Guidance for Industry

Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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TABLE OF CONTENTS

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Guidance for Industry[1]

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I. INTRODUCTION

This guidance is intended to assist the pharmaceutical industry and other investigators engaged in new drug development in evaluating how variations in the human genome could affect the clinical pharmacology and clinical responses of drugs.[2] The guidance provides recommendations on when genomic information should be considered to address questions arising during drug development, and in some cases, during regulatory review. While the application of pharmacogenomic approaches during drug development is an evolutionary process that begins with discovery and continues through confirmation of clinical efficacy and safety outcomes, it is the focus of this guidance to provide advice on general principles of study design, data collection, and data analysis.

This guidance does not address statistical considerations for later phase randomized controlled clinical trials for which genomic hypotheses are prospectively planned, and that are intended to draw definitive conclusions from genomic subgroup effects (e.g., enrichment designs, adaptive enrichment designs, simultaneous hypothesis testing overall and within subgroup(s)). Rather, the statistical considerations here are more relevant for exploratory and observational studies. For instance, early phase data on genomic-dependent dosing, where not definitive, can provide guidance on dose selection in later phase studies or inform the strategy for further collection of genetic and related biomarker data in a larger number of patients in controlled trials.

[1] This draft guidance has been prepared by the Office of Clinical Pharmacology, Office of Translational Sciences, and an Interdisciplinary Working Group with representatives from the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA).

[2] For the purposes of this guidance, the term "drug" includes both small molecule and biological products.

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II. BACKGROUND

Pharmacogenomics (PGx) broadly refers to the study of variations of DNA and RNA characteristics as related to drug response (see ICH E15 Guideline: *Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories*, http://www.emea.europa.eu/pdfs/human/ich/43798606en.pdf). Drug exposure refers to the administered dose, drug levels, or the pharmacokinetic (PK) profile following administration. Drug response refers to the pharmacodynamics (PD) of the drug (i.e., all of the effects of the drug on various physiologic and pathologic processes, including effectiveness and adverse effects). Genetic variations can also influence the exposure-response (E/R) relationship of drugs, including both the shape of the E/R curve and the maximum effect. The definition of PGx in this document is not intended to include other related sciences such as proteomics and metabolomics, but many of the study design issues discussed should be considered in these areas.

A. Genetic Differences

Genetic differences between individuals can affect virtually all aspects of a disease and its treatment, such as the rate of disease occurrence, the risk of disease progression or recurrence, the drug or drug class most likely to result in benefit, the therapeutic dose, the nature and extent of beneficial responses to treatment, and the likelihood of drug toxicity. Differences likely to be of most relevance in drug development are those that occur with genes in three broad categories: (1) genes relevant to the drug's pharmacokinetics (absorption, distribution, metabolism (including formation of active metabolites), and excretion (ADME)), (2) genes that affect the drug's intended and unintended targets and therefore its effect on these targets, and (3) genes that predict the occurrence of disease development (e.g., genes that predict likelihood of tumor development or metastasis), sometimes called prognostic markers.

To date, PK effects of genetic differences are much more familiar and more numerous than PD effects. Individual differences in PK measurements associated with patient genetic profiles are easier to quantify, as measuring drug and metabolite levels in biological fluids over time is straightforward. In many cases, there is a recognized mechanism that predicts differences in PK (e.g., drugs metabolized or transported by enzymes or proteins with well-established genetic polymorphisms, as is the case for CYP2C9, CYP2C19, CYP2D6, or SLCO1B1) (see Addendum) so that such differences can be anticipated. In these cases, DNA sample collection, blood and/or urine drug concentration data, and well-characterized phenotypic information are needed to determine the extent to which genetic polymorphisms in metabolism and/or transporter genes influence exposure to drugs and/or active metabolites and responses.

In contrast to genetic differences affecting PK, genetic differences affecting PD are more difficult to detect because, generally, clinical effects are more variable among individuals, and influenced by many factors, including imprecision in measurement. Genomic effects on PD can, however, profoundly affect dose-response, safety, and efficacy, as is the case for warfarin (see section C.3 below).

Drug product labeling has increasingly included preapproval information on the likelihood of treatment response based on genetic/genomic status (e.g., trastuzumab (Her2) and maraviroc (CCR5)), or the need to genotype before a specified dose can be prescribed (e.g., tetrabenazine). Drug product labeling has also been revised after approval to include PGx information that can alter the benefit/risk (B/R) relationship, or allow dosing of the medicine to be adjusted for individuals. Examples include 6-mercaptopurine and azathioprine, with thiopurine methyltransferase (TPMT) genetic information; warfarin, with CYP2C9 (PK) and VKORC1 (PD) genetic information; and abacavir with HLA-B*5701 information related to likelihood of toxicity. Each of these examples involved dose adjustments needed to address drug safety issues or effectiveness or identification of high risk people. More recently, the label of clopidogrel has been updated to include information on the formation of the active metabolite of clopidogrel by CYP2C19 and the contribution of CYP2C19 polymorphisms to antiplatelet response and clinical outcomes. Because these recent postmarketing examples have, in most cases, been based on data from postmarketing experience, their discoveries were relatively late. It is hoped that full ascertainment of genomic information on all subjects during early development will allow early discovery of clinically important genomic differences. This guidance suggests approaches to improve the quality of the data collected and the ability to assess genomic relationships.

B. Pharmacogenomics Studies

PGx studies can contribute to a greater understanding of interindividual differences in the efficacy and safety of investigational drugs. PGx research depends on the collection and use of biological samples to generate data. Across the drug development continuum, genomic data may be used for several purposes, including (1) identifying the basis for PK outliers and intersubject variability in clinical response, (2) prioritization of drug-drug interaction studies, (3) elucidating the molecular basis of lack of efficacy or adverse events, and (4) designing clinical trials to test for effects in identified subgroups, possibly for use in study enrichment strategies. Genomic tests (i.e., diagnostics) can identify individuals who (1) are most likely to have an efficacious response to an investigational drug, (2) are more at risk for drug-induced adverse events, (3) are unlikely to benefit from treatment, and (4) are in need of a genotype-modified dose or dosing interval. Examples of genetic tests that are intended to make drug therapy more effective and safe continue to increase at a rapid rate, particularly in the therapeutic area of cancer, and there is increasing interest in their use in cardiovascular disease, epilepsy, and HIV, where PK and PD are influenced by genetic differences in metabolic enzymes, membrane transporters, and/or receptors. Even when the results of a PGx assessment are neutral (i.e., no genomic effect is found), the information can streamline drug development by confirming that certain suspected pathways are not likely to contribute significantly to interindividual variability in PK, PD, efficacy, or safety.

