Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
March 14, 2012

Location: Gaylord National Resort & Convention Center, National Harbor, Maryland

Topic: The committee discussed the clinical pharmacology aspects of pediatric clinical trial design and dosing to optimize pediatric drug development. The FDA sought input on how to strategically inform pediatric clinical trial design and dosing by utilizing existing knowledge, including available adult and nonclinical data. The discussion included the role of modeling and simulation including physiologically-based pharmacokinetic modeling in pediatric drug development. Modeling and simulation is the application of mathematical approaches to predicting what will happen in a clinical trial with pediatric patients when a particular dose of a drug is used.

These summary minutes for March 14, 2012, Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration were approved on June 5, 2012 .

I certify that I attended the March 14, 2012, 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/	/s/
Yvette Waples, Pharm.D.	Jürgen Venitz, M.D., Ph.D.
Designated Federal Officer, ACPS-CP	*Chair, ACPS-CP*

Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting
March 14, 2012

The following is the final report of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology meeting held on March 14, 2012. A verbatim transcript will be available in approximately four weeks, sent to the Office of Clinical Pharmacology and posted on the FDA website at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm286697.htm.

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

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 March 14, 2012 at the Gaylord National Resort & Convention Center, National Harbor, 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 Jürgen Venitz, M.D., Ph.D. (Chair). The conflict of interest statement was read into the record by Yvette Waples, Pharm.D. (Designated Federal Officer). There were approximately 400 people in attendance. There were two Open Public Hearing speakers.

Issue: The committee discussed the clinical pharmacology aspects of pediatric clinical trial design and dosing to optimize pediatric drug development. The FDA sought input on how to strategically inform pediatric clinical trial design and dosing by utilizing existing knowledge, including available adult and nonclinical data. The discussion included the role of modeling and simulation including physiologically-based pharmacokinetic modeling in pediatric drug development. Modeling and simulation is the application of mathematical approaches to predicting what will happen in a clinical trial with pediatric patients when a particular dose of a drug is used.

Attendance:
ACPS-CP Members Present (Voting): Jeffrey S. Barrett, Ph.D., FCP; Rose Marie Caballero, M.S.N., R.N., CCM (Consumer Representative); Arthur F. Harralson, Pharm.D., BCPS; Howard L. McLeod, Pharm.D.; Mary V. Relling, Pharm.D. (*did not participate in the Questions to the Committee/Committee Discussion session)*; Jürgen Venitz, M.D., Ph.D. (Chair)

ACPS-CP Members Not Present (Voting): Prabir K. Basu, Ph.D., M.B.A.; Jerry M. Collins, Ph.D.; David A. Flockhart, Ph.D.; Joseph S. Kosler, Ph.D.; Fernando J. Muzzio, Ph.D.; Harriet B. Nembhard, Ph.D.; James E. Polli, Ph.D.; Fadia T. Shaya, Ph.D., M.P.H.; Elizabeth M. Topp, Ph.D.

Temporary Members (Voting): Edmund V. Capparelli, Pharm.D.; Bruce Carleton, Pharm.D.; James C. Cloyd, Pharm.D.; Donald E. Mager, Pharm.D., Ph.D.; Kathleen A. Neville, M.D., M.S.; Michael D. Reed, Pharm.D. FCCP, FCP; Kenneth E. Thummel, Ph.D.; Alexander A. Vinks, Pharm.D., Ph.D., FCP

Acting Industry Representatives to the Committee (Non-Voting): Jack Cook, Ph.D. (Acting Industry Representative); Edwin Hemwall, Ph.D. (Acting Industry Representative); Peter Honig, M.D., M.P.H. (Acting Industry Representative); James Keirns, Ph.D. (Acting Industry Representative)

Guest Speakers: Andrea N. Edginton, Ph.D.; Samuel D. Maldonado, M.D., M.P.H., FAAP

FDA Participants (Non-Voting): Suzie McCune, M.D.; Shiew-Mei Huang, Ph.D.; Gilbert J. Burckart, Pharm.D.

Designated Federal Officer (Non-Voting): Yvette Waples, Pharm.D.

