November 3-4, 2004
Clinical Pharmacology Subcommittee, ACPS
Hilda F. Scharen
Clinical Pharmacology Subcommittee (CPSC)
Advisory Committee for Pharmaceutical Science (ACPS)
November 3-4, 2004

This is the final report of the Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science meeting held on November 3-4, 2004. A verbatim transcript will be available in about 2 weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder04.html#PharmScience

All external requests should be submitted to the Freedom of Information office.
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The Advisory Committee for Pharmaceutical Science of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 3-4, 2004, at the Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. Jurgen Venitz, M.D., Ph.D. chaired the meeting.

Advisory Committee for Pharmaceutical Science Members (voting):
Nozer Singpurwalla, Ph.D., Jurgen Venitz, M.D., Ph.D.

Clinical Pharmacology Subcommittee, Advisory Committee for Pharmaceutical Science Consultants (voting):
Jeffrey S. Barrett, Ph.D., FCP; Terrence F. Blaschke, M.D.; Edmund V. Capparelli, Pharm.D.; David D'Argenio, Ph.D.; Marie Davidian, Ph.D.; Hartmut Derendorf, Ph.D.; Kathleen M. Giacomini, Ph.D.; Stephen D. Hall, Ph.D.; William J. Jusko, Ph.D.; Howard L. McLeod, Pharm.D.; Wolfgang Sadee, Ph.D.; Paul B. Watkins, M.D.

Industry Representative (non-voting):
Paul H. Fackler, Ph.D., Gerald Migliaccio, Ph.D.

Guest Speakers:
Keith Gottesdiener, M.D., Edward L. LeCluyse, Ph.D.; Mark J. Ratain, M.D.; John A. Wagner, Ph.D., M.D.

FDA Guest Speakers:
Shiew-Mei Huang, Ph.D.; Lawrence Lesko, Ph.D., Nam Atiqur Rahman, Ph.D.; Kellie Reynolds, PharmD; Janet Woodcock, M.D.

FDA Participants:
Peter Lee, Ph.D.; Richard Pazdur, M.D.; Donald Stanski, M.D.; John Strong, Ph.D.; Grant Williams, M.D.

Open Public Hearing Speakers:
November 3, 2004:
Mary Relling, Ph.D. (written submission)

November 4, 2004: None.

These summary minutes for the November 3 and 4, 2004 of the Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration were approved on ____11/12/04_____.

I certify that I attended the November 3 and 4, 2004, 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 F. Scharen, M.S.   Jurgen Venitz, M.D., Ph.D.
Executive Secretary   Chair

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The subcommittee received topic updates for ongoing FDA activities previously presented to the subcommittee; discussed and provided comments on the evidence for updating labels of approved drugs to include integrating pharmacogenetic, pharmacokinetic and prognostic biomarkers for the purpose of optimizing therapeutic response and reducing risks of toxicity, with Camptosar (irinotecan hydrochloride), by Pfizer Inc., as an example. The subcommittee discussed and provided comments on metabolism-and transporter-based drug-drug interactions included as recommendations in a concept paper. The subcommittee discussed and provided comments on a new critical path project related to general aspects of the transition of biomarkers to surrogate endpoints, with a focus on planning and process, rather than on specific biomarkers or surrogate endpoints.

Jurgen Venitz, M.D., Ph.D. (Committee Chair), called the meeting to order at 8:03 a.m. on November 3, 2004. 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: Wednesday, November 3, 2004

8:15   **Update on previous meeting discussions**   Lawrence Lesko, Ph.D.
        Introduction to the topics of this meeting   Director, Office of Clinical Pharmacology and Biopharmaceutics
                                                          (OCPB), CDER, FDA

Topic 1   Pharmacogenetics of Irinotecan: Scientific and Clinical Impact of UGT1A1 Polymorphism

8:45   **Introduction**   Lawrence Lesko, Ph.D.

9:10   **Scientific and Clinical Evidence**   Nam Atiqur Rahman, Ph.D.
                                                          Acting Deputy Director, Division of Pharmaceutical Evaluation I,
                                                          OCPB, CDER, FDA

9:50   **Current and future perspectives on**   Luis Parodi, Ph.D.
        Irinotecan phamacogenomics   Director & Site Head, Clinical Pharmacogenomics, Pfizer Inc.

