Pharmacogenomics

a new paradigm for drug development

Pharmacogenomics offers the opportunity to adopt a new paradigm in drug development. The pharmaceutical industry is faced with a number of challenges including relatively low productivity and success in bringing new drugs to market. Investors demand that pharmaceutical companies deliver several new drugs to the marketplace each year. Additional pressure in the form of price control comes from government, managed care and insurance reimbursement institutions. Pharmaceutical companies are rethinking the old drug development paradigm and many are investing in pharmacogenomics as a new approach to the discovery, development and marketing of new drugs.

By Michael P. Murphy, MSc

Pharmacogenomics will increase the number of new viable drug targets and decrease the risks associated with development. Incorporating pharmacogenomics into drug development will eliminate the unpredictable response of drug treatment due to genetic polymorphisms that affect metabolism, clearance and tolerance. The efficacy of new drugs will become more predictable as we correlate genetic changes in drug targets, receptors and transporters with associated patient response. Ultimately, pharmacogenomics promises to change how physicians choose drugs and the correct dose based on each individual's unique genetic profile. For now, this important tool can impact the way pharmaceutical companies develop drugs provided they are willing to accept a new paradigm that recognises that drugs rarely work in all patients.

The promises of pharmacogenomics

Pharmaceutical companies, physicians and the public are anticipating the promise of significant advancements in medicine brought on by the 'genomics revolution'. Pharmacogenomics, the study of heritable traits affecting patient response to drug treatment, holds its own promises (**Figure 1**); to forever change the way drugs are developed and ultimately, the way in which drugs are chosen for patients based on their individual genetic make-up. Understanding the underlying genetics behind a patient's response to therapy should allow pharmaceutical companies to develop safer and more effective drugs. In addition, understanding how individuals are genetically predisposed to risk of disease may result in new drug targets, thereby leading to new classes of drugs designed to delay or prevent disease onset. Many in the pharmaceutical industry have made significant investments in pharmacogenomics with the expectation that it will help eliminate the unpredictable nature of drug development, bring new products to market aimed at preventing common diseases and create premium pricing for their products[1]. A new paradigm in drug development and healthcare has begun and some would argue that Pandora's box has been opened, leaving pharmaceutical companies not with the decision of whether they will or will not participate, but how and when[2-5]. This article hopes to examine those factors that have brought pharmacogenomics to the forefront of drug development. The opportunities and hurdles facing pharmaceutical companies embracing the pharmacogenomics paradigm are presented in the context of the major business challenges facing the pharmaceutical industry.

Figure 1
The promises of pharmacogenomics

Evolution from pharmacogenetics

Pharmacogenomics has evolved from pharmacogenetics, focused primarily on genetic polymorphisms (mutations) responsible for interindividual differences in drug metabolism and disposition. Genotype-phenotype correlation studies have validated that inherited mutations result in two or more distinct phenotypes causing very different responses following drug administration[6]. For example, mutations in the cytochrome P450 gene CYP2D6, results in poor, intermediate, extensive, and ultra-rapid metabolisers[7]. Each of these phenotypic subgroups experience different responses to drugs extensively metabolised by the CYP2D6 pathway ranging from severe toxicity to complete lack of efficacy.

There are several examples where prospective genotyping could be used to ensure that those with appropriate metabolism and efficacy phenotypes are targeted for therapy (**Table 1**)[6,8,9,10]. Using pharmacogenomic testing to choose the proper drug and dose prior to therapy has been validated in case controlled studies[6,11,12]. These studies evaluated patient's predicted phenotype (ie, poor metabolisers) to determine their ability to metabolise approved drugs. This approach has not yet taken hold for new drugs being developed. In fact, with the exception of Trastuzumab (Herceptin®) no other compounds have been advanced through clinical trials and later approved based on their linkage to pharmacogenomic traits.

Future pharmacogenomic studies will incorporate all of the genetic factors that affect patient outcome including metabolism, drug target, transporter proteins and receptors. Bridging new findings from genomics and the human genome project will further expand the scope of useful genetic markers. How quickly will this evolution take place? Consider that despite our well-established knowledge of variants found in drug metabolism genes (some discovered more than 20 years ago) it is still not routine practice to incorporate pharmacogenetic studies while drugs are developed. There are still not enough documented cases demonstrating the cost-benefit of this approach. Pharmacogenomics companies working in partnership with the pharmaceutical industry will need to provide further evidence that pharmacogenomics can provide safer, more focused clinical studies that also save development time and expense.

