Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
July 26, 2011

Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland

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

These summary minutes for July 26, 2011, Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration were approved on Friday August 5, 2011.

I certify that I attended the July 26, 2011, 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/_____
Yvette Waples, Pharm.D.
Designated Federal Officer, ACPS-CP

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

Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
July 26, 2011

The Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on July 26, 2011 at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA. The meeting was called to order by Elizabeth M. Topp, Ph.D. (Acting Chair). The conflict of interest statement was read into the record by Yvette Waples, Pharm.D. (Designated Federal Officer). There were approximately 120 people in attendance for Topic 1 and 60 people in attendance for Topic 2. There were four (4) Open Public Hearing speakers for Topic 1 and none for Topic 2.

Issues: The committee discussed presentations by the Office of Generic Drugs (OGD) on bioequivalence issues and quality standards relative to narrow therapeutic index (NTI) drug products as a class. In response to feedback during the April 13, 2010 Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) meeting, the committee further discussed the definition and list of NTI drugs, as well as proposed bioequivalence standards for these products. The committee also received awareness presentations relevant to OGD's ongoing focus on quality and safety of generic drug products. Presentations outlined current activities seeking to better understand the impact of formulation and quality on the performance of generic drug products and current thinking related to potential regulatory pathways for these issues.

Attendance:
ACPS-CP Members Present (Voting): Merrill Goozner (Consumer Representative); Fernando J. Muzzio, Ph.D.; Harriet B. Nembhard, Ph.D.; James E. Polli, Ph.D.; Fadia T. Shaya, Ph.D., M.P.H.

ACPS-CP Members Not Present: Mukul A. Agrawal, Ph.D. (Industry Representative); Jeffrey S. Barrett, Ph.D.; Prabir K. Basu, Ph.D, M.B.A; Edmund V. Capparelli, Pharm.D.; Jerry M. Collins, Ph.D.; David A. Flockhart, Ph.D. Kathleen M. Giacomini, Ph.D. Arthur F. Harralson, Pharm.D.; Gregory L. Kearns, Pharm.D., Ph.D.; Juan J.L. Lertora, M.D., Ph.D.; Donald E. Mager, Pharm.D., Ph.D.; Philip R. Mayer, Ph.D. (Industry Representative); Howard L. McLeod, Pharm.D.; Mary V. Relling, Pharm.D; Richard J. Stec, Jr., Ph.D. (Industry Representative); Jurgen Venitz, M.D., Ph.D.

ACPS-CP Members Present (Non-Voting): Patricia C. Tway, Ph.D. (Industry Representative)

Temporary Members (Voting): Arthur Kibbe, Ph.D.; Melvin Koch, Ph.D.; Joseph S. Kosler, Ph.D.; Kenneth R. Morris, Ph.D. (participated by telephone); Marilyn E. Morris, Ph.D.; Gokaraju K. Raju, Ph.D.; Anne S. Robinson, Ph.D.; Elizabeth M. Topp, Ph.D. (Acting Chair)

Guest Speakers (Non-Voting): Kamal K. Midha, C.M., Ph.D., D.Sc. (Topic 1); Gordon Johnston, R.Ph., M.S. (Topic 2)

FDA Participants (Non-Voting): Helen N. Winkle; Keith Webber, Ph.D.; Lawrence X. Yu, Ph.D. (Topic 1 only); Laurie Muldowney, M.D. (Topic 2 only)

Designated Federal Officer: Yvette Waples, Pharm.D.

Open Public Hearing Speakers: James V. Hennessey M.D. (American Thyroid Association, American Association Clinical Endocrinology, and The Endocrine Society); Rich Denness (Epilepsy Foundation); Göran B.G. Klintmalm M.D., Ph.D., FACS (Annette C. and Harold C. Simmons Transplant Institute Baylor University Medical Center); Rita Alloway, Pharm.D., FCCP (Transplant Clinical Research University of Cincinnati)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	***Elizabeth Topp, Ph.D.*** *Acting Chair, ACPS-CP*
Conflict of Interest Statement	***Yvette Waples, Pharm.D.*** *Designated Federal Officer, ACPS-CP*
Introduction/Background	***Helen Winkle*** *Director* *Office of Pharmaceutical Science (OPS),CDER, FDA*

Topic 1: Bioequivalence (BE) and Quality Standards for Narrow Therapeutic Index (NTI) Drug Products

Topic Introduction: Approaches to Demonstrate Bioequivalence of Narrow Therapeutic Index Drugs	***Lawrence Yu, Ph.D.*** *Deputy Director for Science and Chemistry* *Office of Generic Drugs (OGD), OPS, CDER, FDA*
Narrow Therapeutic Index Drugs: An Approach to Bioequivalence and Interchangeability	***Kamal K. Midha, Ph.D.*** *University of Saskatchewan*
Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs – OGD Simulation Efforts *Pharmaceutical Quality of NTI Drug Products*	***Donald Schuirmann*** *Mathematical Statistician, Office of Biostatistics* *Office of Translational Sciences, CDER, FDA* ***Wenlei Jiang, Ph.D.*** *Pharmacologist, OGD, OPS, CDER, FDA*

