Pharmacogenetics and Pharmacogenomics in Drug Development and Regulatory Decision Making: Report of the First FDA-PWG-PhRMA-DruSafe Workshop

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The use of pharmacogenetics and pharmacogenomics in the drug development process, and in the assessment of such data submitted to regulatory agencies by industry, has generated significant enthusiasm as well as important reservations within the scientific and medical communities. This situation has arisen because of the increasing number of exploratory and confirmatory investigations into variations in RNA expression patterns and DNA sequences being conducted in the preclinical and clinical phases of drug development, and the uncertainty surrounding the acceptance of these data by regulatory agencies. This report summarizes the outcome of a workshop cosponsored by the Food and Drug Administration (FDA), the Pharmacogenetics Working Group (PWG), the Pharmaceutical Research and Manufacturers of America (PhRMA), and the PhRMA Preclinical Safety Committee (DruSafe). The specific aim of the workshop was to identify key issues associated with the application of pharmacogenetics and pharmacogenomics, including the feasibility of a regulatory "safe harbor" for exploratory genome-based data, and to provide a forum for industry-regulatory agency dialogue on these important issues.

Keywords: *Pharmacogenetics; pharmacogenomics; drug development process; regulatory agencies; safe harbor*

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A workshop was held in Rockville, Maryland, on May 16-17, 2002, under the sponsorship of the U.S. Food and Drug Administration (FDA), the Pharmacogenetics Working Group (PWG), the Pharmaceutical Research and Manufacturers of America (PhRMA), and the PhRMA Preclinical Safety Committee (DruSafe), the latter consisting of members of pharmaceutical companies actively engaged in pharmacogenetics.[a] This was the first agency-industry workshop on pharmacogenetics and pharmacogenomics. The goal of the workshop was to discuss the following:

1. use of genomic technology in nonclinical and clinical drug development;
2. issues, limitations, and questions related to the application of pharmacogenetics and pharmacogenomics; and
3. future direction of regulatory policy and guidances for industry.

The purpose of this report is to summarize the key ideas and recommendations that were identified and

a. The workshop agenda and workbook can be found at www.fda.gov/cder/calendar/meeting/phrma52002/default.htm and www.fda.gov/cder/calendar/meeting/phrma52002/workbook.pdf, respectively.

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discussed at the workshop. There has been no attempt to summarize each individual plenary lecture; rather, the report is organized by key topic areas that emerged during the workshop.

DEFINITIONS

There is a diversity of opinion regarding definitions and benefits of pharmacogenetics and pharmacogenomics.[1-3] For example, pharmacogenetics is often considered to be the study of interindividual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics). Polymorphic variation in the genes that encode the functions of transporters, metabolizing enzymes, receptors, and other proteins can result in individual differences in the dose-plasma concentration-response relationships for many important therapeutic agents. In contrast, pharmacogenomics is thought to be the application of genomic technologies to the study of drug discovery, pharmacological function, disposition, and therapeutic response. Whole-genome or candidate gene single-nucleotide polymorphism (SNP) maps, haplotype markers, and alterations in gene expression or inactivation represent global tools for the discovery of new drugs and genetic variations that influence drug action. This workshop did not attempt to harmonize on these definitions. For the purposes of this workshop, *pharmacogenetics* was used to define applications of single gene sequences or a limited set of multiple gene sequences, but not gene expression or genomewide scans, to study variation in DNA sequences related to drug action and disposition. *Pharmacogenomics* was used to define applications of genomewide SNP scans and genomewide gene expression analyses to study variations that influence drug action.

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OVERVIEW OF PHARMACOGENETICS AND PHARMACOGENOMICS

An important application of pharmacogenetics and pharmacogenomics to public health is the ability to determine a priori who will respond favorably (or unfavorably) to a given type of drug treatment. A major challenge is the interindividual variability (population variance) and intraindividual repeatability in a clinical outcome measure (efficacy or safety) in a target population. There is substantial variability in treatment response, and data already exist to indicate that a component of variability is genetic in nature. Repeatability of a clinical response in a given subject with a chronic recurrent disease requiring continued therapy (e.g., asthma) reflects the heritability in that subject that modulates the response.[4] A challenge of future pharmacogenetic clinical trials will be to design the research in a way that provides information both on population variance and on individual repeatability.

Pharmacogenetics and pharmacogenomics allow one to look at research with a fresh perspective (i.e., a new way to ask old questions). In this context, it is important to clearly define research goals in terms of pharmacokinetics, drug safety, and drug efficacy. For example, pharmacogenetics can now be used to explain (1) the well-known differences in metabolism of 6-mercaptopurine by thiopurine methyltransferase that are due to distinct population genotypes and may result in at-risk subpopulations,[5] (2) the underlying rationale (KCNE2 genotype) for trimethoprim-sulfamethoxazole-induced toxicity in the form of prolongation in QTc in some individuals,[6] and (3) the interindividual variability in peak flow (efficacy) in asthmatics receiving albuterol due to polymorphisms in the beta-adrenergic receptor.[7]

Sample size requirements, as well as the role of ethnicity, will need thorough exploration for the integration of pharmacogenetics into clinical trials, depending on whether the trial goal is to identify efficacy response genotypes or exclude at-risk genotypes due to safety concerns. Study power, and thus sample size, will depend on allele frequency in the trial subjects, the effect of ethnicity on allele frequency, and the nature or type of gene action (e.g., dominant, recessive, additive, etc.).[8]

While human DNA variation as it relates to pharmacogenetic differential drug response is a static marker, RNA expression patterns as they relate to pharma-

cogenomic differential drug response are dynamic and change with disease state and in response to drug treatment. Therefore, expression profiling may serve as a prognostic marker of patient response based on pretreatment profiles and also provide molecular biomarkers of patient response by observed changes during treatment. Differential drug responses may result from individual heterogeneity of the molecular mechanism of disease that can be identified at the level of gene expression. RNA expression profiling can target specific genes using quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) or produce a global profile using DNA chip technology. The identification of RNA patterns that correlate with patient response will allow clinicians to select patients based on their predicted responses and avoid adverse reactions.

GENOMIC TESTING AND DATA QUALITY ISSUES

Single-Nucleotide Polymorphisms Assay Validation

Various assay technologies are used to genotype SNPs or detect variant alleles in human genomic DNA samples. These include but are not limited to the following methods: (1) direct sequencing, (2) primer extension-based methods, (3) hybridization methods (including DNA "chips" of various sorts), and (4) restriction enzyme analyses. Assay validation is generally accomplished using a panel of reference samples (standards) of known genotype. The most widely accepted assay technology is bidirectional dideoxy sequencing of DNA of individual alleles. However, on occasion, sequencing may be problematic because of a high guanine-cytosine (GC) content. An unresolved issue, not directly related to the technology, is evaluating the ability of a genotyping assay to identify homozygotes for rare alleles because of the difficulty in finding such individuals. The inclusion of such individuals in a reference panel may be impractical.

Haplotypes may be determined directly by sequencing individual, cloned chromosomal subsegments, or they can be derived by genotyping relevant SNPs in multigenerational families. Because these methods are considered impractical for routine application to clinical trial samples, various computational algorithms have been developed to infer haplotypes probabilistically, given the directly determined genotypes of individual, closely linked SNPs. Studies of large populations often reveal a number of less prevalent haplotypes. Comparing performance to standard assays can validate these methods. How uncommon haplotypes should be handled remains an unresolved issue.

