Summary Minutes of the
Advisory Committee Pharmaceutical Science
Clinical Pharmacology Subcommittee
October 18-19, 2006
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 October 18-19, 2006 of the Advisory Committee for Pharmaceutical Science, Clinical Pharmacology Subcommittee of the Food and Drug Administration were approved on 11/02/06

I certify that I attended the October 18-19, 2006, meeting of the Advisory Committee for Pharmaceutical Science, Clinical Pharmacology Subcommittee of the Food and Drug Administration meeting and that these minutes accurately reflect wha transpired.

Mimi T. Phan, Pharm.D., R.Ph.
Designated Federal Officer

Jürgen Venitz, M.D., Ph.D.
Subcommittee Chair

Meeting of the Advisory Committee for Pharmaceutical Science
Clinical Pharmacology Subcommittee
October 18, 2006

Prior to the meeting, the members and the invited consultants were provided the background materials from the FDA and any written statements submitted by the public. The meeting was called to order by Jürgen Venitz, M.D., Ph.D. (Subcommittee Acting Chair); the conflict of interest statement was read into the record by Mimi T. Phan, Pharm.D., R.Ph (Designated Federal Officer). There were approximately 100 individuals in attendance.

On October 18, 2006, the subcommittee will: (1) hear an update on previous CPSC meeting recommendations and receive an introduction to the three new topics of this meeting; (2) discuss and provide comments on the first new topic: the scope and strength of evidence to support the inclusion of pharmacogenetic information on CYP2D6 polymorphism in a revision of the label for tamoxifen to improve the benefit/risk of the drug; and (3) to discuss and provide comments on the second new topic: evaluation of transporter-based drug interactions.

Attendance:

Advisory Committee for Pharmaceutical Science Members Present (voting):
Meryl Karol, Ph.D.; Jürgen Venitz, M.D., Ph.D. (Subcommittee Acting Chair)

Advisory Committee for Pharmaceutical Science Consultants (non-voting):
Jeffrey S. Barrett, Ph.D., FCP; Edmund V. Capparelli, Pharm.D.; David D'Argenio, Ph.D.; Marie Davidian, Ph.D.; Kathleer M. Giacomini, Ph.D.; William J. Jusko, Ph.D.(recused from Tamoxifen discussion); Howard L. McLeod, Pharm.D.; Joanne E. Mortimer, M.D.; Mary V. Relling, Pharm.D.; Paul B. Watkins, M.D.

Guest Speakers (non-voting):
Matthew P. Goetz, M.D.; David J. Greenblatt, M.D.; Mitchell E. Taub, Ph.D.

FDA Participants at the Table:
Shiew-Mei Huang, Ph.D.; Lawrence Lesko, Ph.D.; Richard Pazdur, M.D.; Atiqur Rahman, Ph.D.; John Strong, Ph.D.; Sally Yasuda, M.S., Pharm.D.; Lei Zhang, Ph.D.

FDA & Guest Speakers Presentations:

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

Topic 1: Scientific and Clinical Evidence Related to CYP2D6 Polymorphism and Response to Tamoxifen Therapy

Importance of Pharmacogenetics in Oncology Products	Richard Pazdur, M.D Director, Office of Oncology Drug
Tamoxifen Pharmacogenetics: An FDA Perspective	Atiqur Rahman, Ph.D. Director, Division of Clinical Pharmacology V
Tamoxifen, Endoxifen and CYP2D6 Polymorphism	Sally Yasuda, Pharm.D. OCP, CDER, FDA
Tamoxifen Pharmacogenetics and Prediction of Breast Cancer Relapse After Administration of Tamoxifen	Matthew Goetz, M.D. Assistant Professor in Oncology College of Medicine, Mayo Clinic

Open Public Hearing Speakers (October 18, 2006)

1) Ryan Phelan (DNAdirect, San Francisco, California)
2) David A. Flockhart, M.D., Ph.D. (Indiana University, School of Medicine)

