Drug Development and Regulation in the Age of Pharmacogenomics

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
April 25, 2003

Translation of innovative science to bedside medicine

Issue:

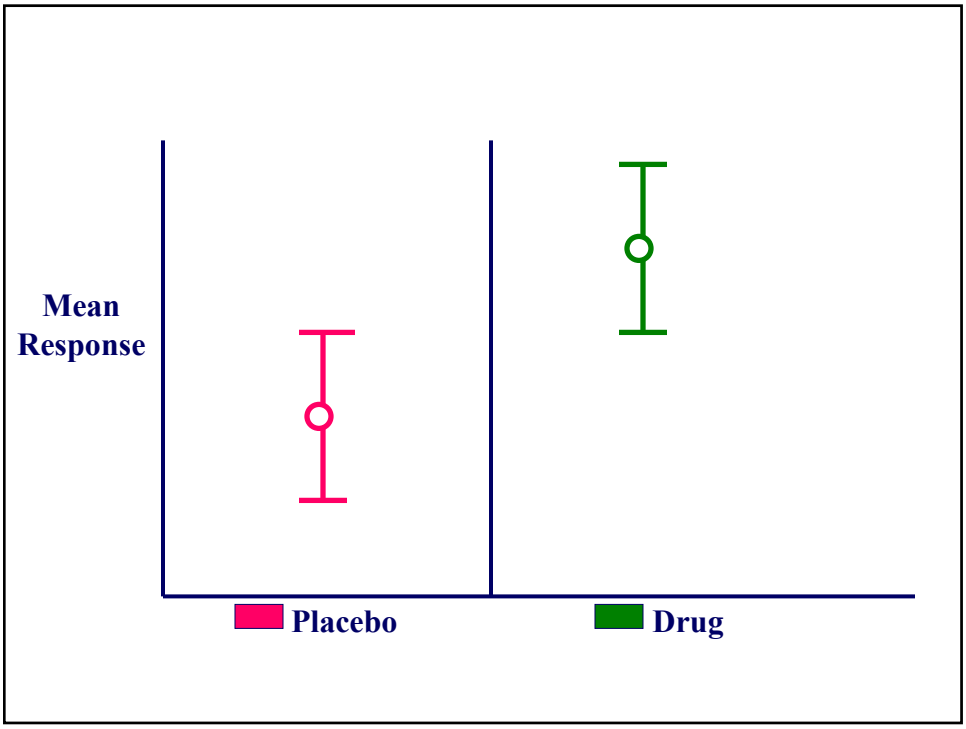
- New science of pharmacogenomics (and increasingly, proteomics) applied extensively in drug development
- Potential to revolutionize process
- Most of the data not seen by regulatory agencies, partly out of concern for how it will be used
- Need an approach that will enable free exchange of information, help advance the science & technology & aid in the timely development of appropriate regulatory policies

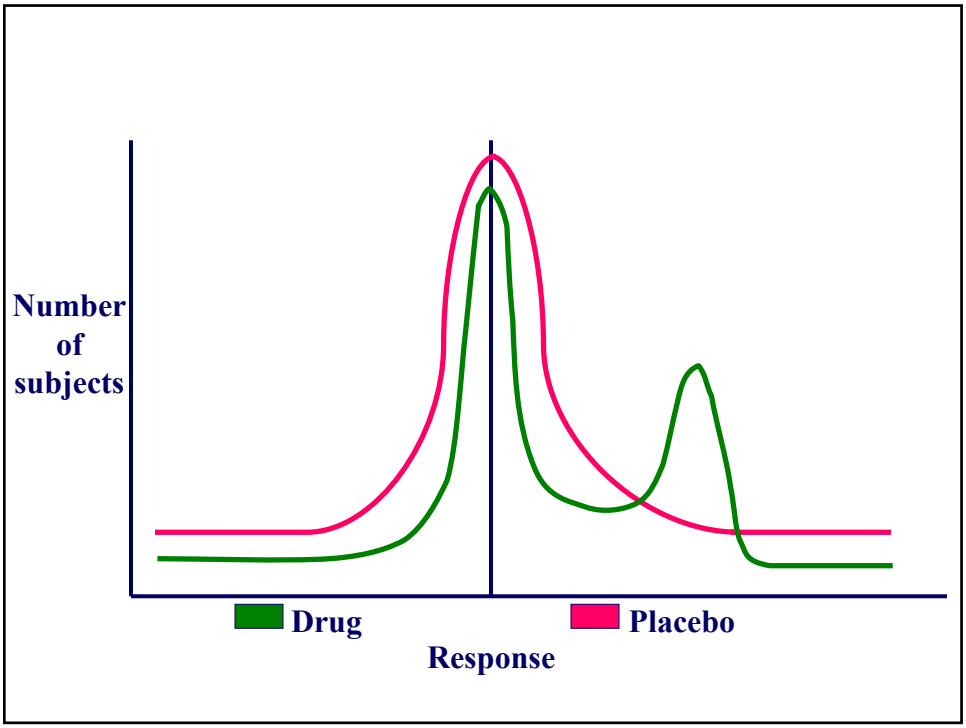
Background

VARIABILITY IN HUMAN RESPONSE TO DRUGS: A major barrier to effective therapeutics

