Food and Drug Administration
Center for Drug Evaluation and Research

Sheraton College Park Hotel, The Ballroom, 4095 Powder Mill Road, Beltsville, MD.

Summary Minutes of the Anti-Infective Drugs Advisory Committee on April 1& 2, 2008.

On April 1 and2, 2008 , the committee discussed product development and clinical trial design for both mild/moderate and moderate/severe community acquired pneumonia (CAP). A primary objective for committee deliberations was to discuss issues relating to the identification of an appropriate noninferiority margin for active controlled trials.

These summary minutes for the April 1 & 2, 2008 meeting of the Anti-Infective Drugs Advisory Committee were approved on Friday June 27, 2008.
I certify that I attended the April 1 & 2, 2008 meeting of the Anti-Infective Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/S/_____ 6/27/2008
Designated Federal Official
LCDR Sohail Mosaddegh, PharmD., R.Ph.

_____/S/_____6/27/2008
Gregory Townsend, M.D
Acting Chair

Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)

A verbatim transcript will be available in about 2 weeks, sent to the Office of Anti-Microbial Products and posted on the FDA website at
http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Gregory Townsend, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by LCDR Sohail Mosaddegh, Pharm.D., R.Ph. (Designated Federal Officer). There were approximately 250 persons in attendance. There were 4 speakers for the Open Public Hearing sessions.

Attendance:

Anti-Infective Drugs Advisory Committee Members Present (voting):
Annie Wong-Beringer, Pharm.D., Bernhard L. Wiedermann, M.D , Gregory Townsend, M.D., Carol A. Kauffman, M.D.

Anti-Infective Drugs Advisory Committee Members Present (Non-voting):
John H. Rex, M.D., F.A.C.P. (industry representative)

Anti-Infective Drugs Advisory Committee Members Absent:
Kathleen M. Gutierrez, M.D., Margo Smith, M.D., Allan R. Tunkel, M.D., Ph.D.

Special Government Employee Consultants Present (voting):
William J. Calhoun, M.D., F.A.C.P., Scott Dowell, M.D., M.P.H., Thomas R. Fleming, Ph.D., Kenneth R. Makowka (patient representative), Jan E. Patterson, M.D., Jürgen Venitz, M.D., Ph.D.

Regular Government Employee Consultants Present (voting):
Dean A. Follmann, Ph.D., Daniel M. Musher, M.D., Cynthia G. Whitney, M.D., M.P.H.

Guest Speaker Present (Non-Voting):
David Gilbert, M.D., Brad Spellberg, M.D., George H. Talbot, M.D., FIDSA, Richard Wunderink, M.D.

FDA Participants:
John Jenkins, M.D., Robert Temple, M.D., Edward Cox, M.D., M.P.H., Mary Singer, M.D., Ph.D., Sumathi Nambiar M.D., M.P.H., Katie Laessig, M.D., Steve Gitterman, M.D., Ph.D.

Open Public Hearing Speakers:
Michael T. Flavin, Ph.D. representing Advanced Life Sciences, Roger Echols, M.D. representing Replidyne, Inc., Alan Goldhammer, Ph.D. representing PhRMA, George Talbot M.D.

Designated Federal Official:
LCDR Sohail Mosaddegh, Pharm.D., USPHS, FDA

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Issue:
The committee discussed product development and clinical trial design for both mild/moderate and moderate/severe community acquired pneumonia (CAP). A primary objective for committee deliberations was to discuss issues relating to the identification of an appropriate noninferiority margin for active controlled trials.

The agenda was as follows:

Day One: April 1, 2008

Call to Order and Opening Remarks	Gregory Townsend, M.D. Acting Chair, Anti-infective Drugs Advisory Committee
Introduction of Committee Conflict of Interest Statement	LCDR Sohail Mosaddegh, Pharm.D., R.Ph. Designated Federal Officer FDA – USPHS
FDA Introductory Remarks and Regulatory Background	Edward Cox, M.D., M.P.H. Director, Office of Antimicrobial Products CDER, FDA
Key Issues from FDA-IDSA Workshop	John Alexander, M.D., M.P.H. Medical Team Leader Division of Anti-Infective and Ophthalmology Products CDER, FDA
IDSA perspective	Dave Gilbert, M.D. Chief of Infectious Diseases Providence Portland Medical Center Portland, Oregon
	Brad Spellberg, M.D. Assistant Professor of Medicine Geffen School of Medicine at UCLA Division of Infectious Diseases Harbor-UCLA Medical Center Los Angeles, California
Break	

