jects understand whether the pharmacogenetic analysis will provide data about an already recognised, clinically valid measurement or will generate new hypotheses about the genetic basis for drug response that may have to be explored further. Researchers will have to explain to subjects that the latter is only exploratory, with no immediate application to healthcare of the individual patient.

3. Issues for the Educator

3.1 Coping with patient fears and expectations about genetic testing and individually targeted therapy

Healthcare professionals and researchers will have to provide high quality information, outlining what genetic measurements and the pharmacogenetic analysis actually include; for example, CYP2D6 polymorphism and the implications for dose adjustment of a drug metabolised by that enzyme. Patients will also have to be informed that pharmacogenetic testing cannot predict with absolute certainty which patients will respond or experience an adverse event, but that the knowledge gained may help a physician select an appropriate medicine and its dose and thereby improve the overall risk/benefit of the medicine individually for each patient. Thus the individualisation of therapy does not come with a guarantee. Patients will also have to be informed of the evolutionary nature of pharmacogenetics. Genetic applications such as blood grouping prior to blood transfusions have existed for many years, and not all medicines will suddenly appear with pharmacogenetic information. Only by successfully communicating objective information regarding the advances and limitations of pharmacogenetic testing will the achievements of genetics and genomics over the last few decades reach their full potential in furtherance of human health [3].

3.2 Societal, legal and ethical implications

Key stakeholders such as healthcare professionals, researchers, policy makers, purchasers and others will have to play an important role in managing the implementation of pharmacogenetics. If pharmacogenetics is to be used as a tool to achieve improved cost-effectiveness, companies involved in research and development of drugs and healthcare purchasers must have in place the systems to evaluate long-term costs and savings.

Pharmacogenetic profiles do not cause adverse events or lack of efficacy. These profiles are merely a scientific tool that allows one to understand better the variability in patient response to a pharmacological agent.

However, the ability to predict a response will potentially restrict access to certain treatments, for example, only to those patients predicted to have a favourable response. Such restriction may be arguably in the best interests of the patient. However, unless the correlation between genotype and drug response is robust, and all other interventions have been explored, a seriously ill patient might feel that his/her last, and perhaps the only, chance of benefit has been taken away. The physician will have to play a key role in managing the expectations of the patient and making appropriate prescribing decisions.

Physician education will have to improve in terms of molecular medicine, pharmacokinetics, pharmacodynamics and factors, including genetic factors that modulate these parameters. Members of non-medical Institutional Review Boards or Independent Ethics Committees (IRB or IEC) may also require education about genetic testing and its advantages and limitations. Currently there exists a considerable variation, both within and between committees, in terms of opinion and requirements.

Regarding the protection of data, the parties involved must understand and discuss how genetic data should be generated, handled, stored, and used as well as restrictions on access to these data by insurers, employers, and others not involved in the research (see Chapter 9 on "Ethical Issues"). Investigators involved directly in research on patients should inform and assure patients that all of their medical data will be used only for the purposes the patients have authorised. Assurances of privacy and confidentiality will be key to increasing the public level of confidence. There must be agreement among all involved parties regarding how genetic data will be generated, handled, stored and used (especially access by insurers and employers to this information) and if appropriate, ultimately destroyed. This will be essential to assure the patients of their personal privacy and protection.

3.3 Need for information to all stakeholders

Education of all stakeholders is essential in order to realise the potential benefits of pharmacogenetics and to assimilate into future healthcare the knowledge acquired through pharmacogenetic investigations. Information about the impact of pharmacogenetics in terms of demand on healthcare across the society is an important area of education and should be encouraged at all levels, from schools to the general population and especially targeted at the interest groups. In particular physicians, pharmacists and other healthcare providers, upon whom many patients rely totally for advice, must have pharmacogenetics built into their core training.

Acceptance for health-related applications of biotechnology should not prevent continuing balanced communication about the benefits and risks. Key stakeholders include:

- Physicians, pharmacists and laboratory personnel
- Patients and patient groups
- General population
- Healthcare professionals (providers)
- Third party payers (e.g. public health insurance, private insurance)
- Regulatory authorities and policy makers (governments)
- Healthcare industries – pharmaceutical, biotechnology and diagnostic companies
- Academia (researchers and educators)

The ultimate incentive for continued education will be the potential benefits of more effective and safer therapies.

3.4 Educational approach

The promotion of education and provision of information to health professionals about advances in pharmacogenetics and pharmacogenomics are based on the belief that:

- Healthcare globally will be transformed by genetically-driven medicine in the next several decades
- Health professionals will require understanding of the core principles of genetics and the basics of genetics in medicine
- Scientific information about genetics and pharmacogenetics must be current and accurate for education of healthcare professionals

The requirements of each of the stakeholder groups differ. Therefore, programmes of communication and education will have to be well targeted and appropriate to each clinical speciality. Healthcare professionals will not only need to receive appropriate information themselves but also need the skills to manage the concerns and questions from their patients. This is likely to mean a retraining and restructuring of current healthcare services in which education and communications efforts will be pivotal.

3.5 Language

For all stakeholders, the use of clear and relatively simple language is crucial. It should be at a level that is understandable, informative, and appropriate to the target audience. Global consensus definitions of all relevant terminology should be precisely followed when educating stakeholders or conveying instructions to patients. In addition, researchers must

distinguish carefully the different types of genetic testing to ensure that pharmacogenetics (and disease gene testing) is not confused with gene therapy, genetic modification, cloning or genetic engineering. Cultural sensitivities regarding genetic-based information must also be recognised as well as delivering services to patients in a multilingual society.

3.6 The message

Educators must convey clearly the following messages:

- Advances in the field of pharmacogenetics offer opportunities and bring benefits – both therapeutic and economic – for patients, healthcare providers and payers and the health industries alike.
- The ability to potentially prescribe at the outset, the right medicine, for the right patient in the right dose and at the right time, should lead to improved effectiveness, improved efficacy through minimising non-response or delayed response, and safety by avoiding serious adverse drug reactions.
- Advances in pharmacogenetics will be gradual, and acceptance will be accompanied by challenges.
- Pharmacogenetics is distinct from testing for disease-related genes, gene therapy, genetic modification, cloning or genetic engineering.

4. Role of the regulatory authorities

The regulatory aspects of pharmacogenetics are discussed in detail in Chapter 7 "Regulatory Perspectives in Pharmacogenetics". With regard to communication and education of stakeholders including the public, one key area is the development and access to genetic tests and their inclusion in product-related information.

4.1 Genetic tests

The growing connection between diagnostics and therapeutics and the increasing availability of direct-to-public genetic tests will require regulatory authorities to address the level of regulation that is appropriate for various individual tests.

The Human Genetics Commission (HGC) in the UK has recently proposed consideration of regulatory controls and safeguards. For example, genetic tests predictive of serious illnesses should be available only after medical consultation, while other tests may be suitable for wider access. The HGC report "Genes Direct" can be accessed at: http://www.hgc.gov.uk/genesdirect/

However, the debate on which tests should be subject to greater and more stringent regulatory controls is yet to be resolved and harmonised.

4.2 Product information

Regulatory agencies anticipate seeing greater use of cytochrome P450-based genotyping tests in drug development. In turn, this will necessitate inclusion of more information on the use and value of such tests in package inserts.

Since patient information leaflets now require fairly detailed information on tests to be undertaken before a drug is prescribed and dosing regimen as well as contraindications, there will be increasing expectations of appropriate pre-treatment tests from the patients. These would include not only the traditional laboratory-based tests such as an electrocardiogram or liver or renal function tests but also genotyping tests.

5. Role of the media

The media is an important source of healthcare information for the general public. Media descriptions of pharmacogenetics are therefore likely to strongly influence the public perception of the benefits and risks of such applications. Information, knowledge and potential outcomes should be communicated without unduly raising the expectations. Therefore, it is imperative that a strong educational and communication foundation is built so that information can be understood and positioned appropriately by journalists and the sensationalist stories of genetic findings do not prove hurdles to healthcare improvement.

6. Communication and education strategy

6.1 Goals

It is the responsibility of policy makers as well as the industry to provide stakeholders with accurate information on pharmacogenetics.

Reaching and educating these groups with effective communications will require planning and strategic design. It will also require continual effort as new information is applied to everyday life.

These goals should remain at the forefront:

- Create awareness of how the applications of pharmacogenetic research will impact human health, including patient treatment and care
- Communicate research initiatives and findings to educate and update stakeholders especially on their relevance to clinical practice
- Organize and harmonise realistic policy on provision of information (wording and content) by all players (at least within groups such as physicians and companies developing drugs and/or diagnostic kits).

