November 17-18, 2003
Clinical Pharmacology Subcommittee, ACPS
Hilda F. Scharen

**Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science**
**November 17-18, 2003**

The following is an internal report, which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov.dockets/ecomments. Slides shown at the meeting will be available at the same website.

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

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The Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science, Food and Drug Administration, Center for Drug Evaluation and Research met on November 17-18, 2003, at the Advisors and Consultants Conference Room, 5630 Fishers Lane, Rockville, Maryland. The meeting was chaired by Jürgen Venitz, M.D., Ph.D.

**Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science Members (voting):**
Jürgen Venitz, M.D., Ph.D., David D'Argenio, Ph.D., Marie Davidian, Ph.D., Hartmut Derendorf, Ph.D., David Flockhart, M.D. Ph.D., Marc Swadener, Ed.D., William J. Jusko, Ph.D., Gregory L. Kearns, Pharm.D., Ph.D., Ph.D., Howard L. McLeod, Pharm.D., Mary V. Relling, Pharm.D., Wolfgang Sadee, Dr.rer.nat., Lewis B. Sheiner, M.D.

**Advisory Committee for Pharmaceutical Consultants (voting):**

**Acting Industry Representative (non-voting):**
Efraim Shek, Ph.D.

**Guest Speakers:**
Peter Bonate, Ph.D., Richard Hockett, MD, Pertti Neuvonen M.D.

**FDA Guest Speakers**:
Hae-Young Ahn, Ph.D., Albert Chen, Ph.D., Joga Gobburu, Ph.D., Peter Hinderling, M.D., Ph.D., Shiew-Mei Huang, Ph.D., Leslie Kenna, Ph.D., Peter Lee, Ph.D., Lawrence Lesko, Ph.D., Stella Machado, Ph.D., Ameeta Parekh, Ph.D., William Rodriguez, M.D.

**FDA Participants:**
Lawrence Lesko, Ph.D., Shiew-Mei Huang, Peter Lee, Ph.D.

**Open Public Hearing Speakers:**
**November 17-18, 2003:**
No speakers were signed-up to orally present at the Open Public Hearing. Pfizer submitted a written document, for Committee members' comment, entitled: "Quantitative analysis using exposure-response for End-of-Phase 2A (EOP2A) meeting and use of clinical trial simulation for PK-QT study design.

These summary minutes for the November 17 and 18, 2003 of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration were approved on ___12/12/03_____.

I certify that I attended the November 17-18, 2003, meeting of the Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration meeting and that these minutes accurately reflect what transpired.

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Hilda Scharen, M.S.
Executive Secretary

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Jürgen Venitz, M.D., Ph.D.
Chair

The Subcommittee discussed the following: 1) quantitative analysis using exposure-response: proposal for End-of-Phase2A (EOP2A) meeting and use of clinical trial simulation for PK-QT study design; and 2) pediatric decision tree: examples for applying the pediatric decision tree.

Jürgen Venitz, M.D., Ph.D. (Committee Chair), called the meeting to order at 8:30 a.m. on November 17, 2003. The Committee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record by Hilda Scharen, M.S. The agenda proceeded as follows:

**Day 1: Monday, November 17, 2003**

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|---|---|
| **Introduction** | **Lawrence Lesko, Ph.D., FDA** |
| ***Quantitative analysis using exposure-response*** | |
| **Proposal for End-of-Phase-2A (EOP2A) meetings** | **Lawrence Lesko, Ph.D., FDA** |
| **Issues proposed to be discussed at EOP2A and their impact** | **Peter Lee, Ph.D., FDA** |
| **Case Studies** | **Ameeta Parekh, Ph.D., FDA**<br>**Hae-Young Ahn, Ph.D., FDA**<br>**Joga Gobburu, Ph.D., FDA** |
| *Break* | |
| **Committee discussion** | |
| *Lunch* | |
| **PK-PD (QT) study design: points-to-consider** | **Peter Lee, Ph.D., FDA** |
| **Use of clinical trial simulation (CTS) for PK-PD QT studies** | **Peter Bonate, Ph.D., Ilex Oncology** |
| **Case Studies** | **Leslie Kenna, Ph.D., FDA** |
| **Committee discussion** | |
| ***Pediatric Bridging: Pediatric decision tree*** | |
| **Introduction** | **Lawrence Lesko, Ph.D., FDA** |
| **Case Studies** | **Peter Hinderling, M.D., FDA**<br>**Albert Chen, Ph.D., FDA** |
| **Methods for determining similarity of exposure-response between pediatric and adult populations** | **Stella Machado, Ph.D., FDA** |
| *Break* | |
| **Research experience in the use of pediatric decision tree** | **Gregory Kearns, Pharm D., Ph.D.**<br>**Children's Mercy Hospital** |
| **Regulatory experience in using the pediatric decision tree** | **Bill Rodriguez, M.D., FDA** |
| **Committee Discussion** | |
| **Concluding Remarks** | **Jürgen Venitz, M.D., Ph.D.** |