Drug development is commonly described in "phases" (21 CFR 312.21). The first two phases provide information about safety, efficacy, and a broad range of doses, so that the larger, later (phase 3) adequate and well-controlled trials needed to support marketing approval can be efficiently designed (e.g., with a reasonable range of doses, good patient selection criteria, appropriate endpoints). Information about PK and pertinent pharmacodynamic effects (generally effects on biomarkers considered predictive of effectiveness or on short-term effectiveness), can provide "proof-of-concept" supporting the likely success of the later trials. Information on PD often includes evidence of exposure-response (usually dose-response but sometimes supplemented by concentration-response modeling) and, where possible, pertinent subset information (demographic, disease severity, and response predictive) that can help target the phase 3 trials by identifying patients with potentially greater responses.

Early studies can:

(1) Identify populations that should receive lower or higher doses of a drug because of excretory or metabolic differences. The latter are generally identified by genetic abnormalities defining metabolic status for enzymes with genetic polymorphisms.

(2) Identify responder populations based on phenotypic, receptor, or genetic characteristics, a critical element in treatment individualization that has been used primarily in the oncologic setting. Predicted differences in response can lead to enrichment strategies based on such predictive markers.

(3) Help define the dose range for later trials by identifying the dose-response for pertinent biomarkers and/or early effectiveness and more common adverse effects. In many cases, the phase 3 trials would evaluate several doses to define benefit and risk further. It would be of particular interest to identify subsets with different dose-response relationships. However, the study of several doses is not common in phase 3 oncology trials of cell and gene therapy products.

(4) Identify high risk groups. Although the ability to cause serious adverse effects will not be generally acceptable in most settings, even if they can be predicted, it is possible that such effects could be linked to factors (metabolic, genetic) that could be managed in later trials, and support approval of drugs with particular value. To date, the most likely use of such information would be to identify poor metabolizers or ultra-rapid metabolizers (e.g., CYP2D6) whose blood levels of parent or relevant metabolites could be markedly affected; in trials they could be excluded or their doses modified to account for genetic variations.

The phase 1 and 2 studies considered in this guidance are often described as "exploratory," in that they are not intended to provide the definitive evidence of safety and effectiveness needed to support drug approval. Nonetheless, they can provide mechanistic support for the later "confirmatory" trials and potentially greatly improve their efficiency, especially if they can help predict the likelihood and magnitude of response.

Typically, phase 2 studies that suggest genomic influences can lead to phase 3 trials that incorporate findings into prespecified hypotheses, such as enriching the study with genomically defined individuals, determining a dose based on demonstrated variability in earlier studies, or defining a priori hypothesis testing of a primary endpoint in a genomic subset. Genomic analyses are common analyses in phase 3 studies (although often not prespecified). In almost all cases these post hoc analyses of efficacy will be considered exploratory; however, strong subset findings on safety (i.e., lack of efficacy) have on occasion been included in labeling (e.g., *KRAS* mutations with cetuximab and panitumumab indicated for colon cancer).

C. The Value of Pharmacogenomics

PGx information obtained from genomic investigations during the course of drug development and from postmarketing studies/trials can improve the effectiveness and safety of drugs. The following examples illustrate the value of genomic information. Although the information was discovered postmarketing, it supports the potential values of having such data earlier when it could be linked to the findings in the clinical trials supporting safety and effectiveness.[3]

1. Abacavir (Ziagen): Improving the Benefit/Risk (B/R) Relationship by Identifying Patients at High Risk for a Serious Adverse Event

Abacavir, which is used alone or in combination with other drugs, is an antiretroviral drug used in the treatment of HIV-1 infection. An abacavir hypersensitivity reaction (HSR) was observed in about 5 to 8% of clinical trial patients, so that hypersensitivity was a well-recognized problem at the time of marketing. The clinical manifestations of the HSR included fever and/or rash, and to a lesser degree, gastrointestinal (nausea, vomiting, diarrhea, and stomach pain) and/or respiratory (cough, shortness of breath, and sore throat) symptoms that emerged within the first 6 weeks of treatment in more than 90% of patients with HSR. Symptomatology worsened with continued therapy and could be life-threatening, but usually resolved upon discontinuation of the drug. Clinical diagnosis was imprecise because of the patients' concurrent illness or drug treatments, and there was an HSR rate of 2-3% in the standard of care arm without abacavir in blinded clinical trials. The hypersensitivity events were an important limitation to the use of abacavir.

Approximately 3 to 4 years after marketing approval of abacavir, new PGx research identified an allele (HLA-B*5701) that appeared to be associated with the hypersensitivity reactions, but the sensitivity and specificity of this predictor of HSR varied between studies and racial populations. A 6-week, randomized controlled trial (called PREDICT-1) (Mallal, S. et al. 2008) was undertaken to assess the clinical utility of HLA-B*5701 screening before beginning abacavir treatment. Abacavir-naïve patients (n = 1956) were randomized 1:1 to an abacavir-containing regimen with HSR monitoring according to standard of care (control arm), or to an abacavir-containing regimen with

[3] The examples provided represent a historical approach to relabeling of drugs. Currently, FDA expects that if a diagnostic test is essential for the safe and effective use of a therapeutic product, that there be a cleared/approved test with the appropriate intended use available concurrent with the drug label change.

HSR monitoring preceded by prospective HLA-B*5701 screening (PGx arm). In the PGx arm, patients who tested positive for HLA-B*5701 were excluded and only HLA-B*5701 negative patients were enrolled.

The trial had two co-primary endpoints: the rate of clinically-suspected HSR, and the rate of immunologically confirmed HSR, defined as HSR with a positive patch test reaction. The incidence of clinically suspected HSR was 7.8% and 3.4% in the control and PGx arms respectively (P<0.001). The positive predictive value of the HLA-B*5701 test for clinically-suspected HSR was 61.2% and the negative predictive value was 95.5%. For immunologically confirmed HSR, the rate was 2.7% for the control arm and 0% for the PGx arm (P<0.001). The positive predictive value of the HLA-B*5701 test for immunologically confirmed HSR was 47.9% and the negative predictive value was 100%, that is, about half of the patients with a positive HLA-B*5701 test developed confirmed HSR while no patient with a negative HLA-B*5701 test did.