Shifting to the new paradigm

Most companies proactively conduct preclinical studies to determine the contribution that cytochrome P450s might have on metabolism and distribution given the well-established fact that many of these genes exhibit genetic polymorphisms[1]. Including specific phenotypic subgroups during Phase I studies ensures that toxicity and safety issues are identified early in clinical development. Indeed, drugs that appear to have less than desirable toxicity are discovered when companies use pharmacogenomics to ensure the inclusion of volunteers with the poor metaboliser phenotype in Phase I clinical trials[1].

When a compound demonstrates efficacy or safety in a subset of patients as demonstrated by pharmacogenomic studies, companies must decide if there is a viable market to justify continued development. Continuing development of a compound

Figure 2
Citation from FDA Guidance document outlining the importance of identifying genetic polymorphisms in order to allow the approval and use of drugs

> **"When a genetic polymorphism affects an important metabolic route of elimination, large dosing adjustments may be necessary to achieve the safe and effective use of the drug... indeed in some cases understanding how to adjust dose to avoid toxicity may allow the marketing of a drug that would have an unacceptable level of toxicity were its toxicity unpredictable and unpreventable."**
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> *From FDA's "Guidance for Industry, Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro" April 1997.*

that appears to demonstrate less than full efficacy in the intended patient group carries uncertain risks for companies. The drug may not be approved and if it is, it may be labelled with restrictions concerning marketing claims and use. Not considering pharmacogenomic studies can also carry risks. The ultimate failure of the current development paradigm occurs when a drug is approved and marketed and later withdrawn from the market due to unforeseen toxicity in a subpopulation of patients. Propulsid®, Rezulin®, Seldane® and Duract® serve as examples of drugs pulled from the market because the companies did not appreciate the extent of adverse events that occurred in a subset of patients.

These drugs were developed under the old development paradigm that largely ignores the fact that humans are genetically different, resulting in a variable response to drugs. These companies assumed the 'one dose fits all' philosophy that presumes that patients studied during clinical development had a common biological background with respect to metabolism and efficacy. Genetic studies confirm that this is not the case, leaving the question of why we would continue to develop drugs under the old paradigm. As early as 1997, the FDA advised pharmaceutical companies to consider a new approach and incorporate the knowledge regarding genetic polymorphisms into drug development (**Figure 2**). Importantly, the FDA recognised that identifying genetic polymorphisms might allow for the safe dosing, marketing and approval of drugs that would otherwise not be approved. Companies incorporating pharmacogenomic testing throughout drug development can significantly increase the likelihood of developing drugs that benefit most patients without severe adverse events in a relative few.

Factors influencing pharmacogenomics adoption by pharmaceutical companies

The pharmaceutical industry faces enormous challenges in the near term due to mounting pressures to produce high revenue generating 'blockbuster' drugs in the face of tighter regulation and controls over pricing. The many challenges the industry faces include:

'Pharmaceutical companies need to improve on the productivity and success of bringing new products to market'

- **Tremendous pressure to get 3-4 new chemical entities (NCE) through the drug development pipeline and approved each year in order to sustain the expected double-digit growth.** Investors have come to expect this rate of growth from the pharmaceutical industry and hence the value of a company's stock depends in large part on their ability to bring several competitive new drugs to market each year.

- **A 'crisis' in the number of novel drugs entering the development pipeline[13].** Despite new technology in high throughput screening and combinatorial chemistry, there is a significant decrease in the number of novel lead compounds. The number of new break through drugs approved has steadily declined since 1996[13]. Many of these compounds fail because they lack appropriate biological activity (efficacy) and tolerance profiles (toxicity) to

allow continued development. Mergers among large pharmaceutical companies witnessed of late are in part oriented towards accumulating promising leads to feed the development pipeline. In addition, an increased number of companies are buying or licensing new compounds from smaller biotechnology companies.

● **Relatively poor percentage of lead compounds that survive the clinical trial process to approval.** Only about 10% of compounds that enter clinical development are ever approved as drugs. Given the investment required for clinical development there is an enormous waste of time and money spent to bring drugs to market. An improvement of even a few percent could have a dramatic effect on the costs associated with drug development.