With regard to the use of SNP and haplotype assay technology and the validation of these methods, there was consensus for a need for standardized reference materials, standards for assay validation, and specific regulatory guidance for validation criteria of the methods. There were various suggested mechanisms to address these needs, including the formation of national repositories for reference materials, specific cooperative efforts to develop standards and reference materials, and alternative strategies that could be used in the interim or in special circumstances. It was concluded that sequencing should not be the only standard that could serve as the basis for development of SNP and haplotype assays. Development of standards for use in this capacity should be a high-priority issue, although how this should be done was not delineated in the workshop. For now, ad hoc mechanisms such as interactions with the FDA through pre-IDE (preinvestigation of device evaluation) and pre-IND (preinvestigational new drug) meetings, use of recommendations from the American College of Medical Genetics (ACMG) and the College of American Pathologists (CAP), and the draft genetics template from the Secretary of Advisory Committee on Genetic Testing (SACGT) should be used until or unless more specific direction becomes available.

Reference Populations

Allele (and haplotype) frequencies typically differ among historically divergent populations. In pharmacogenetic studies, spurious associations may arise if the case (e.g., responder) and control (e.g., nonresponder) groups are drawn from genetically distinct subpopulations (e.g., based on race), even when matched for demographics or other characteristics. One approach to this problem is to test for association in cases and controls that are "genetically matched." Another is to use statistical methods based on allele frequencies at "reference" loci (e.g., in genes selected because they are unlikely to be related to drug response) to account for differences in genetic background. As pharmacogenetic data accumulate, there will be an increasing demand for population-specific data. However, there is a current need for the identification and use of reference populations, despite the inherent difficulties and ambiguities in defining such populations. In summary, the main point was that some form of defining reference population is better than none and better than each individual sponsor defining reference populations on a case-by-case basis.

Gene Expression Arrays

Gene expression arrays are being used nonclinically to explore associations with clinical outcomes to predict drug response, to better understand mechanisms of drug action, and to identify biomarkers of drug response that may be used to assess effectiveness or toxicity in clinical settings. The unique aspect of microarray gene expression technology is the ability to explore "genomewide" expression in a given sample. A huge number of measurable analytes from each experiment, even with the application of 99% statistical confidence limits, could yield a significant number of false-positive and false-negative signals. Gene expression microarray technology is evolving, and its performance is not standardized among numerous platforms now available with various probes designed from different gene sequences for the same targets. The scope of information that microarrays provide requires data reduction applications to analyze, visualize, comprehend, and communicate the data output. To use these data effectively and correctly, we need reliable experimental data, sound data reduction algorithms, and publicly available biologically linked reference information. With regard to validation, each feature of an array would not necessarily need validation, but subsets of features should be evaluated with respect to performance. The development of a reference standard, such as mixed-tissue aliquots of species-specific RNA, was recognized as important for increasing confidence in this technology.

There are varying interpretations as to whether, when, or what type of microarray data on lead compounds in drug development would need to be submitted to regulatory agencies as part of an IND. The format for presentation of such data is undefined. It is not clear if the data quality is sufficiently high and convincingly reliable, given the state of the technology, for regulatory authorities to make decisions on microarray data submitted under an investigational new drug application. Many of the workshop participants suggested that all microarray data conducted under either good laboratory practice (GLP) or non-GLP conditions should be submitted to the FDA if the lead compound is covered by an IND. If microarray databases are needed for regulatory scientists to place individual sponsor microarray experimental results into proper perspective, it is not clear how this database can be built since, to date, very little data have been submitted to the agency and publicly available databases have not matured. As databases become more populated with examples, and scientific knowledge and interpretation of gene expression responses expand, there is concern that the microarray data generated today may become more informative over time and might, therefore, affect assessments of products later during development, prior to making a final regulatory marketing approval decision. There was a strong suggestion, with general agreement, that the FDA needs to be transparent in collecting micro- array data and in using it for regulatory decisions. By sharing collective knowledge gained from reviewing across applications, the FDA can improve the quality of microarray use in drug development.

Even before gene expression microarray results can be interpreted with confidence, some critical assessment of the integrity of gene expression data is required. Concerns exist about the reliability, precision, accuracy, and interlaboratory reproducibility of data derived from global gene expression technologies. Numerous statistical, image analysis, pattern recognition, and data reduction clustering algorithms are being applied to microarray data. For screening compounds and improving understanding of drug effects on a target tissue, applying such approaches will provide a "bigpicture" overview of patterns based on drug class similarities but could also draw attention to the discriminating details that will distinguish among individual agents within a class. The biological interpretations, regulatory implications, and potential legal ramifications of such evaluations of product performance using global gene expression data are not well articulated at the present time.

While there may be efforts by end-users to establish standard procedures to consistently ensure and evaluate sample quality, as well as to calibrate microarrays and microarray instrumentation to ensure the integrity of their complete data sets, there is little regulatory experience to document the analytical reliability of these methods. There is a need for consensus on a standardized set of information required to fully annotate the data generated from microarray experiments. The degrees of quality control and validation that microarray manufacturers apply to their products, as well as the extent to which good manufacturing practices (GMPs) are relevant, are not always apparent. Information on manufacturing controls and post-manufacturing lot-to-lot quality control functional performance/pass-fail measures by microarray providers is important but lacking for many but not all manufacturers. There are little data from well-controlled clinical trials showing that gene expression microarray-based tests are appropriately precise, accurate, and reproducible between laboratories to be clinically valid for patient selection. Communication at the early stages of clinical development between regulatory agencies, diagnostic compa-

nies that are developing genome-based tests, and pharmaceutical companies developing drugs will enhance the possibility that test performance can be validated during clinical trials for utility in the clinical setting.

PRECLINICAL PHARMACOLOGY, SAFETY, AND TOXICOGENOMICS

Definitions

The development of genome-based technology and subsequent genetic information has led to an entirely new field in preclinical safety and pharmacology, and toxicogenomics. As with the terms *pharmacogenetics* and *pharmacogenomics*, there are many diverse definitions of *toxicogenomics*.[9] For the purposes of this workshop, *toxicogenomics* was defined as the application of genomic concepts and technologies to the study of drug toxicity. This definition includes studies of global approaches to study alterations of gene expression that influence, predict, or help define drug toxicity.

Overview of Toxicogenomics in Drug Development

Toxicogenomics is applied in modern drug development in three ways.

1. Predictive toxicogenomics. Used for screening in drug discovery and prioritization of lead compounds to improve the quality of compounds selected for development and to reduce total development time and cost.

2. Investigative toxicogenomics. Used to generate testable hypotheses. An example was presented of an application of investigative toxicogenomics to identify specific predictive biomarkers and better understand mechanisms of drug-induced vasculitis, which is a major safety concern raised by histopathology findings in animal studies with a variety of drugs. Gene expression markers of an acute phase response, normally considered a liver response, were seen in isolated mesenteric arteries from a rat model of fenoldopam-induced vasculitis. However, further studies were needed to identify specific biomarkers of vasculitis that will define human relevance and clinical significance.

