Impact of Pharmacogenomics on FDA's Drug Review Process

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No Clear or Consistent Definition: For This Presentation

Pharmacogenomics (PG)

The study of hereditary differences in either gene expression profiles at the RNA level or nucleotide sequences at the DNA level for the purposes of better understanding variability in disease phenotypes, disease progression, and dose-response. PG data can help in choosing a drug and selecting a dose.

PG Data: Microarrays

- Quantitative gene expression profiling at the RNA level using target tissue or surrogate tissue
- Goal is to identify biomarkers
  - to diagnosis disease or molecular subtypes of disease
  - to monitor disease progression or assess severity
  - to predict clinical outcome of drug treatment *a priori*
  - to measure drug response *posteriori*
  - to develop a diagnostic or drug response predictive test

PG Data: Genotyping

- Whole genome scans or sequence profiling of specific gene nucleotides at the DNA level using blood or tissue samples
- Goal is to identify SNPs (alleles) or haplotypes
  - common validated variants of drug metabolism genes
  - custom set of SNPs related to safety or efficacy
  - population analysis of responders vs nonresponders
  - to include or exclude patients from treatment
  - to guide dose selection *a priori*

Regulatory Pathway for Submission of PG Data Is Unclear

- When PG data should be submitted to FDA?
  - most data is exploratory and not suitable for regulatory decisions
  - exception is drug metabolism genotypes
- What formats can be used for submission?
  - standardization of assays and reports is evolving
- How will PG data be used in decision-making?
  - based on validity of biomarkers

Current Regulations: Submission of PG Data During IND Phase

"Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, *on the basis of which* the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations"

CFR Section 312.23(a)(8)

Current Regulations: Submission of PG Data To Unapproved NDAs

"The NDA is required to contain reports of all investigations of the drug product sponsored by the applicant and all other information about the drug product *pertinent to an evaluation of the application*…..from any source"

CFR Section 314.50

Draft Guidance to Interpret Regulations and Facilitate Progress in PG

Guidance for Industry

Pharmacogenomic Data Submissions

October 31, 2003

CBER, CDER, CDRH

Genomic Data Submission Workshop

November 13-14, 2003

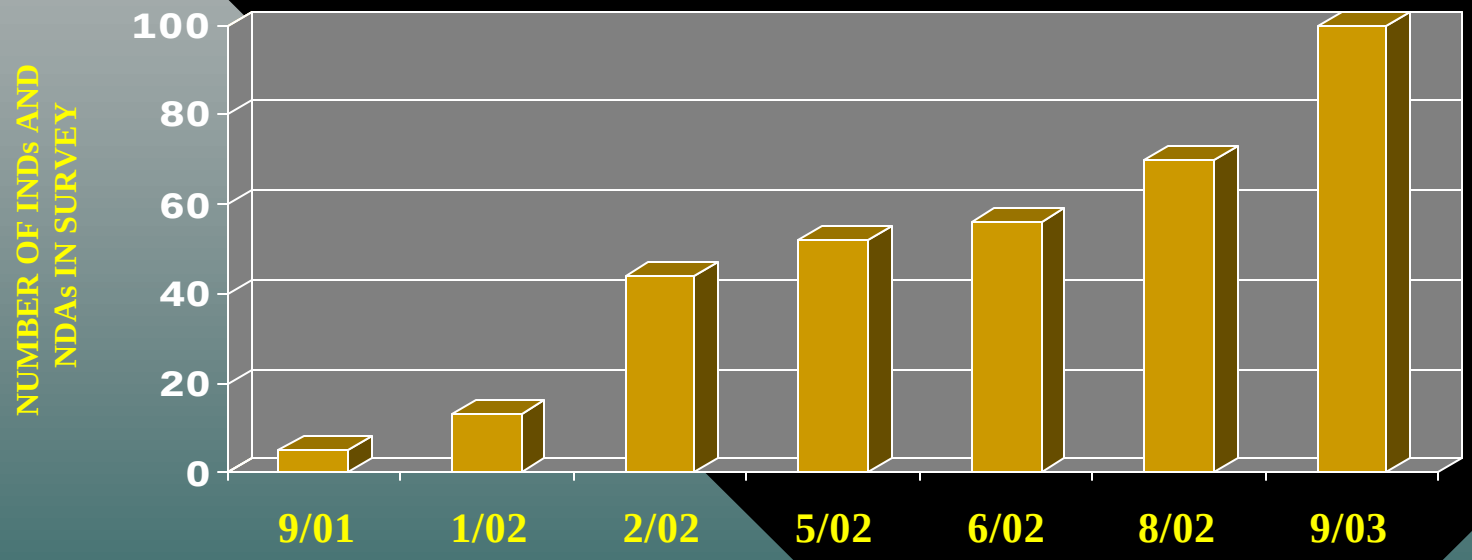
Washington, DC

When Is Sponsor Required to Submit PG Data?

