Summary Minutes of the Clinical Pharmacology Subcommittee Meeting
of the Advisory Committee for Pharmaceutical Science
November 14-15, 2005
Location: Center for Drug Evaluation and Research Advisory Committee
5630 Fishers Lane, Rockville Md. Rm: 1066

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

These summary minutes for the November 14-15, 2005 Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration were approved on January 15, 2006.

I certify that I attended the November 14-15, 2005, Clinical Pharmacology Subcommittee meeting 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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Mimi T. Phan, Pharm.D.
Executive Secretary

_____//S//_____
David Flockhart, M.D., Ph.D.
Chair Topic 1A &1B

_____//S//_____
Jeffrey S. Barrett, Ph.D., FCP
Chair Topic 2

_____//S//_____
Mary V. Relling, PHarm.D.
Chair Topic 3

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

Prior to the meeting, the members and the invited consultants had been provided the background materials from the FDA and any written statements submitted by the public. The a.m. session of the meeting was called to order by David Flockhart, M.D., Ph.D. (Chair, CPSC- Topic 1). The p.m. session of the meeting was called to order by Jeffrey Barrett, Ph.D., FCP (Chair, CPSC- Topic 2). The conflict of interest statements (one statement was prepared for the general issues sessions: Topic 1A and Topic 2 and one statement was prepared for the party matter issue: Topic 1B)was read into the record by Mimi T. Phan, Pharm.D. (Executive Secretary). There were approximately 75 individuals in attendance.

Issues: On November 14, 2005, the subcommittee 1) received an update on previous Clinical Pharmacology Subcommittee meeting recommendations and an introduction to the topics of this meeting, 2) **Topic 1A:** discussed and provided comments on the evidence and process for translation of pharmacogenetic information (e.g., CYP 2C9 polymorphisms) into label updates for approved products, 3) **Topic 1B:** discussed current evidence related to the pharmacogenetics of warfarin as a potential basis for label updates, and 4) **Topic 2:** discussed and provided comments on the critical path pilot project, the End-of-Phase 2A (EOP2A) meetings which will include a case study.

Attendance:

[Question: Are all members of CPSC "ad hoc"?]
ACPS Members (voting – all topics): Carol Gloff, Ph.D., Nozer Singpurwalla, Ph.D.

Ad Hoc CPSC Members (voting – all Topics): David Flockhart, M.D., Ph.D. **(Chair Topic 1A and 1B)**, David D'Argenio, Ph.D., Edmund Capparelli, Pharm.D., Wolfgang Sadee, Ph.D., Gregory Kearns, Pharm.D., Jeffrey Barrett, Ph.D., FCP **(Chair Topic 2)**, Mary Relling, Pharm.D, Marie Davidian, Ph.D.

Ad Hoc CPSC Member (voting – Topic 1A and 2; recused – Topic 1B): William Jusko, Ph.D.

Ad Hoc CPSC Members (voting – Topic 1A and Topic 2; presentation only and no vote Topic 1B): Howard McLeod, Pharm.D., Michael Caldwell, M.D., Ph.D., Brian Gage, M.D., MSc

FDA Participants at the Table:
Lawrence Lesko, Ph.D.; Sheiw-Mei Huang, Ph.D., Robert Powell, Pharm.D., Yaning Wang, Ph.D.

Open Public Hearing Speaker (Topic 1A):
Sean X. Hu, Ph.D., M.B.A
IMS Management Consulting

Presentations:

8:45	Update on Previous Meeting Recommendations and Background to the Topics of the Meeting	Lawrence Lesko, Ph.D. Director, Office of Clinical Pharmacology and Biopharmaceutics (OCPB), CDER, FDA

Topic 1: Translation of Pharmacogenomics (PGx) Information Into Label Updates for Approved ProductsTopic

Topic 1A: Evidence and Process for Translation of Pharmacogenetic Information (e.g., CYP 2C9 polymorphisms) into Label Updates for Approved Products

9:30	How New Insights into Pharmacogenetics Lead to Revisions of Product Labels.	Shiew-Mei Huang, Ph.D. Deputy Director for Science, OCPB
9:45	FDA Pharmacogenetic Labels: A Clinical Perspective	David A. Flockhart, M.D., Ph.D.