3. Mechanistic toxicogenomics. Used to improve human risk assessment by expanding accessible interspecies biomarkers of toxicity and improving the understanding of interspecies similarities and differences. A case example was presented involving identification of gene expression alterations in the rat lens associated with formation of cataracts following administration of a 5-lipoxygenase inhibitor. The pattern of gene expression confirmed that the compound inhibited the synthesis of cholesterol and that lens crystalline structural proteins were targets of drug cataractogenesis. Further studies were needed to investigate interspecies relevance of the mechanistic-based markers of the onset and progression of cataracts.

These examples provide evidence that toxicogenomics can assist with investigations of toxicological mechanisms that involve generating and testing hypotheses, as well as identifying biomarkers useful for making interspecies predictions. However, it may not be appropriate for toxicogenomics to be used in a definitive manner at present to disprove hypotheses, confirm causality, predict safety, or replace any existing traditional safety assays. Definitive follow-up studies are needed to more fully evaluate and confirm the mechanistic insights generated by toxicogenomics. Applications of the technology, formation of strategic partnerships, peer-reviewed publication of toxicogenomic data, and clarification of regulatory and industry uncertainties represent ways to advance the usefulness of toxicogenomic technology.

Toxicogenomics to Predict Potential Human Toxicity

A major potential use of toxicogenomics is as a more efficient alternative to traditional preclinical toxicology studies, with an added value of providing a more mechanistic understanding of different types of toxicity. The assumption is that each chemical entity acts through particular mechanisms of action that will induce, either directly or indirectly, a unique and diagnostic gene expression profile under a given set of conditions.[10] In some cases, changes in early gene expression result in pathological outcomes.[11] Pilot studies in lower eukaryotes and mammals have demonstrated that it is possible to identify common gene expression profiles of drugs with similar mechanisms of action. For example, Waring et al[12] were able to use gene expression profiling to cluster hepatotoxins based on their mechanism of toxicity. In addition, with the growing availability of DNA chips from several different species, it may become possible for toxicity DNA expression measures to be extrapolated across at least some species, thus providing insight into more appropriate species selection for long-term toxicology studies.

However, the utility of toxicogenomics in replacing traditional preclinical toxicology studies is controversial, with many believing that gene expression profil-

ing should be used for hypothesis generation rather than for predicting or confirming toxicity or the lack of toxicity. Here the concerns are as follows:

1. that there are many different effects of toxicants aside from changes in gene expression, such as effects on membrane integrity, and these effects might not be extrapolated from single endpoint gene expression data;
2. in tissues with diverse cell populations, critical gene expression alterations in minor cell populations that will deleteriously affect organ or tissue function may be missed; and
3. without functional knowledge of what observable alterations in gene expression might mean, it is difficult to associate such changes with toxicity. To do so, there needs to be an understanding of how the molecular changes are manifest at the cellular and tissue levels, including correlation of changes of gene expression with changes in protein expression. As a result, there is a need for a multidisciplinary approach to understanding mechanistic toxicology.[13]

Routine Use of Toxicogenomic Data for Making Safety Decisions

There were many diverse opinions about the routine use of genomic data in toxicology studies and whether such studies should be conducted under GLP conditions. On one hand, many participants suggested that genomic data from animal studies are not sufficiently understood to be predictive of human toxicity and should not be routinely collected in GLP toxicity studies. In contrast to traditional toxicology data, it is not yet certain how to interpret genomic data, particularly when they are collected under various nonstandardized experimental conditions, at different points in time after dosing, and by using diverse genomic technologies. The value of non-GLP studies, however, is that they may be exploratory of drug safety or even hypothesis generating and, as such, might not need to be reported to the FDA under an IND. On the other hand, others suggested that all genomic data from animal studies with lead compounds should be part of the preclinical safety database, especially if these data provide biomarkers associated with pathology data, and should be integrated into the overall safety evaluation of a new molecular entity (NME). In some cases, expression microarray data will give a snapshot of activity in many different biological pathways of importance, but in terms of risk assessment, the specific pathways would have to be well understood in high functional detail to be predictive of human toxicity. This is especially true because gene expression changes do not necessarily correlate with changes in protein expression. In a few other cases, genomic data may be considered reportable as strong evidence of human adverse events. Currently, the FDA has not seen many preclinical genomic expression profiles in new drug applications, even though these genomic data may be regarded as toxicology or possibly pharmacology data that are required to be submitted to the agency.

Value of Toxicogenomic Data to Industry and Regulatory Authorities

Most workshop participants agreed that toxicogenomic data have their greatest utility in preclinical mechanistic studies when used in conjunction with other global "-omics" assessments to generate hypotheses and provide possible explanations of observable toxicity. The transition of toxicogenomic data from mechanistic to predictive will be an evolutionary process and not a revolutionary one. It is important for industry and regulatory agencies to work together to advance the science by sharing data and exchanging knowledge.

Use of Genomic Microarray Data with Standard, Short-Term Toxicology Studies to Guide Study Design or Species Selection for Long-Term Toxicology Studies

Workshop participants concluded that results from genomic studies are not mature enough to have predictive utility, especially when considering species selection for long-term toxicology studies. The main concerns were that genomic approaches are primarily used to evaluate toxicity in selected tissues, primarily liver and kidney. In addition, while the human, rat, and mouse genomes are fairly well characterized, the genomes for monkey or dog, two species that are vital in traditional preclinical safety studies, are not. However, genomic technologies may be useful in understanding the genomic makeup of "new species" such as in animal knockout models and may eventually provide a scientific rationale for not selecting rats or dogs under certain circumstances as the conventional target species in traditional toxicology studies.

Use of Reference Databases to Interpret Toxicogenomic Results and Predict Potential Human Toxicity

A contemporary example was presented that described the building of a reference toxicogenomic database us-

ing rat and human microarrays. A large database containing gene expression data, histopathology outcomes, and hematology and clinical chemistry data was constructed from samples of rat and human hepatocytes exposed in vitro and from samples from livers of rats exposed to commercially available pharmaceuticals and chemical toxicants at multiple doses and time points. By applying statistical and clustering algorithms to this database, sets of multiple discriminator genes were identified to predict human drug toxicity. While sets of "common toxicology markers" had predictive power, no single dysregulated gene demonstrated the power to predict toxicity. The database and modeling algorithms were then used to assess the gene expression changes observed at 6 and 24 hours postdose in livers from rats exposed to three acetylcholinesterase inhibitors. Doses of each chemical were chosen to achieve similar numbers of total expression changes but without observable liver pathology. A model was used to predict human liver toxicity for one but not for the other two inhibitors. Subsequently, using 18 blinded sets of 24-hour gene expression data that were generated by seven different laboratories, 15 of 18 sets were accurately identified ("predicted") as being derived from animals exposed to known liver toxicants, peroxisome proliferators, enzyme inducers, or vehicle. However, the ability to confidently make such assessments using data generated at different sites can be compromised if the data are not compared with each other or with information in the reference database. Thus, an assessment of a set of "invariant genes" offered potential for standardization among experiments. Standards were under development to harmonize different data sets. Preliminary data comparing common sets of compounds in vitro using primary rat hepatocytes and in vivo using rat liver samples supported the working hypothesis that coupling in vitro models with toxicogenomics was advantageous. This approach may then be used to screen and help pharmaceutical sponsors to prioritize drugs being considered for clinical development by helping predict and avoid compounds that may be more likely to lead to specific types of human toxicity.

