

**Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
March 2, 2011**

Location: Hyatt Regency Dallas at Reunion, 300 Reunion Boulevard, Dallas Texas.

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

These summary minutes for March 2, 2011, Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration were approved on Tuesday March 15, 2011.

I certify that I attended the March 2, 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/_____
**Jürgen Venitz, M.D., Ph.D.
Acting Committee Chair**

**Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
March 2, 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 March 2, 2011 at the Hyatt Regency Dallas at Reunion, 300 Reunion Boulevard, Dallas Texas. The ACPS-CP Members and Temporary Voting Members were provided copies of the background material from the FDA ahead of the meeting. 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 Yvette Waples, Pharm.D. (Acting Designated Federal Officer). There were approximately 250 persons in attendance. There were four speakers for the Open Public Hearing session.

Issue: The committee discussed innovative approaches to the development of drugs for orphan and rare diseases to support decisions such as dose and trial design selection. FDA sought input and comment on how to optimally utilize mechanistic biomarkers and apply clinical pharmacology tools, such as pharmacogenetics and modeling and simulation, to facilitate efficient and informative drug development and regulatory review. FDA presented and sought input from the committee on how lessons learned from other applications of clinical pharmacology tools in pediatrics and oncology can be applied to orphan and rare disease drugs. The committee was asked to comment on the current status and future direction for clinical pharmacology studies (e.g., dose-response, drug-drug interactions, pharmacokinetics in patients with renal or hepatic impairment) as they pertain to drug development for orphan and rare diseases.

Attendance:

ACPS-CP Members Present (Voting)

Jeffrey S. Barrett, Ph.D., Jerry M. Collins, Ph.D., Kathleen M. Giacomini, Ph.D., Merrill Goozner (Consumer Representative), Arthur F. Harralson, Pharm.D., Juan J.L. Lertora, M.D., Ph.D., Donald E. Mager, Pharm.D., Ph.D., Howard L. McLeod, Pharm.D., Mary V. Relling, Pharm.D., Jürgen Venitz, M.D., Ph.D. (Acting Chair)

ACPS-CP Members Present (Non-voting)

Philip R. Mayer, Ph.D. (Industry Representative)

Temporary Members (Voting)

Michael D. Caldwell, M.D., Ph.D., James C. Cloyd, Pharm.D., Michael D. Reed, Pharm.D., Kenneth E. Thummel, Ph.D.,

Guest Speaker (Non-Voting)

Trevor Mundel, M.D., Ph.D.

FDA Participants (Non-Voting)

Lawrence Lesko, Ph.D., Shiew Mei Huang, Ph.D., Tim Cote, M.D., M.P.H., Dennis Bashaw, Pharm.D., Anne Pariser, M.D., Christine Garnett, Pharm.D.

Open Public Hearing Speakers:

Andrew J. Emmett, M.P.H. (Managing Director, Science and Regulatory Affairs, Biotechnology Industry Organization); Emil D. Kakkis, M.D., Ph.D. (Founder, Kakkis EveryLife Foundation); Stephen Shrewsbury, M.D. (Chief Medical Officer & SVP, AVIBioPharma); Dr. Jim Stocks (Alpha-1 Foundation)

The agenda proceeded as follows:

Call to Order

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

Conflict of Interest Statement

Yvette Waples, Pharm.D.
Designated Federal Officer

Introduction and Background

Lawrence Lesko, Ph.D.
Director, Office of Clinical Pharmacology
(OCP), Office of Translational Science (OTS),
CDER, FDA

FDA perspective on rare disease drug
development and regulation

Tim Cote, M.D., MPH
Director, Office of Orphan Products
Development, FDA

A Paradox in Orphan Drug Development

Trevor Mundel, M.D., Ph.D.(Guest Speaker)
Global Head of Development
Novartis Pharma AG

A clinical pharmacology decision tree for
orphan drugs

Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology
III, OCP, OTS, CDER, FDA

Clinical pharmacology tools for developing
drugs for rare diseases

Christine Garnett, Pharm.D.
Associate Director of Operations,
Pharmacometrics, OCP, OTS, CDER, FDA

BREAK

Future perspectives on academic-industry-government
collaboration on orphan drug development

James Cloyd, Pharm.D.
Professor, Director of Center for Orphan
Drug Development, University of Minnesota

Open Public Hearing

LUNCH

Committee Questions and Discussions

FDA next steps

Anne Pariser, M.D.
Associate Director for Rare Diseases
Office of New Drugs (OND), CDER, FDA

FDA Closing Remarks/Adjourn

Lawrence Lesko, Ph.D.

Questions to the Committee:

Topic 1: Mechanistic Understanding of Disease and Response Biomarkers

- 1-1. How can prior preclinical and early clinical information on rare disease/orphan drug biology and understanding of pharmacology, when available, be best leveraged to inform the design and analysis of clinical pharmacology studies and phase 2/3 clinical trials?