6.2 Implementation

There are a number of means by which to communicate and educate. Methods that are highly effective in promoting good communication and achieving educational goals, especially with regard to pharmacogenetics, include:

- Production of core support materials to ensure consistency and appropriate messages, such as videos, websites, etc.
- Communication of successful research as well as its clinical relevance. This would mean proposing and sharing best practices
- Media outreach programmes
- Organized meetings to coordinate educational and communication efforts
- Sharing of knowledge with key audiences through organized activities
- Roundtable discussions to explain benefits and discuss issues
- Drawing on experience of professions where genetic medicine is a significant part of the practice for information and support; use core competencies of medical schools, regulatory authorities and industry
- Partnerships with advocacy groups

6.3 Development of key messages

Key messages are most effective when relevant and developed with regard to the stakeholders' interests, current knowledge and level of understanding. The interdependency of stakeholders for the effective management of pharmaco-genetics in healthcare should be taken into account. The messages should be the same for both educational and communication activities.

Key message development should:

- Increase awareness of pharmacogenetics and its benefits and impact on healthcare
- Help stakeholders organize and evaluate information about pharmacogenetics and genetics research
- Create a promising, but realistic future with realistic expectations and time frames.
- Differentiate genetic research for preventing or treating disease (related to medicines) from cloning and genetic engineering
- Increase understanding by relating genetic concepts and knowledge to specific applications and benefits

All communications and educational efforts should enhance the stakeholders' understanding of pharmacogenetics, laying the groundwork for its support, acceptance and implementation.

REFERENCES

[1] Zuehlsdorf MT.
Relevance of pheno- and genotyping in clinical drug development.
Int J Clin Pharmacol Ther. 1998; 36: 607-612

[2] *Foot E, Bieber F, Kroll W, et al.*
Impact of pharmacogenetics on healthcare and health economics.
Int J Pharm Med. 2001; 15: 95-100

[3] Lindpaintner K, Foot E, Caulfield M, Hall I.
Pharmacogenetics: Focus on pharmacodynamic.
Int J Pharm Med. 2001; 15: 74-82

SOME USEFUL WEBSITES

A. National Institute of Health – USA:
http://www.nigms.nih.gov/pharmacogenetics/

B. *Human Genetics Commission* – UK
http://www.hgc.gov.uk

C. Human Genetics Advisory Commission – UK
http://www.doh.gov.uk/genetics/hgac.htm

D. Nuffield Council on Bioethics
http://www.nuffieldbioethics.org

E. Pharma Genomics:
http://genomics.phrma.org/

F. Pharma Genomics:
http://genomics.phrma.org/pharmacogenomics.html

G. UK Dept of Health Genetics White Paper
http://www.doh.gov.uk/genetics/whitepaper.htm

H. Public Health Genetics Unit (PHGU), Cambridge
http://www.cgkp.org.uk/index.php

I. The Human Genome Organization (HUGO)
http://www.gene.ucl.ac.uk/hugo/

J. *Council of Europe Steering Committee on Bioethics.*
Working document on the applications of genetics for health purposes
http://www.coe.int/T/E/Legal%5Faffairs/Legal%5Fco%2Doperation/Bioethics/Activities/Human_genetics/INF(2003)3e_genetics_working_doc.asp#TopOfPage
[Accessed on 1 April 2003]

K. Australian Law Reform Commission
Australian Health Ethics Committee – Paper 96,
Essentially Yours: Protection of Human Genetic Information in Australia. 2003
http://www.austlii.edu.au/au/other/alrc/publications/reports/96/
[Accessed on 30 January 2004]

L. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
http://elj.warwick.ac.uk/jilt/dp/material/directiv.htm
[Accessed on 30 January 2004]

M. DHHS, Administrative Simplification Under HIPAA:
National Standards For Transactions, Security And Privacy, March 3, 2003
http://www.hhs.gov/news/press/2002pres/hipaa.html

Chapter 12
Unresolved Issues and Barriers to Progress

1. Introduction

Pharmacogenetics has captured the public's attention as a new means of providing safer and more efficacious medicines. The possibility of selecting, using, and developing drugs based on the patient's individual genotype is highly appealing. Pharmacogenetics has been featured in medical and scientific journals, and also in the popular press, such as *Newsweek* and *Business Week*. Indeed, the possibility of using the right drug at the right dose the first time has a universal appeal – greater therapeutic benefit faster for patients, less guesswork for physicians, and lower costs for payers. Why, then, are there so few instances in which genetics is used in the prescription and development of drugs?

The answer is complex. In part, the time needed to advance from scientific discovery to practical application in any field often takes longer than we would expect. However, in the case of pharmacogenetics there are also specific factors that are impediments to progress.

1. Biological complexity: The current limit to our understanding of the intricacies of biological systems, including drug responses, is that of a simple application of genotyping to clinical decision making.
2. Technical obstacles: Practical and technical obstacles can slow down the discovery of genes related to drug responses and impede the development of simple tests that can be used for patient management.
3. Business-related obstacles including drug development, regulatory and commercial issues: Business concerns about appropriate use of resources can put pharmacogenetic approaches at a disadvantage to more conventional approaches to the development and marketing of drugs.
4. Obstacles in medical practice: Physicians and other caregivers must be convinced of the medical value of pharmacogenetics.
5. Public perception: Variable perception of risks and benefits on the part of potential users adds further uncertainty for the future of pharmacogenetics.

This chapter will review these factors and project expectations for the future.

2. Biological complexity

Genetics is seldom a simple, predictive biological process. In some cases it is, such as with rare inherited disorders like Huntington's disease, or biochemical characteristics like ABO blood types. But most phenotypes, even in clearly inherited conditions, are seldom unequivocal. Genes may have multiple alleles (thalassemias), variable expressivity (male pattern baldness), or multiple, independent genes (height). As a consequence, there remains considerable interindividual variation in phenotypes among people who have the same genotype for a particular relevant gene.

The same is the case for interindividual differences in responses to drugs. While drug metabolism may be strongly affected by one's genotype for drug metabolising enzymes, this does not always translate into meaningful differences in drug response. For instance, CYP2D6 poor metabolisers (PMs) treated with tricyclic antidepressants will develop elevated drug levels [1-4] but the clinical responses these individuals will exhibit can be highly variable. One individual might have nervousness and agitation while another might suffer from intolerable sleepiness [5]. Indeed one recent study concluded that inability to efficiently metabolise antidepressants that are CYP2D6 substrates does not necessarily lead to increased frequency of antidepressant-related adverse drug reactions [6]. Paradoxically, some PM subjects with high drug levels may fail to respond at all. Much of the variability may be due to the influence of other genes that affect drug transport and deposition or the drug target itself. Such genes may have major, moderate or minor effect, and can contribute to the variability in patient responsiveness even when plasma drug levels are the same.

This is exacerbated by complexity in the diseases themselves, even when the disease has a strong genetic component. In many clinical conditions there may be multiple pathways that can lead to similar outcomes, and not all of these may be under the same genetic influence. In asthma, patients who are deficient in 5-lipoxygenase due to the genotype in the ALOX-5 gene are non-responsive to 5-lipoxygenase inhibitors [7]. However, most of the 5-lipoxygenase inhibitor non-responders have normal ALOX-5 genes, and the basis of their non-responsiveness lies in other factors, probably related to the nature of their asthma. This complexity is further complicated by the effect of additional genes, which can enhance or reduce the primary effect.

Additional complexity is imparted by the differences in allele frequencies among different ethnic and racial groups [8]. Clinically important alleles

may be rare in one ethnic group but common in another, such as alleles that confer PM status of CYP2C19 in Asians and Caucasians. Investigation of only a single ethnic population may lead to results that are poorly representative of the target population as a whole.

Effective use of pharmacogenetics will require either the discovery of gene effects clearly correlated to clinical outcomes, or wider acceptance of laboratory results as the basis for prescription. Laboratory results, such as plasma drug levels, tend to reflect genotypes more closely than do clinical outcomes. The use of a laboratory result is a reasonable and attainable goal. A mere demonstration that an individual is a PM may be adequate to make decisions on drug selection or dosing, irrespective of the direct correlation to a particular adverse event.

3. Technological obstacles

Applying genetics to the selection and appropriate use of drugs requires both the identification of the genes that influence drug response and the development of genetic tests that are easy to use and highly predictive. Both of these present practical and technical challenges that have yet to be overcome.

Since the publication of the complete human genome sequence, the discovery of genes related to specific functions has been advancing rapidly. Nevertheless, genes related to drug responses will be among the more difficult to identify. This is especially the case with genes that are involved with a specific drug or disease. In order to identify genes that relate to a response to a particular drug, for instance, it is necessary to obtain and analyse DNA samples from several hundred patients who are clear responders and clear non-responders. Access to this number of well-characterised patients usually involves a controlled clinical trial. Such trials are generally supported only for purposes of drug evaluation and regulation, and do not always have a sufficient number of patients to provide the numbers necessary for gene discovery. In the case of genes related to adverse drug reactions, the relative rarity of adverse responses to a drug that has advanced to large clinical trials will make it especially difficult to obtain DNA samples from adequate numbers of cases and controls.