Topic 1B: Current Evidence Related to the Pharmacogentics of Warfarin as a Potential Basis for Label Updates

10:30	Evidence Supporting Relabeling of Warfarin	Shiew-Mei Huang, Ph.D. Deputy Director for Science, OCPB
10:45	New Insights on Warfarin: How CYP 2C9 and VKORC1 Information May Improve Benefit-Risk Ratio	Brian F. Gage, M.D., M.Sc. Washington University School of Medicine
11:05	Commentary on Current Status and Next Steps with Integrating PGx Information into Safe and Effective Prescribing of Warfarin	Michael D. Caldwell, M.D.,Ph.D. Marshfield Clinic Research Foundation

Open Public Hearing

11:15	Effective Prescribing of Warfarin Commentary on Current Status and Next Steps with Integrating PGx Information into Safe and Effective Prescribing of Warfarin	Howard L. McLeod, Pharm.D. Washington University School of of Medicine

11:40 Committee Discussion of Questions (Topics 1A and !B)

Topic 2: A Critical Path Pilot Project in Pharmacometrics (Quantitative Methods)

2:05	FDA Experience with End of Phase IIa Meetings An Attempt to Improve Drug Development Decisions	Robert Powell, Pharm.D. OCPB, CDER, FDA
2:45	Case Study: A Quantitative Approach to Assess a Genomic Design and a Biomarker Titration Design for a Phase III Clinical Study	Yaning Wang, Ph.D. OCPB, CDER, FDA
3:25	Commentary on the Case Study	Jeffrey S. Barrett, Ph.D., FCP

4:05 Committee Discussion of Questions

Questions to the Subcommittee

Topic 1A- Labeling (No votes taken):

1. Does the committee agree with our labeling recommendations (as delineated in document Topic 1A), in particular, those related to metabolizing enzymes?

After undertaking extensive discussion, the subcommittee proposed the following general labeling recommendations:

a) Avoid excessive descriptive information in labeling language to avoid information overload; focus mainly on clinical information such as adverse drug reactions;
b) Incorporate language regarding the value of the included genomic data to clinical decisions;
c) Include a high-light section to provide clear guidance regarding evolving drug development information;
d) Include dosage individualization recommendations as related to renal and/or liver dysfunction in the highlight section;

e) Include dosing information specific to identified sub-populations.

While the subcommittee recognized the importance of what should be included into the label, they also acknowledged the FDA's sensitivity to information in the indication section and its role in expanding the indication in context of narrowly defining differences between effectiveness in target populations and at risk populations (e.g. pediatric) by improving in the dose prescribing method.

Some subcommittee participants cautioned that while current/updated pharmacogenomic information should be made available, care should be taken with wording not to "overload" the label so as to make it confusing to providers and to patients.

2. In the future, what is the best way to present genetic information in the labeling (section and content) for use by providers and patients?

a. Phenotyping info? (e.g., PM, EM, or IM)

The subcommittee strongly advocated for the inclusion of phenotype information in the labeling. They noted that it would be helpful to include information regarding the importance of identifying and defining the range of "metabolizer types" via genetic definitions. They also noted that both genetics and environment can impact metabolic status (i.e., activity) and that whichever is the case with a specific drug, this should be noted in the label.

b. Specific alleles? (e.g., *4, 5, etc for CYP2D6; *28 for UGT1A1)

c. Nucleotide changes? (e.g., 1846G>A; for CYP2D6*4A)

d. Ethnic/racial prevalence of the above info

In general, the subcommittee felt that while ethnic and racial information might be useful to prescribers, if objective information (e.g., scientific or clinical evidence) were available, the objective information would be more valuable to the prescriber for use in dosing.

3. How should the results of a genotype test be reported when technology allows measurement of genotypes where clinical significance is uncertain or incomplete? (e.g., 5 and 8 for UGT1A1) Do we rely solely on evidence of clinical genotype- response association data to report out certain genotypes, or would in vitro data be sufficient in certain cases where alleles are rare and clinical data are difficult to obtain?

The subcommittee suggested that reporting of specific genotypes (e.g., UGT *X) in the label might not be useful for practitioners to apply. Instead, they recommended that the label could be modified to include a table with terms (the use of "synonyms" do describe these effects, i.e., "poor metabolizers" was suggested) that describe the enzyme activity of a specific genotype make-up. Useful, practical information that translates the genotype or phenotype findings as they relate to clinical decision making should be provided to assist physician's in selecting treatment and dose.

The subcommittee also suggested that only frequent population-based polymorphisms be included in device labels. The label could reference other additional, useful materials for information on less frequent polymorphism.

Topic 1B - Warfarin:

Original Question*:*

1. Does the committee agree that sufficient mechanistic and clinical evidence exists to support the recommendation?

    a. to use lower starting doses of warfarin for patients with genetic variations in CYP2C9 that lead to reduced activities?

    b. to use lower starting doses of warfarin for patients with genetic variations in VKORC1 that lead to reduced activities?