- Guides decision-making in animal studies or human trials
- Supports a claim related to dosing, safety or efficacy
- Provides information or recommend uses of PG tests in drug labels

Valid biomarker: measured in an analytical test system with well-established performance characteristics, and described within a framework that establishes its toxicological or clinical significance

Informal Survey of INDs and NDAs Shows Increased Use of PG



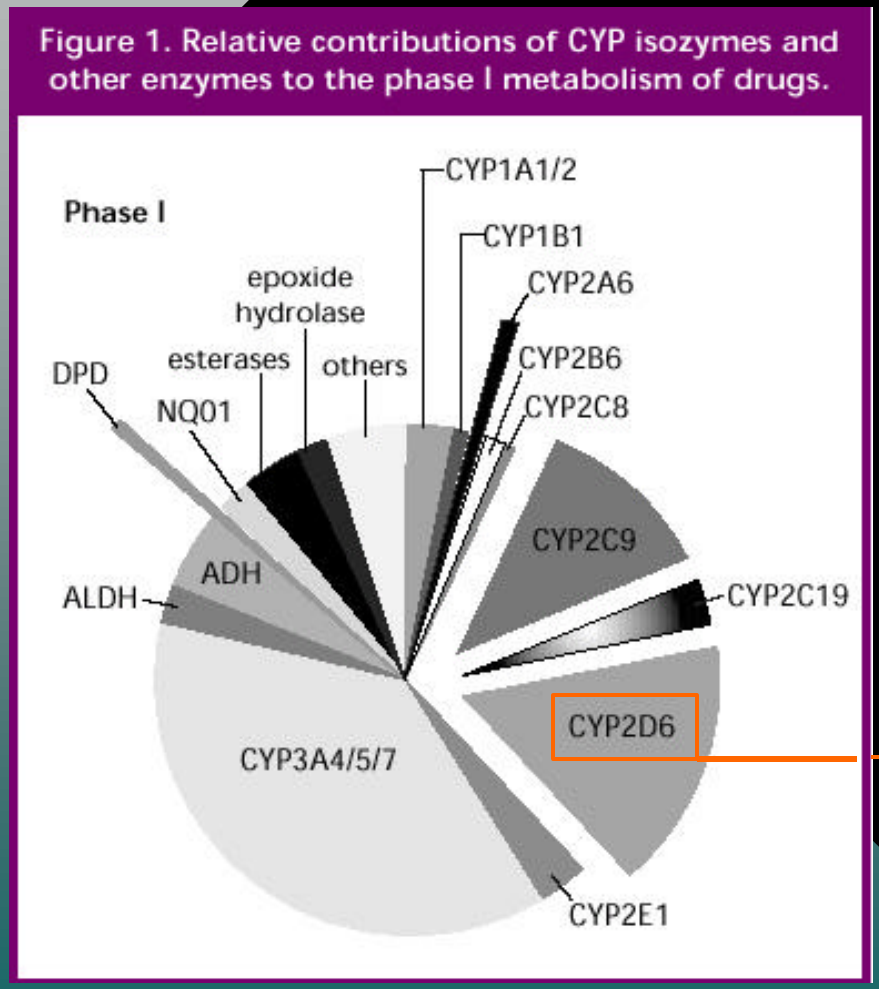
Types of PG Data

- Microarrays
  - relatively new, techniques and test procedures not well validated, exploratory
  - interpretation of toxicological or clinical significance unclear, hypothesis-generating
  - extrapolation of findings across species or patient population tenuous
  - few examples in INDs but some informal meetings with sponsors

Types of PG Data

- Genotyping
  - more mature techniques and test procedures with several well-established biomarkers
  - interpretation of toxicological or clinical significance unclear, hypothesis-generating in some cases
  - extrapolation of findings across patient populations depends on racial distribution of alleles
  - most of the examples in INDs and some examples in NDAs

