2002 WORKSHOP ON PHARMACOGENETICS/PHARMACOGENOMICS IN DRUG DEVELOPMENT AND REGULATORY DECISION-MAKING

MAY 16-17th, 2002

University of Maryland
Shady Grove Conference Center
9630 Gudelsky Drive
Rockville, MD 20850-3480

Sponsored by the FDA, and companies represented on the Pharmaceutical Research and Manufacturers Of America(PhRMA) Preclinical Safety Committee (DruSafe), and the Pharmacogenetics Working Group (PWG).

Organizing and Program Committee Co-Chairpersons

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WORKSHOP ON
PHARMACOGENETICS/PHARMACOGENOMICS
IN DRUG DEVELOPMENT
AND REGULATORY DECISION-MAKING

<u>Intended Audience</u>

This workshop is intended for scientists and clinicians with an interest in the role of pharmacogenomics and pharmacogenetics in drug development, and for regulatory scientists in these disciplines who are responsible for regulatory decision-making. These include pharmacologists, toxicologists, chemists, biologists, clinical scientists, biostatisticians, and physicians.

<u>Scope of the Workshop</u>

The development of technologies that provide genomic or genetic information to predict a drug's efficacy or toxicity and to explain inter-individual differences in response to a drug has accelerated in the past 5 years. This workshop is focused on the regulatory implications and related questions resulting from the application of these technologies rather than on the technical details of the technologies themselves. The intent of this workshop is to provide a forum for discussion on the use and application of genetic science and high-capacity technologies, which include monitoring of gene expression and identification of genetic heterogeneity, with specific application in nonclinical and clinical studies conducted as part of the drug development process. Issues specific to other applications of rapidly evolving, high-capacity "-omics" technologies such as proteomics or metabonomics, however, will not be addressed in this workshop. It is envisioned that the issues addressed and raised will provide a basis for future regulatory guidance.

<u>Goals of Workshop</u>

1. Educational: to provide participants with an understanding of the state-of-the-art pharmacogenetic and pharmacogenomic issues that are relevant to drug development and regulatory review.
2. Awareness: to determine areas of agreement or disagreement on issues of genomic-based drug development, and where there is need for additional information.
3. Direction: to develop a platform for encouraging the application of pharmacogenetic/pharmacogenomic information to drug development and regulatory review: "where are we now, where do we want to go, and how do we get there?"
4. Guidance: to gather input on how the Agency could best help or promote Pharmacogenetic/Pharmacogenomic science and technology and its use in genetic/genomic-based drug applications, e.g. to develop a guidance.
5. Terminology: to begin to promote the use of a set of common and well understood terms based on harmonized definitions.

ORGANIZING COMMITTEE

Committee Co-Chairpersons	Larry Lesko, Ph.D. Director Office of Clinical Pharmacology and Biopharmaceutics CDER, FDA	Ronald A. Salerno, Ph.D Director Experimental Medicine Liaison Worldwide Regulatory Affairs Wyeth Research
Committee members	Shiew-Mei Huang, Ph.D. Deputy Office Director for Science, Office of Clinical Pharmacology and Biopharmaceutics CDER, FDA. Jerry Collins, Ph.D. Director Office of Testing and Research CDER, FDA Frank Sistare, Ph.D. Director Division of Applied Pharmaceutical Research Office of Testing and Research CDER, FDA Joseph Hackett, Ph.D Associate Director, Special Programs Division of Clinical Laboratory Devices Office of Device Evaluation CDRH, FDA David Essayan, M.D. Medical Officer Office of Therapeutics Research and Review Division of Clinical Trial Design and Analysis CBER, FDA James T. MacGregor, Ph.D. Deputy Director National Center for Toxicological Research FDA	Andrew Dorner, Ph.D. Director Molecular Medicine and Pharmacogenomics Wyeth Research Joanne Killinger, Ph.D. Vice President Drug Safety and Metabolism Wyeth Research Timothy Anderson, Ph.D. Vice President Drug Safety Evaluation Pfizer Global Research and Development Peter Shaw, Ph.D. Associate Director Pharmacogenetics Bristol-Myers Squibb Pharmaceutical Research Institute Brian Spear, Ph.D. Director Pharmacogenetics Abbott Laboratories Gillian Woollett, Ph.D. Associate Vice President Biologics and Biotechnology PhRMA

PROGRAM COMMITTEE

Committee	Program Chairperson	Session or Track
Session Chairpersons	Ronald A. Salerno, Ph.D.	Session I: *Expectations/Terminology and Keynote address*
	Frank Sistare, Ph.D.	Session II: *Toxicogenomics and Pharmacogenomics*
	Celia Brazell, Ph.D. Genetics Science and Technology Senior Advisor, Genetics Research GlaxoSmithKline	Session III: *Pharmacogenetics*
	Larry Lesko, Ph.D.	Session IV: *Regulatory Perspectives*
	Shiew-Mei Huang, Ph.D.	Session V: *Workshop Tracks*
	Larry Lesko, Ph.D.	Session VI: *Workshop Track Summaries*
Track Chairpersons	Joseph Hackett, Ph.D	Track I: *Genomic Testing and Data Quality Issues*
	Timothy Anderson, Ph.D.	Track II: *Preclinical, Pharmacology and Safety*
	Shiew-Mei Huang, Ph.D.	Track III co-chair: *Early Clinical Development*
	Virginia Schmith, Ph.D. Medical Genetics Advisor, PK/PD Medical Genetics GlaxoSmithKline	Track III co-chair: *Early Clinical Development*
	Peter Shaw, Ph.D.	Track IV co-chair: *Clinical Trial Safety and Efficacy*
	Donald Anderson, M.D. Director of Genomics, Pharmacogenomics Pharmacia Corporation	Track IV co-chair: *Clinical Trail Safety and Efficacy*

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Workshop on Pharmacogenetics/Pharmacogenomics in Drug Development and Regulatory Decision-Making
May 16, 2002 Day 1 Program

Time	Topics/Speakers
08:15-08:30	**Call to order, brief introduction to Workshop** *Session I Chair: Dr. Ronald A. Salerno, Wyeth Research*
08:30-08:45	**"Workshop Expectations"** **Steve Galson, M.D.** Deputy Center Director CDER, FDA
08:45-09:15	**"Pharmacogenetic and Pharmacogenomic Terminology"** **Brian Spear, Ph.D.** Director, Pharmacogenetics Abbott Laboratories
09:15-10:00	**Keynote address:** **"Shotguns to Rifles: Pharmacogenetics in Drug Discovery and Treatment"** **Jeffrey M. Drazen, M.D.** Editor-in-Chief, NEJM Professor of Medicine, Harvard Medical School
10:00-10:30	**Break** *Session II Chair: Dr. Frank Sistare, CDER*
10:30-11:00	**"Use of Toxicogenomics to Predict Potential Human Toxicity"** **Donna L. Mendrick, Ph.D.** Vice President of Toxicology Gene Logic, Inc.
11:00 – 11:30	**"Toxicogenomics in Drug Development: Where we are and Where we are going"** **James T. Mayne, Ph.D.** Group Director, DSE Laboratories Pfizer Global Research and Development
11:30- 12:00	**"Pharmacogenomics in Phase I/II Clinical Trials: Application of Expression Profiling in Clinical Testing of Immunomodulatory Treatments of Psoriasis"** **Andrew Dorner, Ph.D.** Director of Molecular Medicine Wyeth Research
12:00 – 1:10	**Lunch**

	Day 1 continued
1:10 – 1:15	*Session III Chair: Dr. Celia Brazell, GSK*

1:15 – 2:00	*"Pharmacogenetics in Phase I and II Clinical Studies: Utility and Issues"*
	      Wayne Anderson, Ph.D.
	      Director, Exploratory Clinical Target Genetics
	      GlaxoSmithKline

2:00 – 2:45	*"Pharmacogenetic Scenarios for Phase III/IV Trails in Subjects with a Complex Trait"*
	      Baltazar Gomez-Mancilla, M.D., Ph.D.
	      Director of Clinical Genomics
	      Pharmacia Corporation

2:45 - 3:10	*Break*
3:10 - 3:15	*Session IV Chair: Dr. Larry Lesko, CDER*

3:15 – 4:00	*"Genotyping and Clinical Trials"*
	      Robert Temple, M.D.
	      Associate Director for Medical Policy, CDER
	      Director of the Office of Medical Policy and Director of Office of Drug Evaluation I, CDER, FDA

4:00 – 4:30	*"European Regulatory Perspectives towards Pharmacogenetics"*
	      Marisa Papaluca-Amati, M.D.
	      Deputy Head of Sector
	      EMEA, Sector Clinical Safety and Efficacy

4:30-5:00	**Panel Discussion with ALL speakers**

5:00	**Introduction into Day 2 and evening assignment**
	      Larry Lesko, Ph.D.
	      Director of Office of Clinical Pharmacology
	      CDER, FDA

Program on Workshop on Pharmacogenetics/Pharmacogenomics in Drug Development and Regulatory Decision-Making
May 17, 2002, Day 2 Program

Time	Topic
8:00 – 8:15	**Introduction to Workshop Tracks –** *Dr. Shiew-Mei Huang, CDER* *Interactive discussions among facilitators and attendees*
Time	*Track 1*
8:30-10:00	**Genomic Testing and Data Quality Issues** ***Session Leaders:*** ***(*chair)*** <u>**FDA:**</u> 1. ***Joseph Hackett, Ph.D.**** 2. Frank Sistare, Ph.D. 3. Elizabeth Mansfield, Ph.D. <u>**Industry:**</u> 1. Stephen Ryan, M.D., Director, Clinical Research and Exp. Med., Astra-Zeneca 2. Baltzar Gomez-Mancilla, Ph.D. M.D. Pharmacia Corporation
8:30-10:00	*Track 2*
	Preclinical Pharmacology and Safety ***Session Leaders:*** ***(*chair)*** <u>**FDA:**</u> 1. John Leighton, Ph.D, Office of Review Management, DODP, CDER 2. Alexandra Worobec, M.D., OTRR Div of Clin Trial Design and Analysis, CBER <u>**Industry**</u> 1. ***Tim Anderson*Ph.D.* Pfizer** *2.* Susan Ide, Ph.D., Novartis
8:30-10:00	*Track 3*
	Early Clinical Development ***Session Leaders:*** ***(*chair)*** <u>**FDA:**</u> 1. Jerry Collins, Ph.D. 2. ***S-M. Huang*, Ph.D*** <u>**Industry**</u> 1. Andy Dorner, Ph.D. Wyeth 2. Mark Watson, M.D., Associate Research Director, Clinical Genomics, Merck Research 3. ***Ginny Schmith*, Ph.D., GSK***

	Day 2 continued
8:30-10:00	*Track 4*
	Clinical Trial Safety and Efficacy ***Session Leaders:*** ***(*chair)*** **FDA:** 1. R. J. Meyer, M.D. Div. of Pulmonary and Allergy Drug Products, ODE-II, CDER 2. D. Essayan, M.D., OTRR, CBER **Industry** *1. B. Spear, Ph.D. , Abbott Labs* **2. *P. Shaw, Ph.D.**, Bristol-Myers Squibb** **3. *D. Anderson**, M.D., Pharmacia**
10:00 – 10:30	***Break***
10:00- 12:00	*Tracks continued*
12:00 – 1:30	***Lunch***

Time	**Topic: Track Summaries** – - Where we are now - Where do we want to go - How do we get there	**Speaker**
1:30 – 2:00	**Track 1 – Genomic Testing and Data Quality**	**Joseph Hackett, Ph.D.**
2:00 – 2:30	**Track 2 – Preclinical Pharmacology and Safety**	**Tim Anderson, Ph.D.**
2:30 – 3:00	**Track 3 – Early Clinical Development**	**Shiew-Mei Huang, PhD.**
3:00 - 3:30	**Track 4 – Clinical Trial Safety and Efficacy**	**Peter Shaw, Ph.D.**
3:30 –4:00	***Break***	
4:00 –4:30	**Panel Discussion and Closing**	**Larry Lesko, Ph.D.**

Program Abstracts
and
Workshop Discussion Issues

"Pharmacogenetic and Pharmacogenomic Terminology"

Brian Spear, Ph.D.

Director, Pharmacogenetics
Abbot Laboratories

Uniform definitions of critical technical terms are necessary for clear and productive interactions within the Pharmacogenetics and Pharmacogenomics workshop. A group of scientists from FDA and industry convened to develop a common set of definitions to be used during the Workshop. We found that, for some terms, no consensus exists, particularly for "pharmacogenetics" and "pharmacogenomics". Nevertheless, we arrived at definitions we believe can be useful to focus discussion and encourage clear communications. These definitions are not endorsed by any of the organizations taking part in the workshop, and are intended only for use within the context of the workshop's discussions.

Pharmacogenetics: The study of variations in DNA sequence related to drug action or drug disposition

Pharmacogenomics: The application of genomic concepts and technologies to the study of drug function and disposition. This includes studies of gene expression or inactivation and global approaches to identifying genetic variations that influence drug action

Toxicogenomics: The application of genomic concepts and technologies to the study of drug toxicity. This includes studies of gene expression or inactivation and global approaches to identifying genetic variations that influence drug toxicity.

Identified Samples/Data are those labeled with personal identifiers such as Name or Social Security Number. Use of a clinical trial subject number does not make the sample/data identified.

Coded Samples/Data are those labeled with a clinical trial subject number that can be traced or linked back to the subject only by the investigator. Samples do not carry any personal identifiers.

Double coded or De-Identified Samples/Data are double coded and labeled with a unique second number. The link between the clinical study subject number and the unique second number is maintained, but unknown to investigators and patients. Samples do not carry any personal identifiers.

Anonymized Samples/Data are double coded and labeled with a unique second number. The link between the clinical study subject number and the unique second number is deleted. Samples do not carry any personal identifiers.

Anonymous Samples/Data are those that do not have any personal identifiers, and the identity of the subject is unknown. Anonymous samples may have population information (e.g., the samples may come from patients with diabetes) but no additional individual clinical data.