The impact of the PREDICT-1 results was substantial because the study was a prospectively planned randomized trial with essentially full ascertainment of genomic status of every randomized subject. The study provided demonstration of clinical usefulness (i.e., near total ability to avoid abacavir-induced HSR with an acceptable false positives rate in the screening). The results of this study influenced the inclusion of strong recommendations for HLA-B*5701 screening in professional guidelines and in the U.S. prescribing information (label updated July 2008).

2. Clopidogrel (Plavix): Identifying Patients with Reduced Response to a Drug

Clopidogrel is a platelet adenosine diphosphate (ADP)-receptor antagonist that is indicated for reduction of atherothrombotic events in patients with recent myocardial infarction, recent stroke, peripheral artery disease, and acute coronary syndrome. Clopidogrel is a prodrug with no antiplatelet activity, but about 15% of the dose is metabolized to an active metabolite in a two-step process involving multiple cytochrome P450 (CYP) enzymes, one of which is the polymorphic CYP2C19. CYP2C19 has four different metabolizer phenotypes: ultrarapid, extensive, intermediate, and poor (refer to Addendum for a more detailed description of various alleles in different ethnic/racial groups).

Analyses of data from several PK/PD studies demonstrated that carriers of at least one loss-of-function (LOF) allele of CYP2C19 showed reduced exposure to the active metabolite and less inhibition of platelet aggregation (Mega, J. et al. 2009). These observations have been independently replicated in numerous clinical pharmacology studies. The relationship between the CYP2C19 genotype and PK/PD was further extended to clinical outcomes in several population- or clinical trial-based cohort studies (Mega, J. et al. 2010). For example, CYP2C19 genotypes were determined in patients enrolled in the TRITON-TIMI 38 trial who voluntarily consented to provide their blood samples for DNA analysis. In TRITON-TIMI 38, carriers of LOF CYP2C19 alleles had a higher rate of death, nonfatal myocardial infarction, or nonfatal stroke as compared to

non-carriers (no LOF allele) following percutaneous coronary intervention. Additionally, the rate of stent thrombosis over the same time period was approximately three times higher in carriers (Mega, J. et al. 2009; Mega, J. et al. 2010).

Based on the results from multiple clinical pharmacology and outcomes studies, the label of clopidogrel was updated in May 2009 and again in March 2010 to include PGx information related to the diminished antiplatelet responses and the increased risk of cardiovascular events in patients with reduced CYP2C19 function. Collection of DNA in phase 3 trials helped substantiate the findings of several clinical pharmacology studies.

3. Warfarin (Coumadin): Selecting Optimal Doses Based on Genotype-Based Differences in PK and/or PD

Warfarin is a coumarin-based anticoagulant that is widely used for the short- and long-term management of thromboembolic disorders, such as deep-vein thrombosis, and to prevent stroke and systemic embolic events in patients with atrial fibrillation and those undergoing orthopedic surgeries. A relatively large number of patients experience life-threatening bleeding complications from warfarin. It has been consistently a top ten-ranked cause of drug-induced serious adverse events. Major bleeding frequencies as high as 10-16% have been reported. However, it is also essential to achieve adequate anticoagulation to prevent thromboembolic events that warfarin is intended to prevent.

Warfarin has a narrow therapeutic range, with wide variation in dose requirements for individual patients, and dose is modified by testing of INR (International Normalized Ratio), a measure of coagulation inhibition. Titrating warfarin-naïve patients to a stable INR range (e.g., 2-3, sufficient but not excessive anticoagulation) in a reasonable time is a significant challenge for health care providers because of the many genetic (e.g., CYP2C9 and VKORC1) and nongenetic (e.g., sex, body size, drug-drug interactions, diet) factors affecting the PK and PD of warfarin. Underlying genetic factors have been shown to account for approximately 35-40% of the variation in the maintenance dose. CYP2C9 is the hepatic enzyme responsible for metabolizing S-warfarin, which is 3-5 times more potent than the R-enantiomer. Genetic polymorphisms affecting CYP2C9 (i.e., the *2 and *3 alleles) are common in the general population, resulting in decreased clearance and higher blood levels of S-warfarin.

Warfarin works by inhibiting Vitamin K epoxide reductase (VKOR), which is encoded by the VKORC1 gene. Polymorphisms in this gene affect an individual's response to warfarin. The major polymorphism, mutation in VKORC1 (1639GA), for example, decreases the expression of the gene and increases the responsiveness to warfarin. Patients with these polymorphisms (either heterozygous 1639GA genotype or 1639AA homozygous genotype) will generally require lower doses than patients with the 1639GG genotype. There is a relatively high frequency of the 1639AA genotype, from approximately 4–5% in African Americans, 14-17% in Caucasians, to 72-78% in Asians (Marsh, S. et al. 2006, and Yuan, H.Y. et al. 2006).

Studies have shown that patients carrying variant CYP2C9 and/or VKORC1 genotypes had a higher chance of major hemorrhage during warfarin therapy, and genotypes play an important role in determining the dose of warfarin (Limdi, N.A. et al. 2008; Caraco, Y. et al. 2008; and Klein, T.E. et al. 2009). In August 2007, the FDA updated the warfarin package insert to provide general information about genetic testing and to encourage health care providers to use this information for initial dosing to reduce the risk both of bleeding and of undertreatment. Subsequently in January 2010, the warfarin labeling was updated to include a dosing table to be used for initial dosing based specifically on CYP2C9 and VKORC1 genotypes.

III. PROSPECTIVE DNA SAMPLE COLLECTION

An important prerequisite to successful use of genetic information in drug development is the appropriate collection and storage of DNA samples from all clinical trials, both exploratory studies and the *adequate and well-controlled* trials intended to support effectiveness and safety. Potential PGx differences in efficacy and/or safety can arise from gene variants not yet as well characterized as the metabolism or transporter genes. Therefore, plans for general DNA sample collection should be prespecified at the time of randomization or initiation of a study to minimize the potential for sample selection bias, even if these samples are studied only at a later time during or after a study. It then becomes possible to seek explanations for differences in exposure, efficacy, tolerability, or safety not anticipated prior to beginning the study, noting, of course, potential multiplicity and bias issues.

