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Regulatory Perspectives on Pharmacogenomics

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Introduction

Since Genes determine our susceptibility to disease and how we respond to medicine, Pharmacogenomics (PGx), the use of genetic information to individualize drug therapy, is one of the most immediate and important applications of the human genome project. PGx has been advocated as a way to improve the success of drug development and clinical trials and for prescribing decisions based on genetic test results. The increased interest in PGx and "personalized medicine" is accelerating because of ongoing concerns about adverse drug reactions and the high failure rates in drug development.

The advent of PGx-based tests and drug therapies presents challenges to the US FDA in pursuing its mandate of protecting the health and safety of the public. It has become a major priority for the FDA to develop knowledge in the area of PGx and to use regulatory processes to guide the development and approval of PGx-based drugs and diagnostics that will be safe and effective for public use as well as "least burdensome" to industry sponsors.

This review will summarize current challenges for international harmonization and faced issues about the regulation of PGx for improving public health safety and translating research to the clinic.

Potential benefits

Pharmacogenomics is one of the fields most likely to have a large potential to influence the safety and efficacy of new products. There are three main ways that pharmacogenomics is applied; The first is to help predict the appropriate dose of a drug. So, we can avoid some of the toxicity of the drug by testing all the patients who come in and making dose adjustments based on their genetic test and response to therapy. The second is to target therapy to a subset of a disease ("tumor genomics"). This means picking the most effective drug for the disease subset. And the third is to test for drug resistance. Resistance testing can help doctors choose the drug that will best match the pathogen and suppress it. If drug resistance is discovered, a doctor can decide to try another treatment option.

The main benefit of pharmacogenomics for consumers is the availability of drugs that have a greater chance of benefit in terms of treating illness. The hope for the future is that through personalized medicine, doctors and patients will be able to make better-informed choices about treatment. Genetic information could lead them to decide which drug to use, whether to lower a dose, or whether closer monitoring of the patient for side effects is needed. The potential of pharmacogenomics for drug companies lies in the discovery stage--being able to create new drugs based on genetic information. A better understanding of genetics and disease helps identify new targets for drugs. This could bring drugs to the market sooner.

Accumulating information related to pharmacogomics will be useful to support reasonable decision making for regulatory agency, to facilitate scientific progress in clinical trials, and to get the best medical outcome, especially effective in treatment of life-threatening illness such as cancer; the right dose of the right drug to the right patients at the right time. Ultimately, this will be contributing to lower the cost of health care.

Pharmacogenetics and Regulatory framework

Given that genetic factors frequently determine inter-individual and inter-ethnic differences in pharmacokinetics and pharmacodynamics of a drug-with all the associated implications for failure of efficacy in some patients and predisposition to adverse drug reactions (ADRs) and drug interactions in others-it is not surprising that regulatory authorities have long recognized the significance of pharmacogenetics in drug development and are now increasingly directing their attention to addressing issues that may arise from genetic heterogeneity of the target patient population.

A number of guidelines from the European Union's Committee for Medicinal Products for Human Use (CHMP), and the Inter-national Conference on Harmonization (ICH) already make direct or indirect references to the need for addressing genetic factors when developing an new chemical entities (NCE). The US FDA was provided guideline of Voluntary Genomic Data Submissions (VGDSs) that are a novel way to share information with the FDA. At the current time, most pharmacogenomic data are of an exploratory or research nature and FDA regulations do not require that these data be submitted to an IND, or that complete reports be submitted to an NDA or BLA. However, voluntary submissions can benefit both the industry and the FDA in a general way by providing a means for sponsors to ensure that regulatory scientists are familiar with and prepared to appropriately evaluate future genomic submissions.

Recently, FDA and the EMEA have agreed to expand the VGDS process to include the option for sponsors to have joint FDA-EMEA VGDS Briefing meetings. This document explains how such requests are received, processed and reviewed by the Agencies. The Japanese Ministry of Health, Labour and Welfare's drug regulatory authority (PMDA) has also issued guidelines in June 2001 that recommend genotyping in all drug development programmes for drugs that are metabolized by cytochrome P450s.