"From shotguns to rifles: Pharmacogenetics in drug discovery and treatment"

Jeffrey M. Drazen, M.D.

Editor-in-Chief, The New England Journal of Medicine, Parker B. Francis Professor of Medicine, Emeritus Harvard Medical School; Member Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115

There are data demonstrating substantial variability in the treatment response to a variety of medications among members of a population. There are fewer data about the variability of treatment response over time in a given member of a population. If there is substantial variance in the treatment response among population members and less variability in treatment response in a given patient, the possibility exists that there is a substantial pharmacogenetic effect on treament. Data from clinical trials in asthma will be reviewed that indicate that the variation in treatment response among individuals substantially exceeds the variation in treatment response within a given individual. On the basis of these data, we calculated the repeatability (r) of the asthma treatment response, using outcomes from treatment trials with each of the major classes of asthma treatments, and found that r constituted 50 to 85% of the total treatment variance. Repeatability, r, provides an upper-bound estimate of the fraction of the total phenotypic variance that is genetic in origin, i.e. H^2. Thus, we have good reason to believe that a substantial component of the variability of the asthmatic treatment response is genetic.

In patients with mild-to-moderate persistent asthma, we will provide data that indicates that there is a pharmacogenetic influence the response to inhaled β_2-agonists, and leukotriene modifier agents.

There is known to be genetic variation in the coding region of the β_2-adrenergic receptor. These variants are associated with differential responses of the receptor to stimulation with β-agonists in vitro and have been associated with different clinical responses to this treatment. The key point here is that the majority of patients with asthma have functional β_2-adrenergic receptors but that the type of response to recurrent stimulation at this receptor varies among patients. In the second example, asthma patients possessing polymorphic forms of the core promoter of the ALOX5 gene, which have been associated with decreased promoter-reporter activity in vitro, failed to respond to treatment with an inhibitor of ALOX5. This example shows that a DNA sequence variant in the promoter region of a drug target gene can influence treatment responses.

"Use of Toxicogenomics to Predict Potential Human Toxicity"

Donna L. Mendrick, Ph.D.

Vice President of Toxicology
Gene Logic, Inc

Gene Logic is building ToxExpress™, a reference database containing gene expression alterations in *in vivo* and *in vitro* model systems following exposure to a multitude of toxicants. Commercially available pharmaceuticals and environmental toxicants are used in studies conducted in Sprague Dawley rats, primary rat cells, and human cells. The samples are profiled on Affymetrix's rat (>24,000 genes and ESTs) or human (>33,000 genes and ESTs) GeneChip® microarrays. Using proprietary algorithms along with commercially available statistical and clustering packages to mine this reference database, predictive models are built using gene expression changes observed with model toxicants and the changes are correlated with classical toxicologic parameters such as clinical chemistry, hematology, and histopathology. The compounds chosen represent agents that induce toxicity only in rats, only in humans, or in both species so that questions addressing species specificity can be evaluated. The proprietary modeling approaches have demonstrated the ability to predict toxicity across structural and pharmacological compound classes in multiple tissue types. Further analysis of the models has been performed with data not used in the development of the models and this data was obtained from both internal and external sources. For the latter, customers are generating GeneChip® microarray data at their site and submitting it to Gene Logic in a blinded fashion. Compounds have been classified successfully as toxic or nontoxic even when they are not present in the ToxExpress™ reference database. Toxicity prediction has been achieved with data from Sprague Dawley, Wistar and Fischer rat strains. The software ranks the compounds as to their toxicity potential, assigns likely pathology types, and matches them to the closest compound in the reference database. From this extensive database of information, informed prioritization of compounds can be accomplished and additional information regarding mechanism of action can be gleaned.

"Toxicogenomics in Drug Development: Where we are and Where we are going"

James T. Mayne, Ph.D.

Group Director DSE Laboratories, Pfizer Global Research & Development, Groton CT

Revolutionary advances in the science of molecular biology have driven the emergence of the relatively new field of toxicogenomics. This new field holds dramatic potential for redefining the very foundations of toxicology and pathology, however, as a new field there is still much to be learned about the practical strengths and weaknesses, applications and limitations of toxicogenomics. At present, application of toxicogenomics in the drug development process may be described in three categories: predictive or screening toxicogenomics and drug discovery, investigative toxicogenomics and the generation of testable hypotheses, and mechanistic toxicogenomics and the assessment of the genomic basis of toxicities. This presentation will provide comment and perspective on all three categories, as well as recent examples of each from pharmaceutical industry experience. Learnings from these examples will be summarized to highlight current practice, and to indicate where additional developmental work is needed to broaden the usefulness of toxicogenomics. Finally, comments will be offered on how academic, industry and regulatory scientists may collaborate to enhance the growth rate and yield from this new field.

"Pharmacogenomics in PhaseI/II Clinical Trials: Application of Expression Profiling in Clinical Testing of Immunomodulatory Treatments of Psoriasis"

Andrew Dorner, Ph.D.

Director of Molecular Medicine and Experimental Medicine
Wyeth Research

William L. Trepicchio*, Judy L. Oestreicher*, Ullrich Schwertschlag[+], Toyoko Kikuchi^, Ian B. Walters^, Patricia Gilleaudeau^, James G. Kreuger^, Charles W. Richard*, John Ryan[+] and Andrew J. Dorner*,
*Molecular Medicine and [+]Experimental Medicine, Wyeth Research
^Rockefeller University

Currently, 80% of drugs fail in the clinic due to safety concerns or poor efficacy. It has been estimated that 2 million hospitalized patients have severe adverse drug reactions and that such reactions were between the fourth and sixth leading cause of death in the United States as measured in 1994. Another study suggested that the expense of unnecessary, ineffective or harmful drugs is $100 billion per year in health care and societal costs. The application of pharmacogenomics and pharmacogenetics to the drug development process holds the potential to personalize treatment based on a molecular understanding of disease and drug response for each patient. While DNA variation as it relates to differential drug response (pharmacogenetics) is a static marker, RNA and protein expression patterns as they relate to differential drug response (pharmacogenomics) are dynamic and change with disease state and in response to drug treatment. Therefore, expression profiling may be used as a prognostic marker of patient response based on pretreatment profiles as well as providing molecular surrogate markers 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 RT-PCR or produce a global profile using gene chip technology. The identification of RNA or protein patterns that correlate with patient response will allow clinicians to select patients based on their predicted response and avoid adverse reactions, resulting in improved power and safety of clinical trials and increased benefit/risk ratio for drugs. Pharmacogenomic markers identified in Phase I clinical trials can be validated in Phase II trials with larger patient numbers and used to select patients for optimal Phase III trials. As the discipline and application of pharmacogenomics is rapidly evolving, multiple issues are being addressed, such as the technical validation of the assays (variability and reproducibility) and data analysis (significance thresholds and prediction algorithms) as well as confirmation of the biological and clinical relevance of the results.

In this presentation, we will describe the results of a longitudinal pharmacogenomic analysis using global and gene-specific RNA expression profiling of the response of psoriasis patients to treatment with the immunomodulatory agents Cyclosporin A or recombinant human Interleukin-11 (rhIL-11). Psoriasis is a chronic cutaneous inflammatory disease characterized by hyperplastic epidermal growth and Type 1 T cell mediated inflammation. Psoriasis is particularly amenable to expression profiling since the target disease tissue, skin, is accessible for biopsy. Therefore, changes in mRNA expression patterns associated with

disease and therapeutic intervention can be easily monitored. In a phase I open-label clinical trial, lesional and uninvolved skin biopsies were obtained before, during and after treatment with Cyclosporin A or rhIL-11. These drugs impact the calcineurin or NF-κB pathways, respectively. A target lesion was identified at trial initiation and repeatedly sampled for the longitudinal biopsies. Based on the known pathophysiology of psoriasis, expression of a set of 35 genes was selected for analysis by quantitative RT-PCR. Using the Affymetrix gene chip, a global expression screen of over 7000 known genes was also performed. Clinical response to drug was measured by histological assessment and changes in the global (PASI) and local (PSI) clinical assessment scores. 159 disease-associated genes were identified as being differentially expressed in psoriatic lesions compared to uninvolved skin and serve as a predictor set of disease. The functions of many of these genes are consistent with disease etiology and numerous genes map to known psoriasis susceptibility loci. Patients were classified as responding and non-responding to drug treatment based on PASI score and histological criteria. Gene expression changes in psoriatic lesions correlating with response over the course of treatment were identified. Expression of a subset of the disease-associated genes changed significantly in response to effective therapy. Amelioration of disease by rhIL-11 or Cyclosporin A therapy was associated with a reduction in hyperplastic epidermal growth and modulation of the Type 1 T cell response. Decreased lesional expression of inflammatory genes such as IFI56, IL-12 p40, IFNγ, iNOS, TNFα and S100A12 and genes associated with hyperkeratosis and a regenerative phenotype such as K16 and SCCA2 was observed. In this pharmacogenomic Phase I study, we have shown the ability of RNA expression profiling to identify disease-associated genes that may have value to further elucidate the molecular mechanism of psoriasis, serve as novel therapeutic targets or have utility as surrogate markers of clinical response. We are currently validating these results in a Phase II pharmacogenomic trial using rhIL-11 for psoriasis. Building upon Phase I and II clinical results, Phase III trials applying these surrogate endpoints of efficacy and safety will define patient selection and treatment regimen for the drug's "Indications and Usage".

"Pharmacogenetics in Phase I and II Clinical Studies: Utility and Issues"

Wayne Anderson, Ph.D.

Director, Exploratory Genetics Research
GlaxoSmithKline

Wayne Anderson, Ph.D, Virginia D. Schmith, Ph.D., Elizabeth Foot, Ph.D., Celia Brazell, Ph.D., Linda McCarthy, Ph.D., and Alun McCarthy, Ph.D. Genetics Research, GlaxoSmithKline

Pharmacogenetics and the genotype/phenotype relationships it yields in Phase I/II can lay the foundation for identifying populations of subjects or patients with a better safety profile, a better efficacy rate, and/or a need for a different dosage regimen. The overarching goals of Phase I/II are to develop an understanding of the therapeutic index of a compound and to get an early indication of whether it will meet its' targeted profile. To this end, the objectives of Phase I-II studies are to generate data providing an understanding of: (i) the safety and tolerability of a compound, (ii) its pharmacokinetics (PK) and pharmacodynamics (PD), and (iii) the dose likely to produce efficacy (while maintaining safety). Collecting pharmacogenetic information in these early clinical studies can significantly supplement a traditional dataset by providing a deeper understanding of factors contributing to variability in response. These genotype/phenotype relationships may then be validated in later phase clinical trials.

Phase I studies provide a unique opportunity to couple pharmacogenetic information with clinical safety, PK, and PD data measured frequently over time from healthy subjects and patients. In Phase I, the greatest number of compounds from a variety of drug classes are studied over a wide dosage range, including doses higher than those studied during any other phase of clinical development. Traditionally, the focus in Phase I has been to evaluate the relationship between variants in drug metabolizing enzyme genes and the PK of a compound, with particular attention paid to outliers. The focus of Phase I is now expanding to explain variability in drug response due to variants in genes related to PD (e.g., drug target or mechanisms for adverse events) as well as PK in the general population. Phase I studies also provide the opportunity to evaluate the contribution of pharmacogenetics to drug interactions and differences in drug response due to ethnicity. One perceived limitation, however, is the relatively small subject numbers studied in Phase I. This limitation can be managed by pooling data across studies; by using a prospectively data-driven approach with a focus on variants in the drug target or ADME genes with known or theoretical functional significance; and by acknowledging that only effects of a large magnitude may be uncovered.

Phase II dose-ranging studies provide additional opportunities to couple pharmacogenetic information with relevant and comprehensive efficacy and safety data in larger numbers of patients receiving a range of doses. In some cases, validated genotype/phenotype relationships uncovered during Phase I can be used to define patient populations or the dose targeted to achieve an improved safety profile and/or efficacy rate in Phase II studies. In other cases where genotype/phenotype data from Phase I remains unclear or a surrogate marker could not be measured in Phase I, genotype/phenotype relationships can be further

explored in the larger and broader Phase II patient population. Variants associated with PK, efficacy, and/or safety can be used to explain patient populations at risk for common adverse events or non response. The use of pharmacogenetics as inclusion/exclusion criteria in Phase II changes the paradigm for clinical drug development. This use is still in its infancy and requires a thorough evaluation of multiple issues including: (i) the knowledge of the variant, (ii) the frequency of the variant in the population, (iii) the validity of the association and the test; (iv) the magnitude of the effect relative to the therapeutic index; and (v) whether or not it is appropriate to exclude patients at risk for non-response or adverse events.

Pharmacogenetic information in Phase I/II can be used to make earlier, data-driven, decisions affecting clinical drug development such as defining and optimizing Phase II/III clinical trial design. If appropriate, the potential for utility of a medicine response test can also be evaluated at an earlier stage. Practical and unsettled issues related to the collection and use of pharmacogenetic information in early clinical studies will be addressed using relevant examples. The application of this data to the design of studies will also be discussed.

"Pharmacogenetic Scenarios for Phase III/IV Trails in Subjects with a Complex Trait"

Baltazar Gomez-Mancilla, M.D., Ph.D.

Director of Clinical Genomics
Pharmacia Corporation

The development of technologies that provide genomic or genetic information to predict drug efficacy or toxicity and to explain inter-individual difference in response to a drug has accelerated in the past 5 years. At the same time, Genomics Technologies are becoming more reliable and cost-effective. More and more clinical trials have a PGx component as part of their objectives. The acquisition of this information in clinical trials has been influencing strategic decisions in drug development. Therefore, development and refinement of methodologies and regulations are needed to support registration studies.

This presentation's intent is to open a dialogue between researchers, clinical scientists, and regulatory agencies related to the collection of Pharmacogenetic data in Phase III/IV trials in a complex disease. The data presented shows the potential application of genetic markers in any drug development project as well as limitations. At the same time, many questions are raised to start this dialogue with regulatory agencies.

