U.S. Food and Drug Administration

Notice: Archived Document

The content in this document is provided on the FDA's website for reference purposes only. This content has not been altered or updated since it was archived.

Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
March 17, 2010

Location: Atlanta Marriott Marquis, Atlanta, Georgia

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

These summary minutes for March 17, 2010, Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology of the Food and Drug Administration were approved on March 30, 2010.

I certify that I attended the March 17, 2010, 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.

Yvette Waples

Yvette Waples
Designated Federal Officer, ACPS-CP

Jürgen Venitz

Jürgen Venitz, M.D., Ph.D.
Acting Committee Chair

Summary Minutes of the
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
March 17, 2010

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 17, 2010 at the Atlanta Marriott Marquis, Atlanta, Georgia. 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 Official). There were over 400 persons in attendance. There were no speakers for the Open Public Hearing session.

Issue: The Committee discussed and provided comments on the following topics: (1) General scientific issues related to the application of pharmacogenomics in the early stages of drug development. Pharmacogenomics examines the genetic differences that influence a person's responses, both beneficial and harmful, to certain drugs; (2) a new patient-centric clinical pharmacology approach to drug safety; (3) the design and analysis of clinical pharmacology studies focusing on how the renal function changes in the way the body absorbs, distributes, metabolizes and excretes a drug in patients with kidney impairment; (4) scientific considerations and recent developments in transporter-mediated drug interactions. These interactions are between two or more drugs that either inhibit or enhance the roles of specialized proteins known as "transporters" and, in turn, the interactions can affect a drug's safety and/or efficacy.

Attendance:

ACPS-CP Members Present (Voting)

Jeffrey S. Barrett, Ph.D., Michael D. Caldwell, M.D., Ph.D., Edmund V. Capparelli, Pharm.D., Jerry M. Collins, Ph.D., David A. Flockhart, Ph.D., Kathleen M. Giacomini, Ph.D., Merrill Goozner (Consumer Representative), Arthur F. Harralson, Pharm.D., Gregory L. Kearns, Pharm.D., Ph.D., Juan J.L. Lertora, M.D., Ph.D., Donald E. Mager, Pharm.D., Ph.D., Howard L. McLeod, Pharm.D.

ACPS-CP Members Present (Non-voting)

Mukul A. Agrawal, Ph.D. (Industry Representative), Philip R. Mayer, Ph.D. (Industry Representative)

Temporary Members (Voting)

Thomas C. Dowling, Pharm.D., Ph.D., Lesley A. Stevens, M.D., M.S., Kenneth E. Thummel, Ph.D., Jürgen Venitz, M.D., Ph.D. (Acting Chair)

Guest Speaker (Non-Voting)

Richard L. Lalonde, Pharm.D.
Joseph W. Polli, Ph.D.

Designated Federal Official (Acting)

Yvette Waples, Pharm.D.

FDA Participants (Non-Voting)

Lawrence Lesko, Ph.D., Shiew Mei Huang, Ph.D., Darrell Abernethy, M.D., Ph.D., Issam Zineh, Pharm.D., M.P.H., Lei Zhang, Ph.D.

Open Public Hearing Speakers:

None

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. Acting Designated Federal Official ACPS-CP
Introduction to the Topics of the Meeting	Lawrence Lesko, Ph.D. Director, Office of Clinical Pharmacology (OCP), Office of Translational Science (OTS), CDER, FDA
Mechanistic ("Systems") Approach to Drug Safety	Darrell Abernethy, M.D., Ph.D. Associate Director for Drug Safety OCP, OTS, CDER, FDA
Clinical Pharmacogenomics in Early Drug Development	Issam Zineh, Pharm.D., M.P.H. Associate Director for Genomics Group OCP, OTS, CDER, FDA
Break	
Open Public Hearing	
Committee Questions and Discussions	Jürgen Venitz, M.D., Ph.D. Acting Chair, ACPS-CP
New Study Design and Dosing Adjustment Issues in Renal Impairment	Shiew Mei Huang, Ph.D. Deputy Director, OCP, OTS, CDER FDA
Perspectives on Pharmacokinetic Studies in Patients with Renal Impairment	Richard L. Lalonde, Pharm.D. Vice President and Global Head of Clinical Pharmacology Pfizer, Inc.
Lunch	
Transporter-Mediated Drug Interactions	Lei Zhang, Ph.D. Special Assistant to Office Director OCP, OTS, CDER, FDA
Perspectives of Transporter-Mediated Transporters In Drug Development	Joseph W. Polli, Ph.D. Director Preclinical Drug Metabolism and Pharmacokinetics GlaxoSmithKline, Inc
Open Public Hearing	
Committee Questions and Discussion	Jürgen Venitz, M.D., Ph.D. Acting Chair, ACPS-CP
Closing Remarks/Adjournment	Lawrence Lesko, Ph.D. Director, OCP, OTS, CDER, FDA