Ideally, consent for DNA collection should be obtained from all participants in clinical trials. An effort should be made to collect genetic samples at enrollment and/or at baseline to avoid potential bias associated with delayed collection. This is particularly important in trials where many patients do not complete the study, do not comply with the protocol, or withdraw from the trials before experiencing a clinical outcome. In cases of incomplete sample acquisition, the specific reasons should be described and any potential bias estimated where possible. Samples should be collected in all arms of the trial. DNA should be retained in the event that new genomic issues arise after the completion of the studies.

Why certain individuals experience a beneficial effect or a serious adverse event after drug administration while other individuals do not is usually not known in advance of a study unless genetically influenced PK differences are recognized. It is anticipated, however, that genomic differences among individuals will prove to be important causes of such differences in drug response. Such differences are emerging rapidly in the oncology setting and there are now a number of genetically related toxicities in other areas such as the HLA-B*5701 relationship to abacavir toxicity and the HLA-B*1502 relationship to carbamazepine toxicity. In some cases, for example, when the receptor for a cancer therapy is known, genomic differences can be predicted, but non-PK related response differences between individuals often do not have any obvious mechanism and cannot be anticipated.

Routine collection of DNA samples should provide applicants with an opportunity to investigate the causes of lack of efficacy or the occurrence of toxicity in different individuals, using such

approaches as exploratory genome-wide association investigations, and candidate gene or targeted pathway analyses. The need for genomic tests and possible relationship to clinical phenotypes of efficacy or safety may not be suspected at the time of initiating a study and will become of interest only at a later time. Therefore, where possible, informed consent procedures should anticipate this possibility, and attention should be given to the appropriate sample handling, storage, and sample retention duration so that exploring these genotype-phenotype relationships can be performed after completion of the study.

Samples that can be used for DNA analysis include a range of biological materials such as blood or buccal cells. In addition to germline mutations, there are also somatic or acquired mutations to be considered, for example, in biopsies from tumors. Like germline mutations, not only can they be related to drug response, but they may also predict the severity of a disease and disease prognosis (e.g., likelihood of metastasis) and can be used to identify subgroups of patients most suited for outcome trials because of a relatively large rate of events.

Information to support the quality and integrity of DNA during sample collection and storage, along with information to show that the DNA material can be used for consistent and reproducible analysis, should be provided in an applicant's study report. Examples of best practices for biospecimen collection, storage, and data handling can be found in the National Cancer Institute "Best Practices for Biospecimen Resources" (2007) (http://biospecimens.cancer.gov/global/pdfs/NCI_Best_Practices_060507.pdf) and the FDA draft guidance for industry on *Pharmacogenomic Data Submissions — Companion Guidance* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079855.pdf). There are also harmonized definitions for coding of DNA samples and implications for using different sample coding categories in the ICH E15 guideline entitled *Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories* (http://www.emea.europa.eu/pdfs/human/ich/43798606en.pdf).

IV. CLINICAL EVALUATION OF PHARMACOGENOMICS

A. General Considerations

The value of DNA sample collection and the information that analysis of these samples can provide will vary for different drugs and indications. Considering known PGx factors during preclinical assessment is critical. Exploratory human PGx investigations generally begin with in vitro studies followed by clinical pharmacology studies in humans to assess the PK and PD properties of the drug that might be associated with gene variants in metabolizing enzymes, transporters, and drug target receptors. For example, if in vitro studies show a high percentage of a molecule's metabolism in human cell systems relies on a well-established polymorphic gene, such as CYP2C19, it would almost always be important to determine the contribution of genomic factors to variability in PK and subsequently to dose or dosing regimen selection. These data inform decisions as to whether subsequent clinical studies need to take PGx differences into account (e.g., in dose-response studies). Various technology platforms are available to rapidly characterize the contribution of established and evolving allelic variations of

hundreds of metabolism and transporter genes simultaneously in clinical pharmacology studies to allow thorough understanding of variability in PK and/or PD related to genomics.

To design informative studies and interpret study results appropriately, careful attention should be given in clinical pharmacology studies to differences, if known, in the prevalence of ADME-related gene variants among racial or ethnically distinct groups (e.g., African-Americans/Blacks, Asians, Caucasians/Whites, Hispanics or Non-Hispanics) (FDA guidance for industry on *Collection of Race and Ethnicity Data in Clinical Trials*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071596.pdf) (see Addendum).

B. Clinical Pharmacogenomic Studies

In vitro studies of metabolism, transport, or drug targets could help identify the need for human PGx studies and contribute to the design and analysis of these studies. The following clinical pharmacology studies represent opportunities to integrate PGx factors for assessing interindividual variability and its implications for subsequent clinical studies. To date, many of these studies have not involved prospective randomization of genomically characterized subjects to treatment groups. In later stage clinical trials intended to support efficacy and safety conclusions in genomic subsets, stratified randomization or planned subset assessment would generally be expected.

1. PK and PD Studies in Healthy Volunteers

Single and multiple ascending dose PK studies provide important initial information on drug PK and can suggest the level of interindividual variability in PK that can be expected in later trials. These studies can provide information on common gene variants affecting ADME, and collection of DNA samples from all participants is recommended so that analysis of collected DNA can be performed on individual subjects to evaluate the causes of PK outliers and to help explore the PK parameter distribution. In the case of biologics, PD in addition to PK is particularly important. Where there are concerns about the toxicity of an investigational drug because of excess exposure at higher doses in individuals with genetically-mediated alteration in metabolism (e.g., for drugs with anticipated dose-limiting toxicity and polymorphically mediated metabolism), prospectively genotyping subjects will identify those subjects who are at risk, so that they can (1) receive lower doses, or (2) be excluded from PK studies until there is a better understanding of the in vivo relevance of the metabolic pathway.

When in vitro studies suggest that an investigational drug is metabolized to a large degree by a polymorphic pathway (e.g., CYP2D6), single- and/or multiple-dose PK studies should be conducted in healthy volunteers representing various common genotypes (prevalence $\geq$ 1%) to determine the extent of variability and the maximal differences in systemic exposure between genotypes. In some cases, genotyping could be done retrospectively (after completion of the study) to evaluate observed variability in PK and PD, if relevant PD measurements are available.

