Summary Minutes of the
Anti-Infective Drugs Advisory Committee Meeting
December 9, 2009

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the December 9, 2009, Meeting of the Anti-Infective Drugs Advisory Committee of the Food and Drug Administration were approved on February 8, 2010.

I certify that I attended the December 9, 2009, meeting of the Anti-Infective Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/ Minh Doan, Pharm.D.
Designated Federal Official

/s/ Thomas A. Moore, M.D.
Acting Committee Chair
Minutes of the Anti-Infective Drugs Advisory Committee  
December 9, 2009

The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 9, 2009, at the Hilton Washington, DC/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Thomas A. Moore, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Minh Doan, Pharm.D. (Designated Federal Official). There were approximately 200 persons in attendance. There were seven speakers for the Open Public Hearing session.

Issue: The committee met to discuss endpoints and other clinical trial design issues in the development of antibacterial products for the treatment of community-acquired bacterial pneumonia.

Attendance:

Anti-Infective Drug Advisory Committee Members Present (Voting):
W. Kemper Alston, M.D., Dean Follmann, Ph.D., Matthew Goetz, M.D., Peter Katona, M.D., Susan Rehm, M.D., Kent Sepkowitz, M.D., Melvin Weinstein, M.D.

Anti-Infective Drug Advisory Committee Member Present (Non-Voting):
John Rex, M.D. (Industry Representative)

Special Government Employee Consultants Present (Voting):
John Bartlett, M.D., William Calhoun, M.D., Thomas Fleming, Ph.D., Ken Makowka (Patient Representative), Thomas Moore, M.D., Donald Poretz, M.D., Barth Reller, M.D., Yu Shyr, Ph.D., Kathleen Young (Acting Consumer Representative)

Regular Government Employee Consultants Present (Voting):
None

Guest Speaker Present (Non-Voting):
Nancy Leidy, Ph.D.

Anti-Infective Drugs Advisory Committee Members Not Present:
Archana Chatterjee, M.D., Sheldon Kaplan, M.D.

FDA Participants (Non-Voting):
Edward Cox, M.D., M.P.H., Katherine Laessig, M.D., Sumati Nambiar, M.D., M.P.H., Mary Singer, M.D., Ph.D., Joseph Toerner, M.D., M.P.H., Thamban Valappil, Ph.D.

Designated Federal Official:
Minh Doan, Pharm.D.

Open Public Hearing Speakers:
Barry Eisenstein, M.D., F.A.C.P., FIDSA, PhRMA, James Floyd, M.D., University of Washington, David Gilbert, M.D. and Brad Spellberg, M.D., Infectious Diseases Society of America, John Powers, M.D., George Washington University, David Shlaes, M.D., Anti-infectives Consulting, LLC., Ph.D., Diana Zuckerman, Ph.D., National Research Center for Women and Families
**The agenda was as follows:**

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<td>Thomas A. Moore, M.D., Acting Committee Chair</td>
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<td>Minh Doan, Pharm.D., Designated Federal Officer</td>
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<td>Background</td>
<td>Edward Cox, M.D., M.P.H., Director OAP</td>
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<td>Community-Acquired Pneumonia: Regulatory Background</td>
<td>Joe Toerner, M.D., M.P.H., Associate Director for Medical Affairs OAP</td>
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<td>Non-Inferiority Trial Design and Treatment Effect Measures</td>
<td>Thamban Valappil, Ph.D., Statistical Team Leader Division of Biometrics IV Office of Biostatistics</td>
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<td>Treatment Effect of Antibacterial Drugs in Community-Acquired Bacterial Pneumonia</td>
<td>Mary Singer, M.D., Ph.D., Acting Medical Team Leader Division of Anti-Viral Drug Products (DAVP), OAP</td>
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<td>Community-Acquired Bacterial Pneumonia: Draft Guidance and Comments</td>
<td>Sumati Nambiar, M.D., M.P.H., Deputy Director for Safety Division of Anti-Infective and Ophthalmology Products (DAIOP), OAP</td>
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<td>Patient-Reported Outcomes (PRO) Endpoints in Clinical Trials: Challenges and Opportunities</td>
<td>Nancy Leidy, Ph.D., Senior Vice President, Scientific Affairs United BioSource Corporation</td>
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<td>Path Forward: Some Options</td>
<td>Katherine Laessig, M.D., Deputy Director DAIOP, OAP</td>
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<td>Charge and Questions to the Committee</td>
<td>Edward Cox, M.D., M.P.H., Director OAP</td>
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<td>Adjourn</td>
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Questions to the committee:

1. Do the historical data presented support the use of all-cause mortality as the primary endpoint in a CABP noninferiority trial? (Vote Yes/No)

   If Yes:
   
   a. Please explain your rationale.
   
   b. Please comment on the acceptable noninferiority margin and timepoint for assessment of all-cause mortality.