BREAK

FDA Proposal for Bioequivalence of Generic Narrow Therapeutic Index Drugs	***Barbara M. Davit, Ph.D.*** *Acting Director, Division of Bioequivalence II OGD OPS, CDER, FDA*

Open Public Hearing Session

LUNCH

Topic Wrap-up	***Lawrence Yu, Ph.D.***
Questions to the Committee/Committee Discussion	

Topic 2: Impact of Formulation and Quality on the Safety and Performance of Generic Drug Products

Topic Introduction: Quality and Safety of Generic Drug Products	***Keith Webber, Ph.D.*** *Deputy Director, OPS and* *Acting Director, OGD, OPS* *CDER, FDA*
Postmarketing Drug Safety: Considerations for Abbreviated New Drug Applications (ANDAs)	***Laurie Muldowney, M.D.*** *Medical Officer, OPS, CDER, FDA*
Equivalence by Design – Consumer Concern	***Vilayat Sayeed, Ph.D.*** *Director, Division of Chemistry III* *OGD, OPS, CDER, FDA*

BREAK

Regulatory Research to Support the Office of Generic Drugs	***Mansoor Khan, R.Ph., Ph.D.*** *Director* *Division of Product Quality Research* *Office of Testing and Research, OPS, CDER, FDA*
Impact of Formulation and Quality on Safety and Acceptance of Generic Drug Products	***Gordon Johnston, R.Ph., M.S.*** *Representing the Generic Pharmaceutical Association (GPhA)*
Open Public Hearing Session	
Topic Wrap-up and Future Directions	***Keith Webber, Ph.D.***

ADJOURNMENT

Questions to the Committee:

Topic 1: Bioequivalence (BE) and Quality Standards for Narrow Therapeutic Index (NTI) Drug Products

1) Is the draft definition for narrow therapeutic index (NTI) drugs, proposed by the FDA, reasonable and appropriate? ***[Voting Question]*** *Yes, No, or Abstain*

   a) If not, what revisions would you suggest?

YES: 11 NO: 0 ABSTAIN: 2

Committee Discussion*: The majority of the committee agreed that the draft definition for narrow therapeutic index (NTI) drugs, proposed by the FDA, is reasonable and appropriate; however the committee suggested the following revisions to the draft definition:*

- *The definition should be more quantitative*
- *The draft definition does not address sources of variability; different variables (example patient, batch, manufacturer, etc.) should be taken into account*
- *The first two sentences should be the draft definition and the rest of the wording should be a subsequent paragraph to expand on the definition for clarification*
- *Examples should be included*

Please see the transcript for details of the Committee discussion.

2) Should the following be used for bioequivalence studies of NTI drugs:

a) The two-treatment, four-period, fully replicated crossover design
[Voting Question] *Yes, No, or Abstain*

YES: 12 NO: 1 ABSTAIN: 0

Committee Discussion*: The majority of the committee agreed that the two-treatment, four-period, fully replicated crossover design should be used for bioequivalence studies of NTI drugs in that it will provide additional important data. A few of the members who voted "Yes" commented that this study design should be a recommendation and not a requirement. The panel member who voted "No" noted this study design was overly restrictive and that there are other types of study designs that would also provide this information. Please see the transcript for details of the Committee discussion.*

b) The reference-scaled average bioequivalence approach
[Voting Question] *Yes, No, or Abstain*

YES: 12 NO: 0 ABSTAIN: 1

Committee Discussion*: The majority of the committee agreed that the reference-scaled average bioequivalence approach should be used for bioequivalence studies of NTI drugs in that it will provide more qualitative data. The panel member who abstained was uncertain in the logic of using the scaling approach along with tightening the criteria. Please see the transcript for details of the Committee discussion.*

3) Is it appropriate to tighten the assayed potency standard for NTI drugs to 95.0 – 105.0%?
[Voting Question] *Yes, No, or Abstain*

YES: 13 NO: 0 ABSTAIN: 0

Committee Discussion*: The committee unanimously agreed that it is appropriate to tighten the assayed potency standard for NTI drugs to 95.0 – 105.0%. The committee noted that this is a step in the right direction and is favorable with having the limits consistent with the standards in the European Union (EU) and other areas. However, the committee agreed that this change is necessary but not sufficient as there are underlying issues, such as stability, content uniformity, and variability that need to be addressed. Please see the transcript for details of the Committee discussion.*

Topic 2: Impact of Formulation and Quality on the Safety and Performance of Generic Drug Products

The committee received awareness presentations relevant to OGD's ongoing focus on quality and safety of generic drug products. There were no voting questions or committee discussion for Topic 2.

The meeting was adjourned at approximately 5:10 p.m.