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ATS/ACCP statement	Richard Wunderink, M.D. Professor of Medicine Pulmonary and Critical Care Division Northwestern University Feinberg School of Medicine Chicago, Illinois
Ethical Considerations for Trials of CAP	Robert Nelson, M.D., Ph.D. Pediatric Ethicist Office of Pediatric Therapeutics Office of the Commissioner, Food and Drug Administration Sara F. Goldkind, M.D., M.A. Senior Bioethicist Good Clinical Practice Program Office of the Commissioner, FDA
Non-inferiority Issues in Trials of Community Acquired Pneumonia	Thomas R. Fleming, Ph.D. Professor of Biostatistics University of Washington Seattle, Washington
Questions/clarifications	
Lunch	
Treatment Effect of Antibacterial Drugs in CAP: A Historical Perspective	Mary Singer, M.D., Ph.D. Medical Officer Office of Antimicrobial Products CDER, FDA
Contemporary CAP Trials and Determination of Treatment Effect	Sumathi Nambiar M.D., M.P.H. Medical Team Leader Division of Anti-infective and Ophthalmology Products, CDER FDA
Non-inferiority Margin for CAP Studies: Issues and Approaches	Thamban Valappil, Ph.D. Statistical Team Leader CDER, FDA

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Exposure-Response Analysis for CAP	Christoffer Wenzel Tornoe, Ph.D. Pharmacometrics Reviewer Pharmacometrics, Office of Clinical Pharmacology CDER, FDA

Break

Critical Considerations in CAP Trial Design: A Consultant's Perspective	George Talbot, M.D. George H. Talbot, Talbot Advisors, LLC 564 Maplewood Avenue Wayne, Pennsylvania

Questions/clarifications

Adjourn

Day two: April 2, 2008

Call to Order and Opening Remarks	Gregory Townsend, M.D. Acting Chair, Anti-infective Drugs Advisory Committee
Introduction of Committee Conflict of Interest Statement	LCDR Sohail Mosaddegh, Pharm.D., R.Ph. Designated Federal Officer FDA – USPHS
A Clinician's Scientific Approach to Pneumonia	Daniel M. Musher, M.D. Head of Infectious Diseases Veterans Affairs Medical Center, Houston, Texas
Considerations in the Design of CAP Studies	Steve Gitterman, M.D., Ph.D. Deputy Director, Division of Special Pathogen and Transplant Products CDER, FDA

Questions/clarifications

Break

Questions/Discussion

Open Public Hearing

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Lunch

Charge to the Committee & Advisory Committee Questions	Edward Cox, M.D., M.P.H. Director, Office of Antimicrobial Products CDER, FDA

Adjournment

Questions to the Committee:

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?

YES: 13 NO: 0 Abstain: 0 Absent: 0

(See transcripts for detailed discussion)

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

The committee was unable to provide a consensus or specific recommendation, however, suggested the use of a modified PORT system and emphasized that the PORT score is not sufficient alone to assess severity since it takes into account age and co-morbidities but not other baseline risk factors such as bacteremia status which affect outcomes. Some members ventured to say that the historical data appear to be applicable primarily to patients with a greater risk of death. Admission to the ICU, and/or the need for mechanical ventilation or pressors were suggested as indicating greater severity. The committee also agreed that although mortality is a highly clinically relevant endpoint, it [mortality] is the minimum parameter by which to measure severity. However, the committee did not point to specific information which would allow justification of a non-inferiority trial on outcomes other than all-cause mortality.

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)?

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The committee did not offer detailed discussion on the topic but suggested that in order to evaluate a drug in treating the disease; we need to know that subjects have the disease of interest and therefore a microbiological diagnosis in as many patients as possible is preferable. Pneumonia due to influenza, mycoplasma, Chlamydia, pneumococcus, or Staphylococcus aureus behave differently and respond differently to antimicrobial agents. The population enrolled should have a similar mortality rate to groups of patients studied in the historical data. Enrollment of subjects with lower mortality rates or without bacterial pneumonia may dilute the treatment effects and result in false conclusions of non-inferiority. The committee also suggested that focus be made to developing a rapid diagnostic test for suspected CAP microbes.
(See transcripts for detailed discussion)

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

The committee felt that it was important to enrich the population for patients with bacterial pneumonia, perhaps by modifying study enrollment criteria to include signs and symptoms of acute bacterial pneumonia. The committee further discussed the matter and agreed that the emergency room (E.R.) is a good source to obtain first-seen patients who have not yet received a dose of traditional antibiotics to treat suspected organisms for CAP. Including subjects who have not received prior antimicrobial agents is important because of the findings in the recent publication by Pertel et al. Enrichment for specific organisms such as pneumococcus may help to enroll similar patients in whom the previous studies demonstrated the historical effects of antibiotics.
(See transcripts for detailed discussion)

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.)

