Food and Drug Administration  
Center for Drug Evaluation and Research  

Summary Minutes of the Anti-Infective Drugs Advisory Committee Meeting  
December 4, 2014  

Location: The Marriott Inn and Conference Center, University of Maryland University College  
The Ballroom, 3501 University Blvd. East, Hyattsville, Maryland 20783  

Topic: The committee discussed issues related to clinical development programs and clinical  
trial designs for antibacterial products for the treatment of patients with serious bacterial  
infections for which there are limited or no therapeutic options.  

These summary minutes for the December 4, 2014 meeting of the Anti-Infective Drugs Advisory  
Committee of the Food and Drug Administration were approved on January 16, 2015.  

I certify that I attended the December 4, 2014 meeting of the Anti-Infective Drugs Advisory  
Committee of the Food and Drug Administration and that these minutes accurately reflect what  
transpired.  

______________________________   ______________________________  
/s/ Moon Hee V. Choi, PharmD    /s/ CAPT Monica E. Parise, MD  
Acting Designated Federal Officer, AIDAC    Chairperson, AIDAC
Summary Minutes of the Anti-Infective Drugs Advisory Committee Meeting  
December 4, 2014

The following is the final report of the Anti-Infective Drugs Advisory Committee meeting held on December 4, 2014. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anti-Infective Products and posted on the FDA website at:  
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm385739.htm

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

The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on December 4, 2014, at the College Park Marriott Hotel and Conference Center, University of Maryland University College (UMUC), 3501 University Blvd, East, Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA. The meeting was called to order by CAPT Monica Parise, MD (Chairperson). The conflict of interest statement was read into the record by Moon Hee Choi, PharmD (Acting Designated Federal Officer). There were approximately 150 people in attendance. There were 11 Open Public Hearing speakers.

**Issue:** The committee discussed issues related to clinical development programs and clinical trial designs for antibacterial products for the treatment of patients with serious bacterial infections for which there are limited or no therapeutic options.

**Attendance:**

**Anti-Infective Drugs Advisory Committee Member Present (Voting):** Ellen M. Andrews, PhD (Consumer Representative); Lindsey R. Baden, MD; Alan J. Magill, MD; Luis Z. Ostrosky, MD; CAPT Monica E. Parise, MD (Chairperson); Marc H. Scheetz, PharmD, MSc

**Anti-Infective Drugs Advisory Committee Members Not Present (Voting):** Antonio Carlos Arrieta, MD; Yu Shyr, PhD

**Anti-Infective Drugs Advisory Committee Member Present (Non-Voting):** Patrick Robinson, MD (Industry Representative)

**Temporary Members (Voting):** Diane M. Cappelletty, PharmD; John P. Dekker, MD, PhD; Dean Follmann, PhD; Nicole Mayer Hamblett, PhD; Debra McCall, BS, MBA (Patient Representative); Thomas A. Moore, MD, FACP, FIDSA; L. Barth Reller, MD; Paul C. Schreckenberger, PhD, D(ABMM), F(AAM); Paige E. Waterman, MD
FDA Participants (Non-Voting): Edward Cox, MD, MPH; Sumati Nambiar, MD, MPH; Katherine Laessig, MD; Joseph Toerner, MD, MPH; Lisa LaVange, PhD

Open Public Hearing Speakers: John Fratti, Margaret Dayhoff-Branigan, PhD (National Center for Health Research); Susan Molchan, MD; Ian Friedland, MD (Achaogen, Inc.); Roger Echols, MD (Shionogi, Inc.); Barry Eisenstein, MD, FACP, FIDSA, FAAM (Cubist Pharmaceuticals, Inc.); Joseph Brodine; Drusilla Scott, PhD (Cempra Pharmaceuticals), Michael Dudley, PharmD (The Medicines Company); Reshma Ramachandran (National Physicians Alliance FDA Task Force), Paul Ambrose, PharmD, FIDSA

The meeting agenda proceeded as follows:

Call to Order and Introduction of Committee
CAPT Monica Parise, MD
Chairperson, AIDAC

Conflict of Interest Statement
Moon Hee V. Choi, PharmD
Acting Designated Federal Officer, AIDAC

FDA PRESENTATIONS

FDA Introductory Remarks
Edward Cox, MD, MPH
Director
Office of Antimicrobial Products (OAP)
Office of New Drugs (OND), CDER, FDA

History of Antibacterial Drug Development
Katherine Laessig, MD
Deputy Director
Division of Anti-Infective Products (DAIP)
OAP, OND, CDER, FDA

Clinical Development Issues for Antibacterial Drugs for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases
Joseph Toerner, MD, MPH
Acting Deputy Director for Safety
DAIP, OAP, OND, CDER, FDA

Statistical Considerations in Evaluating Products for Unmet Medical Need
Daniel Rubin, PhD
Statistical Reviewer
Division of Biometrics IV
Office of Biostatistics
Office of Translational Sciences, CDER, FDA

Trial Considerations for Unmet Need
Sumati Nambiar, MD, MPH
Director
DAIP, OAP, OND, CDER, FDA

Clarifying Questions

BREAK
PRESENTATIONS BY PROFESSIONAL ORGANIZATIONS

American Thoracic Society (ATS): A Clinician/Clinical Investigator’s Perspective
Richard G. Wunderink, MD
Chairman, ATS Microbiology, Tuberculosis, and Respiratory Infections Assembly
Member, ATS Board of Directors
Northwestern University Feinberg School of Medicine