"Genotyping and Clinical Trials"

Robert Temple, M.D.

Associate Director for Medical Policy, CDER, FDA

Dr. Temple will discuss the potential role of genotyping in clinical trials. His discussion reflects developing policy, questions that need to be considered, not questions that as yet have clear answers. Dr. Temple will attempt to link pharmacogenetic/genomic questions to more familiar matters, because many of the questions are not as unfamilar as they may appear. In particular, many of the things genotyping can do represent kinds of "enrichment" ways of selecting (or excluding) particular patients or groups of patients for clinical trials.

"European Regulatory Perspectives toward Pharmacogenetics"

Marisa Papaluca-Amati, M.D.

Deputy Head of Sector
EMEA, Sector of Clinical Safety and Efficacy

Abstract
Pharmacogenetics and Pharmacogenomic in drug development
European regulatory perspectives

The knowledge that genetic factors are involved in the differential clinical response of individuals to a given medicinal product is a long standing one as the correlation between different efficiency of metabolic enzymes was identified in the late sixties responsible for diverse safety and efficacy outcomes.

Genetic polymorphisms have been proven with in vitro and in vivo studies to be determinant of phenotypic variants of metabolic enzymes, transporter molecules, ion channels, receptor affinity and density and therefore likely to affects the pharmacokinetic behaviour and the pharmacodynamic response of a number of medicinal products. The knowledge accrued over time is reflected in the European and International Regulatory guidelines laying down the technical requirements for the pre-clinical and clinical development for the purpose of medicinal products regulatory approval. Modern drug development programs have been conceived to address the potential of interference of genetic factors on drug response over and above more traditional and known variables such as concomitant diseases, food, tobacco, age, weight. The major contribution given so far by pharmacogenetic and pharmacogenomic studies have been in terms of elucidation of drug-to-drug interactions, of occurrence of some severe Adverse Drug Reactions, suboptimal efficacy at standard doses of certain medicinal products.

The progress of genetic and genomic knowledge, enahnced dramatically by new analytical methods, bioinformatics tools and models, is focussing now towards more and more precision in the understanding molecular mechanisms of the diseases, the interplay between environment and individuals and the better targeting and personalisation of the medical interventions. In this direction pharmacogenetic indicators would provide for new additional criteria for prediction of efficacy and safety, which will hopefully increase homogeneity in the outcomes and identify more precisely the population and the individuals to be treated.
The robustness of the predictive value of the pharmacogenetic indicator, its clinical relevance, the validation and availability of reliable pharmacogenetic test

methodology and knowledge of genetic "epidemiology" might establish in the future new grounds for global access to the product.

The CPMP having launched the dialogue on pharmacogenetics with Pharmaceutical Industry, Research professionals and Patients associations in 2000, established in April 2001an ad hoc working group on Pharmacogenetics, chaired by the CPMP Vice-President Dr. Eric Abadie.

The CPMP in December 2001 released for six months external consultation a position paper on terminology in Pharmacogenetics. In order to prepare for the likely gradual more extended use of pharmacogenetics in the clinical trials it was considered helpful to tackle basic communication issues among regulators and citizens such as the definition of critical terms describing both the technology and the implications for individual subjects genetic sample handling. In EU it was considered particularly important to have a set of terms with commonly agreed definitions in the light of the upcoming implementation of the Directive 2001/20/EC on the conduct of clinical trials on medicinal products for human use.

The international dimension of the debate has been taken on board as a main feature of the CPMP activities in this rapidly evolving field likely to generate in a not too distant future global impact on the development and use of medicines. Contribution to a number of international initiatives is being undertaken progressively, such as the participation of the Chairman and a number of members of the group to the CIOMS working group on Pharmacogentics and Pharmacoeconomics, exchange of views and discussion with the FDA and increasing dialogue with MHW contacts.

However the experience is limited from both Regulatory and Industy side. At present, with very few exceptions, pharmacogenetics is unlikely to be a primary determinant of clinical decisions The integration of "predictive pharmacogentic indicators" in the development plans is at present implemented by the Industry with a stepwise approach in order to ensure appropriate management of the knowledge available and rapidly upcoming. The level of accuracy and robustness of pharmacogenetic methods and models appropriate for regulatory purposes should be discussed on a case-by-case basis and taking in to account all the above elements.

TRACK 1. WORKSHOP

Genomic Testing and Data Quality Issues
Session Leaders:
(*chair)

<u>FDA:</u>
1. ***Joseph Hackett, Ph.D.* , ODE, CDRH***
2. Frank Sistare, Ph.D. **,** OTR, CDER
3. Elizabeth Mansfield, Ph.D., DCLD, CDER

<u>Industry</u>**:**
1. Stephen Ryan, M.D., Astra-Zeneca
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This workshop will discuss five specific areas involving pharmacogenetic and pharmacogenomic testing:

I.   Issues in the validation of assays of SNPs and haplotypes
II.   Reference populations, allelle frequency estimation, and population stratification
III.   Data quality issues surrounding application of gene expression microarrays to include nonclinical pharamacology/toxicology investigations and clinical trial performance
IV.   Issues in array and chip validation
V.   Validation issues in analytical and clinical trials, and approval of drugs and associated *in vitro* diagnostic devices

I.   Issues in the validation of assays of SNPs and haplotypes

Where are we now?
Various assays are used to genotype SNPs or detect alleles in human genomic DNA samples. These include, but are not limited to, direct sequencing (e.g., dideoxy), primer extension-based methods, hybridization methods (including DNA "chips" of various sorts), and restriction enzyme analysis. Most involve a preliminary PCR step. Each has advantages and limitations in specificity, sensitivity, throughput, and reliability/reproducibility. Assay validation is generally accomplished with a panel of reference samples of known genotype. The most widely accepted standard assay is bidirectional, dideoxy sequencing of DNA of individual alleles that have been isolated by molecular cloning.

Occasionally, dideoxy sequencing may be problematic (e.g., because of very high GC content). An additional unresolved issue is the ability of a genotyping assay to identify homozygotes for rare alleles. The inclusion of such individuals in a reference panel may be impractical.

Haplotypes may be determined directly by sequencing individual, cloned chromosomal sub-segments. Alternatively, they can be derived by genotyping relevant SNPs in multigenerational families. These methods are obviously impractical for clinical trial samples. Various computational algorithms have been developed to infer haplotypes probabilistically, given the (directly determined) genotypes of individual, closely linked SNPs. Comparing performance to a direct assay can validate these methods.

The theoretical number of haplotypes defined by a string of n SNPs is 2^n. The number of haplotypes observed in practice is usually much smaller, but studies of large populations often reveal a number of less prevalent haplotypes. How uncommon haplotypes should be handled is an unresolved issue in pharmacogenetics.

Where do we want to be?

View A	View B
We need to specify a standard procedure for establishing the genotype of reference samples.	Best scientific practice should be used to decide on appropriate genotyping methods for reference samples.
We need guidelines for deciding when rare, homozygous persons should be included in the validation of a genotyping assay.	The inclusion of rare, homozygous persons in a reference panel is often impractical, particularly in early stages of drug development.
Haplotype assays should have very high analytical performance – i.e., should nearly always report the true haplotype.	Prediction of the "true" haplotype is not important. It is only important that an inferred haplotype assay perform clinically.
We need to specify when it is essential to measure haplotype and genotype frequencies, the populations in which this must be done, and with what accuracy and precision – especially for relatively uncommon haplotypes.	Issues regarding the measurement of haplotype and genotype frequencies should be resolved on an ad hoc basis. In general, it is only important that a haplotyping assay reliably specify the most prevalent haplotypes in a population. There will never be enough statistical power in clinical trials to establish and validate correlations between rare haplotypes and various outcomes.
OTHER ISSUES	OTHER ISSUES

How should we get to where we want to be? A few ideas to get us started

1. *Idea* We should define, for situations where dideoxy sequencing (or another proposed reference sequencing method) is ambiguous, how well other sequencing methods correlate with one another. Another view: it is better to use best scientific practice to deal with this issue on an *ad hoc* basis.

2. *Idea* We should determine how well current genotyping and haplotyping assays perform in identifying persons who are homozygous for rare, minor alleles when such persons have not been included in validation protocols.

3. *Idea* We should determine what the consequences are, in various clinical situations, of incorrectly specifying the genotypes of individuals who are homozygous for rare alleles.

4. *Idea* We should compare the ability of statistically inferred haplotypes and directly determined haplotypes to predict clinical outcomes. This data might be generated, e.g., by studying individuals with pharmacokinetic variants (e.g., CYP2D6, TPMT, etc.). These persons would be haplotyped directly and also by various statistical methods.

5. *Idea* We should define a set of "standard" scenarios in drug development and clinical practice, and determine, for each of them, what advantages are provided by precise knowledge of haplotype frequencies.

6. *Idea* We should establish an industry/government/academia working group to address any/all of the above.

II.   Reference populations, allele frequency estimation, and population stratification

Where are we now?
Allele (and haplotype) frequencies typically differ among populations with distinct histories. In pharmacogenetic studies, spurious associations may arise if the case (e.g., responder) and control (nonresponder) groups are drawn from genetically distinct subpopulations. This can occur when the outcome of interest is correlated with race – a common situation in US clinical trials. 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 – i.e., genes selected because they are unlikely to be related to drug response – to account for differences in genetic background.

Assuming that a pharmacogenetic association is valid, its strength may vary among populations. Clinicians already consider race and ethnicity in formulating diagnoses and recommending treatment. As pharmacogenetic data accumulate, there will be an increasing demand for group-specific data.

These issues raise important questions about the need for measuring allele frequencies in various control or reference populations, the degree of precision required for allele frequency estimation, and how such populations should be defined. Is there, for example, a need to identify a standard, reference panel (e.g., analogous to the National Institute of General Medical Sciences Human Diversity Panel) for allele frequency estimation in the development of a DNA diagnostic linked to a drug? If so, who should be responsible?

Where do we want to be?

View A	View B
Estimation of allele and haplotype frequencies in appropriate control populations should be required whenever pharmacogenetics data is used to support an application for a new drug or diagnostic test. We need to establish specific guidelines on precision and accuracy in allele frequency estimation.	The decision on the necessity to estimate SNP allele frequencies, or haplotype frequencies, depends heavily on the proposed use of the test or the way in which pharmacogenetic data is being used to support a drug application.
We need publicly available, reference DNA panels for the estimation of allele frequencies. Sponsors of pharmacogenetic tests should be required to estimate allele frequencies in these panels.	Allele frequencies should be determined in "clinical use" trials that approximate "real-world" clinical practice in anticipated target populations.
We need to articulate specific requirements or recommendations for optimal matching of cases and controls in pharmacogenetic studies. The best way to accomplish this is to develop a standard "race/ethnicity questionnaire," the validation of which is based on its ability to predict known genetic differences among various races/ethnic groups. Sponsors of a diagnostic test should be required to use such a questionnaire in supporting studies.	It is inherently impossible to define race/ethnicity precisely. A better approach would be to conduct pharmacogenetic studies in target populations that appear racially or ethnically homogeneous. For example, a genetic association observed in a US clinical trial that included African and European Americans should be validated in European and African populations.
Statistical "correction" for ethnic mismatching should be used to resolve the difficult issues posed by population stratification in clinical trials. A standard statistical approach should be developed and required.	Statistical approaches to population stratification in the clinical trial setting are inherently flawed and will necessarily dilute power. They show little promise.
OTHER ISSUES	OTHER ISSUES

How should we get to where we want to be? A few ideas to get us started.

1. *Idea* We should to study the impact of mis-specification of allele frequency in a set of "standard" scenarios in clinical practice and drug development.
2. *Idea* We should assess the impact that the required use of reference DNA panels would have on the development and clinical use of drugs and diagnostic tests.
3. *Idea* We should support the development of statistical approaches to correction for genetic mismatching in clinical trials.
4. *Idea* We should support research into novel approaches to improve prospective "genetic matching" in clinical trials.
5. *Idea* We should establish an industry/government/academia working group to address any/all of the above.

III. **Data Quality Issues surrounding Application of Gene Expression Microarrays to Nonclinical Pharmacology/Toxicology Investigations and Clinical Trial Performance**

Expression arrays are being used nonclinically to predict clinical drug performance, to generate hypotheses and better understand mechanisms of drug action, and to identify biomarkers of drug response that may be used to assess human risk potential. Expression arrays have been applied clinically to tumor diagnostics and in many other areas of medicine to better predict or to monitor early patient drug response. The unique aspect of microarray gene expression technology is the parallel access it provides to query what is happening "genome wide" in any given sample. This 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. Routinely repeating hybridizations to reduce error is very costly. The technology is in a constant state of evolution with new developments appearing at a regular pace. Numerous platforms are available with probes designed from different gene sequences for the same targets. The huge scope that microarrays provide also requires data reduction applications to first fine-tune the raw data, and then to manage, analyze, visualize, comprehend and communicate the data output. One of the consequences of simultaneously investigating more revealing endpoints is the fear that certain results that may not be easily explainable (and may not be "real") could raise concerns with regulatory authorities over ambiguities in interpretations. Good judgment is critical to avoid raising false concerns and to recognize legitimate toxicological responses. To help make these judgements wisely, reliable experimental data, reliable data reduction algorithms, and publicly available sound scientific reference information are needed. Furthermore, easily queried strong experiential reference databases can be crucial for achieving certain goals. Presently the majority of such data exist in proprietary repositories.

Where are we now?

(1) There are varying interpretations as to whether or when microarray data on lead compounds would need to be submitted to regulatory agencies as part of an IND data set. It is not clear if the data quality is sufficiently high and convincingly reliable for regulatory authorities to take an action on "voluntarily submitted supplemental" microarray data. Individual sponsors are likely to migrate toward a single favored microarray platform of their choice to generate their data, to use to guide their product development decisions, and to develop their own internal reference databases. Some will choose a commercially available array, while others will develop their own proprietary platform. Regulatory authorities are likely, therefore, to see and learn from data sets derived from multiple different platforms from multiple laboratories presenting data associated with similarly labeled gene identities.