Nevertheless, progress is being made. Genes related to drug metabolising enzymes, for example, have been well investigated. These investigations have taken advantage of the role of genetic polymorphism in each enzyme that metabolises many different drugs and the existence of DNA samples

from a large number of individuals treated with these drugs under controlled conditions. There are, however, only a few examples at present of discovery of genes that relate to specific drugs or idiosyncratic toxicity. The discovery of the involvement of specific genes in hypersensitivity to the HIV protease inhibitor, abacavir sets an excellent example of how such studies can succeed. Roses and his collaborators [9] collected DNA samples from 200 abacavir patients, 85 of whom had well characterised hypersensitivity reaction and 115 did not. DNA sequence polymorphisms were compared at 114 loci in 12 gene families. The results clearly showed disproportionate frequencies of alleles in two loci within HLA-B, from which the authors concluded that, within the Caucasoid population studied, HLA genotyping has the sensitivity to identify hypersensitive patients of 55%. A similar study relating HLA genotypes to this hypersensitivity reaction found even higher sensitivity [10]. This example takes advantage of a clearly defined adverse reaction that can be attributable to the drug treatment in most cases, and access to appropriate number of patients with (cases) and without (controls) the reaction in a post-marketing observational study. Advances in the pharmacogenetics of adverse reactions will require circumstances such as this for success in the foreseeable future.

Although the development of clinical tests to detect DNA polymorphisms is often regarded as a significant hurdle to be overcome, technologies for clinical nucleic acid testing are largely available today [11]. The most serious practical impediment to the implementation of these tests is the need for thorough validation of the assays. Clinical validation will require testing of numerous cases and controls in a clinical setting, which in the case of a test related to a particular drug response, may require the exposure and monitoring of hundreds of patients or more. If a test is intended to match a dose level with a genotype, the validation study will need to be even bigger to accommodate different doses.

4. Business-related obstacles

The discovery of genes related to drug responses and the application of genetic knowledge to the use of drugs is highly dependent upon active participation by pharmaceutical companies. Pharmaceutical companies have access to clinical data relating to response of most investigational drugs, and sponsor the clinical trials in which the genetic research can be carried out. In order for pharmaceutical companies to fully embrace pharmacogenetics, it must be demonstrated first that the use of these approaches will enhance the companies' primary business goals of profitability and growth.

4.1 Drug development

Pharmaceutical companies more and more are including genetic analysis as part of the design of clinical trials, particularly in studies that assess pharmacokinetics. Genetic data can contribute to better interpretation of results, better design of trials, and in some cases, to the avoidance of unnecessary exposure of patients who might be at risk for toxicity. The number of genetic studies submitted to the US FDA has been increasing at a rate that has doubled annually (Lesko L and Huang S-M, personal communication). A similar increase has been noted at the European Medicines Agency (EMEA).

Nevertheless, many drug developers remain sceptical of the value of pharmacogenetics and continue to question the appropriateness of including genetic analysis in clinical trials. Pharmacogenetics may add to the expense and complexity of clinical studies, and could lengthen the time needed to enrol subjects and complete the trial. This concern can be attributed to several factors.

1. Collection of genetic data might slow clinical trials by complicating review of protocols by Independent Ethics Committees or Institutional Review Boards or discouraging some patients from enrolling.
2. Genetic studies may require additional training of clinical trial staff and investigators.
3. Gathering genetic information may increase the informational risk to trial subjects.

These drawbacks are readily apparent before the study is initiated and at the time that funding must be committed, but the benefits of the results will only be known after the trial has been completed. It is difficult to tell which drug candidates will tangibly benefit from knowledge of gene-based patient responses. In many clinical trials, these drawbacks are considered to outweigh the expected benefits of obtaining pharmacogenetic results.

Many believe the greatest benefits from pharmacogenetics will arise from the targeting of drugs for genetically defined sets of patients who will have high likelihood of beneficial response and low risk for side effects. However, this approach to pharmacogenetics is one that often meets the greatest resistance. Testing of a drug within a genetically defined group of patients in a drug registration trial is likely to lead to restrictive labelling such that the product would not be promoted to the entire population [12]. This niche marketing approach is not favoured in the pharma-

ceutical industry, despite the successes of trastuzumab (Herceptin® Roche), imatinib (Gleevec® or Glivec® Novartis), and a few other targeted drugs. A new compound that is directed toward the entire disease population will likely be favoured over one that has a restricted patient base.

Uncertainty is one of the greatest drawbacks to application of pharmacogenetics in the development of drugs. It is impossible today to predict how well a genetic marker will correlate to a particular drug response, whether positive or negative. The research needed to find genes related to a response and then to demonstrate the benefit of pre-selection of patients is expensive and time consuming and at its initiation has no clear measure of the likelihood of success. Uncertainty is a nightmare to business managers. Overcoming the problem will require more information on the genetics of drug responses, on the decision making behaviour of physicians and patients, and on the medical impact of the results. Until there are more publicised examples of drugs that have been made successful through the application of pharmacogenetics, progress in this area will be slow.

4.2 Regulatory obstacles

There is growing recognition by regulatory bodies of the role of genetics in drug use and development, and an apparent eagerness to use genetics as a means of evaluating the potential risks and benefits of drug usage [13-15]. Nevertheless, the role of genetics in the regulatory process is not well established. For instance, the description of genetic contribution to drug effects may appear at any of a number of sites in a drug label. A review of labels of drugs that are primarily metabolised by polymorphic cytochrome P450s (CYPs) found mention of genetic-based effects in several different sections, including dose recommendations, contraindications, adverse reactions, drug interactions, warnings, precautions and pharmacokinetics, or no mention at all. Neither the drug developer nor the prescribers have a clear idea of how such information should be dealt with, nor where the information can be found.

New techniques of genomics have presented regulatory concerns that are new to both scientists and regulators. A single high-density array analysis of gene expression of SNP genotypes can produce tens of thousands of data points. These data are then analysed either by focusing on only a subset of the data, or by statistical methods that perceive patterns among many data points. Such results, if submitted to a regulatory agency, might be subjected to various *post hoc* analyses or interpretations. For instance, a reviewer might concentrate on a different subset of data or might use alternative statistical methods of pattern recognition. These re-analyses

may or may not be appropriate for the particular study design, and may or may not use validated methods. Therefore, drug developers are reluctant to submit or even generate data that might lead to additional questions from the reviewers, or to contrary conclusions about the efficacy or safety of the compound. This concern has had a dampening effect on the use of these new and powerful methods in drug development.

In November 2003, the United States (US) Food and Drug Administration (FDA) put forward, for consultation, its "Guidance for Industry for Pharmacogenetic Data Submissions" [16]. It is proposed that if a pharmacogenomic test shows promise for enhancing the dose selection, safety, or effectiveness of a drug, a sponsor may wish to fully integrate pharmacogenomic data into the drug development programme. This could occur in two ways:

1. Pharmacogenomic data are intended to be included in the drug label in an informational manner and
2. Dose selection, safety, or efficacy of a drug as described in its label will be contingent upon the performance of a pharmacogenomic test or tests.

It is conceded that most pharmacogenomic data are of an *exploratory* or *research* nature, and FDA regulations do not require either that these data be submitted with an investigational new drug (IND) or that complete reports be submitted with a new drug application (NDA) or biologics license applications (BLA). The FDA is requesting that sponsors conducting such programmes consider providing pharmacogenomic data to the Agency voluntarily, when such data are not otherwise required under IND and NDA or BLA regulations. Under this FDA guidance, *Voluntary Genomic Data Submissions* (VGDS) can be used for the submission of results from pharmacogenomic studies that are not obligatory to be submitted. The FDA intends to establish a cross-center Interdisciplinary Pharmacogenomic Review Group (IPRG) to review VGDS, to work on ongoing policy development, and to advise review divisions dealing with pharmacogenomic data. Under VGDS , data submitted with an IND will not be used for making regulatory decisions. However, after the sponsor submits a VGDS, if additional information becomes available that renders the results obligatory to be submitted under appropriate legislation, the sponsor must submit the data to the IND, NDA, or BLA, respectively, by following an established appropriate procedure.

The regulators in Europe have also shown a great deal of interest in pharmacogenetics with regard to exploring the benefits it can deliver to

the patient in terms of potentially more effective and safer medicines. Over the past few years there have been a number of activities including the announcement of a framework that would facilitate exploration of pharmacogenetic data. In January 2003, the EMEA released a concept paper titled "Concept Paper on Pharmacogenetics – Briefing Meetings" (CPMP/4445/03) [17]. This paper outlines the procedure for individual pharmaceutical companies who wish to discuss informally pharmacogenetic data and strategies with the CPMP Ad-hoc Expert Group on Pharmacogenetics.

4.3 Commercial obstacles

Successful pharmaceutical businesses have been built upon product concepts and selling processes that have been carefully developed and time-tested. The idea of targeting a drug at a subgroup of the population defined by a clinical or laboratory test is generally at odds with conventional practices. A process for combining testing with prescribing would have to be developed, sales and marketing staff would require basic training in genetic testing, and reimbursement practices may have to be revised. These would all require significant attention from a staff that is already fully occupied. These concerns could be exacerbated by the potential perception, certainly encouraged by competitors, that a drug that requires prior testing is somehow inferior or incorporates greater risk than the conventional product.