Questions to the Committee:

Topic 1: Clinical Pharmacogenomics in Early Drug Development

1. In 2008, the ACPS-CP AC reached a consensus that DNA samples should be collected from all patients in all clinical trials in drug development (Phase 1-3). Since then, drug developers have stated that it is not possible to obtain this degree of sample acquisition, i.e., ascertainment rate, because of heterogeneity in how ethics committees, IRBs, and regulatory health agencies view DNA sample collection and storage processes. Some have argued that the potential usefulness of routine sample collection may be different for exploratory studies than for confirmatory studies.*

[*Note: From a drug development standpoint, exploratory studies are planned clinical trials that may or may not have a prespecified statistical hypothesis (e.g., PK, dose-ranging, special population studies, drug-drug interactions) and may not necessarily be expected to obtain statistical significance. Confirmatory studies are those with prespecified statistical hypothesis (e.g., adequate and well-controlled phase 3 efficacy/safety studies) mostly intended to confirm ($p<0.05$) efficacy of new treatments.]

Question 1: Should it be mandatory to collect DNA samples in any of the following drug development contexts:

a. Exploratory clinical studies in the pre-approval phase of drug development
b. Confirmatory clinical studies in the pre-approval phase of drug development
c. Post-approval studies required by FDA to assess a safety issue or question

How would the absence of an *a priori* genomic hypothesis influence DNA sample collection?

The majority of the Committee felt that the collection of DNA samples from patients cannot be 'mandated" in clinical trials; however the Committee agreed the collection should be "strongly encouraged". For exploratory (i.e., not hypothesis-driven) PG sampling, PG sampling should be optional, i.e., patients can participate in the trial while declining PG sampling. For hypothesis-driven PG sampling, patients should be urged to participate in PG sampling; if PG information is used for a-priori safety and/or efficacy stratification/inclusion/exclusion criteria, patients may be required to agree to participate in PG sampling in order to be enrolled in the trial.

Please see the transcript for details of the Committee discussion.

2. In pharmaceutical drug development, investigators use either candidate gene and/or target genotypes (and in some cases, phenotypes), or high-throughput approaches [e.g., chips with multiple ADME markers, genome wide association studies (GWAS)] to assess genetic associations with interindividual variability in D/R, PK, PD, and in efficacy, or safety endpoints. For example, candidate genes studies (e.g., CYP2C19) allow for focused hypothesis testing but would not necessarily identify significant, otherwise unknown, gene determinants of inter-subject variability. On the other hand, hypothesis-free, high-throughput strategies allow for greater coverage of a wide range of genetic variations to explain the basis for PK and/or PD outliers.

Question 2: Can the committee enumerate the specific advantages and disadvantages of among these different approaches and in what specific drug development context would one method be preferred over the other?

Selected statements from the Committee include:

With the candidate approach, two issues can be assessed: the magnitude of exposure variability and the potential clinical significance. In addition, with the candidate approach, you can get an understanding of the mechanism and relate it to clinical outcomes.

The Candidate approach is robust, cheap, and fast. On the other hand, the GWAS is not robust, cheap, nor fast.

Please see the transcript for details of the Committee discussion.

If time-permitting,

3. *In silico, in vitro* and *pre-clinical in vivo* drug metabolism experiments are used to determine the putative metabolic pathway for new drugs. These data could in principle inform decisions about whether to conduct pharmacogenetic *(*Pgx) studies in people and their study design, and drug-drug interaction (DDI) studies. In 2008, the ACPS-CP AC was presented with a decision tree that suggested how to perform subsequent Pgx studies in patients depending on whether or not *in vitro* experiments showed that at least 25% of the drug's metabolism is through a polymorphic gene (CYP2C19, CYP2C9, UGT1A1, etc).