Most workshop participants concluded that while much progress using internal, proprietary, or public toxicogenomic databases has been made, such databases are not yet evolved to be fully predictive of human toxicity. A key issue is how to interpret these databases. Many also cautioned that exploratory mining and cluster analyses of this database may digress from the basic biology of the chemical or drug since there are many different ways to query a database and arrange a clustering algorithm output.

Guidance for Industry on Toxicogenomics

The workshop participants concluded that it is premature for the FDA to write a guidance for industry since the science of genomics and its applicability to preclinical toxicogenomics assessment is rapidly evolving. If a guidance were to be developed in the future, questions and concerns would be raised about the following:

1. the purpose of the guidance,
2. recommendations on the format and analytical strategy for submitting genomic data,
3. the process to be followed and the action taken if a gene expression pattern seems to be linked to a toxic event,
4. whether a specific type of microarray platform for certain experimental conditions would be recommended,
5. whether a guidance would compel a company to engage in genomics research even if it was not prepared to do so.

PHARMACOGENETICS AND PHARMACOGENOMICS IN EARLY CLINICAL DEVELOPMENT (PHASE I/II TRIALS)

Background

Pharmacogenetics and pharmacogenomics are beginning to be integrated more into early clinical development programs and as important components in plans to achieve the overall goals of Phase I and II trials, such as safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD), dose ranging, drug-drug interactions, and potentially proof of concept for efficacy hypotheses.

Genetic variants have been identified in gene coding for proteins affecting the processes leading up to a drug response. For several drug-metabolizing enzymes, as well as some drug targets or related receptors, the frequency and functional significance of these variants have been explored in clinical studies. For most genes, the functional consequences of genetic variation remain poorly characterized or relatively unknown.

Candidate gene approaches, in which there is a sufficient hypothesis, are often used in early phase clinical trials. Because drug response is likely to involve variants from multiple genes and from genes not previously hypothesized to be involved in drug response, an alternative to a candidate gene approach is the use of "unbiased" or "hypothesis-generating" full-genome scans using an SNP map. This approach remains exper-

imental and may require larger subject numbers, but because of the larger number of markers examined, this approach could increase the cost, time, and efforts of the study. However, it is anticipated that technological advances will make these studies more affordable in the future. Such proof-of-concept research also involves significant use of novel biostatistical techniques in the assessment of linkage disequilibrium, haplotype maps, and the identification of informative SNP sets.

The number of controlled clinical studies seeking to identify and validate protein or RNA expression profiles as prognostic markers of drug response (e.g., cDNA microarray analyses of primary breast tumors and prognosis) lags behind traditional pharma-cogenetics. For example, an informal survey by the FDA examined more than 70 INDs and NDAs that integrated pharmacogenetic and pharmacogenomic tests into early phase development. Eighty percent of these applications were related to cytochrome P450 (CYP) DNA variants affecting drug metabolism. There were no examples of expression profiling identified in this survey.

Rationale for Use of Pharmacogenetics and Pharmacogenomics

A major goal of pharmacogenetic and pharmacogenomic analyses in early phase clinical studies is to identify subpopulations of subjects with an improved safety and efficacy profile. However, there are various views on how pharmacogenetics and pharmacogenomics could be used in the design of clinical trials. Some examples are as follows:

- Some believe that once a genotype or mRNA expression profile demonstrates a relationship with a phenotype of potential clinical importance, inclusion/exclusion criteria based on this association should be added to future studies. Others believe it is important to validate the association by replication prior to selecting patients based on genotype or phenotype.
- Some believe subjects potentially at risk for adverse events or nonresponse based on prior pharmacogenetic and pharmacogenomic studies could be excluded from future studies. Others believe that because these at-risk patients may receive the drug in the real-world setting, they should be included but possibly studied in a closely monitored setting.

Various approaches have been used to determine when blood samples should be collected for pharmacogenetic and pharmacogenomic research, ranging from collecting samples in all early phase studies to collecting samples in only those studies with narrowly defined and limited hypotheses. Another approach is to collect samples in certain types of studies (e.g., drug interaction studies) or in studies from certain development phases only (e.g., Phase I, II, or III). Some sponsors and contract clinical research organizations routinely collect blood to screen their volunteer panels to determine their genotype for important metabolic enzymes with known polymorphisms such as CYP2D6.

When Is It Appropriate to Use Pharmacogenetics and Pharmacogenomics for Inclusion/Exclusion Criteria (or Stratification), or When Is It Appropriate for Pharmacogenetic and Pharmacogenomic Relationships to Be Explored Post Hoc?

Participants concluded that the use of pharmacogenetics and pharmacogenomics in early Phase I would be an important step in generating information that could be confirmed or validated in Phase II. Most participants thought that pharmacogenetic and pharmacogenomic objectives in Phase I should be considered exploratory (not confirmatory) in nature and that pharmacogenetics and pharmacogenomics should not be used as inclusion/exclusion criteria for a single- or multiple-dose first-time-in-humans (FTIH) study. However, in a few circumstances for variants with well-established functional significance (e.g., alleles of CYP2D6, CYP2C19), a Phase I study may be confirmatory and still use small numbers of patients. Also, in drug interaction studies for drugs metabolized by polymorphic CYP enzymes (e.g., CYP2D6, CYP2C9, and CYP2C19), pharmacogenetics and pharmacogenomics should be considered as inclusion/exclusion criteria or for stratification.

Because of the availability of plasma concentration-time data following administration of many doses, Phase I provides a unique opportunity to explore the relationships between genetic variants in genes related to metabolic enzymes and transporters and the PK properties of the compound. Since Phase I dose-ranging studies include a broader range of doses of drugs administered to subjects (and possibly resulting in a higher rate of adverse events), and since some of these doses are rarely repeated in later trials, Phase I provides a unique opportunity to explore the relationships among genetic variants in the drug target and adverse events. In addition, when an appropriate tissue is available, Phase I provides an early opportunity to evaluate gene expression profiles to identify associations with safety and efficacy at a wide range of doses.

When pharmacogenetics and pharmacogenomics are included in Phase I, gene variants that should be studied should include those encoding for the activity

of drug-metabolizing enzymes and transporters, the drug target, and any pharmacological pathways related to important safety outcomes in healthy volunteers. In addition, if patients are studied, validated disease genes (that could affect drug response) should be evaluated. Investigators should attempt to identify trends and how well the clinical data correspond with preclinical data.

In regard to Phase Ib/IIa (dose-ranging and proof-of-concept [PoC] studies), there is a need to have some confirmation and/or validation before using pharmacogenetics and pharmacogenomics as inclusion/exclusion criteria or for stratification in a Phase Ib/IIa study. There could be a benefit to include all genotypes in PoC studies if all patients have a potential to benefit. However, the dose may require adjustment for subjects with genotypes resulting in reduced enzyme activity (e.g., CYP2D6).