Select comments include:

- *Methods of multi-scale modeling and mechanism-based approaches for understanding drug safety would be useful in leveraging preclinical biology, pharmacology, and pathophysiology and focus on the biology of the system would allow better extrapolation and dose selection for pivotal phase II/III studies.*
- *Showing the smaller pharmaceutical and biotech companies, who may not be aware of quantitative approaches, that modeling approaches are available and could be useful to move the drug forward.*
- *It would be useful to build quantitative models upward starting from the fundamental mechanism of action of the drug and incorporate these models into disease progression models all the way up to clinically relevant endpoints.*
- *The more one understands the biology of disease and pharmacology of the drug, the better one will choose a biomarker and that biomarker will predict the disease progression; this is essential to streamlining orphan disease drug development. The potential disconnect is between the biomarker and the disease progression.*

Please see the transcript for details of the Committee discussion.

Topic 2: Clinical Pharmacology Decision Tree for Rare Diseases/Orphan Drugs

- 2-1 Are the drug development paradigms for regulatory approval of pediatric and oncologic drugs well suited as model processes for **re-purposing** of approved drugs for new rare diseases/orphan drug indications, and for providing the substantial evidence of efficacy/clinical benefit needed to meet statutory standards for orphan drugs? [**Voting Question**] *Yes, No, or Abstain*

If yes, what new types of data or modifications to the pediatric and/or oncology paradigms, if any, would strengthen these paradigms for application to rare diseases/orphan drugs?

If no, what deficiencies in the pediatric and/or oncology paradigms would need to be addressed for use with rare diseases/orphan drugs?

YES: 14 NO: 0 ABSTAIN: 0

The majority of the committee felt that there is no need to reinvent the wheel. There are enough useful paradigms and approaches that have been developed for pediatrics and oncology that could be applied to orphan drugs.

FDA should consult with the various orphan disease advocacy groups and their medical advisory boards as to what relevant clinical endpoints in phase II/III studies should be to support evidence of efficacy.

Given that for numerous orphan diseases patient registries exist, sponsors and FDA should rely on long-term post-marketing safety studies rather than requiring these studies pre-approval.

Appropriate consideration should be given to accelerate approval, i.e., relying on premarketing efficacy trials using surrogate markers, followed by post-marketing efficacy studies using long-term clinical outcomes – using patient registries.

Please see the transcript for details of the Committee discussion.

- 2-2 For **new molecular entities** intended for rare diseases/orphan drugs, does the committee have recommendations on how the FDA should exercise its flexibility and judgment to require different types and quantity of primary (required) and secondary (optional) clinical pharmacology information and data which would be needed for safe and effective use of the drugs, i.e., to meet regulatory standards?

Select comments include:

- Need to identify key information (i.e., PK/PD) that is needed preapproval in the support of efficacy and postpone other information to post-marketing requirements.*
- Disease progression needs to be highlighted. For example, organ dysfunction studies prior to approval may be key in some disease states and postapproval in others.*
- Drug-drug interaction studies need to be identified on a case-by-case basis to determine if they are needed preapproval versus postapproval.*

Please see the transcript for details of the Committee discussion.

- 2-3 Do the current drug development programs and clinical pharmacology studies for rare diseases/orphan drugs provide sufficient information on drug safety (i.e., benefit/risk ratio) given the limitations that exist to conduct relatively large pivotal efficacy trials with safety data collection? [**Voting Question**] *Yes, No, or Abstain*

If yes, what can be done to further strengthen the acquisition of safety information derived from preapproval clinical studies and postapproval clinical practice use of orphan drugs?

If no, what additional safety issues or data requirements may not have been addressed preapproval and what is the best way to address them either before or after market authorization?

YES: 10 NO: 3 ABSTAIN: 1

Those who voted “YES” feel the current drug development programs and clinical pharmacology studies for rare diseases/orphan drugs provide sufficient information on drug safety given the limitations that exist. Post-marketing surveillance programs would be beneficial to further strengthen the acquisition of safety information. In addition, active early engagement with patient advocacy groups and with clinicians would be beneficial.

Those who voted “NO” would like to see patient registries, REMS and other post-marketing surveillance plans required as part of the approval process.

Topic 3: Clinical Pharmacology Tools for Developing Drugs for Rare Diseases

- 3-1. Does the committee agree with, and endorse, a quantitative model-based (pharmacometrics) approach to drug development and regulatory decision-making (e.g., for decisions pertaining to trial design, dose selection, labeling and approvals) for new and re-purposed orphan drugs for rare diseases?
- 3-2. Are there other innovative tools and approaches that FDA should consider to enable drug development and meet regulatory challenges such as novel study designs, DNA collection and genetic analysis or new qualification of clinical efficacy and safety endpoints (biomarkers)?

NOTE: The Committee felt questions 3-1 and 3-2 were previously discussed at length. In the interest of time, the Committee moved forward to Question 4-1.

Please see the transcript for details of the Committee discussion.

Topic 4: FDA Next Steps

- 4-1. Does the committee have recommendations for the future direction that FDA should be taking to address scientific challenges in clinical pharmacology or other scientific or non-scientific areas of rare/orphan diseases drug development, including such things as collaboration with academia and other government agencies, establishment of databases, etc?

Select Comments include:

- *Emphasis should be placed on the importance of addressing exposure-response relationship of re-purposing drugs.*
- *While the items presented are reasonable, the needed specificity and details are lacking at this point.*
- *Thought need to be given to collaboration models that take into account economics.*

Please see the transcript for details of the Committee discussion.

The meeting was adjourned at approximately 2:40 p.m.