Infectious Diseases Society of America and Pediatric Infectious Diseases Society (IDSA and PIDS): Antibiotic Development for Patients with Serious Infections and Unmet Need
Jason Newland, MD, MEd, FPIDS
Member, IDSA Antimicrobial Resistance Committee
Chair, PIDS Pediatric Committee on Antimicrobial Stewardship
Medical Director of Patient Safety and Systems Reliability
Children's Mercy Hospitals & Clinics

Biotechnology Industry Organization (BIO): Clinical Development Issues with Antibacterial Drugs for Unmet Medical Needs – Patients, Pathogens, and Streamlined Drug Development
Jeff Alder, PhD
Senior Director
Global Clinical Development, General Medicine
Bayer HealthCare

BIO: Balancing Expectations – Dataset Size vs. Feasibility
John H. Rex, MD, FACP
Senior Vice President and Head of Infection Global Medicines Development
AstraZeneca

Clarifying Questions

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT
Question to the Committee:

1. **DISCUSSION:** Please discuss the acceptability from a clinical perspective of a streamlined development program that has greater uncertainty about the safety and efficacy of a new drug because of the smaller size of the clinical studies.

   **Committee Discussion:** The majority of the committee members were in support of streamlined development programs in the areas of unmet medical need given limited treatment options currently available for particular organisms. The committee noted that the Agency should have flexibility about the amount of data for different unmet need indications, but the standard for demonstrating the efficacy and safety of drugs should remain the same. Several committee members noted the importance of Phase IV studies and the need to obtain better meaningful data, as well as, to implement better mechanisms for data sharing. Several committee members mentioned the importance of stewardship and the need for the medical community to do a better job, including using drugs with narrow indication properly. One committee member stated that the clinical studies should be designed by looking at the site of infection as opposed to specific pathogen. Another committee member noted that the clinical studies should be done in patients with resistant organisms. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Please discuss the following options for trial designs for streamlined development programs:

   a. Non-inferiority trials
      i. Non-inferiority trials at a single body site of infection (e.g., cUTI, cIAI) using larger than usual non-inferiority margins (e.g., M2 is closer to M1 than is usual in traditional development programs)

   b. Superiority trials
      i. Pooling across different body sites of infection
      ii. Selection of the control group for inference testing (e.g., best-available therapy, external control)

   **Committee Discussion:** The majority of the committee agreed that the Agency should have flexibility in determining what would be appropriate in developing streamlined non-inferiority and superiority trials. Several committee members had concerns with widening the margin in the non-inferiority trials. It was noted that if using a larger than usual non-inferiority margin is the appropriate tool, the Agency would need to determine the appropriate backup steps needed if a less than effective drug was to come out (e.g. phase 4 trials). Several committee members were in favor of the superiority trials over non-inferiority trials. It was noted by some of the committee members that pooling subjects with infections at different body sites would be acceptable if the appropriate statistical
methodology is used and if other supportive evidence (e.g., no other treatment option, drug getting into body fluids) is available to clinicians. Some committee members noted that preclinical data such as genomics and knowing the mechanism of action would be useful in determining best available therapy. A few of the committee members raised concerns with using the external controls and one member noted the issue of the host factors would be problematic in terms of using these controls. Please see the transcript for details of the committee discussion.

3. DISCUSSION: Please discuss trial design options for a product that has a spectrum of activity limited to one or two particular microorganisms (e.g., *Pseudomonas aeruginosa*, *Acinetobacter baumanii*).

**Committee Discussion:** The majority of the committee members agreed that, at this point, a trial design for a product that has a spectrum of activity limited to one or two particular microorganisms is problematic due to the lack of rapid diagnostics. Some of the committee members noted that even if there was a test for a particular bacterial genus or species, there are no rapid diagnostics to determine susceptibility. One committee member suggested initiating treatment by starting out broad and to randomize and test the drug once the infecting organism is determined. Another committee member noted that there could be specific patient populations where supportive evidence can be gathered to identify particular organisms (e.g. patients with cystic fibrosis that are prone to pseudomonas infections). Please see the transcript for details of the committee discussion.

4. DISCUSSION: Please discuss the acceptability of a smaller safety database (e.g., 300 – 400 patients exposed to the investigational drug at the dose and duration of therapy).

**Committee Discussion:** Some of the committee members noted that exposing healthy patients to the drug to determine the adverse event profile, although healthy patients are very different from ill patients, drug-drug interaction information and PK/PD data may help interpret the data in the targeted patients who may have multiple comorbidities and be on multiple medications. In addition, it was suggested that PK information from patients with renal and hepatic impairment would be useful, because the patients who are likely to receive the medication may also have renal or hepatic impairment. One committee member noted that the database for drugs being approved under the 505(b)(2) regulatory authority may need to be augmented with additional numbers to ensure an adequate safety database which could include drug susceptible and drug resistant organisms. Some of the committee members in general agreed with a smaller safety database, but noted that robust supportive preclinical data would be needed, as well as obtain more data in Phase IV as the safety database gets smaller. One committee member noted that these antibiotics can have immunomodulatory effects and those assays should be considered as part of the whole evaluation. Some of the committee members again mentioned that the Agency should have
flexibility on determining the numbers in the safety database by considering how limited the options in determining where to set the bar. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:24 p.m.