(2) If reliable databases are needed for regulators to place individual sponsor microarray experimental results into proper perspective, it is not clear how this should be fairly and transparently accomplished since very little data have been submitted to the agency and publicly available databases have not matured. As databases become more mature, and scientific knowledge of gene expression

responses expands, there is concern that the data generated today may become more revealingly informative over time, and might, therefore, negatively impact products later during development, prior to making a marketing approvability decision.

(3) Even before gene expression responses can be interpreted, 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. We lack convincing testimony to a high level of reliability, precision, accuracy and intra- and inter-laboratory reproducibility of data derived from global gene expression technologies applied across platforms to identical samples derived from nonclinical pharmacology or toxicology studies. On the other hand there are data demonstrating that the technology has been applied in very convincing and reproducible ways to investigate drug actions both nonclinically and clinically, or to stratify and predict patient response.

(4) The degree of quality control and validation microarray manufacturers apply to their products (GMP's ?) is not always apparent. We lack information on manufacturing controls and post-manufacturing lot-to-lot quality control functional performance/pass-fail measures by microarray providers.

(5) We lack information on efforts by end users to establish standard procedures to consistently assure and evaluate sample quality, and to calibrate microarrays and microarray instrumentation to assure the integrity of their complete data sets. And we lack consensus on a standardized set of information required to fully annotate the data generated from microarray experiments.

(6) Numerous statistical algorithms, image analysis, pattern recognition, 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 help to provide "big picture" overview categorizations 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 interpretation(s), regulatory implications, and potential legal ramifications of such evaluations of product performance using global gene expression data are not clear.

Where do we want to be?

View A	View B
(1) Data generated from microarray experimentation are of sufficient quality, are being generated routinely on lead compounds, and is reported to FDA as pharmacology data, reflecting tremendous insight into the agent's mechanism of action. Over time, such data will be used to reduce the length and number of regulatory animal studies.	(1) Data generated from microarray experimentation on lead compounds are not accurately interpretable, have no predictive safety implications, and are therefore a waste of FDA reviewers' time and need not be reported to FDA. They are only of value to sponsors who may feel that they can interpret the information to make better (but still not always accurate) predictions.
(2) The FDA will develop internal databases from sponsor submitted data, and will tap NIH, and other publicly available microarray gene expression databases. These will become rich sources of information to make better regulatory decisions in the interest of the American public – both for consumers and sponsors.	(2) We will continue to rely on traditional histopathological observations and $20\forall$ measurements in serum and continue to generate and review product data as is current practice.
(3) We want to establish minimal performance characteristics needed to demonstrate data integrity. Every data point should be generated in sufficient replicate to represent a reliable measure of precision of that analyte. The linear dynamic range for each analyte on their platform should be calibrated by manufacturers under diverse conditions of use. Accuracy for every analyte must be defined. Different degrees of validation, or different levels of assurances of data validity may be expected, however, depending on the pivotal or nonpivotal role that the data will be expected to play in regulatory product performance evaluation.	(3) When assessing alterations in 1000's of RNA molecules at one time, it is unreasonable to expect all Tm's to match and for all cross-hybridizations to be zero. It should be accepted that each analyte is somewhat of an approximation, and some will represent the truth more accurately than others. This will vary from experiment to experiment. Genome-scale arrays, therefore should be reserved for hypothesis generation, candidate selection screening purposes, and potential biomarker discovery. Samples will be appropriately stored and available for critical analytes to be independently verified by either sponsor or regulator.

VIEW A	VIEW B
(4) GMP's need to be established for all microarrays used in drug development tox studies on lead compounds, and all clinical studies. GMP's will include a rigorous set of manufacturing guidelines and post-manufacture q.c. parameters applied to each lot. GMP's need not be applied for arrays that will be used for research and screening purposes. The 2 levels of data sets should be kept in separate databases.	(4) GMP's are not necessary for any large (> 100?, >??…) microarray platform used either for research, lead compound toxicology, or clinical investigations of product development. The end user is responsible for the quality of the data and for sensing and demonstrating any errors in array measurements. GMP's are needed only for platforms and reagent sets that will be used in a clinical diagnostic mode.
(5) A minimal set of information must be established to accurately annotate how the data are generated from microarray experiments, and how the data should be archived. MIAME efforts underway may provide such a solution (Brazma, et al (2001) Nature Genetics 29: 365-371)	(5) Microarray data annotation details need not be shared nor archived with any concept toward standardization. Individual data generators need only provide and store the final data and relevant information.
(6) A standard data reduction algorithm should be established and a rigorous validation procedure adopted for microarray data that is generated for specific purposes.	(6) Data reduction algorithms will continue to evolve and no attempt should be made to limit creative applications or to standardize approaches. End users and regulators will be free to apply such algorithms and com-municate their respective interpretations.

How do we get to where we want to be? (just a few ideas to get us started)

1) *Ideas:* All of below, plus train review staff how to integrate expression data into traditional studies; expert committee & include outside expert consultation early on.
2) *Ideas:* Contract to initiate formation of FDA database with web access to public databases and firewall protection of proprietary data.
3) *Ideas:* Encourage development and applications of instrumentation standards?; define standard control procedures for running arrays?; define internal standards?; define RNA quality standards for samples?; develop SOP's for defining and reporting threshold signal intensity, threshold fold-induction, statistical significance, signal-to-noise limits?; independent verification of critical analytes to be revisited in ongoing dialogs/guidances?; define differential level of data integrity of pharm/tox study, versus Phase 1/ 2, versus Phase 3?;
4) *Ideas:* Establish working group of array manufacturers, FDA, and end users to establish interpretation of minimal GMP requirements; FDA to define types of studies for which GMP arrays are needed or for which non-GMP arrays are acceptable;
5) *Ideas:*   Join MIAME effort; stay tuned to other public database efforts;
6) *Ideas:* Joint working group to establish a single (set of) data reduction algorithm applications; list other optionals.

IV.   ISSUES IN ARRAY/CHIP VALIDATION

Background
Array and chip manufacturers control the substrate, synthesis/printing and identity/addressing aspects of the assay, i.e. the production of the array platform. This may include placement of "control" features that allow comparative assessment of hybridization and reading performance by the end-user. Some manufacturers also control the array reader platform, the optics, and algorithms used to analyze and reduce data.

Some of the most recognized problems in manufacture of arrays are purity and identity of probe solutions, print head status, robot movement, quality of substrate and uniformity of substrate coating. Difficulties would also arise from incorrect identification/addressing of spots, and mixed probes, although these are not a widely cited problem at the moment.

Validation of array quality may be performed by either the manufacturer or the user, or both. The initial quality check of the appearance of properly formed spots can be done to ensure that the array has been printed uniformly and that no pin, jet, or synthesis failure occurred. Functional validation is the most stringent method, in which arrays are hybridized using standardized hybridization probes and conditions and then analyzed for comparison to expected results and for uniformity of results. Arrays and chips that incorporate control spots are likely to be the easiest to validate, but it is important that the control spots are distributed in such a way as to ensure the integrity of the whole array or chip. A number of other methods such a spot replicates, dye reversal, double-labeling, and multiple replicates of arrays can be used to validate arrays. Computational analysis of data using multiple statistical strategies may aid in assessing statistical significance of expression data.

VIEW A	VIEW B
Manufacturer should validate microarray/ Chips via GMP parameters (eg. Chip to chip; lot to lot; site to site)	Microarray/chips used in CLIA High Complexity laboratory are of acceptable quality to allow incorporation of data into studies
Efforts should be made to develop unified standards and procedures	Standards should be applied as they become available
Array targets (features) should be identified and validated	Array targets (features) do not need to be identified or validated as long as they are consistent between arrays
Where are we today?	
Where would we like to be?	
How do we get there?	

Questions:

1. Are microarrays and gene chips being validated or at least are their performance characteristics evaluated by the chip manufacturers? By the end users? How are they validated or being evaluated?

2. Can manufacturers develop validation and standardization methods? What standards exist to ensure the quality and integrity of data? What additional standards/guiding principles are needed and could be offered? Can standards be developed that are flexible enough to admit new technologies?

3. Is it important to know what area the features that are detected on an array (i.e. is there a need to understand what genes/transcripts are being detected? Can the same result be gained if the identity of the detected genes/transcripts is not known?)

V. VALIDATION ISSUES IN ANALYTICAL AND CLINICAL TRIALS and IN APPROVAL OF DRUGS AND ASSOCIATED IN VITRO DIAGNOSTIC DEVICES

"Personalized" pharmacotherapy is on the brink of becoming a reality, and several drugs that are prescribed based on expression levels of certain genes are already on the market. Ideally, drugs with a (genetically) defined treatment population will be evaluated clinically along with an in vitro diagnostic in order to improve selection and efficacy. Selection tests have been required to be FDA approved or cleared for several drugs. Any test that is commercially distributed requires FDA oversight, but a requirement for oversight is not currently in place for in-house developed ("home brew") testing. It is possible that CDER and/or CBER will mandate the use of an FDA approved diagnostic assay for any drug whose use indicates patient selection for safety and efficacy.

Current selection tests use traditional (established) technologies. New genetic testing technologies are rapidly evolving and many are reaching a stage where they can be considered for clinical use in selecting patients or making diagnoses. Few have been validated for their intended use, their indications for use, and appropriate populations to be evaluated. There are little or no data showing that any current pharmacogenomic (or other "new technology") test would be reliable, have acceptable precision and accuracy (when these are measurable), and between-lab reproducibility, and would be *clinically valid* for patient selection (e.g. Her-2/Neu test can distinguish between different classes of breast cancer cases, and there is clear rationale for using the test to select for therapy). Collaborations of diagnostics and drug developers at early stages will enhance the possibility that tests can be validated for performance and utility in the clinical setting. It is not, however, desirable from the standpoint of innovation that the market be closed to diagnostics developers who were not represented at the initial drug/diagnostic planning.

VIEW A	VIEW B
Performance of "research grade" genetic testing technologies should be clinically validated before use for patient selection in clinical trials.	Full clinical performance evaluation of "research grade" tests is not needed for patient selection
Selection is important for safety and efficacy	Selection is important for safety only
Validate the patient selection assay early in the process before clinical trial, or Phase I/II	Validate the patient selection assay during the clinical trial, or Phase II/III
Population frequencies should be determined in order to include as many populations as possible in the trial.	Population frequencies can be determined after the fact and study results extrapolated to include "new" populations
Ensure that diagnostic tests manufactured by different entities measure the same thing	Diagnostic tests only need to correlate to disease state, and do not need to measure the same thing
A drug specific for a genetically defined patient group will require an FDA-approved in vitro diagnostic test	A drug specific for a genetically defined patient group will need an in-house test.
Where are we today?	
Where would we like to be?	
How do we get there?	

Questions

1. What is the best way to establish a dialog between researchers and manufacturers and users that sets out analytical and clinical validation rules for tests that are non-traditional genetic tests, e.g., arrays, MS? How should professional societies, government agencies, and manufacturers be integrated?

2. How can "rules" be established on which type of samples would require informed consent and which would not in the development phase? Can development of diagnostics fit into the current federal use of records/informed consent scenario, e.g. HIPAA?

3. Clinical validation, especially for predictive tests, may present some difficulties in terms of informed consent for archived samples. How should this be addressed?

4. What are the concerns about the reliability, precision, accuracy, and interlaboratory reproducibility of "research grade" genetic testing technologies used to identify subjects to be used in drug trials?

5. Will approval of a drug specific for a genetically defined patient group require an FDA approved in vitro diagnostic assay? Will it make a difference if the selection is for safety *and* efficacy, or for efficacy or safety alone?

6. Can a test that measures gene expression level be used instead of a test for the genotype to predict patient response to drug?

7. What action is desirable in order that in vitro diagnostic manufacturers and developers and manufacturers of drugs with genetic selection indications cooperate at early stages to decide the best way to select patients? Preferably should not the selection assay be analytically validated early in the process? Should not the developers of the drug and test be able to identify a clear rationale for measuring the selected marker, and show that different populations differ in either possession or expression of the marker (depending on how it is to be measured)?

8. How should standards and/or sample banks, or some other appropriate mechanism be established that 1) allow modified diagnostics to be evaluated and validated, 2) allow secondary diagnostics manufacturers to enter the market with established clinical validity, and 3) ensure that diagnostics manufactured by different entities (and at different times) are measuring the same thing. Is this an important issue for diagnostic development?

TRACK 2. WORKSHOP

Preclinical Pharmacology and Safety

Session Leaders:
(*chair)

FDA:
3. John Leighton, Ph.D, ORM, DODP, CDER
4. Alexandra Worobec, M.D., OTRR, DCTDA, CBER

Industry
3. *Tim Anderson*Ph.D.* **Pfizer**
4. Susan Ide, Ph.D., Novartis

This workshop will discuss five issues regarding preclinical safety genomics technology:

1. Is toxicogenomic science and validation technology sufficiently mature to rely upon genomic data for safety decisions and to justify the routine use of genomic data in GLP toxicology studies?
2. What is the value of toxicogenomic date to Industry and the FDA?
3. How could data from genomic arrays, in conjunction with standard short-term toxicology studies, be used to assist in study design or in species selection for long-term toxicology studies?
4. Is there a need for guidances in the toxicogenomics area? If guidance's existed what would be their main purpose and what would be the potential impact?
5. Development of "historic databases" in interpreting toxicogenomic findings may be useful if the data are robust and reliable and if toxicogenomic profiles predict toxicology. If this is correct, how should such databases be developed and utilized?

Where are we now?