Variable Effectiveness

- For many drugs (leaving aside antibiotics, antivirals, etc)…
- Size of treatment effect from randomized trials is < 10% of outcome measure
- Many conclude that effect is "small" or that "drug doesn't work"





Variability in Drug Toxicity

- Drug vs placebo: each drug has consistent pattern of side effects over placebo rate.
- Observed with common as well as rare events
- Some attributable to known pharmacologic effects; others "idiosyncratic"
- Current medical approach is at the level of organ function, or is observational

There is an Inherited (Genetic) Component to Variability in Drug Response

- Pharmacogenomics (PG): Application of genome-wide RNA or DNA analysis to study differences in drug actions
- Pharmacogenetics : Study of genetic basis for interindividual PK differences

Efficacy Response: Three Types of Genetic Variables Contribute

- Genetic diversity of disease pathogenesis:
- Variable drug metabolism:
- Genetically based pharmacodynamic effects

Drug Toxicity: Genetic Contributions to Variability

- Genetically based interacting state
- Differences in drug metabolism
- "Toxicodynamic" interactions

How Important are these Differences?

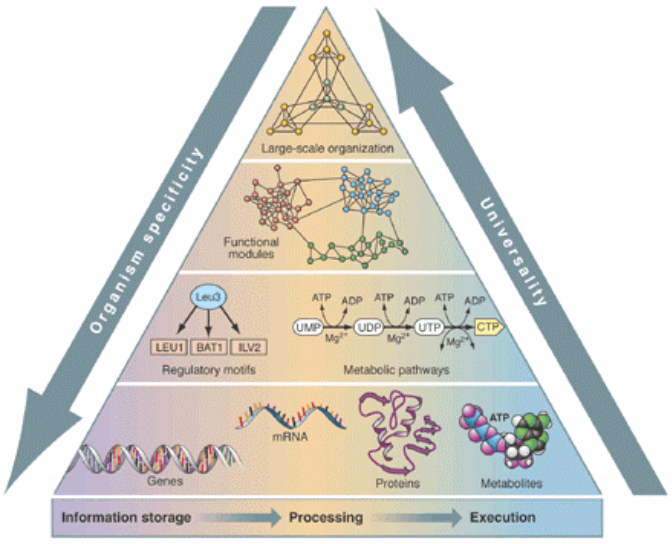
How much of the variability will be explained by genetic differences?

At the Level of the Individual, a Genetic Difference may:

- *Determine* drug response
  Enzyme deficiency disease
- *Highly influence* drug response
  Polymorphic drug metabolizing enzymes

Individual Drug Response

- However, many responses will be---
  Emergent Property of multiple gene product interactions with each other and with environmental factors
- Many individual genetic differences - or even patterns of differences - may have a small effect on drug response



Oltvai and Barabasi, Science, 298, 25 Oct 02.

Current Drug Development

- Satisfactory determination of efficacy--but on a population basis
- Determination of drug toxicity is observational--based on animal and then human exposures
- Carcinogenic and reproductive toxicity potential based on *in vitro* and animal studies

Potential Uses of PG in Drug Development

- Improve candidate drug selection
- Develop new sets of biomarkers for toxic responses in animals and humans--eventually minimize animal studies
- Predict who will respond to a drug
- Predict who will have serious side effects
- Rationalize drug dosing

Potential Impact of PG on Drug Development

- Move from current empirical process to mechanism-based process, hypothesis driven
- Lower cost, faster process resulting in more effective, less toxic drugs for smaller population

How is PG being used now?

PG and Drug Development: Discovery and Lead Candidate

- Target identification
- Evaluating cellular or animal responses to different candidates
- Not part of regulatory submissions

PG and Drug Development: Nonclinical

- Exploratory studies: cells and animals
- Directed studies: genes of interest
- Explanatory studies: evaluate an observed toxic response
- "Toxicogenomics": develop predictive response patterns

PG and Drug Development: Human Studies

- Sort disease syndromes into subgroups based on genetic differences in pathogenesis and evaluate differential responses to treatment
- Evaluate use of genetic/phenotypic tests for metabolizer status to predict dosing

Human Studies

- Search for genetic differences in "responders" vs "nonresponders-- markers for different PD response
- Seek genetic explanation for severe or catastrophic side effects
- SNP and gene expression screening

