Developing Pharmacogenetic Evidence Throughout Clinical Development

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Genetics as a discipline is fundamental for the pharmaceutical industry; it contributes to all therapeutic areas and has an impact throughout the research and development continuum, right up to and including clinical practice. Pharmacogenetics is seen as a significant contributor to increasing the efficiency and effectiveness of pharmaceutical R&D, and it enhances the growing interest in personalized medicine. This article discusses some contemporary issues that influence drug development and examines the potential of pharmacogenetics to reduce the risk and uncertainty that are inherent in the drug development process.

A variety of factors have converged to put unprecedented pressure on the pharmaceutical industry. Lower R&D productivity, an increasing demand from payers that medicines have demonstrated effectiveness, a perception that regulatory barriers have become more rigid, a larger number of patent medicines being converted to generics, an increasing emphasis on drug safety profiles, and dramatic corporate downsizing and mergers are casting doubts on the sustainability of the current business model of the pharmaceutical industry.1 Despite decades of success in drug development, clinical development of a new drug remains a risky and uncertain enterprise. An analysis of the pharmaceutical industry suggests that nearly 90% of clinical programs that initiate human trials fail to achieve registration.2 In addition, the increasing fragmentation of and greater demands placed on clinical development and the accelerated pace of biomedical and genomic discovery are forcing a transformation in traditional clinical development processes.

One of the significant new factors transforming clinical development is the concept of individual benefit/risk and its definition. Personalized medicine is recognized to be an important element in reducing dependence on trial-and-error medicine and improving the efficiency and effectiveness of health-care delivery.3 The Human Genome Project has led to a better understanding of the role that genetic factors play in mediating an individual’s disease risk and response to therapeutics (pharmacogenetics) and provides an opportunity to reduce the uncertainty that is intrinsic to clinical development.4 The question is whether clinical development strategies are keeping pace with the emergent science, the changing requirements of regulatory agencies, and the rising expectations of the healthcare community.

Throughout the drug development process, there are two simple realities: (i) people exhibit variable responses to medicines and (ii) unexpected findings are routine. This article discusses the application of pharmacogenetics to some of the challenges encountered in drug development. Figure 1 is a general representation of the stages of pharmaceutical development and the opportunities for pharmacogenetics to reduce the risks of failure.

**Sampling**

Utilizing pharmacogenetics in pharmaceutical development necessitates a DNA sample obtained with appropriate consent, readiness to incorporate pharmacogenetic strategies into early development planning, and an assessment of the performance of the drug, based on data generated in the course of clinical development. This requires a focus on the response of the individual patient, not simply the mean or average population response. Is the treatment effective in all the subjects or only in some of the subjects? Do some patients experience side effects or adverse events?

A recent survey of industry practices shows that many companies collect DNA samples during some stage of the clinical development pipeline of a drug (A. Warner, A. Bhathena, S. Gilardi, D. Mohr, D. Leong, K.L. Bienfait et al., personal communication). However, there is wide variability with respect to sampling rates among and within individual companies. It is important that every effort be made to collect DNA samples, after obtaining the required consent, from all the subjects enrolled in a clinical trial, throughout the development continuum. Full collection (a DNA sample from all the subjects enrolled in a clinical trial) ensures that the pharmacogenetic results are reflective of the intent-to-treat population, an important consideration for regulators.5 Samples should be collected early in the clinical trial to

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ensure that they are available from all the subjects, even those who withdraw from the trial at a later date. This is particularly important when pharmacogenetics is applied retrospectively to investigate adverse events because these cannot always be anticipated. Having genetic samples already on hand saves valuable time and protects patients from undesirable aspects of exposure to new chemical entities. Recently, a US Food and Drug Administration (FDA)/Drug Information Association Pharmacogenomics Workshop identified a number of proposals that could foster more complete genetic sampling in clinical trials (A. Warner, A. Nelsen, A. Bhathena, K. Fitzgerald, S. Gilardi, E. Kelso et al., personal communication).

The increasing trend toward adopting globally sourced clinical trial designs bears mention in the context of pharmacogenetics. Although this approach offers the opportunity to evaluate drug properties in a diverse population that is more representative of real-world conditions than traditional designs are, it has raised some concerns; it also increases the heterogeneity of the clinical data, thereby potentially confounding the analysis. It is well established that ethnicity-related variability in the frequency of alleles that have an impact on drug disposition is an important contributor to variability in response to drugs. Therefore, it is particularly important to include DNA sampling in the design of globally sourced trials.

**PHARMACOKINETICS/PHARMACODYNAMICS**

It is well established that variations in genes involved in the absorption, distribution, metabolism, and excretion (ADME) of xenobiotics contribute significantly to the pharmacokinetic and pharmacodynamic properties of a drug candidate. As a result, many pharmaceutical companies investigate the associations between these gene variants and the observed interindividual pharmacokinetic and pharmacodynamic variability of drugs in early clinical development (phases I and II). Recently, the European Medicines Agency published a guidance on the use of pharmacogenetics to investigate pharmacokinetic properties of new medicines. ADME pharmacogenetics appears in an increasing number of drug labels approved by the FDA. Emerging evidence with regard to antiplatelet therapy and variations in cytochrome P450 2C19 highlights the importance of ADME genetics in the clinical application of therapeutics. Clopidogrel, one of the top-selling prescription medicines, is a prodrug that is converted to its active metabolite by cytochrome P450s. Individuals carrying loss-of-function variants in the CYP2C19 gene showed reduced response to the drug. Not surprisingly, the frequency of prevalence of the CYP2C19 null alleles varies considerably among ethnic groups, with obvious implications for patient care. In 2010, the clopidogrel label was updated by the FDA to include information on the relationship between metabolizer type and efficacy. Pharmacogenetic observations in phases I and II should not be thought of as meeting medical utility evidentiary standards; however, they do provide an increasing refinement of the individual benefit/risk profile that can be further evaluated in later stages of development.

