

Draft Questions to the Committee
(DRAFT 10/12)

Topic 1

Topic 1A- labeling

1. Does the committee agree with our labeling recommendations (as delineated in document Topic1A), in particular, those related to metabolizing enzymes?
2. In the future, what is the best way to present genetic information in the labeling (section and content) for use by providers and patients?
 - a. Phenotyping info? (e.g., PM, EM, or IM)
 - b. Specific alleles? (e.g., *4, 5, etc for CYP2D6; *28 for UGT1A1)
 - c. Nucleotide changes? (e.g., 1846G>A; for CYP2D6*4A)
 - d. Ethnic/racial prevalence of the above info
3. How should the results of a genotype test be reported when technology allows measurement of genotypes where clinical significance is uncertain or incomplete? (e.g., 5 and 8 for UGT1A1) Do we rely solely on evidence of clinical genotype- response association data to report out certain genotypes, or would in vitro data be sufficient in certain cases where alleles are rare and clinical data are difficult to obtain?

Topic IB- warfarin

1. Does the committee agree that sufficient evidence exists to support the recommendation to use lower starting doses of warfarin for patients with genetic variations in CYP2C9 and VKORC1 that lead to reduced activities?
2. Does the committee believe that genotyping some or all patients prior to beginning warfarin therapy would reduce adverse events and improve achievement of stable INR?
3. Does the committee believe that the existing evidence of the influence of CYP2C9 and VKORC1 genotypes warrants relabeling of warfarin?
 - If yes, what information should be provided in the label?
 - If not, what additional information is needed to provide the necessary evidence for labeling update?

Topic 2

1. What are the committee's comments on the quantitative approach used in this case study ?

2. What are the committee's recommendations on how we would incorporate & evaluate genotype clinical trial design recommendations in different scenarios:

- metabolism genotype
- pharmacodynamic genotype
- disease genotype
- narrow vs wide therapeutic index

Topic 3

Clinical biomarkers are used during drug development for identification of individuals at risk (e.g. QT interval), prediction of treatment outcomes (e.g. viral load), selection of appropriate doses for individual patients (e.g. TPMT genotype), and monitoring therapeutic effects of treatments (e.g. plasma drug concentrations). With regard to the latter:

1. When is it desirable or necessary to include plasma drug concentration information in package inserts, and where in the label would this information be most useful to providers and patients?
2. What evidence should be available to support the use of plasma drug concentration information in package inserts?
3. What is the best approach to obtaining this evidence: during the course of clinical drug development preapproval, or as part of a recommended post-marketing study?
4. To what extent is it necessary to have actually studied the efficacy and safety at doses recommended in the package insert, based upon existing relationships between plasma drug concentrations and clinical outcome?
5. What analytical validation data are appropriate for recommending therapeutic drug monitoring information in the package insert?