Committee Discussion and Questions

Topic 2: Evaluation of transporter-based drug interactions

Key issues in the Evaluation of Drug Interactions	Shiew-Mei Huang, Ph.D. Deputy Director for Science, OCP
Boehringer Ingelheim Experience/Opinion: Transporter-based Drug Interactions	Mitch Taub, Ph.D. Boehringer Ingelheim Pharmaceuticals
Clinical Significant Transporter-based Interactions	David Greenblatt, M.D. Turfs University
Clinical Significant Interactions of OATP1B1 and Their Transporter-base Interactions	Kathleen Giacomini, Ph.D. University of California, SF
Subcommittee Discussion and Questions	Jürgen Venitz, M.D., Ph.D. Acting Chair, CPSC of ACPS
Wrap for Day 1	Lawrence Lesko, Ph.D. Director, OCP, CDER, FDA

Questions to the Subcommittee on Topic 1: Scientific & Clinical Evidence Related to CYP2D6 Polymorphism & Response to Tamoxifen Therapy

1. The scientific evidence on the metabolism of tamoxifen demonstrates that CYP2D6 is an important pathway in the formation of endoxifen.

There was no disagreement among the Subcommittee members (Please refer to the transcript for detailed discussion)

2. The pharmacologic and clinical evidence are sufficient to demonstrate that endoxifen significantly contributes to the pharmacologic (anti-estrogenic) effect of tamoxifen.

While the Subcommittee felt that CYP2D6 contributed clinically to the level of endoxifen in vitro data, there was no direct concentration/response information to indicate that endoxifen is a major contributor to the clinical effect of Tamoxifen. In addition, some members of the Subcommittee indicated that two issues should be addressed separately. 1) CYP2D6-genotype effects (in its relationship to the outcomes of some of the studies being presented), and 2) the CYP2D6 drug interaction effect; some members proposed to consider the combined effects. (Please refer to the transcript for detailed discussion)

2. Does the clinical evidence demonstrate that postmenopausal women with ER-positive breast cancer who are CYP2D6 poor metabolizer are at increased risk for breast cancer recurrence?

The Subcommittee asked the FDA to re-phrase the question to:
Does the clinical evidence demonstrate that postmenopausal women with ER-positive breast cancer who are CYP2D6 poor metabolizer (by genotype or drug interaction) are at increased risk for breast cancer recurrence? (Please refer to the transcript for detailed discussion)

If yes, should the tamoxifen label include information about increased risk for breast cancer recurrence in CYP2D6 poor metabolizers prescribed tamoxifen?

The consensus of the Subcommittee is: the label should be updated to reflect the increased risk for breast cancer along with the mechanistic data presented. (Please refer to the transcript for detailed discussion)

If not, what additional types of clinical evidence will demonstrate that postmenopausal women with ER-positive breast cancer who are CYP2D6 poor metabolizer may be at increased risk for breast cancer recurrence?

