



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London 27 July 2000
EMEA/CPMP/1483/00

**REPORT TO THE CPMP
ON THE EMEA SEMINAR ON THE USE OF PHARMACOGENETICS IN THE DRUG
DEVELOPMENT PROCESS - 5 JUNE 2000**

Introduction

On Monday, 5 June 2000, a meeting was held between CPMP experts, EMEA Scientific Administrators and an informal group of pharmaceutical industry representatives specialised on the use of pharmacogenetics in the drug development process. The first session of the meeting gave an overview of pharmacogenetics and the second session addressed key areas of processes, terminology and validation protocols in clinical studies incorporating pharmacogenetic evaluations.

Today a typical drug development programme usually proceeds on the broad assumption that patients are homogenous groups with little inter-individual variability. However, all patients do not respond to the same medicines in the same way. Some patients may display adverse drug reactions that do not occur in other patients taking the same drug at the same dose. The efficacy of a drug may also display differences between patients.

The differences in the risk/benefit ratio between patients taking the same drug may be caused by differences in their genetic make-up and it is the impact of these genetic differences on therapeutic use that the science of pharmacogenetics aims to unravel.

Pharmacogenetics may be defined as the study of variability in drug response due to genetic factors.

Pharmacogenetics is an area of intense research; in some areas, such as oncology, is already beginning to be used as a tool to aid therapeutic decisions.

In contrast, pharmacogenomics encompasses a broader range of analyses and may be defined as the determination and analysis of the genome (DNA) or its products (RNAs) as they relate to drug response.

However, at present there is not an agreed working definition of pharmacogenomics.

Discussion

- *Disease genetics versus pharmacogenetics*

The analysis of genetics began with the investigation of single gene disorders where there is a high correlation between the presence of an altered gene and the presence of disease.

Genetic analysis now encompasses the investigation of more complex gene disorders where susceptibility genes and environmental factors may interact in the presence of disease.

Pharmacogenetics is a logical extension of the evolution in genetic knowledge and is expected to assist both for more accurate risk and outcome predictions in drug response, and for a more detailed understanding of the molecular basis of diseases. Pharmacogenetic analysis requires a form of genetic testing and this brings with it certain considerations.

It is important to distinguish between genetic testing for the diagnosis or prognosis of disease and the form of genetic testing performed for pharmacogenetics.

In the case of disease genetics, the test is carried out to identify causative gene mutations or polymorphism of disease susceptibility genes, which alter the risk of disease. Testing for these mutations and

7 Westferry Circus, Canary Wharf, London E14 4HB, UK

Tel. (+44-20) 74 18 84 00 Fax: (+44-20) 74 18 85 45

E-Mail: mail@emea.europa.eu <http://www.europa.europa.eu/emea.html>

EMEA 2000 Reproduction and/or distribution of this document is authorised for non commercial purposes only provided the EMEA is acknowledged

polymorphisms, particularly in cases where there may be no effective interventions raises a number of important social, legal and ethical considerations for the individual patient and for their family members.

In pharmacogenetics, genes or genetic markers associated with drug response are tested, this analysis will provide an understanding of the probability or possibility of observing a specific therapeutic response and generally carries a different magnitude of social, legal and ethical considerations for the patient.

- *Methodology: the candidate gene and single nucleotide polymorphisms (SNPs)*

At present, most pharmacogenetic studies are based on correlating patient outcome with variations in genes involved in the medicine's mode of action (e.g. genes for receptors) or metabolic pathway (e.g. genes for cytochrome P450 enzymes). This "candidate gene" approach relies on researchers generating hypotheses relating to the genes and polymorphisms, which may be involved in the variation in therapeutic response.

Any two unrelated human beings will differ by at about 3 million positions in their genetic material (or DNA sequence). Such common variation is called polymorphism and single nucleotide polymorphisms (SNPs) are the commonest form, where the DNA varies by only a single base, or nucleotide. Most of this variation to date has no detectable consequence; whereas some of it is functional and defines variable features such as blood groups etc.

Analysis of SNPs can be used as an adjunct to the candidate gene approach. Advances in the identification and mapping of single nucleotide polymorphisms over the next 1-3 years will provide a high density set of markers across the genome that can be used to identify regions of the genome which may be associated with therapeutic response. In addition, it may be possible to use pharmacogenetic analysis to identify regions of the genome associated with rare serious adverse events.

- *Pharmacogenetics and drug development*

Changes are likely to occur in the way drug development is conducted as a result of pharmacogenetics. While this may lead to a smaller number of patients being investigated in phase III clinical trials it is unclear how many patients will be required in phase I and II as this would involve testing in patients with known polymorphisms of the metabolising enzymes for the drug. Alternatively the SNPs map of the human genome may obviate the need to evaluate the drug in patients with known polymorphisms.

It would seem that a large number of patients have to be studied in Phase I and II in order to find the markers of polymorphism that can predict response. This new scientific approach would have the potential to enable physicians to identify susceptible patients and enhance the risk/benefit ratio for many medicines. This topic will need further discussion.

It is important to have realistic expectations about pharmacogenetics as the information it can provide, especially in early years is unlikely to be an absolute yes/no gate. The analysis of a broad set of genetic markers may only show that a genotypically defined subgroup of patients with a certain disease may have a higher probability of responding in a certain way to a certain drug. In this respect pharmacogenetic analysis during the discussion has been compared to the assessment of blood pressure or lipid levels: raised blood pressure and/or lipid levels are accepted risk factors for cardiovascular disease, however, they do not imply that the patient will definitely suffer a specific cardiovascular disease. During the seminar a statement to the effect that a genetic test is essentially equivalent to a biochemical test was debated. In the context of pharmacogenetics all implications around this point must be highlighted and discussed further.

Conclusions

The practice of pharmacogenetics is a challenge to the pharmaceutical industry, regulatory authorities, medical community, patients and society as a whole with new questions and issues.

Pharmacogenetics is expected to have a wide impact not only on the drug development and regulatory processes but it might also impact on how drugs are prescribed and delivered to patients. There may also be implications for the development and approval of in vitro diagnostics, which apply the techniques of genetic analysis.

Communication and continued education are vital in this rapidly evolving scientific area and it was therefore agreed that discussions of issues arising in pharmacogenetics should take place with a range of audiences (regulators, physicians, and patients) as all interested parties need to share information.

Pharmacogenetics may bring with it implications about how clinical trials are designed and how, in the future, new drugs may be approved and prescribed. In view of the wide range of implications of the pharmacogenetics knowledge in product development, there should be ongoing discussion between the pharmaceutical industry and the regulatory authorities.

In order to develop the necessary technical tools, the informal industry group should work with European Federation of Pharmaceutical Industry Associations towards elaborate proposals for:

- a harmonised terminology for genetics terms required for pharmacogenetic trial protocols and guidelines. The scope and selection of these terms should be defined and agreed by interested parties. As initial step the informal industry group shall submit to the EMEA a proposal on the rationale for the selection of those terms that need to be defined for technical use in pharmacogenetics protocols and guidelines.
- a harmonised approach to pharmacogenetics protocols in clinical trials, where feasible