   If No:
   
   c. Please explain your rationale.

   Vote: Yes 14  No 2  Abstain 0

A majority of the Committee felt the historical data presented supported the use of all-cause mortality as a primary endpoint in CABP noninferiority trials, but not necessarily the primary endpoint. All-cause mortality would be a ‘hard’ endpoint with less chance of bias.

Most of the Committee felt that a noninferiority margin of 10% was acceptable and margins of <10% were also suggested. The Committee also felt consideration was needed for the use of odds ratio as the treatment effect measure for all-cause mortality due to the potential for low control mortality rates. There was also a general consensus that 14 days or less would be an appropriate timepoint for assessment of all-cause mortality. Members discussed the ability for doctors to delay death (i.e. mechanical ventilation), and a timepoint of 30 days might lead to more ambiguity.

Members who voted ‘no’ to the question felt that all-cause mortality should not be the primary endpoint in CABP noninferiority trials because the outcome is uncommon, and again noted the ability of doctors to delay death as an issue.

2. Do the historical data presented support the use of clinical response as the primary endpoint in a CABP noninferiority trial? (Vote Yes/No)

   If Yes:
   
   a. Please explain your rationale.
   
   b. Please comment on the acceptable noninferiority margin and timepoint (e.g., at 48-72 hours) for assessment of clinical response.

   If No:
   
   c. Please explain your rationale.

   Vote: Yes 12  No 4  Abstain 0

A majority of the Committee felt the historical data presented supported the use of clinical response as a primary endpoint in CABP noninferiority trials, but not necessarily the primary endpoint. Members expressed that the patient’s perception is an important component of the equation and should be augmented by clinical data. It was noted that the clinical response data from historical studies is relevant, but may need to be reassessed in the current setting of CAP. Several members referred to the daptomycin studies as a rationale for the use of clinical response as a primary endpoint.

A timepoint of 48-72 hours for assessment was mentioned as appropriate for clinical response.
Members who voted ‘no’ felt that clinical response would introduce bias as it was a subjective measure. It was noted that clinical response measures have not been validated, well-defined, or standardized and cannot be used to demonstrate efficacy.

3. For the primary endpoint(s) for a noninferiority CABP trial that you believe are supported by the historical data, please discuss the appropriate study population for

   a. A trial with all-cause mortality as its primary endpoint
   b. A trial with clinical response at an earlier time point (e.g., at 48-72 hours) as its primary endpoint.

In your comments for a. and b. above, you might consider:

- the characteristics of the patient population(s) from which the historical information is derived.
- to what CABP populations (e.g., degree of CABP severity or mortality rate in the study population) the treatment effect for the proposed primary endpoint would apply.
- If you believe that a clinical response endpoint is an appropriate primary endpoint, are there any comments you wish to provide on how mortality should be analyzed considering that the trial likely would not be powered to analyze mortality.

*The general consensus of the Committee was that all-cause mortality studies could involve PORT IV and V patients and in those with disease severity of lesser degrees, clinical response could be used as a primary endpoint. It was expressed that age greater than 50 and no prior therapy were important considerations. Most of the members did not have much to add and referred to their answers for questions 1 and 2.*

**Assessing CABP Severity at time of Enrollment**

4. Should scoring systems such as PORT/CURB-65 be used to enroll patients or would it suffice to enrich the population based on age ≥50 years? (Non-voting question, please explain your rationale.)

   Several members of the Committee stated that they did not feel strongly about either option presented in the question. Most members felt that either system could be used as long as there was consistency in use. Members stated that PORT is more extensive and its use has been better documented whereas CURB-65 is easier to use.

*Prior to the vote for question 5, one member left the meeting, which resulted in a total of 15 voting members for the remainder of the meeting.*

**Legionella pneumophila**

5. Should patients with documented *L. pneumophila* be enrolled in noninferiority CABP trials? (Vote Yes/No)

   If Yes:
   a. Please explain your rationale.
   b. Please describe the characteristics of patients (e.g., disease severity) with *L. pneumophila* appropriate for inclusion in a non-inferiority CABP trial.
   c. What is the appropriate primary endpoint for a noninferiority trial which includes patients with *L. pneumophila*?