'The pharmacogenomics solution'

Completing the sequencing of the human genome and the discovery of mutations that are responsible for human disease will bring new targets for intervention by pharmaceutical researchers. The increase in new drug targets will create the opportunity for new lead compounds with a significant impact on the drug development process. No longer will drugs be directed at disease symptoms but at preventing or delaying disease onset. Linking specific mutations to disease risk will however, require significant investment in both family linkage and population studies. Once these associations are made they will have to be validated by case-controlled studies. Pharmaceutical companies willing to invest in these types of studies will have the opportunity to develop proprietary pharmacogenomic markers thereby positioning their products apart from others still operating under the old drug development paradigm.

There are several pharmacogenomic service companies available to provide genetic testing for clinical development. Every clinical trial patient can be tested prospectively for known genetic polymorphisms, including those responsible for metabolism. Those who are ready to invest in the pharmacogenomics opportunity will extend their analyses to Phase II-IV clinical trials to stratify the patient population and target responders based on linkage to efficacy markers. Retrospective analyses can be done at the conclusion of studies provided proper informed consent is taken along with a patient sample (typically 5-6 milliliters of whole blood). Pharmacogenomic service companies can help to identify possible unknown variants found in target or receptor genes by resequencing the

Gene	Drug	Responder Genotype or Phenotype	Nonresponder Genotype or Phenotype
TPMT	Thioguanine, azathioprine, mercaptopurine	Extensive Metaboliser	Poor Metaboliser
CETP	Pravastatin	B1	B2
ACE	Enalapril	Insertion (I)	Deletion (D)
5-HTT	Fluvoxamine	Long (l)	Short (s)
CYP2C9	Warfarin	Extensive Metaboliser	Poor Metaboliser
CYP2D6	Desipramine	Extensive Metaboliser	Poor Metaboliser
HER2	Trastuzumab	HER2neu positive	HER2neu negative

Table 1
Examples of genes that have well-established responder or non-responder genotypes and phenotypes

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appropriate candidate genes. Several of these service companies are capable of providing clinical diagnostic testing so that physicians can refer patients for testing prior to prescribing newly approved drugs linked to pharmacogenomic traits.

Pharmaceutical companies need to develop a pharmacogenomic profile for those patients who respond to therapy. This knowledge can be used throughout clinical trials to decrease the total number of patients enrolled in trials by studying a homogeneous population without compromising the power of these studies. By focusing on the responder subgroup, companies can eliminate much of the variability in drug development. The drug development period offers an ideal opportunity to identify and optimise treatment based on inherited genetic traits.

'The development and marketing of new drugs requires a substantial investment on the part of the pharmaceutical companies'

● **The relatively high cost of marketing and developing new drugs.** Spending on research and development has tripled since 1990 to $26.4 billion. On average, pharmaceutical companies spend more on marketing than on research and development. Companies spend more than $7bn per year on marketing and sales[13]. Frustrated by the unsuccessful launch of new drugs these companies have shifted their focus from pharmaceutical research and development to drug marketing. Investment in development, marketing and sales requires a return of $300-$600 million for each new approved drug. Obviously, companies can no longer afford to bring drugs to market only to discover that a subset of the population suffers from life threatening adverse events.

● **Pharmaceutical companies are facing pressures to lower drug prices and competition from generic branding following patent expiration.** In the US, states such as Maine have instituted price controls on drug prescriptions. The US congress and other states are considering similar legislation. Countries including Australia, the UK, Germany, France, Italy and Spain all have limitations on either reimbursement to patients for drug prescription or out right pricing limitations imposed on the pharmaceutical industry[14]. Companies must now justify the cost-benefit before their new drugs can be integrated into the national healthcare system in these countries. Given the competitive landscape for today's pharmaceutical industry they must go beyond demonstrating medical need and justify the cost in comparison to previously accepted treatment.

● **An increased awareness of the morbidity and mortality costs associated with Adverse Drug Reactions (ADR) and the need to minimise toxicity and improve efficacy for new drugs.** Most in the industry are aware of recent findings published in the *Journal of the American Medical Association*[15] that found that ADRs are between the fourth and sixth leading cause of death in the US. Regulatory agencies will increasingly require that companies establish any toxicity or safety issues in those individuals who are genetically predisposed to ADRs due to either deficiencies in metabolism (clearance) or those individuals lacking the appropriate phenotype to benefit from treatment (efficacy). Examples of approved drugs with genetic traits linked to response are shown in **Table 1**. If these drugs were being developed today would it not benefit the pharmaceutical companies, physicians and their patients if treatment were in part based on pharmacogenomic testing? These are just a few examples where genotyping patients prior to therapy can ensure safe and effective treatment.

