DRUG DEVELOPMENT

Can pharmacogenomics make a difference in drug development?

Fred D. Ledley

Pharmacogenomics is expected to improve the efficiency of discovering and developing new drugs. To date, however, the benefits of genomics have been restricted to drug discovery. Genetic maps, expression arrays, and molecular methods for studying gene function and expression are now used routinely to find new therapeutic targets, identify lead compounds, and demonstrate pharmacological effects. The question is whether pharmacogenomics can also make a difference in drug development.

There are important differences between drug discovery and drug development. Discovery is an expansive process involving research into the mechanisms of disease, the selection of biological targets, and the identification of compounds that modulate the disease. Development is focused on establishing the efficacy and safety of a single compound through phased clinical trials to achieve marketing approval. Drug development is constrained by the high cost of clinical investigation and fact that each day required to achieve marketing approval can reduce the economic value of a product by many millions of dollars.

The problem is that many pharmacogenomic approaches and technologies cannot be applied within the scope of conventional clinical trials. The biggest problem is the limited statistical power of pivotal clinical trials. Multicenter trials designed to test drugs in diverse populations do not provide the genetically defined subgroups, sib pairs, or families required for linkage analysis. Therefore, pharmacogenomic approaches must rely on less powerful methods for demonstrating association with genetic markers.

The limited number of patients who are treated with a new chemical entity (NCE) before a new drug application (NDA) is submitted also limits the scope of studies that can be performed. The average number of patients who receive a drug before an NDA is <4,000. A statistical analysis of genetic effects requires a sufficient number of patients with each possible combination of genetic factors to achieve statistical significance. The number of patients that is required increases exponentially with the number of genes studied and the number of variances within each gene. Therefore, it is difficult to perform any meaningful analysis of multigenic effects in conventional clinical trials.

And even if the effects of each gene are considered independently, the number of genes that can be tested is still limited. It is important to recall that, by definition, a p value of $p < 0.01$ means that random chance will provide a "false" positive result 1% of the time. Thus, an analysis of 1–500,000 single nucleotide polymorphisms (SNPs) in a conventional clinical trial design will predictably produce 1–5,000 false positive results, in addition to any true genetic associations. While statistical corrections can be made for multiple ascertainment, these can require large numbers of patients, increasing the time and cost of the trials.

Finally, the use of pharmacogenomic data in an NDA to achieve drug approval requires genetic analysis to be incorporated prospectively in the design of pivotal trials. Thus, the association between an NCE and a specific gene must be established based on the limited number of patients enrolled in phase II or non-pivotal phase III studies. In this setting, genome-wide SNP maps or arrays with thousands of genes are unlikely to provide useful information.

Pharmacogenomics will have an impact on drug development only if the complexity of the questions that must be asked in clinical trials can be reduced. This can be accomplished in several ways.

There is accumulating evidence that the genetic influence on drug action may involve significant single gene effects. While common diseases are highly multifactorial, discrete genetic effects on the kinetics, safety, or efficacy of major classes of drugs have been described. These include genetic effects on metabolism that alter pharmacokinetics and effects on pathways of drug action that alter pharmacodynamics. By focusing on the genes that affect drug action, rather than on the genes involved in the pathogenesis of disease, the likelihood of achieving a commercially meaningful result within the constraints of a clinical trial can be increased.

Focusing on those genes and variances that are most likely to have significant pharmacological effects rather than on randomly selected genetic markers can further reduce complexity. Informatic tools and experimental models of drug action can be used to identify genes that are most likely to affect the action of a drug. Molecular methods can also be used to identify all common variances within a gene and characterize those variances that alter the structure and function of the expressed product or its level of expression.

Genetic methods can also be used to increase the statistical power of genetic analysis. A critical contribution will come from identifying multiple variances within each gene and performing association studies based on the haplotype (the specific set of variances present on each allele in an individual) rather than on individual SNPs. Association studies based on the haplotype have far greater sensitivity than the analysis of individual SNPs. Haplotype studies, however, require new diagnostic technologies to localize variances on specific chromosomes of the individual. Many conventional genotyping technologies for SNPs are not applicable to haplotyping.

Finally, studies of variances that are present in the population at high frequency or those that exert dominant effects will be more feasible than studies of rare or recessive genetic effects. While pharmacogenomics may be used to exclude patients from clinical trials, thus reducing the total number of patients that receive the drug, it may be necessary to screen large numbers of patients to identify the appropriate subset. The process of simply identifying prospective patients for clinical trials is often the rate-limiting step in patient accrual and the timeline of clinical investigation.

The potential benefits of pharmacogenomics on drug development are profound. Achieving these benefits requires a clear focus on technologies that can be applied within the paradigm of conventional development. With the economics of drug development already constrained to the point that many approved drugs never recover their development costs, it is unlikely that pharmacogenomic strategies that require any significant increase in the scope or cost of development will be adopted by the industry. The challenge then for pharmacogenomics is to invent and implement the novel technologies that can meet drug development's needs. ///

Fred D. Ledley is president and chief scientific officer of Variagenics, Cambridge, MA. (fledley@variagenics.com)