Question 3: How, if at all, should the results of *in vitro* drug metabolism studies be used to decide whether an *in vivo* Pgx study should be conducted and how would be the purpose of such studies? Also, Pgx PK studies and drug-drug interaction (DDI) studies are inter-related: therefore should a known PGx association with PK variability be used to determine the need for, and the design of DDI studies? How can the results from DDI studies involving CYP enzymes with polymorphism be used to determine the need for, and design of, a PGx study?

Due to time constraints, Question 3 was not discussed.

Topic 2: Mechanistic ("Systems") Approach to Drug Safety

1. What is the best way to integrate the mechanism-based clinical pharmacology plan with what currently exists in pharmacoepidemiology and biostatistics for understanding adverse reactions?

2. How can one develop a "systems approach" to adverse reactions that combines disease pathology and drug pharmacology at the molecular level, the cellular level and the phenotype level?

Questions 1&2 were discussed together:

Selected statements from the Committee include:

Although bioinformatics and various biology tools are available, there is lack of knowledge in linking and applying these tools to clinical pharmacology.

FDA's futuristic approach of linking mechanism-based clinical pharmacology to the epidemiologic surveillance is favored.

Using the GWAS data with pathway data is excellent for integrating the mechanism based clinical pharmacology plan with post-surveillance studies.

Looking at the approach to adverse drug events (ADEs), databases can provide effective ways of being able to get ADEs data in a non-biased manner.

The FDA approach of focusing on the pathways is favored as it lays the platform that the qualitative measures can be brought in at the beginning, but it then evolves to add in the differential equations and kinetics that are learn through collaboration with scientists in academia, industry, etc.

Please see the transcript for details of the Committee discussion.

Topic 3: New Study Design and Dosing Adjustment Issues in Renal Impairment

1. For a "Reduced PK Study", we propose to conduct a PK study comparing the exposure of a drug/active metabolite (e.g., AUC, Cmax) between a "control group" (i.e., otherwise healthy subjects with normal renal function) with a "renally-compromised group" (i.e., patients with end stage renal disease (ESRD)-- not yet on dialysis) to provide the worst case estimate of the effects of severe renal disease on exposure and PK relative to a control group.

   Question 1:

   a. Is it feasible or necessary to recruit **ESRD** patients "not yet on dialysis" that may represent the worst case estimate in increase in exposure in order to conduct "reduced" PK studies? ***[VOTING]***

   Yes: 2 *No: 13* *Abstain: 1*

   The majority of the committee felt that is was not feasible and would be difficult to recruit ESRD patients not yet on dialysis. Those who voted "YES" disagreed, stating that this population does exist and collecting data would be beneficial.

   b. If it is not necessary or feasible to recruit and study ESRD patients not yet on dialysis, what other patients with compromised renal impairment should be enrolled to provide the best estimate of worst case scenario?

   The Committee felt for the hemodialysis patients, studies during off-dialysis periods would be better to provide the best estimate of worst case scenario. In addition, the committee felt the collection of data in patients with GFR<30ml/min is sufficient.

   Please see the transcript for details of the Committee discussion.

2. In 2008 ACPS-CP, the advisory committee voted Modification of Diet in Renal Disease **(MDRD)** as the preferred method for renal function classification for recommending dosing in renal impairment patients. To accommodate the fact that both methods may be used in clinical practice, we propose that the sponsor provide recommendations for dose adjustments in patient with impaired renal function, when needed, from data analysis that group patients with varying degrees of renal impairment based on both eGFR (using an MDRD equation) AND estimated creatinine clearance (using the C-G equation) as a table in the "Dosage and Administration" section of the labeling (see the table below for an example of groupings of patients based on renal function and associated dosing).

   Question 2:

   a. Do you agree that this type of table is the best way to present these data and would provide clear recommendations to prescribers? ***[VOTING]***

   Yes: 5 *No: 11* *Abstain: 0*

   Those who voted "NO" felt the proposed table is too confusing and the Agency should make amendments to the table (i.e., same units for eGFR and CLcr, provide for BSA calculation). Those who voted "YES" agreed that the table is not optimal at this point, but once the Agency takes into account the recommendations from the Committee, the table would be acceptable and beneficial.

b. Would this presentation of renal impairment groups and associated dosing be confusing in terms of dosing adjustments for older drugs for which dose adjustments are based only on patient groupings based only on estimated creatinine clearance (using the C-G equation)? Is there a better way?