Despite these impediments, it is possible to have a successful drug under these conditions. Trastuzumab, a successful monoclonal antibody treatment for metastatic breast cancer, has been labelled to be used only in patients whose tumours have HER2 protein over expression, as detected with a diagnostic kit. While trastuzumab is an unusual case, in as much as it is for a life-threatening condition and has a very high price, it nevertheless has set an example for success of a targeted drug.

Little stimulus has come from commercialisation of pharmacogenetic tests themselves either as kits or in testing laboratories. Despite the promotion of individualised medicine in the public press and scientific journals, there is little use of genotyping as a means of selecting among prescription drugs. For instance, there are no *in vitro* diagnostic kits for pharmacogenetic markers that have been approved and licensed by the FDA. Most physicians have dealt with patient-to-patient variability in response to antidepressants, warfarin or antiarrhythmic agents without the use of prior testing, and they probably will not see the need for the additional cost and complexity. However, during the clinical use of some thiopurine

drugs, genotyping is becoming the norm. Patients with low or deficient activity of thiopurine S-methyltransferase (TPMT) have a high risk for fatal overdose. As further examples of such associations develop, it is reasonable to believe that pharmacogenetic testing will become a more regular part of medical practice. This is likely to happen in chronic diseases in which drug response tends to be slow in onset, such as depression or schizophrenia, or in therapies with narrow therapeutic range.

5. Obstacles in medical practice

Most physicians have had little training in genetics since their undergraduate education, and much of what they have learned may be out of date. Therefore, few would have a serious awareness of the role of genetics in drug response, and fewer still would consider this to be an important part in their medical decision making. The prospect of explaining the results of a genetic test to a patient would likely make the average physician uncomfortable. The lack of an effective interface between the basic science and clinical practice only serves to make the situation worse. Scientific jargon and reliance on a large body of technical literature is a significant impediment to the acceptance of genetics as a diagnostic or prescribing tool among physicians. Fortunately, there are a growing number of continuing education courses that bring genetics to the level of a clinician's practical needs. Furthermore, demand from patients and payers may become a significant driver for greater acceptance by the medical community.

6. Public perceptions

Genetics plays a role in many aspects of our everyday lives, and the public has developed both a respect for and a suspicion of genetic testing. Because of the simplified versions of reports of genetic studies that appear in the press, there is a tendency to believe that genetics is highly predictive of everything from disease to behaviour to appearance to drug responses. This over-acceptance of the role of genetics only serves to amplify any concerns that individuals might have with the possible uses and misuses of genetic testing. These issues, which have been addressed elsewhere in this Report, include:

1. Insurability and consideration of a gene-based condition as pre-existing condition
2. Discrimination in employment
3. Psychological distress
4. Invasion of patient privacy

Many of these issues do not apply to pharmacogenetics, since the patient already has been diagnosed with a disease, and the results of a pharmacogenetic test merely serve to select the most appropriate drug. However, the perception of a problem persists, and is unlikely to go away without significant public education. Nevertheless, the public, especially in the United States, supports the use of genetics in medicine, and one hopes that a reasoned approach from all sides will lead to the use of pharmacogenetics for the benefit of all.

Other public medical policies impact pharmacogenetics more directly. Since allele frequencies differ between racial or ethnic groups [8], would a pharmacogenetic test be restricted to only certain countries or populations, resulting in "race-based" medicine? Also, what about individuals who, due to their genotypes, are not appropriate patients for certain medicines? Will these individuals get adequate care? All in all, the use of genetic testing for drug responses will not change significantly the number of drugs available, but will only help direct the choice among existing drugs. Nevertheless, new choices can lead to new questions.

7. Looking forward

The use of genetics in the development and use of pharmaceuticals is a new and largely unfamiliar concept. Consequently, there is a need to demonstrate the value of the approach in order to induce researchers, physicians, payers, and patients to change. The contrast between the hype surrounding individualised medicine, and the modest rate at which pharmacogenetics has been applied indicates that acceptance will require tangible benefits rather than promises. How will these tangible benefits come about? First, scientifically, the advances in understanding the human genome organization, cataloguing human polymorphisms and determining gene function will eliminate much of the scientific uncertainty. Second, there must be more examples of the success of targeted medicines. These are likely to come initially from drugs that, because of safety concerns will require special labelling for approval, but which nonetheless provide new solutions for unmet medical needs. Herceptin® is an excellent example, but there will need to be more. Third, education of physicians and others involved directly or indirectly in providing healthcare, regulators, and potential patients will eliminate much of the concern over the unknown aspects of genetic testing and drug use.

Pharmacogenetics offers the possibility of more effective development of new and needed drugs, and the potential for targeting the right drug to the patient. Attaining these goals in the face of the obstacles that face them will require intellect, persistence, and hard work.

REFERENCES

[1] Brosen K.
Drug-metabolising enzymes and therapeutic drug monitoring in psychiatry.
Ther Drug Monit. 1996; 18: 393-396

[2] Gram LF.
Dose-effect relationships for tricyclic antidepressants: the basis for rational clinical testing of new antidepressants.
Psychopharmacol Ser. 1993; 10: 163-173

[3] Shimoda K, Morita S, Hirokane G, Yokono A, Someya T, Takahashi S.
Metabolism of desipramine in Japanese psychiatric patients: the impact of CYP2D6 genotype on the hydroxylation of desipramine.
Pharmacol Toxicol. 2000; 86: 245-249

[4] Spina E, Gitto C, Avenoso A, Campo GM, Caputi AP, Perucca E.
Relationship between plasma desipramine levels, CYP2D6 phenotype and clinical response to desipramine: a prospective study.
Eur J Clin Pharmacol. 1997; 51: 395-398

[5] Chen S, Chou WH, Blouin RA, et al.
The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry.
Clin Pharmacol Ther. 1996; 60: 522-534

[6] Roberts RL, Mulder RT, Joyce PR, Luty SE, Kennedy MA.
No evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolisers treated with fluoxetine or nortriptyline.
Hum Psychopharmacol. 2004; 19: 17-23

[7] Drazen JM, Yandava CN, Dube L, et al.
Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment.
Nat Genet. 1999; 22: 168-170

[8] Xie HG, Kim RB, Wood AJ, Stein CM.
Molecular basis of ethnic differences in drug disposition and response.
Annu Rev Pharmacol Toxicol. 2001; 41: 815-850

[9] Hetherington S, Hughes AR, Mosteller M, et al.
Genetic variations in HLA-B region and hypersensitivity reactions to abacavir.
Lancet. 2002; 359: 1121-1122

[10] Mallal S, Nolan D, Witt C, et al.
Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir.
Lancet. 2002; 359: 727-732

[11] Spear BB, Heath-Chiozzi, M, Huff, J.
Clinical application of pharmacogenetics.
Trends in Mol Med. 2001; 7: 201-204

[12] Lesko LJ, Salerno RA, Spear BB, et al.
Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: Report of the first FDA-PWG-PhRMA-DruSafe Workshop
J Clin Pharmacol. 2003; 43: 342-358

[13] Shah RR.
Implications of pharmacogenetics for the regulatory assessment of new chemical entities.
Pharmaceutical News. 2000; 7: 32-38
[14] Lesko LJ, Woodcock J.
Pharmacogenomic-guided drug development: regulatory perspective.
Pharmacogenomics J. 2002; 2: 20-24
[15] Shah RR.
Regulatory aspects of pharmacogenetics and pharmacogenomics.
Bundesgesundheitsbl - Gesundheitsforsch – Gesundheitsschutz. 2003; 46: 855–867
[16] Anon.
Guidance for Industry Pharmacogenomic Data Submissions.
Food and Drug Administration: Rockville, 1997 Maryland, USA
(Draft Guidance) November 2003
http://www.fda.gov/cder/guidance/index.htm
[Accessed on 30 January 2004]
[17] Anon.
Concept paper on pharmacogenetics 'Briefing meetings'.
(CPMP/4445/03)
Committee for Proprietary Medicinal Products, EMEA: 2003 London.
http://www.emea.eu.int/pdfs/human/pharmacogenetics/444503en.pdf
[Accessed on 24 January 2004]

Annex 1

Process and Membership of CIOMS Working Group on Pharmacogenetics

Before establishing the CIOMS Working Group on Pharmacogenetics, two planning meetings were organized in Geneva in January and September 2001. At these two planning meetings, a Core Group agreed on the outline of the project and the topics to be addressed.

CIOMS Working Group on Pharmacogenetics met in a series of five meetings in Europe and the United States from February 2002 to April 2004 as follows:

February 2002	EMEA, London, UK
August 2002	BfArM, Bonn, Germany
February 2003	FDA, Washington DC, USA
September 2003	Warsaw, Poland
April 2004	Windsor, UK

Listed below alphabetically are the senior scientists from drug regulatory authorities, pharmaceutical companies and academia who participated or otherwise contributed to the project (*see note overleaf*).

