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:
Thomas R. Fleming, PhD, Professor of Biostatistics, University of Washington

David Gilbert, MD, Chief of Infectious Diseases and Director of Earle A. Chiles Research Institute, Providence Portland Medical Center and Professor of Medicine, Oregon Health and Science University

Edward Cox, MD, MPH, Director, Office of Antimicrobial Products, Office of New Drugs, CDER, FDA

Rapporteur:
Brad Spellberg, MD, FIDSA, Assistant Professor of Medicine, Geffen School of Medicine at UCLA, Division of Infectious Diseases, Harbor-UCLA Medical Center

IDSA/FDA-SPONSORED WORKSHOP
January 17-18, 2008
Silver Spring, MD

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

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 to 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

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, III, MD, FIDSA, Science Applications International Corporation in support of the Collaborative Clinical Research Branch, NIAID, NIH and University of Maryland School of Medicine, Baltimore, Maryland and George Washington University School of Medicine and Health Sciences, Washington, DC

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, PhD, D(ABMM), F(AAM), Professor of Pathology and Laboratory Medicine, and Director of Clinical Laboratories, Medical University of South Carolina, Charleston

9:50 – 9:55 a.m. Q&A Panel

9:55 – 10:15 a.m. Prospects for procalcitonin as a new biomarker

Michael Niederman, MD, Chairman, Department of Medicine, Winthrop-University Hospital Professor of Medicine, & Vice-Chairman, Department of Medicine, SUNY at Stony Brook

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, MD, MSc, Director, Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System

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?
Thomas R. Fleming, PhD, Professor of Biostatistics, University of Washington

11:20 – 11:35 a.m. Q&A Panel

11:35 – 12:05 a.m. Clinical endpoints of therapy to include patient-recorded observations
David Gilbert, MD, Chief of Infectious Diseases and Director of Earle A. Chiles Research Institute, Providence Portland Medical Center and Professor of Medicine, Oregon Health and Science University

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, MD, UB Distinguished Professor, Departments of Medicine and Microbiology & Chief of Infectious Diseases, University at Buffalo, State University of New York

1:30 – 1:50 p.m. Overview of Recent CAP Trials: Non-inferiority trial Design and Endpoints
Karen Higgins, PhD, Statistical Team Leader for the Division of Special Pathogen and

Transplant Products, Center for Drug Evaluation and Research, FDA

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 (Thomas M. File), Jr., MD, MSc, MACP, FIDSA, FCCP, Professor, Internal Medicine; Master Teacher; Head, Infectious Disease Section, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio; Chief, Infectious Disease Section and Director of HIV Research

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, MD, Chief Medical Officer, Replidyne

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, MD, PhD, Professor, Medicine, Epidemiology, and Health Services,

Cardiovascular Health Research Unit,
University of Washington

4:20 – 4:40 p.m. Evaluation of drug safety in CAP
Tatiana Oussova, MD, MPH, Medical Officer,
Division of Anti-Infective and Ophthalmic
Products, CDER, FDA

4:40 – 5:10 p.m. Industry experience and importance in monitoring safety
George Talbot, MD
President, Talbot Advisors LLC

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, MD, Professor of Medicine, Northwestern University, Feinberg School of Medicine

8:45 – 9:10 a.m. The spectrum of the microbial etiology of hospitalized CAP: Implications for selecting the population for enrollment

Lionel Mandell, MD, Professor of Medicine, McMaster University (Ontario, Canada)

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, DO, MPH, QIOSC Medical Director, Oklahoma Foundation for Medical Quality

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, MD, William H. Foege, Professor of Global Health, Rollins School of Public Health, Emory University

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, III, MD, FIDSA, Science Applications International Corporation in support of the Collaborative Clinical Research Branch, NIAID, NIH and University of Maryland School of Medicine, Baltimore, Maryland and George Washington University School of Medicine and Health Sciences, Washington, DC

11:00 – 11:15 a.m. Clinical and microbiologic endpoints
Daniel Musher, MD, Head of Infectious Diseases, VA Medical Center, Houston & Professor of Medicine, Baylor College of Medicine

11:15 – 11:45 a.m. Is it possible to "blind" a trial of CAP?
Helen Boucher, MD, Director, Infectious Diseases Fellowship Program & Assistant Professor of Medicine, Division of Infectious Diseases, Tufts-New England Medical Center

11:45 – 12:10 p.m. The lessons of history: Immunotherapy and penicillin for pneumococcal pneumonia.
Mary Singer, MD, PhD, Medical Officer, Division of Special Pathogen and Transplant Products, CDER Office of Antimicrobial Products, FDA

12:10 – 12:30 p.m. Can pharmacodynamics predict clinical and/or microbiologic success or failure?
Paul Ambrose, Pharm. D, FIDSA, Director of the Institute for Clinical Pharmocodynamics in Albany, New York & Associate Research Professor, School of Pharmacy and Pharmaceutical Sciences, University of Buffalo

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, MD, FIDSA, Chief, Division of ID, Johns Hopkins University School of Medicine

1:55 – 2:25 p.m. FDA experience and perspective on non-inferiority trials

Robert Temple, MD, Associate Director for Medical Policy, FDA

2:25 – 2:40 p.m. BREAK

2:40 – 3:00 p.m. The perspective of industry: non-inferiority trials for CAP

Eddie Power, MD, Senior Global Medical Director, Anti-Infectives / Virology,, Global Medical Affairs, Schering-Plough Corporation

3:00 – 3:30 p.m. How to define an evidence-based non-inferiority margin with degrees of unavoidable uncertainty

Thomas R. Fleming, PhD, Professor of Biostatistics, University of Washington

3:30 – 3:40 p.m. Q&A Panel

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)