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

1. Is the pharmacokinetic and clinical evidence presented sufficient to demonstrate that homozygous UGT1A1*28 genotypes (7/7 genotype) are at significantly greater risk for developing a) neutropenia, and b) acute and delayed diarrhea?

2. Based on available dose (300 mg/m2) – response (grade 4 neutropenia) data, what would be the benefits and risks of excluding patients with a UGT1A1*28 homozygous genotype from receiving the standard dose of irinotecan?

3. 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?

4. Would the addition of pharmacogenetic information to the label improve the treatment of patients with irinotecan?

**Topic 2: Updating In Vitro and In Vivo Drug-Drug Interaction Guidances: Issues Related to Transporter- and Induction-Based Interactions and Multiple Inhibitor Drug Interaction Studies**

<u>Questions associated with inhibition of CYP enzymes and transporters</u>

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 or No

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 or No

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 or No

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 or No

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 or No

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 or No

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) or more than 2-fold of the negative control, then there IS a need to recommend an in vivo induction study.

   Yes or No

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, CYP2B6, and CYP2C19?.

   Yes or No

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 or No

10. What issues should be considered before recommending the type of clinical study be conducted on a NME that is described in (9) above?

Others

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

**Topic 3 Transition of Biomarkers to Surrogate Endpoints: A New Critical Path Initiative**

1. In what therapeutic areas, and in what scenarios, do the benefits of using biomarkers as surrogate endpoints outweigh the risks, that is, where is both the biggest need for surrogate endpoints, and the greatest chance to succeed for identifying new surrogate endpoints?

2. What decision criteria for biomarkers as surrogate endpoints should be considered for clinical trials?

3. What are the options for validating biomarkers as surrogate endpoints, in drug development or otherwise?

4. What are the major statistical considerations for validation of biomarkers as surrogate endpoints?

5. What role does causal evidence (preclinical models, mechanistically understood pharmacology and modeling/simulation play in validating biomarkers as surrogate endpoints?

6. What strategies, and where, can be applied for using multiple biomarker sets as surrogates?

7. What needs to be done to assure the accuracy and precision, also standardization, of biomarker assays?

8. What are the theoretical and practical barriers to transitioning biomarkers to surrogate endpoints?