Food and Drug Administration
Center for Drug Evaluation and Research

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

March 19, 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 19, 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 19, 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 seventy (70) persons in attendance. There was no speaker for the Open Public Hearing session.

Issue: The committee discussed and provided comments on the Renal Impairment Concept Paper. Key issues discussed were the effects of renal impairment on CYP/transporter, methods of evaluation of renal function and the effects of hemodialysis on drug clearance.

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; Bruce Mueller, PharmD, FCCP; Mary V. Relling, PharmD; Domenic Sica, MD; Jürgen Venitz, MD, PhD (Acting Chair)

Industry Representative (Non-Voting):

Mukul A. Agrawal, PhD (Acting Industry Representative), Philip Mayer, PhD (Acting Industry Representative)

FDA Participants (Non-Voting):
Shiew-Mei Huang, PhD; Lawrence Lesko, PhD; John Strong, PhD; Shen Xiao, MD; Derek Zhang, PhD

Guest Speakers (Non-Voting)
Vincent Pichette, MD, PhD; William E. Smoyer, MD; John A. Wagner, MD; 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. Designated Federal Official, ACPS-CP

Topic 3: Renal Impairment Concept Paper

When to conduct a study in renal impairment?	Shiew-Mei Huang, Ph.D. Deputy Director, Office of Clinical Pharmacology (OCP), CDER, FDA
Effect of Renal Impairment on CYP/transporter	Vincent Pichette, M.D., Ph.D. University of Montreal, Québec, Canada
Methods of Evaluation of Renal Function Products,	Shen Xiao, M.D. Division of Cardio-Renal Drug Products, Office of New Drugs (OND), CDER, FDA
Effect of Hemodialysis on drug clearance	William Smoyer, M.D. The Research Institute at Nationwide Children's Hospital, Columbus, Ohio
Break	
PhRMA Perspectives	John A. Wagner, M.D., Ph.D. Merck & Co., Inc.
Open Public Hearing	
Advisory Committee Discussion & Recommendations	Jürgen Venitz, M.D., Ph.D.

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March 19, 2008

Summary of recommendations — Lawrence Lesko, Ph.D., Director, OCPB, CDER, FDA

Adjourn

Questions to the Committee:

Topic 3- Concept Paper on PK Studies in Patients with Renal Impairment

1. Does the committee agree that renal impairment can affect metabolism or transport of drugs that are substrates of metabolizing enzymes and transporters?

Yes: 14 ***No: 0*** ***Abstain: 0***

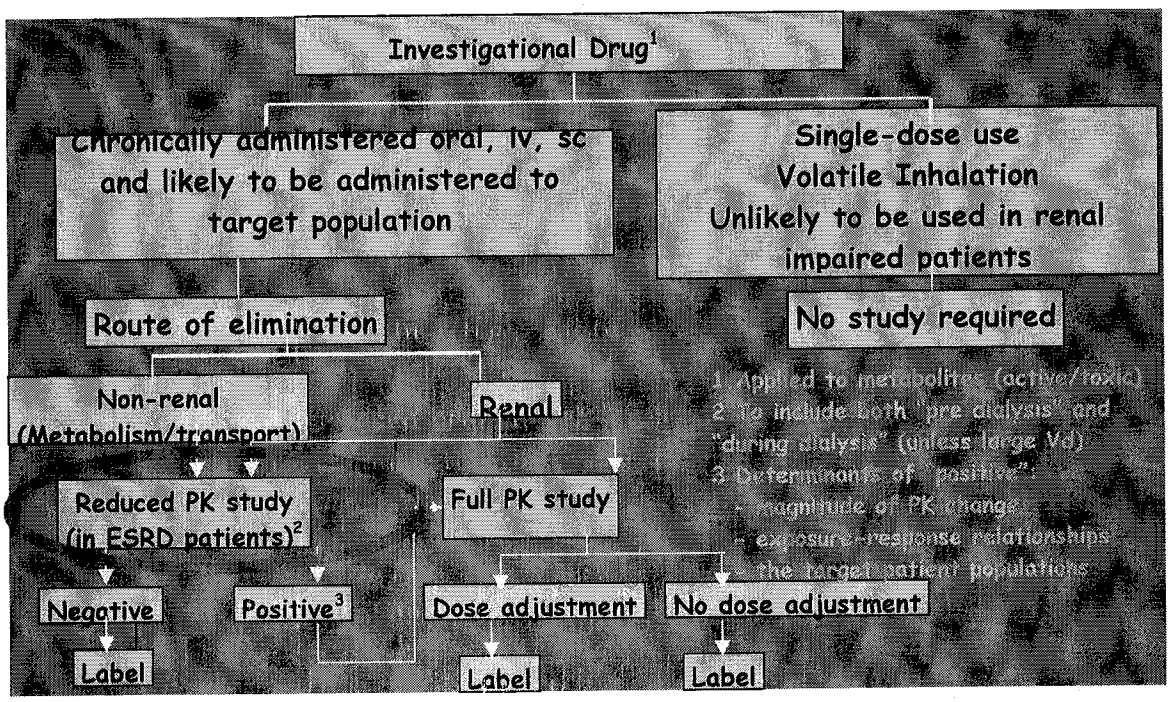
(Please see the transcript for detailed discussion)

2. Does the committee agree with the recommended methods of determining renal function and the proposed stratification of patients based on renal function?

Yes: 14 ***No: 0*** ***Abstain: 0***

(Please see the transcript for detailed discussion)

3. What comments or recommendations does the committee have on applying the following decision tree (Figure 1) to the determination of when a renal impairment study is needed for an investigational drug?



The committee recommended the following when a renal impairment study is needed:

1) ***Since renal study expectation will be extended to the vast majority of drugs, regardless of the route of elimination of these drugs, the intended use (or the likelihood use) for patients with***

chronic kidney disease should be considered in assessing the need for such a study for a given indication.

2) ***The reduced PK Study may provide false negative (i.e., reduced metabolism offset by decreased plasma protein binding, leading to apparent equivalence in systemic exposures) or false positive (e.g., non-obvious drug-drug interactions) conclusions and should not be recommended; it could be replaced by a population PK screen.***
3) ***eGFR method for pediatrics should be included***
4) ***Recommend plasma protein binding studies for highly plasma protein bound drugs with an emphasis on the measurements of active metabolites/metabolite-safety information.***

(Please see the transcript for detailed discussion)

4. What studies in hemodialysis patients does the committee recommend for drugs intended for chronic administration?

The committee recommended the following studies in hemodialysis patients: Acute dialysis study, Interval dialysis study and peritoneal dialysis study.
In addition, the committee suggested that the Agency update and standardize hemodialysis (HD) requirements and consider in vivo PK in intermittent HD population and in vitro drug removal for various devices with continuous renal replacement therapy. **(Please see the transcript for detailed discussion)**

The meeting adjourned for the day at approximately at 12:00 p.m.