Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

March 18, 2005

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

I certify that I attended the March 18, 2008 meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology and that these minutes accurately reflect what transpired.

Mimi T. Phan, PharmD, R.Ph
Designated Federal Officer, ACPS-CP

Jürgen Venitz, M.D., Ph.D.
Acting Chair, ACPS-CP

The Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration, Center for Drug Evaluation and Research met on March 18, 2008 at the Food and Drug Administration, Center for Drug Evaluation and Research Advisory Committee Conference Room, Rm. 1066, 5630 Fishers Lane, Rockville, MD. Prior to the meeting, the members and the invited consultants had been provided the background materials from the FDA. The meeting was called to order by Jürgen Venitz, M.D., Ph.D. (Acting Chair); the conflict of interest statement was read into the record by Mimi T. Phan, Pharm.D., R.Ph. (Designated Federal Official). There were approximately one hundred ten (110) persons in attendance. There was no speaker for the Open Public Hearing session.

Issue: The committee discussed and provided comments on the new topics of this meeting; (1) The New Clinical Pharmacogenomics (PGx) concept paper. Key issues in the concept paper included an industry survey on the collection of PGx samples, and the applications of PGx in clinical development were presented; and (2) discussed and provided comments on Quantitative Clinical Pharmacology: Critical Path Opportunities. An example of a disease model and its applications were presented. The regulatory experience, designs and implications of pediatric studies were discussed.

Attendance:

ACPS-CP Committee Members Present (Voting):
Marilyn E. Morris, PhD; Elizabeth Topp, PhD

Special Government Employee Consultants (Voting):
Jeffrey S. Barrett, PhD, FCP; Michael D. Caldwell, MD, PhD; Edmund V. Capparelli, PharmD; David A. Flockhart, MD, PhD; Kathleen Giacomini, PhD; Merrill Goozner; Gregory L. Kearns, PharmD, PhD; Juan J.L. Lertora, MD, PhD; Donald E. Mager, PharmD, PhD; Howard McLeod, PharmD; Mary V. Relling, PharmD; Jürgen Venitz, MD, PhD (Acting Chair)

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March 18, 2008

Industry Representative (Non-Voting):
Mukul A. Agrawal, PhD (Acting Industry Representative), Philip Mayer, PhD (Acting Industry Representative)

FDA Participants (Non-Voting):
Felix Frueh, PhD (Topic 1); Joga Gobburu, PhD (Topic 2); Shiew-Mei Huang, PhD (Topic 1); Parvin Jadhav, PhD (Topic 2); Ike Lee, PhD (Topic 1); Lawrence Lesko, PhD; Lisa Mathis, MD (Topic 2); Robert O'Neill, PhD (Topic 2); Norman Stockbridge, MD (Topic 2); Yaning Wang, PhD (Topic 2)

Guest Speakers (Non-Voting)
Rene Bruno, PhD; Eric Lai, PhD; Lisa A. Shipley, PhD

Designated Federal Official:
Mimi T. Phan, PharmD, RPh

The agenda was as follows:

Call to Order	Jürgen Venitz, M.D., Ph.D. Acting Chair, ACPS-CP
Conflict of Interest Statement	Mimi Phan, Pharm.D., R.Ph. Designated Federal Official, ACPS-CP
Introduction to the meeting Topics	Lawrence Lesko, Ph.D. Director, Office of Clinical Pharmacology (OCP), CDER, FDA
Topic 1: **New Clinical PGx concept paper**	
Key issues in the concept paper Pharmacogenomics,	Felix Frueh, Ph.D. Associate Director, OCP, CDER, FDA
An industry survey on collection of PGx samples	Lisa Shipley, Ph.D. Eli Lilly & Co.
Use of Pharmacogenetics Information in Clinical Settings- Are We Ready for Prime Time?	Eric Lai, Ph.D. Glaxo-Smith Kline
Break	
Open Public Hearing	
Committee Discussion and Questions	
Lunch	
Topic 2: ***Quantitative Clinical Pharmacology: Critical Path Opportunities***	