The committee was in consensus that the table is not optimal at this point, but once the Agency takes into account the recommendations from the committee, the table would be acceptable and beneficial. Some of the recommendations from the committee included: using same units (mL/min) for eGFR and Clcr and ensuring the table is in agreement with the Guidance.

Please see the transcript for details of the Committee discussion.

Table 1. An Example of Hypothetical Dosing Recommendation in Various Renal Function Groups Based on Estimated GFR (eGFR) or Estimated Creatinine Clearance (CLcr).

Stage	Description[a]	eGFR[b] (mL/min/ 1.73m^2)	Dose (mg)	Frequency	CLcr[c] (mL/min)	Dose (mg)	Frequency
1	Control (normal) GFR	≥ 90	200	Every 12 hours	≥ 90	200	Every 12 hours
2	Mild decrease in GFR	60-89	200	Every 12 hours	60-89	200	Every 12 hours
3	Moderate decrease in GFR	30-59	100	Every 12 hours	30-59	100	Every 12 hours
4	Severe decrease in GFR	15-29	100	Every 24 hours	15-29	100	Every 24 hours
5	End Stage Renal Disease (ESRD)	<15 not on dialysis	50	Every 24 hours	<15 not on dialysis	50	Every 24 hours
		Requiring dialysis		Supplemental dose, if appropriate, should be given after dialysis[d]	Requiring dialysis		Supplemental dose, if appropriate, should be given after dialysis[d]

[a] Stages of renal impairment are based on *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from the National Kidney Foundation* in 2002; GFR: glomerular filtration rate;
[b] eGFR: estimate of GFR based on MDRD equation;
[c] Clcr: estimated creatinine clearance based on the C-G equation;
[d] The need for supplemental dose is dependent on the drug dialyzability.

Topic 4: Transporter-Mediated Drug Interactions

One of the goals of the drug interaction guidance is to provide recommendation to the sponsor on the data that may be collected during drug development for drug interaction evaluation for the safe and effective use of the medications concomitantly. Although the sponsor has the option to study drug interactions directly *in vivo*, appropriately designed *in vitro* studies may be used as a screening tool to help prioritize and design of *in vivo* drug interaction studies. For example, *in vitro* studies have often served as a screening tool for CYP-mediated drug interaction evaluation to rule out the importance of a metabolic pathway and the drug-drug interactions that occur through this pathway so that subsequent *in vivo* testing is unnecessary. Similarly, appropriately designed *in vitro* studies for transporters may help to determine the need to the interaction studies to be conducted *in vivo* during drug development. The *in vitro* studies include the determination of whether a drug is a substrate or an inhibitor for a transporter.

1. With regard to evaluation of a new molecular entity (NME) as a substrate for transporters, the proposal is to study all NMEs to determine NME's potential as a substrate for P-glycoprotein (P-gp, MDR1, ABCB1) or breast cancer resistance protein (BCRP, ABCG2) and, depending on the NME's clearance pathways, organic anion transporting polypeptides (OATP1B1/1B3, SLCO1B1/1B3), organic anion transporters (OAT1/3, SLC22A6/8), and organic cation transporter (OCT2, SLC22A2) may be evaluated (see the proposed flow chart, Figure 1, below).

   Question 1: For evaluation of NMEs as potential substrates of transporters:

   a. Do you agree that P-gp, BCRP, OATP1B1/1B3, OAT1/3 and OCT2 are the major transporters that should be routinely evaluated based on the proposed flow chart (Figure 1) during drug development? ***[VOTING]***

      Yes: 12 *No: 4* *Abstain: 0*

      The Committee agreed that the above transporters are great start. Those who voted "Yes" considered the International Transporter Consortium (ITC) recommended decision trees as sufficiently mature for all transporters involved and favored their implementation; they commended FDA for their efforts on this initiative. Those who voted "NO" agreed that the area of drug transporter effects is rapidly emerging and maturing, but are concerned with the lack of availability of selective substrates/inhibitors (in-vitro and in-vivo), full and open validation of the in-vitro-in-vivo extrapolation approach implied in the decision trees and the lack of specific recommendations for any required in-vivo follow-up DDI studies. They recommended to first invest the resources in improving the tools before requiring these studies.

   b. What transporter(s) should be included in the flow chart for routine study and why?