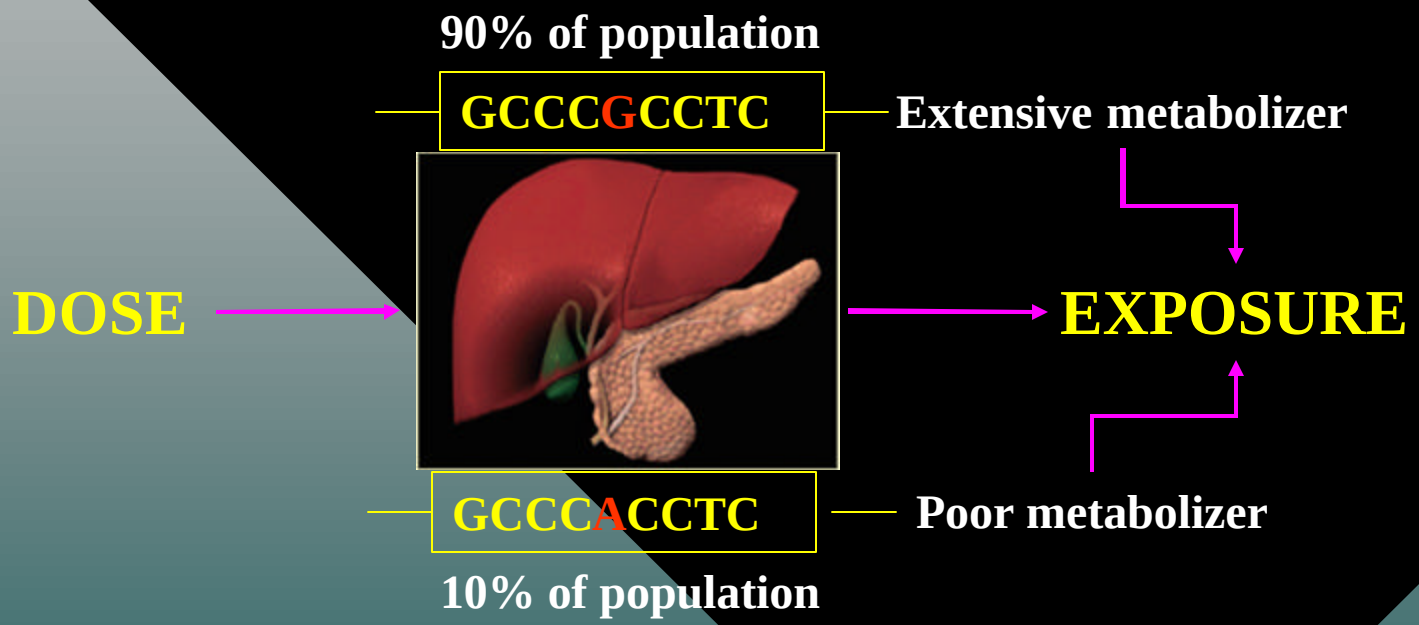
Example of Well-Established Biomarkers: CYP P450 Enzyme Alleles



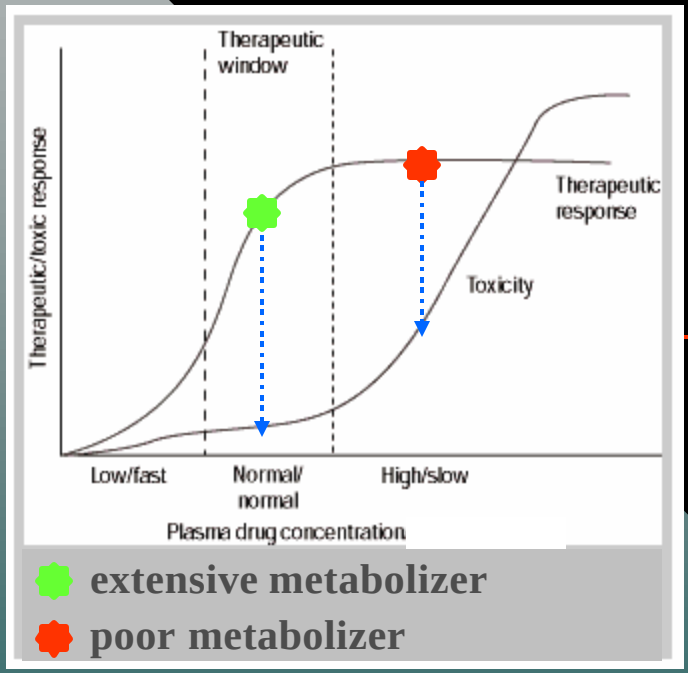
- **Responsible for metabolism of 30 % of all Rx drugs**
- **Over 200 million Rx's for CYP2D6 drugs per year**