Revised Question (as revised by the subcommittee)*:*

1. Does the committee agree that sufficient mechanistic and clinical evidence exists to support the recommendation:
    a. to use lower doses of warfarin for patients with genetic variations in CYP2C9 that lead to reduced activities?

    b. to use lower doses of warfarin for patients with genetic variations in VKORC1 that lead to reduced VKORC1 activities?

Note: The word, "starting", was deleted in subsections a. and b. to clarify that the question is related more specifically to determining warfarin maintenance doses in the early part or induction of therapy and to relate these doses to INR, rather than the first dose used to begin initial therapy. In addition, in subsection b. the abbreviation, "VKORC1" was added prior to the word, "activities".

By consensus/unanimously without a vote, the subcommittee adopted the language of the revised questions.

By consensus/unanimously without a vote, the subcommittee agreed with both subparts a. and b., as amended.

Original Question:

2. Does the committee believe that genotyping some or all patients prior to beginning warfarin therapy would reduce adverse events and improve achievement of stable INR?

a. in patients with genetic variations in CYP2C9

b. in patients with genetic variations in VKORC1

Revised Question (as revised by the subcommittee):

2. Does the committee believe that genotyping patients in the induction phase of warfarin therapy would reduce adverse events and improve achievement of stable INR?

a. in patients with genetic variations in CYP2C9

b. in patients with genetic variations in VKORC1

By consensus/unanimously without a vote, the subcommittee adopted the revised language of the introductory section of the question. The subcommittee deleted the words, "some or all" before the word "patients" and replaced the phrase, ""prior to beginning" with "in the induction phase".
By consensus/unanimously without a vote, the subcommittee agreed with both subparts a. and b. to the question.
3. Does the committee believe that existing evidence of the influence of CYP2C9 genotypes warrants relabeling of warfarin to include genomic and test information?

If yes, what information should be provided in the label?

If no, what additional information is needed to provide the necessary evidence for labeling update?

Subcommittee Vote:

Yes: 8 (D'Argenio, Capparelli, Sadee, Flockhart, Barrett, Relling, Gloff, Davidian)
No: 2 (Singpurwalla, Kearns)

See transcripts for subcommittee feedback regarding information to include in the label.

4. Does the committee believe that existing evidence of the influence of VKORC1 genotypes warrants relabeling of warfarin to include genomic and test information?

If yes, what information should be provided in the label?

If no, what additional information is needed to provide the necessary evidence for labeling update?

Subcommittee vote:
Yes: 8 (D'Argenio, Capparelli, Sadee, Flockhart, Barrett, Relling Gloff, Davidian)
No: 2 (Sinpurwalla, Kearns)

Topic 2: Case Study

1. What are the committee's comments on the quantitative approach used in this case study?

The subcommittee endorsed the modeling and simulation approach used in the case study. The members felt that the model was outstanding and a good concept. It is a logical culmination of work that has been going on for some time. It is a useful to use models/simulation as a process for assistance in informed decision making about dose and study design. The subcommittee emphasized that there is a need for further development of disease progression models that are useful for the drug development process rather than one that addresses only academic/esoteric endeavors.

2. What are the committee's recommendations on how we would incorporate & evaluate genotype clinical trial design recommendations in different scenarios?

- metabolism genotype
- pharmacodynamic genotype
- disease genotype
- narrow vs wide therapeutic index

The committee commented that they felt, in general that there has been relatively good progress made in the metabolism genotype arena. However, they felt that there was a lack of good genotype predictive markers in the pharmacodynamic and disease areas.

The subcommittee discussed pursuing targeted collaborations with academia because there may not be appropriate disease and drug datasets available to support modeling and simulation studies of the type described here which would be valuable. The subcommittee emphasized that improvements in the area of pharmacogenomics should not be isolated to new molecular entities; much benefit can still be gained from research on approved products already on the market.

The meeting adjourned for the day at approximately 4:30 p.m.

November 15, 2005

Prior to the meeting, the members and the invited consultants had been provided the background materials from the FDA and any written statements submitted by the public. The meeting was called to order by Mary Relling, Pharm.D. (Chair, CPSC- Topic 3); the conflict of interest statement was read into the record by Mimi T. Phan, Pharm.D. (Executive Secretary). There were approximately 75 individuals in attendance.

On November 15, 2005, the subcommittee discussed and provided comments on: 1)the critical path biomarker-surrogate endpoint project, 2) the use of biomarker information in labels to facilitate individualizing pharmacotherapy, and 3) the analytical and clinical validation criteria for approving a clinical assay ("diagnostic test").