Obligations of Drug Regulators

- Determine if drug is safe and effective
- Protect human subjects enrolled in trials

Legal requirements: FD &C Act

- Safety: evaluate reports of "all methods reasonably applicable to show whether or not such drug is safe for use under the conditions…in the proposed labeling"
- Effectiveness: "adequate and well controlled trials" to show that "the drug will have the effect it purports to have under the conditions of use"

IND Submission requirements: 21 CFR 312.23(a) (8)

- Pharmacology and toxicology information "on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations"

NDA Submission requirements: 21 CFR 314.50

- Nonclinical studies. d (2) (I): submit "studies that are pertinent to possible adverse effects"
- Clinical d (5) (iv): submit "data or information relevant to an evaluation of the safety and effectiveness of the drug product"

Issues to Resolve

- When/how to use developing PG information in regulatory decisions?
- When is the information "reasonably applicable" to safety?"
- Under what circumstances is submission to FDA needed?

Plan

- FDA to establish policies on PG data
  - What types of data required/not required to be submitted
  - What types of data appropriate for /not appropriate for regulatory decision - making

Submission Requirement?

- Based on interpretation of regulations cited above
- Any data actually used in protocol decision-making in people needs to be submitted
- Sponsor may submit data to bolster claim or scientific position
- For most results, submission NOT required

Submission of Data

- If submission not required, how will FDA develop a knowledge base about the field?
- We will request voluntary submission of results--these results will not be used in regulatory decision making

When will FDA use the data for regulatory decision-making?

- FDA will apply a threshold determination to required data
- Data submitting voluntarily (for information purposes) will not be used in decision making
- Data submitted by sponsor to make a case will be evaluated

Valid Biomarker

- When the meaning of a genetic test is well understood and of known predictive value, results from testing animals or patients should be submitted to FDA
- Research or exploratory tests are not suitable for making decisions on safety or efficacy of a drug

Public Input

- FDA will develop threshold and policies using public and transparent process with advisory committee oversight

Plan

- Publish Guidance for Industry
  - Decision tree for submission requirements
  - Decision tree for use in regulatory decision making
- FDA would establish Interdisciplinary PG Review Group (IPGRG)
  - Centralized review of information
  - Ongoing policy development

Plan

- **FDA is also actively working with the private sector on standardization issues**
- **FDA will issue guidance on format of submission and data**

Examples: Toxicology Studies

- Required submisison: No current example
- Voluntary submission: We are interested
- Explain an animal toxicity finding: up to sponsor

Example: Toxicology

- Q: What if a study shows increased expression of a (proto)oncogene after drug exposure
- A: Many common drugs have elicited this finding in toxicity studies

Example: Clinical Pharmacology Studies

- Genotyping/phenotyping trial subjects for CYP450 isoenzyme polymorphism
- Value and meaning of information is well known and relevant to assessing
  - assessing outliers in PK studies
  - evaluating toxicity
- Should be submittted to FDA

Example: Clin Pharm studies of CYP450 Isoenzymes

- Q: Might this information need to go in the drug label?
- A: Yes , if it is clinically relevant (Strattera)
- Q: Will FDA force the sponsor to limit the drug to certain phenotypes?
- A: No, but dosage modification may be proposed if clinically useful

Example: Clin Pharm Studies of P-glycoprotein Efflux Transporter Genotype

- Q: If patients are screened in a clinical study, is submission needed
- A: No, if correlation is observed, more study would be needed to establish usefulness and predictability of information
- FDA would be interested in voluntary submission

Example: Screening patient in a clinical trial to predict response

- Q: Would results be used in regulatory decision-making?
- A: No, value not understood
- Q: If sponsor submitted data showing greater response in one subgroup, would FDA limit label indication to that group?
- A: NO

Example: Screening patients to predict response

- What if screen were used to select patients for a clinical trial (enrichment)?
- A: Data and rationale would need to be submitted to FDA
- Would sponsor be required to limit indication to specific patients?
- A: Only if they were studied exclusively

Screening Patients to Correlate Adverse Event

- Does genomic data gathered on patients during trial need to be submitted to FDA ?
- A: No
- If analysis indicates a potential correlation with an adverse event, how would this finding be interpreted by FDA?
- A: As a potential biomarker, would need more evaluation in additional trials and diverse populations

Summary

- Pharmacogenomics holds great promise for drug development and rational therapeutics
- The pharmaceutical industry is increasing the use of these techniques
- Free and open exchange of results between industry and FDA is needed to ensure appropriate development of regulatory policies

Summary

- Concerns about how data will be used by regulators has stifled exchange
- FDA will develop clear policies on use of pharmacogenomic data in regulatory decision-making
- We all look forward to the advances in medicine and health that these techniques will bring