The progress of technology and information has led to an entirely new field in toxicology and preclinical safety, that of toxicogenomics. One definition of toxicogenomics is: "the study of the relationship between the structure and activity of the genome (the cellular component of genes) and the adverse biological effects of exogenous agents" (Aardema and MacGregor, 2002). Another definition calls it the "integration of genomics, bioinformatics, and toxicology" (Fielden and Zacharewski, 2001). The "-omics" part of the term indicates the global aspect of studies in which the entire genome of an organism is sequenced, or the expression of entire genomes can be identified in a single experiment. Such experiments allow for toxicity pathways to be identified and mechanisms to be elucidated. For the purposes of this workshop, toxicogenomics is defined as the application of genomic concepts and technologies to the study of drug toxicity. This includes studies of gene expression or inactivation and global approaches to identifying genetic variations that influence drug toxicity.

A commonly used genomic assay platform is the Affymetrix GeneChip® (www.affymetrix.com). This platform has arrays which include genomes from yeast, rat, mouse, human, and arabidopsis. Of special interest to toxicology and preclinical safety, rat genomes are one of the more extensive Affymetrix arrays available. These arrays include chips which query 7,000 full length genes, 17,000 expressed sequence tags (ESTs), a neurobiology gene array, and a toxicology specific array which contains the genes known to be related to toxic or stress related responses. Alternatively, many companies and research institutions are constructing their own microarrays designed to answer specific questions. More recently a microarray chip has become available as 2 chips that contain 500,000 human oligonucleotide sequences/chip and represents the entire repertoire of human genes and toxicology specific human arrays may be custom designed to evaluate specific cDNA profiles.

One of the major ideas of toxicogenomics is to utilize it as alternative to or in addition to traditional preclinical safety studies by providing a means to understand the mechanisms of toxicity, and use that knowledge as predictive of human risk in future preclinical studies. The assumption is that each chemical entity acts through a "particular mechanism of action which will induce a unique and diagnostic gene expression profile under a give set of conditions" (Fielden and Zacharewski, 2001 and references therein). Pilot studies in lower eukaryotes have demonstrated that it is possible to identify common expression profiles of drugs of similar therapeutic action (Marton et al, 1998) and there are similar studies in mammals. For example, Waring et al were able use gene expression profiling to cluster hepatoxins based on their mechanism of toxicity (Waring et al, 2001).

Others doubt this utility of toxicogenomics, believing that gene expression profiling should be used as a hypothesis generating tool rather than a predictive one. One concern is that the data, at least as currently generated with today's technology, is simply not robust enough for predictive value. Additionally, there is concern is that there are many different effects of toxicants that are not elucidated by changes in gene expression, including effects on membrane and DNA integrity, generation of reactive intermediates, etc, and these effects are not amenable to being extrapolated from single timepoint gene expression data. Without functional knowledge of what alterations in gene expression might mean, it is difficult to correlate such changes with toxicity. In order to do so, there needs to be an understanding of how the molecular changes manifest at the cellular and tissue levels, indicating a need for a multi-disciplinary approach to understanding mechanistic toxicology (Pennie et al, 2000).

Although these views are different in the degree of usefulness toxicogenomics provides, they both point to the same need, which is for industry and regulatory to come to an understanding in how to utilize the information, and begin to anticipate where it may go. From experience we know that "…gene expression is either altered directly or indirectly as a result of toxicant exposure in almost all cases examined" (Corton et al, 1999) and pathological outcomes are the end result of early gene expression changes. In addition, the availability of gene chips from many different species allows for toxicity gene expression measures to be taken across species, including evaluation of bridging biomarkers from laboratory models to humans, thus providing insight into more appropriate species selection for long term toxicology studies. Such decision making requires input and commitment from both industry and regulatory officials.

The field of toxicogenomics is currently fairly small; a search of "toxicogenomics" in PubMed yields 26 articles as of April, 2002. The term wasn't coined until recently, so such

an analysis is a bit misleading, but the important thing is that it highlights the fact that it is groundbreaking science. Despite the limited number of references in this field, the interest is great because there is significant potential that toxicogenomics could greatly improve the methods used to identify and evaluate potentially toxic drugs.

Our mission today in this workshop is to raise issues related to the introduction of pharmacogenomics in preclinical drug development and develop a framework to prioritize and address concerns. The workshop format will focus on a set of key questions, common to industry and regulatory scientists, with a set of alternative views to be debated in the workshop. The outcome will be a summary of where are we today in toxicogenomics, where would we like to be, and how do we get there?

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Workshop Questions

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<td colspan="2">1) Is toxicogenomic science and validation technology sufficiently mature to rely upon genomic data for safety decisions and to justify the routine use of genomic data in GLP toxicology studies?</td>
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<td>View A</td>
<td>View B</td>
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<td>Genomic data from animal studies are not sufficiently understood to be predictive of clinical (human) toxicity. Therefore, genomic data are not routinely collected in GLP toxicity studies.

If collected in GLP studies, and the genomic data indicate a potential adverse event, the data would not be reportable unless confirmed in more established or validated systems. A follow-on, more established experimental system would supercede initial genomics data for safety assessment purposes.</td>
<td>Genomic data from animal studies, following administration of a new molecular entity (NME) should be part of the safety database and integrated into the safety evaluation of the NME. Genomic data, in general, are considered "reportable" as stand-alone evidence of adverse events. Sponsors of Clinical Studies should notify the FDA. Investigators and IRB's, under existing IND requirements, of genomic results indicating potential for adverse events. The Agency would react to activation of genes that might signal human health issues in the same manner as they would react to any other findings from animal toxicity studies that indicate a potential for adverse effects in humans.</td>
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<td colspan="2">*Consensus view to be determined in workshop*

Where are we today?

Where would we like to be?

How do we get there?</td>
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2) What is the value of toxicogenomic date to Industry and the FDA?	
View A	View B
Toxicogenomic data should be included in Safety Assessments as "stand-alone" data. They can be interpreted as single gene patterns and are indicative of potential adverse events in humans.	Toxicogenomic data are most useful to provide mechanistic explanations for drug effects that have already been characterized in animal models using standard procedures. They should not be used as "stand-alone" data but rather should be interpreted in accordance with other findings from animal studies (Clinical pathology, Histopathology, Metabolism, etc.)

Consensus view to be determined in workshop

Where are we today?

Where would we like to be?

How do we get there?

3) How could data from genomic arrays, in conjunction with standard short-term toxicology studies, be used to assist in study design or in species selection for long-term toxicology studies?	
View A	View B
Because animal genomic data is not understood well enough to be predictive of human clinical toxicities, it would not be useful in selecting the species most likely to represent the human response. Rather, the established methodologies of species metabolism, receptor homology, in vitro enzymology, etc, should be used to select the best species for toxicology studies. Chronic animal toxicity studies are still the best means to characterize chronic toxicity.	Use of animal genomic data could refine the study design (e.g., incorporating novel biomarkers) and assist in the selection of best species for toxicology studies. Because of it's ability to predict chronic toxicity it would reduce the need for long-term toxicology studies for safety assessment.
Consensus view to be determined in workshop Where are we today? Where would we like to be? How do we get there?	

4) Is there a need for guidances in the toxicogenomics area? If guidance's existed what would be their main purpose and what would be the potential impact?	
View B	View A
Guidelines are necessary because genomic data are being used for safety decisions in a non-transparent and inconsistent manner.	There is no necessity for guidelines because this is still an "embryonic" technology that is not routinely used in risk identification, risk management, or safety decisions. Once we have a better understanding of appropriate study design and data interpretation, guidelines might be useful.

Consensus view to be determined in workshop

Where are we today?

Where would we like to be?

How do we get there?

5) Development of "historic databases" in interpreting toxicogenomic findings may be useful if the data are robust and reliable and if toxicogenomic profiles predict toxicology. If this is correct, how should such databases be developed and utilized?	
View A Toxicogenomic databases are not yet useful to predict human toxicity because the data are not robust, reproducible, or reliable. We are still learning from our study design mistakes. However, there is value is such databases if they are based on robust, reproducible, and reliable data.	View B Toxicogenomic databases are useful to predict human relevant toxicities because they are based on robust, reproducible, and reliable data.
Consensus view to be determined in workshop Where are we today? Where would we like to be? How do we get there?	

TRACK 3. WORKSHOP
Early Clinical Development
Session Leaders:
*(*chair)*

<u>**FDA**</u>:
1. Jerry Collins, Ph.D., OTR, CDER
2. ***S-M. Huang*, Ph.D, OCPB, CDER***

<u>Industry</u>
3. Andy Dorner, Ph.D. Wyeth Research
4. Mark Watson, M.D, Merck Research laboratories

Recorder: Virginia. Schmith, Ph.D., GSK*

This workshop session will present four issues for discussion when utilizing pharmacogenetics and pharmacogenomics in early clinical development studies.

<u>Where are we now?</u>

Variants have been identified in the candidate genes for proteins involved in the disposition pathways of drugs, in the drug targets, and in other proteins affecting drug response. For many of the drug metabolizing enzymes (e.g., CYP2D6, NAT-2, TPMT) and more recently drug targets or related receptors (e.g., 5-hydroxytryptamine receptor, cholesteryl ester transfer protein, 5-lipoxygenase), the frequency and functional significance of these variants has been explored. For other genes, the functional consequences of genetic variation may be less well-characterized or unknown, particularly at the start of a clinical development program. The amount of data available is important in determining how pharmacogenetics is integrated into the early clinical plan and the design of individual studies, particularly when using a candidate gene approach. Since drug response is likely to involve variants from multiple genes and from genes not previously hypothesized to be involved in drug response, another approach that does not rely on *a priori* assumptions about candidate genes is the use of "unbiased" or "hypothesis generating"full genome scans using SNP (single nucleotide polymorphism) map. This approach remains experimental, requires larger subject numbers, and larger number of markers examined, increasing the cost and effort of the study. It is currently being explored in larger clinical studies associated with later stage development programs of high priority (including post-marketing). Such proof of concept work also involves assessment of biostatistical techniques such as linkage disequilibrium, haplotype maps and the identification of informative SNP sets

The identification and validation of RNA or protein expression profiles, as prognostic markers of response, significantly lags behind the knowledge base of pharmacogenetics. Recent papers have described the use of RNA expression profiling of tumor tissue to predict clinical outcome (e.g., Affymetrix gene chip and genes associated with predicted outcome of diffuse large cell lymphoma; cDNA microanalyses of primary breast tumors and prognosis).

An informal survey by FDA of INDs and NDAs identified over 54 applications integrating Pharmacogenetics/pharmacogenomic tests into early phase development. Eighty percent of these applications were related to CYP450 variants affecting drug metabolism. Even though functionally important genetic variations in key metabolic pathways are known for a variety of drugs, validated assays to guide drug prescription are not widely used. One test that is used in product labeling, widely accepted and used in the clinic, is the assay for HER2 prior to use of trastuzumab(Herceptin) for breast cancer. While it is debatable whether this technically employs a 'genetic test', (it utilizes protein expression, not candidate genes, SNPs or expression profiles, which are commonly used test techniques in many current pharmacogenetic/pharmacogenomic studies), it is a good example of a biomarker being used to define drug development, and treatment strategy.

Clearly, it is anticipated that adding pharmacogenetics/pharmacogenomics to early clinical studies will identify sub-populations with a better safety and efficacy profile, possibly by use of a different dosing regimen. However, as genotype/phenotype relationships are uncovered in early drug development, there are various views on how pharmacogenetics/pharmacogenomics should be used in the design of future clinical trials:

- Some believe that once a genotype/phenotype relationship of potential clinical importance has been found, inclusion/exclusion criteria should be added to future studies. Others believe it is important to validate the results by replication prior to selecting patients based on genotype/phenotype. Similar issues apply to mRNA expression profiling.

- Some believe subjects at risk for adverse events or non-response should be screened out of all studies, while others believe that since at-risk patients may possibly receive the drug in the real world setting, these subjects should be included, but possibly studied in a more closely monitored setting.

In addition to these issues, various approaches have been used to decide when blood samples should be collected for pharmacogenetics/pharmacogenomics research ranging from collecting samples in all studies to collecting in studies with narrowly defined and limited hypotheses. Another approach collects samples in certain types of studies (e.g., drug interaction studies) or in studies from certain Phases only (e.g., Phase III). Furthermore, some sponsors and CROs routinely screen their volunteer panels to determine their genotype for important CYP isoenzymes such as CYP2D6. The sampling population and sampling techniques becomes more of an issue for RNA expression profiling since optimal timing and special tissue handling is required.

Where do we want to be?

Pharmacogenetics/pharmacogenomics (e.g., SNP maps, candidate genes, expression profiles) will be optimally integrated in early clinical development programs and be seen as an important component to reaching the overall goals of Phase I and II: safety, tolerability, PK/PD, dose ranging, drug-drug interactions. Pharmacogenetics/pharmacogenomics will also support early decision-making.

1. Apply pharmacogenetics/pharmacogenomics analyses to identify markers of drug activity or toxicity in Phase I and II studies. Select the optimal drug dose and/or population based on genetic information predictive of response

   - Pharmacogenetics/pharmacogenomics will be considered in the design (e.g., inclusion/exclusion criteria, stratification, dose selection, power and subject number calculations) and in the interpretation of studies (ethnic differences in allele frequency, bridging strategy, dose response, drug-interaction studies, and risk/benefit), when it is appropriate and feasible.
   - Pharmacogenetics will be added to PK/PD modeling and simulation as an additional component (an extension of what is already done) to explain variability in response and to design and interpret future studies.
   - Pharmacogenetics data from early clinical development will identify sub-populations with a better safety profile, a better efficacy rate, and/or a need for a different dosage regimen.

2. Identify and confirm markers of drug response in human disease tissue and Phase I/II clinical trials;

3. Apply markers in Phase III trials to optimize power and safety of trial in patients with genetic profiles that predicts favorable responses.

4. Develop validated marker in parallel with the drug approval process for use by clinicians to identify patients with best-predicted response rate and lowest possibility of adverse reaction. This may result in the labeling requiring a molecular diagnostic assay (issues are addressed under Track 4).

5. Consensus on validation of pharmacogenetic/pharmacogenomic markers and development of validated assays with high predictive strength (issues are addressed under Track 1)

How do we get there?