1.	Eric ABADIE	AFSSAPS, France
2.	Larry ALTSTIEL	Schering-Plough
3.	Ariel BERESNIAK	Serono
4.	Celia BRAZELL	GlaxoSmithKline
5.	Michel EICHELBAUM	Dr Margarete Fischer-Bosch-Institut für Klinische Pharmakologie, Germany
6.	Csilla FOLDES	Aventis
7.	Andrew GALAZKA	Serono
8.	Hiroshi GUSHIMA	Yamanouchi
9.	Juhana E. IDÄNPÄÄN-HEIKKILÄ	CIOMS, Switzerland
10.	Agnes V. KLEIN	Health Canada
11.	Chie KOJIMA	MHLW, Japan
12.	Gottfried KREUTZ	BfArM, Germany
13.	David LEPAY	FDA, USA
14.	Larry LESKO	FDA, USA
15.	Klaus LINDPAINTNER	Roche
16.	Duncan McHALE	Pfizer
17.	Odette MORIN	IFPMA, Switzerland
18.	Marisa PAPALUCA-AMATI	EMEA, London, UK
19.	Olavi PELKONEN	University of Oulu, Finland

20.	Mihael POLYMEROPOULOS	Novartis
21.	Lembit RAGO	WHO, Switzerland
22.	Jens S. SCHOU	University of Copenhagen, Denmark
23.	Rashmi R. SHAH	MHRA, UK
24.	Brian SPEAR	Abbott Laboratories
25.	Jacek SPLAWINSKI	Narodowy Instytut Zdrowia Publicznego, Poland
26.	Noboru TAKAHASHI	National Institute of Health Sciences, Japan
27.	Mieko TAMAOKI	Yamanouchi
28.	Kiichiro TSUTANI	University of Tokyo, Japan
29.	Jan VENULET	CIOMS, Switzerland
30.	Mark WATSON	Merck & Co
31.	Thomas R. WEIHRAUCH	Bayer
32.	Elora J. WERINGER	Pfizer

Note:
Because the affiliation or the responsibility of some members listed above changed during the current tenure of this Working Group, they were unable to continue their full participation and did not have an input in the preparation of the final report

Non-members who contributed specific sections or items for inclusion in this Report include

1. Dr Leonie Hunt, Director, Drug Safety & Evaluation Branch, Therapeutic Goods Administration, Australia.
2. Prof Hong-Hao Zhou, Pharmacogenetics Research Institute, Central South University, Changsah, Hunan, China.
3. Prof Sang-Goo Shin, Professor of Clinical Pharmacology/Pharmacology, Department of Pharmacology, Seoul National University College of Medicine & Clinical Pharmacology Unit/SNUH, Leader, Korean Pharmacogenomics Research Network/KMHW, Republic of Korea.
4. Dr Kerwin Low, Assistant Director Centre for Drug Administration, Health Sciences Authority, Singapore.
5. Dr Yi-Jin Chiou, Pharmacokinetics Reviewer, Division of Preclinical Sciences, Centre for Drug Evaluation in Taiwan, Chinese Taipei.

The Editorial Board of the report was constituted of Drs. Celia Brazell, Larry Lesko, Rashmi Shah, Brian Spear and Elora Weringer.

Dr Rashmi Shah also acted as the Chief Editor of the final report.

Annex 2

Pharmacogenetics and Pharmacogenomics in Australia

Contribution by:
Dr Leonie Hunt, MBBS, FRACGP, BEc, MBA
Director, Drug Safety & Evaluation Branch,
Therapeutic Goods Administration, Australia

1. General Guidelines

The Therapeutic Goods Administration (TGA) is the therapeutic goods regulator for Australia. It has adopted the European Common Technical Document (CTD) for applications lodged in Australia, and most associated guidelines from the Committee for Medicinal Products for Human Use, (CHMP) (formerly the Committee for Proprietary Medicinal Products (CPMP).

These are listed on the TGA website
www.tga.gov.au/pmeds.htm#guidelines

2. Guidelines on Bioethics

The Australian Health Ethics Committee (AHEC) is one of four principal committees of Australia's National Health and Medical Research Council (NHMRC). Established under an Act of Parliament, the NHMRC is Australia's national organization for funding health research, promoting the development and maintenance of public health standards through the provision of evidence-based health advice, and providing ethical guidelines and advice in relation to health research and health practice.

Although it forms part of the NHMRC, AHEC has statutory independence and is effectively Australia's 'national bioethics commission'. The membership of 15 people includes categories of persons with expertise, knowledge or experience in philosophy, ethics, medical research, public health, social science research, clinical medical practice, nursing or allied health, law, religion and people with understanding of health consumer issues and of the concerns of people with disabilities. Members are appointed by the federal Minister for Health and Ageing and serve for three years.

The following AHEC publications may be relevant to pharmaceutical regulation and the areas of pharmacoeconomics and pharmacogenomics.

- *The National Statement on Ethical Conduct in Research involving Humans* (1999) is the primary guideline for Australia's Human Research Ethics Committees (HRECs) and for researchers and others on the ethical principles and values, which should govern research activities that involve humans.

  Available at http://www.nhmrc.gov.au.publications/ehome.htm

- *Essentially Yours: the Protection of Human Genetic Information in Australia* (2003) (joint publication with the Australian Law Reform Commission). This Inquiry was prompted by concerns about privacy and discrimination, especially in the contexts of insurance and employment, and about ethical and other oversight of medical and scientific research, clinical practice, and the use and collection of genetic databases. The final report covers a spectrum of health and related issues including research, privacy, clinical practice, the delivery of health services, and workforce issues. Its two volumes of 1200 pages contain 144 recommendations, which include the establishment of a Human Genetics Commission of Australia, the amendment of discrimination laws to prohibit unlawful discrimination based on a person's real or perceived genetic status, and the strengthening of ethical oversight of genetic research. The report is available at http:// www.alrc.gov.au.

- *Guidelines for Genetic Registers and Associated Genetic Material* (1999)

- *Ethical Aspects of Human Genetic Testing: an Information Paper* (2000)

  Available at http://www.nhmrc.gov.au.publications/ehome.htm

A full list of AHEC publications is available at

http://www.nhmrc.gov.au/publications

Annex 3

Pharmacogenetics and Pharmacogenomics in Canada

Health Canada's approach to pharmacogenomics reflects its mandate as the federal department responsible for helping the people of Canada maintain and improve their health. With respect to biotechnology, its primary role is to ensure the prudent use of products and procedures that are derived from biotechnology and consumed by, or applied to, humans.

Pharmacogenomics is a transformative technology that will usher in a new generation of diagnostics and therapies, and could lead to measurable population health impacts. It has the potential to deliver impressive outcomes – better drug safety and efficacy, new tools for evidence-based healthcare decision making and targeted and more effective clinical trials. At the same time, it raises new challenges for Health Canada and the public it serves, from establishing a good clinical evidence base, to regulating the co-marketing of diagnostics and therapeutics, to assessing and addressing economic and ethical issues.

In response to these challenges, the Department, as policy maker and regulator, strives for a balanced and integrated approach that will maximise the potential health and safety benefits of pharmacogenomics, while minimising possible risks. This approach conforms not only to Health Canada's mandate, but also to key priorities in the departmental biotechnology framework, including enhanced regulatory capacity, addressing the social impacts of genetic technology, and robust stewardship pertaining to the impact of biotechnology on Canadians' health and healthcare system.

Canada has been involved closely with the WHO work in genomics and ethics. For example, the University of Toronto's Joint Centre for Bioethics heads a PAHO/WHO Collaborating Centre for Bioethics. The Centre hosted a WHO meeting on Collaboration in Medical Genetics in April 2002 which adopted several recommendations to strengthen the role of WHO in human genetics, to develop comprehensive medical genetics services linked to primary healthcare, to develop ethics capacity and related regulatory systems, to enhance training capacity and to "promote a global public dialogue". In the latter half of 2002, this Centre published an excellent document entitled "Top 10 Biotechnologies for Improving Health in Developing Countries".

The Office of Biotechnology in the Health Products and Food Branch (HPFB) of Health Canada is in charge of coordinating all genetics and related activities within Health Canada. This includes the regulatory activities around pharmacogenomic testing.

The following activities are included in this project:

There exists a Pharmacogenomics Working Group which has developed an analysis and a complete environmental scan in order to provide a basis for developing a Canadian Guidance document that will be a good fit with the Canadian Drug Regulatory Framework. This group has now evolved into a Health Canada-wide group that is developing regulatory guidance on pharmacogenetics/pharmacogenomics and the co-regulation or development of *in-vitro* diagnostics together with the drugs.

This HPFB Pharmacogenomics Working Group had been created in part to support HC participation in the Council of International Organizations of Medical Sciences.

The following activities are going on into which there are regulatory and other inputs:

- Development of commercial testing kits,
- In-house genetic tests;
- Quality assurance; quality control;
- Pharmacogenomics issues – Pharmacogenomics Working Group
- Ethics as part of the regulatory assessment of various products;
- Input from Health Canada into issues around patenting of genetic and related materials
- Canadian Biotechnology Strategy Genetic Information and Privacy Working Group.
- Linkages between the various activities related to genetics, pharmacogenetics and pharmacogenomics with the regulator.