Open Public Hearing Speakers: John Mondick, Ph.D. (Metrum Research Group LLC); Joga Gobburu, Ph.D., FCP, M.B.A. (Professor, Executive Director, Center for Translational Medicine, University of Maryland School of Pharmacy)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Jürgen Venitz, M.D., Ph.D.** Chair, ACPS-CP
Conflict of Interest Statement	**Yvette Waples, Pharm.D.** Designated Federal Officer, ACPS-CP
Introduction and Background	**Shiew-Mei Huang, Ph.D.** Acting Director, Office of Clinical Pharmacology (OCP) Office of Translational Sciences (OTS), CDER, FDA
FDA PRESENTATIONS	
Lessons Learned from BPCA and PREA Studies Under FDAAA	**Gilbert J. Burckart, Pharm.D.** Associate Director of Regulatory Policy OCP, OTS, CDER, FDA
Adolescent PK Studies Under PREA and BPCA	**Lily Mulugeta, Pharm.D.** Clinical Pharmacology Reviewer – Pediatrics OCP, OTS, CDER, FDA

SPEAKER PRESENTATION

Role of Modeling and Simulation to Support Pediatric Drug Development: Academic Perspective	**Jeffrey S. Barrett, Ph.D., FCP** Director, Laboratory for Applied PK/PD Director, Pediatric Pharmacology Research Unit The Children's Hospital of Philadelphia Professor of Pediatrics Kinetic Modeling and Simulation (KMAS) Core Director University of Pennsylvania Medical School

FDA PRESENTATION

Regulatory Perspective of Modeling and Simulation in Pediatric Drug Development	**Kevin M. Krudys, Ph.D.** Pharmacometrics Reviewer OCP, OTS, CDER, FDA

Clarifying Questions

BREAK

GUEST SPEAKER PRESENTATION

Pediatric PBPK Models: Development and Application for Dose Guidance	**Andrea N. Edginton, Ph.D.** Assistant Professor, Pharmaceutical Science University of Waterloo School of Pharmacy

FDA PRESENTATION

Regulatory Experience in Physiologically-Based Pharmacokinetic (PBPK) Models in Pediatric Submissions	**Ping Zhao, Ph.D.** Clinical Pharmacology Reviewer – PBPK OCP, OTS, CDER, FDA

GUEST SPEAKER PRESENTATION

A Perspective From A Drug Sponsor on Pediatric Drug Development	**Samuel D. Maldonado, M.D., M.P.H., FAAP** Vice President Pediatric Drug Development, Center of Excellence Janssen Research & Development

Clarifying Questions

Open Public Hearing Session

LUNCH

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. Should modeling and simulation methods be considered in all pediatric drug development programs? (**VOTE**)

   In addressing this question, please comment on the following: **(DISCUSSION)**

   a) The gaps in knowledge that might limit the application of modeling and simulation approaches to pediatric drug development programs (e.g., neonates, critically-ill children, specific disease states, biologics/small molecules).

   b) The barriers and incentives for industry to perform modeling and simulation (M&S) for these programs.

   c) How regulatory agencies can serve as change agents to foster M&S in these programs.

   d) The scope of guidelines developed by FDA for the efficient use of modeling and simulation in these programs.

   YES: 13 NO: 0 ABSTAIN: 0

   Committee Discussion: *The committee unanimously agreed that modeling and simulation methods should be considered in all pediatric drug development programs. However, the committee acknowledged that there are knowledge gaps and limitations regarding the application of modeling and simulation approaches in pediatric drug development programs. In addition, some committee members agreed that the appropriateness of utilizing these approaches should be determined on a case-by-case basis. Committee members also urged FDA to help develop a "Best Practices in M&S" document jointly with all stakeholders. Please see the transcript for details of the Committee discussion.*

2. The FDA Office of Clinical Pharmacology has proposed a framework to derive sample size in pediatric pharmacokinetic (PK) studies to ensure the quality of pediatric PK data. Is the quality standard based on this framework reasonable? (**VOTE**)