We need to discuss the following issues for early clinical development programs:

1. When is it appropriate for pharmacogenetics/pharmacogenomics to be used as inclusion/exclusion criteria (or stratification) in a Phase II dose ranging study or drug-drug interaction studies vs. when is it appropriate for pharmacogenetics/pharmacogenomics relationships to be explored post-hoc based on multiple considerations?

   - Is the answer to this question different based on
     - stage of knowledge of the variants or expression profile?
     - magnitude of effect relative to the therapeutic index?
     - frequency of the variant?
     - timing and special tissue handling (e.g., RNA expression profiling)?
     - validity of results (are results consistent with theoretical or in vitro data? How have they been replicated?)?
     - number of candidate genes or SNPs affecting the phenotype?

   - When is it appropriate to exclude or to include subjects at risk for adverse events or non-response in a study?

- Does the benefit to patient selection outweigh the risk, e.g. false negative results in-patient being denied beneficial therapy compared with false positive resulting in serious adverse event?
- When dealing with RNA expression profiles, can one assess uncertainties associated with prediction using supervised machine learning programs?
- Is there a rationale for pharmacogenetics/pharmacogenomics to affect dose response?

2. When is it appropriate to adjust doses for Phase II studies based on pharmacogenetics/pharmacogenomics (considerations should be given to points raised in question #1)? Would a higher overall response rate be required for success? Do we need to increase the number of subjects enrolled if we do not prescreen?

3. When/how should samples be collected for genotyping/mRNA expression profile/SNP profiling? Are we at the point where there is a strong rationale for collecting samples in all studies? Or just in those studies with predicted hypotheses? Consideration can be given to the stage of development and potential development issues (e.g., issues with similar compounds).

4. How will pre-knowledge of genetic susceptibility to pharmacologically predictable adverse events or non-response obtained in early phase development affect the risk/benefit assessment? How will this information be used in product labeling? What will regulatory requirement be for label to state for the use or non-use of a diagnostic test before treatment with the drug? When will specific genotype/phenotype assays be indicated in the labeling? (issues also discussed in Track 4).

TRACK 4. WORKSHOP

Clinical Trial Safety and Efficacy

Session Leaders:
(*chair)

<u>FDA:</u>
1.   R. Meyer, Ph.D., ORM, DPDP, CDER
2.   D. Essayan, M.D., OTRR, CBER

<u>Industry</u>
4.   B. Spear, Ph.D. , Abbott Labs
5.   P. Shaw, Ph.D.*, Bristol-Myers Squibb
6.   D. Anderson*, M.D. Pharmacia

Introduction
The six questions below have been written to cover a wide variety of topics for discussion when using Pharmacogenetics during the clinical development of drugs.   They are meant for discussion and to stimulate thoughts about a way forward.

Session 1 Question 1

Pharmacogenetic tests can be used both in a clinical trial setting and with marketed drugs. Pharmacogenetic tests aim to provide information that can identify either subsets of individuals from the broader patient population who might selectively benefit from a therapy or subsets of patients with a higher/lower probability of an observed adverse event.

How might conducting a clinical trial in a pharmacogenetically defined subset of patients influence requirements for collection of adequate safety and efficacy data prior to registration?

Consider the following scenarios:
a) A clinical trial that uses genotype to exclude those patients who are unlikely to respond (Non responders)?
b) A clinical trial that uses genotype to exclude those patients who are at risk for a particular adverse drug response/adverse event (AE)?
c) A clinical trial in which the efficacy population is selected by genotype, but in which safety is assessed in all subjects?

Debate the following
a.   How do the scenarios differ from studies that currently employed enrichment designs or strict inclusion criteria?
b.   Are there specific product profiles (efficacy and safety) and illnesses that might necessitate collection of additional data in a wider population? If it is considered necessary to collect data for a more heterogeneous group, what would be the extent of this and would it be needed pre or post registration?

c. What are the scientific and ethical implications of conducting studies in patients thought unlikely to respond or at increased risk of having an AE?

d. Will an approved *in vitro* diagnostic kit be required for use during the phase III pivotal trial when a Pharmacogenetic marker is used for selecting patients with better efficacy/safety profiles or will a home brew assay available at a commercial company or academic center suffice?

e. Will an approved *in vitro* diagnostic kit need to be available for the approval of the drug if the data indicates a benefit to a pharmacogenetic selected population.

f. What types of trial design for registration and approval of a drug are suitable which use pharmacogenetic markers for efficacy and safety

Session 1 Question 2

The clinical development of a drug is a process involving the completion of multiple clinical trials, over several years, to determine the efficacy and safety of a compound. During clinical development samples from patients can be collected and stored in anticipation of the need to perform pharmacogenetic research. The collection of samples for future pharmacogenetic research is considered to be much more cost effective and likely to capture important cases for future statistical analyses than retrospective collection procedures.

Consider these scenarios
a) Pharmacogenetic samples are collected in the clinical phase, but the desire/need/rational/ability to analyze is not clear and no prospective pharmacogenetic research is carried out. However, as work progresses, the product profile indicates a variability in response that may benefit from some pharmacogenetic understanding.

b) Pharmacogenetic samples are not collected during the clinical phase. However, as work progresses, the product profile indicates a variability in response that may benefit from some pharmacogenetic understanding. Options are therefore to initiate a new pharmacogenetic study. This may be alongside a clinical trial with a prospective collection and analysis or there may be a scenario in which one needs to go back to patients who have taken the drug in an earlier study or in the post marketing phase and ask for their participation in pharmacogenetic research. In the latter situation the phenotype information will come from earlier records, so both the phenotype and the analyses are retrospective. For a rare drug profile, setting up a new prospective clinical study has severe practical constraints and retrospective work may be the only viable option.

Under what circumstances can a "pharmacogenetic clinical trial" be conducted that uses samples and/or clinical data from a previously completed drug clinical study or in the post marketing environment.

Discuss
a) If discoveries are made subsequent to original filing that show that pharmacogenetic variation affected drug response, can the new data from the previous trial be re-presented for registration and if so what criteria would need to be met? For example in a pivotal Phase III, in which a compound is found to be less or equal in efficacy to the control arm, could a retrospective subset analysis using a pharmacogenetic marker, which then demonstrates superior efficacy with no significant safety issues, support a registration?
b) Is a new clinical trial required in the newly defined subset to show efficacy and safety?

Session 1 Question 3

In clinical trials in which data is used for registration purposes an audit trail is maintained which links the laboratory and clinical data back to an individual patient. Perceptions surrounding any field of genetic research have impacted upon pharmacogenetics. As a result the potential use or miss-use of exploratory pharmacogenetic research data generated in clinical trials has lead to the establishment of processes and procedures that add additional levels of security to prevent linking exploratory pharmacogenetic research data with the identity of an individual. Anonymized samples/data is one such category which adds an extra level of protection for an individuals privacy/confidentiality when participating in clinical trials that have exploratory pharmacogenetic research.

a) Is it appropriate or possible to use anonymized samples/data (The key which links genotype information to the patients study number has been destroyed) rather than coded or de-identified/double-coded samples (the key continues to exist which links genotype information to the patients study number) to support a filing or registration of a drug? And if it is possible what requirements would need to be met? e.g. audit of the anonymization process?

b) Is it more appropriate to avoid maintaining a link which can potentially identify individuals when performing pharmacogenetic research

c) When does Pharmacogenetic research data need to have an audit trail back to the Physicians office and patient study number?
    1. Only hypothesis testing in pivotal phase III studies,
    2. Data generated in Phase II studies if the data is going to be used to support a hypothesis test in a pivotal Phase III study.

In the context of the development and registration of pharmacogenetic drugs, guidance is needed concerning what pharmacogenetic data is sufficient to identify and treat those individuals most likely to benefit from drug treatment as well as to exclude subjects at high risk for adverse events or low probability of benefit. Definition is needed concerning the characteristics of genotype-phenotype associations (or other possible associations based on haplotypes/complex genetic markers incorporated into a pharmacogenetic diagnostic test) in the process of using data in drug registration dossiers.

What special considerations, if any, should be addressed in a registrational clinical trial linking a genetic marker to:
  a) An efficacy response (patients who are shown, through a pharmacogenetic test, to be at an increased chance of responding to the drug compared to placebo/SOC)? or,
  b) An adverse event (patients who are shown, through a pharmacogenetic test, to be at increased risk for toxicity or a side effect)?

Specific questions to consider:

a) What strength of genetic associations (e.g. differential of allelic/genotypic or haplotypic frequencies) will be required for a pharmacogenetic efficacy marker?

b) What proportions of study populations with defined genetic variants would be required for analysis and interpretation?

c) What level of validation/replication will be required for a pharmacogenetic efficacy marker? Would additional pivotal trials be required to validate identified genetic markers in general populations, and would specific replication response studies be required in all ethnic sub-populations if not represented in initial registration trials?

d) What therapeutic advantage of a pharmacogenetic marker would be sufficient to allow use in a drug label; e.g. what odds ratio (or other statistical value) for drug response vs. non-response would be sufficient to allow use of a pharmacogenetic marker to select responder populations or exclude non-responder populations?

e) What level of false positive or false negative results (sensitivity & specificity) would be allowed/required for predictive pharmacogenetic markers of: drug response, drug non-response, non-serious adverse events or serious adverse events in drug labeling?

Session 2 Question 2

With the current technological advances in the field of exploratory pharmacogenetic research it is conceivable that whole genome studies will be rapid and cost effective in the future. Exploratory pharmacogenetic research is expected to lead to unanticipated new discoveries about the safety and efficacy of drugs on the market and in clinical development as well as the treatment of diseases. The results of current and future exploratory pharmacogenetic research studies are expected to lead to better drugs and therapies for the future.

If exploratory pharmacogenetic research is performed during the clinical development of a compound, that is not part of the basic clinical study design (for example through a sample banking amendment for future exploratory pharmacogenetic research), under what circumstances would the results of a pharmacogenetic analyses warrant reporting to a regulatory agency?

Debate the following points
a) All cases, even if the research study is a data-mining exercise to look for a pharmacogenetic correlation to clinical responses,
b) Only when the pharmacogenetic study is hypothesis-driven and adequately powered to draw meaningful conclusions,
c) Only in a hypothesis-driven study when validated assays (tests) have been used to obtain pharmacogenetic data,
d) Only in a study such as "c" when the results relate to patient safety,
e) Only when data suggests drug hazards not apparent from the primary study conclusion, e.g. activation of oncogenes.
f) Under what circumstances would the FDA require such data to be submitted? And in what time frame e.g. expedited, annual? How would this differ for a marketed compound?

Session 2 Question 3

In clinical development, between 80% to 90% of the population enrolled in clinical studies is Caucasian. Therefore, if data for a gene-based response are developed, it is assumed that the large amount of genotypic information generated from such studies pertain to Caucasians.

What would be the implications for ethnic diversity derived from these data?

Would additional information based on allelic frequency be required for other ethnic groups when results indicate an "ethnicity difference" in safety and efficacy?

Discussion Points

a) How should ethnicity be defined [self reporting, or based on additional information requested from patients on biological parents (for example 1/2, 2/2 of parents for the same reported ethnic group)]? Should grandparents be considered?
a) Would additional information based on allelic frequency from ethnic reference populations be required?
b) What are the regulatory implications of genetic profile screening of patients during IND therapy?
c) How would this information affect the product label?
d) How would existing guidelines on bridging studies be carried out with data generated within the same ethnic group? Among different ethnic groups?
e) Will additional data in ethnic populations be required if the original trial was not powered to show differences appropriately?
f) Should alleles that associate with safety or efficacy be tested in all people regardless of ethnicity or expected frequency?

SPEAKER, SESSION AND TRACK LEADERS
PROFESSIONAL SUMMARIES

Anderson, Donald	Dr. Anderson is currently Director of Genomics and Pharmacogenomics at the Pharmacia Corporation. He has responsibilities for genomics initiatives within the Discovery and other divisions of its R&D organization, and he represents Pharmacia on the Pharmacogenetics Working Group. He is the corresponding author of a submitted publication from this pharmaceutical consortium on the topic of Informed Consent for Pharmacogenetic Studies.
Anderson, Timothy	
Anderson, Wayne	Dr. Anderson earned a Bachelor of Science degree in biology and a Master of Education degree in science education at Springfield College in Springfield, Massachusetts. He then obtained a Doctor of Philosophy degree in pharmacology from the University of South Florida College of Medicine in Tampa, where he also served as a postdoctoral research fellow and an instructor in the Department of Pharmacology and Therapeutics. Over the past 12 years, Dr. Anderson has held various positions in respiratory clinical research and genetics at Glaxo, and in 2000, he was awarded the Glaxo Wellcome Discovery Genetics Award for Innovation in Pharmacogenetics. Before joining the staff of Glaxo, Dr. Anderson was a Research Manager and Group Leader in the Pulmonary Pharmacology Research Division of Ciba-Geigy in Basel, Switzerland, where he won a research prize for his work on leukotrienes and leukotriene receptor antagonists. He had also held the titles of Senior Scientist and Assistant Research Group Chief in the Department of Pharmacology at Hoffmann-La Roche in Nutley, New Jersey. Dr. Anderson is a member of the American Thoracic Society and is the Past President and current member of the Board of Directors of the Carolinas Chapter of the Cystic Fibrosis Foundation. He has authored or coauthored more than 40 articles, book chapters, abstracts, and presentations in the field of respiratory diseases and cystic fibrosis.
Brazell, Celia	Dr Celia Brazell is the Genetics Science and Technology Advisor for Genetics Research at GlaxoSmithKline. In this role Celia works with research ethics committees, drug/device regulators, policy makers and healthcare providers to explore the application of genetics to healthcare improvement. After completing her PhD in Neuropharmacology at the Queen's Medical Centre, Nottingham University, Celia joined Merck Sharp & Dohme in the US. Here she worked on the effectiveness of novel slow release formulations designed to treat Parkinson's Disease. In 1986 she transferred to the Merck Sharp & Dohme Neuroscience Research Centre (UK) to establish and manage the Clinical Unit Laboratory. Here the goal was to evaluate surrogate markers of Central Nervous System function. Celia joined Glaxo Group Research in 1991 as part of the Neurology & Psychiatry Clinical Group evaluating treatments for Alzheimer's disease. Since that time she has been involved with projects for depression, anxiety, acute hospital care and respiratory, including pharmaecoeconomic evaluations. In November 1997 she accepted an appointment in the new Clinical Genetics Division of Genetics Research at Glaxo Wellcome with the responsibility of incorporating and evaluating genetic research in the drug development and commercialisation process for CNS. She is a member of the British Pharmacological Society and has over 50 publications
Collins, Jerry	Director, Laboratory of Clinical Pharmacology, Food & Drug Administration. Dr. Collins received his Ph.D. in 1976 from the University of Pennsylvania, and completed a postdoctoral fellowship in Clinical Pharmacology at Johns Hopkins University School of Medicine. He spent a total of 10 years at the National Institutes of Health, including 5 years as Chief of the Pharmacokinetics Section at the National Cancer Institute. In 1988, he joined the FDA. He has authored or co-authored over 150 papers in the field of clinical pharmacology, primarily

