Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
April 13, 2010

Location: Hilton Silver Spring/Washington D.C., The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland.

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

These summary minutes for April 13, 2010, Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration were approved on April 28, 2010.

I certify that I attended the April 13, 2010, meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Anuja Patel, M.P.H.
Designated Federal Official, ACPS-CP

_____/s/_____
Elizabeth M. Topp, Ph.D.
Committee Chair

The Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 13, 2010 at the Hilton Silver Spring/Washington D.C., The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA. The meeting was called to order by Elizabeth M. Topp, Ph.D. (Committee Chair); the conflict of interest statement was read into the record by Anuja Patel, M.P.H. (Designated Federal Official). There were more than 300 persons in attendance. There was one (1) speaker for the Open Public Hearing session for Topic 1 and seven (7) speakers for Topic 2.

Issue: On April 13th, the committee will receive presentations from the Office of Generic Drugs (OGD) and discuss two bioequivalence (BE) topics relevant to generic drug approval: (1) revising the BE approaches for critical dose drugs; and (2) the use of partial area under the curve (AUC) for the evaluation of abbreviated new drug applications (ANDAs) for products with complex pharmacokinetic profiles. Bioequivalence refers to the evaluation of equivalence in the rate and extent of drug absorption between two preparations of the same drug. Critical dose drugs are medicines that require a narrow (or "critical") dose range to achieve and maintain their intended effects and to reduce serious adverse drug reactions. The "area under the curve" is the area under a plot of drug concentration in the bloodstream versus time; it is a measure of the extent of exposure to a drug after a dose is administered.

Attendance:

Pharmaceutical Science and Clinical Pharmacology Drug Advisory Committee Members Present (Voting):
Jessie L-S. Au, Pharm.D., Ph.D., Jerry M. Collins, Ph.D., Merrill Goozner *(Consumer Representative),* James E. Polli, Ph.D., Anne S. Robinson, Ph.D., Elizabeth M. Topp, Ph.D. *(Chair)*

Special Government Employee Consultants (Temporary Voting Members):
Maureen Donovan, Ph.D., Meryl H. Karol. Ph.D., Arthur Kibbe, Ph.D., Melvin Koch, Ph.D., Bernd Meibohm, Ph.D., FCP, Marilyn E. Morris, Ph.D., Kenneth R. Morris, Ph.D. *(participated by telephone)*

Non-voting Participants:
Richard J. Stec, Jr., Ph.D. *(Industry Representative)*
Patricia C. Tway, Ph.D. *(Industry Representative)*
Kamal K. Midha, C.M., Ph.D., D.Sc. *(Guest Speaker)*

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Members Not Present:
Mukul A. Agrawal, Ph.D.
Jeffrey S. Barrett, Ph.D.
Michael D. Caldwell, M.D., Ph.D.
Edmund V. Capparelli, Pharm.D.
John F. Carpenter, Ph.D.
David A. Flockhart, Ph.D.
Kathleen M. Giacomini, Ph.D.
Howard L. McLeod, Pharm.D.
Fernando J. Muzzio, Ph.D.
Harriet B. Nembhard, Ph.D.
Mary V. Relling, Pharm.D
Philip R. Mayer, Ph.D.
Donald E. Mager, Pharm.D., Ph.D.
Juan J.L. Lertora, M.D., Ph.D.
Gregory L. Kearns, Pharm.D., Ph.D.
Arthur F. Harralson, Pharm.D.
Kathleen M. Giacomini, Ph.D.

FDA Participants (Non-Voting):
Helen N. Winkle
Gary J. Buehler, R.Ph.
Keith Webber, Ph.D.
Lawrence X. Yu, Ph.D.

Designated Federal Official:
Anuja Patel, M.P.H.

Open Public Hearing Speakers:
Topic 1: Russell J. Rackley, Ph.D, Generic Pharmaceutical Association (GPhA)
Topic 2: Russell J. Rackley, Ph.D, Generic Pharmaceutical Association (GPhA); Victor Bernet, MD, American Thyroid Association; Mohamed A. Iqbal, Jr.; Donald Heald, Ph.D, Johnson and Johnson; Keith Gallicano, Ph.D.; Laszlo Endrenyi, Ph.D., D.Sci.; Doug Sporin (Consultant)

The agenda was as follows:

Call to Order and Opening Remarks	**Elizabeth Topp, Ph.D.** Chair, Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP)
Conflict of Interest Statement	**Anuja Patel, M.P.H.** Designated Federal Official
Welcome and Introductory Remarks	**Helen N. Winkle** Director, Office of Pharmaceutical Science (OPS) Center for Drug Evaluation and Research (CDER), FDA

Topic 1: Open Public Hearing

Topic 1: Revising the Bioequivalence (BE) Approaches for Critical Dose Drugs
Agency Presentations:

Topic Introduction: History of BE for Critical Dose Drugs	**Gary Buehler, R.Ph.** Acting Deputy Director for Operations, OPS, CDER, FDA
Medical Perspectives of Critical Dose Drugs	**Laurie Frueh, MD** Medical Officer, OPS, CDER, FDA

BREAK

Agency Presentations continued: Approaches to Demonstrate Bioequivalence of Critical Dose Drugs	**Lawrence Yu, Ph.D.** Deputy Director for Science, OGD, OPS, CDER, FDA
Topic wrap-up - Questions to the Committee	**Lawrence Yu, Ph.D.**