Several participants felt that pharmacogenetics and pharmacogenomics should not be treated differently from any other covariate. In some cases, more confirmation would be required prior to using these data as inclusion/exclusion criteria (or for stratification), and pharmacogenetics and pharmacogenomics would be viewed as a covariate in the post hoc analyses.

In this regard, the following factors should be considered in the context of stratification or use as inclusion/exclusion criteria.

Therapeutic area. For life-threatening indications such as oncology, many participants felt that there is more willingness in clinical practice to stratify based on pharmacogenetics and pharmacogenomics. In other therapeutic areas in which many effective agents are already available and physicians are accustomed to titrating the dose in individual patients (e.g., depression), it was thought that there was less willingness to stratify based on pharmacogenetics and pharmacogenomics until differences in response are linked to genotype differences. For many other therapeutic areas (e.g., asthma and respiratory), there is some interest in using pharmacogenetics and pharmacogenomics for stratification.

Safety or efficacy. Many participants expressed that there is more willingness to stratify based on pharmacogenetics and pharmacogenomics for safety than for efficacy. For example, it was felt that for a CYP2D6 substrate (confirmed by in vitro and Phase I data), a stratified design in Phase II, with CYP2D6 poor metabolizers (PMs) being randomized to a standard or low dose, was appropriate. Consideration needs to be given to the seriousness and consequences of nonresponse or an adverse event and the ethical implications of these outcomes. Using pharmacogenetics and pharmacogenomics was suggested as being analogous to the study of patients with reduced renal function. In the case of low creatinine clearance, patients may be excluded from Phase II/III studies until a small study in the renally impaired population is conducted. Then the Phase II/III studies may be amended to include such patients, or these patients may continue to be excluded, depending on results of the small study.

Magnitude of effect relative to the therapeutic index. If a drug has a narrow therapeutic index, it may be appropriate to stratify based on pharmacogenetics and pharmacogenomics. If the therapeutic index is wide, some large effects may not be important enough to warrant stratification.

Stage of knowledge of the variants or expression profile. For gene variants with known functional significance, less information may be required prior to using pharmacogenetics and pharmacogenomics as inclusion/exclusion criteria or for stratification. For example, if Phase I results along with relevant in vitro data showed a reasonable relationship between CYP2D6 status and pharmacokinetic interindividual variability, then this would be considered a valid reason to stratify or use as inclusion/exclusion criteria in Phase II. For a drug with a narrow therapeutic index, stratification should be done by CYP2D6 status and not exclude PMs when all patients can benefit, although CYP2D6 PMs may require lower doses. For variants in the drug target in which the functional consequences are unknown, one should consider "all comers" and analyze data using the genetic variant as a covariate in a post hoc analysis. Even after one or two Phase I studies show that a variant in the drug target may affect drug response, there may not be enough information to exclude a population from Phase II studies, unless more is understood about the functional consequences of the genetic variants.

Allele frequency of the variant. If the allele frequency is common (e.g., > 15%), the optimal approach would be to conduct a single trial and stratify by genotype. However, if the frequency is low (e.g., < 10%), it may be less feasible to evaluate both genotypes in the same study because recruitment of subjects with the minor allele would be much slower than for those with the dominant allele. Two separate trials would allow the drug to be progressed more quickly in the dominant population. However, if separate studies were conducted, there would be less information about the analytical and clinical sensitivity and specificity of a pharmacogenetic and pharmacogenomic test. There may be some cases when safety data, but not efficacy

data, from a pharmacogenetic and pharmacogenomic subgroup may be studied or other cases when a dose-ranging study in the minor pharmacogenetic and pharmacogenomic subgroup may be conducted postmarketing. One should not assume that PMs should be treated the same for all substrates (i.e., there is a need for case-by-case review).

Dose response. If there were a rationale for pharmacogenetics and pharmacogenomics to affect dose response, then the optimal approach would be to evaluate dose response in both groups (e.g., CYP2D6 extensive and poor metabolizers).

Other factors. These include factors that need to be considered, such as (1) biological validity of results (i.e., are the results consistent with theoretical or in vitro data?), (2) the extent to which they have been replicated, (3) the number of candidate genes or SNPs affecting the phenotype, (4) the need for the optimal timing and special tissue handling for RNA expression profiling, and (5) the validity of supervised machine learning programs, if used for RNA expression profiling.

When or How Should Samples Be Collected for Genotyping/mRNA Expression Profile/SNP Profiling?

While pharmacogenetic and pharmacogenomic information could be useful in Phase I/II studies, the science is not at the point where samples should be collected in all studies. If there is a strong scientific rationale for obtaining pharmacogenetic and pharmacogenomic data, then the samples should be collected. However, it should be kept in mind that if the results of Phase I/II studies show the value of sample collection, it might be too late to initiate sample banking.

Some examples of scientific rationale to perform pharmacogenetic and pharmacogenomic studies include (1) a compound metabolized by a polymorphic enzyme, (2) drug interaction studies involving any substrates with polymorphic enzymes (e.g., probe cocktail), and (3) variants in the drug target or pathways known to affect safety (e.g., long QT genes).

If the metabolism of a compound is not fully understood during FTIH studies, pharmacogenetic and pharmacogenomic samples should be collected from early Phase I studies to provide the ability to examine genotype-outcome associations that may be pertinent in the later development phases.

Although DNA sample collection is independent of time, RNA samples require critical timing of the sample and more time-critical tissue processing. Thus, DNA collection may be easier to justify scientifically than RNA. Some believe RNA sample collection should only be done when there are preclinical data to suggest optimal timing. Others believe that optimal timing in animals in preclinical studies might not be predictive of optimal timing in humans; therefore, the stringency for RNA should be no different than for DNA. With RNA, one must consider what tissue is available, which for most studies is linked to blood, skin, or a pathological tissue biopsy.

How Will Preknowledge of Genetic Susceptibility to Pharmacologically Predictable Adverse Events or Nonresponse Obtained in Early Phase Development Affect the Risk/Benefit Assessment and Product Labeling?

If a pharmacogenetic and pharmacogenomic subgroup had improved efficacy and/or safety, how the information is included in the label would be dependent on the risk/benefit assessment, with life-threatening events being considered different from less severe adverse events. The pharmacogenetic and pharmacogenomic relationship may be described under "Clinical Pharmacology," "Indications and Usage," "Warnings or Precautions," or "Dosage and Administration." The label would inform clinicians that there is a genotype or phenotype test available, but it may not have to be done prior to dosing unless warranted. If the diagnostic test must be done prior to dosing, then it may be stated under "Indications and Usage" (e.g., approved labeling for Herceptin® [trastuzumab]).

The decision of whether a pharmacogenetic and pharmacogenomic test is necessary prior to dosing will be dependent on many factors, including the following: (1) if safety, the seriousness of the adverse event; (2) if efficacy, the consequences of nonresponse; (3) the incidence of the clinical outcome; (4) the variability in the clearance of the drug; (5) how well an adverse event can be managed (i.e., if it can be recognized easily without a genetic test and whether toxicity is reversible); (6) need for education of physicians and third-party payers; and (7) feasibility of accessing and using the test in clinical practice. For example, oncologists would be more likely to use a pharmacogenetic and pharmacogenomic test prior to treatment if it would improve efficacy and/or safety. On the other hand, an allergist who has a patient with allergies may want immediate relief for the patient and is unlikely to wait several days to a week before writing a prescription so that a genetic test can be run to predict whether the patient is at risk for a drug-related headache.