Although the requirements to address these genetic factors are stated in different terms by different regulatory bodies, the net effect of these requirements is that new knowledge concerning pharmacogenetic variations in drug disposition or responsiveness of pharmacological targets will lead to additional requirements for pharmacogenetic documentation for NCE.

Current Situation of Korea

The regulatory agency has to take a leadership role by initiating discussions about pharmacogenomics and work on guidance on how to develop genomic tests and drugs together and on the quality of DNA analysis. Therefore, in Korea, PGx in drug development process is also emphasized and we need to take account that most drugs marketed in Korea have developed by multinational companies. Since Ethnic differences is shown in drug responses, supplementary pharmacogenomic tests with IND done in Korea has been increased. So, these are emphasizing that we need to consider PGx characteristics of Korean in clinical trials and drug evaluation.

Drug Evaluation Department of KFDA is also planning to start the project for establishment of draft guidance and organize the pharmacogenomic information evaluation committee in 2007. They will provide "Guidance for PGx information submission" and Guidance for PGx Data Evaluation of clinical trials in NDA and INDs.

As one of projects to support the above, National Institute of Toxicology Research published reference book that is including ethnic differences information in drug responses and genotypes of interested genes. Based on this PGx information, the PGx database is going to open to the public in October, 2006. So far, there are two official PGx databases (KPGRN DB and PGRC DB) established for personalized medicine and pharmaco-therapy.

Future Regulatory Approaches

In future, substantial pharmacogenetic data will be accumulated and submitted, raising issues that will be important for regulatory integration of these data in the overall drug evaluation and approval processes. Regulatory aspects most likely to be influenced are assessment of efficacy, dose-schedules, ADRs and drug interactions in relation to genotype and communicating this assessment to the prescribing community. Sponsors will seek guidance on how pharmacogenetic data ought to be presented and analysed and may form part of the labeling. Regulators need to start addressing these issues and articulate specific guidance. To this end, both the CHMP and the FDA have already implemented measures for 'briefing meetings' or 'voluntary submissions of genomic data', respectively. The PMDA in Japan recently issued a public consultation document requesting comments on their proposal for preparation of guideline for the use of pharmacogenomics in clinical trials. The outcome of this consultation has resulted in March 2005 in a final guidance note that is very similar to the FDA.

Regulatory action can be taken at the level of providing information to physicians, patients, and other health-care providers via drug labels. Regulatory agencies also need to consider following issues; In the meantime, people & clinician will be resistant to incorporating PGx into prescribing decision due to complexity, cost

and requiring times for individualization. Even Drug companies will consider if there is enough financial benefit from drugs that treat only small segment of people. Legal assurance will be needed so that insurance companies can't use genetic information to discriminate against people having genetic risk for health problems.

Conclusion

It remains to be seen that advances resulting from genome-wide pharmacogenetic studies translate into safe and effective individualized therapy. In the mean time before clearly demonstrating clinical validity and utility in relevant clinical trials, prescribing should comply with the genetic information provided without unrealistic expectations.

Pharmaco-economic assessments may well be required to determine the cost-effectiveness of pharmacogenetically driven prescribing of each 'genetically vulnerable' drug on a case-by-case basis. The important paradigms should include specificity and sensitivity of the genotyping tests, and positive and negative predictive values of the genotype-phenotype associations as well as pharmaco-economic considerations.

We are at a critical stage in pharmacogenomics: the science is not new, but has experienced a significant boost since the human genome project has been completed. Now is the time to capitalize on what basic science has provided and translate it into clinical practice. However, this can only happen if the prescribing community (physicians and other health-care professionals, as well as patients) is being educated and become knowledgeable about pharmacogenomics. Good educators must address: pharmacogenomics will not replace, but enhance, existing good medical practice.