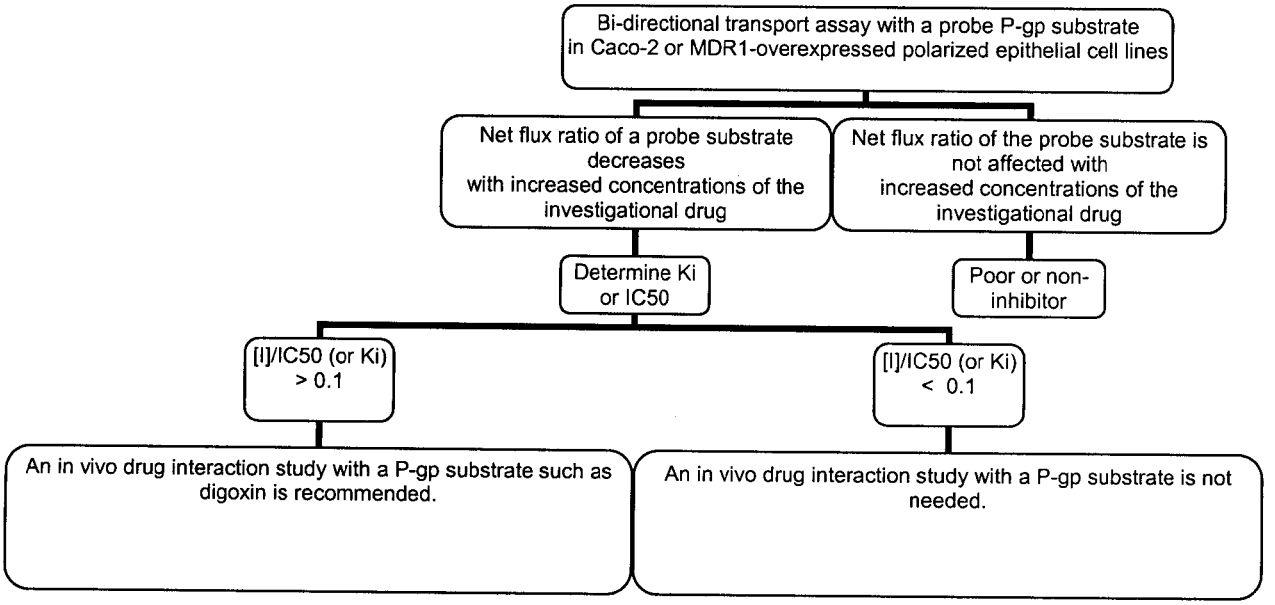
4. Is there sufficient scientific and clinical evidence to support revisions of the tamoxifen label that recommends CYP2D6 genotype testing for post-menopausal patients before they are prescribed tamoxifen for adjuvant treatment?

The Subcommittee did not reach a consensus on this question. Some members felt that the genetic test should be RECOMMENDED while others felt that it should be mentioned in the label as an OPTION for discussion between the health care provider and patient. However, the majority indicated that it should be include in an appropriate section of the package insert. (Please refer to the transcript for detailed discussion)

Questions to the Subcommittee on Topic 2: Evaluation of Transporter-based Drug Interactions

1. Are the criteria for determining whether an investigational drug is an inhibitor of P-gp and whether an in vivo drug interaction study is needed, as described in the following figure, are appropriate?

Figure 1. Decision tree to determine whether an investigational drug is an inhibitor for p-gp and whether an in vivo drug interaction study with a P-gp substrate such as digoxin is needed