Family: CYP 2
Subfamily: CYP 2D6
Gene: CYP 2D6*3

Genotype-Phenotype Associations Recognized in Scientific Community



Example: SSRI (2D6 Substrate) for Childhood Depression



Efficacy: childhood depression rating scale, improvement in up to 9 different symptoms

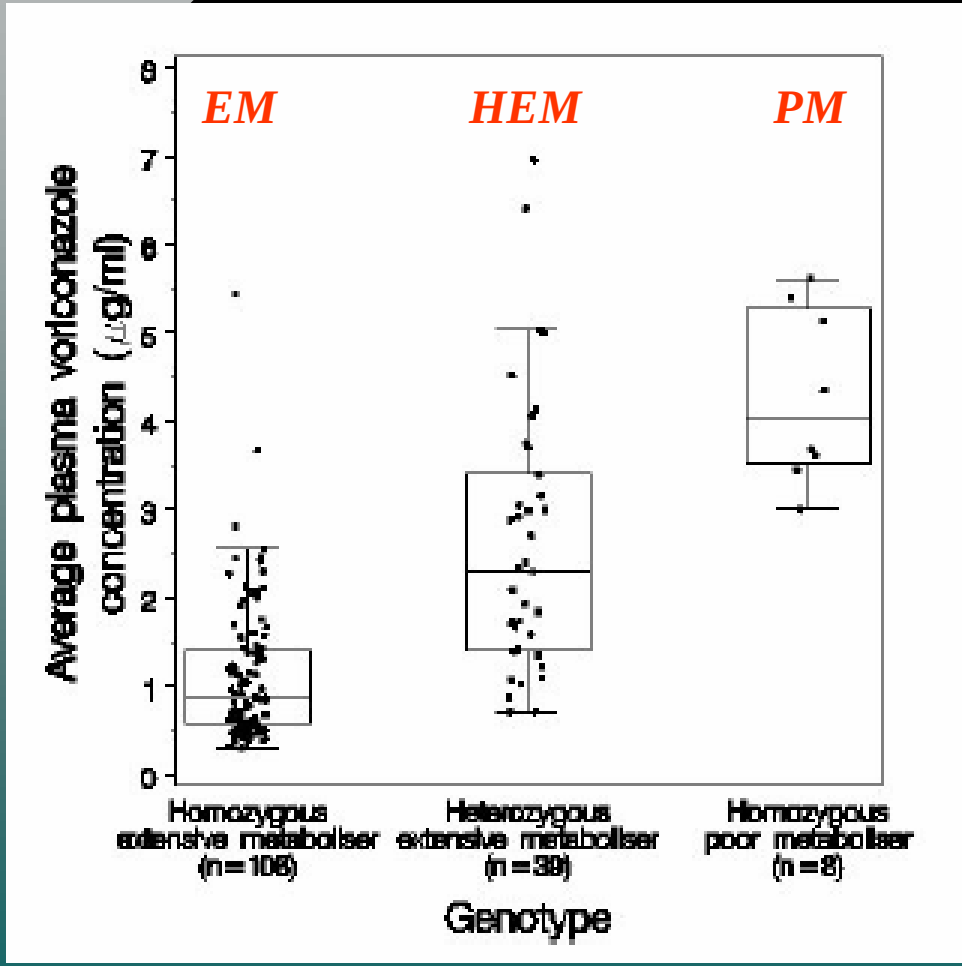
Safety: CNS difficulties, long-term growth and suicide potential

Voriconazole (Vfend^{R})

- Antifungal approved in May 2002 at an oral dose of 100-200 mg BID
- CYP2C19 is major metabolic enzyme controlling clearance and exposure
- Most common side effect is visual distrubances (34%) and most serious *potential* adverse event is QT prolongation (drug interactions)

FDA Antiviral Drugs Advisory Committee Briefing Document from Pfizer, 8/30/01

Genotype as a Covariate in Early Clinical Pharmacology Studies



Genotyping of patients was not done in the Phase 3 RCTs

Co-Variates and Dosage Adjustments

Co-Variate	*Changes in Exposure*	*Recommended Dosing Adjustment*	*Prevalence in Population*
Body Weight < 40 kg	2.0-fold	50 % reduction	2.3 %
Hepatic Impairment	3.2-fold	50 % reduction	???
2C19 Genotype*	2.0-fold (HEM) 4.0-fold (PM)	No dose reduction	26% (HEM) 2% (PM)