Leveraging Prior Knowledge to Guide Drug Development Decisions	Joga Gobburu, Ph.D. Director, Pharmacometrics OCP, CDER, FDA
An example of disease model: Non Small Cell Lung Cancer (NSCLC)	Yaning Wang, Ph.D. OCP, CDER, FDA
Application of FDA's NSCLC model	Rene Bruno, Ph.D. Pharsight, France
Committee Discussions	
Break	
FDAAA: Implications on Pediatric Studies New	Lisa Mathis, M.D. Associate Director Pediatric & Maternal Health, Office of Drugs (OND), CDER, FDA
Pediatric Studies in Cardiovascular area: Experience & Opportunities	Norman Stockbridge, M.D. Division of Cardio-Renal Products OND, CDER, FDA
Leveraging Prior Knowledge to Design a Pediatric Study	Pravin Jadhav, Ph.D. Reviewer, Pharmacometrics OCP, CDER, FDA
Committee Discussion	
Wrap for Day 1	Lawrence Lesko, Ph.D. Director, OCP, CDER, FDA
Adjourn	

Questions to the Committee:

Topic 1: Clinical Pharmacogenomics Preliminary Draft Concept Paper

1. It is proposed to collect DNA samples from all participants in clinical trials.
   - What issues or barriers should be addressed to facilitate routing collection of DNA samples?
   - When (under what circumstances, to what degree) should DNA be collected during drug development for use in exploratory analysis?

The committee addressed question 1a and 1b together as below:

There was a consensus from the committee that DNA samples should be collected and stored throughout the clinical (pre-marketing, phase I-III) development, and that samples should be collected for subjects/patients and controls. There should be mechanism in place to ensure the privacy (in compliance with Investigational Review Boards) and long-term storage to protect the patients/subjects and samples, respectively; if the patient decides to withdraw from the study (especially in pediatric population).
When storing the samples, there should be a well planned so that they could be traceable for post-hoc analysis.
(Please see the transcript for detailed discussion)

2. A decision tree depicting the integration of pharmacogenetic studies into the drug development process is proposed.
    - What comments and/or recommendations does the committee have on the scientific rationale and thought process embodied in the proposed decision tree?

The committee recommended the following information be included in the decision tree: 1) when to analyze DNA samples, 2) how to use the DNA information (other than labeling), 3) the tree should apply all drugs, biologics, and active metabolites, and 4) to include pharmacodynamic/biomarkers and disease markers in addition to the pharmacokinetics (ADME) markers. **(Please see the transcript for detailed discussion)**

3. Different study types for clinical pharmacogenetic studies are proposed.
    - What comments and/or recommendations does the committee have on the design of clinical pharmacogenetic studies and their proposed impact on subsequent clinical trials?

The committee recommended the Agency utilize modeling and simulations (in-silico approach), and those that are being used by the pharmaceutical companies. These simulation models should assist in designing a better study (such as how to identify a poor metabolizer or an extensive metabolizer).
(Please see the transcript for detailed discussion)

Topic 2: Quantitative Clinical Pharmacology (Critical Path Initiatives)

Disease Models

1. What comments or suggestions does the committee have for improving the mathematical, statistical or clinical concepts in the model?

The committee indicated that the NSCLC model may be useful for better planning of clinical trials, but needed refinement, particularly in the exposure-response part. The committee suggested that the pharmaceutical sponsor and NIH are in the best position to generate data to perform this task. **(Please see the transcript for detailed discussion)**

2. How does the committee envision such a model can be best utilized to improve drug development?

The committee recommended that the Agency bridge preclinical (animal) to clinical (human) data to have a more mechanistic model. **(Please see the transcript for detail discussion)**

3. Does the committee have any general recommendations for further exploratory research into drug disease models?

The committee was in favor of further exploratory research and recommended that the Agency collaborate with National Institutes of Health, academic institutions, industries to on large clinical trials to generate pertinent datasets. **(Please see the transcript for detailed discussion)**

Designing Pediatric Trials

1. Do you think that such an approach will render pediatric trials more informative with respect to better dosing and study designs given the difficulties in conducting pediatric clinical trials?

Yes: 13 ***No: 0*** ***Abstain: 0***

2. Given limited resources, please advice us on how to prioritize pediatrics programs for applying model-based trial design?

The committee recommended the Agency to prioritize in the areas where the disease characteristics in pediatrics and adults are well defined, and to collaborate with industries to perform these analyses. **(Please see the transcript for detailed discussion)**

3. Do you have any suggestions on how to improve the approach with respect to closing our knowledge gaps in pediatric pharmacotherapy?

The committee suggested that the Agency leverage adult data to help in designing pediatric studies. These studies should be drug specific focusing on the physicochemical properties, pharmacokinetic parameters and other pediatric disease markers. **(Please see the transcript for detailed discussion)**

The meeting adjourned for the day at approximately at 5 p.m.