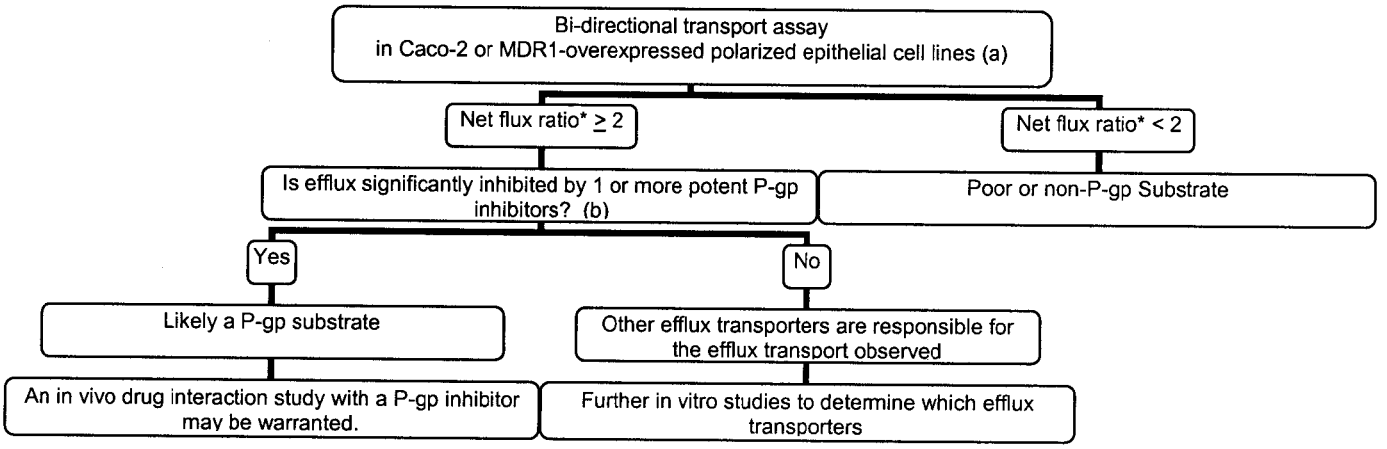


* For Caco-2 cells, net flux ratio is calculated as (Permeability $_{app, B-A}$/Permeability $_{app, A-B}$); For MDR1-overexpressed cell lines, net flux ratio is calculated as ratio of (Permeability $_{app, B-A}$/Permeability $_{app, A-B})_{MDR1}$ to (Permeability $_{app, B-A}$/Permeability $_{app, A-B})_{wild-type}$. Note that [I] represents the mean steady-state Cmax value for total drug (bound plus unbound) following administration of the highest proposed clinical dose.

While it is a good intention that the Agency tried to set a guidance that would decrease the cost of unnecessary studies, however, the Subcommittee felt the current decision tree is not ready yet. There is still lack of knowledge in the areas of the proper "I" value (GI concentration of drug, bound vs. unbound drug in plasma). The Subcommittee suggested more experience is needed to set better criteria to justify the numbers (i.e. Ki, P-gp). (Please refer to the transcript for detailed discussion)

2. Are the criteria for determining whether an investigational drug is a substrate of P-gp and whether an in vivo drug interaction study is needed, as described in the following figure, are appropriate?

Figure 2. Decision tree to determine whether an investigational drug is a substrate for P-gp and whether an in vivo drug interaction study with a P-gp inhibitor is needed



*For Caco-2 cells, net flux ratio is calculated as (Permeability $_{app, B-A}$/Permeability $_{app, A-B}$); For MDR1-overexpressed cell lines, net flux ratio is calculated as ratio of (Permeability $_{app, B-A}$/Permeability $_{app, A-B})_{MDR1}$ to (Permeability $_{app, B-A}$/Permeability $_{app, A-B,})_{wild-type}$.
(a) An acceptable system produces next flux ratios of probe substrates similar to the literature values. A net flux ratio ≥2 for the investigational drug is a positive signal for further evaluation. Note: there is a concern that this value is too liberal and will lead to too may positive results. An alternative is to use a % value (net flux of investigation drug relative to a probe substrate, such as digoxin).
(b) reduction of the flux ratio significantly (> 50%) or to unity

The Subcommittee suggested the Agency to collect further information to improve the application of the decision tree to determine its appropriateness. Furthermore, the decision tree needs to be more refining to include more specific, clinical P-gp inhibitors and consideration of other inhibitor effects, mechanistic level of interaction (GI, renal, CNS, etc). (Please refer to the transcript for detailed discussion)

3. If a NME is a P-gp substrate and an in vivo interaction study is indicated, are the inhibitors listed in page 11 (i.e., ritonavir, cyclosporine, verapamil) appropriate?

3a. Should different inhibitors be considered, if NME is also a substrate for CYP3A? For example, a strong dual inhibitor of P-gp and CYP3A (e.g., ritonavir)

There was a consensus among the Subcommittee members that NME is a substrate of CYP3A and different inhibitors should be considered. (Please refer to the transcript for detailed discussion)

4. Does the current knowledge base support the recommendation of drug interaction studies for other transporters such as OATP1B1, MRP2, BCRP, OCTs and OAT

The Subcommittee recognized that there are compelling data (with Cyclosporin, Gemfibrozil, Probenecid) to support the role of transporters such as OATP1B1, MRP2. However, current knowledge is insufficient to recommend prospective drug interaction studies for other transporters (i.e. BCRP, OCTs and OATs). (Please refer to the transcript for detailed discussion)

The Meeting adjourned for the day at approximately 1720 hours and reconvened on October 19, 2006 at 0830 hours.