**SAFETY**

Often, the unexpected observations in drug development occur on the risk side, with the appearance of adverse events. One of the earliest examples of a pharmacogenetic marker associated with a drug-related adverse event is provided by abacavir, a nucleoside reverse inhibitor used for treating patients infected with HIV. It was observed during drug development, as well as during postapproval use, that 5–8% of patients using abacavir experienced a hypersensitivity reaction. Through a combination of retrospective and prospective studies, the genetic marker HLA-B*5701 was identified as a significant risk factor for abacavir-associated hypersensitivity reaction. Although the initial finding was reported and independently replicated in 2002, it was not until a prospective study provided the weight of evidence for the utility of a pharmacogenetic test that changes to treatment guidelines and drug labels were made; subsequently, the adoption of the HLA-B*5701 test by physicians has increased sharply. This remains a persuasive example of the use of genetics to reduce the risk of an adverse event for an individual patient prior to drug exposure. Furthermore, recent groundbreaking work has identified genetic variants that inform the risk for idiosyncratic hepatotoxicity associated with the use of fluvoxacinill and lumiracoxib.

**BENEFIT/RISK**

The benefit/risk relationship is dynamic and is continually refined with increasing experience and knowledge of a drug’s properties. “Knowledge turns” have been described as the time necessary for a new scientific idea to move from hypothesis to application. Routine clinical development often takes 5–8 years, and drug developers and regulators must be prepared to harness new biomedical insights to improve the understanding of the benefit/risk profile of a drug. A recent example of how quickly a knowledge turn can occur that alters development plans is that of KRAS/panitumumab. Panitumumab, a monoclonal antibody directed against the epidermal growth factor receptor, was given accelerated approval by the FDA in 2006 for
treatment of colorectal cancers. Subsequently, evidence emerged that indicated that somatic mutations in KRAS, a component of the epidermal growth factor receptor signaling pathway, were prognostic of a favorable drug response. Fortunately, the drug sponsor had implemented a biospecimen acquisition component in the clinical development program and was able to evaluate this hypothesis with the samples and data on hand. The prognostic value of KRAS mutation status was substantiated and became part of the European Medicines Agency regulatory approval of panitumumab. The FDA asked for an update of the drug label to reflect these new findings.

The increase in the number of drugs directed at specific molecular targets has fostered an interest in new clinical trial designs that incorporate the use of biomarkers, including pharmacogenetic markers. The use of adaptive clinical trials has been the subject of numerous conferences, workshops, and papers. Recently, results were reported for an adaptive clinical trial design incorporating biomarkers to inform treatment decisions for lung cancer patients. Widespread use of adaptive designs will require partnership between regulatory authorities and the drug sponsor to ensure that appropriate consideration is given to the clinical trial design, assessment of the biomarker and its performance metrics, and the end points for the therapeutic agent and biomarker; it is also essential to stress the importance of understanding the performance of the therapeutic in the marker-negative group. To some extent, the uncertainties along the evidentiary path have led to a slower-than-anticipated uptake of adaptive designs in clinical development planning by pharmaceutical companies.

DEFINING “VALUE”

A significant trend in the health-care discussion is the focus on clinical utility and comparative effectiveness. Recent analysis and recommendations by the National Institute for Health and Clinical Excellence in the UK have catalyzed discussions on clinical value and are reshaping the benchmarks for the development of new medicines. The increasing emphasis on demonstrated therapeutic utility, in particular, “personal utility,” will continue to have significant impact on clinical development strategies. The examples cited in this article (panitumumab, clopidogrel, and abacavir) clearly demonstrate the utility of pharmacogenetics in establishing individual benefit/risk profiles, and this information is being reflected in treatment guidelines, drug labels, and reimbursement decisions. However, utility can mean different things to the various stakeholders in the health-care continuum. Traditionally, clinical development establishes the benefit/risk profile in order to support registration of a new treatment. Today, there is increased pressure to use clinical trials to produce evidence for relative efficacy and comparative effectiveness as compared with alternative courses of therapy. Clearly, this shift will require all parties to reevaluate what constitutes a successful clinical development program. Another noteworthy development is the role of health-care payers in promoting the gathering of evidence to support the use of pharmacogenomics to inform treatment decisions.

Pharmaceutical development is undergoing a period of unprecedented pressures and change, and with change comes opportunity. Is it time to broaden the evidence path beyond the randomized controlled clinical trial design focused on assessing population mean values or average benefit/risk? Pharmaceutical innovation will continue to be a risky and uncertain endeavor. However, it is now clear, from numerous examples, that pharmacogenetics can contribute to reducing this uncertainty and improving the benefit/risk profile for individual patients. Furthermore, the evidence regarding the utility of a pharmacogenetic biomarker can be produced during the course of clinical development. There continues to be a general reluctance to integrate pharmacogenetics into routine clinical development, but this reluctance is diminishing, and much progress is evident. To date, pharmacogenetics has often been considered a rescue strategy used to salvage a troubled drug development program. Going forward, pharmacogenetics should be an integral component of a clinical development plan to produce differentiated molecules of value. A general perception is that genetic research has yet to deliver on its early promise. However, the growing number of drug labels with pharmacogenetic information, treatment guideline recommendations based on genetics, and escalating investment in pharmacogenetics by industry, academia, governments, and institutions are all evidence to the contrary. Integrating pharmacogenetics into routine clinical care to benefit patients will require cooperation from all stakeholders to develop the evidence path necessary to define utility.

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CONFLICT OF INTEREST

The author declared no conflict of interest.