	emphasizing the applications of PK/PD principles in the field of cancer. His current work is focused upon extending these principles with positron emission tomography. In addition to research and administrative duties at the FDA, Dr. Collins holds adjunct faculty appointments at Johns Hopkins, Georgetown and the Uniformed Services University.
Dorner, Andrew	Received Ph.D. from State University of New York at Stony Brook for research on poliovirus protein synthesis under the direction of Eckard Wimmer in 1983. Post-doctoral research (1983-1985) on the molecular basis of avian retrovirus host range at Tufts University School of Medicine under the direction of John Coffin. Joined Genetics Institute in 1985. Initial research in Mammalian Expression group focused on the processing and secretion of human proteins in CHO cells. Studied the pathway of wt and B domain deleted FVIII synthesis and secretion and identified the role of BIP binding in the inefficient secretion of wt FVIII. Contributed to the successful development and FDA approval of Recombinate (FVIII), BeneFix (FIX) and Neumega (rhIL-11). Initiated program in Preclinical Research and Development to apply expression profiling to animal models and clinical trials that led to development of Molecular Medicine group. As Director of Molecular Medicine group leads effort at Wyeth Research to apply pharmacogenomics and pharmacogenetics in preclinical and clinical studies. First clinical pharmacogenomic study identified therapy-induced RNA expression changes in psoriatic lesions following rhIL-11 treatment. Adjunct Professor of Pharmacology and Experimental Therapeutics in the Boston University School of Medicine. CV lists over 60 publications.
Drazen, Jeffrey	Dr. Drazen was born in Missouri, attended Tufts University with a major in Physics, and Harvard Medical School. He did his internship at Peter Bent Brigham Hospital and thereafter joined the Pulmonary Divisions of the Harvard Hospitals. He has served as Chief of Pulmonary at the Beth Israel Hospital, the combined Divisions of the Beth Israel and Brigham and Women's Hospitals, and finally as the Chief of Pulmonary at Brigham and Women's Hospital. Through his research program he defined the role of novel endogenous chemical agents in asthma. This has led to four new licensed pharmaceuticals for asthma with over 1.5 million people on treatment world wide. His work identified a genetic component of the variability of the asthma treatment response and is an important example of the intersection between individual responses to drug treatment and genetics. He is currently Professor of Medicine at Harvard Medical School and Editor-in-Chief of the *New England Journal of Medicine.*
Essayan, David	
Galson, Steve	Dr. Steven Galson is the Deputy Director of the Center for Drug Evaluation and Research at the Food and Drug Administration. Dr. Galson's current responsibilities include agencywide coordination of patient safety activities and CDER's evolving risk management strategies. He was the Acting Director of CDC from November 2001 – March 2002. Prior to his arrival at FDA in May, 2001, Dr. Galson was the Director of the Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, at the US Environmental Protection Agency EPA. He was previously the Scientific Director of EPA's Office of Children's Health Protection. At EPA, he organized the first national conference on preventable causes of children's cancer, managed the Science Advisory Panel and EPA's Endocrine Disrupter Screening Program. Dr. Galson holds a BS from the University of Stony Brook, an M.D from Mt. Sinai School of Medicine and a MPH from Harvard. He is Board Certified in Preventive Medicine & Public Health and Occupational Medicine. Until June 1997, Dr. Galson was the Chief Medical Officer at the U.S. Department of Energy where he worked on a wide range of public health issues related to the nuclear weapons complex and advised the Secretary of science. Among many varied activities as an officer in the US Public Health Service, Dr. Galson has conducted epidemiologic studies at the National Institute for Occupational Safety and Health, been an environmental health officer at the NY State Health Department and worked

	overseas on refugee emergencies.
Gomez-Mancilla, B.	Dr. Baltazar Gomez-Mancilla is currently Director of Clinical Genomics and Biobank at Pharmacia Corporation; His research group utilizes genomic approaches for target and biomarker identification, as well as the discovery of markers that can be developed to predict efficacy and safety of drugs. His group supports the genomic efforts in Discovery and Drug Development to apply and integrate pharmacogenetic studies in the discovery and development of novel therapeutics. Baltazar serves as a Chairman on the Pharmacogemonics Protocol Review Committee at Pharmacia.. This committee reviews the overall scientific, medical, statistical, and ethical aspects of all Pharmacogenomics Programs. Baltazar is also on the steering committee of the Pharmacogenetics Working Group. This group, comprised of representatives from pharmaceutical companies, advances the understanding and development of pharmacogenetics by openly addressing and disseminating information on non-competitive topics such as ethical, legal, and regulatory issues. Baltazar received his MD degree from University of Mexico in1981, MSc and PhD degrees in Experimental Neurology at Laval University., and a Postdoctoral degree in Neurology (Movement Disorders, and Epilepsy) and in Clinical Pharmacology (Drug Metabolism and Pharamacogenetics) at the University of Toronto. For the last 8 years Baltazar has been working at Pharmacia involved in Drug Development.
Hackett, Joseph	After working in industry for 7 years, Dr. Hackett joined what is now FDA's Center for Devices and Radiological Health (CDRH) in 1974. During his time at FDA he has been involved in and had partial responsibility for several programs such as Standards, Investigational Device Exemptions (IDE), and Premarket Approval (PMA), primarily with In Vitro Diagnostic devices. Dr. Hackett is employed in the Office of Device Evaluation's Division of Clinical Laboratory Devices (DCLD), where he is an Associate Director for that Division. Currently he is the Project Officer for the Agency's Clinical Laboratory Improvement Amendments (CLIA) Program. He also oversees the education and training of DCLD personnel in the area of DNA microarrays/SNP's. In addition he is assisting in the development of proposals for possible oversight of Genetic testing by FDA.
Huang, Shiew-Mei	Shiew-Mei is currently Deputy Office Director for Science, Office of Clinical Pharmacology and Biopharmaceutics (OCPB), Center for Drug Evaluation and Research (CDER), FDA. She received her B.S. in Pharmacy from the National Taiwan University, Taipei, Taiwan in 1975 and a Ph.D. in Pharmacokinetics and Biopharmaceutics in 1981 from the University of Illinois at the Medical Center, Chicago, Illinois. From 1981 to 1989, she was Senior Scientist at the Ortho Pharmaceutical Company. She joined the DuPont Pharmaceutical Company in 1989 and was Director of the Pre-Clinical ADME Group of the Drug Metabolism and Pharmacokinetics Section at the DuPont Merck Pharmaceutical Company prior to joining the FDA in 1996. Shiew-Mei is an AAPS Fellow and was board certified by the American Board of Clinical Pharmacology (Applied Pharmacologist). She has published over 60 peer-reviewed articles focusing on the topics of clinical pharmacology, drug metabolism/drug-drug and drug-herb interactions, biopharmaceutics and pre-clinical drug disposition. Since joining OCPB, Shiew-Mei has assumed responsibility for a wide variety of scientific activities relating to review, policy development, research, and scientific communications. She chaired a working group (WG) that published a guidance for industry on drug interactions in vivo. Currently, She chairs a WG that is developing a guidance for reviewers on drug interactions in vitro and an OCPB Good Review Practices WG. She is a member of various working groups including the CDER Race/Ethnicity WG, CDER QTc WG, CDER Pharmacogenetics/pharmacogenomics WG, and the FDA's Gender Effects Science Council.
Ide, Susan	Dr. Ide received her PhD in Human Genetics from the George Washington University in 2000, and a BS in Biology from Bucknell University in 1992.

	Prior to joining Novartis in 1998, she was a Research Scientist at the National Human Genome Research Institute while doing her graduate studies part time. Her research involved extensive work on the Human Genome Project, including linkage and physical mapping of disease genes, candidate gene sequence analysis, and mapping of expressed sequence tags (ESTs). She was part of the group to identify mutations in alpha synuclein, the first gene identified for Parkinson's disease. Her linkage work turned into her dissertation project, "Cloning of the Ellis van Creveld Syndrome Gene". Susan implements and oversees Pharmacogenetic studies at Novartis and serves as the Novartis representative to the Pharmacogenetics Working Group.
Killinger, Joanne	
Leighton, John	Dr. Leighton received his PhD from the Department of Physiology and Biophysics at the University of Illinois, Urbana-Champaign. His thesis work involved investigating the molecular biology of phenobarbital-inducible cytochrome P450s, where he cloned and sequenced several novel P450s and studied their regulated expression in different tissues and their time course of expression. He then received postdoctoral training at the University of Colorado Health Sciences Center in Denver in lipid metabolism, where his research focus was in drug and dietary (fasting and non-fasting) effects of cholesterol and bile acid metabolism and lipoproteins (apo B and apo E). Dr. Leighton is a supervisor of the pharmacology and toxicology team in the Division of Oncology Drug Products (DODP) at FDA's Center for Drug Evaluation and Research. In DODP, Dr. Leighton and other members of the pharmacology/toxicology team review the safety of oncology drugs. Dr. Leighton is also serving as ODE III Associate Director of Pharmacology and Toxicology. He is a Diplopmate of the American Board of Toxicology.
Lesko, Larry	Lawrence J. Lesko, Ph.D. is Director of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (1995-present). This Office is responsible for the review and evaluation of the biopharmaceutic, pharmacokinetic and pharmacodynamic data contained in IND's and New Drug Applications (NDA's). Dr. Lesko is Chair of the Clinical Pharmacology Section of the Medical Policy Coordinating Committee, and Co-Chair of the Biopharmaceutics Coordinating Committee, in CDER that is responsible for developing guidances for industry. Dr. Lesko currently represents FDA on the Common Technical Document (Efficacy) Working Group in the International Conference on Harmonization. Dr. Lesko was previously Associate Director of Research at the FDA where he was responsible for developing and managing the Product Quality Research Program in the Office of Generic Drugs (1992-95). Prior to joining FDA, Dr. Lesko was Vice President of PharmaKinetics Laboratories (1988-92) and Associate Professor of Pharmaceutics at the University of Maryland at Baltimore (1981-88). He also held an appointment in the Laboratory of Neuroscience, National Institute on Aging, National Institutes of Health, from 1985-1988 investigating the effects of age on the pharmacokinetics and pharmacodynamics of drug substances. He was a Laboratory Director in the Clinical Pharmacology Division of the University of Massachusetts Medical Center from 1979-1981 and was on the faculty of the Massachusetts College of Pharmacy from 1973-1979. Dr. Lesko received his B.S. and Ph.D. degrees in pharmaceutics from Temple University in Philadelphia, Pennsylvania and was board certified in Clinical Pharmacology by the American Board of Clinical Pharmacology in 1992. In 1998, Dr. Lesko was awarded the Outstanding Alumni Award from Temple University. He has been conferred the Honor of Fellow by AAPS and was awarded Fellowship status by ACCP. As a member of ACCP, he serves as a Regent of the College. He also serves as Chair of the Drug Development and Regulatory Science Section of ASCPT and as FDA's Federal Liaison to EUFEPS. Dr. Lesko is an Adjunct Professor at the University of Florida College of Pharmacy. He has authored or co-authored over 110 peer-reviewed articles in biopharmaceutics and clinical

	pharmacology and he is a frequent speaker at national and international meetings.
MacGregor, James	James T. MacGregor, Ph.D., D.A.B.T., is Deputy to the Director of the FDA National Center for Toxicological Research, responsible for Washington Operations. Previously, he was Director of the Office of Testing and Research (OTR) at the FDA Center for Drug Evaluation and Research (1997-2001), Director of the Toxicology and Metabolism Laboratory at SRI International (formerly the Stanford Research Institute) in Menlo Park, CA (1990-97) and Manager of the Food Safety Research Unit at the USDA Western Regional Research Center, Berkeley, California (1972 –1988). Jim received his B.S. in chemistry in 1965 and a Ph.D. in toxicology from the University of Rochester School of Medicine in 1971. He has held academic appointments in toxicology at the University of California, Berkeley and the University of San Francisco. He is a Diplomate of the American Board of Toxicology and has served on numerous national and international expert toxicology groups and advisory boards. He has been active in professional societies (including President and Treasurer of the Environmental Mutagen Society, President of the Genetic and Environmental Toxicology Assn. of Northern California, and committees of the Society of Toxicology) and has served on the editorial boards of *Environmental and Molecular Mutagenesis*, *Mutation Research*, and *Mutagenesis*. He has published more than 200 journal articles, abstracts, and book chapters in the field of toxicology.
Mansfield, Elizabeth	Geneticist, Review Staff, Immunology and Molecular Devices Branch, DCLD/CDRH, FDA. Dr. Mansfield reviews regulatory submissions, helps to develop policy related to molecular devices in genomics/proteomics areas, and is working with the Genetics team on the potential implementation of FDA oversight of in-house genetic testing. Prior to joining the FDA, she worked as a Research Fellow at the NIAMS at NIH on the identification of genes and mutations, and the function of proteins, in auto-inflammatory pathways. As a postdoctoral fellow at NCI, Dr. Mansfield constructed and performed pre-clinical development of a therapeutic immunotoxin, which is currently in clinical trials. She earned her Ph.D. in biochemistry at the Johns Hopkins University and her B.A. at the University of Pennsylvania.
Mayne, James, T.	Dr. James Mayne is Group Director, DSE Laboratories in the Drug Safety Evaluation section of Pfizer Global Research and Development in Groton, Connecticut. In this capacity, Dr. Mayne oversees the Departments of Molecular and Investigative Toxicology, Genetic Toxicology and Safety Pharmacology. He has been actively involved in the application of in vitro and molecular technologies to toxicology problem solving throughout his tenure at Pfizer. Dr. Mayne received his Ph.D. and post-doctoral training in Toxicology from Cornell University. He was board certified in General Toxicology in 1990 and has been an active participant in a number of professional societies including the Society of Toxicology and the American College of Toxicology. Dr. Mayne has published over 25 original research articles and book chapters dealing with mechanisms of toxicity and issues in preclinical drug development, and has made numerous presentations to professional, academic and industrial groups regarding strategies for incorporating emerging technologies into preclinical drug testing.
Mendrick, Donna	Dr. Donna Mendrick is the Vice President of Toxicology at Gene Logic, Inc. She was on the Editorial Board of the Journal of Histochemistry and Cytochemistry for 8 years, a member of the NIH SBIR Immunology Study Section for 8 years, and a member of the Board of Directors of the National Kidney Foundation of Massachusetts for 4 years. Prior to joining Gene Logic in 1998, Dr. Mendrick was a Group Leader in Pharmacology at Human Genome Sciences, Inc. where she planned and directed acute and chronic toxicity, developmental, and ADME studies for IND submissions, performed in-house pharmacology experiments, and directed two Project Teams. She was an Assistant Professor in the Department of Pathology at Harvard Medical School