   YES: 1 NO: 11 ABSTAIN: 1

   Committee Discussion: *The majority of the committee did not agree that the quality standard based on the FDA's Office of Clinical Pharmacology currently proposed framework is reasonable. The members who voted "No" stated that the proposed framework is not adequately constructed, thus is not suitable for all studies and should not be the gold standard. Particular concern was expressed about basing sample size calculations solely on planned inferential testing of means across pre-specified age groups; committee members*

recommended instead to use age as a continuous variable for modeling of age-dependent changes in PK endpoints. However, there was a committee consensus that quality standards to justify sample size for pediatric PK studies are needed in the full context of study objectives, existing prior PK information as well as other study design features such as dose(s) and sampling schedule. FDA was also encouraged to consider clinical covariates other than age in their future framework for sample size justification. The committee member who voted "Yes" viewed the framework as a reasonable starting point. The committee member who abstained expressed that the information was outside of her expertise to make a knowledgeable decision. Please see the transcript for details of the Committee discussion.

a) Please discuss other available methods to ensure precise estimation of important PK parameters. **(DISCUSSION)**

Committee Discussion: *Some committee members stated that other covariates would need to be taken into consideration to ensure precise estimation of important PK parameters. These include the various determinants of individual variability such as how a drug is metabolized and any genetic polymorphisms that may be relevant. Please see the transcript for details of the Committee discussion.*

3. Can dose(s) for the adolescent (>12 years) population be derived using adult data without the need for a dedicated PK study? (**VOTE**)
   In addressing this question, please comment on the following: **(DISCUSSION)**

   a) Whether sparse PK sampling from this population should be collected during safety/efficacy studies if there is no dedicated PK study.

   b) Whether the drug would then be given as the adult dose or scaled. If scaled, comment on whether allometric scaling or other approaches should be used.

YES: 12 NO: 1 ABSTAIN: 0

Committee Discussion: *The majority of the committee agreed that doses for the adolescent (>12 years) population can be derived using adult data without the need for a dedicated PK study; however, some committee members recommended that this approach should be considered on a drug specific basis; in particular CYP1A2-metabolized drugs (such as theophylline) may have higher clearance values in adolescents than adults. Some committee members were in favor of the collection of sparse PK sampling from the adolescent population during safety/efficacy studies if there is no dedicated PK study. In addition, some members opined that allometric scaling to determine doses for the adolescent population is a reasonable approach, but drug specific PK or PD properties and the therapeutic benefit versus risks would need to be taken into consideration. Please see the transcript for details of the Committee discussion.*

4. Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time? (**VOTE**)

   In addressing this question, please discuss the following: **(DISCUSSION)**

   a) If PBPK modeling can be useful in pediatric drug development for: (1) identifying the dose for first-in-pediatric studies, and (2) pediatric clinical trial design (e.g. sampling times).

   b) If the potential for a drug-drug interaction can be reasonably modeled from adult data, if available, for all pediatric age groups.

   c) If dosage adjustments for renal and hepatic impairment in pediatric patients could be modeled from adult data using PBPK.

   YES: 7 NO: 6 ABSTAIN: 0

   Committee Discussion: *A plurality of the committee (mainly committee members with PK/PD modeling background and expertise) agreed that the routine use of PBPK in pediatric drug development, when possible, should be recommended at the present time. The committee members who voted "Yes" expressed their agreement that the PBPK modeling approach would be beneficial in better anticipating and understanding the PK variability in the pediatric populations. However, limitations in PBPK modeling need to be acknowledged and addressed as part of its use in pediatric pharmacology; in particular, the need for prospective validation of PBPK models for their intended use in pediatric PK, e.g. by assessing their predictive performance after IV and PO administration in adults, prediction of the impact of drug-drug interactions, chronic renal failure, chronic hepatic failure etc. or prediction of adult/pediatric PK for a chemically/PK similar drug. There was also recognition by committee members of the limited pool of experts in PBPK modeling, the lack of formal comparisons of existing PBPK software packages, the added time and resource commitment and potentially additional regulatory burden for sponsors. The committee members who voted "No" stated that pediatric PBPK models still have significant knowledge gaps, and a great amount of work will need to be done in order for this tool to be useful for routine use, e.g., pharmacogenetic effects on drug metabolism/transport, ontogeny of transporters, etc.. There was also concern that investigator-initiated pediatric study protocols may not have access to and resources available for prospective PBPK modeling as part of protocol development. Finally, the committee strongly recommended the FDA develop a guidance or best practices approach for PBPK modeling using their in-house experience/database with pediatric PBPK. Please see the transcript for details of the Committee discussion.*

The meeting was adjourned at approximately 1:50 p.m.