***Questions to the Committee**:*

**Topic #1: EOP2A Meetings**

1. **Please comment on the goals of the proposed EOP2A meeting and the impact that such meetings could have on optimizing dose selection strategies and efficiency in clinical pharmacology drug development. What major obstacles would be expected to stand in the way of achieving the goals of the EOP2A meeting and how can they be avoided?**

*The Committee agreed that an EOP2A meeting could be helpful because brings to attention to exposure-response at EOP2 (sponsor and agency) and may prevent suboptimal dose finding, which is often the reason for non-approval. The Committee acknowledged that there is a fair amount of uncertainty in the drug development process and the reasons for failure of clinical trials are also unknown. The members recognized that discussing perspectives on dose response and risk benefits earlier on in this voluntary meeting could be beneficial; however, additional "red-tape" was to be avoided.*

*It was discussed that this is a pilot program for EOP2A meetings over a period of two to three years that will allow for improvements if needed; the primary outcome of the pilot program is likely to be customer satisfaction since other development outcomes are subject to other uncontrollable factors.*

*The Committee concluded that flexible expectations have to be set and a collaborative meeting with congruence of FDA and the sponsor is crucial to a successful outcome. The Committee agreed the approach should be quantitative and mechanistic, where biomarkers and utility functions along with quantitative integration of in-vitro and preclinical PK/PD data should be discussed, while considering the end point goal of improving the approval and labeling process.*

2. **Based on the examples of quantitative analysis of exposure-response data to assess benefit/risk presented to the committee, are these the approaches that are best used to optimize dose selection strategies? What considerations should be given to the prerequisite studies and data, methods of analysis, assumptions and certainty of results at this point in time of drug development, in order to maximize the value of an EOP2A meeting?**

*The Committee proposed that the concept of a utility function may be necessary for optimal dose finding. The members defined this meeting would serve to identify the problem issues and how they could impact the development process. The Committee emphasized that retrospective data could identify issues that need to be studied prospectively.*

*The Committee agreed that pre-clinical and in vitro information need to be part of the quantitative analysis. The Committee concluded that the goal is to give guidance to Industry and define what will be at stakes for the different issues. It was also agreed upon that other items should include the potential payoff and impact on the guidance process.*

3. **What benchmark measurements and metrics for measuring the future impact of the EOP2A meeting should FDA consider?**

*The Committee suggested that customer satisfaction may be the only way to measure the outcome of a change in the development process. The Committee agreed that dose change or dose reduction in post approval may be a useful metric that can be measured over time.*

*The members felt that the benchmarks were defined in the FDA strategic planning steps as reducing the: time, cost, and uncertainty of developing new drugs. It was agreed that the goal is defined and the outcome can be measured.*

*The Committee identified specific scenarios where EOP2 meeting would be the most helpful. The members emphasized that for newer drugs, where less prior information is available, such a meeting may be less advantageous. The members concluded that such a meeting would be most beneficial for drugs where a fair amount of knowledge is available ie. preferably drugs used to treat symptomatic versus chronic conditions, as the payoff may be earlier regardless of the pharmacology of the drug. The Committee concluded that the EOP2 meeting could also be quite helpful in bringing forward necessary studies for special populations the sponsor will need to address.*

**Topic #2: PK-PD (QT) Study Design**

1. **What additional study design points would the committee recommend for consideration in the analysis of PK-QT data?**

*The Committee agreed that the use of standard "corrections" for heart rate (Bazet's or Fridericia's formula) do not remove all influence of heart rate and that bivariate analysis of QT (unoicffected) and HR (or its reciprocal RR) might better separate drug*

2. **Please comment on the case studies presented to the committee and the pros and cons of using clinical trial simulation (CTS) approaches to evaluate PK-PD (QT) study design. Are there other methods of analyzing PK-QT data that FDA should consider?**