PHARMACOGENETICS AND PHARMACOGENOMICS IN LATE CLINICAL DEVELOPMENT (PHASE III TRIALS)

Background

Clinical studies intended to evaluate the safety and efficacy of new drugs in development generally involve large numbers of patients and are critical to the evaluation and approval of a new drug. The role of pharmacogenetics in late clinical development (Phase III trials) is to focus on either the further exploration of genetically defined populations or the confirmation of pharmacogenetic data from these populations to support efficacy, safety, and/or the labeling of the drug. When subsets of patients respond to a drug differently, clinical trials can be designed to take advantage of these differences. For instance, trials could be limited to individuals who are more likely to receive a clinical benefit or less likely to suffer an adverse response. However, in so doing, the trials may not adequately determine the safety and efficacy of the drug in all individuals who might be exposed to it. Approaches to having the study power for genotypes need to be reconciled to take into account the need for a thorough assessment of the beneficial and harmful effects of the drug once it is in clinical practice.

In another potential use of pharmacogenetics, drugs that have not been shown to be adequately safe and effective in a clinical trial on an entire population may achieve that goal in a genetically defined subset of the population. Since genotypes do not change in an individual, it should be possible to detect a group who will derive a clear clinical benefit by reanalyzing the data from a previously completed trial through genetic stratification. In this way, a drug that is otherwise unregisterable might be approved for the genetically defined group. However, this use of pharmacogenetics poses a number of questions for which there are no definitive answers at present:

- Are there conditions under which such a retrospective study would be acceptable for drug registration?
- To what extent do these studies need to be replicated?
- Can the data from such studies, not specifically designed as a pharmacogenetic study or even from investigative studies with no genetic hypothesis, be used for registration?
- What constitutes acceptable data in such studies?
- How do these data apply from one racial or ethnic group to another when there may be significant differences in allele frequencies between groups?

To date, there appears to have been relatively little application of pharmacogenetics in Phase III studies and subsequently in regulatory decision making. Few examples exist that can be used to assess various models for pharmacogenetic trials. The workshop focused discussion on the types of trials that might be conducted and to estimate the likely reception that such trials might receive. In practice, any such trial, especially those with novel pharmacogenetic approaches, should be discussed in detail between the sponsors and the regulatory authorities and would likely be evaluated on a case-by-case basis. Only after numerous examples exist will it be possible to develop a general guidance for industry that will provide recommendations to direct the conduct of these trials.

How Will Conducting a Clinical Trial in a Pharmacogenetically Defined Subset of Patients Influence the Collection of Adequate Safety and Efficacy Data Prior to Registration?

While the integration of pharmacogenetics into clinical trials is based on newer technologies and newly discovered knowledge of the genome, the issues raised by using pharmacogenetic information in selecting patients is very similar to the issues raised by other forms of enrichment. The utility of pharmacogenetic data will depend on the following:

- the robustness of the study results (i.e., how well established is the association between the pharmacogenetic enrichment biomarkers, drug exposure, and clinical endpoints?),
- whether patients can be readily identifiable in a practice setting (i.e., can they be preidentified with readily available tests or assessments?), and
- whether there is an expectation that the drug will be used only in this enriched population in practice.

In many cases, pharmacogenetically defined patient groups will not display a dichotomous relationship between their genetic status and their response to treatment but rather will show a gradation of responses. The smaller the difference in response (efficacy or safety) between the genetically defined group and the general population, the more important it becomes to compare the response in patients who are positive for the genetic biomarkers and negative for the genetic biomarkers. This will be necessary not only to help establish the clinical utility of the biomarkers but also to establish an overall risk/benefit ratio for the treatment if used in the general population, including those negative for the genetic

biomarkers. If there is reasonable expectation that drug use would occur in the wider population (with or without knowledge of the genetic status of the patient), or if availability of the relevant pharmacogenetic test may be limited, preapproval testing in the negative population will be necessary to ensure that the overall risk/benefit of the drug in the general population is acceptable.

The amount of clinical data needed to confirm the clinical value of a pharmacogenetic biomarker will differ depending on the prior knowledge of the genetics involved and the mechanistic understanding of the way the drug therapy works in relationship to the genetics. For example, polymorphisms in a receptor that is understood to affect drug binding will require less data for confirmation than will polymorphisms in genes whose biological role is unknown.

In most cases, there appears to be no overarching ethical reason to exclude certain subsets of patients from pharmacogenetic-based clinical trials, even those who may be at increased risks of a particular toxicity. However, each situation would need to be considered in context, and the decision to include such patients would depend on the severity of the disease being treated, the severity and the reversibility of the known or anticipated toxicities, and the current strength of evidence on the predictive value of the pharmacogenetic assessment for that treatment and disease.

Finally, for regulatory authorities to approve a drug only for a defined pharmacogenetic subset of patients, especially if tested only in that subset for safety and efficacy, it is highly likely that a clinical diagnostic assay should be available at the time of approval of the drug. While ideally this would be an approved in vitro diagnostic kit, this is not an absolute necessity since many hospital or laboratory tests are not kits but are developed and validated within the testing laboratory ("home brews"). In situations when regulatory agencies will not formally regulate the test, it is advisable to involve experts such as the College of American Pathologists in the consideration of test standardization and other quality control aspects.

Under What Circumstances Can a "Pharmacogenetic Clinical Trial" Be Conducted Using Samples and/or Clinical Data from a Previously Completed Drug Clinical Study?

Discussion at the workshop focused on whether the results from a pharmacogenetic study can be used for drug evaluation and registration if the clinical data came from a previously completed study not originally designed for genetic stratification. Such a study would be both retrospective with respect to the collection of samples and clinical data and prospective with respect to testing a genetic hypothesis. Initially, there were two contrasting views. On one hand, some maintained that any trial that had already been unblinded was a retrospective trial and so would not be acceptable as confirmatory evidence for regulatory approval. However, it would be an acceptable hypothesis-generating trial. On the other hand, others viewed that such a trial could have its own design, separate from the original study protocol, and that the analysis would be thoroughly blinded with respect to the clinical outcomes and so should be an acceptable study for drug registration.

Specific considerations that emerged from this discussion were the following:

- While the original study would be adequately powered for the expected outcome, the genetic study might be underpowered. However, it was pointed out that, depending on the degree of association of the genotype with the response, power in the genetic study could be sufficient. Statistical power in the genetic study could be determined at the time of protocol design if there was sufficient preliminary knowledge of the association.
- Caution is needed because the original study may have been designed for a particular population, but the genetic study comprises a restricted, different population such that the randomization may not have been considered appropriate for the genetic study.

Another key factor with regard to the acceptance of a genotype study is the biology of the gene used as a marker for stratification. In cases in which the genetic biomarker is plausibly linked with the response of interest (e.g., a polymorphism in the drug target or a drug-metabolizing enzyme), the retrospective-prospective trial may provide data that would be useful in the evaluation of the drug. Nevertheless, it was generally accepted that, under any circumstances, an independent prospective trial with genotyping included in the basic study design would be necessary. The requirement for single or multiple confirmatory trials could differ depending on whether the relevant outcome was efficacy or safety and the strength of the association.