Special consideration should be given to a drug for which conversion to an active metabolite from an inactive parent compound occurs through a polymorphic metabolism pathway. It is advisable to characterize the metabolism of the drug and study the biological activity of the relevant metabolites early in drug development. In these cases, differences in metabolite exposure among individuals may have implications for dosing, efficacy, and safety. Where drug metabolites have important clinical effects (e.g., tamoxifen, clopidogrel), failure to form the active metabolite may have profound effects on disease recurrence and/or sequelae. It is particularly critical from the beginning of development in these cases to include subgroups of subjects with genetic variants of metabolic or transporter pathways.

Strategies other than a targeted candidate gene approach can also be useful for probing the causes of variability early in drug development, even before there is understanding of the influence of genetic factors on drug response. These strategies include routine screening of subjects in early phase clinical trials using a gene chip that includes a large number of possible candidate metabolism and transporter genes, some of which may influence PK and/or PD.

For a drug that is a substrate of a polymorphic enzyme or transporter, the evaluation of comparative PK in the subgroups genetically defined as UM (ultra-rapid metabolizers), EM (extensive metabolizers) and PM (poor metabolizers) of certain enzymes or transporters often provides essential information on potential drug-drug interactions. This is helpful in prioritizing subsequent drug interaction studies and in estimating the extent of interactions by that specific pathway. For example, the difference in drug exposures between EM and PM subgroups would generally represent the most extreme change that could be caused by a strong inhibitor of that pathway. Similarly, an alternative to a genotype-specific PK study in the case of a polymorphic metabolizing enzyme is to administer the investigational drug to extensive metabolizers with and without concomitant administration of a known strong inhibitor of the metabolic pathway. For example, an individual who is a CYP2D6 EM can be converted to a de facto CYP2D6 PM by concomitant administration of a strong CYP2D6 inhibitor, and the increase in exposure provides a reasonable estimate of the increase in exposure that would be expected in the CYP2D6 PMs. For drug interaction study design and selection of strong inhibitors of metabolic pathways, refer to the FDA guidance for industry on *Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling* (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm).

2. PK and PD Studies in Patients

If important variability in PK of active species (i.e., parent drug and/or its active metabolite) is observed in healthy volunteers, the significance of this finding should be considered in the design of subsequent studies in patients (e.g., in dose/response studies

in genotype-defined subgroups). When a test to identify genotypes is found to be important in predicting blood levels and drug effect, this knowledge can be used in the subsequent design of other clinical trials, for example, by using genotypes to (1) select patients for trials (i.e., enrichment with potential responders and elimination of patients likely to experience toxicity), (2) stratify groups within trials, and (3) adjust doses in trials. These steps can increase the average effect, decrease toxicity, and improve the chances of overall success of the study. The trials can also reveal exposure differences that are not clinically critical.

3. Dose-Response (D/R) Studies

D/R studies are usually conducted in phase 2 using biomarkers or clinical endpoints which are relevant to clinical efficacy and safety to (1) provide "proof of concept," (2) identify doses for phase 3 trials, and (3) establish dose-response for relatively common adverse effects. Both PK differences (i.e., metabolism and transport) and PD differences (i.e., shift in concentration-response curves) can lead to differences in D/R in individuals. If previous PK and/or PD studies suggest that a genotype is important in influencing systemic exposure-response or efficacy and safety responses, D/R studies that stratify dose groups by genotype or specific genotype-guided D/R studies (PK adjusted D/R or even a concentration controlled study) should be considered. In the latter studies, doses are defined by expected blood levels in individuals rather than by administered dose.

Drug plasma level evaluation in D/R studies, even if the study was not planned to assign patients to groups by blood levels, can help interpret results when there are major differences in blood levels resulting from genomic factors as well as apparent variability in D/R relationships. Explanations related to genomic factors can sometimes be persuasive on their own or can lead to hypotheses to be tested in further studies, where patients would be stratified by genotype. Any of these possibilities necessitates at least population PK efforts in those studies (FDA guidance for industry on *Population Pharmacokinetics*, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm.

C. Specific Considerations in Study Design

1. Overview

The choice of study design depends on prior knowledge and the purpose of the study. The study is straightforward when the goal is to compare PK in genomically defined subgroups of healthy volunteers or patients. PK is then assessed in the relevant subgroups, often, but not necessarily, in the same study. This design is similar to the studies in people with hepatic or renal impairment. These studies provide information on exposure in genomically defined subgroups and depending on an understanding of the PD consequences of blood levels (i.e., concentration/response relationships), could influence

dosing in later randomized controlled trials. The information and results would generally be included in product labeling.

Less well developed than such PK studies are study designs used to understand genomically distinguished PD responses. Where a particular genomic influence is reasonably well understood, patients can be stratified and responses analyzed by subsets. This would be possible, for example, for oncology settings where tumor markers (ER, EGFR, KRAS) are thought to predict response, and historically where other markers have had similar potential (e.g., high vs. low renin, systolic or diastolic dysfunction in heart failure). In a more exploratory setting, PK-PD studies or D/R studies measuring a biomarker can be examined for genomic predictors of PD effects. Earlier studies in drug development will generally look for effects on such a marker, while studies of clinical endpoints would be assessed later in drug development. In some cases, of course, there is no marker and only clinical outcomes can be studied. In later trials, such relationships, if not anticipated, will in most cases be considered exploratory (i.e., needing prospectively defined confirmation).

Analytical validation of genotyping and phenotyping methods should be established before initiating a clinical PGx study. Appropriate quality control materials, standards, and calibrators (where applicable), as well as validated protocols, should be established to provide assurance of continuing analytical performance over time and across testing sites (Dickinson, G.L., Rezaee, S., et al. 2007). For specific advice on analytical and clinical validity requirements for FDA approval or clearance of a genomic assay, sponsors should consult the Office of In Vitro Diagnostic Device Evaluation and Safety in CDRH.