*The Committee felt that the main challenge in this approach is determining the maximum and differentiating from random fluctuations. The Committee agreed that clinical trial simulation is very difficult and there are limitations to what the QT interval should be, as there are many variants and genes, there is a need for positive control. The members discussed that prospective genotyping and preselecting of patients at risk for TdP may be appropriate. The Committee agreed FDA is on the right track, as FDA can do these simulations based on available in-house real-life data; models for drug effects should not be limited to only concentration. The Committee recommended reviewing and modeling heart rate along with QTc and considering any drug effects on heart rate. The members agreed that a more realistic and forward thinking approach needs to used, including available in- vitro and preclinical information.*

3. **What critical design elements influence the outcome of a PK-QT study that has as its goal to identify a meaningful change in QT?**

*The Committee proposed that in drug interaction studies, it is crucial to understand the potential effect both drugs have on QT. The Committee agreed that generalizations can only be made if drugs are tested independently; as the implications of a pharmcodynamic interaction may be far greater than a pharmacokinetic interaction. The Committee discussed a meaningful change in terms of a risk benefit analysis for drugs with real benefits, in extreme situations. The Committee concluded that clinical significance varies a lot depending on the benefits of the drug and the parameters of risk versus benefit and suggested further exploration of the definition of "meaningful QTc effect".*

**Topic #3: Pediatric Bridging: Pediatric Decision Tree**

1. **Please provide feedback on the pros and cons of the current pediatric decision tree and the changes that have been proposed in light of the examples that have been presented?**

*The Committee agreed with the proposed changes to the current pediatric decision tree. The Committee proposed that an approach of exposure-response mechanism be used to guide the development of drugs, that are well understood (e.g., have a well-characterized mechanism of action and/or known concentration-effect data in adults) or that have a wide therapeutic index.*

*The Committee discussed that pharmacodynamic endpoints to be evaluated in the context of a clinical trial must be directly linked to drug effect through its mechanism of action and also, must be appropriate (i.e., technically feasible without adding more than minimal risk, scientifically valid), for assessment in infants and children. . The members felt that, in the course of pediatric drug development, testing of certain drugs is quite difficult because some methods/techniques recommended for use to assess drug effect/efficacy cannot be validated with clinical data in pediatric subjects. . In addition, the committee discussed that in the context of the trials, one is sometimes forced to examine endpoints that may be unrelated to the effect of the drug. The Committee agreed that pediatric investigation should be driven by the known clinical pharmacology of the drug (i.e., mechanism of action, concentration-effect determined in adults) using the E-R based decision tree.*

2. **Please comment on the relevant adult data and information, as well as quantitative methods of analysis that determine the similarity between E-R in adults and pediatric patients.**

*The Committee discussed that there is a tremendous amount of interpretation that needs to go on between the Office of Clinical Pharmacology and the Review divisions so there can be agreement earlier on in the process, to ensure that the studies that are truly necessary in children are completed. The Committee argued that disease presentation and progression in adults and children can be very different. They also noted that much off-label (i.e., contrary to the approved adult indication) drug use in pediatric patients is not driven by specific disease based indications but rather, by the expected pharmacologic effect (i.e., mechanism of action) for a given drug. , However, the Committee felt that if the decision tree is appropriately revised and correctly implemented, it could facilitate pediatric drug development by improving its efficiency, maximizing the amount of information produced from clinical trials while reducing the overall risk and providing valid scientific and clinical information that would support pediatric drug labeling as intended by the Best Pharmaceuticals for Children Act. Finally, the Committee suggested that in certain instances, the decision tree could be utilized to incorporate preclinical information (e.g., primate data, in vitro reaction phenotyping using pediatric livers) to facilitate use of an E-R approach.*

3. **How do we know that by adjusting dose and exposure we achieve efficacy and safety in all populations? Under what circumstances do they predict deviations will occur?**

*The Committee argued that adjusting dose and exposure does not necessarily optimize clinical outcomes. The Committee felt that extrapolation is predicated by reasonable assumptions derived from a scientific and clinical perspective and successful methods.*

*The Committee concluded that the pediatric initiative has made some great advances and is a work in progress. The Committee argued that when adjusting dose based on exposure of parent drug, one has to be careful in the case of highly metabolized drugs, as it is unknown how any active metabolite exposure may change as a result.*

The meeting was adjourned at approximately 5:00 p.m. on November 17, 2003.

On November 18, 2003 the Subcommittee discussed the following: 1) drug interactions; and 2) pharmacogenetics: integration into new drug development.