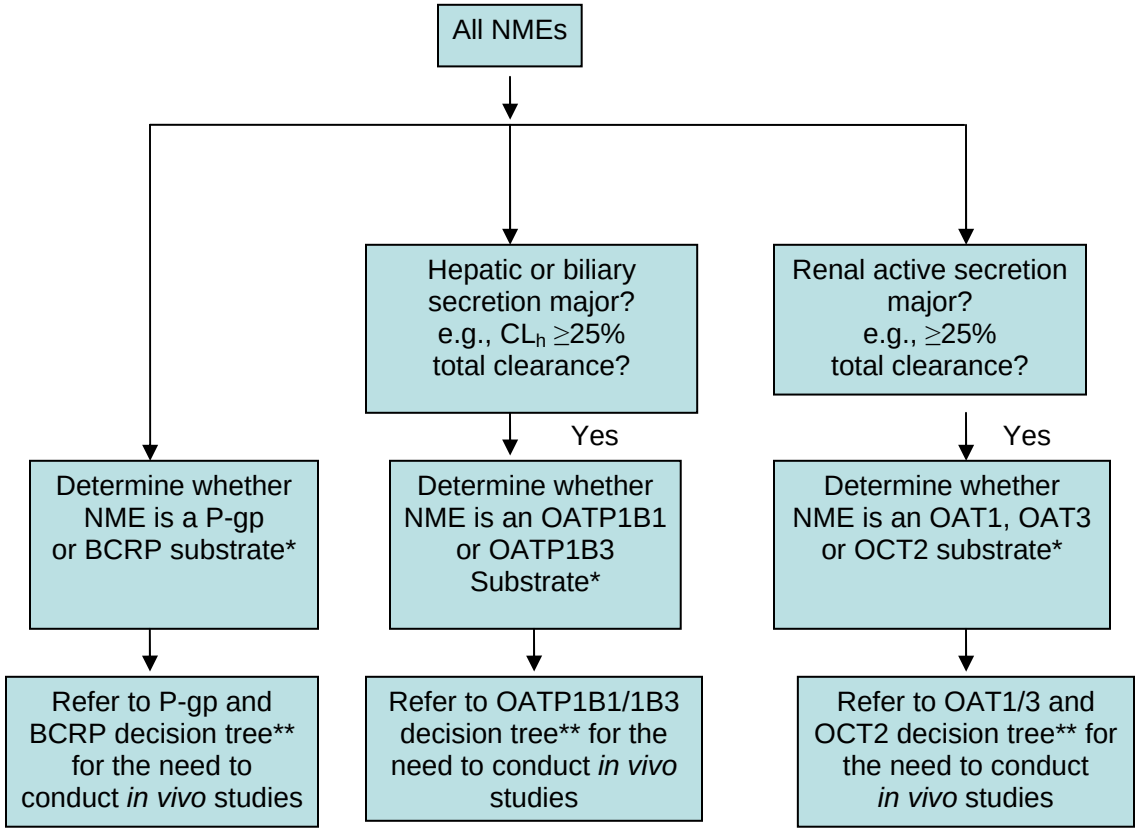
      The Committee felt the transporters listed above are sufficient and well vetted.

   c. What alternative criteria would you suggest to identify transporters that would have clinical significance and should be studied?

      Modeling and simulation were suggested as alternate criteria to extrapolate the PK effects of transporters that would have clinical significance.

      Please see the transcript for details of the Committee discussion.

Figure 1. Evaluation of NMEs as Substrates for Transporters.



* The sponsor has the option to use *in vitro* tools first for the evaluation.
** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, 2010:9:215-236) for the decision tree for each transporter.

2. With regard to evaluation of an NME <u>as an inhibitor</u> for transporters, the proposal is to study all NMEs as an inhibitor for P-gp, BCRP, or OATP1B1/1B3. Many drugs are shown to be substrates of these transporters, including statin drugs that are widely used in various patient populations. We propose that the need to determine NME's potential as an inhibitor for OAT1/3 or OCT2 will depend on the therapeutic areas and likely co-administered drugs. For example, if an NME is likely to be used with a known OAT1 or OAT3 substrate (e.g., methotrexate, tenofovir, zidovudine) or a known OCT2 substrate (e.g., metformin), an evaluation of its inhibition potential on OAT1/3 or OCT2 should be carried out (see the proposed flow chart, Figure 2, below).