2. Study Population

Clinical PGx studies focused on pharmacokinetics are usually performed in phase 1 using healthy volunteers, with additional attention to the effects of gender, age, and race/ethnicity. Safety considerations may preclude the use of healthy volunteers for certain drug classes (e.g., cytotoxic anticancer drugs). Studies of patients for whom the investigational drug is intended provide the opportunity to explore PD or clinical endpoints not measurable in healthy volunteers.

The exclusion of patients with certain genotypes from a clinical trial may be appropriate when the concentration/response relationship is reasonably well known and it is clear that subjects with certain genotypes would not respond to the low exposure of active drug that would be achieved. Similarly, the clear absence of a drug target (e.g., the gene for a cell surface receptor needed for anti-cancer activity) might lead to exclusion of such patients. A potential problem, however, may be lack of information as to what receptor level is needed for response, so that in most cases there should be some response, perhaps for biomarker endpoints, of the group with low expression of the target. Subjects may also be excluded from a clinical trial when it is known that certain genotypes would be at risk because of high exposure to the active drug. When a drug-drug interaction study is intended to evaluate the impact of an investigational drug as an inhibitor of enzyme

metabolism, it would not be appropriate to enroll poor metabolizers of that enzyme, if it is polymorphic. In some instances, an evaluation of the extent of drug interactions in subjects with various genotypes may be helpful (refer to the FDA guidance for industry on *Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf).

3. Multiple Covariate Considerations

Many observable phenotypes of drug response in humans result from the interactions of multiple factors or covariates, including genetic, demographic, and environmental factors. The understanding of specific covariates (e.g., age, gender, and race) and gene-covariate interactions on variability in drug response could be useful in understanding the relative impact of genetics, versus other nongenetic factors, on the PK, PD, dosing, efficacy, and safety of the drug. For example, some clinical studies have found that genetic variants in CYP2C9 and VKORC1 increase the risk of bleeding in patients taking standard doses of warfarin. However, genetic variations are not the only factors that increase the risk of bleeding. The dose of warfarin in the context of a patient's body surface area (BSA) and age may also influence the bleeding risk. In some cases, therefore, it is important to understand the risk associated with multiple factors —both genetic and nongenetic.

Mathematical simulations using population-based, physiological PK/PD models (i.e., physiologically-based pharmacokinetic (PBPK) models) that simultaneously integrate various patient-intrinsic and -extrinsic factors can provide an understanding of the potential complex changes in E/R relationships in patients where multiple covariates are present. Some applications of these models, including the design of clinical trials to evaluate the effects of drug metabolizing enzyme polymorphisms on PK and PD, can be found in the literature (Dickinson, G,L,, Rezaee, S., et al. 2007, and Dickinson, G.L., Lennard, M.S., et al. 2007). Further discussion of the utility and limitations of PBPK modeling and simulation can be found in the FDA guidance for industry on *Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf).

4. Dose Selection

A clinical PGx study should be conducted at relevant clinical doses. A lower dose may be used for subjects with certain genotypes that could result in high and unsafe exposure or excessive pharmacological response to the drug. Interpretation of findings in a clinical PGx study, such as changes in exposure in specific genotypes, may be aided by a good understanding of dose- or concentration-response relationships for both desirable and undesirable drug effects in the general population and in subpopulations with different genetic variations. The FDA guidance for industry on *Exposure-Response Relationships*

— *Study Design, Data Analysis, and Regulatory Applications* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf) provides considerations in the evaluation D/R and concentration/response (C/R) relationships.

5. Measurements of Interest

PK Parameters

PK measurements and parameters that should be useful for consideration of genotypic effects on drug exposure include AUC, Cmax, and time-to-Cmax (Tmax), as well as PK parameters such as clearance, volumes of distribution, and half-lives. Additional measures, such as trough drug concentrations in multiple-dose PK studies, if associated with a PD measurement, an efficacy endpoint, or an adverse effect, may help to determine appropriate dosing strategies to achieve similar exposure across different subsets of the population.

Biomarkers of Drug Response (PD)

Biomarkers of drug response related to efficacy and/or safety should be incorporated into clinical PGx studies to measure whether or not genetic factors influencing exposure or target response will have an impact on clinical outcomes.

6. Statistical Considerations

Statistical considerations are important so that the hypotheses and conclusions arising from early phase clinical studies (e.g., need for different doses for different CYP genotypes) are sufficiently supported with credible data, and where not definitive, can define a hypothesis to be pursued later in drug development with more rigorous study designs. As a general matter, early studies should be able to identify definitively large differences in PK resulting from genomic differences (e.g., CYP2D6 poor metabolizers), but genomic PD differences will generally need further study.

Clinical studies evaluating the effect of PGx factors during early drug development are intended to address questions concerning variability in PK and short-term PD endpoints in healthy volunteers and patient groups. Although there are well-established variants in metabolism (e.g., CYP2D6 and CYP2C19 poor metabolizers; see Addendum), most pharmacogenomic research is exploratory at this stage and is often intended to discover relationships for which no prior hypotheses exist. Even where genomic factors are expected to be important (e.g., genetic determinants of receptor characteristics), there may be considerable uncertainty as to clinical consequences.

In addition to candidate gene approaches, high density SNP maps may be developed to explore SNP profiles that may influence PK, PD, and/or clinical outcomes.

For exploratory and observational studies, which generally do not involve randomization of subjects to treatment, the statistical concepts that are most relevant to clinical

pharmacogenomics are (1) controlling for the multiplicity and the risk of incorrectly identifying associations in genomic data when many undirected searches are performed; (2) quantitatively characterizing the preliminary marker classifier performance (sensitivity, specificity, predictive values), and exploring the prognostic and predictive attributes of the marker where appropriate; (3) minimizing bias in estimates of associations where there are no prior hypotheses; and (4) assessing the reproducibility of a genetic finding (strength of association, magnitude of association, subgroup response) so that it can reliably be used and evaluated in follow-up development research in later phase clinical trials.

Statistical issues for early pharmacogenomic assessments, discussed in section II.C of this guidance (The Value of Pharmacogenomics), can be divided roughly into the use of the PGx information for the following three purposes:

To define differences in metabolism or clearance that will affect the PK of a drug.