10:10   Break

10:40   **Clinical utility of genotyping**   Mark Ratain, M.D.
                                                          Professor of Medicine
                                                          Chairman, Committee on Clinical Pharmacology and
                                                          Pharmacogenomics, University of Chicago

11:00   **Committee Discussions and Recommendations**

12:00   Lunch

1:00   **Open Public Hearing**

Topic 2   Drug-Drug Interaction Concept Paper: Issues related to CYP, Transporter-and Induction-based Interactions and multiple Inhibitor Drug Interaction Studies

1:30   **Conflict of Interest Statement**   Hilda Scharen, M.S.

        Relevant principles on drug interaction   Shiew-Mei Huang, Ph.D.
        concept paper   Deputy Director for Science, OCPB, CDER, FDA

2:15   **A scientific perspective**   Keith Gottesdiener, M.D.
                                                          Vice President, Clinical Pharmacology
                                                          Merck Research Laboratories, Merck & Co., Inc

2:45   **Induction-based interactions**   Edward LeCluyse, Ph.D.
                                                          Chief Scientific Officer, CellzDirect, Inc.

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		John Strong, Ph.D. Deputy Director, Division of Clinical Pharmacology, Office of Testing and Research, Office of Pharmaceutical Science, CDER, FDA
3:15	**Multiple inhibitor studies**	Kellie Reynolds, PharmD Team Leader, Division of Pharmaceutical Evaluation 3, OCPB, CDER, FDA
3:30	Break	
4:00	**Committee Discussions and Recommendations**	
5:30	**Wrap-up of Day 1**	Lawrence Lesko, Ph.D.

The meeting was adjourned at approximately 5:50 p.m. on November 3, 2004.

Day 2: Thursday, November 4, 2004

8:00	**Call to Order**	Jurgen Venitz, M.D., Ph.D.
	Conflict of Interest Statement	Hilda Scharen, M.S.
8:05	**Tribute to Dr. Lewis Sheiner**	Terrence Blaschke, M.D. Professor of Medicine and Molecular Pharmacology, Stanford Medical Center, Stanford University
8:20	**Framing the issues: what needs to be done and how?**	Janet Woodcock, M.D. Acting Commissioner for Operations, FDA
9:05	**Introduction to the topic, background and project plan**	Lawrence Lesko, Ph.D.
9:20	**What are Industry's expectations of the project and process?**	John Wagner, M.D., Ph.D. Senior Director, Department of Clinical Pharmacology Merck Research Laboratories, Merck & Co., Inc
9:50	**Opportunities, challenges & some ways forward How can Academia-Industry-Government collaborations facilitate the development of biomarkers and surrogates?**	Terrence Blaschke, M.D.
10:20	Break	
10:50	**Committee Discussions and Recommendations**	
12:00	**Summary of recommendations**	Lawrence Lesko, Ph.D.
12:30	**Open Public Hearing**	

The meeting was adjourned at approximately 11:43 a.m. on November 4, 2004.

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<u>*Questions to the Committee*</u>:

Topic# 1: Pharmacogenetics of Irinotecan: Scientific and Clinical Impact of UGT Polymorphism

1. Is the scientific and clinical evidence presented sufficient to demonstrate that homozygous UGT1A1*28 genotypes (7/7 genotype) are at significantly greater risk for developing:
    a) neutropenia,
    >   Yes: 12
    >   No: 0
    >   Abstain: 0
    b) acute & delayed diarrhea from irinotecan therapy?
    >   Yes: 0
    >   No: 11
    >   Abstain: 1

    Discussion: *The subcommittee added the data indicates that there may be a relationship between genotype and diarrhea, but it appears to be limited to patients who have colorectal cancer i.e. the drug induces diarrhea.*

2. Based on what is known about the relationship between various irinotecan-containing regimens and grade 3/4 toxicities, for UGT1A1*28 genotypes
    a) Do we know enough to recommend the starting dose of irinotecan in the single-agent and in the combination therapy?
    b) What would be the risks and benefits of the recommended starting dose?
    c) What is an appropriate study to evaluate dosing for UGT1A1*28 patients?

