FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP)
Atlanta Marriott Marquis, Atlanta, Georgia

March 17, 2010

QUESTIONS

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?

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?

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?

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?

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:

   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, No, or Abstain*

   a. 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?

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, No, or Abstain

   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?

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).

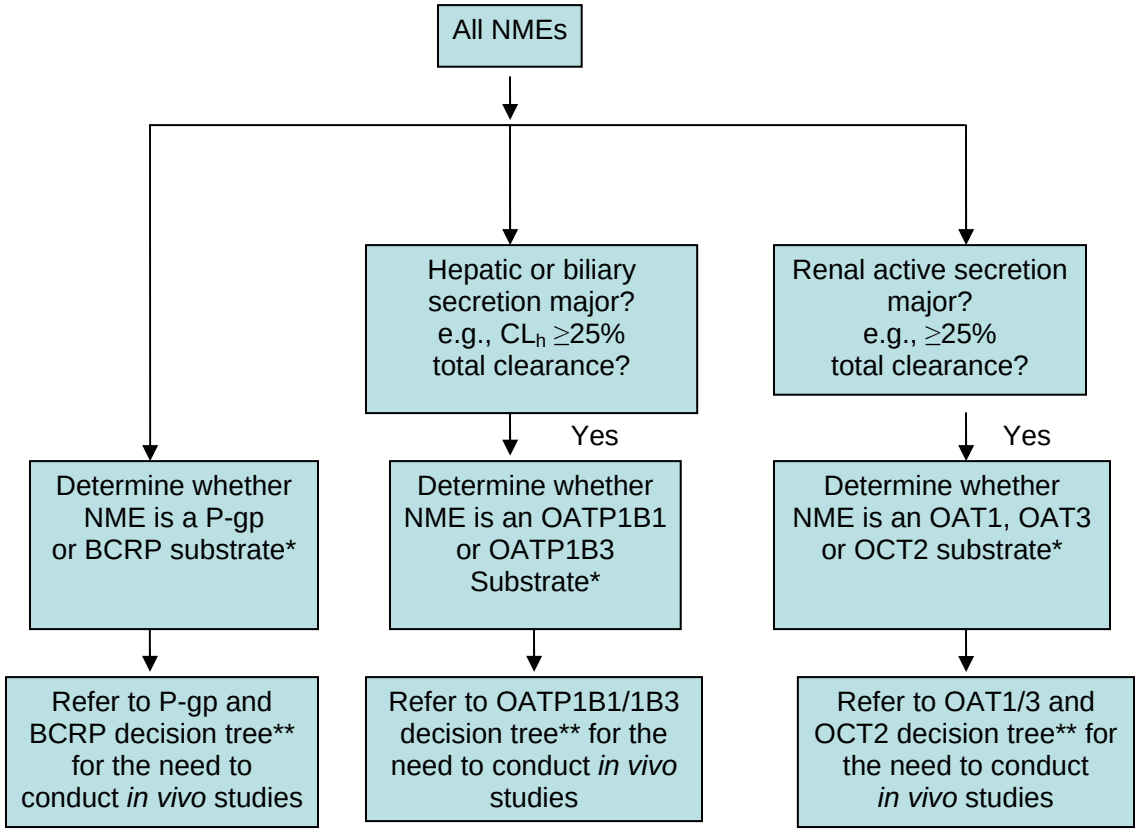
   Question 1: For evaluation of NMEs as potential substrates of transporters:

   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, No, or Abstain

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

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

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 as an inhibitor 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).

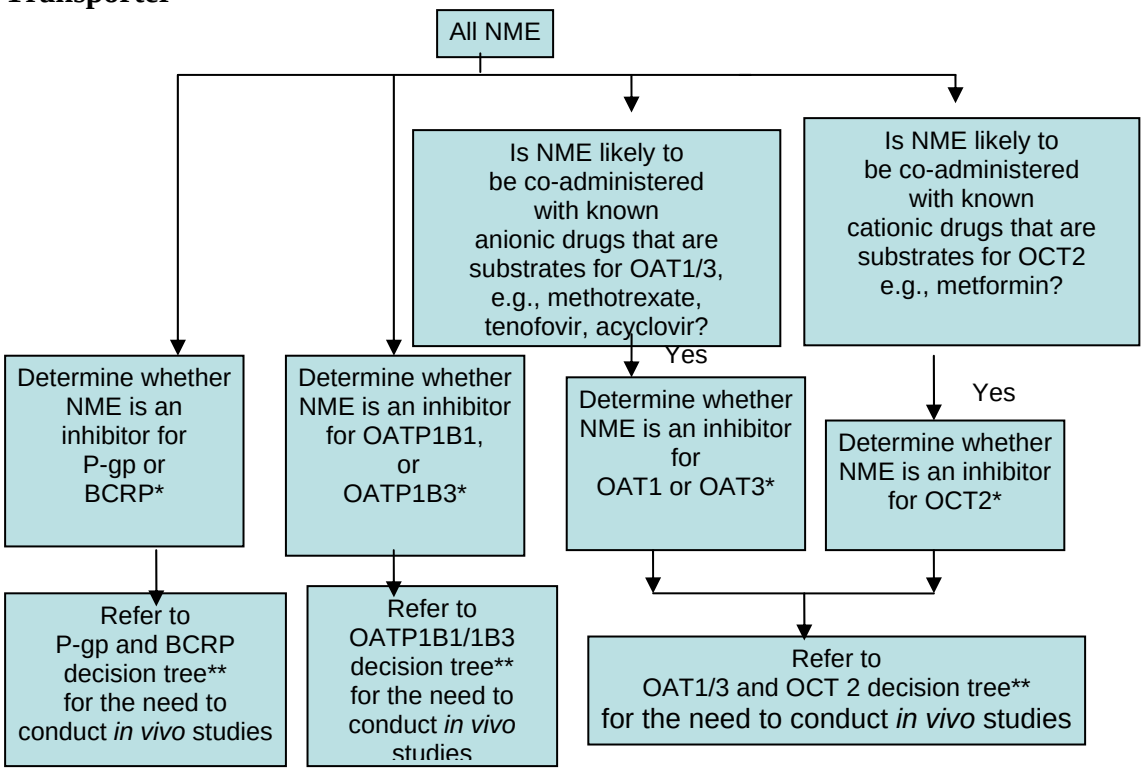
Question 2: For evaluation of NMEs as potential <u>inhibitors</u> of transporters:

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, No, or Abstain*

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

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

Figure 2. Evaluation of NMEs as Inhibitors for Transporter



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