	prior to leaving in 1995 to join Human Genome Sciences. Dr. Mendrick received her Ph.D. degree from S.U.N.Y. at Buffalo in the field of immunopathology.
Meyer, Robert	Dr. Robert J. Meyer joined the FDA as a medical reviewer for the Division of Oncologic and Pulmonary Drug Products in July of 1994. In February of 1996, he was named Medical Team Leader within the newly formed Division of Pulmonary Drug Products. In August of 1999, Dr. Meyer was named Director of the division. This division, now called the Division of Pulmonary and Allergy Drug Products has regulatory responsibility for all drugs (excluding biologics) indicated for the treatment of diseases of the upper and lower respiratory tract, including drugs for asthma, COPD and allergic rhinitis. In addition to his work within the Division, Dr. Meyer chairs the Chlorofluorocarbon Work Group for CDER, and is a member of the Aerosol Technical Options Committee (ATOC) of the United Nations Environmental Programme (UNEP). Dr. Meyer came to the FDA from the Oregon Health Sciences University (OHSU) in Portland where he was an Assistant Professor of Medicine in the Pulmonary and Critical Care Division and was Co-Medical Director of Lung and Heart/Lung Transplantation at OHSU. Dr. Meyer received his B.A. degree in Natural Science from Lehigh University in Bethlehem PA in 1980 and his M.D. degree from the University of Connecticut Medical School in Farmington in 1984. Dr. Meyer completed a Residency in Internal Medicine (1984-1987) and a Chief Medical Residency (1987-1988) at the University of Connecticut / Newington VAMC Internal Medicine Program. He then performed a Fellowship in Pulmonary and Critical Care Medicine (1988-1991) at the University of Vermont in Burlington.
Papaluca-Amati	Dr. Marisa Papaluca Amati is the Deputy Head of Sector for Safety and Efficacy of medicines, EMEA. She has a Degree in medicine and surgery (University of Rome). She completed a Research fellowship in the State University of Rome in the area of clinical immunology, oncology and cellular immunology till 1983. Her speciality is in internal medicine, and has done Post-graduate studies in cardiology and endocrinology. From 1984 to 1994, Dr. Papaluca Amati was the Medical Director of the Pharmaceutical Department of the Italian Ministry of Health. In charge of the Operative Centre for Community Procedures, Italian member of the CPMP (Committee for Proprietary Medicinal Products), EU rapporteur and expert for a number of ICH topics (E5, S6). Member of the International CIOMS Working Groups I and II on pharmacovigilance. She joined the EMEA in 1994as Scientific Secretary of the CPMP Biotechnology Working Party from 1995 till 2000. Dr. Papaluca Armati's increasing responsibilities in the EMEA included the following: Deputy Head of Sector in the Biotech/Biologicals 1998- 2000; Deputy Head of Sector for Safety and Efficacy of medicines and Group leader of the therapeutic group Oncology/Cardiovascular 2001 to date; EMEA Project leader for innovative therapies and product development strategies (gene therapy, cell therapy, pharmacogenetics etc).
Ryan, Stephen	Dr. Ryan joined AstraZeneca in April, 2001 as Director and Genetics Advisor in Experimental Medicine. He is engaged in the practical application of pharmacogenetics in drug development, with emphasis on neuropsychiatric disorders. Dr. Ryan has a longstanding research interest in the genetic basis of human epilepsies and related disorders. He and his colleagues demonstrated that mutations with the strychnine-sensitive glycine receptor caused hereditary startle disease, thereby establishing this disorder as the first example of a brain disease due to a genetically defective neurotransmitter receptor. Dr. Ryan graduated from Georgetown University with honors and received his MD from Duke University in 1980. He completed residency training in and is boarded in Pediatrics and Neurology. From 1987-1995 he served in the Department of Pediatrics at the University of Texas Health Science Center at San Antonio, where he directed the Division of Child Neurology. He then joined the faculty of the University

	of Pennsylvania and the medical staff of the Children's Hospital of Philadelphia, where he was co-director of the Division of Child Neurology until 2001. Dr. Ryan co-represents AstraZeneca in the Pharmacogenetics Working Group.
Salerno, Ronald A	Recently employed by Wyeth Research as Director, Worldwide Regulatory Affairs Liaison for the Experimental Medicine Department. The clinical research focuses on the application of pharmacogenomics, pharmacogenetics and proteomics to define biomarkers predictive of drug response and new targets for discovery research. Dr. Salerno is currently an active representative of Wyeth Research in the Pharmacogenetics Working Group. Prior to joining Wyeth, he was employed by Merck & Co. for 28 years and contributed significantly to Merck's vaccine programs while in Research and Manufacturing positions. There he accumulated 11 years of experience in Worldwide Regulatory Affairs for Biologics and Drugs with noted expertise in U.S. and European regulations. During this period he worked as a Regulatory Affairs Liaison Director which included a two-year assignment in Europe. Before retiring, he directed the staff of the Biologics Licensing Department responsible for Worldwide Chemistry and Manufacturing Submissions. Prior to Merck, Dr. Salerno worked in the field of viral-chemical oncology for NCI-sponsored contracts. He earned his B.A. from St. Vincent College, an M.S. from Villanova University and an M.S. and Ph.D. from the University of Maryland in the Biological Sciences.
Schmith, Virginia	Dr. Schmith has over 13 years of experience in clinical pharmacology and experimental medicine working across therapeutic areas such as anesthesia, CNS, oncology, cardiovascular, respiratory, and metabolic. She has advocated the use of novel PK/PD methods (e.g., unique PK/PD and population PK/PD models, clinical trial simulation, surrogate markers, and pharmacogenetics) during drug development at Burroughs Wellcome, GlaxoWellcome, and GlaxoSmithKline. During this time she received numerous performance awards within the company including the President's Award and the Vice President's Award. For the past two years, Ginny has developed and implemented the strategy for incorporation of pharmacogenetics in Phase I/IIa studies in the US. Ginny recently moved to the Genetics Research Division as a Medical Genetics Advisor in PK/PD and is now responsible for implementing the overall strategy for using pharmacogenetics in early drug development, focussing on issues that span across therapeutic areas. Ginny received her B.S. in Pharmacy in 1984 and her Ph.D. in Clinical Pharmaceutical Sciences in 1989 from the University of Pittsburgh. She is also currently an Adjunct Assistant Professor at the University of North Carolina-Chapel Hill School of Pharmacy.
Shaw, Peter	Dr. Peter Shaw is currently an Associate Director in the Pharmacogenomics department at Bristol Myers-Squibb. His research group utilizes genomic approaches for target and biomarker identification, as well as, the discovery of markers that can be developed into reagents to predict efficacy and safety of drugs. The group interacts with different divisions across the whole drug development pipeline from early discovery to life cycle management to apply and integrate pharmacogenetic studies in the discovery and development of novel therapeutics. Peter is also on the steering committee of the Pharmacogenetics Working Group. This group is comprised of representatives from pharmaceutical companies that meet to advance the understanding and development of pharmacogenetics by openly addressing and disseminating information on non-competitive topics such as ethical, legal, and regulatory issues. Peter received his Ph.D. from Aberdeen University in1987 and then, at NYU Medical Center, studied gene regulation. Prior to joining BMS he headed the drug metabolism group at the Pan Vera Corporation which was involved in characterizing and developing novel commercial systems using recombinant human enzymes.

Sistare, Frank	Dr. Sistare has served since 1995 as Director of the Division of Applied Pharmacology Research within the US Food and Drug Administration's Center for Drug Evaluation and Research. The Division is responsible for implementing research strategies in pharmacology and toxicology to strengthen the scientific basis for regulatory decision making and to minimize human risks to pharmaceuticals. He served previously as Branch Chief of this Division's Molecular Pharmacology Branch. Since coming to the FDA his research has focused on the conversion of costly and labor-intensive animal hormone bioassays to *in vitro* alternatives, and more recently on the infusion of emerging molecular toxicology technologies into pharmaceutical safety evaluation strategies. These strategies have included transgenic mouse models for carcinogenicity and photocarcinogenicity assessment, and applications of genomic and proteomic approaches to a number of insidious drug-induced toxicities including vasculitis, cardiotoxicity, nephrotoxicity, and hepatotoxicity. He received his BS in Pharmacy from the University of Rhode Island, and earned his Ph.D. in Pharmacology at the University of Virginia. He was awarded a postdoctoral PRAT Fellowship and later a Senior Staff Fellowship at the National Institutes of Health. Dr. Sistare is a Captain in the Public Health Service Commissioned Corps and has received several PHS Unit Commendations, as well as PHS Meritorious Service, Commendation, and Achievement Awards, and CDER and FDA awards for excellence in laboratory research. He is a member of the Society of Toxicology and the National Capital Area Chapter of SOT, and serves or chairs numerous FDA regulatory committees and working groups including co-chair of FDA's Genomics and Proteomics Intercenter Working Group.
Spear, Brian	Dr. Brian Spear is Director of Pharmacogenetics within Global Pharmaceutical Research and Development at Abbott Laboratories. Dr. Spear graduated from Amherst College with honors, and received his Ph.D. from Yale University after which he carried out research at the University of Colorado as a Jane Coffin Childs Fellow. From 1976 to 1982 he was an assistant professor in Biological Sciences at Northwestern University where he headed a laboratory studying chromosome structure and genome organization. At Abbott Laboratories since 1982, Dr. Spear has held positions as Laboratory Head in Molecular Biology, Director of Research and Development in Agricultural Products, and Director of Technology Assessment and Acquisition in the Abbott Diagnostics Division. In his current position he is responsible for directing activities in pharmacogenetics and cellular and molecular toxicology. Dr. Spear has published numerous papers on chromosome structure, function and evolution, biological pesticides, and pharmacogenetics.
Temple, Robert	Dr. Robert Temple is Director of the Office of Medical Policy of FDA's Center for Drug Evaluation and Research and is also Acting Director of the Office of Drug Evaluation I (ODE-I). ODE-I is responsible for the regulation of cardio-renal, oncologic and neuropharmacologic/psychopharmacologic drug products. The Office of Medical Policy is responsible for regulation of promotion though the Division of Drug Marketing, Advertising, and Communication, for assessing quality of clinical trials through the Division of Scientific Investigations, and for a variety of other policy initiatives.
Watson, Mark	
Woollett, Gillian	Dr. Gillian R. Woollett is Associate Vice President Biologics and Biotechnology at the Pharmaceutical Research and Manufacturers of America (PhRMA) - the trade association of the research-based pharmaceutical industry in the US. She earned her M.A. from the University of Cambridge, and D.Phil from the University of Oxford. Her research began on immunochemical isolation of cell-surface antigens of rat leucocytes using the then newly-developed monoclonal antibody technologies, and later focused on immunological responses to malarial parasites as pertinent to the potential for the development of a human vaccine. In 1987, Dr. Woollett joined the

	American Institute of Biological Sciences (AIBS) to manage scientific merit peer review on behalf on USAID, NASA and DOD. In the latter capacity, she was Program Manager for the 1992, 1993 and 1994 scientific peer review for the Army Breast Cancer Research Program with awards totaling over a quarter of a billion dollars, as well as for the Army programs in infectious disease and trauma. She also conducted scientific program reviews for the USAMRDC chemical and biological defense research programs. In 1996, Dr. Woollett joined PhRMA with responsibilities for all activities concerning biologics and biotechnology, including staffing the PhRMA Biomedical Research subcommittee to the FDA and Biomedical Research Key Issue Team, which has the active participation of the CEOs of major pharmaceutical and biotechnology companies. The BR Subcommittee is a forum for the discussion of the promise, ethics and impact of the rapidly-developing new DNA technologies in health care as an area of particular interest. She is publisher of the PhRMA "Genomics - a Global Resource" World Wide Web page accessible from the PhRMA home page at www.phrma.org. Additionally, her responsibilities include staffing the PhRMA Biologics and Biotechnology Committee of expert company scientists; liaising with the Center for Biologics Evaluation & Research at FDA; being the PhRMA media representative for biotechnology, especially genomics; and expressing appropriate industry concerns and coordinating responses, domestically and internationally, to the proposed Protocol to be added to the Biological Weapons Convention and other issues of significance to the pharmaceutical industry such as BSE.
Worobec, Alexandra	

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