    The subcommittee underlined that the effect of UGT1A1genotype on survival is not known, because not enough studies have been done. The subcommittee suggested that UGT1A1 may have an effect on response, but it does not appear to have an impact on disease progression nor survival. The members added that any one study is not sufficient to give a complete answer on survival. The subcommittee underlined that there is not a lot of difference in the median survival rate across dose reduction groups; however the numbers are too small for a firm conclusion.

    The members agreed that although there is not a good understanding of the optimal dose and its eventual clinical outcomes, similar outcomes have been reached with a reduced dose. The subcommittee suggested that Irinotecan has some influence on disease stabilization or time to progression, which may be far more important than tumor reduction. The subcommittee discussed that there isn't a good understanding of dose response for this drug in the general population, as dose has been based only on toxicity. The members argued that although there is indication to start with a lower dosage, it is not necessarily an indication that sensitive patients will do well with this dosage. In summary, the subcommittee added that as a result of a lower dosage, efficacy may actually be improved over time by keeping the patient on the drug.

    The members discussed that control theory has been used to answer this question with limited success, as the clinical endpoints are crude. The consultants suggested that a Phase I dose escalation study could be conducted in the 7/7 patients looking at toxicity and using SN38 AUC (area under the curve), which correlates with neutropenia but is not a useful guide for efficacy. The subcommittee added the AUC would be extremely important to measure and then use as a guide with other measures to determine what the appropriate dose would be. In conclusion, the subcommittee acknowledged that several on-going studies will be looking at different dosage and genotyping and exposure PK to predict appropriate dose.

3. How can information about genotype be used in combination with bilirubin levels, prior pelvic and abdominal radiotherapy, performance status, and age in clinical decision-making?
    The subcommittee highlighted that although bilirubin is not as good a biomarker as genotyping, it is a built-in "safety valve" to supplement genotyping for very sensitive groups. The members agreed that there is missing information on the variability within genotypes. The subcommittee recognized that there is clear evidence of a correlation with neutropenia but that the second step would be to determine how often this is predicted.

4. Is the measurement of UGT1A1*28 sufficiently robust in terms of sensitivity and specificity to be used as a response predictor test for irinotecan dosing?
    >   Yes: 9

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No: 0
Abstain: 3

Discussion: The subcommittee underlined that as the toxicity data presented as function UGT1A1*28 genotype show a high negative predictive value(90-95 %), while the positive predictive value appears lower at 50%. Therefore utility functions are necessary to determine if 50% is enough to ensure starting treatment in a patient. The members added that the measurement of UGT1A1*28 is sufficiently robust a predictive test based on clinical judgment but not statistics given the clinical consequences of Grade IV neutropenia.

The subcommittee concluded this test should not be used in isolation but coupled with other information (such as: monitoring the patient, using a lower dose, pre-existing risk factors) and with the knowledge of the bilirubin for a physician to make a decision.

Topic# 2: Drug-Drug Interaction Concept Paper: Issues Related to Transporter-and- Induction-Based Interactions and Multiple Inhibitor Drug Interaction Studies

Questions associated with inhibition of CYP enzymes and transporters:

1. If a NME is NOT an inhibitor of the following 5 major CYP enzymes (CYP1A2, 2C9, 2C19, 2D6, 3A) based upon in vitro data, then there is NO need to conduct in vivo interaction studies based on these CYPs.
    Yes: 12
    No: 0
    Abstain: 1
    Discussion: The subcommittee recommended that if there is in vitro evidence there is no inhibition, there is no need to do an in vivo interaction study. However, the members added that the in the absence of inhibition the in vitro 0.02 value may be is too conservative.

2. If a NME IS an inhibitor of P-gp in vitro, then there IS a need to conduct an in vivo study using digoxin or other suitable substrates.
    Yes: 8
    No: 2
    Abstain: 3
    Discussion: The subcommittee emphasized that if a drug is a P-gp inhibitor, there may be many other clinical studies which may de done, but it is an appropriate starting point. The members suggested there is a need to further quantify the degree of inhibition and concentration level. The subcommittee agreed that although digoxin is a reasonable substrate for use in safety studies, from a scientific perspective it has some deficiencies. The members added other clinical P-gp substrates have limitations as well.

