:15 a.m. CAP scenario #1: “CAP in adults not requiring hospitalization”**  
*David Gilbert*
- 9:15 – 9:20 a.m. Clarification and comment by panel

### How can we best define the subjects eligible for a CAP trial?

- 9:20 – 9:50 a.m. Molecular diagnostics to detect viral and bacterial pathogens  
*Frederick Nolte*
- 9:50 – 9:55 a.m.. Q&A Panel
- 9:55 – 10:15 a.m. Prospects for procalcitonin as a new biomarker  
*Michael Niederman*
- 10:15 – 10:20 a.m. Q&A Panel
- 10:20 – 10:35 a.m. BREAK
- 10:35 – 10:50 a.m. How severe is the pneumonia: PORT scores  
*Michael Fine*

### Endpoints

#### Current knowledge of the “treatment effect” in clinical trials of outpatient pneumonia

- 10:50 – 11:20 a.m. What criteria should be addressed to do a credible non-  
inferiority trial and why is this clinically important?  
*Tom Fleming*
- 11:20 – 11:35 a.m. Q&A Panel

- 11:35 – 12:05 a.m. Clinical endpoints of therapy to include patient-recorded observations  
*Jack Edwards*
- 12:05 – 12:15 p.m. Q&A Panel
- 12:15 – 1:00 p.m. LUNCH
- 1:00 – 1:30 p.m. Does literature document a treatment effect relative to placebo? How does this aid design of future superiority or non-inferiority trials?  
*Tim F. Murphy*
- 1:30 – 1:50 p.m. Statistical issues in endpoint selection and non-inferiority trial design from an FDA perspective  
*Karen Higgins*
- 1:50 – 2:20 p.m. What are potential designs for a superiority trial for mild CAP? Are there adequate data to define an evidence-based margin in a non-inferiority trial for mild to moderate CAP?  
*Tom File*
- 2:20 – 2:30 p.m. Q&A Panel
- 2:30 – 2:45 p.m. BREAK
- 2:45 – 3:05 p.m. The perspective of industry  
*Roger Echols*
- 3:05 – 3:30 p.m. Q&A Panel
- 3:30 – 4:00 p.m. **Panel Discussion of CAP scenario #1:**
- Discussion points
    - What are the possible designs for an ethical controlled clinical trial designed to show superiority of a test drug in mild to moderate CAP?
    - Within the limitations of what we know, how likely is it that superiority could be demonstrated in a controlled clinical trial of an antibacterial drug for mild to moderate CAP?
    - If superiority in an active controlled trial is unlikely to be demonstrated for a clinically meaningful effect, can an informative, non-inferiority trial be designed based upon our current knowledge base of mild to moderate CAP?

## **Drug safety in trials of CAP**

- 4:00 – 4:20 p.m.    Issues in evaluating drug safety in CAP  
*Bruce Psaty*
- 4:20 – 4:40 p.m.    Evaluation of drug safety in CAP  
*Tatiana Oussova (FDA)*
- 4:40 – 5:10 p.m.    Industry experience and importance in monitoring safety  
*George Talbot*
- 5:10 – 5:30 p.m.    Q&A and Discussion

## Friday, January 18

- 8:00 – 8:30 a.m. Co-Chairs summary of day 1 and introduction of day 2
- 8:30 a.m. **Scenario #2: CAP pneumonia requiring hospitalization but not requiring ICU care**  
*Richard Wunderink*
- 8:45 – 9:10 a.m. The spectrum of the microbial etiology of hospitalized CAP: Implications for selecting the population for enrollment  
*Lionel Mandell*
- 9:10 – 9:15 a.m. Q&A Panel
- 9:15 – 9:40 a.m. The power of the Medicare database. Antibiotic selection makes a difference.  
*Dale Bratzler*
- 9:40 – 9:45 a.m. Q&A Panel
- 9:45 – 10:10 a.m. Can we improve the detection of *S. pneumoniae*? Implications for selecting the population for enrollment.  
*Keith Klugman*
- 10:10 – 10:15 a.m. Q&A Panel
- 10:15 – 10:30 a.m. BREAK
- 10:30 a.m. **How to assess a drug treatment effect?**
- 10:30 – 11:00 a.m. Primary and secondary and composite endpoints  
*John Powers*
- 11:00 – 11:15 a.m. Clinical and microbiologic endpoints  
*Daniel Musher*
- 11:15 – 11:45 a.m. Is it possible to “blind” a trial of CAP?  
*Helen Boucher*
- 11:45 – 12:10 p.m. The lessons of history: Immunotherapy and penicillin for pneumococcal pneumonia.  
*Mary Singer (FDA)*

- 12:10 – 12:30 p.m. Can pharmacodynamics predict clinical and/or microbiologic success or failure?  
*Paul Ambrose*
- 12:30 – 12:40 p.m. Q&A Panel
- 12:40 – 1:25 p.m. LUNCH
- 1:25 – 1:55 p.m. Is activity vs “atypical” pathogens necessary in treatment of protocols for CAP? Issues with combination therapy.  
*John Bartlett*
- 1:55 – 2:25 p.m. FDA experience and perspective on non-inferiority trials  
*Robert Temple*
- 2:25 – 2:40 p.m. BREAK
- 2:40 – 3:00 p.m. The perspective of industry: non-inferiority trials for CAP  
*Eddie Power*
- 3:00 – 3:30 p.m. How to define an evidence-based non-inferiority margin with degrees of unavoidable uncertainty  
*Tom Fleming*
- 3:30 – 3:40 p.m.
- 3:40 – 4:30 p.m. **Panel discussion of Scenario #2**
- What constitutes severe CAP and how should severity be classified for the purposes of a clinical trial?
  - What superiority and non-inferiority designs in trials for severe CAP would be reasonable?
  - What is the appropriate primary analysis population(s) for a trial of severe CAP and is it influenced by the antimicrobial spectrum of the test drug?
- 4:30 – 5:00 p.m. Closing remarks (Co-Chairs)