** Caucasian data*

Racial Differences in Phenotype and Genotype

Racial Group	CYP 2C19 Phenotype (PM)	CYP 2C19 Genotype (Alleles)
Caucasions	2 – 5 %	*2A, *2B (2 – 5 %)
Asians	13 – 23 %	*2A, *2B (20 – 30 %) *3 (15%)

Atomoxetine (Strattera^{R})

- NE reuptake inhibitor of ADHD approved in January 2003
- CYP2D6 is major metabolic enzyme controlling clearance and exposure
  - 7% Caucasians, 2% African-Americans ~ PMs
    - 10-fold higher AUC, 5-fold longer $t_{1/2}$ compared to EMs
- CYP 2D6 genotype obtained under double-blind conditions in clinical trials
  - 3017 EMs and 237 PMs (7.3%)

CYP 2D6 and Treatment Outcomes: Retrospective Analysis

Patient Discontinuations

All Patients	EMs	PMs	p-value
Adverse Event	5.8%	8.9%	0.063
Lack of Efficacy	26.0%	17.3%	0.002

At doses < 1.2 mg/kg/day (Source: R. Hockett, DIA Annual Meeting, 2003

Strattera® Label

Human PK

A fraction of the population are PM's resulting in ...

Drug-Drug Interactions

Inhibitors of CYP2D6 in EM's increase exposure...similar to PM's

Adverse Reactions

The following ADR's were either twice as frequent or statistically significantly more frequent in PM's compare to EM's...

Laboratory Tests

Laboratory tests are available to identify CYP 2D6 PM's...

This Is Consistent With Labeling Regulations

- 21 CFR 201.57
  - if evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug

Improving Risk/Benefit of Approved Drugs Using PG

Updating Information in the Approved Label for 6-Mercaptopurine: Introduction

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Pediatric Oncology Subcommittee Meeting
Rockville, Maryland
July 15, 2003

6-Mercaptopurine (6MP) and Childhood Acute Lymphoblastic Leukemia (ALL)

- ALL is a life-threatening disease and 6MP can cause life-threatening toxicities
- Dose titration (dosing size, duration and intensity) is major determinant of long-term EFS and myelosuppressive effects
- 6MP is metabolized to pharmacologically active thiopurine nucleotides by thiopurine methyltransferase (TPMT)

TPMT Genetic Polymorphism

- Well-documented, causal link between TPMT polymorphism and clinical effects, including toxicity

Table 3
Genetic Determinants of Thiopurine Methyltransferase Activity

Gene Frequency	Enzyme Activity	Allele
89%	Normal to high	$TPMT^{H}/TPMT^{H}$
11%	Intermediate	$TPMT^{H}/TPMT^{L}$
0.33%	Low to Absent	$TPMT^{L}/TPMT^{L}$

If heterozygote: approximately 50% activity, yielding less 6-MMP and more 6-TG. Very likely to respond to therapy; however, much higher risk of myelotoxicity; requires reduction in dose (33% of usual).
If homozygous mutation: minimal activity, yielding negligible 6-MMP and high 6-TG. Very high risk for severe myelotoxicity; drug contraindicated.
If wild type: normal to high activity, yielding normal to excessive 6-MMP levels; variable outcome.
TPMT, thiopurine methyltransferase; 6-MMP, 6-methylmercaptopurine; 6-TG, 6-thioguanine.

TPMT Testing

- PG tests are available and feasible to use for identifying these patients and guide optimal dosing
  - TPMT *2 (~ 5%), *3A (~85%) and *3C (~5%)
- Commercial laboratories operating under CLIA, and in some cases, GLP conditions
- Academic laboratories operating under research protocols

Pediatric Oncology Subcommittee recommended revision of the 6MP label to include update information on TPMT

Summary

- While the technology and biomarkers are new, the fundamental concept of using PG to enrich populations, exclude patients from studies and guide dosing is not new
- For co-development of a PG test and drug, FDA would recommend submission of complete information on both test (e.g., IDE) and drug (e.g., NDA)
- Analytical validity of established PG tests rely on internal QC programs typical of CLIA and/or GLP laboratories (sample handling, incoming RNA and DNA integrity tests, + and - controls, duplicates, etc), voluntary proficiency testing results