Jürgen Venitz, M.D., Ph.D. (Committee Chair), called the meeting to order at 8:30 a.m. on November 18, 2003. The Committee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record by Hilda Scharen, M.S. The agenda proceeded as follows:

**Day 2: Tuesday, November 18, 2003**

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| **Introduction** | **Lawrence Lesko, Ph.D., FDA** |
| ***Drug Interactions*** | |
| **Introduction** | **Shiew-Mei Huang, Ph.D., FDA** |
| **Evaluation of CYP2B6-based interactions** | **David Flockhart, M.D., Ph.D., FDA** |
| **Evaluation of CYP2C8-based interactions** | **Pertti Neuvonen, M.D., University of Helsinki** |
| **Committee Discussion** | |
| ***Pharmacogenetics: Integration into new drug development*** | |
| **Introduction** | **Lawrence Lesko, Ph.D., FDA** |
| **Academic perspectives** | **David Flockhart, M.D., Ph.D., FDA** |
| **Industry perspectives** | **Richard Hockett, M.D., Eli Lilly** |
| **"Practitioner perspectives"** | **Mary V. Relling, Pharm.D., St. Jude Children's Research Hospital** |
| **Committee Discussion** | |
| **Committee Discussion and Concluding Remarks** | **Lawrence Lesko, Ph.D.** |

***Questions to the Committee****:*

**Topic #3: Drug Interactions**

**Please discuss the implications of drug interactions involving CYP2B6 and CYP2C8, and what recommendations that FDA should provide to sponsors with regard to *in vitro* and *in vivo* drug-drug interaction studies?**

*The Committee recommended for CYP2B6 the following substrates in-vitro: efavirenz, bupropion, and in some cases S-mephenytoin. The Committee suggested the only selective in vitro inhibitor to be thioTEPA. However, the Committee felt that that were not any specific inducers, nor any specific in-vivo probes.*

*In addition, the Committee recommended as a CYP2C8 substrate (in-vivo and in-vitro) repaglinide, because it is the most sensitive marker. The Committee suggested that gemfibrozil be used in-vivo or in-vitro as a non-selective*

*inhibitor, because it is most potent; trimethoprime is less potent but more selective. Further studies are needed to find optimal probe substrates and inhibitors, particularly for in vivo evaluations.*

*As for other in-vitro DDIs, the in-vitro concentrations need to be considered in the determination of relative contribution of specific metabolic pathways.*

*The Committee advised to consider not only two-way but multiple drug interactions given the increasing polypharmacy in clinical practice. In addition to the mean exposure, the variability in the in-vivo DDI should be considered in evaluating the clinical significance. Assessment o population variability will depend on corresponding population-based clinical studies. Furthermore, the Committee recommended that large medication use databases be mined for drug interactions these databases are becoming more available and reliable, and can be used to assess clinical significance and estimates of prevalence for drug interactions*

**Topic #4: Pharmacogenetics**

**Are the approaches presented to study the influence of pharmacogenetics on exposure-response sufficient and appropriate? Are there other criteria or approaches that FDA should consider recommending to sponsors?**
*The Committee defined that it is necessary to find a way to formulate individualized dosages for patients, though there may be different dosage requirement for different patients. A utility function is necessary to address the issue of clinical significance (safety, efficacy) of PG information. Population-based studies may be necessary to determine the prevalence of clinical significant genetic polymorphisms in practice as part of risk assessment.*

*The Committee recognized that in order to use PG optimally, there needs to be a high level of mechanistic, quantitative understanding of the contribution of PG to PK and PD. The Committee suggested that product labels should include all information that is known with respect to the different factors, because the complexity can help clarify the information that otherwise could be misleading.*

*The Committee felt that only the known genetic polymorphisms be included in the label, and others can be added as they are better understood. Also, the Committee discussed that is difficult to distill down incomplete pieces of PG information and use it to educate practitioners how to adjust dosages. However, there was disagreement as to how detailed PG information should be provided in the drug product label in order to effectively and efficiently translate PG knowledge into clinical practice.*

*The Committee suggested that PG testing be recommended/required in areas of the most clinical relevance where the stakes are high for inadvertent over-/underdosing, and the PG mechanisms are well understood quantitatively, e.g., genotyping differences can be measured in terms of exposure response, and the clinical relevance is high.*

*Finally, there was lively discussion on how PG information may be similar to or different from other clinical covariates used in dosage adjustment. It was recognized the PG information adds to the multidimensional nature of covariate effects on drug exposure and/or response.*

The meeting was adjourned at approximately 12:00 p.m. on November 18, 2003.