Food and Drug Administration
Center for Drug Evaluation and Research

Food and Drug Administration, Center for Drug Evaluation and Research Advisory Committee Conference Room, Rm. 1066
5630 Fishers lane, Rockville, MD

Summary Minutes of the Anti-Infective Drugs Advisory Committee on April 12, 2007.

On April 12, 2007, the committee discussed clinical trial designs for products that seek indications for the prevention and/or treatment of disease caused by Shiga toxin-producing bacteria.

These summary minutes for the April 12, 2007 meeting of the Anti-Infective Drugs Advisory Committee were approved on Monday May 7, 2007.
I certify that I attended the April 12, 2007 meeting of the Anti-Infective Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/S/_____ 5/07/2007
Designated Federal Official
Lt. Sohail Mosaddegh, PharmD., R.Ph.

_____/S/_____5/07/2007
L. Barth Reller M.D.
Acting Primary Co-Chair

_____/S/_____5/07/2007
Marsha D. Rappley, M.D.
Acting Co-Chair

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/cder07.html#AntiInfective

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the Sponsor. The meeting was called to order by L. Barth Reller M.D. (Acting Committee Co-Chair); the conflict of interest statement was read into the record by Lt. Sohail Mosaddegh, Pharm.D., R.Ph. (Designated Federal Officer). There were approximately 85 persons in attendance. There was 1 speaker for the Open Public Hearing sessions.

Attendance:

Anti-Infective Drugs Advisory Committee Members Present (voting):
John E. Edwards Jr., M.D., Joan Hilton, Sc.D., M.P.H., Margo Smith, M.D., Gregory Townsend, M.D., Bernard Wiedermann, M.D., Annie Wong-Beringer, Pharm.D..

Anti-Infective Drugs Advisory Committee Members Present (non-voting):
Samuel D. Maldonado, M.D., M.P.H.

Anti-Infective Drugs Advisory Committee Members Absent:
Kathleen M. Gutierrez, M.D., Carol A. Kauffman, M.D., Allan R. Tunkel, M.D..

Pediatric Advisory Committee Members Present (voting):
Avital Cnaan, Ph.D., M.S., Robert S. Daum, M.D., Deborah L. Dokken, MPA , Michael E. Fant, M.D. Ph.D., Richard L. Gorman, M.D., Melissa Maria Hudson, M.D., Keith Kocis, M.D., M.S., Marsha D. Rappley, M.D. (Acting Co-Chair), Robert Ward, M.D..

Pediatric Advisory Committee Members Absent (voting):
Leon Dure, M.D., Elizabeth A. Garofalo, M.D., John W. M. Moore, M.D., M.P.H., Thomas B. Newman, M.D., M.P.H..

Special Government Employee Consultants Present (voting):
Frederick Kaskel, Ph.D., Susan Rehm, M.D., L. Barth Reller, M.D.(Acting primary Co-Chair), Geoffrey L Rosenthal, M.D., Ph.D., Phillip Tarr, M.D..

Federal Employee Consultants Present (voting)
Patricia M. Griffin, M.D., Marva Moxey-Mims, M.D., F.A.A.P. , David Acheson, Ph.D..

Guest Speaker Present:
Martin Bitzan, M.D

FDA Participants:
Edward Cox, M.D., M.P.H., Amy Nostrandt, Ph.D., Thomas Smith, MD., Janice Soreth, M.D., Yan Wang, Ph.D..

Open Public Hearing Speakers:
Jonathon Stern (Inverness Medical)

Issue: The committee discussed clinical trial designs for products that seek indications for the prevention and/or treatment of disease caused by Shiga toxin-producing bacteria.

The Agenda was as follows:

April 12, 2007

Call to Order and Introductions	L. Barth Reller, M.D. Acting Co-Chair Anti-Infective Drugs Advisory Committee (AIDAC) Marsha D. Rappley, M.D. Acting Co-Chair Pediatric Advisory Committee (PAC)
Conflict of Interest Statement	Lt. Sohail Mosaddegh, RPh., Pharm.D., Designated Federal Official, Anti-Infective Drugs Advisory Committee