Differences in metabolism are, in most cases, well understood, and the main issue will be to examine the magnitude of the effect on PK parameters, which can be large if the genetically affected pathway has an important role in the drug's metabolism. In some cases the effect of the altered PK will confer an important effect on PD or clinical endpoints (as in the clopidogrel and warfarin examples), depending on the C/R relationship. Studies will initially simply compare PK in groups with normal and gene variant metabolism, and often the differences will be large and readily described. If the clinical consequences of the genetic differences need to be investigated, clinical or PGx studies in patients with normal and genetic variant profiles should be studied (in separate studies, or preferably as strata within a single study), and the differences in response between the two groups should be noted. Thus, for clopidogrel, normal and CYP2C19 poor metabolizer genotypes would be studied for clopidogrel's ability to inhibit platelet aggregation and, if needed, for clopidogrel's effect on cardiovascular outcome.

To define differences in the magnitude or presence of a favorable response to a treatment

Where genetic differences do not lead to differences in blood levels of active drug or metabolite, but rather to changes in the C/R relationship (e.g., slope in C/R curve or at the extreme, lack of any PD effect), validation and precise definition of the genomic difference would be evaluated in a trial in which genetic strata could be studied, preferably in the same trial. Thus, cancer patients whose tumors bear a particular genetic marker and patients without the marker would be stratified in a control trial and differences in response between the groups studied. A critical question would be how such markers would be identified initially as an a priori hypothesis. If not understood as a mechanism of drug action initially, they could be identified later, after studying the exposure of an unselected population to the drug. Response would then be explored in relation to a wide range of markers. Even if a strong association were seen, it would generally be prudent to examine the relationship again in a separate independent data set,

in recognition of the possibility of false findings stemming from issues of multiple testing and bias within the initial data set. Prior to using a novel multivariate test for investigational management of patients, it is important to ensure that the marker effect replicates in a truly independent population. In addition, use of the test result in investigational patient management may require the approval by CDRH of an Investigational Device Exemption submission.

To identify genomic predictors of an increased likelihood of an adverse effect.

Relating a PGx characteristic to a relatively uncommon adverse drug reaction (ADR) requires, first, analysis of patients who experience the ADR in order to seek a common PGx characteristic. This would generally involve a case-control approach, comparing the rate of the putative PGx predictor in patients with and without the adverse reaction. Given the substantial multiplicity in such searches and the potential for bias when comparing cases with improperly selected controls, a large risk-ratio would generally be needed to be persuasive. In the abacavir case described in section II.C, HLAB*5701 was strongly identified as the marker predicting susceptibility to toxicity, and a clinical trial comparing ADR ratios in a marker-screened population versus an unscreened population was carried out to show definitively that elimination of marker-positive patients (those at risk for HSR) eliminated the well-defined adverse effect almost entirely (with an odds ratio of 0.40 with clinically diagnosed method and 0.03 with immunologically confirmed method).

V. PRINCIPLES OF INCLUDING PHARMACOGENOMIC INFORMATION IN LABELING

In general, information on PGx in labeling is intended to inform prescribers about the impact, or lack of impact, of genotype on phenotype, and indicate whether a genomic test is available and if so, whether testing should be considered, recommended, or necessary. A "Pharmacogenomics" subsection should be created in the CLINICAL PHARMACOLOGY section and should include details on the clinically relevant information on the effect of genetic variations affecting drug therapy.

Pharmacogenomic information can include, but is not limited to, the following:

- Description of polymorphic enzymes (for example, genetic-based differences in enzyme activity such as reduced cytochrome P450 enzyme activity attributable to polymorphisms in a CYP gene).
- Subpopulation-based information on the prevalence or frequencies of alleles, genotypes, haplotypes, or other genomic markers.
- Positive and negative predictive values associated with the use of the genomic marker for safety and/or efficacy purposes.
- Effect of genotype on important PK parameters, such as clearance, half-life, and AUC.

- The pharmacogenomic studies that provided evidence of genetically based differences in drug benefit or risk.
- Changes in dose based on genotype.

When the information has important implications for the safe and effective use of the drug and the consequences of the genetic variations result in recommendations for restricted use, dosage adjustments, contraindications, or warnings, this information should be included in other sections of the labeling, as appropriate, such as the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and/or DRUG INTERACTIONS sections, with a cross reference to the section that contains the detailed information. The detailed information will most often appear in the Pharmacogenomics subsection of CLINICAL PHARMACOLOGY (12.5) or CLINICAL STUDIES section (14). In addition, PGx information that needs to be conveyed to patients should be summarized in the PATIENT COUNSELING INFORMATION section (17).

Detailed information about clinically relevant genetic information should be consolidated into the most appropriate labeling section. Often, other sections of labeling may briefly describe or refer to the information and provide a cross-reference to the section that contains the detailed information, but should not repeat the detailed information. The following are types of PGx information that would be appropriate to include in the specified labeling section or sections.

- PGx information related to proper patient selection (e.g., the need for PGx testing) — INDICATIONS AND USAGE
- Different dosing recommendations for subgroups of patients based on genetic makeup — DOSAGE AND ADMINISTRATION
- PGx information affecting drug safety — BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and/or ADVERSE REACTIONS
- Relevant information concerning the role of genetic variations in drug-drug interactions and the clinical consequences of the combination of genetic polymorphisms in protein(s) in the context of the drug's metabolism, transport and action — DRUG INTERACTIONS
- PGx impact on PK or PD (if not included in another section)— CLINICAL PHARMACOLOGY
- Efficacy differences related to PGx — CLINICAL STUDIES (if studied and the evidence is substantial)
- Genotype(s) that are known to be associated with an adverse reaction in a specific population — WARNINGS AND PRECAUTIONS and USE IN SPECIFIC POPULATIONS

For more information on general recommendations for product labeling, refer to the guidance for industry on *Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf).

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ADDENDUM

Ethnic Differences in Allele Frequencies for Selected Enzymes, Transporters, and Pharmacologic Targets (modified from Reference Yasuda S, et al., The Role of Ethnicity in Variability in Response to Drugs: Focus on Clinical Pharmacology Studies. *Clin Pharmacol Ther.*, 84 (3), 417-423, 2008).