Question 2: For evaluation of NMEs as potential <u>inhibitors</u> of transporters:

a. Do you agree that P-gp, BCRP, OATP1B1/1B3, OAT1/3 and OCT2 are the major transporters that should be routinely evaluated based on the proposed flow chart (Figure 2) during drug development? ***[VOTING]***
Yes: 11 *No: 5* *Abstain: 0*

As stated in 4a, the Committee agreed that the above transporters are great start. Those who voted "NO" agreed the transporters are reasonable, but are concerned with the lack of specific inhibitors. In addition, those who voted "NO" believed there is a thin line between guidance versus a requirement. Also, a comment was made that FDA and the committee keep on adding additional studies to the drug development process, but do not seem to remove anything, leading to constantly increasing costs.

b. What transporter(s) should be included in the flow chart for routine study and why?

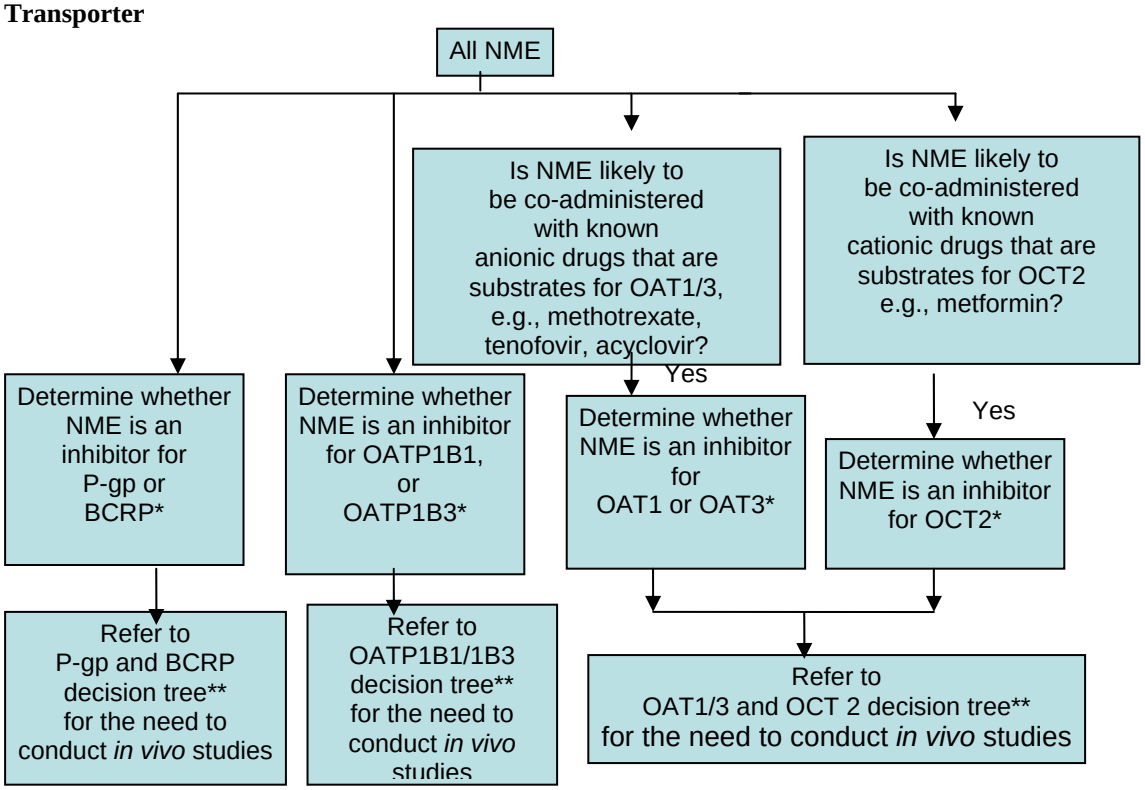
As stated in 4a, the Committee felt the transporters listed above are sufficient and well vetted.

c. What alternative criteria would you suggest to identify transporters that would have clinical significance and should be studied?

As stated in 4a, Modeling and simulation were suggested as alternate criteria to identify those transporters that would have clinical significance for a given drug.

Please see the transcript for details of the Committee discussion.

Figure 2. Evaluation of NMEs as Inhibitors for Transporter



* The sponsor has the option to use *in vitro* tools first for the evaluation.
** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, 2010; 9:215-236) for the decision tree for each transporter.