   If No:
d. Please explain your rationale.

e. Please comment on other clinical trial designs to evaluate patients with pneumonia due to *L. pneumophila*.

Vote: Yes 13  No 1  Abstain 1

A majority of the Committee agreed that patients with documented *L. pneumophila* should be enrolled in noninferiority CABP trials because there would never be clinical studies of Legionella as the sole etiology of CAP. It was noted that *L. pneumophila* would be the only atypical organism that could be included, but it would be rare to find patients to enroll.

Members who voted ‘no’ did not feel that it would not be practical to include patients with documented *L. pneumophila* in the trials. Reasons included the presence of different species of Legionella, low rate of occurrence in the population, and feasibility concerns. It was also expressed that they could be included in the trials, but analyzed separately.

**Primary Analysis Population**

6. Should the Microbiological Intent-to-Treat (MITT) population be the primary analysis population in noninferiority clinical trials of CABP? (Vote Yes/No)

   If Yes:
   
   a. Please explain your rationale.
   
   b. Please comment on including patients with positive non culture-based tests (e.g. antigen tests, PCR, serologies) for pathogens known to cause CABP in the MITT population.

   If No:
   
   c. Please explain your rationale.
   
   d. Please provide any other comments on the appropriate analysis population(s).

Vote: Yes 12  No 3  Abstain 0

A majority of the Committee agreed that the MITT (all randomized patients who have the relevant pathogen, e.g. *Streptococcus pneumoniae* isolated at baseline) population as the primary analysis population in noninferiority clinical trials of CABP would help to minimize bias.

The members commented that non culture-based tests would help to enrich the MITT population, but some have not been FDA approved. The Agency responded that although some of the tests are not approved, they are allowed to be used in trials as long as they have the appropriate performance characteristics and are discussed with the Agency first.

Members who voted ‘no’ felt that the MITT population should not be the primary analysis population. It was noted that it would not be practical to use the MITT population as the primary analysis population because microbiological data is not always available.

**Prior Effective Antibacterial Therapy**

7. Should noninferiority clinical trials of CABP permit enrollment of patients who have received prior effective antibacterial drug therapies? (Vote Yes/No)

   If Yes:
a. Please provide your rationale and describe the circumstances that would permit meaningful interpretation of the treatment effect of an antibacterial drug in patients who have received prior effective antibacterial therapy.

If No:

b. Please provide your rationale.

Vote: Yes 4 No 11 Abstain 0

A majority of the Committee agreed that noninferiority clinical trials of CABP should not permit enrollment of patients who have received prior effective antibacterial drug therapies due to the potential to introduce bias in the treatment effect. It was also noted that because of the nature of the infection because treatment can result in rapid improvement, prior therapy would dilute treatment effect and can falsely conclude non-inferiority.

Members who voted ‘no’ felt that it was not practical to exclude these patients. It was stated that prior antibacterial drug therapy might not have any effect.

Several members from both voting categories expressed that they could have answered the question either way.

Patient Reported Outcome Endpoint in Mild/Moderate CABP

8. Should active-controlled superiority clinical trial designs using a Patient Reported Outcome (PRO) endpoint be recommended for the evaluation of new antibacterial drugs for treatment of mild-to-moderate CABP? (Vote Yes/No)

If Yes:

a. Please explain your rationale.

b. Please comment on the enrollment of patients with atypical pathogens, such as C. pneumoniae or M. pneumoniae.

If No:

c. Please explain your rationale.

d. Please comment on the clinical trial design(s) and endpoints for the evaluation of antibacterial drugs in patients with mild-to-moderate CABP.

Vote: Yes 10 No 4 Abstain 1

A majority of the Committee felt that using a Patient Reported Outcome (PRO) endpoint should be recommended for the evaluation of new antibacterial drugs for the treatment of mild-to-moderate CABP. Information gathered from a PRO instrument would be subjective, but could supplement clinical data. Some members commented that currently there is limited utility, but it should be further explored.

Members who voted ‘no’ were concerned about the use of PROs because none have been validated for use in community-acquired pneumonia. It was noted that this is an opportunity for such an instrument to be developed and validated.

Members who abstained from the vote felt they could not recommend PROs because of practical problems related to such instruments, but did see utility in their use.

Please see the transcript for detailed discussion.
The session adjourned @ approximately 6:00 p.m.