Some committee members agreed that treatment effect based on mortality might be extrapolated to endpoints which are used in current non-inferiority CAP trials. The committee deliberated at length on the topic of the use of mortality data. Many committee members believed that, in double blind studies, we could use a combination of symptoms and signs. There needed to be enough patients enrolled at each site so that variations in the results based on subjective factors would average out with the randomization. Mortality rates are generally too low (and almost absent in the group of mild to moderate pneumonias) to be very useful; in hospitalized patients mortality up to 10-14 days can be used, but not beyond. Clarification was made that mortality is a powerful endpoint but may not be the only appropriate endpoint for current measure. A modern day equivalent of mortality could be the need for rescue therapy. The committee commented that more severely ill patients are not being enrolled; therefore, clinical response is highly relevant. However, while pointing to the clinical relevance of endpoints other than mortality, the committee did not point to validated evidence from historical studies which would allow definition of a quantifiable and reproducible treatment effect on such endpoints to permit justification of non-inferiority trials on endpoints other than all-cause mortality. The committee suggested that the PRO instrument should be validated. The committee commented that it is critical for trials to be blinded as data captured is highly subjective and high success rates should be clarified as to the liberal assertion of such stated success.

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(See transcripts for detailed discussion)

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.

(See transcripts for detailed discussion)

The committee did not recommend that choice of comparator agents for future trials be limited to penicillin, sulfonamides, or tetracycline as long as we have evidence that new agents have preserved the treatment effect of previous therapies. The committee also suggested the most effective antibiotic should be used as the comparator agent, head-to-head to avoid loss of effect of the control agent through serial non-inferiority trials, (biocreep). Also, comparator agents should be selected on the basis of treatment guidelines.

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?

To further clarify, the committee recommended that the historical data can be used to select a noninferiority margin (M2) for CAP trials of intravenous drugs in hospitalized patients. The committee consensus was that a 10 percent margin is reasonable for moderate-to-severe pneumonia with a mortality endpoint Also, there was some support for using relative risk reduction in mortality. In addition, demonstration of internal exposure-response relationships, consistent with prior expectations, can provide supportive evidence of treatment effectiveness in an NI trial.
(See transcripts for detailed discussion)

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).

a) Can a treatment effect be reliably quantified for a noninferiority study of outpatient CAP (i.e., for an oral drug)?

YES: 10 NO: 3 Abstain: 0

Members voting yes agreed treatment effect can be reliably quantified for a noninferiority study of outpatient CAP but also suggested that outpatient CAP may not have sufficient historical data, therefore this patient population would benefit from further study. Several members discussed that since the severity of the patients in the historical studies isn't well-described and anybody with pneumonia was likely to have been hospitalized at that time, the historical data may be applicable to mild-moderate pneumonia as well. Thus, a margin of 10% for mortality may be reasonable in

this setting as well. A concern was expressed about extrapolation of this margin to other endpoints.

Members voting 'no' suggested that the plausibility of extrapolation of treatment effect based on the all-cause mortality endpoint to other endpoints in mild/moderate disease may be unrealistic given the lack of historical data to validate this assumption and suggests that the Infectious Disease Society of American (IDSA) position paper summary conclusion recommending use of all-cause mortality to test a non-inferiority hypothesis along with validated patient reported outcome instruments to test a superiority hypothesis is valid. The group voting 'no' also agreed that study within the mild/moderate patient populations does not provide an appropriate setting for use of the non-inferiority trial design given the lack of evidence to support a margin on endpoints other than all-cause mortality. Non-inferiority trials could be designed in this population using a relative risk calculation of the treatment difference between the test and control groups; however the smaller mortality rate in this population would result in a larger sample size. The group voting "no" agreed that demonstration of non-inferiority with a justifiable margin based on an endpoint of all-cause mortality could result in granting of a general indication for "community acquired pneumonia" without further specification. The group pointed out that current oral drugs have been studied in patients with more severe disease.