Other important issues that need to be considered are the following:

- Careful collection and storage of the DNA samples would be necessary, both from a stability standpoint (generally not a problem) and for tracking and inventory.
- It is also crucial that the samples be collected with adequate informed consent for whatever genotyping may later take place.
- The nature of the test to be used to genotype patients in the trial and subsequently in general use is also critical.

This is especially so in tests that might involve multiple sequences or multiple genes.

There was general agreement in the workshop that a trial involving genotypic stratification using clinical data from a completed study might be considered as evidence for regulatory purposes if it were to meet several specific conditions or criteria. Those conditions would involve having (1) adequate power in the genetically defined subsets, (2) appropriate informed consent, (3) proper sample handling procedures, (4) an adequately validated genotyping test, (5) clear biological relation between the response and the gene(s), (6) a prospective hypothesis for assessing the response-genotype relationship, and (7) follow-up by an independent prospective trial. In the absence of these conditions, the prospective-retrospective trial would be useful only for purposes of hypothesis generation. Given the complexities of the possible study designs and genetic associations, the determination that a retrospectively genotyped study would be acceptable for regulatory purposes should be considered on a case-by-case basis.

Is It Appropriate or Possible to Use Anonymized Samples or Data in Registration Studies?

Several processes are currently being used during drug development for the collection of DNA samples and associated patient data. One recent article[14] and one regulatory guidance[15] summarize and describe terminology and processes for the collection of samples and data. Concerns exist that genetic data might be used discriminatorily, for instance, for employment or insurance. Therefore, procedures for collection and data generation have been developed to provide additional confidentiality and privacy to patients by dissociating genetic data from patient identifiers. The workshop discussion focused on the merits of two types of pharmacogenetics data: (1) data that can be linked back to a patient's code number and thus to a patient identity (coded, single-coded, de-identified, double-coded) and (2) data that cannot be linked back to a patient's record (anonymized, anonymous).

From the discussions, several important points were highlighted:

- From a regulatory standpoint, it was emphasized that data to be used for registrational purposes require an audit trail back to the medical record, as is standard for all other data submitted for this purpose. Anonymous or anonymized data[14] are not auditable and would not be appropriate for registrational use.
- Eliminating the link between samples or data and the patient record provides additional privacy and confidentiality as long as there is strict adherence to standard operating procedures that prevent matching of multiple recorded clinical phenotypes to reidentify an individual. Such samples are not auditable but are useful for research purposes and might be especially suited for hypothesis generation.
- Anonymized or anonymous data and samples can be collected in registrational studies but cannot be used to support the primary objective of the trial in which they were collected.
- Samples without a link to the patient record cannot be used to validate and support new results and hypotheses discovered during later stage development of a drug, for example, in validating the relationship between a diagnostic reagent and clinical response observed in subsequent trials or during postregistrational use.

Most workshop participants recommended that data to be used to support drug safety and efficacy for registration should have a link to the patient record. In addition, samples linked to patients' data have potential for use in subsequent validation studies for uses unanticipated at the outset of drug development.

What Characteristics of Association Data Are Expected in Exploratory or Registration Studies?

Until there is greater experience with pharmacogenetics, the participants concluded that specific requirements for the use of pharmacogenetic data in exploratory drug development or in registration trials should be defined on a case-by-case basis. Currently, there are few examples of pharmacogenetic-based drugs on which regulatory guidance criteria can be based. In general, the requirements for using predictive genetic biomarkers are similar to those for nongenetic biomarkers and should be based on equally compelling scientific concepts and arguments.

Several limitations are inherent in applying pharmacogenetic associations derived from case control data sets, even if statistically significant results are observed. Replication of pharmacogenetic associations identified in an initial study population may not always be possible in separate studies and populations. Association studies also pose several inherent statistical challenges,[16] and sponsors are unlikely to repeat large Phase III trials solely for the purpose of confirming the genetic results. Nevertheless, the confirmation of identified genetic associations is mandatory if pharmacogenetic biomarkers are to be included in drug labeling. To accomplish this goal, researchers should identify such biomarkers in smaller exploratory studies and then confirm them in larger trials in which sta-

tistical validation can be achieved. Informed consent for genetic studies and routine collection/archiving of genetic samples also should be considered, whether there is a rationale or not, early in the drug development process[17] and should be adequate for future marker identification, drug regulation, and assay development. This will allow for genetic analysis of responses that may appear only at later stages of drug development or marketing.

While such markers may be widely employed in the design of exploratory trials to enable validation of pharmacogenetics signals and to provide "proof of concept," the specific characteristics of genetic association data for registration and labeling of a drug will depend on the context of the experimental questions and the pharmacogenetics objectives to be addressed. For example, a predictive genetic biomarker of drug response should be sufficiently common in applicable patient populations, and the degree of enrichment of response afforded should be clinically meaningful. These requirements, in relative terms, will depend on clinical factors, including the nature and severity of disease and the extent of the unmet medical need, if any. Use of genetic biomarkers to exclude individuals or populations at risk for adverse events will require rigorously validated genetic associations, especially for serious toxicity. Acceptability for false-negative results of genetic biomarkers to predict drug toxicity will be very low. Acceptability for false positives may be higher, especially if alternative therapies are available. It was pointed out that while such biomarkers may be widely employed in the design of exploratory trials to enable validation of pharmacogenetics signals and to provide proof of concept, the regulatory requirements for application of such biomarkers in registration trials or in drug labeling are uncertain and yet to be defined. The confidence with which any pharmacogenetic biomarker can be applied in clinical studies or practice will be enhanced by supportive biologic experimental data providing a credible scientific rationale for a pharmacogenetic hypothesis.

If Exploratory Pharmacogenetic Research Is Performed during the Clinical Development of a Compound outside the Basic Clinical Study Design, under What Circumstances Would the Results of a Pharmacogenetic Analysis Warrant Reporting to a Regulatory Agency?

FDA regulations (e.g., CFR312.23) cover the reporting obligations for exploratory studies of this type. Pharmacogenetic data are to be considered a part of the drug development process and should not be segregated or differentially reported and, if relevant to the safe and effective use of a product, should be reported to the appropriate regulatory agencies for review. The course of action by the regulatory agencies in response to such data will depend in part on the quality of these data (i.e., the validation of the study methodology) and statistical power of any associations. Future actions may be modified in the near term by the concept of a "safe harbor" for exploratory genomic data (discussed below), when and if this concept becomes better defined and accepted as suggested by the FDA.

What Would Be the Implications for Ethnic Diversity in Clinical Trials?

Throughout the workshop discussion, as well as in scientific and nonscientific literature, the terms *ethnicity* and *race* are often used interchangeably. There are sensitivities surrounding these terms, and trying to get consensus on the definitions was beyond the scope of the workshop. It was recognized that both risk for disease and desirable and undesirable drug responses are variable across the human species, and the variability is dependent on both genetic and environmental factors, many of which may differ between populations.