FDA Presentation

Regulatory Pathways for Products for the Prevention or Treatment of Disease Caused by Shiga Toxin-Producing Bacteria	Thomas Smith, M.D. Medical Officer Division of Anti-Infective and Ophthalmology Products (DAIOP) CDER, FDA
Epidemiology of Shiga toxin-producing *E. coli* infections, focusing on North America	Patricia Griffin, M.D. Chief, Enteric Diseases Epidemiology Branch Division of Foodborne, Bacterial and Mycotic Diseases National Center for Zoonotic, Vectorborne, and Enteric Diseases
Clinical course and consequences of infections with *Escherichia coli* O157:H7 and other Shiga toxin-producing Bacteria	Phillip I. Tarr, M.D. Melvin E. Carnahan Professor of Pediatrics Professor of Molecular Microbiology Director, Division of Pediatric Gastroenterology and Nutrition Washington University School of Medicine
Break	
Experimental Animal Models for the Evaluation of Therapeutic Products Indicated for Shiga-toxin Producing Infections	Amy C. Nostrandt, D.V.M., Ph.D. Pharmacologist, DAIOP, CDER, FDA
Study Design Issues and Considerations in HUS Trials	Yan Wang, Ph.D. Statistical Reviewer, Division of Biometrics IV CDER, FDA
Lunch	
Open Public Hearing	
STEC Disease Severity Score	Martin Bitzan, M.D. Assistant Professor Department of Pediatrics and Pediatric Nephrology, McGill University, Montreal Children's Hospital

Industry Perspective

Thallion Pharmaceuticals

Trial Design for Shiga Toxin-Producing Bacterial Infection	Thomas G. Cleary, M.D. Center for Infectious Diseases University of Texas School of Public Health

Teijin America, Inc.

Strategy, Issues, and Alternative Approaches in Development of a Treatment for HUS Prevention	Sheldon Brookman, Ph.D. Executive Director, Research and Regulatory Affairs, Teijin America, Inc. Allen Cato, M.D., Ph.D. President, Cato Research Myron Peterson, M.D., Ph.D. M.P.H. Acting Director, Medical Affairs, Cato Research

Break

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

Committee Discussion and Vote

Adjourn

Questions to the committee:

1. While the Agency does not believe that product approval for this indication can rely solely on efficacy data from animal models for approval (i.e., Animal Efficacy Rule), we would like the Committee to consider whether animal data may provide supportive evidence of efficacy.
    a. Does the Committee believe that the pathophysiology of Shiga toxin-producing bacterial infection and the resulting complications in animal models are sufficiently understood so that we may conclude a model exists that is predictive of the disease process in humans? If so, which animal model(s)?
    Discussion: After some discussion, the Committee Chair called for a vote on the following question:
    Do any of the animal models discussed today adequately mirror the disease process in humans?
    After some discussion the committee came to the consensus that: There is no single animal model that mimics the disease process in humans, but there are components of the disease process represented in different animal models. Either a better single animal model is needed or a composite model would be required. The suckling pig and the greyhound are two animal models that the committee felt were most promising to be studied further to predict aspects of disease .

    b. If the answer to the preceding question is yes, does the Committee believe that the animal model(s) may be used to provide supporting data for drug and/or biologic products that seek to intervene in the disease process?
    Discussion: After some discussion the committee reached the consensus that animal models (single or aggregate animal models) could not be a substitute for adequately controlled clinical trials. Futhermore, supportive use of animal data would require independent validation of the model(s) used

2. At this time it is anticipated that any product seeking approval or licensure for treatment of Shiga toxin-producing bacterial infection would be studied in a clinical study(ies) of superiority design, in which the product + standard of care would be compared to standard of care alone. For products seeking to intervene in the disease process prior to the onset of HUS, what primary endpoint should used to determine efficacy?
    a. Prevention of HUS only?
    Discussion: After some discussion the committee voted on the question: should prevention of HUS be the only endpoint?
    Yes: 9 No:11 Absent: 3
    There was a consensus, however, that HUS should be the primary endpoint, if not the only endpoint.

    See transcript for further discussions

    b. Are there alternative clinical endpoints that the Committee considers clinically meaningful that may be included in a composite endpoint with prevention of HUS?
    Discussion: **See transcript for further discussions.**

3. The enrollment of patients in clinical studies to assess the safety and efficacy of products to prevent the complications of Shiga toxin-producing bacterial infection is challenging due to the low incidence of infection and the sporadic nature of outbreaks. In addition, there may be a limited therapeutic window in which an intervention may be efficacious. Does the Committee have any suggestions regarding strategies that may enhance trial enrollment?

    Discussion: **See transcript for further discussions**

Anti-Infective Drugs Advisory Committee in a joint Session with the Pediatric Advisory Committee meeting Final minutes

April 12, 2007 – Shiga-Toxin