'The pharmacogenomics solution'

Companies that utilise pharmacogenomic profiling during clinical trials to include only those predicted responder phenotypes should see considerable cost savings by limiting clinical trial enrollment. A recently published study in which poor metabolisers were excluded from enrollment allowed the sponsor to decrease the trial population by 10% for a pivotal Phase IIIb study[11]. The cost per patient for a Phase III trial for a central nervous system (CNS) product is estimated at between $8,000 and $12,000 per patient. Therefore, eliminating 10% of the trial population of known non-responders in a trial involving more than 450 subjects, can save between $360,000 and $540,000 for a single trial. Additionally, some predict that the contribution of pharmacogenomics to medical outcome is expected to add $500m in extra revenue per drug[16]. Obviously, companies will not appreciate the financial impact of pharmacogenomics in development or following approval until a careful pharmacoeconomic assessment is done to compare the current development and marketing approaches with those incorporating this new paradigm. More studies are needed to convince the industry that revising current business models and incorporating pharmacogenomics (with a possible segmented market)

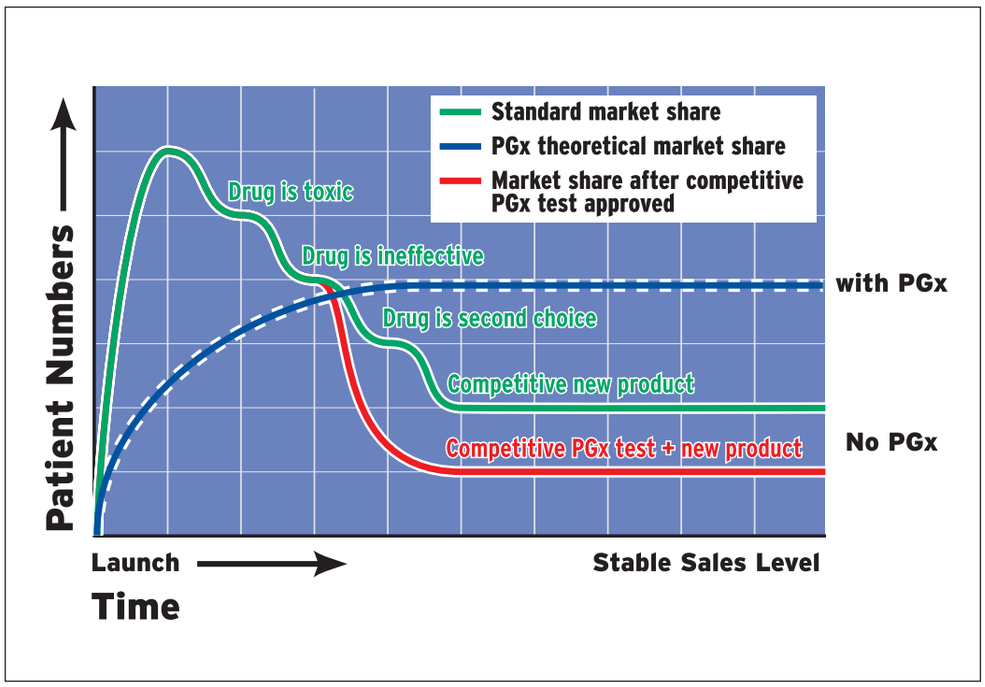

Illustration courtesy of Ken Conway, Millenium Predictive Medicine

Figure 3
Theoretical model demonstrating the impact of pharmacogenomic tests associated with newly marketed drugs

will be more than offset by the potential savings using this approach.