3. If a NME IS a substrate for P-gp in vitro AND a CYP3A4 substrate based on either in vitro and/or in vivo data, then a clinical study with a P-gp- and CYP3A4-inhibitor (e.g., ritonavir) should be conducted.
    Yes: 7
    No: 4
    Abstain: 2

4. If a NME IS a substrate for P-gp in vitro AND NOT a CYP3A4 substrate based on either in vitro and/or in vivo data, then a clinical study with a P-gp-inhibitor (e.g., cyclosporine, verapamil) should be conducted.
    Yes: 6
    No: 5
    Abstain: 2
    Discussion: The subcommittee suggested the wording in the guideline should be revised to indicate that if the test is conducted , no other additional tests would be required.

5. Is the current evidence and in vitro methodologies sufficiently mature to recommend that drug-drug interactions be studied clinically for CYP2B6, CYP2C8 or UGT1A1 for certain drugs?
    Yes: 11
    No: 0
    Abstain: 2

Discussion: The subcommittee suggested 2C8 be considered quite mature. The pathway in question needs to be a major pathway of metabolism.

6. Does the current evidence support recommendations that drug-drug interactions based on OATP and/or MRP be recommended for clinical study during drug development?
   Yes: 3
   No: 7
   Abstain: 3

   Discussion: The members stressed that although transporters are and will be increasingly important in the disposition of drugs; the science is so new that there are no good probes or full understanding of clinical consequences.
   The members agreed with the principle that wherever a single gene product is found to be important in drug-drug interaction, it is essential to study it further; however, some members felt clinical studies could not be prescribed at this point. In conclusion, the members felt it is important to encourage more research in the area be done and a better understanding of specific transporters and probe inhibitors.

Questions associated with induction of CYP enzymes:

7. If the in vitro induction (increase in enzyme activity) is more than 40% of the positive control (e.g., rifampin) then there IS a need to recommend an in vivo induction study.
   Yes: 3
   No: 8
   Abstain: 2

   Discussion: The subcommittee felt there was not enough evidence to support the more than 40% cut-off value of the positive control for in vitro induction.

8. If a NME's induction effect on CYP3A4 in vitro is NEGATIVE, is it acceptable to NOT recommend any in vivo studies with substrates of CYP3A, CYP2C9, CYP2C19 and CYP2B6.
   Yes: 9
   No: 1
   Abstain: 3

   Discussion: The subcommittee agreed with the statement if rephrased to not recommend both in vivo and in vitro studies with substrates of CYP2C9 and CYP2C19.

Questions associated with multiple-inhibitor studies:

9. Is it acceptable to recommend that under certain conditions (e.g., to estimate QT effects) it is important to determine the maximum exposure of a NME that a patient may experience by increasing the exposure to the NME in the presence of either a) a single inhibitor, b) multiple inhibitors (when there are more than one pathway responsible for its metabolic clearance) or c) under multiple-impaired conditions (e.g., renal impairment and co-administration of a metabolic inhibitor)?
   Yes: 0
   No: 12
   Abstain: 1

   Discussion: The subcommittee argued the maximum exposure could be predicted based on the known individual interactions and by using modeling and simulation. The subcommittee added this should be done for drugs where the stakes are high i.e. where there are concerns for toxic effects.

   In addition, the subcommittee emphasized such a study cannot be done unless the dose is reduced. In order to do this, the members indicated there needs to be an understanding of the expectations and such studies are difficult because modeling and simulation would need to be used to figure out how to adjust the dose.

10. What issues should be considered before recommending the type of clinical study be conducted on a NME that is described in (9) above?
    The subcommittee voted in majority against question 9., therefore this question was determined to be irrelevant.

Others questions:

11. Are there other areas of drug interactions that should have been addressed in the concept paper?

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The members felt stimulation should be removed from the concept paper as there are no examples of clinical interactions due to stimulation and it seems to be an unnecessary burden.
In addition, the subcommittee expressed some concern that this guidance does not end up as a check list of required studies from a response point of view, independent of whether they are really needed.

The members added that each drug is different and each interaction has a different significance, thus the subcommittee emphasized there needs to be some flexibility based on the individual drug.

In conclusion, the subcommittee felt it was important to better describe the decision making process used to make decisions in the guidance and this would be helpful to the subcommittee members to make better recommendations.