Gene	Variant Allele	Alteration in Allele Function	Allele Frequencies (%)				
			White	Black	Asian	Chinese	Japanese
CYP2A6	*1	Normal	46	54		34	
	*4	Deletion	0; 1.2	0.6; 1.9	10.8 [a]	6.7	19; 24.2
	*7	Reduced	0; 0.3	0	9.8 [a]	3.1	9.8; 6.3
	*9	Reduced	8.0; 7.1	8.5; 7.1	19.3 [a]	15.6	19.0; 20.3
	*10	Reduced or virtually absent	0	0		0.4	1.6
	*17	Reduced	0	10.5	0		0
CYP2B6	*1	Normal	50.7	44.3	30		68.0
	*4	Increased	6	2	4		
	*5	No change	3; 12	5; 3	3		
	*6	Reduced	28; 25.6	34; 32.8	23	16.2	18
	*7	Reduced	3	1	0		
	*9	Reduced	1	1	0		
	*11	Reduced	1	0	0		
	*15	Unknown	0.4	0	0		
	*16	Reduced					
	*17	Unknown	0	6; 7.1	0		
	*18	Reduced	0	9; 2.9	0		

Gene	Variant Allele	Alteration in Allele Function	Allele Frequencies (%)				
			White	Black	Asian	Chinese	Japanese
	*22	Unknown	3.3	1.1	0		
CYP2C8	*1	Normal	87;77.5	80		100	
	2	Reduced	0.4	18			0
	3	Reduced	13-15	2			0
	4	Reduced	7.5				0
CYP2C9	*1	Normal	80	>90	>90	96.3	98.9
	*2	Reduced	10-13	3	Absent or rare		
	*3	More Reduced	5.6-8	1			3.5
CYP2C19	*1	Normal	86; 85.3	75; 81.4; 82.3	62	54.1; 64.7	67
	*2	Non-functional	13.6-15	17		none 30	34.5 [e]
	*3	Non-functional	<1	<1		5	9 [e]
CYP2D6[b]	EM	Normal	71; 70; 73.4	37; 48	51.5	45	55.2
	PM	Non-functional	7.7	1.9-7.3	0-4.8		
	IM	Decreased	1-2		51		
	UM	Increased	4.3	4.9	0.9		
CYP3A5 WE = white European WC=White Canadian AA African American Z=Zimbabwean	*1A	Normal	8-15; 5-7 WE	45; 40 AA	23-40; 25	22	23
	*1B	None (controversial)	0 WC 0.5-3.0 WE	0AA 0Z			
	*1C	Unknown	4.6 WC 3.0 WE	7.0 AA 0 Z	0		
	*2	Unknown	0.7WC 2.0 WE	0 AA 0 Z			
	*3	No function	92.9 WC 70 WE	27.0-50.0 AA 77.6 Z	75.0		

Gene	Variant Allele	Alteration in Allele Function	Allele Frequencies (%)				
			White	Black	Asian	Chinese	Japanese
	*5	Unknown	0 WC	0Z	0.9		
	*6	Decreased Function	0 WC 0WE	13.0 AA 22.0Z	0		
	*7	No function	0	10.0 (AA) 10.0 (Zimbabwean	0		
ABCB1 (P-gp) [c]	Wild Type (C1236T) C allele	Normal	34	6		20.0	45.5
	*1	Unknown	15	15	15		
	*13	Unknown	34	5	34-37		
	*26	Unknown	10	9	5		
	*21	Unknown	3	8			
	*11	Unknown	1	2	23		
	*14	Unknown	10	2	2		
ABCG2 (BCRP)	Wild Type (34G>A; V12M)	Normal	81; 94.4	93.7			82.4
	34G>A		2	4	45 [d]	20	15
	421C>A	Reduced	14, 10	0	15 [d]	35	35
SCLCO1B1 (OATP1B1)	*1a	Normal	32.5				35
	*1b (388A>G)	Increased (possibly protein expression)	30; 30-51; 38	74; 75; 77	57-88	59.9	46.9; 53.7; 63-67
	*2	Unknown	2	0			0
	*4	Unknown	16	2			0
	*5 (521T>C)	Decreased	14; 2.7%	2			

Gene	Variant Allele		Alteration in Allele Function	Allele Frequencies (%)				
				White	**Black**	**Asian**	**Chinese**	**Japanese**
				(Finnish)				
	*6		Unknown	2	0			
	*7		Unknown	1	0			
	*8		Unknown	1	0			
	*9		Unknown	0	9			
	*10		Unknown	2	0			
	*11		Unknown	2	34			
	*15 (both 388A>G and 521T>C)		Decreased	2.4 (Finnish)			14	3.7; 10.3
	*16		Unknown	7.9 (Finnish)				3.7
	*17 (388A>G and 521T>C, and -11187G>C)		Decreased	6.9 (Finnish)				13.3
UGT1A1	*1		Normal	45.1	15		87.5; 61	
	*6 (211G>A)	Homo-zygous	Reduced	0	0			4
		Hetero-zygous	Reduced	1.3	0			23
	*27 (229C>A)		Reduced	0	0	<1-3		
	*28	($TA_{7/7}$)	Reduced	12; 13	23	5	8	2
		($TA_{6/7}$)	Reduced	39		20	14	
UGT2B7	*1a		Normal	33; 38.6				47
	*1 *1		None	25 ; 23.75				43; 45
	*1 *2		None	43				37
	*2 *2		Reduced transcription	23				4

Gene	Variant Allele		Alteration in Allele Function	Allele Frequencies (%)				
				White	**Black**	**Asian**	**Chinese**	**Japanese**
VKORC1	Wild Type		Normal	60	80	1		
	-1639G>A	AA	Lower dose requirement	14		82-83	88	
		AG		47			18	
		GG		39			0	
	1173C>T	CC		37.5	80.4	89		
		CT			18.7			
				12.5	0.9			15.2

Note: Data from different references are separated by semicolons. Blank cells indicate that data are not found in the literature.

[a] for CYP2A6, Asian refers to Korean

[b] for CYP2D6, TT 50

PM: denotes individuals with 2 of the following non-functional alleles: *3, *4, *5, *6, *7, *8, *14, *18, *21, and *44.

IM: denotes individuals with one non-functional alleles and one functional allele or two reduced function alleles: *10 and *17.

UM: denotes individuals with 2 or more copies of the functional alleles.

[c] Mexican Americans had allele frequencies of 34% for *26 and 20% for *11; Asian refers to Asian-Americans[d] South East Asia (non-Chinese, non-Japanese); allele frequencies are approximate based on the figure in reference 28.

[e] Native Japanese.