'Challenges and obstacles affecting the pharmaceutical industry's adoption of pharmacogenomics'

● **The linkage between a pharmacogenomic trait and response in a subset of the patient population will fragment the market for new drugs and may result in labelling restrictions.** The reality is that most drugs do not work in all patients. By current estimates the percentage of patients who will react favourably to a specific drug range from 20% to 80%[16]. Drugs that have known adverse events in a subset of the population such as those caused by deficiency in metabolism (potential liver toxicity) have warnings regarding dosing and may require regular testing of liver function. Of course marketing groups within the industry believe that market fragmentation will result in lost market share, hence decreased revenues and possibly the end of so-called 'blockbuster' drugs. The reality is that drugs that benefit a majority of the patient population and stand in the marketplace with little or no competition still have the potential as blockbusters. Over time the market share can be eroded in the absence of significant competition due to lack of efficacy or worse, toxicity. Physicians are reluctant to continuing to try new drugs when a subgroup of patients fail to respond and the reasons for lack of response are not clear. Patients who do not get better following therapy typically become non-compliant and fail to use drugs at the appropriate dose or schedule.

'The pharmacogenomics solution'

Figure 3 illustrates the theoretical differences in the stability of drug sales from the conventional paradigm to one that incorporates pharmacogenomic testing as a crucial element of product launch. The model accounts for the loss in market share when drugs ultimately demonstrate either toxicity or lack of efficacy in a subgroup of patients (**Figure 3, Green Line**). Additional loss of market potential occurs when the drug ends up as second choice and physicians choose competing products because of uncertainties regarding both toxicity and efficacy in drugs prescribed to patients. In theory, the market share will be further eroded when competitor compounds linked to pharmacogenomics enter the market (**Figure 3, Red Line**). The basis, in part, for this theory is that physicians will initiate therapy and continue patients on drugs based on personalised medicine, that is, prescribing drugs based on previously established pharmacogenomic tests that predict efficacy and lack of toxicity (**Figure 3, Blue Line**). For now the industry is waiting for the first

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successful launch of a drug that requires genetic testing prior to prescribing. Several companies are contemplating the co-development and approval of pharmacogenomic drugs and diagnostic tests, primarily for compounds that demonstrate very good efficacy in a patient subpopulation. The floodgates may be opened after the first successful demonstration of this new approach.

Future of pharmacogenomics-based drug development

The long-term future of pharmacogenomics-based drug development looks something like:
Lead compounds coming out of preclinical pharmacogenomic testing will ideally be chosen based on the fact that they are metabolised and eliminated by several alternative pathways. Phase I volunteers who might be at risk for toxicity due to metabolic status for these same paths of elimination might be identified and studied for dose limiting tolerance. Genetic traits that predict efficacy (ie, receptor status) will be a focus of pharmacogenomic studies during Phase II-IV clinical studies to optimise the population of patients who will respond positively to treatment. Pharmacogenomic tests validated as positive markers of response will be developed as molecular diagnostic tests. Pharmaceutical companies will partner with pharmacogenomic and diagnostic companies to develop panels of tests that will be submitted for regulatory approval in parallel with the new drug applications.

In the near term, pharmaceutical companies are likely to use pharmacogenomics in drug development for the following applications:

- Development rescue, rather than rescue old drugs which have been long abandoned. Companies are more likely to use pharmacogenomics to determine if a genetic element is involved in the subpopulation of patients who either demonstrate toxicity or lack of efficacy for an otherwise promising lead compound. As outlined in this review, they will either decide to terminate development or those companies embracing the new paradigm will develop the necessary tests to isolate the responder phenotype using genetics and later co-market the appropriate diagnostic tests to allow approval of the drug.

- Drugs targeted to those individuals with an underlying genetic component predictive of disease onset. Diseases such as cardiovascular disease (coronary heart disease and restenosis) with a clear genetic component will be targeted to those individuals at predisposed risk.

- Drugs targeted to life threatening disease. Cases when the treatment involves drugs that are either expensive or quite toxic will utilise those pharmacogenomic tests that clearly differentiate potential responders. Examples include targeting Herceptin® for Her2neu positive breast cancer patients and fluorouracil for dihydropyrimidine dehydrogenase (DPD) efficient metabolisers.

Pharmacogenomics has already made an impact on drug development. Pharmacogenetics is used in preclinical and Phase I studies to identify important drug metabolism genetic polymorphisms. The list of genetic traits linked to efficacy continues to grow and be used for selecting drug treatment. Within the next five years, pharmacogenomics will evolve as an integral part of the drug development process. In concert with this paradigm shift will be the development of new diagnostic tests designed to assist physicians in selecting the right drug at the right dose. Ultimately patients will be the real benefactors of gene-based drug selection. Personalised medicine will enhance drug therapy by minimising adverse reactions and increasing the chances of successful treatment. DDW

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