There is still an ongoing need for complete identification of the full range of interested parties and issues and options within the Canadian context. To that end, a series of round table and workshops were organized and continue to be organized. The most recent one was a round table conference on Pharmacogenetics/Pharmacogenomics on November 4, 2004 in Ottawa, while the OECD expert meeting on Pharmacogenetics, held in Paris on 15 October 2004, was co-chaired by Canada.

Annex 4

Pharmacogenetics and Pharmacogenomics in China

Contribution by:
Prof Hong-Hao Zhou, MD
Pharmacogenetics Research Institute,
Central South University,
Changsah,
Hunan,
China.

1. Guidelines

1. Guidelines for Bioethics and Biosafety
2. Clinical Studies and post-marketing surveillance are regulated by the National Pharmaceutical Affairs Law (revised in 2001).

2. Projects to establish a foundation for Pharmacogenomic researches

1. The International Hap Map Project
   - 1.1 Schedule: FY2002-FY2004 (3 years-term)
   - 1.2 Participants: Canada, China, Japan, UK and US
   - 1.3 Aim: clinical application to pharmacogenomics
   - 1.4 Scope: a total of 200-400 blood samples from Mongolian, Caucasian, and African-American donors are to be collected for haplotype mapping. China will bear tenth of the responsibility for analysis. The data will be published in 2004.
2. Chinese Pharmacogenomics Research
   - 2.1 Scheduled: FY1999-FY2005 (7 years-term)
   - 2.2 Budget: 2.2 million RMB
   - 2.3 Aim: Discovery of polymorphisms related to drug safety and efficacy in Chinese population and clinical application of Pharmacogenomics information
   - 2.4 Scope: The research is focused on genetic basis for different response and efficacy of drugs used in patients with hypertension, hyperlipemia, etc.
   - 2.5 Project Leader: Professor Hong-Hao Zhou (Central South University), et al.
3. Project on relationship of genomics and severe diseases
   - 3.1 Schedule: FY2001-2010
   - 3.2 Budget: 10.0 million RMB

3.3 Aim: Elucidation of genetic background for susceptibility to various severe diseases.
3.4 Scope: Genes that relate to oncogenesis will be elucidated using DNA from approximately 10,000 patients, covering more than a dozen of severe diseases including cancers and diabetes, with the prior informed consent of each patient.
3.5 Project leader: Professor Qiang Bo-qing, et al. (Chinese Human Genome Center, CHGC)

4. Bioinformatics on gene functions and drug designing
   4.1 Schedule: FY2002-FY2005
   4.2 Budget: 5.0 million RMB
   4.3 Aim: Development of bioinformatics platforms for studying gene functions and potential targets for drug therapy.
   4.4 Scope: *Database of genomics and proteomics, bioinformatics* methods and softwares.
   4.5 Project leader:

5. Xiang-Ya, CSU Demonstrative Lab on Pharmacogenetics
   5.1 Schedule: FY2002-FY2007 (6 years-term)
   5.2 Budget: 300,000 USD for 6 years
   5.3 Aim: Determination of SNP of different drug metabolising enzymes and their phenotype-genotype relationship of clinical drugs.
   5.4 Scope: Pharmacogenomics of common diseases
   5.5 Project Leader: Professor Hong-Hao Zhou (Central South University)

6. Pharmacogenomics and modernisation of Chinese herbs
   6.1 Schedule: FY2001-FY2005
   6.2 Budget: 5.0 million RMB
   6.3 Aim: Application of pharmacogenomics to modernisation of Chinese herbs
   6.4 Scope: Rationalisation of Chinese herbs
   6.5 Project leader: Guo De-An (Peking University), et al.

7. Research Center for Medication in Minorities
   7.1 Schedule: FY1993-FY2004 (12 years-term)
   7.2 Budget: 2.2 million RMB for 12 years
   7.3 Aim: Application of pharmacogenomics to clinical practice
   7.4 Scope: Ethnic differences of drug metabolism and response in Chinese minorities.
   7.5 Project Leader: Professor Hong-Hao Zhou (Central South University)

8. Individualisation of drug therapy for patients with hypertension
   8.1 Schedule: FY2001-FY2005
   8.2 Budget: 2.0 million RMB
   8.3 Aim: Individualisation of treatment for some major antihypertensive drugs
   8.4 Scope: Application of gene chips to determine individual's genotype for genes that closely relate to drug response and adverse effect. Types of drugs and their doses will be rationalised according to individual's genotype.
   8.5 Project Leader: Professor Hong-Hao Zhou (Central South University)

3. Activities

1. Ministry of Health and Welfare: funding the disease genomics and Chinese pharmacogenomics research work.
2. Chinese Pharmacology Society (CNPHARMS): the Committee on clinical pharmacology to consider the measure to make use of pharmacogenomics.
3. CHGC and Institute of Environment & Occupational Health (USA): International study meeting concerning Environmental Genomics and Pharmacogenomics to promote pharmacogenomics.
4. Forum of Chinese Pharmacogenomics: Forum held by National Natural Science Foundation of China (NSFC) and Bureau of Science & Technology discussing application of pharmacogenomics to clinical practice.
5. Satellite Meeting on Pharmacogenomics, IUPHARM World Congresses of Pharmacology (2006)

4. Pharmaceutical Industry

The ethnic differences of drug metabolism and response and relationship of phenotype and genotype of drug metabolising enzymes have been studied and elucidated. A personalised-therapy advice center will be established soon to give more precise prescription for patients, especially those with cardiovascular diseases (including hypertension and heart failure, etc.) and gastrointestinal ulcer, etc. Several pharmaceutical companies will sponsor several clinical trials searching relationship between drug efficacy/adverse effect and specific genotype. More drugs will be administered using a personalised approach.

Annex 5

Pharmacogenetics and Pharmacogenomics in Chinese Taipei

Contribution by:
Dr Yi-Jin Chiou, Ph.D.
Pharmacokinetics Reviewer,
Division of Preclinical Sciences,
Center for Drug Evaluation in Taiwan,
Chinese Taipei.

1. Guidelines

1. Guidelines on Bioethics
   Although life science research has steadily advanced in Taiwan, there are no nation-wide guidelines on bioethics concerning human genome/gene research or genetic testing at present except for some general bioethics guidelines such as "Guideline on Collection and Use of Human Samples for Research Purpose". Research institutes basically follow individual research guidelines and regulations enforced by in-house boards and/or general guidelines of clinical studies regulated by the Department of Health (DoH). Comprehensive research guidelines for ethical issues related to human genome studies including pharmacogenetics/nomics are currently under discussion at DoH.
2. "Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data"
   This guideline and relevant notifications issued by DoH in 2000 regulating the necessity of conducting bridging studies of a new drug based on evaluation of its potential ethnic sensitivity are considered important and related to pharmacogenetics. Since the evaluation of clinical data package involves determining whether genetically polymorphic enzymes and/or transporters play a significant role in the pharmacokinetics of the drug, the implementation of this guideline is expected to encourage pharmaceutical companies to involve Asians in multinational clinical trials incorporating genetic polymorphism analysis.

2. Projects to establish a foundation for pharmacogenomics

1. National Research Program for Genomic Medicine
   1.1 This is a 5-year nation-wide program starting from 2002 including research projects of four main areas: genomic medicine, bioinformatics, proteomics and structural genomics, and ELSI (Ethics, Legal and Social Implications). It is initiated by the National Science Council and DoH and involves the most outstanding physicians and scientists from medical centers and research institutes all over the country.
   1.2 Aims (pharmacogenomics-related): (i) Development of new technologies to identify disease targets and to facilitate therapeutic discovery, which includes gene delivery technology, genomic sequencing, genotyping, microarray and proteomics technology, and drug discovery platform; (ii) Identification of genetic polymorphisms/mutation associated with human diseases such as cancers, metabolic diseases, immune disorders, neurological diseases and mental disorders, cardiovascular diseases and infectious diseases; (iii) Promotion of ELSI-related research projects and transformation of achievements of ELSI projects into concrete reports or recommendations for policy makers in enacting laws and guidelines concerning bioethics of human genome research.
   1.3 Progress: Many projects derived from this national program have been initiated and making progress in all areas including pharmacogenomics this year.
2. Establishment of "Super Control Genomic Database"
   2.1 Aims: Establishment of a control pool that has large enough sample size to serve as multiple controls for various endemic diseases.
   2.2 Progress: Normal subjects of Han Chinese origin residing in Taiwan (N= 3312) have been recruited. A pilot study to establish the disease entities, sample size, ELSI concerns, operational methodology and governing body will be done by 2005. A plan to collect several hundred thousand DNA samples with disease information will be prepared afterwards. Single nucleotide polymorphisms (SNPs) of candidate genes potentially involved in drug metabolism and transport mechanisms and adverse drug reactions have been selected for high-throughput genotyping. Allele and haplotype frequencies of SNPs will be determined in the subjects randomly selected from the "Super Control" pool.
3. The Pharmacogenomics Program at Institute of Biomedical Sciences, Academia Sinica
   3.1 Aims: (i) Establishment of genetic susceptibility database of adverse drug reactions caused by drugs such as warfarin, azathioprine and carbamazepine; (ii) Identification of genetic determinants underlying individual's difference in drug efficacy; (iii) Elucidating pharmacokinetics and pharmacodynamics using pharmacogenomics profiling.
   3.2 Progress: Patients suffering from moderate to severe adverse drug reactions are being recruited, and genetic variants responsible for the risk of specific adverse drug reactions in clinical patients are being identified, including a severe life-threatening condition (Stevens Johnson Syndrome) caused by carbamazepine.