However, the link between a particular genotype and a clinical phenotype can only be established by analysis of individuals. This information may be best uncovered through understanding genetic diversity within a given population. Observation of phenotype-genotype relationships in different "population groups" should be driven by analysis of genetic variation and clinical parameters in parallel with classical assessments that are socially and culturally acceptable. There are several recent reviews and discussions covering genetic diversity related to risk of diseases and the probability of drug response in different populations.[18,19]

REGULATORY PERSPECTIVES ON PHARMACOGENETICS AND PHARMACOGENOMICS

"Safe Harbor"

Pharmacogenetics and pharmacogenomics are being integrated into drug development by most, if not all, pharmaceutical research companies. Submission of pharmacogenetic and pharmacogenomic data to regulatory agencies has been limited, but regulatory authorities are very interested in enabling this technology because of its potential to improve the drug development process and public health.

Regulatory agencies are encouraging pharmaceutical companies to explore and apply toxicogenomic, pharmacogenetic, and pharmacogenomic technologies in drug development and to submit such data for regulatory review. However, sponsors have concerns that genomic-based data would be acted on prematurely by regulatory authorities to interfere with or add to the cost of drug development. The FDA expressed a willingness to explore the feasibility of a "safe harbor" for genome-based data on both lead and nonlead compounds. This term was used to describe a process in which exploratory genomic-based data generated and submitted under an active IND would be submitted to the FDA but would not undergo formal regulatory review until more is known about the validity of the technology used and the appropriate interpretation of the data. An example of exploratory genomic-based data that might have tenuous or uncertain interpretation is the activation or overexpression of an oncogene in a DNA microarray assay in rat cells. The linkage of this event to human adverse events is unknown or extremely uncertain and may be valuable only for generating new hypotheses but would not be appropriate as the basis of a regulatory decision. The value of a safe-harbor toxicogenomic database would be (1) to gain a better understanding of the relationship between RNA expression biomarkers and pathology, (2) to discover integrated knowledge from data mining across submissions, and (3) to learn how to interpret different data sets over multiple technology platforms.

There are many details of a safe harbor that would have to be worked out, including the format for the safe-harbor presentation of data, the process for submitting such data, and the procedure for regulatory review.

The FDA acknowledges the importance of having a transparent process for decision making related to the transition or bridging of genomic data from a safe harbor to a database subject to a formal regulatory review. One suggestion by the FDA was to cosponsor additional public meetings or workshops as part of a process to develop guidance on safe harbor or on pharmacogenetics and pharmacogenomics in general.

FDA Perspective on Genotyping and Clinical Efficacy/Safety Trials

While genomic-based technology may be at an early stage, the issues and questions surrounding pharmacogenetics and pharmacogenomics are not necessarily new. For example, genotyping in clinical trials represents a form of mechanistic or empirical "enrichment" (i.e., a process for selecting or excluding individual patients or groups of patients for clinical trials). Regulatory agencies are quite familiar with criteria that have been used in the past for routinely enriching clinical efficacy or safety trials for drugs such as inotropic agents, topical nitrates, antiviral drugs, and antibacterials and in diseases such as hypertension, stroke, and sepsis. A well-known example of enrichment is the enrollment of women with breast cancer who overexpress the HER-2 protein in clinical trials of trastuzumab (Herceptin®).

In the broadest sense, genotyping can also be used in proof-of-principle trials and for individualization and modification of dose based on genotype. Associations between genotypes and clinical outcomes can also be explored retrospectively, as was the case for abacavir,[20,21] but these are mainly exploratory and would need confirmation in a clinical trial prospectively. An important distinction was made between two types of genome-based enrichment: the first type (preferred) is when there is a well-understood, genome-based pathophysiological ability to select responders and nonresponders, and the second type is when genomic-based predictions of differences in response are observational, but the basis for pathophysiology is not well understood. Some key points were (1) that if a treatment cannot be limited to a genomically defined patient population, then effects in the overall population, especially safety in the nonselected patients, need to be determined to assess the true risk/benefit of the drug, and (2) confirmation of outcomes from genomically guided clinical trials almost always need repeating in a prospective trial to be persuasive. Several study designs for clinical pharmacogenomic studies were discussed, and while all were acceptable, it is important to clearly consider the objectives of the investigation (e.g., bioanalytical performance of a genome-based diagnostic test, clinical utility of a diagnostic test, safety in nonselected patients) in deciding on the design of the clinical trial.

European Agency for the Evaluation of Medicinal Products (EMEA) Perspective on Pharmacogenetics and Pharmacogenomics

It is important to consider the impact of the known pharmacogenetics (e.g., polymorphism in genes that code for drug-metabolizing enzymes) in dealing with the new pharmacogenomics in delineating a way forward. Concern was expressed about the high percentage of patients who do not respond or respond incompletely to drugs, as well as the substantial morbidity and mortality due to adverse drug reactions, and that perhaps greater attention should be paid to the known

pharmacogenetics. Principles related to genes and drug response are already included in several European and international regulatory guidances. It was pointed out that the new pharmacogenomics is in a transitional phase where genome-based science is moving from research to the clinic and from exploratory to confirmatory research. Regulatory agencies are preparing themselves for the anticipated increase in submissions that include pharmacogenetics or pharmacogenomics. Within Europe, a Committee for Proprietary Medicinal Products (CPMP) expert group was formed in April 2001 and a CPMP position paper on terminology[15] was released for consultation and comment in December 2001; this position paper was adopted by the CPMP in November 2002. Two concerns were expressed in regard to post hoc genomic-based association studies, similar to the FDA concerns: first, the reliability and repro-ducibility of findings and, second, the need to confirm findings in a prospective clinical study that defines the sensitivity and specificity of the genetic marker. It was emphasized that regulatory agencies and industry must continue to maintain dialogue as the field moves forward quickly and that regulatory agencies should consider future guidances depending on the level of scientific knowledge, experience, and applicability of pharmacogenetics and pharmacogenomics.

SUMMARY AND CONCLUSIONS

The workshop concluded with a panel discussion, along with questions and answers from the audience related to future deployment of pharmacogenetics and pharmacogenomics in drug development and regulatory decision making. The broad conclusions from the workshop were as follows:

1. Pharmacogenetics and pharmacogenomics should be considered in all phases of drug development because these sciences will only improve our understanding of the safety and efficacy of new drugs and improve the development of optimal dosing regimens. The use of genetic and genomic technologies, however, should be driven by science and applied where it can improve decision making from lead compound selection to allowing market access.
2. Greater clarity on the most appropriate applications of pharmacogenetic and pharmacogenomic biomarkers in drug development is needed to advance the field.
3. Continued dialogue between academic researchers, industry scientists, and regulatory agencies is needed to help guide strategies for exploiting pharmacogenetic and pharmacogenomic information to optimize risk/benefit ratios.

The challenge of advancing pharmacogenetics and pharmacogenomics has many dimensions: scientific, economic, social, and political. In light of the huge potential for these sciences to improve the drug development process and address future public health needs, professionals from academia, industry, and regulatory agencies need to work together to achieve the potential that pharmacogenetics and pharmacogenomics offers to society. Given this challenge and the impact that these sciences can have as they evolve rapidly in the upcoming years, there are plans to conduct follow-up public workshops that will focus on subsets of issues identified in this workshop to develop a blueprint for a way forward.

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