Attendance:
ACPS Members (voting): Carol Gloff, Ph.D., Nozer Singpurwalla, Ph.D.

Ad Hoc CPSC Members (voting): David Flockhart, M.D., Ph.D., David D'Argenio, Ph.D., Edmund Capparelli, Pharm.D., Wolfgang Sadee, Ph.D., Gregory Kearns, Pharm.D., Jeffrey Barrett, Ph.D., FCP, Mary Relling, Pharm.D (**Chair)**, Marie Davidian, Ph.D., William Jusko, Ph.D., Howard McLeod, Pharm.D., Brian Gage, M.D., MSc

FDA Participants at the Table:
Lawrence Lesko, Ph.D., Janet Woodcock, M.D., Steven Gutman, M.D.

Guest Industry Speaker:
Douglas Mayers, M.D.
Boehringer Ingelheim Pharmaceuticals, Inc.

Presentations:

Topic 3: Biomarkers in the Critical Path and Their Use in Drug Development and Drug Product Labels

8:30 Call to Order	Mary V. Relling, Pharm.D. St. Jude Children's Research Hospital Chair: Topic 3
Conflict of Interest Statement	Mimi Phan, Pharm.D. Executive Secretary, ACPS, CPSC
8:45 Update on the Critical Path Biomarker-Surrogate Endpoint Project	Janet Woodcock, M.D. Deputy Commissioner for Operations FDA
9:30 Use of Biomarker Information in Drug Product Labels to Individualize Pharmacotherapy	Lawrence Lesko, Ph.D. Director, OCPB, CDER, FDA
10:00 Use of Biomarkers in Clinical Development and Labeling: An Industry Perspective	Douglas Mayers, M.D. Boehringer Ingelheim Pharmaceuticals,
11:00 CDRH Perspective on Analytical and Clinical Considerations that go into a FDA Approval of a (OIVD) a "diagnostic test". Presentation of Case Studies	Steven Gutman, M.D. Director, Office of In Vitro Diagnostics Center for Devices and RadiologicalHealth (CDRH)

11:20 Open Public Hearing

11:50 Committee Discussion of Questions

1:00 Summary of Recommendations Lawrence Lesko, Ph.D.

Questions to the Sub-Committee
Topic 3

Clinical biomarkers are used during drug development for identification of individuals at risk (e.g. QT interval), prediction of treatment outcomes (e.g. viral load), selection of appropriate doses for individual patients (e.g. TPMT genotype), and monitoring
therapeutic effects of treatments (e.g. plasma drug concentrations). With regard to the latter:

1. When is it desirable or necessary to include plasma drug concentration information in package inserts, and where in the label would this information be most useful to providers and patients?

The subcommittee emphasized the need and importance to including dose response, or exposure-response information in the label; particularly with certain drugs and diseases, such as drugs with a narrow therapeutic index or with drugs used to treat diseases that are life threatening. This would include drugs that are potentially life-saving, and when there are good analytical tests to measure biomarkers that predict either outcome or toxicity or both available to the health care providers. It was suggested that an appropriate place in the label for this information would be in the section where dose adjustment is discussed.

2. What evidence should be available to support the use of plasma drug concentration information in package inserts?

Please refer to the transcript for a complete discussion.

3. What is the best approach to obtaining this evidence: during the course of clinical drug development pre-approval, or as part of a recommended post-marketing study?

Please refer to the transcript for a complete discussion.

4. To what extent is it necessary to have actually studied the efficacy and safety at doses recommended in the package insert, based upon existing relationships between plasma drug concentrations and clinical outcome?

The subcommittee noted that clinicians would need the results of the actual efficacy/safety studies included in the package insert to assist them with dose interpolation or extrapolation. However, in certain sub-populations when using extrapolation to select dose, there are safety concerns that the therapy should be based on the clinical sensitivity of the population, and the interindividual variability of the dose exposure relationship in that population. In addition, the subcommittee discussed that the recommended dose range could be different than that which was utilized in the pivotal clinical trials because subjects in the clinical trials are usually younger and healthier.

5. What analytical validation data are appropriate for recommending therapeutic drug monitoring information in the package insert?

The subcommittee acknowledged that much uncertainty exists in the area of assay development and assay correlation with clinical outcomes in the context of using assays for therapeutic drug monitoring (TDM). This is so because there is little standardization across labs for demonstrating the clinical utility of testing and its use in clinical practice. There is variability in TDM between practice settings

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The meeting adjourned for the day at approximately 12:30 p.m.