4. Hepatitis B and C Pharmacogenomic Project
   4.1 Aim: Differentiating genetic variant patterns between interferon responders and non-responders by identifying host SNPs that can predict Interferon (IFN) response in new chronic hepatitis C patients contemplating interferon therapy.
   4.2 Progress: There are two ongoing studies through collaboration of National Taiwan University Hospital and one of the leading genomics company in Taiwan. In these studies, patients are divided into responder and non-responder groups for an IFN alpha drug regime. More than 10 SNPs on eight genes in the antiviral pathway that may influence IFN response in hepatitis B and C patients have been successfully identified.

3. Activities

1. Symposium and workshop
   A number of scientific meetings in relation with pharmacogenetics/genomics have been held during past years or will be this year. Below are the examples:
   1.1 Taipei Science and Technology Law Forum – Legal Reform in Response to the Bio-Tech Revolution in the 21st Century: pharmacogenomics for personalised medicine, the use of genetic testing and protection of personal genetic information were included in the discussion. (August 2002)
   1.2 Clinical Research Seminar Series- Pharmacogenomics and Population Pharmacokinetics: The role of pharmacogenomics in drug development and regulatory decision making were addressed. (December 2002)
   1.3 Workshop on Biomedicine Research and Bioinformatics: The issues to be discussed are challenges, application and regulations of pharmacogenomics, as well as application of bioinformatics. (March 2004)
2. Center for Drug Evaluation (CDE): internal taskforce meetings to look into current pharmacogenetics/nomics-related research projects and clinical trials and to promote the cooperation between DoH, ELSI and CDE to enactment of pharmacogenomics-related regulations and laws.

4. Present situation of pharmacogenomics in academia and industry in Taiwan

Research projects investigating pharmacokinetics- and/or pharmacodynamics-related genetic polymorphism are a booming area in academia and major medical centers in Taiwan, mostly through collaboration between the two groups. Although the area of pharmacogenomics has not yet become a focus to the local pharmaceutical companies, a few of genomics companies are making endeavours to understand the genes and pathways involved in major endemic diseases and the responsiveness of patients to drug therapy using pharmacogenomics approaches and thus to improve the diagnosis, treatment, and eventual cure of the diseases.

1. Major projects by collaboration between industry and clinical research institutes
   1.1 Asthma: One study is currently ongoing to look for the naturally occurring genetic variation affecting the function and regulation of genes that are critical for the pathogenesis of asthma, a disease mediated by allergen- specific IgE. This project has identified certain SNPs that are related to the increased IgE levels in paediatric asthma, and the patent application has been filed.
   1.2 Diabetes: This ongoing study aims to examine the genetic mechanism underlying the renal complications of diabetics.
   1.3 Pharmacogenomics-oriented development of traditional Chinese medicine: This genome-based biomedical research project aims to improve diagnosis of major diseases such as hypertension and hepatitis by identifying their genetic markers and to develop Chinese herbal medicine to better treat such diseases.
2. Clinical Research and Clinical Trials
   2.1 Phenytoin: a clinical study was performed in a total of 169 epileptic patients receiving phenytoin treatment for more than one month, and the results indicated that the dosage of phenytoin can be optimised based on the metabolic activities of CYP2C9 and CYP2C19 polymorphisms genotyped by PCR-RFLP analysis.
   2.2 A number of multi-national phase III and post-marketing clinical trials including blood sample collection for pharmacogenomics analysis and evaluation of pharmacokinetics-related genetic polymorphism have been started.
3. Development of Diagnostic Kits
   3.1 Treatment of hepatitis C: a proprietary DNA-based diagnostic technology was successfully developed using pharmacogenomic approaches to "fish out" patients and carriers who are susceptible to the current single and combination therapies involving IFN drugs. The patent application of this diagnostic technique has been filed.
   3.2 More molecular diagnostic related technology and products are being developed through collection and analysis of samples from patients with progressive illnesses and samples from patients being treated with various drugs to help early detection and better treatment of major diseases such as cirrhosis, hepatoma, asthma, breast cancer, diabetes and diabetic nephropathy.

Annex 6

Pharmacogenetics and Pharmacogenomics in the European Union

The development of pharmacogenetics and pharmacogenomics in the European Union (EU) should be considered in the wider framework of policies for a dynamic knowledge-driven economy, supporting the establishment of a European Area of research and innovation. These policies impact on public health, industrial and social sectors with the objective of enhancing an EU-integrated innovation's performance[1]. In 2000, the European Parliament set up a Temporary Committee on Human Genetics and New Technologies in Modern Medicine to assess the ethical, legal, economic and social implications of human genetics. The draft report from this Committee, dated November 2001, and the European Parliament Report on the Commission communication Life Sciences and Biotechnology – A Strategy for Europe – adopted in November 2002, both indicated the need for policy actions regarding the use of genetic testing for medical and non-medical purposes to lay down a harmonised regulatory framework.

Many initiatives have been undertaken within the European Commission services, in collaboration with other EU Institutions, tackling different aspects of genetic testing and aiming to contributing to i) developing novel or improved genetic tests, ii) improving the quality of genetic services, iii) analysing the ethical, legal and social aspects, iv) providing support for the development of related responsible policies, v) fostering societal dialogue and vi) encouraging international dialogue.

In order to ensure that different services of the European Commission share information, support each others' initiatives and avoid the risk of duplication, an "inter-service" group on genetic testing has been set up. The group meets at regular intervals and provides progress reports to the Biological Steering Committee in preparation of the main policy discussions taking place at the level of the Council of Ministers and the European Parliament. Initiatives have also been undertaken by the European Commission for the establishment of a high level working party with the participation of the representatives of Member States with the objective of exchanging information and coordinating the many important national initiatives taking place in the field of genetics such as the creation of DNA biobanks and the issuance of national guidelines.

The European Medicines Agency (EMEA) launched its activities on pharmacogenetics in June 2000 with a facts-finding seminar on pharmacogenetics where experts from the Committee for Proprietary Medicinal Products (CPMP, now known as the Committee for Medicinal Products for Human use, CHMP), industry and patients' organisations contributed. A multidisciplinary Ad Hoc Expert Group on Pharmacogenetics was set up by the CPMP in 2001 to address priorities identified during the workshop.

[1] Presidency conclusions Lisbon March 2000
http://ue.eu.int/ueDocs/cms_Data/docs/pressData/en/ec/00100-r1.en0.htm

A Position Paper on Terminology on Pharmacogenetics was released by the CPMP in 2002. This is attached herewith. The document addresses the use of key terms applicable to the handling of samples and data generated in pharmacogenetic testing during clinical trials. The document provides the position of CPMP on technical, regulatory and privacy protection aspects. This document has already been accepted as one of the reference documents on terminology in pharmacogenetics at international level. The CPMP document on terminology has also been adapted into lay language in consultation with the CPMP Working Party with Patients Associations. It will be made available in all EU languages for wider use by early 2005.

Since 2002, the EMEA is also contributing as requested to a number of initiatives of the European Commission, especially on technical research aspects and ethical issues specific to pharmacogenetics and pharmacogenomics. The EMEA is also active member of the inter-service co-ordination group on genetic testing.

In 2003, the CPMP implemented a new initiative called Briefing Meetings on Pharmacogenetics which provided for an informal forum for discussion between sponsors and regulators on the main technical issues associated with pharmacogenetics in drug development and scientific and regulatory assessment. As of July 2004, 10 pharmaceutical companies had applied for such informal meetings at the EMEA.

Looking forward to the necessary international dialogue in the field, the EMEA joined the CIOMS Working Group on Pharmacogenetics in late 2001 and also started an exchange of contributions with the FDA in a number of international meetings (Washington May 2002, London October 2003, Washington July 2004).

Further initiatives will be pursued at the EU and international levels to ensure that there will not be significant regulatory differences creating hurdles at a regional or global level to the best exploitation of this new technology in drug development, approval and clinical use.

For additional information the following websites are available for consultation:

http://europa.eu.int/index.htm
http://heads.medagencies.org
http://www.emea.eu.int/index/indexh1.htm
http://pharmacos.eudra.org/

London 21 November 2002
EMEA/CPMP/3070/01

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POSITION PAPER ON TERMINOLOGY IN PHARMACOGENETICS

1. Introduction

Pharmacogenetic research started from the observations that not all subjects respond in the same way to the same medicine and that these differences between individuals may be caused partially by their genetic profile.

Today the drug development programmes consider (usually for practical reasons) the subjects as coming from a rather homogenous population since it is not possible to accommodate fully in the drug development programme the whole range of inter-individual variability observed within a population. When differences in drug response are anticipated, e.g. in subjects with renal or hepatic disease, or with age-related differences, then studies are requested in the specific subgroup identified.