Committee voting, discussion, and recommendations

LUNCH

Topic 2: Open Public Hearing

Topic 2: Use of Partial Area Under the Curve (AUC) for Products with a Complex Pharmacokinetic (PK) Profile

Topic 2: Agency Presentations- Topic Introduction	**Lawrence Yu, Ph.D.**
Early Exposure Metrics to Demonstrate Bioequivalence – A View Point	**Kamal K. Midha, Ph.D.** University of Saskatchewan, Canada

BREAK

Topic 2: Agency Presentations continued:

PK Profile Comparison for Modified Release Products	**Robert A. Lionberger, Ph.D.** Chemist, Office of Generic Drugs (OGD), OPS, CDER, FDA
Case Studies and BE Approaches	**Barbara M. Davit, Ph.D., J.D.** Acting Director, Division of Bioequivalence 2 (DBE 2), OGD, OPS, CDER, FDA
Topic wrap-up -- Questions to the Committee	**Barbara M. Davit, Ph.D.**

Committee voting, discussion, and recommendations

Questions to the Committee:

TOPIC ONE

Revising the Bioequivalence (BE) Approaches for Critical Dose (CD) Drugs

1. Are CD drugs a distinct group of products? (Yes/No/Abstain)

Yes= 12 *No= 0* *Abstain= 1*

(It was noted that the abstention was based upon lack if information on the Agency's status in developing a list with specialized criteria; if the Agency does intend to develop a list then the vote would have been "yes").

Please refer to transcript for additional details

a. What terminology should be used to delineate this group and how should it be defined?

Members of the committee, including the industry representatives, preferred to call this group of products Narrow Therapeutic Index (NTI) Drugs as opposed to Critical Dose Drugs. The Committees advised the Agency on defining NTI drugs by considering therapeutic drug monitoring and true clinical need for therapy.

Please refer to transcript for additional details

b. Should the FDA develop a list of CD drugs? (Yes/No/Abstain)

Yes= 13 *No= 0* *Abstain= 0*

The committee further recommended that the Agency develop a list of NTI drugs with clear, specialized criteria for including drugs on the list. The following are recommendations from the Committee:

- *The list should be made public by the FDA and clearly define the mechanism for addition to the list.*
- *The list should be dynamic and constantly monitored.*
- *The list should focus on bioequivalence issues.*

Please refer to transcript for additional details

2. Are the current BE standards sufficient for CD drugs? (Yes/No/Abstain)

Yes= 2 *No= 11* *Abstain= 0*

After a request from the committee for clarification on the question as it was stated, the Agency explained that advice on whether or not the bioequivalence criteria of 80-125% confidence intervals is sufficient as opposed to NTI. The Committee noted that data presented on the point estimates was fine, however issue remains with confidence intervals in general. The Committee made the following suggestions:

- *The Agency has not provided sufficient information to determine whether the criterion should be debated.*
- *Additional data mining efforts should be performed by the Agency using information provided in the drug applications.*
- *The Agency should evaluate the reliability of data on the failed bioequivalence studies.*
- *Replicate studies are important.*
- *The Agency should look at manufacturing data on excipients from existing of formularies.*
- *The requirements for confidence intervals should perhaps be narrower (90-111%) and should include 100% (or 1.0).*
- *International Harmonization on this issue should be considered by the Agency.*
- *Members voting "yes" agreed that products currently on the market are not at issue based upon current standards, however they do not feel the Agency is ready, at this point, to change these standards.*

Please see transcript for additional details.

a. Should more rigorous BE standards be adopted? (Yes/No/Abstain)

The committee did not vote on this question but did suggest a need for more rigorous standards during the earlier discussion.

Please see transcript for additional details.

b. What should these standards be?
Please see Question 2

Please refer to transcript for additional details

3. Does the Committee have recommendations for future research?

The Committee made the following recommendations:

- *Increased pharmacodynamic (PD) modeling is needed.*
- *The agency should increase efforts to assist in both consumer and healthcare provider education on generic drug bioequivalence.*
- *The Agency should determine whether or not therapeutic failure impact is related to generic switching or other factors.*

Please refer to transcript for additional details

TOPIC TWO

Use of Partial Area Under the Curve (AUC) for Products with a Complex Pharmacokinetic (PK) Profile

DISCUSSION QUESTIONS

1. FDA is considering the use of partial AUC for these products. Please comment on our suggestion and the use of pAUC/profile comparison as a potential general tool to evaluate the significance of test to reference formulation differences.

2. Are there other profile comparison metrics that FDA should consider? We want to identify a metric that will give sponsors and reviewers clarity about when to evaluate the clinical impact of profile differences.

Questions one and two were addressed together. The Committee made the following recommendations:

- *The committee is concerned with the large number of subjects required (100 subjects) to obtain a meaningful power of differences from the partial AUC calculation.*
- *Time of onset should be evaluated through rate of release of initial onset.*
- *Comparison of the area under the difference of partial AUC to determine the difference between the curves was suggested; however, the problem was that was that it didn't help measure the time to onset.*
- *T max could be used as a starting point to measure partial AUC.*

Please refer to transcript for additional details

The meeting adjourned at 5:30 p.m.