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

The committee agreed the population should be enriched for pneumococcal pneumonia, but would include other bacterial pneumonias and would primarily consist of patients who are not ill enough to require hospitalization and are judged able to be treated with an oral agent. The population should be enriched with older patients who have greater risk for bacterial pneumonia rather than younger patients who are less ill and more likely to have viral or atypical pneumonias.
(See transcripts for detailed discussion)

ii. What endpoint(s) should be utilized?

The Committee agreed that a composite clinical outcome possibly incorporating fever and other parameters that may be affected based on disease severity should be used to evaluate the response to treatment. This would consist of information on symptoms noted by the patient and signs noted by the clinician; implicit in this endpoint is the notion that careful follow-up of patients is essential in order to obtain valid data. It was noted that a PRO instrument would need validation. The committee also agreed mortality should not be a primary endpoint in this population. However, as noted above, the committee did not point to evidence from historical studies to justify the use of a composite endpoint in the setting of non-inferiority trials. Some committee members held that an all-cause mortality endpoint is not relevant today because current "rescue therapy" has decreased mortality in pneumonia. However, others on the committee pointed out that there is lack of evidence that "rescue therapy" has altered mortality in pneumonia since data presented to the committee showed that the mortality rate in pneumonia has not decreased since the 1940s.
(See transcripts for detailed discussion)

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

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(Clarification was made by FDA that historical data remains relevant today, and should still be considered in forming responses)

The committee agreed that the proposed non-inferiority margins should be based on interpretation of the earlier data and the supposition that a large percentage of these patients would have gone on to more severe disease in the pre-antibiotic era. However, as noted above, others on the committee pointed out that the lack of data to support this supposition, the lack of change in overall mortality rates in pneumonia over the last 60 years, and data showing most patients with pneumonia who die do so early in the course of the disease do not support the conclusion that current patients are "rescued" from death when they would have died in the past. The committee also agreed that the same M1/M2 groups should be used if historical trials are of focus and the results from historical data should be extrapolated to current patient populations' data without defining severity. Some on the committee pointed out those non-inferiority trials based on an all-cause mortality endpoint could be used if a relative risk rather than absolute risk measure of treatment effect is used. The historical data could support a relative risk margin of 1.67 on all-cause mortality in all patient groups, but this would result in larger sample sizes for patient populations with lower mortality. As noted previously, some members thought a 10% NI margin was reasonable.
(See transcripts for detailed discussion).

b) Can placebo-controlled trials be carried out in less severely ill patients with CAP?

YES: 0 NO: 13 Abstain: 0 Absent: 0

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

The committee agreed that placebo controlled trials are not appropriate, even in less severe CAP, because patients expect to be treated with an active drug and there is evidence of a treatment effect on all-cause mortality in all patient groups. Institutional Review Boards are unlikely to approve a placebo-controlled study, and the risk of progression to more severe disease is a reality that must be considered.
(See transcript for further discussions.)

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.

After some debate on this question the committee was not able reach a consensus on alternative strategies. There was discussion of dose-ranging, with the caveat that a clinically small dose, which might be expected to be ineffective, would come dangerously close to a placebo trial. There was discussion of the potential impact of cumulative non-inferiority margins allowing the theoretical possibility of approval for a drug that is no more effective than placebo. The general belief of the committee was that although there may be a theoretical possibility, it is unlikely to be a serious concern. Delayed therapy was also discussed, but there were ethical and practical concerns with this approach as well, since there is evidence to suggest that early therapy of CAP improves outcome.
(See transcript for further discussions.)

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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?

YES: 13 NO: 0 Abstain: 0 Absent: 0

After voting on question 3 the committee members discussed the question further and came to the general consensus that if a drug is found to be effective in severe CAP, this fact can support the drug's effectiveness in patients with mild and moderate CAP, even though the drug has not been directly studied in less severe CAP. Even though the committee voted unanimously on this issue some of the members had reservations on the matter. Some did not believe the organisms causing less severe CAP would be the same as those causing severe CAP but still voted yes because providing coverage for those organisms causing severe pneumonia while treating patients with mild pneumonia would presumably keep them out of serious trouble. Members also commented that sufficient oral bioavailability of the oral formulation needs to be documented.
(See transcript for further discussions.)

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?

YES: 12 NO: 0 Abstain: 1 Absent: 0

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*

After the vote was taken the committee members discussed their reasoning and came to the general consensus that they would include patients with etiologies other than S.pneumoniae. This was partly due to the realization that identification of the true causative organism would be uncertain and untimely. Several members expressed concern about the evolving significance of S. aureus in CAP.
(See transcript for further discussions.)

The meeting was adjourned at approximately 4:30 p.m. on April 2, 2008.