The contribution of genetic influences to variability in drug response often far exceeds that of any other variable and is what the science of pharmacogenetics aims to unravel. The analysis of a broad set of genetic variations may show that a genotypically defined subgroup of subjects may have a higher probability of responding to a certain drug differently from others in the population. The overall genetic profile may vary according to ethnicity.

As a result of the development within the areas of genetics and genomics, changes are likely to occur in the way drug development is currently being conducted and the way medicines will be used.

The use of terms that are harmonised and widely accepted by the stakeholders would contribute greatly to clarity in the dialogue. At present there is not an agreed set of working definitions crucial for pharmacogenetic clinical research. This is urgently required for protocols and guidelines addressing pharmacogenetic testing to ease communication particularly between ethics committees, investigators and subjects.

Following extensive consultation, the CPMP has agreed on a specific set of definitions directly relevant to the current practices in clinical research,

with the understanding that they may have to be revisited in the light of future scientific advance and taking into account emerging legislation. The definitions discussed hereafter are highly relevant to the scenario of individual clinical protocols including pharmacogenetic testing; the principles might however be relevant also for trials involving testing other than pharmacogenetics.

The terms "pharmacogenetics" and "pharmacogenomics" as well as the terms used in the handling of samples and data for pharmacogenetic testing have been defined from the scientific-technical point of view.

The same definitions, following appropriate consultation will then be written in lay-terms and made available in all EU official languages to constitute a useful technical asset for regulatory authorities, ethics committees, health professionals and subjects when confronted with pharmacogenetic testing protocols and consent documents for medicinal product clinical trials.

2. Scope

This position paper focuses on a specific set of critical terms that are frequently used in protocols for pharmacogenetic testing and that are relevant to define appropriate levels of protection for the privacy of the subjects when describing how the results and samples will be used in clinical trials.

The choice of the level depends on the extent to which it is desired or considered possible to link the data and samples to an identifiable subject and corresponds to the defined category of sample linkage.

The most appropriate level for a particular study depends on the nature of the research, the intended use of the data, the regulatory and legal environment and the specific concerns of the investigator and study sponsor. This choice must respect the needs for the privacy of subjects participating in a clinical study.

Generally, the greater the subject privacy in a study, the less are the opportunities for the subject after sample collection and pharmacogenetic testing have been performed to withdraw the individual samples from further analyses or to receive individual results from the study. Privacy of information, control over the use of samples, and knowledge of study results may all contribute to a subject's willingness to take part in a study, and as a consequence the choice of process may significantly affect enrolment in a clinical trial in which pharmacogenetic testing is planned.

Sample coding procedures should be documented according to Good Clinical Practices (GCPs) and as provided for by relevant EU directives and accompanying guidance documents. Primary study data and original study-

related records should be accessible to the competent regulatory authority in order to validate the evidence that is reported. While the regulatory authority can accept different levels of documentation, depending on the particulars of the study and the availability of other evidence or records, there may be times when it is necessary to link a clinical outcome to a particular patient. In principle, there is a framework for protecting patients enrolled in clinical trials now, and this framework may be adequate, perhaps with small changes, to apply to clinical pharmacogenetic trials.

Complete anonymity of the subject without any possibility of linking the samples/data to an individual will have great impact on the usefulness of the results and on what aspects might be verified during a GCP inspection from a competent authority or a sponsor audit. The individual subject record is an important component of data for submission to regulatory agencies ad so the use of data from a study involving anonymised samples might not be acceptable for the submission of a claim to be included in the label of a drug or clinical diagnostic assay.

In designing clinical trials, investigators and sponsors should attempt, in consultation with competent authorities and ethics committees, to find the optimum balance between achieving the aims of the study and protecting the subject's safety or right to privacy.

It is recognised that DNA data unique to a subject could potentially be used to reconstruct a link between a subject's medical record and genotype information. Procedures should ensure that in order to respect the subject's wishes and privacy, such links are not reconstructed. For the same reasons, it is further recommended that the code should comprise randomly assigned numbers/letters and should not be based on protocol and site number (and perhaps gender) because if a particular site has included only a few subjects, it might be theoretically possible to reconstruct a link to individual subjects.

3. Pharmacogenetics and Pharmacogenomics

There is at present no consensus in the literature on the definitions of "pharmacogenetics" and "pharmacogenomics". Actually the terms are frequently used interchangeably. The achievement of widely accepted working definitions of the two would be a useful first approach to applying pharmacogenetics and pharmacogenomics in clinical trials. It is important to single out pharmacogenetics and pharmacogenomics from the wider field of genetic testing as the latter encompasses different level of concerns especially in terms of sensitivity of sample handling, data and trial results management.

Pharmacogenetics is the study of interindividual variations in DNA sequence related to drug response.

Pharmacogenomics is the study of the variability of the expression of the individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development.

4. Definitions applicable to DNA samples and data in clinical trials including pharmacogenetic testing

Different terminologies relate to the collection of human samples for pharmacogenetic research and the management of the data therefrom. The set of terms described in this paper are a key to correct handling of the samples and the data and to transparency of communication among industry, ethics committees, regulatory authorities and subjects about the pharmacogenetic approach in clinical research, regulatory assessment of medicinal products and clinical practice.

The processes by which samples and data are collected, labelled and stored have a direct effect on how the samples and the results obtained can be used in the future and on the obligations of the investigator and sponsor to the sample subject. This pertains particularly to situations when a subject withdraws his or her consent to further participation in a study and affects the possibility to return information to the subject or his/her physician, the possibility to withdraw a sample from future analyses and verification of data ascribed to a subject in reports and regulatory submissions. Additionally, the readiness and willingness with which a subject would or would not want to take part in a study may be affected by such factors as the uses of the results, the nature of the information the subject might receive, and the perceived risk resulting from disclosure of genetic information to third parties.

Five definitions (See table 1) for the labeling and coding of pharmacogenetic samples and data are proposed describing direct implications for the handling methodology of samples for pharmacogenetic testing and corresponding consequences for the level of privacy protection and use of the information for regulatory purposes. Duration of retention of the sample or its destruction needs to be defined in the protocol and in the consent form. Otherwise, if and when relevant, the timepoint and the procedure for anonymisation of the sample itself should be defined in these documents.

4.1 Identified samples and data

are those labeled with personal identifiers such as Name or Social Security Number.

Identified samples and data are treated in much the same way as those acquired in everyday medical practice. Because the sample and the data generated from it are directly traced to the subject, it is easy to withdraw the sam-

Table 1 Summary table of the five terms of sample labelling

SAMPLE LABELLING CATEGORY	Link Between Subject Identity and Pharmacogenetic Data	Records Identifiable for Clinical Monitoring	Actions Possible if subject withdraws Consent	Return of Individual Results to Subject	Scope of Subject Privacy protection
Identified	Yes, directly	Yes	Sample can be withdrawn with immediate effect for any prospective use	Possible	Similar to general healthcare confidentiality
Single coded	Indirectly, via code key	Yes, via protocol-specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Standard for clinical research Conforms to principles of GCP
Double coded	Very indirectly, via two sets of code keys	Yes, via protocol-specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Double code offers added privacy protection over single code
Anonymised	No. Key(s) identifying the link between pharmacogenetic data and the identity of the subject is deleted	No	Sample and data are not identifiable. Sample cannot be withdrawn once key is deleted	Not possible	Pharmacogenetic data not linked to individuals
Anonymous	No	No	None	Not possible	Complete

ple or the data from the study, update subject information, and return results to the subject. Also, at an inspection of the study it will be possible to verify the connection between the subject and the reported results. On the other hand, since a subject's genotyping results are directly linked to the subject's identity, the use of identified samples offers no extra privacy protection in addition to those generally provided.

Identified samples and relevant data might be coded at the given point in time in order to provide for extra long-term privacy protection following the closure of the trial. The protocol should also specify when and whether the samples and data might be destroyed or anonymised.

4.2 Single coded samples and data

are those to which a single specific code is attributed for protecting individuals. It is recommended that the code should compromise randomly assigned numbers/letters.

The investigator stores the key connecting the code of the sample to the individual's data. This step separates the subject's identity from the results of the pharmacogenetic analysis. The researcher with knowledge of the pharmacogenetic data would not have ready access to the identity of the subject.

Only breaking the code can reveal the subject's identity.

It is possible to withdraw a subject's sample for prospective use or return individual results to the subject or physician if desired.

The maintenance of a link between the subject and the pharmacogenetic information by a single code allows verification of data ascribed to an individual subject. Because the investigator who has coded the sample might also have access to the pharmacogenetic data, the safeguards of the subject's privacy, including doctor-subject confidentiality, are equivalent to those in current clinical trials practice.

4.3 Double-coded samples and data

have an additional privacy safeguard imposed by the use of a second coding system. Adding an additional code to the samples and data provides further protection.

The investigator who only knows the first code does not know this second code. In this way, anyone with knowledge of the pharmacogenetic results can only trace a subject identity to a coded identifier but no further, unless a key is used to link the codes between the data set with subject identifiers and the data set containing the pharmacogenetic information.